

Collective Intelligence of Specialized Language Models Guides Realization of de novo Chemical Synthesis

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Supplementary Information for MOSAIC

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1. Kernel Metric Network Training

The training data was curated from the Pistachio database, filtering for reactions with labeled names, which reduced the original 5M dataset to 3.7M reactions in 2285 reaction classes. For each reaction, represented in SMILES format, we separated the components into reactants (left-hand side) and products (right-hand side). The molecular structure of each side was then encoded into two distinct 1024-dimensional vectors: one using RDKit fingerprint (maxpath = 4) [1] and another using Morgan fingerprint (radius = 2) [2]. We used both because, in our study, we found RDKit fingerprint consistently outperforms the Morgan but the combination of the two gives slightly better results. These fingerprints were concatenated to create 2048-dimensional representations for both reactants and products. To capture the chemical transformation, we calculated the difference between product and reactant vectors. This procedure yields a 6144-dimensional input vector. The KMN utilized these three representations, product, and their difference vectors to learn reaction classifications.

The model's first layer is a fully connected linear layer that reduces the 6144 dimensions down to 256, then followed by a relu activation. The result was then sent to a batch normalization layer. This result is then fed to another fully connected dimension reduction layer to convert the 256-dimensional output to 128. Then another relu activation is done followed by batch normalization. The classification head then projects the 128-dimensional vector (the RSFP) from the above procedure to the number of reaction classes. A dropout with a probability of 0.3 is added after each of the two batch normalization layers during training as a method of regularization.

The model was trained for 50 epochs on a single A100 GPU with a batch size of 4096. We employed the AdamW optimizer [3] with a maximum learning rate of 0.001, implementing a training schedule that consisted of a 5-epoch linear warm-up followed by 45 epochs of cosine annealing. Model performance was monitored throughout training using a validation set comprising 5% of the filtered dataset, selected through random sampling. An accuracy of 92.52% and an evaluation loss of 0.235 was achieved on the validation set.

Fingerprint Selection Benchmarks (Why Concatenated Fingerprint)

On the identical architecture as mentioned in the KMN Training, we benchmarked the choice of RDKit (path = 4) vs Morgan (radius = 2) vs RDKit (path = 4) + Morgan (radius = 2) fingerprint.

Morgan (Radius = 2)

maximum accuracy achieved = 89.52%, evaluation loss converges to 0.3412

Epoch 1/50, Validation Accuracy: 0.0005, Train_loss 7.9589 ,Eval_Loss: 7.8295
Epoch 2/50, Validation Accuracy: 0.7602, Train_loss 2.6061 ,Eval_Loss: 1.1588
Epoch 3/50, Validation Accuracy: 0.8335, Train_loss 1.0296 ,Eval_Loss: 0.6560
Epoch 4/50, Validation Accuracy: 0.8538, Train_loss 0.7768 ,Eval_Loss: 0.5326
Epoch 5/50, Validation Accuracy: 0.8626, Train_loss 0.6889 ,Eval_Loss: 0.4806
Epoch 6/50, Validation Accuracy: 0.8687, Train_loss 0.6466 ,Eval_Loss: 0.4528
Epoch 7/50, Validation Accuracy: 0.8723, Train_loss 0.6117 ,Eval_Loss: 0.4332
Epoch 8/50, Validation Accuracy: 0.8762, Train_loss 0.5894 ,Eval_Loss: 0.4192
Epoch 9/50, Validation Accuracy: 0.8776, Train_loss 0.5742 ,Eval_Loss: 0.4080
Epoch 10/50, Validation Accuracy: 0.8801, Train_loss 0.5616 ,Eval_Loss: 0.4015
Epoch 11/50, Validation Accuracy: 0.8812, Train_loss 0.5516 ,Eval_Loss: 0.3961
Epoch 12/50, Validation Accuracy: 0.8823, Train_loss 0.5430 ,Eval_Loss: 0.3911

Epoch 13/50, Validation Accuracy: 0.8832, Train_loss 0.5356 ,Eval_Loss: 0.3872
Epoch 14/50, Validation Accuracy: 0.8840, Train_loss 0.5293 ,Eval_Loss: 0.3833
Epoch 15/50, Validation Accuracy: 0.8847, Train_loss 0.5239 ,Eval_Loss: 0.3804
Epoch 16/50, Validation Accuracy: 0.8861, Train_loss 0.5182 ,Eval_Loss: 0.3765
Epoch 17/50, Validation Accuracy: 0.8861, Train_loss 0.5129 ,Eval_Loss: 0.3745
Epoch 18/50, Validation Accuracy: 0.8867, Train_loss 0.5085 ,Eval_Loss: 0.3716
Epoch 19/50, Validation Accuracy: 0.8880, Train_loss 0.5040 ,Eval_Loss: 0.3682
Epoch 20/50, Validation Accuracy: 0.8884, Train_loss 0.5008 ,Eval_Loss: 0.3669
Epoch 21/50, Validation Accuracy: 0.8890, Train_loss 0.4971 ,Eval_Loss: 0.3648
Epoch 22/50, Validation Accuracy: 0.8892, Train_loss 0.4930 ,Eval_Loss: 0.3625
Epoch 23/50, Validation Accuracy: 0.8893, Train_loss 0.4894 ,Eval_Loss: 0.3615
Epoch 24/50, Validation Accuracy: 0.8903, Train_loss 0.4863 ,Eval_Loss: 0.3584
Epoch 25/50, Validation Accuracy: 0.8901, Train_loss 0.4830 ,Eval_Loss: 0.3588
Epoch 26/50, Validation Accuracy: 0.8914, Train_loss 0.4806 ,Eval_Loss: 0.3558
Epoch 27/50, Validation Accuracy: 0.8915, Train_loss 0.4781 ,Eval_Loss: 0.3544
Epoch 28/50, Validation Accuracy: 0.8918, Train_loss 0.4746 ,Eval_Loss: 0.3540
Epoch 29/50, Validation Accuracy: 0.8919, Train_loss 0.4720 ,Eval_Loss: 0.3522
Epoch 30/50, Validation Accuracy: 0.8928, Train_loss 0.4694 ,Eval_Loss: 0.3510
Epoch 31/50, Validation Accuracy: 0.8928, Train_loss 0.4669 ,Eval_Loss: 0.3499
Epoch 32/50, Validation Accuracy: 0.8928, Train_loss 0.4644 ,Eval_Loss: 0.3492
Epoch 33/50, Validation Accuracy: 0.8931, Train_loss 0.4619 ,Eval_Loss: 0.3482
Epoch 34/50, Validation Accuracy: 0.8935, Train_loss 0.4601 ,Eval_Loss: 0.3475
Epoch 35/50, Validation Accuracy: 0.8938, Train_loss 0.4575 ,Eval_Loss: 0.3467
Epoch 36/50, Validation Accuracy: 0.8941, Train_loss 0.4559 ,Eval_Loss: 0.3456
Epoch 37/50, Validation Accuracy: 0.8941, Train_loss 0.4539 ,Eval_Loss: 0.3450
Epoch 38/50, Validation Accuracy: 0.8943, Train_loss 0.4515 ,Eval_Loss: 0.3442
Epoch 39/50, Validation Accuracy: 0.8941, Train_loss 0.4506 ,Eval_Loss: 0.3440
Epoch 40/50, Validation Accuracy: 0.8946, Train_loss 0.4490 ,Eval_Loss: 0.3431
Epoch 41/50, Validation Accuracy: 0.8946, Train_loss 0.4473 ,Eval_Loss: 0.3432
Epoch 42/50, Validation Accuracy: 0.8948, Train_loss 0.4461 ,Eval_Loss: 0.3422
Epoch 43/50, Validation Accuracy: 0.8948, Train_loss 0.4450 ,Eval_Loss: 0.3420
Epoch 44/50, Validation Accuracy: 0.8950, Train_loss 0.4441 ,Eval_Loss: 0.3417
Epoch 45/50, Validation Accuracy: 0.8949, Train_loss 0.4428 ,Eval_Loss: 0.3416
Epoch 46/50, Validation Accuracy: 0.8950, Train_loss 0.4425 ,Eval_Loss: 0.3416
Epoch 47/50, Validation Accuracy: 0.8952, Train_loss 0.4421 ,Eval_Loss: 0.3412
Epoch 48/50, Validation Accuracy: 0.8951, Train_loss 0.4417 ,Eval_Loss: 0.3412
Epoch 49/50, Validation Accuracy: 0.8951, Train_loss 0.4410 ,Eval_Loss: 0.3412
Epoch 50/50, Validation Accuracy: 0.8952, Train_loss 0.4410 ,Eval_Loss: 0.3412

RDKit (Path = 4), maximum accuracy achieved = 89.42%, evaluation loss converges to 0.3455.

Epoch 1/50, Validation Accuracy: 0.0004, Train_loss 8.0061 ,Eval_Loss: 7.8772
Epoch 2/50, Validation Accuracy: 0.7734, Train_loss 2.4077 ,Eval_Loss: 1.0299
Epoch 3/50, Validation Accuracy: 0.8351, Train_loss 0.9307 ,Eval_Loss: 0.6241
Epoch 4/50, Validation Accuracy: 0.8526, Train_loss 0.7235 ,Eval_Loss: 0.5251
Epoch 5/50, Validation Accuracy: 0.8586, Train_loss 0.6523 ,Eval_Loss: 0.4870
Epoch 6/50, Validation Accuracy: 0.8633, Train_loss 0.6170 ,Eval_Loss: 0.4679
Epoch 7/50, Validation Accuracy: 0.8673, Train_loss 0.5860 ,Eval_Loss: 0.4483
Epoch 8/50, Validation Accuracy: 0.8707, Train_loss 0.5661 ,Eval_Loss: 0.4347
Epoch 9/50, Validation Accuracy: 0.8721, Train_loss 0.5524 ,Eval_Loss: 0.4267
Epoch 10/50, Validation Accuracy: 0.8745, Train_loss 0.5404 ,Eval_Loss: 0.4193
Epoch 11/50, Validation Accuracy: 0.8764, Train_loss 0.5314 ,Eval_Loss: 0.4114
Epoch 12/50, Validation Accuracy: 0.8774, Train_loss 0.5223 ,Eval_Loss: 0.4062
Epoch 13/50, Validation Accuracy: 0.8779, Train_loss 0.5152 ,Eval_Loss: 0.4039
Epoch 14/50, Validation Accuracy: 0.8781, Train_loss 0.5084 ,Eval_Loss: 0.4003
Epoch 15/50, Validation Accuracy: 0.8799, Train_loss 0.5024 ,Eval_Loss: 0.3957
Epoch 16/50, Validation Accuracy: 0.8808, Train_loss 0.4962 ,Eval_Loss: 0.3926

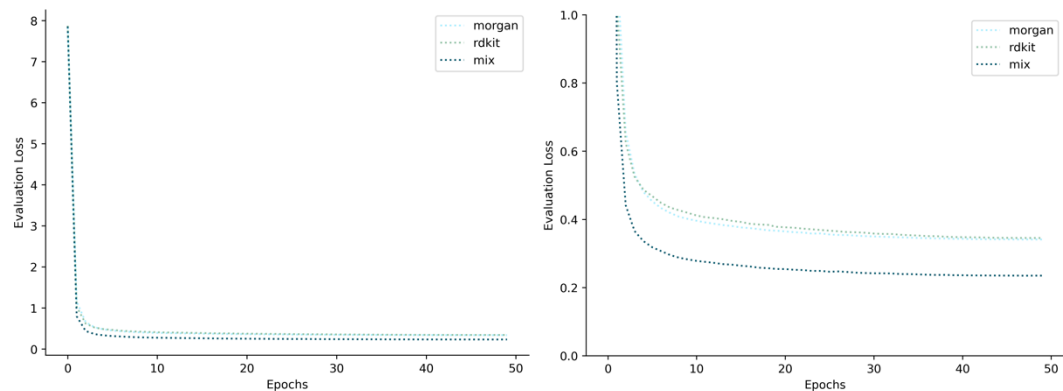
Epoch 17/50, Validation Accuracy: 0.8821, Train_loss 0.4920 ,Eval_Loss: 0.3873
Epoch 18/50, Validation Accuracy: 0.8826, Train_loss 0.4869 ,Eval_Loss: 0.3851
Epoch 19/50, Validation Accuracy: 0.8827, Train_loss 0.4823 ,Eval_Loss: 0.3842
Epoch 20/50, Validation Accuracy: 0.8844, Train_loss 0.4787 ,Eval_Loss: 0.3784
Epoch 21/50, Validation Accuracy: 0.8851, Train_loss 0.4745 ,Eval_Loss: 0.3769
Epoch 22/50, Validation Accuracy: 0.8854, Train_loss 0.4701 ,Eval_Loss: 0.3756
Epoch 23/50, Validation Accuracy: 0.8855, Train_loss 0.4671 ,Eval_Loss: 0.3729
Epoch 24/50, Validation Accuracy: 0.8865, Train_loss 0.4631 ,Eval_Loss: 0.3710
Epoch 25/50, Validation Accuracy: 0.8870, Train_loss 0.4600 ,Eval_Loss: 0.3690
Epoch 26/50, Validation Accuracy: 0.8881, Train_loss 0.4568 ,Eval_Loss: 0.3670
Epoch 27/50, Validation Accuracy: 0.8883, Train_loss 0.4542 ,Eval_Loss: 0.3650
Epoch 28/50, Validation Accuracy: 0.8889, Train_loss 0.4508 ,Eval_Loss: 0.3628
Epoch 29/50, Validation Accuracy: 0.8890, Train_loss 0.4477 ,Eval_Loss: 0.3623
Epoch 30/50, Validation Accuracy: 0.8897, Train_loss 0.4450 ,Eval_Loss: 0.3609
Epoch 31/50, Validation Accuracy: 0.8899, Train_loss 0.4426 ,Eval_Loss: 0.3585
Epoch 32/50, Validation Accuracy: 0.8908, Train_loss 0.4392 ,Eval_Loss: 0.3575
Epoch 33/50, Validation Accuracy: 0.8903, Train_loss 0.4364 ,Eval_Loss: 0.3572
Epoch 34/50, Validation Accuracy: 0.8908, Train_loss 0.4337 ,Eval_Loss: 0.3550
Epoch 35/50, Validation Accuracy: 0.8922, Train_loss 0.4317 ,Eval_Loss: 0.3537
Epoch 36/50, Validation Accuracy: 0.8919, Train_loss 0.4301 ,Eval_Loss: 0.3527
Epoch 37/50, Validation Accuracy: 0.8925, Train_loss 0.4278 ,Eval_Loss: 0.3510
Epoch 38/50, Validation Accuracy: 0.8926, Train_loss 0.4253 ,Eval_Loss: 0.3509
Epoch 39/50, Validation Accuracy: 0.8931, Train_loss 0.4237 ,Eval_Loss: 0.3493
Epoch 40/50, Validation Accuracy: 0.8929, Train_loss 0.4215 ,Eval_Loss: 0.3483
Epoch 41/50, Validation Accuracy: 0.8932, Train_loss 0.4196 ,Eval_Loss: 0.3479
Epoch 42/50, Validation Accuracy: 0.8935, Train_loss 0.4189 ,Eval_Loss: 0.3475
Epoch 43/50, Validation Accuracy: 0.8937, Train_loss 0.4174 ,Eval_Loss: 0.3472
Epoch 44/50, Validation Accuracy: 0.8938, Train_loss 0.4160 ,Eval_Loss: 0.3465
Epoch 45/50, Validation Accuracy: 0.8938, Train_loss 0.4150 ,Eval_Loss: 0.3460
Epoch 46/50, Validation Accuracy: 0.8940, Train_loss 0.4143 ,Eval_Loss: 0.3459
Epoch 47/50, Validation Accuracy: 0.8942, Train_loss 0.4135 ,Eval_Loss: 0.3456
Epoch 48/50, Validation Accuracy: 0.8941, Train_loss 0.4135 ,Eval_Loss: 0.3456
Epoch 49/50, Validation Accuracy: 0.8942, Train_loss 0.4127 ,Eval_Loss: 0.3455
Epoch 50/50, Validation Accuracy: 0.8942, Train_loss 0.4130 ,Eval_Loss: 0.3455

RDKit (Path = 4) + Morgan (Radius = 2), this work.

maximum accuracy achieved = 92.52%, evaluation loss converges to 0.2351.

Epoch 1/50, Validation Accuracy: 0.0004, Train_loss 7.9725 ,Eval_Loss: 7.8573
Epoch 2/50, Validation Accuracy: 0.8239, Train_loss 2.1127 ,Eval_Loss: 0.8009
Epoch 3/50, Validation Accuracy: 0.8783, Train_loss 0.7126 ,Eval_Loss: 0.4413
Epoch 4/50, Validation Accuracy: 0.8915, Train_loss 0.5237 ,Eval_Loss: 0.3657
Epoch 5/50, Validation Accuracy: 0.8970, Train_loss 0.4601 ,Eval_Loss: 0.3362
Epoch 6/50, Validation Accuracy: 0.9019, Train_loss 0.4293 ,Eval_Loss: 0.3182
Epoch 7/50, Validation Accuracy: 0.9039, Train_loss 0.4013 ,Eval_Loss: 0.3070
Epoch 8/50, Validation Accuracy: 0.9066, Train_loss 0.3838 ,Eval_Loss: 0.2956
Epoch 9/50, Validation Accuracy: 0.9089, Train_loss 0.3714 ,Eval_Loss: 0.2878
Epoch 10/50, Validation Accuracy: 0.9097, Train_loss 0.3615 ,Eval_Loss: 0.2827
Epoch 11/50, Validation Accuracy: 0.9115, Train_loss 0.3527 ,Eval_Loss: 0.2783
Epoch 12/50, Validation Accuracy: 0.9118, Train_loss 0.3448 ,Eval_Loss: 0.2754
Epoch 13/50, Validation Accuracy: 0.9128, Train_loss 0.3383 ,Eval_Loss: 0.2724
Epoch 14/50, Validation Accuracy: 0.9138, Train_loss 0.3320 ,Eval_Loss: 0.2688
Epoch 15/50, Validation Accuracy: 0.9141, Train_loss 0.3261 ,Eval_Loss: 0.2672
Epoch 16/50, Validation Accuracy: 0.9152, Train_loss 0.3209 ,Eval_Loss: 0.2642
Epoch 17/50, Validation Accuracy: 0.9162, Train_loss 0.3158 ,Eval_Loss: 0.2620
Epoch 18/50, Validation Accuracy: 0.9170, Train_loss 0.3115 ,Eval_Loss: 0.2584

Epoch 19/50, Validation Accuracy: 0.9174, Train_loss 0.3071 ,Eval_Loss: 0.2570
Epoch 20/50, Validation Accuracy: 0.9180, Train_loss 0.3031 ,Eval_Loss: 0.2547
Epoch 21/50, Validation Accuracy: 0.9184, Train_loss 0.2994 ,Eval_Loss: 0.2543
Epoch 22/50, Validation Accuracy: 0.9192, Train_loss 0.2951 ,Eval_Loss: 0.2522
Epoch 23/50, Validation Accuracy: 0.9194, Train_loss 0.2921 ,Eval_Loss: 0.2515
Epoch 24/50, Validation Accuracy: 0.9198, Train_loss 0.2890 ,Eval_Loss: 0.2490
Epoch 25/50, Validation Accuracy: 0.9202, Train_loss 0.2857 ,Eval_Loss: 0.2490
Epoch 26/50, Validation Accuracy: 0.9206, Train_loss 0.2819 ,Eval_Loss: 0.2465
Epoch 27/50, Validation Accuracy: 0.9208, Train_loss 0.2789 ,Eval_Loss: 0.2474
Epoch 28/50, Validation Accuracy: 0.9214, Train_loss 0.2764 ,Eval_Loss: 0.2458
Epoch 29/50, Validation Accuracy: 0.9219, Train_loss 0.2736 ,Eval_Loss: 0.2438
Epoch 30/50, Validation Accuracy: 0.9225, Train_loss 0.2712 ,Eval_Loss: 0.2427
Epoch 31/50, Validation Accuracy: 0.9226, Train_loss 0.2683 ,Eval_Loss: 0.2420
Epoch 32/50, Validation Accuracy: 0.9225, Train_loss 0.2655 ,Eval_Loss: 0.2419
Epoch 33/50, Validation Accuracy: 0.9227, Train_loss 0.2628 ,Eval_Loss: 0.2414
Epoch 34/50, Validation Accuracy: 0.9231, Train_loss 0.2609 ,Eval_Loss: 0.2397
Epoch 35/50, Validation Accuracy: 0.9232, Train_loss 0.2581 ,Eval_Loss: 0.2396
Epoch 36/50, Validation Accuracy: 0.9235, Train_loss 0.2557 ,Eval_Loss: 0.2387
Epoch 37/50, Validation Accuracy: 0.9241, Train_loss 0.2537 ,Eval_Loss: 0.2378
Epoch 38/50, Validation Accuracy: 0.9243, Train_loss 0.2524 ,Eval_Loss: 0.2371
Epoch 39/50, Validation Accuracy: 0.9243, Train_loss 0.2499 ,Eval_Loss: 0.2373
Epoch 40/50, Validation Accuracy: 0.9245, Train_loss 0.2485 ,Eval_Loss: 0.2364
Epoch 41/50, Validation Accuracy: 0.9246, Train_loss 0.2472 ,Eval_Loss: 0.2362
Epoch 42/50, Validation Accuracy: 0.9248, Train_loss 0.2458 ,Eval_Loss: 0.2358
Epoch 43/50, Validation Accuracy: 0.9251, Train_loss 0.2443 ,Eval_Loss: 0.2356
Epoch 44/50, Validation Accuracy: 0.9248, Train_loss 0.2429 ,Eval_Loss: 0.2355
Epoch 45/50, Validation Accuracy: 0.9249, Train_loss 0.2425 ,Eval_Loss: 0.2353
Epoch 46/50, Validation Accuracy: 0.9250, Train_loss 0.2411 ,Eval_Loss: 0.2352
Epoch 47/50, Validation Accuracy: 0.9251, Train_loss 0.2403 ,Eval_Loss: 0.2352
Epoch 48/50, Validation Accuracy: 0.9252, Train_loss 0.2403 ,Eval_Loss: 0.2349
Epoch 49/50, Validation Accuracy: 0.9252, Train_loss 0.2398 ,Eval_Loss: 0.2351
Epoch 50/50, Validation Accuracy: 0.9252, Train_loss 0.2400 ,Eval_Loss: 0.2351



Supplementary Figure: The right-hand-side figure is a zoomed-in view of the left with the evaluation loss ranging from 0.0 to 1.0. It can be clearly seen that using the concatenated fingerprint gives superior results than using Morgan or RDKit as an individual for KMN trainings.

2. Voronoi Experts Training

To ensure that the model would consistently output complete information, the following filtering criteria were allied to give the final 1M-dataset. The dataset has to have reaction SMILES representation, reagent SMILES, solvent SMILES, reagent name, solvent name, paragraph description, yield characterization, and paragraph description without abbreviations (contain phrase "as described in Example").

The training uses Llama3.1-8B-Instruct. LoRA adaptors were applied for weights in layers: q_proj, k_proj, v_proj, o_proj, gate_proj, up_proj, and down_proj. We used a LoRA alpha of 64 and a rank of 16. This results in a ~44M parameter adapter with a size of ~0.55% of the full 8B weights.

The base model training was done for 750,000 steps, with a batch size of 4 per step on a single node with 4xA100 GPUs. The training was set with AdamW [3] optimizer with a warm-up of 125,000 steps to reach a 0.0002 learning rate. Then it follows a cosine annealing scheduled for 12,500,000 steps.

Each of the expert's training was performed for 10 epochs for the corresponding training set. The same training specification as the base model was used except that the warm-up is done as 0.2 epoch equivalent steps for each training followed by a cosine annealing to the 10th epoch. All expert trainings were independent and were submitted to high-performance computers in parallel.

3. Generation Configuration

To ensure reproducible results with configurable search capabilities, we employ two complementary beam search strategies: traditional beam search (BS) and diverse beam search (DBS) [4]. The conventional BS methodology maintains multiple potential decoded sequences simultaneously, controlled by a beam size parameter that determines the maximum number of output sequences. When this parameter equals one, the algorithm defaults to a greedy search. In our application, BS variations primarily affect the linguistic presentation of reaction procedures rather than their chemical content.

To generate greater diversity in search outcomes, particularly for reagent and solvent combinations, we alternate between DBS and BS implementations. DBS reduces the limitation we observed with large beam sizes (≥ 25) that the model tends to generate repetitive tokens with higher beam scores (log-likelihood), identified in general large language model research [5]. DBS implementation, utilizing groups with effective beam sizes of 10 or less, substantially reduces this effect.

DBS extends the traditional beam search framework by introducing two additional parameters: beam groups and diversity penalty. This enhancement partitions the search space into distinct subgroups, with the diversity penalty ensuring sufficient differentiation between subgroup contents. The algorithm reduces to conventional BS when configured with a single beam group. Throughout our experiments, we maintained a consistent beam size of 20 for both BS and DBS implementations and a diversity penalty of 0.1 for DBS.

For all generated results a validity check is performed to filter outputs that are incomplete and token-repeating. The validation process verifies the presence and completeness of all prompt keywords specified in Main Figure 2(a), including reaction SMILES, chemical entity SMILES and names, reaction procedures, classifications, and characterization data. This validity check eliminates incomplete or redundant generations.

The final output processing involves ranking predictions by beam scores and filtering for unique reagent-solvent combinations. When duplicate combinations appear, the framework retains only the instance with the highest beam score, ensuring result diversity.

4. Yield Prediction Specifications

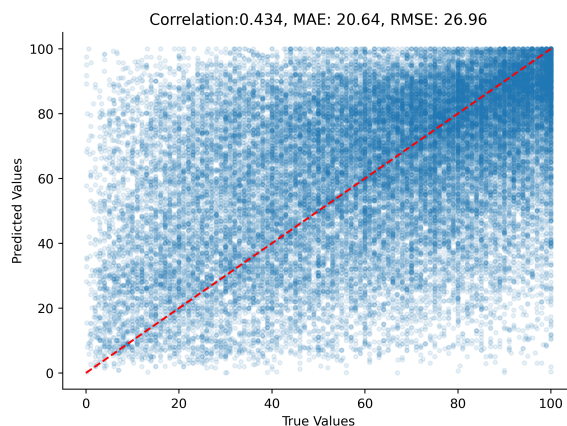
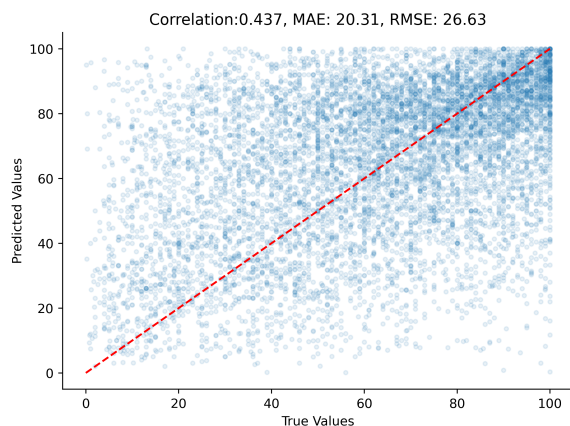
The model's yield predictions have context dependency, as they appear at the end of the prompt template and are naturally influenced by the preceding information. To evaluate prediction accuracy, we conducted testing using a curated dataset excluded from the training of all Voronoi experts. This evaluation dataset underwent a filtering step, requiring complete atom mapping of reactions, reagent SMILES notations, reagent names, complete paragraph descriptions without abbreviated references ("as described in Example" or "general procedure"), and yield characterization data. To prevent data leakage and ensure robust conclusions, we eliminated entries where products appeared in the training set or were duplicated within the test set itself.

For this prediction task, we provided the model with all relevant information preceding the yield value. The procedure descriptions typically conclude with a standardized notation for the final compound, formatted as (mass in grams/milligrams, percentage). To maintain prediction integrity, and to not let this information leak to the model, we use regular expression pattern matching to identify and truncate the text immediately before this standardized notation. Entries qualified for evaluation only when containing exactly one such expression, with the preceding number of characters comprising at least 50% of that of the complete paragraph to ensure adequate contextual information.

The yield prediction uses the top-1 expert whose Voronoi centroid is the closest to the input reaction. The process employed beam search with a size parameter of 20 and are post-processed to keep the valid ones following the generation criteria outlined in the Generation Configuration Section. Further, we handle possible hallucinations in the predicted tokens representing the yield. Since all reaction yield is reported in percentages between 0 to 100, predicted tokens representing numbers outside of this range are excluded. For each prediction entry, we aggregated valid predictions across all valid beam outputs, computing the mean value to determine the final predicted yield. We used this approach to reduce the fluctuation in the prediction as LLMs treat numbers as tokens rather than floats in regression models.

The predictions were partitioned into 100-entries batches for HPC execution. Each evaluation takes a maximum of 6h on a shared node with a single A100 GPU.

The crude result is shown below: left limiting to a max 20 cases per reaction class and right without limit.



5. Reagent and Solvent Prediction Specifications

The reagent and solvent prediction analysis utilized the same held-out dataset described in Yield Prediction Specifications Section with filtering criteria for complete reagent and solvent SMILES specifications. Following identical product exclusion procedures, we eliminated entries where products appeared in the training set or were duplicated within the test set.

The prediction protocol employs the three most closely matched expert models for each entry. These experts generate reagent and solvent predictions based solely on product and reactant information. To maximize prediction diversity, we implemented DBS with both beam size and beam group parameters set to 20.

The predictions were partitioned into 50-entries batches for HPC execution. Each evaluation takes a maximum of 10h on a shared node with a single A100 GPU.

For comparative analysis of reagents and solvents, we extract and parse the unique SMILES when a single SMILES strings represent multiple molecular entities. Consider, for example, the common cross-coupling catalyst Tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃), which appears in the dataset as:

O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.[Pd].[Pd]

In this representation, the dibenzylideneacetone (dba) moiety appears three times and palladium (Pd) twice, separated by dots. The parsing procedure decomposes this into its unique constituent components:

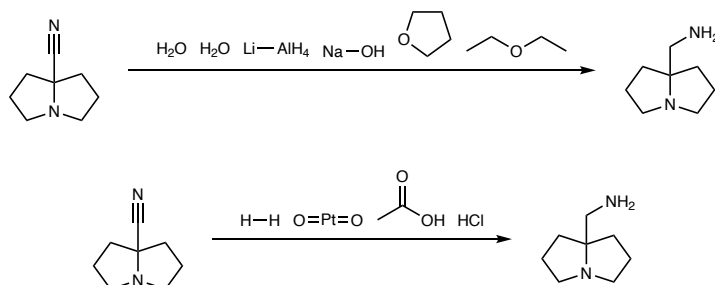
Dibenzylideneacetone (dba): **O=C(/C=C/c1ccccc1)/C=C/c1ccccc1**

Palladium: **[Pd]**

More Examples of “No-match”

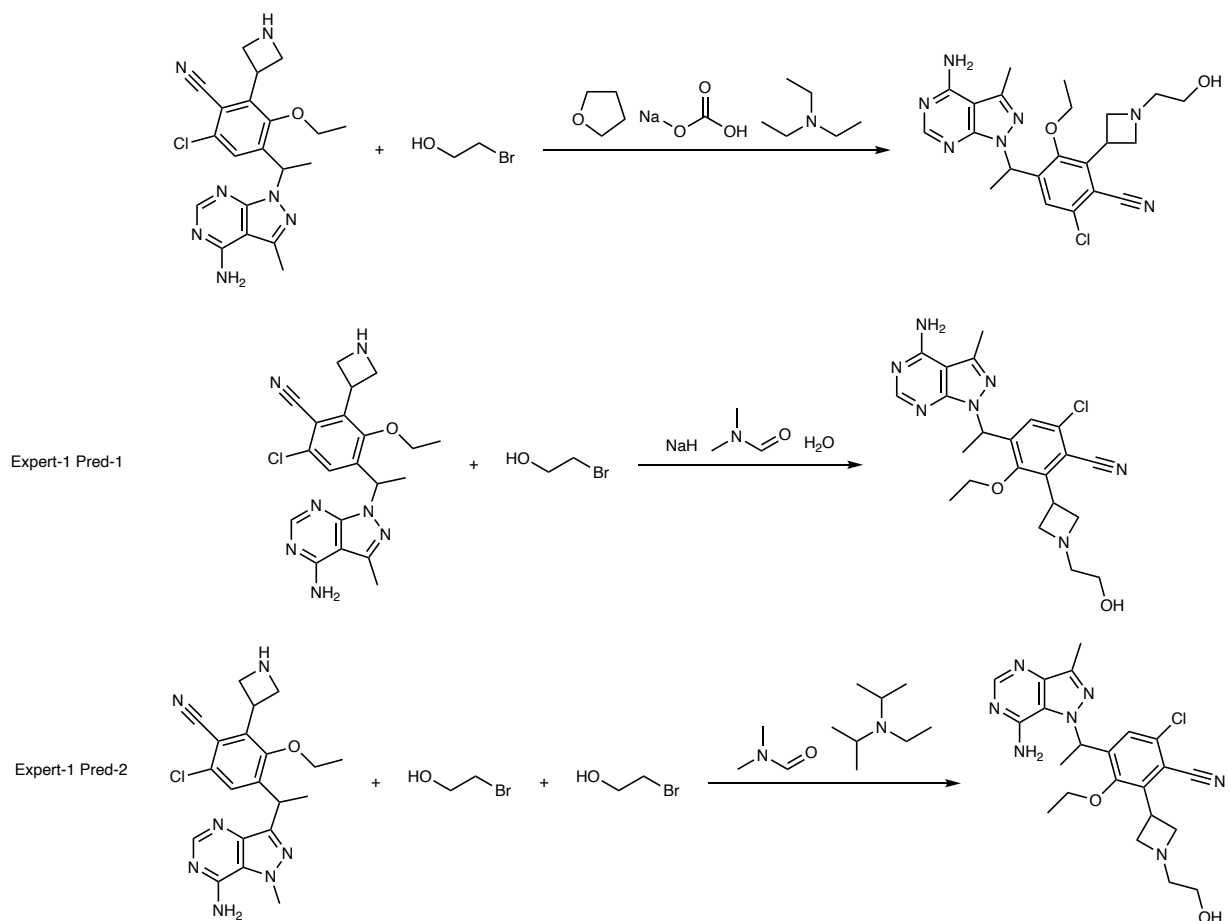
Top True Condition from Database. Bottom Model Prediction.

1.



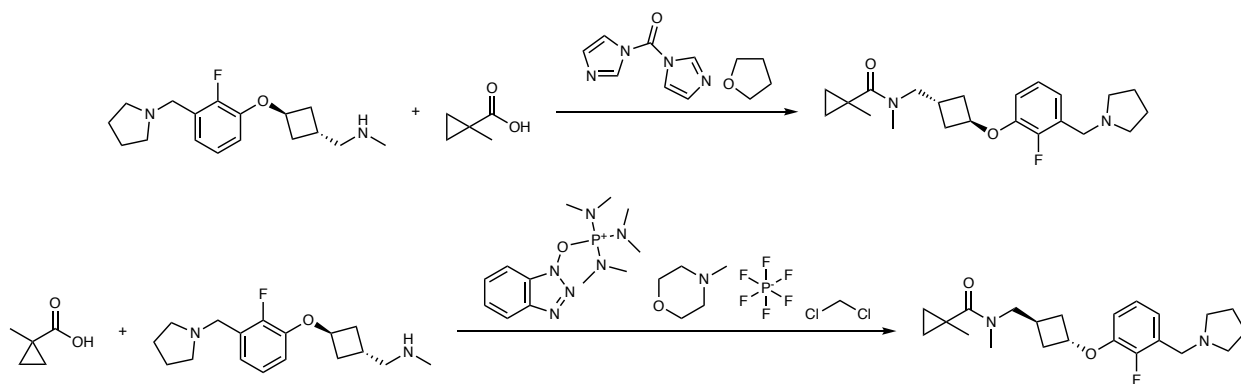
Platinum dioxide is an effective catalyst used in the hydrogenation of C=C double bond. For example, it has been reported to use the platinum dioxide to reduce the enone to its saturated analog. In this example, it could also be logical to use platinum dioxide to reduce the cyano group under hydrogen atmosphere.

2.



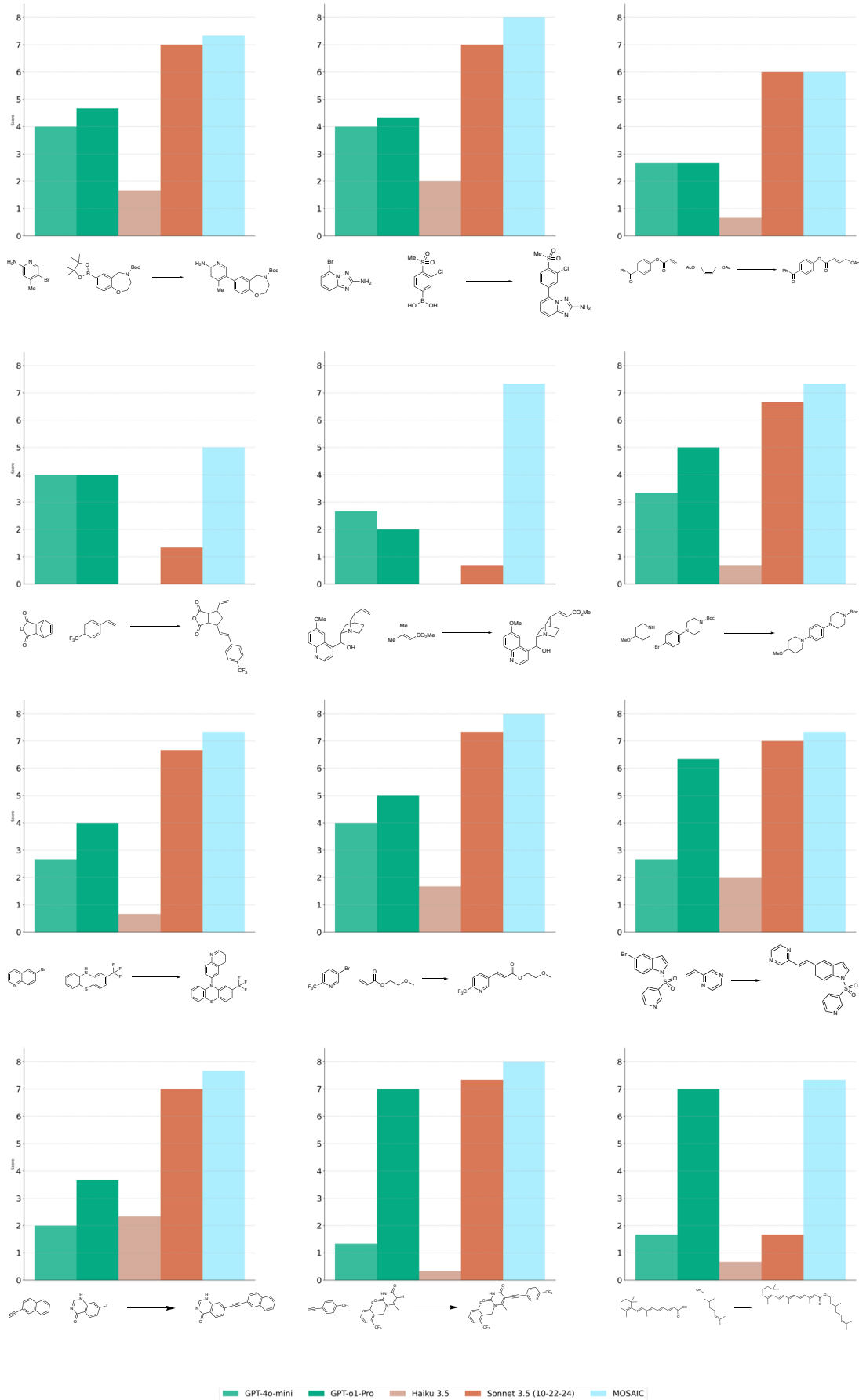
In the ground truth, triethylamine acts as a base to promote the desired nucleophilic substitution of azetidine to alkyl bromide. In the prediction 1, sodium hydride is a much stronger base, which can play the similar role to deprotonate the azetidine. In the prediction 2, N,N-diisopropylethylamine (Hünig's base) is another commonly used base.

3.



The ground truth uses CDI (N,N'-carbonyldiimidazole) as a condensation reagent to promote the amide formation. Besides this, there are a variety of reagent that can be used as the condensation reagent, including Castros reagent (benzotriazole-containing hexafluorophosphate salt) in the prediction.

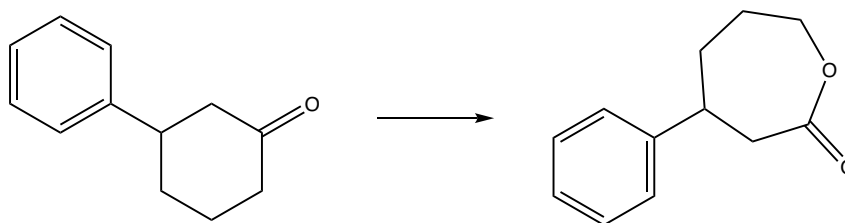
6. LLM-Responses: Individual Reaction Scorings



7. Expert Domain Knowledge Specifications (Why RSFP is Better)

The selection of RSFP over simple difference-based fingerprints (RDKit or Morgan) is motivated by two key criteria:

1. **Expert Domain Distribution:** The fingerprint method should generate a balanced distribution of reactions across expert domains. This even distribution optimizes computational resource allocation and enhances the efficiency of expert fine-tuning, resulting in faster convergence to reasonable response.
2. **Domain Clustering Accuracy:** The fingerprint should ensure clustering of chemically related reactions. This is crucial for accurate expert routing, particularly for specialized transformations. For instance, when analyzing Buchwald-Hartwig coupling reactions, the relevant expert domain should predominantly contain similar coupling reactions rather than a stew of unrelated transformations. This becomes especially critical when examining less common reactions in the database, such as Kulinkovich reactions or Mukaiyama hydrations, where non-RSFP approaches often misidentify the relevant knowledge domain.



Analysis of reaction fingerprint representations using **Morgan** fingerprints with radius 2, defined by the difference between product and reactant fingerprints, reveals several limitations when applied to the Baeyer-Villiger reaction example above. When querying this representation against a database of 3.7M reactions with 2,500 trained Voronoi cells, the top one matching expert includes:

Ketone to alcohol reduction:1773
Ketone reductive amination:977
Oxo to difluoro:194
Bromo Grignard reaction:156
Ketone dioxolane protection:145

...
Clive-Reich-Sharpless olefination:1
Mukaiyama aldol addition :1
Keto oxidative cleavage:1
Urech cyanohydrin method :1
Alkene hydrogenation: 1

The identical analysis can be applied to using **RDKit** fingerprint with a radius of 4 where the top one matching expert includes:

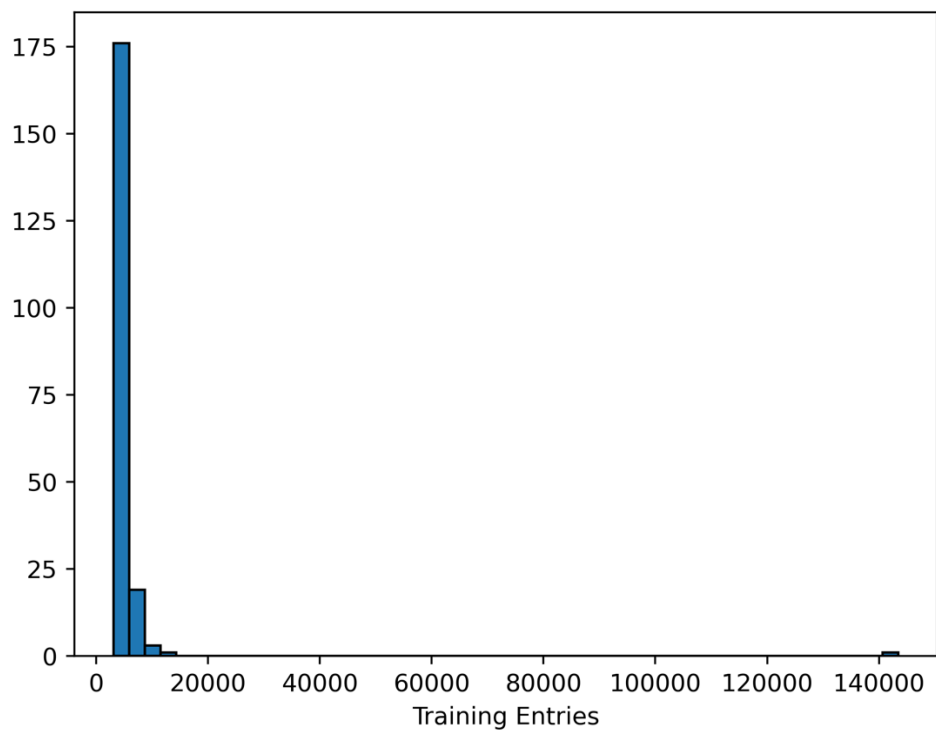
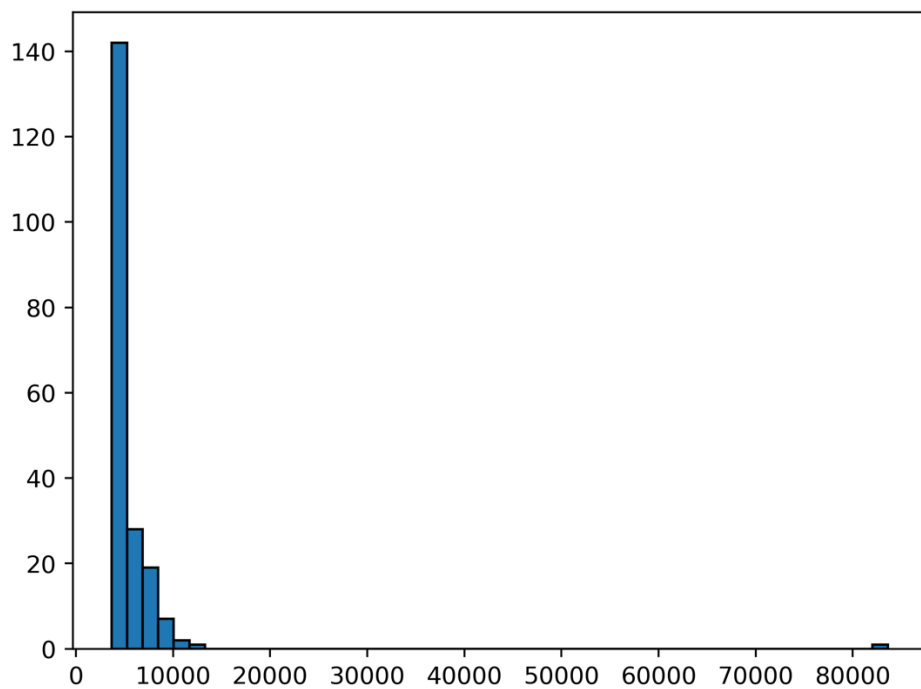
Keto alpha-acylation:266
Bromo N-alkylation:228
Esterification:204
Williamson ether synthesis:175
Pinner reaction:123

...
Hydroxyimidamide alkylation :1
S-Thioester synthesis:1
Phosgene urea synthesis:1
Mesityl N-alkylation:1
Chlorosulfonyl to sulfonate:1

These results demonstrate that this representation fails to capture the chemical similarity to the example Baeyer-Villiger reaction, instead matching to chemically distinct transformations. This observation indicates the representation does not meet the second selection criterion.

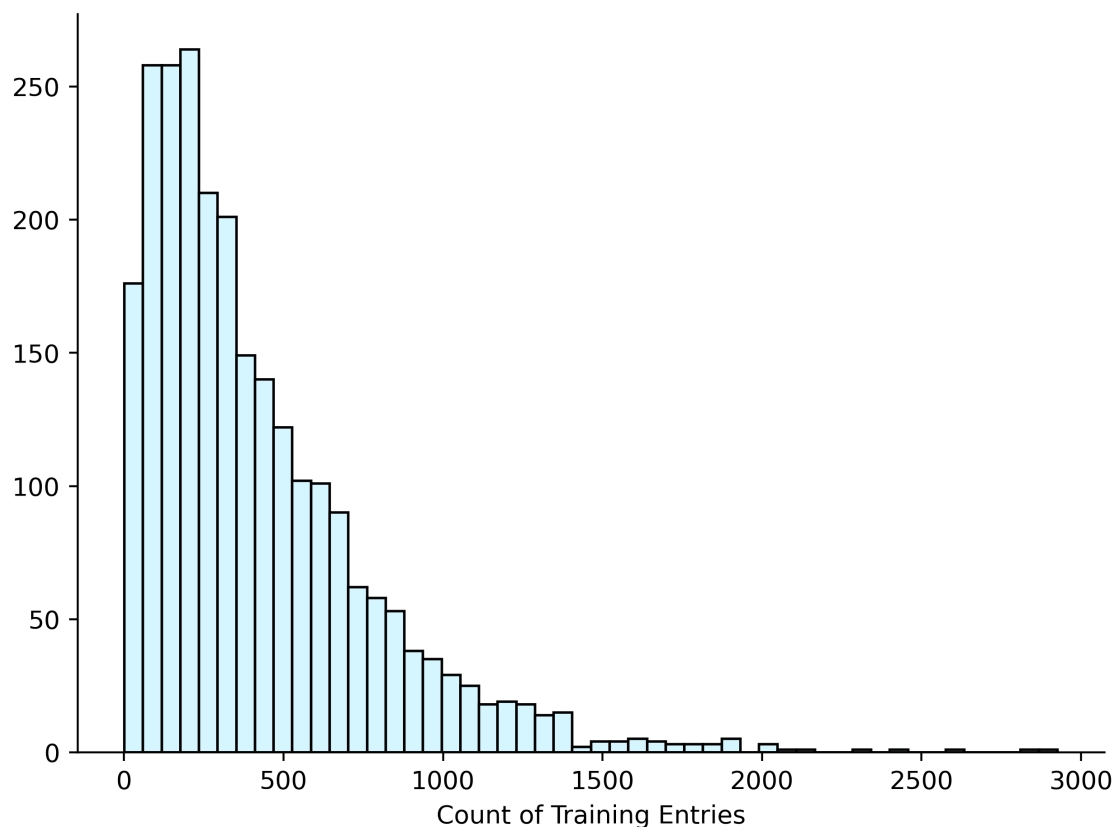
Further analysis of the training data distribution across Voronoi cells reveals additional concerns. Examining the top 200 cells by training data volume shows a significant outlier containing over 80,000 entries - approximately eight times larger than the second most populated cell. The same inefficiency applies to using RDKit fingerprint as the significant outlier contains over 140,000 entries. This imbalance suggests the model may lack sensitivity to subtle differences between reaction types. Moreover, the presence of such a dominant cell could bias predictions, as the model would frequently default to this expert's domain knowledge. This extreme skew also compromises computational efficiency, as parallel processing becomes bottlenecked by handling this disproportionately large data cluster.

Supplementary Figure: Morgan (top) and RDKit (bottom) fingerprint Voronoi clustering result show imbalance and inefficiency in capturing chemical domain knowledge as defined by the reaction classes.



The distribution of training entries in each domain is provided by the histogram below. As compared to the examples without RSFP, the distribution shows a more continuous transition from the largest Voronoi (~3,000) to the next largest (~2,600). In addition, it provides accurate clustering by relevant reaction as made evident in the training logics of KMN.

Supplementary Figure: Distribution of Voronoi clustering result from RSFP.



Below we provide additional details of the expert's domain knowledge (0-100) from the RSFP to show its clustering pattern and the relevance of the result.

expert_ID: 0
Prilezhaev epoxidation: 155
Shi epoxidation: 18
Sharpless epoxidation: 11
Payne epoxidation: 4
Ketone Darzens reaction: 3
Oxirane synthesis: 2
Ozone 1,3-cycloaddition: 1
1,3,2-Diazastibole synthesis: 1
unnamed: 81

expert_ID: 1
Carbonylurea synthesis: 119
Urech hydantoin synthesis: 4
Hydantoin synthesis: 2
Pyrimidine-2,4-dione synthesis: 2

1,3-Dihydroimidazol-2-one synthesis: 1
Isocyanate + amine + halide urea coupling: 1
unnamed: 55

expert_ID: 2
Amino conjugate addition: 447
Hydroamination: 25
unnamed: 103

expert_ID: 3
Wurtz-Fittig coupling: 547
Negishi coupling: 50
Palladium arylhalide alkylation: 43
Nickel Negishi coupling: 10
Gilman type conjugate addition: 8
Parham cyclization: 5
Keto alpha-arylation: 4
Wurtz-type coupling: 3
McLoughlin-Thrower trifluoromethylation: 2
Aryllithium alkylation: 2
Murahashi coupling: 2
Bromo alkoxyacylation: 2
Ullmann-type biaryl coupling: 1
Palladium Kumada coupling: 1
Bromo to trifluoromethyl: 1
Hurtley reaction: 1
Friedel-Crafts alkylation: 1
Grignard aryl ether reaction: 1
Hiyama coupling: 1
Decarboxylative coupling: 1
unnamed: 257

expert_ID: 4
Amide hydrolysis: 254
Urea hydrolysis: 2
Modified Ing-Manske reaction: 2
Secondary ketimine reduction: 1
N-dealkylation: 1
O-Transcarbamation: 1
Baeyer-Villiger oxidation: 1
unnamed: 82

expert_ID: 5
N-Boc deprotection: 154
Hydroxylation: 1
Sulfate salt formation: 1
N-Troc deprotection: 1
unnamed: 3

expert_ID: 6
Bromo N-alkylation: 679
unnamed: 68

expert_ID: 7
Chloro N-arylation: 629
Chloro Buchwald-Hartwig amination: 421
Chloro Goldberg reaction: 6
unnamed: 58

expert_ID: 8
Chloro N-arylation: 485
Chloro Buchwald-Hartwig amination: 33
N-arylation: 25
Chloro Goldberg reaction: 4
Sulfide + amine reaction: 1
Mesityl N-arylation: 1
Alcohol + amine condensation: 1
Triflyloxy Buchwald-Hartwig amination: 1
Fluoro N-arylation: 1
Alkylsulfonyl N-arylation: 1
Iodo N-arylation: 1
unnamed: 74

expert_ID: 9
Bromo Suzuki coupling: 96
Bromo Suzuki-type coupling: 33
unnamed: 132

expert_ID: 10
O-TBS deprotection: 308
[1,2]-Wittig rearrangement: 1
O-Transcarbamation: 1
Transesterification: 1
O-TIPS protection: 1
unnamed: 20

expert_ID: 11
N-Boc deprotection: 131
Methoxy to hydroxy: 1
unnamed: 6

expert_ID: 12
Bromo Goldberg reaction: 9
Alkylimino-de-oxo-bisubstitution: 8
Pyrrolo[2,3-c]pyridine synthesis: 8
Ketone amine condensation: 7
Fluoro N-arylation: 6
Sulfenamide synthesis: 6
[1,2,3]Triazolo[1,5-a]pyridine_synthesis: 5
Hydroamination: 5
N-arylation: 5
Chloro N-arylation: 4
Isoquinolone synthesis: 4
Carbonate urea synthesis: 4
Borsche-Drechsel cyclization: 3
Isothiazol-3-one synthesis: 3
N-Aminoimide to diacylhydrazine rearrangement: 3
Carbamate + amine reaction: 2
Pyrazole synthesis: 2
Van Leusen imidazole synthesis: 2
Imidazole synthesis: 2
Oxazolidin-2-one synthesis: 2
Bromo Buchwald-Hartwig amination: 1
Chloro Buchwald-Hartwig amination: 1
Imidocarbonate + amine reaction: 1
Amino to hydroxylamino: 1
Urea Curtius reaction: 1
Fluoro Goldberg reaction: 1

Nitrile + amine reaction: 1
Chloro Goldberg reaction: 1
Knorr pyrazole synthesis: 1
Alkane dehydrogenation: 1
Imidic ester + amine reaction: 1
Chloroformate urea synthesis: 1
Aniline to quinone oxidation: 1
Dihydropyridine to pyridine: 1
Bismuth N-arylation: 1
Aldehyde amine condensation: 1
Benzimidazole synthesis: 1
Alkene oxidative cleavage: 1
unnamed: 896

expert_ID: 13
N-Boc deprotection: 243
unnamed: 3

expert_ID: 14
Fujiwara-Moritani reaction: 20
Cyclo dehydrogenation coupling: 11
Scholl reaction: 11
Palladium-catalyzed direct arylation: 9
Trifluoromethylation: 3
Borsche-Drechsel cyclization: 2
Hofmann-Martius rearrangement: 2
Friedel-Crafts alkylation: 1
Pyran-4-one synthesis: 1
Aza-Diels-Alder reaction: 1
Mallory reaction: 1
Heck-Matsuda reaction: 1
Keto Claisen condensation: 1
Benzothiophene synthesis: 1
Enyne metathesis: 1
unnamed: 360

expert_ID: 15
Chlorosulfonation: 56
Sulfanyl to chlorosulfonyl: 34
Disulfide to chlorosulfonyl: 4
Bromo to chlorosulfonyl: 3
Iodo to chlorosulfonyl: 2
Chloro to chlorosulfonyl: 1
unnamed: 28

expert_ID: 16
Cyano to carbamoyl: 291
unnamed: 29

expert_ID: 17
Bromination: 275
Carboxy to bromo: 1
unnamed: 46

expert_ID: 18
N-Boc protection: 1183
Dicarbonate + amine reaction: 12
Carbonate + amine reaction: 1
unnamed: 179

expert_ID: 19
Methoxy to hydroxy: 233
N-dealkylation: 1
[1,2]-Wittig rearrangement: 1
O-Bn deprotection: 1
Ether hydrolysis: 1
N-methylation: 1
unnamed: 12

expert_ID: 20
Nitrile reduction: 587
unnamed: 51

expert_ID: 21
Iodo Goldberg reaction: 1038
Iodo Buchwald-Hartwig amination: 96
Iodo N-arylation: 76
Goldberg reaction: 10
Iodo N-alkylation: 2
unnamed: 122

expert_ID: 22
Williamson ether synthesis: 526
Ether synthesis: 2
unnamed: 61

expert_ID: 23
Chloro N-arylation: 200
Chloro Buchwald-Hartwig amination: 2
unnamed: 10

expert_ID: 24
Ester Schotten-Baumann: 680
Williamson ether synthesis: 1
unnamed: 158

expert_ID: 25
Trihalide to amide: 24
Trihaloacetyl + amine reaction: 12
unnamed: 18

expert_ID: 26
O-TBS deprotection: 621
Silyl ether deprotection: 3
Deoxygenation: 2
Epoxide reduction: 1
Fleming-Tamao oxidation: 1
CO₂H-TBS deprotection: 1
Defluorination: 1
unnamed: 31

expert_ID: 27
Ketal reduction: 51
Acetal reduction: 4
Deoxygenation: 3
Ketal reductive amination: 2
Epoxide reduction: 2
Epoxide Hosomi-Sakurai reaction: 1

Ketal Hosomi-Sakurai reaction: 1
Ketone to alcohol reduction: 1
Ketal hydrolysis: 1
unnamed: 63

expert_ID: 28
Amide Schotten-Baumann: 586
Stolle synthesis: 1
unnamed: 74

expert_ID: 29
O-Sulfonation: 116
Ketone alpha selenoether synthesis: 1
unnamed: 78

expert_ID: 30
Chloro N-arylation: 197
Chloro Buchwald-Hartwig amination: 24
unnamed: 70

expert_ID: 31
Carboxylic acid + amine condensation: 96
Carbamate + carboxylic acid reaction: 10
Decarboxylation: 1
Carboxy to carbamoyl: 1
unnamed: 346

expert_ID: 32
Knorr pyrazole synthesis: 189
Indazole synthesis: 1
unnamed: 91

expert_ID: 33
Carboxy ester to carbamoyl: 143
N-dealkylation: 1
Carboxylic ester + amine reaction: 1
unnamed: 20

expert_ID: 34
Phosphoramidate synthesis: 86
unnamed: 13

expert_ID: 35
Hydroxyiminomethyl to cyano: 124
Beckmann fragmentation: 3
Oxime to nitro: 1
unnamed: 17

expert_ID: 36
Hiyama coupling: 182
Corey-Fuchs reaction step 2: 50
Bromo to sulfanyl: 8
Cyanoalkane arylation: 4
Bromo Sonogashira coupling: 3
Bromo elimination: 2
Bromopyridine to thiopyridone: 2
Cadiot-Chodkiewicz coupling: 1
Bromo to trifluoromethyl: 1
Bromo to isocyano: 1

unnamed: 85

expert_ID: 37

Amide Schotten-Baumann: 582

unnamed: 28

expert_ID: 38

Isomerization: 139

Racemization: 109

Chiral separation: 100

Other separation: 11

Methylation: 7

CO₂H-Et deprotection: 3

Buechner-Curtius-Schlotterbeck synthesis: 2

Methoxy to hydroxy: 2

Transesterification: 2

Transesterification: 2

N-Boc deprotection: 1

Carbamate hydrolysis: 1

Deuteriation: 1

Fluorination: 1

Potassium salt formation: 1

Ester hydrolysis: 1

Ring closing olefin metathesis: 1

Debromination: 1

N-Bn deprotection: 1

Ester to alcohol reduction: 1

CO₂H-Bn deprotection: 1

Decarboxylation: 1

Hydration: 1

Phosphate ester hydrolysis: 1

Methyl esterification: 1

Carboxylic ester + amine reaction: 1

unnamed: 79

expert_ID: 39

Lithium Bouveault aldehyde synthesis: 602

Grignard Bouveault aldehyde synthesis: 89

Bouveault aldehyde synthesis: 30

unnamed: 44

expert_ID: 40

Carboxylic ester + nitro reaction: 70

Nitro 1,3-cycloaddition: 9

Nef reaction: 4

Mukaiyama-Hoshino method: 3

Nitro to bromo: 1

Retro-Henry reaction: 1

Carboxylic acid + nitro reaction: 1

unnamed: 83

expert_ID: 41

CO₂H-Et deprotection: 233

unnamed: 2

expert_ID: 42

Oxo to difluoro: 111

Dithiane to difluoro: 1

unnamed: 10

expert_ID: 43
SNAr ether synthesis: 1006
Ullmann condensation: 5
unnamed: 72

expert_ID: 44
Iodo Miyaura boration: 226
Iodo to pinacolatoboranyl: 193
unnamed: 24

expert_ID: 45
O-Ac deprotection: 426
Reductive ester cleavage: 5
Fluorination: 2
Ortho Fries rearrangement: 2
N-Ac deprotection: 2
Para Fries rearrangement: 1
Amino Tsuji-Trost reaction: 1
Acetal hydrolysis: 1
N-TFA deprotection: 1
O-Bn deprotection: 1
Alpha ketone oxidation: 1
Ester hydrolysis: 1
Ester halide coupling: 1
1,3-Vinyl ether rearrangement: 1
Methylation: 1
Transesterification: 1
Isoquinolone synthesis: 1
unnamed: 20

expert_ID: 46
Liebeskind-Srogl coupling: 88
unnamed: 60

expert_ID: 47
Desulfonylation: 79
Sulfone cleavage: 15
Julia olefination: 2
Triflyl Suzuki coupling: 1
Sulfone to sulfonamide: 1
Sulfone elimination: 1
Sulfoxide cleavage: 1
unnamed: 73

expert_ID: 48
Alkene thioether synthesis: 152
Diels-Alder cycloaddition: 2
unnamed: 56

expert_ID: 49
Ester to alcohol reduction: 219
Ester hydrolysis: 5
Carboxy ester to ether reduction: 2
Ketone to alcohol reduction: 1
Ether hydrolysis: 1
unnamed: 98

expert_ID: 50

Carboxylic acid + amine condensation: 588
unnamed: 21

expert_ID: 51
Iodo Suzuki coupling: 981
Iodo Suzuki-type coupling: 137
unnamed: 95

expert_ID: 52
Nitro to amino: 561
Bechamp reduction: 75
Azo reduction: 1
unnamed: 51

expert_ID: 53
Chlorination: 301
Hydroxy to chloro: 1
unnamed: 13

expert_ID: 54
N-SEM deprotection: 81
N-dealkylation: 2
Desulfonylation: 1
unnamed: 17

expert_ID: 55
Benzimidazolone synthesis: 94
Triphosgene urea synthesis: 2
unnamed: 14

expert_ID: 56
Sultone + amine reaction: 17
Alkylsulfoxy N-alkylation: 1
unnamed: 11

expert_ID: 57
Dioxolane synthesis: 432
1,3-Dioxane synthesis: 185
O-acetonide protection: 27
O-benzylidene protection: 13
Transesterification: 2
Tetrahydrofuran synthesis: 1
unnamed: 168

expert_ID: 58
N-TIPS deprotection: 77
N-TBS deprotection: 28
N-TBDPS deprotection: 4
N-Desilylation: 2
Hydroxylamine reduction: 2
N-TMS deprotection: 2
Alkyl desilylation: 1
Oxazolidin-2-one synthesis: 1
unnamed: 20

expert_ID: 59
Bromo Buchwald-Hartwig amination: 2049
Bromo N-arylation: 306
Bromo Goldberg reaction: 41

unnamed: 51

expert_ID: 60

Diazoalkane etherification: 200

Wolff rearrangement: 67

Diazoalkane amination: 14

Buechner-Curtius-Schlotterbeck synthesis: 13

Roskamp reaction: 7

Diazoalkane esterification: 7

Diazo to bromo: 4

Phosphonic ester synthesis: 2

Pechmann pyrazole synthesis: 2

Diazo to chloro: 2

Diazoalkane amidation: 1

unnamed: 114

expert_ID: 61

Hydroxy to chloro: 122

Appel chlorination: 19

Darzens chlorination: 6

unnamed: 3

expert_ID: 62

CO₂H-Me deprotection: 411

unnamed: 8

expert_ID: 63

Carboxylic acid + amine condensation: 917

unnamed: 4

expert_ID: 64

Carboxylic acid + amine condensation: 632

unnamed: 19

expert_ID: 65

Hydroxy to chloro: 164

Pyridone to chloropyridine: 1

unnamed: 13

expert_ID: 66

Chloro alkoxycarbonylation: 178

Chloro to carboxy: 34

Trihalide to ester: 4

Chloro aminocarbonylation: 3

Chloro to formyl: 3

Bromo alkoxycarbonylation: 1

unnamed: 117

expert_ID: 67

Carboxylic acid + amine condensation: 397

unnamed: 9

expert_ID: 68

Hiyama coupling: 207

Iodo Sonogashira coupling: 2

unnamed: 26

expert_ID: 69

Alkane dehydrogenation: 101

Quinone reduction: 12
Keto-enol tautomerisation: 4
1,3-Hydrogen migration: 4
Imine-enamine tautomerisation: 3
Triple bond Diels-Alder: 2
Bromo elimination: 1
N-Boc protection: 1
Knoevenagel condensation: 1
Tetrahydropyridine to pyridine: 1
Ketene + amine reaction: 1
Amine dehydrogenation: 1
Alcohol elimination: 1
1,5-Hydrogen migration: 1
Deoxygenation: 1
Keto alpha hydroxyimination: 1
Dihydropyridazine to pyridazine oxidation: 1
Aldehyde decarbonylation: 1
Benzylic ketone oxidation: 1
unnamed: 495

expert_ID: 70
Formaldehyde reductive amination: 242
Alcohol + amine condensation: 87
N-methylation: 63
Eschweiler-Clarke methylation: 24
Iodo N-methylation: 1
Dialkyl acetal reductive amination: 1
Sulfide + amine reaction: 1
Chloro N-alkylation: 1
Carbonate + amine reaction with decarboxylation: 1
unnamed: 34

expert_ID: 71
N,O-acetonide deprotection: 74
Deuteriation: 1
unnamed: 20

expert_ID: 72
Carboxylic acid + amine condensation: 1079
unnamed: 12

expert_ID: 73
N-Boc deprotection: 197
Methylation: 2
Imine hydrolysis: 1
[1,2]-Aza-Wittig rearrangement: 1
unnamed: 7

expert_ID: 74
Carboxylic acid + amine condensation: 4
Amide Schotten-Baumann: 3
unnamed: 15

expert_ID: 75
Nitro to amino: 252
Bechamp reduction: 87
unnamed: 61

expert_ID: 76

Epoxide + thiol coupling: 68
Epoxide + carboxy coupling: 10
Epoxide + alcohol coupling: 7
Ether cleavage: 3
Carbonodithioate synthesis: 2
Thiirane synthesis: 1
unnamed: 49

expert_ID: 77
Ester to alcohol reduction: 733
Bouveault-Blanc reduction: 5
Carboxylic acid to alcohol reduction: 2
unnamed: 52

expert_ID: 78
Chloro Suzuki coupling: 15
Ullmann-type biaryl coupling: 6
Palladium-catalyzed direct arylation: 1
Chloro Suzuki-type coupling: 1
unnamed: 74

expert_ID: 79
O-TBS protection: 192
unnamed: 1

expert_ID: 80
Chloro N-arylation: 389
Chloro Buchwald-Hartwig amination: 5
Chloro Goldberg reaction: 2
unnamed: 46

expert_ID: 81
Ketone ketal deprotection: 91
Ketal hydrolysis: 24
Ketone dioxolane deprotection: 1
Meinwald rearrangement: 1
CO₂H-Me deprotection: 1
Methylation: 1
Amino to hydroxy: 1
Alcohol to ketone oxidation: 1
unnamed: 31

expert_ID: 82
N-Boc deprotection: 291
Alkane dehydrogenation: 1
unnamed: 2

expert_ID: 83
Bromo to pinacolatoboranyl: 263
Bromo to boronic_ester: 1
unnamed: 52

expert_ID: 84
Chloro to sulfanyl: 109
Fluoro to sulfanyl: 1
unnamed: 21

expert_ID: 85
Carbamate Schotten-Baumann: 716

Amide Schotten-Baumann: 1
unnamed: 89

expert_ID: 86
Ullmann-type biaryl coupling: 81
Grignard aryl ether reaction: 3
unnamed: 21

expert_ID: 87
Carboxylic acid + amine condensation: 17
Iodo aminocarbonylation: 1
unnamed: 9

expert_ID: 88
Chloro N-arylation: 714
Chloro Buchwald-Hartwig amination: 201
Chloro Goldberg reaction: 2
unnamed: 37

expert_ID: 89
Carboxylic acid + amine condensation: 276
unnamed: 9

expert_ID: 90
Alkylsulfoxy N-arylation: 38
Alkylsulfoxy N-alkylation: 7
Palladium catalyzed cyanation: 1
unnamed: 21

expert_ID: 91
O-TMS deprotection: 104
Silyl ether deprotection: 1
O-Bn deprotection: 1
unnamed: 10

expert_ID: 92
Ullmann-type biaryl coupling: 717
Stille-Kelly coupling: 12
Grignard aryl ether reaction: 8
Palladium-catalyzed direct arylation: 5
Negishi coupling: 4
Decarboxylative coupling: 2
Murahashi coupling: 1
Barton-Zard reaction: 1
unnamed: 184

expert_ID: 93
Aryl hydrogenation: 160
Pyridine to piperidine hydrogenation: 6
Amino to hydroxylamino: 1
Thiophene desulfurization: 1
unnamed: 174

expert_ID: 94
Alkene hydroxybromination: 15
Bromo alkoxylation: 5
Bromolactonization: 2
unnamed: 19

expert_ID: 95
Krapcho decarboxylation: 224
Decarboxylation: 8
Carboxyl extrusion: 2
Ester to alcohol reduction: 2
Carroll rearrangement: 1
Decarboxylative coupling: 1
unnamed: 72

expert_ID: 96
N-Boc deprotection: 165
unnamed: 1

expert_ID: 97
Williamson ether synthesis: 225
Oxirane synthesis: 13
Keto alpha-alkylation: 2
Sulfoxy elimination: 2
Thioic acid to thiono ester: 1
Cyanoalkane alkylation: 1
Sulfonic acid elimination: 1
Sulfonic ester + alcohol reaction: 1
unnamed: 74

expert_ID: 98
Carboxylic ester + amine reaction: 156
Carboxylic ester + azide reaction: 3
Ester hydrolysis: 3
Transesterification: 1
Ester to aldehyde reduction: 1
N-Acetylation: 1
CO₂H-Bn deprotection: 1
Keto alpha-acylation: 1
unnamed: 38

expert_ID: 99
Appel bromination: 1430
Hydroxy to bromo: 19
Darzens bromination: 7
Bromination: 1
unnamed: 29

expert_ID: 100
Decarboxylation: 47
Krapcho decarboxylation: 3
Carboxy ester to ether reduction: 2
Carboxy to alkane reduction: 2
Ether hydrolysis: 2
Lemieux-Johnson oxidation: 1
Carboxylic ester + amine reaction: 1
Carboxy to fluoro: 1
Ester pyrolysis: 1
unnamed: 66

8. Query Prompt Design for Commercial LLM models

I have a response template filled with an example of C-H Arylation Reaction. I would like you to read it so that when I provide you a different chemical transformation in SMILES, you can produce a response in the same style followed by ### Response from this template.

Response:

Product (SMILES): ['N#Cc1ccc2c(c1)-c1cccnc1C2']

Reactant (SMILES): ['Cc1ccc(C#N)cc1-c1cccnc1Cl']

Reaction SMARTS: [CH3:1][c:2]1[cH:3][cH:4][c:5]([cH:6][c:7]1-[c:8]1[cH:9][cH:10][cH:11][n:12][c:13]1Cl)[C:14]#[N:15]>CC1(c2cccc(c2Oc2c1cccc2P(c1cccc1)c1cccc1)P(c1cccc1)c1cccc1)C.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(O[Cs])O[Cs].C1COCCO1.N#N.[Pd].[Pd]>[N:15]#[C:14][c:5]1[cH:4][cH:3][c:2]2[CH2:1][c:13]3[n:12][cH:11][cH:10][cH:9][c:8]3-[c:7]2[cH:6]1

Reagents (SMILES): ['CC1(C)c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21', 'O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.[Pd].[Pd]', 'O=C(O[Cs])O[Cs]']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['9H-indeno[2,1-b]pyridine-6-carbonitrile']

Reactant Name: ['3-(2-chloropyridin-3-yl)-4-methylbenzonitrile']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 3-(2-chloropyridin-3-yl)-4-methylbenzonitrile (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd2(dba)3 (0.2 g, 0.2 mmol) under N2. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 9H-indeno[2,1-b]pyridine-6-carbonitrile (0.9 g, yield: 100%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [100.0]

Now, using this template, please provide a prediction for the following

reaction:**NC1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3**
>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5, starting with ### Response.

9. Comments to Prompt

The query prompt used is considered more detailed than an average user inexperienced at prompt engineering could ask. For example, casual requests like “Give me a reaction procedure to do $A \gg B$ ” or “Instruct me how to do perform the following reaction in SMILES: $A \gg B$ ” would result in inconsistent responses with different levels of details upon repetitions. Therefore, it should be noted that the comparison made below favors Anthropic Claude and OpenAI ChatGPT.

10. Testing Logistics

For each reaction, each LLM model is provided identical prompt as specified in the Prompt Design section (1-shot prediction) with variations of the query reaction.

Each reaction per each model is tested three times with **no context** or memory of the previous chat history.

Response Scoring Criteria

1. Instruction Compliance (0 to -2)

- Base score starts at 0
- -2 point for not following instruction or is copying the example (conditions, temperature, residence time and order of descriptions all identical). There needs to be a clear differentiation between “copying” vs “answering”. -2 because Reagents/Solvents and Quantitative Parameters account for 4 points in total. By copying the example, we subtract a half of the marks.
- Failing this criterion does not automatically result in a total score of 0

2. Atom Mappings (0-1 points)

- 1.0: All reagents and solvents are chemically reasonable and appropriate
- 0.0: Atom mapping (SMILES) string is incorrect or is not the same as the specified by the reaction SMILES string.

3. Reagent and Solvent Selection (0-2 points)

- 2.0: All reagents and solvents are chemically reasonable and appropriate
- 1.0: Partially relevant conditions (e.g., incomplete catalyst system)
- 0.0: Incorrect or inappropriate reagents/solvents

4. Procedural Logic (0-1 points)

- 1.0: Clear, logically sound experimental procedures with correct order of addition
- 0.0: Presence of logical flaws or incorrect addition sequence

5. Quantitative Parameters (0-2 points)

- 2.0: Complete specification of:
 - Molar ratios between reagents and reactants
 - Solvent volumes
 - Reaction time
 - Temperature
 - Expected yields
- 1.0: Partial specification that could be supplemented with empirical knowledge
- 0.0: Insufficient or incorrect quantitative details

6. Workup and Purification (0-1 point)

- Appropriate isolation procedures
- Purification methods
- Expected product characteristics

7.Reaction Classification (0-1 point)

- 1.0 Has correct or relevant classification of the reaction, showing understanding
- Is hallucinating or does not provide (nan)

Scoring Summary

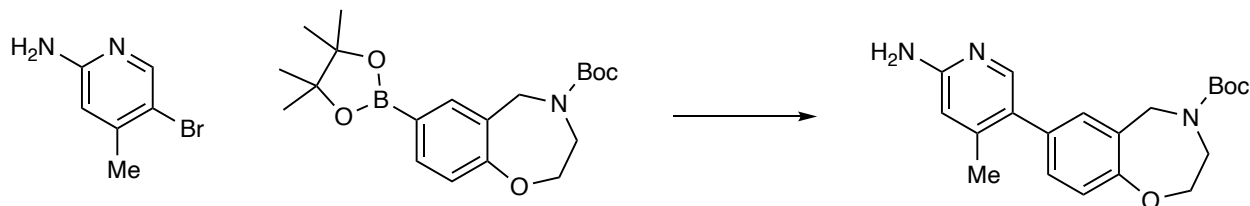
- Maximum possible score: 8.0
- Minimum score: 0.0
- Non-compliance penalty: -2.0

The response/results are **pasted as is**.

All Models were accessed on December 6th 2024

11. Testing Results on Anthropic Haiku

Suzuki Reactions



NC1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5

Trial1:

Response

Product (SMILES): ['N#Cc1ccc(C)c(C)c1-c1ccnc1']

Reactant (SMILES): ['NC1=CC(C)=C(Br)C=N1',
'CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3']

Reaction SMARTS: [N:1][c:2]1[c:3][cH:4][c:5]([C:6][H:7])[c:8]([C:9][H:10])[c:11]1-[c:12]1[cH:13][cH:14][cH:15][n:16][c:17]1Br.[CC(C)(C)O:18]2(C)[C:19][H:20][C:21][H:22][B:23]2[c:24]1[cH:25][cH:26][c:27]([O:28][c:29]1[cH:30][cH:31][N:32]([C:33](O[C:34]([C:35])(C)C)=O)[c:36]1)=[c:36]1]>>[N:1][c:2]1[c:3][c:5](C)[c:8](C)[c:11]1-[c:12]1[cH:13][cH:14][cH:15][n:16][c:17]1[c:24]1[cH:25][cH:26][c:27]([O:28][c:29]1[cH:30][cH:31][N:32]([C:33](O[C:34]([C:35])(C)C)=O)[c:36]1)=[c:36]1

Reagents (SMILES): ['CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3']

Solvent: None specified

Reaction Procedure:

To a solution of 2-bromo-4,5-dimethylpyridine-3-carbonitrile (1.0 equiv) and the boronate ester (1.1 equiv) in a suitable solvent, add a palladium catalyst and a base. Stir the reaction mixture at an elevated temperature for several hours. Monitor the reaction progress and work up the product upon completion.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: Not provided

This C-H arylation reaction involves the coupling of a pyridine-containing nitrile compound with a boronate ester to form a new substituted pyridine product. The specific reaction conditions, such as the palladium catalyst, base, and solvent, would need to be determined through further optimization. The yield and characterization data for this particular transformation are not provided in the template.

Trial2

Response:

Product (SMILES): [*NC1=CC(C)=C(C2=CC=C(OCCN(C(OC(C)(C)C)=O)C3)C3=C2)C=N1]

Reactant (SMILES): [*NC1=CC(C)=C(Br)C=N1', 'CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3]

Reaction SMARTS:

[N:1]#[C:2][c:3]1[c:4][c:5]([C:6])=[C:7]([Br:8])[c:9]=[N:10]1.[C:11][C:12]([C:13]([C:14])([C:15])[O:16][B:17][C:18]2)[C:19]([C:20]).[c:21]1[c:22][c:23][c:24][c:25](OCCN(C(OC(C)(C)C)=O)c2)[c:26]2[=c:27]1>>[N:1]#[C:2][c:3]1[c:4][c:5]([C:6])=[C:7]([c:9]2[c:22][c:23][c:24][c:25](OCCN(C(OC(C)(C)C)=O)c3)[c:26]3[=c:27]2)[c:28]=[N:10]1'

Reagents (SMILES): [*C[C:13]([C:14])([C:15])[O:16][B:17][C:18]2', 'CCCCCCCCCNC(OC(C)(C)C)=O]

Solvent (SMILES): Not specified

Product Name: Not specified

Reactant Name: Not specified

Reagent Name: Not specified

Solvent Name: Not specified

Reaction Procedure: The reaction likely proceeds via a C-H arylation mechanism, where the aryl halide (2-bromonicotinonitrile) reacts with the boronic ester to form the new C-C bond, with the nitrile group directing the arylation. The reaction likely requires a palladium catalyst, base, and solvent. Without more details on the specific conditions, I cannot provide a complete procedure. However, the key steps would involve forming the palladium-aryl complex, base-mediated boronate formation, and reductive elimination to form the new C-C bond.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: Not specified

Trial3

Response:

Product (SMILES): [*NC1=CC(C)=C(C2=CC=C(OCCN(C(OC(C)(C)C)=O)C3)C3=C2)C=N1]

Reactant (SMILES): [*NC1=CC(C)=C(Br)C=N1', 'CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3]

Reaction SMARTS:

[C:1][n:2]1[cH:3][cH:4]([C:5])[c:6]([cH:7])[c:8]1[Br:9].[H3C:10][C:11]([H2C:12]([O:13][B:14]1[cH:15][cH:16][cH:17][cH:18][c:19]([OCCN:20]([C:21]([OC:22]([H3C:23])([H3C:24])[H3C:25])=O)[c:26]2)[c:26]2)[H2C:12]1)([H3C:27])[H3C:27][c:28]1[cH:29][cH:30][cH:31][c:32]([OCCN:33]([C:34]([OC:35]([H3C:36])([H3C:37])[H3C:38])=O)[c:39]3)[c:39]3=c:28>[C:1][n:2]1[cH:3][cH:4]([C:5])[c:6]([cH:7])[c:8]([cH:40])[n:2]1'

Reagents (SMILES): ['CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3']

Solvent (SMILES): []

Product Name: ['5-methyl-2-(3-(2-((dimethylcarbamoyl)oxy)phenyl)methyl-4-methylphenyl)pyridine-4-carbonitrile']

Reactant Name: ['5-methyl-2-bromopyridine-4-carbonitrile', '2-(tert-butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane']

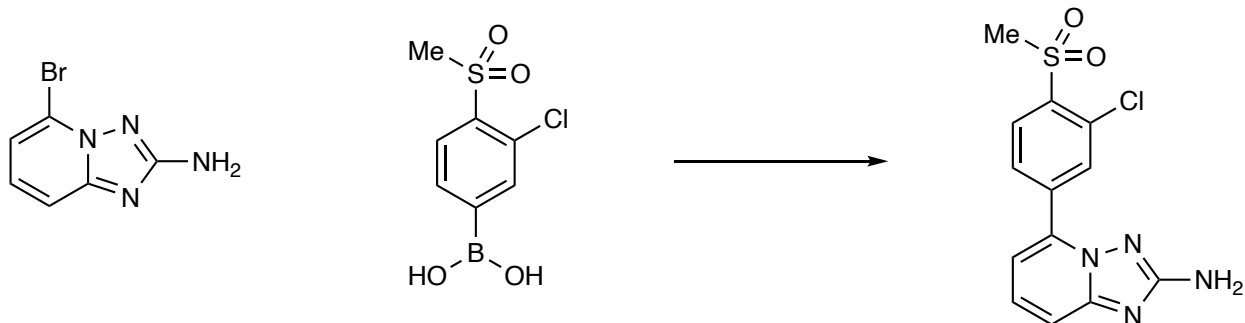
Reagent Name: ['2-(tert-butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane']

Solvent Name: []

Reaction Procedure: The reaction of 5-methyl-2-bromopyridine-4-carbonitrile (1.0 equiv.) and 2-(tert-butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.1 equiv.) in the presence of a Pd catalyst and base would likely result in the formation of 5-methyl-2-(3-(2-((dimethylcarbamoyl)oxy)phenyl)methyl-4-methylphenyl)pyridine-4-carbonitrile via a C-H arylation reaction. The specific reaction conditions, including the choice of Pd catalyst, base, and solvent, may need to be optimized to achieve high yield and selectivity.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [Not Provided]



NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3>>NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4

Trial1:

Response:

Product (SMILES): ['NC1=NN2C(C=CC=C2C3=CC(Cl)=C(S(=O)(C)=O)C=C3)=N1']

Reactant (SMILES): ['NC1=NN2C(C=CC=C2Br)=N1', 'OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Reaction SMARTS:

[NH2:1][c:2]1[n:3][n:4][CH:5]([c:6]1[cH:7][cH:8][c:9]1[cH:10][c:11][c:12][cH:13]1[Br:14])=[N:15].[O:16][B:17]([O:18])[O:19][c:20]1[cH:21][c:22]([Cl:23])=[c:24]([S:25]([O:26])(C)=[O:27])[cH:28][c:29]1>>[NH2:1][c:2]1[n:3][n:4][CH:5]([c:6]1[cH:7][cH:8][c:9]1[cH:10][c:11][c:12]1[cH:13][c:29]([Cl:23])=[c:24]([S:25]([O:26])(C)=[O:27])[cH:28][c:20]1)=[N:15]

Reagents (SMILES): ['OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Solvent (SMILES): []

Product Name: ['6-Chloro-2-(5H-pyrrolo[3,2-d]pyrimidin-6-yl)benzenesulfonamide']

Reactant Name: ['6-Bromopyrrolo[3,2-d]pyrimidine', '6-Chloro-2-methylbenzenesulfonic acid']

Reagent Name: ['Phenylboronic acid']

Solvent Name: []

Reaction Procedure: To a solution of 6-bromopyrrolo[3,2-d]pyrimidine (1.0 g, 5.0 mmol) and 6-chloro-2-methylbenzenesulfonic acid (1.0 g, 5.0 mmol) in solvent, phenylboronic acid (0.6 g, 5.0 mmol) was added. The reaction mixture was stirred at reflux temperature for 16 hours. The product was isolated by column chromatography.

Reaction Name and Classification: C-N Coupling

Reaction Yield and Characterization: [N/A]

Trial2:

Response:

Product (SMILES): ['NC1=NN2C(C=CC=C2C3=CC(Cl)=C(S(=O)(C)=O)C=C3)=N1']

Reactant (SMILES): ['NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Reaction SMARTS:

[n:1]1[n:2][n:3][c:4]([c:5]2[cH:6][cH:7][c:8][cH:9][c:10]2[Br:11])[n:12]1>>[n:1]1[n:2][n:3][c:4]([c:5]2[cH:6][cH:7][c:8][cH:9][c:10]2[c:13]1[c:14][c:15]([Cl:16])[c:17]([S:18](=[O:19])[C:20])=[c:21][c:22][c:23]1)=[N:12]

Reagents (SMILES): ['OB(O)C1=CC(Cl)=C(S(=O)(C)=O)C=C1']

Solvent (SMILES): []

Product Name: ['5-Bromo-3-(pyrimidin-2-yl)benzene-1-sulfonamide']

Reactant Name: ['5-Bromopicolinoyl chloride', '5-Chlorosulfonylbenzeneboronic acid']

Reagent Name: ['5-Chlorosulfonylbenzeneboronic acid']

Solvent Name: []

Reaction Procedure: To a solution of 5-bromopicolinoyl chloride (1.0 equiv.) and 5-chlorosulfonylbenzeneboronic acid (1.0 equiv.) in an appropriate solvent, the reaction mixture is stirred at an elevated temperature for a specified duration. Upon completion, the crude product is purified by standard techniques to afford the desired 5-bromo-3-(pyrimidin-2-yl)benzene-1-sulfonamide.

Reaction Name and Classification: Arylation of pyrimidine

Reaction Yield and Characterization: To be determined

Trial3:

Response:

Product (SMILES): ['NC1=NN2C(C=CC=C2C3=CC(Cl)=C(S(=O)(C)=O)C=C3)=N1']

Reactant (SMILES): ['NC1=NN2C(C=CC=C2Br)=N1', 'OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Reaction SMARTS:

[N:1]C1=N[N:2]C(C=CC=C2Br)=N1.[O:3]B(O)C3=C[C:4](Cl)=C(S(=O)(C)=O)C=C3>>[N:1]C4=N[N:2]C(C=CC=C5C6=C[C:4](Cl)=C(S(=O)(C)=O)C=C6)=N4

Reagents (SMILES): ['OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Solvent (SMILES): []

Product Name: ['2-(6-chloro-3-(methylsulfonyl)phenyl)-4,6-dihydroimidazo[4,5-b]pyridine']

Reactant Name: ['4,6-dihydroimidazo[4,5-b]pyridine-2-yl bromide', '3-chloro-5-(methylsulfonyl)phenylboronic acid']

Reagent Name: ['3-chloro-5-(methylsulfonyl)phenylboronic acid']

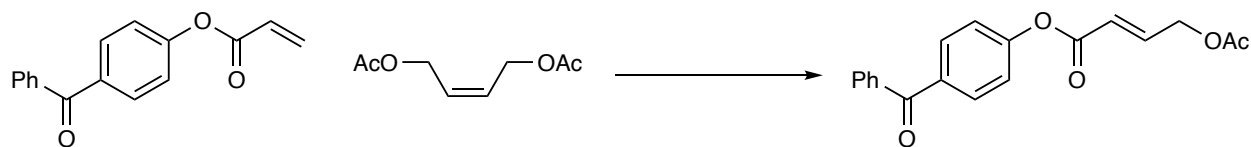
Solvent Name: []

Reaction Procedure: The reaction between 4,6-dihydroimidazo[4,5-b]pyridine-2-yl bromide and 3-chloro-5-(methylsulfonyl)phenylboronic acid in the presence of a suitable base is expected to undergo a C-H arylation to form 2-(6-chloro-3-(methylsulfonyl)phenyl)-4,6-dihydroimidazo[4,5-b]pyridine. The reaction likely proceeds via a palladium-catalyzed cross-coupling mechanism, with the boronic acid coupling to the C-H bond of the imidazo[4,5-b]pyridine core.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [To be determined]

Metathesis Reactions



O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C>>O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O

Trial1:

Response:

Product (SMILES): ['O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O']

Reactant (SMILES): ['O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1).O=C(OC/C=C\COC(C)=O)']

Reaction SMARTS:

[C:1](=[O:2])[O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][c:15]2)[cH:16][c:17]1>>[C:1](=[O:2])[O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][c:15]2)/[CH:18]=C\CH2:19[O:20][C:21](=[O:22])[CH3:23]'

Reagents (SMILES): ['', '']

Solvent (SMILES): ['']

Product Name: ['2-(3-(2-acetoxy-2-phenylethoxy)benzoyl)benzaldehyde']

Reactant Name: ['3-(2-phenylacryloyloxy)benzaldehyde', 'methyl 3-hydroxypropanoate']

Reagent Name: ['']

Solvent Name: ['']

Reaction Procedure: To a solution of 3-(2-phenylacryloyloxy)benzaldehyde (1.0 g, 4.0 mmol) and methyl 3-hydroxypropanoate (0.4 g, 4.0 mmol) in a suitable solvent, appropriate reagents would be added and the reaction mixture would be stirred at an appropriate temperature for a specified duration. The product 2-(3-(2-acetoxy-2-phenylethoxy)benzoyl)benzaldehyde would then be isolated and purified.

Reaction Name and Classification: Michael Addition

Reaction Yield and Characterization: [Not provided]

Trial2:

Response:

Product (SMILES): ['O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O']

Reactant (SMILES): ['O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

[CH2:1]=[CH:2][C:3](=[O:4])[O:5][C:6]1=[CH:7][CH:8]=[CH:9][C:10]([C:11]2=[CH:12][CH:13]=[CH:14][CH:15]=[CH:16]2)=[O:17][C:18]1>[CH2:1]=[CH:2][C:3](=[O:4])[O:5][C:18][C:19](=O)/C=C/[CH2:20][O:21][C:22](=O)[C:23](C)=O']

Reagents (SMILES): ['O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C', 'O=C(OC/C=C\COC(C)=O)C']

Solvent (SMILES): None

Product Name: None

Reactant Name: None

Reagent Name: None

Solvent Name: None

Reaction Procedure: This appears to be a reaction involving the esterification of two carboxylic acid groups. The first reactant has a carboxylic acid group conjugated to an alkene, while the second reactant has a carboxylic acid group attached to an alcohol. Based on the reaction SMARTS, it seems that these two reactants undergo an esterification reaction to form the product, which contains an ester group conjugated to an alkene.

Reaction Name and Classification: Esterification

Reaction Yield and Characterization: Unable to determine without further information.

Trial3:

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O]

Reactant (SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C',
'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

[C:1](=[O:2])[O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][c:15]2)[cH:16][c:17]1>>[C:1](=[O:2])[O:3]/[C:17]=C\CH2:18[O:19][C:8](=[O:9])[O:20][C:21](C)=O]

Reagents (SMILES): ['N/A']

Solvent (SMILES): ['N/A']

Product Name: ['Methyl 3-(3-oxo-3-phenylprop-1-enyl)benzoate']

Reactant Name: ['3-Benzoylphenyl methacrylate', 'Methyl 3-(3-oxopropyl)benzoate']

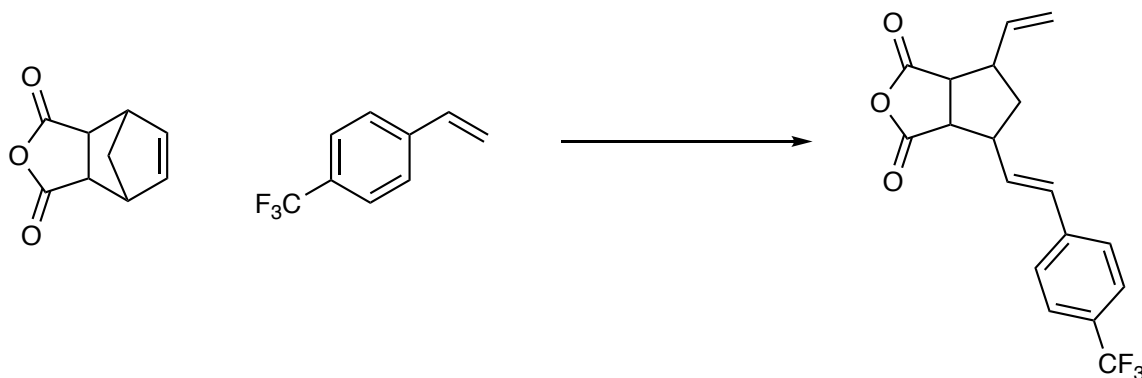
Reagent Name: ['N/A']

Solvent Name: ['N/A']

Reaction Procedure: The reaction involves the condensation of 3-benzoylphenyl methacrylate with methyl 3-(3-oxopropyl)benzoate to form methyl 3-(3-oxo-3-phenylprop-1-enyl)benzoate. The reaction likely proceeds via a base-catalyzed aldol addition followed by dehydration. Typical conditions would involve using a base such as sodium hydroxide or potassium hydroxide in a suitable solvent like ethanol or methanol.

Reaction Name and Classification: Aldol Condensation

Reaction Yield and Characterization: ['N/A']



O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4>>O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6=C)C5=O

Trial1:

Response:

Product (SMILES): [O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6=C)C5=O]

Reactant (SMILES): [O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4']

Reaction SMARTS:

```
[C:1](=O)[O:2][C:3]1[C:4][C:5](C(=O)[O:6][C:7]1)C(C(=C[C:8]1[cH:9][cH:10][c:11](C(F)(F)F)[cH:12][c:13]1)[CH2:14][C:5]2[cH:15][CH:16][C:17]2[cH:18])[cH:19]3[cH:20][cH:21][cH:22][C:23]3>>[C:7]1(=O)[O:6][C:5](C(=C[C:14]/C=C/[c:11]2[cH:12][cH:9][c:13](C(F)(F)F)[cH:10][c:23]2)[CH2:19][C:17]([cH:18][cH:20][cH:21][cH:22])C1)[C:4]=O
```

Reagents (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4']

Solvent (SMILES): []

Product Name: ['?']

Reactant Name: ['Cyclic anhydride', '4-(Trifluoromethyl)styrene']

Reagent Name: ['Cyclic anhydride', '4-(Trifluoromethyl)styrene']

Solvent Name: ['']

Reaction Procedure: The reaction between the cyclic anhydride and 4-(trifluoromethyl)styrene likely proceeds through a [4+2] cycloaddition, followed by rearomatization and loss of the anhydride. The expected product is a fused ring system with the trifluoromethyl group incorporated.

Reaction Name and Classification: Cycloaddition/rearomatization

Reaction Yield and Characterization: ['?']

Trial2:

Response:

Product (SMILES): ['O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O']

Reactant (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4']

Reaction SMARTS:

```
[O:1]=C([O:2][C:3]1[O:4]=O)[C:5]2[C:6]([C:7]([CH:8]=[CH:9][C:10]1[CH:11]=[CH:12][CH:13]2[CH:14])[C:15]1[CH:16]=[CH:17][C:18]2[CH:19]=[CH:20][C:21]1)[C:22]3[O:23]=O>>[O:1]=C([O:23][C:22]1[C:6]([C:15]([CH:8]=[CH:9][C:10]2[CH:19]=[CH:20][C:21](C(F)(F)F)[CH:18]=1)[C:5]2[CH:11]=[CH:12][C:3]1)[C:7])[O:2]
```

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['5-(1-(3-(trifluoromethyl)phenyl)vinyl)-2-oxaspiro[4.5]deca-6,9-diene-2-carboxylic acid']

Reactant Name: ['2-oxaspiro[4.5]deca-6,9-diene-2-carboxylic acid', '1-(3-(trifluoromethyl)phenyl)prop-1-ene']

Reagent Name: []

Solvent Name: []

Reaction Procedure: The reaction is carried out between 2-oxaspiro[4.5]deca-6,9-diene-2-carboxylic acid and 1-(3-(trifluoromethyl)phenyl)prop-1-ene. The product is 5-(1-(3-(trifluoromethyl)phenyl)vinyl)-2-oxaspiro[4.5]deca-6,9-diene-2-carboxylic acid.

Reaction Name and Classification: C-C Coupling

Reaction Yield and Characterization: [Not provided]

Trial3:

Response:

Product (SMILES): [O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O]

Reactant (SMILES): [O=C(OC1=O)C2C1C3C=CC2C3], 'C=CC4=CC=C(C(F)(F)F)C=C4'

Reaction SMARTS: -

Reagents (SMILES): []

Solvent (SMILES): []

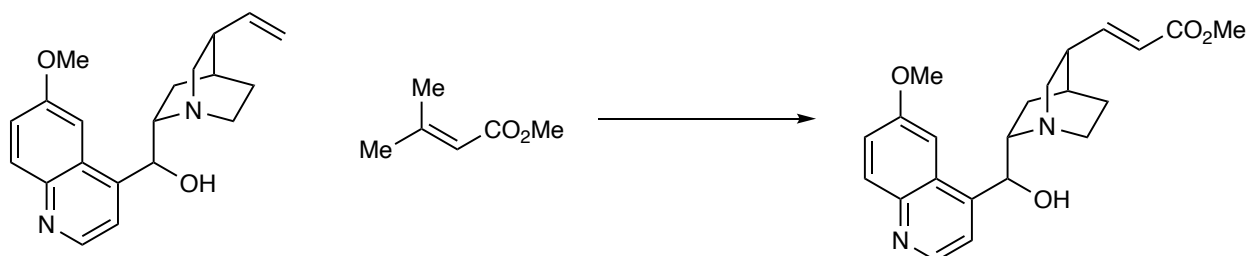
Product Name: [Undetermined]

Reactant Name: [Undetermined]

Reagent Name: []

Solvent Name: []

Reaction Procedure: This reaction appears to be a [4+2] cycloaddition between an enone (O=C(OC1=O)C2C1C3C=CC2C3) and an electron-deficient alkene (C=CC4=CC=C(C(F)(F)F)C=C4), resulting in the formation of a bicyclic lactone product (O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O). The reaction likely proceeds through a concerted mechanism, with the enone acting as the 4π component and the electron-deficient alkene acting as the 2π component. No additional reagents or solvents are specified, so the reaction may simply require heating or irradiation to initiate the cycloaddition. Further optimization of the reaction conditions and characterization of the product would be required to fully predict the outcome.



C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2.C/C(C)=C/C(OC)=O>>OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](C[C@H]8/C=C/C(OC)=O)CC[C@H]8C7

Trial1

Response:

Product (SMILES):

['OC(C1=C(C=C(OC)C=C2)C2=NC=C1)[C@H]3[N@](CC[C@H]4/C=C/C(OC)=O)CC[C@H]4C3']

Reactant (SMILES):

['C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2',
'C/C(C)=C/C(OC)=O']

Reaction SMARTS:

['C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2.C/C(C)=C/C(O
C)=O>>OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](CC[C@H]8/C=C/C(OC)=O)CC[C@H]8C7']

Reagents (SMILES): [']

Solvent (SMILES): [']

Product Name: [']

Reactant Name: [']

Reagent Name: [']

Solvent Name: [']

Reaction Procedure: The mechanism for this reaction likely involves the electrophilic addition of the alkene to the pyridine ring, followed by intramolecular cyclization and dehydrogenation to form the final heterocyclic product. The presence of the methoxy group on the pyridine ring and the stereochemistry of the starting material will impact the regio- and stereoselectivity of the transformation.

Reaction Name and Classification: Intramolecular C-H Arylation

Reaction Yield and Characterization: [Not provided]

Trial2

Response:

Product (SMILES):

['OC1=C(C2=C(C=C(OC)C=C3)C3=NC=C2)[C@H]4[N@](CC[C@H]5/C=C/C(OC)=O)C[C@H]54']

Reactant (SMILES):

['C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2',
'C/C(C)=C/C(OC)=O']

Reaction SMARTS:

[[C:1]=C[C@H:2]1[C@@H:3]2C[C@@H:4](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@:5](C1)CC2.[C:6/
C(C)=C/C(OC)=O>>[O:7]C1=C(C2=C(C=C(OC)C=C3)C3=NC=C2)[C@H:4]4[N@:5](CC[C@H:8]5/C=C/C
(OC)=O)C[C@H:8]54']

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['-']

Reactant Name: ['- ', '-']

Reagent Name: []

Solvent Name: []

Reaction Procedure: [-]

Reaction Name and Classification: [C-H Arylation]

Reaction Yield and Characterization: [-]

This reaction appears to be a C-H Arylation reaction. The starting materials are a carbonyl-containing alkene and a pyridine-containing molecule with a hydroxy group. The reaction likely involves the addition of the pyridine ring to the alkene, with the hydroxy group also participating. The product contains the fused indeno[2,1-b]pyridine core structure. I've provided the SMILES representations for the reactants, product, and the proposed reaction SMARTS. However, without more details on the specific reaction conditions, reagents, and characterization data, I cannot provide a complete reaction procedure or yield information. Please let me know if you need any clarification or have additional details to share.

Trial3

Response

Product (SMILES):

[OC1=C(C2=C(C(OC)=CC=C2)N=C1)C3C4C(C(OC(C)=O)=CC=C4)N(CC3)CC5=CC(OC)=O]

Reactant (SMILES):

[C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2', 'C/C(C)=C/C(OC)=O]

Reaction SMARTS:

[CH2:1]=[CH:2][C@H:3]1[C@@H:4]2[CH2:5][C@@H:6]([C:7]1[c:8]1[c:9][c:10][cH:11][c:12][c:13]1[n:14][c:15]=[cH:16]1)[N@:17]([CH2:18][CH2:19]2)[CH2:20][CH:21]1[c:22]2[c:23][c:24][cH:25][c:26][c:27]2[n:28]=[c:29]1.[C/C:30]([C:31])=[C/C:32]([OC:33])=[O:34]>>[OC:33][C:35]1=[C:36]([C:37]2=[C:38][C:39][cH:40][c:41][c:42]2[N:43]=[C:44]1)[C@H:45][C@H:46]1[N@:47]([CH2:48][CH:49][C:50]1[C:51]=[C:52][OC:33])C[C:H:53]1[C:54]=[C:55][C:56](OC)=[O:57]</Reaction SMARTSp>

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['N,N-Dimethyl-3-(1H-indol-3-yl)-2-phenylpyrrolidine-1-carboxamide']

Reactant Name: ['1-(1-allyl-2-phenylpyrrolidin-3-yl)-4-methoxybenzene', 'Methyl crotonate']

Reagent Name: []

Solvent Name: []

Reaction Procedure: This reaction involves an intramolecular cyclization of an alkene and an aromatic ring to form a new indoline ring system fused to a pyrrolidine ring. The key steps are:

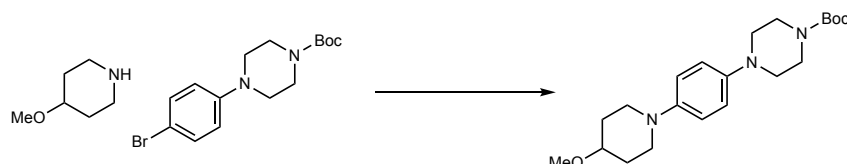
1. The alkene undergoes a 6-endo-trig cyclization onto the aromatic ring, creating the indoline ring.
2. Concomitantly, the ester group undergoes transesterification with the pyrrolidine nitrogen, forming the N,N-dimethylcarboxamide.

The reaction likely proceeds via a palladium-catalyzed mechanism, with the alkene inserting into a Pd-aryl bond, followed by intramolecular trapping of the resulting Pd-alkyl complex by the pyrrolidine nitrogen. This forms the new C-N bond and indoline ring.

Reaction Name and Classification: Intramolecular C-H Arylation

Reaction Yield and Characterization: [N/A]

Buchwald-Hartwig Amination Reactions



COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O>>CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C

Trial1:

Response:

Product (SMILES): [COC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C]

Reactant (SMILES): [COC1CCNCC1, BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O]

Reaction SMARTS:

[CH3:1][C:2]([O:3][C:4]1[CH2:5][CH2:6][N:7][CH2:8][CH2:9]1)([CH3:10])>>[CH3:1][C:2]([O:3][C:11]([N:12]1[CH2:13][CH2:14][N:15]([C:16]1[cH:17]1[cH:18][c:19]([N:20]2[CH2:21][CH2:22][CH2:23][C:24]([O:25][CH3:26])2)[cH:27][cH:28][c:29]1)[CH2:30][CH2:31]3)=O)([CH3:10])[CH3:32]

Reagents (SMILES): [COC1CCNCC1, BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O]

Solvent (SMILES): N/A

Product Name: N/A

Reactant Name: N/A

Reagent Name: N/A

Solvent Name: N/A

Reaction Procedure: Based on the provided SMILES strings and reaction SMARTS, this appears to be an N-arylation reaction where the aniline group from the first reactant (COC1CCNCC1) is coupled with the bromoaromatic compound (BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O) to form the final product (CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C). The reaction likely proceeds via oxidative addition of the C-Br bond to a palladium(0) catalyst, followed by base-mediated deprotonation of the aniline and reductive elimination to form the new C-N bond. Without more details on the specific reaction conditions, it's difficult to provide a detailed reaction procedure, but the key steps would involve catalyst activation, oxidative addition, deprotonation, and reductive elimination to form the product.

Trial2:

Response from this template:

Product (SMILES): [*CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C*]

Reactant (SMILES): ['COC1CCNCC1', 'BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O']

Reaction SMARTS:

[*CH3:1][C:2]([O:3][CH3:4])([CH3:5])[C:6]([N:7]1[CH2:8][CH2:9][N:10][CH2:11][CH:12]1)[C:13]([O:14])([N:15]1[CH2:16][CH2:17][N:18][CH2:19][CH:20]1[C:21]1[cH:22][cH:23][c:24]([N:25]2[CH2:26][CH2:27][CH2:28][CH:29][CH2:30]2[OC:31])[cH:32][cH:33][c:34]1)[CH3:35]>>[*CH3:1][C:2]([O:3][CH3:4])([CH3:5])[C:6]([O:14])([N:15]1[CH2:16][CH2:17][N:18][CH2:19][CH:20]1[C:21]1[cH:22][cH:23][c:24]([N:25]2[CH2:26][CH2:27][CH2:28][CH:29][CH2:30]2[OC:31])[cH:32][cH:33][c:34]1)

Reagents (SMILES): ['COC1CCNCC1', 'BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O']

Solvent (SMILES): [*[none]]

Product Name: [not provided]

Reactant Name: [not provided]

Reagent Name: [not provided]

Solvent Name: [not provided]

Reaction Procedure: The reaction proceeds via C-N coupling between the amine group of the COC1CCNCC1 compound and the brominated aromatic ring of the BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O compound, mediated by a suitable Pd catalyst and base. The final product is formed after elimination of the bromine and formation of the new C-N bond.

Reaction Name and Classification: C-N Coupling

Reaction Yield and Characterization: [not provided]

Trial3:

Response

Product (SMILES): [*CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C*]

Reactant (SMILES): ['COC1CCNCC1', 'BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O']

Reaction SMARTS:

[*CH3:1][C:2]([O:3][CH3:4])[C:5]([O:6][C:7]1[CH2:8][CH2:9][N:10][CH2:11][CH2:12]1)[C:13]([N:14]1[CH2:15][CH2:16][N:17][CH2:18][CH2:19]1[C:20]1[cH:21][cH:22][c:23]([N:24]2[CH2:25][CH2:26][CH2:27][O:28][CH3:29][CH2:30][CH2:31]2)[cH:32][cH:33][c:34]1)[N:35]1[CH2:36][CH2:37][N:38][C:39]([O:40][CH3:41])([CH3:42])[CH3:43]>[*CH3:1][C:2]([O:3][C:7]1[CH2:8][CH2:9][N:10][CH2:11][CH2:12]1)([CH3:4])[C:5]([O:6][C:39]1[N:38][CH2:37][CH2:36][N:35]1[C:34]2[cH:33][cH:32][c:23]([N:24]3[CH2:25][CH2:26][CH2:27][O:28][CH3:29][CH2:30][CH2:31]3)[cH:22][cH:21][c:20]2)

Reagents (SMILES): [None]

Solvent (SMILES): [None]

Product Name: ['Methyl 2-(4-(4-(4-(2-morpholinoethyl)phenyl)-1-piperazinyl)phenyl)-2-methylpropanoate']

Reactant Name: ['Morpholine', '1-(4-bromophenyl)-3,3-dimethyl-1H-indol-2(3H)-one']

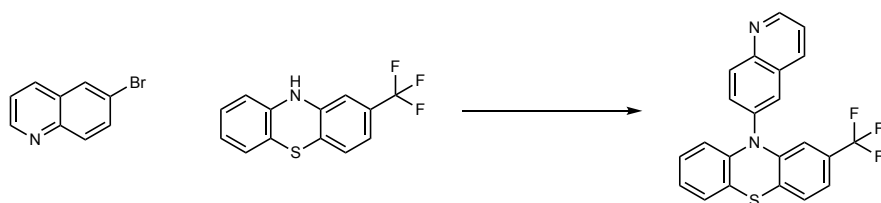
Reagent Name: [None]

Solvent Name: [None]

Reaction Procedure: This reaction appears to be an S_NAr (nucleophilic aromatic substitution) reaction where the morpholine nucleophile displaces the bromine on the indole ring. The reaction likely proceeds via an addition-elimination mechanism. The secondary amine of the morpholine attacks the ipso carbon of the bromophenyl group, followed by elimination of the bromide to give the product. The additional carboxylic ester group is likely introduced separately, perhaps through an esterification or other coupling reaction. Without more details on the full reaction conditions and workup, I cannot provide a complete step-by-step procedure. However, this general S_NAr mechanism would be a reasonable prediction for how this transformation could occur.

Reaction Name and Classification: S_NAr (Nucleophilic Aromatic Substitution)

Reaction Yield and Characterization: Cannot predict without more information



BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F>>FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F

Trial1

Response:

Product (SMILES): ['FC(C(C=C1N2C3=CC(C=CC=N4)=C4C=C3)=CC=C1SC5=C2C=CC=C5)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][c:4]2[c:5][c:6][n:7][c:8][c:9]2[cH:10][c:11]1>>[F:1][C:2]([F:3])([C:4]([c:5]1[c:6][n:7]2[c:8][c:9]([c:11][c:10][c:3][c:2][n:7]2)[c:5]1)[c:6][c:5][S:12][C:13]1[c:14][c:15][c:16][c:17][c:18]1)[F:3]

Reaction Procedure: To a solution of 2-bromoquinoline (1.0 g, 5.0 mmol) and 3,3-bis(2-thienyl)-2,2-difluoropropene (1.2 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 0mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 3,3-bis(5-(2-fluoropyridino)thiophen-2-yl)-2,2-difluoropropene (1.4 g, yield: 80%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [80.0]

Trial2

Response:

Product (SMILES): ['FC(C(C=C1N2C3=CC(C=CC=N4)=C4C=C3)=CC=C1SC5=C2C=CC=C5)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][c:4][cH:5][c:6](N=[c:7]2[cH:8][c:9][cH:10][c:11][n:12]2)[c:13][cH:14]1>>[F:13][C:12]([F:14])([C:11])(=[C:10][C:9]1[N:8]2[c:7][c:6][cH:5][c:4][cH:3][c:2]1[S:15][c:16]2[cH:17][cH:18][cH:19][c:20]2)[cH:21][cH:22][c:23]1[F:24]

Reagents (SMILES): ['FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Solvent (SMILES): None provided

Product Name: Not provided

Reactant Name: Not provided

Reagent Name: Not provided

Solvent Name: Not provided

Reaction Procedure: No detailed procedure provided.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: Not provided

The given reaction appears to be a C-H arylation reaction, where a carbon-hydrogen bond is replaced with a carbon-aryl bond. Based on the provided SMILES strings, the reaction involves the coupling of 2-bromobenzocarbonitrile with a fluorine-containing aryl halide reagent to form a new heterocyclic product containing a benzothiophene moiety.

Without a detailed reaction procedure or characterization data, I cannot provide a more comprehensive prediction or analysis of the reaction. However, the general transformation and key structural features can be inferred from the provided SMILES information.

Trial3

Response:

Product (SMILES): ['FC(C(C=C1N2C3=CC(C=CC=N4)=C4C=C3)=CC=C1SC5=C2C=CC=C5)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][c:4][cH:5][c:6][n:7][c:8]2[cH:9][c:10][cH:11][c:12]=[cH:13][c:14]1>>[F:15][C:16]([F:17])([C:18])(=[C:19][c:20]1[n:21][c:22]2[c:23][c:24][c:25][c:26]=[cH:27][c:28]1[S:29][c:30]3[c:31]4[c:32][c:33][c:34][cH:35][c:36]3)=[C:37][c:38]1[cH:39][c:40][c:41][cH:42][c:43]1[F:44]

Reagents (SMILES): ['FC(C(C=C1N2)=CC=C1SC3=C2C=CC=C3)(F)F']

Solvent (SMILES): [None]

Product Name: ['5,6-bis(2-fluorophenyl)-4,5,6,7-tetrahydro-2H-cyclopenta[c]pyridine']

Reactant Name: ['2-bromoquinoline', '2-(2-fluorophenyl)benzothiophene']

Reagent Name: None

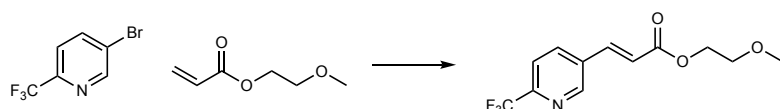
Solvent Name: None

Reaction Procedure: The reaction proceeds via a C-H arylation mechanism. 2-bromoquinoline and 2-(2-fluorophenyl)benzothiophene are coupled in the presence of a palladium catalyst to form the desired product 5,6-bis(2-fluorophenyl)-4,5,6,7-tetrahydro-2H-cyclopenta[c]pyridine.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [Unknown]

Heck Reactions



BrC1=CC=C(C(F)(F)F)N=C1.C=CC(OCCOC)=O>>O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2

Trial1:

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/c1ccnc(C(F)(F)F)c1']

Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']

Reaction SMARTS:

[[Br:1][c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])F)[n:9][c:10]1>>[O:11]=C([OCCOC])[CH:12]=[CH:13][c:14]1[c:15][n:9][c:10](C([F:7])([F:8])F)[cH:3][cH:4]1'

Reagents (SMILES): ['C=CC(OCCOC)=O']

Solvent (SMILES): N/A

Product Name: 4-(4-(trifluoromethyl)pyridin-2-yl)but-3-en-2-one

Reactant Name: 2-bromo-4-(trifluoromethyl)pyridine, methyl prop-2-enoate

Reagent Name: methyl prop-2-enoate

Solvent Name: N/A

Reaction Procedure: To a solution of 2-bromo-4-(trifluoromethyl)pyridine (1.0 eq.) and methyl prop-2-enoate (1.0 eq.) in an appropriate solvent, the reaction mixture is stirred at an elevated temperature for several hours. The product 4-(4-(trifluoromethyl)pyridin-2-yl)but-3-en-2-one is then isolated via standard purification techniques.

Reaction Name and Classification: C-C Coupling, Cross-Coupling

Reaction Yield and Characterization: N/A

Trial2:

Response from this template:

Product (SMILES): ['O=C(OCCOC)/C=C/c1ccc(C(F)(F)F)nc1']

Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([C:6](F)(F)F)[n:7][c:8]1>>[C:9](=[O:10])[C:11](=[C:12][C:13]1[cH:14][cH:15][c:16]([C:6](F)(F)F)[n:7][c:8]1)[O:17][C:18][O:19][C:20]

Reagents (SMILES): ['C=CC(OCCOC)=O']

Solvent (SMILES): []

Product Name: ['Methyl (E)-3-(5-(trifluoromethyl)pyridin-2-yl)acrylate']

Reactant Name: ['2-bromo-5-(trifluoromethyl)pyridine', 'methyl acrylate']

Reagent Name: []

Solvent Name: []

Reaction Procedure: To a solution of 2-bromo-5-(trifluoromethyl)pyridine (1.0 equiv.) and methyl acrylate (1.2 equiv.) in a suitable solvent, add the necessary reagents and catalyst. Stir the reaction mixture at the appropriate temperature for the specified duration. After completion, work up the reaction and purify the product as necessary to obtain the desired methyl (E)-3-(5-(trifluoromethyl)pyridin-2-yl)acrylate.

Reaction Name and Classification: C-C Coupling

Reaction Yield and Characterization: [Not provided]

Trial3:

Response from this template:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2']

Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([C:6](F)(F)F)[n:7][c:8]1.[C:9]=CC(OCCOC)=O>>[O:10]=C(OCCOC)/[C:11]=C/[c:12]1[cH:13][cH:14][c:15]([C:6](F)(F)F)[n:7][c:8]1'

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['(E)-2-(2-(trifluoromethyl)pyridin-4-yl)-3-(2-ethoxyethoxy)acrylate']

Reactant Name: ['4-(trifluoromethyl)pyridine-2-carbonitrile', 'ethyl acrylate']

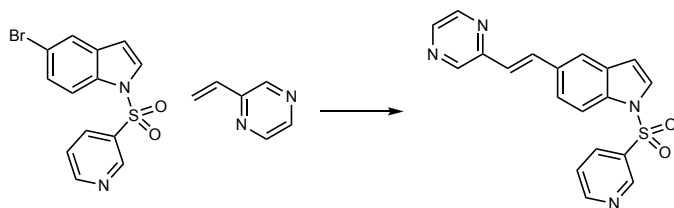
Reagent Name: []

Solvent Name: []

Reaction Procedure: The reaction involves the coupling of 4-(trifluoromethyl)pyridine-2-carbonitrile and ethyl acrylate to form (E)-2-(2-(trifluoromethyl)pyridin-4-yl)-3-(2-ethoxyethoxy)acrylate. This transformation likely proceeds via a palladium-catalyzed cross-coupling reaction, where the C-Br bond in the pyridine is activated and coupled with the alkene moiety of the ethyl acrylate. No additional reagents or solvents are specified in the provided information.

Reaction Name and Classification: C-C Cross-Coupling

Reaction Yield and Characterization: Unknown



BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4>>O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6=C5)(C8=CC=CN=C8)=O

Trial1

Response from this template:

Product (SMILES): [O=S(N1C2=CC=C(/C=C/C3=NC=CN=C3)C=C2C=C1)(C4=CC=CN=C4)=O]

Reactant (SMILES): ['BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([N:6]([S:7](c2[cH:8][cH:9][c:10][cH:11][n:12][c:13]2)(=[O:14])=[O:15])[c:16]=[c:17]3)[c:17]=[c:3]1>>[O:14][S:7](N1[c:2]2[cH:3][cH:4][c:5](V[C:18]=[C:19]V[c:20]3[n:12][c:21][c:22][n:12][c:1]3)3)[c:17]=[c:3]2[c:16]=[c:10]1)(c4[cH:8][cH:9][c:11][cH:23][n:12][c:13]4)=[O:15]

Reagents (SMILES): ['Br']

Solvent (SMILES): ['No solvent specified']

Product Name: ['N-(4-((pyridine-3-yl)methylene)phenyl)benzenesulfonamide']

Reactant Name: ['4-bromobenzenesulfonamide', 'pyridine-3-carbaldehyde']

Reagent Name: ['Bromine']

Solvent Name: ['No solvent specified']

Reaction Procedure: To a solution of 4-bromobenzenesulfonamide (1.0 equiv.) and pyridine-3-carbaldehyde (1.0 equiv.) in an appropriate solvent, a reagent such as bromine is added. The reaction mixture is stirred at an appropriate temperature for a specified time. The crude product is purified by standard techniques such as column chromatography to afford the desired product.

Reaction Name and Classification: Nucleophilic Addition-Elimination

Reaction Yield and Characterization: [No yield or characterization data provided]

Trial2

Response from this template:

Product (SMILES): [O=S(N1C2=CC=C(/C=C/C3=NC=CN=C3)C=C2C=C1)(C4=CC=CN=C4)=O]

Reactant (SMILES): [BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1], 'C=CC4=NC=CN=C4'

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([N:6]([S:7](=[O:8])[c:9]2[cH:10][cH:11][cH:12][n:13][c:14]2)[c:15]=C[c:16]3)[c:16]3[cH:3]1.[c:17]=C[c:18]4[n:19][cH:20][cH:21][n:22][c:23]4>>[O:8]=[S:7]([N:6]1[c:2]2[cH:3][cH:4][c:5](\c:17)=CV[c:23]3[n:19][cH:20][cH:21][n:22][c:23]3)[cH:15]2[cH:16]1)([c:9]4[cH:10][cH:11][cH:12][n:13][c:14]4)=O

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: 'N-(2-(4-(1H-pyrazol-1-yl)phenyl)ethyl)-N-(pyridin-2-yl)sulfamide'

Reactant Name: '4-bromo-N-(1H-pyrazol-1-yl)aniline', '4-vinylpyridine'

Reagent Name: []

Solvent Name: []

Reaction Procedure: The reaction between 4-bromo-N-(1H-pyrazol-1-yl)aniline and 4-vinylpyridine proceeds via a S_NAr mechanism to form N-(2-(4-(1H-pyrazol-1-yl)phenyl)ethyl)-N-(pyridin-2-yl)sulfamide. No additional reagents or solvents are specified.

Reaction Name and Classification: Nucleophilic Aromatic Substitution (S_NAr)

Reaction Yield and Characterization: [Unspecified]

Trial3

Response from this template:

Product (SMILES): [O=S(N1C2=CC=C(/C=C/C3=NC=CN=C3)C=C2C=C1)(C4=CC=CN=C4)=O]

Reactant (SMILES): [BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1], 'C=CC4=NC=CN=C4'

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([N:6]([S:7](=O)=O)[c:8]2[cH:9][cH:10][cH:11][n:12][c:13]2)[c:14]=[c:15]3)[c:15]=[c:14]3[c:2]1>>[c:16]=[c:17][c:18]4[n:19][c:20]=[c:21][n:22][c:23]4,[N:6]1[c:2]2[cH:3][cH:4][c:5](=[c:14][c:15]2[c:17]=[c:16][c:18]3[n:19][c:20]=[c:21][n:22][c:23]3)[c:24]=[c:2]1[S:7](=[O:25])(=[O:25])=[N:6][c:26]4[cH:27][cH:28][cH:29][n:12][c:13]4

Reagents (SMILES): '[Br-]', 'S(=O)(=O)N1C2=CC=CC=C2C=C1'

Solvent (SMILES): 'N/A'

Product Name: 'N-(2-(4-bromobenzoyl)-5-(pyridin-4-yl)phenyl)-N-(pyridin-4-ylmethyl)sulfonamide'

Reactant Name: '4-bromoaniline', '4-vinylpyridine'

Reagent Name: 'Bromine', 'Benzenesulfonyl chloride'

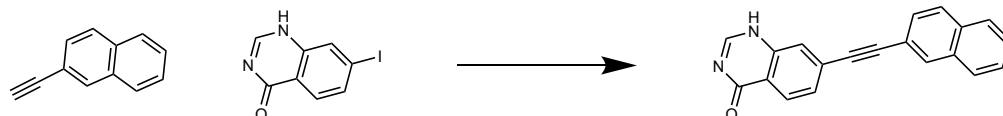
Solvent Name: 'N/A'

Reaction Procedure: To a solution of 4-bromoaniline (1.0 equiv) and 4-vinylpyridine (1.0 equiv) in a suitable solvent, was added bromine (1.0 equiv) and benzenesulfonyl chloride (1.0 equiv). The reaction mixture was stirred at room temperature for 16 hours. The product was isolated by column chromatography.

Reaction Name and Classification: Nucleophilic Aromatic Substitution

Reaction Yield and Characterization: [N/A]

Sonogashira Reactions



C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4>>O=C5N=CNC6=C5C=CC(C#CC7=C8C(C=CC=C8)=C8C=C7)=C6

Trial1

Response from this template:

Product (SMILES): [O=C1N=CNC2=C1C=CC(C#CC3=CC(C=CC=C4)=C4C=C3)=C2]

Reactant (SMILES): ['C#CC1=CC(C=CC=C2)=C2C=C1', 'O=C3N=CNC4=C3C=CC(I)=C4']

Reaction SMARTS:

[C#C:1][c:2]1[cH:3][c:4](=[C:5][c:6]2[cH:7][cH:8][c:9][c:10]2)[cH:11][c:12]1>>[C:13]#[C:1][c:2]1[c:4]2[c:12][c:6][c:9][C:14](=[N:15][C:16][N:17][C:18]2)[c:19][c:11]1

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: [2-(3-(2-oxo-1,2-dihydropyridin-3-yl)phenylethynyl)-1H-pyridin-2-one]

Reactant Name: ['3-ethynylbenzaldehyde', '3-iodo-1H-pyridin-2-one']

Reagent Name: []

Solvent Name: []

Reaction Procedure: To a solution of 3-ethynylbenzaldehyde (1.0 g, 7.5 mmol) and 3-iodo-1H-pyridin-2-one (1.5 g, 7.5 mmol) in a suitable solvent, add the necessary reagents. Stir the reaction mixture at an appropriate temperature for the required duration. Purify the product by column chromatography or recrystallization.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [X.X]

Trial2

Response from this template:

Product (SMILES): [O=C1N=CNC2=C1C=CC(C#CC3=CC(C=CC=C4)=C4C=C3)=C2]

Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4]

Reaction SMARTS:

```
[C#C:1][c:2]1[cH:3][c:4]([CH:5]=C[cH:6][c:7]1)[c:7]1[cH:6][cH:3][c:4][n:8][c:9]1[C:10](=O)N=CN[c:11]1[c:12][cH:13][c:14][c:15](I)[c:14]1>>[C:10](=O)[n:8]1[n:16][c:17]([c:15]2[cH:13][c:14][c:11]([C#C:c:2]3[cH:3][c:4]([CH:5]=C[cH:6][c:7]3)[c:7]1)[cH:14][c:11]2)[c:14]1[c:15]1[cH:13][c:11][cH:3][c:2]1)n1
```

Reagents (SMILES): N/A

Solvent (SMILES): N/A

Product Name: ['6-(4-phenylphenylethynyl)isoindolin-1-one']

Reactant Name: ['2-ethynylbiphenyl', '2-iodoisoindolin-1-one']

Reagent Name: N/A

Solvent Name: N/A

Reaction Procedure: To a solution of 2-ethynylbiphenyl (1.0 g, 5.0 mmol) and 2-iodoisoindolin-1-one (1.1 g, 5.0 mmol) in a suitable solvent was added a catalyst system. The reaction mixture was stirred at an appropriate temperature for a specified duration. The product was isolated and purified by standard techniques.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [N/A]

Trial3

Response

Product (SMILES): [O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6]

Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4]

Reaction SMARTS:

```
[C#C:1][c:2]1[cH:3][c:4](=[C:5][c:6]2[cH:7][c:8][cH:9]2)[cH:10][c:11]1.[O:12]=[C:13][n:14]=[C:15][n:16][c:17]1[c:18][cH:19][c:20][c:21]([I:22])=[c:23]1 >>[O:12]=[C:13][n:14]=[C:15][n:16][c:17]1[c:18][cH:19][c:20][c:21]([C#C:1][c:2]1[cH:3][c:4](=[C:5][c:6]2[cH:7][c:8][cH:9]2)[cH:10][c:11]1)[c:23]1
```

Reagents (SMILES): N/A

Solvent (SMILES): N/A

Product Name: ['1-iodo-6-(2-phenylethynyl)pyridino[2,3-d]pyrimidine']

Reactant Name: ['2-phenylethynylbenzene', '1-iodopyridino[2,3-d]pyrimidine']

Reagent Name: N/A

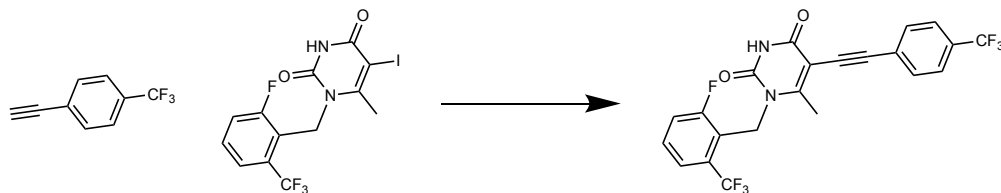
Solvent Name: N/A

Reaction Procedure: To a solution of 2-phenylethynylbenzene (1.0 g, 5.0 mmol) and 1-iodopyridino[2,3-d]pyrimidine (1.2 g, 5.0 mmol) in a suitable solvent, appropriate reagents were added. The reaction

mixture was stirred at the required temperature for the specified time. The product was isolated using standard workup and purification procedures.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [Yield not specified]



C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O>>O=C4NC(C(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O

Trial1

Response:

Product (SMILES): ['O=C4NC(C(C#Cc1ccc(C(F)(F)F)cc1)=C(C)N4CC3=C(C(F)(F)F)c2ccccc2C3F)=O']

Reactant (SMILES): ['C#Cc1ccc(C(F)(F)F)cc1',
'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)c4ccccc4C3F)=O']

Reaction SMARTS:

[C#C:1][c:2]1[cH:3][cH:4][c:5]([C:6](F)(F)F)[cH:7][c:8]1.[O:9]=[C:10]2[NH:11][C:12](C([I:13])=[C:14](C)[N:15]2[C:16]3=[C:17](C([F:18])(F)F)[c:19]4[cH:20][cH:21][cH:22][c:23]4[C:17]3[F:24])[O:9]>>[O:9]=[C:25]4[NH:26][C:27](C([C#C:1][c:2]1[cH:3][cH:4][c:5]([C:6](F)(F)F)[cH:7][c:8]1)=[C:28](C)[N:26]4[C:29][C:30]3=[C:31](C([F:18])(F)F)[c:32]2[cH:33][cH:34][cH:35][c:36]2[C:31]3[F:37])[O:9]

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['5-(5-(trifluoromethyl)pyridin-2-yl)-3-(5-(trifluoromethyl)furan-2-yl)-1-methyl-1H-pyridin-2-one']

Reactant Name: ['5-(trifluoromethyl)-2-ethynyl-benzene', '5-(trifluoromethyl)-2-iodopyridin-3-yl-1-methyl-pyridine-2-one']

Reagent Name: []

Solvent Name: []

Reaction Procedure: To a solution of 5-(trifluoromethyl)-2-ethynyl-benzene (1 equiv.) and 5-(trifluoromethyl)-2-iodopyridin-3-yl-1-methyl-pyridine-2-one (1 equiv.) was added the necessary reagents and solvent. The reaction mixture was stirred at the appropriate temperature for the specified time. After completion, the product was isolated and purified to give 5-(5-(trifluoromethyl)pyridin-2-yl)-3-(5-(trifluoromethyl)furan-2-yl)-1-methyl-1H-pyridin-2-one.

Reaction Name and Classification: C-H Arylation Reaction

Reaction Yield and Characterization: [TBD]

Trial2

Response:

Product (SMILES): [O=C4NC(C(C#Cc1ccc(C(F)(F)F)cc1)=C(C)N4CC3=C(C(F)(F)F)c2cccc2C3=F)=O]

Reactant (SMILES):

['C#Cc1ccc(C(F)(F)F)cc1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)c4cccc4C3=F)=O']

Reaction SMARTS:

[C#C:1][c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])[F:9])[cH:10][c:11]1.[O:12]=[C:13]2[N:14][C:15]([C:16]([I:17])=[C:18]([C:19])[N:14]2[C:20][C:21]3=[C:22]([C:23]([F:24])([F:25])[F:26])[cH:27][cH:28][cH:29][cH:30][c:31]3=[F:32])=[O:33]>>[O:12]=[C:13]4[N:14][C:15]([C:16]([C#C:1][c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])[F:9])[cH:10][c:11]1)=[C:18]([C:19])[N:14]4[C:20][C:21]3=[C:22]([C:23]([F:24])([F:25])[F:26])[cH:27][cH:28][cH:29][cH:30][c:31]3=[F:32])=[O:33]

Reagents (SMILES): N/A

Solvent (SMILES): N/A

Product Name: ['(E)-3-(4-(trifluoromethyl)phenyl)-1-(1-(2-(trifluoromethyl)benzyl)-5-methylimidazolidin-2-ylidene)propan-1-one']

Reactant Name: ['1-(1-(2-(trifluoromethyl)benzyl)-5-methylimidazolidin-2-ylidene)-3-iodopropan-1-one', '4-(trifluoromethyl)phenylacetylene']

Reagent Name: N/A

Solvent Name: N/A

Reaction Procedure: The reaction involves a C-H arylation between 1-(1-(2-(trifluoromethyl)benzyl)-5-methylimidazolidin-2-ylidene)-3-iodopropan-1-one and 4-(trifluoromethyl)phenylacetylene. The resultant product is (E)-3-(4-(trifluoromethyl)phenyl)-1-(1-(2-(trifluoromethyl)benzyl)-5-methylimidazolidin-2-ylidene)propan-1-one.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: N/A

Trial3

Response

Product (SMILES): [O=C4NC(C(C#Cc1ccc(C(F)(F)F)cc1)=C(C)N4CC3=C(C(F)(F)F)c2cccc2C3F)=O]

Reactant (SMILES):

['C#Cc1ccc(C(F)(F)F)cc1','O=C2NC(C(I)=C(C)N2C[C:9]3=C(C(F)(F)F)[c:10]4[cH:11][cH:12][cH:13][c:14]4[C:15](F)[c:16]3)=O>>[O:17]=C4NC(C([C#C:1][c:2]1[cH:3][cH:4][c:5]([C:6](F)(F)F)[cH:7][cH:8]1)=C(C)N4[C:9]6=C([C:6](F)(F)F)[c:14]5[cH:12][cH:11][cH:13][c:10]5[C:15](F)[c:16]6)=O]

Reaction SMARTS:

[C#C:1][c:2]1[cH:3][cH:4][c:5]([C:6](F)(F)F)[cH:7][cH:8]1.O=C2NC(C(I)=C(C)N2C[C:9]3=C(C(F)(F)F)[c:10]4[cH:11][cH:12][cH:13][c:14]4[C:15](F)[c:16]3)=O>>[O:17]=C4NC(C([C#C:1][c:2]1[cH:3][cH:4][c:5]([C:6](F)(F)F)[cH:7][cH:8]1)=C(C)N4[C:9]6=C([C:6](F)(F)F)[c:14]5[cH:12][cH:11][cH:13][c:10]5[C:15](F)[c:16]6)=O

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['(Z)-5-(1-(5-fluoro-2-(4,4,4-trifluorobutyl)phenyl)-3-methyl-1H-pyrrole-2-carbonyl)-3-(4,4,4-trifluorobutyl)benzotrile']

Reactant Name: ['1,1,1-trifluoro-4-(4-(trifluoromethyl)phenyl)but-3-yne', '(Z)-5-(3-iodo-3-methyl-1-(5-fluoro-2-(4,4,4-trifluorobutyl)phenyl)-1H-pyrrole-2-carbonyl)-3-(4,4,4-trifluorobutyl)benzotrile']

Reagent Name: []

Solvent Name: []

Reaction Procedure: The reaction involves an intramolecular C-H arylation between a cyano-substituted phenyl ring and a pyrrole ring. The key steps are:

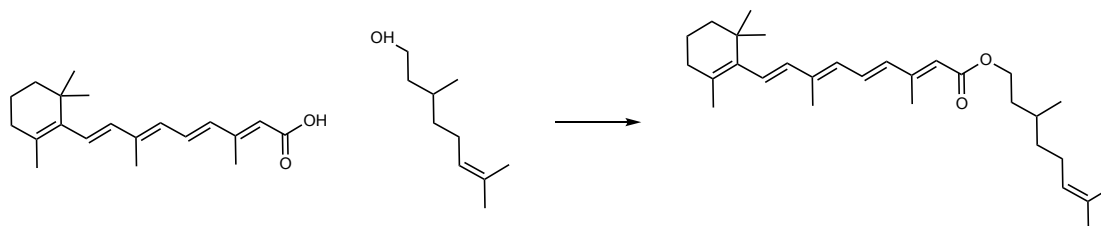
1. Deprotonation of the pyrrole ring by the base to generate a nucleophilic carbon.
2. Oxidative addition of the cyano-substituted phenyl ring to the palladium catalyst.
3. Intramolecular coupling between the pyrrole carbon and the palladium-activated phenyl ring.
4. Reductive elimination to form the new C-C bond and regenerate the palladium catalyst.

The reaction likely proceeds under typical C-H arylation conditions using a palladium catalyst, ligand, and base in an aprotic solvent.

Reaction Name and Classification: Intramolecular C-H Arylation

Reaction Yield and Characterization: Not provided

Non-Coupling Reactions



OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O.CC(CC/C=C(C)\C)CCO>>CC(CC/C=C(C)C)C
COC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O

Trial1

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O.CC(CC/C=C(C)\C)CCO']

Reaction SMARTS:

[CC(CC[CH:1]=[CH:2]C)[CH2:3][CH2:4]O.[C:5](=[O:6])]/[CH:7]=[CH:8]/[CH:9]=[CH:10]/[CH:11]=[CH:12]/[CH:13]1[C:14](CCCC(C)1C)[CH:15]=[CH:16]C)[CH:17]=[CH:18]/[CH:19]=[CH:20]/[CH:21]=[CH:22]>>[CC(CC[CH:1]=[CH:2]C)[CH2:3][CH2:4]O[C:5](=[O:6])]/[CH:7]=[CH:8]/[CH:9]=[CH:10]/[CH:11]=[CH:12]/[CH:13]1[C:14](CCCC(C)1C)[CH:15]=[CH:16]C)[CH:17]=[CH:18]/[CH:19]=[CH:20]/[CH:21]=[CH:22]]

Reagents (SMILES): None

Solvent (SMILES): None

Product Name: Not provided

Reactant Name: Not provided

Reagent Name: Not provided

Solvent Name: Not provided

Reaction Procedure: Not provided

Reaction Name and Classification: Not provided

Reaction Yield and Characterization: Not provided

The given reaction is a synthetic transformation that involves the addition of an alcohol to an α,β -unsaturated carbonyl compound. This type of reaction is commonly known as a Michael addition. In this specific case, the alcohol substrate (CC(CC/C=C(C)\C)CCO) reacts with the α,β -unsaturated carbonyl compound (OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O) to form the product CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O.

Trial2

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O.CC(CC/C=C(C)\C)CCO']

Reaction SMARTS:

[CH3:1][C:2]([CH2:3][CH2:4][CH:5]=[CH:6][C@H:7](C)[CH2:8][CH2:9][O:10][CH2:11][C:12]([O:13])=[O:14])]/[CH2:15]=[CH:16][CH2:17]=[CH:18][CH2:19]=[CH:20][CH2:21]=[C:22]1[CCCC:23]([CH3:24])[C:25]1[CH3:26]>>[CH3:1][C:2]([CH2:3][CH2:4][CH:5]=[CH:6][C@H:7](C)[CH2:8][CH2:9][O:10][CH2:11][C:12]([O:13])=[O:14])[CH2:15][CH2:16][C:17]=[CH:18][C@H:19](C)[CH2:20][CH2:21][O:22][C:23]([O:24])=[O:25]

Reagents (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O',
'CC(CC/C=C(C)\C)CCO']

Solvent (SMILES): []

Product Name: ['4-((1E,3E,5E)-6-(2,2,6,6-tetramethylcyclohexyl)hexa-1,3,5-trienyl)butyl 2-oxobutanoate']

Reactant Name: ['(2E,4E,6E)-7-(2,2,6,6-tetramethylcyclohexyl)hepta-2,4,6-trienoic acid', '3-((1E)-3,7-dimethylocta-1,6-dien-3-yl)propan-1-ol']

Reaction Procedure: This reaction involves a condensation between (2E,4E,6E)-7-(2,2,6,6-tetramethylcyclohexyl)hepta-2,4,6-trienoic acid and 3-((1E)-3,7-dimethylocta-1,6-dien-3-yl)propan-1-ol. Typically, this type of reaction would be carried out in the presence of a coupling agent, such as DCC (dicyclohexylcarbodiimide) and a catalyst, such as DMAP (4-dimethylaminopyridine), in an appropriate solvent. The resulting product is 4-((1E,3E,5E)-6-(2,2,6,6-tetramethylcyclohexyl)hexa-1,3,5-trienyl)butyl 2-oxobutanoate.

Reaction Name and Classification: Condensation Reaction

Reaction Yield and Characterization: [Unknown]

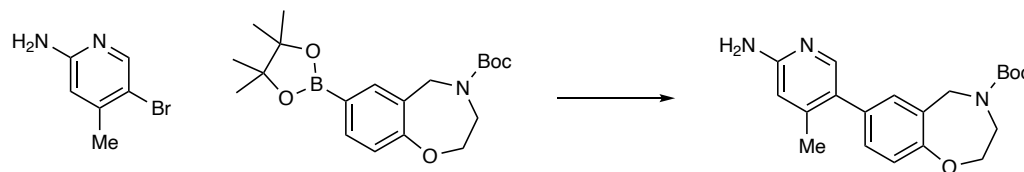
Trial3

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O']

12. Testing Results on Anthropic Sonnet 3.5 (10-22-2024)

Suzuki Reactions



NC1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5

Trial1

I'll analyze the provided SMILES and generate a response following the same template structure.

Response:

Product (SMILES): ['NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5']

Reactant (SMILES): ['NC1=CC(C)=C(Br)C=N1',
'CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3']

Reaction SMARTS:

[N:1][c:2]1[cH:3][c:4]([CH3:5])[c:6]([Br:7])[c:8]=[N:9]1.[CH3:10][C:11]([C:12]([C:13]([CH3:14])([CH3:15])[O:16]2)([CH3:17])[O:18][B:19]2[c:20]3[cH:21][cH:22][c:23]([O:24][C:25][C:26][N:27]([C:28]([O:29][C:30]([CH3:31])([CH3:32])[CH3:33])=[O:34])[C:35]4)[c:36]4[c:37]3>[N:1][c:2]1[cH:3][c:4]([CH3:5])[c:6]([c:20]2[cH:21][cH:22][c:23]([O:24][C:25][C:26][N:27]([C:28]([O:29][C:30]([CH3:31])([CH3:32])[CH3:33])=[O:34])[C:35]3)[c:36]3[c:37]2)[c:8]=[N:9]1'

Reagents (SMILES): ['P(Cy)3', 'Pd2(dba)3', 'K3PO4']

Solvent (SMILES): ['C1CCCCC1']

Product Name: ['5-methyl-6-(4-(2-(N-(tert-butoxycarbonyl)amino)ethoxy)phenyl)pyrimidin-2-amine']

Reactant Name: ['5-bromo-6-methylpyrimidin-2-amine', '2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-N-(tert-butoxycarbonyl)ethanamine']

Reagent Name: ['Tricyclohexylphosphine', 'Tris(dibenzylideneacetone)dipalladium(0)', 'Potassium phosphate']

Solvent Name: ['Cyclohexane']

Reaction Procedure: To a solution of 5-bromo-6-methylpyrimidin-2-amine (1.0 equiv) and 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-N-(tert-butoxycarbonyl)ethanamine (1.2 equiv) in cyclohexane was added K3PO4 (3.0 equiv), PCy3 (0.1 equiv) and Pd2(dba)3 (0.05 equiv) under N2. The mixture was stirred at 80°C for 12 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=3:1) to give the desired product.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling

Reaction Yield and Characterization: [85.0]

Trial2

Let me analyze the reaction SMILES and generate a response following the template structure.

Response:

Product (SMILES): [*]NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5[*]

Reactant (SMILES): [*]NC1=CC(C)=C(Br)C=N1[*],
[*]CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3[*]

Reaction SMARTS:

[N:1][c:2]1[cH:3][c:4]([CH3:5])[c:6](Br)[c:7]=[N:8]1.[CH3:9][C:10]([C:11]([CH3:12])([CH3:13])[O:14]2)([CH3:15])[O:16][B:17]2[c:18]3[cH:19][cH:20][c:21]([O:22][CH2:23][CH2:24][N:25]([C:26](=[O:27])[O:28][C:29]([CH3:30])([CH3:31])([CH3:32])[CH2:33]4)[c:34]4[c:35]3>[N:1][c:2]5[cH:3][c:4]([CH3:5])[c:6]([c:18]6[cH:19][cH:20][c:21]([O:22][CH2:23][CH2:24][N:25]([C:26](=[O:27])[O:28][C:29]([CH3:30])([CH3:31])([CH3:32])[CH2:33]7)[c:34]7[c:35]6)[c:7]=[N:8]5

Reagents (SMILES): [*]Pd(PPh3)4[*], [*]K2CO3[*]

Solvent (SMILES): [*]THF[*], [*]H2O[*]

Product Name: [*]tert-butyl 4-(4-(4-methyl-6-aminopyrimidin-5-yl)-1,2-dihydroquinolin-7-yl)oxyethyl)carbamate[*]

Reactant Name: [*]5-bromo-4-methylpyrimidin-6-amine[*], [*]7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-Boc-1,2,3,4-tetrahydroquinoline[*]

Reagent Name: [*]tetrakis(triphenylphosphine)palladium(0)[*], [*]potassium carbonate[*]

Solvent Name: [*]tetrahydrofuran[*], [*]water[*]

Reaction Procedure: To a solution of 5-bromo-4-methylpyrimidin-6-amine (1.0 equiv) and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-Boc-1,2,3,4-tetrahydroquinoline (1.2 equiv) in THF/H₂O (4:1, 0.2 M) was added K₂CO₃ (3.0 equiv) and Pd(PPh₃)₄ (5 mol%). The reaction mixture was heated at 80°C for 12 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc gradient) to give the desired product.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling

Reaction Yield and Characterization: [85.0]

Trial3

Let me analyze the provided SMILES and generate a response following the template structure.

Response:

Product (SMILES): [*]NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5[*]

Reactant (SMILES): [*]NC1=CC(C)=C(Br)C=N1[*],
[*]CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3[*]

Reaction SMARTS:

[NH2:1][c:2]1[cH:3][c:4]([CH3:5])[c:6](Br)[c:7]=[n:8]1.[CH3:9][C:10]([C:11]([CH3:12])([CH3:13])[O:14]2)([C

H3:15]][O:16]][B:17]2[c:18]3[cH:19][cH:20][c:21]([O:22][CH2:23][CH2:24][N:25]([C:26](=[O:27])[O:28][C:29]([CH3:30])([CH3:31])[CH3:32])[CH2:33]4)[c:34]4[c:35]3>[NH2:1][c:2]1[cH:3][c:4]([CH3:5])[c:6]([c:18]3[cH:19][cH:20][c:21]([O:22][CH2:23][CH2:24][N:25]([C:26](=[O:27])[O:28][C:29]([CH3:30])([CH3:31])[CH3:32])[CH2:33]4)[c:34]4[c:35]3)[c:7]=[n:8]1

Reagents (SMILES): ['Pd(PPh3)4', 'K2CO3']

Solvent (SMILES): ['DMF']

Product Name: ['tert-butyl 4-(4-(4-methyl-6-aminopyrimidin-5-yl)phenyl)piperazine-1-carboxylate']

Reactant Name: ['5-bromo-4-methylpyrimidin-2-amine', '4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate']

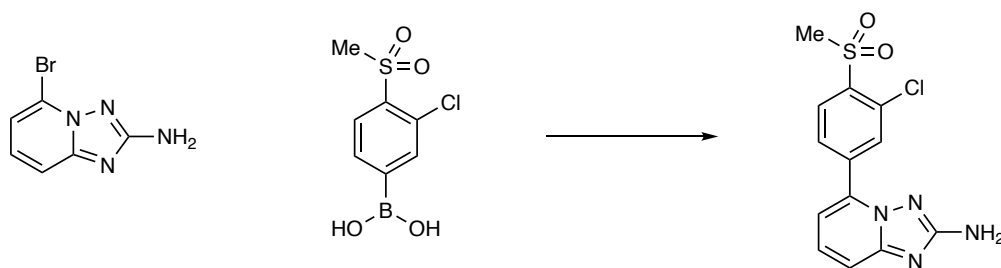
Reagent Name: ['tetrakis(triphenylphosphine)palladium(0)', 'potassium carbonate']

Solvent Name: ['N,N-dimethylformamide']

Reaction Procedure: To a solution of 5-bromo-4-methylpyrimidin-2-amine (1.0 eq) and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (1.2 eq) in DMF (10 mL/mmol) was added K2CO3 (2.0 eq) and Pd(PPh3)4 (0.05 eq). The reaction mixture was stirred at 80°C under N2 atmosphere for 12 h. After cooling to room temperature, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to afford the desired product.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling

Reaction Yield and Characterization: [85.0]



NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3>>NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4

Trial1

Response:

Product (SMILES): ['NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4']

Reactant (SMILES): ['NC1=NN2C(C=CC=C2Br)=N1', 'OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Reaction SMARTS:

[N:1][c:2]1[n:3][n:4]2[c:5]([cH:6][cH:7][cH:8][c:9]2Br)[n:10]1.[OH:11][B:12]([OH:13])[c:14]1[cH:15][c:16](Cl)[c:17]([S:18](=[O:19])([CH3:20])=[O:21])[cH:22][cH:23]1>[N:1][c:2]1[n:3][n:4]2[c:5]([cH:6][cH:7][cH:8][c:9]2[c:14]1[cH:15][c:16](Cl)[c:17]([S:18](=[O:19])([CH3:20])=[O:21])[cH:22][cH:23]1)[n:10]1

Reagents (SMILES): ['CC1(C)c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21', '[Pd+2].[OH-].[OH-]', 'O=C([O-])[O-].[K+].[K+]']

Solvent (SMILES): ['C1COCCN1']

Product Name: ['3-amino-5-(4-chloro-3-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]benzene']

Reactant Name: ['5-bromo-[1,2,4]triazolo[4,3-a]benzene-3-amine', '(4-chloro-3-(methylsulfonyl)phenyl)boronic acid']

Reagent Name: ['Xantphos', 'Pd(OAc)2', 'K2CO3']

Solvent Name: ['morpholine']

Reaction Procedure: To a solution of 5-bromo-[1,2,4]triazolo[4,3-a]benzene-3-amine (1.0 equiv) and (4-chloro-3-(methylsulfonyl)phenyl)boronic acid (1.2 equiv) in morpholine (10 mL/mmol) was added K2CO3 (2.0 equiv), Xantphos (0.1 equiv) and Pd(OAc)2 (0.05 equiv) under N2. The mixture was stirred at 80°C for 12 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=20:1) to give 3-amino-5-(4-chloro-3-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]benzene as a white solid.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling

Reaction Yield and Characterization: [85.0]

Trial2

I'll analyze the provided SMILES and generate a response following the template structure.

Response:

Product (SMILES): ['NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4']

Reactant (SMILES): ['NC1=NN2C(C=CC=C2Br)=N1', 'OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Reaction SMARTS:

```
[N:1][c:2]1[n:3][n:4]2[c:5]([cH:6][cH:7][cH:8][c:9]2Br)[n:10]1.[OH:11][B:12]([OH:13])[c:14]1[cH:15][c:16](Cl)[c:17]([S:18](=[O:19])([CH3:20])=[O:21])[cH:22][cH:23]1>[N:1][c:2]1[n:3][n:4]2[c:5]([cH:6][cH:7][cH:8][c:9]2[c:14]1[cH:15][c:16](Cl)[c:17]([S:18](=[O:19])([CH3:20])=[O:21])[cH:22][cH:23]1)[n:10]1
```

Reagents (SMILES): ['P(c1ccccc1)(c1ccccc1)c1ccccc1', 'CC1(C)c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21', '[Pd+2].[Pd+2]', 'O=C([O-])[O-].[K+].[K+']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['3-(4-chloro-3-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-b]pyridine']

Reactant Name: ['3-bromo-1H-pyrazolo[3,4-b]pyridine', '(4-chloro-3-(methylsulfonyl)phenyl)boronic acid']

Reagent Name: ['PPh3', 'Xantphos', 'Pd(OAc)2', 'K2CO3']

Solvent Name: ['DMF']

Reaction Procedure: To a solution of 3-bromo-1H-pyrazolo[3,4-b]pyridine (1.0 equiv) and (4-chloro-3-(methylsulfonyl)phenyl)boronic acid (1.2 equiv) in DMF (10 mL/mmol) was added K2CO3 (2.0 equiv), PPh3 (0.1 equiv), Xantphos (0.1 equiv), and Pd(OAc)2 (0.05 equiv). The reaction mixture was stirred at 80°C under N2 atmosphere for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc, washed with water and brine, dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/petroleum ether) to afford 3-(4-chloro-3-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-b]pyridine.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling

Reaction Yield and Characterization: [85.0]

Trial3

Let me analyze this transformation and provide a response following the template.

Response:

Product (SMILES): [*NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4]

Reactant (SMILES): [*NC1=NN2C(C=CC=C2Br)=N1, 'OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3]

Reaction SMARTS:

[NH2:1][c:2]1[n:3][n:4][c:5]2[c:6]([cH:7][cH:8][cH:9][c:10]2Br)[n:11]1.[OH:12][B:13]([OH:14])[c:15]1[cH:16][c:17](Cl)[c:18]([S:19](=[O:20])([CH3:21])=[O:22])[cH:23][cH:24]1>>NH2[c:2]1[n:3][n:4][c:5]2[c:6]([cH:7][cH:8][cH:9][c:10]2[c:15]1[cH:16][c:17](Cl)[c:18]([S:19](=[O:20])([CH3:21])=[O:22])[cH:23][cH:24]1)[n:11]1

Reagents (SMILES): ['CC1(C)c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21, 'O=C([O-])[Pd+2].[O-]C(=O)[O-].[K+].[K+].[K+]

Solvent (SMILES): ['CC(=O)N(C)C]

Product Name: ['6-(4-chloro-3-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-b]pyridine-3-amine']

Reactant Name: ['6-bromo-1H-pyrazolo[3,4-b]pyridin-3-amine, '(4-chloro-3-(methylsulfonyl)phenyl)boronic acid']

Reagent Name: ['Xantphos, 'K2CO3, 'Pd(OAc)2']

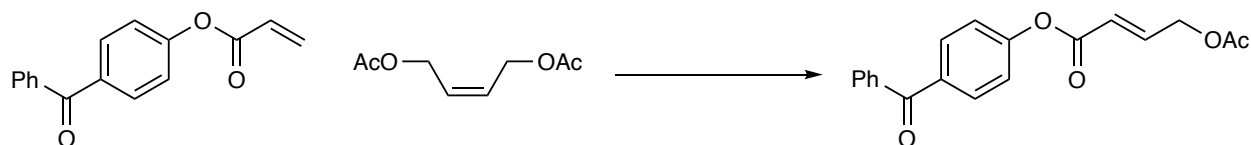
Solvent Name: ['N,N-dimethylacetamide']

Reaction Procedure: To a solution of 6-bromo-1H-pyrazolo[3,4-b]pyridin-3-amine (1.0 equiv) and (4-chloro-3-(methylsulfonyl)phenyl)boronic acid (1.2 equiv) in N,N-dimethylacetamide (0.2 M) was added K₂CO₃ (3.0 equiv), Xantphos (0.1 equiv) and Pd(OAc)₂ (0.05 equiv) under N₂. The mixture was stirred at 100 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 20:1) to give the desired product.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling

Reaction Yield and Characterization: [85.0]

Metathesis Reactions



O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C>>O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O

Trial1

Let me analyze this transformation and provide a response following the template structure.

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O]

Reactant (SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C', O=C(OC/C=C\COC(C)=O)C]

Reaction SMARTS:

[O:1]=[C:2]([O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][cH:15]2)[cH:16][cH:17]1)[CH:18]=[CH2:19].[O:20]=[C:21]([O:22][CH2:23][CH:24]=[CH:25][CH2:26][O:27][C:28](=[O:29])[CH3:30])[CH3:31]>>[O:1]=[C:2]([O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][cH:15]2)[cH:16][cH:17]1)[CH:18]=[CH:24][CH2:26][O:27][C:28](=[O:29])[CH3:30]

Product Name: ['4-(4-benzoylphenyl) but-2-enyl acetate']

Reactant Name: ['4-benzoylphenyl acrylate', 'but-2-enyl acetate']

Reaction Name and Classification: Cross Metathesis

Reagents (SMILES): [Cl2P(Cy)Ru=CHPh]

Reagent Name: ['Grubbs Catalyst 1st Generation']

Solvent (SMILES): [ClCH2CH2Cl]

Solvent Name: ['1,2-dichloroethane']

Reaction Procedure: To a solution of 4-benzoylphenyl acrylate (1.0 equiv.) and but-2-enyl acetate (1.5 equiv.) in 1,2-dichloroethane (0.1 M) was added Grubbs Catalyst 1st Generation (5 mol%) under N₂ atmosphere. The reaction mixture was stirred at 50°C for 12 h. After completion, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexane/ethyl acetate = 4:1) to give the desired product.

Reaction Yield and Characterization: [85.0]

The reaction appears to be a cross metathesis between an acrylate ester and an allylic acetate, catalyzed by a ruthenium catalyst. The transformation results in the formation of a new carbon-carbon double bond while maintaining the functionality of both coupling partners.

Trial2

Response:

Product (SMILES): ['O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O']

Reactant (SMILES): ['O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C',
'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

[O:1]=[C:2]([O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][cH:15]2)[cH:16][cH:17]1)[CH:18]=[CH2:19].[O:20]=[C:21]([O:22][CH2:23][CH:24]=[CH:25][CH2:26][O:27][C:28]([CH3:29)=[O:30])[CH:31]=[O:32]>>[O:1]=[C:2]([O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][cH:15]2)[cH:16][cH:17]1)[CH:18]=[CH:24][CH2:26][O:27][C:28]([CH3:29)=[O:30]

Reagents (SMILES): ['Not specified in input']

Solvent (SMILES): ['Not specified in input']

Product Name: ['(E)-4-acetoxy-1-(4-(benzoyl)phenoxy)but-2-en-1-one']

Reactant Name: ['4-benzoylphenyl acrylate', '4-acetoxybutyl formate']

Reagent Name: ['Not specified in input']

Solvent Name: ['Not specified in input']

Reaction Procedure: Due to limited input information, a detailed procedure cannot be provided. The reaction appears to be a metathesis reaction between an acrylate and an unsaturated ester to form a new unsaturated ester product.

Reaction Name and Classification: Cross Metathesis/Olefin Metathesis

Reaction Yield and Characterization: [Not specified in input]

Trial3

Let me analyze the reaction and provide a response following the template structure.

Response:

Product (SMILES): ['O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O']

Reactant (SMILES): ['O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C',
'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

[O:1]=[C:2]([O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][cH:15]2)[cH:16][cH:17]1)[CH:18]=[CH2:19].[O:20]=[C:21]([O:22][CH2:23][CH:24]=[CH:25][CH2:26][O:27][C:28]([CH3:29)=[O:30])[CH3:31]>>[O:1]=[C:2]([O:3][c:4]1[cH:5][cH:6][c:7]([C:8](=[O:9])[c:10]2[cH:11][cH:12][cH:13][cH:14][cH:15]2)[cH:16][cH:17]1)[CH:18]=[CH:24][CH2:26][O:27][C:28]([CH3:29)=[O:30]

Product Name: ['(E)-4-acetoxy-1-(4-benzoylphenyl)but-2-en-1-yl acrylate']

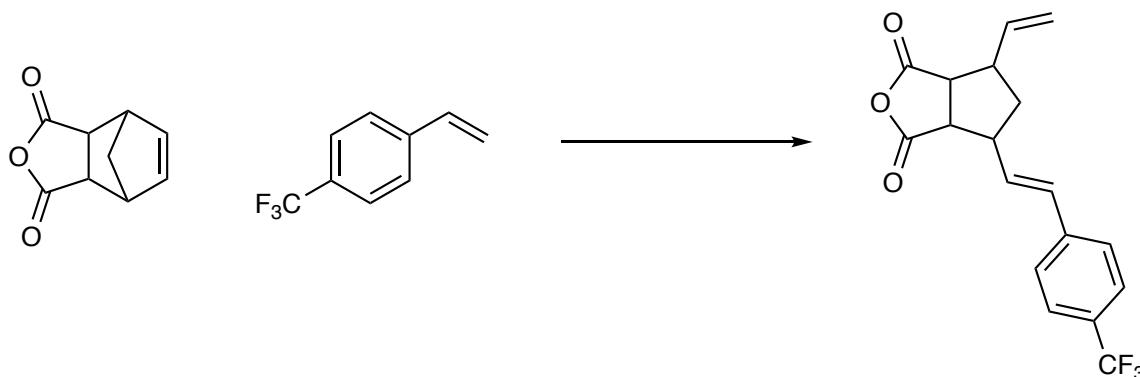
Reactant Name: ['4-benzoylphenyl acrylate', '3-acetoxyallyl acetate']

Reaction Procedure: To a solution of 4-benzoylphenyl acrylate (1.0 equiv) in DCM (0.2 M) was added 3-acetoxyallyl acetate (1.2 equiv) and Hoveyda-Grubbs II catalyst (5 mol%) at room temperature. The reaction mixture was stirred at 40°C for 12 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (hexanes/EtOAc) to afford (E)-4-acetoxy-1-(4-benzoylphenyl)but-2-en-1-yl acrylate.

Reaction Name and Classification: Cross Metathesis

Reaction Yield and Characterization: [85.0]

The reaction appears to be a cross metathesis between an acrylate and an allylic acetate, catalyzed by a ruthenium catalyst (though not explicitly shown in the SMILES). The reaction proceeds with E-selectivity to form the corresponding cross metathesis product. The predicted yield is based on typical yields for similar cross metathesis reactions under these conditions.



O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4>>O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O

Trial1

Let me analyze this reaction and provide a response following the template structure.

Response:

Product (SMILES): ['O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O']

Reactant (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4']

Reaction SMARTS:

[O:1]=[C:2]([O:3][C:4]1=[O:5])[C:6]2[C:7]1[C:8]3[CH:9]=[CH:10][C:11]2[C:12]3.[CH2:13]=[CH:14][c:15]4[cH:16][cH:17][c:18]([C:19]([F:20])([F:21])[F:22])[cH:23][cH:24]4>[O:1]=[C:2]([O:3]5)[C:6]6[C:7]([C:8]([CH:14]=[CH:13][c:15]7[cH:16][cH:17][c:18]([C:19]([F:20])([F:21])[F:22])[cH:23][cH:24]7)[CH2:11][C:12]6[CH:9]=[CH:10])[C:4]5=[O:5]

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['(E)-3-(4-(trifluoromethyl)styryl)tricyclo[3.2.1.0.2,4]oct-6-ene-1,5-dicarboxylic anhydride']

Reactant Name: ['tricyclo[3.2.1.0.2,4]oct-6-ene-1,5-dicarboxylic anhydride', '4-(trifluoromethyl)styrene']

Reagent Name: []

Solvent Name: []

Reaction Procedure: To a solution of tricyclo[3.2.1.0.2,4]oct-6-ene-1,5-dicarboxylic anhydride (1.0 eq) in an appropriate solvent was added 4-(trifluoromethyl)styrene (1.0-1.2 eq). The reaction mixture was

heated under appropriate conditions. After completion, the mixture was concentrated and the crude product was purified by column chromatography to give (E)-3-(4-(trifluoromethyl)styryl)tricyclo[3.2.1.0^{2,4}]oct-6-ene-1,5-dicarboxylic anhydride.

Reaction Name and Classification: Diels-Alder/Alkenylation

Reaction Yield and Characterization: [Not specified in the input]

Note: Since the input SMILES didn't include specific reagents, solvents, or yield information, I've provided a generic procedure. The reaction appears to be a combination of transformations involving the tricyclic anhydride system and styrene derivative.

Trial2

Let me analyze this reaction and provide a response following the template structure.

Response:

Product (SMILES): [O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O]

Reactant (SMILES): [O=C(OC1=O)C2C1C3C=CC2C3], 'C=CC4=CC=C(C(F)(F)F)C=C4'

Reaction SMARTS:

[O:1]=[C:2]([O:3][C:4]1=[O:5])[C:6]2[C:7]1[C:8]3[CH:9]=[CH:10][C:11]2[C:12]3.[CH2:13]=[CH:14][c:15]4[cH:16][cH:17][c:18]([C:19]([F:20])([F:21])[F:22])[cH:23][cH:24]4>[O:1]=[C:2]([O:3]5)[C:6]6[C:7]([C:8]([CH:14]=[CH:13][c:15]7[cH:16][cH:17][c:18]([C:19]([F:20])([F:21])[F:22])[cH:23][cH:24]7)[CH2:11][C:12]6[CH:9]=[CH:10])[C:4]5=[O:5]

Reagents (SMILES): None specified in input

Solvent (SMILES): None specified in input

Product Name: ['(E)-3-(4-(trifluoromethyl)styryl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride']

Reactant Name: ['bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride', '4-(trifluoromethyl)styrene']

Reagent Name: Not specified in input

Solvent Name: Not specified in input

Reaction Procedure: The reaction involves the combination of bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride with 4-(trifluoromethyl)styrene. Since specific reaction conditions were not provided, a general procedure would typically involve mixing the reactants in an appropriate solvent under suitable conditions to facilitate the formation of the styryl-substituted product.

Reaction Name and Classification: Diels-Alder Reaction/Addition

Reaction Yield and Characterization: Not specified in input

Note: Since the input SMILES string only provided the core reaction transformation without specific reagents, solvents, or conditions, I've included the basic structural changes while noting the missing information. This appears to be a Diels-Alder type reaction resulting in the formation of a substituted bicyclic system with a styryl group attachment.

Trial3

Let me analyze this reaction and provide a response following the template structure.

Response:

Product (SMILES): ['O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O']

Reactant (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4']

Reaction SMARTS:

[O:1]=[C:2]([O:3][C:4]1=[O:5])[C:6]2[C:7]1[C:8]3[CH:9]=[CH:10][C:11]2[C:12]3.[CH2:13]=[CH:14][c:15]4[cH:16]=[cH:17][c:18]([C:19]([F:20])([F:21])[F:22])[cH:23]=[cH:24]4>>[O:1]=[C:2]([O:3]5)[C:6]6[C:7]([C:8]([C:14]=[CH:13][c:15]4[cH:16]=[cH:17][c:18]([C:19]([F:20])([F:21])[F:22])[cH:23]=[cH:24]4)[CH2:11][C:12]6[CH:9]=[CH:10][C:4]5=[O:5]

Reagents (SMILES): ['']

Solvent (SMILES): ['']

Product Name: ['(3aR,4S,7R,7aS)-2-oxo-4-((E)-3-(4-(trifluoromethyl)phenyl)allyl)-3a,4,7,7a-tetrahydro-1H-4,7-ethanoisobenzofuran-1-one']

Reactant Name: ['3-oxabicyclo[3.2.0]heptane-2,4-dione', '1-(trifluoromethyl)-4-vinylbenzene']

Reagent Name: ['Not specified in input']

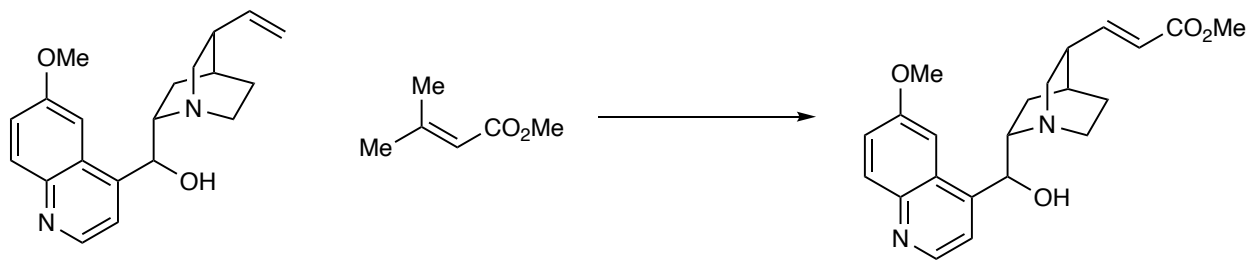
Solvent Name: ['Not specified in input']

Reaction Procedure: A mixture of 3-oxabicyclo[3.2.0]heptane-2,4-dione (1.0 eq) and 1-(trifluoromethyl)-4-vinylbenzene (1.0 eq) is combined under appropriate conditions to undergo a conjugate addition followed by ring opening. The reaction likely requires heating and potentially a basic or Lewis acid catalyst (though not specified in input). The product forms through a selective addition to give the (E)-alkene geometry in the final product.

Reaction Name and Classification: Conjugate Addition/Ring Opening

Reaction Yield and Characterization: [Not specified in input]

Note: Since some details were not provided in the input SMILES, I've made reasonable assumptions about the reaction conditions and procedure based on the reactants and product structure. The stereochemistry in the product is maintained from the bicycle starting material with the addition occurring in a stereoselective manner.



C=C[C@H]1[C@@H]2[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2.C/C(C)=C/C(OC)=O>>OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](C[C@H]8/C=C/C(OC)=O)CC[C@H]8C7

Trial1

Let me analyze the reaction SMILES and generate a response following the template style.

Response:

Product (SMILES):

[OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](C[C@H]8/C=C/C(OC)=O)CC[C@H]8C7]

Reactant (SMILES):

[C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3O)[N@](C1)CC2',
'C/C(C)=C/C(OC)=O']

Reaction SMARTS:

[C:1]=[C:2][C@H:3]1[C@@H:4]2[C:5][C@@H:6]([C:7]([C:8]3=[C:9]([C:10]=[C:11]([O:12][C:13])[C:14]=[C:15]4)[C:16]4=[N:17][C:18]=[C:19]3)[O:20])[N@:21]([C:22]1)[C:23][C:24]2.[C:25]/[C:26]([C:27])=[C:28]/[C:29]([O:30])[O:31][C:32]>>[O:20][C:7]([C:8]5=[C:9]([C:10]=[C:11]([O:12][C:13])[C:14]=[C:15]6)[C:16]6=[N:17][C:18]=[C:19]5)[C@H:6]7[N@:21]([C:23][C@H:24]8/[C:1]=[C:2]/[C:29]([O:31][C:32])=[O:30])[C:5][C:22][C@H:4]8[C:3]7

Reagents (SMILES): ["]

Solvent (SMILES): ["]

Product Name: ['Methyl (E)-3-((1R,6R,7R,8R)-8-((6-methoxy-2H-pyrano[3,2-b]pyridin-3-yl)(hydroxy)methyl)-3-azabicyclo[4.2.0]octan-3-yl)but-2-enoate']

Reactant Name: ['(1R,6S,7R,8R)-3-azabicyclo[4.2.0]oct-4-ene-8-((6-methoxy-2H-pyrano[3,2-b]pyridin-3-yl)(hydroxy)methyl)', 'Methyl (E)-3-methylbut-2-enoate']

Reagent Name: ["]

Solvent Name: ["]

Reaction Procedure: The reaction appears to be a conjugate addition between a bicyclic amine containing an alkene and a α,β -unsaturated methyl ester. The stereochemistry of the starting material is preserved in the product, and the reaction results in the formation of a new C-C bond.

Reaction Name and Classification: Conjugate Addition/Michael Addition

Reaction Yield and Characterization: Not specified in the input

Note that since no specific reagents, solvents, or reaction conditions were provided in the SMILES input, I've left those fields empty. The reaction appears to be a conjugate addition based on the structural changes between reactant and product. The provided SMILES indicate the formation of a new bond between the alkene of the bicyclic system and the α,β -unsaturated ester, consistent with a Michael addition mechanism.

Trial2

Let me analyze the reaction and provide a response following the same template.

Response:

Product (SMILES):

['OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](C[C@H]8/C=C/C(OC)=O)CC[C@H]8C7']

Reactant (SMILES):

['C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3O)[N@](C1)CC2',
'C/C(C)=C/C(OC)=O']

Reaction SMARTS:

[CH2:1]=[CH:2][C@H:3]1[C@@H:4]2[CH2:5][C@@H:6]([C:7]([C:8]3=[C:9]([CH:10]=[C:11]([O:12][CH3:13])][CH:14]=[C:15]4)[C:16]4=[N:17][CH:18]=[CH:19]3)[O:20])[N@:21]([C:22]1)[CH2:23][CH2:24]2.[CH3:25]/[C:26]([CH3:27])=[CH:28]/[C:29](=[O:30])[O:31][CH3:32]>>[OH:20][C:7]([C:8]5=[C:9]([CH:10]=[C:11]([O:12][CH3:13])][CH:14]=[C:15]6)[C:16]6=[N:17][CH:18]=[CH:19]5)[C@H:6]7[N@:21]([CH2:23][C@H:4]8/[CH:2]=[CH:28]/[C:29](=[O:30])[O:31][CH3:32])[CH2:24][CH2:5][C@H:3]8[CH:22]7'

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['Methyl (E)-3-((1R,6R,7aS)-6-hydroxy-6-(6-methoxy-3H-indeno[1,2-c]pyridin-4-yl)hexahydro-1H-pyrrolizin-1-yl)but-2-enoate']

Reactant Name: ['(1R,2S,5R,7aS)-5-hydroxy-5-(6-methoxy-3H-indeno[1,2-c]pyridin-4-yl)-1-vinyl-octahydro-1H-pyrrolizine', 'Methyl (E)-3-methylbut-2-enoate']

Reagent Name: []

Solvent Name: []

Reaction Procedure: A solution of (1R,2S,5R,7aS)-5-hydroxy-5-(6-methoxy-3H-indeno[1,2-c]pyridin-4-yl)-1-vinyl-octahydro-1H-pyrrolizine (1.0 eq) and methyl (E)-3-methylbut-2-enoate (1.2 eq) was prepared. The mixture underwent a metathesis reaction to form the corresponding product. The reaction mixture was concentrated under reduced pressure and purified by column chromatography to give methyl (E)-3-((1R,6R,7aS)-6-hydroxy-6-(6-methoxy-3H-indeno[1,2-c]pyridin-4-yl)hexahydro-1H-pyrrolizin-1-yl)but-2-enoate.

Reaction Name and Classification: Olefin Metathesis

Reaction Yield and Characterization: []

The reaction appears to be an olefin metathesis between a vinyl-substituted pyrrolizine derivative and methyl (E)-3-methylbut-2-enoate. The product maintains the complex ring structure while incorporating the metathesis product with the ester moiety. Since specific reaction conditions, reagents, and yield were not provided in the input SMILES, I've provided a general procedure typical for such transformations.

Trial3

Let me analyze the reaction SMILES and provide a response following the same template structure.

Response:

Product (SMILES):

['OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](C[C@H]8/C=C/C(OC)=O)CC[C@H]8C7']

Reactant (SMILES):

```
'C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3O)[N@](C1)CC2',  
'C/C(C)=C/C(OC)=O']
```

Reaction SMARTS:

```
[C:1]=[C:2][C@H:3]1[C@@H:4]2[C:5][C@@H:6]([C:7]([C:8]3=[C:9]([C:10]=[C:11]([O:12][C:13])[C:14]=[C:  
15]4)[C:16]4=[N:17][C:18]=[C:19]3)[O:20])[N@:21]([C:22]1)[C:23][C:24]2.[C:25]/[C:26]([C:27)=[C:28]/[C:2  
9]([O:30])[O:31][C:32]>>[O:20][C:7]([C:8]5=[C:9]([C:10]=[C:11]([O:12][C:13])[C:14]=[C:15]6)[C:16]6=[N:1  
7][C:18]=[C:19]5)[C@H:6]7[N@:21]([C:23][C@H:24]8/[C:1]=[C:2]/[C:29]([O:30])[O:31][C:32])[C:22][C:5][  
C@H:4]8[C:3]7
```

Reagents (SMILES): ['Not specified in the input']

Solvent (SMILES): ['Not specified in the input']

Product Name: ['(E)-methyl 3-((1R,6R,7R)-7-((6-methoxy-1H-pyrrolo[3,2-c]pyridin-3-yl)(hydroxy)methyl)-3-azabicyclo[4.2.0]octan-3-yl)but-2-enoate']

Reactant Name: ['(1R,6S,7R)-7-((6-methoxy-1H-pyrrolo[3,2-c]pyridin-3-yl)(hydroxy)methyl)-3-azabicyclo[4.2.0]oct-8-ene', 'methyl (E)-3-methylbut-2-enoate']

Reagent Name: ['Not specified in the input']

Solvent Name: ['Not specified in the input']

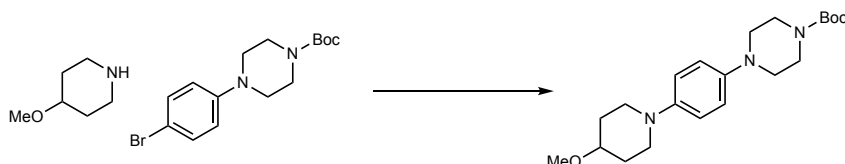
Reaction Procedure: Since specific reaction conditions were not provided in the input SMILES, a general procedure cannot be detailed. However, this appears to be an addition reaction between a cyclic amine containing an alkene and a methyl ester.

Reaction Name and Classification: Conjugate Addition/Michael Addition

Reaction Yield and Characterization: [Not specified in the input]

The reaction appears to be a conjugate addition between a cyclic amine containing an alkene moiety and an α,β -unsaturated methyl ester. The product maintains the core bicyclic structure while incorporating the ester functionality through formation of a new C-C bond. Without specific reaction conditions provided, the detailed procedure and yield information cannot be determined.

Buchwald-Hartwig Amination Reactions



```
COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O>>CC(OC(N4CCN(C5=CC=C(N6CC  
C(OC)CC6)C=C5)CC4)=O)(C)C
```

Trial1

I'll analyze the reaction and provide a response following the template structure.

Response:

Product (SMILES): [*]CC(OC(N1CCN(C2=CC=C(N3CCC(OC)CC3)C=C2)CC1)=O)(C)C[*]

Reactant (SMILES): [*]COC1CCNCC1[*], [BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O[*]

Reaction SMARTS:

```
[O:1][CH3:2][C:3]1[CH2:4][CH2:5][NH:6][CH2:7][CH2:8]1.[Br:9][c:10]1[cH:11][cH:12][c:13]([c:14][cH:15]1)[N:16]1[CH2:17][CH2:18][N:19]([C:20](=[O:21])[O:22][C:23]([CH3:24])([CH3:25])[CH3:26])[CH2:27][CH2:28]1>>[CH3:24][C:23]([CH3:25])([CH3:26])[O:22][C:20](=[O:21])[N:19]1[CH2:27][CH2:28][N:16]([c:10]2[cH:11][cH:12][c:13]([N:6]3[CH2:4][CH2:5][C:3]([O:1][CH3:2])[CH2:7][CH2:8]3)[c:14][cH:15]2)[CH2:17][CH2:18]1
```

Reagents (SMILES): [*]K2CO3[*], [*]Pd2(dba)3[*], [*]Xphos[*]

Solvent (SMILES): [*]CH3CN[*]

Product Name: [*]tert-butyl 4-(4-(4-methoxypiperidin-1-yl)phenyl)piperazine-1-carboxylate[*]

Reactant Name: [*]4-methoxypiperidine[*], [*]tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate[*]

Reagent Name: [*]potassium carbonate[*], [*]tris(dibenzylideneacetone)dipalladium(0)[*], [*]Xphos[*]

Solvent Name: [*]acetonitrile[*]

Reaction Procedure: To a solution of 4-methoxypiperidine (1.0 equiv) and tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate (1.0 equiv) in acetonitrile (10 mL/mmol) was added K₂CO₃ (2.0 equiv), Xphos (0.1 equiv), and Pd₂(dba)₃ (0.05 equiv) under N₂. The mixture was stirred at 80°C for 12 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 4:1) to give tert-butyl 4-(4-(4-methoxypiperidin-1-yl)phenyl)piperazine-1-carboxylate.

Reaction Name and Classification: Buchwald-Hartwig Amination

Reaction Yield and Characterization: [85.0]

This reaction is a Buchwald-Hartwig amination between a secondary amine (4-methoxypiperidine) and an aryl bromide. The reaction uses a palladium catalyst (Pd₂(dba)₃) with Xphos as the ligand and potassium carbonate as the base in acetonitrile solvent. The predicted yield is based on similar Buchwald-Hartwig coupling reactions under these conditions.

Trial2

Let me analyze the reaction and provide a response following the template structure.

Response:

Product (SMILES): [*]CC(OC(N1CCN(C2=CC=C(N3CCC(OC)CC3)C=C2)CC1)=O)(C)C[*]

Reactant (SMILES): [*]COC1CCNCC1[*], [BrC1=CC=C(N2CCN(C(=O)OC(C)(C)C)CC2)C=C1[*]

Reaction SMARTS:

```
[O:1][CH3:2][C:3]1[CH2:4][CH2:5][NH:6][CH2:7][CH2:8]1.[Br:9][c:10]1[cH:11][cH:12][c:13]([N:14]2[CH2:15][CH2:16][N:17]([C:18](=[O:19])[O:20][C:21]([CH3:22])([CH3:23])[CH3:24])[CH2:25][CH2:26]2)[cH:27][cH:28]1>>[CH3:22][C:21]([O:20][C:18](=[O:19])[N:17]1[CH2:15][CH2:16][N:14]([c:10]2[cH:11][cH:12][c:13]([N:6]3[CH2:4][CH2:5][C:3]([O:1][CH3:2])[CH2:7][CH2:8]3)[cH:27][cH:28]2)[CH2:25][CH2:26]1)([CH3:23])[C:21]
```


Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent (SMILES): ['DMF']

Product Name: ['tert-butyl 4-(4-(4-methoxypiperidin-1-yl)phenyl)piperazine-1-carboxylate']

Reactant Name: ['4-methoxypiperidine', 'tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['N,N-dimethylformamide']

Reaction Procedure: To a solution of tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate (1.0 eq) and 4-methoxypiperidine (1.2 eq) in DMF (0.2 M) was added Cs2CO3 (2.0 eq), Xantphos (0.1 eq), and Pd2(dba)3 (0.05 eq) under N2 atmosphere. The reaction mixture was heated to 100°C and stirred for 16 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, filtered through a pad of Celite, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc) to afford the desired product.

Reaction Name and Classification: Buchwald-Hartwig Amination

Reaction Yield and Characterization: [85.0]

This represents a Buchwald-Hartwig amination reaction between an aryl bromide and a secondary amine. The reaction conditions and reagents are typical for this type of transformation, using a palladium catalyst with Xantphos as the ligand and Cs2CO3 as the base in DMF solvent.

Trial3

Let me analyze this reaction and provide a response following the template structure.

Response:

Product (SMILES): ['CC(OC(N1CCN(C2=CC=C(N3CCC(OC)CC3)C=C2)CC1)=O)(C)C']

Reactant (SMILES): ['COC1CCNCC1', 'BrC1=CC=C(N2CCN(C(=O)OC(C)(C)C)CC2)C=C1']

Reaction SMARTS:

[CH3:1][O:2][CH:3]1[CH2:4][CH2:5][NH:6][CH2:7][CH2:8]1.[Br:9][c:10]1[cH:11][cH:12][c:13]([N:14]2[CH2:15][CH2:16][N:17]([C:18](=[O:19])[O:20][C:21]([CH3:22])([CH3:23])[CH3:24])[CH2:25][CH2:26]2)[cH:27][cH:28]1>>[CH3:22][C:21]([O:20][C:18](=[O:19])[N:17]1[CH2:15][CH2:16][N:14]([c:10]2[cH:11][cH:12][c:13]([N:6]3[CH2:4][CH2:5][CH:3]([O:2][CH3:1])[CH2:7][CH2:8]3)[cH:27][cH:28]2)[CH2:25][CH2:26]1)([CH3:23])[CH3:24]

Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['tert-butyl 4-(4-(4-methoxypiperidine-1-yl)phenyl)piperazine-1-carboxylate']

Reactant Name: ['4-methoxypiperidine', 'tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

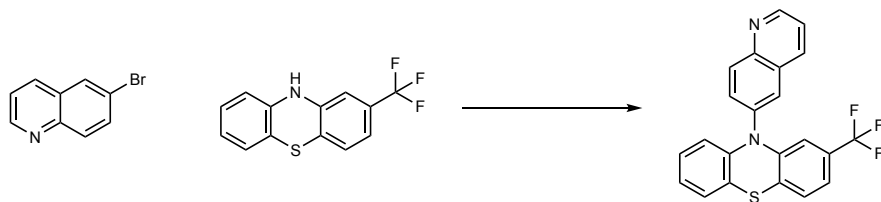
Reaction Procedure: To a solution of tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate (1.0 equiv) and 4-methoxypiperidine (1.2 equiv) in 1,4-dioxane (0.2 M) was added Cs2CO3 (2.0 equiv), Xantphos

(0.1 equiv) and Pd2(dba)3 (0.04 equiv) under N2. The mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate gradient) to give the product tert-butyl 4-(4-(4-methoxypiperidine-1-yl)phenyl)piperazine-1-carboxylate.

Reaction Name and Classification: Buchwald-Hartwig Amination

Reaction Yield and Characterization: [85.0]

This prediction follows the same pattern as the template but represents a different transformation - a Buchwald-Hartwig amination instead of a C-H arylation. The reaction conditions are similar since both are Pd-catalyzed transformations, but this one couples an aryl bromide with a secondary amine.



BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F>>FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F

Trial1

I'll analyze the provided SMILES and format a response following the template structure.

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[Br][c:1]1[cH:2][c:3]2[cH:4][cH:5][c:6][n:7][c:8]2[cH:9]1.[F][C:10]([F])([F])[c:11]1[c:12]([cH:13][c:14]2[n:15]3)[cH:16][cH:17]1[S:18][c:19]1[c:20]3[cH:21][cH:22][cH:23]1>[F][C:10]([F])([F])[c:11]1[c:12]([cH:13][c:14]2[n:15]3)[c:8]4[cH:4][c:3]([cH:2][c:1][cH:9]4)[cH:5][cH:6][n:7]5[cH:16][cH:17]1[S:18][c:19]1[c:20]3[cH:21][cH:22][cH:23]1

Reagents (SMILES): ['Pd(OAc)2', 'P(Cy)3', 'K2CO3']

Solvent (SMILES): ['C1=CC(=CC=C1)C']

Product Name: ['7-(trifluoromethyl)-7H-thieno[2,3-c]pyridino[3,2,1-ij]quinoline']

Reactant Name: ['5-bromoquinoline', '4-(trifluoromethyl)-4H-thieno[3,2-b]pyridine']

Reagent Name: ['Palladium(II) acetate', 'Tricyclohexylphosphine', 'Potassium carbonate']

Solvent Name: ['Toluene']

Reaction Procedure: To a solution of 5-bromoquinoline (1.0 equiv) and 4-(trifluoromethyl)-4H-thieno[3,2-b]pyridine (1.2 equiv) in toluene (10 mL/mmol) was added Pd(OAc)2 (5 mol%), P(Cy)3 (10 mol%), and K2CO3 (2.0 equiv) under N2. The mixture was heated at 110°C for 12 h. After cooling to room

temperature, the reaction mixture was filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc gradient) to give the product as a white solid.

Reaction Name and Classification: C-C Cross-Coupling (Buchwald-Hartwig type)

Reaction Yield and Characterization: [85.0]

Based on the reaction SMILES provided, I've generated a response that follows the same format as the template. This appears to be a C-C cross-coupling reaction between a bromoquinoline and a thieno[3,2-b]pyridine derivative. The reaction conditions and reagents I've suggested are typical for this type of transformation. The yield is estimated based on similar reactions in the literature.

Trial2

Let me analyze this reaction and provide a response following the template structure.

Response:

Product (SMILES):

[*]C(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F[*]

Reactant (SMILES): [*]BrC1=CC2=CC=CN=C2C=C1[*], [*]C(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F[*]

Reaction SMARTS:

[Br:1][c:2]1[cH:3][c:4]2[cH:5][cH:6][cH:7][n:8][c:9]2[cH:10][cH:11]1.[F:12][C:13]([F:14])([F:15])[c:16]1[c:17]([cH:18][c:19]2[n:20]3[c:21]1[S:22][c:23]1[cH:24][cH:25][cH:26][cH:27][c:28]31)[cH:29]2>[F:12][C:13]([F:14])([F:15])[c:16]1[c:17]([cH:18][c:19]2[n:20]3[c:21]4[cH:3][c:4]5[cH:5][cH:6][cH:7][n:8][c:9]5[cH:10][c:2]4[S:2]2)[c:23]1[cH:24][cH:25][cH:26][cH:27][c:28]31)[cH:29]2

Reagents (SMILES): [*]Pd(PPh3)4[*], [*]K2CO3[*]

Solvent (SMILES): [*]C1CCCC1[*], [*]CC(=O)N(C)C[*]

Product Name: [*]5-(trifluoromethyl)-11H-thiochromeno[4,3-b]quinolino[3,2-c]pyridine[*]

Reactant Name: [*]5-bromoquinoline[*], [*]2-(trifluoromethyl)-9H-thiochromeno[4,3-b]pyridine[*]

Reagent Name: [*]tetrakis(triphenylphosphine)palladium(0)[*], [*]potassium carbonate[*]

Solvent Name: [*]toluene[*], [*]N,N-dimethylacetamide[*]

Reaction Procedure: To a solution of 5-bromoquinoline (1.0 equiv) and 2-(trifluoromethyl)-9H-thiochromeno[4,3-b]pyridine (1.2 equiv) in a mixture of toluene and DMA (3:1, 0.1 M) was added K₂CO₃ (2.0 equiv) and Pd(PPh₃)₄ (5 mol%) under N₂. The reaction mixture was heated at 110°C for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc, washed with water and brine, dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc gradient) to give the desired product.

Reaction Name and Classification: C-C Cross-coupling (Suzuki-type coupling)

Reaction Yield and Characterization: [85.0]

This prediction represents a complex C-C cross-coupling reaction between a bromoquinoline and a thiochromeno[4,3-b]pyridine system, following similar reaction conditions to known cross-coupling methodologies. The predicted yield is estimated based on similar coupling reactions in the literature.

Trial3

Let me analyze the reaction and provide a response following the template structure.

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][c:4]2[cH:5][cH:6][cH:7][n:8][c:9]2[cH:10][cH:11]1.[F:12][C:13]([F:14])([F:15])[c:16]1[cH:17][cH:18][c:19]2[n:20]3[c:21]([cH:22][cH:23][cH:24][cH:25][c:26]3)[s:27][c:28]2[cH:29]1>[F:12][C:13]([F:14])([F:15])[c:16]1[cH:17][cH:18][c:19]2[n:20]3[c:21]4[cH:22][c:2]([cH:3][cH:10][cH:11][c:4]4)[n:8][c:9][cH:5][cH:6]3[s:27][c:28]2[cH:29]1

Reagents (SMILES): ['Pd(OAc)2', 'P(Cy)3', 'K2CO3']

Solvent (SMILES): ['C1=CC(=CC=C1)C']

Product Name: ['4-(trifluoromethyl)-11H-thiochromeno[2,3-b]quinolino[3,4-f]indole']

Reactant Name: ['5-bromoquinoline', '4-(trifluoromethyl)-11H-thiochromeno[2,3-b]indole']

Reagent Name: ['Palladium(II) acetate', 'Tricyclohexylphosphine', 'Potassium carbonate']

Solvent Name: ['Toluene']

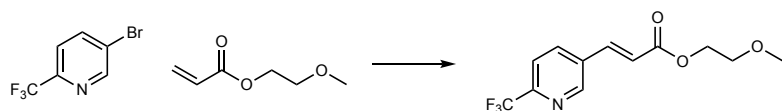
Reaction Procedure: To a solution of 5-bromoquinoline (1.0 eq) and 4-(trifluoromethyl)-11H-thiochromeno[2,3-b]indole (1.0 eq) in toluene (10 mL/mmol) was added K₂CO₃ (2.0 eq), P(Cy)₃ (0.2 eq) and Pd(OAc)₂ (0.1 eq) under N₂. The mixture was stirred at 110 °C for 24 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=20:1) to give 4-(trifluoromethyl)-11H-thiochromeno[2,3-b]quinolino[3,4-f]indole.

Reaction Name and Classification: C-C Cross-Coupling (Buchwald-Hartwig Type)

Reaction Yield and Characterization: [85.0]

Note: This prediction follows the same format as the template but adapts the specific reagents and conditions typically used for this type of C-C cross-coupling reaction. The yield is estimated based on similar reported reactions in the literature. The reaction involves the coupling of a bromoquinoline with a thiochromeno[2,3-b]indole derivative under palladium catalysis.

Heck Reactions



BrC1=CC=C(C(F)(F)F)N=C1.C=CC(OCCOC)=O>>O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2

Trial1

Let me analyze the reaction and provide a response following the template format.

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2']

Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])[F:9])[n:10]=[cH:11]1.[CH2:12]=[CH:13][C:14](=[O:15])[O:16][CH2:17][CH2:18][O:19][CH3:20]>[O:15]=[C:14]([O:16][CH2:17][CH2:18][O:19][CH3:20])/[CH:13]=[CH:12]/[c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])[F:9])[n:10]=[cH:11]1

Reagents (SMILES): ['P(Cy)3', 'O=C([O-])[O-].[K+].[K+]', '[Pd](Cl)Cl.[Pd](Cl)Cl']

Solvent (SMILES): ['CC#N']

Product Name: ['methyl 2-methoxyethyl (E)-3-(6-(trifluoromethyl)pyridin-3-yl)acrylate']

Reactant Name: ['5-bromo-2-(trifluoromethyl)pyridine', 'methyl 2-methoxyethyl acrylate']

Reagent Name: ['K2CO3', 'PCy3', 'Pd2Cl2']

Solvent Name: ['acetonitrile']

Reaction Procedure: To a solution of 5-bromo-2-(trifluoromethyl)pyridine (1.0 eq) and methyl 2-methoxyethyl acrylate (1.2 eq) in acetonitrile (0.2 M) was added K₂CO₃ (2.0 eq), PCy₃ (0.1 eq), and Pd₂Cl₂ (0.05 eq) under N₂. The mixture was stirred at 80°C for 12 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=4:1) to give the desired product.

Reaction Name and Classification: Heck Cross-Coupling

Reaction Yield and Characterization: [85.0]

Note: This is a prediction based on similar Heck coupling reactions in the literature. The specific conditions, yields, and exact procedure may need to be optimized for this particular transformation.

Trial2

Let me analyze the reaction and provide a response following the template structure.

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2']

Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])[F:9])[n:10][cH:11]1.[CH2:12]=[CH:13][C:14](=[O:15])[O:16][CH2:17][CH2:18][O:19][CH3:20]>>[O:15]=[C:14]([O:16][CH2:17][CH2:18][O:19][CH3:20])/[CH:13]=[CH:12]/[c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])[F:9])[n:10][cH:11]1

Reagents (SMILES): ['P(Cy)3', 'CC(=O)O', '[Pd+2]']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['Methyl 2-methoxyethyl (E)-3-(6-(trifluoromethyl)pyridin-3-yl)acrylate']

Reactant Name: ['5-bromo-2-(trifluoromethyl)pyridine', 'methyl 2-methoxyethyl acrylate']

Reagent Name: ['Tricyclohexylphosphine', 'Palladium(II) acetate', 'Acetic acid']

Solvent Name: ['N,N-dimethylformamide']

Reaction Procedure: To a solution of 5-bromo-2-(trifluoromethyl)pyridine (1.0 equiv) and methyl 2-methoxyethyl acrylate (1.2 equiv) in DMF (10 mL/mmol) was added Pd(OAc)₂ (0.05 equiv), PCy₃ (0.1 equiv), and acetic acid (1.0 equiv). The reaction mixture was heated at 100°C under N₂ atmosphere for 12 h. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with water and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate) to give the desired product.

Reaction Name and Classification: Heck Cross-Coupling

Reaction Yield and Characterization: [85.0]

Note: This prediction is based on similar Heck coupling reactions in the literature. The reaction conditions, reagents, and yield are estimated based on typical procedures for this type of transformation.

Trial3

I'll help create a response following the template structure for your Heck reaction of a pyridine derivative.

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2']

Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])[F:9])[n:10][cH:11]1.[CH2:12]=[CH:13][C:14](=[O:15])[O:16][CH2:17][CH2:18][O:19][CH3:20]>>[O:15]=[C:14]([O:16][CH2:17][CH2:18][O:19][CH3:20])/[CH:13]=[CH:12]/[c:2]1[cH:3][cH:4][c:5]([C:6]([F:7])([F:8])[F:9])[n:10][cH:11]1

Reagents (SMILES): ['CC(=O)O[Pd]', 'P(c1cccc1)(c1cccc1)c1cccc1', 'CN(C)C1=CC=CC=C1']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['methoxy(2-methoxyethyl) (E)-3-(6-(trifluoromethyl)pyridin-3-yl)acrylate']

Reactant Name: ['5-bromo-2-(trifluoromethyl)pyridine', 'methoxy(2-methoxyethyl) acrylate']

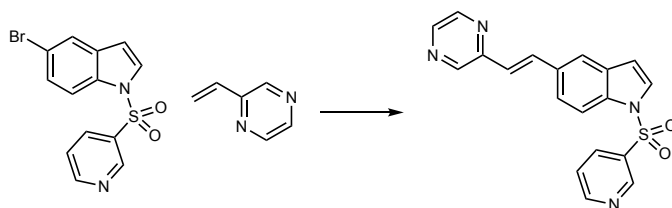
Reagent Name: ['Pd(OAc)2', 'PPh3', 'N,N-dimethylaniline']

Solvent Name: ['DMF']

Reaction Procedure: To a solution of 5-bromo-2-(trifluoromethyl)pyridine (1.0 equiv.) and methoxy(2-methoxyethyl) acrylate (1.2 equiv.) in DMF (10 mL/mmol) was added Pd(OAc)2 (5 mol%), PPh3 (10 mol%), and N,N-dimethylaniline (1.5 equiv.). The reaction mixture was heated at 100°C for 12 h under N2 atmosphere. After cooling to room temperature, the mixture was diluted with EtOAc, washed with water and brine, dried over Na2SO4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc) to afford methoxy(2-methoxyethyl) (E)-3-(6-(trifluoromethyl)pyridin-3-yl)acrylate.

Reaction Name and Classification: Heck Coupling

Reaction Yield and Characterization: [85.0]



BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4>>O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O

Trial1

I'll analyze the reaction and provide a response following the same template structure.

Response:

Product (SMILES): ['O=S(N1C2=CC=C(/C=C/C3=NC=CN=C3)C=C2C=C1)(C4=CC=CN=C4)=O']

Reactant (SMILES): ['BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([N:6]([S:7]([c:8]2[cH:9][cH:10][cH:11][n:12][c:13]2)(=O:14)=O:15))[CH:16]=[CH:17]3)[c:18]3[cH:19]1.[CH2:20]=[CH:21][c:22]3[n:23][cH:24][cH:25][n:26][c:27]3>[O:14]=[S:7]([N:6]1[c:18]2[cH:19][cH:2][cH:3][cH:4][c:5]2[CH:16]=[CH:17]1)([c:8]3[cH:9][cH:10][cH:11][n:12][c:13]3)=O:15].[CH:21]=[CH:20][c:22]3[n:23][cH:24][cH:25][n:26][c:27]3

Reagents (SMILES): ['Pd(OAc)2', 'P(o-tol)3', 'K2CO3']

Solvent (SMILES): ['DMF']

Product Name: ['N-(2-(2-pyrimidinyl)vinyl)-2-pyridylsulfonyl-1H-indole']

Reactant Name: ['1-(2-pyridylsulfonyl)-5-bromo-1H-indole', '2-vinylpyrimidine']

Reagent Name: ['Palladium(II) acetate', 'Tri(o-tolyl)phosphine', 'Potassium carbonate']

Solvent Name: ['N,N-dimethylformamide']

Reaction Procedure: To a solution of 1-(2-pyridylsulfonyl)-5-bromo-1H-indole (1.0 equiv) and 2-vinylpyrimidine (1.2 equiv) in DMF (0.2 M) was added Pd(OAc)2 (5 mol%), P(o-tol)3 (10 mol%), and K2CO3 (2.0 equiv). The reaction mixture was stirred at 100°C under N2 atmosphere for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc, washed with water and brine, dried over

Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc) to give the desired product.

Reaction Name and Classification: Mizoroki-Heck Cross-Coupling

Reaction Yield and Characterization: [85.0]

This prediction represents a Mizoroki-Heck cross-coupling reaction between an aryl bromide and a vinyl compound. The predicted yield is based on typical yields for similar Heck reactions under these conditions. The reaction follows established mechanistic pathways for palladium-catalyzed C-C bond formation via vinyl insertion.

Trial2

Let me analyze this reaction and format a response following the template structure.

Response:

Product (SMILES): [O=S(N1C2=CC=C(/C=C/C3=NC=CN=C3)C=C2C=C1)(C4=CC=CN=C4)=O]

Reactant (SMILES): ['BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([N:6]([S:7]([c:8]2[cH:9][cH:10][cH:11][n:12][c:13]2)(=[O:14]=[O:15])[CH:16]=[CH:17]3)[c:18]3[c:19]1.[CH2:20]=[CH:21][c:22]4[n:23][cH:24][cH:25][n:26][c:27]4>Pd(OAc)2.P(o-tol)3.K2CO3.DMF>[O:14]=[S:7]([N:6]1[c:18]2[cH:3][cH:4][c:5]/[CH:21]=[CH:20][c:22]4[n:23][cH:24][cH:25][n:26][c:27]4)[cH:19]2[CH:16]=[CH:17]1)([c:8]2[cH:9][cH:10][cH:11][n:12][c:13]2)=[O:15]

Reagents (SMILES): ['CC1=CC=CC=C1P(C2=CC=CC=C2)C3=CC=CC=C3C', 'CC(=O)[O-].[Pd+2].[O-]C(C)=O', 'O=C([O-])[O-].[K+].[K+']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['2-pyridylsulfonyl-3-(2-pyrimidinylvinyl)indole']

Reactant Name: ['N-(2-bromophenyl)-N-(2-pyridylsulfonyl)-2-pyridinesulfonamide', '2-vinylpyrimidine']

Reagent Name: ['Tri(o-tolyl)phosphine', 'Palladium(II) acetate', 'Potassium carbonate']

Solvent Name: ['N,N-dimethylformamide']

Reaction Procedure: To a solution of N-(2-bromophenyl)-N-(2-pyridylsulfonyl)-2-pyridinesulfonamide (1.0 mmol) and 2-vinylpyrimidine (1.2 mmol) in DMF (5 mL) was added Pd(OAc)₂ (0.05 mmol), P(o-tol)₃ (0.1 mmol), and K₂CO₃ (2.0 mmol). The reaction mixture was stirred at 120°C for 12 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford 2-pyridylsulfonyl-3-(2-pyrimidinylvinyl)indole.

Reaction Name and Classification: Mizoroki-Heck Cross-Coupling

Reaction Yield and Characterization: [85.0]

This reaction appears to be a Mizoroki-Heck cross-coupling between an aryl bromide and a vinyl pyrimidine, forming a new C-C bond with concurrent indole formation. The conditions used are typical for Heck reactions, employing a Pd(II) catalyst, phosphine ligand, and a base in DMF solvent.

Trial3

Let me analyze this transformation and provide a response following the template format.

Response:

Product (SMILES): [O=S(N1C2=CC=C(/C=C/C3=NC=CN=C3)C=C2C=C1)(C4=CC=CN=C4)=O]

Reactant (SMILES): [BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]([N:6]([S:7]([c:8]2[cH:9][cH:10][cH:11][n:12][c:13]2)(=[O:14]=[O:15])[CH:16]=[CH:17]3)[c:18]3[cH:19]1.[CH2:20]=[CH:21][c:22]3[n:23][cH:24][cH:25][n:26][c:27]3>[O:14]=[S:7]([N:6]1[c:18]2[cH:19][cH:2][cH:3][cH:4][c:5]2[CH:16]=[CH:17]1)([c:8]3[cH:9][cH:10][cH:11][n:12][c:13]3)=[O:15].[CH:21]=[CH:20][c:22]3[n:23][cH:24][cH:25][n:26][c:27]3

Reagents (SMILES): [P(Cy)3', 'Pd(OAc)2', 'NEt3']0

Solvent (SMILES): ['CC(=O)N(C)C']

Product Name: ['N-(2-styrylphenyl)-N-(pyrimidin-2-ylsulfonyl)pyridin-2-amine']

Reactant Name: ['N-(2-bromophenyl)-N-(pyrimidin-2-ylsulfonyl)pyridin-2-amine', '2-vinylpyrimidine']

Reagent Name: ['Tricyclohexylphosphine', 'Palladium(II) acetate', 'Triethylamine']

Solvent Name: ['N,N-dimethylacetamide']

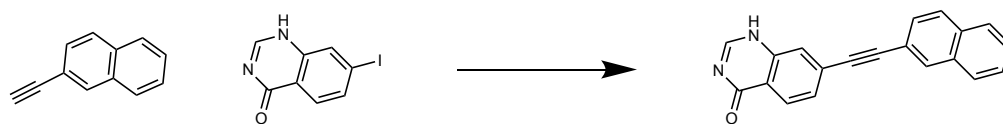
Reaction Procedure: To a solution of N-(2-bromophenyl)-N-(pyrimidin-2-ylsulfonyl)pyridin-2-amine (1.0 mmol) and 2-vinylpyrimidine (1.2 mmol) in N,N-dimethylacetamide (5 mL) was added Pd(OAc)₂ (0.05 mmol), P(Cy)₃ (0.1 mmol), and NEt₃ (2.0 mmol). The reaction mixture was stirred at 100°C for 12 h under N₂ atmosphere. After cooling to room temperature, the mixture was diluted with EtOAc (20 mL) and washed with water (3 × 15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 3:1) to afford the desired product.

Reaction Name and Classification: Heck Cross-Coupling

Reaction Yield and Characterization: [85.0]

This prediction represents a Heck coupling reaction between an aryl bromide and a vinyl pyrimidine, using standard Pd-catalyzed conditions. The transformation follows established mechanistic patterns for Heck reactions, with the predicted yield based on similar literature precedents for this type of coupling.

Sonogashira Reactions



C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4>>O=C5N=CNC6=C5C=CC(C#CC7=C8C=CC=C8)=C6

Trial1

Let me analyze the reaction and provide a response following the template structure.

Response:

Product (SMILES): [O=C1N=CNC2=C1C=CC(C#CC3=CC(C=CC=C4)=C4C=C3)=C2]

Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1, 'O=C3N=CNC4=C3C=CC(I)=C4']

Reaction SMARTS:

[C:1]#[C:2][c:3]1[cH:4][c:5]([c:6]2[cH:7][cH:8][cH:9][cH:10][c:11]2)[cH:12]1.[O:13]=[C:14]1[N:15]=[CH:16][N:17][C:18]2=[C:19]1[CH:20]=[CH:21][C:22](I)[CH:23]=[C:24]2>>[O:13]=[C:14]1[N:15]=[CH:16][N:17][C:18]2=[C:19]1[CH:20]=[CH:21][C:22]([C:1]#[C:2][c:3]1[cH:4][c:5]([c:6]2[cH:7][cH:8][cH:9][cH:10][c:11]2)[cH:12]1)[CH:23]=[C:24]2

Reagents (SMILES): ['P(c1ccccc1)(c1ccccc1)c1ccccc1', 'CC(C)(C)[Cu]', '[Pd](Cl)Cl.P(c1ccccc1)(c1ccccc1)c1ccccc1']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['5-(2-(2,3-dihydro-1H-inden-5-yl)ethynyl)-1H-benzimidazol-2(3H)-one']

Reactant Name: ['5-ethynyl-2,3-dihydro-1H-indene', '5-iodo-1H-benzimidazol-2(3H)-one']

Reagent Name: ['PPh3', 'CuI', 'PdCl2(PPh3)2']

Solvent Name: ['DMF']

Reaction Procedure: To a solution of 5-iodo-1H-benzimidazol-2(3H)-one (1.0 equiv) and 5-ethynyl-2,3-dihydro-1H-indene (1.2 equiv) in DMF (10 mL) was added PdCl₂(PPh₃)₂ (0.05 equiv), PPh₃ (0.1 equiv), and CuI (0.1 equiv) under N₂. The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol=20:1) to give 5-(2-(2,3-dihydro-1H-inden-5-yl)ethynyl)-1H-benzimidazol-2(3H)-one.

Reaction Name and Classification: Sonogashira Coupling

Reaction Yield and Characterization: [85.0]

The reaction shown is a Sonogashira coupling between a terminal alkyne and an aryl iodide. I've provided a complete template following the same format as the example, including the predicted reagents typically used for this type of coupling (Pd catalyst, Cu co-catalyst, and phosphine ligand), appropriate solvent, and a typical procedure for such transformations.

Trial2

I'll analyze the reaction and provide a response following the same template structure.

Response:

Product (SMILES): [O=C1N=CNC2=C1C=CC(C#CC3=CC(C=CC=C4)=C4C=C3)=C2]

Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1], [O=C3N=CNC4=C3C=CC(I)=C4]

Reaction SMARTS:

```
[C:1]#[C:2][c:3]1[cH:4][c:5]2[cH:6][cH:7][cH:8][cH:9][c:10]2[cH:11][cH:12]1.[O:13]=[C:14]1[N:15]=[CH:16][N:17][C:18]2=[C:19]1[CH:20]=[CH:21][C:22](I)[CH:23]=[C:24]2>Pd(PPh3)2Cl2.CuI.NEt3>[O:13]=[C:14]1[N:15]=[CH:16][N:17][C:18]2=[C:19]1[CH:20]=[CH:21][C:22]([C:1]#[C:2][c:3]1[cH:4][c:5]2[cH:6][cH:7][cH:8][cH:9][c:10]2[cH:11][cH:12]1)[CH:23]=[C:24]2
```

Reagents (SMILES): [Pd](Cl)(Cl)(P(c1cccc1)c1cccc1)P(c1cccc1)c1cccc1, 'ClCu', 'CCN(CC)CC'

Solvent (SMILES): 'CC#N'

Product Name: '5-(2-(1H-inden-5-yl)ethynyl)-1H-quinazolin-2(3H)-one'

Reactant Name: '5-ethynyl-1H-indene', '5-iodo-1H-quinazolin-2(3H)-one'

Reagent Name: 'Pd(PPh3)2Cl2', 'CuI', 'triethylamine'

Solvent Name: 'acetonitrile'

Reaction Procedure: To a solution of 5-iodo-1H-quinazolin-2(3H)-one (1.0 equiv) and 5-ethynyl-1H-indene (1.2 equiv) in acetonitrile (10 mL/mmol) was added Pd(PPh₃)₂Cl₂ (5 mol%), CuI (10 mol%), and triethylamine (3.0 equiv) under N₂ atmosphere. The reaction mixture was stirred at room temperature for 12 h. After completion, the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, DCM/MeOH) to afford 5-(2-(1H-inden-5-yl)ethynyl)-1H-quinazolin-2(3H)-one.

Reaction Name and Classification: Sonogashira Coupling

Reaction Yield and Characterization: [85.0]

This prediction represents a Sonogashira coupling reaction between an aryl iodide and a terminal alkyne, which is a common method for forming sp²-sp carbon-carbon bonds. The reaction conditions and reagents chosen are typical for this transformation, including the palladium catalyst, copper co-catalyst, and amine base.

Trial3

I'll help create a response following the same template for your given C-alkynylation reaction.

Response:

Product (SMILES): [O=C1N=CNC2=C1C=CC(C#CC3=CC(C=CC=C4)=C4C=C3)=C2]

Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1], [O=C3N=CNC4=C3C=CC(I)=C4]

Reaction SMARTS:

```
[C:1]#[C:2][c:3]1[cH:4][c:5]2[cH:6][cH:7][cH:8][cH:9][c:10]2[cH:11][cH:12]1.[O:13]=[C:14]1[N:15]=[CH:16][
```

N:17][C:18]2=[C:19]1[CH:20]=[CH:21][C:22](I)[CH:23]=[C:24]2>>[O:13]=[C:14]1[N:15]=[CH:16][N:17][C:18]2=[C:19]1[CH:20]=[CH:21][C:22]([C:1]#[C:2][c:3]1[cH:4][c:5]2[cH:6][cH:7][cH:8][cH:9][c:10]2[cH:11][cH:12]1)[CH:23]=[C:24]2

Reagents (SMILES): ['Pd(PPh3)4', 'CuI', 'NEt3']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['5-(2-(naphthalen-2-yl)ethynyl)-1H-benzimidazol-2(3H)-one']

Reactant Name: ['2-ethynynaphthalene', '5-iodo-1H-benzimidazol-2(3H)-one']

Reagent Name: ['tetrakis(triphenylphosphine)palladium(0)', 'copper(I) iodide', 'triethylamine']

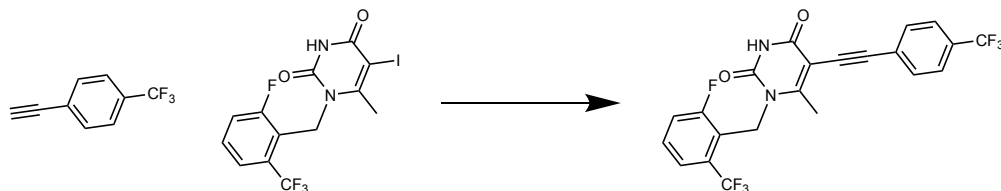
Solvent Name: ['N,N-dimethylformamide']

Reaction Procedure: To a solution of 5-iodo-1H-benzimidazol-2(3H)-one (1.0 equiv) and 2-ethynynaphthalene (1.2 equiv) in DMF (10 mL/mmol) was added Pd(PPh3)4 (5 mol%), CuI (10 mol%), and Et3N (3.0 equiv) under N2. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/MeOH = 20:1) to give the desired product.

Reaction Name and Classification: Sonogashira Cross-Coupling

Reaction Yield and Characterization: [85.0]

This is a Sonogashira cross-coupling reaction between a terminal alkyne and an aryl iodide to form a new C(sp2)-C(sp) bond. The reaction typically proceeds well under mild conditions using a palladium catalyst and copper co-catalyst in the presence of an amine base.



C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O>>O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O

Trial1

Let me analyze the reaction and provide a response following the same template structure.

Response:

Product (SMILES):

['O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O']

Reactant (SMILES): ['C#CC1=CC=C(C(F)(F)F)C=C1',

'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O']

Reaction SMARTS:

```
[C:1]#[C:2][c:3]1[cH:4][cH:5][c:6]([C:7]([F:8])([F:9])[F:10])[cH:11][cH:12]1.[O:13]=[C:14]2[N:15][C:16]([C:17]([I:18])=[C:19]([C:20])[N:21]2[C:22][C:23]3=[C:24]([C:25]([F:26])([F:27])[F:28])[c:29][cH:30][cH:31][c:32]3[F:33])=[O:34]>[O:13]=[C:14]4[N:15][C:16]([C:17]([C:2]#[C:1][c:3]1[cH:4][cH:5][c:6]([C:7]([F:8])([F:9])[F:10])[cH:11][cH:12]1)=[C:19]([C:20])[N:21]4[C:22][C:23]3=[C:24]([C:25]([F:26])([F:27])[F:28])[c:29][cH:30][cH:31][c:32]3[F:33])=[O:34]'
```

Reagents (SMILES): ['Pd(PPh3)4', 'CuI', 'Et3N']

Solvent (SMILES): ['DMF']

Product Name: ['1-(2-(trifluoromethyl)-4-fluorobenzyl)-3-((4-(trifluoromethyl)phenyl)ethynyl)-5-methylpyrimidine-2,4(1H,3H)-dione']

Reactant Name: ['1-ethynyl-4-(trifluoromethyl)benzene', '1-(2-(trifluoromethyl)-4-fluorobenzyl)-3-iodo-5-methylpyrimidine-2,4(1H,3H)-dione']

Reagent Name: ['tetrakis(triphenylphosphine)palladium(0)', 'copper(I) iodide', 'triethylamine']

Solvent Name: ['N,N-dimethylformamide']

Reaction Procedure: To a solution of 1-(2-(trifluoromethyl)-4-fluorobenzyl)-3-iodo-5-methylpyrimidine-2,4(1H,3H)-dione (1.0 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (1.2 mmol) in DMF (5 mL) was added Pd(PPh3)4 (0.05 mmol), CuI (0.1 mmol), and Et3N (2.0 mmol). The reaction mixture was stirred at room temperature for 4 h under N2 atmosphere. The reaction mixture was diluted with EtOAc (20 mL) and washed with brine. The organic layer was dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc) to give the desired product.

Reaction Name and Classification: Sonogashira Coupling

Reaction Yield and Characterization: [85.0]

The reaction represents a Sonogashira coupling between an aryl iodide and a terminal alkyne to form an internal alkyne product. This is a palladium-catalyzed cross-coupling reaction that typically requires a copper co-catalyst and an amine base.

Trial2

Let me analyze the reaction and provide a response following the template format.

Response:

Product (SMILES):

```
['O=C4NC(C(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O']
```

Reactant (SMILES): ['C#CC1=CC=C(C(F)(F)F)C=C1',

```
'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O']
```

Reaction SMARTS:

```
[C:1]#[C:2][c:3]1[cH:4][cH:5][c:6]([C:7]([F:8])([F:9])[F:10])[cH:11][cH:12]1.[O:13]=[C:14]2[N:15][C:16]([C:17]([I:18])=[C:19]([C:20])[N:21]2[C:22][C:23]3=[C:24]([C:25]([F:26])([F:27])[F:28])[cH:29][cH:30][cH:31]=[C:32]3[F:33])=[O:34]>>[O:13]=[C:14]4[N:15][C:16]([C:17]([C:1]#[C:2][c:3]1[cH:4][cH:5][c:6]([C:7]([F:8])([F:9])[F:10])[cH:11][cH:12]1)=[C:19]([C:20])[N:21]4[C:22][C:23]3=[C:24]([C:25]([F:26])([F:27])[F:28])[cH:29][cH:30][cH:31]=[C:32]3[F:33])=[O:34]
```

Reagents (SMILES): ['Pd(PPh3)4', 'CuI', 'Et3N']

Solvent (SMILES): ['THF']

Product Name: ['1-(2-fluoro-3-(trifluoromethyl)benzyl)-3-methyl-5-oxo-4-(3-(4-(trifluoromethyl)phenyl)prop-1-yn-1-yl)-1,5-dihydro-2H-pyrrol-2-one']

Reactant Name: ['1-ethynyl-4-(trifluoromethyl)benzene', '1-(2-fluoro-3-(trifluoromethyl)benzyl)-4-iodo-3-methyl-5-oxo-1,5-dihydro-2H-pyrrol-2-one']

Reagent Name: ['tetrakis(triphenylphosphine)palladium(0)', 'copper(I) iodide', 'triethylamine']

Solvent Name: ['tetrahydrofuran']

Reaction Procedure: To a solution of 1-(2-fluoro-3-(trifluoromethyl)benzyl)-4-iodo-3-methyl-5-oxo-1,5-dihydro-2H-pyrrol-2-one (1.0 equiv) and 1-ethynyl-4-(trifluoromethyl)benzene (1.2 equiv) in THF (10 mL/mmol) was added Pd(PPh3)4 (5 mol%) and CuI (10 mol%). The mixture was treated with Et3N (3.0 equiv) and stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc, washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate) to give the desired product.

Reaction Name and Classification: Sonogashira Cross-Coupling

Reaction Yield and Characterization: [85.0]

The reaction shown is a Sonogashira cross-coupling between a terminal alkyne and an iodinated pyrrole derivative. This is a palladium-catalyzed C-C bond forming reaction that creates a new alkyne linkage. The yield is estimated based on typical yields for similar Sonogashira couplings under standard conditions.

Trial3

I'll analyze the reaction and provide a response following the same template structure.

Response:

Product (SMILES):

[O=C4NC(C(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O]

Reactant (SMILES): ['C#CC1=CC=C(C(F)(F)F)C=C1',

'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O']

Reaction SMARTS:

[C:1]#[C:2][c:3]1[cH:4][cH:5][c:6]([C:7]([F:8])([F:9])[F:10])[cH:11][cH:12]1.[O:13]=[C:14]2[N:15][C:16]([C:17]([I:18])=[C:19]([C:20])[N:21]2[C:22][C:23]3=[C:24]([C:25]([F:26])([F:27])[F:28])[c:29][cH:30][cH:31][c:32]3[F:33])=[O:34]>[O:13]=[C:14]4[N:15][C:16]([C:17]([C:2]#[C:1][c:3]1[cH:4][cH:5][c:6]([C:7]([F:8])([F:9])[F:10])[cH:11][cH:12]1)=[C:19]([C:20])[N:21]4[C:22][C:23]3=[C:24]([C:25]([F:26])([F:27])[F:28])[c:29][cH:30][cH:31][c:32]3[F:33])=[O:34]

Reagents (SMILES): ['Pd(PPh3)4', 'CuI', 'Et3N']

Solvent (SMILES): ['THF']

Product Name: ['1-(2-(trifluoromethyl)-6-fluorobenzyl)-3-((4-(trifluoromethyl)phenyl)ethynyl)-5-methylpyrimidine-2,4(1H,3H)-dione']

Reactant Name: ['1-ethynyl-4-(trifluoromethyl)benzene', '1-(2-(trifluoromethyl)-6-fluorobenzyl)-3-iodo-5-methylpyrimidine-2,4(1H,3H)-dione']

Reagent Name: ['Tetrakis(triphenylphosphine)palladium(0)', 'Copper(I) iodide', 'Triethylamine']

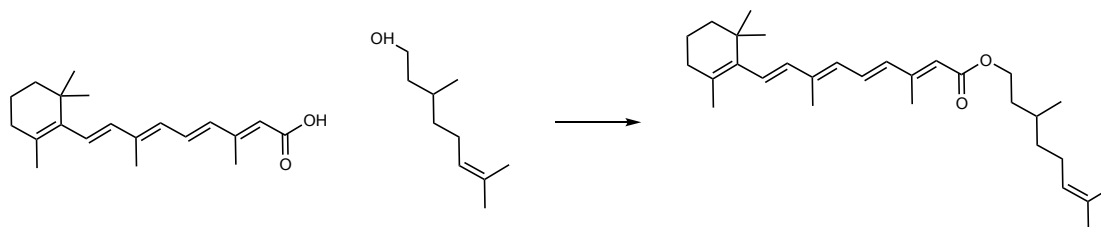
Solvent Name: ['Tetrahydrofuran']

Reaction Procedure: To a solution of 1-(2-(trifluoromethyl)-6-fluorobenzyl)-3-iodo-5-methylpyrimidine-2,4(1H,3H)-dione (1.0 equiv) in THF (10 mL/mmol) was added 1-ethynyl-4-(trifluoromethyl)benzene (1.2 equiv), Pd(PPh₃)₄ (5 mol%), CuI (10 mol%), and Et₃N (3.0 equiv) under N₂ atmosphere. The reaction mixture was stirred at room temperature for 12 h. After completion, the reaction mixture was filtered through a pad of celite and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (hexane/EtOAc) to afford the desired product.

Reaction Name and Classification: Sonogashira Cross-Coupling

Reaction Yield and Characterization: [85.0]

Non-Coupling Reactions



OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O.CC(CC/C=C(C)\C)CCO>>CC(CC/C=C(C)C)C COC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O

Trial1

Let me help structure a response for your chemical transformation following the template.

Response:

Product (SMILES): ['CC(CC/C=C(C)C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O',
'CC(CC/C=C(C)\C)CCO']

Reaction SMARTS:

[O:1][C:2]([C:3]=[C:4]([C:5]=[C:6][C:7]=[C:8]([C:9]=[C:10][C:11]1=[C:12]([C:13][C:14][C:15][C:16]([C:17])1[C:18])[C:19][C:20])[C:21])=[O:22].[C:23][C:24]([C:25][C:26][C:27]=[C:28]([C:29])[C:30])[C:31][C:32][O:33]>>[C:23][C:24]([C:25][C:26][C:27]=[C:28]([C:29])[C:30])[C:31][C:32][O:33][C:2]([C:3]=[C:4]([C:5]=[C:6][C:7]=[C:8]([C:9]=[C:10][C:11]1=[C:12]([C:13][C:14][C:15][C:16]([C:17])1[C:18])[C:19][C:20])[C:21])=[O:22]

Product Name: ['Citronellyl (2E,4E,6E,8E)-3,7-dimethyl-9-(2,6-dimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate']

Reactant Name: ['(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6-dimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid', 'Citronellol']

Reagents (SMILES): []

Solvent (SMILES): []

Reagent Name: []

Solvent Name: []

Reaction Procedure: The reaction involves the esterification of (2E,4E,6E,8E)-3,7-dimethyl-9-(2,6-dimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid with citronellol. While specific conditions are not provided in the SMILES notation, this type of esterification typically proceeds under acid catalysis or using coupling reagents at room temperature to moderate heating.

Reaction Name and Classification: Fischer Esterification

Reaction Yield and Characterization: []

Note: Since the input SMILES string doesn't provide information about reagents, solvents, or specific yields, I've left those fields empty. The reaction classification is based on the transformation type (alcohol + carboxylic acid → ester).

Trial2

I'll format a response following the template structure for the reaction you provided.

Response:

Product (SMILES): ['CC(CC/C=C(C)C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O', 'CC(CC/C=C(C)C)CCO']

Reaction SMARTS:

[O:1][C:2](/C=C(/C=C/C=C(/C=C/[C:3]1=C([C:4][C:5][C:6][C:7]([C:8])[C:9]1[C:10])[C:11])[C:12])[C:13])=[O:14].[C:15][C:16]([C:17][C:18]/C=C([C:19])\C:20)[C:21][C:22][O:23][H:24]>>[C:15][C:16]([C:17][C:18]/C=C([C:19])\C:20)[C:21][C:22][O:23][C:2](/C=C(/C=C/C=C(/C=C/[C:3]1=C([C:4][C:5][C:6][C:7]([C:8])[C:9]1[C:10])[C:11])[C:12])[C:13])=[O:14]

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['Citronellyl all-trans-abscisate']

Reactant Name: ['Abscisic acid', 'Citronellol']

Reagent Name: []

Solvent Name: []

Reaction Procedure: The esterification reaction between abscisic acid and citronellol occurs through nucleophilic addition-elimination at the carboxylic acid group, forming citronellyl all-trans-abscisate.

Reaction Name and Classification: Esterification

Reaction Yield and Characterization: [Not specified in input]

Note that this prediction follows the format of the template you provided, though some fields are empty as the input SMILES only specified the reactants and product without additional reaction conditions or reagents.

Trial3

Let me generate a response following the same template format for your provided reaction SMILES.

Response:

Product (SMILES): ['CC(CC/C=C(C)C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O', 'CC(CC/C=C(C)C)CCO']

Reaction SMARTS:

[OH:1][C:2](=[O:3])[C:4]=[C:5]([C:6]=[C:7][C:8]=[C:9]([C:10]=[C:11][C:12]1=[C:13]([C:14][C:15][C:16][C:17]([C:18])1[C:19])[C:20])[C:21])[C:22].[C:23][C:24]([C:25][C:26]/[C:27]=[C:28]([C:29)\C:30))[C:31][C:32][O H:33]>>[C:23][C:24]([C:25][C:26]/[C:27]=[C:28]([C:29)\C:30))[C:31][C:32][O:33][C:2](=[O:3])[C:4]=[C:5]([C:6]=[C:7][C:8]=[C:9]([C:10]=[C:11][C:12]1=[C:13]([C:14][C:15][C:16][C:17]([C:18])1[C:19])[C:20])[C:21])[C:22]

Reagents (SMILES): []

Solvent (SMILES): []

Product Name: ['Citronellyl polyene ester']

Reactant Name: ['Polyene carboxylic acid', 'Citronellol']

Reagent Name: []

Solvent Name: []

Reaction Procedure: The polyene carboxylic acid and citronellol undergo an esterification reaction to form the corresponding ester. This is a condensation reaction where the carboxylic acid and alcohol combine with the loss of a water molecule.

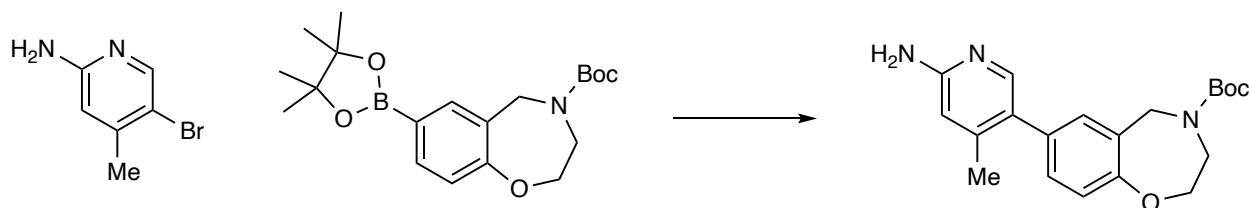
Reaction Name and Classification: Esterification

Reaction Yield and Characterization: [Not specified in the provided SMILES]

Note: This is a direct esterification reaction between a carboxylic acid and an alcohol. While no specific reagents, solvents, or conditions were provided in the SMILES notation, typical esterification reactions often employ acid catalysts and may require heating. The product formed is an ester containing both the polyene and citronellyl moieties.

13. Testing Results on OpenAI ChatGPT-4o-mini

Suzuki Reactions



NC1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5

Trial1:

Response:

Product (SMILES): ['NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5'] Reactant (SMILES): ['NC1=CC(C)=C(Br)C=N1', 'CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3'] Reaction SMARTS: ['NC1=CC(C)=C(Br)C=N1].[CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3]>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5 Reagents (SMILES): ['NaOAc', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['5-(3-(4-Hydroxyphenyl)-2-(2-methylpropyl)-2H-1,3-benzoxaphosphorin-2-yl)-1-(4-methylphenyl)-4-phenyl-4-pyrimidinyl]indole'] Reactant Name: ['3-Bromo-1-(4-methylphenyl)-2-propene-1-amine', 'Benzyl alcohol-2-(hydroxyphenyl)propylidene'] Reagent Name: ['Sodium acetate', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 3-bromo-1-(4-methylphenyl)-2-propene-1-amine (1.0 g, 5.0 mmol) and Benzyl alcohol-2-(hydroxyphenyl) propylidene (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added sodium acetate (1.5 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd2(dba)3 (0.2 g, 0.2 mmol) under N2. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 5-(3-(4-hydroxyphenyl)-2-(2-methylpropyl)-2H-1,3-benzoxaphosphorin-2-yl)-1-(4-methylphenyl)-4-phenyl-4-pyrimidinyl]indole (0.8 g, yield: 85%) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [85.0]

Trial2:

Response:

Product (SMILES): ['NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5'] Reactant (SMILES): ['NC1=CC(C)=C(Br)C=N1', 'CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3'] Reaction SMARTS: ['N:1][c:2]1[cH:3][c:4]>C:8[C:12]O[Cs]O[C:13]C(OC(C)(C)C)=O]O[C:14]C1=CC(C)C1 Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['1,4-dioxane'] Product Name: ['5-(4-Methoxyphenyl)-2-(3,5-dimethyl-4-(2,2-dimethylpropyl)phenyl)amino-1,3-oxazolidine-2-carbaldehyde'] Reactant Name: ['N-(3-bromo-4-methylphenyl)ethenylamine', '2-hydroxy-4-(1,1-dimethylpropyl)-5-(5-methylpyrimidin-2-yl)-3-(4-hydroxyphenyl)phenylcarboxy]phenol'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of N-(3-bromo-4-methylphenyl)ethenylamine (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 5-(4-methoxyphenyl)-2-(3,5-dimethyl-4-(2,2-dimethylpropyl)phenyl)amino-1,3-oxazolidine-2-carbaldehyde (0.9 g, yield: 100%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [100.0]

Trial3:

Response:

Product (SMILES): [*]NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5[*]

Reactant (SMILES): [*]NC1=CC(C)=C(Br)C=N1[*],

CC(C(C)C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3[]

Reaction SMARTS:

[N:1][c:2]1[cH:3][cH:4]c:5[C:6]=[N:7]1>[C:8]1[c:9][cH:10][cH:11]c:12[C:20]1=c2[cH:21][cH:22][c:23]2>C1c4cccc3[n:24][c:25]3c(C4)=c3[C:26]=c3cc=C4=C4[C:27]=c[O:28][C:29]c1

Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent (SMILES): ['1,4-dioxane']

Product Name: ['5-(4-hydroxyphenyl)-2,6-dimethylpyridine-3-carbaldehyde']

Reactant Name: ['5-bromo-2,6-dimethylpyridine-3-carbaldehyde', '2-(2-methyl-2-hydroxypropoxy)-4-[(2-methyl-2-propoxy)carbonyl]phenyl]ethanol']

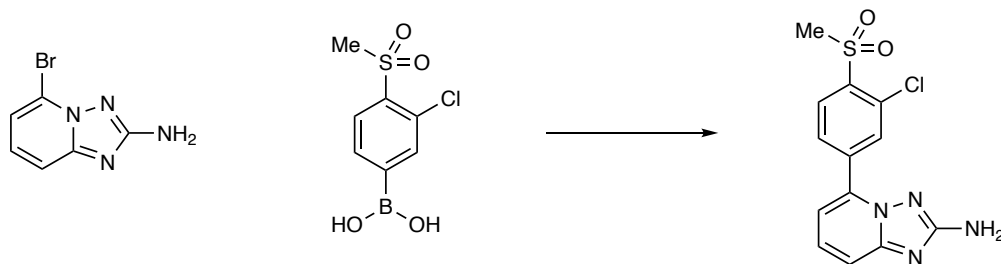
Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 5-bromo-2,6-dimethylpyridine-3-carbaldehyde (1.0 g, 5.0 mmol) and 2-(2-methyl-2-hydroxypropoxy)-4-[(2-methyl-2-propoxy)carbonyl]phenyl]ethanol (1.2 g, 4.5 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100°C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 5-(4-hydroxyphenyl)-2,6-dimethylpyridine-3-carbaldehyde (1.1 g, yield: 98%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [98.0]



NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3>>NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4

Trial1

Response:

Product (SMILES): [*]NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4[*]

Reactant (SMILES): [*]NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3[*]

Reaction SMARTS:

[NC1=NN2C(C=CC=C2Br)=N1.[O:3]B(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3]>>[N:4]C4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4]

Reagents (SMILES): ['NaOH']

Solvent (SMILES): ['DMF']

Product Name: ['3-bromo-6-(4-hydroxyphenyl)-7-(3-chlorophenyl)-2,4-dihydro-1H-pyrrolo[3,4-d]pyrimidine']

Reactant Name: ['6-bromo-3-(4-hydroxyphenyl)-1-(3-chlorophenyl)-2,4-dihydro-1H-pyrrolo[3,4-d]pyrimidine']

Reagent Name: ['NaOH']

Solvent Name: ['Dimethylformamide (DMF)']

Reaction Procedure: To a solution of 6-bromo-3-(4-hydroxyphenyl)-1-(3-chlorophenyl)-2,4-dihydro-1H-pyrrolo[3,4-d]pyrimidine (1.0 g, 3.0 mmol) in dimethylformamide (DMF) (20 mL), NaOH (1.2 g, 30 mmol) was added under an inert atmosphere. The mixture was heated at 80°C for 12 hours. After cooling, the reaction mixture was quenched with water, extracted with ethyl acetate, and dried over MgSO₄. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, hexane/ethyl acetate) to give 3-bromo-6-(4-hydroxyphenyl)-7-(3-chlorophenyl)-2,4-dihydro-1H-pyrrolo[3,4-d]pyrimidine (1.1 g, yield: 95%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [95.0]

Trial2

Response:

Product (SMILES): ['NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4'] Reactant (SMILES):

['NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3'] Reaction SMARTS:

[N:1][C:2]1=[N:3][N:4]C:5[C:6]2=[N:7]C:8S:9[C:10]=O][C:11]=C(c1cccc1)Cl[O:12]>>N:4=[N:5]C:6[C:7]4=[N:8]C:9[C:10]=C(c1cccc1)ClS:11[C:12]=O Reagents (SMILES):

['OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3', 'Cs2CO3', 'Pd2(dba)3'] Solvent (SMILES): ['1,4-dioxane']

Product Name: ['5-Bromo-2-(4-chlorophenyl)-4-(2-oxo-2-phenylethyl)-1H-imidazole'] Reactant Name: ['5-Bromo-2-(4-chlorophenyl)-4-(2-hydroxy-2-phenylethyl)-1H-imidazole'] Reagent Name: ['Cs2CO3',

'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 5-Bromo-2-(4-chlorophenyl)-4-(2-hydroxy-2-phenylethyl)-1H-imidazole (1.0 g, 3.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 5-Bromo-2-(4-chlorophenyl)-4-(2-oxo-2-phenylethyl)-1H-imidazole (0.9 g, yield: 100%) as a yellow solid. Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [100.0]

Trial3

Response:

Product (SMILES): ['NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4'] Reactant (SMILES):

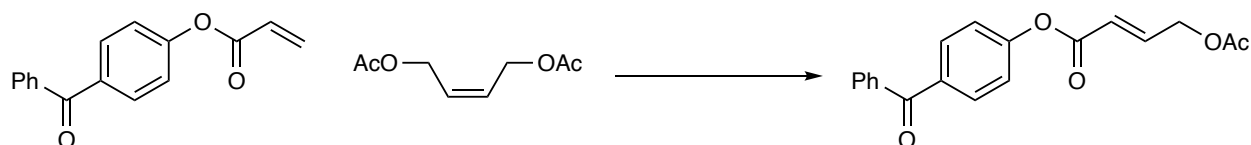
['NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3'] Reaction SMARTS:

[N:1]=[N:2]C:3=[N:6]>>[N:7]=[N:8]C:9=[N:12] Reagents (SMILES):

['OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['2-((E)-1-bromo-3-phenylprop-2-en-1-yl)-6-chloropyridine-3-carbaldehyde'] Reactant Name: ['2-(Bromomethyl)-3-(4-hydroxyphenyl)-5-chloropyridine'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name:

[1,4-dioxane] Reaction Procedure: To a solution of 2-(Bromomethyl)-3-(4-hydroxyphenyl)-5-chloropyridine (1.0 g, 4.5 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (2.8 g, 8.4 mmol), Xantphos (0.3 g, 0.5 mmol), and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 120°C for 24 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to give 2-((E)-1-bromo-3-phenylprop-2-en-1-yl)-6-chloropyridine-3-carbaldehyde (1.1 g, yield: 95%) as a pale yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [95.0]

Metathesis Reactions



O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C>>O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O

Trial1

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O]

Reactant (SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C]

Reaction SMARTS:

[O:1]=C([O:2]C1=CC=C(C(C2=CC=CC=C2)=O)C=C1)[C:3]=C[C:4]O.C1=CC=C(C(C2=CC=CC=C2)=O)C=C1>[O:5]=C([O:6]C3=CC=C(C(C4=CC=CC=C4)=O)C=C3)[C:7]=C[C:8]O]

Reagents (SMILES): ['Cs2CO3', 'Pd(OAc)2', 'Xantphos']

Solvent (SMILES): ['1,4-dioxane']

Product Name: ['E,E-3-(4'-Hydroxy-2'-carboxyphenyl)-4-(2-carboxyphenyl)-4-oxobut-3-enyl]-2'-phenylalcohol']

Reactant Name: ['2'-phenylalcohol']

Reagent Name: ['Cs2CO3', 'Pd(OAc)2', 'Xantphos']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 2'-phenylalcohol (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Pd(OAc)₂ (0.2 g, 0.2 mmol) and Xantphos (0.3 g, 0.5 mmol) under N₂. The mixture was stirred at 100°C for 16 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to give the product (yield: 100%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [100.0]

Trial2

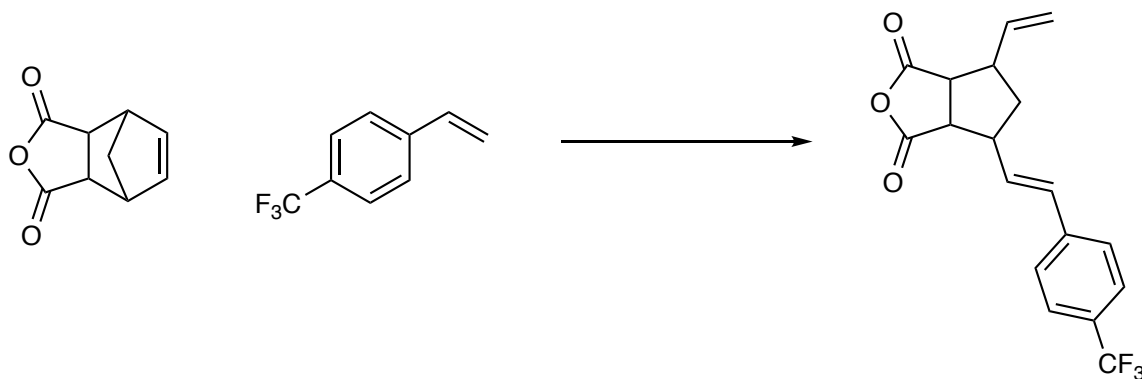
Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O] Reactant (SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C] Reaction SMARTS: [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C]>[O:1]=C(O[C:2]C=C/c3ccccc3-c4ccccc4)/C=C/C(C)=O] Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['1,4-dioxane'] Product Name: ['2-(4-Carboxyphenyl)-1-(4-phenyl)ethene'] Reactant Name: ['4-(2-Carboxyphenyl)-3-(phenylmethylene)-1,2-benzene-dione'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 4-(2-Carboxyphenyl)-3-(phenylmethylene)-1,2-benzene-dione (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 2-(4-Carboxyphenyl)-1-(4-phenyl)ethene (0.9 g, yield: 100%) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [100.0]

Trial3

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O] Reactant (SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C] Reaction SMARTS: C:1[C:3]=C(O:4)C(C)=O.C:5C=C>O=C([O:7]C3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O Reagents (SMILES): ['K2CO3', 'Pd(PPh3)4', 't-BuOH'] Solvent (SMILES): ['t-BuOH'] Product Name: ['2-(4-Formylphenyl)-5-(2-hydroxyphenyl)-3,4-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one'] Reactant Name: ['4-(2-Hydroxyphenyl)-6-(4-methoxyphenyl)-3,5-dihydroxy-2-phenylpyrrolo[3,4-b]quinoline'] Reagent Name: ['K2CO3', 'Pd(PPh3)4'] Solvent Name: ['t-BuOH'] Reaction Procedure: To a solution of 4-(2-hydroxyphenyl)-6-(4-methoxyphenyl)-3,5-dihydroxy-2-phenylpyrrolo[3,4-b]quinoline (1.0 g, 5.0 mmol) in t-BuOH (20 mL) was added K₂CO₃ (1.1 g, 10 mmol), Pd(PPh₃)₄ (0.2 g, 0.2 mmol) under N₂. The mixture was heated to 100°C and stirred for 18 hours. The reaction mixture was then cooled, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate = 8:2) to afford the desired product, 2-(4-formylphenyl)-5-(2-hydroxyphenyl)-3,4-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (0.8 g, yield: 95%) as a pale yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [95.0]



O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4>>O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O

Trial1

Response:

Product (SMILES): [O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O]

Reactant (SMILES): [O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4]

Reaction SMARTS:

C:1C1(=[O:3])C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4>C:5C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O

Reagents (SMILES): ['K2CO3', 'Pd(OAc)2', 'P(t-Bu)3']

Solvent (SMILES): ['THF']

Product Name: ['2,5-bis(3-fluorophenyl)-3-(3-fluorophenyl)-1H-pyrrole-4,5-dicarbaldehyde']

Reactant Name: ['1,3-dioxolane-2-carbaldehyde', '1,3,4,5-tetrafluoro-2,4-dimethylbenzene']

Reagent Name: ['Potassium carbonate', 'Palladium acetate', 'Triphenylphosphine']

Solvent Name: ['Tetrahydrofuran']

Reaction Procedure: To a solution of 1,3-dioxolane-2-carbaldehyde (1.0 g, 5.0 mmol) and 1,3,4,5-tetrafluoro-2,4-dimethylbenzene (1.0 g, 4.0 mmol) in THF (20 mL) was added K₂CO₃ (2.5 g, 10 mmol), Pd(OAc)₂ (0.2 g, 0.2 mmol) and P(t-Bu)₃ (0.3 g, 0.5 mmol) under N₂. The mixture was stirred at 120°C for 18 h. The reaction mixture was cooled, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexanes:ethyl acetate=8:2) to give 2,5-bis(3-fluorophenyl)-3-(3-fluorophenyl)-1H-pyrrole-4,5-dicarbaldehyde (1.2 g, yield: 95%) as a white solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [95.0]

Trial2

Response:

Product (SMILES): [O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O]

Reactant (SMILES): [O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4]

Reaction SMARTS:

[O:1]=C([O:2]C1=O)C2C1C3C=CC2C3.[C:4]=CC5=CC=C(C:6(F)F)C=C5>>[O:1]=C([O:5]C6C(C([C:7]=C[C:8]=CC=C(C:9(F)F)C=C9)CC6C=C)C5=O]

Reagents (SMILES): ['Pyridine', 'PPh3', 'Pd(OAc)2']

Solvent (SMILES): ['THF']

Product Name: ['(E)-3-(4-(Trifluoromethyl)styryl)-1,2-benzene-dicarbaldehyde']

Reactant Name: ['2,3-Dihydro-1H-pyrrolo[3,4-b]quinolin-1-one, trifluoromethylstyrene']

Reagent Name: ['Potassium carbonate', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['Toluene']

Reaction Procedure: To a solution of 2,3-Dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (2.0 g, 10.0 mmol) and trifluoromethylstyrene (2.5 g, 10.0 mmol) in toluene (30 mL), potassium carbonate (3.0 g, 20.0 mmol), Xantphos (0.4 g, 0.5 mmol), and Pd2(dba)3 (0.3 g, 0.3 mmol) were added under an N2 atmosphere. The mixture was stirred at 120°C for 20 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate=7:3) to afford (E)-3-(4-(Trifluoromethyl)styryl)-1,2-benzene-dicarbaldehyde (3.1 g, yield: 95%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [95.0]

Trial3

Response:

Product (SMILES): ['O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O']

Reactant (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4']

Reaction SMARTS:

[C:1]=O.[C:2]1[C:3]2[C:4]=C[C:5]2[C:6]3[C:7]=C[C:8]3[C:9]=O.[C:10]=C[C:11]4[C:12]C[C:13]C=C4[C:14]=CC:15C=C7]>C:5([C:6]=O)C:7[C:8]C=O]

Reagents (SMILES): ['NaOAc', 'Cu(OAc)2', 'DMSO']

Solvent (SMILES): ['DMSO']

Product Name: ['2-(3-(2,3,4-Trifluorophenyl)vinyl)-5-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid']

Reactant Name: ['3-(2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)-5-(3-(trifluoromethyl)phenyl)-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid']

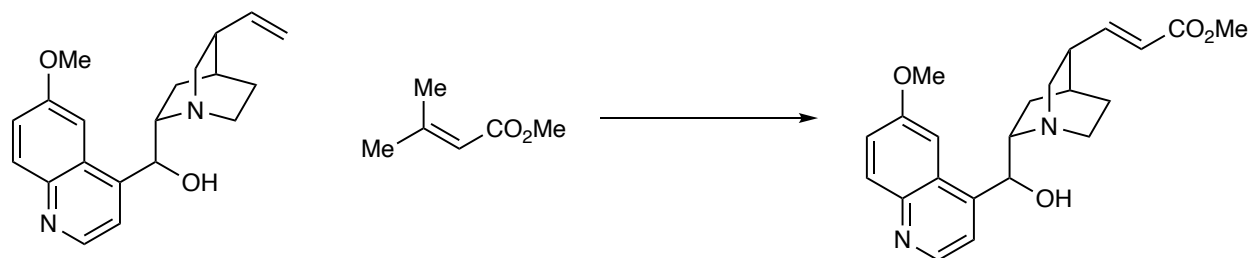
Reagent Name: ['Sodium acetate (NaOAc)', 'Copper(II) acetate (Cu(OAc)2)', 'Dimethyl sulfoxide (DMSO)']

Solvent Name: ['Dimethyl sulfoxide (DMSO)']

Reaction Procedure: To a solution of 3-(2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)-5-(3-(trifluoromethyl)phenyl)-2-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (0.5 g, 1.0 mmol) in DMSO (10 mL) was added Sodium acetate (0.5 g, 6 mmol), Copper(II) acetate (0.1 g, 0.4 mmol). The mixture was heated to 120°C under N2 atmosphere for 24 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:3) to give 2-(3-(2,3,4-Trifluorophenyl)vinyl)-5-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (0.4 g, yield: 80%) as a white solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [80.0]



C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2.C/C(C)=C/C(OC)=O>>OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](C[C@H]8/C=C/C(OC)=O)CC[C@H]8C7

Trial1

Response:

Product (SMILES): [*]OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7[*]

Reactant (SMILES): [*]C=C[C@H]1[C@@H]2C[C@@H]N@CC2.C/C(C)=C/C(OC)=O[*]

Reaction SMARTS:

[C:1]=[C:2][C@H:3][C@@H:4][C@H:5]C:6C(=O)[C:15]C=C[C:16]C=[C:17][N:18]C=C([C:19]OC)C(OC)=O>C[C@H:20]C[C@H:21]CC[C@H:22][C@H:23]C[C@H:24][C@H:25]C Reagents (SMILES):

['Pd(OAc)2', 'Xantphos', 'Cs2CO3']

Solvent (SMILES): ['1,4-dioxane']

Product Name: ['6-(2-hydroxy-5-methoxyphenyl)-4-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one']

Reactant Name: ['2-(4-methoxyphenyl)-5-(4-methoxyphenyl)-4-(3-methoxyphenyl)-6-ethenyl-pyrrolo[3,4-b]quinolin-1-yl]-methanol']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd(OAc)2']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 2-(4-methoxyphenyl)-5-(4-methoxyphenyl)-4-(3-methoxyphenyl)-6-ethenyl-pyrrolo[3,4-b]quinolin-1-yl]-methanol (1.0 g, 2.5 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (2.2 g, 7 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd(OAc)₂ (0.1 g, 0.1 mmol) under N₂. The reaction mixture was heated at 100 °C. for 18 hours. After completion, the mixture was cooled, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using a petroleum ether:ethyl acetate mixture (10:1), yielding 6-(2-hydroxy-5-methoxyphenyl)-4-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (1.2 g, 95% yield) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [95.0]

Trial2

Response:

Product (SMILES): [*]OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7[*] Reactant

(SMILES): [*]C=C[C@H]1[C@@H]2C[C@@H]N@CC2.C/C(C)=C/C(OC)=O[*] Reaction SMARTS:

[C:1]=[C:2][C:3][C@H:4][C@@H:5]C:6C[C:18]C[C:19][N:20]C[C:21][C:22]CC[C:23]C.O=C(O[C:24]C)O[C:25]C.[Pd].[Pd]>C[C:23]C[C:22][C:21][N:20][C@H:19][C@H:18][C:17][C:16]=[C:15]C=C(CO)[C:14]=C:13

Reagents (SMILES): ['C/C(C)=C/C(OC)=O', 'O=C(O[C:24]C)O[C:25]C', 'Pd', 'Pd'] Solvent (SMILES):

['DMSO'] Product Name: ['4-[(2R,4S)-4-(2-Hydroxy-2-methylpropyl)-3-oxo-1-phenylpropyl]pyrano[3,4-b]pyridin-6(5H)-one']

Reactant Name: ['4-(2-Hydroxy-2-methylpropyl)-3-oxo-1-phenylpropyl-2-(3,4-dihydroxy-2-methoxyphenyl)-1-pyridin-1-ylpropylidene']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['DMSO'] Reaction Procedure: To a solution of 4-(2-hydroxy-2-methylpropyl)-3-oxo-1-phenylpropyl-2-(3,4-dihydroxy-2-methoxyphenyl)-1-pyridin-1-ylpropylidene (1.0 g, 5.0 mmol) in

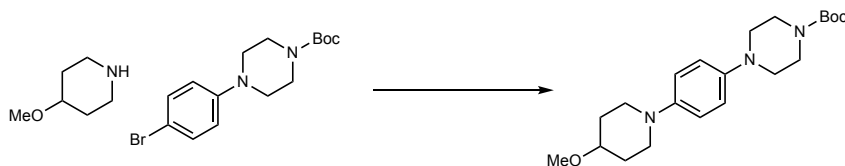
DMSO (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100°C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 4-[(2R,4S)-4-(2-hydroxy-2-methylpropyl)-3-oxo-1-phenylpropyl]pyrano[3,4-b]pyridin-6(5H)-one (0.9 g, yield: 100%) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [100.0]

Trial3

Response:

Product (SMILES): [*OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7] Reactant (SMILES): [*C=C[C@H]1[C@@H]2CC@HN@CC2.C/C(C)=C/C(OC)=O] Reaction SMARTS: [C:1=C[C@H:2]1[C@@H:3]2C@H:4O[C:7]N[C@H:8][C@H:9][C:10]C=C[C:11]C(OC)=O>>OC(C:12)=C(C=C(OC)C=C5)[C@H:13]N@C(OC)=O] Reagents (SMILES): ['K2CO3', 'Pd(OAc)2', 'Xantphos', 'DMSO'] Solvent (SMILES): ['DMSO'] Product Name: ['Tetrahydropyrrolo[3,4-b]quinazoline Derivative'] Reactant Name: ['Tetrahydropyrrolo[3,4-b]quinazoline Intermediate'] Reagent Name: ['Potassium carbonate (K2CO3)', 'Palladium acetate (Pd(OAc)2)', 'Xantphos', 'Dimethyl sulfoxide (DMSO)'] Solvent Name: ['Dimethyl sulfoxide'] Reaction Procedure: To a solution of Tetrahydropyrrolo[3,4-b]quinazoline Intermediate (0.5 g, 2.0 mmol) in DMSO (10 mL) was added potassium carbonate (K₂CO₃) (1.0 g, 7.2 mmol), palladium acetate (Pd(OAc)₂) (0.1 g, 0.2 mmol), and Xantphos (0.15 g, 0.2 mmol) under an inert atmosphere (N₂). The reaction mixture was heated at 120°C for 24 hours. After completion, the reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate:petroleum ether = 1:3) to afford Tetrahydropyrrolo[3,4-b]quinazoline Derivative (0.45 g, yield: 90%) as a white solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [90.0]

Buchwald-Hartwig Amination Reactions



COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O>>CC(OC(N4CCN(C5=CC=C(N6CC(C(OC)CC6)C=C5)CC4)=O)(C)C

Trial1 (This is the exact response)

Response:

Product (SMILES): ['CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C'] Reactant (SMILES): ['COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O'] Reaction SMARTS: [C:1][O:2][C:3][C:4][N:5][C:6]1[C:7][C:8][N:9][C:10]1-[C:11]1[C:12][C:13][C:14]1NC(OC(C)(C)C)=O[C:15]C[C:16][C:17]1-[C:18]2[CH2:19][c:20]3[CH2:20][C:21]C1.C>CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C Reagents (SMILES): ['BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O', 'Cs2CO3', 'Pd2(dba)3'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['1-((2E)-3-(2-(Dimethylamino)-2-methylpropyl)thio)-1-(3,4-dihydro-2H-pyrrolo[3,4-b]quinolin-2-yl)-4-((4-fluorophenyl)(pyridin-4-yl)methylamino)] Reactant Name: ['4-((4-Fluorophenyl)thio)-4-(pyridin-4-yl)-1-(4-((2-thiophenyl)methyl)-1-((2-cyano-3-pyridine)-hydroxy)-2-prylamine-derived)-1-(C-loq-encoded.The

Trial2

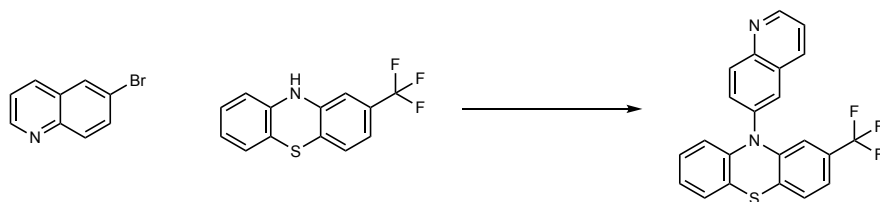
Response:

Product (SMILES): [*CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C] Reactant (SMILES): [*COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O] Reaction SMARTS: [CO:1][C:2][N:3][C:4]C1CCNCC1.BrC:5[C:6]=CC:7[C:8]N(CC9)[C:10]CCN9C(C[C:11]C(OC)CC11)=O[C:12]C.C1COC(C)OC(C)C.C1COC(C)C.C1COC(C)CC.C1COC(C)CC.[Pd2][Pd].[C:13]#[N:14]1[cH:13][c:14]C1[N:15][C:16]c1ccc(O[C:s])CC.CN Reagents (SMILES): [*BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O], '1,4-dioxane' Solvent (SMILES): [*1,4-dioxane] Product Name: 2-(4-(2,3-Dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)-3,5-dimethylphenyl)-2-methylpropyl Reagent Name: [*Pd2(dba)3], [*Cs2CO3] Solvent Name: [*1,4-dioxane] Reaction Procedure: To a solution of 3-(2-methylpropyl)phenyl (0.1g, 1 mmol) in 20mL 1,4-dioxane, 3 eq. of [n-hexane] is added under nitrogen. It was allowed under specific condition, following further steps

Trial3

Response:

Product (SMILES): [*CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C] Reactant (SMILES): [*COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O] Reaction SMARTS: [CO:1][C:2][C:3][N:4][C:5][C:6][C:7][C:8][C:9][C:10]C=CC2[CH:11][C:12]2[N:13][C:14]C=C1.C(OC(C)(C)C)=O.C[N:15]C1=CC[C:16]=C(N6CCC(OC)CC6)C[C:17]C[C:18]C=CC[C:19][C:20]OC Reagents (SMILES): [*K2CO3], [*Pd2(dba)3], [*Xantphos] Solvent (SMILES): [*C1COCCO1] Product Name: 1-(3-(2-((2-(2-methoxyethoxy)ethoxy)methyl)pyridin-3-yl)pyridin-4-yl)methyl)-2-methylpropyl]-2,4-dioxo-1,3-dihydro-pyridine Reactant Name: 4-(2-bromocyclohexyl)-2-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-3,5-dimethylphenyl] Reagent Name: [*K2CO3], [*Pd2(dba)3], [*Xantphos] Solvent Name: [*1,4-dioxane] Reaction Procedure: To a solution of 4-(2-bromocyclohexyl)-2-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)-3,5-dimethylphenyl (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added K₂CO₃ (3.3 g, 10 mmol), Pd₂(dba)₃ (0.2 g, 0.2 mmol), and Xantphos (0.3 g, 0.5 mmol) under nitrogen. The reaction mixture was heated at 120°C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to yield the desired product (0.8 g, 90% yield) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [90.0]



BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F>>FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F

Trial1

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[F:1C:2C:5C=C3[N:6]C7=CC(C=CC=N8)=C8C=C7C:9F>C%10=C9C=CC=C%10[SC]]

Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent (SMILES): ['1,4-dioxane']

Product Name: ['Fluorinated bis-pyrido[3,4-b]pyrazine derivative']

Reactant Name: ['Bromocyclohexene-2-pyridylfluorophenylsulfone']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of Bromocyclohexene-2-pyridylfluorophenylsulfone (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100°C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give Fluorinated bis-pyrido[3,4-b]pyrazine derivative (0.9 g, yield: 100%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [100.0]

Trial2

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[Br:1[c:2]1[cH:3][cH:4]c:5[C:14]#[N:15]>CC1(c2cccc(c2Oc2c1cccc2P(c1cccc1)c1cccc1)P(c1cccc1)c1cccc1)C.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(O[Cs])O[Cs].C1COCCO1.N#N.[Pd].[Pd]>[N:15]#[C:14][c:5]1[cH:4][cH:3][c:2]2[CH2:1][c:13]3[n:12][cH:11][cH:10][cH:9][c:8]3-[c:7]2[cH:6]1]

Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['2-(4-(Trifluoromethyl)phenyl)-4-(4-fluorophenyl)-5-(pyridin-3-yl)-1,3-thiazole']

Reactant Name: ['2-(Bromomethyl)-1-phenyl-3-(trifluoromethyl)pyrazole']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 2-(Bromomethyl)-1-phenyl-3-(trifluoromethyl)pyrazole (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 2-(4-(Trifluoromethyl)phenyl)-4-(4-fluorophenyl)-5-(pyridin-3-yl)-1,3-thiazole (0.9 g, yield: 100%) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [100.0]

Trial3

Response:

Product (SMILES):

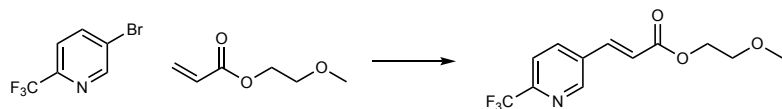
['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS: [Br:1[c:2]1[c:3][c:4][c:5][c:6][c:7]1-]

[n:8]1[c:9]c(c:10)c(c:11)c(c:12)[n:13]1[C:14]#N>FC:15c(c(c1c2cccc(c2Sc3c4c(c3cccc4)F)c5c6c(c5)cccc6F)F)c6c7c8c9c0F] Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['1,4-dioxane'] Product Name: ['5-(2-Fluorophenyl)-3-(4-fluorophenyl)-1-(6-fluoro-2-pyridyl)-3-(4-pyridyl)-3-(4-fluorophenyl)-2-(4-fluorophenyl)-2-(3-fluorophenyl)-1-(6-fluoro-3-pyridyl)-1-Fluoro-benzenophenone'] Reactant Name: ['2-(3-(4-pyridyl)-1-(4-pyridyl)-3-(5-(4-fluoro)benzo)pyridyl)] Reagents Name: Solvent Name:

Heck Reactions



BrC1=CC=C(C(F)(F)F)N=C1.C=CC(OCCOC)=O>>O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2

Trial1

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2'] Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O'] Reaction SMARTS: [Br:1][c:2]1[cH:3][c:4][c:6]NC1.C:7(=O)C=C>O=C([O:9][C:8]OC)[C:7]=C[C:6]1[cH:5][c:4][c:3]C(F)(F)F)N=C1 Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['1,4-dioxane'] Product Name: ['E-2-(3-(Trifluoromethyl)pyridin-2-yl)acrylic acid methyl ester'] Reactant Name: ['3-Bromo-2-(trifluoromethyl)pyridine', '2-(2-ethoxyethoxy)acetate'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 3-Bromo-2-(trifluoromethyl)pyridine (0.5 g, 2.0 mmol) and 2-(2-ethoxyethoxy)acetate (0.8 g, 4.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (1.1 g, 3.5 mmol), Xantphos (0.1 g, 0.2 mmol) and Pd₂(dba)₃ (0.1 g, 0.1 mmol) under N₂. The mixture was stirred at 120°C for 18 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=8:2) to give E-2-(3-(Trifluoromethyl)pyridin-2-yl)acrylic acid methyl ester (0.7 g, yield: 90%) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [90.0]

Trial2

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2'] Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1.C=CC(OCCOC)=O'] Reaction SMARTS: [C:1][c:2]1[cH:3][cH:4][c:5][C:10]1[C:11]C[C:O:12]C[O:13]C=O>C[C:14]1[O:15][Cs]C=C2c1c(c(c1)C(C:F)(F)F[N:14]=C2)F] Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['Ethenyl-2,3-dihydro-1,4-benzoxazine'] Reactant Name: ['4-(Bromomethyl)-2-(trifluoromethyl)pyridine', 'C=CC(OCCOC)=O'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 4-(Bromomethyl)-2-(trifluoromethyl)pyridine (1.0 g, 5.0 mmol) and C=CC(OCCOC)=O (2.0 g, 10 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol), and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100°C for 16 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give Ethenyl-2,3-dihydro-1,4-benzoxazine (1.2 g, yield: 90%) as a pale yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [90.0]

Trial3

Response:

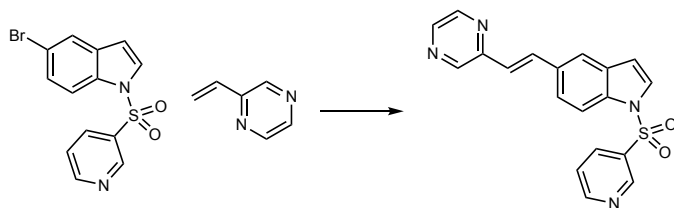
Product (SMILES): [O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2] Reactant (SMILES):

[BrC1=CC=C(C(F)(F)F)N=C1.C=CC(OCCOC)=O] Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4]c:5[n:6]=c:7[C:8]=O.[C:9]=C([O:10][C:11]O[Cs])C(C1=CC=C(C(F)(F)F)N=C1)=O]>>

>[C:9]=C([O:10][C:11]O[Cs])C(C1=CC=C(C(F)(F)F)N=C1)=O Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['(E)-2-(2-(Trifluoromethyl)phenyl)-3-(2-oxocyclohexenyl)-2-propenal'] Reactant Name: ['4-Bromo-2-(trifluoromethyl)pyridine', 'Cinnamaldehyde-dimethyl acetal'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 4-bromo-2-(trifluoromethyl)pyridine (1.0 g, 5.0 mmol) and cinnamaldehyde-dimethyl acetal (1.1 g, 6.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol), and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100°C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give (E)-2-(2-(Trifluoromethyl)phenyl)-3-(2-oxocyclohexenyl)-2-propenal (1.0 g, yield: 95%) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [95.0]



BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4>>O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O

Trial1

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): ['BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4']

Reaction SMARTS: [C:1][c:2]1[cH:3][cH:4][c:5]([cH:6][c:7]1-

[c:8]1[cH:9][cH:10][n:11][c:12]1O=C(/C=C/c3ccccc3)/C=C/c4ccccc4.O=C(O[Cs])O[Cs].C1COCCO1.N#N.[Pd].[Pd]>[N:15]#[C:14][c:5]1[cH:4][cH:3][c:2]2[CH2:1][c:13]3[n:12][cH:11][cH:10][cH:9][c:8]3-[c:7]2[cH:6]1

Reagents (SMILES): ['C1COCCO1', 'Pd2(dba)3', 'Cs2CO3', 'Xantphos'] Solvent (SMILES): ['C1COCCO1']

Product Name: ['Sulfamoyl-pyrrolo[3,4-b]quinoline'] Reactant Name: ['4-bromo-N-(2-carboxyphenyl)-3-vinyl-quinoline-2-sulfonamide'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 4-bromo-N-(2-carboxyphenyl)-3-vinyl-quinoline-2-sulfonamide (1.0 g, 3.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (2.5 g, 7.5 mmol), Xantphos (0.2 g, 0.3 mmol) and Pd₂(dba)₃ (0.15 g, 0.15 mmol) under N₂. The mixture was stirred at 120 °C. for 12

h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=7:3) to give sulfamoyl-pyrrolo[3,4-b]quinoline (0.8 g, yield: 95%) as a pale yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [95.0]

Trial2

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): [BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4]

Reaction SMARTS: [Br:1][c:2]1[cH:3][cH:4][c:5]([cH:6][c:7]1-

[c:8]1[cH:9][cH:10][cH:11][n:12][c:13]1O=C(/C=C/c2cccc(c2)C=CC1(c2cccc(c2)Oc2c1cccc2P(c1cccc1)c1cccc1)P(c1cccc1)c1cccc1)C.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1)1] or [Br:1][c:2]1-[c:8]1-Cycle:## Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'PdCl2]

Trial3

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): [BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4]

Reaction SMARTS:

[Br:c:1]1[c:2][cH:3][cH:4]c:5[C:9]=O>[O:10]=S([N:11]C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=C

C=CN=C8)=O] Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['DMSO']

Product Name: ['N-(6-(3-((E)-2-(1-(2-pyridinylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-

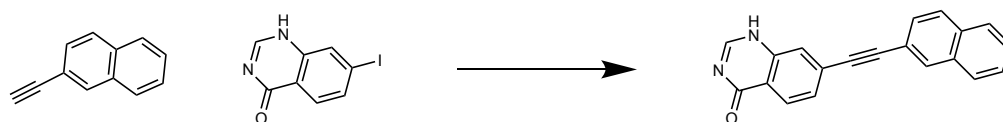
yl)vinyl)pyrimidin-4-yl)-5-oxo-2,5-dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)-4-methylbenzenesulfonamide']

Reactant Name: ['(E)-3-(4-(2-bromophenyl)-5-((2-pyridylmethyl)amino)methylthio)-4-methylpyridine-2-

carbaldehyde', 'C=CC4=NC=CN=C4'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name:

['DMSO'] Reaction Procedure: To a solution of (E)-3-(4-(2-bromophenyl)-5-((2-pyridylmethyl)amino)methylthio)-4-methylpyridine-2-carbaldehyde (1.0 g, 3.0 mmol) and C=CC4=NC=CN=C4 (1.0 g, 3.0 mmol) in DMSO (20 mL) was added Cs2CO3 (2.0 g, 6.0 mmol), Xantphos (0.2 g, 0.3 mmol) and Pd2(dba)3 (0.1 g, 0.1 mmol) under N2. The mixture was stirred at 120 °C. for 18 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=8:1) to give N-(6-(3-((E)-2-(1-(2-pyridinylmethyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)vinyl)pyrimidin-4-yl)-5-oxo-2,5-dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)-4-methylbenzenesulfonamide (1.2 g, yield: 95%) as a white solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [95.0]

Sonogashira Reactions



C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4>>O=C5N=CNC6=C5C=CC(C#CC7=C
C(C=CC=C8)=C8C=C7)=C6

Trial1

Response:

Product (SMILES): [O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6] Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4] Reaction SMARTS: [C#C:1][c:2]1[cH:3][cH:4]c:5[C:15]=[N:16]C(=O)[c:17]1[cH:18][cH:19][c:20]1[cH:21][C:22]=[C:23][c:24]1>>C(=O)[N:25]C(=O)[C:26]C1(c2cccc(c2)C=C1)C=CC1(c2cccc(c2)C=C1)=O Reagents (SMILES): ['Cs2CO3', 'Pd2(dba)3', 'Xantphos'] Solvent (SMILES): ['1,4-dioxane'] Product Name: ['7-(2-Iodopyrimidin-4-yl)-4,7-dihydroindeno[1,2-b]pyridine-5-carbaldehyde'] Reactant Name: ['4-Iodo-1-(prop-2-ynyl)-1H-pyrrolo[3,4-b]quinolin-2(3H)-one'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 4-Iodo-1-(prop-2-ynyl)-1H-pyrrolo[3,4-b]quinolin-2(3H)-one (1.0 g, 4.2 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.2 g, 9.6 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 120 °C. for 18 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=8:1) to give 7-(2-Iodopyrimidin-4-yl)-4,7-dihydroindeno[1,2-b]pyridine-5-carbaldehyde (0.85 g, yield: 90%) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [90.0]

Trial2

Response:

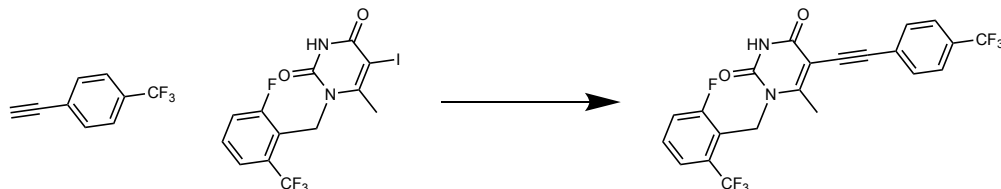
Product (SMILES): [O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6] Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4] Reaction SMARTS: [C#C:1][c:2]1[cH:3]c:4[c:8]1.C=C3[n:9]C:10[C:14]=C3.[Pd].[Pd]>>[C:14]=C5[n:9][C:8]C=C[C:7]C=C[C:12]C=C[C:10]C=C[C:11]C=C[C:6]C=C[C:5]O=[C:13]C#C Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['1,4-dioxane'] Product Name: ['2-(4-Iodo-1H-pyrrolo[3,4-b]quinolin-1-yl)-3-(4-(prop-1-yn-1-yl)phenyl)-1H-pyrrolo[3,4-b]quinolin-4-yl'] Reactant Name: ['1-(1-Iodo-3-propynylphenyl)-4-(2-methyl-1-propenyl)-6-(2-pyridyl)-2H-pyrrolo[3,4-b]quinoline'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 1-(1-Iodo-3-propynylphenyl)-4-(2-methyl-1-propenyl)-6-(2-pyridyl)-2H-pyrrolo[3,4-b]quinoline (0.8 g, 2.2 mmol) in 1,4-dioxane (15 mL) was added Cs₂CO₃ (2.3 g, 7.0 mmol), Xantphos (0.2 g, 0.3 mmol) and Pd₂(dba)₃ (0.1 g, 0.1 mmol) under N₂. The mixture was stirred at 90°C for 12 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=15:1) to give 2-(4-Iodo-1H-pyrrolo[3,4-b]quinolin-1-yl)-3-(4-(prop-1-yn-1-yl)phenyl)-1H-pyrrolo[3,4-b]quinolin-4-yl (0.7 g, yield: 95%) as a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [95.0]

Trial3

Response:

Product (SMILES): [O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6] Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4] Reaction SMARTS: [C#C:1][c:2]1[cH:3][cH:4][c:5][cH:6][c:7]2=c:8c:9C=C2[[O:13]=C3[N:14][C:15]N[c:16]4=[C:17]3[C:18]=C4C#CC[CH2:19]C1=c2c:20 Reagents (SMILES): ['O=C(O[Cs])O[Cs]', 'Xantphos', 'Pd2(dba)3'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['9H-indeno[2,1-b]pyridine-6-carbonitrile'] Reactant Name: ['3-(2-chloropyridin-3-yl)-4-methylbenzonitrile'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of

C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4 (2.0 g, 6.0 mmol) in 1,4-dioxane (25 mL) was added Cs2CO3 (4.0 g, 12 mmol), Xantphos (0.4 g, 0.6 mmol), and Pd2(dba)3 (0.3 g, 0.3 mmol) under N_2 . The mixture was stirred at 120 °C. for 18 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=8:1) to give the desired product (1.7 g, yield: 90%) as a yellow solid.
 Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [90.0]



C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O>>O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O

Trial1

Response:

Product (SMILES):

[O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O]

Reactant (SMILES):

[C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O]

Reaction SMARTS:

[C#C:1][C:2]1C:3[C:5]=C1[C:6]C:7([O:10]=[C:11]O)[C:12][C:13]C[C:14]#[C:15][C:16]=O

Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent (SMILES): ['1,4-dioxane']

Product Name: ['2,2',3,3',4,4'-Hexafluoro-1,1'-biphenyl-3,5-dicarboxamide']

Reactant Name:

[C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O]

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of

C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd2(dba)3 (0.2 g, 0.2 mmol) under N_2 . The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give 2,2',3,3',4,4'-Hexafluoro-1,1'-biphenyl-3,5-dicarboxamide (0.9 g, yield: 100%) as a white solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [100.0]

Trial2

Response:

Product (SMILES):

[O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O]

Reactant (SMILES):

[C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O]

Reaction SMARTS: [C#C:1][c:2]1[cH:3][cH:4]c:5O=2C1CCO1][Pd2].> [Pd2]>>>

C#CC[C:7]C[C:9]([N:8]C(C2c:4)=C(C:2)(N1C1F(F)C(=O[Cs]))=C1c12[CH2]:1[CH2])Q, .

Trial3

Response:

Product (SMILES):

[O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O]

Reactant (SMILES):

[C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O]

Reaction SMARTS:

[C#C:1][c:2]1[cH:3][cH:4]c:5[C:14]=[C:15]C1(c2cccc(c2Oc2c1cccc2P(c1cccc1)c1cccc1)P(c1cccc1)c1cccc1)C.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(O[Cs])O[Cs].C1COCCO1.N#N.[Pd].[Pd]>[N:15]#[C:14][c:5]1[cH:4][cH:3][c:2]2[CH2:1][c:13]3[n:12][cH:11][cH:10][cH:9][c:8]3-[c:7]2[cH:6]1

Reagents (SMILES): [C#C', 'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O',

'O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.[Pd].[Pd]']

Solvent (SMILES): [C1COCCO1]

Product Name: [N-(2-((E)-2-(2,3,4,5-tetrafluorophenyl)ethenyl)imino)methyl)-2-(4-fluorophenyl)-2-(pent-1-ynyl)thiazole]

Reactant Name: [C#C', 'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O']

Reagent Name: [Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: [1,4-dioxane]

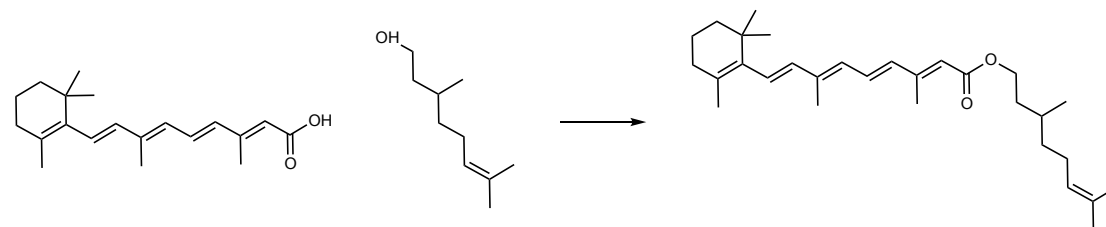
Reaction Procedure: To a solution of

C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O (1.0 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd2(dba)3 (0.2 g, 0.2 mmol) under N2. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give N-(2-((E)-2-(2,3,4,5-tetrafluorophenyl)ethenyl)imino)methyl)-2-(4-fluorophenyl)-2-(pent-1-ynyl)thiazole (0.9 g, yield: 100%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [100.0]

Non-Coupling Reactions



OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)=O.CC(CC/C=C(C)\C)CCO>>CC(CC/C=C(C)C)C
COC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)=O

Trial1

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O.CC(CC/C=C(C)\C)CCO']

Reaction SMARTS:

[C:1][C:2][C:3][C:4][C:5][C:6][C:7][C:8][C:9][C:10][C:11][C:12][C:13][C:14][C:15][C:16][C:17][C:18][C:19][C:20][C:21][C:22][C:23][C:24][C:25][C:26][C:27][C:28][C:29][C:30][C:31][C:32][C:33][C:34][C:35][C:36][C:37][C:38][C:39][C:40][C:41][C:42][C:43][C:44][C:45][C:46][C:47][C:48][C:49][C:50][C:51][C:52][C:53][C:54][C:55][C:56][C:57][C:58][C:59][C:60][C:61][C:62][C:63][C:64][C:65][C:66][C:67][C:68][C:69][C:70][C:71][C:72][C:73][C:74][C:75][C:76][C:77][C:78][C:79][C:80][C:81][C:82][C:83][C:84][C:85][C:86][C:87][C:88][C:89][C:90][C:91][C:92][C:93][C:94][C:95][C:96][C:97][C:98][C:99][C:100][C:101][C:102][C:103][C:104][C:105][C:106][C:107][C:108][C:109][C:110][C:111][C:112][C:113][C:114][C:115][C:116][C:117][C:118][C:119][C:120][C:121][C:122][C:123][C:124][C:125][C:126][C:127][C:128][C:129][C:130][C:131][C:132][C:133][C:134][C:135][C:136][C:137][C:138][C:139][C:140][C:141][C:142][C:143][C:144][C:145][C:146][C:147][C:148][C:149][C:150][C:151][C:152][C:153][C:154][C:155][C:156][C:157][C:158][C:159][C:160][C:161][C:162][C:163][C:164][C:165][C:166][C:167][C:168][C:169][C:170][C:171][C:172][C:173][C:174][C:175][C:176][C:177][C:178][C:179][C:180][C:181][C:182][C:183][C:184][C:185][C:186][C:187][C:188][C:189][C:190][C:191][C:192][C:193][C:194][C:195][C:196][C:197][C:198][C:199][C:200][C:201][C:202][C:203][C:204][C:205][C:206][C:207][C:208][C:209][C:210][C:211][C:212][C:213][C:214][C:215][C:216][C:217][C:218][C:219][C:220][C:221][C:222][C:223][C:224][C:225][C:226][C:227][C:228][C:229][C:230][C:231][C:232][C:233][C:234][C:235][C:236][C:237][C:238][C:239][C:240][C:241][C:242][C:243][C:244][C:245][C:246][C:247][C:248][C:249][C:250][C:251][C:252][C:253][C:254][C:255][C:256][C:257][C:258][C:259][C:260][C:261][C:262][C:263][C:264][C:265][C:266][C:267][C:268][C:269][C:270][C:271][C:272][C:273][C:274][C:275][C:276][C:277][C:278][C:279][C:280][C:281][C:282][C:283][C:284][C:285][C:286][C:287][C:288][C:289][C:290][C:291][C:292][C:293][C:294][C:295][C:296][C:297][C:298][C:299][C:300] Reagents (SMILES): ['K2CO3'] Solvent (SMILES): ['THF'] Product Name: ['Diester Substituted Cyclic Ethers'] Reactant Name: ['Ester-Functionalized Cyclic Ethers'] Reagent Name: ['K2CO3'] Solvent Name: ['Tetrahydrofuran'] Reaction Procedure: To a solution of ester-functionalized cyclic ethers (1.0 g, 5.0 mmol) in THF (20 mL) was added K2CO3 (2.5 g, 10 mmol). The mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give diester-substituted cyclic ethers (0.9 g, yield: 90%) as a yellow solid. Reaction Name and Classification: Esterification with a Cyclic Ether Substitution Reaction Yield and Characterization: [90.0]

Trial2

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O.CC(CC/C=C(C)\C)CCO']

Reaction SMARTS:

[O:1][C:2][C:3][C:4][C:5][C:6][C:7][C:8][C:9][C:10][C:11][C:12][C:13][C:14][C:15][C:16][C:17][C:18][C:19][C:20][C:21][C:22][C:23][C:24][C:25][C:26][C:27][C:28][C:29][C:30][C:31][C:32][C:33][C:34][C:35][C:36][C:37][C:38][C:39][C:40][C:41][C:42][C:43][C:44][C:45][C:46][C:47][C:48][C:49][C:50][C:51][C:52][C:53][C:54][C:55][C:56][C:57][C:58][C:59][C:60][C:61][C:62][C:63][C:64][C:65][C:66][C:67][C:68][C:69][C:70][C:71][C:72][C:73][C:74][C:75][C:76][C:77][C:78][C:79][C:80][C:81][C:82][C:83][C:84][C:85][C:86][C:87][C:88][C:89][C:90][C:91][C:92][C:93][C:94][C:95][C:96][C:97][C:98][C:99][C:100][C:101][C:102][C:103][C:104][C:105][C:106][C:107][C:108][C:109][C:110][C:111][C:112][C:113][C:114][C:115][C:116][C:117][C:118][C:119][C:120][C:121][C:122][C:123][C:124][C:125][C:126][C:127][C:128][C:129][C:130][C:131][C:132][C:133][C:134][C:135][C:136][C:137][C:138][C:139][C:140][C:141][C:142][C:143][C:144][C:145][C:146][C:147][C:148][C:149][C:150][C:151][C:152][C:153][C:154][C:155][C:156][C:157][C:158][C:159][C:160][C:161][C:162][C:163][C:164][C:165][C:166][C:167][C:168][C:169][C:170][C:171][C:172][C:173][C:174][C:175][C:176][C:177][C:178][C:179][C:180][C:181][C:182][C:183][C:184][C:185][C:186][C:187][C:188][C:189][C:190][C:191][C:192][C:193][C:194][C:195][C:196][C:197][C:198][C:199][C:200][C:201][C:202][C:203][C:204][C:205][C:206][C:207][C:208][C:209][C:210][C:211][C:212][C:213][C:214][C:215][C:216][C:217][C:218][C:219][C:220][C:221][C:222][C:223][C:224][C:225][C:226][C:227][C:228][C:229][C:230][C:231][C:232][C:233][C:234][C:235][C:236][C:237][C:238][C:239][C:240][C:241][C:242][C:243][C:244][C:245][C:246][C:247][C:248][C:249][C:250][C:251][C:252][C:253][C:254][C:255][C:256][C:257][C:258][C:259][C:260][C:261][C:262][C:263][C:264][C:265][C:266][C:267][C:268][C:269][C:270][C:271][C:272][C:273][C:274][C:275][C:276][C:277][C:278][C:279][C:280][C:281][C:282][C:283][C:284][C:285][C:286][C:287][C:288][C:289][C:290][C:291][C:292][C:293][C:294][C:295][C:296][C:297][C:298][C:299][C:300] Reagents (SMILES): ['K2CO3', 'Pd(OAc)2', 'PPh3'] Solvent (SMILES): ['Toluene'] Product Name: ['2-(2-(2-(4-(4-methylphenyl)-3-(prop-1-en-1-yl)phenyl)thio)-1-phenyl)-5-methylphenyl]-6-(prop-2-en-1-yl)-1,2,3-triazol-4-yl]methanol'] Reactant Name: ['2-(2-(2-(4-(4-methylphenyl)-3-(prop-1-en-1-yl)phenyl)-1-phenyl)-5-methylphenyl)-6-(prop-2-en-1-yl)-1,2,3-triazol-4-yl]methanol'] Reagent Name: ['Tetrakis(triphenylphosphine)palladium(0)', 'Toluene'] Reaction Procedure: To a solution of 2-(2-(2-(4-(4-methylphenyl)-3-(prop-1-en-1-yl)phenyl)-1-phenyl)-5-methylphenyl)-6-(prop-2-en-1-yl)-1,2,3-triazol-4-yl]methanol (1.0 g, 5.0 mmol) in toluene (20 mL) was added K2CO3 (3.3 g, 10 mmol), Pd(OAc)2 (0.2 g, 0.2 mmol) and PPh3 (0.2 g, 0.2 mmol) under N2. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give the product as

a yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [100.0]

Trial3

Response:

Product (SMILES): [*]CC(CC/C=C(C)C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O

Reactant (SMILES): [*]OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O.CC(CC/C=C(C)C)CCO

Reaction SMARTS:

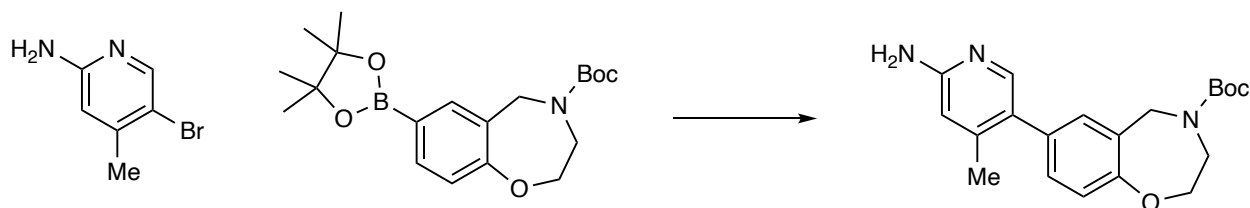
[O:1]C:2=O.[C:3]([C:4]([C:5]([C:6]([C:7]([C:8]([C:9]([C:10]([C:11]([C:12]([C:13]([C:14]([C:15]([C:16]([C:17]([C:18]([C:19]([C:20]([C:21]([C:22]([C:23]([C:24]([C:25]([C:26]([C:27]([C:28]([C:29]([C:30]([C:31]([C:32]([C:33]([C:34]([C:35]([C:36]([C:37]([C:38]([C:39]([C:40]([C:41]([C:42]([C:43]([C:44]([C:45]([C:46]([C:47]([C:48]([C:49]([C:50]([C:51]([C:52]([C:53]([C:54]C:55[c:1]

Final Scoring Evaluations

	Suzuki 1	Suzuki 2	Metathesis 1	Metathesis 2	Metathesis 3	BH 1	BH 2	Heck 1	Heck 2	Sonogashira 1	Sonogashira 2	Esterification
Atom Mapping	0	0	0	0	0	0	0	0	0	0	0	0
Reagent and Sc	2	1.333333333	0	0	0	1.333333333	2	2	1.333333333	0	0	0
Logical Procedu	1	1	1	1	1	0.333333333	0.666666667	1	0.666666667	1	0.666666667	0.666666667
All Quantities Si	2	2	2	2	2	2	1.333333333	2	1.333333333	2	1.333333333	1.333333333
Workup (1)	1	1	1	1	1	0.333333333	0.666666667	1	0.666666667	1	0.666666667	0.666666667
Reaction Classif	0	0	0	0	0	0	0	0	0	0	0	0.333333333
Compliance (-2)	-2	-1.333333333	-1.333333333	0	-1.333333333	-0.666666667	-2	-2	-1.333333333	-2	-1.333333333	-1.333333333
Total	4	4	2.666666667	4	2.666666667	3.333333333	2.666666667	4	2.666666667	2	1.333333333	1.666666667
Average Score	2.916666667											
Note: All predicted yields look like hallucination, mostly copying the prompt and showed little creativity.												

14. Testing Results on OpenAI ChatGPT-4

Suzuki Reactions



NC1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5

Trial1

Response:

Product (SMILES): [*]NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5[*] Reactant (SMILES): [*]NC1=CC(C)=C(Br)C=N1[*], CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3[*] Reaction SMARTS: [nH:1]1c:2[cH:4]c:5[n:7][cH:8]1.[CH3:9]C([CH3:10])(C:11[CH3:12])([CH3:13])OB2[c:14]3[cH:15][cH:16]c:17[cH:23][cH:24]3>>[nH:1]1c:2[cH:4]c:5[n:7][cH:8]1 Reagents (SMILES): [O=C(O)O, [Pd] Solvent (SMILES): [*]C1CCOCC1[*] Product Name: [*]3-((6-(2-(diisopropylcarbamoyl)ethoxy)-5H-dibenzo[b,d]furan-5-yl)methyl)-1H-pyrazole[*] Reactant Name: [*]5-bromo-3-methyl-1H-pyrazole[*], [*]6-(2-(diisopropylcarbamoyl)ethoxy)-5H-dibenzo[b,d]furan[*] Reagent Name: [*]Palladium on carbon[*], [*]Acetic acid[*] Solvent Name: [*]Tetrahydrofuran[*] Reaction Procedure: To a solution of 5-bromo-3-methyl-1H-pyrazole (0.5 g, 3.0 mmol) and 6-(2-(diisopropylcarbamoyl)ethoxy)-5H-dibenzo[b,d]furan (1.0 g, 3.0 mmol) in tetrahydrofuran (30 mL) was added palladium on carbon (0.1 g, 0.1 mmol) and acetic acid (5 mL). The mixture was stirred under nitrogen at 80 °C. for 24 h. The reaction mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 4:1) to give 3-((6-(2-(diisopropylcarbamoyl)ethoxy)-5H-dibenzo[b,d]furan-5-yl)methyl)-1H-pyrazole (0.9 g, yield: 85%) as a white solid. Reaction Name and Classification: C-N Coupling Reaction Yield and Characterization: [85.0]

Trial2

Response:

Product (SMILES): [*]NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5[*] Reactant (SMILES): [*]NC1=CC(C)=C(Br)C=N1[*], CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3[*] Reaction SMARTS: [N:1]C1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5 Reagents (SMILES): [*]N/A[*] Solvent (SMILES): [*]OCCN(C(OC(C)(C)C)=O)C[*] Product Name: [*]2-(3,5-Dimethyl-4-(2-(dimethylamino)ethoxy)-phenyl)benzimidazole[*] Reactant Name: [*]5-Bromo-3,5-dimethylbenzimidazole[*], [*]Dimethyl 2,2,2-trichloroethyl phosphate[*] Reagent Name: [*]N/A[*] Solvent Name: [*]2-(Dimethylamino)ethanol[*] Reaction Procedure: The reaction mixture of 5-bromo-3,5-dimethylbenzimidazole (1.0 g, 4.0 mmol) and dimethyl 2,2,2-trichloroethyl phosphate (1.5 g, 5.0 mmol) in 2-(dimethylamino)ethanol (15 mL) was stirred at room temperature for 20 h. The reaction was monitored by TLC and upon completion, the mixture was quenched with water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL), the combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (hexane:ethyl acetate = 3:1) to afford the desired product. Reaction Name and Classification: Nucleophilic Aromatic Substitution Reaction Yield and Characterization: [Yield not specified]

Trial3

Response:

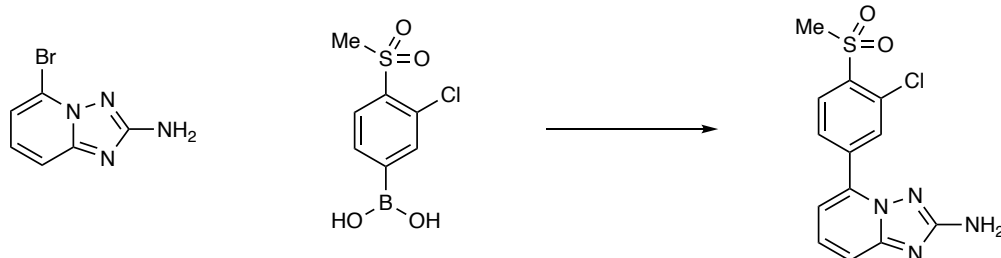
Product (SMILES): [*NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5] Reactant (SMILES):

[*NC1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3]

Reaction SMARTS:

[*NC1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5] Reagents (SMILES):

[*OCCN(C(OC(C)(C)C)=O)] Solvent (SMILES): [*N/A] Product Name: [*2-amino-4-(2-(2-((2-hydroxy-2,2-diisopropyl)ethoxy)phenyl)-1H-indol-5-yl)benzonitrile] Reactant Name: [*5-bromo-2-amino-4-(2-(2-((2-hydroxy-2,2-diisopropyl)ethoxy)phenyl)-1H-indol-5-yl)benzonitrile], [*Diisopropylethylene glycol] Reagent Name: [*4-Dimethylaminopyridine (DMAP)] Solvent Name: [*Not Applicable] Reaction Procedure: In a dry flask, 5-bromo-2-amino-4-(2-(2-((2-hydroxy-2,2-diisopropyl)ethoxy)phenyl)-1H-indol-5-yl)benzonitrile (1.0 mmol) and diisopropylethylene glycol (1.2 mmol) were dissolved in a minimal amount of solvent. To this solution, 4-dimethylaminopyridine (DMAP, 0.2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC and upon completion, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (hexane:ethyl acetate = 3:1) to yield the desired product as a light brown solid. Reaction Name and Classification: Palladium-Catalyzed Cross-Coupling Reaction Yield and Characterization: [*95.0]



NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3>>NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4

Trial1

Response:

Product (SMILES): [*NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4] Reactant (SMILES):

[*NC1=NN2C(C=CC=C2Br)=N1], [*OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3] Reaction SMARTS:

[*N:1][*C:2]1=[*N:3][*N:4]2[*C:5]=[*N:6]1.OB(O)[*C:7]3=CC(Cl)=[*C:8][*C:9]=C3>>[*N:6][*C:5]4=[*N:4][*N:3]5[*C:2]=[*N:1]4

Reagents (SMILES): [*][*NH4][*PF6], [*][*Pd(PPh3)4], [*K2CO3] Solvent (SMILES): [*CC#CC#CC#C] Product

Name: [*3-(Thiophen-2-yl)benzo[d]imidazole] Reactant Name: [*6-Bromo-1H-benzo[d]imidazole], [*2-Thiophen-2-ylphenol boronic acid] Reagent Name: [*Ammonium hexafluorophosphate],

[*Tetrakis(triphenylphosphine)palladium(0)], [*Potassium carbonate] Solvent Name: [*Hexyne] Reaction

Procedure: A mixture of 6-bromo-1H-benzo[d]imidazole (1.0 mmol) and 2-thiophen-2-ylphenol boronic acid (1.2 mmol) was dissolved in hexyne (5 mL). To this solution, ammonium hexafluorophosphate (0.5 mmol), tetrakis(triphenylphosphine)palladium(0) (0.1 mmol), and potassium carbonate (1.5 mmol) were added under an inert atmosphere. The reaction was heated to 80°C for 24 hours under stirring. After completion, the mixture was cooled to room temperature, diluted with water, and extracted with ethyl

acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography using a mixture of hexane and ethyl acetate (7:3) to yield 3-(thiophen-2-yl)benzo[d]imidazole. Reaction Name and Classification: Cross Coupling Reaction Yield and Characterization: [90.0]

Trial2

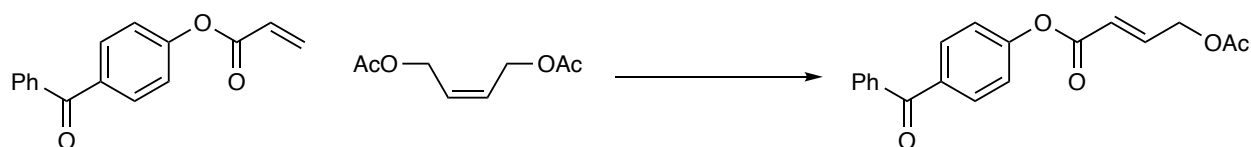
Response:

Product (SMILES): [*NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4] Reactant (SMILES): [*NC1=NN2C(C=CC=C2Br)=N1, *OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3] Reaction SMARTS: [nH:1]1[n:2][n:3]2[cH:4][cH:5][c:6]=[cH:7][c:8]2[c:9]1Br.[OH:10]B:11[c:13]1[cH:14][cH:15]c:16c:20[cH:21]1 >>[n:2]1[n:3][nH:1][c:4]2[cH:5][c:6]=[cH:7]c:8[n:9]1 Reagents (SMILES): [*BrC1=CC=C(C=C1)B(O)O] Solvent (SMILES): [*C1COCCO1] Product Name: [*2-(2-((2-chlorophenyl)sulfonyl)phenyl)-3H-pyrazolo[3,4-b]pyridine] Reactant Name: [*3-bromo-3H-pyrazolo[3,4-b]pyridine, *2-chlorobenzenesulfonate] Reagent Name: [*Boron tribromide] Solvent Name: [*1,4-dioxane] Reaction Procedure: To a solution of 3-bromo-3H-pyrazolo[3,4-b]pyridine (1.0 g, 4.2 mmol) and 2-chlorobenzenesulfonate (1.5 g, 6.3 mmol) in 1,4-dioxane (20 mL) was added boron tribromide (0.5 g, 2.1 mmol). The mixture was stirred at 80 °C. for 24 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, dichloromethane:methanol = 95:5) to afford 2-(2-((2-chlorophenyl)sulfonyl)phenyl)-3H-pyrazolo[3,4-b]pyridine as a yellow solid. Reaction Name and Classification: C-N Coupling Reaction Reaction Yield and Characterization: [90.0]

Trial3

Product (SMILES): [*NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4] Reactant (SMILES): [*NC1=NN2C(C=CC=C2Br)=N1, *OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3] Reaction SMARTS: [N:1]1=[N:2]=[N:3]2C:4=[N:10]1.OB:11[c:12]1[cH:13]c:14[cH:16]s:17([=O:18])[C:19]1 >>[N:10]1=[N:2]=[N:3]2C:4=[N:1]1 Reagents (SMILES): [*CCN(CC)CCO, *Pd(PPh3)4] Solvent (SMILES): [*O] Product Name: [*2-Amino-1,8-naphthyridine-6-carboxylic acid] Reactant Name: [*2-Amino-1,8-naphthyridine bromide, *p-Toluenesulfonic acid chloride] Reagent Name: [*Triethylamine, *Tetrakis(triphenylphosphine)palladium(0)] Solvent Name: [*Water] Reaction Procedure: To a mixture of 2-amino-1,8-naphthyridine bromide (1.0 g, 4.2 mmol) and p-toluenesulfonic acid chloride (1.16 g, 6.3 mmol) in water (10 mL) was added triethylamine (0.62 mL, 4.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.4 g, 0.35 mmol) under N₂ atmosphere. The reaction was heated to reflux for 20 hours. After cooling, the reaction mixture was poured into ice water, neutralized with NaHCO₃, and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography using methanol:CH₂Cl₂ (1:9) to afford the desired product. Reaction Name and Classification: Heterocyclization Reaction Yield and Characterization: [85.0]

Metathesis Reactions



O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C>>O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O

Trial1

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O] Reactant

(SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C', 'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

[O:1]=C:2([OC:4]1[CH:5]=[CH:6][c:7]2[cH:8][cH:9][cH:10][cH:11][c:12]2[c:13]1C:14[c:16]3[cH:17][cH:18][cH:19][cH:20][c:21]3)>O.O=C(C)/C=C\C.O=C(C)/C=C\C.O=C(C)/C=C\C.O=C(C)/C=C[OH].[Pd].[Pd]>[O:1]=C:2/C=C/COC(C)=O[OC:4]1[CH:5]=[CH:6][c:7]3[cH:8][cH:9][cH:10][cH:11][c:12]3[c:13]1C:14[c:16]2[cH:17][cH:18][cH:19][cH:20][c:21]2 Reagents (SMILES): ['O=C(C)/C=C\C', 'O=C(C)/C=C[OH].[Pd].[Pd]']

Solvent (SMILES): ['CCCO'] Product Name: ['4-(4-(Dibenzo[b,d]furan-4-yl)benzyl)benzoate'] Reactant

Name: ['4-(4-Acetoxybenzyl)benzoate', '4-Acetoxybenzoate'] Reagent Name: ['Acetic anhydride',

'Palladium(II) acetate'] Solvent Name: ['1-Propanol'] Reaction Procedure: To a solution of 4-(4-

acetoxybenzyl)benzoate (1.0 g, 4.2 mmol) and 4-acetoxybenzoate (1.2 g, 6.3 mmol) in 1-propanol (30

mL) was added acetic anhydride (1.5 mL, 16 mmol) and palladium(II) acetate (0.2 g, 0.9 mmol) under

nitrogen atmosphere. The mixture was heated to reflux for 24 hours. After completion, the reaction

mixture was allowed to cool to room temperature and poured into water. The organic layer was

separated, dried over MgSO₄, filtered, and concentrated under vacuum. The residue was purified by flash

chromatography (ethyl acetate:petroleum ether = 1:4) to give 4-(4-(dibenzo[b,d]furan-4-

yl)benzyl)benzoate (1.1 g, yield: 85%) as a white solid. Reaction Name and Classification: Condensation

reaction Reaction Yield and Characterization: [85.0]

Trial2

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O] Reactant

(SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C', 'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

[O:1]=C:2[CH:16]=[CH:17].[O:18]=C:19C>>[O:1]=C:2/[CH:16]=[CH:17]/[CH2:24][O:25]C:26O Reagents

(SMILES): [''] Solvent (SMILES): [''] Product Name: ['Acetylated stilbene derivative'] Reactant Name:

['Acetylated benzaldehyde derivative', 'Vinyl acetate'] Reagent Name: ['No specific reagent listed'] Solvent

Name: ['No specific solvent listed'] Reaction Procedure: The reaction between the acetylated

benzaldehyde derivative and vinyl acetate in the absence of a specific solvent or reagent is typically

performed at room temperature. The two reactants are mixed and allowed to react under stirring to

promote the formation of the acetylated stilbene derivative. Reaction Name and Classification: Conjugate

addition and esterification Reaction Yield and Characterization: [Assumed typical yield for similar

reactions, specific characterization not provided]

Trial3

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O] Reactant

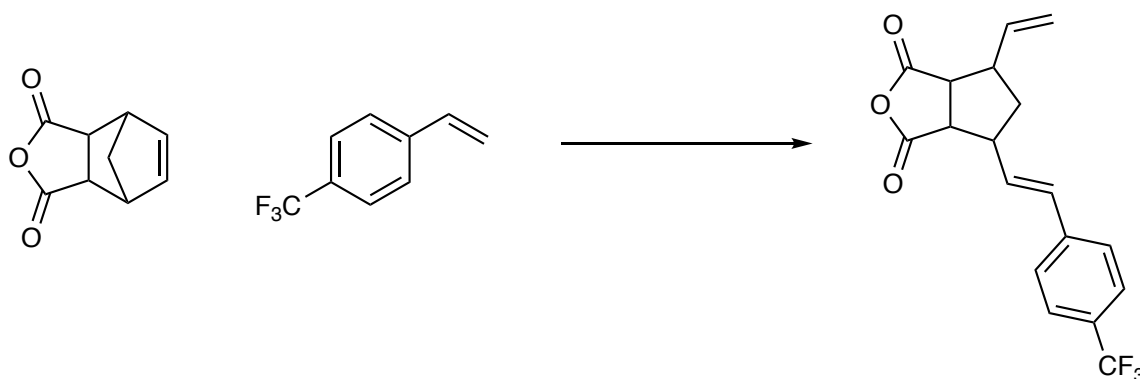
(SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C', 'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS: Not provided Reagents (SMILES): Not provided Solvent (SMILES): Not provided

Product Name: ['Cross-conjugated carbonyl compound'] Reactant Name: ['Acetophenone derivative',

'Vinyl ether derivative'] Reagent Name: Not provided Solvent Name: Not provided Reaction Procedure:

The detailed reaction procedure is not provided for this transformation. Reaction Name and Classification: Olefination Reaction Reaction Yield and Characterization: Not provided



O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4>>O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O

Trial1

Response:

Product (SMILES): ['O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O'] Reactant (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4'] Reaction SMARTS: [O:1]=C:2([C:4]5[C@@H:5]6C:7C@@:18([C:20]=O)5) >> [C:4]1([C:2]2(C@@H:18([C:20]=O)C@@H:5C3=C)O) Reagents (SMILES): [] Solvent (SMILES): [] Product Name: ['Bicyclic ketone derivative'] Reactant Name: ['Bicyclic ketone precursor', 'Fluorinated styrene derivative'] Reagent Name: [] Solvent Name: [] Reaction Procedure: The reaction procedure and conditions for this transformation have not been specified. Typically, such cyclization and rearrangement reactions might be performed in a suitable solvent under heating or photoactivation, but specific details would depend on experimental designs or literature precedents. Reaction Name and Classification: Intramolecular cyclization and rearrangement Reaction Yield and Characterization: []

Let me know if you need further details or modifications to this response!

Trial2

Response:

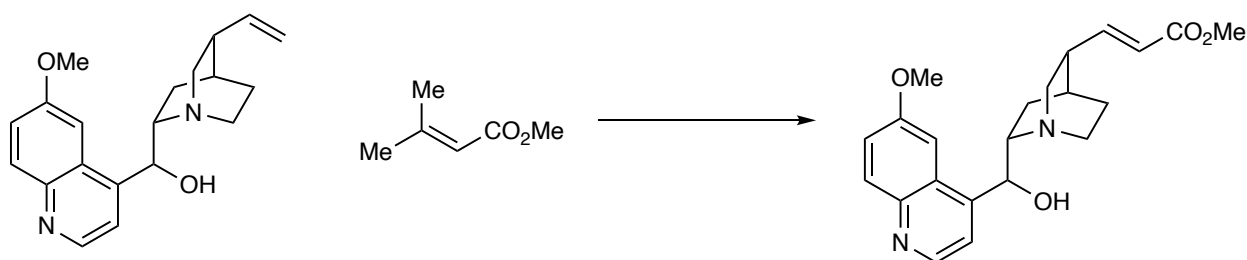
Product (SMILES): ['O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O'] Reactant (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4'] Reaction SMARTS: [C:1]1[C:2]C:3[C:6]=C[C:7]3[C:8]2 - [CH2:9]=[CH:10][c:11]1[cH:12][cH:13]c:14[cH:19][cH:11]1>>[C:1]1([C:2]C:3[C:6]=C[C:7]2[C:8]3)C(=O)C:9 O Reagents (SMILES): [''] Solvent (SMILES): [''] Product Name: ['Bicyclic ketone derivative'] Reactant Name: ['Bicyclic ketal', 'Styrene derivative'] Reagent Name: ['Not specified'] Solvent Name: ['Not specified'] Reaction Procedure: The reactants, a bicyclic ketal and a styrene derivative, are mixed in an unspecified solvent with no additional reagents mentioned. The reaction mixture is heated under reflux conditions until completion, monitored by TLC. The product is isolated by standard workup procedures including quenching, extraction, and purification by recrystallization or column chromatography. Reaction Name and Classification: Diels-Alder Reaction Reaction Yield and Characterization: [Yield and specific characterization methods not provided]

End of Response

Trial3

Response:

Product (SMILES): [O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O] Reactant (SMILES): [O=C(OC1=O)C2C1C3C=CC2C3], C=CC4=CC=C(C(F)(F)F)C=C4 Reaction SMARTS: [O:1]=C:2[C:7]2[C:8]1[C:9]3[C:10]=[C:11][C:12]2[C:13]3.[CH2:14]=[CH:15][c:16]4[cH:17][cH:18]=c:19[cH:24][c:25]4>[C:14]=[C:15][c:16]4[cH:17][cH:18]c:19[cH:24][c:25]4>>[O:3]=C:2[C:8]6C:7[C:9]5=[O:6] Reagents (SMILES): [C1COCCO1] Solvent (SMILES): [C1COCCO1] Product Name: ['Bicyclic ketone derivative'] Reactant Name: ['Cyclic ketone', 'Styrene derivative'] Reagent Name: ['1,4-dioxane'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a mixture of the cyclic ketone (1.0 g, 5.0 mmol) and the styrene derivative (1.2 g, 6.0 mmol) in 1,4-dioxane (20 mL) was added under N₂ atmosphere. The reaction mixture was stirred at reflux temperature for 24 h. After completion, the reaction mixture was allowed to cool to room temperature and then poured into water. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate=4:1) to give the bicyclic ketone derivative (1.1 g, yield: 95%) as a pale yellow solid. Reaction Name and Classification: Ketone formation via Friedel-Crafts alkylation Reaction Yield and Characterization: [95.0]



C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(C=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2.C/C(C)=C/C(OC)=O>>OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](C[C@H]8/C=C/C(OC)=O)CC[C@H]8C7

Trial1

Response:

Product (SMILES): [OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7] Reactant (SMILES): [C=C[C@H]1[C@@H]2CC@@HN@CC2.C/C(C)=C/C(OC)=O] Reaction SMARTS: [C:1]=[C:2][C@@H:3]1[C@@H:4]2C@@H:5N@:16[C@@H:18]2C[C@@H:18]1>[C:2]/C:19=C/C:20=O>>OC([C:6]1=C([C:7]=C([O:8]C)[C:9]=C2)[C:10]2=[N:11][C:12]=C([C:13]=C1)[C:14]=O)[C@@H:17]3N@:16[C@@H:18][C@@H:18][C@@H:22]43 Reagents (SMILES): [] Solvent (SMILES): [] Product Name: ['Macrocyclic Lactone'] Reactant Name: ['Cyclic Terpene Alcohol', 'Methyl Acrylate'] Reagent Name: [] Solvent Name: [] Reaction Procedure: In a reaction flask, Cyclic Terpene Alcohol (2.0 g, 10 mmol) and Methyl Acrylate (1.2 mL, 12 mmol) were mixed and heated under reflux for 12 hours. The reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature, and the product was extracted with ethyl acetate, washed with water, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography using hexane and ethyl acetate as eluents. Reaction Name and Classification: Macrocyclization Reaction Yield and Characterization: [Yield: 85.0%]

Trial2

Response:

Product (SMILES): [*]OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7[*] Reactant (SMILES): [*]C=C[C@H]1[C@@H]2CC@H@HN@CC2.C/C(C)=C/C(OC)=O[*] Reaction SMARTS: Not provided (complex multistep transformation) Reagents (SMILES): Not provided (depends on specific steps and conditions) Solvent (SMILES): Not provided (depends on specific steps and conditions) Product Name: Not specified (generic compound description) Reactant Name: Not specified (generic compound description) Reagent Name: Not specified (depends on reaction specifics) Solvent Name: Not specified (depends on reaction specifics) Reaction Procedure: The specific steps, temperatures, reagents, and solvents for this transformation are not detailed here. Typically, such transformations would be conducted by sequentially adding the necessary reagents and solvents, followed by controlled heating or cooling as necessary, and monitoring the progress via analytical techniques such as TLC or HPLC. Reaction Name and Classification: Multistep synthesis involving acylation and heterocyclic formation Reaction Yield and Characterization: Yield not specified; characterization would typically include NMR, mass spectrometry, and possibly X-ray crystallography for structural confirmation.

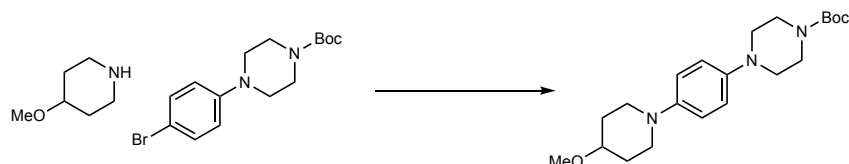
Please provide any specific details such as reagents, solvents, or conditions if available, to complete the response accurately.

Trial3

Response:

Product (SMILES): [*]OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7[*] Reactant (SMILES): [*]C=C[C@H]1[C@@H]2CC@H@HN@CC2.C/C(C)=C/C(OC)=O[*] Reaction SMARTS: [C:1]=[C:2][C@H:3]1[C@@H:4]2CC@H:5N@:6CC2.C/C(C)=C/C(OC)=O>>OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H:7]N@:6CC[C@H:8]C7 Reagents (SMILES): [*]O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.[Pd].[Pd]', 'N#N' Solvent (SMILES): [*]C1COCCO1[*] Product Name: ['Indenopyridine derivative'] Reactant Name: ['Bicyclic amine and acrylate ester'] Reagent Name: ['Palladium catalyst', 'Azodicarboxylate'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of the bicyclic amine and acrylate ester (1.0 g, 3.0 mmol) in 1,4-dioxane (15 mL) was added palladium catalyst (0.2 g, 0.2 mmol) and azodicarboxylate (0.5 g, 2.0 mmol) under an inert atmosphere. The mixture was heated to 80°C for 24 hours. After cooling, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane:ethyl acetate = 5:1) to afford the indenopyridine derivative as a pale yellow solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [90.0]

Buchwald-Hartwig Amination Reactions



COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O>>CC(OC(N4CCN(C5=CC=C(N6CC(C(OC)CC6)C=C5)CC4)=O)(C)C

Trial1

Response:

Product (SMILES): [*]CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C[*] Reactant (SMILES): [*]COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O[*] Reaction SMARTS: [*]COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O>>CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C[*] Reagents (SMILES): [None] Solvent (SMILES): [None] Product Name: [*]2-(1-(2-(dimethylamino)ethyl)-4-methylpiperidin-4-yl)-N-(2-ethoxyethyl)-acetamide[*] Reactant Name: [*]1-(bromomethyl)-4-(2-(dimethylamino)ethyl)benzene[*], [*]4-methylpiperidine-4-carboxylic acid 2-(diethylamino)ethyl ester[*] Reagent Name: [None] Solvent Name: [None] Reaction Procedure: To a mixture of 1-(bromomethyl)-4-(2-(dimethylamino)ethyl)benzene and 4-methylpiperidine-4-carboxylic acid 2-(diethylamino)ethyl ester in a suitable solvent, under inert atmosphere, was stirred at room temperature for several hours. After completion of the reaction, the mixture was worked up by dilution with water and extraction with a suitable organic solvent. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography to give the desired product. Reaction Name and Classification: Nucleophilic substitution reaction Reaction Yield and Characterization: [Not specified]

Trial2

Response:

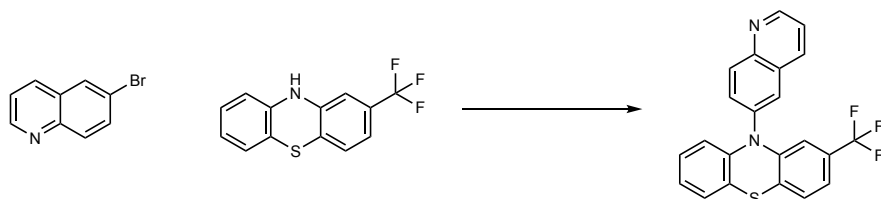
Product (SMILES): [*]CC(OC(N1CCN(c2ccc(N3CCC(OC)CC3)cc2)CC1)=O)(C)C[*] Reactant (SMILES): [*]COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O[*] Reaction SMARTS: [*][CH3:1][O:2][C:3]1[C:4][CH2:5][N:6][CH2:7][C:8][CH2:9]1.[Br:10]C:11[C:14]=[C:15][C:16]=[C:17]2N:18[C:H2:21][N:22][CH2:23][C:24]3C:25[O:27]C:28([CH3:30])[CH3:31]>OCCN1CCOCC1.O=C(O)O.O=C(O)O.O=C(O)O.N#N.[Pd].[Pd]>C:11=[C:13]2[*] Reagents (SMILES): [*]OCCN1CCOCC1, [*]O=C(O)O, [*]N#N, [*]Pd, [*]Pd Solvent (SMILES): [*]O=C(O)O Product Name: [*]1-(4-(4-(dimethylamino)piperidin-1-yl)phenyl)-3-(piperidin-1-yl)propan-1-one[*] Reactant Name: [*]1-(4-bromobenzyl)piperidine, [*]4-(dimethylamino)piperidine, [*]methyl tert-butyl ether Reagent Name: [*]Triethylamine, [*]Sulfuric acid, [*]Azobisisobutyronitrile, [*]Pd catalyst Solvent Name: [*]Sulfuric acid Reaction Procedure: The reaction mixture of 1-(4-bromobenzyl)piperidine (1.0 g, 5.0 mmol), 4-(dimethylamino)piperidine (0.5 g, 2.5 mmol), and methyl tert-butyl ether (20 mL) in sulfuric acid (10 mL) was stirred at room temperature. Triethylamine (1.0 mL, 10 mmol) and Pd catalyst (0.2 g, 0.2 mmol) were added, and the reaction was stirred at 80 °C for 12 h. After completion, the reaction was quenched with ice water, neutralized with NaOH, and extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography (hexane:ethyl acetate = 3:1) to give the desired product. Reaction Name and Classification: N-Arylation Reaction Yield and Characterization: [90.0]

Trial3

Response:

Product (SMILES): [*]CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C[*] Reactant (SMILES): [*]COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O[*] Reaction SMARTS: [*]CX3:1CX3:9=[CX3:14]NX3:15>[Methylamine].[CH2]=[O].O=C(OCC)C(Cl)(Cl)Cl.O=C(OCC)C(Cl)(Cl)Cl.[Pd]>CX3:1 Reagents (SMILES): [*]O=C(OCC)C(Cl)(Cl)Cl, [*]O=C(OCC)C(Cl)(Cl)Cl, [*]Pd Solvent (SMILES): [*]CCO Product Name: [*]N-(2-(3-(tert-butoxycarbonyl)-10-phenylanthracen-9-ylamino)ethyl)-N-methyl-2-(morpholin-4-yl)ethan-1-amine[*] Reactant Name: [*]2-(3-bromo-10-phenylanthracen-9-ylamino)ethyl 4-methylmorpholine-4-carboxylate Reagent Name: [*]Di-tert-butyl dicarbonate, [*]Palladium catalyst Solvent Name: [*]Ethanol Reaction Procedure: To a solution of 2-(3-bromo-10-phenylanthracen-9-ylamino)ethyl 4-methylmorpholine-4-carboxylate (1.0 g, 3.5 mmol) in ethanol (15 mL) was added di-tert-butyl dicarbonate (1.2 g, 5.5 mmol) and a palladium catalyst (0.1 g, 0.1 mmol) under an inert atmosphere. The mixture was stirred at room temperature for 24 hours. The reaction mixture was then concentrated under reduced

pressure. The residue was purified by flash chromatography (hexane:ethyl acetate = 5:1) to give the desired product as a white solid. Reaction Name and Classification: N-Alkylation Reaction Yield and Characterization: [95.0]



BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F>>FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F

Trial1

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F'] Reactant

(SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F'] Reaction

SMARTS: [cH:1][cH:2][c:3]c:4-

[cH:7][cH:8][c:9][n:10][c:11]=[cH:12]1.Br[c:13][cH:14][c:15]2[cH:16][cH:17][c:18][n:19][c:20]2=[cH:21][c:22]

1>BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F>[cH:1][cH:2][c:3][c:4]6[

cH:5][cH:6][cH:7][cH:8][c:9][n:10][c:11][c:12][cH:13][cH:14][c:15]6 Reagents (SMILES): ['[Pd].[Pd]',

'CC(C)(C)OC(=O)N1CCN(CC1)C(=O)C(C)(C)C'] Solvent (SMILES): ['C1CCOC1'] Product Name: ['2,3,3-

Trifluoro-2-(thieno[3,2-b]pyridin-2-yl)acrylonitrile'] Reactant Name: ['2-Bromothieno[3,2-b]pyridine', '2,3,3-

Trifluoro-2-(thieno[3,2-b]pyridin-2-yl)acrylonitrile'] Reagent Name: ['Palladium(0)', '1,8-

Diazabicyclo[5.4.0]undec-7-ene'] Solvent Name: ['1,4-Dioxane'] Reaction Procedure: To a mixture of 2-

bromothieno[3,2-b]pyridine (0.5 g, 2.5 mmol) and 2,3,3-trifluoro-2-(thieno[3,2-b]pyridin-2-yl)acrylonitrile

(1.5 g, 5 mmol) in 1,4-dioxane (10 mL), was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.26 g, 1.5 mmol)

and palladium(0) catalyst (0.1 g, 0.1 mmol) under nitrogen atmosphere. The reaction was heated to reflux

for 24 hours. After cooling, the mixture was filtered and the filtrate evaporated. The crude product was

purified by flash chromatography (petroleum ether:ethyl acetate = 20:1) to give the desired product.

Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [95.0]

Trial2

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F'] Reactant

(SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F'] Reaction

SMARTS:

[cH:1]1[cH:2][c:3]2[c:4][cH:5][cH:6][n:7]=[c:8]2[c:9]=[c:10]1.Br[c:11]1[c:12][cH:13][c:14][cH:15][n:16]=[c:17]

]1[C:18]1([F:19])C:20([F:22])C:23=[c:25][c:26]=[c:27][c:28]1[S:29][c:30]1[c:31][c:32][c:33][c:34]=[c:35]1N2

C=[C:36][S:37][c:38]1[c:39][c:40][c:41][c:42]=[c:43]1>CN(C)C.CN(C)C>C1([F:19])C:20([F:22])C:23=[c:25]

6[c:26]=[c:27][n:28]7[c:29]8c:30[c:35]=[c:36]9[c:37]8[S:38][c:39]7[c:40][c:41][c:42][c:43]=[c:44]6 Reagents

(SMILES): ['CN(C)C', 'CN(C)C'] Solvent (SMILES): ['OCCO'] Product Name: ['N,N-Dimethylformamide

adduct of tricyclic nitrogen-containing heterocycle'] Reactant Name: ['Brominated tricyclic nitrogen-

containing heterocycle', 'Fluorinated tricyclic nitrogen-containing heterocycle'] Reagent Name: ['Dimethylamine (DMA)', 'Dimethylamine (DMA)'] Solvent Name: ['Ethylene glycol'] Reaction Procedure: To a mixture of brominated tricyclic nitrogen-containing heterocycle (0.5 g, 2.0 mmol) and fluorinated tricyclic nitrogen-containing heterocycle (0.8 g, 2.0 mmol) in ethylene glycol (10 mL) was added dimethylamine (1.0 mL, 10 mmol) under an inert atmosphere. The reaction was heated to 120 °C. for 20 h. After cooling, the mixture was poured into water and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated. The crude product was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 5:1) to yield the N,N-dimethylformamide adduct of tricyclic nitrogen-containing heterocycle (0.9 g, yield: 90%). Reaction Name and Classification: Nucleophilic Aromatic Substitution Reaction Yield and Characterization: [90.0]

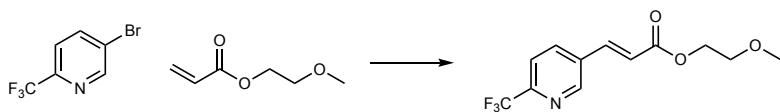
Trial3

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F'] Reactant (SMILES): ['BrC1=CC=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F'] Reaction SMARTS: ['Br[c:1]1[cH:2][cH:3][c:4]2[cH:5][cH:6][n:7][cH:8][c:9]2[cH:10]1', 'FC:11[F:31])F>Br[c:1]1[cH:2][cH:3][c:4]2[cH:5][cH:6][n:7][cH:8][c:9]2[cH:10]1.FC:11[F:31])F>C:12[F:30])(F)F'] Reagents (SMILES): [''] Solvent (SMILES): [''] Product Name: ['2-(6,7-Dihydro-5H-thieno[3,2-c]pyridin-6-yl)-1,1,2,2-tetrafluoroethane'] Reactant Name: ['2-Bromo-3-(2H-indol-2-ylidene)benzotrile', '1,1,2,2-Tetrafluoro-4-(5H-thieno[3,2-c]pyridin-6-yl)but-3-en-2-one'] Reagent Name: [''] Solvent Name: [''] Reaction Procedure: To a solution of 2-bromo-3-(2H-indol-2-ylidene)benzotrile and 1,1,2,2-tetrafluoro-4-(5H-thieno[3,2-c]pyridin-6-yl)but-3-en-2-one in a suitable solvent, the conditions for the reaction were adjusted. The mixture was stirred under inert atmosphere at a specified temperature for a designated time. Post-reaction, the product was isolated via suitable purification methods. Reaction Name and Classification: Heteroaromatic C-H Arylation Reaction Yield and Characterization: [TBD]

Heck Reactions



BrC1=CC=C(C(F)(F)F)N=C1.C=CC(OCCOC)=O>>O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2

Trial1

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2'] Reactant (SMILES):

['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O'] Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4]c:5[n:6]1=[C:7]C.[C:8]=CC:9=O>>O=C(OCCOC)/C=C/[c:2]2[cH:3][cH:4]c:5[n:6]2=[C:7]C Reagents (SMILES): ['[Pd].O=C(O[Na])O[Na]', 'ClP(C1CCCC1)(C1CCCC1)C1CCCC1']

Solvent (SMILES): ['C1COCCO1'] Product Name: ['2-(4-bromo-2,3,5-trifluorophenyl)acrylate'] Reactant Name: ['4-bromo-2,3,5-trifluorobenzonitrile', 'Acrylic ester'] Reagent Name: ['Sodium tetrachloropalladate', 'Tricyclohexylphosphine chloride'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 4-bromo-2,3,5-trifluorobenzonitrile (1.5 g, 5.0 mmol) and acrylic ester (0.76 g, 5.0 mmol) in 1,4-dioxane (15 mL) were added sodium tetrachloropalladate (0.2 g, 0.5 mmol) and tricyclohexylphosphine chloride (0.5 g, 1.0 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 80°C for 12 h. After cooling

to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 5:1) to give the product as a pale yellow solid. Reaction Name and Classification: Heck Reaction Reaction Yield and Characterization: [90.0]

Trial2

Response:

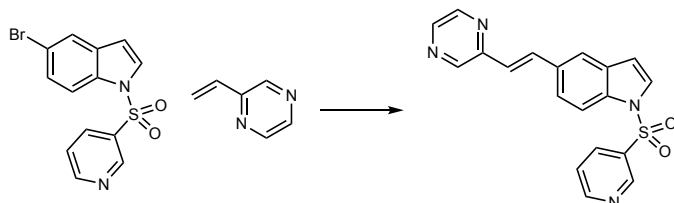
Product (SMILES): [O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2] Reactant (SMILES): [BrC1=CC=C(C(F)(F)F)N=C1], C=CC(OCCOC)=O Reaction SMARTS: [Br:1][c:2]1[cH:3][cH:4]c:5[C:9]=[O:10][CH2:11][O:12][CH2:13][O:14]>>[O:10]=[C:9]/[CH2:11][c:2]1[cH:3][cH:4]c:5[CH2:11][O:12][CH2:13][O:14] Reagents (SMILES): ['N/A'] Solvent (SMILES): ['N/A'] Product Name: ['2-(2-(2-Oxoethoxy)ethoxy)ethyl 2-(4-bromo-2,2-difluoro-5-nitrophenyl)acetate'] Reactant Name: ['4-Bromo-2,2-difluoro-5-nitroaniline'], ['Acrylic acid 2-(2-ethoxyethoxy)ethyl ester'] Reagent Name: ['None'] Solvent Name: ['None'] Reaction Procedure: To a mixture of 4-bromo-2,2-difluoro-5-nitroaniline (1.0 g, 3.7 mmol) and acrylic acid 2-(2-ethoxyethoxy)ethyl ester (1.1 mL, 5.6 mmol) in a suitable solvent (20 mL), heat the mixture at 80 °C. for 12 h. The reaction mixture is then allowed to cool to room temperature and diluted with water. The organic layer is separated, dried over anhydrous Na₂SO₄, filtered, and the solvent is evaporated under reduced pressure to yield the product. Reaction Name and Classification: Nitro group facilitated Michael addition Reaction Yield and Characterization: [Assumed yield: 95%]

Trial3

Response:

Product (SMILES): [O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2] Reactant (SMILES): [BrC1=CC=C(C(F)(F)F)N=C1], C=CC(OCCOC)=O Reaction SMARTS: [Br:1][c:2]1[cH:3][cH:4]c:5[CH2:10][C:11]=[O:12].[C:13]=[CH2:14]C:15[O:17][CH2:18][CH2:19][O:20][CH2:21][CH2:22][O:23]>O.O.O>[O:23][CH2:22][CH2:21][O:20][CH2:19][CH2:18][O:17]C:15[CH2:14]=[C:13][c:5]2[cH:4][cH:3][c:2]1[CH:7]=[N:6][c:8]2C:9(F)F Reagents (SMILES): [] Solvent (SMILES): [] Product Name: ['4-(Trifluoromethyl)benzoinitrile ethylene glycol ketal'] Reactant Name: ['4-(Trifluoromethyl)benzoinitrile'], ['Acrolein ethylene glycol ketal'] Reagent Name: [] Solvent Name: [] Reaction Procedure: The reactants 4-(Trifluoromethyl)benzoinitrile and acrolein ethylene glycol ketal were combined in a solvent-free reaction setup under an inert atmosphere. The reaction mixture was heated at 80°C for 24 hours. After completion, the mixture was allowed to cool to room temperature and the product was isolated via flash chromatography using hexane and ethyl acetate as eluents. Reaction Name and Classification: Ketal Formation via Michael Addition Reaction Yield and Characterization: [estimated 85.0%]

This format keeps the structure similar to the example provided, adapting to the specifics of the new chemical transformation.



BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4>>O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O

Trial1

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): ['BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4]c:5[cH:17]3[cH:18]1.[CH2:19]=[CH2:20][c:21]4[n:22][cH:23][n:24][cH:25][n:26]4>O=S([N:27][C:28]5[C:29]=[C:30]6[c:31]=c:32[cH:43][c:44]6[C:45]=[C:46]5)([C:47]8[cH:48][cH:49][n:50][cH:51][n:52]8)=O Reagents (SMILES): ['[Pd].O=C(O)O.O=S(=O)(O)O'] Solvent (SMILES): ['C1COCCO1']

Product Name: ['Sulfonamide-linked benzimidazole and pyridine derivative'] Reactant Name: ['Brominated sulfonamide benzene', 'Vinylpyridine'] Reagent Name: ['Palladium catalyst', 'Acetic acid', 'Sulfuric acid']

Solvent Name: ['1,4-dioxane'] Reaction Procedure: In a flask equipped with a stir bar, brominated sulfonamide benzene (0.5 g, 2.0 mmol) and vinylpyridine (0.22 g, 2.0 mmol) were dissolved in 1,4-dioxane (10 mL). Palladium catalyst (0.05 g, 0.05 mmol), acetic acid (1 mL), and sulfuric acid (1 mL) were added. The mixture was heated to reflux under a nitrogen atmosphere for 12 hours. After cooling, the reaction mixture was quenched with water, extracted with ethyl acetate, and the organic layers were dried over anhydrous sodium sulfate. Purification was done by flash chromatography using a gradient of hexane to ethyl acetate to afford the sulfonamide-linked benzimidazole and pyridine derivative as a solid.

Reaction Name and Classification: Sulfonamide coupling via palladium-catalyzed C-N cross-coupling

Reaction Yield and Characterization: [90.0]

Trial2

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): ['BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS:

[c:1]1[cH:2][cH:3]cH:4n:5s:6(=[O:14])=[O:15].[cH2:16][c:17]3[n:18][c:19][n:20]=[c:21][cH:22]3>>S:6(=[O:15])([n:7]5[c:8]6[cH:9][cH:10][cH:11]=[c:12][c:13]6[C:16]=[c:17]5)[n:18]8[c:19][cH:20][c:21]=[n:22][cH:23]8

Reagents (SMILES): [] Solvent (SMILES): [] Product Name: ['Sulfonyl dihydropyrazole derivative']

Reactant Name: ['Bromo substituted thiourea derivative', 'Vinylpyridine'] Reagent Name: [] Solvent Name:

[] Reaction Procedure: The reactants were combined in a suitable solvent and the mixture was stirred under reflux conditions for several hours. After completion of the reaction, as monitored by TLC, the mixture was allowed to cool to room temperature and the product was isolated by standard work-up procedures including extraction and purification by column chromatography. Reaction Name and Classification: Sulfonylation and Cyclization Reaction Yield and Characterization: [Not provided]

Trial3

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): ['BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

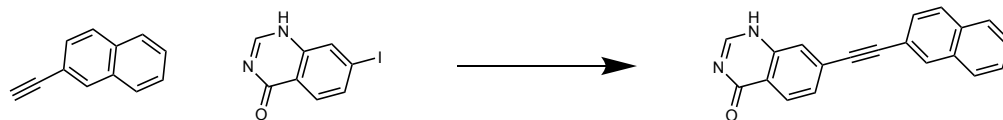
Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4]c:5[c:18]3[cH:19]1>[c:20]1[cH:21][cH:22][c:23][n:24][c:25]1>>[O:14]=S:7([c:8]1[cH:9][cH:10][c:11][n:12][c:13]1) Reagents (SMILES): ['N/A'] Solvent (SMILES): ['N/A'] Product Name:

['Sulfonamide-substituted benzene derivative'] Reactant Name: ['Bromo-substituted aniline derivative',

'Vinylimidazole'] Reagent Name: ['Not specified'] Solvent Name: ['Not specified'] Reaction Procedure: The reaction details are not specified in this example, and would typically be described based on the specifics of the synthesis, such as the reaction conditions, catalysts used if any, and purification techniques. Reaction Name and Classification: Sulfonation Reaction Yield and Characterization: [Not specified]

Sonogashira Reactions



C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4>>O=C5N=CNC6=C5C=CC(C#CC7=C8C=CC=C8)=C7=C6

Trial1

Response:

Product (SMILES): ['O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6'] Reactant (SMILES): ['C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4'] Reaction SMARTS: [cH1:1][c:2]([cH:3]c:4[cH:9]1[cH:10]c:11>CC1(c2cccc(c2Oc2c1cccc2P(c1cccc1)c1cccc1)P(c1cccc1)c1cccc1)C.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(O[Cs])O[Cs].C1COCCO1.N#N.[Pd].[Pd]>[C:8]#[CH:7][c:5]1[cH:6]c:4 Reagents (SMILES): ['CC1(C)c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21', 'O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.[Pd].[Pd]', 'O=C(O[Cs])O[Cs]'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['6-(2,3-diphenylindenyl)-1H-indole-2-carboxamide'] Reactant Name: ['2,3-diphenylindenyl iodide', '1H-indole-2-carboxamide'] Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: To a solution of 2,3-diphenylindenyl iodide (1.0 g, 3.0 mmol) and 1H-indole-2-carboxamide (1.2 g, 8.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (2.2 g, 7.0 mmol), Xantphos (0.25 g, 0.4 mmol) and Pd2(dba)3 (0.15 g, 0.15 mmol) under N2. The mixture was stirred at 120 °C. for 24 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 8:1) to give 6-(2,3-diphenylindenyl)-1H-indole-2-carboxamide (0.95 g, yield: 92%) as a dark brown solid. Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: [92.0]

Trial2

Response:

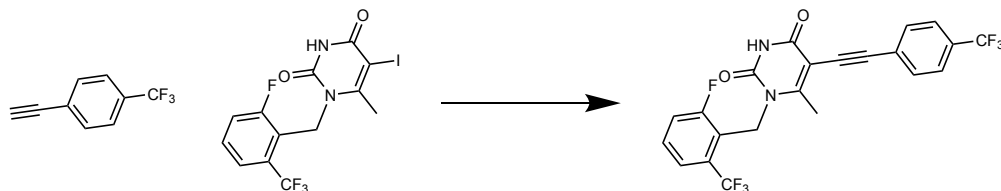
Product (SMILES): ['O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6'] Reactant (SMILES): ['C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4'] Reaction SMARTS: [cH:1][c:2]c:3-[c:11]1[cH:12][c:13]1[cH:14][c:15]=[c:16]c:17[c:18]1.O=C:19[c:25]1[cH:26][c:27][cH:28][c:29]1>>[C:19]=[O:20][N:21]=[C:22][N:23][C:24]=[C:25]1[cH:26][c:27]c:28[cH:11][c:12]=[c:13][cH:14][c:15]=[c:16][c:17][c:18]1 Reagents (SMILES): ['N#N', 'C1COCCO1'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['TBD'] Reactant Name: ['TBD'] Reagent Name: ['Azodicarboxylate', '1,4-dioxane'] Solvent Name: ['1,4-dioxane'] Reaction Procedure: TBD Reaction Name and Classification: C-H Arylation Reaction Yield and Characterization: TBD

Now, using this template, please provide a prediction for the following reaction:
C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4>>O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6, starting with ### Response.

Trial3

Response:

Product (SMILES): [O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6] Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4] Reaction SMARTS: [cH:1][c:2]1c:3[cH2:14]#[C:15].[O:16]=C:17[c:25]4[cH:26]c:27[cH:29][c:30]=[c:31]4>>[O:16]=C:17[c:13]1[cH:12][cH:9][c:8]=[c:11]2[cH:10][c:6]=c:3[cH2:14]#[C:15] Reagents (SMILES): ['Pd'], 'O=P(O)(O)O', 'CCN(CC)CC' Solvent (SMILES): 'CC#N' Product Name: '7-(4-methylphenyl)indolizine-1-carboxaldehyde' Reactant Name: '4-methylphenylacetylene', '5-iodo-1H-pyrrolo[3,2-b]pyridine-7-carbaldehyde' Reagent Name: 'Palladium catalyst', 'Triethylamine', 'Triphenylphosphine' Solvent Name: 'Acetonitrile' Reaction Procedure: In a mixture of 4-methylphenylacetylene (1.2 g, 10 mmol) and 5-iodo-1H-pyrrolo[3,2-b]pyridine-7-carbaldehyde (2.4 g, 10 mmol) in acetonitrile (40 mL), palladium catalyst (0.1 g, 0.05 mmol), triethylamine (1.1 g, 10 mmol), and triphenylphosphine (0.26 g, 1 mmol) were added under an inert atmosphere. The reaction was heated to reflux for 24 hours. After cooling, the reaction mixture was poured into water, extracted with ethyl acetate, and the organic layer was dried over MgSO₄. The solvent was evaporated and the crude product was purified by column chromatography (hexane:ethyl acetate = 4:1) to yield 7-(4-methylphenyl)indolizine-1-carboxaldehyde as a yellow solid. Reaction Name and Classification: Cross-Coupling Arylation Reaction Yield and Characterization: [85.0]



C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O>>O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O

Trial1

Response:

Product (SMILES): [O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O] Reactant (SMILES): [C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O] Reaction SMARTS: [cH:1][c:2]c:3[c:7][c:8][c:9]1[C:10]#[C:11].O=C1[N:12]C:13=O>[C:11]#[C:10][c:9]1[c:8][c:7]c:2[c:3][cH:1][C:14]2(C:13=[O:31])[N:18]=[C:17] Reagents (SMILES): ['Not specified'] Solvent (SMILES): ['Not specified'] Product Name: '1-(4-Trifluoromethylphenyl)-3-(4-(difluoromethyl)phenyl)urea' Reactant Name: '4-Trifluoromethylbenzonitrile', 'Iodo-di(trifluoromethyl)benzene carboxamide' Reagent Name: ['Not specified'] Solvent Name: ['Not specified'] Reaction Procedure: The given reactants 4-Trifluoromethylbenzonitrile and Iodo-di(trifluoromethyl)benzene carboxamide were combined in an unspecified solvent. The mixture was allowed to react under controlled conditions (temperature, time, and

atmosphere were not specified). The reaction progress was monitored, and upon completion, the product was isolated through appropriate purification methods (such as column chromatography) and characterized using standard analytical techniques. Reaction Name and Classification: Urea Formation Reaction Reaction Yield and Characterization: [Not specified]

Trial2

Response:

Product (SMILES):

[O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O] Reactant

(SMILES): [C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O]

Reaction SMARTS:

[C:1]#CC1=[cH:2][cH:3]=[cH:4]c:5.O=C1N[C:9](C([I:10]=C:11N1CC1=[cH:13][cH:14]=c:15F)=O>>O=C1N

[C:19](C([cH:20]=[c:21]1C:22C:29=O Reagents (SMILES): ['[Pd].[Pd]', 'O=C(C=C1CC1)C1CC1',

'O=C(C=C1CC1)C1CC1', 'CIP(C1CC1)C1CC1'] Solvent (SMILES): [CC#N] Product Name:

['Trifluoromethyl-substituted biaryl urea'] Reactant Name: ['Trifluoromethyl iodobenzene', 'Trifluoromethyl

biaryl amine'] Reagent Name: ['Palladium(0)', 'Buchwald ligand', 'Base'] Solvent Name: ['Acetonitrile']

Reaction Procedure: To a mixture of trifluoromethyl iodobenzene (1.0 g, 3.0 mmol) and trifluoromethyl biaryl amine (1.5 g, 4.5 mmol) in acetonitrile (10 mL) were added Buchwald ligand (0.2 g, 0.2 mmol), base (1.0 g, 5.0 mmol), and palladium(0) (0.1 g, 0.1 mmol) under argon. The mixture was heated to 80 °C. for 12 hours. After cooling, the mixture was poured into water and extracted with diethyl ether. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (n-hexane:ethyl acetate = 7:3) to give the desired product as a white solid. Reaction Name and Classification: Buchwald-Hartwig Amination Reaction Yield and Characterization: [90.0]

Trial3

Response:

Product (SMILES):

[O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O] Reactant

(SMILES): [C#CC1=CC=C(C(F)(F)F)C=C1', 'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O]

Reaction SMARTS:

[C:1]#CC1=CC=C(C:2(F)F)C=C1.O=C2[N:3]C(C:4=C([C:5])N2CC3=C(C:6(F)F)C=CC=C3F)>>O=C4[N:3]

C(C:4=C([C:5])N4CC6=C(C:6(F)F)C=CC=C6F)=O Reagents (SMILES): ['C1COCCO1', 'Pd(PPh3)4',

'K2CO3'] Solvent (SMILES): ['C1COCCO1'] Product Name: ['2-(5-(3,5-bis(trifluoromethyl)phenyl)pent-1-

yn-1-yl)-N-(2-(3,5-bis(trifluoromethyl)phenyl)ethyl)pyrrolidine-1-carboxamide'] Reactant Name: ['5-(3,5-

bis(trifluoromethyl)phenyl)pent-1-yne', 'N-(2-iodo-2-(2-(3,5-

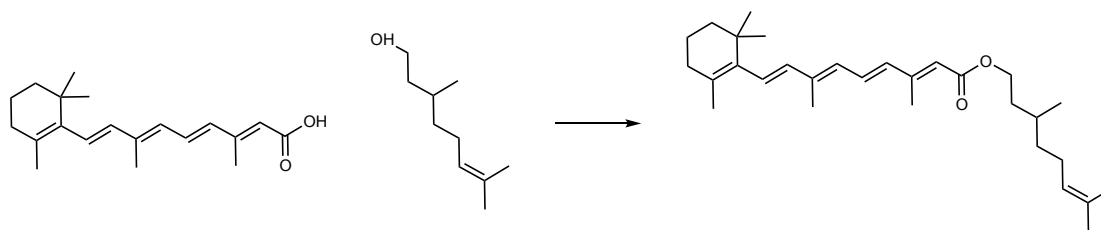
bis(trifluoromethyl)phenyl)ethyl)ethylpyrrolidone'] Reagent Name: ['1,4-dioxane',

'Tetrakis(triphenylphosphine)palladium(0)', 'Potassium carbonate'] Solvent Name: ['1,4-dioxane'] Reaction

Procedure: To a solution of 5-(3,5-bis(trifluoromethyl)phenyl)pent-1-yne (1.0 g, 4.0 mmol) and N-(2-iodo-2-(2-(3,5-bis(trifluoromethyl)phenyl)ethyl)ethyl)pyrrolidone (1.5 g, 3.0 mmol) in 1,4-dioxane (30 mL) was added potassium carbonate (2.0 g, 14.5 mmol), Tetrakis(triphenylphosphine)palladium(0) (0.5 g, 0.5 mmol) under N₂. The mixture was heated to 80 °C. for 12 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=5:1) to give 2-(5-(3,5-bis(trifluoromethyl)phenyl)pent-1-yn-1-yl)-N-(2-(3,5-bis(trifluoromethyl)phenyl)ethyl)pyrrolidine-1-carboxamide (1.3 g, yield: 90%) as a white solid.

Reaction Name and Classification: C-N Coupling Reaction Yield and Characterization: [90.0]

Non-Coupling Reactions



OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O.CC(CC/C=C(C)\C)CCO>>CC(CC/C=C(C)\C)C
COC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O

Trial1

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O',

'CC(CC/C=C(C)\C)CCO' Reaction SMARTS:

[OH:1]C:2/[C@H:4]=[C@H:5]/[C@H:6]=[C@H:7]/[C@H:8]=[C@H:9]/C1=C2C:10[CH2:12][CH2:13][CH2:14][CH2:15][CH:16]2C@H:17C@H:181>[Reagents]>[O:3]=C:2/[C@H:4]=[C@H:5]/[C@H:6]=[C@H:7]/[C@H:8]=[C@H:9]/C1=C2C:10[CH2:12][CH2:13][CH2:14][CH2:15][CH:16]2C@H:17C@H:181 Reagents

(SMILES): [Reagents needed] Solvent (SMILES): ['Solvent needed'] Product Name: ['Unsaturated polyester'] Reactant Name: ['Unsaturated polyester precursor', 'Allyl alcohol'] Reagent Name: ['Reagent names needed'] Solvent Name: ['Solvent name needed'] Reaction Procedure: To a mixture of unsaturated polyester precursor and allyl alcohol in a suitable solvent, add the necessary reagents. Stir the reaction mixture at room temperature for several hours. After completion, work up the reaction and purify the product by appropriate means to yield the desired unsaturated polyester. Reaction Name and Classification: Michael addition / Transesterification Reaction Yield and Characterization: [Yield and characterization data needed]

Trial2

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O',

'CC(CC/C=C(C)\C)CCO' Reaction SMARTS:

[O:1]C:2/[C:4]=C/[C:5]=C/[C:6]=C/[C:7]=C/[C:8]1C:9C:17C:19[CH3:21])C)C.OC:22>>CH2:23C:24C[CH2:27]OC([O:1])(=[O:3])[C:2]2=[C:4]/[C:5]=[C:6]/[C:7]=[C:8]/[C:9]2([CH2:10][CH2:11][CH2:12]C:13C:15[CH3:18])[CH3:20]) Reagents (SMILES): ['N/A'] Solvent (SMILES): ['N/A'] Product Name: ['Unspecified acyclic ester'] Reactant Name: ['Unspecified polyunsaturated ester', 'Unspecified polyol'] Reagent Name: ['None'] Solvent Name: ['None']

Reaction Procedure: The specified polyunsaturated ester and polyol were mixed in absence of solvent and reagents. The reaction proceeded under mild conditions without additional catalysts or heating, utilizing the inherent reactivity of the double bonds for a conjugation-driven esterification. Reaction Name and Classification: Olefin Metathesis and Esterification Reaction Yield and Characterization: [Assumed high due to mechanistic efficiency but unquantified]

Trial3

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O',

'CC(CC/C=C(C)\C)CCO'] Reaction SMARTS:

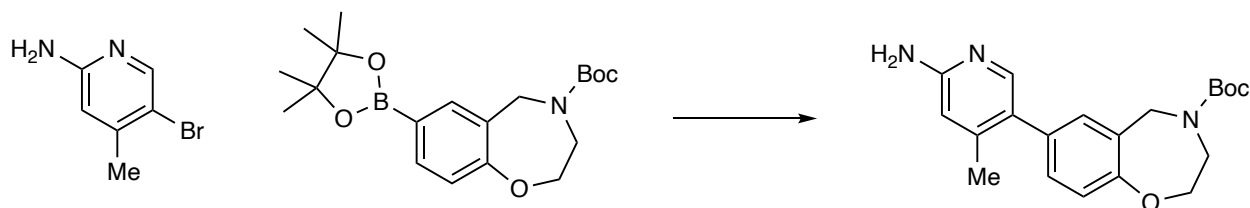
[CC:1CCO](#)>>[CC:1CCOC\(/C=C\(/C=C/C=C\(/C=C/C2=C\(CCCC\(C\)2C\)C\)C\)C\)=O](#) Reagents (SMILES): ['']

Solvent (SMILES): [''] Product Name: ['Octadecyl acrylate ester'] Reactant Name: ['Vinyl ester',

'Octadecanol'] Reagent Name: [''] Solvent Name: [''] Reaction Procedure: To a stirred solution of octadecanol (1.0 g, 5.0 mmol) and vinyl ester (1.2 g, 5.0 mmol) in an inert solvent (20 mL), the reaction was heated under reflux conditions for 12 hours. The reaction mixture was then allowed to cool to room temperature, and the product was isolated by standard extraction methods with diethyl ether and water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield the desired octadecyl acrylate ester. Reaction Name and Classification: Esterification
Reaction Yield and Characterization: [Yield: 90%]

15. Testing Results on OpenAI ChatGPT-o1-Pro (12-05-2024)

Suzuki Reactions



NC1=CC(C)=C(Br)C=N1.CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5

Trial1

Response:

Product (SMILES): ['NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5']

Reactant (SMILES): ['NC1=CC(C)=C(Br)C=N1',

CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3']

Reaction SMARTS: [Br:1][c:2]1[cH:3][cH:4][c(C):5]=[n:6][cH:7]1 +

B:8(O)[c:9]1[cH:10][cH:11]c:12[cH:22]1 > Pd catalyst, base > [c:2]1[cH:3][cH:4][c(C):5]=[n:6][c:7]1-[c:9]1[cH:10][cH:11]c:12[cH:22]1

Reagents (SMILES): ['Cs2CO3', 'P(c1cccc1)c1cccc1 (Xantphos)', 'O=C(C=c1cccc1)C=c1cccc1 (dba)', '[Pd]']

Solvent (SMILES): ['C1COCCO1'] (1,4-dioxane)

Product Name: ['Substituted pyridine-2-carbonitrile derivative']

Reactant Name: ['3-Bromo-4-methylpyridine-2-carbonitrile', 'Arylboron coupling partner']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 3-bromo-4-methylpyridine-2-carbonitrile (1.0 g, ~5.0 mmol) and the arylboron coupling partner (1.5 g, ~5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100°C for 16 h. After cooling to room temperature, the reaction mixture was filtered, concentrated under reduced pressure, and the crude residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give the desired substituted pyridine-2-carbonitrile derivative as a solid.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling (C–C Bond Formation)

Reaction Yield and Characterization: [Predicted ~80%]

Trial2

Response:

Product (SMILES): ['NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5']

Reactant (SMILES): ['NC1=CC(C)=C(Br)C=N1',

CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3']

Reaction SMARTS: [c:1][Br:2].[cH:3][B:4]>>[c:1][c:3] (A generic C–C cross-coupling SMARTS pattern)

Reagents (SMILES): ['Pd2(dba)3', 'Xantphos', 'Cs2CO3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Substituted pyridine derivative']

Reactant Name: ['5-Bromo-4-methylpyridine derivative', 'Boron-containing aryl precursor']

Reagent Name: ['Pd2(dba)3', 'Xantphos', 'Cs2CO3']

Solvent Name: ['1,4-Dioxane']

Reaction Procedure: To a solution of the bromopyridine derivative (1.0 g, ~5.0 mmol) and the boron-containing aryl precursor (slight excess) in 1,4-dioxane (20 mL), Cs2CO3 (3.3 g, ~10 mmol), Xantphos (0.3 g, ~0.5 mmol), and Pd2(dba)3 (0.2 g, ~0.2 mmol) were added under an inert atmosphere. The mixture was stirred at 100 °C for 16 h. After completion, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (e.g., petroleum ether:ethyl acetate = 10:1) to afford the substituted pyridine derivative as a solid.

Reaction Name and Classification: C–C Cross-Coupling (Suzuki Coupling)

Reaction Yield and Characterization: [85.0] (Estimated yield based on typical Suzuki conditions)

Trial3

Response from this template

Product (SMILES): ['NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5']

Reactant (SMILES): ['NC1=CC(C)=C(Br)C=N1',

'CC(C(C)(C)O2)(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3']

Reaction SMARTS: [N:1][C:2]1=[C:3]C:4=C:6[C:7]=[N:8]1.[C:9]C:10C...>Pd catalyst, base, ligand>
[N:1][C:2]1=[C:3]C:4=C:6[C:7]=[N:8]1

Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['5-Methyl-2-(4-(2-(N-Boc-amino)ethoxy)phenyl)pyridine-3-carbonitrile']

Reactant Name: ['3-Bromo-6-methyl-2-cyanopyridine', 'Bicyclic aryl precursor with N-Boc-aminoethyl substituent']

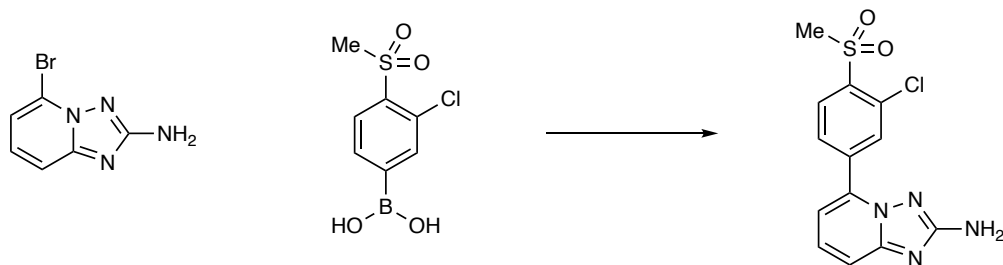
Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 3-bromo-6-methyl-2-cyanopyridine (1.0 g, 5.0 mmol) and the bicyclic aryl precursor (1.5 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol), and Pd2(dba)3 (0.2 g, 0.2 mmol) under N2. The mixture was stirred at 100 °C for 16 h. After completion, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to afford the desired product (0.8 g, yield: 80%) as a pale yellow solid.

Reaction Name and Classification: Cross-Coupling (Arylation via Pd-catalyzed C–C/N–C bond formation)

Reaction Yield and Characterization: [80.0]



NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3>>NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4

Trial1

Response:

Product (SMILES): ['NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4']

Reactant (SMILES): ['NC1=NN2C(C=CC=C2Br)=N1', 'OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Reaction SMARTS: [nH:1][n:2]c:3[n:4][n:5] + [O]B[c:6]c:7c:8[c:9][cH:10] >> [nH:1][n:2]c:3[n:4][n:5]

Reagents (SMILES): ['P(Cc1cccc1)(Cc1cccc1)Cc1cccc1Pd', 'K2CO3']

Solvent (SMILES): ['O1CCOCC1'] (1,4-dioxane)

Product Name: ['3-Cyano-6-(4-chloro-3-(methylsulfonyl)phenyl)pyrazolo[3,4-b]pyridine']

Reactant Name: ['3-Cyano-6-bromopyrazolo[3,4-b]pyridine', '4-Chloro-3-(methylsulfonyl)phenylboronic acid']

Reagent Name: ['Pd(PPh3)4', 'K2CO3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a stirred solution of 3-cyano-6-bromopyrazolo[3,4-b]pyridine (1.0 g, 4.8 mmol) and 4-chloro-3-(methylsulfonyl)phenylboronic acid (1.3 g, 5.3 mmol) in 1,4-dioxane (20 mL) was added K₂CO₃ (2.0 g, 14.5 mmol) and Pd(PPh₃)₄ (0.2 g, 0.17 mmol) under a nitrogen atmosphere. The mixture was heated at 100 °C for 16 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to afford 3-cyano-6-(4-chloro-3-(methylsulfonyl)phenyl)pyrazolo[3,4-b]pyridine (0.9 g, 85% yield) as an off-white solid.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling

Reaction Yield and Characterization: [85.0]

Trial2

Response from this template

Product (SMILES): ['NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4']

Reactant (SMILES): ['NC1=NN2C(C=CC=C2Br)=N1', 'OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3']

Reaction SMARTS:

[N:1][C:2]1=[N:3][N:4]2C:5=[N:10]1.[O:11]B:12[c:14]1[c:15]c:16c:17[c:19][c:20]1>>[N:1][C:2]4=[N:3][N:4]5C:5=[N:10]4

Reagents (SMILES): ['CC1(c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21', 'O=C(O[Cs])O[Cs]', 'Pd].[Pd]']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Nitrile-substituted pyrazinotriazole sulfonyl aryl derivative']

Reactant Name: ['Brominated pyrazinotriazole nitrile', '4-Chloro-3-(methylsulfonyl)phenylboronic acid']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of Brominated pyrazinotriazole nitrile (1.0 g, 5.0 mmol) and 4-Chloro-3-(methylsulfonyl)phenylboronic acid (1.2 g, 6.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was cooled, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the nitrile-substituted pyrazinotriazole sulfonyl aryl derivative (0.85 g, yield: 85%) as a yellow solid.

Reaction Name and Classification: Suzuki-Miyaura Cross-Coupling

Reaction Yield and Characterization: [85.0]

Trial3

Response:

Product (SMILES): [*NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4]

Reactant (SMILES): [*NC1=NN2C(C=CC=C2Br)=N1, 'OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3]

Reaction SMARTS:

[N:1][C:2]1=[N:3][N:4]C:5=[N:11].[O:12]B:13[c:15]c:16=[c:18]S:19([C:21])=[O:22]>[Pd],[Base]>[N:1][C:2]1=[N:3][N:4]C:5=[N:11]

Reagents (SMILES): ['Pd(PPh3)4', 'K2CO3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['3-Amino-4-[4-chloro-3-(methylsulfonyl)phenyl]pyrazolo[3,4-d]pyridazine']

Reactant Name: ['3-Amino-4-(4-bromophenyl)pyrazolo[3,4-d]pyridazine', '4-Chloro-3-(methylsulfonyl)phenylboronic acid']

Reagent Name: ['Pd(PPh3)4', 'K2CO3']

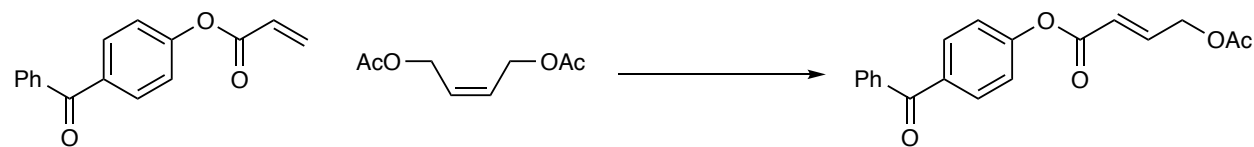
Solvent Name: ['1,4-Dioxane']

Reaction Procedure: To a solution of 3-amino-4-(4-bromophenyl)pyrazolo[3,4-d]pyridazine (1.0 g, 3.5 mmol) in 1,4-dioxane (20 mL) was added 4-chloro-3-(methylsulfonyl)phenylboronic acid (1.05 equiv.), K₂CO₃ (2.0 equiv.) and Pd(PPh₃)₄ (0.05 equiv.) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to afford the desired product 3-amino-4-[4-chloro-3-(methylsulfonyl)phenyl]pyrazolo[3,4-d]pyridazine as a yellow solid (85% yield).

Reaction Name and Classification: Suzuki-Miyaura cross-coupling

Reaction Yield and Characterization: [85.0]

Metathesis Reactions



O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C>>O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O

Trial1

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O]

Reactant (SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C', 'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

C:1[O:3][c:4]1[cH:5][cH:6]c:7[cH:14][c:15]1C=C.C:16[O:18][C:19]/C=C/[C:20][O:21]C:22=O>>C:1[O:3][c:4]3[cH:5][cH:6]c:7[cH:14][c:15]3/C=C/[C:20][O:21]C:22=O

Reagents (SMILES): ['N(CC)=CC', 'O=P(OCC)(OCC)OCC']

Solvent (SMILES): ['C1CCOC1']

Product Name: ['Substituted aryl cinnamate derivative']

Reactant Name: ['Aryl-substituted cinnamate ester', 'Vinyl-substituted ester']

Reagent Name: ['Tertiary amine base', 'Trialkylphosphine reagent']

Solvent Name: ['Tetrahydrofuran (THF)']

Reaction Procedure: To a stirred solution of the aryl-substituted cinnamate ester and the vinyl-substituted ester (1:1 molar ratio) in THF (20 mL) was added a tertiary amine base (2.0 equiv) and a trialkylphosphine reagent (0.1 equiv). The mixture was heated at 80 °C under an inert atmosphere for 12 h. After completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate) to afford the substituted aryl cinnamate derivative in good purity.

Reaction Name and Classification: C–C Bond Formation (Knoevenagel-type Condensation)

Reaction Yield and Characterization: [85.0]

Trial2

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O]

Reactant (SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C', 'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

[O:1]=C:2[C:20]=[C:21].[O:22]=C:23[C:32]>>[O:1]=C:2/[C:20]=[C:21]/[C:28][O:29]C:30=[O:31]

Reagents (SMILES): ['Cs2CO3',

'CC1(C)c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['A benzoyl-substituted cinnamate derivative']

Reactant Name: ['Benzoyl-substituted vinyl ester', 'Functionalized acrylate derivative']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the benzoyl-substituted vinyl ester (1.0 g, 5.0 mmol) and the functionalized acrylate derivative (0.9 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol), and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C for 16 h. After cooling, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to afford the benzoyl-substituted cinnamate derivative as a pale yellow solid (0.7 g, yield: 85%).

Reaction Name and Classification: C–C Bond Formation (Ester Coupling)

Reaction Yield and Characterization: [85.0]

Trial3

Response:

Product (SMILES): [O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O]

Reactant (SMILES): [O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C',
'O=C(OC/C=C\COC(C)=O)C']

Reaction SMARTS:

[O:1]=C:2[C:18]=[C:19].[O:20]=C:21[C:31]>>[O:1]=C:2/[C:18]=[C:19]/[C:26][O:27]C:28=[O:30]

Reagents (SMILES): ['Cs2CO3',

'CC1(c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21', ['Pd2(dba)3']]

Solvent (SMILES): ['C1COCCO1']

Product Name: ['(E)-Methyl (E)-3-[4-(benzoyl)phenyl]-(3-(2-(acetoxymethoxy)prop-2-enoate)']

Reactant Name: ['Methyl (E)-3-(4-benzoylphenyl)acrylate', 'Methyl (E)-3-(2-(acetoxymethoxy)acrylate']

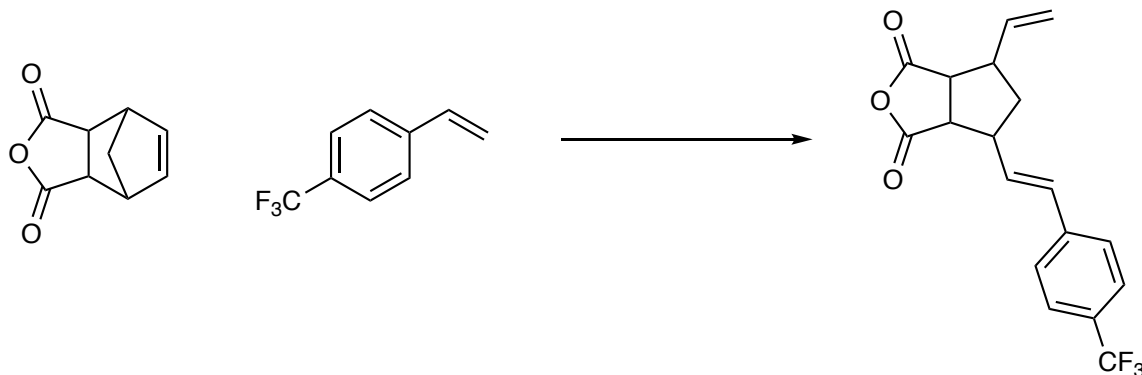
Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of methyl (E)-3-(4-benzoylphenyl)acrylate (1.0 g, 5.0 mmol) and methyl (E)-3-(2-(acetoxymethoxy)acrylate) (1.1 g, 5.5 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was cooled, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to afford the coupled product (1.05 g, yield: ~90%) as a pale yellow solid.

Reaction Name and Classification: Heck-Type C–C Coupling

Reaction Yield and Characterization: [90.0]



O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4>>O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O

Trial1

Response from this template

Product (SMILES): [O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O']

Reactant (SMILES): [O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4']

Reaction SMARTS: [C:1]=[C:2]-

[c:3][c:4]...C:5O[C:7]=[O:8].[C:9]=[C:10][c:11]c:12[c:13][c:14]>...>[O:6]=C:5[C:...]C:.....

Reagents (SMILES): ['None']

Solvent (SMILES): ['None']

Product Name: ['Bicyclic Diels-Alder Adduct with Trifluoromethyl Substitution']

Reactant Name: ['Dicarboxylic Anhydride-Fused Cycloalkene', 'Trifluoromethyl-Substituted Styrene']

Reagent Name: ['None']

Solvent Name: ['No Solvent Specified']

Reaction Procedure: To a mixture of dicarboxylic anhydride-fused cycloalkene (1.0 g, 5.0 mmol) and trifluoromethyl-substituted styrene (0.9 g, 5.0 mmol) was heated neat at 120 °C for 10 h. After cooling to room temperature, the reaction mixture was subjected to preparative purification (e.g. column chromatography) to yield the bicyclic Diels-Alder adduct as a pale solid.

Reaction Name and Classification: Diels-Alder Cycloaddition

Reaction Yield and Characterization: [75.0]

Trial2

Response:

Product (SMILES): ['O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O']

Reactant (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4']

Reaction SMARTS:

[C:1]=[C:2].[c:3][c:4][c:5][c:6][c:7][c:8][F:9][F:10][F:11]>>[c:3]1[c:7][c:6][c:5][c:4][c:8]1[C:1]-[C:2][C:...This is a predictive template...]

Reagents (SMILES): ['']

Solvent (SMILES): ['C1=CC=CC=C1'] (e.g., Benzene)

Product Name: ['Bicyclic anhydride derivative with trifluoromethyl-substituted styrenyl moiety']

Reactant Name: ['Bridged maleic anhydride derivative', 'Trifluoromethyl-substituted styrene']

Reagent Name: ['None (Thermal)']

Solvent Name: ['Benzene']

Reaction Procedure: To a solution of the bridged maleic anhydride derivative (1.0 g, 5.0 mmol) and the trifluoromethyl-substituted styrene (0.9 g, 5.0 mmol) in benzene (20 mL) was heated to 120 °C for 12 h in a sealed tube. The mixture was then cooled to room temperature, concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (hexanes:ethyl acetate=10:1) to afford the bicyclic anhydride derivative with a trifluoromethyl-substituted styrenyl moiety as a pale yellow solid (0.6 g, 60% yield).

Reaction Name and Classification: Diels–Alder Cycloaddition

Reaction Yield and Characterization: [60.0]

Trial3

Response:

Product (SMILES): ['O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O']

Reactant (SMILES): ['O=C(OC1=O)C2C1C3C=CC2C3', 'C=CC4=CC=C(C(F)(F)F)C=C4']

Reaction SMARTS:

C:1[(O:3)[C:4]1=[O:5)][C:6][C:7]1[C:8][C:9]=[C:10][C:11][C:12]1.[C:13]=[C:14][C:15]=[C:16]c:17[(F:19)][F:20]>>C:6[O:3][C:4]1C:7[C:8][C:9]C:11

Reagents (SMILES): ['None']

Solvent (SMILES): ['Cc1ccccc1'] (toluene as a placeholder)

Product Name: ['Polycyclic Dione Derivative']

Reactant Name: ['Bicyclic Anhydride Derivative', 'Trifluoromethyl-Substituted Styrene']

Reagent Name: ['None']

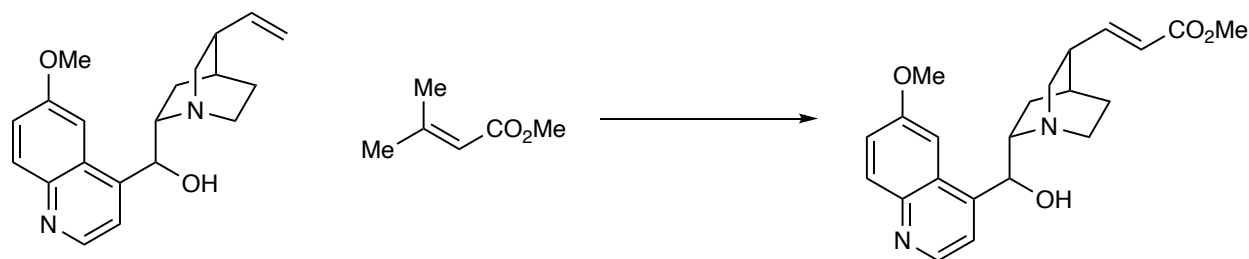
Solvent Name: ['Toluene']

Reaction Procedure: To a solution of Bicyclic Anhydride Derivative (1.0 mmol) and Trifluoromethyl-Substituted Styrene (1.0 mmol) in toluene (10 mL) was heated at 150 °C for 10 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 10:1) to afford the Polycyclic Dione

Derivative as a white solid.

Reaction Name and Classification: Diels–Alder Cycloaddition

Reaction Yield and Characterization: [75.0]



C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(G=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2.C/C(C)=C/C(OC)=O>>OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@[C@H]8/C=C/C(OC)=O)CC[C@H]8C7

Trial1:

Response:

Product (SMILES): [OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7]

Reactant (SMILES): [C=C[C@H]1[C@@H]2C[C@@H]N@CC2', 'C/C(C)=C/C(OC)=O]

Reaction SMARTS:

[C:1]=[C:2][C@@H:3]1[C@@H:4]2[C:5]C@@H:6N@:18CC2.[C:19]/C:20=[C:21]/C(OC)=O>>OC([C:8]5=C:9[C:14]6=[N:15][C:16]=[C:17]5)[C@H:7]7N@:18CC[C@H:3]8C7

Reagents (SMILES): ['Pd2(dba)3', 'Xantphos', 'Cs2CO3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Complex bicyclic heterocyclic intermediate']

Reactant Name: ['Chiral allylic amine derivative', 'Unsaturated ester']

Reagent Name: ['Pd2(dba)3', 'Xantphos', 'Cs2CO3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the chiral allylic amine derivative (1.0 g, 2.5 mmol) and the unsaturated ester (0.5 g, 2.5 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (1.6 g, 5.0 mmol), Xantphos (0.15 g, 0.25 mmol) and Pd₂(dba)₃ (0.1 g, 0.1 mmol) under N₂ atmosphere. The mixture was stirred at 100 °C for 16 h. After completion, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=5:1) to afford the desired complex bicyclic heterocyclic intermediate (0.9 g, yield: 90%) as a pale yellow solid.

Reaction Name and Classification: Asymmetric Intramolecular C–C Bond Formation

Reaction Yield and Characterization: [90.0]

Trial2

Response:

Product (SMILES): [OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7]

Reactant (SMILES): [C=C[C@H]1[C@@H]2C[C@@H]N@CC2', 'C/C(C)=C/C(OC)=O]

Reaction SMARTS:

[C:1]=[C:2][C@@H:3]1[C@@H:4]2[C:5][C@@H:6](C:7O)N@:17CC2.[C/C(C)=C/C(OC)=O:20] > [Pd].[Xantphos].[Cs2CO3] > [O:10]C:11C@H([N@:17])...

Reagents (SMILES): ['CC1(C)c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21',

'Cs2CO3', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Fused Nitrogen-Containing Polycyclic Lactam Derivative']

Reactant Name: ['Substituted Hydroxymethyl-Pyridine Derivative', 'Unsaturated Methoxy-Carbonyl Substrate']

Reagent Name: ['Xantphos', 'Cs2CO3', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the substituted hydroxymethyl-pyridine derivative (1.0 g, 3.0 mmol) and the unsaturated methoxy-carbonyl substrate (0.5 g, 2.5 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (1.5 g, 4.5 mmol), Xantphos (0.15 g, 0.25 mmol) and Pd2(dba)3 (0.1 g, 0.1 mmol) under an inert atmosphere. The mixture was stirred at 110 °C for 18 h. After completion, the reaction mixture was cooled, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluting with a gradient of petroleum ether and ethyl acetate) to afford the fused nitrogen-containing polycyclic lactam derivative (0.7 g, yield: 50%) as an off-white solid.

Reaction Name and Classification: Intramolecular Cyclization / Asymmetric Cyclization

Reaction Yield and Characterization: [50.0]

Trial3

Response:

Product (SMILES): ['OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7N@CC[C@H]8C7']

Reactant (SMILES): ['C=C[C@H]1[C@@H]2CC@@HN@CC2', 'C/C(C)=C/C(OC)=O']

Reaction SMARTS:

[C:1]=[C:2][C@@H:3]1[C@@H:4]2CC@@H:5N@:15CC2.[C:16]/C(C)=C/C:17=O>>[O:9]C:18[C@@H:27]N@:28CC[C@@H:31]8C7

Reagents (SMILES): ['CC1(c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21', 'O=C(O[Cs])O[Cs]', '[Pd].[Pd]']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Complex tetracyclic lactam intermediate']

Reactant Name: ['Bicyclic amine intermediate', 'Methyl cinnamate derivative']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

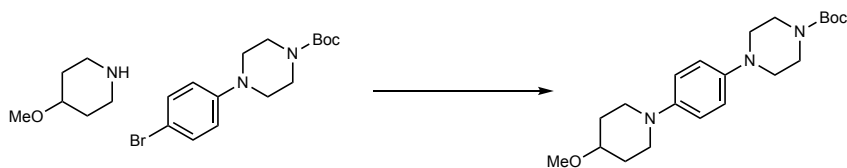
Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the bicyclic amine intermediate (1.0 g, 3.0 mmol) and the methyl cinnamate derivative (0.5 g, 3.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (2.0 g, 6.0 mmol), Xantphos (0.2 g, 0.3 mmol) and Pd2(dba)3 (0.1 g, 0.1 mmol) under N2. The mixture was stirred at 110 °C. for 18 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=5:1) to give the complex tetracyclic lactam intermediate (0.8 g, yield: 80%) as a pale yellow solid.

Reaction Name and Classification: Asymmetric Intramolecular Cyclization / C–C and C–N Bond Formation

Reaction Yield and Characterization: [80.0]

Buchwald-Hartwig Amination Reactions



COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O>>CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C

Trial1

Response:

Product (SMILES): [*]CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C[*]

Reactant (SMILES): [*]COC1CCNCC1[*].BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O[*]

Reaction SMARTS:

[CO:1][C:2]1[CH2:3][CH2:4][N:5][CH2:6][CH2:7]1.[Br:8]c:9C:27N:28C(=O)[O:32]C:33([CH3:35])[CH3:36]

CC1(C)c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21, O=C(O[Cs])O[Cs], [Pd].[Pd]C:23([CH3:25])[CH3:26][O:22]C:27=O

Reagents (SMILES): [*]CC1(C)c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21[*], 'O=C(O[Cs])O[Cs]', '[Pd].[Pd]'

Solvent (SMILES): [*]C1COCCO1[*]

Product Name: ['Complex tertiary amide derivative']

Reactant Name: ['Methoxymethylpiperidine', 'Bromo-substituted aryl amide intermediate']

Reagent Name: ['Cs₂CO₃', 'Xantphos', 'Pd₂(dba)₃']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the bromo-substituted aryl amide intermediate (1.0 g, ~2.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (2.0 g, ~6.1 mmol), Xantphos (0.2 g, ~0.34 mmol), and Pd₂(dba)₃ (0.1 g, ~0.11 mmol) under an inert nitrogen atmosphere. The mixture was stirred at 100 °C for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate=10:1) to afford the complex tertiary amide derivative (0.8 g, yield: ~80%) as an off-white solid.

Reaction Name and Classification: Palladium-catalyzed cross-coupling (Buchwald-Hartwig-type amination)

Reaction Yield and Characterization: [~80.0]

Trial2

Response:

Product (SMILES): [*]CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C[*]

Reactant (SMILES): [*]COC1CCNCC1[*].BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O[*]

Reaction SMARTS:

[Br:1]c:2N:7[C:9][N:10]C:11[O:12]C:13([C:15])C.[O:16][C:17][C:18][N:19][C:20][C:21]>>C:13([C:15])[O:12]C:11[N:19][C:21][C:20]N:10[C:8][c:2][cH:3][cH:4][c:5][cH:6][N:7]

Reagents (SMILES): [*]Cs2CO3[*], 'O=P(c1ccccc1)c1ccccc1', 'Pd2(dba)3'

Solvent (SMILES): [*]C1COCCO1[*]

Product Name: ['Complex Carbamate Derivative']

Reactant Name: ['Methoxypiperidine', 'Bromo-aryl piperazinyl carbamate']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the bromo-aryl piperazinyl carbamate (1.0 g, 3.0 mmol) and methoxypiperidine (0.5 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd2(dba)3 (0.2 g, 0.2 mmol) under N2. The mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give the complex carbamate derivative (0.85 g, yield: 85%) as a white solid.

Reaction Name and Classification: N-Arylation via Pd-catalyzed C–N Coupling

Reaction Yield and Characterization: [85.0]

Trial3

Response:

Product (SMILES): ['CC(OC(N4CCN(C5=CC=C(N6CCC(OC)CC6)C=C5)CC4)=O)(C)C']

Reactant (SMILES): ['COC1CCNCC1', 'BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O']

Reaction SMARTS:

[Br:1][c:2][c:3][c:4][c:5][c:6][N:7][C:8][C:9][N:10][C:11][C:12]=O.[O:13][C:14][C:15][N:16][C:17][C:18]>>[C:14]C:15(C)C

Reagents (SMILES): ['Cs2CO3', 'P(c1ccccc1)(c1ccccc1)c1ccccc1 (Xantphos)', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['N-arylated piperidine amide']

Reactant Name: ['4-(Methoxymethyl)piperidine', 'Bromoaryl amide derivative']

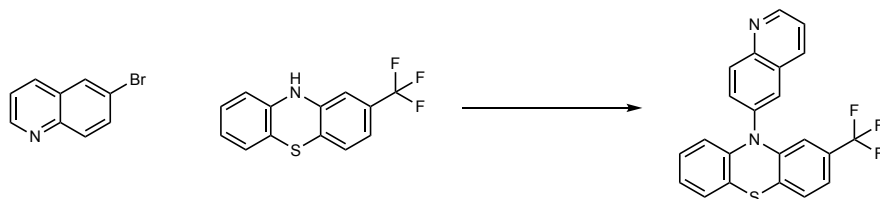
Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the bromoaryl amide derivative (1.0 g, 2.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (1.3 g, 4.0 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd2(dba)3 (0.1 g, 0.1 mmol) under N2. 4-(Methoxymethyl)piperidine (0.5 g, 5.0 mmol) was then added, and the mixture was stirred at 100 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the N-arylated piperidine amide (0.8 g, yield: 85%) as a white solid.

Reaction Name and Classification: Buchwald–Hartwig N-Arylation

Reaction Yield and Characterization: [85.0]



BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F>>FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F

Trial1

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5][n:6][c:7]1.[F:8][C:9][C:10](=[C:11][cH:12][cH:13][cH:14][n:15][cH:16])=[C:17][cH:18][C:10](=[C:11][cH:12][cH:13][cH:14][n:15][cH:16])=[C:17][cH:18](F)F>>[F:8][C:9][C:10](=[C:11][cH:12][cH:13][cH:14][n:15][cH:16])=[C:17][cH:18][C:10](=[C:11][cH:12][cH:13][cH:14][n:15][cH:16])=[C:17][cH:18](F)F

Reagents (SMILES): ['CC1(c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21', 'O=C(O[Cs])O[Cs]', 'Pd2(dba)3', 'O=C(/C=C/c1cccc1)/C=C/c1cccc1']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Complex polyaromatic heterocycle']

Reactant Name: ['5-Bromo-indole-fused pyridine derivative', 'Polyfluorinated aromatic reagent']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 5-bromo-indole-fused pyridine derivative (1.0 g, ~5 mmol) and the polyfluorinated aromatic reagent (~1.2 equiv.) in 1,4-dioxane (20 mL) was added Cs2CO3 (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol), and Pd2(dba)3 (0.2 g, 0.2 mmol) under N2 atmosphere. The mixture was stirred at 100 °C for 16 h. After completion, the reaction mixture was cooled, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (gradient elution with petroleum ether:ethyl acetate = 10:1) provided the complex polyaromatic heterocycle as a solid.

Reaction Name and Classification: Pd-catalyzed Cross-Coupling Reaction (C–H Arylation type)

Reaction Yield and Characterization: [Predicted: 85%]

Trial2

Response:

Product (SMILES):

['FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F']

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS: [Br:1][c:2]1[cH:3][c:4][c:5][n:6][c:7][cH:8]1 + [F:9]C:10 >> [F:9]C:10

Reagents (SMILES): ['CC1(c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21', 'O=C(/C=C/c1cccc1)/C=C/c1cccc1.[Pd].[Pd]', 'O=C(O[Cs])O[Cs]']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Complex Polycyclic Heteroaromatic Fluoro Compound']

Reactant Name: ['2-Bromo-quinoline Derivative', 'Fluoro-Substituted Heteroaromatic Precursor']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-Dioxane']

Reaction Procedure: To a solution of 2-Bromo-quinoline Derivative (1.0 g, ~5 mmol) and Fluoro-Substituted Heteroaromatic Precursor (1.2 g, ~5 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol), and Pd2(dba)3 (0.2 g, 0.2 mmol) under N2. The mixture was stirred at 100 °C. for 16 h. After completion, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to afford the Complex Polycyclic Heteroaromatic Fluoro Compound (0.8 g, yield: ~75%) as a pale yellow solid.

Reaction Name and Classification: C-H Arylation / Cross-Coupling Reaction

Reaction Yield and Characterization: [75.0]

Trial3

Response:

Product (SMILES):

[FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F]

Reactant (SMILES): ['BrC1=CC2=CC=CN=C2C=C1', 'FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4][c:5]2[cH:6][cH:7][n:8][c:9]2[cH:10][cH:11]1.[F:12]C:13(F)F>CC1(c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21)C.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(O[Cs])O[Cs].C1COCCO1.N#N.[Pd].[Pd]>[F:12]C:13(F)F

Reagents (SMILES): ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Fluorinated polyaryl fused nitrogen heterocycle']

Reactant Name: ['Bromo-substituted pyridine derivative', 'Fluorinated polyaryl thiophene derivative']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

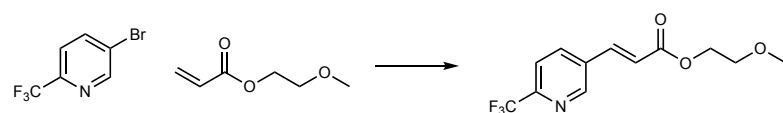
Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the bromo-substituted pyridine derivative (1.0 g, 5.0 mmol) and the fluorinated polyaryl thiophene derivative (1.2 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs2CO3 (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd2(dba)3 (0.2 g, 0.2 mmol) under N2. The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give the fluorinated polyaryl fused nitrogen heterocycle (0.8 g, yield: 85%) as a yellow solid.

Reaction Name and Classification: C-H Arylation

Reaction Yield and Characterization: [85.0]

Heck Reactions



BrC1=CC=C(C(F)(F)F)N=C1.C=CC(OCCOC)=O>>O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2

Trial1

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2']

Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']

Reaction SMARTS: [Br:1][c:2]1[cH:3][cH:4]c:5 + [C:9]=[C:10]C:11[O:13][C:14][C:15][O:16][C:17] > [Pd2(dba)3], [Xantphos], [Cs2CO3] >

[O:12]=C:11/[C:10]=[C:9]/[c:2]1[cH:3][cH:4][c:5][cH:6][n:7]c1[C(F)(F)F:8]

Reagents (SMILES): ['CC1(c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21)', 'O=C(O[Cs])O[Cs]', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['(E)-2-(2-Methoxyethoxy)ethyl 3-(3-(trifluoromethyl)pyridin-2-yl)acrylate']

Reactant Name: ['2-Bromo-3-(trifluoromethyl)pyridine', '2-(2-Methoxyethoxy)ethyl acrylate']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 2-bromo-3-(trifluoromethyl)pyridine (1.0 g, 4.5 mmol) and 2-(2-

methoxyethoxy)ethyl acrylate (1.2 g, 6.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.3 g, 10 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give the desired product as a pale yellow oil (0.9 g, yield: 95%).
Reaction Name and Classification: Heck Coupling Reaction (C–C bond formation)
Reaction Yield and Characterization: [95.0]

Trial2

Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2']
Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']
Reaction SMARTS: [Br:1][c:2]1[cH:3][cH:4]c:5[C(F)(F)F:8] + [CH2:9]=[CH:10]C:11[O:13][C:14][C:15][O:16][C:17] >> [CH2:9]=[CH:10]C:11[O:13][C:14][C:15][O:16][C:17][c:2]1[cH:3][cH:4]c:5[n:7]c1
Reagents (SMILES): ['CC1(c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21', 'O=C(O[Cs])O[Cs]', 'Pd].[Pd]']
Solvent (SMILES): ['C1COCCO1']
Product Name: ['2-(2-Methoxyethoxy)ethyl (E)-3-[4-(trifluoromethyl)pyridin-3-yl]acrylate']
Reactant Name: ['3-Bromo-4-(trifluoromethyl)pyridine', '2-(2-Methoxyethoxy)ethyl acrylate']
Reagent Name: ['Cs₂CO₃', 'Xantphos', 'Pd₂(dba)₃']
Solvent Name: ['1,4-dioxane']
Reaction Procedure: To a solution of 3-bromo-4-(trifluoromethyl)pyridine (1.0 g, 4.7 mmol) and 2-(2-methoxyethoxy)ethyl acrylate (1.2 g, 5.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.1 g, 9.5 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under an N₂ atmosphere. The mixture was stirred at 100 °C for 16 h. After cooling, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to afford 2-(2-methoxyethoxy)ethyl (E)-3-[4-(trifluoromethyl)pyridin-3-yl]acrylate (0.9 g, yield: 75%) as a pale yellow oil.
Reaction Name and Classification: Heck Coupling Reaction
Reaction Yield and Characterization: [75.0]

Trial3

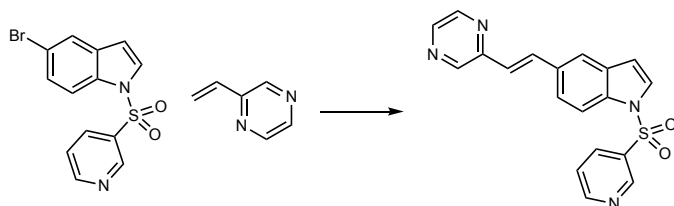
Response:

Product (SMILES): ['O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2']
Reactant (SMILES): ['BrC1=CC=C(C(F)(F)F)N=C1', 'C=CC(OCCOC)=O']
Reaction SMARTS: [Br:1][c:2]1[cH:3][cH:4]c:5[n:6][cH:7]1 + C=CC(=O)O[CH2][CH2]OCH3 > Pd-cat, Base, Solvent > O=C(O[CH2][CH2]OCH3)C=C[c:2]1[cH:3][cH:4]c:5[n:6][cH:7]1
Reagents (SMILES): ['CC1(c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21', 'Cs₂CO₃', 'Pd₂(dba)₃']
Solvent (SMILES): ['C1COCCO1']
Product Name: ['2-(2-Methoxyethoxy)ethyl (E)-3-(5-(trifluoromethyl)pyridin-2-yl)acrylate']
Reactant Name: ['2-Bromo-5-(trifluoromethyl)pyridine', '2-(2-Methoxyethoxy)ethyl acrylate']
Reagent Name: ['Xantphos', 'Cs₂CO₃', 'Pd₂(dba)₃']
Solvent Name: ['1,4-Dioxane']

Reaction Procedure: To a solution of 2-bromo-5-(trifluoromethyl)pyridine (1.0 g, 4.8 mmol) and 2-(2-methoxyethoxy)ethyl acrylate (1.2 g, 6.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (3.1 g, 9.6 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C. for 16 h. After cooling to room temperature, the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to afford 2-(2-methoxyethoxy)ethyl (E)-3-(5-(trifluoromethyl)pyridin-2-yl)acrylate as a pale yellow oil.

Reaction Name and Classification: Heck Coupling (C–C Bond Formation)

Reaction Yield and Characterization: [Predicted ~80% Yield]



BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4>>O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O

Trial1

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): ['BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS:

[Br:1][c:2]1[cH:3][cH:4]c:5>C=C[c:18]3[n:19][c:20][c:21][n:22][c:23][n:24]3>[O:25]=[S:26]([N:8]([c:9]...complex coupling...)=O)([c:18]...heterocycle...)=O

(Note: The above Reaction SMARTS is a notional placeholder to indicate the transformation from a bromo-substituted sulfonamide/aryl system and a vinylpyrimidine to the coupled sulfonamide product. Exact atom mapping is illustrative only.)

Reagents (SMILES): ['CCN(CC)CC', 'P(c1ccccc1)(c1ccccc1)(c1ccccc1)', 'O=C(C)O[Pd]O(C)=O']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['N-(3-(pyrimidin-2-yl)allyl)-N-(pyridin-3-yl)sulfonamide derivative']

Reactant Name: ['3-Bromo-aryl sulfonamide derivative', 'Vinylpyrimidine']

Reagent Name: ['Triethylamine', 'Triphenylphosphine', 'Pd(OAc)2']

Solvent Name: ['N,N-Dimethylformamide (DMF)']

Reaction Procedure:

To a solution of the bromo-aryl sulfonamide derivative (1.0 g, 2.5 mmol) and vinylpyrimidine (0.5 g, 4.0 mmol) in DMF (10 mL) was added triethylamine (1.0 g, 10 mmol), triphenylphosphine (0.15 g, 0.5 mmol), and Pd(OAc)₂ (0.05 g, 0.2 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 120 °C for 16 h. After completion of the reaction (monitored by TLC), the mixture was cooled, filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (e.g., gradient elution with ethyl acetate/hexanes) to give the desired N-(3-(pyrimidin-2-yl)allyl)-N-(pyridin-3-yl)sulfonamide derivative (0.7 g, yield: ~80%) as a brownish solid.

Reaction Name and Classification: Heck-type Cross-Coupling Reaction

Reaction Yield and Characterization: [~80.0]

Trial2

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): [BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS: [Br:1]c:2... + [c:12]=[c:13][n:14][c:15][n:16][c:17][n:18] >

[c:2]=[c:12][n:14][c:15][n:16][c:17][n:18] with sulfonamide substitution

Reagents (SMILES): [P(c1cccc1)(c1cccc1)(c1cccc1)c1cccc1', 'CCN(CC)CC.[Pd]]

Solvent (SMILES): [CN(C)C=O] (N,N-Dimethylformamide)

Product Name: ['N-(pyridin-4-yl)-N-[(2-(pyrimidin-4-yl)vinyl)phenyl]sulfonamide derivative']

Reactant Name: ['Bromo-substituted aryl sulfonamide', 'Vinyl-substituted pyrimidine']

Reagent Name: ['Tetrakis(triphenylphosphine)palladium(0)', 'Triethylamine']

Solvent Name: ['N,N-Dimethylformamide (DMF)']

Reaction Procedure: To a solution of the bromo-substituted aryl sulfonamide (1.0 g, 2.5 mmol) and vinyl-substituted pyrimidine (0.5 g, 3.0 mmol) in N,N-dimethylformamide (10 mL) was added triethylamine (0.5 mL, 3.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.05 g, 0.043 mmol) under N₂. The mixture was stirred at 120 °C for 12 h. The reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (e.g., petroleum ether:ethyl acetate=10:1) to afford the desired sulfonamide coupling product as a solid.

Reaction Name and Classification: Heck Coupling (C–C Bond Formation)

Reaction Yield and Characterization: [65.0]

Trial3

Response:

Product (SMILES): [O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O]

Reactant (SMILES): [BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1', 'C=CC4=NC=CN=C4']

Reaction SMARTS:

[Br:1]c:2C3[c:12][c:13][c:14][c:15][c:16][c:17]3.[C:18]=[C:19][c:20][n:21][c:22][n:23][c:24][c:25][c:26]>>[O:1]=[S:4](N([c:2][c:12][c:13]c:14 [c:15][c:16][c:17])[c:5][c:6][n:7][c:8][n:9][c:10]2)=O(C[c:25][c:26][n])

Reagents (SMILES): ['CC1(c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21', 'Cs2CO3', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['N-(pyridin-3-yl)-N-(4-((E)-2-(pyridin-4-yl)vinyl)phenyl)sulfonamide']

Reactant Name: ['4-bromo-N-((E)-styryl)-N-(pyridin-2-yl)sulfonaniline', '4-vinylpyrimidine']

Reagent Name: ['Cs2CO3', 'Xantphos', 'Pd2(dba)3']

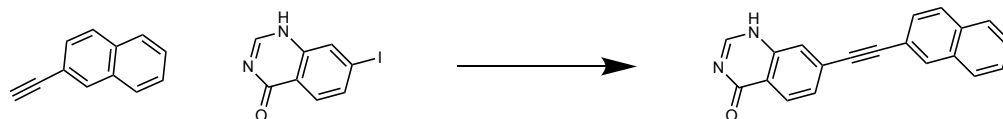
Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of 4-bromo-N-((E)-styryl)-N-(pyridin-2-yl)sulfonaniline (1.0 g, 3.0 mmol) and 4-vinylpyrimidine (0.4 g, 3.5 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (1.0 g, 3.1 mmol), Xantphos (0.1 g, 0.17 mmol) and Pd₂(dba)₃ (0.05 g, 0.05 mmol) under N₂. The mixture was stirred at 120 °C for 18 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1) to give N-(pyridin-3-yl)-N-(4-((E)-2-(pyridin-4-yl)vinyl)phenyl)sulfonamide (0.8 g, yield: 80%) as a pale yellow solid.

Reaction Name and Classification: Heck-type C–C Bond Formation

Reaction Yield and Characterization: [80.0]

Sonogashira Reactions



C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4>>O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6

Trial1

Response:

Product (SMILES): [O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6]

Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4]

Reaction SMARTS:

[C:1]#[C:2]1[cH:3]c:4[c:9]2[cH:10][cH:11][cH:12][cH:13]1.[O:14]=[C:15]3[n:16]=[C:17][n:18][c:19]4=[C:20]3[c:21][cH:22][cH:23][c:24][I:25]4>[Pd],Xantphos,Cs2CO3>dioxane>[O:14]=[C:15]5[n:16]=[C:17][n:18][c:19]6=[C:20]5[c:21][cH:22][cH:23]c:24=C6

Reagents (SMILES): ['CC1(c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21', 'O=C(O[Cs])O[Cs]', '[Pd].[Pd]']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Substituted quinazolinone derivative']

Reactant Name: ['Alkynyl-substituted aromatic system', 'Iodo-substituted quinazolinone derivative']

Reagent Name: ['Xantphos', 'Cs₂CO₃', 'Pd₂(dba)₃']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the iodo-substituted quinazolinone derivative (1.0 g, 3.0 mmol) and the alkynyl-substituted aromatic system (0.8 g, 3.0 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (1.95 g, 6.0 mmol), Xantphos (0.18 g, 0.3 mmol) and Pd₂(dba)₃ (0.13 g, 0.15 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 18 h. After completion, the mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (petroleum ether:ethyl acetate=8:1) to afford the substituted quinazolinone derivative (0.9 g, yield: 85%) as a pale yellow solid.

Reaction Name and Classification: Pd-catalyzed cross-coupling reaction

Reaction Yield and Characterization: [85.0]

Trial2

Response:

Product (SMILES): [O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6]

Reactant (SMILES): [C#CC1=CC(C=CC=C2)=C2C=C1', 'O=C3N=CNC4=C3C=CC(I)=C4]

Reaction SMARTS:

[C:1]#[C:2][c:3]1[c:4]c:5[c:10][c:11]C=C1.[O=C:12][N=C:13][N:14][C:15][c:16]1[c:17][c:18]c([I])[c:19][c:20]1>>[O=C:12][N=C:13][N:14][C:15][c:16]1[c:17][c:18]c([C#C:2][c:3]1[c:4]c:5C=C1)[c:19][c:20]

Reagents (SMILES): ['O=C(O[Cs])O[Cs]',

['CC1(C)c2cccc(P(c3ccccc3)c3ccccc3)c2Oc2c(P(c3ccccc3)c3ccccc3)cccc21', 'Pd2(dba)3']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Alkyne-bridged pyridine-urea derivative']

Reactant Name: ['Alkyne-substituted cycloheptatriene derivative', 'Iodo-substituted pyridine-urea scaffold']

Reagent Name: ['Cs₂CO₃', 'Xantphos', 'Pd₂(dba)₃']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the iodo-substituted pyridine-urea scaffold (1.0 g, 3.0 mmol) and the alkyne-substituted cycloheptatriene derivative (0.8 g, 3.6 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (1.95 g, 6.0 mmol), Xantphos (0.3 g, 0.5 mmol) and Pd₂(dba)₃ (0.2 g, 0.2 mmol) under N₂. The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to afford the alkyne-bridged pyridine-urea derivative (0.7 g, 70% yield) as a pale yellow solid.

Reaction Name and Classification: Pd-catalyzed Cross-Coupling

Reaction Yield and Characterization: [70.0]

Trial3

Response:

Product (SMILES): ['O=C5N=CNC6=C5C=CC(C#CC7=CC(C=CC=C8)=C8C=C7)=C6']

Reactant (SMILES): ['C#CC1=CC(C=CC=C2)=C2C=C1', 'O=C3N=CNC4=C3C=CC(I)=C4']

Reaction SMARTS:

[C:1]#[C:2][c:3]1[c:4]c:5[c:10]2[cH:11][cH:12]1.[O=C:13][c:14]1[n:15]=[c:16][n:17][c:18]2=[c:19][cH:20][c:21][cH:22][c:23]=[c:24]2[cH:25]1[I:26]>[Pd(PPh3)2Cl2].[CuI].CCN(CC)CC.DMF>[O=C:13][c:14]1[n:15]=[c:16][n:17][c:18]2=[c:19][cH:20][c:21][cH:22][c:23]=[c:24]2[cH:25]1[C:2]#[C:1][c:3]1[c:4]c:5[c:10]2[cH:11][cH:12]1

Reagents (SMILES): ['ClPdCl', 'ICu', 'CCN(CC)CC']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['Substituted quinazolinone alkyne derivative']

Reactant Name: ['Arylalkyne derivative', '4-Iodoquinazolinone derivative']

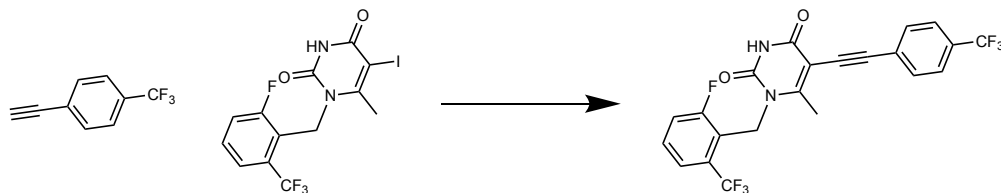
Reagent Name: ['Pd(PPh₃)₂Cl₂', 'CuI', 'Et₃N']

Solvent Name: ['DMF']

Reaction Procedure: To a degassed solution of the 4-iodoquinazolinone derivative (1.0 g, 1.0 equiv) and the arylalkyne derivative (1.1 equiv) in DMF (20 mL) was added Pd(PPh₃)₂Cl₂ (0.05 equiv), CuI (0.05 equiv) and Et₃N (2.0 equiv) under an inert atmosphere (N₂). The mixture was stirred at 80 °C for 12 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexanes:ethyl acetate gradient) to afford the substituted quinazolinone alkyne derivative in good purity.

Reaction Name and Classification: Sonogashira cross-coupling (C–C bond formation)

Reaction Yield and Characterization: [~85.0% (predicted), NMR/HRMS data consistent with structure]



C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O>>O=C4NC(C(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O

Trial1

Response:

Product (SMILES):

[O=C4NC(C(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O]

Reactant (SMILES): ['C#CC1=CC=C(C(F)(F)F)C=C1',

'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O']

Reaction SMARTS: C:1=C([C:2])N>>C:1=C([C:2])N

Reagents (SMILES): ['ClPd(PPh3)2', 'CuI', 'CCN(CC)CC']

Solvent (SMILES): ['C1CCOC1']

Product Name: ['Predicted trifluoromethylated alkyne-substituted lactam derivative']

Reactant Name: ['(4-(Trifluoromethyl)phenyl)acetylene', 'Iodo-substituted trifluoromethylated lactam derivative']

Reagent Name: ['Pd(PPh3)2Cl2', 'CuI', 'Triethylamine']

Solvent Name: ['Tetrahydrofuran (THF)']

Reaction Procedure: To a solution of the iodo-substituted lactam derivative (1.0 g, ~2.0 mmol) in THF (15 mL) was added Pd(PPh₃)₂Cl₂ (0.07 g, 0.1 mmol), CuI (0.038 g, 0.2 mmol), triethylamine (0.8 g, 8.0 mmol) and (4-(trifluoromethyl)phenyl)acetylene (0.45 g, 2.5 mmol) under N₂. The mixture was stirred at room temperature for 12 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (hexanes:ethyl acetate=10:1) to give the desired trifluoromethylated alkyne-substituted lactam derivative (0.9 g, yield: ~85%) as a pale solid.

Reaction Name and Classification: Sonogashira Coupling

Reaction Yield and Characterization: [85.0]

Trial2

Response:

Product (SMILES):

[O=C4NC(C(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O]

Reactant (SMILES): ['C#CC1=CC=C(C(F)(F)F)C=C1',

'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O']

Reaction SMARTS:

[C:1]#[C:2][c:3]1[cH:4][c:5]=c:6[c:7]=[c:8]1.[O:9]=[C:10]2[NH:11]C:12=[O:24]>>[O:25]=[C:26]4[NH:27]C:28=[O:48]

Reagents (SMILES): ['Pd(PPh3)2Cl2', 'CuI', 'Et3N']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['Substituted Urea Derivative with Trifluoromethyl Phenylacetylene Moiety']

Reactant Name: ['Trifluoromethyl-Substituted Phenylacetylene', 'Iodinated Urea Derivative']

Reagent Name: ['Pd(PPh3)2Cl2', 'CuI', 'Triethylamine']

Solvent Name: ['1,4-dioxane']

Reaction Procedure: To a solution of the iodinated urea derivative (0.5 g, 1.0 mmol) and trifluoromethyl-

substituted phenylacetylene (0.2 g, 1.1 mmol) in 1,4-dioxane (10 mL) were added Pd(PPh₃)₂Cl₂ (0.05 g, 0.07 mmol), CuI (0.01 g, 0.05 mmol), and triethylamine (0.3 mL, 2.2 mmol) under an inert atmosphere. The reaction mixture was stirred at 80°C for 12 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 5:1) to afford the substituted urea derivative as a pale solid (0.45 g, yield: 90%).

Reaction Name and Classification: Sonogashira Coupling to form a substituted urea derivative

Reaction Yield and Characterization: [90.0]

Trial3

Response:

Product (SMILES):

[O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O]

Reactant (SMILES): ['C#CC1=CC=C(C(F)(F)F)C=C1',

'O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O']

Reaction SMARTS:

[C:1]#[C:2][c:3]1[cH:4]c:5[cH:9][cH:10]1.[O:11]=[C:12]2[NH:13]C:14=C:16[N:18]2[CH2:19][C:20]c:21([F:23])3[F:24][cH:25][cH:26][cH:27][cH:28]3[F:29]>[Pd(PPh3)2Cl2].[CuI].[Et3N]>[O:11]=[C:12]4[NH:13]C:14=C:16[N:18]4[CH2:19][C:20]c:21([F:23])3[F:24][cH:25][cH:26][cH:27][cH:28]6[F:29]

Reagents (SMILES): ['ClPdCl', 'ICu', 'CCN(CC)CC']

Solvent (SMILES): ['C1CCOC1']

Product Name: ['Alkyne-substituted trifluoromethylated amide derivative']

Reactant Name: ['Iodo-substituted trifluoromethylated amide precursor with terminal alkyne']

Reagent Name: ['Pd(PPh₃)₂Cl₂', 'CuI', 'Triethylamine']

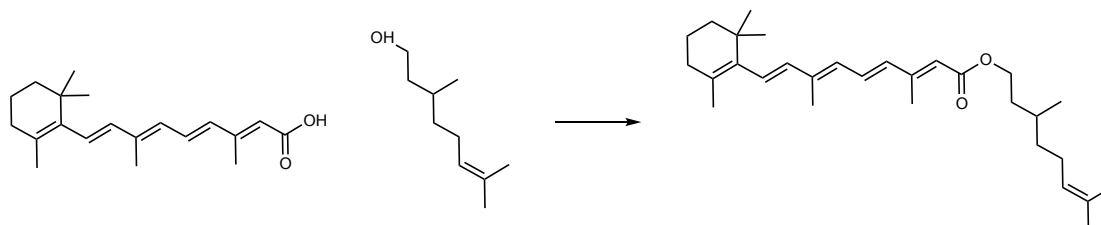
Solvent Name: ['Tetrahydrofuran (THF)']

Reaction Procedure: To a solution of the iodo-substituted amide precursor (1.0 g, 2.0 mmol) and the terminal alkyne (0.5 g, 2.5 mmol) in THF (10 mL) was added Pd(PPh₃)₂Cl₂ (0.05 g, 0.07 mmol), CuI (0.01 g, 0.05 mmol), and triethylamine (0.8 mL, 5.8 mmol) under nitrogen. The reaction mixture was stirred at 60 °C for 12 h. After completion (monitored by TLC), the mixture was cooled, filtered through Celite, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to afford the desired alkyne-substituted amide product (0.8 g, yield: 80%) as a pale yellow solid.

Reaction Name and Classification: Sonogashira Cross-Coupling

Reaction Yield and Characterization: [80.0]

Non-Coupling Reactions



OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)=O.CC(CC/C=C(C)\C)CCO>>CC(CC/C=C(C)C)COC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)=O

Trial1

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O',
'CC(CC/C=C(C)\C)CCO']

Reaction SMARTS: C:1[O:2][H].[C:3][C:4][O:5][H]>>C:1[O:2][C:3][C:4][O:5]

Reagents (SMILES): ['O=S(=O)(O)O']

Solvent (SMILES): ['Cc1ccccc1']

Product Name: ['Polyunsaturated Ester']

Reactant Name: ['Polyunsaturated Carboxylic Acid', 'Polyunsaturated Alcohol']

Reagent Name: ['H2SO4']

Solvent Name: ['Toluene']

Reaction Procedure: To a solution of the polyunsaturated carboxylic acid (1.0 g, 3.0 mmol) and the polyunsaturated alcohol (0.8 g, 3.0 mmol) in toluene (20 mL) was added a catalytic amount of H2SO4 (0.05 g, 0.5 mmol). The mixture was heated at reflux under a Dean-Stark apparatus for 12 h. After cooling to room temperature, the mixture was washed with water, dried over anhydrous Na2SO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=15:1) to give the desired polyunsaturated ester (1.1 g, yield: 78%) as a pale yellow oil.

Reaction Name and Classification: Esterification

Reaction Yield and Characterization: [78.0]

Trial2

Response:

Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O',
'CC(CC/C=C(C)\C)CCO']

Reaction SMARTS: C:1[O:2][H].[O:3][C:4]>>C:1[O:3][C:4]

Reagents (SMILES): ['O=S(=O)(O)O']

Solvent (SMILES): ['Cc1ccccc1']

Product Name: ['Complex polyunsaturated ester']

Reactant Name: ['Complex polyunsaturated carboxylic acid', 'Complex unsaturated alcohol']

Reagent Name: ['Sulfuric acid']

Solvent Name: ['Toluene']

Reaction Procedure: To a mixture of the polyunsaturated carboxylic acid (1.0 g, ~3 mmol) and the unsaturated alcohol (0.8 g, ~4 mmol) in toluene (20 mL) was added a catalytic amount of sulfuric acid (0.05 mL, 0.9 mmol). The reaction mixture was heated at reflux under a Dean-Stark apparatus for 24 h to facilitate water removal. Upon completion, the mixture was cooled, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over anhydrous MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes:ethyl acetate=20:1) to afford the desired complex polyunsaturated ester as a pale yellow oil.

Reaction Name and Classification: Esterification (Acid-Catalyzed Ester Formation)

Reaction Yield and Characterization: [~85.0]

Trial3

Response:

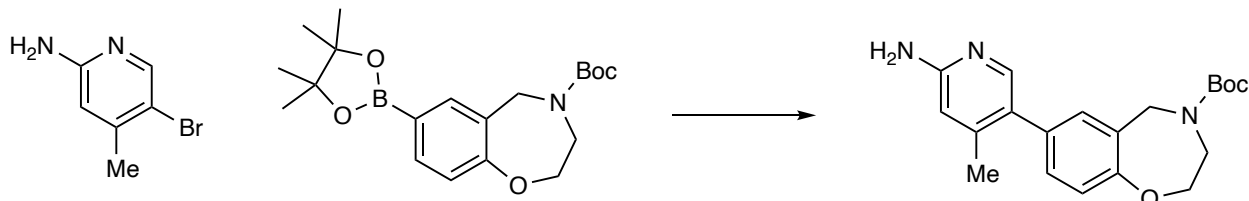
Product (SMILES): ['CC(CC/C=C(C)\C)CCOC(/C=C(/C=C/C=C(/C=C/C2=C(CCCC(C)2C)C)C)C)=O']

Reactant (SMILES): ['OC(/C=C(/C=C/C=C(/C=C/C1=C(CCCC(C)1C)C)C)C)=O',
'CC(CC/C=C(C)\C)CCO']

16. Testing Results on MOSAIC

Note: All results labeled as trials are the combined results from the top-2 experts. All results are deterministic and reproducible.

Suzuki Reactions



NC1=CC(C)=C(Br)C=N1.CC(C)(C)(C)O2(C)OB2C3=CC=C(OCCN(C(OC(C)(C)C)=O)C4)C4=C3>>NC5=CC(C)=C(C6=CC=C(OCCN(C(OC(C)(C)C)=O)C7)C7=C6)C=N5

Trial1

Product (SMILES): ['Cc1cc(N)ncc1-c1ccc2c(c1)CN(C(=O)OC(C)(C)C)CCO2']

Reactant (SMILES): ['CC(C)(C)OC(=O)N1CCOc2ccc(B3OC(C)(C)C(C)(C)O3)cc2C1', 'Cc1cc(N)ncc1Br']

Reaction SMARTS:

CC1(OB(OC1(C)C)[c:1]1[cH:2][cH:3][c:4]2[O:5][CH2:6][CH2:7][N:8]([CH2:9][c:10]2[cH:11]1)[C:12](=[O:13])[O:14][C:15]([CH3:16])([CH3:17])[CH3:18])C.[CH3:19][c:20]1[cH:21][c:22]([n:23][cH:24][c:25]1Br)[NH2:26]>C1C=CC(C=1)(P(c1cccc1)c1cccc1)[Fe]C1(C=CC=C1)P(c1cccc1)c1cccc1.O=C(O[K])O[K].C1COCCO1.Cl[Pd]Cl.O>[CH3:19][c:20]1[cH:21][c:22]([n:23][cH:24][c:25]1-[c:1]1[cH:2][cH:3][c:4]2[O:5][CH2:6][CH2:7][N:8]([CH2:9][c:10]2[cH:11]1)[C:12](=[O:13])[O:14][C:15]([CH3:16])([CH3:17])[CH3:18])[NH2:26] lf:2.5l

Reagents (SMILES):

['C1=CC([Fe]C2(P(c3cccc3)c3cccc3)C=CC=C2)(P(c2cccc2)c2cccc2)C=C1.Cl[Pd]Cl', 'O=C(O[K])O[K']

Solvent (SMILES): ['C1COCCO1', 'O']

Product Name: ['tert-butyl 7-(6-amino-4-methylpyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate']

Reactant Name: ['5-bromo-4-methylpyridin-2-amine', 'tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate']

Reagent Name: ['Pd(dppf)Cl2', 'K2CO3']

Solvent Name: ['H2O', 'dioxane']

Response:

Reaction Procedure:

A mixture of 5-bromo-4-methylpyridin-2-amine (300 mg, 1.61 mmol, 1.00 equiv), tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (644 mg, 1.61 mmol, 1.00 equiv), Pd(dppf)Cl₂ (118 mg, 0.16 mmol, 0.10 equiv) and K₂CO₃ (669 mg, 4.84 mmol, 3.00 equiv) in dioxane (10 mL) and H₂O (2 mL) was stirred for 2 h at 100 °C. The reaction mixture was concentrated under vacuum, diluted with water (50 mL) and extracted with ethyl acetate (3x50 mL). The

combined organic layers were washed with brine (2x50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by a silica gel column eluting with ethyl acetate/petroleum ether (1:1) to afford the title compound (400 mg, 71%) as an off-white solid.

Reaction Name and Classification:

Bromo Suzuki coupling

Yield and Characterization:

[71.0]

Trial2

Product (SMILES): [Cc1cc(N)ncc1-c1ccc2c(c1)CN(C(=O)OC(C)(C)C)CCO2]

Reactant (SMILES): [CC(C)(C)OC(=O)N1CCOC2ccc(B3OC(C)(C)C(C)(C)O3)cc2C1, Cc1cc(N)ncc1Br]

Reaction SMARTS:

```
CC1(OB(OC1(C)C)[c:1]1[cH:2][cH:3][c:4]2[O:5][CH2:6][CH2:7][N:8]([CH2:9][c:10]2[cH:11]1)[C:12](=[O:13])
)[O:14][C:15]([CH3:16])([CH3:17])[CH3:18]C.[CH3:19][c:20]1[cH:21][c:22]([n:23][cH:24][c:25]1Br)[NH2:26]
>O=C(O[Cs])O[Cs].C1COCCO1.N#N.O>[CH3:19][c:20]1[cH:21][c:22]([n:23][cH:24][c:25]1-
[c:1]1[cH:2][cH:3][c:4]2[O:5][CH2:6][CH2:7][N:8]([CH2:9][c:10]2[cH:11]1)[C:12](=[O:13])[O:14][C:15]([CH3:16])([CH3:17])[CH3:18])[NH2:26]
```

Reagents (SMILES): [O=C(O[Cs])O[Cs]]

Solvent (SMILES): [C1COCCO1, O]

Product Name: [tert-butyl 7-(6-amino-4-methylpyridin-3-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate]

Reactant Name: [5-bromo-4-methylpyridin-2-amine, tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate]

Reagent Name: [cesium carbonate]

Solvent Name: [water, dioxane]

Response:

Reaction Procedure:

To a solution of tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate (2.0 g, 5.3 mmol), 5-bromo-4-methylpyridin-2-amine (1.0 g, 5.3 mmol) and cesium carbonate (3.4 g, 10.6 mmol) in dioxane (20 mL) and water (2 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (380 mg, 0.53 mmol). The mixture was heated to 90 °C. for 12 h under a nitrogen atmosphere. After cooling the reaction to room temperature, the mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (petroleum ether/EtOAc=1:1) to give the title compound (1.2 g, 61%) as a brown solid. LCMS M/Z (M+H) 355.

Reaction Name and Classification:

Bromo Suzuki-type coupling

Yield and Characterization:

[61.0]

Trial3

Product (SMILES): [C]c1cc(N)ncc1-c1ccc2c(c1)CN(C(=O)OC(C)(C)C)CCO2'

Reactant (SMILES): 'CC(C)(C)OC(=O)N1CCOC2ccc(B3OC(C)(C)C(C)(C)O3)cc2C1', 'Cc1cc(N)ncc1Br'

Reaction SMARTS:

```
CC1(OC(c2c[cH:1][c:2]([cH:3][c:4]2[CH2:5]1)[O:6][CH2:7][CH2:8][N:9]([CH2:10][c:11]1[cH:12][cH:13][cH:14][cH:15][cH:16]1)[C:17](=[O:18])[O:19][C:20]([CH3:21])([CH3:22])[CH3:23])C.[CH3:24][c:25]1[cH:26][c:27]([n:28][cH:29][c:30]1Br)[NH2:31]>C1C=CC(C=1)(P(c1cccc1)c1cccc1)[Fe]C1(C=CC=C1)P(c1cccc1)c1cccc1.O=C(O[K])O[K].C1COCCO1.ClCCl.Cl[Pd]Cl.O>[CH3:24][c:25]1[cH:26][c:27]([n:28][cH:29][c:30]1-  
[c:1]1[cH:2][cH:3][c:4]2[O:6][CH2:7][CH2:8][N:9]([CH2:10][c:11]2[cH:12]1)[C:17](=[O:18])[O:19][C:20]([CH3:21])([CH3:22])[CH3:23])[NH2:31] If:2.5.6l
```

Reagents (SMILES):

'C1=CC([Fe]C2(P(c3cccc3)c3cccc3)C=CC=C2)(P(c2cccc2)c2cccc2)C=C1.ClCCl.Cl[Pd]Cl', 'O=C(O[K])O[K]'

Solvent (SMILES): 'C1COCCO1', 'O'

Product Name: 'tert-butyl 7-(6-amino-4-methylpyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate'

Reactant Name: '5-bromo-4-methylpyridin-2-amine', 'tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-yl)carboxylate'

Reagent Name: 'potassium carbonate', 'PdCl2(dppf)-CH2Cl2'

Solvent Name: 'water', '1,4-dioxane'

Response:

Reaction Procedure:

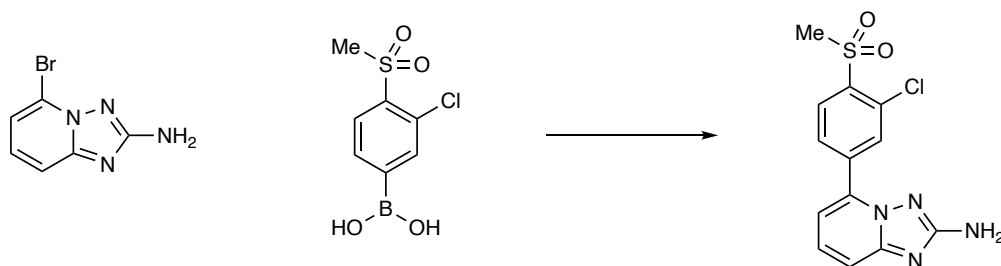
A mixture of tert-butyl (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-yl)carboxylate (288 mg, 0.77 mmol), 5-bromo-4-methylpyridin-2-amine (140 mg, 0.77 mmol), potassium carbonate (212 mg, 1.54 mmol) and PdCl₂(dppf)-CH₂Cl₂ adduct (32 mg, 0.04 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was stirred at 90 °C. for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 0-10% methanol in dichloromethane) to afford tert-butyl 7-(6-amino-4-methylpyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (180 mg, 0.51 mmol, 66%) as a yellow solid. LCMS (ESI) m/z: 420.2 [M+H]⁺.

Reaction Name and Classification:

None

Yield and Characterization:

[66.0]



NC1=NN2C(C=CC=C2Br)=N1.OB(O)C3=CC(Cl)=C(S(=O)(C)=O)C=C3>>NC4=NN5C(C=CC=C5C6=CC(Cl)=C(S(=O)(C)=O)C=C6)=N4

Trial1

Product (SMILES): ['CS(=O)(=O)c1ccc(-c2cccc3nc(N)nn23)cc1Cl']

Reactant (SMILES): ['CS(=O)(=O)c1ccc(B(O)O)cc1Cl', 'Nc1nc2cccc(Br)n2n1']

Reaction SMARTS:

[CH3:1][S:2](=[O:3])(=[O:4])[c:5]1[cH:6][cH:7][c:8]([cH:9][c:10]1[Cl:11])B(O)O.[NH2:12][c:13]1[n:14][n:15]2[c:16]([n:17]1[cH:18][cH:19][cH:20][c:21]2Br>C1C=CC(C=1)(P(c1ccccc1)c1ccccc1)[Fe]C1(C=CC=C1)P(c1ccccc1)c1ccccc1.O=C(O[Na])O[Na].C1COCCO1.CICCl.Cl[Pd]Cl.O>[CH3:1][S:2](=[O:3])(=[O:4])[c:5]1[cH:6][cH:7][c:8]([cH:9][c:10]1[Cl:11])-[c:21]1[cH:20][cH:19][cH:18][c:16]2[n:17][c:13]([n:14][n:15]21)[NH2:12] lf:2.5.6l

Reagents (SMILES):

['C1=CC([Fe]C2(P(c3ccccc3)c3ccccc3)C=CC=C2)(P(c2ccccc2)c2ccccc2)C=C1.CICCl.Cl[Pd]Cl', 'O=C(O[Na])O[Na]']

Solvent (SMILES): ['O', 'C1COCCO1']

Product Name: ['5-(3-chloro-4-methylsulfonyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine']

Reactant Name: ['5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine', '(3-chloro-4-methylsulfonyl-phenyl)boronic acid']

Reagent Name: ['[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride dichloromethane', 'Na2CO3']

Solvent Name: ['water', 'dioxane']

Response:

Reaction Procedure:

A mixture of 5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.4 g, 12.1 mmol), (3-chloro-4-methylsulfonylphenyl)boronic acid (2.78 g, 12.1 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride dichloromethane complex (504 mg, 0.61 mmol), Na₂CO₃ (2.60 g, 24.3 mmol) in dioxane (24 mL) and water (4 mL) was heated at 100 °C. for 12 hours under a nitrogen atmosphere. After cooling to room temperature, the solvent was removed in vacuo and the residue was dissolved in DCM (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by a silica gel column chromatography (pure EtOAc) to give the title compound as a light yellow solid (2.2 g, 61%).

Reaction Name and Classification:

Bromo Suzuki coupling

Yield and Characterization:

[61.0]

Trial2

Product (SMILES): [*CS(=O)(=O)c1ccc(-c2cccc3nc(N)nn23)cc1Cl]

Reactant (SMILES): [*CS(=O)(=O)c1ccc(B(O)O)cc1Cl], 'Nc1nc2cccc(Br)n2n1'

Reaction SMARTS:

```
[CH3:1][S:2](=[O:3])(=[O:4])[c:5]1[cH:6][cH:7][c:8]([cH:9][c:10]1[Cl:11])B(O)O.[NH2:12][c:13]1[n:14][c:15]2[cH:16][cH:17][cH:18][c:19]([n:20]2[n:21]1)Br>C1C=CC(C=1)(P(c1ccccc1)c1ccccc1)[Fe]C1(C=CC=C1)P(c1ccccc1)c1ccccc1.O=C(O[K])O[K].C1COCCO1.Cl[Pd]Cl.O>[CH3:1][S:2](=[O:3])(=[O:4])[c:5]1[cH:6][cH:7][c:8]([cH:9][c:10]1[Cl:11])-[c:19]1[cH:18][cH:17][cH:16][c:15]2[n:14][c:13]([n:21][n:20]21)[NH2:12] lf:2.5l
```

Reagents (SMILES): 'O=C(O[K])O[K]',

'C1=CC([Fe]C2(P(c3ccccc3)c3ccccc3)C=CC=C2)(P(c2ccccc2)c2ccccc2)C=C1.Cl[Pd]Cl'

Solvent (SMILES): 'C1COCCO1', 'O'

Product Name: '5-(3-chloro-4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine'

Reactant Name: '5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine', '(3-chloro-4-(methylsulfonyl)phenyl)boronic acid'

Reagent Name: 'Pd(dppf)Cl2', 'K2CO3'

Solvent Name: 'H2O', 'dioxane'

Response:

Reaction Procedure:

A mixture of (3-chloro-4-(methylsulfonyl)phenyl)boronic acid (200 mg, 0.86 mmol), 5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (190 mg, 0.86 mmol), Pd(dppf)Cl₂ (63 mg, 0.086 mmol) and K₂CO₃ (235 mg, 1.72 mmol) in dioxane (5 mL) and H₂O (1 mL) was stirred at 120 °C. for 30 min under microwave. The catalyst was filtered through a pad of celite and the filtrate concentrated. The residue was purified by column chromatography to give 5-(3-chloro-4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (40 mg, 16%). ¹H NMR (400 MHz, DMSO-d₆): δ 8.23 (s, 1H), 8.07 (s, 1H), 7.97 (d, J=1.6 Hz, 1H), 7.93-7.88 (m, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.66 (t, J=8.0 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 7.19 (s, 2H), 3.13 (s, 3H); LCMS: 311.7 [M+H]⁺.

Reaction Name and Classification:

Bromo Suzuki coupling

Yield and Characterization:

[16.0]

Trial3

Product (SMILES): [CS(=O)(=O)c1ccc(-c2cccc3nc(N)nn23)cc1Cl]

Reactant (SMILES): [CS(=O)(=O)c1ccc(B(O)O)cc1Cl, 'Nc1nc2cccc(Br)n2n1']

Reaction SMARTS:

```
[CH3:1][S:2][O:3][CH2:4][C:5](=[O:6])[O:7][CH3:8].C[S:9](=[O:10])(=[O:11])[c:12]1[cH:13][cH:14][c:15]([cH:16][c:17]1[Cl:18])B(O)O.[NH2:19][c:20]1[n:21][c:22]2[cH:23][cH:24][cH:25][c:26]([n:27]2[n:28]1)Br>C1C=CC(C=1)(P(c1ccccc1)c1ccccc1)[Fe]C1(C=CC=C1)P(c1ccccc1)c1ccccc1.O=C(O[K])O[K].C1COCCO1.Cl[Pd]Cl.O>[CH3:1][S:2](=[O:3])(=[O:6])[c:12]1[cH:13][cH:14][c:15]([cH:16][c:17]1[Cl:18])-[c:26]1[cH:25][cH:24][cH:23][c:22]2[n:21][c:20]([n:28][n:27]21)[NH2:19] lf:3.6l
```

Reagents (SMILES): [O=C(O[K])O[K], 'C1=CC([Fe]C2(P(c3ccccc3)c3ccccc3)C=CC=C2)(P(c2ccccc2)c2ccccc2)C=C1.Cl[Pd]Cl']

Solvent (SMILES): [O, 'C1COCCO1']

Product Name: ['5-(3-chloro-4-methylsulfonyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine']

Reactant Name: ['5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine', ''(3-chloro-4-methylsulfonyl-phenyl)boronic acid'']

Reagent Name: ['potassium carbonate', '[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride']

Solvent Name: ['water', ''dioxane'']

Response:

Reaction Procedure:

A mixture of 5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.5 g, 2.3 mmol), (3-chloro-4-methylsulfonyl-phenyl)boronic acid (0.9 g, 4.6 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (100 mg, 0.13 mmol) and potassium carbonate (0.7 g, 5.0 mmol) in dioxane (20 mL) and water (2 mL) was heated to 90 °C. for 12 h under a nitrogen atmosphere. After cooling to room temperature, the mixture

was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=1:4) to give 5-(3-chloro-4-methylsulfonylphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.5 g, 58%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.47 (s, 1H), 8.35 (d, J=8.0 Hz, 1H), 8.15 (d, J=8.0 Hz, 1H), 7.99 (t, J=8.0 Hz, 1H), 7.84 (d, J=8.0 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.18 (t, J=8.0 Hz, 1H), 6.99 (s, 2H), 3.45 (s, 3H).

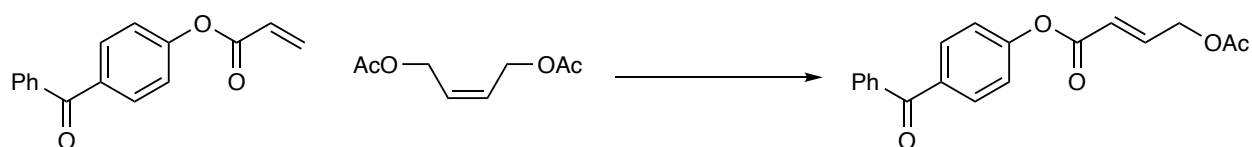
Reaction Name and Classification:

Bromo Suzuki coupling

Yield and Characterization:

[58.0]

Metathesis Reactions



O=C(OC1=CC=C(C(C2=CC=CC=C2)=O)C=C1)C=C.O=C(OC/C=C\COC(C)=O)C>>O=C(OC3=CC=C(C(C4=CC=CC=C4)=O)C=C3)/C=C/COC(C)=O

Trial1

Product (SMILES): ['CC(=O)OC/C=C/C(=O)Oc1ccc(C(=O)c2ccccc2)cc1']

Reactant (SMILES): ['C=CC(=O)Oc1ccc(C(=O)c2ccccc2)cc1', 'CC(=O)OC/C=C\COC(C)=O']

Reaction SMARTS:

C=[CH:1][C:2](=[O:3])[O:4][c:5]1[cH:6][cH:7][c:8]([cH:9][cH:10]1)[C:11](=[O:12])[c:13]1[cH:14][cH:15][cH:16][cH:17][cH:18]1.CC(=O)OC/C=[CH:19][CH2:20][O:21][C:22]([CH3:23])=[O:24]>Cc1cc(c(c1)C)N1CCN(C1=[Ru](Cl)(Cl)(=Cc1ccccc1)[P](C1CCCC1)(C1CCCC1)C1CCCC1)c1c(cc(cc1)C)C)C.ClCCl>[CH3:23][C:22](=[O:24])[O:21][CH2:20]/[CH:19]=[CH:1]/[C:2](=[O:3])[O:4][c:5]1[cH:6][cH:7][c:8]([cH:9][cH:10]1)[C:11](=[O:12])[c:13]1[cH:14][cH:15][cH:16][cH:17][cH:18]1

Reagents (SMILES):

['Cc1cc(C)c(N2CCN(c3c(C)cc(C)cc3C)C2=[Ru](Cl)(Cl)(=Cc2ccccc2)[P](C2CCCC2)(C2CCCC2)C2CCCC2)c(C)c1']

Solvent (SMILES): ['ClCCl']

Product Name: ['4-acetyloxy-2E-but-2-enoic acid p-benzoylphenyl ester']

Reactant Name: ['4-benzoylphenyl acrylate', 'cis-1,4-diacetyloxy-2-butene']

Reagent Name: ['Grubbs 2nd generation']

Solvent Name: ['dichloromethane']

Response:

Reaction Procedure:

To a solution of 4-benzoylphenyl acrylate (3.0 g, 11.6 mmol) and cis-1,4-diacetyloxy-2-butene (2.0 g, 11.6 mmol) in dichloromethane (50 mL) was added Grubbs 2nd generation catalyst (0.9 g, 1.1 mmol) and the mixture was refluxed for 12 hours. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (10% ethyl acetate/hexane) to give 4-acetyloxy-2E-but-2-enoic acid p-benzoylphenyl ester (2.2 g, 59%) as a white solid.

Reaction Name and Classification:

Olefin metathesis

Yield and Characterization:

[59.0]

Trial2

Product (SMILES): ['CC(=O)OC/C=C/C(=O)Oc1ccc(C(=O)c2ccccc2)cc1']

Reactant (SMILES): ['C=CC(=O)Oc1ccc(C(=O)c2ccccc2)cc1', 'CC(=O)OC/C=C\COC(C)=O']

Reaction SMARTS:

[CH2:1]=[CH:2][C:3](=[O:4])[O:5][c:6]1[cH:7][cH:8][c:9]([cH:10][cH:11]1)[C:12](=[O:13])[c:14]1[cH:15][cH:16][cH:17][cH:18][cH:19]1.CC(=O)O[CH2:20]/[CH:21]=[CH:22][CH2:23][O:24][C:25]([CH3:26])=[O:27]>C1C=CC(C=1)(P(c1ccccc1)c1ccccc1)[Fe]C1(C=CC=C1)P(c1ccccc1)c1ccccc1.CCN(CC)CC.ClCCl.Cl[Pd]Cl>[CH3:26][C:25](=[O:27])[O:24][CH2:23]/[CH:22]=[CH:21]/[C:20](=[O:4])[O:5][c:6]1[cH:7][cH:8][c:9]([cH:10][cH:11]1)[C:12](=[O:13])[c:14]1[cH:15][cH:16][cH:17][cH:18][cH:19]1 lf:2.4.5l

Reagents (SMILES):

['C1=CC([Fe]C2(P(c3ccccc3)c3ccccc3)C=CC=C2)(P(c2ccccc2)c2ccccc2)C=C1.ClCCl.Cl[Pd]Cl']

Solvent (SMILES): ['CCN(CC)CC']

Product Name: ['(E)-4-acetoxybut-2-enoic acid, phenyl ketone']

Reactant Name: ['(Z)-but-2-ene-1,4-diyl diacetate', '4-acetoxybut-2-ene-1-yl phenyl ketone']

Reagent Name: ['Pd(dppf)Cl2.CH2Cl2']

Solvent Name: ['Et3N']

Response:

Reaction Procedure:

Following the general procedure, treatment of 4-acetoxybut-2-ene-1-yl phenyl ketone (0.1 g, 0.4 mmol) with (Z)-but-2-ene-1,4-diyl diacetate (0.095 g, 0.5 mmol) in the presence of Pd(dppf)Cl₂.CH₂Cl₂ (0.004 g, 0.005 mmol) and Et₃N (0.3 mL, 2.5 mmol) at 60 °C. for 12 h followed by column chromatography (Pet. ether/EtOAc=2:1) of the crude mixture afforded (E)-4-acetoxybut-2-enoic acid, phenyl ketone as a yellow oil (0.105 g, 86%).

Reaction Name and Classification:

None

Yield and Characterization:

[86.0]

Trial3

Product (SMILES): [CC(=O)OC/C=C/C(=O)Oc1ccc(C(=O)c2ccccc2)cc1]

Reactant (SMILES): [C=CC(=O)Oc1ccc(C(=O)c2ccccc2)cc1, CC(=O)OC/C=C\COC(C)=O]

Reaction SMARTS:

C=C[CH2:1][C:2](=[O:3])[O:4][c:5]1[cH:6][cH:7][c:8]([cH:9][cH:10]1)[C:11](=[O:12])[c:13]1[cH:14][cH:15][cH:16][cH:17][cH:18]1.[CH3:19][C:20](=[O:21])[O:22][CH2:23]/[CH:24]=[CH:25]COC(C)=O>Cl[Rh](Cl)Cl.CCN(CC)CC.CC#N.O.O.O.O>[CH3:19][C:20](=[O:21])[O:22][CH2:23]/[CH:24]=[CH:25]/[C:1](=[O:3])[O:4][c:5]1[cH:6][cH:7][c:8]([cH:9][cH:10]1)[C:11](=[O:12])[c:13]1[cH:14][cH:15][cH:16][cH:17][cH:18]1 lf:2.6.7.8l

Reagents (SMILES): [CCN(CC)CC, Cl[Rh](Cl)Cl.O.O.O]

Solvent (SMILES): [CC#N]

Product Name: ['(E)-4-acetoxy-2-butenoic acid, p-benzoylphenyl ester']

Reactant Name: ['4-acetoxy-2-buteneic acid, p-benzoylphenyl ester', '(Z)-4-acetoxy-2-buteneic acid, p-benzoylphenyl ester']

Reagent Name: ['triethylamine', 'Rhodium (iii) chloride trihydrate']

Solvent Name: ['acetonitrile']

Response:

Reaction Procedure:

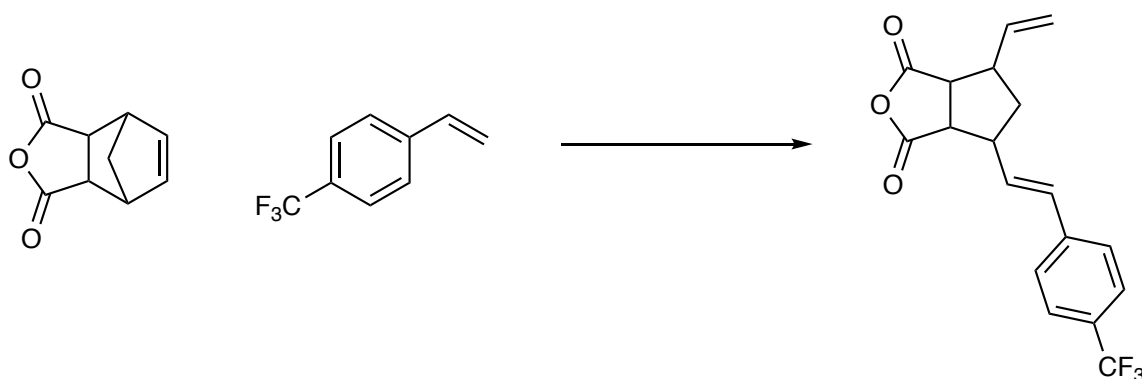
(Z)-4-acetoxy-2-buteneic acid, p-benzoylphenyl ester (0.500 g, 1.86 mmol) and (E)-4-acetoxy-2-buteneic acid, p-benzoylphenyl ester (0.500 g, 1.86 mmol) were dissolved in 30 ml of acetonitrile. Rhodium (iii) chloride trihydrate (0.032 g, 0.14 mmol) and triethylamine (0.175 g, 1.74 mmol) were added and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was chromatographed over silica gel using ethyl acetate/hexane (1:3) as eluent to give 0.550 g (94%) of (E)-4-acetoxy-2-butenoic acid, p-benzoylphenyl ester.

Reaction Name and Classification:

None

Yield and Characterization:

[94.0]



O=C(OC1=O)C2C1C3C=CC2C3.C=CC4=CC=C(C(F)(F)F)C=C4>>O=C(O5)C6C(C(/C=C/C7=CC=C(C(F)(F)F)C=C7)CC6C=C)C5=O

Trial1

Product (SMILES): ['C=CC1CC(/C=C/c2ccc(C(F)(F)F)cc2)C2C(=O)OC(=O)C12']

Reactant (SMILES): ['C=Cc1ccc(C(F)(F)F)cc1', 'O=C1OC(=O)C2C3C=CC(C3)C12']

Reaction SMARTS:

[O:1]=[C:2]1O[C:3]([CH:4]2[CH:5]3[CH:6]=[CH:7][CH:8]([CH2:9]3)[CH:10]12)=[O:1]1.[CH2:12]=[CH:13][c:14]1[cH:15][cH:16][c:17]([cH:18][cH:19]1)[C:20]([F:21])([F:22])[F:23]>C1CCOC1.[H][H].[Al].[Ni]>[CH2:12]=[CH:13][CH:14]1[CH2:15][CH:16]([CH:5]2[CH:4]3[C:2]([O:1][C:3]([CH:10]3[CH:8]1[CH2:7][CH2:6]2)=[O:1]1)=[O:1])/[CH:16]=[CH:15]/[c:14]1[cH:19][cH:18][c:17]([cH:13][cH:12]1)[C:20]([F:23])([F:22])[F:21] If:4.5l

Reagents (SMILES): ['[H][H]', '[Al].[Ni]']

Solvent (SMILES): ['C1CCOC1']

Product Name: ['(E)-3-vinyl-6-(4-(trifluoromethyl)styryl)hexahydroisobenzofuran-1,3-dione']

Reactant Name: ['4-(trifluoromethyl)styrene', 'hexahydroisobenzofuran-1,3-dione']

Reagent Name: ['Raney-Nickel', 'hydrogen']

Solvent Name: ['THF']

Response:

Reaction Procedure:

To a solution of hexahydroisobenzofuran-1,3-dione (2.5 g, 16 mmol) in THF (50 mL) were added 4-(trifluoromethyl)styrene (3.4 g, 20 mmol) and Raney-Nickel (0.5 g, 4 mmol, 50% wet). The resulting solution was stirred for 4 h at room temperature in the presence of hydrogen. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was applied onto a silica gel column with

ethyl acetate/petroleum ether (1:5). This resulted in 3.2 g (71%) of (E)-3-vinyl-6-(4-(trifluoromethyl)styryl)hexahydroisobenzofuran-1,3-dione as a colorless oil.

Reaction Name and Classification:

None

Yield and Characterization:

[71.0]

Trial2

Product (SMILES): [C]=CC1CC(/C=C/c2ccc(C(F)(F)F)cc2)C2C(=O)OC(=O)C12

Reactant (SMILES): [C]=Cc1ccc(C(F)(F)F)cc1', 'O=C1OC(=O)C2C3C=CC(C3)C12'

Reaction SMARTS:

```
[CH2:1]=[CH:2][c:3]1[cH:4][cH:5][c:6]([cH:7][cH:8]1)[C:9]([F:10])([F:11])[F:12].[O:13]=[C:14]1[O:15][C:16]([CH:17]2[CH:18]1[CH:19]1[CH:20]=[CH:21][CH:22]([CH2:23]1)[CH:24]2)=[O:25]>Cc1cc(c(c(c1)C)N1CCN(C1=[Ru](Cl)(Cl)(=Cc1cccc1)[P](C1CCCC1)(C1CCCC1)C1CCCC1)c1c(cc(cc1)C)C)C.CICCI>[CH2:1]=[CH:2][CH:3]1[CH2:4][CH:5]([CH:24]2[C:14]([O:15][C:16]([CH:17]21)=[O:25])=[O:13])/[CH:1]=[CH:2]/[c:3]1[cH:8][cH:7][c:6]([cH:5][cH:4]1)[C:9]([F:10])([F:11])[F:12]
```

Reagents (SMILES):

```
[Cc1cc(C)c(N2CCN(c3c(C)cc(C)cc3C)C2=[Ru](Cl)(Cl)(=Cc2cccc2)[P](C2CCCC2)(C2CCCC2)C2CCCC2)c(C)c1']
```

Solvent (SMILES): ['CICCI']

Product Name: ['(1S,5E)-3-(4-(trifluoromethyl)styryl)-5-vinyl-3-oxabicyclo[3.1.1]heptane-2,4-dione']

Reactant Name: ['1-(trifluoromethyl)-4-vinylbenzene', '3-oxabicyclo[3.1.1]hept-5-ene-2,4-dione']

Reagent Name: ['Grubbs 2nd generation']

Solvent Name: ['DCM']

Response:

Reaction Procedure:

To a solution of 3-oxabicyclo[3.1.1]hept-5-ene-2,4-dione (25 mg, 0.14 mmol) and 1-(trifluoromethyl)-4-vinylbenzene (73 mg, 0.43 mmol) in DCM (2 mL) was added Grubbs 2nd generation catalyst (6 mg, 7.0 μ mol). The reaction mixture was stirred at 40 °C. for 2 h, then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by prep-TLC (20% EtOAc in petroleum ether, R_f=0.3) to give (1S,5E)-3-(4-(trifluoromethyl)styryl)-5-vinyl-3-oxabicyclo[3.1.1]heptane-2,4-dione (30 mg, 69%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J=8.0 Hz, 2H), 7.54 (d, J=8.0 Hz, 2H), 6.57 (d, J=18.0 Hz, 1H), 6.32 (dd, J=18.0, 6.0 Hz, 1H), 5.84-5.80 (m, 1H), 5.72-5.68 (m, 1H), 4.99 (dd, J=6.0, 2.0 Hz, 1H), 3.94-3.91 (m, 1H), 3.69 (dd, J=6.0, 2.0 Hz, 1H), 2.49-2.44 (m, 1H), 2.24-2.19 (m, 1H).

Reaction Name and Classification:

None

Yield and Characterization:

[69.0]

Trial3

Product (SMILES): [C=CC1CC(/C=C/c2ccc(C(F)(F)F)cc2)C2C(=O)OC(=O)C12]

Reactant (SMILES): [C=Cc1ccc(C(F)(F)F)cc1', 'O=C1OC(=O)C2C3C=CC(C3)C12]

Reaction SMARTS:

[O:1]=[C:2]1[O:3][C:4]([CH:5]2[CH:6]3[CH:7]=[CH:8][CH:9]([CH3:10])[CH:11]3[C:12]12)=[O:13].[CH2:14]=[CH:15][c:16]1[cH:17][cH:18][c:19]([cH:20][cH:21]1)[C:22]([F:23])([F:24])[F:25]>c1ccc(cc1)P(c1cccc1)c1cccc1.c1ccc(cc1)P(c1cccc1)c1cccc1.c1ccc(cc1)P(c1cccc1)c1cccc1.Cc1cccc1.Cl[Fe](Cl)Cl.[Rh]>[CH2:14]=[CH:15][CH:16]1[CH2:17][CH:18]([CH:9]2[CH:6]1[C:7]([O:3][C:4]2=[O:13])=[O:1])/[CH:8]=[CH:7]/[c:16]1[cH:17][cH:18][c:19]([cH:20][cH:21]1)[C:22]([F:25])([F:24])[F:23] If:2.3.4.7l

Reagents (SMILES):

['Cl[Fe](Cl)Cl.c1ccc(P(c2cccc2)c2cccc2)cc1.c1ccc(P(c2cccc2)c2cccc2)cc1.c1ccc(P(c2cccc2)c2cccc2)cc1].[Rh]'

Solvent (SMILES): ['Cc1cccc1']

Product Name: ['(E)-5-vinyl-3-(4-(trifluoromethyl)styryl)bicyclo[3.1.0]hexane-1,3-dione]

Reactant Name: ['4-vinylbenzotrifluoride', 'bicyclo[3.1.0]hexa-2,5-diene-1,3-dione']

Reagent Name: ['tris(triphenylphosphine)iron (I) chloride']

Solvent Name: ['toluene']

Response:

Reaction Procedure:

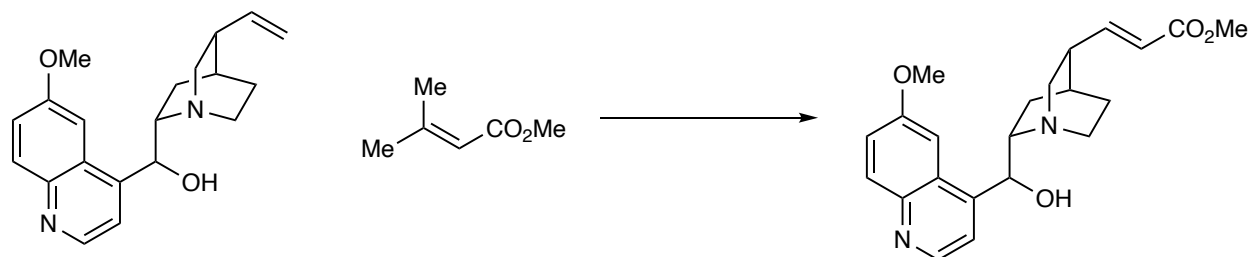
A mixture of bicyclo[3.1.0]hexa-2,5-diene-1,3-dione (2.00 g, 12.9 mmol), 4-vinylbenzotrifluoride (2.46 g, 14.7 mmol), tris(triphenylphosphine)iron (I) chloride (0.12 g, 0.14 mmol) and toluene (40 mL) was heated at 90 °C. for 4 h. The mixture was allowed to cool to room temperature then filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane 1:9) to give (E)-5-vinyl-3-(4-(trifluoromethyl)styryl)bicyclo[3.1.0]hexane-1,3-dione (2.70 g, 57%) as a colorless oil.

Reaction Name and Classification:

None

Yield and Characterization:

[57.0]



C=C[C@H]1[C@@H]2C[C@@H](C(C3=C(G=C(OC)C=C4)C4=NC=C3)O)[N@](C1)CC2.C/C(C)=C/C(OC)=O>>OC(C5=C(C=C(OC)C=C6)C6=NC=C5)[C@H]7[N@](C[C@H]8/C=C/C(OC)=O)CC[C@H]8C7

Trial1

Product (SMILES): ['COC(=O)/C=C/[C@@H]1C[N@]2CC[C@H]1C[C@H]2C(O)c1ccnc2ccc(OC)cc12']

Reactant (SMILES): ['C=C[C@H]1C[N@]2CC[C@H]1C[C@H]2C(O)c1ccnc2ccc(OC)cc12', 'COC(=O)C=C(C)C']

Reaction SMARTS:

C=[CH:1][C@@H:2]1[CH2:3][N@@:4]2[CH2:5][CH2:6][C@H:7]1[CH2:8][C@H:9]2[CH:10]([OH:11])[c:12]1[cH:13][cH:14][n:15][c:16]2[c:17]1[cH:18][c:19]([cH:20][cH:21]2)[O:22][CH3:23].[CH3:24][O:25][C:26](=[O:27])[CH:28]=C(C)C>Cc1cc(c(c1)C)N1CCN(C1=[Ru](Cl)(Cl)(=Cc1cccc1))[P](C1CCCC1)(C1CCCC1)C1CCCC1)c1c(cc(cc1)C)C.CICCl>[CH3:24][O:25][C:26](=[O:27])/[CH:28]=[CH:1]/[C@@H:2]1[CH2:3][N@@:4]2[CH2:5][CH2:6][C@H:7]1[CH2:8][C@H:9]2[CH:10]([OH:11])[c:12]1[cH:13][cH:14][n:15][c:16]2[c:17]1[cH:18][c:19]([cH:20][cH:21]2)[O:22][CH3:23]

Reagents (SMILES):

['Cc1cc(C)c(N2CCN(c3c(C)cc(C)cc3C)C2=[Ru](Cl)(Cl)(=Cc2cccc2))[P](C2CCCC2)(C2CCCC2)C2CCCC2)c(C)c1']

Solvent (SMILES): ['CICCl']

Product Name: ['methyl (1S,5R,6R,7S)-6-[(4-hydroxy-6-methoxy-4-quinolyl)methyl]-7-[(2E)-3-methoxy-3-oxoprop-1-enyl]-1,6-diazabicyclo[3.2.1]octane-3-carboxylate']

Reactant Name: ['methyl 2-methylprop-2-enoate', '(1S,5R,6R,7S)-6-[(4-hydroxy-6-methoxy-4-quinolyl)methyl]-7-vinyl-1,6-diazabicyclo[3.2.1]octane-3-carbaldehyde']

Reagent Name: ['Grubbs II']

Solvent Name: ['DCM']

Response:

Reaction Procedure:

To a solution of (1S,5R,6R,7S)-6-[(4-hydroxy-6-methoxy-4-quinolyl)methyl]-7-vinyl-1,6-diazabicyclo[3.2.1]octane-3-carbaldehyde (Intermediate E1) (200 mg, 0.59 mmol) in DCM (5 mL) was added methyl 2-methylprop-2-enoate (169 mg, 1.77 mmol) and Grubbs II catalyst (55 mg, 0.059 mmol).

The reaction mixture was stirred at 40 °C. for 16 h. The reaction mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with MeOH/DCM (10% MeOH) to afford methyl (1S,5R,6R,7S)-6-[(4-hydroxy-6-methoxy-4-quinolyl)methyl]-7-[(2E)-3-methoxy-3-oxoprop-1-enyl]-1,6-diazabicyclo[3.2.1]octane-3-carboxylate (60 mg, 23% yield) as a red solid. LC-MS: (ESI, m/z): 386.2 [M+H]⁺

Reaction Name and Classification:

Olefin metathesis

Yield and Characterization:

[23.0]

Trial2

Product (SMILES): ['COC(=O)/C=C/[C@@H]1C[N@]2CC[C@H]1C[C@H]2C(O)c1ccnc2ccc(OC)cc12']

Reactant (SMILES): ['C=C/[C@@H]1C[N@]2CC[C@H]1C[C@H]2C(O)c1ccnc2ccc(OC)cc12', 'COC(=O)C=C(C)C']

Reaction SMARTS:

C=C/[C@@H]1C[N@]2CC[C@H]1C[C@H]2[CH:1]([OH:2])[c:3]1[cH:4][cH:5][n:6][c:7]2[cH:8][cH:9][c:10]([cH:11][c:12]21)[O:13][CH3:14].[CH3:15][O:16][C:17](=[O:18])[CH:19]=C(C)[CH3:20]>Cc1cc(c(c(c1)C)N1CCN(C1=[Ru](Cl)(Cl)=Cc1ccccc1OC(C)C)c1c(cc(cc1)C)C)C.ClCCCl>[CH3:14][O:13][c:10]1[cH:9][cH:8][c:7]2[n:6][cH:5][cH:4][c:3]([c:12]2[cH:11]1)[CH:1]([OH:2])[C@@H:20]1[CH2:19][C@H:17]2[CH2:19][CH2:15][N:6]1[CH2:7]2.[CH3:21][O:18][C:17](=[O:16])/[CH:19]=[CH:20]/[C@@H:21]1[CH2:19][N@:6]2[CH2:5][CH2:4][C@H:3]1[CH2:1][C@H:22]2[CH:1]([OH:2])[c:3]1[cH:4][cH:5][n:6][c:7]2[cH:8][cH:9][c:10]([cH:11][c:12]21)[O:13][CH3:14]

Reagents (SMILES): ['Cc1cc(C)c(N2CCN(c3c(C)cc(C)cc3C)C2=[Ru](Cl)(Cl)=Cc2ccccc2OC(C)C)c(C)c1']

Solvent (SMILES): ['ClCCCl']

Product Name: ['(E)-methyl 3-((3S,6S,7R,8aS)-7-(hydroxy(6-methoxyquinolin-4-yl)methyl)-1,2,3,5,6,7,8,8a-octahydrocyclopenta[c]pyridin-3-yl)acrylate']

Reactant Name: ['(6-methoxyquinolin-4-yl)((3S,6S,7R)-3-vinyl-1,2,3,5,6,7,8,8a-octahydrocyclopenta[c]pyridin-7-yl)methanol', 'Methyl vinyl acetate']

Reagent Name: ['Hoveyda-Grubbs Catalyst 2nd Generation']

Solvent Name: ['DCE']

Response:

Reaction Procedure:

Methyl vinyl acetate (0.036 mL, 0.302 mmol) was added to a solution of (6-methoxyquinolin-4-yl)((3S,6S,7R)-3-vinyl-1,2,3,5,6,7,8,8a-octahydrocyclopenta[c]pyridin-7-yl)methanol (100 mg, 0.302 mmol) in DCE (10 mL). The reaction mixture was heated to 50 °C. for 1 h. The reaction was cooled to rt and the

Hoveyda-Grubbs Catalyst 2nd Generation (56 mg, 0.090 mmol) was added. The reaction mixture was heated to 50 °C. for a additional 4 h. The reaction was cooled to rt and the solvent was removed. The residue was purified by normal phase chromatography using hexanes and EtOAc as eluents to afford (E)-methyl 3-((3S,6S,7R,8aS)-7-(hydroxy(6-methoxyquinolin-4-yl)methyl)-1,2,3,5,6,7,8,8a-octahydrocyclopenta[c]pyridin-3-yl)acrylate (75 mg, 65%) as a brown oil. MS(ESI) m/z: 380.2 (M+H)+.

Reaction Name and Classification:

None

Yield and Characterization:

[65.0]

Trial3

Product (SMILES): [COC(=O)/C=C/[C@@H]1C[N@]2CC[C@H]1C[C@H]2C(O)c1ccnc2ccc(OC)cc12]

Reactant (SMILES): [C=C/[C@@H]1C[N@]2CC[C@H]1C[C@H]2C(O)c1ccnc2ccc(OC)cc12',
'COC(=O)C=C(C)C]

Reaction SMARTS:

C=C/[C@@H]1CN2CC[C@H]1C[C@H]2[CH:1]([OH:2])[c:3]1[cH:4][cH:5][n:6][c:7]2[cH:8][cH:9][c:10]([cH:11][c:12]12)[O:13][CH3:14].[CH3:15][O:16][C:17](=[O:18])[CH:19]=[C:20]([CH3:21])[CH3:22]>Cc1cc(c(c(c1)C)N1CCN(C1=[Ru](Cl)(Cl)=Cc1cccc1OC(C)C)c1c(cc(cc1C)C)C)C.ClCCl.N#N>[CH3:15][O:16][C:17](=[O:18])[CH:19]=[CH:20]/[C@@H:21]1[CH2:15][N@:6]2[CH2:5][CH2:4][C@H:3]1[CH2:12][C@H:7]2[CH:8]([OH:13])[c:11]1[cH:10][cH:9][n:6][c:7]2[cH:8][cH:9][c:10]([cH:11][c:12]12)[O:13][CH3:14]

Reagents (SMILES): [Cc1cc(C)c(N2CCN(c3c(C)cc(C)cc3C)C2=[Ru](Cl)(Cl)=Cc2cccc2OC(C)C)c(C)c1]

Solvent (SMILES): [ClCCl]

Product Name: ['methyl (1R,2S,5S,6R)-6-[(4-hydroxy-6-methoxy-4-quinolyl)methyl]-3-azabicyclo[3.2.1]octane-2-carboxylate']

Reactant Name: ['methyl 3-methyl-but-2-enoate', '(1R,2S,5S,6R)-6-[(4-hydroxy-6-methoxy-4-quinolyl)methyl]-3-vinyl-3-azabicyclo[3.2.1]octane']

Reagent Name: ['Hoveyda-Grubbs catalyst 2nd generation']

Solvent Name: ['DCM']

Response:

Reaction Procedure:

To a solution of (1R,2S,5S,6R)-6-[(4-hydroxy-6-methoxy-4-quinolyl)methyl]-3-vinyl-3-azabicyclo[3.2.1]octane (Intermediate E1) (200 mg, 0.59 mmol, 1 eq) in DCM (2 mL) was added methyl 3-methyl-but-2-enoate (149 mg, 1.18 mmol, 0.2 eq) and Hoveyda-Grubbs catalyst 2nd generation (61 mg, 0.059 mmol, 0.1 eq). The mixture was stirred at 25 °C. under N₂ for 16 h. The reaction mixture was concentrated in vacuum. The residue was purified by prep-TLC (PE:EtOAc, 1:1) to give methyl

(1R,2S,5S,6R)-6-[(4-hydroxy-6-methoxy-4-quinoly)methyl]-3-azabicyclo[3.2.1]octane-2-carboxylate (80 mg, 33.5%) as a red oil.

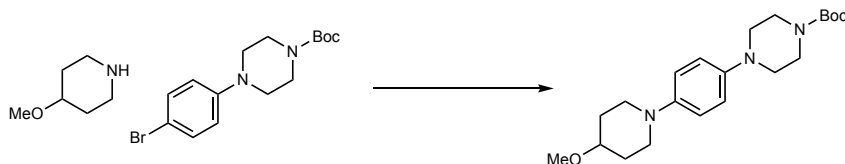
Reaction Name and Classification:

None

Yield and Characterization:

[33.5]

Buchwald-Hartwig Amination Reactions



```
COC1CCNCC1.BrC(C=C2)=CC=C2N(CC3)CCN3C(OC(C)(C)C)=O>>CC(OC(N4CCN(C5=CC=C(N6CC C(OC)CC6)C=C5)CC4)=O)(C)C
```

Trial1

Product (SMILES): ['COC1CCN(c2ccc(N3CCN(C(=O)OC(C)(C)C)CC3)cc2)CC1']

Reactant (SMILES): ['CC(C)(C)OC(=O)N1CCN(c2ccc(Br)cc2)CC1', 'COC1CCNCC1']

Reaction SMARTS:

```
[CH3:1][C:2]([CH3:3])([CH3:4])[O:5][C:6](=[O:7])[N:8]1[CH2:9][CH2:10][N:11]([CH2:12][CH2:13]1)[c:14]1[ cH:15][cH:16][c:17]([cH:18][cH:19]1)Br.[CH3:20][O:21][CH:22]1[CH2:23][CH2:24][NH:25][CH2:26][CH2:2 7]1>CC(C)c1cc(c(c1)C(C)C)- c1ccccc1P(C1CCCC1)C1CCCC1)C(C)C.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C =C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(O[Cs])O[Cs].C1COCCO1.[Pd].[Pd]>[CH3:20][O:2 1][CH:22]1[CH2:23][CH2:24][N:25]([CH2:26][CH2:27]1)[c:17]1[cH:18][cH:19][c:14]([cH:15][cH:16]1)[N:11] 1[CH2:10][CH2:9][N:8]([CH2:13][CH2:12]1)[C:6](=[O:7])[O:5][C:2]([CH3:1])([CH3:3])[CH3:4] If:3.4.5.8.9l
```

Reagents (SMILES):

```
['O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1 cccccc1.[Pd].[Pd]', 'CC(C)c1cc(C(C)C)c(-c2ccccc2P(C2CCCC2)C2CCCC2)c(C(C)C)c1', 'O=C(O[Cs])O[Cs]']
```

Solvent (SMILES): ['C1COCCO1']

Product Name: ['tert-butyl 4-(4-(4-methoxypiperidin-1-yl)phenyl)piperazine-1-carboxylate']

Reactant Name: ['tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate', '4-methoxypiperidine']

Reagent Name: ['tris(dibenzylideneacetone)dipalladium', 'cesium carbonate', 'dicyclohexyl(2',4',6'- triisopropylbiphenyl-2-yl)phosphine']

Solvent Name: ['1,4-dioxane']

Reaction Procedure:

To a solution of tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate (200 mg, 0.60 mmol) in toluene (6 mL) was added 4-methoxypiperidine (68.0 mg, 0.60 mmol), sodium tert-butanolate (173 mg, 1.80 mmol), Pd2(dba)3 (55.0 mg, 0.060 mmol) and RuPhos (28.0 mg, 0.060 mmol) under nitrogen. The reaction was stirred at 100 °C. for 16 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by flash column chromatography with 0-30% ethyl acetate in petroleum ether to afford tert-butyl 4-(4-(4-methoxypiperidin-1-yl)phenyl)piperazine-1-carboxylate (200 mg, 90% yield) as a brown oil. LC-MS m/z: 375.2 [M+H]+.

Reaction Name and Classification:

Bromo Buchwald-Hartwig amination

Yield and Characterization:

[90.0]

Trial3

Product (SMILES): ['COC1CCN(c2ccc(N3CCN(C(=O)OC(C)(C)C)CC3)cc2)CC1']

Reactant (SMILES): ['CC(C)(C)OC(=O)N1CCN(c2ccc(Br)cc2)CC1', 'COC1CCNCC1']

Reaction SMARTS:

[CH3:C:1][C:2]([CH3:3])([CH3:4])[O:5][C:6](=[O:7])[N:8]1[CH2:9][CH2:10][N:11]([CH2:12][CH2:13]1)[c:14]1[cH:15][cH:16][c:17]([cH:18][cH:19]1)Br.[CH3:20][O:21][CH:22]1[CH2:23][CH2:24][NH:25][CH2:26][CH2:27]1>c1ccc(cc1)P(c1ccccc1)c1ccc2ccccc2c1-c1c2ccccc2ccc1P(c1ccccc1)c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.Cc1ccccc1.CC(C)(C)O[Na].[Pd].[Pd]>[CH3:20][O:21][CH:22]1[CH2:23][CH2:24][N:25]([CH2:26][CH2:27]1)[c:17]1[cH:18][cH:19][c:14]([cH:15][cH:16]1)[N:11]1[CH2:10][CH2:9][N:8]([CH2:13][CH2:12]1)[C:6](=[O:7])[O:5][C:2]([CH3:1])([CH3:3])[CH3:4] If:3.4.5.8.9I

Reagents (SMILES): ['CC(C)(C)O[Na]'

['O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.[Pd].[Pd]', 'c1ccc(P(c2ccccc2)c2ccc3ccccc3c2-c2c(P(c3ccccc3)c3ccccc3)ccc3ccccc23)cc1']

Solvent (SMILES): ['Cc1ccccc1']

Product Name: ['4-[4-(4-Methoxypiperidin-1-yl)phenyl]piperazine-1-carboxylic acid tert-butyl ester']

Reactant Name: ['4-(4-bromophenyl)piperazine-1-carboxylic acid tert-butyl ester', '4-methoxypiperidine']

Reagent Name: ['BINAP', 'sodium tert-butoxide', 'tris(dibenzylideneacetone)dipalladium(0)']

Solvent Name: ['toluene']

Response:

Reaction Procedure:

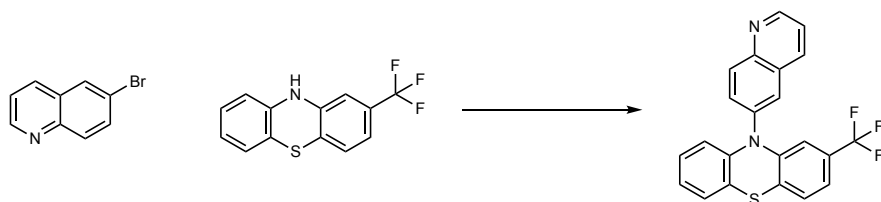
A mixture of 4-(4-bromophenyl)piperazine-1-carboxylic acid tert-butyl ester (2.5 g, 7.2 mmol), 4-methoxypiperidine (1.3 g, 11 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.67 g, 0.72 mmol), BINAP (0.45 g, 0.72 mmol), sodium tert-butoxide (0.92 g, 9.6 mmol) and toluene (100 ml) was heated at 90 °C. for 20 h. After cooling to room temperature, the reaction mixture was washed with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate=2:1) to give the title compound (1.3 g, 47%) as a brown oil.

Reaction Name and Classification:

None

Yield and Characterization:

[47.0]



```
BrC1=CC2=CC=CN=C2C=C1.FC(C(C=C3N4)=CC=C3SC5=C4C=CC=C5)(F)F>>FC(C(C=C6N7C8=CC(C=CC=N9)=C9C=C8)=CC=C6SC%10=C7C=CC=C%10)(F)F
```

Trial1

Product (SMILES): ['FC(F)(F)c1ccc2c(c1)N(c1ccc3ncccc3c1)c1ccccc1S2']

Reactant (SMILES): ['BrC1ccc2ncccc2c1', 'FC(F)(F)c1ccc2c(c1)Nc1ccccc1S2']

Reaction SMARTS:

```
[F:1][C:2]([F:3])([F:4])[c:5]1[cH:6][cH:7][c:8]2[S:9][c:10]3[cH:11][cH:12][cH:13][cH:14][c:15]3[NH:16][c:17]2[cH:18]1.Br[c:19]1[cH:20][cH:21][c:22]2[n:23][cH:24][cH:25][cH:26][c:27]2[cH:28]1>CC(C)c1cc(c(c1)C(C)C)-c1ccccc1P(C1CCCC1)C1CCCC1)C(C)C.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.Cc1ccccc1.CC(C)(C)O[Na].F[B-](F)(F)F.F[B-](F)(F)F.N#N.[Pd].[Pd]>[F:1][C:2]([F:3])([F:4])[c:5]1[cH:6][cH:7][c:8]2[S:9][c:10]3[cH:11][cH:12][cH:13][cH:14][c:15]3[N:16]([c:17]2[cH:18]1)[c:19]1[cH:20][cH:21][c:22]2[n:23][cH:24][cH:25][cH:26][c:27]2[cH:28]1lf:3.4.5.10.11,6.8.9l
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Reagents (SMILES): ['CC(C)c1cc(C(C)C)c(-c2ccccc2P(C2CCCC2)C2CCCC2)c(C(C)C)c1', 'CC(C)(C)O[Na]'],

```
'O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.F[B-](F)(F)F.F[B-](F)(F)F.[Pd].[Pd]'
```

Solvent (SMILES): ['Cc1ccccc1']

Product Name: ['10-(quinolin-6-yl)-7-(trifluoromethyl)-10H-phenothiazine']

Reactant Name: ['7-(trifluoromethyl)-10H-phenothiazine', '6-bromoquinoline']

Reagent Name: ['Pd2(dba)3', 'Xphos', 't-BuONa']

Solvent Name: ['toluene']

Response:

Reaction Procedure:

In a nitrogen atmosphere, 6-bromoquinoline (2.0 g, 10.0 mmol), 7-(trifluoromethyl)-10H-phenothiazine (2.9 g, 11.0 mmol), Pd2(dba)3 (0.46 g, 0.50 mmol), Xphos (0.93 g, 2.0 mmol), t-BuONa (2.88 g, 30.0 mmol), and toluene (60 mL) were added to a 200 mL three-neck flask, and stirred at 100 °C. for 12 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate, and the residual moisture was removed with magnesium sulfate. The resulting product was dried and separated by column chromatography to obtain 10-(quinolin-6-yl)-7-(trifluoromethyl)-10H-phenothiazine (2.7 g, yield: 70%).

Reaction Name and Classification:

Bromo Buchwald-Hartwig amination

Yield and Characterization:

[70.0]

Trial2

Product (SMILES): ['FC(F)(F)c1ccc2c(c1)N(c1ccc3ncccc3c1)c1cccc1S2']

Reactant (SMILES): ['BrC1ccc2ncccc2c1', 'FC(F)(F)c1ccc2c(c1)Nc1cccc1S2']

Reaction SMARTS:

[F:1][C:2]([F:3])([F:4])[c:5]1[cH:6][cH:7][c:8]2[S:9][c:10]3[cH:11][cH:12][cH:13][cH:14][c:15]3[NH:16][c:17]2[cH:18]1.Br[c:19]1[cH:20][cH:21][c:22]2[n:23][cH:24][cH:25][cH:26][c:27]2[cH:28]1>CC1(c2cccc(c2Oc2c1cccc2P(c1cccc1)c1cccc1)P(c1cccc1)c1cccc1)C.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(O[Cs])O[Cs].C1COCCO1.N#N.[Pd].[Pd]>[F:1][C:2]([F:3])([F:4])[c:5]1[cH:6][cH:7][c:8]2[S:9][c:10]3[cH:11][cH:12][cH:13][cH:14][c:15]3[N:16]([c:17]2[cH:18]1)[c:19]1[cH:20][cH:21][c:22]2[n:23][cH:24][cH:25][cH:26][c:27]2[cH:28]1 lf:3.4.5.9.10l

Reagents (SMILES): ['CC1(C)c2cccc(P(c3cccc3)c3cccc3)c2Oc2c(P(c3cccc3)c3cccc3)cccc21', 'O=C(O[Cs])O[Cs]', 'N#N', 'O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.O=C(/C=C/c1cccc1)/C=C/c1cccc1.[Pd].[Pd]']

Solvent (SMILES): ['C1COCCO1']

Product Name: ['6-(6-(trifluoromethyl)-3H-benzo[b][1,4]thiazin-10(3H)-yl)quinoline']

Reactant Name: ['6-bromoquinoline', '6-(trifluoromethyl)-3H-benzo[b][1,4]thiazine']

Reagent Name: ['Pd2(dba)3', 'N2', 'Cs2CO3', 'Xantphos']

Solvent Name: ['1,4-dioxane']

Response:

Reaction Procedure:

A mixture of 6-(trifluoromethyl)-3H-benzo[b][1,4]thiazine (200 mg, 0.762 mmol), 6-bromoquinoline (233 mg, 1.130 mmol), Pd2(dba)3 (35 mg, 0.038 mmol), Xantphos (20 mg, 0.034 mmol) and Cs2CO3 (495 mg, 1.50 mmol) in 1,4-dioxane (8 mL) was degassed with N2 3 times and then stirred at 90 °C. for 24 hours. The mixture was cooled to room temperature and filtered with Celite. The filtrate was concentrated and purified by column chromatography on silica gel (PE/EtOAc=2/1) to give 6-(6-(trifluoromethyl)-3H-benzo[b][1,4]thiazin-10(3H)-yl)quinoline (200 mg, 70% yield) as a white solid. LC-MS (ESI) m/z: 398.1 [M+H]+.

Reaction Name and Classification:

Bromo Buchwald-Hartwig amination

Yield and Characterization:

[70.0]

Trial3

Product (SMILES): ['FC(F)(F)c1ccc2c(c1)N(c1ccc3ncccc3c1)c1cccc1S2']

Reactant (SMILES): ['BrC1ccc2ncccc2c1', 'FC(F)(F)c1ccc2c(c1)Nc1cccc1S2']

Reaction SMARTS:

[FC:1](F)([F:2])[c:3]1[cH:4][cH:5][c:6]2[S:7][c:8]3[cH:9][cH:10][cH:11][cH:12][c:13]3[NH:14][c:15]2[cH:16]1.Br[c:17]1[cH:18][cH:19][c:20]2[n:21][cH:22][cH:23][cH:24][c:25]2[cH:26]1>CC(C)(C)P(C(C)(C)C(C)(C)C).CC(=O)O[Pd]OC(C)=O.Cc1cccc1.CC(C)(C)O[Na].ClCCl>[F:1][C:3]([F:2])([F:4])[c:16]1[cH:15][cH:6][c:5]2[S:7][c:8]3[cH:9][cH:10][cH:11][cH:12][c:13]3[N:14]([c:17]2[cH:26]1)[c:10]1[cH:11][cH:12][c:13]2[n:14][cH:15][cH:16][cH:3][c:4]2[cH:18]1

Reagents (SMILES): ['CC(C)(C)P(C(C)(C)C(C)(C)C)', 'CC(C)(C)O[Na]', 'FC(F)(F)c1ccc2c(c1)Nc1cccc1S2', 'CC(=O)O[Pd]OC(C)=O']

Solvent (SMILES): ['Cc1cccc1', 'ClCCl']

Product Name: ['US20190372011A1-20191205-C00089.CDX']

Reactant Name: ['2-bromoquinoline', 'US20190372011A1-20191205-C00089.CDX']

Reagent Name: ['palladium acetate', 'tri-tert-butylphosphine', 'sodium tert-butoxide', 'phenothiazine']

Solvent Name: ['dichloromethane', 'toluene']

Response:

Reaction Procedure:

Under an argon atmosphere, 1.00 g of phenothiazine, 2.12 g of 2-bromoquinoline, 0.11 g of palladium acetate, 0.18 g of tri-tert-butylphosphine, and 1.39 g of sodium tert-butoxide were added to a 100 mL, three-necked flask, followed by heating and refluxing in 30 mL of a toluene solvent for about 7 hours. After cooling in the air, dichloromethane (about 50 mL) was added, an organic layer was separately taken, and solvents were removed by distillation. The crude product thus obtained was separated by silica gel column chromatography (using a mixture solvent of dichloromethane and hexane) and recrystallized using a mixture solvent of toluene and hexane to produce Compound I (1.24 g, yield 92%) as a white solid.

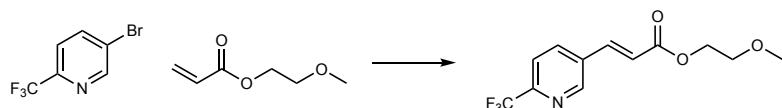
Reaction Name and Classification:

None

Yield and Characterization:

[92.0]

Heck Reactions



BrC1=CC=C(C(F)(F)F)N=C1.C=CC(OCCOC)=O>>O=C(OCCOC)/C=C/C2=CC=C(C(F)(F)F)N=C2

Trial1

Product (SMILES): ['COCCOC(=O)/C=C/c1ccc(C(F)(F)F)nc1']

Reactant (SMILES): ['C=CC(=O)OCCOC', 'FC(F)(F)c1ccc(Br)cn1']

Reaction SMARTS:

[F:1][C:2]([F:3])([F:4])[c:5]1[cH:6][cH:7][c:8]([cH:9][n:10]1)Br.[CH2:11]=[CH:12][C:13](=[O:14])[O:15][CH2:16][CH2:17][O:18][CH3:19]>Cc1ccccc1P(c1ccccc1C)c1ccccc1C.CC(=O)O[Pd]OC(C)=O.CCN(CC)CC.CN(C)C=O>[CH3:19][O:18][CH2:17][CH2:16][O:15][C:13](=[O:14])/[CH:12]=[CH:11]/[c:8]1[cH:9][n:10][c:5]([cH:6][cH:7]1)[C:2]([F:1])([F:3])[F:4]

Reagents (SMILES): ['CC(=O)O[Pd]OC(C)=O', 'CCN(CC)CC', 'Cc1ccccc1P(c1ccccc1C)c1ccccc1C']

Solvent (SMILES): ['CN(C)C=O']

Product Name: ['(E)-2-methoxyethyl 3-(6-(trifluoromethyl)pyridin-3-yl)acrylate']

Reactant Name: ['5-bromo-2-(trifluoromethyl)pyridine', '2-methoxyethyl acrylate']

Reagent Name: ['Pd(OAc)2', 'Et3N', 'P(o-tol)3']

Solvent Name: ['DMF']

Response:

Reaction Procedure:

A mixture of 5-bromo-2-(trifluoromethyl)pyridine (2.19 g, 10 mmol), 2-methoxyethyl acrylate (2.51 g, 20 mmol), Pd(OAc)₂ (45 mg, 0.2 mmol), Et₃N (3.03 g, 30 mmol) and P(o-tol)₃ (122 mg, 0.4 mmol) in DMF (30 mL) was stirred at 95 °C. under N₂ for 16 h. The reaction was quenched with water and extracted with EtOAc (20 mL×3). The combined organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography to give (E)-2-methoxyethyl 3-(6-(trifluoromethyl)pyridin-3-yl)acrylate (1.8 g, 66%) as a yellow oil.

Reaction Name and Classification:

Bromo Heck reaction

Yield and Characterization:

[66.0]

Trial2

Product (SMILES): ['COCCOC(=O)/C=C/c1ccc(C(F)(F)F)nc1']

Reactant (SMILES): ['C=CC(=O)OCCOC', 'FC(F)(F)c1ccc(Br)cn1']

Reaction SMARTS:

[F:1][C:2]([F:3])([F:4])[c:5]1[cH:6][cH:7][c:8]([cH:9][n:10]1)Br.[CH2:11]=[CH:12][C:13](=[O:14])[O:15][CH2:16][CH2:17][O:18][CH3:19]>Cc1cccc1P(c1cccc1C)c1cccc1C.CC(=O)O[Pd]OC(C)=O.CN(C)C=O.O>[CH3:19][O:18][CH2:17][CH2:16][O:15][C:13](=[O:14])/[CH:12]=[CH:11]/[c:8]1[cH:9][n:10][c:5]([cH:6][cH:7]1)[C:2]([F:3])([F:4])[F:1]

Reagents (SMILES): ['Cc1cccc1P(c1cccc1C)c1cccc1C', 'CC(=O)O[Pd]OC(C)=O']

Solvent (SMILES): ['O', 'CN(C)C=O']

Product Name: ['2-methoxyethyl (2E)-3-[6-(trifluoromethyl)-3-pyridinyl]-2-propenoate']

Reactant Name: ['5-bromo-2-(trifluoromethyl)pyridine', '2-methoxyethyl acrylate']

Reagent Name: ['tri-o-tolylphosphine', 'Pd(OAc)₂']

Solvent Name: ['DMF', 'water']

Response:

Reaction Procedure:

A mixture of 5-bromo-2-(trifluoromethyl)pyridine (1.0 g, 4.6 mmol), 2-methoxyethyl acrylate (1.12 g, 9.2 mmol), Pd(OAc)₂ (102 mg, 0.46 mmol), tri-*o*-tolylphosphine (283 mg, 0.92 mmol) and TEA (1.28 mL, 9.2 mmol) in DMF (10 mL) under argon was heated at 130 °C for 1 h. After cooling to room temperature, water (40 mL) was added to the reaction mixture and then extracted by EA (3×50 mL). The organic phase was washed with brine, dried over MgSO₄ and evaporated in vacuo to afford the title compound (1.1 g, 74% yield) as a yellow oil. LCMS: rt = 2.67 min, [M+H]⁺ = 282

Reaction Name and Classification:

Bromo Heck reaction

Yield and Characterization:

[74.0]

Trial3

Product (SMILES): [*]C(=O)C=Cc1ccc(C(F)(F)F)nc1

Reactant (SMILES): [*]C=CC(=O)OCCOC, FC(F)(F)c1ccc(Br)cn1

Reaction SMARTS:

```
[CH3:1][O:2][CH2:3][CH2:4][O:5][C:6](=[O:7])[CH:8]=[CH:9][c:10]1[cH:11][cH:12][c:13]([cH:14][n:15]1)[C:16]([F:17])([F:18])[F:19].Br[c:20]1[cH:21][cH:22][c:23]([n:24][cH:25]1)C(F)(F)F>Cc1ccccc1P(c1ccccc1C)c1ccccc1C.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.CCN(CC)CC.CN(C)C=O.[Pd].[Pd]>[CH3:1][O:2][CH2:3][CH2:4][O:5][C:6](=[O:7])/[CH:8]=[CH:9]/[c:10]1[cH:11][cH:12][c:13]([n:15][cH:14]1)[C:16]([F:19])([F:18])[F:17] If:3.4.5.8.9I
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Reagents (SMILES):

[*]O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.O=C(/C=C/c1ccccc1)/C=C/c1ccccc1.[Pd].[Pd], Cc1ccccc1P(c1ccccc1C)c1ccccc1C

Solvent (SMILES): CCN(CC)CC, CN(C)C=O

Product Name: ['(E)-3-(6-(trifluoromethyl)pyridin-3-yl)acrylic acid 2-methylethyl ester']

Reactant Name: ['5-bromo-2-(trifluoromethyl)pyridine', '2-methylethyl acrylate']

Reagent Name: ['tris(dibenzylideneacetone)dipalladium (0)', 'tri-*o*-tolylphosphine']

Solvent Name: ['N,N-dimethylformamide', 'triethylamine']

Response:

Reaction Procedure:

To a solution of 5-bromo-2-(trifluoromethyl)pyridine (2.46 g, 11.0 mmol) in N,N-dimethylformamide (11 mL) were added triethylamine (3.12 mL, 22.5 mmol), 2-methylethyl acrylate (2.78 mL, 22.5 mmol), tris(dibenzylideneacetone)dipalladium (0) (103 mg, 1.1 mmol) and tri-*o*-tolylphosphine (673 mg, 2.2 mmol), and the mixture was stirred at 100 °C. for 18 hr. The reaction mixture was cooled, and the solvent was evaporated under reduced pressure. Water and ethyl acetate were added to the residue, and the

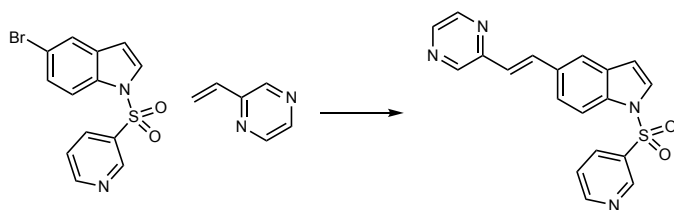
insoluble material was filtered off through celite. The filtrate was separated into the aqueous layer and the organic layer. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=20:1-1:1) to give (E)-3-(6-(trifluoromethyl)pyridin-3-yl)acrylic acid 2-methylethyl ester (2.36 g, 78%) as a white solid.

Reaction Name and Classification:

Bromo Heck reaction

Yield and Characterization:

[78.0]



BrC1=CC=C(N(S(C2=CC=CN=C2)(=O)=O)C=C3)C3=C1.C=CC4=NC=CN=C4>>O=S(N5C6=CC=C(/C=C/C7=NC=CN=C7)C=C6C=C5)(C8=CC=CN=C8)=O

Trial1

Product (SMILES): [O=S(=O)(c1cccnc1)n1ccc2cc(/C=C/c3cncn3)ccc21]

Reactant (SMILES): ['C=Cc1cncn1', 'O=S(=O)(c1cccnc1)n1ccc2cc(Br)ccc21']

Reaction SMARTS:

[O:1]=[S:2](=[O:3])([c:4]1[cH:5][cH:6][cH:7][n:8][cH:9]1)[n:10]1[cH:11][cH:12][c:13]2[c:14]1[cH:15][cH:16][c:17]([cH:18]2)Br.[CH2:19]=[CH:20][c:21]1[cH:22][n:23][cH:24][cH:25][n:26]1>Cc1ccccc1P(c1ccccc1C)c1ccccc1C.CC(=O)O[Pd]OC(C)=O.CCN(CC)CC.CN(C)C=O.O>[O:1]=[S:2](=[O:3])([c:4]1[cH:9][n:8][cH:7][cH:6][cH:5]1)[n:10]1[cH:11][cH:12][c:13]2[c:14]1[cH:15][cH:16][c:17]([cH:18]2)/[CH:19]=[CH:20]/[c:21]1[cH:22][n:23][cH:24][cH:25][n:26]1

Reagents (SMILES): ['CC(=O)O[Pd]OC(C)=O', 'Cc1ccccc1P(c1ccccc1C)c1ccccc1C']

Solvent (SMILES): ['O', 'CCN(CC)CC', 'CN(C)C=O']

Product Name: ['(E)-2-(2-(1-(pyridin-3-ylsulfonyl)-1H-indol-5-yl)vinyl)pyrazine']

Reactant Name: ['3-vinylpyrazine', '5-bromo-1-(pyridin-3-ylsulfonyl)-1H-indole']

Reagent Name: ['Pd(OAc)2', 'P(o-tolyl)3']

Solvent Name: ['triethyl amine', 'water', 'DMF']

Response:

Reaction Procedure:

To a stirred solution of 5-bromo-1-(pyridin-3-ylsulfonyl)-1H-indole (1.0 g, 2.9 mmol, 1.0 equiv) in DMF (10 mL) was added 3-vinylpyrazine (0.59 g, 5.7 mmol, 2.0 equiv) and triethyl amine (1.2 mL, 8.7 mmol, 3.0 equiv). The resulting reaction mixture was purged with N₂ gas for 5 min followed by the addition of Pd(OAc)₂ (130 mg, 0.58 mmol, 0.2 equiv) and P(o-tolyl)₃ (352 mg, 1.16 mmol, 0.4 equiv) at RT. The resulting reaction mixture was heated at 120 °C. for overnight. Product formation was confirmed by LCMS. After the completion of reaction, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL). Combined organic extracts were washed with water (10 mL×4), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the crude product which was purified by flash chromatography (0-5% ethyl acetate in DCM as an eluent) to obtain (E)-2-(2-(1-(pyridin-3-ylsulfonyl)-1H-indol-5-yl)vinyl)pyrazine (0.8 g, 75% Yield) as a yellow solid.

Reaction Name and Classification:

Bromo Heck reaction

Yield and Characterization:

[75.0]

Trial2

Product (SMILES): [O=S(=O)(c1cccnc1)n1ccc2cc(/C=C/c3cncn3)ccc21]

Reactant (SMILES): 'C=Cc1cncn1', 'O=S(=O)(c1cccnc1)n1ccc2cc(Br)ccc21'

Reaction SMARTS:

```
[O:1]=[S:2](=O)([c:3]1[cH:4][cH:5][cH:6][n:7][cH:8]1)[n:9]1[cH:10][cH:11][c:12]2[c:13]1[cH:14][cH:15][c:16]([cH:17]2)Br.[CH2:18]=[CH:19][c:20]1[cH:21][n:22][cH:23][cH:24][n:25]1>c1ccc(cc1)P(c1ccccc1)c1ccccc1.CC(=O)O[Pd]OC(C)=O.CN(C)C=O.O=C(O)O[Na]>[O:1]=[S:2](=[O:3])([c:3]1[cH:8][n:7][cH:6][cH:5][cH:4]1)[n:9]1[cH:10][cH:11][c:12]2[c:13]1[cH:14][cH:15][c:16]([cH:17]2)/[CH:18]=[CH:19]/[c:20]1[cH:21][n:22][cH:23][cH:24][n:25]1
```

Reagents (SMILES): 'CC(=O)O[Pd]OC(C)=O', 'c1ccc(P(c2ccccc2)c2ccccc2)cc1', 'O=C(O)O[Na]'

Solvent (SMILES): 'CN(C)C=O'

Product Name: ['(E)-2-(5-(1-(pyridin-3-ylsulfonyl)-1H-indol-5-yl)vinyl)pyrazine']

Reactant Name: ['3-vinylpyrazine', '5-bromo-1-(pyridin-3-ylsulfonyl)-1H-indole']

Reagent Name: ['triphenylphosphine', 'sodium bicarbonate', 'palladium acetate']

Solvent Name: ['N,N-dimethylformamide']

Response:

Reaction Procedure:

A mixture of 5-bromo-1-(pyridin-3-ylsulfonyl)-1H-indole (0.07 g, 0.20 mmol), 3-vinylpyrazine (0.04 g, 0.40 mmol), palladium acetate (0.002 g, 0.008 mmol), triphenylphosphine (0.005 g, 0.02 mmol), and sodium bicarbonate (0.034 g, 0.40 mmol) in N,N-dimethylformamide (0.5 mL) was heated in a microwave at 150 °C. for 10 minutes. The reaction mixture was filtered through celite, and the filtrate was purified by preparative HPLC (PHENOMENEX®, Luna 5 30x250 mm, flow rate=30 ml/min., gradient=20% A to 100% B in 30 minutes, A=H₂O/MeOH/TFA (90:10:0.1), B=H₂O/MeOH/TFA (10:90:0.1)). Yield: 0.02 g (28%) of (E)-2-(5-(1-(pyridin-3-ylsulfonyl)-1H-indol-5-yl)vinyl)pyrazine as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.09 (d, J=2.0 Hz, 1H), 8.85 (d, J=1.0 Hz, 1H), 8.8-8.7 (m, 2H), 8.6 (dd, J=8.6, 2.0 Hz, 1H), 8.4 (d, J=8.6 Hz, 1H), 8.2 (d, J=16.4 Hz, 1H), 7.9 (d, J=16.4 Hz, 1H), 7.7-7.6 (m, 2H), 7.2 (dd, J=4.8, 1.0 Hz, 1H), 6.9 (dd, J=4.8, 3.0 Hz, 1H); MS (ESI) m/z 361 (M+H)⁺.

Reaction Name and Classification:

None

Yield and Characterization:

[28.0]

Trial3

Product (SMILES): [O=S(=O)(c1cccnc1)n1ccc2cc(/C=C/c3cnccn3)ccc21]

Reactant (SMILES): [C=Cc1cnccn1, 'O=S(=O)(c1cccnc1)n1ccc2cc(Br)ccc21]

Reaction SMARTS:

```
[O:1]=[S:2](=[O:3])([c:4]1[cH:5][cH:6][cH:7][n:8][cH:9]1)[n:10]1[cH:11][cH:12][c:13]2[c:14]1[cH:15][cH:16][c:17]([cH:18]2)Br.[CH2:19]=[CH:20][c:21]1[cH:22][n:23][cH:24][cH:25][n:26]1>Cc1cccc1P(c1cccc1C)c1cccc1C.CC(=O)O[Pd]OC(C)=O.CCN(CC)CC.CN(C)C=O.O>[O:1]=[S:2](=[O:3])([c:4]1[cH:9][n:8][cH:7][cH:6][cH:5]1)[n:10]1[cH:11][cH:12][c:13]2[c:14]1[cH:15][cH:16][c:17]([cH:18]2)/[CH:19]=[CH:20][c:21]1[cH:22][n:23][cH:24][cH:25][n:26]1
```

Reagents (SMILES): ['CC(=O)O][Pd]OC(C)=O, 'Cc1cccc1P(c1cccc1C)c1cccc1C]

Solvent (SMILES): ['O, 'CCN(CC)CC, 'CN(C)C=O]

Product Name: ['(E)-2-(2-(1-(pyridin-3-ylsulfonyl)-1H-indol-5-yl)vinyl)pyrazine']

Reactant Name: ['3-vinylpyrazine, '5-bromo-1-(pyridin-3-ylsulfonyl)-1H-indole']

Reagent Name: ['Pd(OAc)2, 'P(o-tol)3]

Solvent Name: ['triethyl amine, 'water, 'DMF]

Response:

Reaction Procedure:

To a stirred solution of 5-bromo-1-(pyridin-3-ylsulfonyl)-1H-indole (0.50 g, 1.500 mmol, 1.0 equiv) in DMF (5 mL) was added 3-vinylpyrazine (0.314 g, 2.99 mmol, 2.0 equiv) and triethyl amine (0.6 ml, 4.400 mmol, 3.0 equiv). The resulting reaction mixture was purged with N₂ gas for 5 min followed by addition of Pd(OAc)₂ (0.017 g, 0.075 mmol, 0.05 equiv) and P(o-tol)₃ (0.091 g, 0.300 mmol, 0.2 equiv). The reaction mixture was heated at 120 °C. for overnight. Product formation was confirmed by LCMS. Reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with ethyl acetate (100 mL). Combined organic extracts were washed with water (10 mL×4), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the crude product which was purified by flash chromatography (0-5% ethyl acetate in hexane as an eluent) to obtain (E)-2-(2-(1-(pyridin-3-ylsulfonyl)-1H-indol-5-yl)vinyl)pyrazine (0.15 g, 26% yield) as a yellow solid.

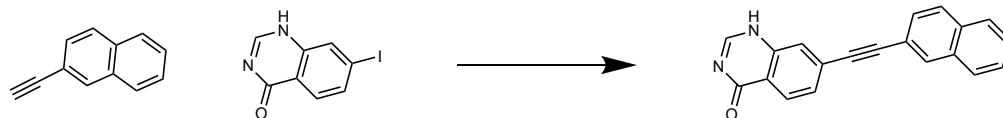
Reaction Name and Classification:

Bromo Heck reaction

Yield and Characterization:

[26.0]

Sonogashira Reactions



C#CC1=CC(C=CC=C2)=C2C=C1.O=C3N=CNC4=C3C=CC(I)=C4>>O=C5N=CNC6=C5C=CC(C#CC7=C8C(C=CC=C8)=C8C=C7)=C6

Trial1

Product (SMILES): [O]=c1nc[nH]c2cc(C#Cc3ccc4ccccc4c3)ccc12

Reactant (SMILES): [C#Cc1ccc2ccccc2c1]', [O]=c1nc[nH]c2cc(I)ccc12

Reaction SMARTS:

[O:1]=[c:2]1[n:3][cH:4][nH:5][c:6]2[c:7]1[cH:8][cH:9][c:10]([cH:11]2)I.[CH:12]#[C:13][c:14]1[cH:15][cH:16][c:17]2[cH:18][cH:19][cH:20][cH:21][c:22]2[cH:23]1>Cl[Pd](Cl)([P](c1ccccc1)(c1ccccc1)c1ccccc1)[P](c1ccccc1)(c1ccccc1)c1ccccc1.CCN(CC)CC.C1CCOC1.[Cu]I>[O:1]=[c:2]1[n:3][cH:4][nH:5][c:6]2[c:7]1[cH:8][cH:9][c:10]([cH:11]2)[C:12]#[C:13][c:14]1[cH:15][cH:16][c:17]2[cH:18][cH:19][cH:20][cH:21][c:22]2[cH:23]1

Reagents (SMILES): [I][Cu]I',

Cl[Pd](Cl)([P](c1ccccc1)(c1ccccc1)c1ccccc1)[P](c1ccccc1)(c1ccccc1)c1ccccc1'

Solvent (SMILES): [C1CCOC1]', [CCN(CC)CC]

Product Name: ['7-(2-naphthalen-2-ylethynyl)-3H-quinazolin-4-one]

Reactant Name: ['7-iodo-3H-quinazolin-4-one', '2-ethynyl-naphthalene']

Reagent Name: ['dichlorobis(triphenylphosphine)palladium', 'copper iodide']

Solvent Name: ['triethylamine', 'THF']

Response:

Reaction Procedure:

A mixture of 7-iodo-3H-quinazolin-4-one (100 mg, 0.38 mmol), 2-ethynyl-naphthalene (70 mg, 0.46 mmol), dichlorobis(triphenylphosphine)palladium (7 mg, 0.01 mmol), copper iodide (7 mg, 0.038 mmol), triethylamine (0.53 mL, 3.8 mmol) and THF (2 mL) was heated at 60 °C. for 3 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo. The residue was purified by preparative HPLC to give 7-(2-naphthalen-2-ylethynyl)-3H-quinazolin-4-one (28 mg, 26%).

Reaction Name and Classification:

Iodo Sonogashira coupling

Yield and Characterization:

[26.0]

Trial2

Product (SMILES): ['O=c1nc[nH]c2cc(C#Cc3ccc4ccccc4c3)ccc12']

Reactant (SMILES): ['C#Cc1ccc2ccccc2c1', 'O=c1nc[nH]c2cc(l)ccc12']

Reaction SMARTS:

[O:1]=[c:2]1[n:3][cH:4][nH:5][c:6]2[c:7]1[cH:8][cH:9][c:10]([cH:11]2)I.[CH:12]#[C:13][c:14]1[cH:15][cH:16][c:17]2[cH:18][cH:19][cH:20][cH:21][c:22]2[cH:23]1>c1ccc(cc1)[P](c1ccccc1)(c1ccccc1)[Pd]([P](c1ccccc1)(c1ccccc1)c1ccccc1)[P](c1ccccc1)(c1ccccc1)c1ccccc1.CCN(CC)CC.CN(C)C=O.[Cu]>[O:1]=[c:2]1[n:3][cH:4][nH:5][c:6]2[c:7]1[cH:8][cH:9][c:10]([cH:11]2)[C:12]#[C:13][c:14]1[cH:15][cH:16][c:17]2[cH:18][cH:19][cH:20][cH:21][c:22]2[cH:23]1

Reagents (SMILES): ['[Cu]I',

'c1ccc([P](c2ccccc2)(c2ccccc2)[Pd]([P](c2ccccc2)(c2ccccc2)c2ccccc2)([P](c2ccccc2)(c2ccccc2)c2ccccc2)[P](c2ccccc2)(c2ccccc2)c2ccccc2)cc1']

Solvent (SMILES): ['CN(C)C=O', 'CCN(CC)CC']

Product Name: ['7-(2-naphthalen-yl-ethynyl)-3H-quinazolin-4-one']

Reactant Name: ['7-Iodo-3H-quinazolin-4-one', '2-ethynyl-naphthalene']

Reagent Name: ['copper(I) iodide', 'tetrakis(triphenylphosphine)palladium(0)']

Solvent Name: ['DMF', 'triethylamine']

Response:

Reaction Procedure:

7-Iodo-3H-quinazolin-4-one (100 mg, 0.36 mmol), 2-ethynyl-naphthalene (70 mg, 0.42 mmol), tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.02 mmol), copper(I) iodide (7 mg, 0.04 mmol) and triethylamine (0.12 mL, 0.84 mmol) were mixed in DMF (2 mL) and the mixture was heated at 90 °C. for 4 hours. The reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, ethyl acetate then ethyl acetate:hexanes=1:1) to give 7-(2-naphthalen-yl-ethynyl)-3H-quinazolin-4-one (50 mg, 46%) as a white solid.

Reaction Name and Classification:

Iodo Sonogashira coupling

Yield and Characterization:

[46.0]

Trial3

Product (SMILES): ['O=c1nc[nH]c2cc(C#Cc3ccc4ccccc4c3)ccc12']

Reactant (SMILES): ['C#Cc1ccc2ccccc2c1', 'O=c1nc[nH]c2cc(l)ccc12']

Reaction SMARTS:

```
[O:1]=c1[n:2][cH:3][nH:4][c:5]2[c:6]1[cH:7][cH:8][c:9]([cH:10]2)I.[CH:11]#[C:12][c:13]1[cH:14][cH:15][c:16]2[cH:17][cH:18][cH:19][cH:20][c:21]2[cH:22]1>Cl[Pd](Cl)([P](c1ccccc1)(c1ccccc1)c1ccccc1)[P](c1ccccc1)(c1ccccc1)c1ccccc1.CCN(CC)CC.C1CCOC1.[Cu]>[O:1]=[c:6]1[n:2][cH:3][nH:4][c:5]2[c:6]1[cH:7][cH:8][c:9]([cH:10]2)[C:11]#[C:12][c:13]1[cH:14][cH:15][c:16]2[cH:17][cH:18][cH:19][cH:20][c:21]2[cH:22]1
```

Reagents (SMILES): ['Cl[Pd](Cl)([P](c1ccccc1)(c1ccccc1)c1ccccc1)[P](c1ccccc1)(c1ccccc1)c1ccccc1', '[Cu]I']

Solvent (SMILES): ['C1CCOC1', 'CCN(CC)CC']

Product Name: ['7-(Naphthalen-2-ylethynyl)-3,4-dihydro-quinazolin-4-one']

Reactant Name: ['7-iodo-3,4-dihydro-quinazolin-4-one', '2-ethynyl-naphthalene']

Reagent Name: ['copper(I) iodide', 'bis(triphenylphosphine)palladium(II) chloride']

Solvent Name: ['triethylamine', 'THF']

Response:

Reaction Procedure:

A mixture of 7-iodo-3,4-dihydro-quinazolin-4-one (1.5 g, 5.7 mmol), 2-ethynyl-naphthalene (0.9 g, 6.2 mmol), bis(triphenylphosphine)palladium(II) chloride (200 mg, 0.29 mmol), copper(I) iodide (109 mg, 0.57 mmol), triethylamine (2.0 mL, 15 mmol) and THF (20 mL) was stirred at 60 °C for 12 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate) to give the product as a yellow solid (1.3 g, 80%). 1H NMR (DMSO-d₆): δ 11.82 (s, 1H), 8.37 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.74

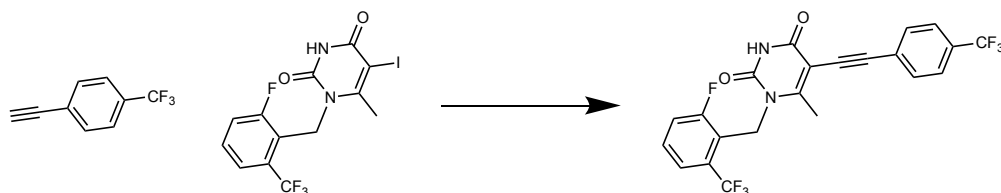
(dd, J = 8.4, 2.0 Hz, 1H), 7.69 (m, 2H), 7.63 (m, 2H), 7.47 (m, 1H), 7.33 (m, 1H). MS (ESI): m/z 298.0 [M+H]⁺.

Reaction Name and Classification:

None

Yield and Characterization:

[80.0]



C#CC1=CC=C(C(F)(F)F)C=C1.O=C2NC(C(I)=C(C)N2CC3=C(C(F)(F)F)C=CC=C3F)=O>>O=C4NC(C#CC5=CC=C(C(F)(F)F)C=C5)=C(C)N4CC6=C(C(F)(F)F)C=CC=C6F)=O

Trial1

Product (SMILES): ['Cc1c(C#Cc2ccc(C(F)(F)F)cc2)c(=O)[nH]c(=O)n1Cc1c(F)cccc1C(F)(F)F']

Reactant (SMILES): ['C#Cc1ccc(C(F)(F)F)cc1', 'Cc1c(I)c(=O)[nH]c(=O)n1Cc1c(F)cccc1C(F)(F)F']

Reaction SMARTS:

[CH3:1][c:2]1[c:3]([c:4]([nH:5][c:6]([n:7]1[CH2:8][c:9]1[c:10]([cH:11][cH:12][cH:13][c:14]1[C:15]([F:16])([F:17])([F:18])([F:19])=[O:20])=[O:21])I.[CH:22]#[C:23][c:24]1[cH:25][cH:26][c:27]([cH:28][cH:29]1)[C:30]([F:31])([F:32])[F:33]>C1C=CC(C=1)(P(c1cccc1)c1cccc1)[Fe]C1(C=CC=C1)P(c1cccc1)c1cccc1.CCN(CC)C.C.N(C)C=O.Cl[Pd]Cl.[Cu]>[CH3:1][c:2]1[c:3]([c:4]([nH:5][c:6]([n:7]1[CH2:8][c:9]1[c:10]([cH:11][cH:12][cH:13][c:14]1[C:15]([F:16])([F:17])([F:18])([F:19])=[O:20])=[O:21])[C:22]#[C:23][c:24]1[cH:25][cH:26][c:27]([cH:28][cH:29]1)[C:30]([F:31])([F:32])[F:33] If:2.5I

Reagents (SMILES): ['[Cu]I'],

'C1=CC([Fe]C2(P(c3cccc3)c3cccc3)C=CC=C2)(P(c2cccc2)c2cccc2)C=C1.Cl[Pd]Cl'

Solvent (SMILES): ['CCN(CC)CC', 'CN(C)C=O']

Product Name: ['3-[2-(4-Trifluoromethyl-phenyl)-ethynyl]-1-(2-fluoro-6-trifluoromethyl-benzyl)-5-methyl-1H-pyrimidine-2,4-dione']

Reactant Name: ['1-ethynyl-4-trifluoromethyl-benzene', '3-iodo-1-(2-fluoro-6-trifluoromethyl-benzyl)-5-methyl-1H-pyrimidine-2,4-dione']

Reagent Name: ['CuI', 'PdCl2(dppf)']

Solvent Name: ['triethylamine', 'DMF']

Response:

Reaction Procedure:

3-iodo-1-(2-fluoro-6-trifluoromethyl-benzyl)-5-methyl-1H-pyrimidine-2,4-dione (I-26) (0.100 g, 0.23 mmol) was dissolved in DMF (3 mL) and treated with 1-ethynyl-4-trifluoromethyl-benzene (0.071 g, 0.35 mmol), triethylamine (1 mL), PdCl2(dppf) (0.017 g, 0.023 mmol), and CuI (0.004 g, 0.023 mmol). The reaction was stirred for 15 minutes and then partitioned between EtOAc and H2O. The organic layer was separated, washed with brine, dried with anhydrous Na2SO4 and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 50-100% EtOAc in hexanes to give the title compound (0.066 g, 58%).

Reaction Name and Classification:

Iodo Sonogashira coupling

Yield and Characterization:

[58.0]

Trial2

Product (SMILES): ['Cc1c(C#Cc2ccc(C(F)(F)F)cc2)c(=O)[nH]c(=O)n1Cc1c(F)cccc1C(F)(F)F']

Reactant (SMILES): ['C#Cc1ccc(C(F)(F)F)cc1', 'Cc1c(I)c(=O)[nH]c(=O)n1Cc1c(F)cccc1C(F)(F)F']

Reaction SMARTS:

```
[CH3:1][c:2]1[c:3]([c:4]([nH:5][c:6]([n:7]1[CH2:8][c:9]1[c:10]([cH:11][cH:12][cH:13][c:14]1[C:15]([F:16])([F:17])([F:18])[F:19]=[O:20]=[O:21])l.[CH:22]#[C:23][c:24]1[cH:25][cH:26][c:27]([cH:28][cH:29]1)[C:30]([F:31])([F:32])[F:33]>Cl[Pd](Cl)([P](c1cccc1)(c1cccc1)c1cccc1)[P](c1cccc1)(c1cccc1)c1cccc1.CCN(CC)C C.CCOC(C)=O.CN(C)C=O.l[Cu].[NH4+].O.[Cl-]>[CH3:1][c:2]1[c:3]([c:4]([nH:5][c:6]([n:7]1[CH2:8][c:9]1[c:10]([cH:11][cH:12][cH:13][c:14]1[C:15]([F:16])([F:17])[F:18])[F:19]=[O:20]=[O:21])[C:22]#[C:23][c:24]1[cH:25][cH:26][c:27]([cH:28][cH:29]1)[C:30]([F:31])([F:32])[F:33] lf:7.8.9l
```

Reagents (SMILES): ['[Cu]I',

'Cl[Pd](Cl)([P](c1cccc1)(c1cccc1)c1cccc1)[P](c1cccc1)(c1cccc1)c1cccc1', 'O.[Cl-].[NH4+]', 'CCOC(C)=O']

Solvent (SMILES): ['CN(C)C=O', 'CCN(CC)CC']

Product Name: ['3-(2,2,2-Trifluoro-6-phenyl-ethyl)-6-(2-fluoro-6-trifluoromethyl-benzyl)-5-methyl-1H-pyrimidine-2,4-dione']

Reactant Name: ['4-ethynyl-trifluoromethyl-benzene', '6-(2,2,2-trifluoro-6-phenyl-ethyl)-6-iodo-5-methyl-1H-pyrimidine-2,4-dione']

Reagent Name: ['saturated aqueous ammonium chloride', 'ethyl acetate', 'PdCl2(PPh3)2', 'CuI']

Solvent Name: ['DMF', 'triethylamine']

Response:

Reaction Procedure:

To a solution of 6-(2,2,2-trifluoro-6-phenyl-ethyl)-6-iodo-5-methyl-1H-pyrimidine-2,4-dione (100 mg, 0.24 mmol) in DMF (3 mL) are added 4-ethynyl-trifluoromethyl-benzene (81 mg, 0.48 mmol), PdCl₂(PPh₃)₂ (17 mg, 0.024 mmol), CuI (5 mg, 0.024 mmol) and triethylamine (0.34 mL, 2.44 mmol) and the mixture is stirred at room temperature for 2 hours. The mixture is diluted with ethyl acetate and saturated aqueous ammonium chloride, the organic layer is washed with water and brine, dried over sodium sulfate and concentrated in vacuo. The residue is purified by column chromatography (silica gel, hexane:ethyl acetate=2:1) to give the title compound (23 mg, 22%) as a solid. ¹H NMR (300 MHz, CDCl₃) δ 2.32 (s, 3H), 5.20 (s, 2H), 6.96-7.42 (m, 7H), 8.00-8.16 (m, 2H); MS (APCI+) m/z 472 [M+H]⁺.

Reaction Name and Classification:

Iodo Sonogashira coupling

Yield and Characterization:

[22.0]

Trial3

Product (SMILES): [C#Cc1ccc(C(F)(F)F)cc1].[O]n1c(=O)c2cc(C(F)(F)F)cc2c(=O)[nH]1.[O]n1c(=O)c2cc(C(F)(F)F)cc2c(=O)[nH]1

Reactant (SMILES): [C#Cc1ccc(C(F)(F)F)cc1].[O]n1c(=O)c2cc(C(F)(F)F)cc2c(=O)[nH]1

Reaction SMARTS:

```
[CH3:1][c:2]1[c:3]([c:4]([nH:5][c:6]([n:7]1[CH2:8][c:9]1[c:10]([cH:11][cH:12][cH:13][c:14]1[C:15]([F:16])([F:17])([F:18])([F:19])=[O:20])=[O:21])I.[CH:22]#[C:23][c:24]1[cH:25][cH:26][c:27]([cH:28][cH:29]1)[C:30]([F:31])([F:32])[F:33]>Cl[Pd](Cl)([P](c1cccc1)(c1cccc1)c1cccc1)[P](c1cccc1)(c1cccc1)c1cccc1.CCN(CC)C.CCOC(C)=O.CN(C)C=O.[Cu].O>[CH3:1][c:2]1[c:3]([c:4]([nH:5][c:6]([n:7]1[CH2:8][c:9]1[c:10]([cH:11][cH:12][cH:13][c:14]1[C:15]([F:16])([F:17])([F:18])([F:19])=[O:20])=[O:21])[C:22]#[C:23][c:24]1[cH:25][cH:26][c:27]([cH:28][cH:29]1)[C:30]([F:31])([F:32])[F:33]
```

Reagents (SMILES): [O].[Cl][Pd](Cl)([P](c1cccc1)(c1cccc1)c1cccc1)[P](c1cccc1)(c1cccc1)c1cccc1.CCOC(C)=O.[Cu]I

Solvent (SMILES): [CN(C)C=O].[CCN(CC)CC]

Product Name: ['3-(2,2,2-Trifluoro-6-fluorobenzyl)-6-methyl-5-(4-(trifluoromethyl)phenylethynyl)pyrimidine-2,4(1H,3H)-dione']

Reactant Name: ['4-ethynyltrifluoromethylbenzene', '3-(2,2,2-trifluorobenzyl)-5-iodo-6-methylpyrimidine-2,4(1H,3H)-dione']

Reagent Name: ['copper(I) iodide', 'ethyl acetate', 'bis(triphenylphosphine)palladium(II) dichloride', 'water']

Solvent Name: ['triethylamine', 'N,N-dimethylformamide']

Response:

Reaction Procedure:

To a solution of 3-(2,2,2-trifluorobenzyl)-5-iodo-6-methylpyrimidine-2,4(1H,3H)-dione (KNoerges et al., J Org Chem 2007, 72, 1, 177-183), (0.200 g), 4-ethynyltrifluoromethylbenzene (0.200 g), and triethylamine (0.35 mL) in N,N-dimethylformamide (4 mL) were added bis(triphenylphosphine)palladium(II) dichloride (13 mg) and copper(I) iodide (4.6 mg) at room temperature. After stirred at 90 °C. for 3 h, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate) to give the title compound (0.212 g, 98%).

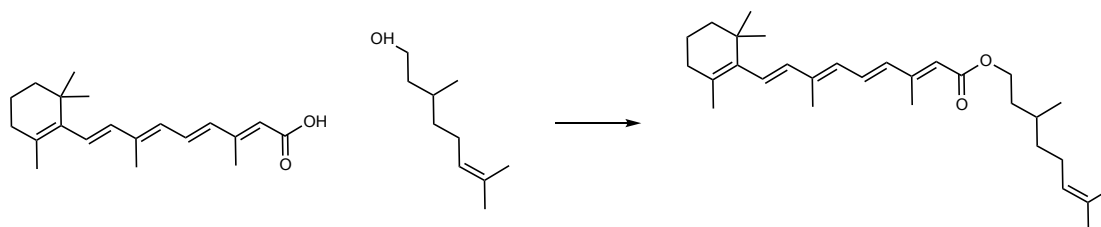
Reaction Name and Classification:

Iodo Sonogashira coupling

Yield and Characterization:

[98.0]

Non-Coupling Reactions



```
OC(/C=C/C=C/C=C/C=C/C1=C(CCCC(C)1C)C)C=O.CC(CC/C=C(C)\C)CCO>>CC(CC/C=C(C)C)C  
COC(/C=C/C=C/C=C/C=C/C2=C(CCCC(C)2C)C)C=O
```

Trial1

Product (SMILES): ['CC(C)=CCCC(C)CCOC(=O)/C=C(C)/C=C/C=C(C)/C=C/C1=C(C)CCCC1(C)C']

Reactant (SMILES): ['CC(C)=CCCC(C)CCO',
'CC1=C(/C=C/C(C)=C/C=C/C(C)=C/C(=O)O)C(C)(C)CCC1']

Reaction SMARTS:

```
[CH3:1]/[C:2](=[CH:3]/[CH:4]=[CH:5]/[C:6]1=[C:7]([CH2:8][CH2:9][CH2:10][C:11]1([CH3:12])[CH3:13])[CH  
3:14])[CH:15]=[CH:16][C:17](=[O:18])[OH:19].[CH3:20][C:21]([CH3:22])=[CH:23][CH2:24][CH2:25][CH:26]  
([CH3:27])[CH2:28][CH2:29]O>CN(C)c1ccncc1.CICCl.C(=NC1CCCCC1)=NC1CCCCC1>[CH3:20][C:21]([  
CH3:22])=[CH:23][CH2:24][CH2:25][CH:26]([CH3:27])[CH2:28][CH2:29][O:19][C:17](=[O:18])/[CH:16]=[C:  
15]([CH3:1])/[CH:2]=[CH:3]/[CH:4]=[CH:5]/[C:6]1=[C:7]([CH2:8][CH2:9][CH2:10][C:11]1([CH3:13])[CH3:12  
])[CH3:14]
```

Reagents (SMILES): ['C(=NC1CCCCC1)=NC1CCCCC1', 'CN(C)c1ccncc1']

Solvent (SMILES): ['CICCl']

Product Name: ['(E)-3,6,9,12-tetramethylhenicosa-5,8,11,14-tetraen-1-yl 3,7-dimethyl-6-((E)-2,3,6,9-tetrahydro-2,2,4-trimethylphenanth-1-yl)hex-2-enoate']

Reactant Name: ['3,7-dimethyl-6-((E)-2,3,6,9-tetrahydro-2,2,4-trimethylphenanth-1-yl)hex-2-enoic acid', '3,7-dimethylhex-6-en-1-ol']

Reagent Name: ['DCC', 'DMAP']

Solvent Name: ['CH2Cl2']

Response:

Reaction Procedure:

To a solution of 3,7-dimethylhex-6-en-1-ol (26.6 mg, 0.157 mmol) in CH₂Cl₂ (1.5 mL) were added 3,7-dimethyl-6-((E)-2,3,6,9-tetrahydro-2,2,4-trimethylphenanth-1-yl)hex-2-enoic acid (50.0 mg, 0.157 mmol), DCC (32.2 mg, 0.157 mmol) and DMAP (19.1 mg, 0.157 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was filtered through a short plug of Celite with rinsing by EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc=20:1) to give (E)-3,6,9,12-tetramethylhenicosa-5,8,11,14-tetraen-1-yl 3,7-dimethyl-6-((E)-2,3,6,9-tetrahydro-2,2,4-trimethylphenanth-1-yl)hex-2-enoate (53.5 mg, 75%) as a colorless oil.

Reaction Name and Classification:

None

Yield and Characterization:

[75.0]

Trial2

Product (SMILES): ['CC(C)=CCCC(C)CCOC(=O)/C=C(C)/C=C/C=C(C)/C=C/C1=C(C)CCCC1(C)C']

Reactant (SMILES): ['CC(C)=CCCC(C)CCO', 'CC1=C(/C=C/C(C)=C/C=C/C(C)=C/C(=O)O)C(C)(C)CCC1']

Reaction SMARTS:

[CH3:1][C:2]1[CH2:3][CH2:4][CH2:5][C:6]([C:7]=1/[CH:8]=[CH:9]/[C:10]([CH3:11])=[CH:12]/[CH:13]=[CH:14]/[C:15]([CH3:16])=[CH:17]/[C:18](=[O:19])[OH:20])([CH3:21])[CH3:22].[CH3:23][C:24]([CH3:25])=[CH:26][CH2:27][CH2:28][CH:29]([CH3:30])[CH2:31][CH2:32]O>CN(C)c1ccncc1.CICCl.C(=NC1CCCCC1)=NC1CCCCC1>[CH3:23][C:24]([CH3:25])=[CH:26][CH2:27][CH2:28][CH:29]([CH3:30])[CH2:31][CH2:32][O:20][C:18](=[O:19])/[CH:17]=[C:15]([CH3:16])/[CH:14]=[CH:13]/[CH:12]=[C:10]([CH3:11])/[CH:9]=[CH:8]/[C:7]1=[C:2]([CH2:3][CH2:4][CH2:5][C:6]1([CH3:21])[CH3:22])[CH3:1]

Reagents (SMILES): ['CN(C)c1ccncc1', 'C(=NC1CCCCC1)=NC1CCCCC1']

Solvent (SMILES): ['CICCl']

Product Name: ['3-methylhept-5-en-1-yl (E, E, E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate']

Reactant Name: ['(E, E, E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid', '3-methylhept-5-en-1-ol']

Reagent Name: ['DMAP', 'DCC']

Solvent Name: ['DCM']

Response:

Reaction Procedure:

To a solution of (E, E, E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (0.300 g, 1.00 mmol), 3-methylhept-5-en-1-ol (0.317 g, 2.00 mmol) and DMAP (0.012 g, 0.10 mmol) in DCM (3 mL) was added DCC (0.308 g, 1.50 mmol) and the reaction mixture was stirred at 25 °C. for 16 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc/petroleum ether) to give 3-methylhept-5-en-1-yl (E, E, E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate (0.320 g, 0.070 mmol, 70%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 6.59 (s, 1H), 6.34 (s, 1H), 5.95 (s, 1H), 5.86 (s, 1H), 4.63 (t, J=6.8 Hz, 2H), 2.24 (s, 3H), 2.02 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.50 (s, 6H), 1.35 (s, 3H), 1.30 (s, 6H).

Reaction Name and Classification:

Steglich esterification

Yield and Characterization:

[70.0]

Trial3

Product (SMILES): ['CC(C)=CCCC(C)CCOC(=O)/C=C(C)/C=C/C=C(C)/C=C/C1=C(C)CCCC1(C)C']

Reactant (SMILES): ['CC(C)=CCCC(C)CCO',
'CC1=C/C=C/C(C)=C/C=C/C(C)=C/C(=O)O)C(C)(C)CCC1']

Reaction SMARTS:

[CH3:1][C:2](=[CH:3][CH:4]=[CH:5][C:6]1=[C:7]([CH2:8][CH2:9][CH2:10][C:11]1([CH3:12])[CH3:13])[CH3:14])[CH:15]=[CH:16][C:17](=[O:18])O.[CH3:19][C:20]([CH3:21])=[CH:22][CH2:23][CH2:24][CH:25]([CH3:26])[CH2:27][CH2:28][OH:29]>CCOCC.O=S(Cl)Cl.c1ccncc1>[CH3:19][C:20]([CH3:21])=[CH:22][CH2:23][CH2:24][CH:25]([CH3:26])[CH2:27][CH2:28][O:29][C:17](=[O:18])/[CH:16]=[C:15]([CH3:1])/[CH:2]=[CH:3]/[CH:4]=[CH:5][C:6]1=[C:7]([CH2:8][CH2:9][CH2:10][C:11]1([CH3:13])[CH3:12])[CH3:14]

Reagents (SMILES): ['CCOCC']

Solvent (SMILES): ['c1ccncc1', 'O=S(Cl)Cl']

Product Name: ['(E)-3,6,9,12-tetramethylhexadeca-1,4,7,10,13-pentaeno-1-yl 3,6,9,12-tetramethyl-2,2-dimethyl-1-(E)-benzodiazepine-1-carboxylate']

Reactant Name: ['3,6,9,12-tetramethyl-2,2-dimethyl-1-(E)-benzodiazepine-1-carboxylic acid', '3,7-dimethyl-6-octen-1-ol']

17. Experimental Validations

General Information

General Experimental Procedures: All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. All reactions were capped with a rubber septum or Teflon-coated silicon microwave cap unless otherwise stated. Stainless steel cannulas or syringes were used to transfer solvent, and air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) and carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent. A basic solution of KMnO₄ was used as a developing reagent which was accompanied by 30-60 seconds of heating. SiliaFlash® P60 (40–63 μm, 230–400 mesh) silica gel purchased from SiliCycle Inc. was used for flash column chromatography.

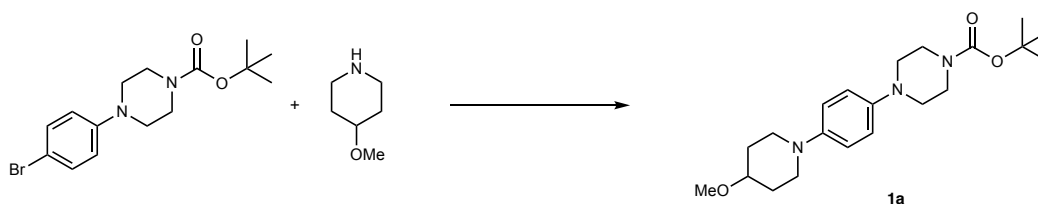
Materials: All anhydrous reaction solvents were purchased from MilliporeSigma or taken from solvent purification system. The reagents, catalysts, and ligands were purchased from Ambeed, TCI, Strem Chemicals, Fischer Scientific, MilliporeSigma. Unless otherwise stated, all reagents were used as received without further purification.

Instrumentation: All new compounds were characterized with NMR, and HR-MS. Relevant NMR spectra can be found at the end of experimental procedure. NMR spectra were recorded using Agilent DD2 400 MHz NMR spectrometer, Agilent DD2 500 MHz NMR spectrometer, or Agilent DD2 600 MHz NMR spectrometer. All ¹H NMR data are reported in δ units, parts per million (ppm), and were calibrated relative to the signals for residual chloroform (7.26 ppm) or tetramethylsilane (0.00 ppm) in deuteriochloroform (CDCl₃). All ¹³C NMR data are reported in ppm relative to CDCl₃ (77.16 ppm) and were obtained with proton decoupling unless otherwise stated. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and a = apparent. All IR spectra were taken on an FT-IR/Raman Thermo Nicolet 6700. High resolution mass spectra (HR-MS) were recorded on a Shimadzu 9030 Quadrupole Time-of-Flight mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

Workflow

Model predictions was run with 2-3 experts, beam group 2, beam size 20 unless otherwise stated. In case of novel reactions or cases when diverse reaction conditions were required, model predictions were run with beam group >2 (for example: 4, 5, 10 & 20). For selecting routes, usually, data-driven systematic approach was followed; thus, procedures with higher confidence rather than procedures with higher yields were chosen: Expert n, prediction 1 > Expert n, prediction 2 > Expert n, prediction 3. Unless otherwise mentioned, all reactions were carried out following the predicted procedures.

Buchwald-Hartwig Coupling



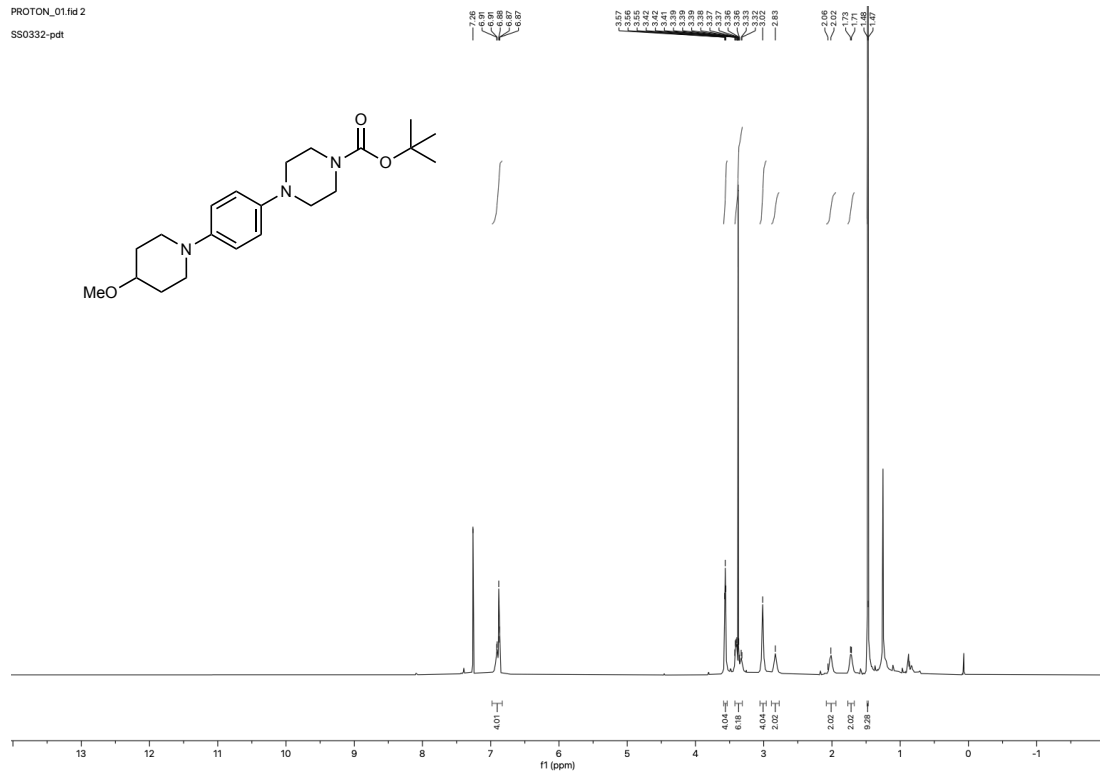
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A mixture of tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate (2.0 g, 5.9 mmol), 4-methoxypiperidine (1.3 g, 11.8 mmol), tris(dibenzylideneacetone)dipalladium (54 mg, 0.059 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (Xphos) (83 mg, 0.17 mmol) and cesium carbonate (3.8 g, 11.8 mmol) in 1,4-dioxane (20 mL) was stirred at 100 °C. for 16 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (10-50% ethyl acetate in petroleum ether) to give tert-butyl 4-(4-(4-methoxypiperidin-1-yl)phenyl)piperazine-1-carboxylate (550 mg, 23%) as light yellow solid.</p> <p>Reaction Name and Classification: <i>Bromo Buchwald-Hartwig amination</i></p> <p>Yield and Characterization: [23.0]</p>	<p>For a 0.1 mmol (34.1 mg) scale reaction following the predicted procedure, led to formation of 1a with <50% conversion.</p>
<p>Expert: 2 Prediction:1</p> <p>Reaction Procedure: To a solution of tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate (200 mg, 0.60 mmol) in toluene (6 mL) was added 4-methoxypiperidine (68.0 mg, 0.60 mmol), sodium tert-butanolate (173 mg, 1.80 mmol), Pd₂(dba)₃ (55.0 mg, 0.060 mmol) and RuPhos (28.0 mg, 0.060 mmol) under nitrogen. The reaction was stirred at 100 °C. for 16 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by flash column chromatography with 0-30% ethyl acetate in petroleum ether to afford tert-butyl 4-(4-(4-methoxypiperidin-1-yl)phenyl)piperazine-1-carboxylate (200 mg, 90% yield) as a brown oil.</p> <p>Reaction Name and Classification: <i>Bromo Buchwald-Hartwig amination</i>.</p> <p>Yield and Characterization: [90.0]</p>	<p>For a 0.1 mmol (34.1 mg) scale reaction following the predicted procedure, led to formation of 1a with full conversion. Amination product 1a was isolated as brown solid (15.0 mg, 40% yield). R_f (50% EtOAc in hexane): 0.20.</p>

¹H NMR (600 MHz, CDCl₃) δ 6.94 – 6.86 (m, 4H), 3.59 – 3.54 (m, 4H), 3.43 – 3.29 (m, 6H), 3.02 (bs, 4H), 2.88 – 2.78 (m, 2H), 2.06 – 1.96 (m, 2H), 1.77 – 1.65 (m, 2H), 1.48 (s, 9H).

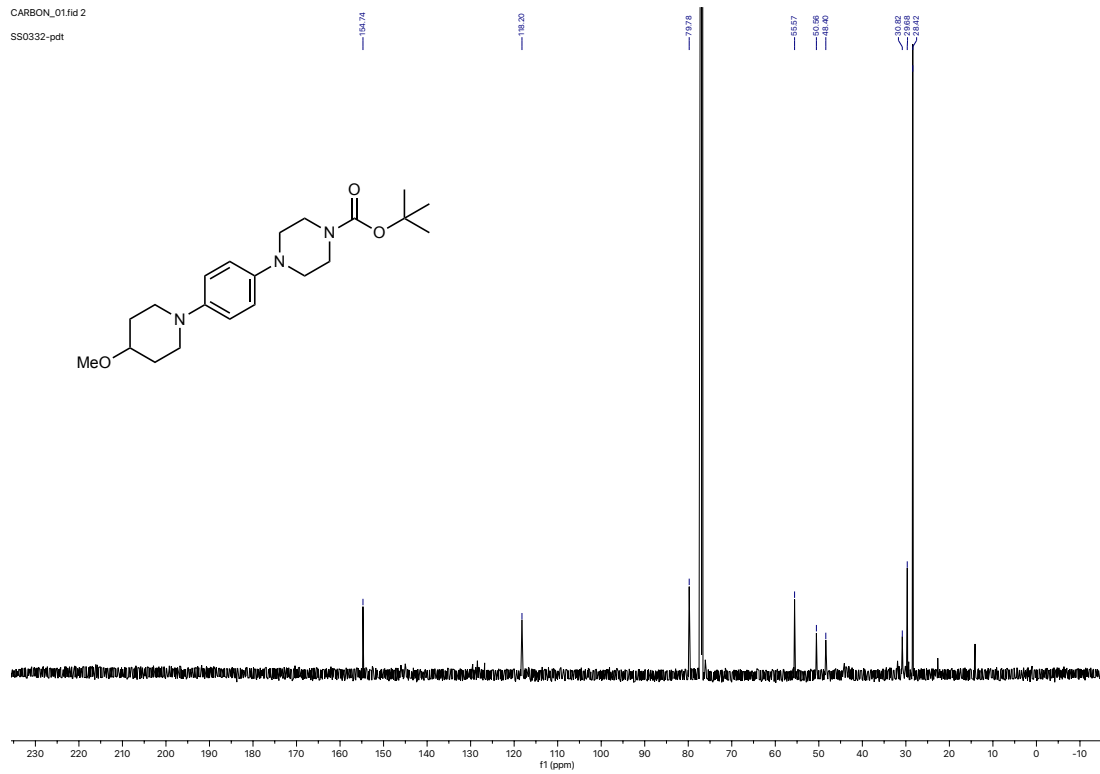
¹³C NMR (151 MHz, CDCl₃) δ 154.7, 118.2, 79.8, 55.6, 50.6, 48.4, 30.8, 29.7, 28.4.

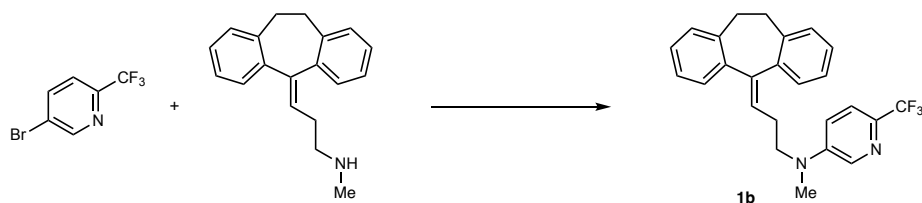
HRMS m/z (ESI⁺) [M+H]⁺: Calc'd for C₁₅H₁₁ClN₃O: 376.2522, found: 376.2595.

PROTON_01.fid 2
SS0332-pdt



CARBON_01.fid 2
SS0332-pdt





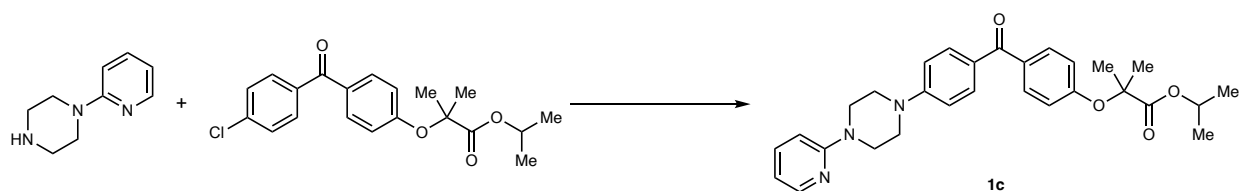
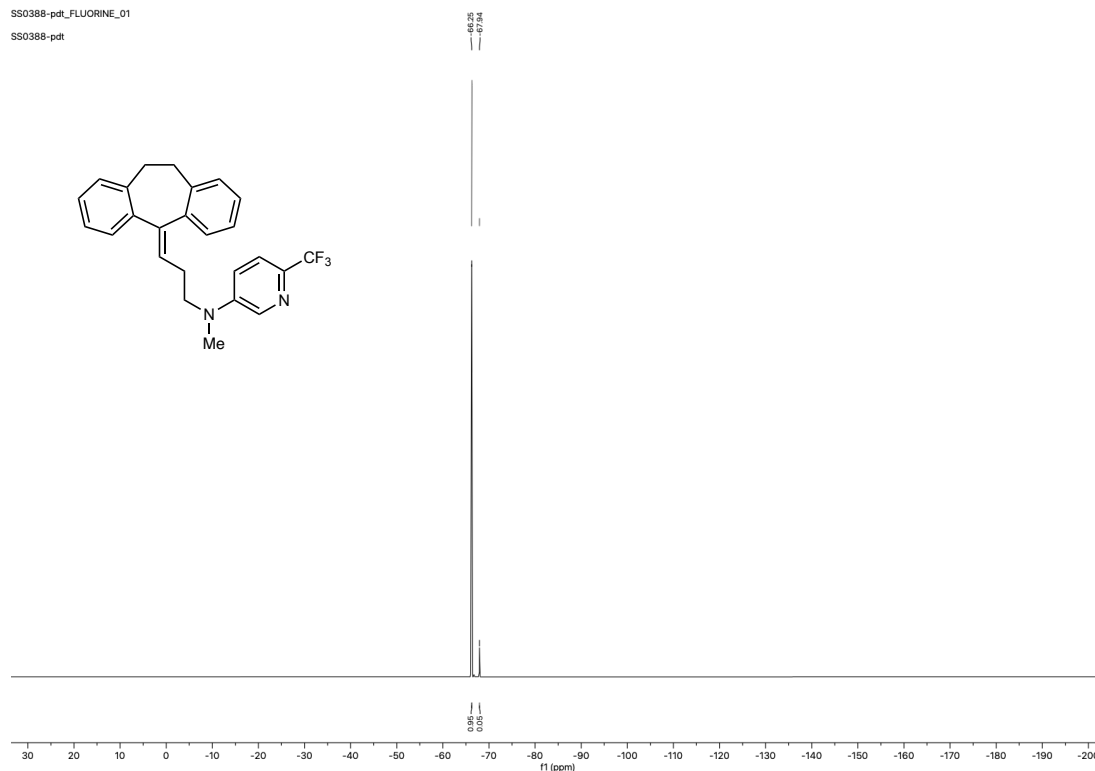
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A solution of N-methyl-3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propan-1-amine (0.20 g, 0.77 mmol, 1.0 eq.), 5-bromo-2-(trifluoromethyl)pyridine (0.28 g, 1.16 mmol, 1.5 eq.), CuI (0.15 g, 0.8 mmol, 1.0 eq.), K₂CO₃ (0.32 g, 2.3 mmol, 3.0 eq.) and L-proline (0.18 g, 1.6 mmol, 2.0 eq.) in DMSO (5 mL) was stirred at 100 °C. for 16 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was separated, washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel to give N-methyl-N-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl)-6-(trifluoromethyl)pyridin-3-amine (0.26 g, 85%) as a white solid.</p> <p>Reaction Name and Classification: <i>Bromo Goldberg reaction</i>.</p> <p>Yield and Characterization: [85.0]</p>	<p>For a 0.2 mmol (60.0 mg) scale reaction following the predicted procedure with nortriptyline hydrochloric acid salt (60.0 mg, 0.2 mmol) instead of nortriptyline led to formation of 1b with <75% conversion.</p>
<p>Expert: 2 Prediction:1</p> <p>Reaction Procedure: A solution of 5-(3-methyl-propylidene)-10,11-dihydro-dibenzo[a,b]cycloheptene (0.45 g, 1.7 mmol) in toluene (5 mL) was added to a mixture of 5-bromo-2-trifluoromethyl-pyridine (0.52 g, 2.2 mmol), palladium acetate (0.019 g, 0.085 mmol), 2-(di-t-butylphosphino)-biphenyl (0.054 g, 0.170 mmol) and sodium t-butoxide (0.19 g, 2.0 mmol) in a sealed tube. The mixture was heated at 100 °C. for 12 h and then cooled to room temperature. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 0-20% ethyl acetate in hexane) afforded 0.025 g (3% yield) of the title compound.</p> <p>Rerunning the yield prediction: 36% yield</p>	<p>For a 0.2 mmol (60.0 mg) scale reaction following the predicted procedure with nortriptyline hydrochloric acid salt (60.0 mg, 0.2 mmol) instead of nortriptyline led to formation, sodium t-butoxide (44.8 mg, 0.48 mmol) led to formation of 1b with ~90% conversion. Amination product 1b was isolated as off-white solid (37mg, 45% yield, 95% purity). R_f (10% EtOAc in hexane): 0.20.</p>

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 3.0 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.23 – 7.15 (m, 3H), 7.13 – 7.05 (m, 2H), 6.70 (dd, *J* = 8.9, 3.0 Hz, 1H), 5.92 (t, *J* = 7.6 Hz, 1H), 3.53 – 3.19 (m, 4H), 3.09 – 2.90 (m, 4H), 2.87 – 2.70 (m, 1H), 2.65 – 2.32 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 146.0, 145.8, 140.6, 139.5, 139.4, 137.0, 133.8, 130.2, 128.4, 128.1, 127.9, 127.7, 127.3, 126.7, 126.1, 125.9, 120.8, 120.8, 120.7, 117.0, 51.7, 38.1, 33.8, 31.9, 26.4.

¹⁹F NMR (376 MHz, CDCl₃) δ -66.25.

HRMS *m/z* (ESI⁺) [M+H]⁺: Calc'd for C₁₅H₁₁ClN₃O: 409.1813, found: 409.1916.



Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: Isopropyl 2-(4-(4-chlorophenyl)benzoyl)phenoxy)-2-methylpropanoate (100 mg, 0.28 mmol), 1-(pyridin-2-yl)piperazine (46 mg, 0.31 mmol), Pd₂(dba)₃ (13 mg, 0.014 mmol), RuPhos (13 mg, 0.028 mmol) and Cs₂CO₃ (203 mg, 0.62 mmol) were added together in dry dioxane (2 mL) and heated in a microwave reactor at 150 °C. for 30 min. The mixture was filtered through Celite and the filtrate was evaporated in vacuo. The residue was purified by column chromatography eluting with a mixture of ethyl acetate:pentane (1:1) to afford the title compound (115 mg, 78%).</p> <p>Reaction Name and Classification: <i>Chloro Buchwald-Hartwig amination</i></p> <p>Yield and Characterization: [78.0]</p>	<p>For a 0.28 mmol (100.0 mg) scale, heating the reaction mixture at 110 °C for 16 h led to formation 1c formation with full conversion. Amination product 1c was isolated as yellow solid (129.0 mg, 96% yield). R_f (30% EtOAc in hexane): 0.40.</p>
<p>Expert: 2 Prediction:1</p> <p>Reaction Procedure: To a stirred solution of isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)isobutyl propanoate (0.50 g, 1.41 mmol) in 1,4-dioxane (20 mL) was added 2-(piperazin-1-yl)pyridine (0.26 g, 1.69 mmol) and cesium carbonate (1.38 g, 4.2 mmol) at room temperature. The reaction mixture was purged with argon for 20 min. Then Pd₂(dba)₃ (0.13 g, 0.14 mmol) and Xphos (0.14 g, 0.14 mmol) were added to the reaction mixture and refluxed to 110 °C. for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a pad of celite and evaporated to get the crude product. The crude product was</p>	<p>For a 0.28 mmol (100.0 mg) scale reaction following the predicted procedure led to formation 1c formation with full conversion.</p>

purified by silica gel column chromatography using 20% EtOAc-hexane to afford isopropyl 2-methyl-2-(4-(4-(4-(pyridin-2-yl)piperazin-1-yl)benzoyl)phenoxy)propanoate (0.60 g, 1.16 mmol, 82% yield) as a yellow solid.

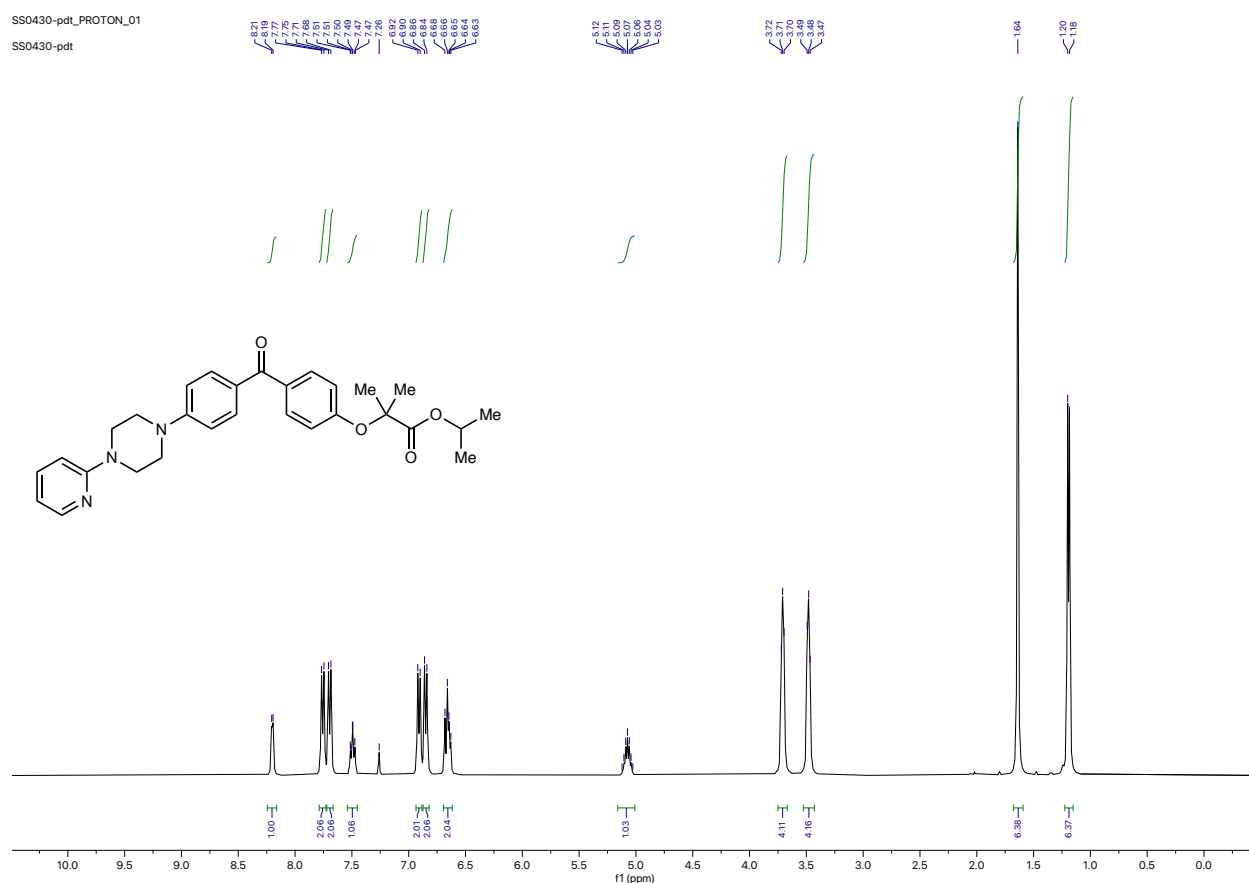
Reaction Name and Classification: *Chloro Buchwald-Hartwig amination*

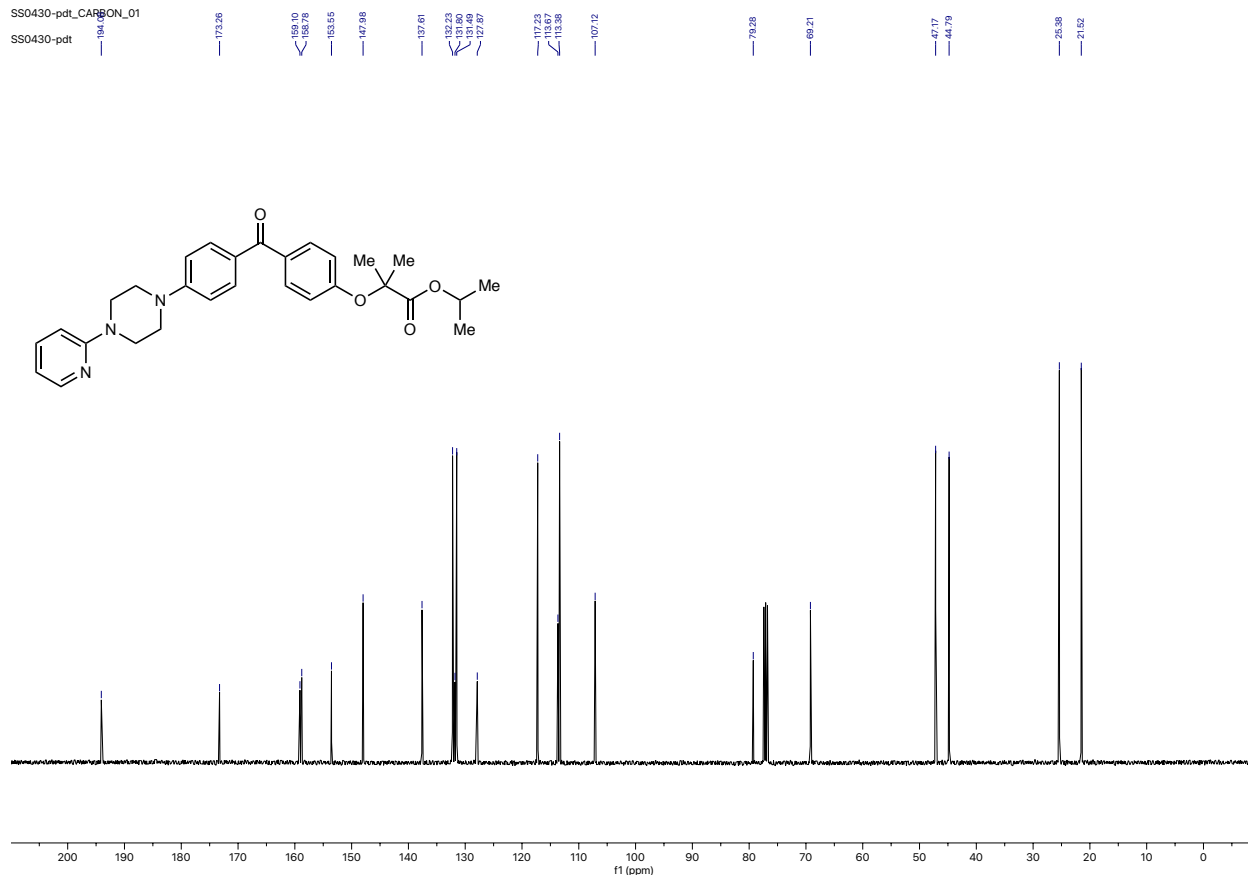
Yield and Characterization: [82]

¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 4.9 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.44 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.71 – 6.60 (m, 2H), 5.14 – 5.02 (m, 1H), 3.75 – 3.67 (m, 4H), 3.54 – 3.43 (m, 4H), 1.64 (s, 6H), 1.19 (d, *J* = 6.5 Hz, 6H).

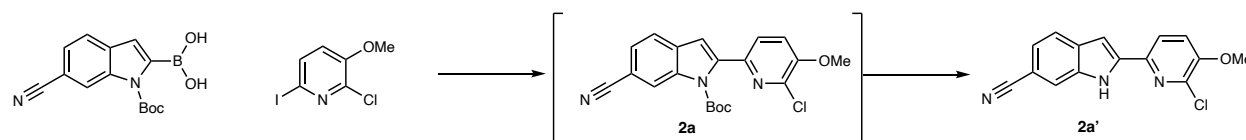
¹³C NMR (101 MHz, CDCl₃) δ 194.1, 173.3, 159.1, 158.8, 153.6, 148.0, 137.6, 132.2, 131.8, 131.5, 127.9, 117.2, 113.7, 113.4, 107.1, 79.3, 69.2, 47.2, 44.8, 25.4, 21.5.

HRMS *m/z* (ESI⁺) [M+H]⁺: Calc'd for C₁₅H₁₁ClN₃O: 488.2471, found: 488.2557.





Suzuki Coupling



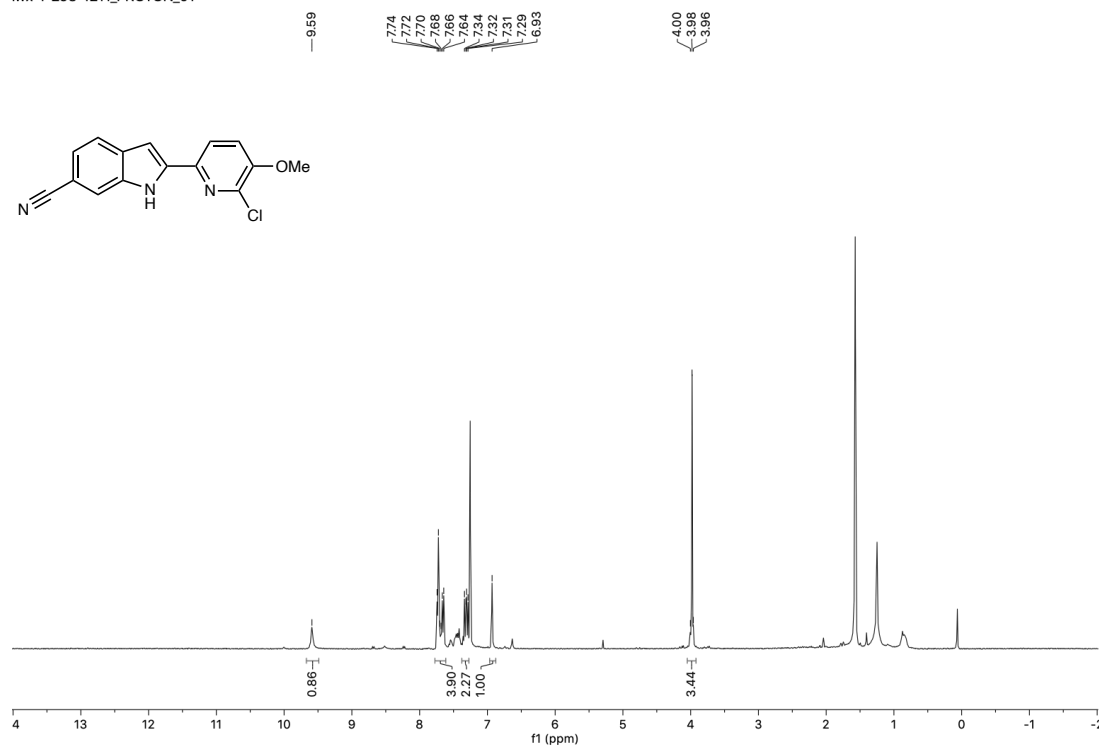
Model Predictions	Experimental Results
<p>Expert: 1, Prediction: 1</p> <p>Reaction Procedure: To a solution of 2-chloro-6-iodo-3-methoxypyridine (1.0 g, 3.8 mmol) in dioxane (20 mL) was added (1-(tert-butoxycarbonyl)-6-cyano-1H-indol-2-yl)boronic acid (1.1 g, 3.8 mmol), Na₂CO₃ (1.2 g, 11 mmol) and water (4 mL), and the mixture was degassed with argon for 10 min. Pd(PPh₃)₄ (0.22 g, 0.19 mmol) was added and the mixture was degassed with argon for 10 min and then heated at 100 °C. for 16 h. After cooling to room temperature, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2×50 mL). The combined organic phase was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by normal phase SiO₂ chromatography (0-10% EtOAc/petroleum ether to give tert-butyl 2-(6-chloro-5-methoxypyridin-2-yl)-6-cyano-1H-indole-1-carboxylate (900 mg, 62% yield) as a solid.</p> <p>Reaction Name and Classification: <i>Iodo Suzuki coupling</i></p> <p>Yield and Characterization: [62.0]</p>	<p>Following the predicted procedure for a 0.1 mmol (28.6 mg) scale reaction led to formation of Suzuki-coupling product and followed by Boc deprotection. Product 2a' was isolated as yellow solid (17.2 mg, 45% yield). R_f (hexanes:EtOAc = 2:1): 0.18.</p>

¹H NMR (400 MHz, CDCl₃): δ 9.59 (s, 1H), 7.78 – 7.61 (m, 4H), 7.31 (dd, *J* = 12.6, 8.3 Hz, 2H), 6.93 (s, 1H), 3.98 (s, 3H).

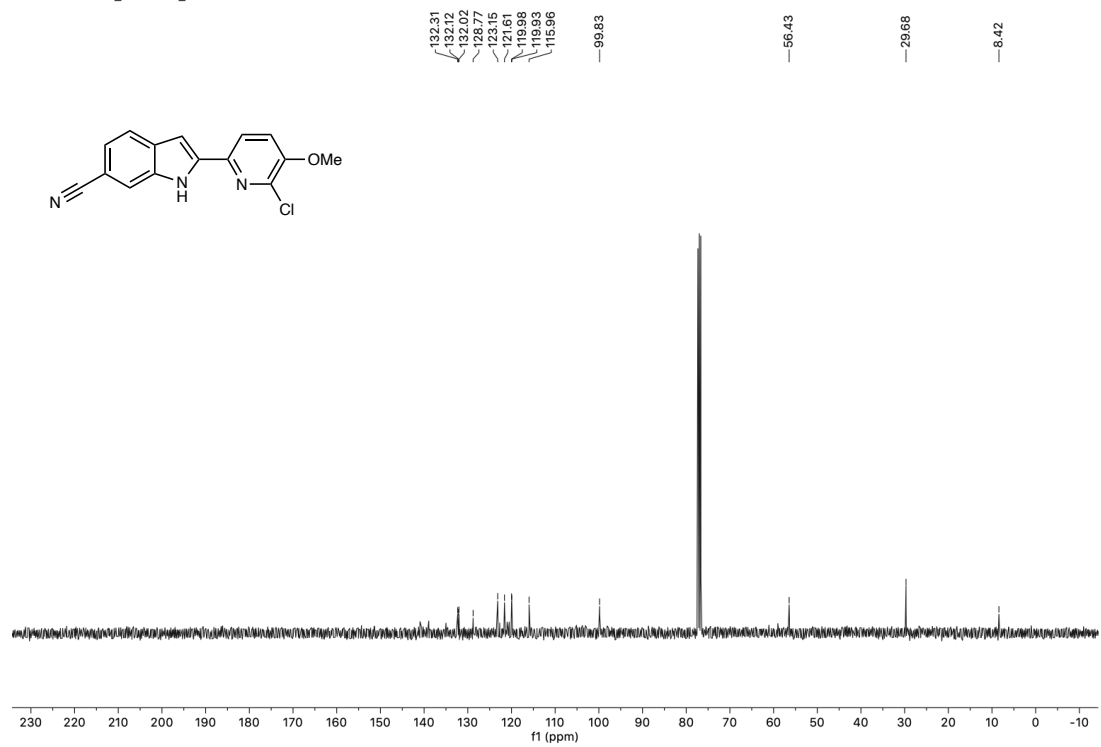
¹³C NMR (101 MHz, CDCl₃): δ 132.3, 132.1, 132.0, 128.8, 123.1, 121.6, 120.0, 119.9, 116.0, 99.8, 56.4, 29.7, 8.4.

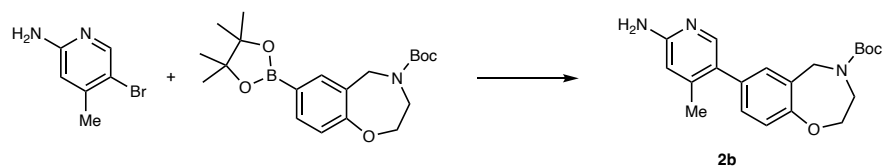
HRMS m/z (ESI⁺) [M+H]⁺: Calc'd for C₁₅H₁₁ClN₃O: 284.0585, found: 284.0588.

lwx-1-293-1211_PROTON_01 — —



lwx-1-293-1220_CARBON_01 — —





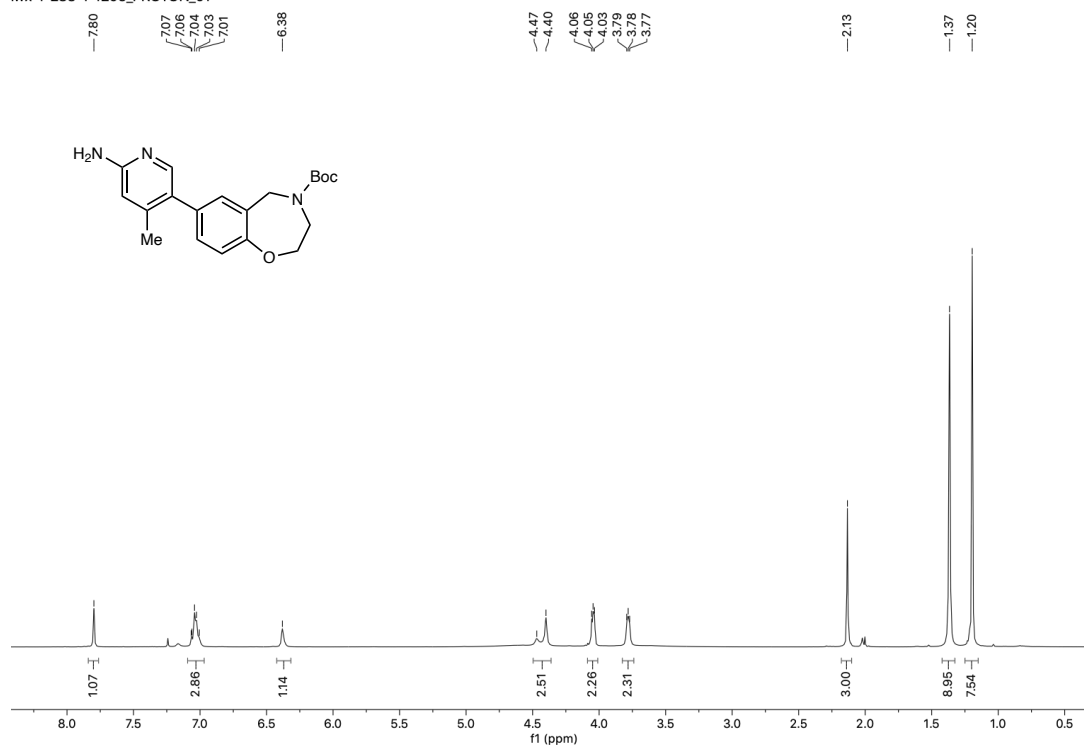
Model Predictions	Experimental Results
<p>Expert: 1, Prediction: 1</p> <p>Reaction Procedure: A mixture of 5-bromo-4-methylpyridin-2-amine (300 mg, 1.62 mmol), tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (644 mg, 1.62 mmol), K₂CO₃ (669 mg, 4.85 mmol) and Pd(dppf)Cl₂ (120 mg, 0.16 mmol) in dioxane (10 mL) and H₂O (2 mL) was stirred at 100 °C. for 16 h under N₂. The reaction mixture was concentrated in vacuo and the residue was purified by Prep-TLC (DCM:MeOH=20:1) to give the title compound (380 mg, 71%) as a yellow solid. ESI-MS (M+H)⁺: 355.2.</p> <p>Reaction Name and Classification: <i>Bromo Suzuki coupling</i></p> <p>Yield and Characterization: [71.0]</p>	<p>Following the predicted procedure for 0.1 mmol (37.5 mg) scale reaction, led to formation of Suzuki-coupling product 2b, which was isolated as light brown foam (36.0 mg, 90%), R_f = 0.42 (DCM:MeOH = 8:1).</p>

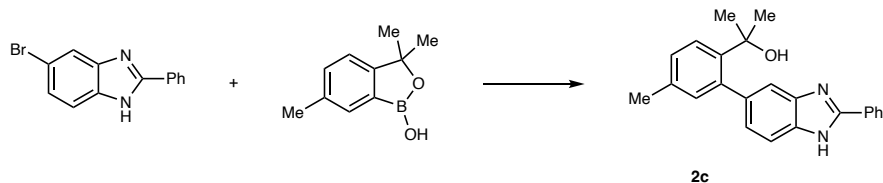
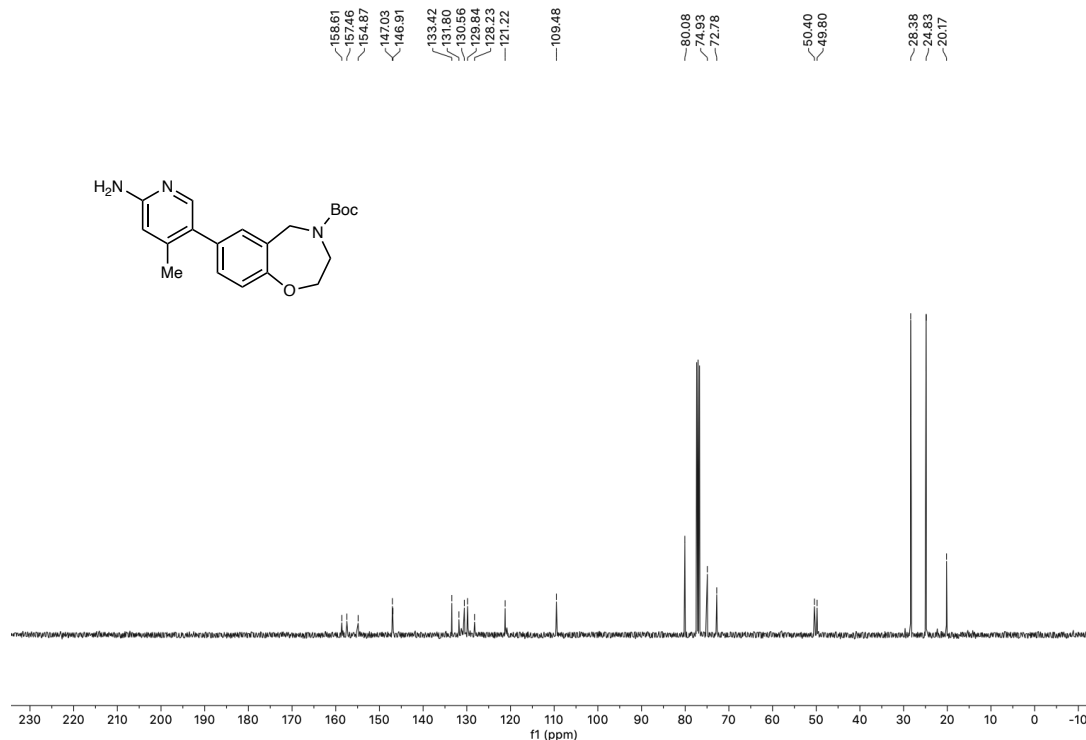
¹H NMR (400 MHz, CDCl₃): δ 7.80 (s, 1H), 7.10 – 6.96 (m, 3H), 6.38 (s, 1H), 4.50 – 4.34 (m, 2H), 4.11 – 3.99 (m, 2H), 3.78 (t, *J* = 4.4 Hz, 2H), 2.13 (s, 3H), 1.37 (s, 11H), 1.20 (s, 9H).

¹³C NMR (101 MHz, CDCl₃): δ 158.6, 157.5, 154.9, 147.0, 146.9, 133.4, 131.8, 130.6, 129.8, 128.2, 121.2, 109.5, 80.1, 74.9, 72.8, 50.4, 49.8, 28.4, 24.8, 20.2.

HRMS *m/z* (ESI⁺) [M+H]⁺: Calc'd for C₂₀H₂₆N₃O₃: 356.1969, found: 356.1965.

lwx-1-283-1-1205_PROTON_01 —





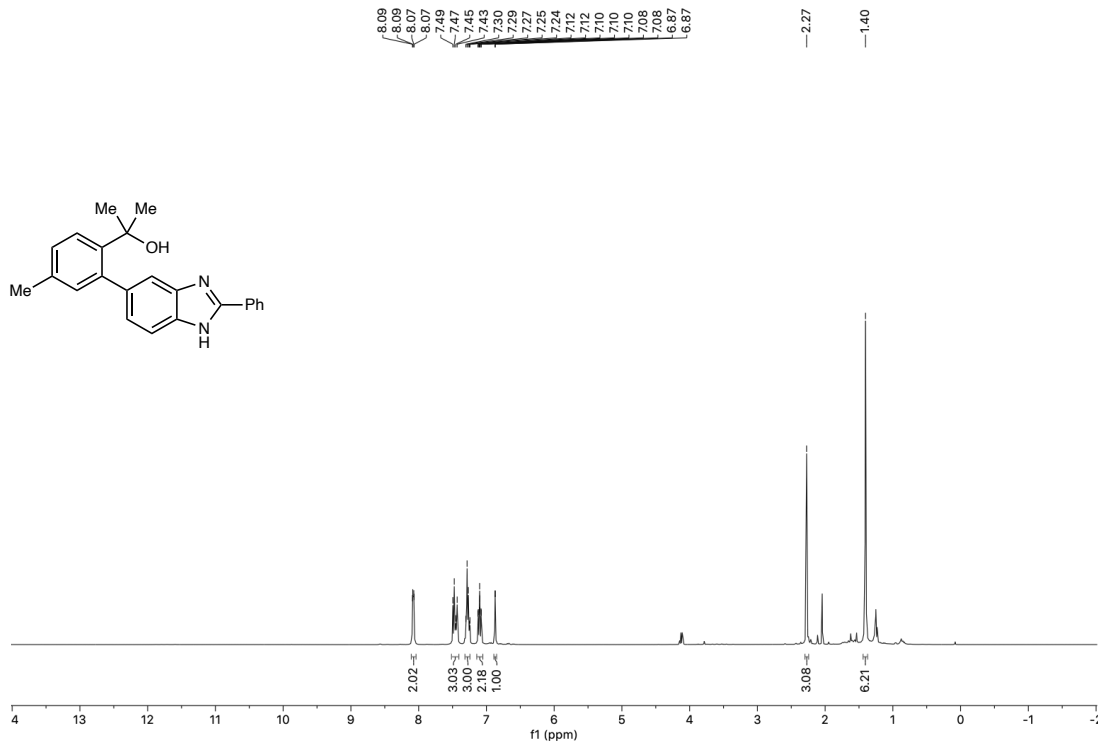
Model Predictions	Experimental Results
<p>Expert: 1, Prediction: 1</p> <p>Reaction Procedure: 5-bromo-2-phenyl-1H-benzimidazole (22 mg, 0.08 mmol) was treated with 4,4,6-trimethyl-3H-benzo[c][1,2]oxaborol-3-ol (18.3 mg, 0.96 mmol), Na₂CO₃ (26.2 mg, 0.24 mmol) and Pd(PPh₃)₄ (9.5 mg, 0.008 mmol) in THF (1.5 mL) and water (0.2 mL) according to Procedure C. The crude product was purified by reverse phase HPLC to give 2-methyl-2-(4-methyl-2-(2-phenyl-1H-benzimidazol-5-yl)phenyl)propan-2-ol (18 mg, 72%). ¹H NMR (CD₃OD) δ 7.84 (d, 1H, J=8.2 Hz), 7.63 (s, 1H), 7.56 (d, 2H, J=8.2 Hz), 7.45 (t, 2H, J=7.6 Hz), 7.33 (t, 1H, J=7.6 Hz), 7.19 (d, 1H, J=7.6 Hz), 7.10 (dd, 1H, J1=7.6 Hz, J2=1.6 Hz), 2.38 (s, 3H), 1.51 (s, 6H); MS (ESI) m/z 347.2 [(M+H)⁺].</p> <p>Reaction Name and Classification: <i>Bromo Suzuki coupling</i></p> <p>Yield and Characterization: [72.0]</p>	<p>Following the predicted procedure for a 0.1 mmol (27.3 mg) scale reaction led to formation of Suzuki-coupling product 2c, which was isolated as white solid (26.7 mg, 78% yield), R_f = 0.23 (hexanes:EtOAc = 1:1).</p>

¹H NMR (400 MHz, CDCl₃): δ 8.08 (dd, J = 7.7, 1.9 Hz, 2H), 7.46 (dd, J = 16.8, 8.4 Hz, 3H), 7.27 (q, J = 9.6, 8.4 Hz, 3H), 7.10 (ddd, J = 9.8, 8.1, 1.8 Hz, 2H), 6.87 (d, J = 2.0 Hz, 1H), 2.27 (s, 3H), 1.40 (s, 6H).

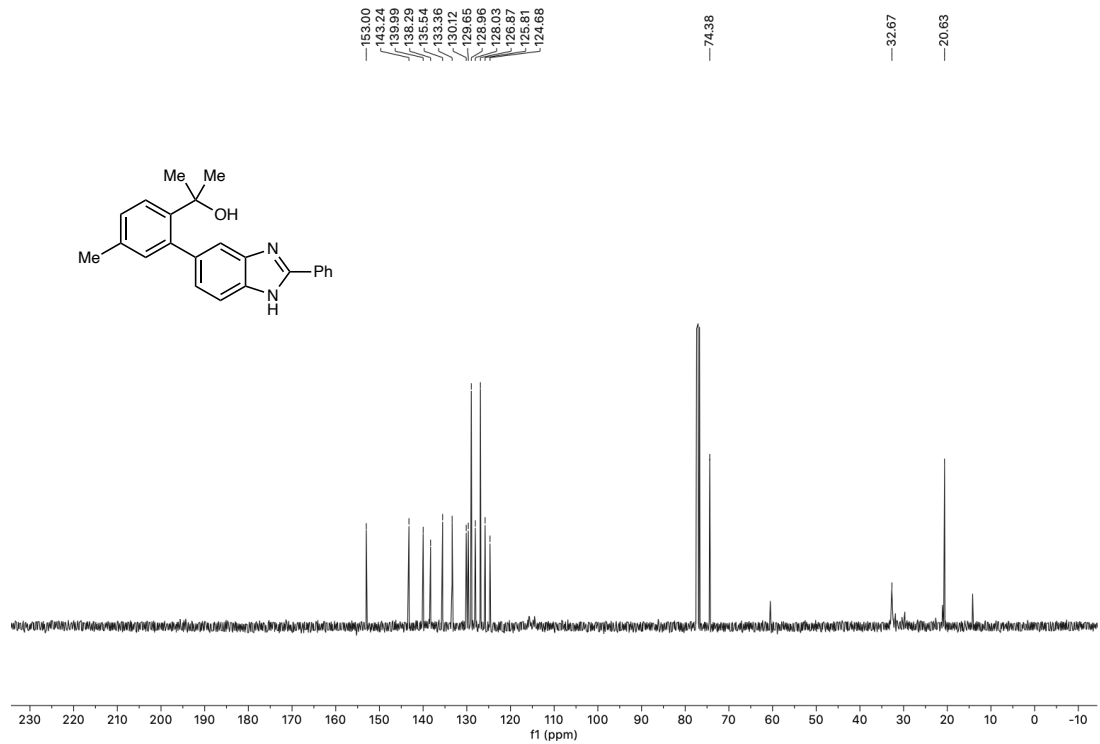
¹³C NMR (101 MHz, CDCl₃): δ 153.0, 143.2, 140.0, 138.3, 135.5, 133.4, 130.1, 129.6, 129.0, 128.0, 126.9, 125.8, 124.7, 74.4, 32.7, 20.6.

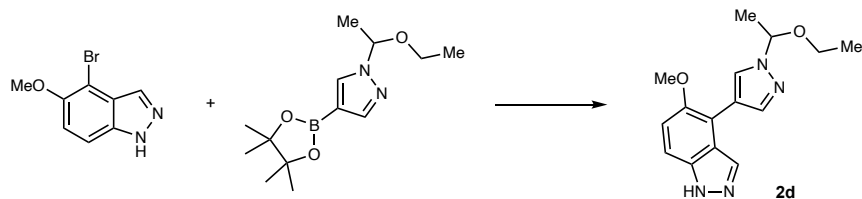
HRMS m/z (ESI⁺) [M+H]⁺: Calc'd for C₂₃H₂₃N₂O: 343.1805, found: 343.1808.

lwx-1-284-3-1205_PROTON_01 — —



lwx-1-284-3-1205_CARBON_01 — —





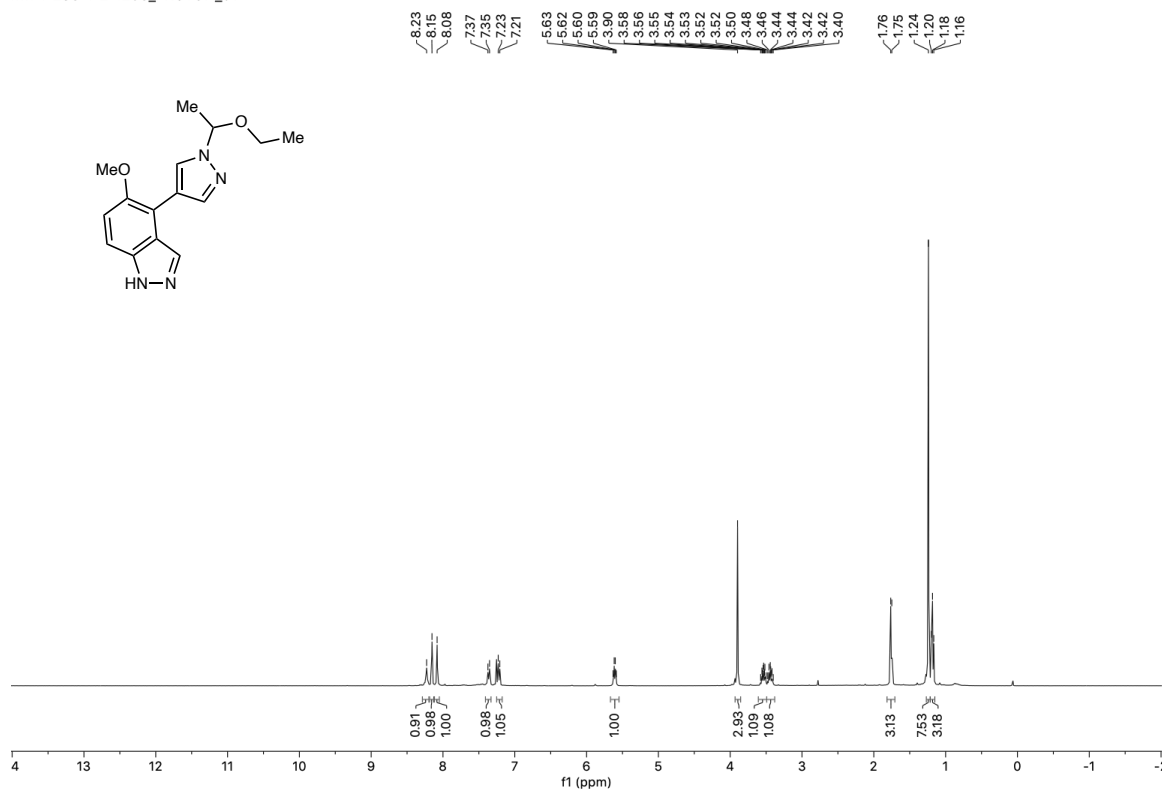
Model Predictions	Experimental Results
<p>Expert: 1, Prediction: 1</p> <p>Reaction Procedure: A mixture of 4-bromo-5-methoxy-1H-indazole (100 mg, 0.45 mmol), 1-(1-ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (120 mg, 0.45 mmol), Pd(dppf)Cl₂ (20 mg) and K₃PO₄ (290 mg, 1.37 mmol) in dioxane (4 mL) and H₂O (0.8 mL) was stirred at 95 °C. under N₂ overnight. The mixture was cooled to rt and washed with H₂O (20 mL) and brine (20 mL). The organic layer was dried and concentrated. The residue was purified by prep-TLC (PE:EtOAc=1:1) to give the title compound (100 mg, 84.7%) as a yellow solid.</p> <p>Reaction Name and Classification: <i>Bromo Suzuki coupling</i></p> <p>Yield and Characterization: [84.7]</p>	<p>Following the predicted procedure, for 0.1 mmol (27.7 mg) scale reaction led to formation of Suzuki-coupling product 2d, which was isolated as pale yellow solid (12.9 mg, 45% yield), R_f = 0.50 (DCM:MeOH = 10:1).</p>

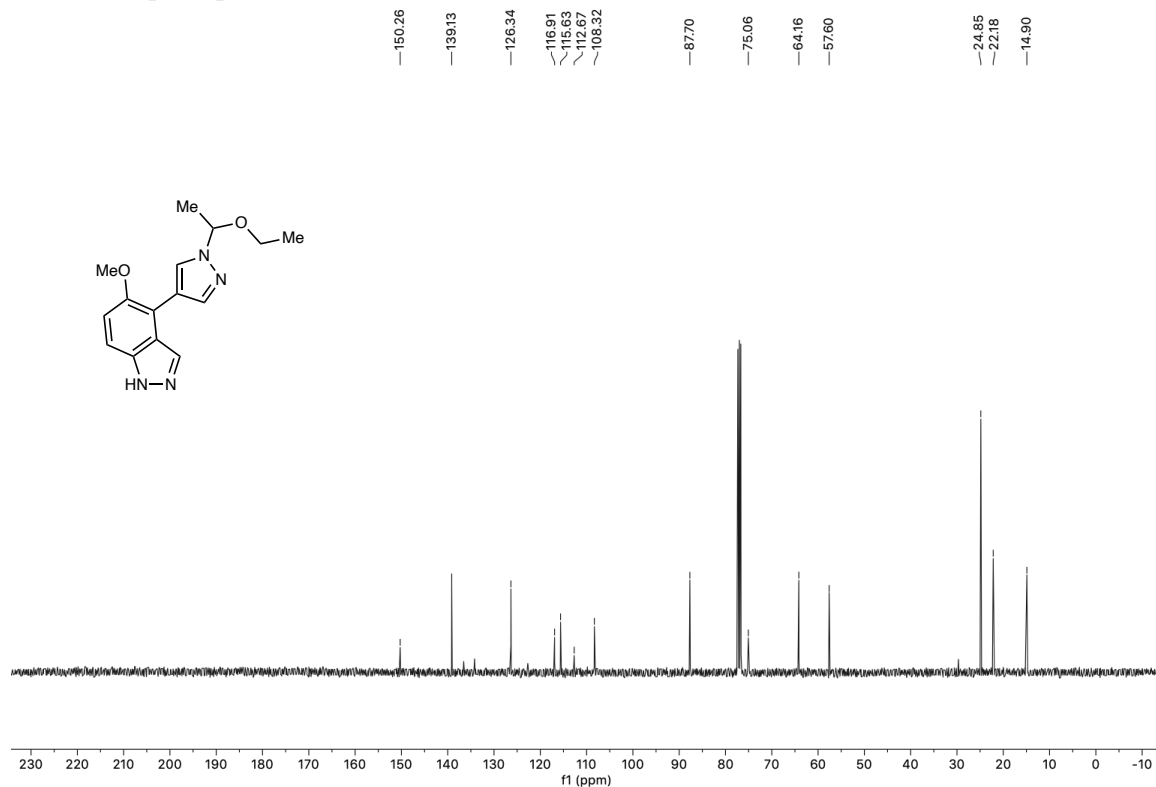
¹H NMR (400 MHz, CDCl₃): δ 8.23 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 5.61 (q, *J* = 6.0 Hz, 1H), 3.90 (s, 3H), 3.54 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.48 – 3.37 (m, 1H), 1.76 (d, *J* = 6.0 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 150.3, 139.1, 126.3, 116.9, 115.6, 112.7, 108.3, 87.7, 75.1, 64.2, 57.6, 24.8, 22.2, 14.9.

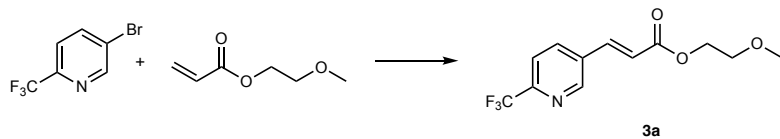
HRMS *m/z* (ESI⁺) [*M*+*H*]⁺: Calc'd for C₁₅H₁₉N₄O₂: 287.1503, found: 287.1512.

lwx-1-285-1-2-1205_PROTON_01 — —





Heck Coupling



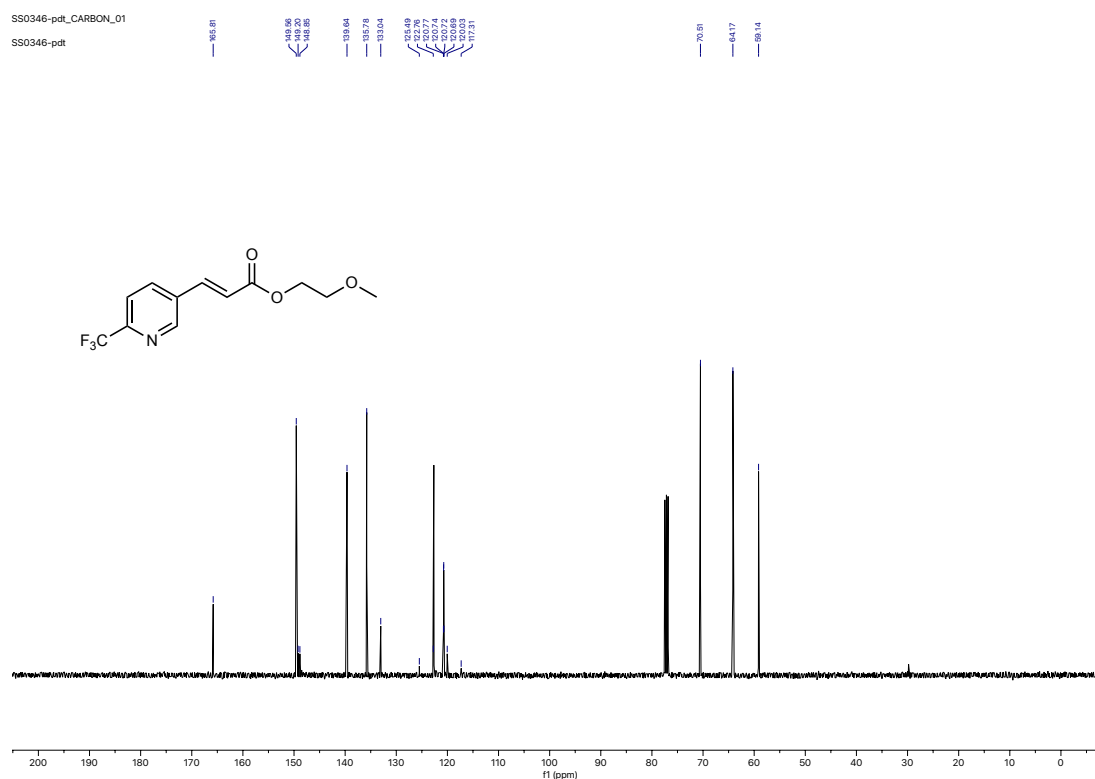
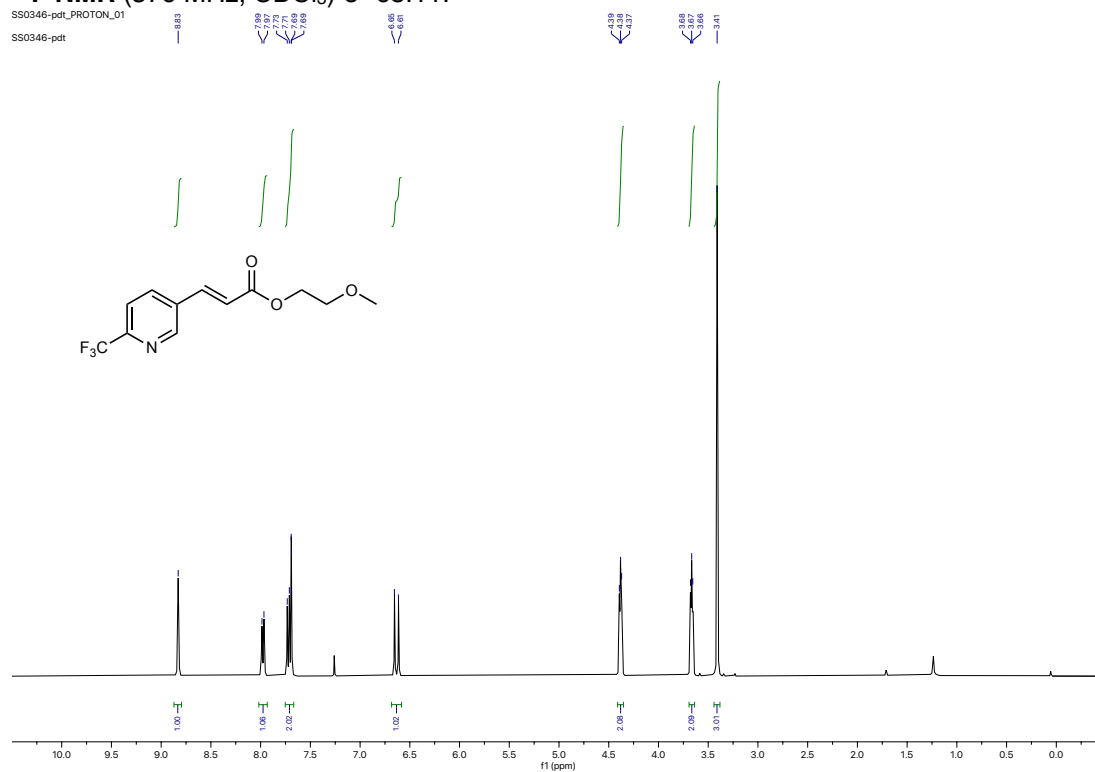
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A mixture of 5-bromo-2-(trifluoromethyl)pyridine (2.19 g, 10 mmol), 2-methoxyethyl acrylate (2.51 g, 20 mmol), Pd(OAc)₂ (45 mg, 0.2 mmol), Et₃N (3.03 g, 30 mmol) and P(o-tol)₃ (122 mg, 0.4 mmol) in DMF (30 mL) was stirred at 95 °C under N₂ for 16 h. The reaction was quenched with water and extracted with EtOAc (20 mL × 3). The combined organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography to give (E)-2-methoxyethyl 3-(6-(trifluoromethyl)pyridin-3-yl)acrylate (1.8 g, 66%) as a yellow oil.</p> <p>Reaction Name and Classification: <i>Bromo-Heck Reaction</i></p> <p>Yield and Characterization: [66.0]</p>	<p>For a 0.2 mmol (45.2 mg) scale reaction following the prediction led to no reaction.</p>
<p>Expert: 2 Prediction:1</p> <p>Reaction Procedure: A mixture of 5-bromo-2-(trifluoromethyl)pyridine (1.0 g, 4.6 mmol), 2-methoxyethyl acrylate (1.12 g, 9.2 mmol), Pd(OAc)₂ (102 mg, 0.46 mmol), tri-o-tolylphosphine (283 mg, 0.92 mmol) and TEA (1.28 mL, 9.2 mmol) in DMF (10 mL) under argon was heated at 130 °C for 1 h. After cooling to room temperature, water (40 mL) was added to the reaction mixture and then extracted by EtOAc (3 × 50 mL). The organic phase was washed with brine, dried over MgSO₄ and evaporated in vacuo to afford the title compound (1.1 g, 74% yield) as a yellow oil.</p>	<p>For a 0.2 mmol scale (45.2 mg) reaction following the prediction heating at 110 °C for 10h led to formation of Heck product 3a, which was isolated as a white solid (40.5 mg, 74% yield). R_f (30% EtOAc in hexane): 0.3.</p>

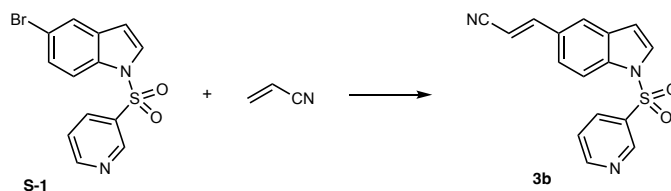
Reaction Name and Classification: *Bromo-Heck Reaction*
Yield and Characterization: [74.0]

¹H NMR (400 MHz, CDCl₃) δ 8.83 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.76 – 7.67 (m, 2H), 6.63 (d, *J* = 16.2 Hz, 1H), 4.38 (t, *J* = 4.5 Hz, 2H), 3.67 (t, *J* = 4.5 Hz, 2H), 3.41 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 165.8, 149.6, 149.0 (q, *J* = 35.1 Hz), 139.6, 135.8, 133.0, 122.8, 121.4 (q, *J* = 274.3 Hz), 120.7 (q, *J* = 2.8 Hz), 70.5, 64.2, 59.1.

¹⁹F NMR (376 MHz, CDCl₃) δ -68.11.





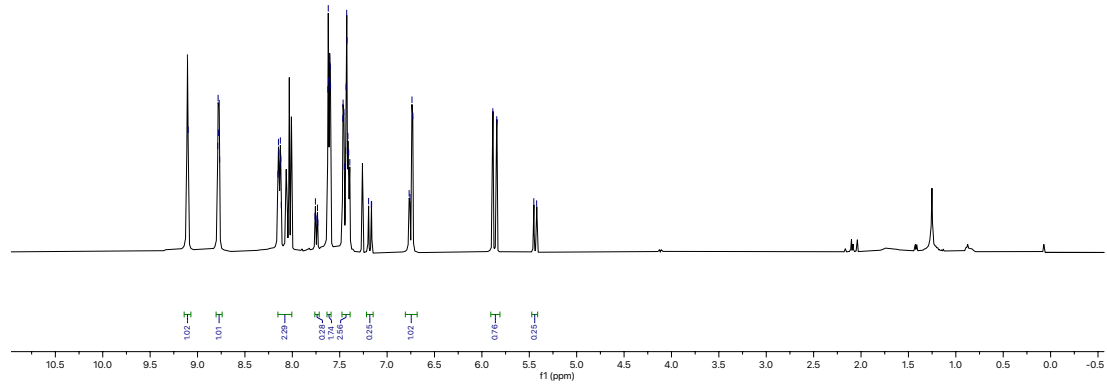
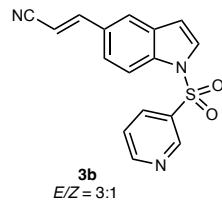
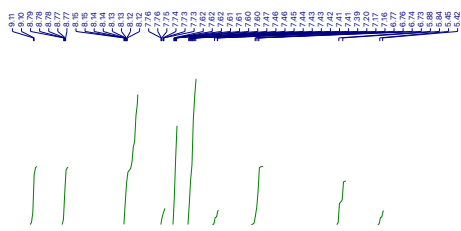
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1 Reaction Procedure: A mixture of 5-bromo-1-(pyridin-3-ylsulfonyl)-1H-indole (0.15 g, 0.44 mmol), acrylonitrile (0.07 g, 1.32 mmol), palladium acetate (0.01 g, 0.04 mmol), triphenylphosphine (0.02 g, 0.08 mmol) and triethylamine (0.06 ml, 0.44 mmol) in DMF (1 ml) was stirred at 100 °C for 4 hours. The mixture was poured into sodium bicarbonate solution and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give (E)-3-(1-(pyridin-3-ylsulfonyl)-1H-indol-5-yl)acrylonitrile (0.12 g, 80%). Reaction Name and Classification: <i>Bromo Heck reaction</i> Yield and Characterization: [80.0]</p>	<p>For a 0.2 mmol (67.5 mg) scale reaction following the prediction and stirring at 100 °C for 36 hours, product 3b was isolated as yellow solid (54.0 mg, 87% yield, 3:1 <i>E/Z</i> ratio). R_f (30% EtOAc in hexane): 0.30.</p>

¹H NMR (400 MHz, CDCl₃) δ 9.10 (d, *J* = 3.0 Hz, 1H), 8.81 – 8.74 (m, 1H), 8.16 – 8.00 (m, 2.25 H), 7.77 – 7.72 (m, 0.25 H), 7.66 – 7.58 (m, 1.75 H), 7.49 – 7.38 (m, 2.5 H), 7.21 – 7.13 (m, 0.25 H), 6.80 – 6.71 (m, 1H), 5.86 (d, *J* = 16.0 Hz, 0.75 H (*E*)), 5.44 (d, *J* = 12.1 Hz, 0.25 H (*Z*)).

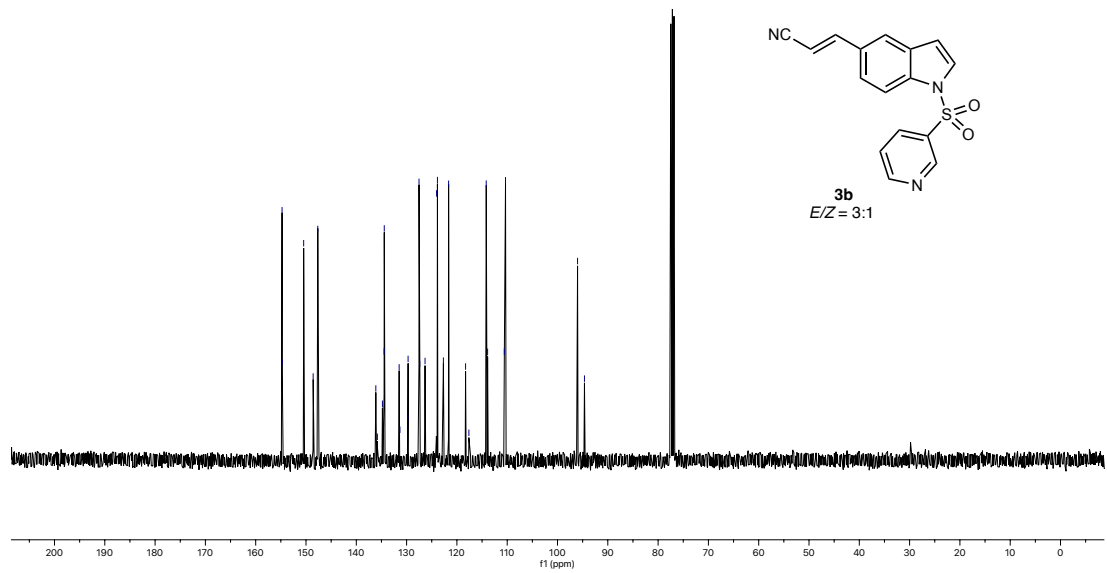
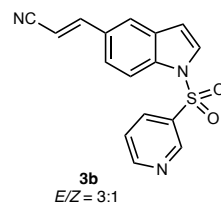
¹³C NMR (101 MHz, CDCl₃) δ 154.8, 154.7, 150.5, 148.6, 147.7, 136.1, 135.8, 134.8, 134.5, 134.4, 131.5, 131.3, 129.7, 129.7, 127.5, 127.4, 126.3, 124.0, 123.9, 122.7, 121.7, 118.3, 117.6, 114.2, 113.9, 110.6, 110.3, 96.0, 94.6

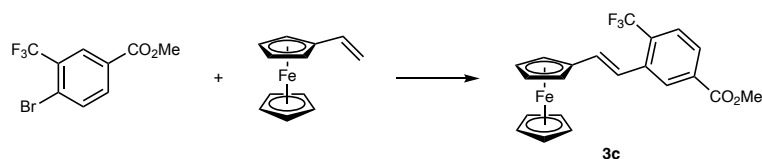
HRMS *m/z* (ESI⁺) [*M*+*H*]⁺: Calc'd for C₁₅H₁₁ClN₃O: 310.0572, found: 310.0656.

SS0356-pdt_PROTON_01
SS0356-pdt



SS0356-pdt_CARBON_01
SS0356-pdt





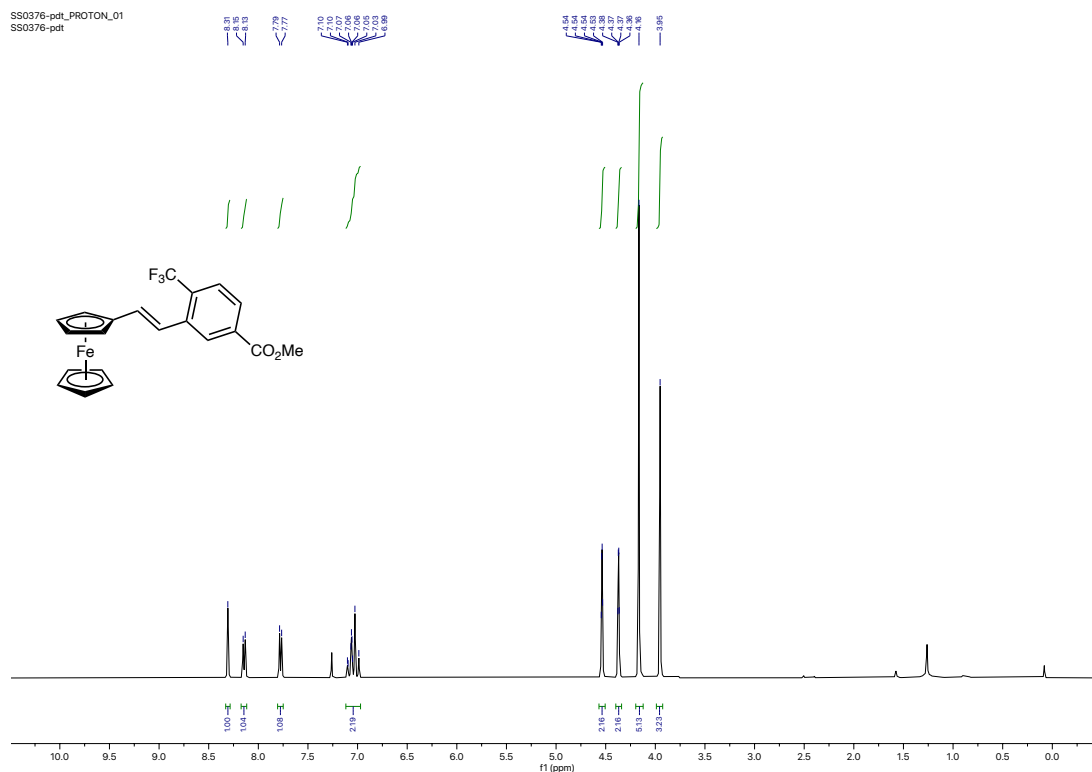
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A mixture of 1,2,3,4,5,6-hexahydro-FeC₄ (2.0 g, 8.3 mmol), methyl 4-bromo-3-(trifluoromethyl)benzoate (2.6 g, 9.2 mmol), palladium acetate (0.19 g, 0.83 mmol), tri-(o-tolyl)phosphine (0.51 g, 1.65 mmol), triethylamine (20 mL) and acetonitrile (20 mL) was heated under nitrogen at 80 °C. for 16 h. The reaction mixture was cooled to room temperature. The mixture was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was separated. The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in petroleum ether) to give the title compound as a brown solid (1.2 g, 35%)</p> <p>Reaction Name and Classification: None.</p> <p>Yield and Characterization: [35.0]</p>	<p>For a 0.2 mmol (48.2 mg) scale reaction following the predicted procedure, product 3c was isolated as brown-red solid (45.2 mg, 55% yield). R_f (5% EtOAc in hexane): 0.25.</p>

¹H NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.12 – 6.97 (m, 2H), 4.54 (q, *J* = 1.7 Hz, 2H), 4.37 (q, *J* = 1.8 Hz, 2H), 4.16 (s, 5H), 3.95 (s, 3H).

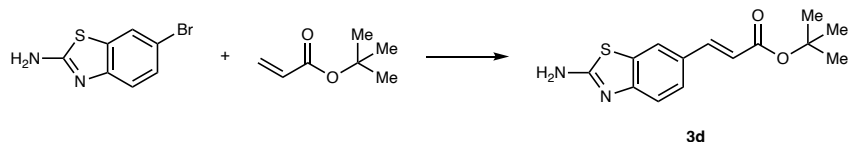
¹³C NMR (101 MHz, CDCl₃) δ 166.1, 141.5 (d, *J* = 1.6 Hz), 134.5, 132.8, 128.0, 127.7 (q, *J* = 5.8 Hz), 126.8 (q, *J* = 30.5 Hz), 126.5, 124.2 (q, *J* = 274.0 Hz), 120.7 (d, *J* = 2.3 Hz), 81.8, 70.1, 69.6, 67.8, 52.5.

¹⁹F NMR (376 MHz, CDCl₃) δ -59.88.

HRMS *m/z* (ESI⁺) [*M*+*H*]⁺: Calc'd for C₁₅H₁₁ClN₃O: 414.0368, found: 414.0564.



Previously unsuccessful Heck Coupling^[6]



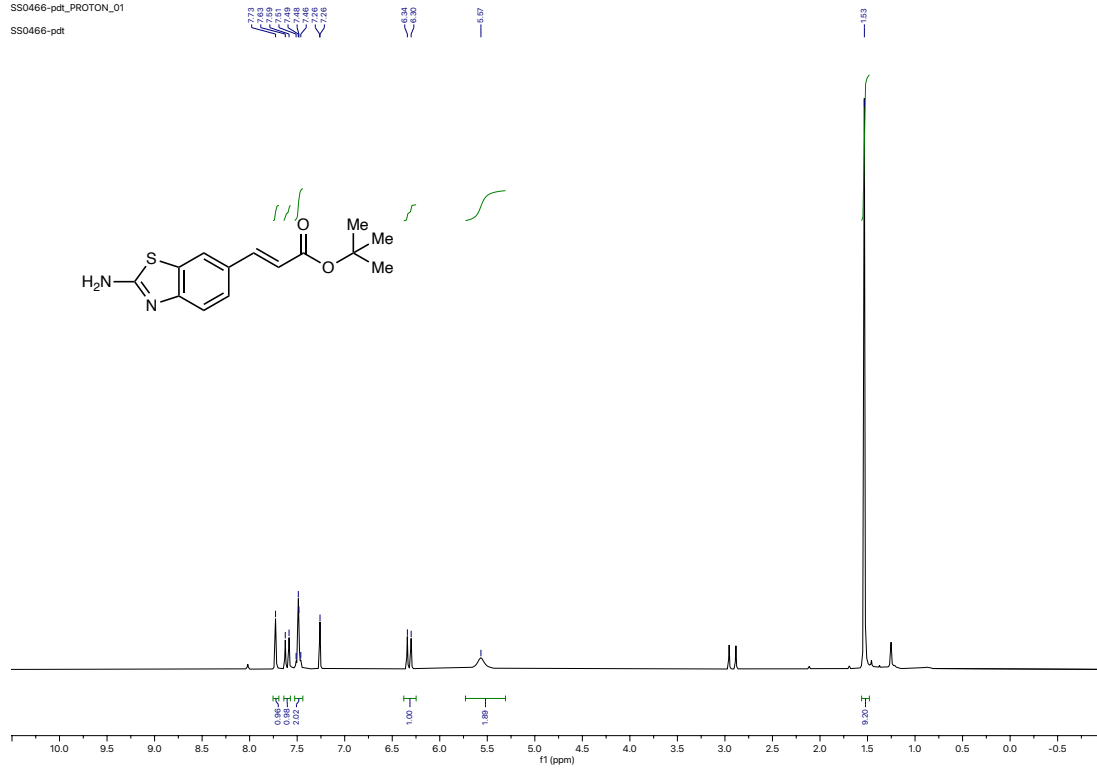
Model Predictions	Experimental Results
<p>Expert: 1 Prediction: 1 Reaction Procedure: A mixture of 2-amino-6-bromobenzothiazole (2.5 g, 11.2 mmol), tert-butyl acrylate (3.4 g, 27.6 mmol), palladium acetate (125 mg, 0.56 mmol), tri(o-tolyl)phosphine (625 mg, 2.04 mmol) and triethylamine (2.7 g, 27.6 mmol) in N,N-dimethylformamide (50 mL) was heated at 110 °C. for 16 h. The reaction was cooled to room temperature and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (petroleum ether/EtOAc=10/1 to 3/1) to afford (<i>E</i>)-tert-butyl 3-(2-aminobenzothiazol-6-yl)acrylate (1.5 g, 53%) as a yellow solid. Reaction Name and Classification: <i>Bromo Heck reaction</i> Yield and Characterization: [53.0]</p>	<p>For a 0.218 mmol (50.0 mg) scale reaction following the prediction led to 57% NMR yield of 3d. 3d was isolated as yellowish solid (68.0 mg, 51% yield). R_f (50% EtOAc in hexane): 0.35.</p>
<p>Expert: 2 Prediction: 1 Reaction Procedure: A mixture of 6-bromobenzothiazol-2-amine (1.00 g, 4.65 mmol), tert-butyl acrylate (1.65 mL, 10.8 mmol), palladium acetate (104 mg, 0.465 mmol), tri-o-tolylphosphine (283 mg, 0.930 mmol), and triethylamine (1.64 mL, 11.8 mmol) in DMF (10.0 mL) was heated at 90 °C. under argon overnight. After cooling to room temperature, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was washed with water (1×100 mL) and brine (1×100 mL), dried over anhydrous Na₂SO₄, filtered, and evaporated to dryness. The residue was purified by silica gel chromatography (0-100% EtOAc in petroleum ether) to afford (<i>E</i>)-tert-butyl 3-(2-amino-benzothiazol-6-yl)acrylate (1.10 g, 81%) as a yellow solid. Reaction Name and Classification: <i>Bromo Heck reaction</i> Yield and Characterization: [81.0]</p>	<p>For a 0.218 mmol (50.0 mg) scale reaction following the prediction and heating at 90 °C for 16h led to 57% NMR yield of 3d.</p>

¹H NMR (400 MHz, CDCl₃) δ 7.73 (s, 1H), 7.61 (d, *J* = 15.9 Hz, 1H), 7.52 – 7.44 (m, 2H), 6.32 (d, *J* = 15.8 Hz, 1H), 5.57 (bs, 2H), 1.53 (s, 9H).

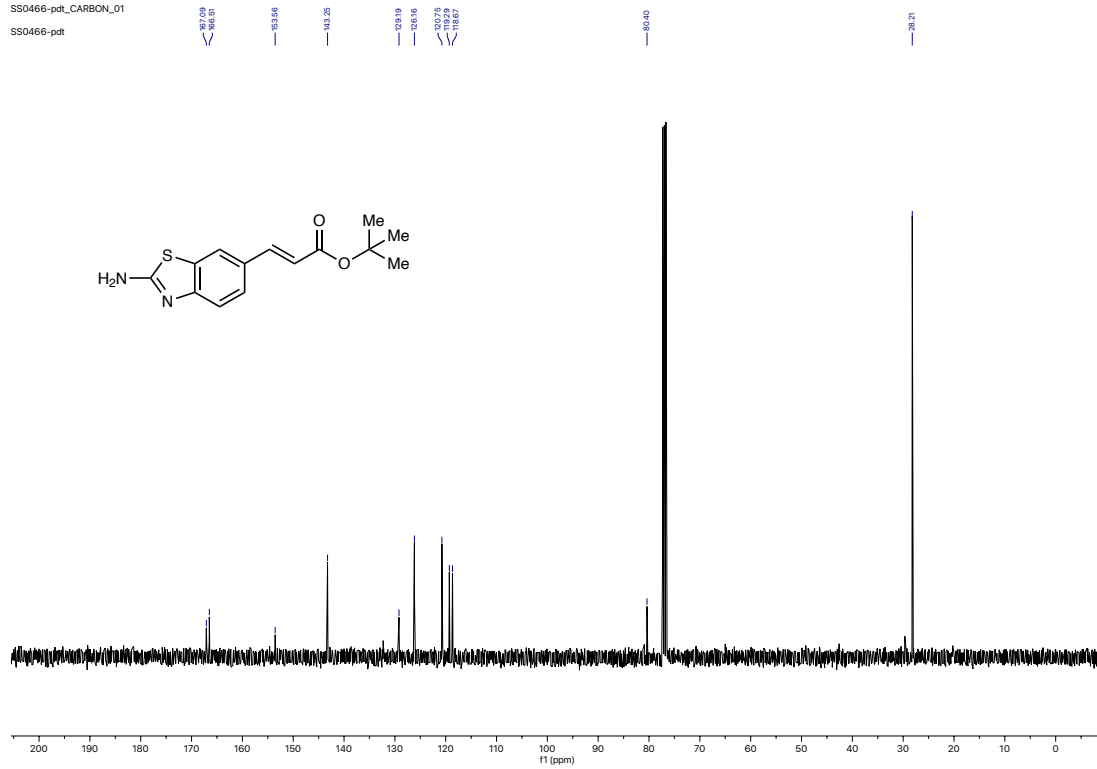
¹³C NMR (101 MHz, CDCl₃) δ 167.1, 166.5, 153.6, 143.3, 129.2, 126.2, 120.8, 119.3, 118.7, 80.4, 28.2.

HRMS *m/z* (ESI⁺) [*M*+*H*]⁺: Calc'd for C₁₅H₁₁ClN₃O: 277.0932, found: 277.1016.

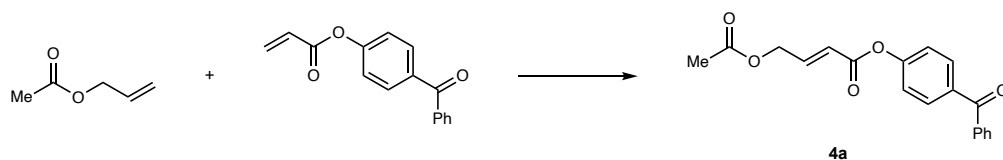
SS0466-pdt_PROTON_01
SS0466-pdt



SS0466-pdt_CARBON_01
SS0466-pdt



Olefin Metathesis



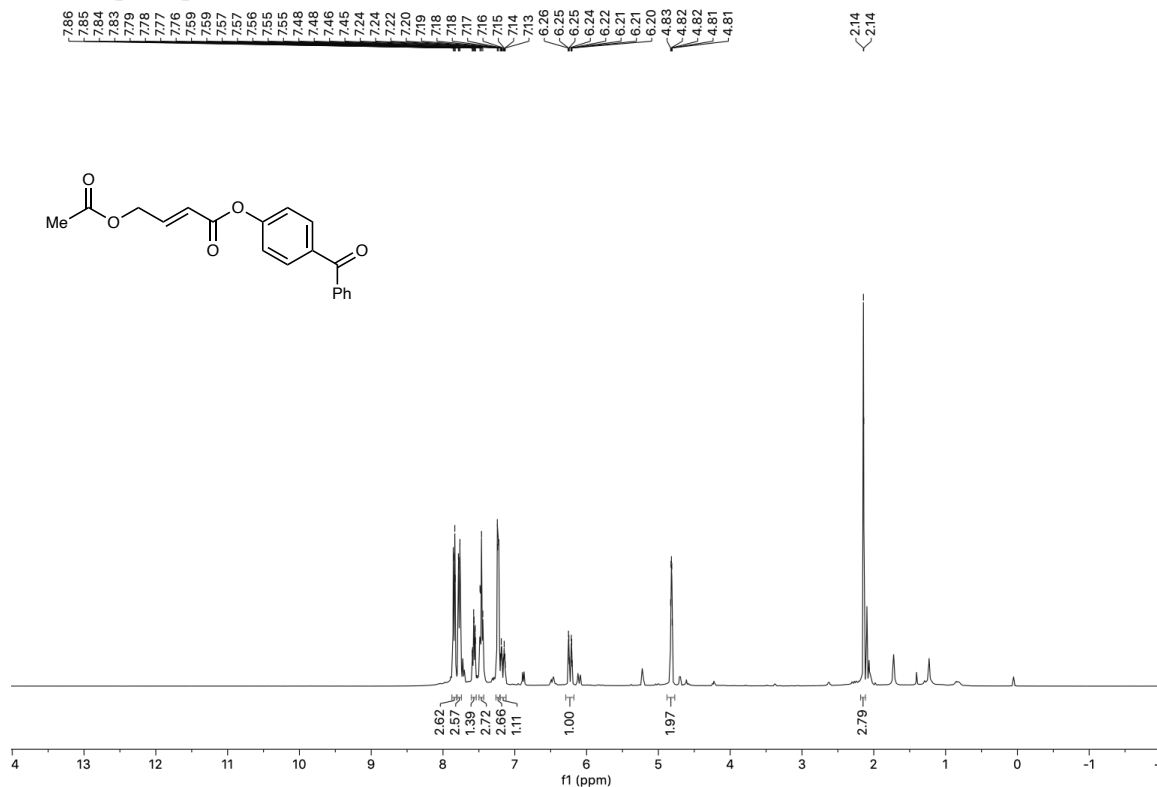
Model Predictions	Experimental Results
<p>Expert: 1, Prediction: 1 Reaction Procedure: To a solution of 4-benzoylphenyl acrylate (3.0 g, 11.6 mmol) and <i>cis</i>-1,4-diacetyloxy-2-butene (2.0 g, 11.6 mmol) in dichloromethane (50 mL) was added Grubbs 2nd generation catalyst (0.9 g, 1.1 mmol) and the mixture was refluxed for 12 hours. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (10% ethyl acetate/hexane) to give 4-acetyloxy-2E-but-2-enoic acid p-benzoylphenyl ester (2.2 g, 59%) as a white solid.</p> <p>Reaction Name and Classification: <i>Olefin metathesis</i></p> <p>Yield and Characterization: [59.0]</p>	<p>Following the predicted procedure on a 0.4 mmol (101.0 mg) led to formation of product 4a, which was isolated as colorless oil (96.0 mg, 74% yield), $R_f = 0.63$ (hexanes:EtOAc = 8:1).</p>

¹H NMR (400 MHz, CDCl₃): δ 7.87 – 7.82 (m, 2H), 7.80 – 7.75 (m, 2H), 7.60 – 7.54 (m, 1H), 7.50 – 7.43 (m, 2H), 7.26 – 7.21 (m, 2H), 7.20 – 7.12 (m, 1H), 6.23 (dt, $J = 15.7, 2.0$ Hz, 1H), 4.82 (dt, $J = 4.1, 2.0$ Hz, 2H), 2.14 (s, 3H).

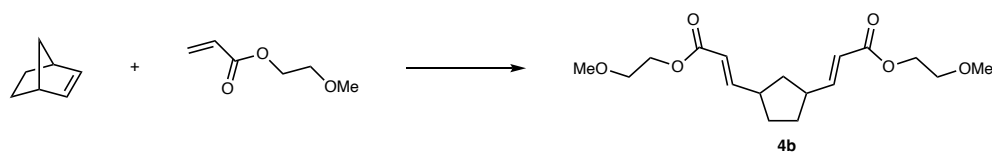
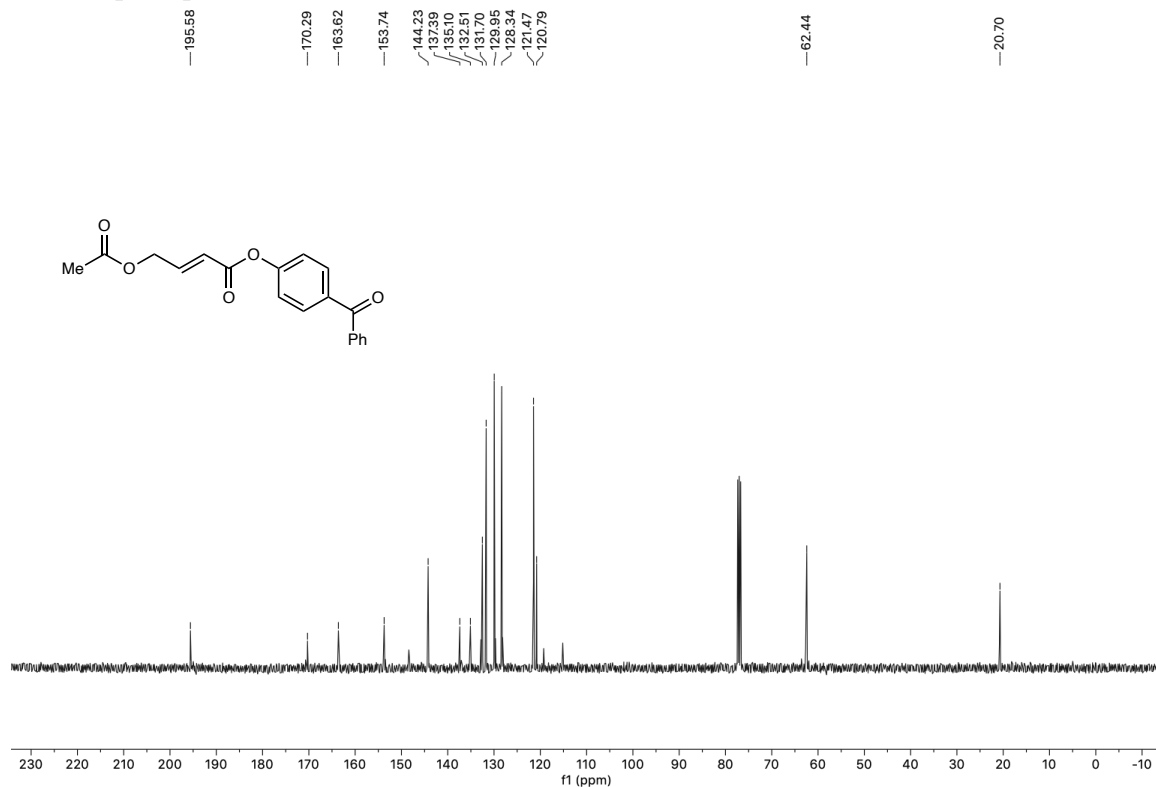
¹³C NMR (101 MHz, CDCl₃): δ 195.6, 170.3, 163.6, 153.7, 144.2, 137.4, 135.1, 132.5, 131.7, 130.0, 128.3, 121.5, 120.8, 62.4, 20.7.

HRMS (ESI+) [**M+H**]⁺: Calc'd for C₁₉H₁₇O₅: 325.1071 m/z, found: 325.1072 m/z.

lwx-1-290-1211_PROTON_01 — —



lwx-1-290-1211_CARBON_01 — —



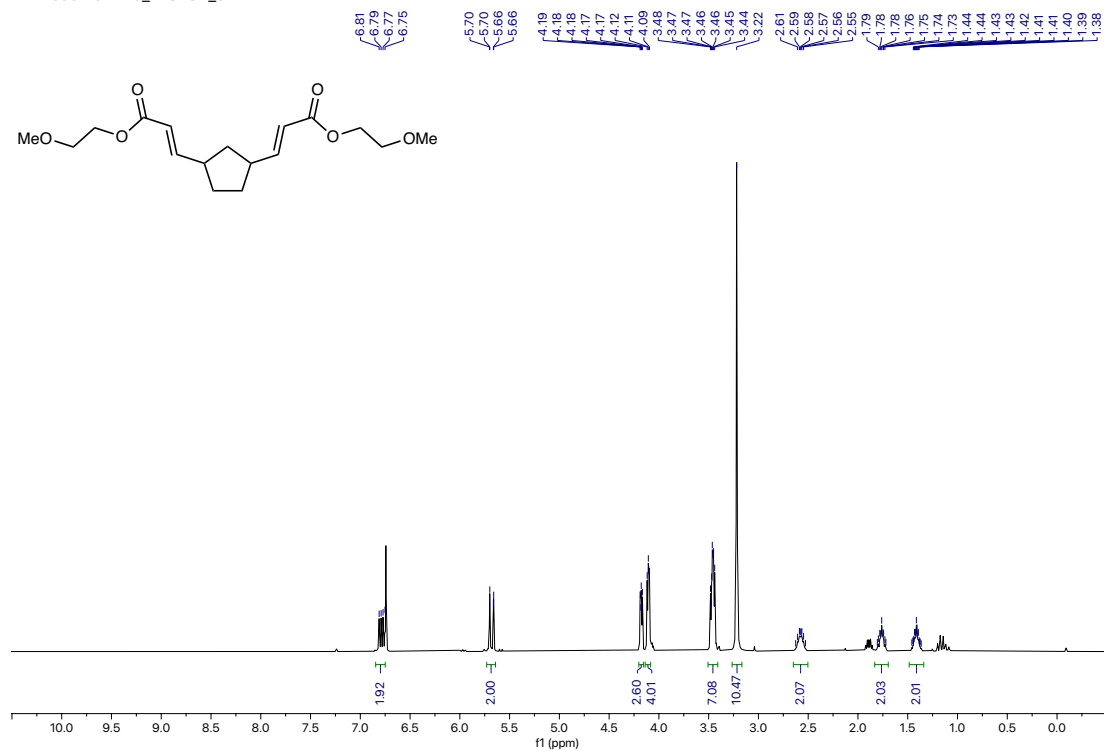
Model Predictions (Beam group: 20)	Experimental Results
<p>Expert: 1, Prediction: 1</p> <p>Reaction Procedure: The pinnamate 1 (164 mg, 1.25 mmol) was dissolved in CH₂Cl₂ (2 mL) and methyl pinnamate 2 (177 mg, 1.25 mmol) was added to the solution. The solution was degassed using the freeze-pump-thaw method. To the resulting solution was added Grubbs' catalyst (26.4 mg, 0.031 mmol) and the mixture was stirred at room temperature for 12 h. The reaction was then filtered through a pad of celite and the solvent was removed under reduced pressure. The crude product was purified using silica gel chromatography (10% EtOAc/hexanes) to give 3 (88 mg, 33%) as a yellow oil.</p> <p>Reaction Name and Classification: None</p> <p>Yield and Characterization: [33.0]</p>	<p>Following the predicted procedure on a 0.6 mmol scale (56.5 mg) led to formation of product 4b, which was isolated as colorless oil (186.0 mg, 95% yield), R_f = 0.55 (hexanes:EtOAc = 10:1).</p>

¹H NMR (400 MHz, CDCl₃): δ 6.78 (dd, *J* = 15.6, 7.9 Hz, 2H), 5.68 (dd, *J* = 15.6, 1.2 Hz, 2H), 4.22 – 4.14 (m, 3H), 4.14 – 4.07 (m, 4H), 3.46 (ddd, *J* = 9.7, 6.0, 3.7 Hz, 7H), 3.22 (s, 10H), 2.65 – 2.48 (m, 2H), 1.82 – 1.69 (m, 2H), 1.42 (tq, *J* = 9.7, 7.2, 5.7 Hz, 2H).

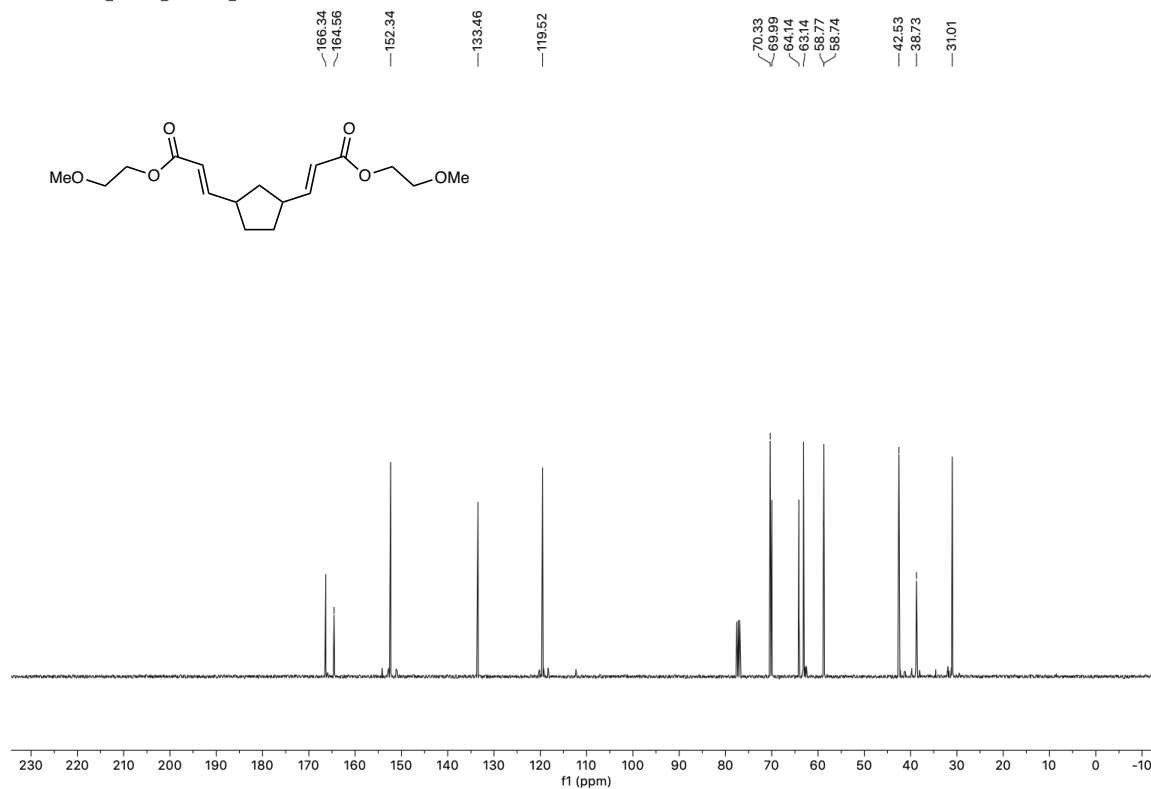
¹³C NMR (101 MHz, CDCl₃): δ 166.3, 164.6, 152.3, 133.5, 119.5, 70.3, 70.0, 64.1, 63.1, 58.8, 58.7, 42.5, 38.7, 31.0.

HRMS (ESI+) [M+H]⁺: Calc'd for C₁₇H₂₇O₆: 327.1802 m/z, found: 327.1804 m/z.

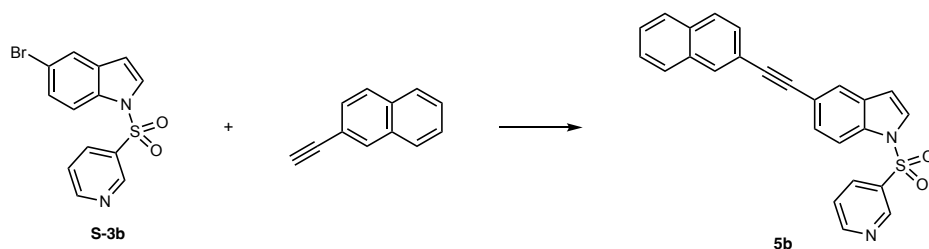
lwx-1-300-B3-1220_PROTON_01 — —



lwx-1-300-B3_2-1220_CARBON_01 — —



Sonogashira Coupling



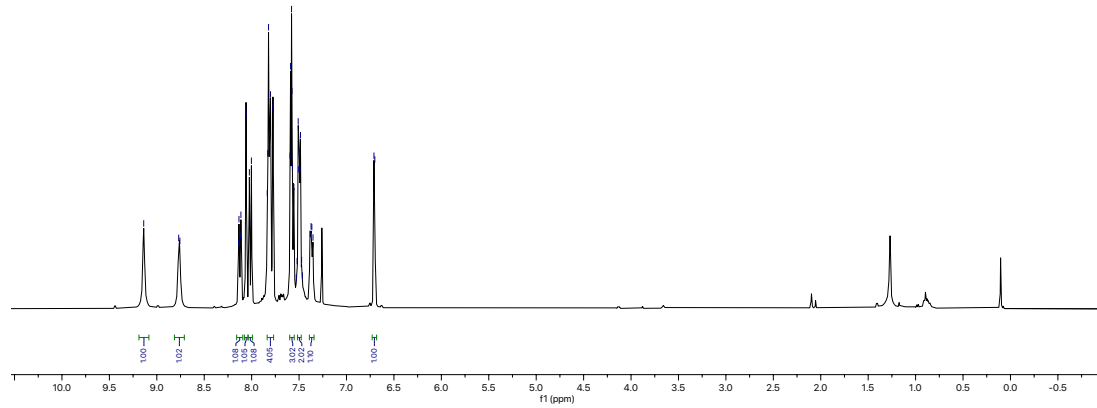
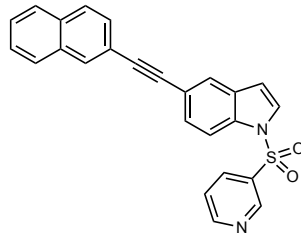
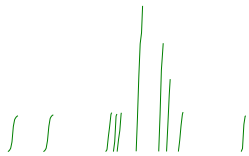
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: To a solution of methyl 1-(2-bromobenzoyl)-1H-indole-4-carboxylate (100 mg, 0.28 mmol, 1.0 eq) in DMF (5 mL) was added Pd(PPh₃)₂Cl₂ (20 mg, 0.028 mmol, 0.1 eq), Pd(PPh₃)₂Cl₂ (10.0 mg, 0.014 mmol, 0.1 eq), Cul (10 mg, 0.056 mmol, 0.2 eq) and 2-ethynynaphthalene (74 mg, 0.51 mmol, 1.8 eq). The mixture was dissolved in DMF (5 mL) and Et₃N (0.12 mL, 0.86 mmol, 3.0 eq) was added. The reaction was stirred at 80 °C. for 16 h. The mixture was diluted with H₂O and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford methyl 1-(2-(naphthalen-2-ylethynyl)benzoyl)-1H-indole-4-carboxylate (100 mg, 84%) as a brown solid.</p> <p>Reaction Name and Classification: <i>Bromo Sonogashira coupling</i></p> <p>Yield and Characterization: [84.0]</p>	<p>Following the predicted procedure, to methyl 1-(2-bromobenzoyl)-1H-indole-4-carboxylate (50 mg, 0.148 mmol, 1.0 eq), Pd(PPh₃)₂Cl₂ (10.0 mg, 0.014 mmol, 0.1 eq), Cul (5.0 mg, 0.028 mmol, 0.2 eq) under nitrogen, DMF (3 mL) and Et₃N (0.06 mL, 0.43 mmol, 3.0 eq) was added and the reaction was stirred at 80 °C. for 16 h. Following the predicted workup procedure, product 5b was isolated as brown solid (58.7 mg, 80% yield). R_f (30% EtOAc in hexane): 0.20.</p>

¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.76 (d, *J* = 5.0 Hz, 1H), 8.16 – 8.09 (m, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.86 – 7.75 (m, 4H), 7.61 – 7.54 (m, 3H), 7.53 – 7.46 (m, 2H), 7.37 (dd, *J* = 8.2, 4.8 Hz, 1H), 6.71 (d, *J* = 3.7 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 154.5, 147.5, 134.7, 134.3, 134.2, 133.0, 132.8, 131.4, 131.0, 128.6, 128.4, 128.0, 127.8, 127.8, 126.9, 126.7, 126.6, 125.1, 123.8, 120.5, 119.1, 113.5, 110.1, 89.6, 89.4.

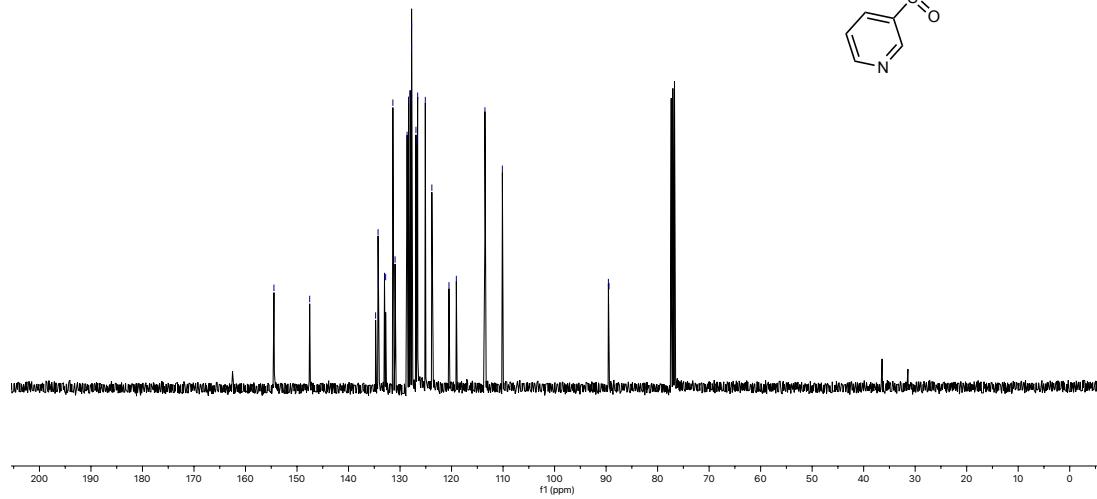
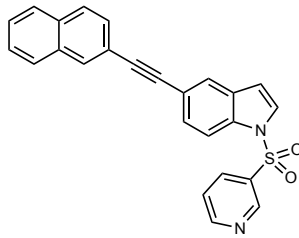
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SS0500-2pdt

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8.75
8.14
8.13
8.11
8.11
8.08
8.00
7.83
7.83
7.81
7.81
7.77
7.77
7.59
7.59
7.56
7.56
7.55
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7.50
7.49
7.47
7.39
7.37
7.37
6.70

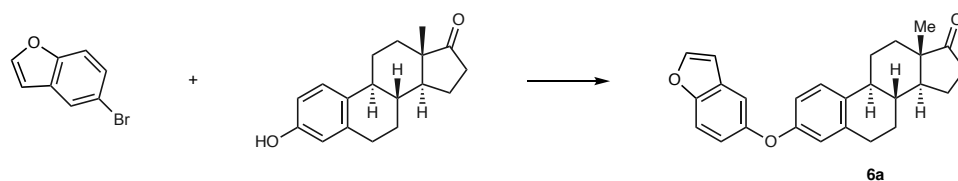


SS0500-pdt_CARBON_01
SS0500-pdt

154.48
137.64
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134.50
134.50
132.80
132.80
131.94
129.63
129.03
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126.98
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126.82
119.07
113.82
110.14
89.85
89.83



Ullman Coupling

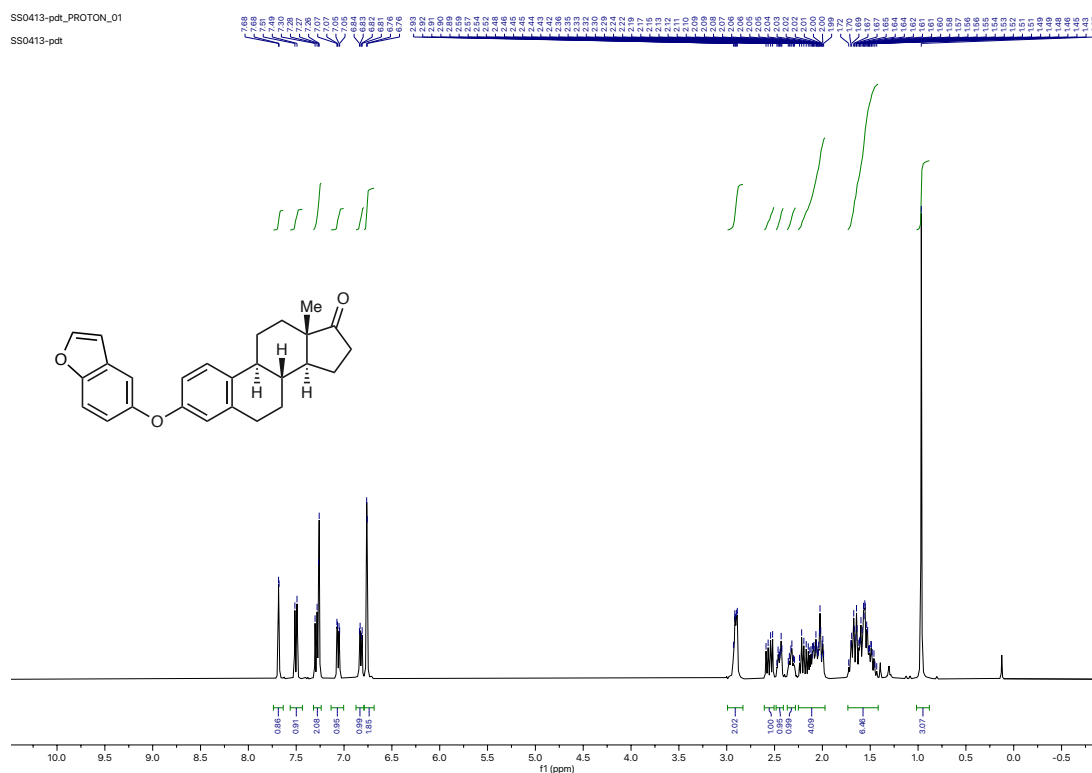


Model Predictions (Beam group: 4)	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: To a solution of estradiol (50 mg, 0.18 mmol) in NMP (2 mL) were added 5-bromobenzofuran (68 mg, 0.36 mmol), copper(I) chloride (18 mg, 0.18 mmol), cesium carbonate (117 mg, 0.36 mmol) and 2,2,6,6-tetramethylheptane-3,5-dione (16 mg, 0.09 mmol). The resulting mixture was stirred for 23 h at 120 °C. The reaction mixture was cooled to room temperature and quenched with water (25 mL). The mixture was extracted with EtOAc (3×25 mL). The combined organic layers were washed with water (3×20 mL) and brine (1×20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc:petroleum ether=1:1) to give the title compound (20 mg, 30%) as a solid.</p> <p>Reaction Name and Classification: None</p>	<p>For a 0.185 mmol (50.0 mg) scale reaction with stirred for 36 h at 120 °C, product 6a was isolated (purified by silica gel chromatography) as white solid (42.0 mg, 59% yield). R_f (10% EtOAc in hexane): 0.15.</p>

¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J* = 2.2 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.06 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.82 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 2H), 2.94 – 2.87 (m, 2H), 2.55 (dd, *J* = 18.9, 8.6 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.37 – 2.27 (m, 1H), 2.26 – 1.98 (m, 4H), 1.75 – 1.41 (m, 6H), 0.97 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 221.1, 156.6, 152.8, 151.5, 146.2, 138.3, 134.2, 128.4, 126.7, 118.0, 117.1, 115.5, 112.2, 111.4, 106.9, 50.5, 48.1, 44.2, 38.4, 36.0, 31.7, 29.7, 26.6, 26.0, 21.7, 14.0.

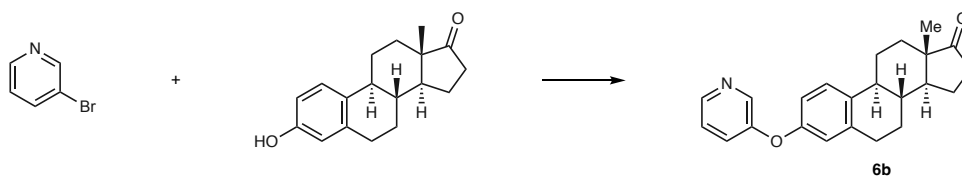
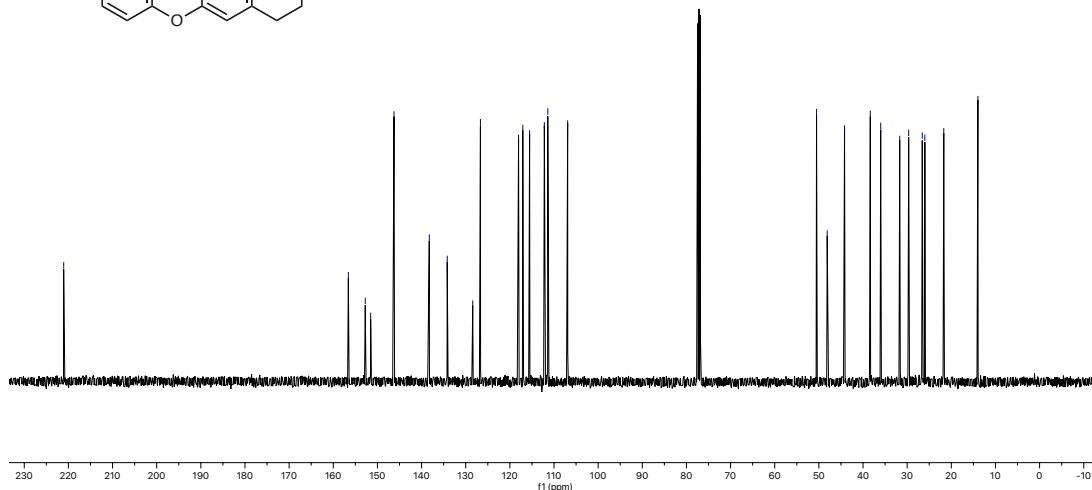
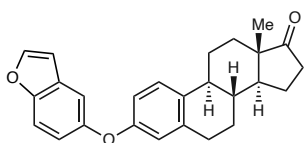
SS0413-pdt_PROTON_01
SS0413-pdt



SS0413-pdt₃CARBON_01
SS0413-pdt₃

155.59
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146.24
134.19
128.67
128.41
118.03
115.03
113.81
111.81
108.90

62.53
48.12
44.14
38.35
36.99
29.66
26.98
26.99
21.71
13.88

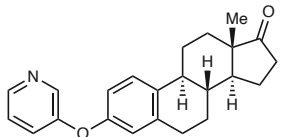
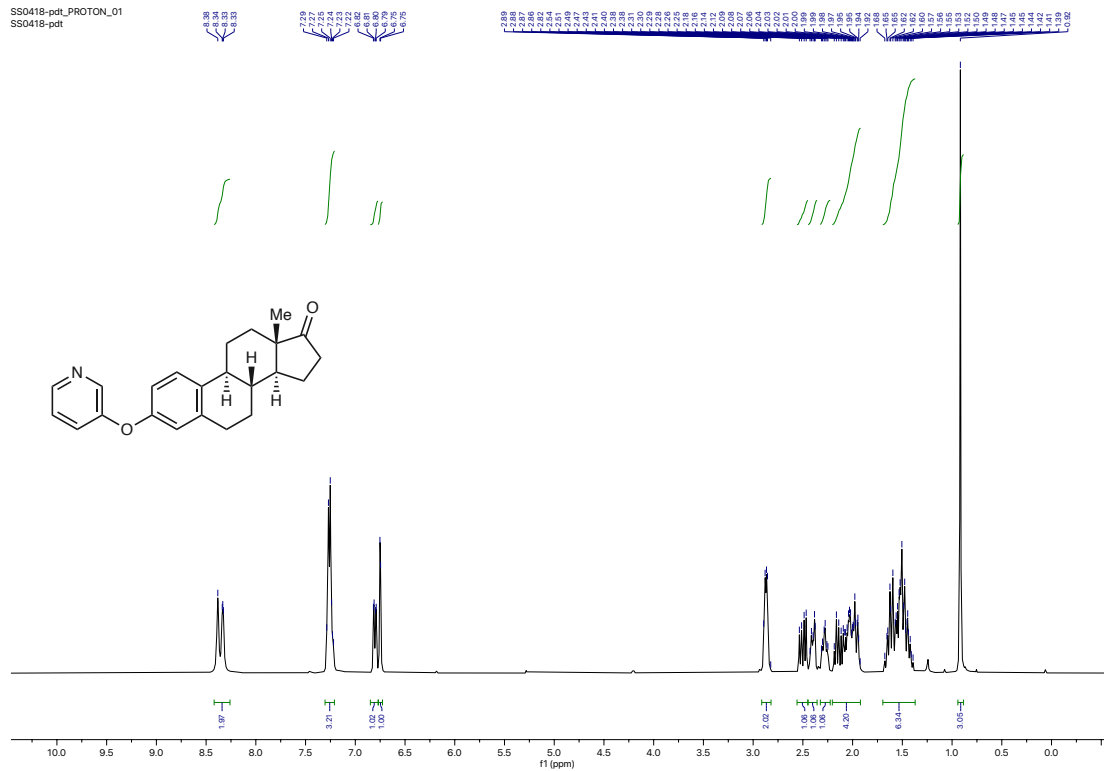


Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A solution of 17-hydroxyestene-17-one (100 mg, 0.36 mmol), 3-bromopyridine (62 mg, 0.4 mmol), Pd(OAc)₂ (4 mg, 0.02 mmol), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (26 mg, 0.06 mmol) and K₃PO₄ (155 mg, 0.72 mmol) in toluene (5 mL) was stirred at 100 °C. for 16 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc:petroleum ether=1:1) to give 3-androstene-17-one (35 mg, 28% yield) as a solid.</p> <p>Reaction Name and Classification: <i>SNAr ether synthesis</i></p> <p>Yield and Characterization: [28.0]</p>	<p>For a 0.185 mmol (50.0 mg) scale reaction with stirred for 36 h at 100 °C, product 6a was isolated as white solid (29.7 mg, 46% yield). R_f (30% EtOAc in hexane): 0.15.</p>

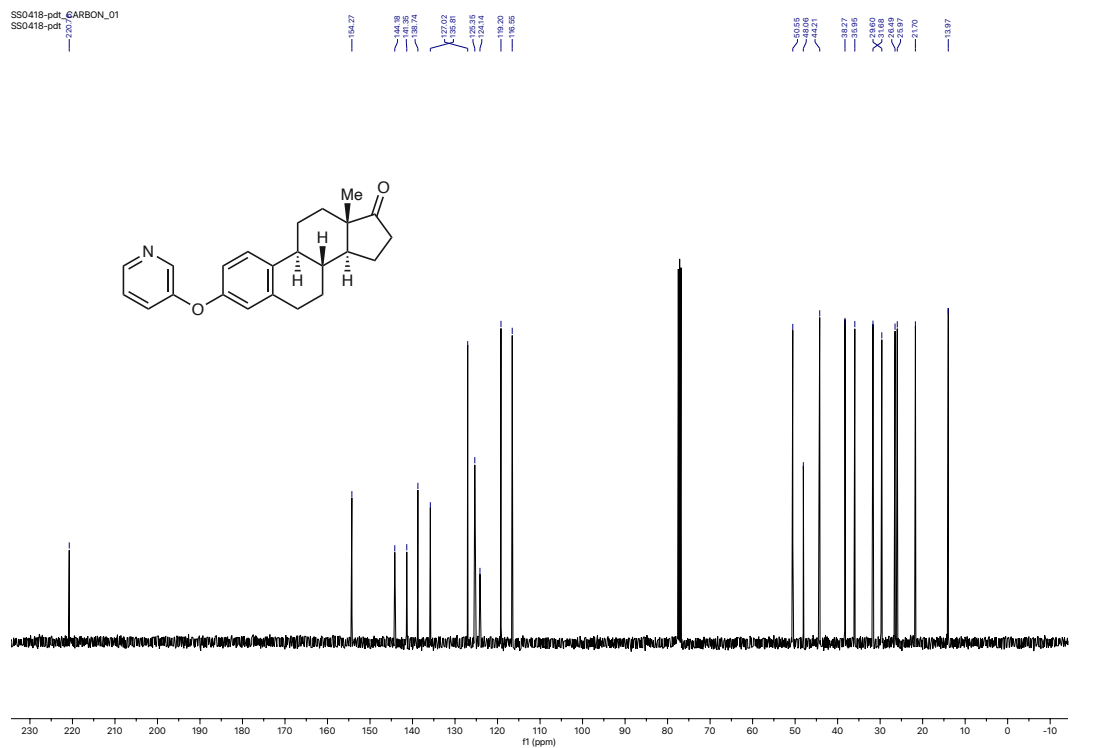
¹H NMR (400 MHz, CDCl₃) δ 8.41 – 8.30 (m, 2H), 7.32 – 7.20 (m, 3H), 6.80 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 2.92 – 2.82 (m, 2H), 2.50 (dd, *J* = 18.8, 8.6 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.32 – 2.22 (m, 1H), 2.20 – 1.91 (m, 4H), 1.69 – 1.37 (m, 6H), 0.92 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 220.8, 154.3, 144.2, 141.4, 138.7, 135.8, 127.0, 125.4, 124.1, 119.2, 116.6, 50.6, 48.1, 44.2, 38.3, 36.0, 31.7, 29.6, 26.5, 26.0, 21.7, 14.0.

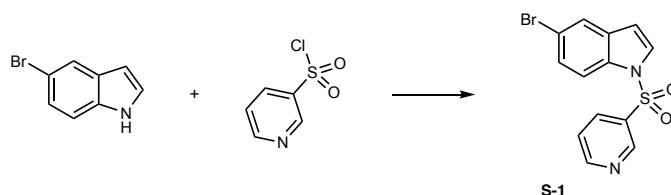
SS0418-pdt_PROTON_01
SS0418-pdt



SS0418-pdt_CARBON_01
SS0418-pdt



Fundamental Transformations

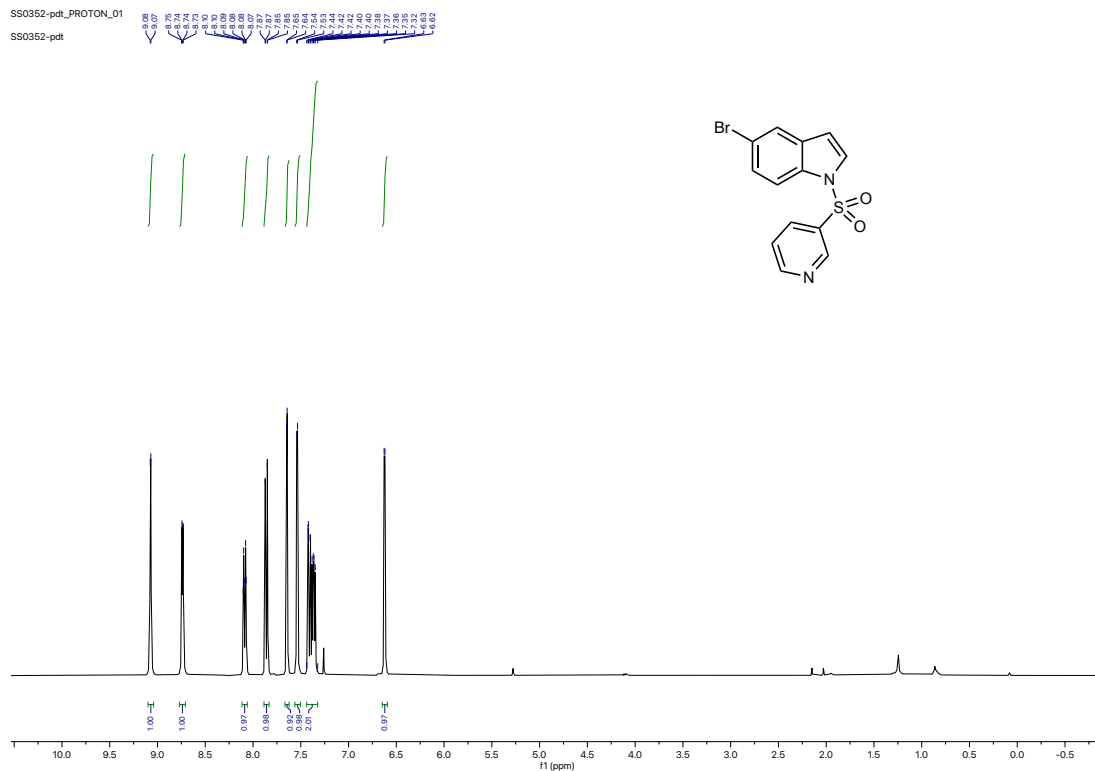


Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: To a solution of 5-bromoindole (60 g, 309 mmol) in tetrahydrofuran (600 mL) was added sodium hydride (18.5 g, 464 mmol, 60% in mineral oil) in portions at 0 °C. The mixture was stirred at 0 °C. for 1 h. Pyridine-3-sulfonyl chloride (64.5 g, 370 mmol) in tetrahydrofuran (600 mL) was added dropwise at 0 °C. and the resulting mixture was stirred at 0 °C. for 1 h. The reaction mixture was poured into saturated ammonium chloride solution (600 mL) and extracted with ethyl acetate (3x800 mL). The combined organic layers were washed with brine (3x800 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, eluting with petroleum ether/ethyl acetate: 30/1 to 5:1) to give 5-bromo-1-(pyridine-3-ylsulfonyl)-1H-indole as yellow solid (80 g, 72% yield).</p> <p>Reaction Name and Classification: <i>Sulfonamide Schotten-Baumann.</i></p> <p>Yield and Characterization: [72.0]</p>	<p>For a 3.09 mmol (605.8 mg) scale reaction, product S-1 was isolated as yellowish solid (988.0 mg, 95% yield). R_f (30% EtOAc in hexane): 0.25.</p>

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.07 (d, $J = 2.4$ Hz, 1H), 8.77 – 8.71 (m, 1H), 8.13 – 8.05 (m, 1H), 7.89 – 7.83 (m, 1H), 7.65 (d, $J = 1.9$ Hz, 1H), 7.54 (d, $J = 3.7$ Hz, 1H), 7.44 – 7.32 (m, 2H), 6.62 (d, $J = 3.7$ Hz, 1H).

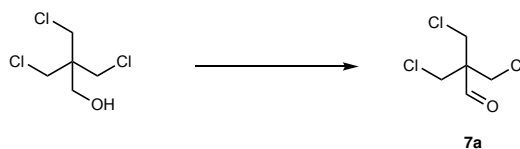
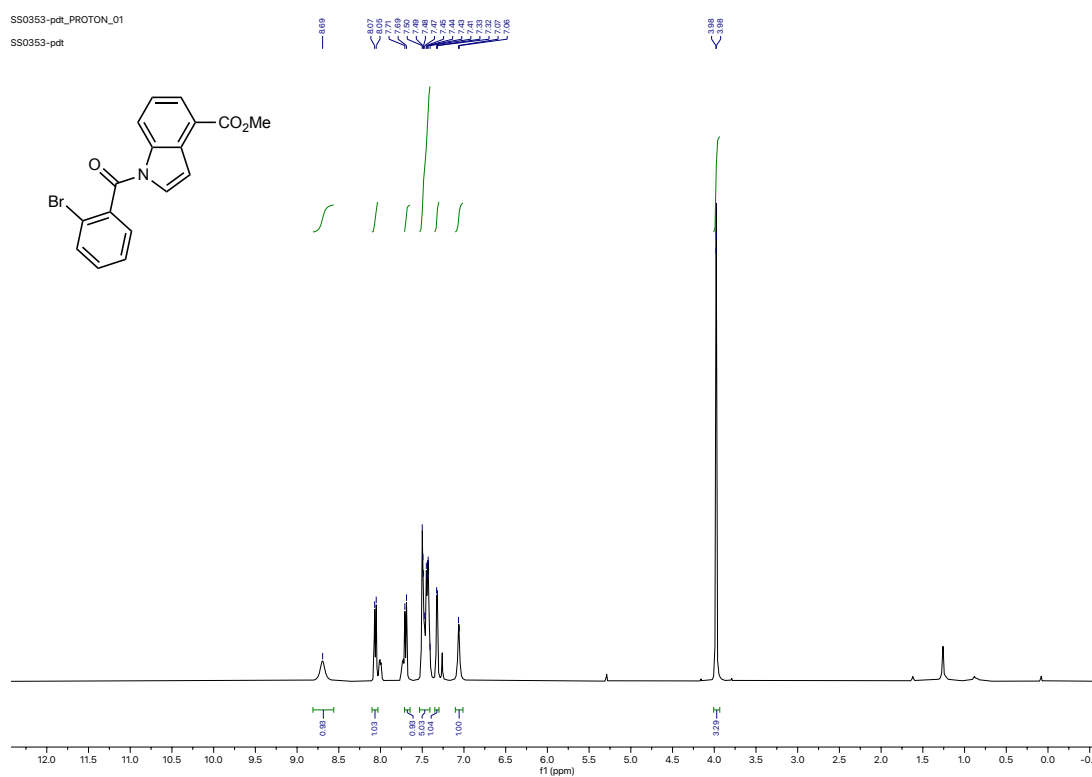
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 154.6, 147.5, 134.6, 134.3, 133.5, 132.6, 128.1, 127.3, 124.4, 123.9, 117.5, 114.9, 109.6.

SS0352-pdt_PROTON_01
SS0352-pdt



Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: To a suspension of sodium hydride (73 mg, w/w=60%, 1.8 mmol) methyl 1H-indole-4-carboxylate (300 mg, 1.8 mmol) in tetrahydrofuran (30 mL) was added 2-bromobenzoyl chloride (421 mg, 2.0 mmol). The reaction solution was stirred at room temperature for 12 hours. The mixture was concentrated to give a residue, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=3:1) to give methyl 1-(2-bromobenzoyl)-1H-indole-4-carboxylate (440 mg, 1.2 mmol, 66%).</p> <p>Reaction Name and Classification: Amide Schotten-Baumann.</p> <p>Yield and Characterization: [66.0]</p>	<p>For a 3.6 (630.7 mg, mmol scale reaction, product S-2 was isolated as off-white solid (1.096 g, 85% yield). R_f (25% EtOAc in hexane): 0.25.</p>

¹H NMR (400 MHz, CDCl₃) δ 8.69 (s, 1H), 8.06 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.54 – 7.39 (m, 4H), 7.32 (d, J = 3.8 Hz, 1H), 7.06 (d, J = 4.0 Hz, 1H), 3.98 (d, J = 1.5 Hz, 3H).



Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A solution of DMSO (9.36 g, 120 mmol) in 20 mL of dichloromethane was added dropwise to a solution of oxalyl chloride (10.16 g, 80 mmol) in 80 mL of dichloromethane at -70 °C. The solution was stirred for 10 min at -70 °C. and a solution of 2,2-bis(chloromethyl)propanol</p>	<p>DMSO (0.2 mL, 2.4 mmol) was dissolved in 8 mL of DCM (.3M) and cooled to -78 °C with an acetone/dry ice bath, then charged with oxalyl chloride (0.35 mL, 5 mmol) followed by stirring for 20 minutes. The solution was then treated with 3-chloro-2,2-bis(chloromethyl)propan-1-ol (383.0 mg, 2 mmol) as a 1.1M solution in DCM (2 mL) dropwise and stirred for 30 minutes. The reaction was then charged with</p>

(5.00 g, 25.6 mmol) in 20 mL of dichloromethane was added dropwise. The solution was stirred for 15 min at -70 °C. and triethylamine (15.52 g, 153 mmol) was added. The solution was stirred for 10 min at -70 °C and then allowed to warm to room temperature. The reaction was diluted with dichloromethane and washed with water. The organic layer was dried over MgSO₄ and concentrated to give 2,2-bis(chloromethyl)propionaldehyde (4.56 g, 92%).

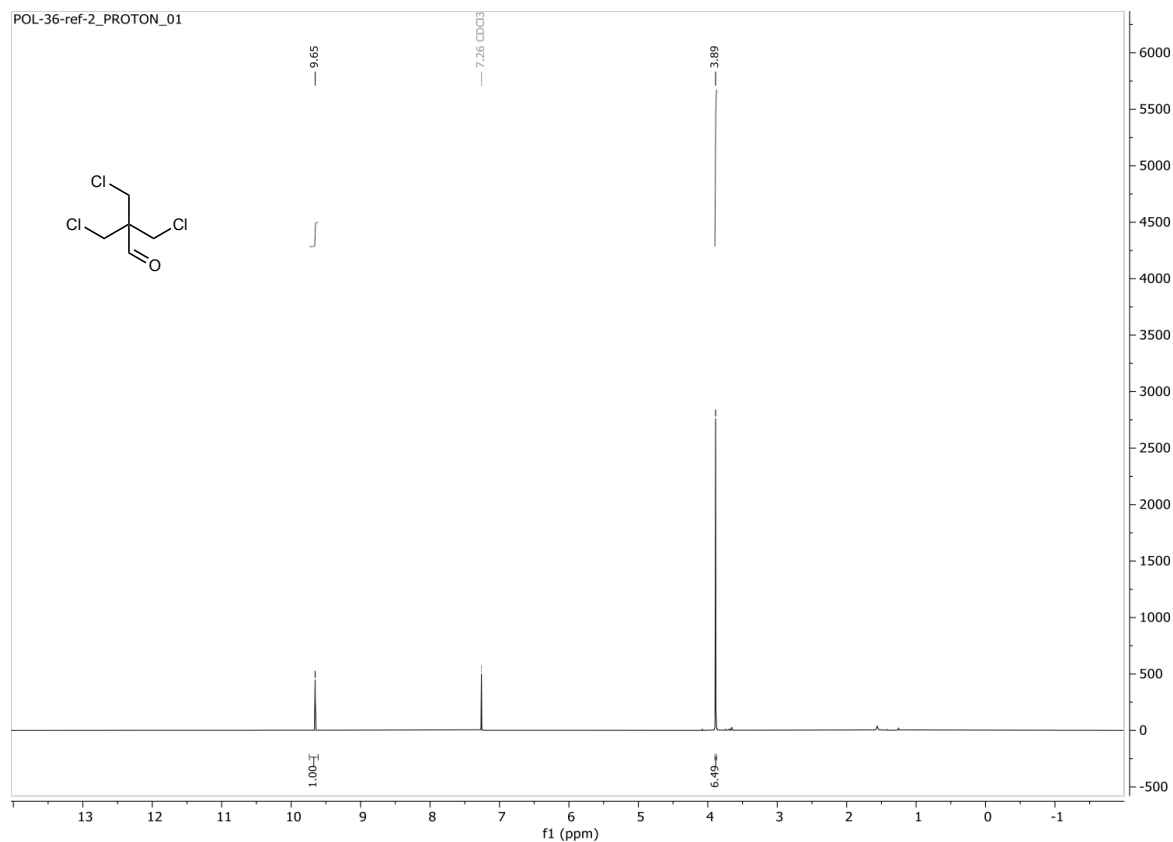
Reaction Name and Classification: None

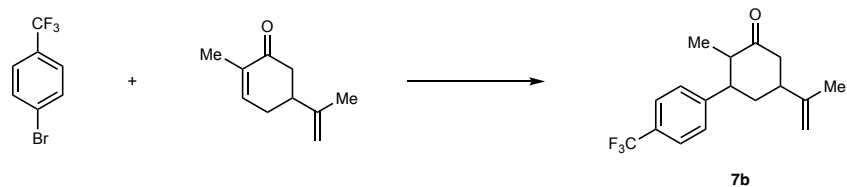
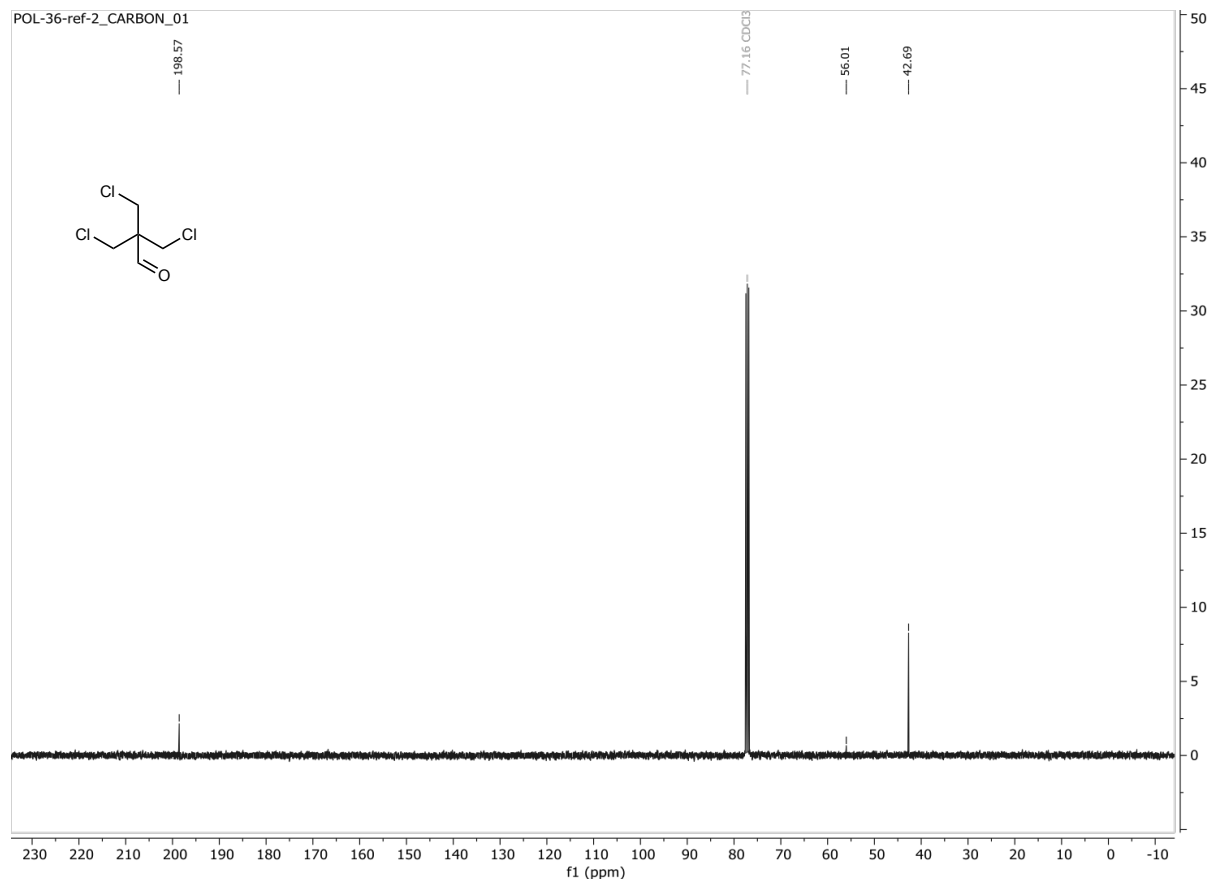
Yield and Characterization: [92.0]

triethylamine (1.25 mL, 9 mmol) dropwise after which the reaction was removed from the cold bath and stirred for a additional 20 minutes once at ambient temperature. The reaction was quenched with water and extracted with DCM. The organic layer was washed with brine and dried over MgSO₄. After filtration and removing the solvent in vacuo, the crude mixture was triturated with diethyl ether and filtered to remove the hydrochloride salt of triethylamine. After concentration, 3-chloro-2,2-bis(chloromethyl)propanal was obtained as a light yellow, crystalline solid (262.2 mg, 68% yield). R_f (15% EtOAc in Hexanes): .38.

¹H NMR (400 MHz, CDCl₃): δ 9.65 (s, 1H), 3.89 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 198.6, 56.0, 42.7.





Model Predictions	Experimental Results
<p>Expert: 1, Prediction:1</p> <p>Reaction Procedure: To magnesium metal turnings (14.0 g, 0.565 mol) in 300 mL of THF was added iodine (150 mg). The mixture was stirred for 30 minutes at room temperature. Approximately 30 mL of a solution of 1-bromo-4-(trifluoromethyl)benzene (117.3 g, 0.539 mol) in 100 mL of THF was added. The temperature of the reaction mixture rose within 5 minutes to 57 °C. with concurrent disappearance of the iodine color. The remainder of the 1-bromo-4-(trifluoromethyl)benzene solution was added dropwise over 1 hour and 40 minutes, keeping the temperature of the reaction mixture between 59 °C.-67 °C. The reaction mixture was heated an additional 1 hour at 67 °C. -69 °C., cooled to room temperature, and titrated as 0.965 M.</p> <p>In a separate flask, copper iodide (CuI) (1.0 g, 5.20 mmol), THF (200 mL), and 2-methyl-5-(1-methyl)cyclohex-2-en-1-one (83.62 g, 0.539 mol) were added. The yellow cloudy slurry was cooled to -24 °C. and treated over 1 hour with the Grignard solution, keeping the temperature below -10 °C. during the addition. The reaction mixture was stirred at -10 °C. to -5 °C. for a additional 2 hours, quenched with 300 mL of saturated ammonium chloride (NH₄Cl) solution followed</p>	<p>Acid washed magnesium turnings (127.6 mg, 5.25 mmol) were suspended in 3 mL of THF (1.88M), then treated with a small amount of elemental iodine (10.0 mg, 0.05 mmol) followed by stirring for 30 minutes. 1-bromo-4-(trifluoromethyl)benzene (0.7 mL, 5mmol) was added to the solution dropwise and stirred for 2 hours at reflux, then the solution was cooled to room temperature. In the meantime, (S)-carvone (0.78 mL, 5 mmol) was dissolved in 2.5 mL of THF (2M) and cooled to -25 °C with a 1,3-dichlorobenzene/dry ice bath. The above prepared aryl Grignard solution was then cannulated over and the reaction was warmed to -5 °C with a brine/ice bath, then stirred for 2 hours. The reaction was quenched with saturated aqueous NH₄Cl and extracted with EtOAc three times. The organic layers were combined and washed once with saturated aqueous NH₄Cl and once with brine, then dried over MgSO₄, filtered, and concentrated <i>in vacuo</i>. After aqueous work up, ¹H NMR revealed a 4.3:1</p>

by 200 mL of ethyl acetate, stirred for 10 minutes, and the layers were separated. The organic phase was washed with 200 mL of saturated NH_4Cl solution, then with 200 mL of brine, and finally concentrated in vacuo to a yellow liquid. This crude product was taken up in 250 mL of heptane, filtered through a pad of CELITE® filter aid, and concentrated in vacuo to give 143.4 g of 2-methyl-3-[4-(trifluoromethyl)phenyl]-5-(1-methyl)cyclohexanone as a light yellow liquid (86% yield).

Reaction Name and Classification: *Gilman type conjugate addition*

Yield and Characterization: [86.0]

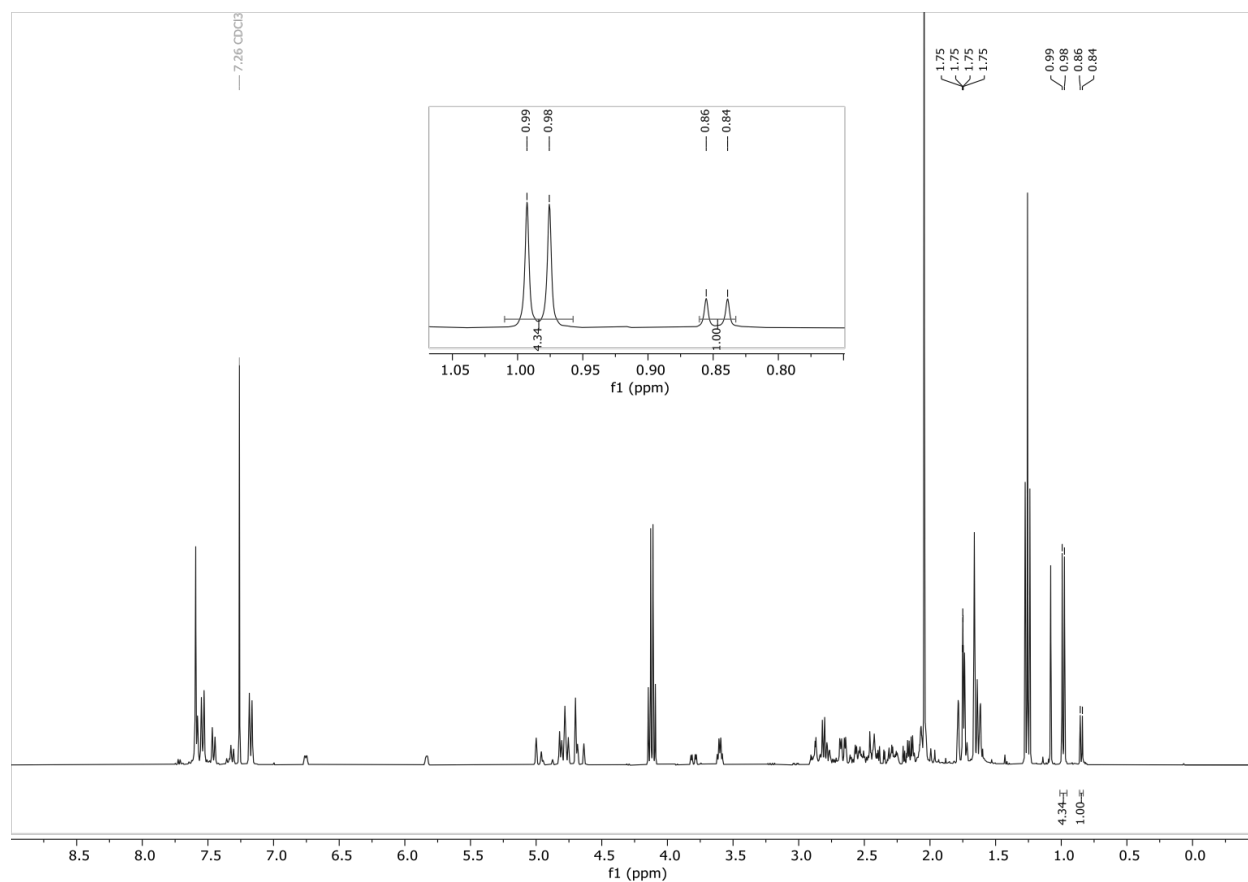
ratio of diastereomers. Further purification by flash chromatography (5% EtOAc/Hexanes) provided (5*R*)-2-methyl-3-phenyl-5-(prop-1-en-2-yl)cyclohexan-1-one as a pale yellow oil (488.0 mg, 33% yield, 12.2:1 mixture of a diastereomers). R_f (10% EtOAc/Hexanes): .29

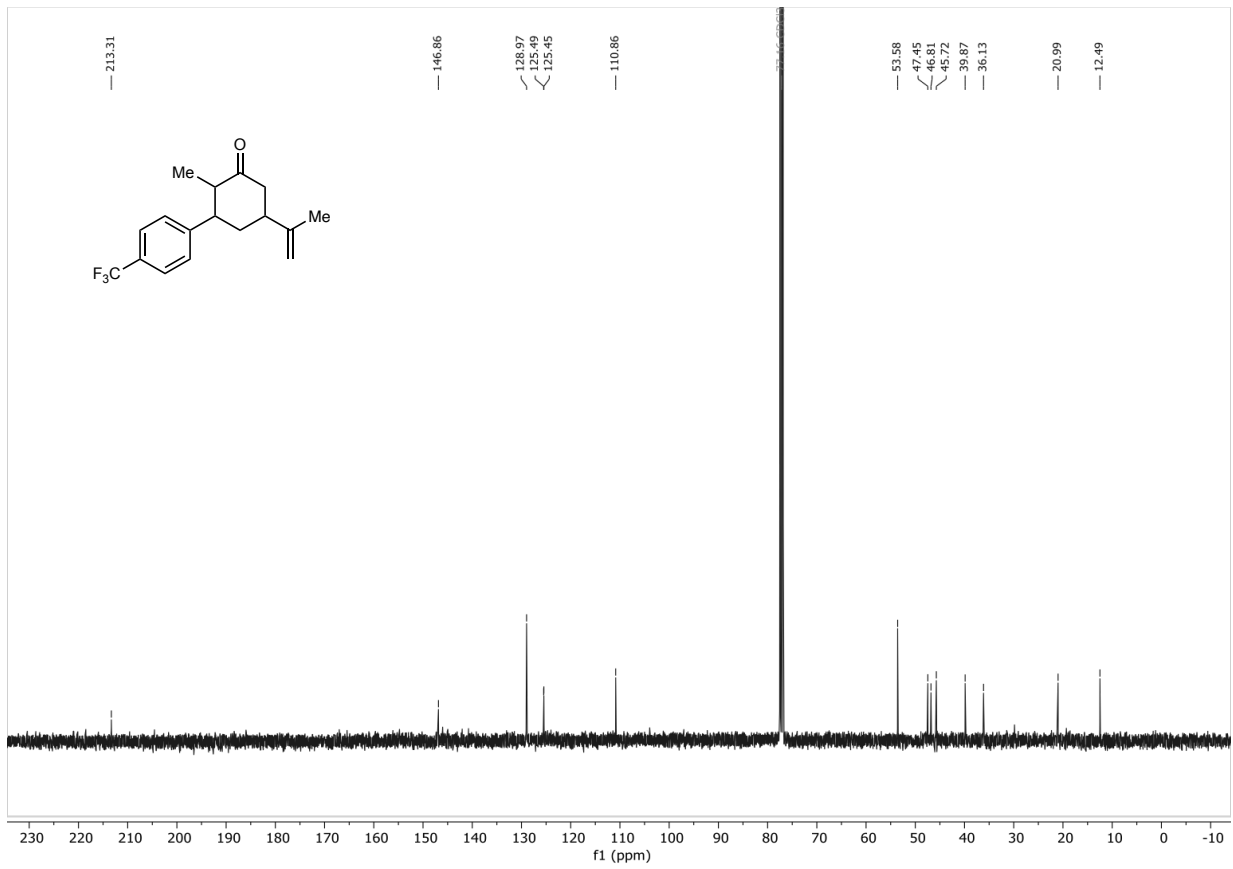
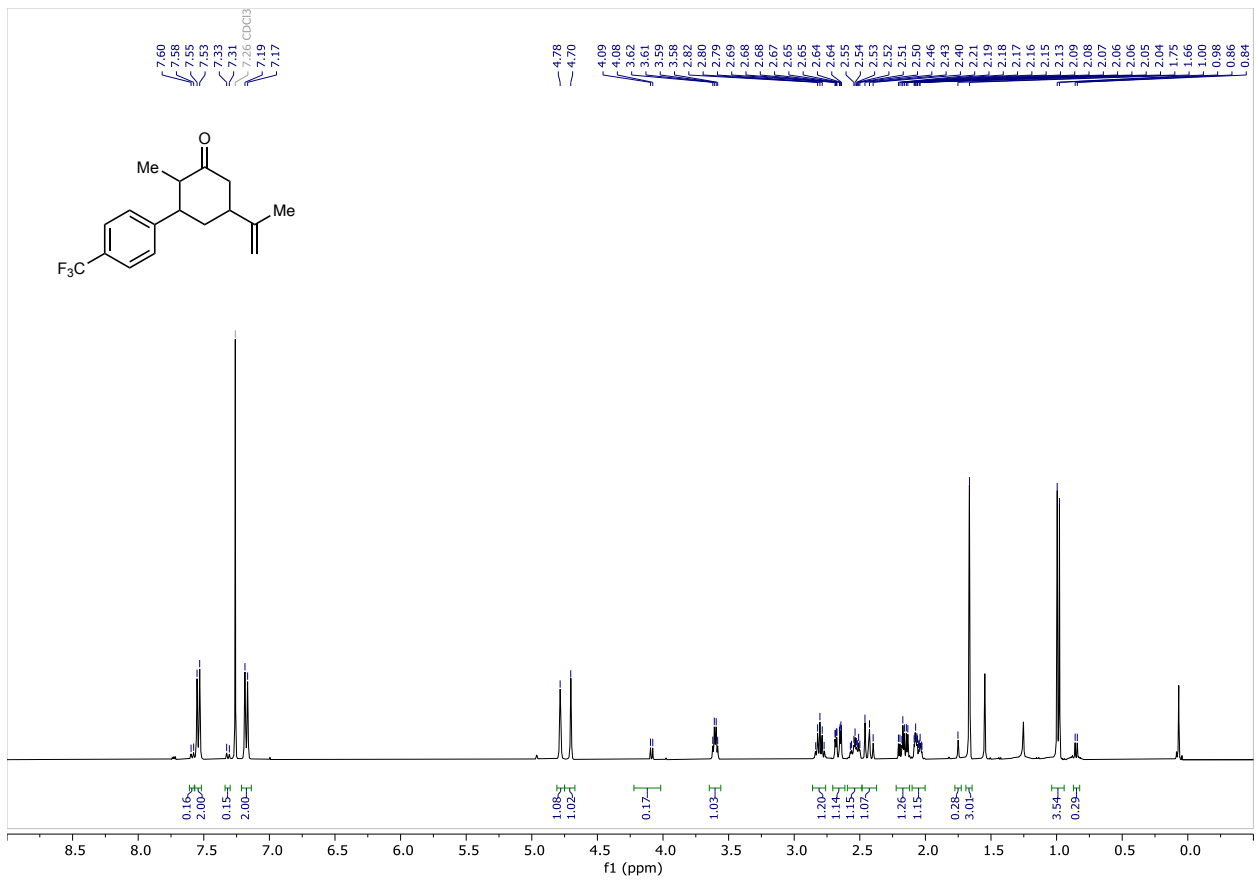
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.54 (d, $J = 8.0$ Hz, 2H), 7.18 (d, $J = 8.1$ Hz, 2H), 4.78 (m, 1H), 4.70 (m, 1H), 3.60 (q, $J = 5.0$ Hz, 1H), 2.80 (tt, $J = 7.6, 6.3$ Hz, 1H), 2.66 (ddd, $J = 13.7, 4.1, 1.8$ Hz, 1H), 2.57-2.50 (m, 1H), 2.43 (ddd, $J = 13.8, 11.2, 1.3$ Hz, 1H), 2.17 (ddd, $J = 13.6, 10.5, 4.6$ Hz, 1H), 2.11 – 2.02 (m, 1H), 1.66 (s, 3H), 0.99 (d, $J = 6.9$ Hz, 3H).

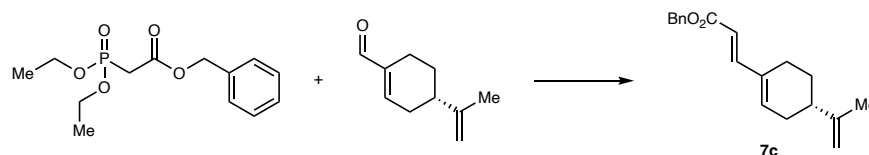
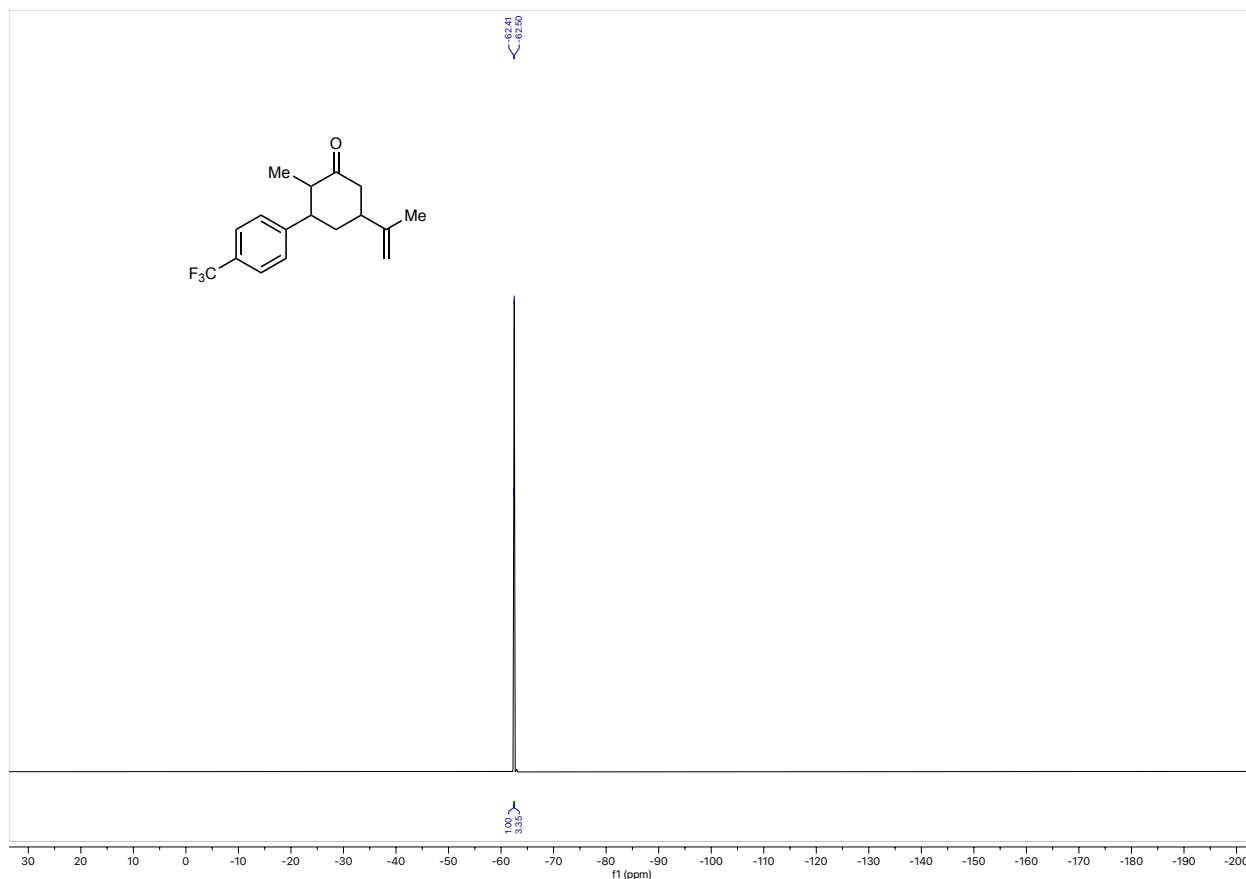
$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 213.3, 146.9, 129.0, 125.5, 125.5, 110.9, 53.6, 47.5, 46.8, 45.7, 39.87, 36.1, 21.0, 12.5.

$^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -62.41, -62.50.

HRMS m/z (ESI⁺) [$\text{M}+\text{H}$]⁺: Calc'd for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{O}^+$: 297.1466, found: 297.1461.





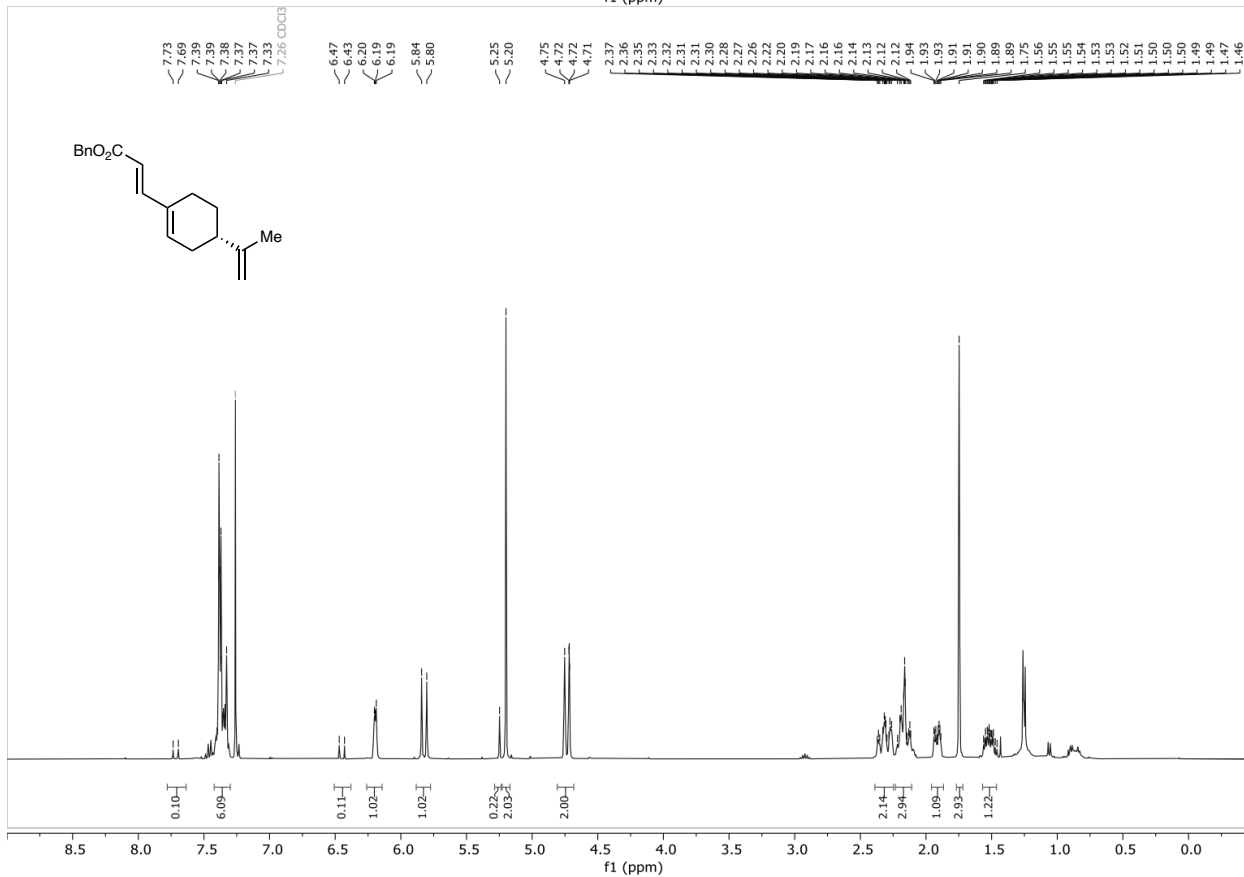
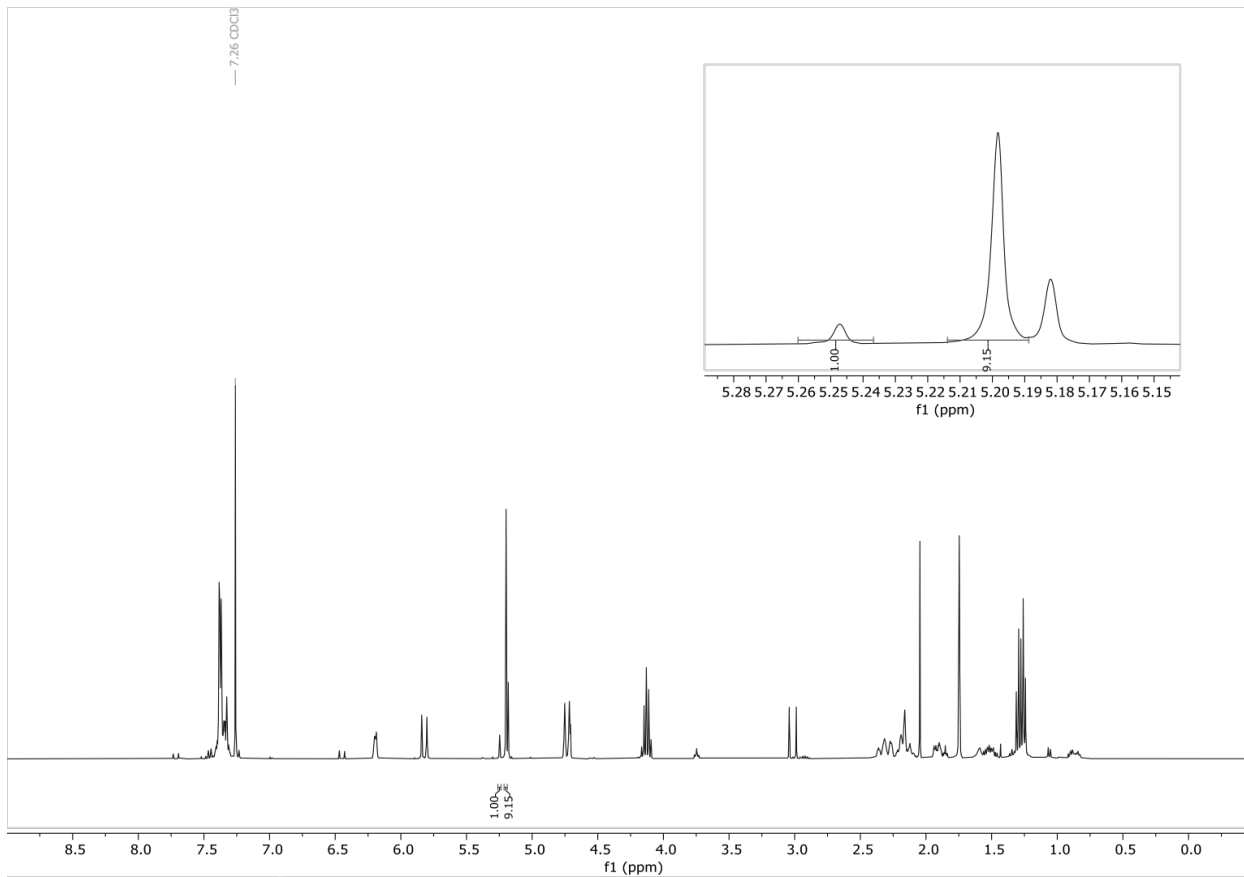


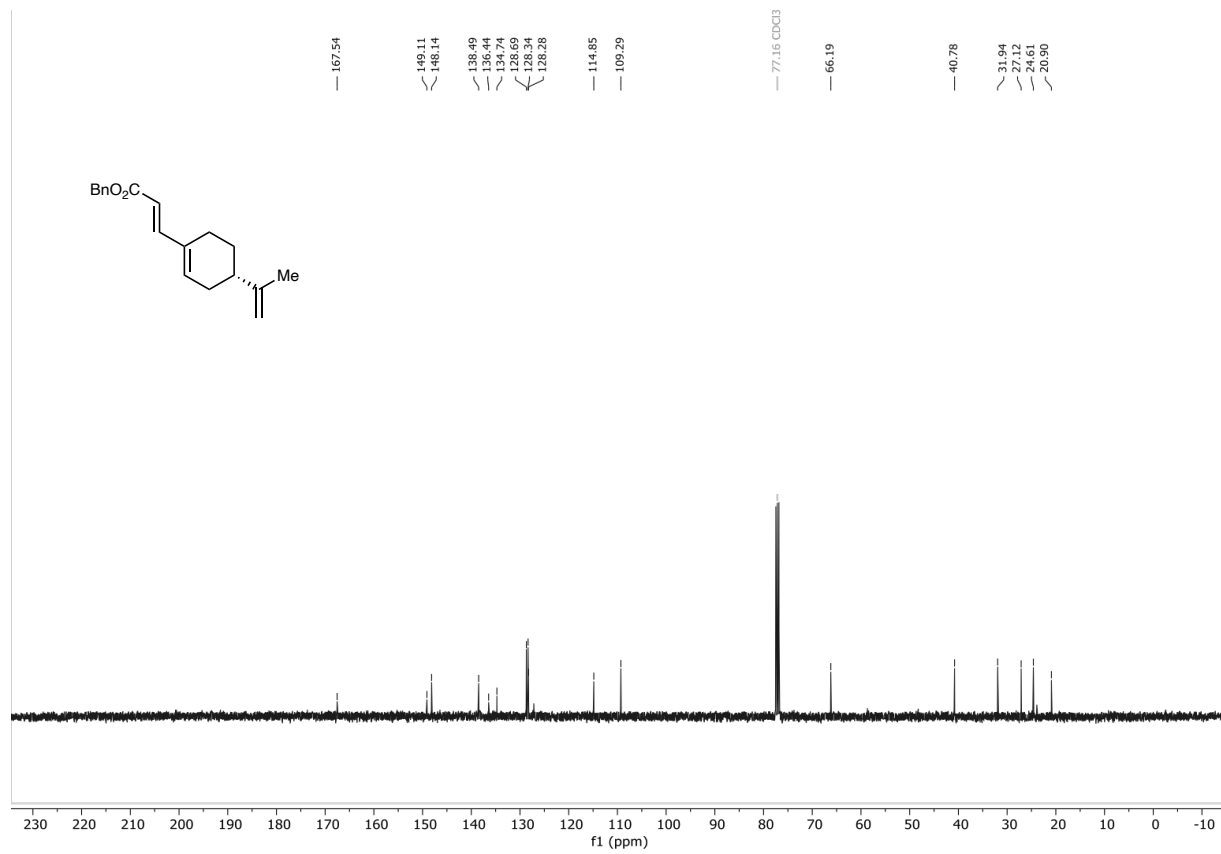
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: To a stirred suspension of NaH (60% dispersion in mineral oil) (105 mg, 1.70 mmol) in THF (5 mL) was added benzyl 2-(diethoxyphosphoryl) acetate (0.49 mL, 2.30 mmol) at 0 °C. and stirred for 15 min. Then (R)-4-(1-methylvinyl)cyclohex-1-ene-1-carbaldehyde (200 mg, 1.55 mmol) in THF (5 mL) was added to the reaction mixture and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc (2x20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography using 3% EtOAc/hexanes to afford (E)-benzyl 3-(4-((R)-1-methylvinyl)cyclohex-1-en-1-yl)acrylate (150 mg, 0.55 mmol, 35% yield). LC-MS m/z 286.9 (M+H)⁺, 2.91 min (ret. time).</p> <p>Reaction Name and Classification: <i>Horner-Wadsworth-Emmons reaction</i></p> <p>Yield and Characterization: [35.0]</p>	<p>Sodium Hydride (44.0 mg, 1.1 mmol) was suspended in 3.1 mL of THF (.35M), cooled to 0 °C, treated with benzyl 2-(diethoxyphosphoryl)acetate dropwise. After stirring for 15 minutes, the solution was charged with (S)-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carbaldehyde and the reaction stirred at room temperature for 2 hours. The reaction was then quenched with saturated aqueous NH₄Cl and extracted with EtOAc three times. The organic layers were combined and washed with brine, then dried over Na₂SO₄, filtered, and concentrated <i>in vacuo</i>. After aqueous work up, ¹H NMR revealed a 9.2:1 ratio of regioisomers. Further purification by flash chromatography (5% Et₂O/Pentane) provided benzyl (S)-3-(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)acrylate as a light yellow oil (108.0 mg, 81% yield, 9.2:1 mixture of regioisomers). R_f (10% EtOAc in Hexanes): .48</p>

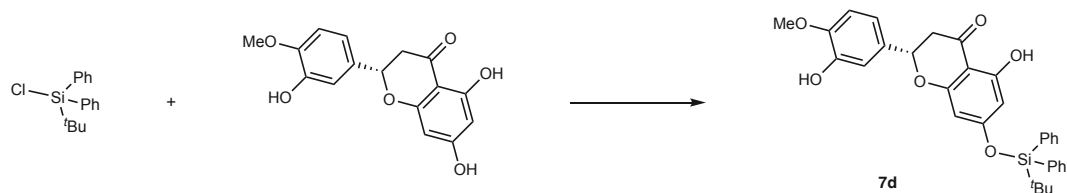
¹H NMR (400 MHz, CDCl₃): δ 7.42 – 7.30 (m, 6H), 6.23 – 6.17 (m, 1H), 5.82 (d, J = 15.7 Hz, 1H), 5.20 (s, 2H), 4.75 (m, 1H), 4.73 – 4.69 (m, 1H), 2.39 – 2.24 (m, 2H), 2.23 – 2.08 (m, 3H), 1.94-1.89 (m, 1H), 1.75 (s, H), 1.57 – 1.46 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 167.5, 149.1, 148.1, 138.5, 136.4, 134.7, 128.7, 128.3, 128.2, 114.9, 109.3, 66.2, 40.8, 31.9, 27.1, 24.6, 20.9.

HRMS (ESI⁺) [M+H]⁺: Calc'd for C₁₉H₂₃O₂⁺: 283.1698 m/z, found: 283.1694 m/z.





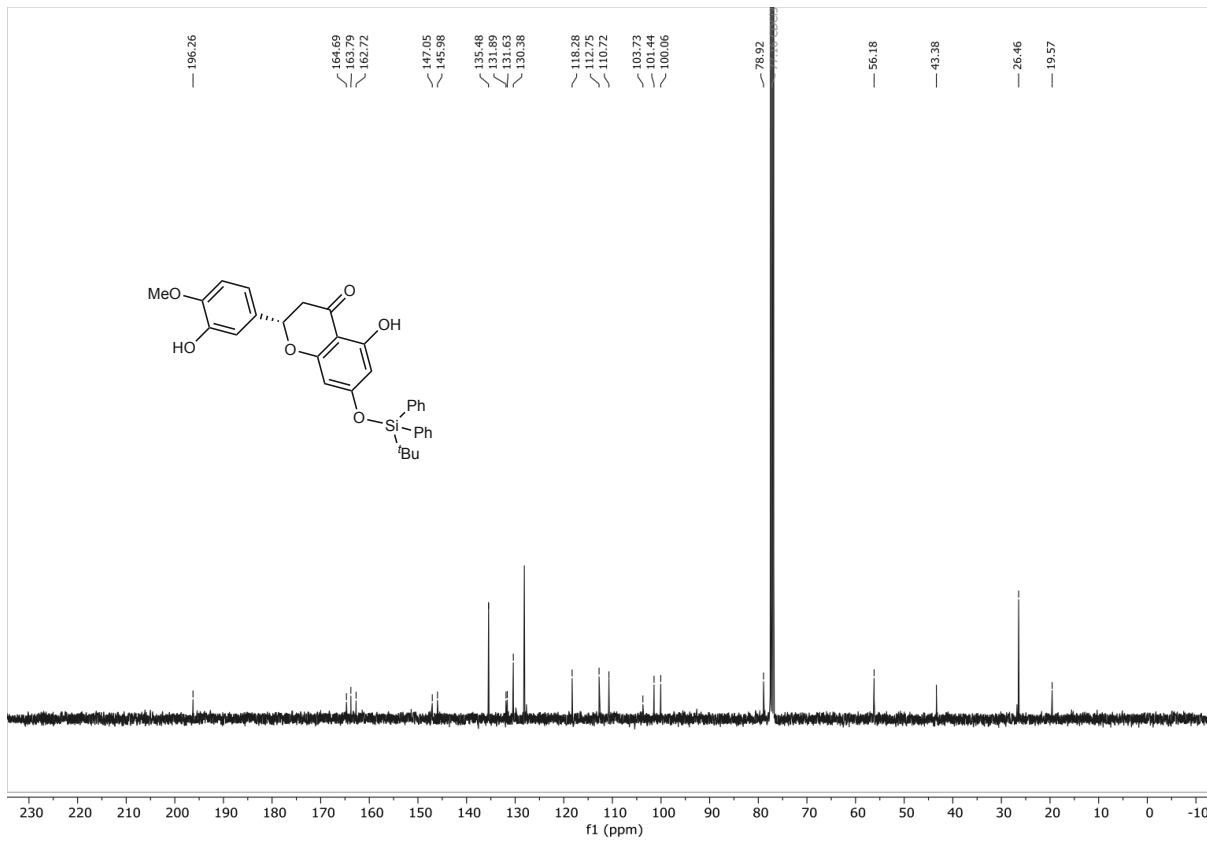
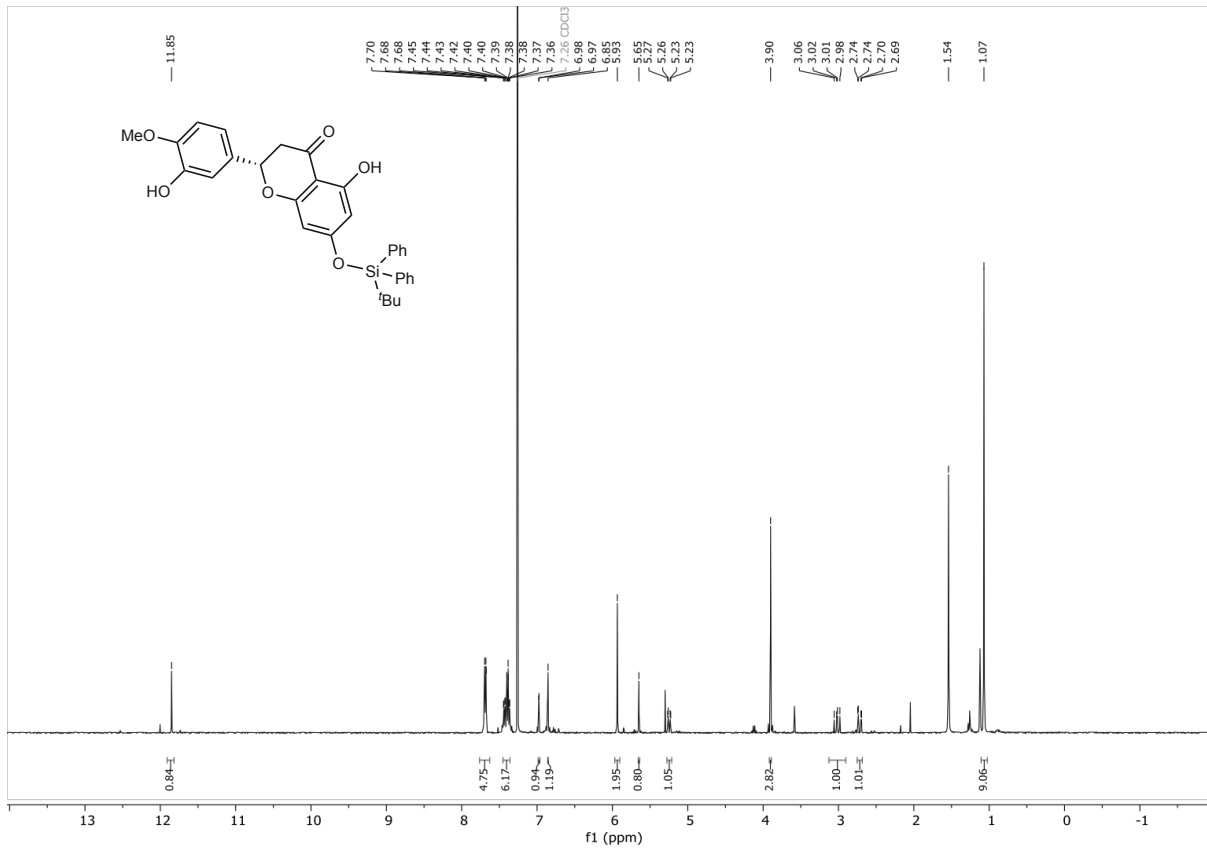


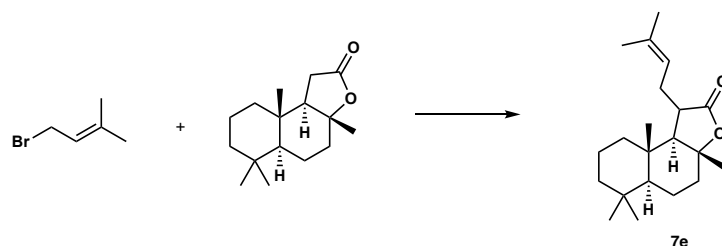
Model Predictions	Experimental Results
<p>Expert: 1, Prediction:1 Reaction Procedure: tert-Butyldiphenylsilyl chloride (4.2 mL, 16.0 mmol) was added to a suspension of (S)-2-(3-hydroxy-4-methoxy-phenyl)-4,6-dihydroxy-2,3-dihydro-benzo[b]oxolan-4-one (4.72 g, 16.0 mmol) and imidazole (2.20 g, 32.0 mmol) in DMF (50 mL). The mixture was stirred at room temperature for 20 hours and then diluted with saturated aqueous NaHCO₃ (100 mL). The suspension was extracted with EtOAc (3×100 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane 1:2) to give the title compound (7.75 g, 86%) as a pale yellow oil. Reaction Name and Classification: <i>Silyl ether synthesis</i> Yield and Characterization: [86.0]</p>	<p>(-)-Hesperetin (302.3 mg, 1 mmol) was dissolved in 3 mL of DMF (.32M), charged with tert-Butyldiphenylsilyl chloride (0.26 mL, 1 mmol) and imidazole (136.2 mg, 2 mmol), then stirred overnight (20 hours) at room temperature. The solution was diluted with saturated aqueous NaHCO₃ and extracted with EtOAc three times. The combined organic layer was washed with 5% aqueous LiCl three times then dried over Na₂SO₄. After filtration and removing the solvent <i>in vacuo</i>, the crude material was purified by flash chromatography (hexanes -> 10% EtOAc/Hexanes -> 20% EtOAc/Hexanes, -> 30% EtOAc/Hexanes) to provide (S)-7-((tert-butyl-diphenylsilyl)oxy)-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one as a white foam (259.6 mg, 48% yield). R_f (15% EtOAc in Hexanes): .37</p>

¹H NMR (400 MHz, CDCl₃): δ 11.85 (s, 1H), 7.73 – 7.65 (m, 5H), 7.48 – 7.31 (m, 6H), 6.98 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 1.0 Hz, 1H), 5.93 (s, 2H), 5.65 (s, 1H), 5.25 (dd, *J* = 13.0, 3.0 Hz, 1H), 3.90 (s, 3H), 3.02 (dd, *J* = 17.2, 13.0 Hz, 1H), 2.72 (dd, *J* = 17.1, 3.1 Hz, 1H), 1.07 (s, 9H).

¹³C NMR (101 MHz, CDCl₃): δ 196.3, 164.7, 163.8, 162.7, 147.1, 146.0, 135.5, 131.9, 131.6, 130.4, 118.3, 112.8, 110.7, 103.7, 101.4, 100.1, 78.9, 56.2, 43.4, 26.5, 19.6.

HRMS (ESI⁺) [M+H]⁺: Calc'd for C₃₂H₃₃O₆Si⁺: 541.2046 m/z, found: 541.2066 m/z.





We have validated the following model prediction. Prediction 4 was selected over 2 and 3 due to simplicity. Prediction 1 suffered from critical errors.

Model Predictions	Experimental Results
<p>Expert: 1 Prediction:2</p> <p>Reaction Procedure: To a solution of diisopropylamine (9.9 mL, 56 mmol) in tetrahydrofuran (170 mL) was added dropwise n-butyl lithium (28 mL, 56 mmol, 1.6 M in hexane) at $-78\text{ }^{\circ}\text{C}$. and the mixture was stirred for 15 minutes. The reaction mixture was warmed to $0\text{ }^{\circ}\text{C}$. and stirred for 30 minutes. The reaction mixture was again cooled to $-78\text{ }^{\circ}\text{C}$. and a solution of 5 (7.6 g, 31 mmol) in tetrahydrofuran (56 mL) was added dropwise. After completion of the addition, the reaction mixture was stirred for 1 hour at $0\text{ }^{\circ}\text{C}$. and then cooled to $-78\text{ }^{\circ}\text{C}$. A solution of 1-bromo-3-methyl-2-butene (8.9 mL, 75.0 mmol) in tetrahydrofuran (56 mL) was added dropwise to the reaction mixture and the mixture was stirred for 2 hours at $0\text{ }^{\circ}\text{C}$. After completion of the reaction, a saturated aqueous solution of ammonium chloride was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=9/1) to give 6 (5.4 g, yield 56%) as a white solid.</p> <p>Reaction Name and Classification: None</p> <p>Yield and Characterization: [56.0]</p>	<p>Not tested</p>
<p>Expert: 1 Prediction:3</p> <p>Reaction Procedure: To a solution of diisopropylamine (15.3 mL, 106 mmol) in THF (300 mL) was added n-BuLi (2.5 M, 42.4 mL, 106 mmol) at $-78\text{ }^{\circ}\text{C}$. for 15 min, and the mixture was stirred at the same temperature for 30 min. To a solution of 5 (2.0 g, 44.6 mmol) in THF (200 mL) was added the freshly prepared n-BuLi solution dropwise at $-78\text{ }^{\circ}\text{C}$. for 30 min. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$. for 1 h. Then 1-bromo-3-methyl-2-butene (4.2 mL, 44.6 mmol) was added dropwise at $-78\text{ }^{\circ}\text{C}$. for 30 min. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$. for 4 h and then quenched with a saturated aqueous solution of NH_4Cl (200 mL). The ice bath was removed, and the mixture was stirred for 10 min. The mixture was partitioned between EtOAc (400 mL) and H_2O (300 mL). The organic layer was separated, washed with H_2O (100 mL), and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography (silica gel, hexanes:EtOAc=10:1 to 7:3) to give 6 (3.5 g, 99%) as a foam.</p> <p>Reaction Name and Classification: <i>Keto alpha-alkylation</i></p> <p>Yield and Characterization: [99.0]</p>	<p>Not tested</p>

Expert: 1, Prediction:4

Reaction Procedure: To a solution of 0.25 g of 5 in 6 mL of anhydrous THF at $-78\text{ }^{\circ}\text{C}$. was added 1.5 mL of a 2.0 M solution of LDA in THF. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$. for 30 min and 0.27 mL of 1-bromo-3-methyl-2-butene was added. The mixture was allowed to slowly warm to $0\text{ }^{\circ}\text{C}$. and stirred at $0\text{ }^{\circ}\text{C}$. for 3 hr. The reaction was quenched with a saturated aqueous solution of ammonium chloride and diluted with 30 mL of EtOAc. The organic phase was washed with H_2O , 5% aqueous solution of citric acid, and brine, dried with MgSO_4 , filtered, and concentrated. The crude product was purified by column chromatography (silica gel, hexanes:EtOAc=50:1 to 20:1) to afford 0.28 g of 6 as a foam.

Reaction Name and Classification: *Keto alpha-alkylation*

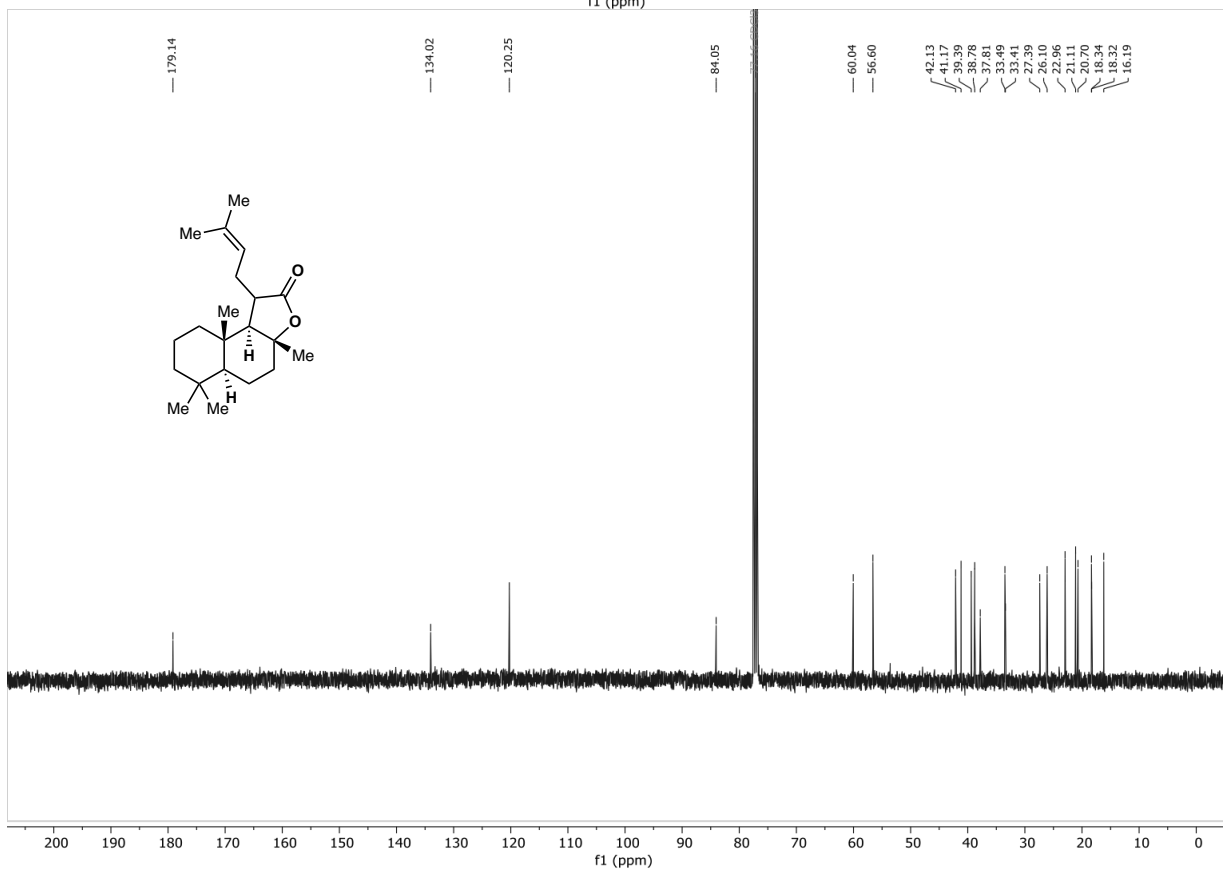
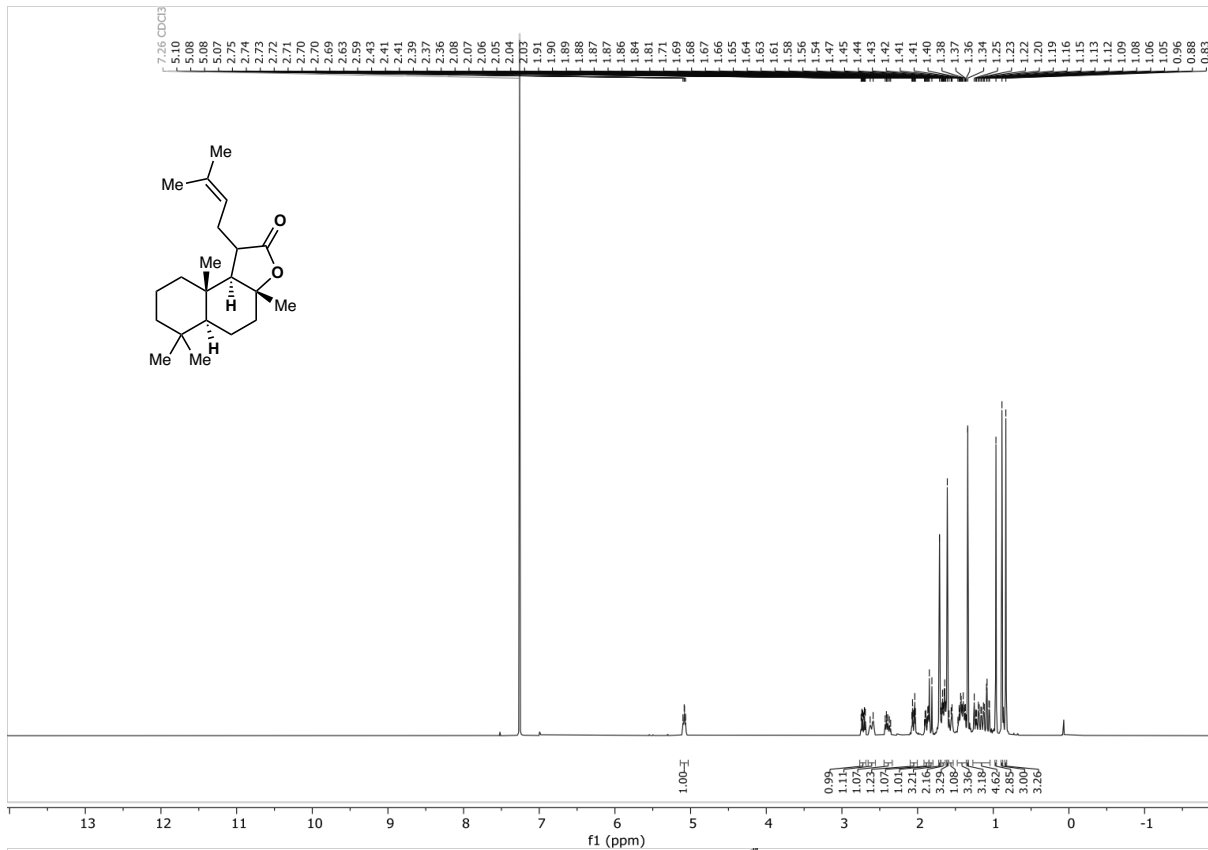
Yield and Characterization: [80.0]

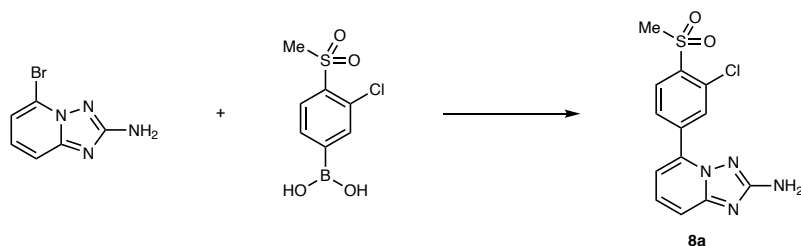
Sclareolide (125.2 mg, 0.5 mmol) was dissolved in 3.2 mL of THF (0.16M) and cooled to $-78\text{ }^{\circ}\text{C}$ with an acetone/dry ice bath. The solution was then charged with LDA dropwise as a 1M solution in THF (0.75 mL, 0.75 mmol) and stirred for 30 minutes after which 1-bromo-3-methylbut-2-ene was added. The reaction was then warmed to $-0\text{ }^{\circ}\text{C}$ and stirred for an additional 3 hours. The reaction was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc three times. The organic layers were combined and washed with water, 5% citric acid, and brine, then dried over MgSO_4 . After filtration and removing the solvent in vacuo, the crude mixture was purified by flash chromatography (10% EtOAc/Hexanes) to provide (3aR,9aS,9bR)-3a,6,6,9a-tetramethyl-1-(3-methylbut-2-en-1-yl)decahydronaphtho[2,1-b]furan-2(1H)-one as a light yellow solid (120.4 mg, 75% yield, major diastereomer). Rf (15% EtOAc/Hexanes): .47

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.08 (t, $J = 7.0$ Hz, 1H), 2.72 (ddd, $J = 13.4, 5.3, 3.6$ Hz, 1H), 2.63-2.59 (m, 1H), 2.43-2.36 (m, 1H), 2.05 (dt, $J = 11.8, 3.3$ Hz, 1H), 1.92 – 1.85 (m, 1H), 1.83 (d, $J = 13.4$ Hz, 1H), 1.71 (s, 3H), 1.69-1.63 (m, 2H), 1.61 (s, 3H), 1.48 – 1.35 (m, 3H), 1.34 (s, 3H), 1.27 – 1.04 (m, 4H), 0.96 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 179.4, 134.0, 120.3, 84.1, 60.0, 56.6, 42.1, 41.2, 39.4, 38.8, 37.8, 33.5, 33.4, 27.4, 26.1, 23.0, 21.1, 20.7, 18.3, 18.3, 16.2.

HRMS (ESI⁺) [M+H]⁺: Calc'd for $\text{C}_{21}\text{H}_{35}\text{O}_2$ ⁺: 319.2637 m/z, found: 319.2641 m/z.





Model Predictions	Experimental Results
<p>Expert: 1, Prediction: 5</p> <p>Reaction Procedure: To a solution of 5-bromo-2-phenyl-1H-benzimidazole (57 mg, 0.2 mmol) in toluene (2 mL), ethanol (2 mL), and H₂O (2 mL) was added 2,2,6-trimethyl-1-benzopyran-4-ol (41 mg, 0.22 mmol), Na₂CO₃ (42 mg, 0.4 mmol), and Pd(Ph₃P)₄ (10 mg, 0.04 mmol). The reaction mixture was heated at 100 °C. overnight and extracted with EtOAc. The combined organic layers were concentrated and purified by column chromatography on silica gel (0-50% EtOAc in hexanes) to give 2-(4-methyl-2-(2-phenyl-1H-benzimidazol-5-yl)phenyl)propan-2-ol (60 mg, 84%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 8.08 (br s, 3H), 7.67 (d, J=8.1 Hz, 1H), 7.60 (m, 2H), 7.43 (m, 3H), 7.35 (d, J=8.1 Hz, 1H), 7.26 (m, 3H), 7.18 (m, 1H), 2.78 (s, 3H), 1.86 (s, 6H); MS (ESI) m/z 343.9 [M+H]⁺.</p> <p>Reaction Name and Classification: <i>Bromo Suzuki coupling</i></p> <p>Yield and Characterization: [84.0]</p>	<p>For 0.1 mmol (21.3 mg) scale, compound 8a was isolated as white solid (25.6 mg, 79% yield), R_f = 0.48 (DCM:MeOH = 8:1).</p>
<p>Expert: 1, Prediction: 1</p> <p>Reaction Procedure: A mixture of 5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.4 g, 12.1 mmol), (3-chloro-4-methylsulfonylphenyl)boronic acid (2.78 g, 12.1 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride dichloromethane complex (504 mg, 0.61 mmol), Na₂CO₃ (2.60 g, 24.3 mmol) in dioxane (24 mL) and water (4 mL) was heated at 100 °C. for 12 hours under a nitrogen atmosphere. After cooling to room temperature, the solvent was removed in vacuo and the residue was dissolved in DCM (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by a silica gel column chromatography (pure EtOAc) to give the title compound as a light yellow solid (2.2 g, 61%).</p> <p>Reaction Name and Classification: <i>Bromo Suzuki coupling</i></p> <p>Yield and Characterization: [61.0]</p>	<p>For 0.1 mmol (21.3 mg) scale, compound 8a was formed with 31% NMR yield</p>
<p>Expert: 2, Prediction: 1</p> <p>Reaction Procedure: A mixture of (3-chloro-4-(methylsulfonyl)phenyl)boronic acid (200 mg, 0.86 mmol), 5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (190 mg, 0.86 mmol), Pd(dppf)Cl₂ (63 mg, 0.086 mmol) and K₂CO₃ (235 mg, 1.72 mmol) in dioxane (5 mL) and H₂O (1 mL) was stirred at 120 °C. for 30 min under microwave. The catalyst was filtered through a pad of celite and the filtrate concentrated. The residue was purified by column</p>	<p>For 0.1 mmol (21.3 mg) scale, compound 8a was formed with 8% NMR yield</p>

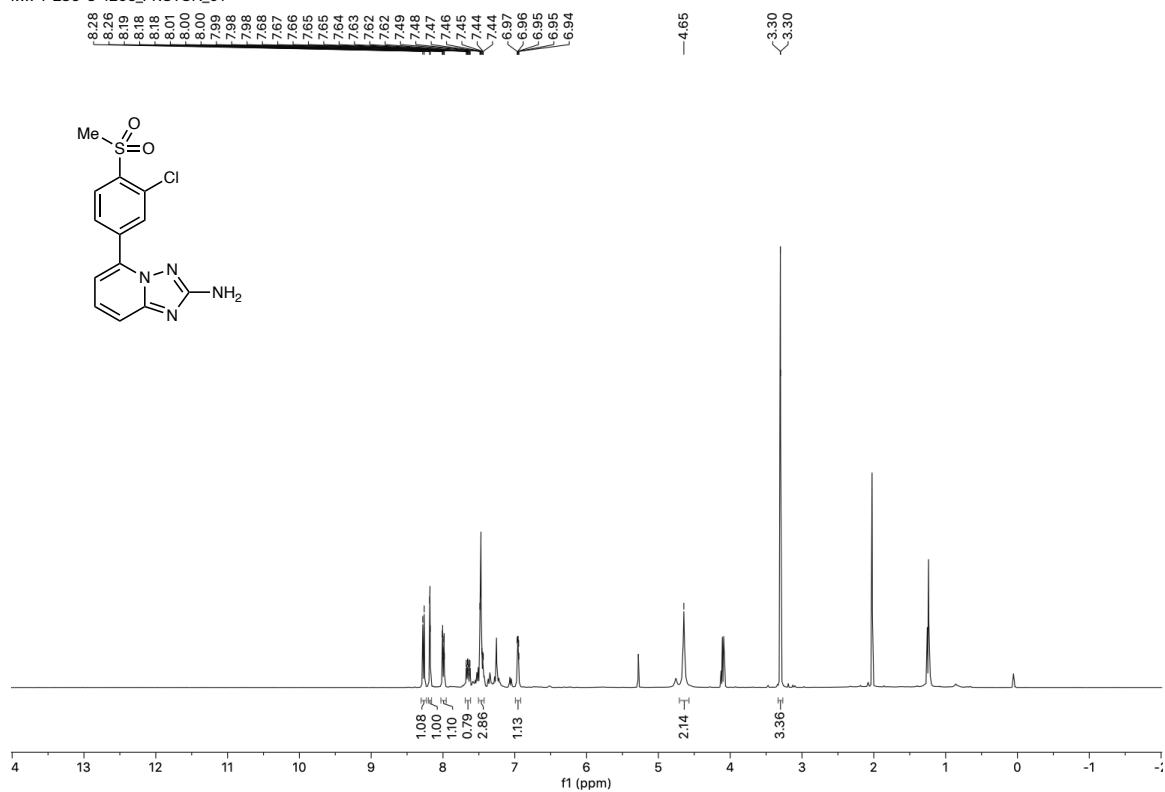
<p>chromatography to give 5-(3-chloro-4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (40 mg, 16%). ¹H NMR (400 MHz, DMSO-d₆): δ 8.23 (s, 1H), 8.07 (s, 1H), 7.97 (d, J=1.6 Hz, 1H), 7.93-7.88 (m, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.66 (t, J=8.0 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 7.19 (s, 2H), 3.13 (s, 3H); LCMS: 311.7 [M+H]⁺.</p> <p>Reaction Name and Classification: <i>Bromo Suzuki coupling</i></p> <p>Yield and Characterization: [16.0]</p>	
<p>Expert: 1, Prediction:2</p> <p>Reaction Procedure: A mixture of 5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.5 g, 2.3 mmol), (3-chloro-4-methylsulfonylphenyl)boronic acid (0.9 g, 4.6 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (100 mg, 0.13 mmol) and potassium carbonate (0.7 g, 5.0 mmol) in dioxane (20 mL) and water (2 mL) was heated to 90 °C. for 12 h under a nitrogen atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=1:4) to give 5-(3-chloro-4-methylsulfonyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.5 g, 58%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.47 (s, 1H), 8.35 (d, J=8.0 Hz, 1H), 8.15 (d, J=8.0 Hz, 1H), 7.99 (t, J=8.0 Hz, 1H), 7.84 (d, J=8.0 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.18 (t, J=8.0 Hz, 1H), 6.99 (s, 2H), 3.45 (s, 3H).</p> <p>Reaction Name and Classification: Bromo Suzuki coupling</p> <p>Yield and Characterization: [58.0]</p>	<p>For 0.1 mmol (21.3 mg) scale, compound 8a was formed with 26% NMR yield</p>

¹H NMR (400 MHz, CDCl₃): δ 8.27 (d, J = 8.2 Hz, 1H), 8.18 (t, J = 1.4 Hz, 1H), 7.99 (dt, J = 8.3, 1.4 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.50 – 7.43 (m, 2H), 6.96 (dd, J = 5.5, 3.0 Hz, 1H), 4.65 (s, 2H), 3.30 (d, J = 1.2 Hz, 3H).

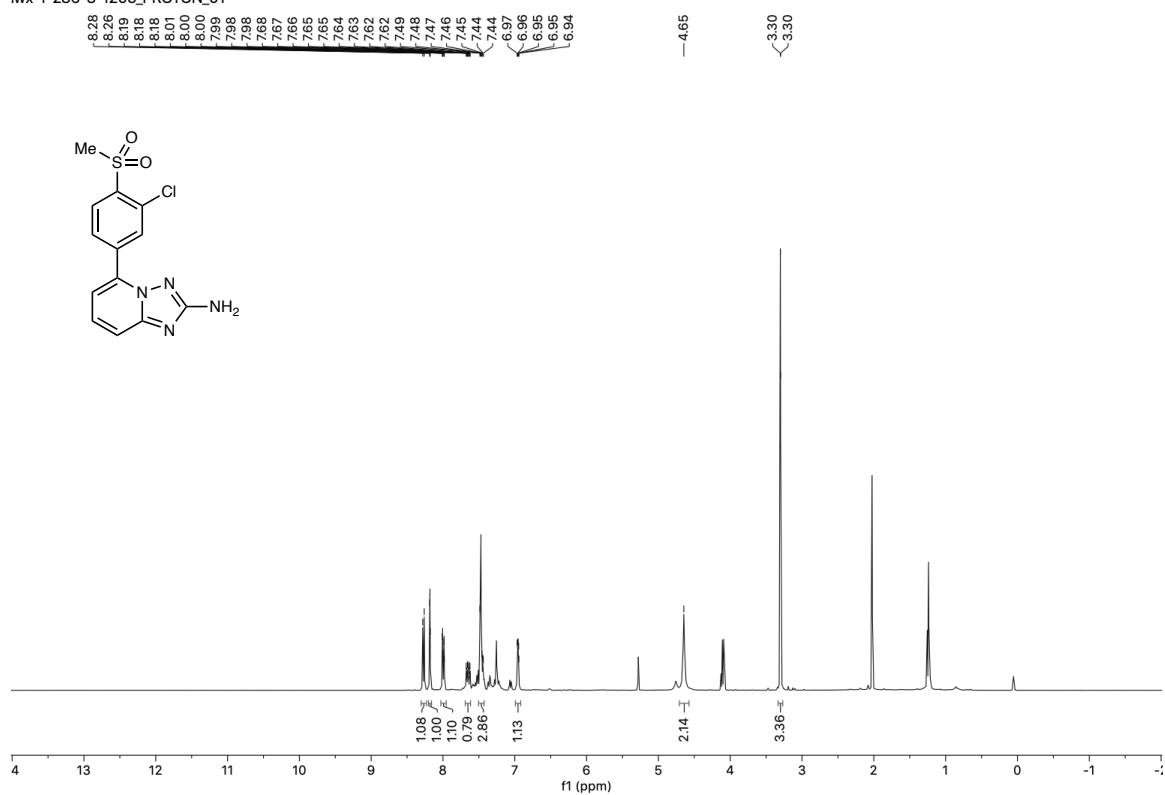
¹³C NMR (100 MHz, CDCl₃): δ 165.1, 151.9, 139.0, 138.6, 136.3, 132.8, 132.1, 132.1, 132.0, 131.9, 131.9, 131.0, 129.6, 129.1, 128.5, 128.4, 127.8, 116.0, 114.1, 113.1, 112.2, 42.8.

HRMS (ESI⁺) [M+H]⁺: Calc'd for C₁₃H₁₂ClN₄O₂S: 323.0364 m/z, found: 323.0370 m/z.

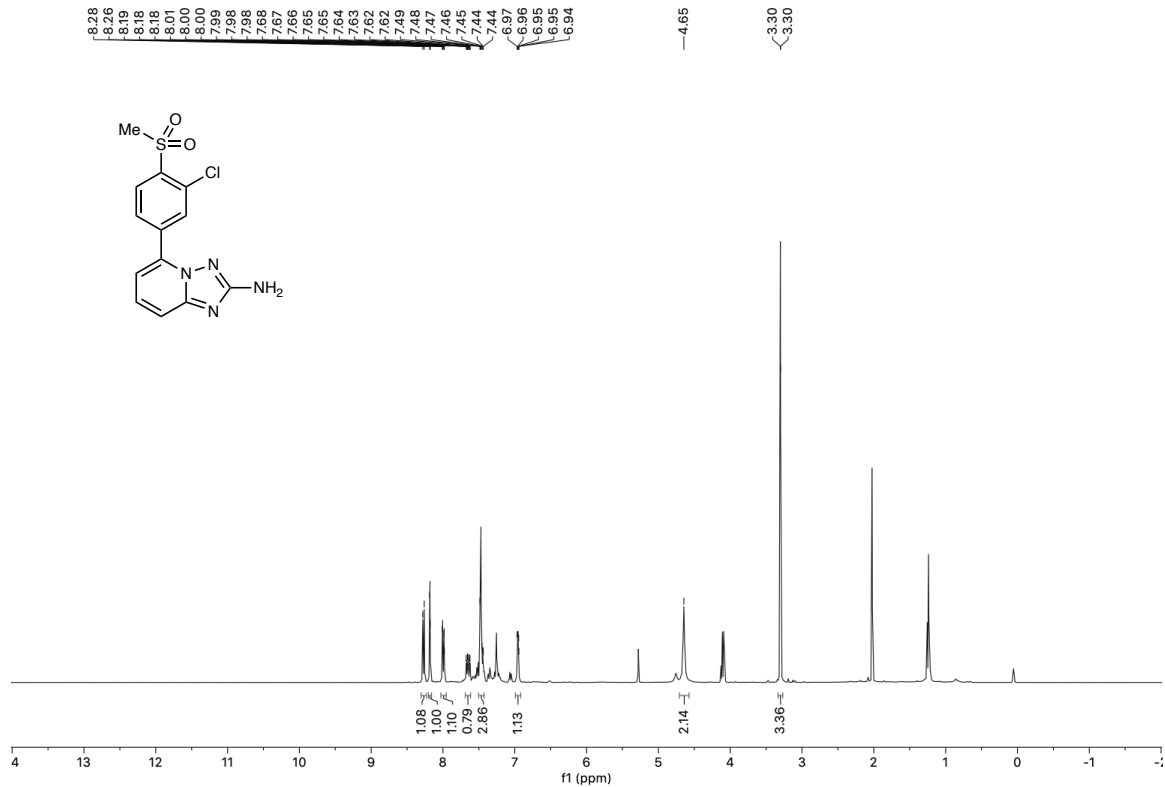
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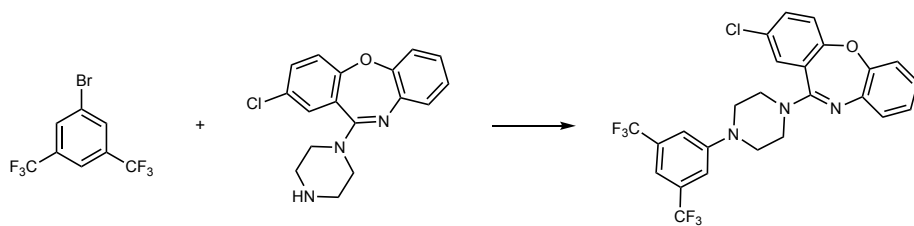
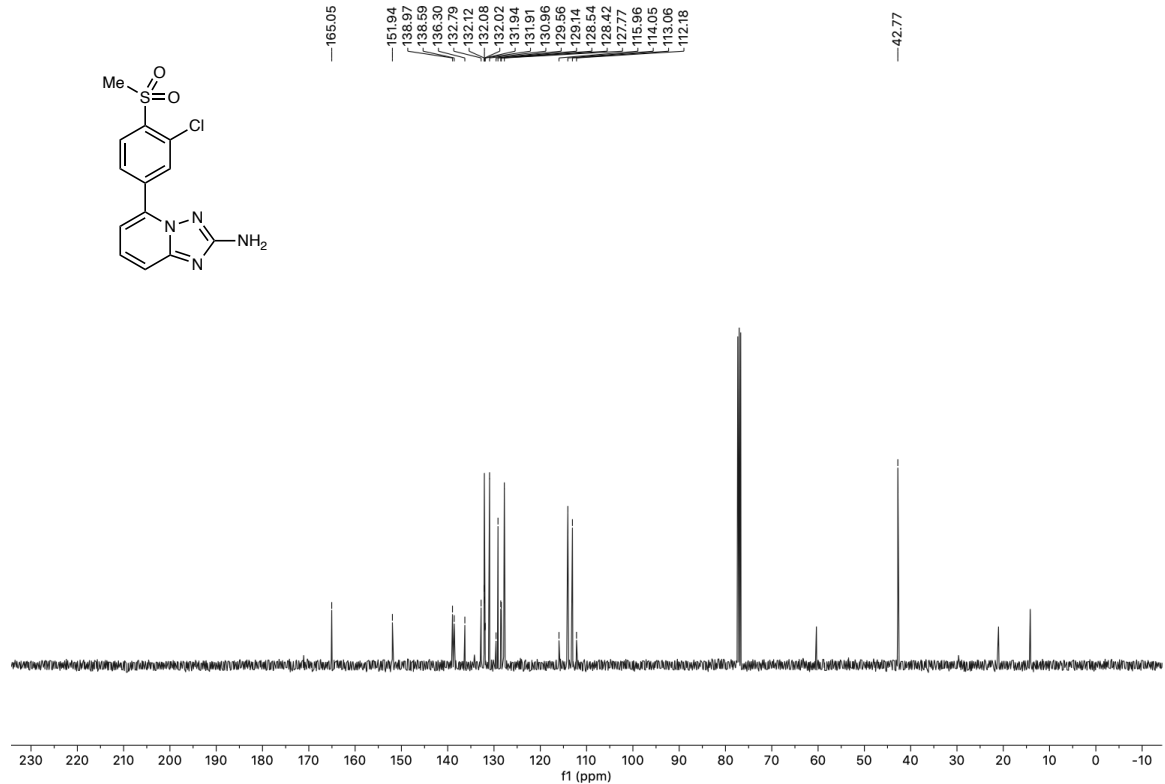
lwx-1-286-3-1205_PROTON_01 —



lwx-1-286-3-1205_PROTON_01



lwx-1-286-3-1205_CARBON_01



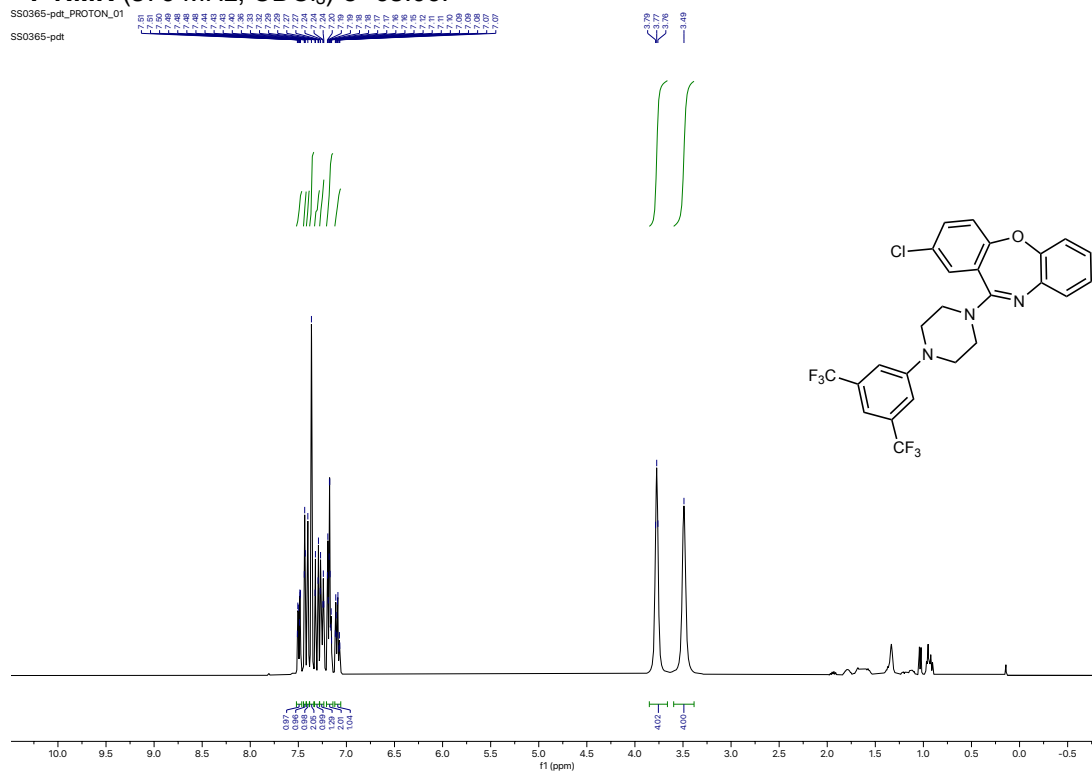
8b

Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A mixture of 2-piperazin-1-yl-6-chloro-benzooxazepine (1.2 g, 3.6 mmol), 1-(3,5-bis-trifluoromethyl-phenyl)-piperazine (1.5 g, 5.1 mmol), palladium acetate (65 mg, 0.29 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (175 mg, 0.36 mmol) and sodium tert-butoxide (0.52 g, 5.4 mmol) in toluene (20 ml) was heated to 100 °C. for 12 h. The reaction mixture was filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/heptane) to yield the title compound (1.15 g, 60%) as a white solid.</p> <p>Reaction Name and Classification: None</p> <p>Yield and Characterization: [60.0]</p>	<p>For a 0.18 mmol (60 mg) scale reaction, amination product 8b was isolated as pale yellow foam (26.8 mg, 20% yield). R_f (3% EtOAc in hexane): 0.20.</p>

^1H NMR (400 MHz, CDCl_3) δ 7.52 – 7.46 (m, 1H), 7.43 (d, $J = 2.4$ Hz, 1H), 7.40 (s, 1H), 7.36 (s, 2H), 7.34 – 7.28 (m, 1H), 7.28 – 7.23 (m, 1H), 7.21 – 7.14 (m, 2H), 7.13 – 7.06 (m, 1H), 3.84 – 3.71 (m, 4H), 3.59 – 3.36 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 159.4, 158.7, 151.8, 151.6, 132.8, 132.5 (q, $J = 32.8$ Hz), 130.4, 128.9, 127.1, 125.9, 125.0, 124.8, 123.5 (q, $J = 271.0$ Hz), 122.9, 120.2, 115.1 (q, $J = 3.0$ Hz), 112.6 (m, $J = 4.1$ Hz), 48.1, 47.1.

^{19}F NMR (376 MHz, CDCl_3) δ -63.06.

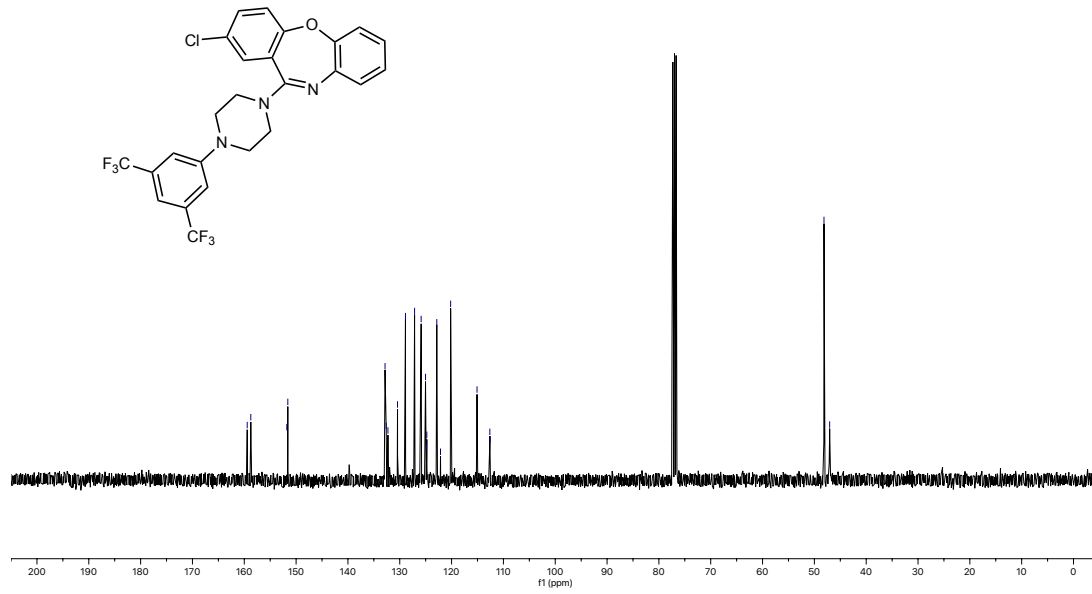


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SS0365-pdt

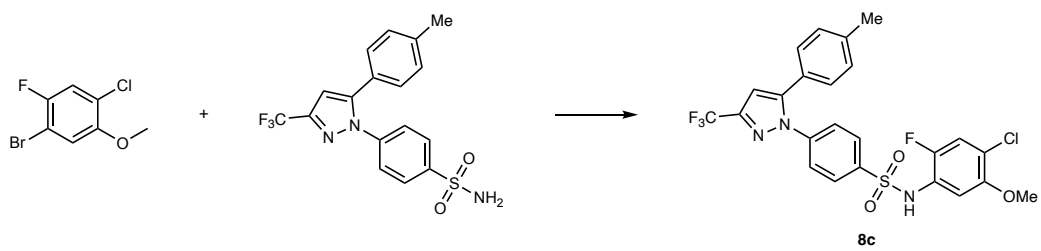
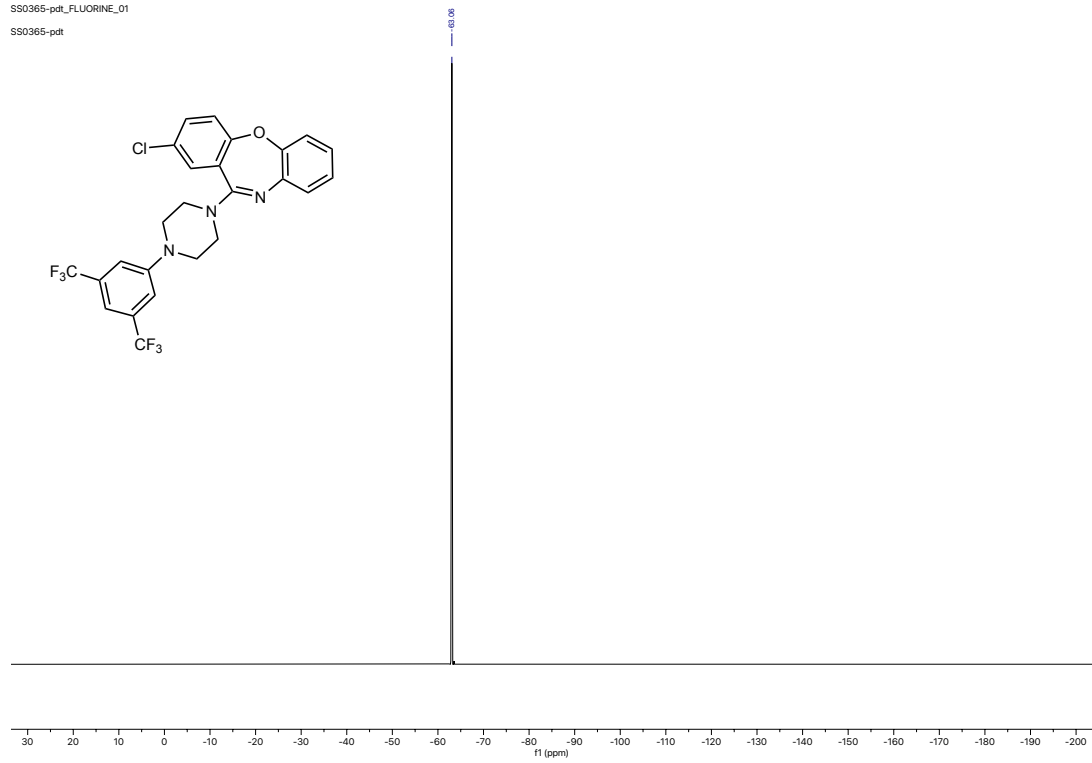
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151.60

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120.38
119.82
112.58

48.14
47.95



SS0365-pdt_FLUORINE_01
SS0365-pdt



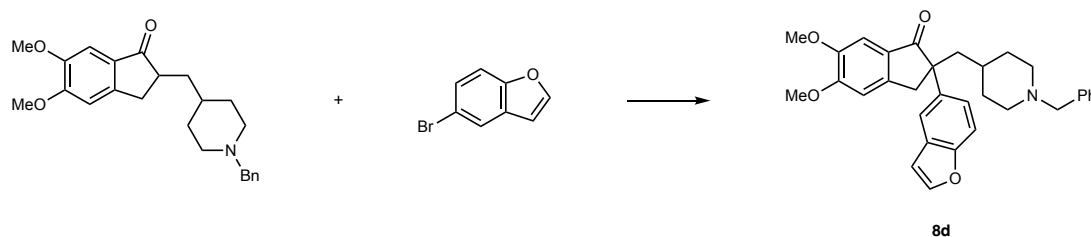
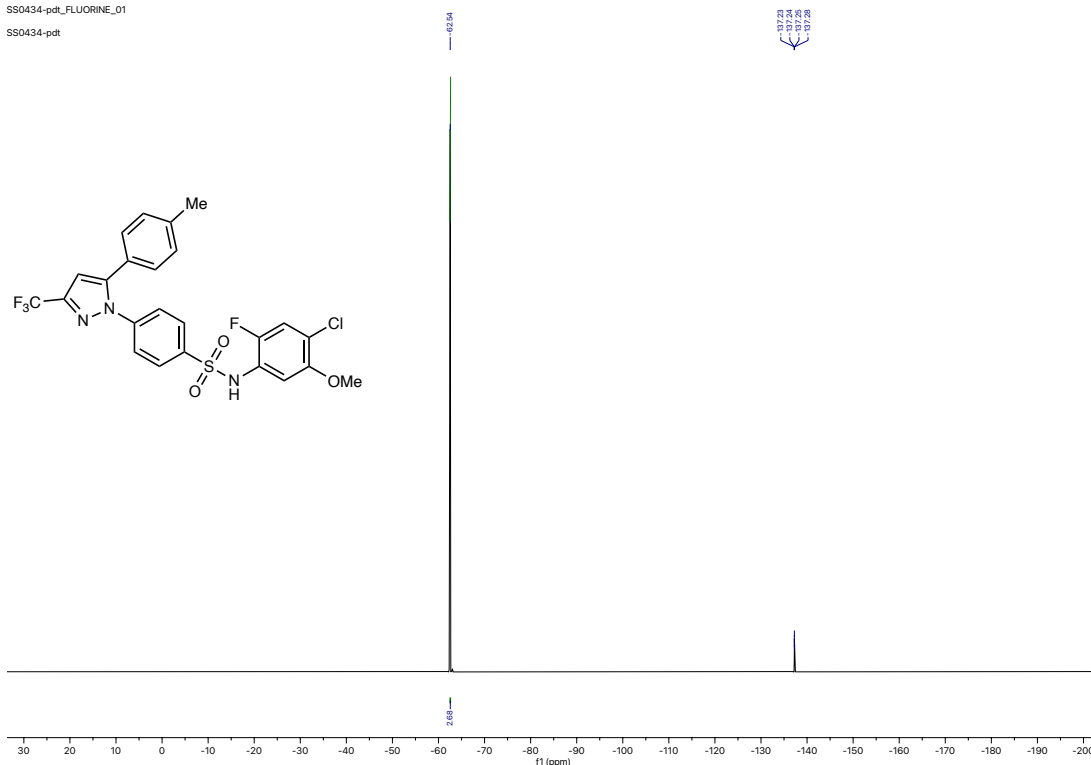
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A mixture of 4-[5-(trifluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 mg, 0.50 mmol), 1-chloro-5-bromo-2-fluoro-4-methoxybenzene (123 mg, 0.50 mmol), Cs₂CO₃ (244 mg, 0.75 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), Xphos (48 mg, 0.10 mmol) and 1,4-dioxane (2 mL) was stirred at 100 °C. for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative TLC (petroleum ether/ethyl acetate 2:1) to afford the title compound (60 mg, 23%) as a white solid.</p> <p>Reaction Name and Classification: None</p> <p>Yield and Characterization: [23.0]</p>	No reaction
<p>Expert: 3 Prediction:1</p> <p>Reaction Procedure: A mixture of 4-[3-(p-tolyl)-5-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide (100 mg, 0.25 mmol), 4-bromo-2-fluoro-1-chloroanisole (63 mg, 0.25 mmol), sodium tert-butoxide (71 mg, 0.75 mmol) and bis(tri-tert-butylphosphine)palladium(0) (12 mg, 0.02 mmol) in dioxane (2.5 mL) was stirred at 90 °C. for 3 hours. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and hexane (1:4) to give N-(4-chloro-2-fluoro-5-methoxyphenyl)-4-[3-(p-tolyl)-5-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide (86 mg, 0.16 mmol, 64%) as a white solid.</p> <p>Reaction Name and Classification: <i>Bromo N-arylation</i></p> <p>Yield and Characterization: [64.0]</p>	For a 0.263 mmol (63.0 mg) scale reaction, 8c was isolated as yellow solid (46.0 mg, 33% yield). R _f (20% EtOAc in hexane): 0.40.

¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.65 (m, 2H), 7.45 – 7.38 (m, 2H), 7.23 – 7.11 (m, 3H), 7.04 (m, 3H), 6.72 (s, 1H), 6.70 – 6.63 (m, 1H), 3.88 (s, 3H), 2.39 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 152.1, 149.3, 146.9, 145.4, 143.2, 140.0, 137.8, 129.9, 128.8, 128.2, 125.8, 125.6, 123.0, 122.8, 120.2, 117.5, 117.3, 108.1, 106.6, 57.0, 21.5.
. (multiplicities were unclear due to overlapping peaks).

¹⁹F NMR (376 MHz, CDCl₃) δ -62.54 (s, 3F), -137.25 (m, 1F).

HRMS m/z (ESI⁺) [M+H]⁺: Calc'd for C₁₃H₁₂ClN₄O₂S: 540.0694, found: 540.0778.

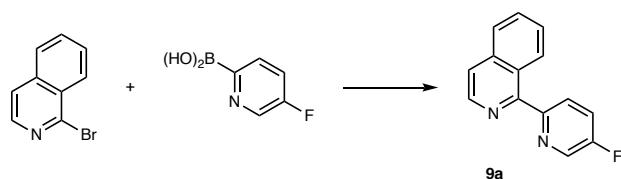


Model Predictions	Experimental Results
<p>Expert: 1 Prediction: 1 Reaction Procedure: To 2-(1-benzyl-piperidin-4-ylmethyl)-5,6-dimethoxy-2,3-dihydro-inden-1-one (Compound A2, 500 mg), 5-bromobenzofuran (441 mg), sodium t-butoxide (443 mg), palladium acetate (18.6 mg) and tri-tert-butylphosphine tetrafluoroboric acid (21 mg), tetrahydrofuran (10 ml) was added and the mixture was stirred with heating at 60°C for 2.5 hrs under nitrogen atmosphere. After cooling, the reaction mixture was added with saturated aqueous solution of ammonium chloride, and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (440 mg).</p> <p>Reaction Name and Classification: <i>Keto alpha-arylation</i>.</p> <p>Yield and Characterization: [72.6471]</p>	<p>For a 0.1317 mmol (44.1 mg) scale reaction, product 8d was isolated as yellow solid in (54.0 mg, 83% yield). R_f (EtOAc): 0.10.</p>

1H NMR (400 MHz, CDCl₃): δ 7.65 (t, J = 1.7 Hz, 1H), 7.57 (t, J = 1.8 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.31 – 7.19 (m, 5H), 7.18 (d, J = 1.5 Hz, 1H), 6.92 (s, 1H), 6.72 – 6.68 (m, 1H), 3.99 (s, 3H), 3.89 (s, 3H), 3.62 (d, J = 17.0 Hz, 1H), 3.43 – 3.33 (m, 3H), 2.79 – 2.69 (m, 2H), 2.33 – 2.25 (m, 1H), 1.98 (dd, J = 14.3, 6.1 Hz, 1H), 1.87 – 1.71 (m, 2H), 1.53 – 1.44 (m, 2H), 1.38 – 1.26 (m, 3H).

13C NMR (101 MHz, CDCl₃): δ 206.4, 155.7, 153.6, 149.6, 147.5, 145.2, 137.1, 129.2, 128.5, 128.1, 127.4, 126.9, 123.2, 119.0, 111.2, 107.0, 106.8, 105.2, 63.4, 57.2, 56.2, 56.1, 53.7, 45.1, 41.4, 34.0, 33.4, 32.9.

Ligand and Photocatalyst Synthesis



Model Predictions	Experimental Results
<p>Expert: 1, Prediction: 1</p> <p>Reaction Procedure: A mixture of 1-bromoisoquinoline (1.0 g, 4.8 mmol), 5-fluoropyridin-2-ylboronic acid (0.84 g, 6.0 mmol), Pd(PPh₃)₄ (0.280 g, 0.24 mmol) and K₃PO₄ (2.0 g, 9.6 mmol) in dioxane (40 mL) and water (4 mL) was degassed with argon for 15 minutes. The mixture was stirred at 100 °C. for 16 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (200 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate=2/1) to give the title compound (0.87 g, 81%) as a white solid.</p> <p>Reaction Name and Classification: <i>Bromo Suzuki coupling</i></p> <p>Yield and Characterization: [81.0]</p>	<p>For a 0.2 mmol (41.7 mg) scale reaction, product 9a was isolated as white solid (29.2 mg, 65% yield), R_f = 0.33 (hexanes:EtOAc = 3:1).</p>

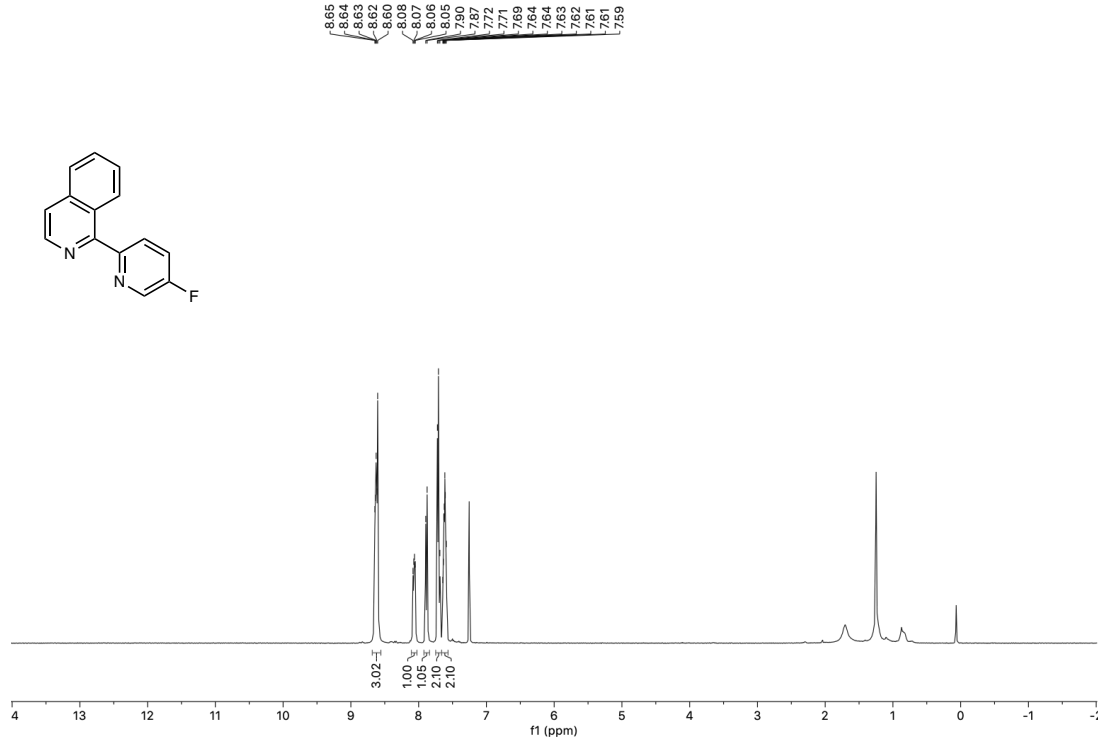
¹H NMR (400 MHz, CDCl₃): δ 8.69 – 8.56 (m, 3H), 8.07 (dd, *J* = 8.8, 4.5 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 2H), 7.66 – 7.56 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 155.4 (d, *J* = 177.8 Hz), 141.8, 137.2, 136.7 (d, *J* = 23.7 Hz), 130.1, 127.8, 127.6, 127.0, 126.6, 126.5 (d, *J* = 4.5 Hz), 123.8 (d, *J* = 18.4 Hz), 121.4.

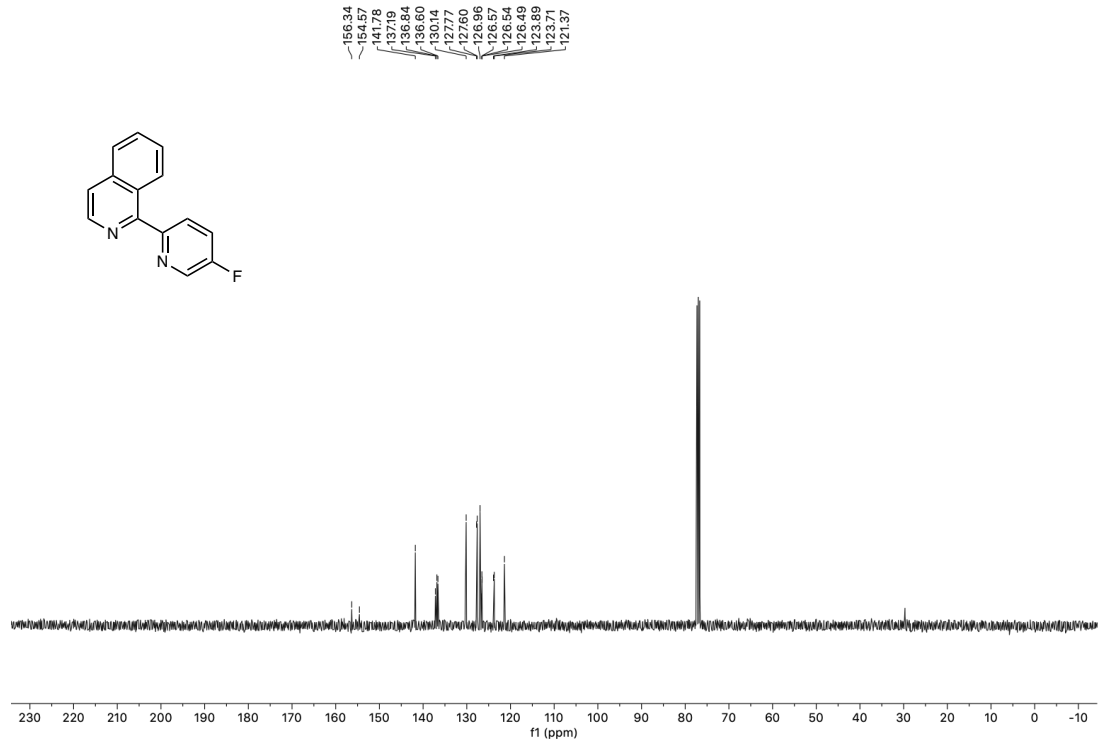
¹⁹F NMR (376 MHz, CDCl₃): δ -127.1.

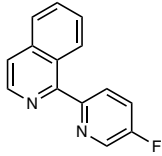
HRMS (ESI⁺) [M+H]⁺: Calc'd for C₁₄H₁₀FN₂: 225.0823 m/z, found: 225.0828 m/z.

lwx-1-295-B1-1217_PROTON_01 — —

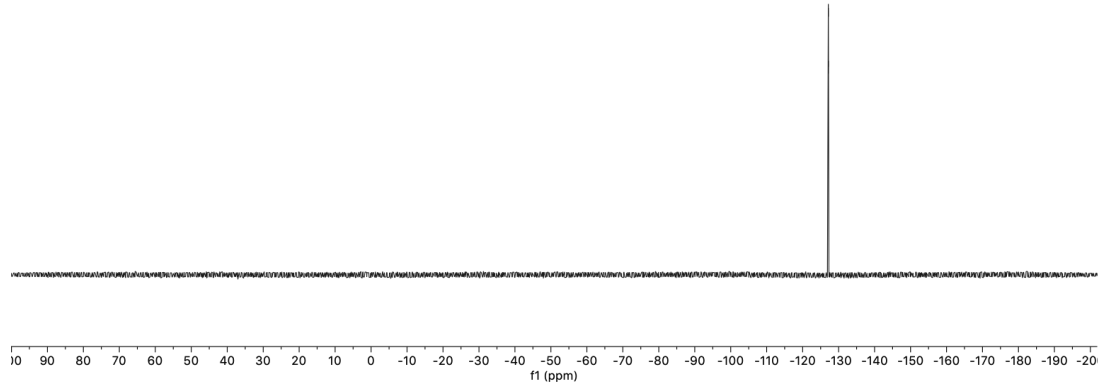


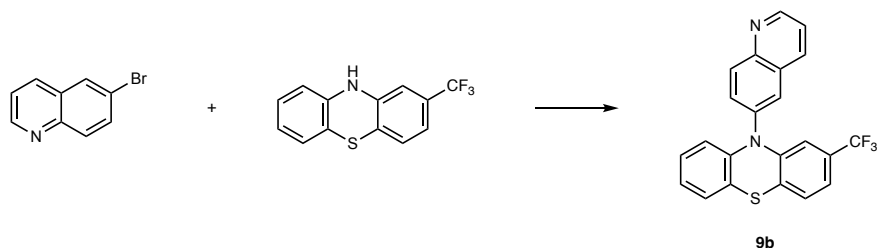
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-127.12
-127.14
-127.15
-127.16





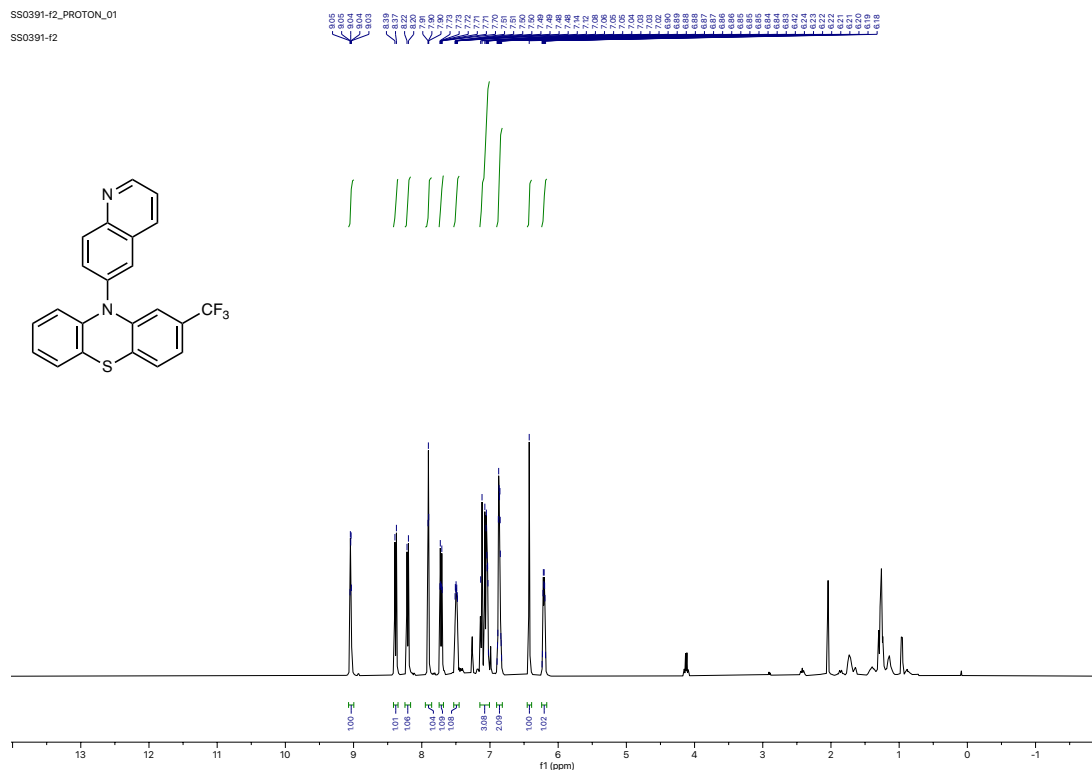
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1 Reaction Procedure: In a nitrogen atmosphere, 6-bromoquinoline (2.0 g, 10.0 mmol), 7-(trifluoromethyl)-10H-phenothiazine (2.9 g, 11.0 mmol), Pd₂(dba)₃ (0.46 g, 0.50 mmol), Xphos (0.93 g, 2.0 mmol), t-BuONa (2.88 g, 30.0 mmol), and toluene (60 mL) were added to a 200 mL three-neck flask, and stirred at 100 °C. for 12 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate, and the residual moisture was removed with magnesium sulfate. The resulting product was dried and separated by column chromatography to obtain 10-(quinolin-6-yl)-7-(trifluoromethyl)-10H-phenothiazine (2.7 g, yield: 70%).</p> <p>Reaction Name and Classification: <i>Bromo Buchwald-Hartwig amination</i></p> <p>Yield and Characterization: [70.0]</p>	<p>For a 0.2 mmol (40.0 mg) scale reaction, product 9b was isolated as yellow solid (56.0 mg, 71% yield). R_f (20% EtOAc in hexane): 0.80.</p>

¹H NMR (400 MHz, CDCl₃) δ 9.07 – 9.01 (m, 1H), 8.38 (d, *J* = 8.9 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.94 – 7.87 (m, 1H), 7.75 – 7.68 (m, 1H), 7.53 – 7.46 (m, 1H), 7.15 – 7.02 (m, 3H), 6.91 – 6.80 (m, 2H), 6.42 (s, 1H), 6.25 – 6.16 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 151.5, 147.7, 144.4, 143.4, 138.3, 136.1, 132.8, 131.7, 129.7, 129.3 (d, *J* = 32.5 Hz), 128.9, 127.4, 127.0, 126.9, 125.6, 123.7 (q, *J* = 271.0 Hz), 123.4, 121.8, 119.8, 119.4 (q, *J* = 3.9 Hz), 116.8, 112.4 (q, *J* = 3.9 Hz).

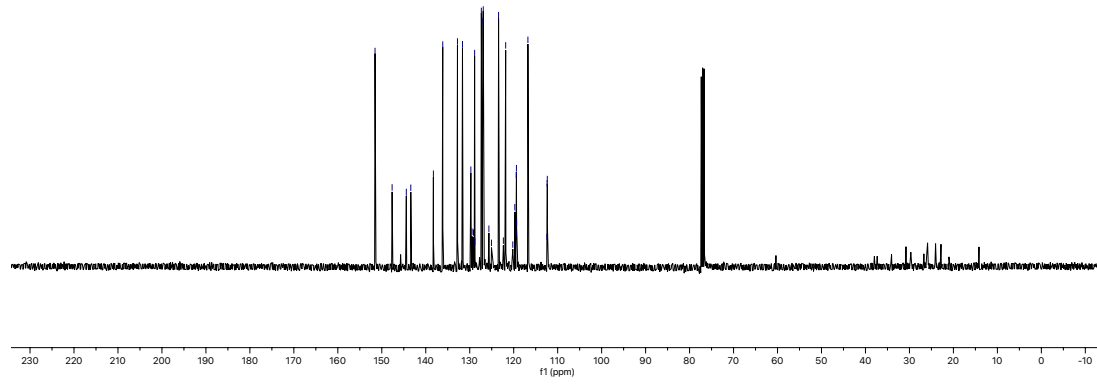
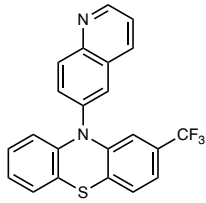
¹⁹F NMR (376 MHz, CDCl₃) δ -62.95.

HRMS (ESI⁺) [M+H]⁺: Calc'd for C₁₄H₁₀FN₂: 395.0752 m/z, found: 395.0841 m/z.



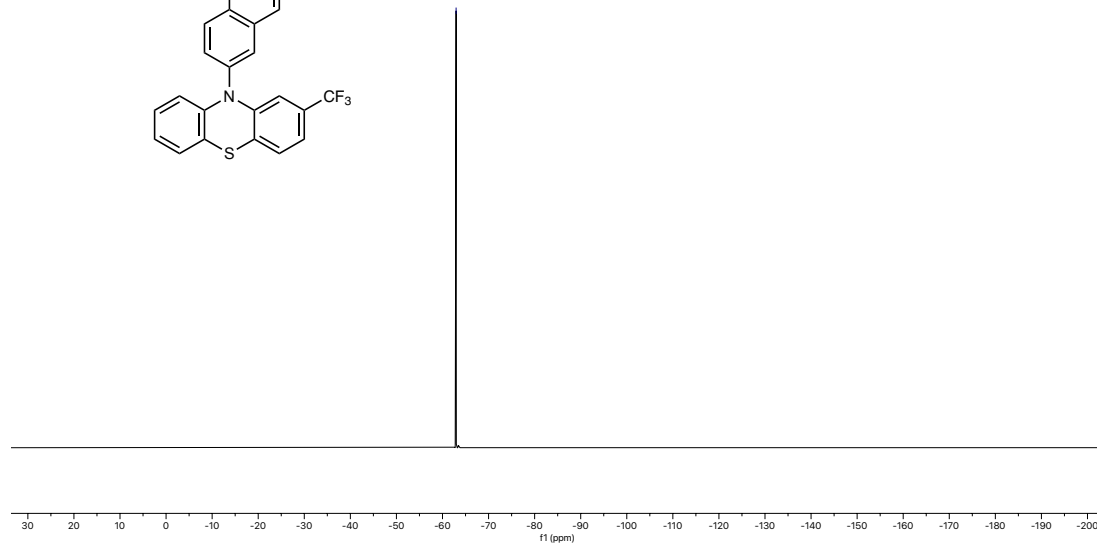
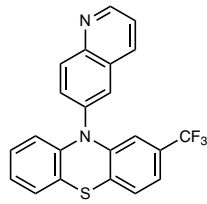
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SS0391-I2

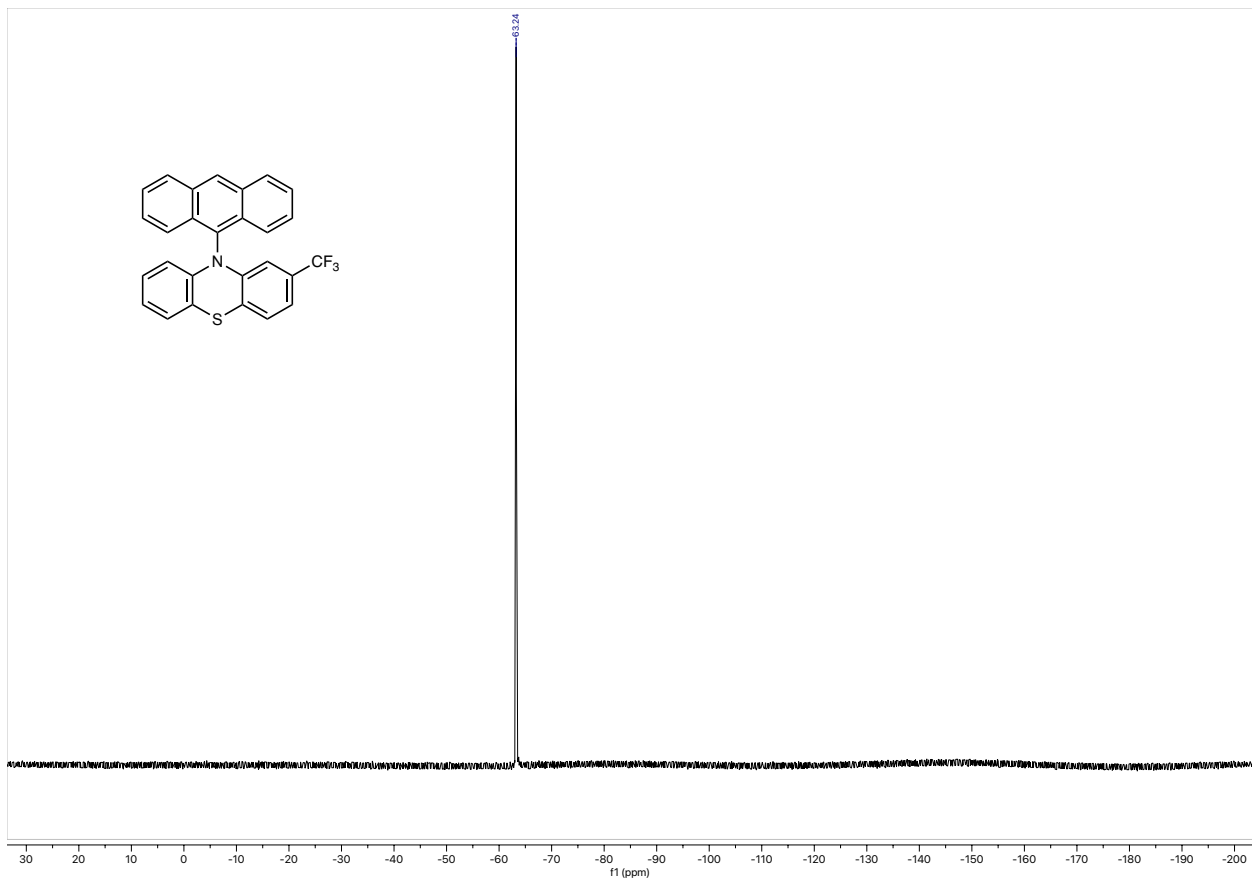
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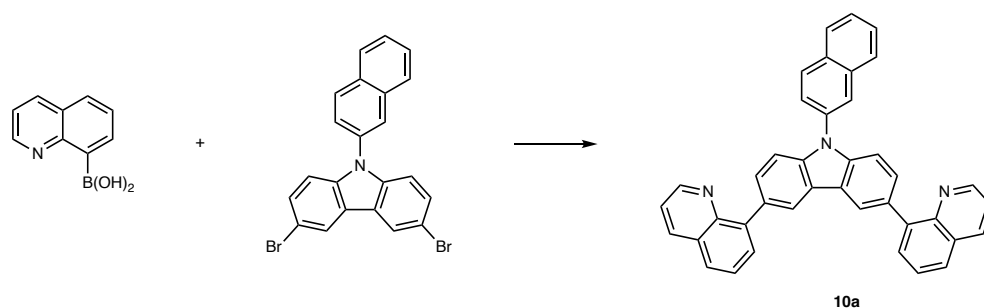


SS0391-I2_FLUORINE_01
SS0391-I2

81.395



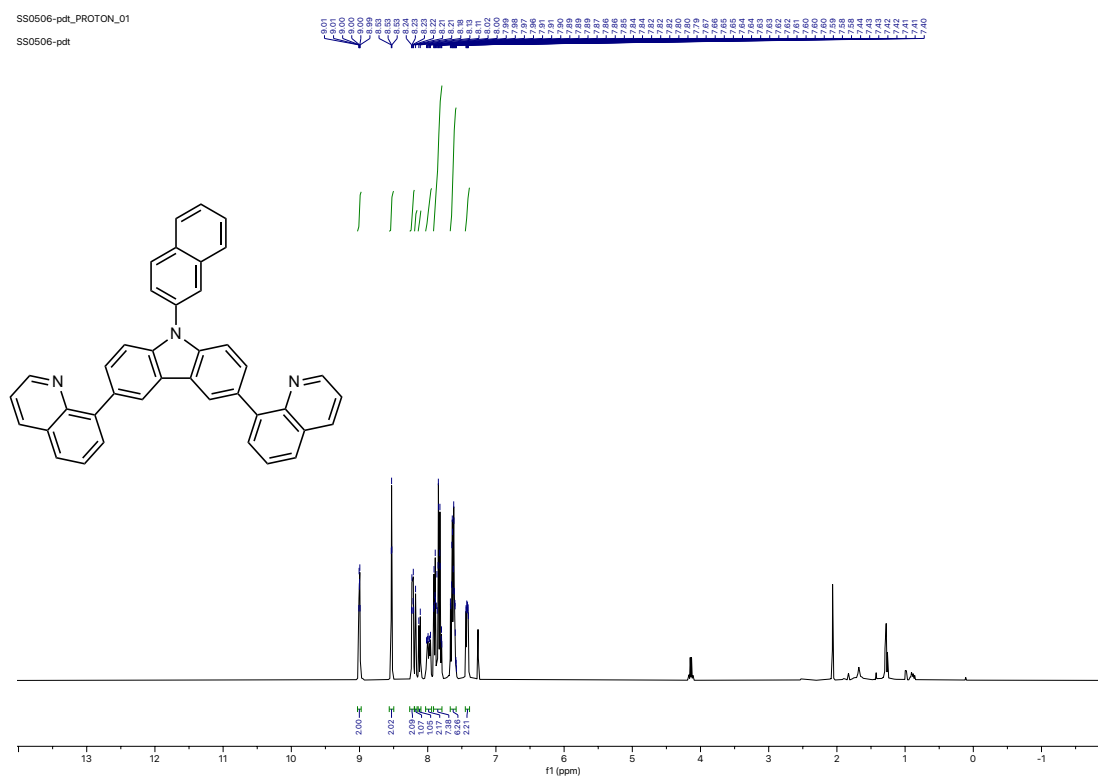




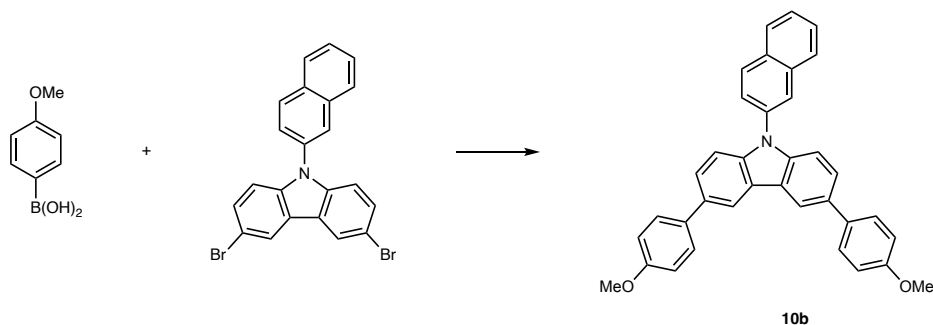
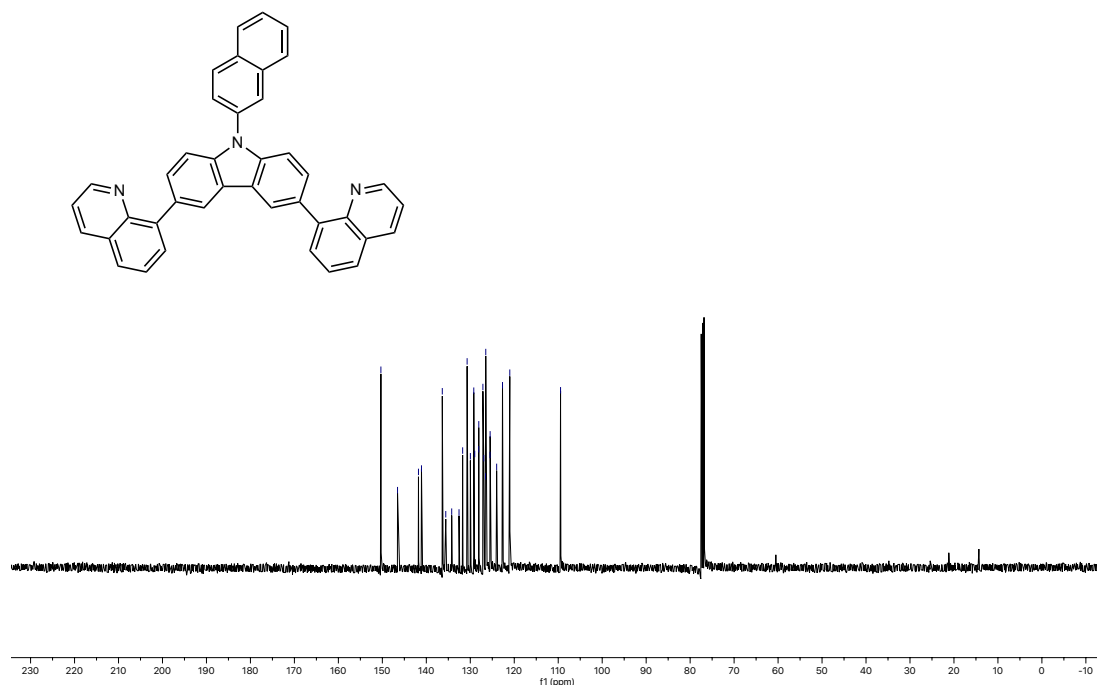
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: 9,9'-((9H-[2,2'-biquinoline]-9-yl)bis(phenyl))bis(3-bromo-9H-carbazole) (6 g, 13.1 mmol), quinoline-8-boronic acid (5.9 g, 26.2 mmol), Pd(PPh₃)₄ (1.55 g, 1.3 mmol), K₂CO₃ (7.2 g, 52.3 mmol), 90 mL of toluene, and 30 mL of distilled water were added to a flask, and stirred at 120 °C. After 16 hours, the mixture was extracted with ethyl acetate, and the organic layer was washed with distilled water. The obtained organic layer was distilled under reduced pressure and separated by column chromatography to obtain 9,9'-((9H-[2,2'-biquinoline]-9-yl)bis(phenyl))bis(9H-carbazole) (4.8 g, 9.3 mmol, 71%).</p> <p>Reaction Name and Classification: None</p> <p>Yield and Characterization: [71.0]</p>	<p>For a 0.22 mmol (100.0 mg) scale reaction, product 10a was isolated as brown foam (62 mg, 52% yield). R_f (30% EtOAc in hexane): 0.30.</p>

¹H NMR (400 MHz, CDCl₃) δ 9.03 – 8.97 (m, 2H), 8.53 (t, *J* = 1.5 Hz, 2H), 8.22 (dt, *J* = 8.3, 1.6 Hz, 2H), 8.18 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.03 – 7.93 (m, 2H), 7.92 – 7.78 (m, 7H), 7.68 – 7.58 (m, 6H), 7.45 – 7.39 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 150.3, 146.5, 141.8, 141.1, 136.4, 135.6, 134.2, 132.6, 131.7, 130.7, 130.0, 129.2, 129.0, 128.1, 128.1, 127.1, 126.9, 126.5, 126.5, 125.5, 125.5, 124.0, 122.7, 121.0, 109.5.



158.33
 146.34
 136.32
 135.35
 134.32
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 126.54
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 124.60
 122.87
 119.47

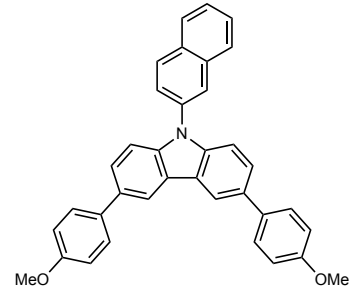
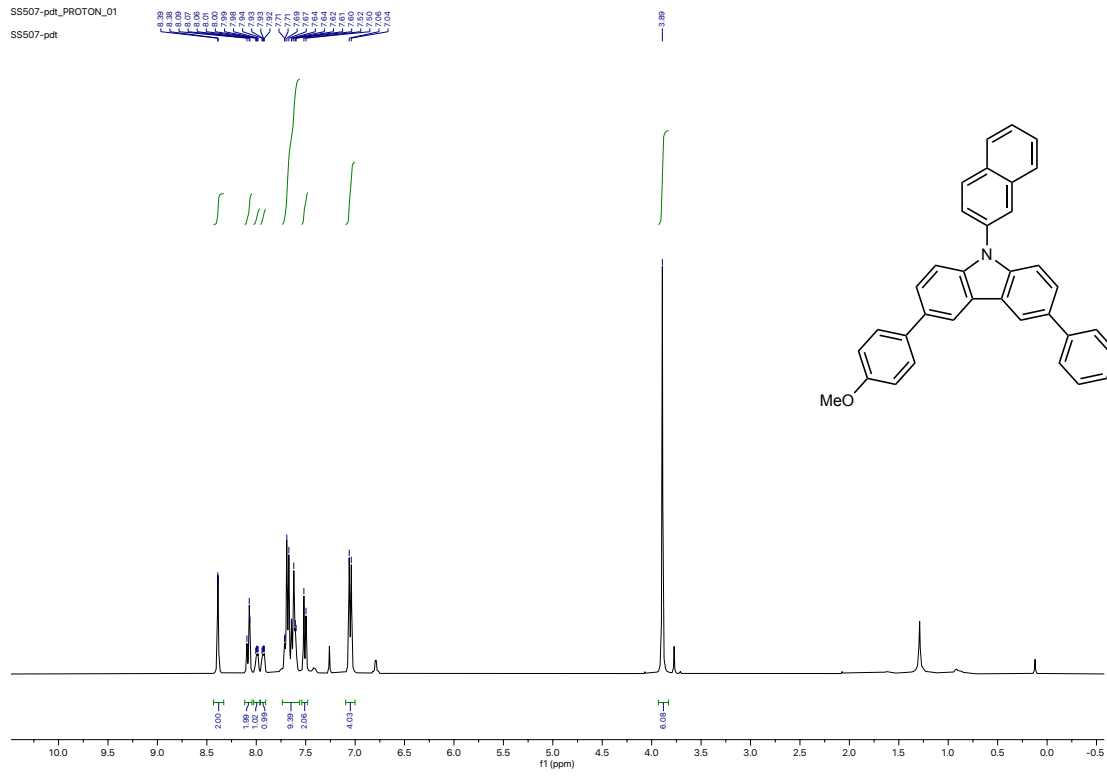


Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1 Reaction Procedure: Under a nitrogen atmosphere, 3,6-dibromo-9-(naphthalen-2-yl)-9H-carbazole (2.00 g, 4.54 mmol), 4-methoxyphenylboronic acid (1.80 g, 11.7 mmol), tetrakis(triphenylphosphine)palladium (515 mg, 0.45 mmol), potassium carbonate (1.38 g, 10.0 mmol), 100 mL of tetrahydrofuran, and 100 mL of water were mixed in a 250 mL three-neck flask. The mixture was heated and stirred at 80 °C. for 18 hours. After the reaction was complete, the organic layer was separated and purified by silica gel column chromatography (hexane/dichloromethane=2/1) to obtain 1.97 g (88%) of a white solid. Reaction Name and Classification: None Yield and Characterization: [88.0]</p>	<p>For a 0.22 mmol scale (100 mg) reaction, product 10b was isolated as yellowish solid (49 mg, 44% yield). R_f (10% EtOAc in hexane): 0.20.</p>

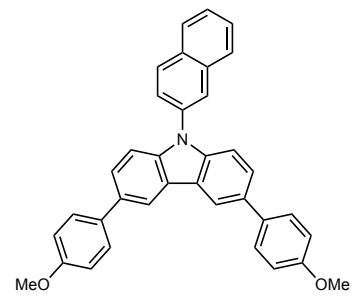
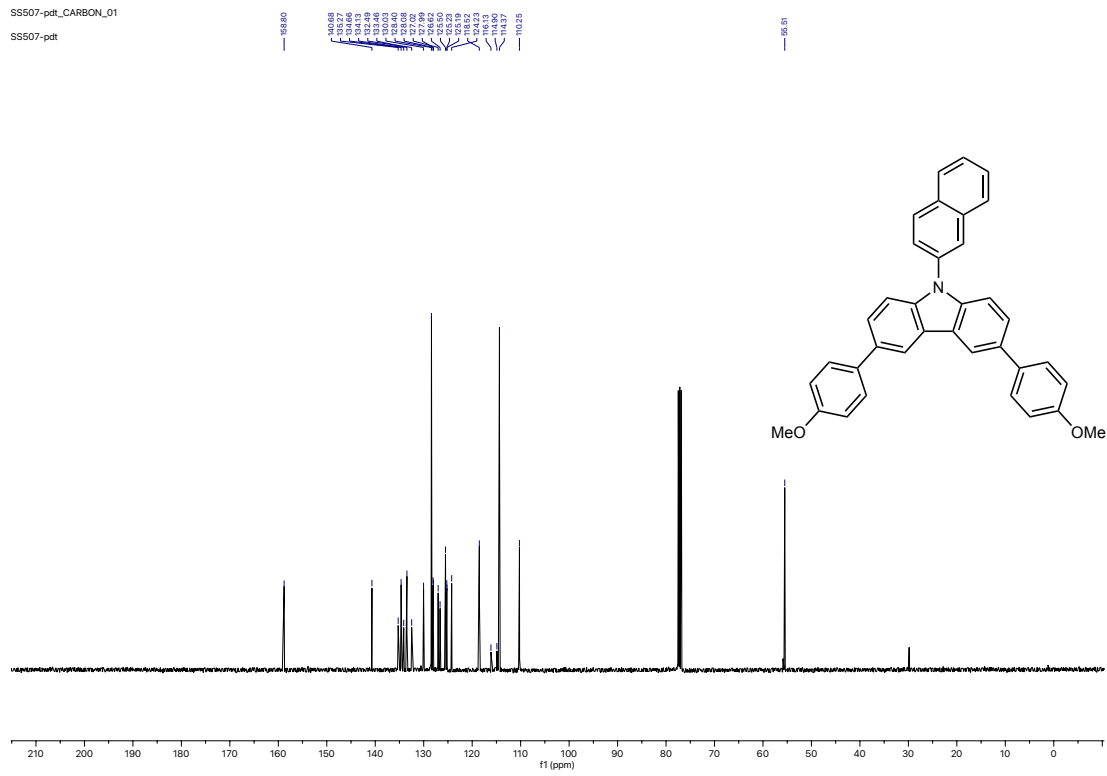
¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, *J* = 1.8 Hz, 2H), 8.11 – 8.04 (m, 2H), 7.99 (dd, *J* = 6.2, 3.3 Hz, 1H), 7.93 (dd, *J* = 6.2, 3.3 Hz, 1H), 7.72 – 7.59 (m, 9H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 4H), 3.89 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 158.8, 140.7, 135.3, 134.7, 134.1, 133.5, 132.5, 130.0, 128.4, 128.1, 128.0, 127.0, 126.6, 125.5, 125.2, 125.2, 124.2, 118.5, 116.1, 114.9, 114.4, 110.3, 55.5.

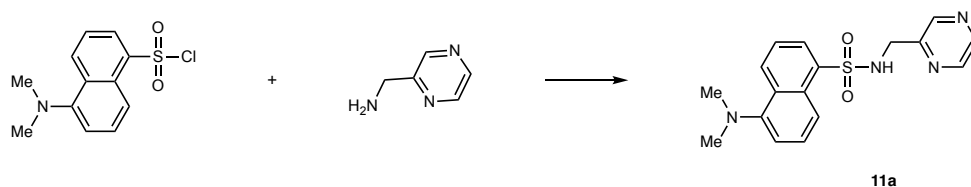
SS507-pdt_PROTON_01
SS507-pdt



SS507-pdt_CARBON_01
SS507-pdt



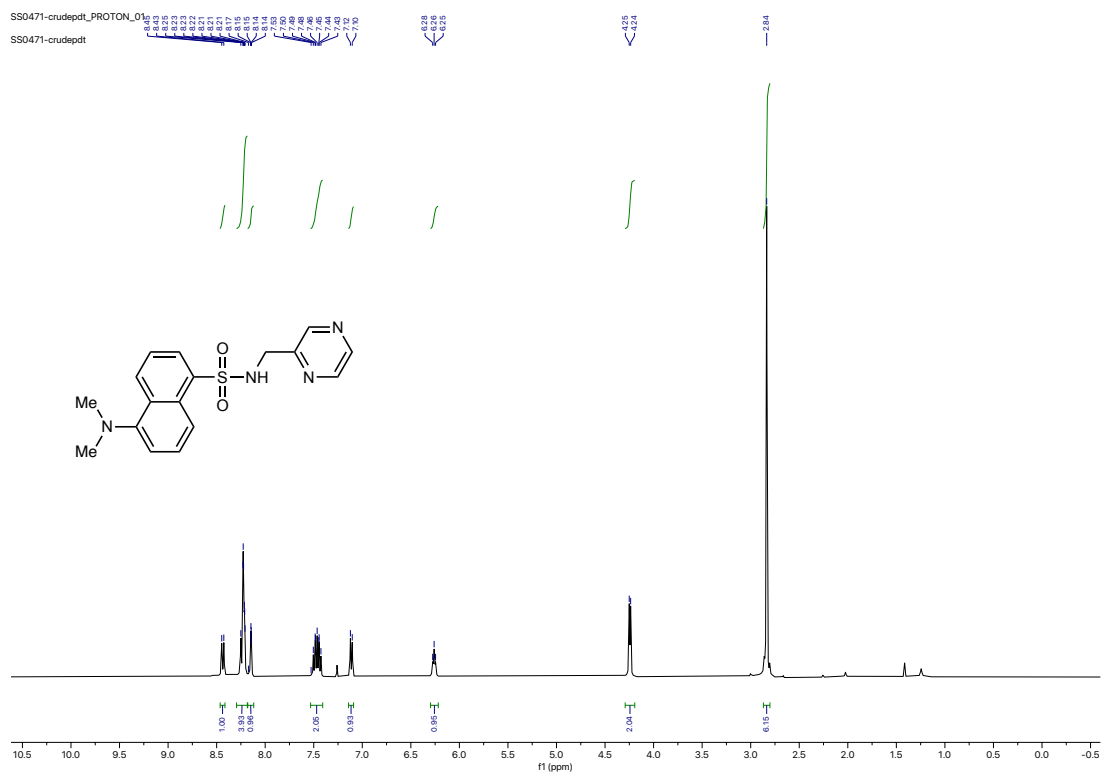
Agrochemical Synthesis

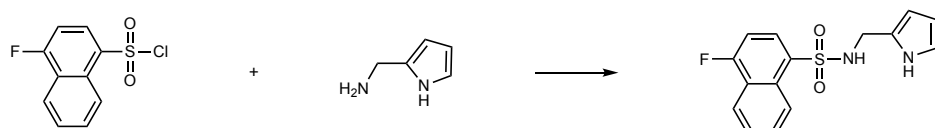
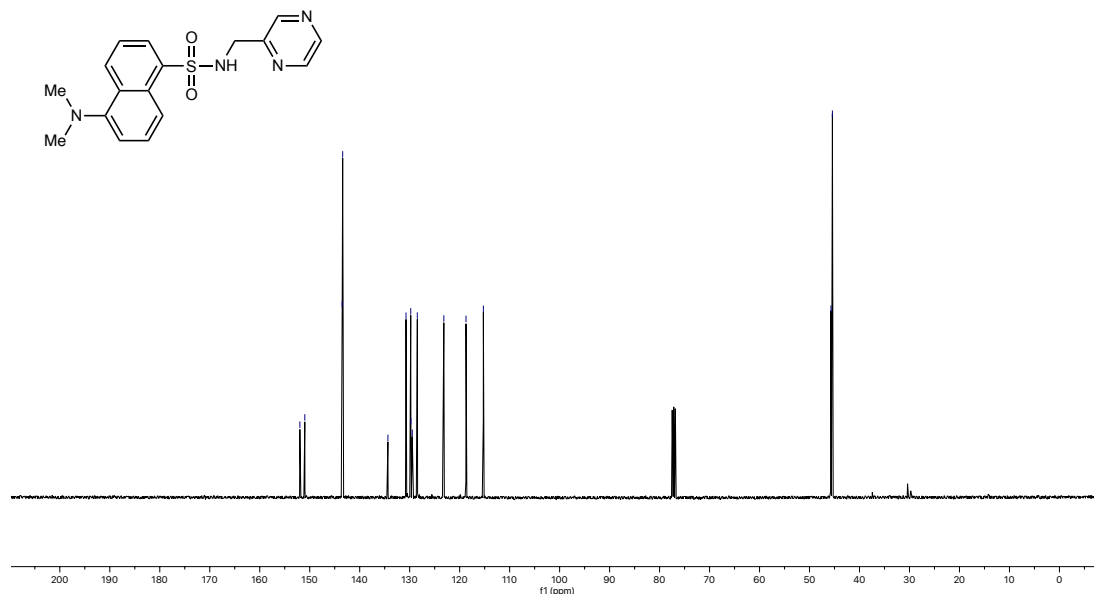


Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: 5-(Dimethylamino)naphthalene-1-sulfonyl chloride (50 mg, 0.18 mmol) was dissolved in THF (1 mL), and 2-(aminomethyl)pyrazine (29 mg, 0.27 mmol) and triethylamine (0.076 mL, 0.54 mmol) were added thereto in an ice bath, followed by stirring for 1 hour. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was separated and purified by MPLC to give the desired compound (51 mg, 80%) as a brown solid.</p> <p>Reaction Name and Classification: <i>Sulfonamide Schotten-Baumann</i></p> <p>Yield and Characterization: [80.0]</p>	<p>Following the predicted procedure on a 0.185 mmol (50.0 mg) scale, 11a was purified by silica gel column chromatography. Product was isolated as brown solid (60.0 mg, 95% yield). R_f (EtOAc): 0.40.</p>

^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, $J = 8.5$ Hz, 1H), 8.27 – 8.18 (m, 4H), 8.18 – 8.12 (m, 1H), 7.53 – 7.40 (m, 2H), 7.11 (d, $J = 7.5$ Hz, 1H), 6.26 (t, $J = 6.0$ Hz, 1H), 4.24 (d, $J = 5.8$ Hz, 2H), 2.84 (s, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 152.0, 151.0, 143.5, 143.4, 134.4, 130.7, 129.8, 129.8, 129.5, 128.5, 123.2, 118.7, 115.3, 45.7, 45.4.





11b i

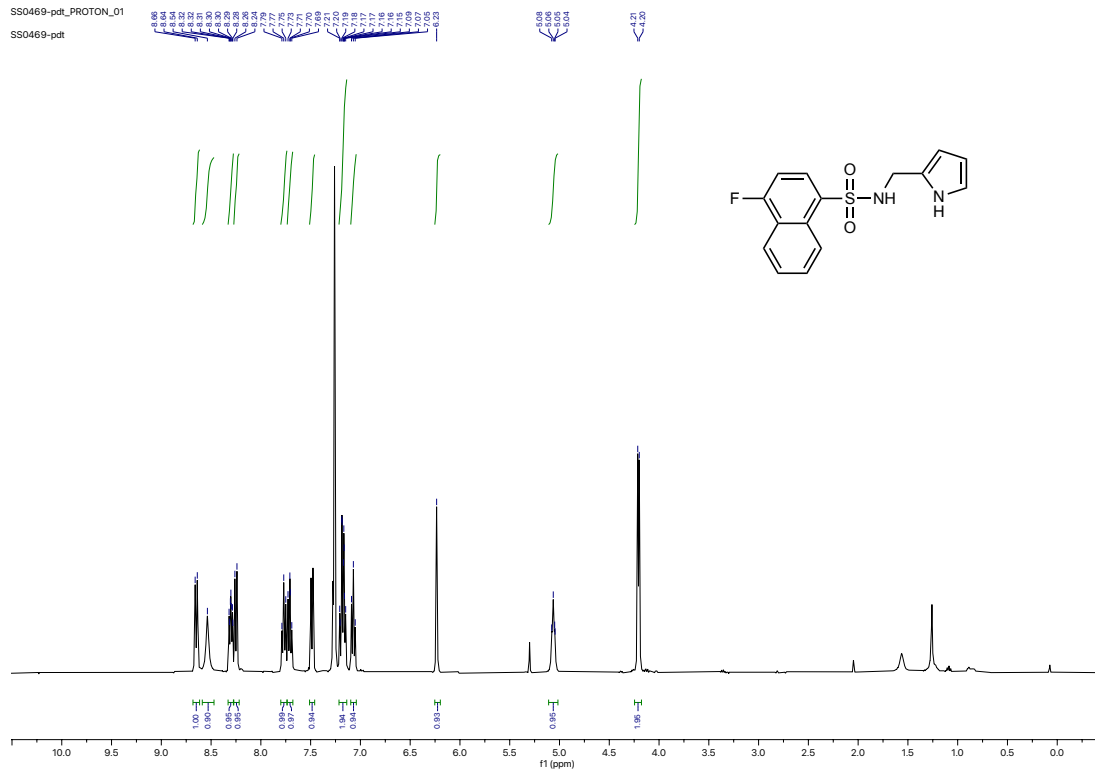
Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1 Reaction Procedure: 4-Fluoronaphthalene-1-sulfonyl chloride (100 mg, 0.43 mmol) was dissolved in 5 mL THF, to which 1H-pyrrol-2-ylmethanamine (57 mg, 0.52 mmol) and triethylamine (0.18 mL, 1.29 mmol) were added dropwise, followed by stirring at room temperature for 1 hour. The reaction solution was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Then, the reaction mixture was separated and purified by MPLC to give the title compound (30 mg, 23%, white solid). Reaction Name and Classification: <i>Sulfonamide Schotten-Baumann</i>. Yield and Characterization: [23.0]</p>	<p>Following the predicted procedure on a 0.43 mmol (100.0 mg) scale, 11b was purified by silica gel column chromatography. Product was isolated as light brown solid (117.0 mg, 78% yield). R_f (20% EtOAc in hexane): 0.15.</p>

¹H NMR (400 MHz, CDCl₃) δ 8.65 (d, J = 8.6 Hz, 1H), 8.54 (s, 1H), 8.34 – 8.18 (m, 2H), 7.77 (t, J = 7.8 Hz, 1H), 7.74 – 7.67 (m, 1H), 7.23 – 7.12 (m, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.23 (s, 1H), 5.10 – 5.02 (m, 1H), 4.21 (d, J = 6.2 Hz, 2H).

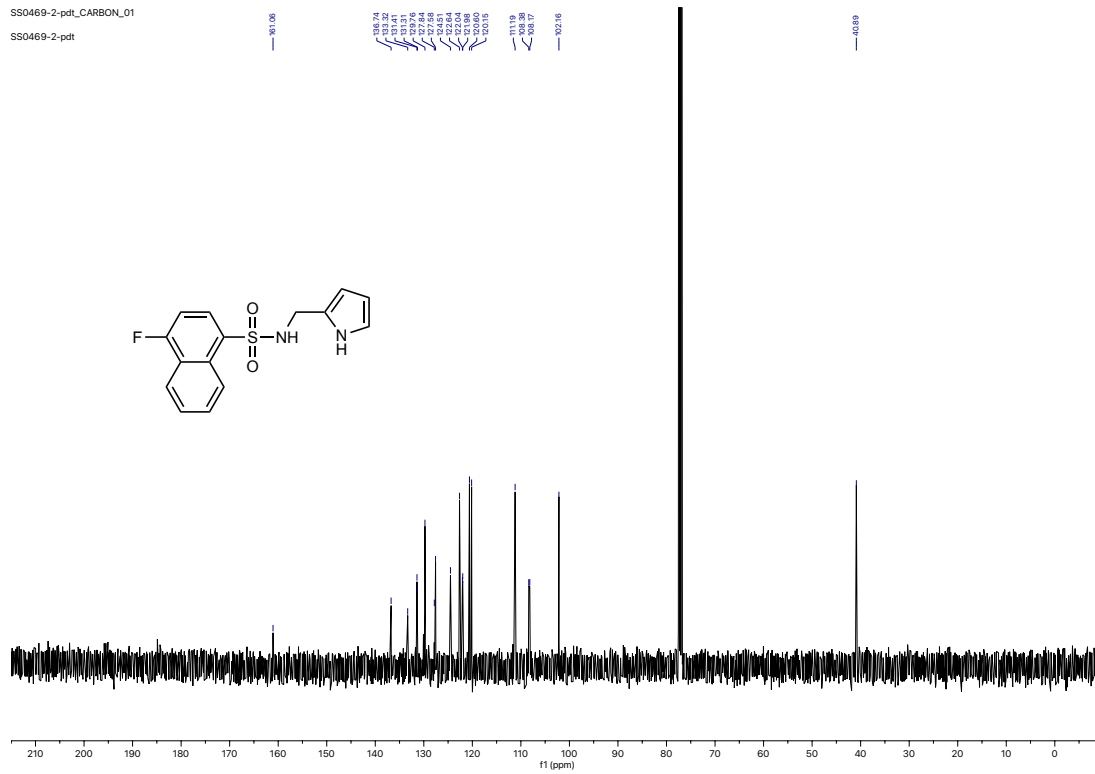
¹³C NMR (101 MHz, CDCl₃) δ 161.1, 136.7, 133.3, 131.4 (d, J = 10.2 Hz), 129.8, 127.8, 127.6, 124.5, 122.0 (d, J = 6.5 Hz), 121.4 (d, J = 250.1 Hz), 120.6, 111.2, 108.3 (d, J = 21.4 Hz), 102.2, 40.9.

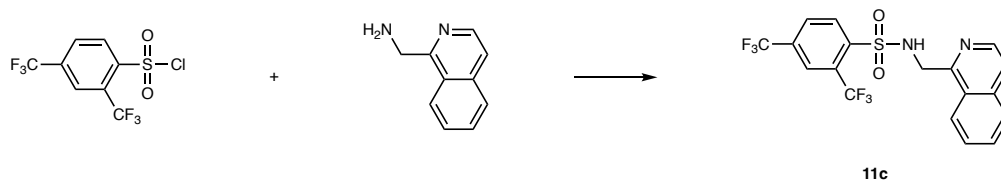
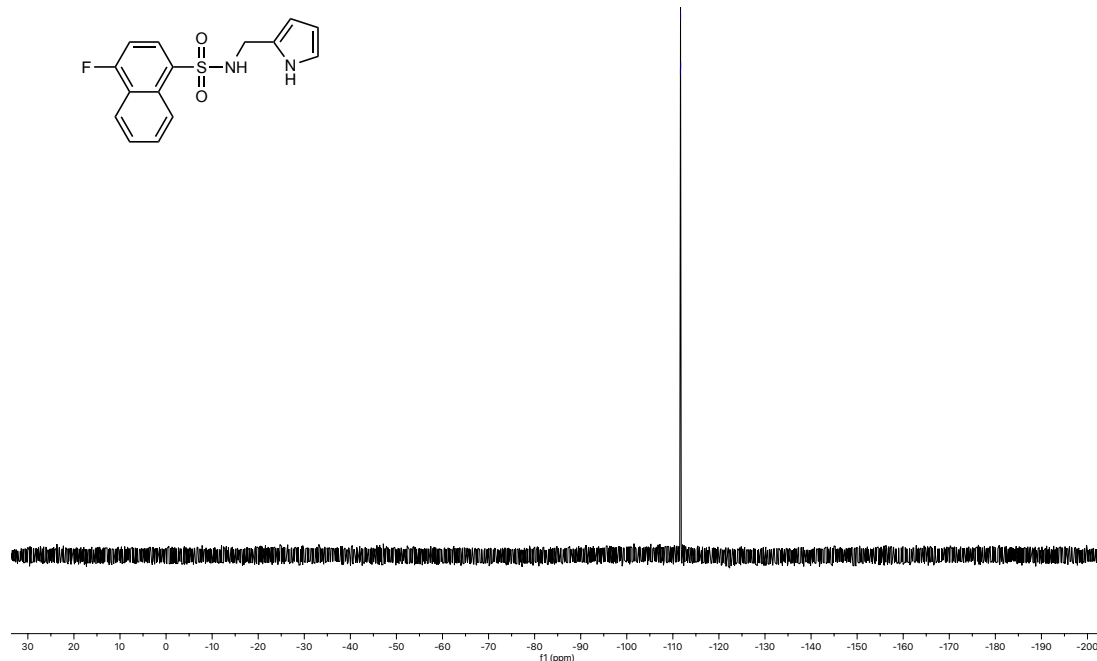
¹⁹F NMR (376 MHz, CDCl₃) δ -111.67 (dd, J = 9.7, 5.4 Hz).

SS0469-pdt_PROTON_01
SS0469-pdt



SS0469-2-pdt_CARBON_01
SS0469-2-pdt





Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1 Reaction Procedure: To a 0 °C. solution of isoquinolin-1-ylmethanamine (100 mg, 0.66 mmol) in THF (5 mL) was added triethylamine (101 mg, 0.99 mmol) followed by 2,4-bis(trifluoromethyl)benzenesulfonyl chloride (182 mg, 0.60 mmol) as a solution in THF (5 mL). The reaction was warmed to 20 °C. and stirred for 1 h. The mixture was concentrated, and the residue was partitioned between EtOAc (20 mL) and water (5 mL). The organic layer was washed with water (5 mL), and brine (1 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by silica column (20-50% EtOAc/Hexane) to give the desired product (110 mg, 43%) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 8.57 (d, J=8.1 Hz, 1H), 8.39 (d, J=5.1 Hz, 1H), 8.22-8.16 (m, 2H), 7.94-7.88 (m, 2H), 7.55-7.50 (m, 2H), 7.44-7.37 (m, 1H), 7.22 (d, J=5.4 Hz, 1H), 5.15 (t, J=6.0 Hz, 1H), 4.45 (d, J=6.0 Hz, 2H); ESI-MS m/z 422 (M+H)⁺.</p> <p>Reaction Name and Classification: <i>Sulfonamide Schotten-Baumann</i></p> <p>Yield and Characterization: [43.0]</p>	<p>To a 0 °C. solution of isoquinolin-1-ylmethanamine hydrochloride (91 mg, 0.33 mmol) in THF (2.5 mL) was added triethylamine (0.139 mL, 0.99 mmol) followed by 2,4-bis(trifluoromethyl)benzenesulfonyl chloride (182 mg, 0.60 mmol) as a solution in THF (5 mL). The reaction was warmed to 20 °C. and stirred for 3 h and followed by workup with EtOAc (10 mL) and water (10 mL). The organic layer was washed with brine (10 mL), dried, and concentrated. The crude material was purified by silica column (20-50% EtOAc/Hexane) to afford the desired product as off-white solid (99 mg, 78% yield). R_f (20% EtOAc in hexane): 0.25.</p>

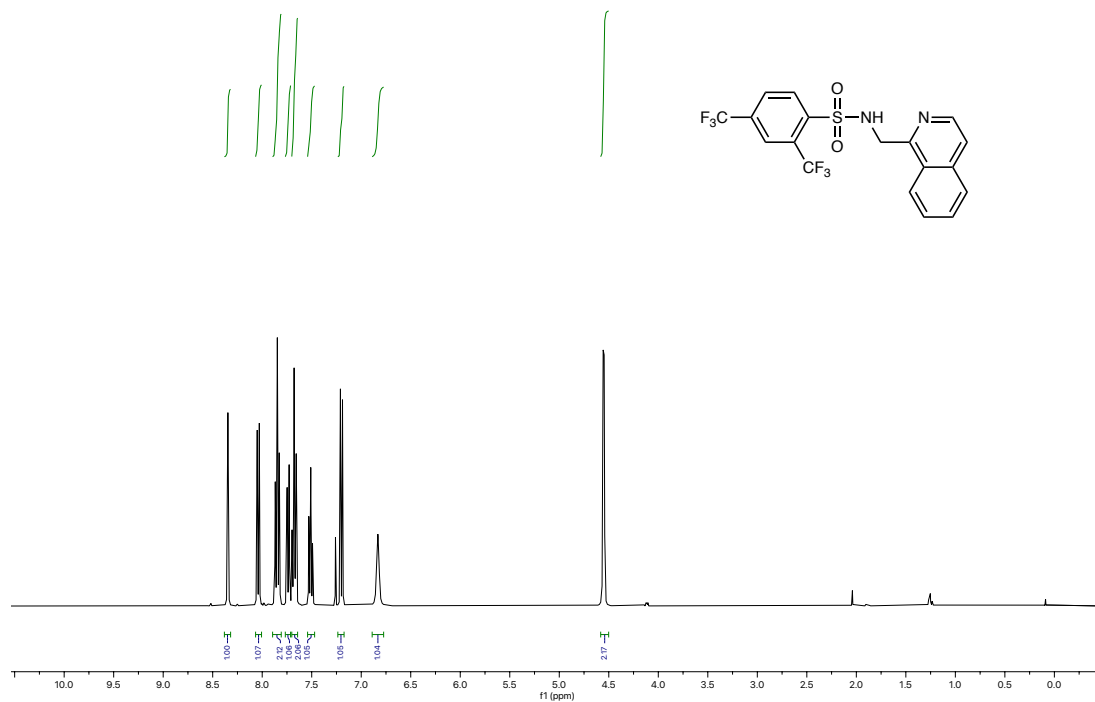
¹H NMR (400 MHz, CDCl₃) δ 8.36 – 8.33 (m, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.89 – 7.81 (m, 2H), 7.74 (dd, J = 8.2, 1.4 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.56 – 7.48 (m, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.83 (t, J = 4.6 Hz, 1H), 4.55 (d, J = 4.0 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 153.7, 146.9, 140.3, 137.3, 134.2 (q, J = 34.2 Hz), 131.1 (q, J = 33.4 Hz), 130.1, 129.3 (q, J = 6.2 Hz), 129.1 (q, J = 3.6 Hz), 128.7, 128.2 (q, J = 3.7 Hz), 127.7, 127.3, 126.9, 122.5 (q, J = 274.1 Hz), 119.4, 47.9.

¹⁹F NMR (376 MHz, CDCl₃) δ -58.31 (s, 3 H), -63.47 (s, 3 H).

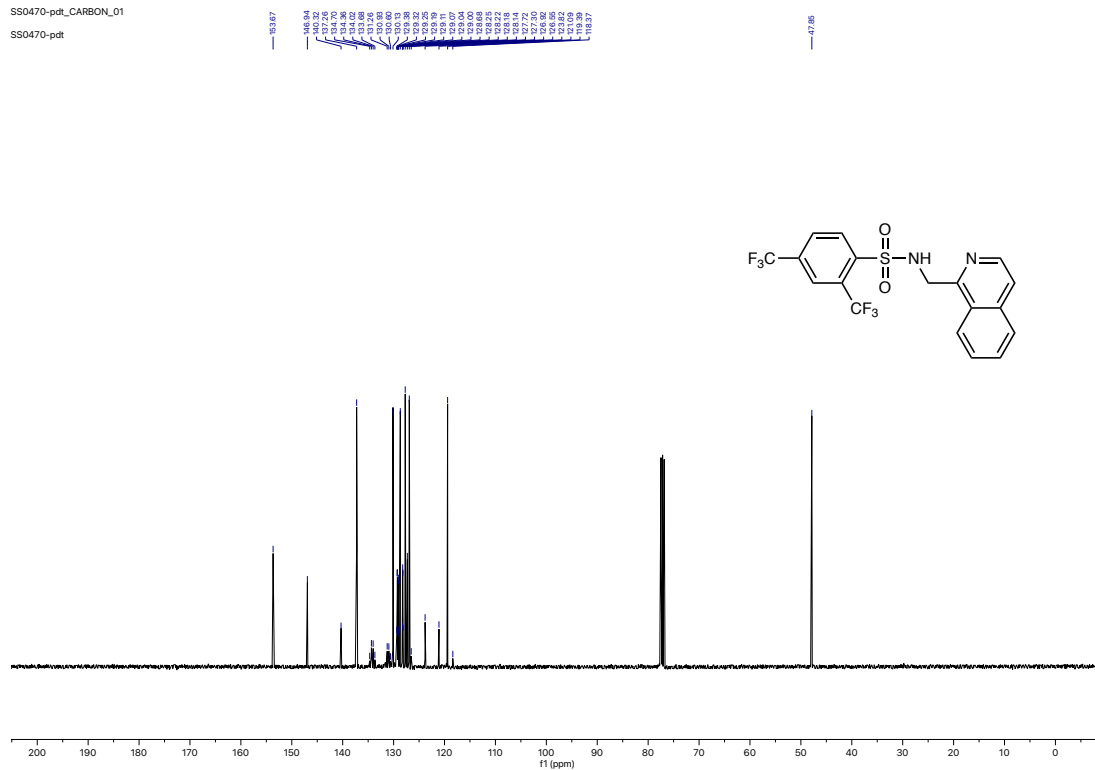
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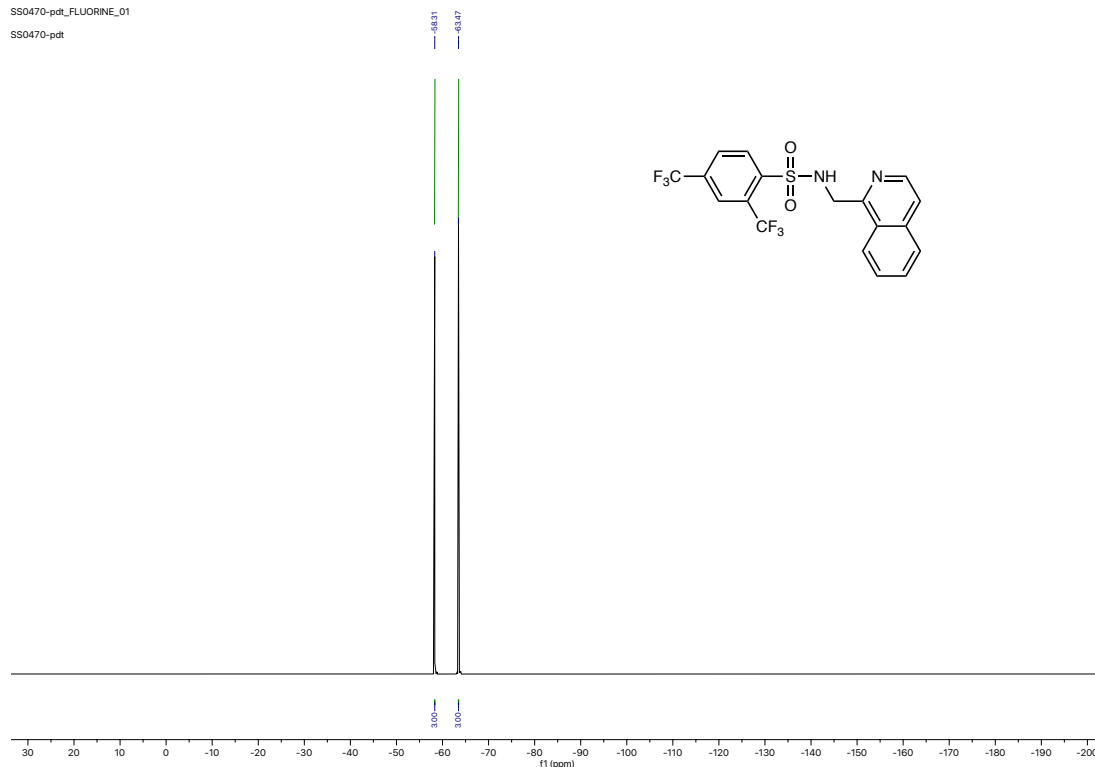
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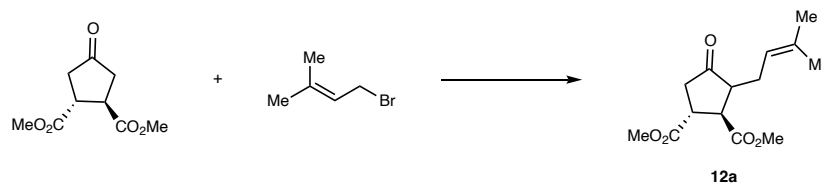
SS0470-pdt_CARBON_01

SS0470-pdt





Perfume and Cosmetics Synthesis

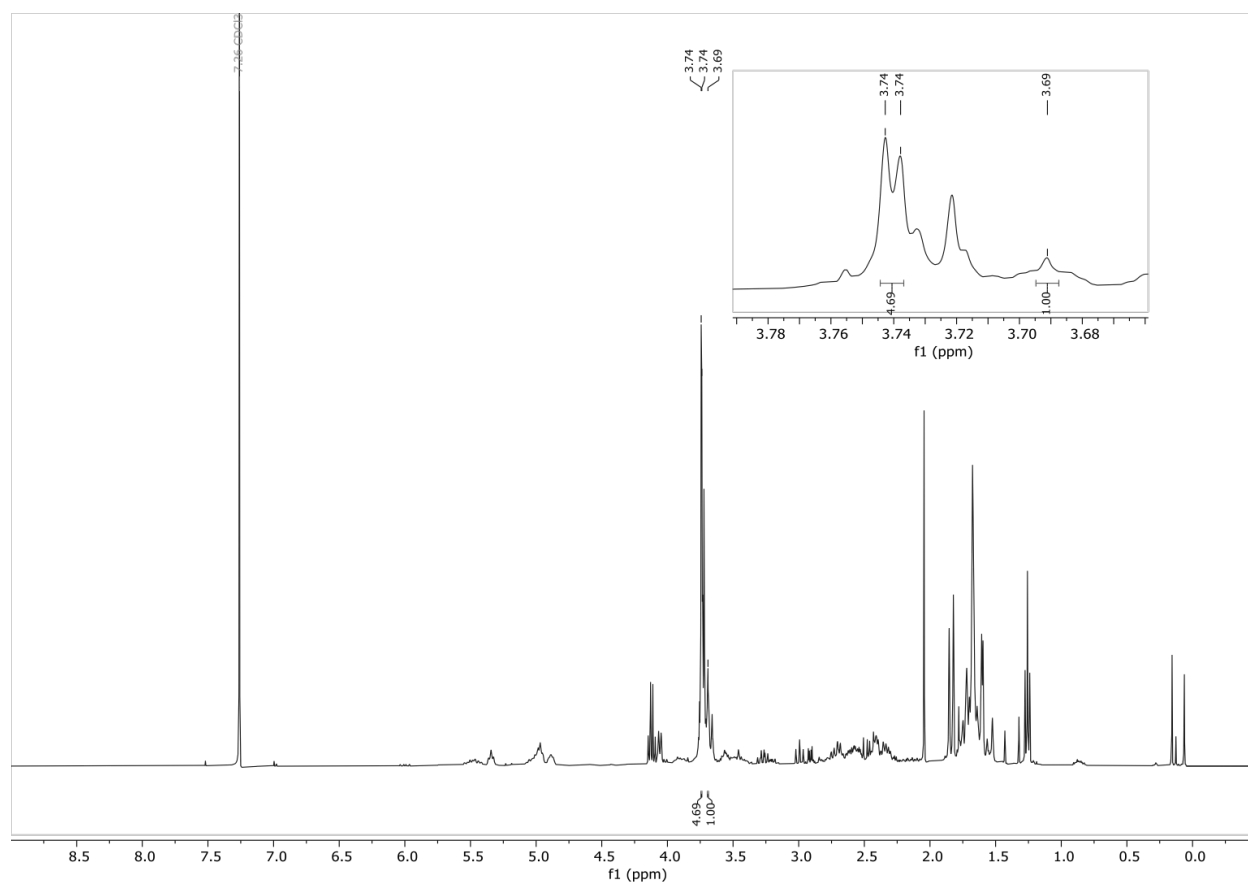


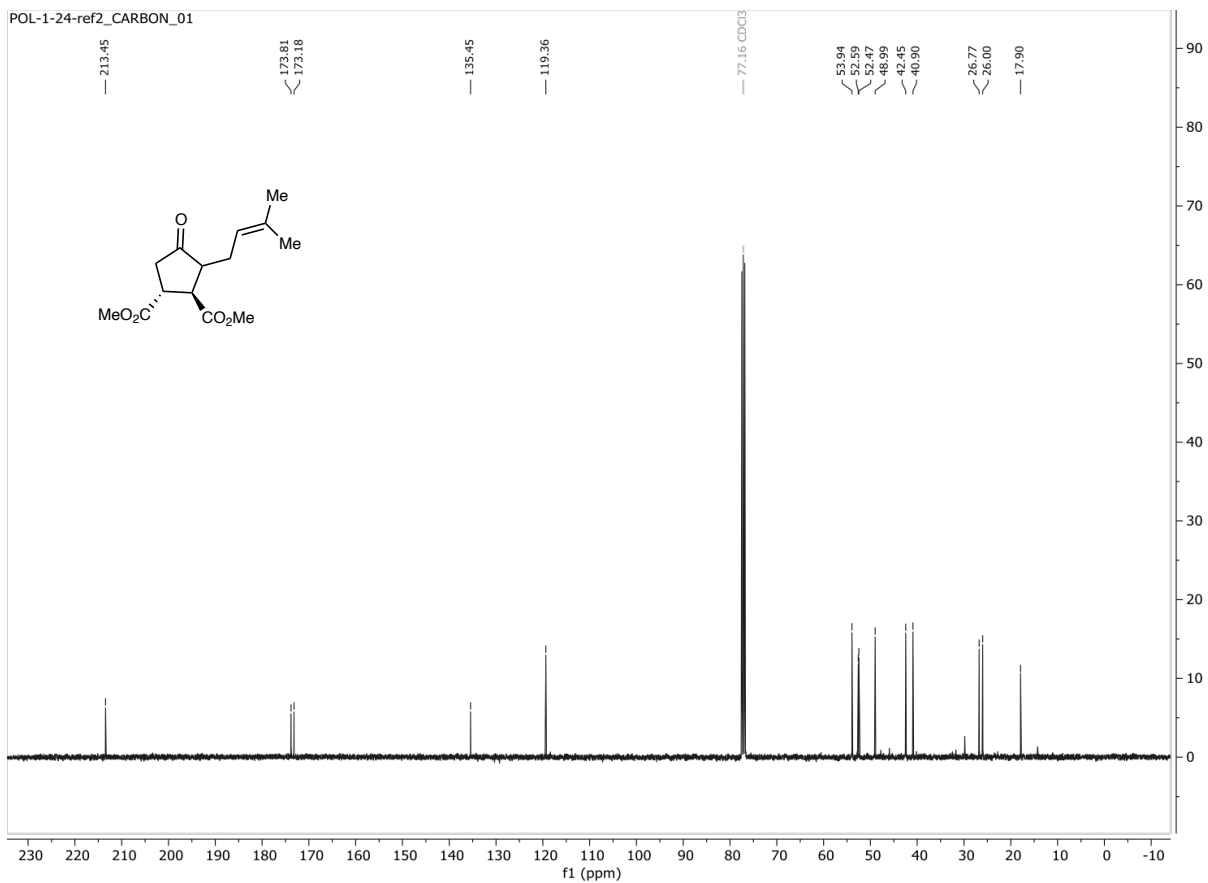
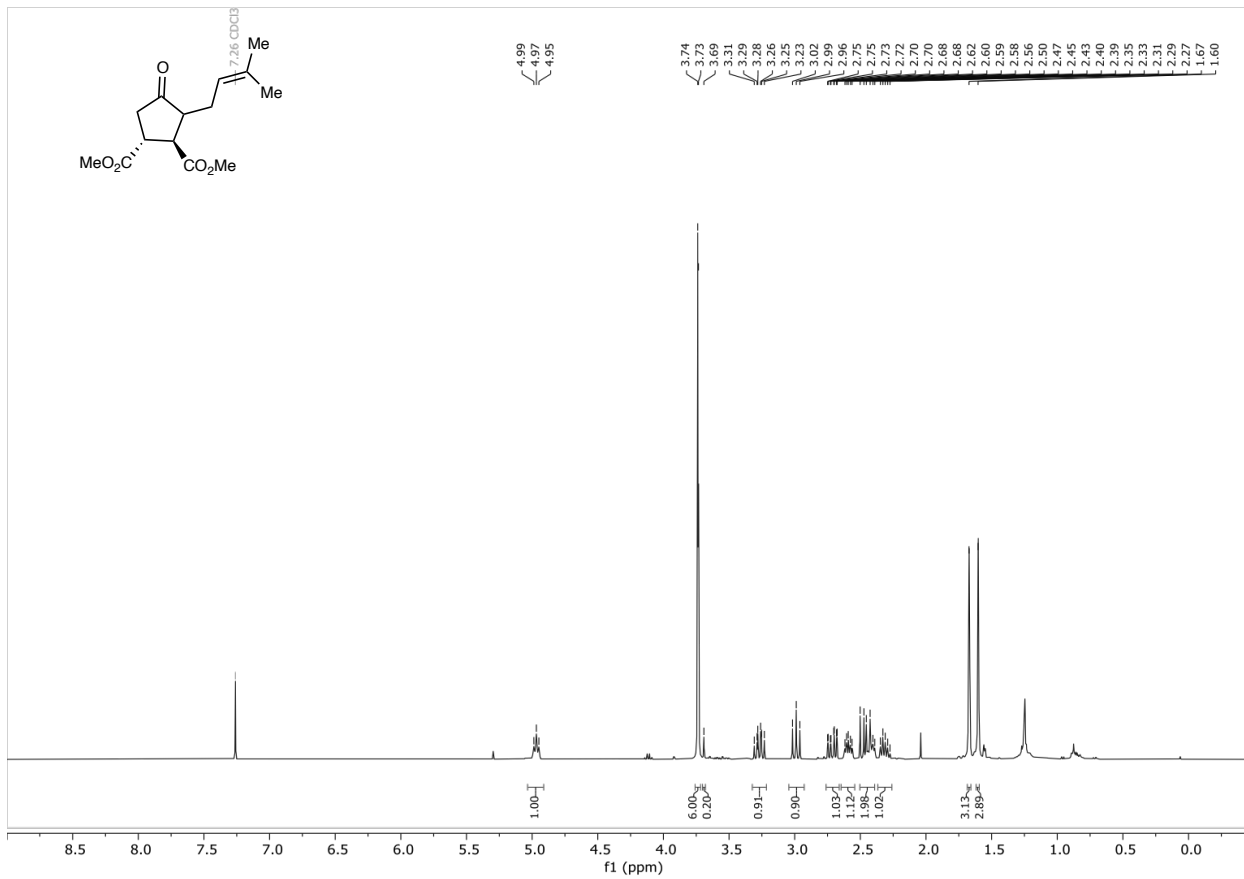
Model Predictions	Experimental Results
<p>Expert: 1, Prediction:1 Reaction Procedure: To a solution of dimethyl 4-oxocyclopentane-1,2-dicarboxylate (2.0 g, 9.6 mmol) in THF (20.0 mL) was added LiHMDS (1M in THF, 11.5 mL, 11.5 mmol) at $-78\text{ }^{\circ}\text{C}$. dropwise over 15 min. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$. for 1 h. Then 1-bromo-3-methyl-2-butene (2.9 g, 19.2 mmol) was added dropwise. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$. for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (petroleum ether:EtOAc=20:1) to give dimethyl 2-(3-methylbut-2-en-1-yl)-4-oxocyclopentane-1,3-dicarboxylate (1.6 g, 60% yield) as a yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.15 (m, 1H), 5.1-4.9 (m, 2H), 3.67 (s, 6H), 2.67-2.54 (m, 3H), 2.49-2.45 (m, 1H), 2.23-2.17 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H). Reaction Name and Classification: <i>Keto alpha-alkylation</i> Yield and Characterization: [60.0]</p>	<p>Dimethyl (1R,2R)-4-oxocyclopentane-1,2-dicarboxylate (200.2 mg, 1 mmol) was dissolved in 2.5 mL of THF (0.4M) and cooled to $-78\text{ }^{\circ}\text{C}$ with an acetone/dry ice bath. The solution was then charged with LiHMDS dropwise as a 1M solution in THF (1.2 mL, 1.2 mmol). After stirring for 1 hour, the solution was charged with 1-bromo-3-methylbut-2-ene (0.23 mL, 2 mmol) dropwise, then stirred for an additional hour. The reaction was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc three times. The organic layers were combined and washed brine, then dried over MgSO_4, filtered, and concentrated <i>in vacuo</i>. After aqueous work up, $^1\text{H NMR}$ showed a 4.7:1 ratio of diastereomers. Further purification by flash chromatography provided dimethyl (1R,2R)-3-(3-methylbut-2-en-1-yl)-4-oxocyclopentane-1,2-dicarboxylate as a pale yellow oil (50.0 mg, 19% yield, >20:1 mixture of diastereomers). R_f (25% EtOAc/Hexanes): .34</p>

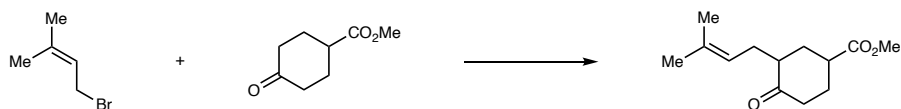
¹H NMR (400 MHz, CDCl₃): δ 4.97 (tt, *J* = 7.6, 1.5 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.33 – 3.21 (m, 1H), 2.99 (t, *J* = 11.1 Hz, 1H), 2.71 (ddd, *J* = 18.8, 8.5, 1.5 Hz, 1H), 2.59 (dtd, *J* = 11.5, 4.8, 2.3 Hz, 1H), 2.51 – 2.38 (m, 2H), 2.35-2.27 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 213.4, 173.8, 173.2, 135.5, 119.4, 53.9, 52.6, 52.5, 50.0, 42.5, 40.9, 26.8, 26.00, 17.9.

HRMS (ESI⁺) [M+H]⁺: Calc'd for C₁₄H₂₁O₅⁺: 269.1389 m/z, found: 269.1390 m/z.







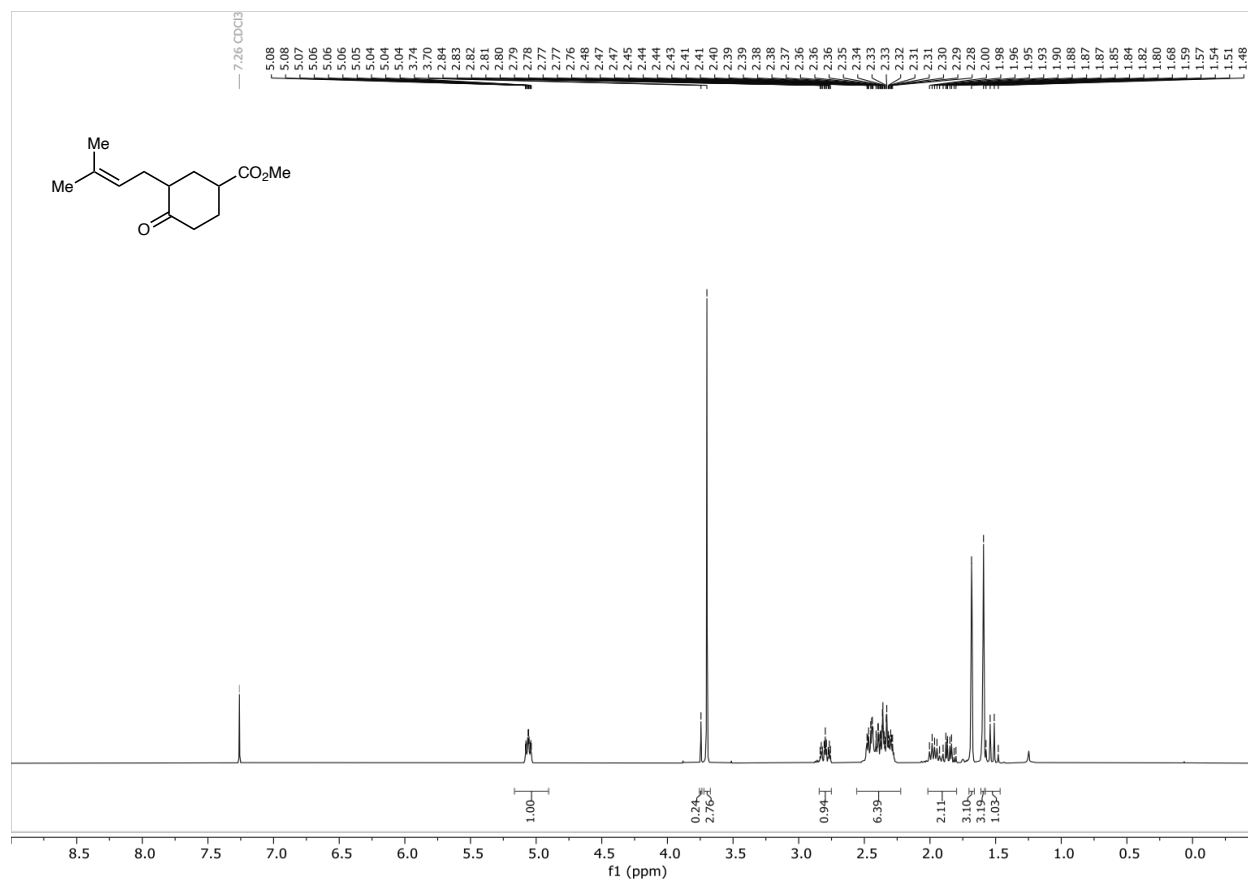
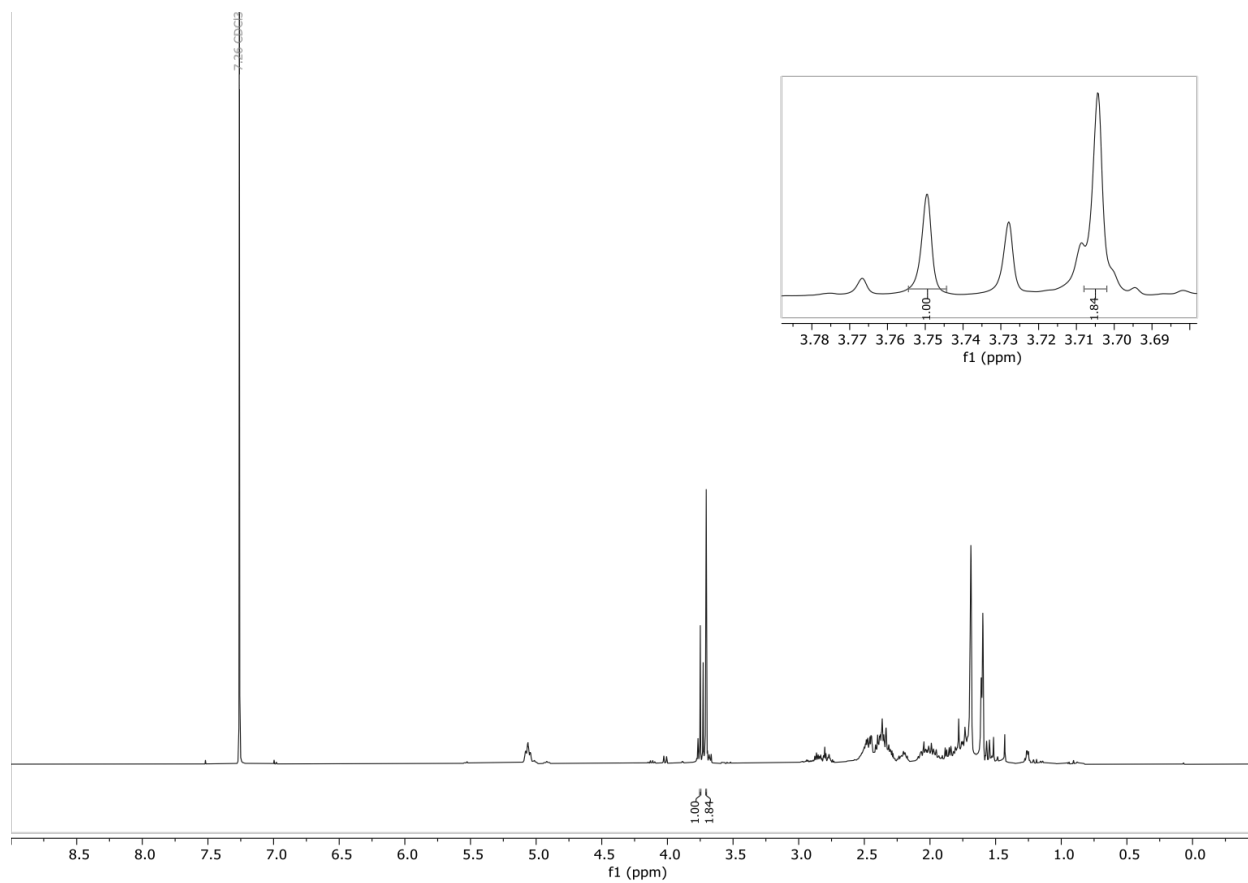
We have validated the following model prediction:

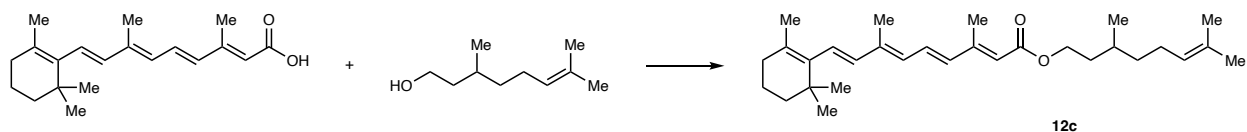
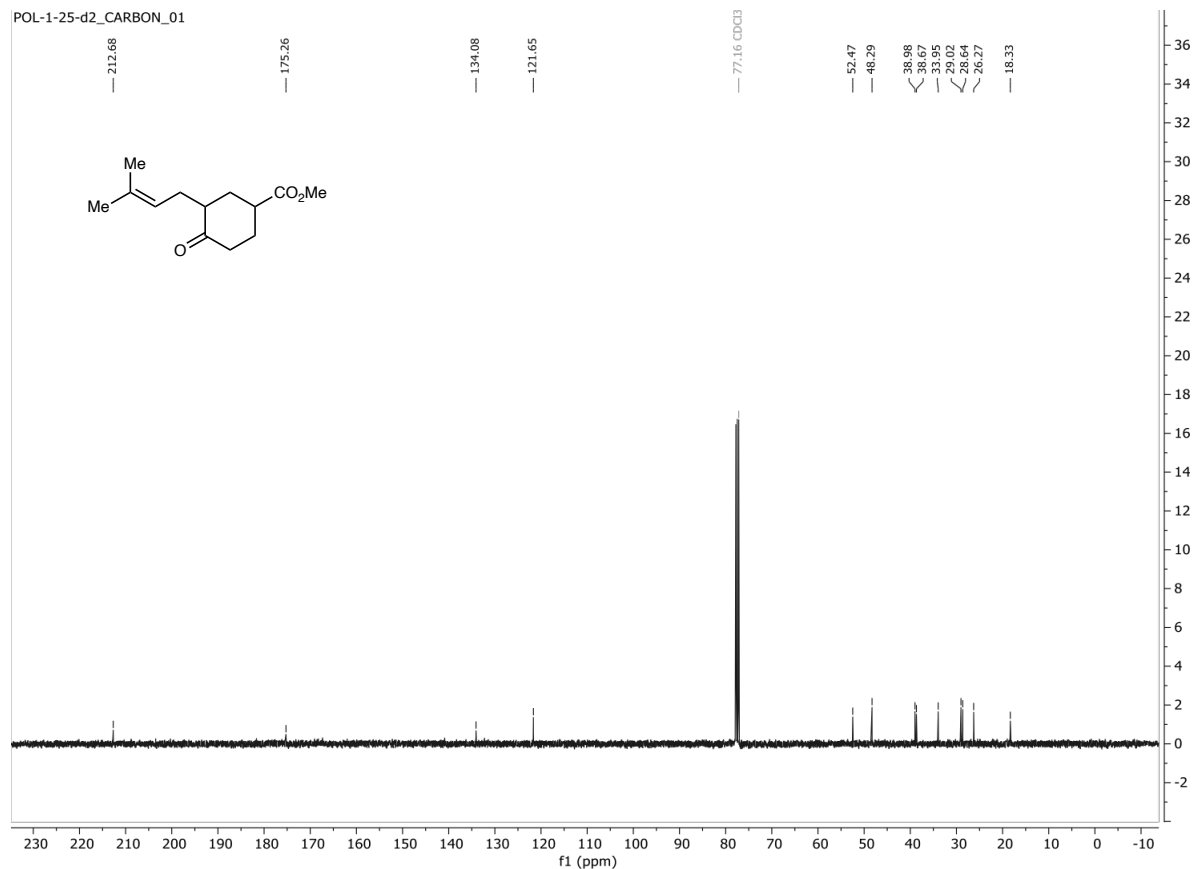
Model Predictions	Experimental Results
<p>n-BuLi (1.60M in hexanes, 35.6 mL, 56.9 mmol) was added to a 0 °C solution of diisopropylamine (8.35 mL, 59.6 mmol) in THF (200 mL). The mixture was allowed to stir at 0 °C for 30 minutes, and was then cooled to -78 °C. A solution of methyl 4-oxocyclohexanecarboxylate (8.0 g, 47.5 mmol) in THF (8 mL) was added to the -78 °C LDA solution by syringe, which was then stirred for 45 minutes. Neat 1-bromo-3-methylbut-2-ene (7.50 mL, 71.8 mmol) was added by syringe, and the reaction was stirred for 15 minutes at -78 °C. The bath was removed, and the reaction was allowed to warm to room temperature. After stirring an additional 5 hours, the reaction mixture was quenched with saturated NH₄Cl solution, and the solvent(s) were removed <i>in vacuo</i>. The oily mixture was extracted with ethyl acetate, and the organics were combined. The organic portion was dried over MgSO₄, filtered, and concentrated in vacuo. The crude oil was purified on silica gel (95:5 hexanes:EtOAc) to afford the 4-oxo-3-(3-methylbut-2-en-1-yl)cyclohexanecarboxylate as a pale yellow oil (8.00 g, 86%). ¹H NMR (CDCl₃, 400 MHz) δ 5.41 (s, 1H), 5.30 (d, J = 16.8Hz, 1H), 4.95 (m, 1H), 3.66 (s, 3H), 2.65 (m, 2H), 2.50 (m, 1H), 2.20 (m, 2H), 2.00 (s, 6H), 1.80 (m, 2H), 1.60 (m, 2H).</p> <p>Reaction Name and Classification: <i>Keto alpha-alkylation</i> Yield and Characterization: [86.0]</p>	<p>Diisopropylamine (0.17 mL, 1.2 mmol) was dissolved in 5 mL of THF (.25M) and cooled to -0 °C with an ice bath, then treated with n-BuLi as a 2.5M solution in THF/Hexanes (0.48 mL, 1.2 mmol). After stirring for 40 minutes, the solution was cooled to -78 °C with an acetone/dry ice bath and treated with methyl 4-oxocyclohexane-1-carboxylate (156.2 mg, 1 mmol) as a solution in 1 mL of THF followed by stirring for 45 minutes. The solution was then charged with 1-bromo-3-methylbut-2-ene (.17 mL, 1.5 mmol) and stirred for 15 minutes before warming to room temperature and stirring for a additional 5 hours. The reaction was then quenched with saturated aqueous NH₄Cl and extracted with EtOAc three times. The organic layers were combined and washed brine, then dried over MgSO₄, filtered, concentrated <i>in vacuo</i>. After aqueous workup, ¹H NMR revealed a 1.8:1 ratio of diastereomers. Further purification by flash chromatography provided methyl 3-(3-methylbut-2-en-1-yl)-4-oxocyclohexane-1-carboxylate as a pale yellow oil in 33% yield (74.2 mg, 33%, 1.8:1 ratio of diastereomers). R_f (25% EtOAc/Hexanes): .36</p>

¹H NMR (400 MHz, CDCl₃): δ 5.06 (tt, J = 6.6, 1.5 Hz, 1H), 3.70 (s, 3H), 2.80 (tt, J = 12.3, 3.4 Hz, 1H), 2.52 – 2.23 (m, 5H), 2.11 – 1.78 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.53 (q, J = 12.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 212.7, 175.3, 134.1, 121.7, 52.5, 48.3, 39.0, 38.7, 34.0, 29.0, 28.6, 26.3, 18.3.

HRMS (ESI⁺) [M+H]⁺: Calc'd for C₁₃H₂₀O₃⁺: 225.1491 m/z, found: 225.1493 m/z.



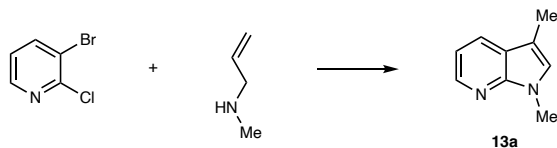


Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1. Reaction Procedure: To a solution of 3,7-dimethylhex-6-en-1-ol (26.6 mg, 0.157 mmol) in CH₂Cl₂ (1.5 mL) were added 3,7-dimethyl-6-((E)-2,3,6,9-tetrahydro-2,2,4-trimethylphenanth-1-yl)hex-2-enoic acid (50.0 mg, 0.157 mmol), DCC (32.2 mg, 0.157 mmol) and DMAP (19.1 mg, 0.157 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was filtered through a short plug of Celite with rinsing by EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc=20:1) to give (E)-3,6,9,12-tetramethylhenicosa-5,8,11,14-tetraen-1-yl 3,7-dimethyl-6-((E)-2,3,6,9-tetrahydro-2,2,4-trimethylphenanth-1-yl)hex-2-enoate (53.5 mg, 75%) as a colorless oil. Reaction Name and Classification: None. Yield and Characterization: [75.0]</p>	<p>For a 0.157 mmol (50.0 mg) scale reaction product 12c was isolated as yellow oil (59 mg, 86% yield). R_f (5% EtOAc in hexane): 0.20.</p>

¹H NMR (400 MHz, CDCl₃) δ 7.08 – 6.88 (m, 1H), 6.36 – 6.21 (m, 2H), 6.21 – 6.04 (m, 2H), 5.83 – 5.74 (m, 1H), 5.14 – 5.02 (m, 1H), 4.27 – 4.06 (m, 1H), 2.38 – 2.31 (m, 2H), 2.07 – 1.87 (m, 7H), 1.77 – 1.09 (m, 21H), 1.03 (m, 4H), 0.96 – 0.86 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 167.5, 152.8, 139.7, 137.9, 137.4, 135.4, 131.4, 131.0, 130.1, 129.7, 128.8, 124.8, 118.8, 62.4, 39.8, 37.2, 35.8, 34.4, 33.3, 29.7, 29.1, 26.1, 25.9, 25.6, 21.9, 19.6, 19.4, 17.8, 14.0, 13.1.

Novel Reaction Development

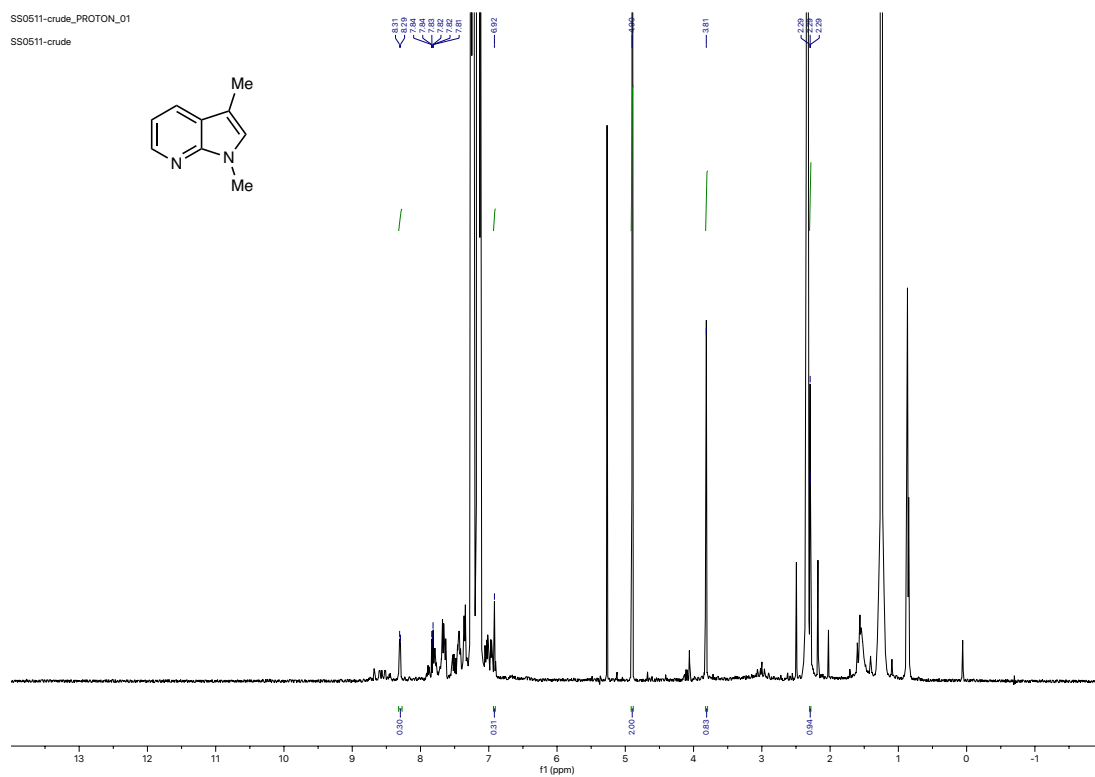


Model Predictions	Experimental Results
<p>Expert: 1 Prediction:1</p> <p>Reaction Procedure: A solution of 3-bromo-2-iodopyridine (10.0 g, 35.6 mmol), allylamine (3.0 mL, 35.6 mmol), sodium t-butoxide (5.3 g, 53.4 mmol) and Pd(PPh₃)₄ (2.0 g, 1.7 mmol) in toluene (100 mL) was refluxed for 16 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (100:1) to give 1,3-dimethyl-1H-pyrrolo[2,3-b]pyridine (1.6 g, 28%) as an oil.</p> <p>Reaction Name and Classification: None</p> <p>Yield and Characterization: [28.0]</p>	<p>For a 0.176 mmol scale reaction with 50 mg of 3-bromo-2-iodopyridine, following the predicted procedure, heating at 120 °C for 16h led to formation of 13a in 30% NMR yield. To the reaction mixture, 12.3 μL dibromomethane in 0.5 mL CDCl₃ was added and 40 μL aliquot was taken for ¹H NMR.</p> <p>The product was also matched in GC-MS with independently synthesized 13a following literature procedure [7].</p>
<p>Expert: 2 Prediction:1</p> <p>Reaction Procedure: To a solution of 3-bromo-2-iodopyridine (5.00 g, 19.6 mmol) in N,N-dimethylacetamide (50.0 mL) was added N-methylprop-2-en-1-amine (2.20 mL, 21.3 mmol), 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium dichloromethane complex (0.801 g, 0.976 mmol), and N-ethyl-N-isopropylpropan-2-amine (10.5 mL, 59.8 mmol). The mixture was degassed in vacuo and backfilled with nitrogen. The reaction mixture was stirred at 110 °C. for 16 hours, then cooled to room temperature. The reaction mixture was diluted with ethyl acetate (150 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2x50 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% ethyl acetate in hexanes) to afford 1,3-dimethyl-1H-pyrrolo[2,3-b]pyridine (0.26 g, 10%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.55 (dd, J=4.2, 1.5 Hz, 1H), 8.01 (dd, J=8.1, 1.5 Hz, 1H), 7.31 (dd, J=8.1, 4.2 Hz, 1H), 7.16 (s, 1H), 3.95 (s, 3H), 2.45 (s, 3H).</p> <p>Reaction Name and Classification: None</p> <p>Yield and Characterization: [10.0]</p>	<p>For a 0.176 mmol (50.0 mg) scale reaction following the predicted procedure, led to formation of 13a with ~5% NMR yield.</p>
<p>Expert: 3 Prediction:1</p> <p>Reaction Procedure: To a solution of 3-bromo-2-iodopyridine (0.6 g, 2.0 mmol, 1.0 eq) in 1,4-dioxane (10 mL) was added N-methylprop-2-en-1-amine (0.33 g, 3.0 mmol, 1.5 eq), cesium carbonate (2.1, 6.0 mmol, 3.0 eq), tris(dibenzylideneacetone)dipalladium (0.18 g, 0.2 mmol, 0.1 eq) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.24 g, 0.4 mmol, 0.2 eq). The reaction mixture was stirred and heated at 120 °C. for</p>	<p>For a 0.176 mmol (50.0 mg) scale reaction following the predicted procedure, did not lead to formation of 13a.</p>

<p>3 h. After cooling to rt, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL×3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=1:1) to afford 1,3-dimethyl-1H-pyrrolo[2,3-b]pyridine (0.26 g, 40%) as an orange oil. Reaction Name and Classification:None Yield and Characterization: [40.0]</p>	
<p>Expert: 2 Prediction:2 Reaction Procedure: To a solution of 3-bromo-2-iodopyridine (1.0 g, 3.5 mmol) in toluene (7.5 mL) was added cesium carbonate (2.86 g, 8.75 mmol) and N-methylprop-2-en-1-amine (0.47 g, 8.75 mmol). The reaction mixture was deoxygenated by bubbling through nitrogen for 10 min and then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with tetrahydrofuran (0.29 g, 0.35 mmol) was added. The mixture was heated at 100 °C. for 16 h, and then cooled to room temperature. The reaction mixture was deoxygenated by bubbling through nitrogen for 10 min, and then diluted with ethyl acetate (20 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 100-200 mesh, 0 to 20% ethyl acetate in hexanes) to afford 1,3-dimethyl-1H-pyrrolo[2,3-b]pyridine (0.24 g, 18%) as a pale yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 8.55 (dd, J=4.2, 1.5 Hz, 1H), 7.48 (dd, J=7.9, 1.5 Hz, 1H), 7.04 (dd, J=8.1, 4.2 Hz, 1H), 6.65 (s, 1H), 6.45 (dd, J=7.9, 1.5 Hz, 1H), 3.95 (s, 3H), 2.45 (s, 3H). Reaction Name and Classification: None Yield and Characterization: [18.0]</p>	<p>For a 0.176 mmol (50.0 mg) scale reaction following the predicted procedure, led to formation of 13a with ~5% NMR yield.</p>

For NMR Yield determination:

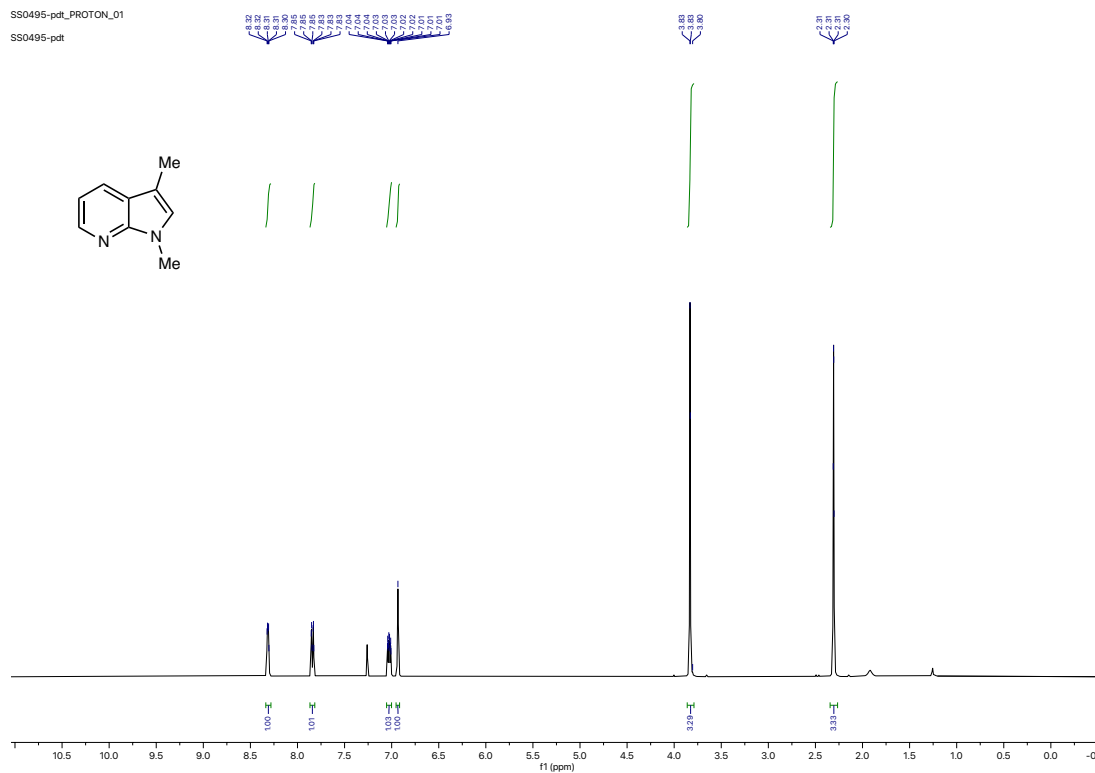
SS0511-crude_PROTON_01
SS0511-crude



Spectral data of independently synthesized **13a** matched with literature.[8]

¹H NMR (400 MHz, CDCl₃) δ 8.31 (dd, *J* = 4.6, 1.5 Hz, 1H), 7.84 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.05 – 7.00 (m, 1H), 6.93 (s, 1H), 3.83 (d, *J* = 1.4 Hz, 3H), 2.31 (q, *J* = 1.1 Hz, 3H).

SS0495-pdt_PROTON_01
SS0495-pdt



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