Carbon−Hydrogen Bond Functionalization using Removable Monodentate Directing Groups

by
Se Hun Kwak

A dissertation submitted to the Department of Chemistry,
College of Natural Sciences and Mathematics
in partial fulfillment of the requirements for the degree of Doctor of Philosophy
in Chemistry

Chair of Committee: Dr. Olafs Daugulis
Committee Members: Dr. Scott R. Gilbertson
Dr. Chengzhi Cai
Dr. Tai-Yen Chen
Dr. Gregory D. Cuny

University of Houston
August 2020

ACKNOWLEDGMENTS

I would like to express my appreciation to Dr. Olafs Daugulis for his guidance and support on my research work. I also would like to thank my dissertation committee members, Dr. Scott Gilbertson, Dr. Chengzhi Cai, Dr. Tai-yen Chen, and Dr. Gregory Cuny.

ABSTRACT

Chapter 1: 3,5-Dimethylpyrazole was employed as a mono-dentate directing group for palladium-catalyzed *ortho*-sp^2 C−H arylation with aryl iodides. The reaction shows good functional group tolerance and outstanding selectivity for mono-ortho-arylation. Ozonolysis of *ortho*-arylated arylpyrazoles gave acylated biphenylamines that were further arylated to afford unsymmetrically substituted 2,6-diarylacetanilides.

Chapter 2: *N*-Aminopyridinium ylides were used as mono-dentate directing groups for copper-promoted C−H/N−H coupling of sp^2 C−H bonds with pyrazoles, imidazoles, and sulfonamides. Reactions proceed in fluorinated alcohol solvents at elevated temperatures and require use of 1.3−3 equiv of copper(II) acetate. This appears to be the first method for copper-promoted C−H/N−H coupling directed by a removable monodentate auxiliary in absence of added ligands.

Chapter 3: *N*-Aminopyridinium ylides are competent monodentate directing groups for cobalt-catalyzed annulation of sp^2 C−H bonds with internal alkynes. Pyridine moiety in ylide serves as an internal oxidant and is cleaved during the reaction. The annulation reactions possess excellent compatibility with heterocyclic substrates, tolerating furan, thiophene, pyridine, pyrrole, pyrazole, and indole functionalities.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

THF	tetrahydrofuran
TFE	2,2,2-trifluoroethanol
Eq	equation
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
AcOH	acetic acid
TFA	trifluoroacetic acid
NMR	nuclear magnetic resonance
mp	melting point
PFB	nonafluoro-*tert*-butanol
TFAA	trifluoroacetic anhydride
rt	room temperature
DCE	dichloroethane
Cp	cyclopentadienyl
KIE	kinetic isotope effect

LIST OF SCHEMES

LIST OF TABLES

LIST OF FIGURES

LIST OF RELATED PUBLICATIONS

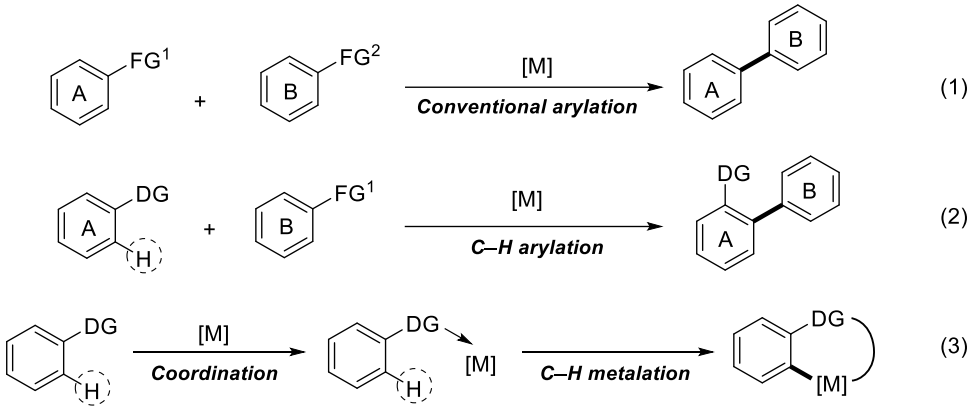
(1) Kwak, S. H.; Gulia, N.; Daugulis, O. Synthesis of Unsymmetrical 2,6-Diarylanilines by Palladium-Catalyzed C–H Bond Functionalization Methodology. *J. Org. Chem.* **2018**, *83*, 5844–5850.

(2) Kwak, S. H.; Daugulis, O. *N*-Aminopyridinium Ylide-Directed, Copper-Promoted Amination of sp^2 C–H Bonds. *J. Org. Chem.* **2019**, *84*, 13022–13032.

CHAPTER 1: Synthesis of Unsymmetrical 2,6-Diarylanilines by Palladium-Catalyzed C−H Bond Functionalization Methodology

1.1 Introduction

Transition metal catalyzed cross coupling reactions play a pivotal role as synthetic tools, allowing discovery of new compounds for material science and medicinal chemistry. Among various transition metals, palladium is the most prominent element since it shows the wide range of different catalytic reactions. Through the continuous efforts on the design of new ligands, optimization of reaction conditions, and detailed mechanism studies, the past decades have witnessed enormous expansion in palladium catalysis.[1]

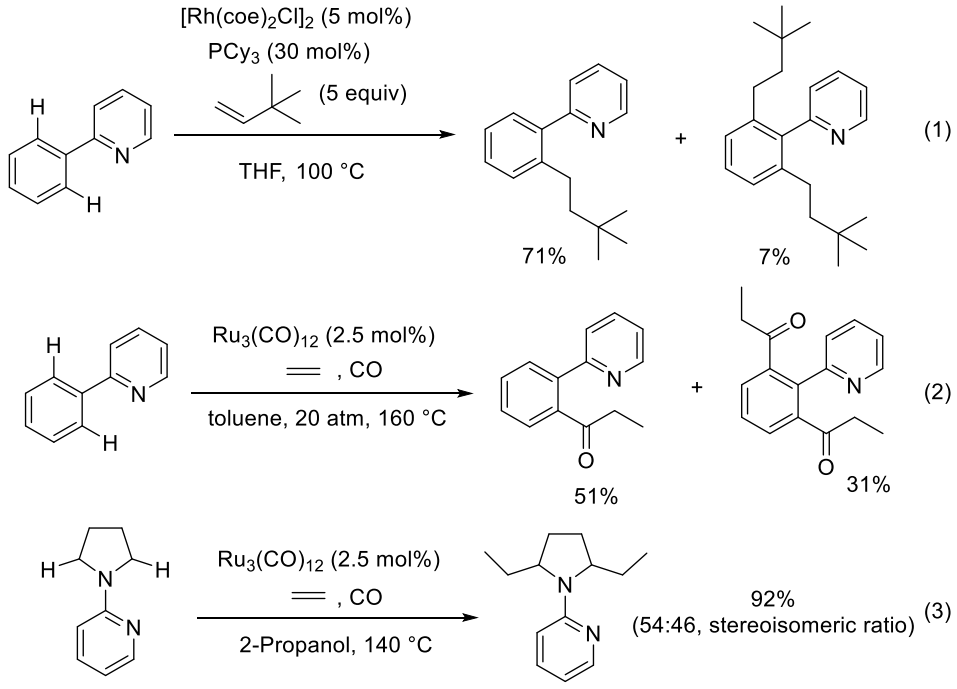


Scheme 1.1 Biaryl synthesis

The palladium catalyzed cross-coupling reactions between aryl halides or related electrophiles and organometallic compound nucleophiles afford the important biaryl motif (Scheme 1.1, Eq 1). While the arylation requires coupling of two functionalized chemicals, C–H arylation utilizing C–H bond as a functional group has been developed as an attractive strategy. The use of directing groups, involving donor atoms such as N, O, P, and S, would be a way to facilitate the activation of C–H bond and to attain high selectivity by ensuring a proximity of transition metal to the C–H bond that is cleaved (Scheme 1.1, Eq 2). Cyclometallated complex formed by the directed C–H

metalation can be used as the organometallic intermediate to react with electrophiles for the arylation (Scheme 1.1, Eq 3).[2]

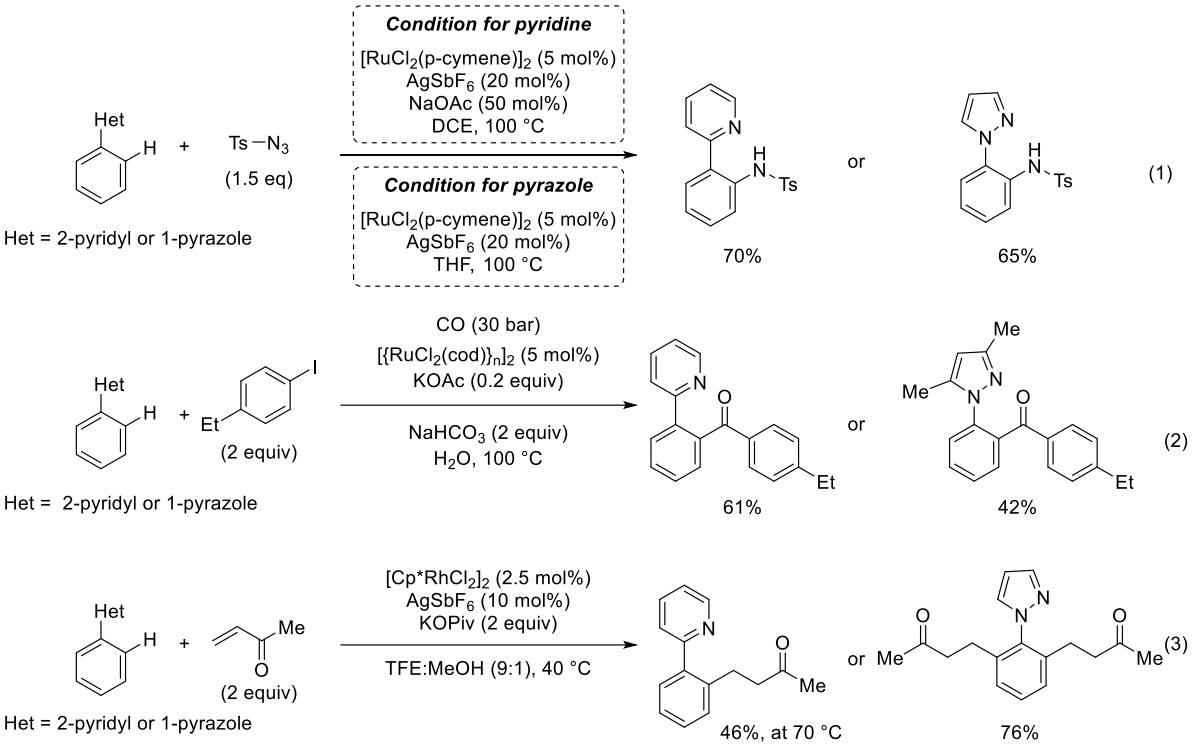
N-Heterocycles as mono-dentate directing groups have been extensively used for various C–H functionalization.[3] Pyridine directing groups were employed in early examples for catalytic sp^2 C–H functionalization. Carbon–hydrogen bond alkylation (Scheme 1.2, Eq 1)[4] and carbonylation (Eq 2)[5] were achieved using 2-phenylpyridine substrate with rhodium (I) and ruthenium (0) catalysts. Furthermore, alkylation of α-C(sp^3)–H bonds of cyclic amines was reported under similar conditions used for sp^2 C–H carbonylation (Eq 3).[6]



Scheme 1.2 Pyridine-directed C–H functionalization

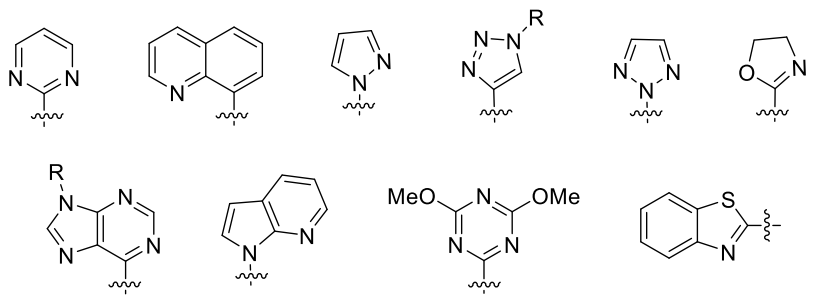
Pyrazoles showed comparable reactivity with pyridine-directed reactions (Scheme 1.3).[7] In rhodium catalyzed alkylation (Eq 3), formation of the dialkylation product and higher yield at

lower temperature showed that pyrazole is a more efficient directing group than pyridine in this particular reaction.



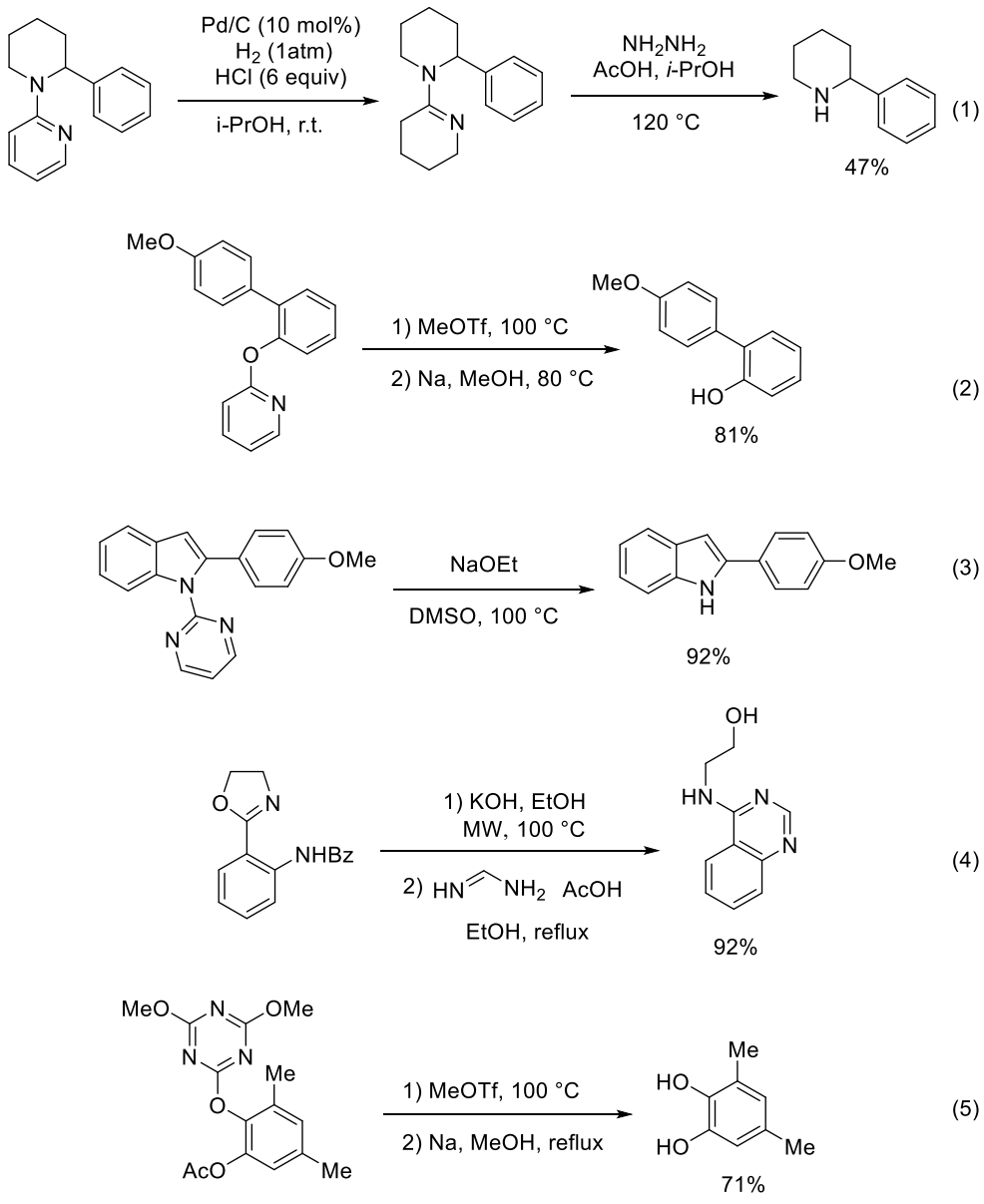
Scheme 1.3 Comparison of pyrazole directed C–H functionalization with pyridine directed reaction

Other heterocycles containing sp^2 hybridized *N* atoms have been explored in directed C–H functionalization catalyzed by transition metals (Scheme 1.4). Pyrimidine is the second most common directing group and has often been used for C2 functionalization of indoles.[3, 8] 8-Methylquinonline sp^3 C–H bond can be functionalized.[7a, 9] Consequently, heterocycles regarded as important scaffolds in biologically active compounds, oxazoles,[10] triazoles,[11] purines,[12] and fused bicycles,[7c, 13] have been used as directing group to expand the synthetic utility of C–H functionalization.



Scheme 1.4 *N*-Heterocycles used as a monodentate directing groups

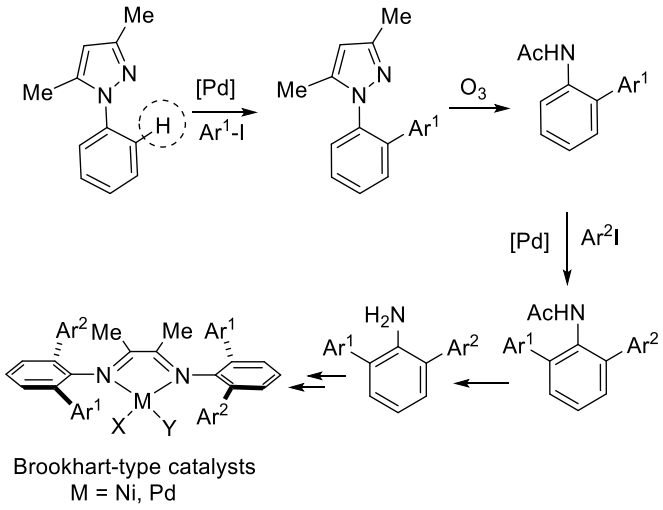
Removal of directing groups is important for directed C–H functionalization because it can render the transformation useful. The removal of pyridine and pyrimidine occurs only when the directing groups are tethered to the heteroatoms of substrates (Scheme 1.5).[3] Pyridine moiety should be either reduced or alkylated before removal of the pyridine (Eq 1 and 2).[14] Pyrimidine can be hydrolyzed directly under harsh conditions (Eq 3).[15] Oxazole directing group was utilized for cyclization to afford 4-aminoquinazoline (Eq 4).[10] Triazine can be removed under the conditions used for pyridine cleavage (Eq 5).[11] It was reported that pyrazole can undergo ozonolysis[16] to give an amide but removal of pyrazole directing group after C–H functionalization has not been disclosed until our investigation.[17]



Scheme 1.5 Removal of directing groups

Our group has developed a palladium catalyzed directed C–H arylation to prepare 2,6-diarylaniline ligands for Brookhart-type α-diimine-nickel or palladium complexes employed as alkene polymerization catalysts.[18] The method was efficient for the synthesis of symmetric 2,6-diarylanilines[19] but it was impractical for the synthesis of unsymmetrically substituted compounds because arylation was not monoselective leading to the formation of poorly separable mixtures.

Consequently, it is desirable to find directed monoselective C–H arylation with a transformable directing group. In addition, due to interest in new olefin polymerization catalysts,[20] we needed a method to selectively prepare unsymmetrical 2,6-diarylanilines from simple starting materials. A route to selective synthesis of such 2,6-diarylanilines would be available if recently reported 1-alkyl-3,5-dimethylpyrazole arylation/ozonolysis[16-17] and arylation of the generated *N*-acetylanilide with a different aryl iodide[21] could be combined (Scheme 1.6). In 2006, we reported a single example of palladium-catalyzed 1-arylpyrazole arylation. For 2,6-diarylamine synthesis, 3,5-dimethylpyrazole directing group is required. After ozonolysis, a robust acetanilide should be obtained for further functionalization. While several examples of 1-arylpyrazole *ortho*-arylation have been reported,[22] use of a 3,5-dimethylpyrazole directing group for sp^2 C–H arylation is rare.[23]

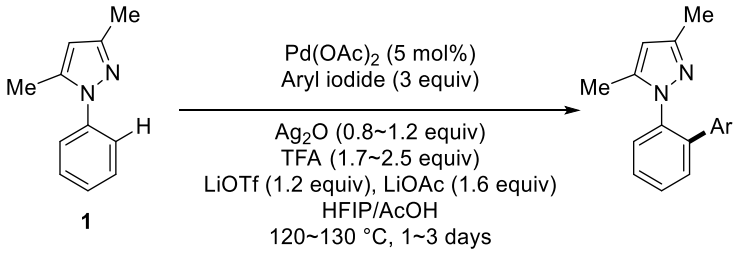


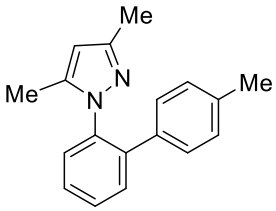
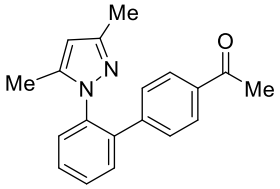
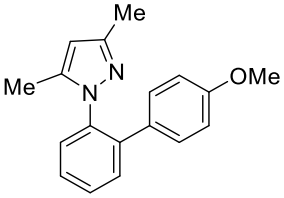
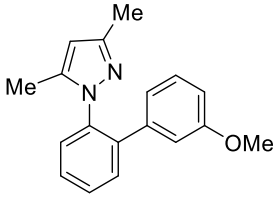
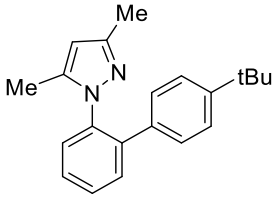
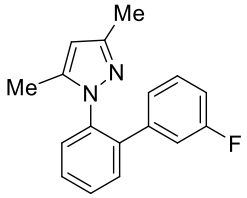
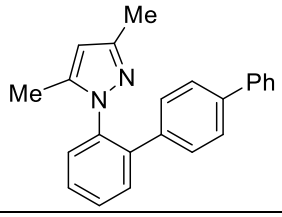
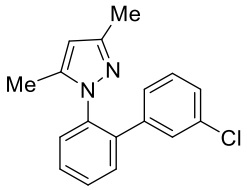
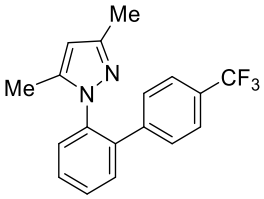
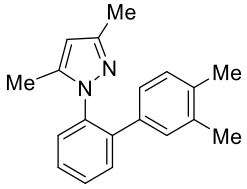
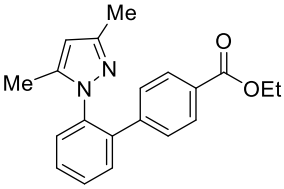
Scheme 1.6 Pyrazole directed C–H arylation

1.2 Results and discussion

Pyrazole-directed sp^3 C−H arylation using the combination of $Pd(OAc)_2$ catalyst, Ag_2O, LiOAc, and LiOTf additives was reported previously.[17a] This protocol was applied to sp^2 C−H arylation of 3,5-dimethyl-1-phenyl-1*H*-pyrazole with 4-iodotoluene (Table 1.1). Gratifyingly, monoarylated product was obtained in 85% yield. Only a trace amount of diarylated product was observed in the crude reaction mixture. To evaluate the arylation scope, a series of aryl iodides bearing either an electron-withdrawing or -donating group were examined. Diverse *para*-substituted aryl iodides furnished the monoarylated products in good yields (entries 1−7). *meta*-Substituted aryl iodides are reactive as well, affording the desired products regardless of the electronic properties of substituents (entries 8−10). Ester (entry 6), ketone (entry 7), alkoxy (entries 2 and 8), trifluoromethyl (entry 5), and halogen (entries 9 and 10) substituents are tolerated well, showing broad functional group compatibility of this protocol. In all cases, at most trace amounts of diarylated product were observed. Unfortunately, 2-iodotoluene was unreactive, and heterocyclic aryl iodides, such as 2- or 3-iodothiophene, afforded low yields of arylation products.

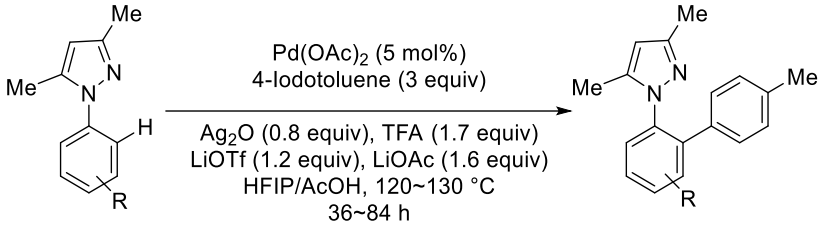
Table 1.1 Arylation with Aryl Iodides

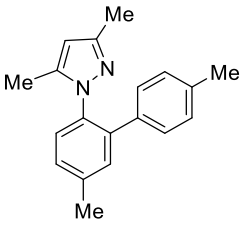
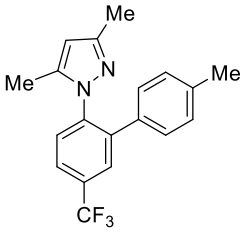
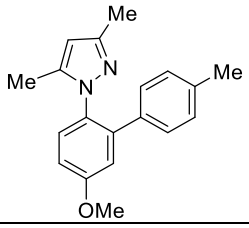
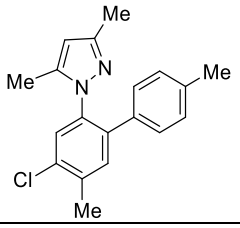


Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		85	7		66
2		83	8		75
3		78	9		80
4		79	10		77
5		81	11		73
6		80			

In addition, several *N*-arylpyrazole derivatives, easily prepared by condensation of acetylacetone with hydrazines or by amination of aryl halides with commercially available and inexpensive 3,5-dimethylpyrazole,[24] were examined for C−H arylation with 4-iodotoluene. The reaction selectively generated the corresponding monoarylated products in good yields (Table 1.2). Pyrazole possessing a meta substituent on the aryl ring was regioselectively functionalized at the less hindered ortho site (entry 4), which is consistent with cyclometalation selectivity.

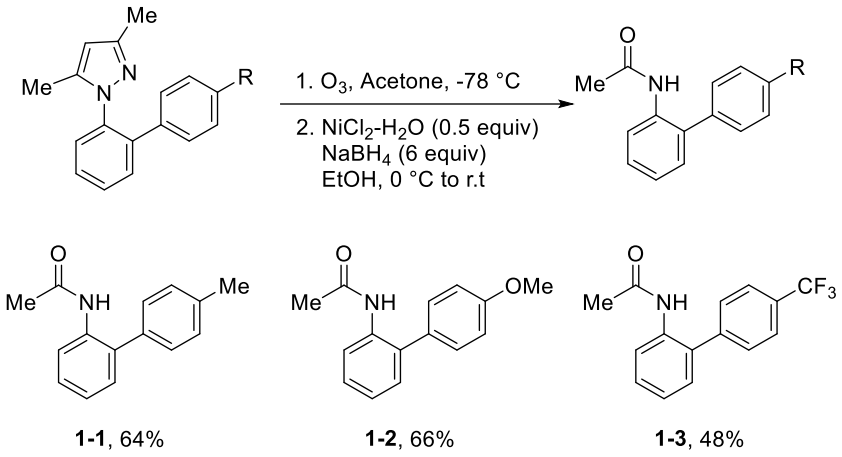
Table 1.2 Arylation of *N*-arylpyrazoles



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		83	3		83
2		87	4		86

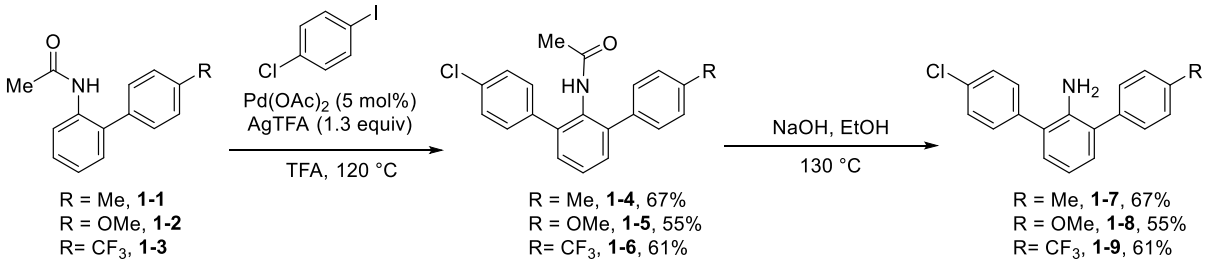
The dimethylpyrazole directing group can be transformed into anilide by ozonolysis followed by nickel-mediated reduction.[16-17] Monoarylated pyrazoles prepared by the palladium-catalyzed C−H arylation were converted to the corresponding acetanilides by ozonolysis followed by reductive

workup (Scheme 1.7). Methyl-, methoxy-, and trifluoromethyl substituted 2-arylacetanilides (**1-1**−**1-3**) were obtained in moderate to good yields.



Scheme 1.7 Directing group removal

Further arylation of arylacetanilides under previously published conditions[21] afforded unsymmetrically substituted 2,6-diarylanilides (**1-4**−**1-6**). Subsequent base hydrolysis of the diarylanilides gave the desired 2,6-diarylanilines (**1-7**−**1-9**) in excellent yields (Scheme 1.8).



Scheme 1.8 Preparation of Unsymmetrically Substituted 2,6-Diarylanilines

1.3 Conclusion

In conclusion, we have shown that 3,5-dimethylpyrazole can be utilized as a removable directing group for palladium-catalyzed monoselective *ortho* sp^2 C−H arylation. The pyrazole moiety of the arylated product is amenable to ozonolysis for the transformation into acetamide, which enables

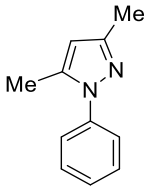
further C−H arylation and hydrolysis for the preparation of unsymmetrically diarylated anilines, useful for ligand synthesis.

1.4 Experimental Section

General Information

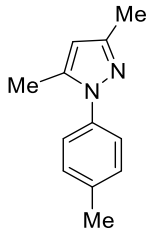
The ^{1}H, ^{13}C NMR spectra were recorded on JEOL EC-400, EC-500 and EC-600 spectrometers using residual solvent peak as a reference. Compounds for HRMS were analyzed by positive mode electrospray ionization (CI or ESI) using Agilent QTOF mass spectrometer in the Mass Spectrometry Facility (MSF) of the Department of Chemistry and Biochemistry of University of Texas-Austin. IR spectra were obtained using a ThermoScientific Nicolet iS10 FT-IR spectrometer. Column chromatography was performed using 60 Å silica gel. Reagents and starting materials were purchased from commercial vendors and used without further purification. The ozonolysis was conducted using Ozone Solution OZV-8 ozone generator and oxygen (oxygen, Matheson, 99.98%). The amount of ozone was regulated by flow rate and the 10-position switch integrated into the device (intensity 1 - 10).

Preparation of pyrazoles

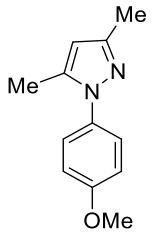


3,5-Dimethyl-1-phenyl-1*H*-pyrazole. The compound was obtained according to a modified reported procedure.[25] A round bottom flask was charged with acetylacetone (52.5 mmol, 5.39 mL) and H_2SO_4-SiO_2 (2 mol%, 158 mg). To this mixture was added phenyl hydrazine (50 mmol, 4.92 mL) dropwise at 0 ^{o}C. The mixture was stirred at room temperature for 3 h. After completion of the reaction, aqueous 1 M NaOH (50 mL) was poured into the mixture. The mixture was extracted

with diethyl ether (3 x 200 mL). Extract was washed with water (3 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford the known pyrazole (7.34 g, 85%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 4H), 7.38 – 7.28 (m, 1H), 5.99 (s, 1H), 2.30 (s, 3H), 2.29 (s, 3H).

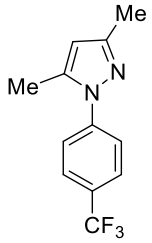


3,5-Dimethyl-1-(*p*-tolyl)-1*H*-pyrazole. The compound was obtained according to a modified reported procedure.[26] To a solution of acetylacetone (5 mmol, 0.51 mL) in ethanol (10 mL) was added *p*-tolylhydrazine hydrochloride (5 mmol, 793 mg). The mixture was refluxed at 90 ^{o}C for 2 h. After removal of ethanol in vacuum, water (30 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over $MgSO_4$ and filtered. The residue was purified by column chromatography on silica gel with EtOAc/hexanes (1/15) eluent to afford the known pyrazole (540 mg, 58%) as a yellow oil. R_f = 0.16 (EtOAc/hexanes = 1/15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.25 – 7.20 (m, 2H), 5.97 (s, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H).[26]

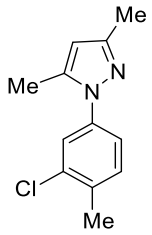


1-(4-Methoxyphenyl)-3,5-dimethyl-1*H*-pyrazole. The compound was obtained according to a modified reported procedure.[26] To a solution of acetylacetone (5 mmol, 0.51 mL) in ethanol (10 mL) was added 4-methoxy-phenylhydrazine hydrochloride (5 mmol, 873 mg). The mixture was

refluxed at 90 °C for 6 h. After completion of the reaction, ethanol was evaporated in vacuum. Water (50 mL) was added to the reaction mixture follower by extraction with ethyl acetate (3 x 50 mL). The combined organic layer was dried over $MgSO_4$ and filtered. The residue was purified via column chromatography on silica gel with EtOAc/hexanes (1/7) eluent to afford the known pyrazole (850 mg, 84%) as a light brown oil. R_f = 0.12 (EtOAc/hexanes = 1/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 5.95 (s, 1H), 3.83 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H).[26]



3,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole. The compound was obtained according to a modified reported procedure.[26] To a solution of acetyl acetone (5 mmol, 0.51 mL) in ethanol (10 mL) was added 4-(trifluoromethyl)-phenylhydrazine (5 mmol, 881 mg) and 1 drop of concentrated H_2SO_4. The mixture was refluxed at 90 ^{o}C for 6 h. After completion of the reaction, ethanol was evaporated in vacuum. Water (50 mL) was added to the reaction mixture follower by extraction with ethyl acetate (3 x 50 mL). The combined organic layer was dried over $MgSO_4$ and filtered. The residue was purified via column chromatography on silica gel with EtOAc/hexanes (1/15) eluent to afford the known pyrazole (978 mg, 81%) as an orange oil. R_f = 0.21 (EtOAc/hexanes = 1/15); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.66 (m, 2H), 7.64 – 7.55 (m, 2H), 6.04 (s, 1H), 2.36 (s, 3H), 2.30 (s, 3H).

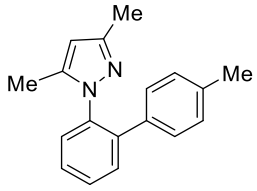


1-(3-Chloro-4-methylphenyl)-3,5-dimethyl-1*H*-pyrazole. The compound was obtained according to a modified reported procedure.[24] A round bottom flask was charged with 3,5-dimethylpyrazole (5.0 mmol, 481 mg), copper(I) oxide (1.5 mmol, 215 mg), cesium carbonate (10 mmol, 3.53 g), 1,10-phenanthroline (1.5 mmol, 270 mg), and DMF (10 mL). To the mixture was added 2-chloro-4-iodotoluene (10 mmol, 1.40 mL) and flask was heated at 120 ^{o}C for 15 h. After completion of the reaction, mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over $MgSO_4$ and filtered. The residue was purified via column chromatography on silica gel with EtOAc/hexanes (1/15) eluent to afford the pyrazole (870 mg, 79%) as a pale yellow solid. mp 56-57 ^{o}C (pentane). R_f = 0.23 (EtOAc/hexanes = 1/15); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.22 (dd, J = 8.1, 2.2 Hz, 1H), 5.98 (s, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.3, 139.5, 138.8, 135.2, 134.6, 131.1, 125.3, 122.8, 107.3, 19.8, 13.6, 12.5; HRMS (ESI) calc. For $C_{12}H_{14}ClN_2$ $[M+H]^+$: 221.0840; found: 221.0843.

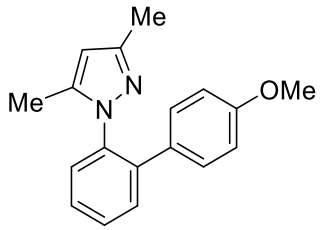
General Procedure for Arylation of Pyrazoles

A 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (0.8 equiv, 93 mg), LiOTf (1.2 equiv, 94 mg), HFIP (0.38 mL), acetic acid (0.13 mL), trifluoroacetic acid (TFA, 1.7 equiv, 65 μL), and iodoarene (3 equiv). The mixture was stirred at room temperature for 10 min until the solution became clear. To the mixture was added 3,5-dimethyl-1-aryl pyrazole (0.5 mmol), LiOAc (1.6 equiv, 53 mg) and the vial was flushed with

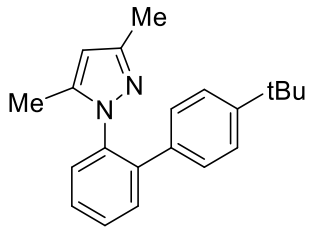
nitrogen. The sealed vial was heated and stirred at 120 °C. After completion of the reaction, the mixture was cooled, diluted with ethyl acetate (20 mL) followed by quenching with aqueous NaOH (1 M, 20 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over $MgSO_4$ and filtered through a short pad of silica gel, washed with EtOAc, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexanes and ethyl acetate eluent to afford pure product.



3,5-Dimethyl-1-(4'-methyl-[1,1'-biphenyl]-2-yl)-1*H*-pyrazole (Table 1.1, entry 1). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 °C for 24 h. Pale yellow oil; 85% yield (112 mg); purification (EtOAc/hexanes = 1/10); R_f = 0.15 (EtOAc/hexanes = 1/15); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.38 (m, 4H), 7.09 – 7.04 (m, 2H), 6.98 (d, J = 8.2 Hz, 2H), 5.76 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 140.7, 139.2, 137.5, 137.2, 135.7, 130.4, 129.2, 129.1, 129.0, 128.4, 128.1, 105.5, 21.3, 13.8, 11.2; FT-IR (neat, cm^{-1}) ν 1648, 1575, 1449, 1347, 1196; HRMS (ESI) calc. For $C_{18}H_{19}N_2$ $[M+H]^+$: 263.1543; found: 263.1547.

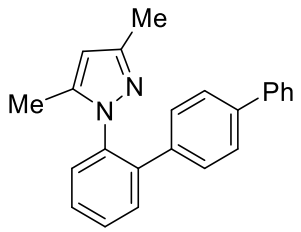


1-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.1, entry 2). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 4-iodoanisole (351 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 °C for 48 h. White solid; mp 86-87 °C (diethyl ether); 83% yield (116 mg); purification (EtOAc/hexanes = 1/8); R_f = 0.25 (EtOAC/hexanes = 1/4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 – 7.31 (m, 4H), 7.01 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 5.76 (s, 1H), 3.78 (s, 3H), 2.30 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.0, 148.7, 140.7, 138.9, 137.4, 131.0, 130.3, 129.7, 129.2, 129.0, 127.9, 113.9, 105.6, 55.3, 13.8, 11.2; FT-IR (neat, cm^{-1}) ν 1607, 1556, 1519, 1490, 1366, 1243, 1181, 1036; HRMS (ESI) calc. For $C_{18}H_{19}N_2O$ $[M+H]^+$: 279.1492; found: 279.1492.

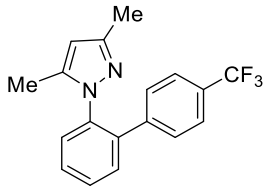


1-(4'-(*tert*-Butyl)-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.1, entry 3). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 4-*tert*-butyliodobenzene (390 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 °C for 24 h. Pale yellow oil; prification (EtOAc/hexanes = 1/8); R_f = 0.12 (EtOAc/hexanes = 1/8); 78% yield (119 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (ddd, J = 7.6, 1.6, 0.7 Hz, 1H), 7.52 – 7.42 (m, 1H), 7.48 – 7.37 (m, 2H), 7.30 – 7.21 (m, 2H), 7.05 – 6.93 (m, 2H), 5.75 (s, 1H), 2.29 (s, 3H), 1.58 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 148.7, 140.8, 139.0, 137.5, 135.5, 130.5, 129.1, 129.0, 128.1, 128.0, 125.4, 105.6, 34.6, 31.4, 13.7, 11.2; FT-IR (neat, cm^{-1}) ν 2962,

1552, 1493, 1364, 1181, 1102; HRMS (ESI) calc. For $C_{21}H_{25}N_2$ $[M+H]^+$: 305.2012; found: 305.2019.

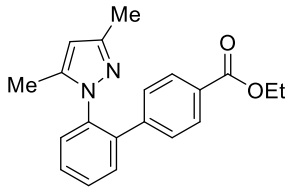


1-([1,1':4',1''-Terphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.1, entry 4). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 4-iodobiphenyl (280 mg, 1 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.75 mL), acetic acid (0.25 mL), TFA (65 μL, 0.85 mmol), 120 ºC for 48 h. Pale yellow solid; mp 127-128 ºC (diethyl ether); 79% yield (128 mg); purification (EtOAc/hexanes = 1/8); R_f = 0.10 (EtOAc/hexanes = 1/8); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 7.7 Hz, 1H), 7.54 – 7.50 (m, 3H), 7.49 – 7.45 (m, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 5.77 (s, 1H), 2.31 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.8, 140.8, 140.6, 140.0, 138.8, 137.6, 137.6, 130.4, 129.2, 129.1, 129.0, 128.9, 128.4, 127.5, 127.1, 127.1, 105.7, 13.8, 11.3; FT-IR (neat, cm^{-1}) v 1551, 1485, 1460, 1416, 1368, 1029, 1007; HRMS (ESI) calc. For $C_{23}H_{21}N_2$ $[M+H]^+$: 325.1699; found: 325.1704.

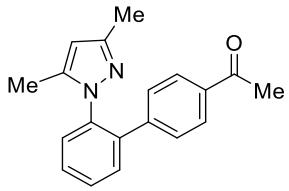


3,5-Dimethyl-1-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-pyrazole (Table 1.1, entry 5). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 4-iodobenzotrifluoride (408 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (140 mg, 0.6 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc

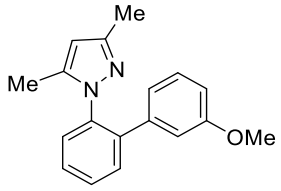
(53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (100 μL, 1.3 mmol), 130 °C for 48 h. Pale yellow solid; mp 102-103 °C (pentane); 81% yield (128 mg); purification (EtOAc/hexanes = 1/8); R_f = 0.10 (EtOAc/hexanes = 1/8); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 – 7.42 (m, 5H), 7.20 (d, J = 8.1 Hz, 2H), 5.78 (s, 1H), 2.28 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 142.2 (q, J_{C-F} = 1.4 Hz), 140.6, 137.9, 137.6, 130.5, 129.5, 129.5 (q, J_{C-F} = 32.4 Hz), 129.2, 129.2, 128.8, 128.9, 128.9, 125.4 (q, J_{C-F} = 3.8 Hz), 124.3 (q, J_{C-F} = 272.1 Hz), 106.0, 13.7, 11.3; FT-IR (neat, cm^{-1}) ν 1616, 1557, 1494, 1405, 1368, 1321, 1158, 1070; HRMS (ESI) calc. For $C_{18}H_{16}F_3N_2$ $[M+H]^+$: 317.1260; found: 317.1262.



Ethyl 2'-(3,5-dimethyl-1*H*-pyrazol-1-yl)-[1,1'-biphenyl]-4-carboxylate (Table 1.1, entry 6). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), ethyl 4-iodobenzoate (414 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 °C for 72 h. Pale yellow oil; 80% yield (128 mg); purification (EtOAc/hexanes = 1/5); R_f = 0.09 (EtOAc/hexanes = 1/8); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, J = 8.4 Hz, 2H), 7.50 (ddd, J = 20.5, 4.1, 1.5 Hz, 4H), 7.16 (d, J = 8.4 Hz, 2H), 5.75 (s, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.28 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, MeOD) δ 166.3, 148.9, 143.0, 141.4, 138.6, 136.9, 130.4, 129.7, 129.3, 129.2, 129.0, 128.8, 128.3, 105.7, 60.9, 13.2, 11.8, 9.8; FT-IR (neat, cm^{-1}) ν 1713, 1609, 1554, 1492, 1366, 1271, 1183, 1100, 1026; HRMS (ESI) calc. For $C_{20}H_{21}N_2O_2$ $[M+H]^+$: 321.1598; found: 321.1604.

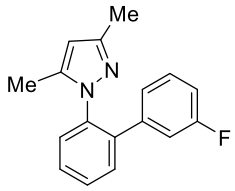


1-(2'-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)ethan-1-one (Table 1.1, entry 7). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 4-iodoacetophenone (369 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 ^{o}C for 72 h. Pale yellow solid; mp 90-91 ^{o}C (diethyl ether); 66% yield (96 mg); purification (EtOAc/hexanes = 1/5); R_f = 0.05 (EtOAc/hexanes = 1/8); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2H), 7.57 – 7.45 (m, 4H), 7.18 (d, J = 8.3 Hz, 2H), 5.76 (s, 1H), 2.58 (s, 3H), 2.28 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.0, 149.0, 143.5, 140.6, 138.1, 137.6, 135.8, 130.4, 129.4, 129.2, 129.2, 128.8, 128.5, 105.9, 26.8, 13.7, 11.3; FT-IR (neat, cm^{-1}) v 1716, 1687, 1489, 1359, 1268, 1183, 1103, 1027; HRMS (ESI) calc. For $C_{19}H_{18}N_2ONa$ $[M+Na]^+$: 313.1311; found: 313.1324.

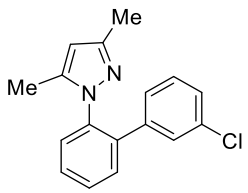


1-(3'-Methoxy-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.1, entry 8). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 3-iodoanisole (351 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 ^{o}C for 36 h. Pale yellow oil; 75% yield (104 mg); purification (EtOAc/hexanes = 1/8); R_f = 0.15 (EtOAC/hexanes = 1/8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.40 (m, 4H), 7.24 – 7.16 (m, 1H), 6.89 – 6.75 (m,

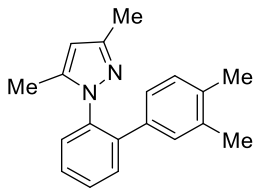
2H), 6.53 (dd, J = 2.5, 1.7 Hz, 1H), 5.77 (s, 1H), 3.63 (s, 3H), 2.29 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.4, 148.6, 141.0, 139.9, 139.2, 137.6, 130.4, 129.4, 129.3, 129.0, 128.5, 121.0, 114.5, 112.7, 105.8, 55.1, 13.7, 11.2; FT-IR (neat, cm^{-1}) ν 1591, 1469, 1417, 1367, 1216, 1181, 1022; HRMS (ESI) calc. For $C_{18}H_{19}N_2O$ $[M+H]^+$: 279.1492; found: 279.1501.



1-(3'-Fluoro-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.1, entry 9). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 3-fluoroiodobenzene (327 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 ºC for 72 h. Pale yellow oil; 80% yield (107 mg); purification (EtOAc/hexanes = 1/10); R_f = 0.17 (EtOAc/hexanes = 1/8); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.40 (m, 4H), 7.21 (td, J = 8.0, 6.0 Hz, 1H), 6.94 (tdd, J = 8.4, 2.6, 0.9 Hz, 1H), 6.88 (ddd, J = 7.7, 1.6, 0.9 Hz, 1H), 6.79 (ddd, J = 10.3, 2.6, 1.6 Hz, 1H), 5.78 (s, 1H), 2.28 (s, 3H), 1.65 (d, J = 0.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7 (d, J_{C-F} = 245.4 Hz), 148.9, 140.7, 140.7, 138.1 (d, J_{C-F} = 2.2 Hz), 137.6, 130.4, 129.9 (d, J_{C-F} = 8.3 Hz), 129.3, 129.1, 128.9, 124.3 (d, J_{C-F} = 3.0 Hz), 115.5 (d, J_{C-F} = 22.4 Hz), 114.3 (d, J_{C-F} = 21.1 Hz), 105.8, 13.7, 11.2; FT-IR (neat, cm^{-1}) ν 1588, 1553, 1480, 1425, 1265, 1184, 1028; HRMS (ESI) calc. For $C_{17}H_{15}FN_2Na$ $[M+Na]^+$: 289.1111; found: 289.1119.

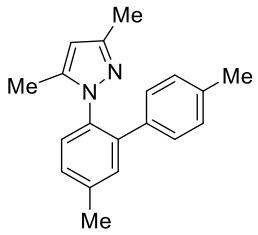


1-(3'-Chloro-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.1, entry 10). 3,5-imethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 3-Chloroiodobenzene (358 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 °C for 72 h. Pale yellow oil; 77% yield (109 mg); purification (EtOAc/hexanes = 1/10); R_f = 0.20 (EtOAc/hexanes = 1/8); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.42 (m, 4H), 7.22 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.10 (t, J = 1.9 Hz, 1H), 6.94 (dt, J = 7.6, 1.4 Hz, 1H), 5.79 (s, 1H), 2.29 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 140.7, 140.3, 138.0, 134.2, 130.3, 129.6, 129.4, 129.1, 128.9, 128.6, 127.5, 126.7, 105.8, 13.7, 11.3; FT-IR (neat, cm^{-1}) ν 1554, 1504, 1408, 1365, 1098, 1028; HRMS (ESI) calc. For $C_{17}H_{15}ClN_2Na$ $[M+Na]^+$: 305.0816; found: 305.0830.

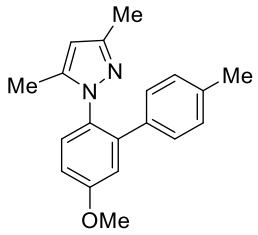


1-(3',4'-Dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.1, entry 11). 3,5-Dimethyl-1-phenyl pyrazole (86 mg, 0.5 mmol), 4-iodo-1,2-dimethylbenzene (348 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 °C for 24 h. Yellow oil; 83% yield (115 mg); purification (EtOAc/hexanes = 1/10); R_f = 0.20 (EtOAc/hexanes = 1/8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.36 (m, 4H), 7.01 (d, J = 7.8 Hz, 1H), 6.84 (s, 1H), 6.80 (dd, J = 7.8, 1.8 Hz, 1H), 5.76 (s, 1H), 2.30 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 141.0, 139.4, 137.3, 136.6, 135.9, 135.9, 130.5, 129.7, 129.3, 128.9, 128.0, 125.8, 122.5, 105.5, 19.8, 19.6, 13.6, 11.3; FT-IR (neat, cm^{-1}) ν

1576, 1492, 1348, 1160, 1136, 1101; HRMS (ESI) calc. For $C_{19}H_{20}N_2Na$ $[M+Na]^+$: 299.1519; found: 299.1526.

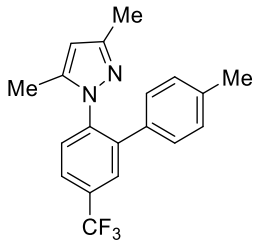


1-(4',5-Dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.2, entry 1). 3,5-Dimethyl-1-(*p*-tolyl)pyrazole (93 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 ºC for 36 h. Pale yellow oil; 83% yield (115 mg); purification (EtOAc/hexanes = 1/10); R_f = 0.22 (EtOAc/hexanes = 1/8); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 1.5 Hz, 1H), 7.22 (dd, J = 8.1, 1.7 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H), 5.74 (s, 1H), 2.44 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.4, 140.7, 139.0, 138.8, 137.0, 135.8, 135.0, 131.0, 129.1, 128.7, 128.7, 128.4, 105.3, 21.4, 21.3, 13.8, 11.3; FT-IR (neat, cm^{-1}) ν 2920, 1552, 1503, 1420, 1187, 1029; HRMS (ESI) calc. For $C_{19}H_{20}N_2Na$ $[M+Na]^+$: 299.1519; found: 299.1529.



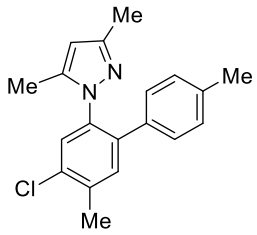
1-(5-Methoxy-4'-methyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.2, entry 2). 1-(4-Methoxyphenyl)-3,5-dimethylpyrazole (101 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol),

LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 ºC for 36 h. Pale yellow solid; mp 92-93 ºC (pentane); 87% yield (127 mg); Purification (EtOAc/hexanes = 1/5); R_f = 0.07 (EtOAc/hexanes = 1/8); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.6 Hz, 1H), 7.06 (dd, J = 8.5, 0.6 Hz, 2H), 7.01 – 6.97 (m, 3H), 6.93 (dd, J = 8.6, 2.9 Hz, 1H), 5.73 (s, 1H), 3.87 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 148.3, 140.9, 140.5, 137.3, 135.7, 130.6, 130.1, 129.2, 128.3, 115.2, 113.3, 105.2, 55.7, 21.3, 13.8, 11.2; FT-IR (neat, cm^{-1}) ν 1609, 1553, 1495, 1421, 1292, 1207, 1029; HRMS (ESI) calc. For $C_{19}H_{21}N_2O$ $[M+H]^+$: 293.1648; found: 293.1655.



3,5-Dimethyl-1-(4'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-pyrazole (Table 1.2, entry 3). 3,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)pyrazole (120 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOAc (53 mg, 0.8 mmol), LiOTf (94 mg, 0.6 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 ºC for 84 h. Pale yellow oil; 83% yield (137 mg); purification (EtOAc/hexanes = 1/10); R_f = 0.27 (EtOAc/hexanes = 1/8); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 1H), 7.71 – 7.65 (m, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.98 (d, J = 8.2 Hz, 1H), 5.79 (s, 1H), 2.33 (s, 2H), 2.30 (s, 2H), 1.60 (d, J = 0.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 140.8, 140.4, 139.8, 138.1, 134.4, 131.2 (q, J_{C-F} = 32.6 Hz), 129.7, 129.5, 128.3, 127.6 (q, J_{C-F} = 3.9 Hz), 124.9 (q, J_{C-F} = 3.7 Hz), 123.9 (q, J_{C-F} = 272.5 Hz), 106.3, 21.3, 13.7,

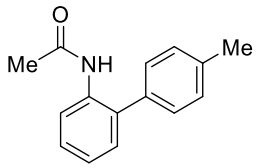
11.2; FT-IR (neat, cm^{-1}) *v* 1615, 1557, 1418, 1334, 1167, 1124, 1029; HRMS (ESI) calc. For $C_{19}H_{18}F_3N_2$ $[M+H]^+$: 331.1417; found: 331.1417.



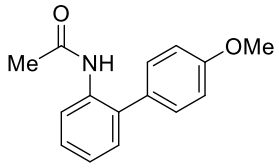
1-(4-Chloro-4',5-dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole (Table 1.2, entry 4). 1-(3-Chloro-4-methylphenyl)-3,5-dimethylpyrazole (110 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL, 0.85 mmol), 120 °C for 60 h. White solid; mp 114-115 °C (pentane); 86% yield (134 mg); purification (EtOAc/hexanes = 1/10); R_f = 0.33 (EtOAc/hexanes = 1/8); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.34 (s, 1H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 8.1 Hz, 2H), 5.75 (s, 1H), 2.45 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.9, 140.8, 137.5, 137.4, 137.1, 136.0, 134.8, 133.4, 132.4, 129.4, 129.3, 128.3, 105.7, 21.3, 20.0, 13.8, 11.2; FT-IR (neat, cm^{-1}) *v* 1557, 1492, 1385, 1128, 1058; HRMS (ESI) calc. For $C_{19}H_{20}ClN_2$ $[M+H]^+$: 311.1310; found: 311.1315.

General Procedure for Ozonolysis. The solution of the pyrazole (1 mmol) in acetone (20 mL) was cooled to -78 °C. A stream of O_3/O_2 was bubbled into the reaction solution for 20 min (2.5 l/min, intensity 2). After completion of the reaction (monitored by TLC), ozone was replaced by nitrogen for 5 min bubbling. Subsequently, acetone was removed under vacuum at room temperature. To the residue was added ethanol (20 mL) and $NiCl_2$•$6H_2O$ (0.5 mmol, 119 mg). The mixture was cooled to 0 °C followed by addition of $NaBH_4$ (6 mmol, 227 mg) portionwise. The

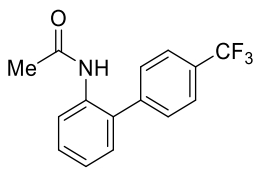
resulting mixture was stirred for 10 min. After removal of ethanol under vacuum, water was (50 mL) added and the mixture was extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over $MgSO_4$ and filtered. The residue was purified by column chromatography on silica gel with hexanes/ethyl acetate eluent to afford the corresponding amide.



***N*-(4'-Methyl-[1,1'-biphenyl]-2-yl)acetamide (1-1).** Pale yellow solid; mp 103-104 ^oC (diethyl ether); 64% yield (144 mg); Purification (EtOAc/hexanes = 1/2); R_f = 0.23 (EtOAc/hexanes = 1/2); ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.2 Hz, 1H), 7.35 (td, J = 8.1, 1.6 Hz, 1H), 7.32 – 7.21 (m, 5H), 7.20 – 7.11 (m, 2H), 2.43 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 137.9, 135.2, 134.9, 132.2, 130.2, 129.9, 129.2, 128.3, 124.4, 121.6, 24.8, 21.3.



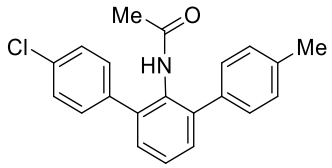
***N*-(4'-Methoxy-[1,1'-biphenyl]-2-yl)acetamide (1-2).** Pale yellow solid; mp 134-135 ^oC (diethyl ether); 66% yield (159 mg); Purification (EtOAc/hexanes = 1/2); R_f = 0.27 (EtOAc/hexanes = 1/2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.2 Hz, 1H), 7.40 – 7.25 (m, 3H), 7.26 – 7.17 (m, 1H), 7.20 – 7.10 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 159.4, 134.9, 131.9, 130.5, 130.3, 130.3, 128.2, 124.4, 121.6, 114.6, 55.5, 24.8.



***N*-(4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)acetamide (1-3).** Pale yellow solid; mp 117-118 ^{o}C (diethyl ether); 48% yield (134 mg); Purification (EtOAc/hexanes = 2/3); R_f = 0.2 (EtOAc/hexanes = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.41 (ddd, J = 8.4, 6.2, 2.9 Hz, 1H), 7.23 (d, J = 5.7 Hz, 2H), 6.96 (s, 1H), 2.04 (s, 3H).

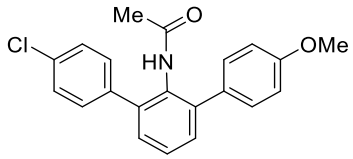
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 142.2, 134.6, 131.6, 130.3 (q, J_{C-F} = 32.7 Hz), 130.2, 129.8, 129.30, 126.1 (q, J_{C-F} = 3.8 Hz), 124.2 (q, J_{C-F} = 272.2 Hz), 125.1, 122.9, 24.6.

General Procedure for C-H Arylation of Acetamides. A 2-dram vial equipped with a magnetic stir bar was charged with amide (0.5 mmol), $Pd(OAc)_2$ (5 mol%, 5.6 mg), $Ag(OCOCF_3)$ (0.65 mmol, 144 mg), 1-chloro-4-iodobenzene (1 mmol, 238 mg), and TFA (1 mL). The reaction mixture was stirred at 120 ^{o}C for 8 h. Subsequently, the reaction was diluted with ethyl acetate (50 mL) and neutralized with saturated aqueous $NaHCO_3$ (50 mL) followed by extraction with ethyl acetate (2 x 30 mL). The solvent was dried over $MgSO_4$ and removed under reduced pressure. The residue was purified by column chromatography.

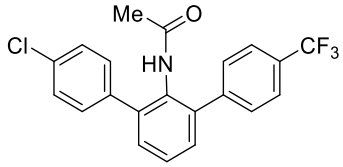


***N*-[2-(4-Chlorophenyl)-6-(*p*-tolyl)phenyl]acetamide (1-4).** *N*-(4'-methyl-[1,1'-biphenyl]-2-yl)acetamide **1-1** (0.5 mmol, 113 mg). Purification (hexanes/EtOAc/dichloromethane = 1/4/0.5); pale yellow solid; mp 239-240 °C (diethyl ether); 67% yield (112 mg); R_f = 0.35 (EtOAc/hexanes = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.04 (m, 11H), 6.57 (s, 1H), 2.39 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 169.5, 140.8, 140.0, 138.6, 137.4, 136.6, 133.4, 131.3, 130.4,

130.2, 129.8, 129.2, 128.8, 128.5, 128.0, 23.1, 21.4; HRMS (ESI) calc. For $C_{21}H_{19}ClNO$ $[M+H]^+$: 336.1150; found: 336.1150.

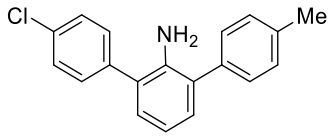


***N*-[2-(4-Chlorophenyl)-6-(4-methoxyphenyl)phenyl]acetamide (1-5).** *N*-(4'-Methoxy-[1,1'-biphenyl]-2-yl)acetamide **1-2** (0.5 mmol, 121 mg). Purification (EtOAc/hexanes = 1/2); pale yellow solid; mp 231-232 °C (diethyl ether); 55% yield (97 mg); R_f = 0.15 (EtOAc/hexanes = 1/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.23 (m, 9H), 6.94 (d, J = 8.7 Hz, 2H), 6.58 (s, 1H), 3.84 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 159.1, 140.6, 140.0, 138.6, 133.4, 131.8, 131.4, 130.4, 130.1, 130.0, 129.7, 128.5, 128.0, 113.9, 55.4, 23.1. HRMS (ESI) calc. For $C_{21}H_{19}ClNO_2$ $[M+H]^+$: 352.1099; found: 352.1100.

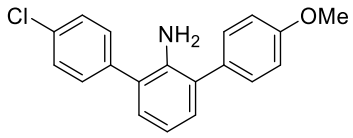


***N*-[2-(4-Chlorophenyl)-6-[4-(trifluoromethyl)phenyl]phenyl]acetamide (1-6).** *N*-(4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)acetamide **1-3** (0.5 mmol, 140 mg). Purification (EtOAc/hexanes = 1/5); pale yellow solid; mp 254-255 °C (diethyl ether); 61% yield (119 mg); R_f = 0.55 (EtOAc/hexanes = 1/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.40 – 7.23 (m, 6H), 6.59 (s, 1H), 1.70 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.6, 143.5, 140.1, 140.0, 137.9, 133.8, 131.3, 130.6, 130.2, 130.2, 129.7 (q, J = 32.4 Hz), 129.2, 128.7, 128.2, 125.3, 124.3 (d, J = 272.1 Hz), 23.0. HRMS (ESI) calc. For $C_{21}H_{16}ClF_3NO$ $[M+H]^+$: 390.0867; found: 390.0870.

General Procedure for Hydrolysis of 2,6-Disubstituted Acetamides. A 2-dram vial equipped with a magnetic stir bar was charged with acetamide (0.23 mmol), sodium hydroxide (2.3 mmol, 92 mg), and EtOH (0.5 ml). The mixture was heated at 130 °C for 24 h. After completion of the reaction, water (20 mL) was added to the reaction mixture and resulting solution was extracted with diethyl ether (3 x 30 mL). Organic layer was dried over $MgSO_4$, filtered, and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel.

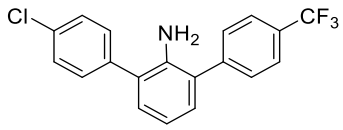


4-Chloro-4''-methyl-[1,1':3',1''-terphenyl]-2'-amine (1-7). Acetamide **1-4** (0.23 mmol, 77 mg). Purification (hexanes/diethyl ether = 20/1); white solid; mp 90-91 °C (pentane); 83% yield (56 mg); R_f = 0.72 (hexanes/diethyl ether = 10/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 7.4 Hz, 2H), 7.27 (d, J = 7.4 Hz, 2H), 7.12 (d, J = 7.4 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 6.90 – 6.84 (m, 1H), 3.81 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.9, 138.3, 137.2, 136.6, 133.3, 130.9, 130.2, 129.7, 129.6, 129.3, 129.1, 128.3, 126.7, 118.4, 21.3; HRMS (ESI) calc. For $C_{19}H_{17}ClN$ $[M+H]^+$: 294.1044; found: 294.1046.



2-(4-Chlorophenyl)-6-(4-methoxyphenyl)aniline (1-8). Acetamide **1-5** (0.22 mmol, 77 mg). Purification (hexanes/diethyl ether = 10/1); white solid; mp 102-103 °C; 81% yield (55 mg); R_f = 0.30 (hexanes/diethyl ether = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.38 (m, 6H), 7.13 (d, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 7.8 Hz, 2H), 6.88 (t, J = 7.5 Hz, 1H), 3.87 (s,

3H), 3.80 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 141.0, 138.3, 133.3, 131.8, 130.8, 130.5, 130.2, 129.5, 129.1, 128.0, 126.7, 118.4, 114.4, 55.4. HRMS (ESI) calc. For $C_{19}H_{17}ClNO$ $[M+H]^+$: 310.0993; found: 310.0994.



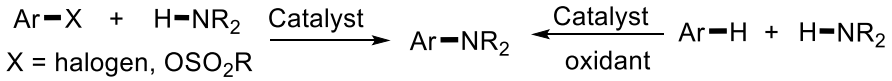
2-(4-Chlorophenyl)-6-[4-(trifluoromethyl)phenyl]aniline (1-9). Acetamide **1-6** (0.20 mmol, 78 mg), heated at 130 °C for 36 h. Purification (hexanes/diethyl ether = 20/1); white solid; mp 68-69 °C; 82% yield (57 mg); R_f = 0.75 (hexanes/diethyl ether = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.46 (s, 4H), 7.13 (d, *J* = 7.4 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 3.79 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 140.7, 137.9, 133.5, 130.8, 130.4, 130.1, 129.8, 129.6 (q, *J* = 33.0 Hz), 129.2, 127.1, 126.6, 126.0 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 272.2 Hz), 118.6. HRMS (ESI) calc. For $C_{19}H_{14}ClF_3N$ $[M+H]^+$: 348.0761; found: 348.0765.

CHAPTER 2: *N*-Aminopyridinium Ylide-Directed, Copper-Promoted Amination of sp^2 C−H Bonds

2.1 Introduction

Copper-mediated *N*-arylation was discovered in early 20th century by Fritz Ullmann and Irma Goldberg. The reaction has served as a useful synthetic tool for the preparation of valuable compounds used in various fields. However, the application of the amination was restricted because it usually required harsh conditions, aryl electrophiles activated with an electron withdrawing group, and presence of strong bases.[27] In line with the development of palladium-catalyzed amination discovered by Buchwald and Hartiwig groups, the limitation of copper-mediated amination has been overcome by employing ligands and additives that facilitate the reaction. Wide substrate scope and good function group tolerance of the transition metal catalyzed amination allowed organic chemists to embrace the protocol.[28]

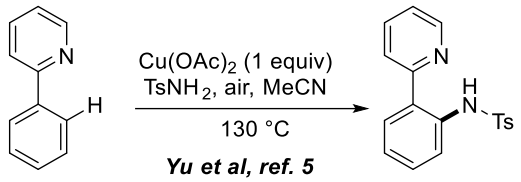
The amination described above is the coupling reaction of aryl (pseudo)halides and amines. Alternative method for the synthesis of arylamines is the amination utilizing aryl C−H bonds instead of aryl (pseudo)halides (Scheme 2.1).[19b, 29] Inertness of unactivated C−H bonds and selectivity issues attributed to the similar reactivity of different C−H bonds are the main challenges of such reactions. However, use of directing groups could assist in selectivity control and activation of C−H bonds by cyclometallation with transition metals.[2b, 2e, 3, 30]



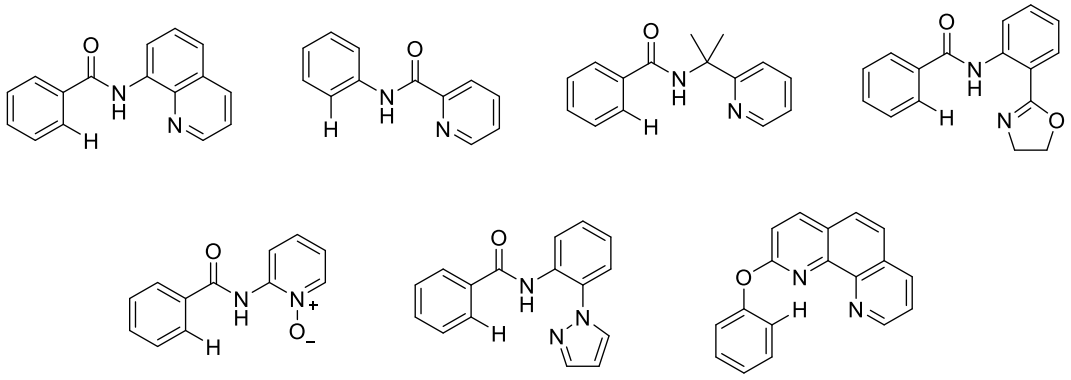
Scheme 2.1 Aryl amine synthesis

The first copper-promoted, directed amination of arene C−H bonds was reported by Yu in 2006 (Scheme 2.2),[31] followed by several other groups showing similar reactivity of 2-phenylpyridine derivatives.[31-32] After this early work, a number of groups have disclosed copper-catalyzed

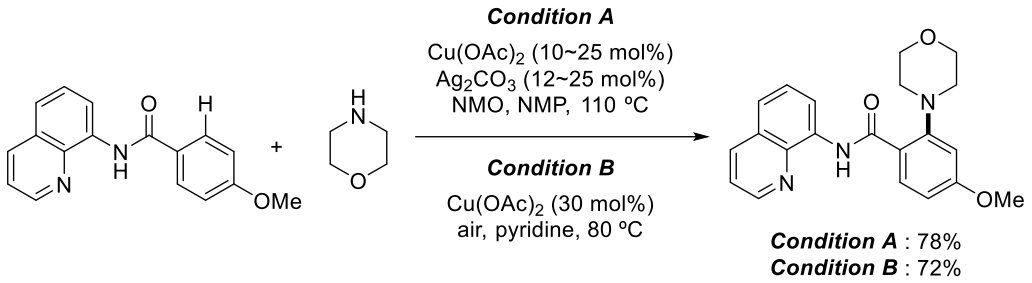
C−H/N−H couplings directed by bidentate auxiliaries (Scheme 2.3).[33] Our group has shown that either NMO or oxygen from air can be used as terminal oxidant for aminoquinoline-directed, copper-catalyzed amination of sp^2 C−H bonds (Scheme 2.4).[33a, 33f] Other first-row metals, such as cobalt and nickel, have also been used for bidentate auxiliary-directed amination of sp^2 C−H bonds.[34] However, it appears that in all examples of Cu-catalyzed, directed C−H/N−H couplings, either a non-removable pyridine or a bidentate directing group is required. A report by the Yu and Dai group shows that a removable, monodentate perfluorinated toluanilide can direct C−H amination of sp^2 C−H bonds in presence of several equivalents of copper and an external ligand (Scheme 2.5).[35] It would be advantageous if a simpler, monodentate directing group could be employed under ligand-free environment.



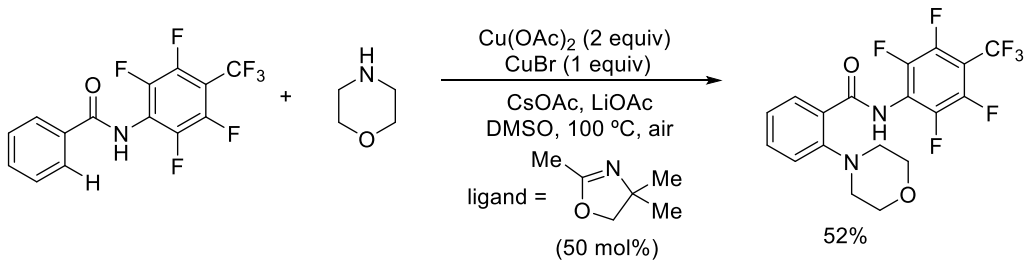
Scheme 2.2 First example of copper mediated C−H amination



Scheme 2.3 Bidentate directing groups used for C−H amination using copper catalysis

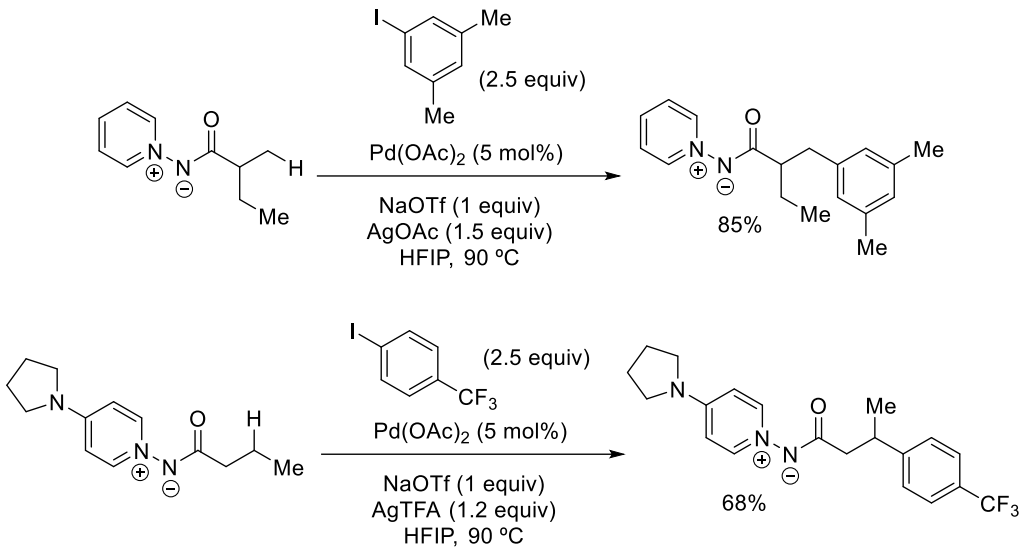


Scheme 2.4 8-Aminoquinoline directed C−H amination



Scheme 2.5 Removable monodentate directing group for C−H amination

We have recently reported that *N*-iminopyridinium ylide functionality can serve as a removable auxiliary for palladium-catalyzed sp^3 C−H bond functionalization (Scheme 2.6).[36] This directing group appears to be nearly as efficient as aminoquinoline, and even aliphatic chains can be arylated. We report here that *N*-iminopyridinium ylides function as competent directing groups for copper-promoted coupling of sp^2 C−H bonds with pyrazoles, imidazoles, and sulfonamides.



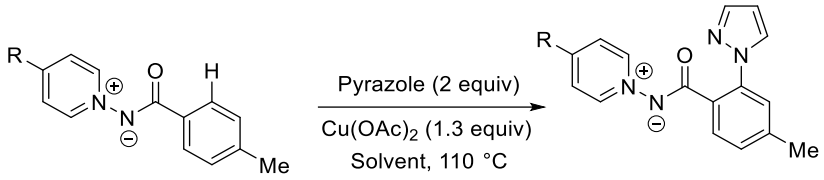
Scheme 2.6 Pyridiniumylide-directed sp^3 C−H arylation

2.2 Results and discussion

The initial optimization experiments were carried out with unsubstituted *N*-iminopyridinium ylide prepared from commercially available 1-aminopyridinium iodide and *p*-toluoyl chloride (Table 2.1). After screening of a number of copper salts and solvents, we found that $Cu(OAc)_2$ in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) afforded superior results (entry 2). Attempts to improve yield with the help of additives, ligands, and external oxidants were not fruitful. Subsequently, modification of ylide pyridine moiety was undertaken. Methoxy and methyl substituents on the pyridine ring did not substantially improve the reaction yield (entries 3-4). When 4-*tert*-butyl-substituted ylide was employed, the yield was improved to 47% (entry 5). Further improvement in yield was achieved if the reaction was performed in nonafluoro-*tert*-butanol (PFB) (entry 6). Finally, 74% yield was reached by increasing amount of $Cu(OAc)_2$ and pyrazole (entry 7). Attempts to perform catalytic reactions under oxygen atmosphere resulted in at most two turnovers

based on $Cu(OAc)_2$ and low conversions. In addition, it should be noted that trace amount of C−H hydroxylation product was observed in addition to the desired amination product.

Table 2.1. Reaction optimization[a]

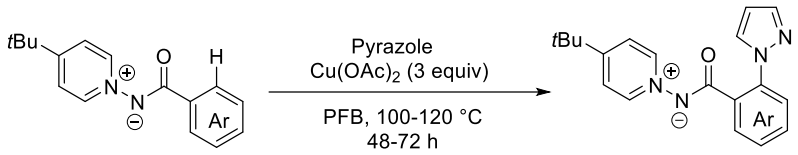


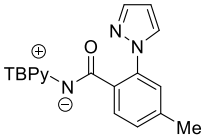
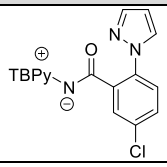
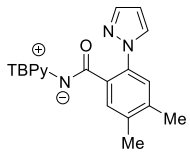
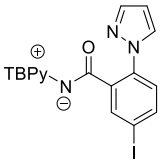
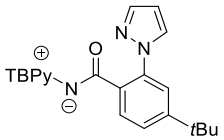
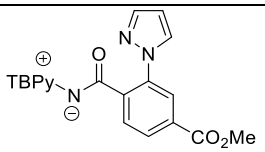
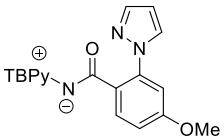
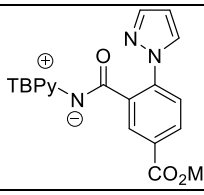
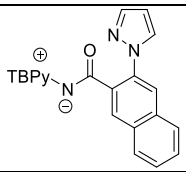
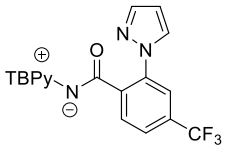
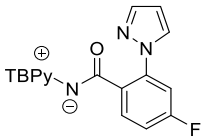
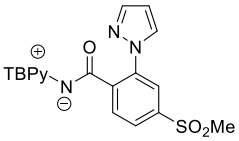
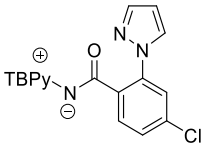
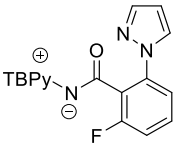
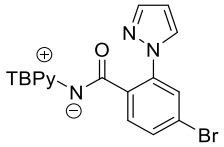
Entry	R	Solvent	Yield (%)
1	H	TFE	-
2	H	HFIP	19
3	4-MeO	HFIP	20
4	3,5-Me_2	HFIP	25
5	4-*tert*-Butyl	HFIP	47
6	4-*tert*-Butyl	PFB	64
7	4-*tert*-Butyl	PFB	74

[a] Scale: 0.1 mmol, time: 24 h, solvent: 0.5 mL. Yields are isolated yields. [b] Substrate 0.4 mmol, $Cu(OAc)_2$ 3 equiv, pyrazole 4.5 equiv, solvent 1.0 mL, 48 h. Abbreviations: TFE = trifluoroethanol, HFIP = hexafluoroisopropanol, PFB = nonafluoro-*t*-butanol.

Reaction scope with respect to substitution on aromatic ring was studied next (Table 2.2). Typically, best results were obtained with electron-donating substituents at *para*-position of the aromatic ring (entries 1, 3, 4). Introduction of electron-withdrawing substituents led to lower yields of products (entries 6-14). Substitution at the *meta* position led to decreased reaction efficiency (entries 9, 10, 12). A range of functional groups, such as fluoro, chloro, bromo, iodo, methoxy, ester, trifluromethyl, and sulfone are well tolerated. The reaction failed if substrate contains nitrile functionality. Substitution at the *ortho* position of the aromatic ring decreases yield (entry 15).

Table 2.2. Reaction Scope with Respect to Ylides[a]

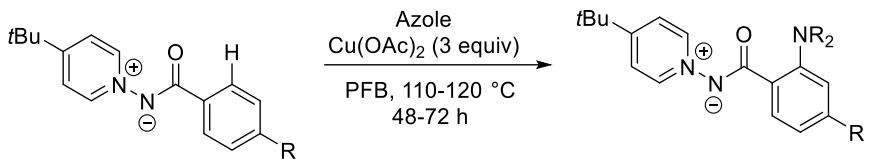


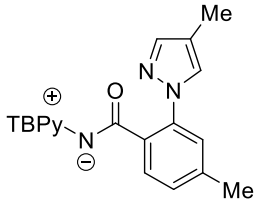
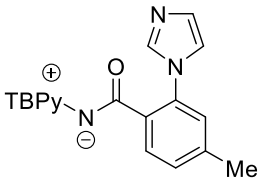
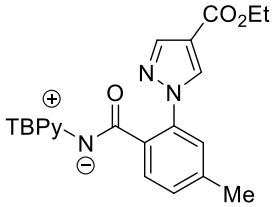
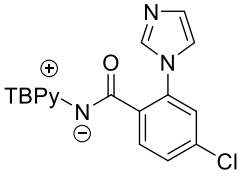
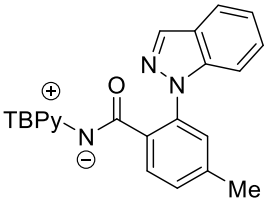
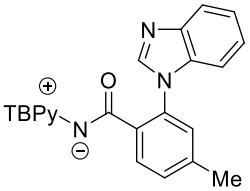
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		74 72[b]	9		54
2		60	10		47
3		75	11		47
4		67	12		46
5		61	13		67
6		64	14		36
7		65	15		54
8		56			

[a] Reaction scale: 0.4 mmol, solvent 1 mL. Isolated yields reported. TBPy = 4-*t*-butyl-1-pyridyl. [b] Reaction scale: 1.2 mmol; 82% PFB recovered.[14]

Substituted pyrazoles and indazole are also compatible with the reaction conditions (Table 2.3). Coupling with methylpyrazole, ester-substituted pyrazole, and indazole gave products in good yields (entries 1−3). Furthermore, imidazole and benzimidazole react to afford the corresponding products (entries 4−6). However, the C−H amination with imidazoles is less efficient and products were obtained in low yields. The main byproduct results from *ortho* C−H hydroxylation of aromatic ring,[37] in line with observations for aminoquinoline-directed reactions. Pyrrole, indole, and triazole failed to give the amination products.

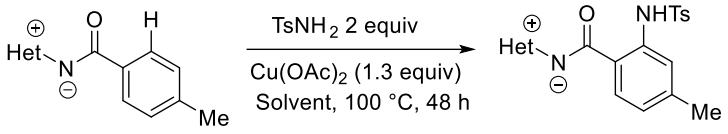
Table 2.3 Amination with pyrazoles and imidazoles



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		74	4		23
2		54	5		41
3		67	6		45

Finally, we investigated amidation reactions with sulfonamides. The initial optimization showed that conditions are somewhat different from those employed for couplings with heterocycles (Table 2.4).

Table 2.4. Amidation with sulfonamides optimization[a]



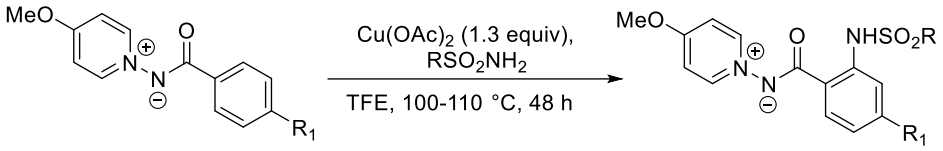
Entry	Het	Solvent	Yield (%)
1	1-pyridyl	PFB	37
2	1-pyridyl	HFIP	45
3	1-pyridyl	TFE	55
4	4-methoxy-1-pyridyl	TFE	60
5	4-pyrrolidino-1-pyridyl	TFE	29
6	4-*tert*-butyl-1-pyridyl	TFE	42
7	3,5-dimethoxy-1-pyridyl	TFE	45
8	4-trifluoromethyl-1-pyridyl	TFE	31
9	1-methyl-2-pyrazoyl	TFE	46
10	1-(2,2'-bipyridyl)	TFE	60
11	1-(1,8-naphthyridinyl)	TFE	44

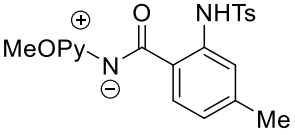
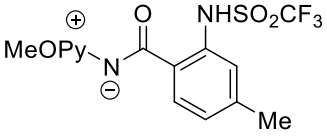
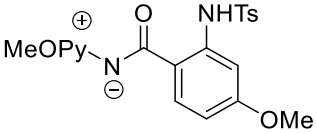
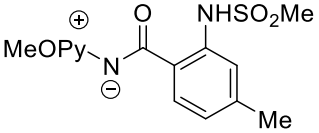
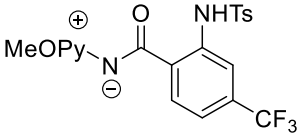
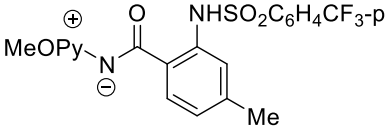
[a] Scale: 0.1 mmol, solvent 0.5 mL. Yields are isolated yields.

In contrast to the amination with azoles, PFB was no longer the most effective solvent among three fluorinated alcohols, and reaction in TFE gave the highest yields of product (Table 2.4, entries 1−3). Subsequently, modification of ylide pyridine moiety was undertaken (entries 4−8). The best results were obtained with a methoxysubstituted iminopyridine ylide (entry 4). Electron-

rich pyrrolidino (entry 5), *tert*-butyl (entry 6), dimethoxy (entry 7), and electron-poor trifluoromethyl-substituted (entry 8) ylides gave lower yields. We investigated also a number of potentially bidentate ligands, such as pyrazolyl- (entry 9), bipyridyl- (entry 10), and naphthyridinyl- (entry 11)-substituted ylides. Only bipyridyl-substituted substrate gave an acceptable yield of coupling product.

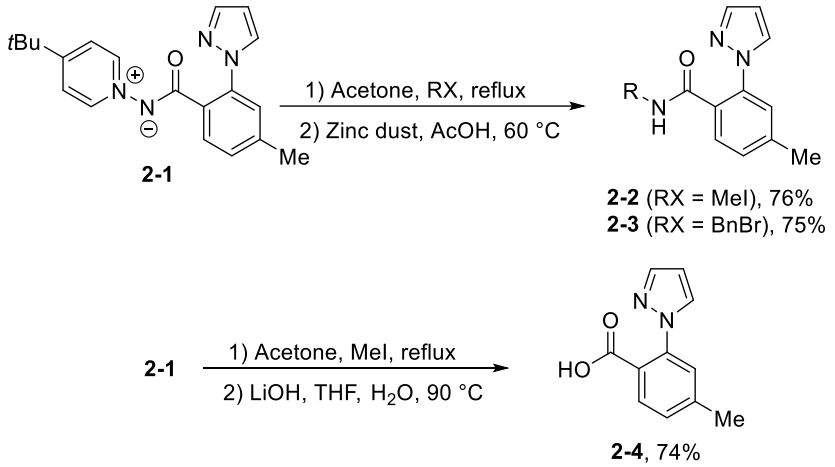
Table 2.5 Amidation with sulfonamides



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		60	4		53
2		56	5		38
3		44	6		52

Consequently, 4-methoxypyridinium ylides were chosen as the substrates for the amidation, affording the desired products in moderate yields (Table 2.5). *p*-Toluenesulfonamide can be coupled with electron-rich methyl- and methoxy-substituted substrates (entries 1 and 2) as well as electron-poor trifluorobenzoic acid derivative (entry 3). Triflamide can be coupled in 53% yield

(entry 4), while methanesulfonamide gave product in 38% yield (entry 5). Electron-withdrawing substituents such as trifluoromethyl group on arylsulfonamide moiety are also tolerated (entry 6).



Scheme 2.7. Directing group removal

Directing group can be removed by a sequence of *N*-alkylation and reduction (Scheme 2.7).[38] Thus, compound **2-1** was reacted with methyl iodide or benzyl bromide followed by treatment with zinc dust in acetic acid at 60 ºC, affording amides **2-2** and **2-3** in 76% and 75% overall yields, respectively. Alternatively, alkylation followed by base hydrolysis gives carboxylic acid **2-4** in 74% yield.

2.3 Conclusion

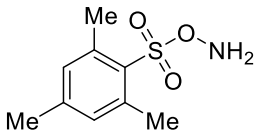
In conclusion, we have shown that *N*-iminopyridinium ylides act as competent monodentate directing groups for copper-promoted C−H/N−H coupling of sp^2 C−H bonds with pyrazoles, imidazoles, and sulfonamides. Reactions proceed in fluorinated alcohol solvents at elevated temperatures and require use of 1.3-3 equivalents of copper(II) acetate. Products are obtained in modest to good yields. This work shows that removable monodentate auxiliaries can be employed for base metal promoted C−H/N−H couplings.

2.4 Experimental Section

General Information.

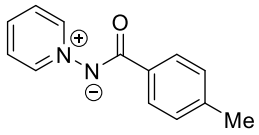
The ^{1}H, ^{13}C NMR spectra were recorded on JEOL EC-400, EC-500 and EC-600 spectrometers using residual solvent peak as a reference. Compounds for HRMS were analyzed by positive mode electrospray ionization (CI or ESI) using Agilent QTOF mass spectrometer in the Mass Spectrometry Facility (MSF) of the Department of Chemistry and Biochemistry of University of Texas-Austin. Column chromatography was performed using 60 Å silica gel. Reagents and starting materials were purchased from commercial vendors and used without further purification unless noted otherwise.

Preparation of *O*-(2,4,6-Trimethylbenzenesulfonyl)hydroxylamine

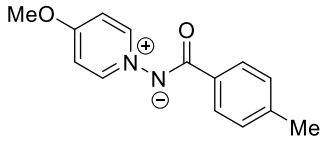


2-Mesitylenesulfonyl chloride (50 mmol, 10.9 g) and *N*-Boc-hydroxylamine (50 mmol, 6.6 g) were dissolved in methyl *tert*-butyl ether (120 mL) and cooled to 0 °C. Triethylamine (50 mmol, 7.0 mL) in methyl *tert*-butyl ether (30 mL) was added dropwise with stirring and stirred at 0 °C for 2 h. The resulting salt was filtered off and washed with methyl *tert*-butyl ether. The filtrate was concentrated in vacuo. To the residue were added methyl *tert*-butyl ether (10 mL) and hexanes (100 mL) and the solution was evaporated slowly in vacuo to give a white solid. The solid was collected by filtration, washed with hexanes. To the filtrate was added methyl *tert*-butyl ether (5 mL) and concentrated slowly in vacuo to give a white solid. The solid was obtained by filtration and washed with hexanes. All the white solids were dried under vacuum. A 500 ml round bottomed flask was charged with trifluoroacetic acid (80 mL) and cooled down to 0 °C. To the solution was added the prepared white solid above portionwise and stirred at 0 °C for 2 h. Crushed ice and cold

water were added to the solution and immediately white solid was appeared, which was collected by filtration, washed with cold water (400 ml X 2). The wet solid was dissolved in diethyl ether and water layer was removed using a separate funnel. The organic layer was evaporated in vacuo at room temperature to afford the title compound (7.5 g, 70%,). This product was used without further drying and purification and was stored in a refrigerator.

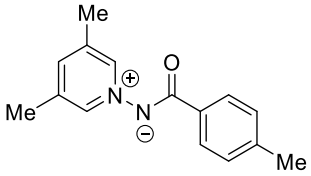


(4-Methylbenzoyl)(pyridin-1-ium-1-yl)amide (SM01). 1-Aminopyridinium iodide (2.22 g, 10 mmol) and triethylamine (5.57 mL, 40 mmol) were dissolved in MeOH (30 mL). The solution was cooled to 0 °C. 4-Methylbenzoyl chloride (1.47 ml, 11 mmol) was added to the solution dropwise. The deep purple solution was stirred for 16 h. The mixture was poured into water and extracted with ethyl acetate (5 × 70 mL), dried over $MgSO_4$, and evaporated to give a pale yellow solid (1.90 g, 90%). Appearance: pale yellow solid; R_f = 0.26 (EtOAc/MeOH = 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (d, J = 6.3 Hz, 2H), 8.03 (d, J = 8.0 Hz, 2H), 7.97 (t, J = 7.7 Hz, 1H), 7.72 (t, J = 7.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.2, 143.9, 141.0, 138.1, 133.2, 128.9, 128.2, 126.4, 21.6. This compound is known.[39]



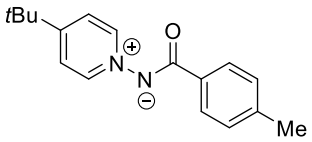
(4-Methoxypyridin-1-ium-1-yl)(4-methylbenzoyl)amide (SM02). This is also a representative procedure for SM03, SM04, and SM06−SM26 preparation. To a 100 mL round bottomed flask were added 4-methoxypyridine (0.41 mL, 4 mmol) and CH_2Cl_2 (20 mL). *O*-(2,4,6-Trimethylbenzenesulfonyl)hydroxylamine (1.03 g, 4.8 mmol) was added to the solution and the

mixture was stirred for 2 h. This step prepares a substituted 1-aminopyridine. To another 100 mL round bottomed flask were added p-toluic acid (0.54 g, 4 mmol) and CH_2Cl_2 (20 mL), and mixture was cooled to 0 °C. Ethyl chloroformate (0.42 mL, 4.4 mmol) was added to the mixture followed by the addition of triethylamine (1.67 mL, 12 mmol). The mixture was stirred for 30 min at room temperature. To this mixture were added the aminopyridinium solution prepared above dropwise and K_2CO_3 (1.66 g, 12 mmol). After stirring the mixture for 24 h, NaOH (50 mL of a 1 N aqueous solution) was poured in and mixture was extracted with CH_2Cl_2 (3 × 100 mL). The extracts were dried over $MgSO_4$ and residue was purified by column chromatography (gradient elution, EtOAc/MeOH, 5% → 15%) to give the product (0.70 g, 72%). Appearance: white solid; mp 194−196 °C (EtOAc/MeOH =10:1); R_f = 0.30 (EtOAc/MeOH = 4/1); 1H NMR (600 MHz, CD_2Cl_2) δ 8.52 (d, J = 6.9 Hz, 2H), 7.96 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 7.08 (d, J = 6.9 Hz, 2H), 3.98 (s, 3H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD) δ 174.2, 169.3, 146.5, 141.9, 134.9, 129.6, 129.0, 113.6, 58.0, 21.5. HRMS (ESI) calcd for $C_{14}H_{15}N_2O_2$ $[M + H]^+$ 243.1128, found 243.1130.

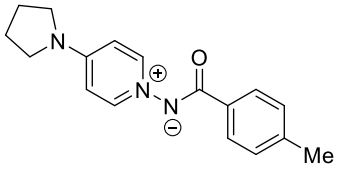


(3,5-Dimethylpyridin-1-ium-1-yl)(4-methylbenzoyl)amide (SM03). General procedure was used with 3,5-dimethylpyridine (0.46 mL, 4 mmol). Yield: 0.64 g, 67%; Appearance: white solid; mp 156−158 °C (EtOAc/MeOH =10:1); R_f = 0.40 (EtOAc/MeOH = 4/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^1H NMR (400 MHz, CD_3OD) δ 8.36 (s, 2H), 7.95 (s, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 2.48 (s, 6H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (101

MHz, CD_3OD) δ 173.7, 142.6, 142.1, 142.0, 139.2, 134.9, 129.6, 129.0, 21.5, 18.1. HRMS (ESI) calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1335, found 241.1338.

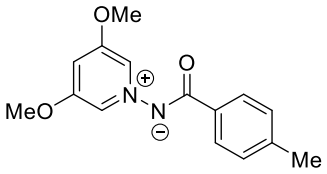


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-methylbenzoyl)amide (SM04). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol). Yield: 0.81 g, 75%; appearance: white solid; mp 231−232 °C (EtOAc/MeOH =10:1); R_f = 0.65 (EtOAc/MeOH = 4/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 7.1 Hz, 2H), 8.04 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 7.1 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 2.38 (s, 3H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 162.6, 142.9, 140.2, 134.6, 128.7, 128.0, 123.1, 35.8, 30.4, 21.6. HRMS (ESI) calcd for $C_{17}H_{21}N_2O$ $[M + H]^+$ 269.1648, found 269.1651.

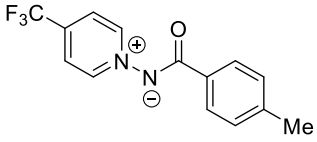


(4-Methylbenzoyl)(4-(pyrrolidin-1-yl)pyridin-1-ium-1-yl)-amide (SM05). To a 100 mL round bottomed flask were added 4-pyrrolidinopyridine (0.59 g, 4 mmol) and CH_2Cl_2 (20 mL). *O*-(2,4,6-Trimethylbenzenesulfonyl)hydroxylamine (1.03 g, 4.8 mmol) was added to the solution. After stirring for 2 h, 4-methylbenzoyl chloride (0.58 mL, 4.4 mmol) and pyridine (0.97 mL, 12 mmol) were added to the solution and stirred for 24 h. After that, NaOH (50 mL of a 1 N aqueous solution) was poured in and mixture was extracted with CH_2Cl_2 (3 ×100 ml). The extracts were dried over $MgSO_4$ and purified by column chromatography (gradient elution, EtOAc/MeOH, 5% → 15%) to give the product (0.27 g, 24%). Appearance: white solid; mp 291−293 °C (EtOAc/MeOH =10:1); R_f = 0.15 (EtOAc/MeOH = 4/1); ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (d, J = 7.6 Hz, 2H), 7.87 (d,

J = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.78 (d, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 6.7 Hz, 4H), 2.38 (s, 3H), 2.17 – 2.06 (m, 4H). $^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3OD) δ 174.7, 153.5, 143.3, 141.7, 135.3, 129.6, 129.0, 108.6, 49.2, 26.3, 21.4. HRMS (ESI) calcd for $C_{17}H_{20}N_3O$ $[M + H]^+$ 282.1601, found 282.1605.

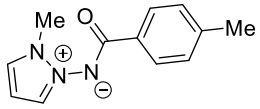


(3,5-Dimethoxypyridin-1-ium-1-yl)(4-methylbenzoyl)amide (SM06). General procedure was used with 3,5-dimethoxypyridine (0.56 g, 4 mmol). Yield: 0.82 g, 75%; appearance: white solid; mp 172−173 °C (EtOAc/MeOH =90:10); R_f = 0.51 (EtOAc/MeOH = 4/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (d, *J* = 2.2 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.46 (t, *J* = 2.2 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 3.99 (s, 6H), 2.39 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3OD) δ 173.5, 160.3, 142.0, 134.9, 129.6, 129.1, 126.3, 111.9, 57.8, 21.5. HRMS (ESI) calcd for $C_{15}H_{17}N_2O_3$ $[M + H]^+$ 273.1234, found 273.1240.

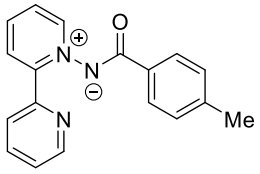


(4-Methylbenzoyl)(4-(trifluoromethyl)pyridin-1-ium-1-yl)amide (SM07). General procedure was used with 4-(trifluoromethyl)pyridine (0.46 mL, 4 mmol). Yield: 0.66 g, 59%; appearance: white solid; mp 198−199 °C (EtOAc/MeOH =10:1); R_f = 0.2 (hexanes/EtOAc = 1/2); purification (gradient elution, hexanes/EtOAc, 25% → 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, *J* = 6.7 Hz, 2H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 6.8 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.8, 143.3, 141.1, 136.1 (q, *J* = 36.1 Hz), 134.1, 128.8,

128.2, 122.6 (q, J = 3.6 Hz), 121.7 (q, J = 273.5 Hz), 21.6. HRMS (ESI) calcd for $C_{14}H_{12}F_3N_2O$ $[M + H]^+$ 281.0896, found 281.0900.

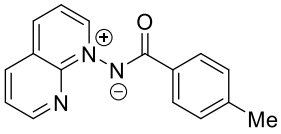


(1-Methyl-1H-pyrazol-2-ium-2-yl)(4-methylbenzoyl)amide (SM08). General procedure was used with 1-methylpyrazole (0.33 mL, 4 mmol). Yield: 0.48 g, 56%; appearance: white solid; mp 208−209 °C (EtOAc/MeOH =10:1); R_f = 0.27 (EtOAc/MeOH = 4/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (dd, J = 2.8, 1.2 Hz, 1H), 8.01 (dd, J = 3.3, 1.1 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 6.67 (t, J = 3.0 Hz, 1H), 3.92 (s, 3H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 175.0, 142.2, 134.6, 133.3, 131.8, 129.7, 129.1, 105.7, 35.5, 21.5. HRMS (ESI) calcd for $C_{12}H_{14}N_3O$ $[M + H]^+$ 216.1131, found 216.1134.

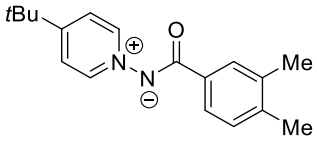


[2,2'-Bipyridin]-1-ium-1-yl(4-methylbenzoyl)amide (SM09). General procedure was used with 2,2′-bipyridyl (0.62 g, 4 mmol). Yield: 0.94 g, 81%; appearance: pale yellow solid; mp 157−158 °C (EtOAc/MeOH =10:1); R_f = 0.24 (EtOAc/MeOH = 4/1); purification (gradient elution, EtOAc/MeOH, 10% → 20%); ^{1}H NMR (400 MHz,CD_3OD) δ 8.72 (d, J = 4.8 Hz, 1H), 8.70 (dd, J = 6.3, 0.7 Hz, 1H), 8.37 (td, J = 7.8, 1.1 Hz, 1H), 8.22 (dd, J = 8.0, 1.7 Hz, 1H), 8.03 – 7.92 (m, 2H), 7.84 (td, J = 7.8, 1.5 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.48 (ddd, J = 7.6, 4.9, 0.8 Hz, 1H), 7.15 (d, J = 8.2 Hz, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 173.3, 152.8, 151.2,

150.9, 146.8, 142.0, 141.6, 137.7, 134.7, 130.5, 129.6, 129.0, 128.0, 126.5, 126.4, 21.4. HRMS (ESI) calcd for $C_{18}H_{16}N_3O$ $[M + H]^+$ 290.1288, found 290.1294.

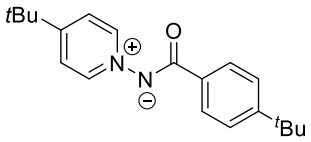


(4-Methylbenzoyl)(1,8-naphthyridin-1-ium-1-yl)amide (SM10). General procedure was used with 1,8-naphthyridine (0.52 g, 4 mmol). Yield: 0.76 g, 72%; appearance: orange solid; mp 173−175 °C (EtOAc/MeOH =10:1); R_f = 0.14 (EtOAc/MeOH = 4/1); purification (gradient elution, EtOAc/MeOH, 10% → 20%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.32 (dd, J = 5.9, 1.4 Hz, 1H), 9.22 (dd, J = 4.1, 1.8 Hz, 1H), 8.47 (dd, J = 8.3, 1.3 Hz, 1H), 8.43 (dd, J = 8.2, 1.7 Hz, 1H), 8.21 (d, J = 8.0 Hz, 2H), 7.78 (dd, J = 8.3, 6.0 Hz, 1H), 7.75 (dd, J = 8.2, 4.2 Hz, 1H), 7.24 (d, J = 7.9 Hz, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.1, 156.2, 148.5, 148.2, 140.2, 138.8, 138.1, 134.4, 128.6, 128.5, 125.4, 125.1, 121.8, 21.6. HRMS (ESI) calcd for $C_{16}H_{14}N_3O$ $[M + H]^+$ 264.1131, found 264.1136.

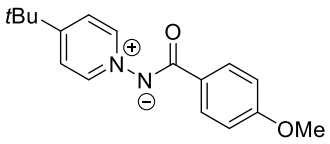


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(3,4-dimethylbenzoyl)amide (SM11). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 3,4-dimethylbenzoic acid (0.60 g, 4 mmol). Yield: 0.95 g, 84%; appearance: white solid; mp 211−212 °C (EtOAc/MeOH =10:1); R_f = 0.30 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 7.2 Hz, 2H), 7.92 (s, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.16 (d, J = 7.8 Hz, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (101

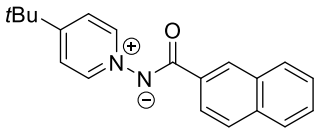
MHz, $CDCl_3$) δ 171.3, 162.6, 142.9, 138.8, 136.0, 134.9, 129.3, 129.1, 125.6, 123.1, 35.7, 30.4, 20.0, 19.9. HRMS (ESI) calcd for $C_{18}H_{23}N_2O$ $[M + H]^+$ 283.1805, found 283.1809.



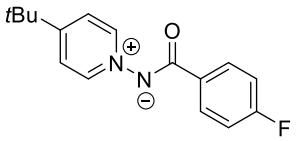
(4-(*tert*-Butyl)benzoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (SM12). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-(*tert*-butyl)benzoic acid (0.71 g, 4 mmol). Yield: 0.96 g, 77%; appearance: white solid; mp 260−261 °C (EtOAc/MeOH =10:1); R_f = 0.33 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 6.0 Hz, 2H), 8.07 (d, J = 7.7 Hz, 2H), 7.58 (d, J = 5.9 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 1.37 (s, 9 H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 162.6, 153.3, 142.9, 134.6, 127.8, 124.9, 123.1, 35.7, 34.9, 31.4, 30.4. HRMS (ESI) calcd for $C_{20}H_{27}N_2O$ $[M + H]^+$ 311.2118, found 311.2124.



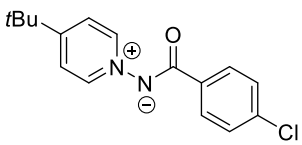
(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-methoxybenzoyl)amide (SM13). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-methoxybenzoic acid (0.61 g, 4 mmol). Yield: 0.69 g, 61%; appearance: white solid; mp 235−237 °C (EtOAc/MeOH =10:1); R_f = 0.11 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 5% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 7.3 Hz, 2H), 8.10 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 7.3 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 3.84 (s, 3H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.8, 162.6, 161.3, 142.9, 129.9, 129.7, 123.1, 113.2, 55.4, 35.8, 30.4. HRMS (ESI) calcd for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1598, found 285.1601.



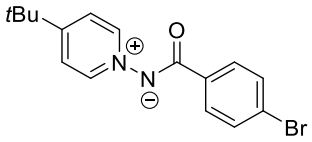
(2-Naphthoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (SM14). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 2-naphthoic acid (0.69 g, 4 mmol). Yield: 1.01 g, 83%; appearance: white solid; mp 215 − 216 °C (EtOAc/MeOH =10:1); R_f = 0.38 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.65 (m, 3H), 8.26 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 7.1 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 6.1 Hz, 2H), 7.54 – 7.42 (m, 2H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.0, 162.9, 142.8, 134.9, 134.6, 133.1, 129.1, 128.1, 127.7, 127.4, 126.6, 125.9, 125.5, 123.2, 35.8, 30.4. HRMS (ESI) calcd for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1648, found 305.1654.



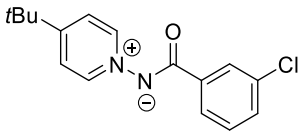
(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-fluorobenzoyl)amide (SM15). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-fluorobenzoic acid (0.56 g, 4 mmol). Yield: 0.86 g, 79%; appearance: white solid; mp 198−199 °C (EtOAc/MeOH =10:1); R_f = 0.28 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 7.2 Hz, 2H), 8.14 (dd, J = 8.8, 5.7 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.05 (t, J = 8.8 Hz, 2H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 164.3 (d, J = 248.3 Hz), 163.9, 142.7, 133.6 (d, J = 2.9 Hz), 130.2 (d, J = 8.5 Hz), 123.2, 114.7 (d, J = 21.4 Hz) 35.8, 30.4. HRMS (ESI) calcd for $C_{16}H_{18}FN_2O$ $[M + H]^+$ 273.1398, found 273.1401.



(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-chlorobenzoyl)amide (SM16). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-chlorobenzoic acid (0.63 g, 4 mmol). Yield: 0.80 g, 69%; appearance: white solid; mp 254−255 °C (EtOAc/MeOH =10:1); R_f = 0.28 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 5.7 Hz, 2H), 8.08 (d, *J* = 7.7 Hz, 2H), 7.60 (d, *J* = 5.8 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8, 162.8, 142.4, 135.8, 135.8, 129.3, 127.8, 122.9, 35.6, 30.1. HRMS (ESI) calcd for $C_{16}H_{18}ClN_2O$ $[M + H]^+$ 289.1102, found 289.1110.

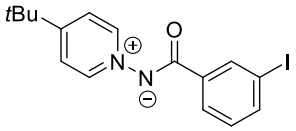


(4-Bromobenzoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (SM17). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-bromobenzoic acid (0.80 g, 4 mmol). Yield: 1.03 g, 77%; appearance: white solid; mp 261−263 °C (EtOAc/MeOH =10:1); R_f = 0.33 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 1.37(s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 163.1, 142.7, 136.5, 131.0, 129.8, 124.6, 123.2, 35.8, 30.4. HRMS (ESI) calcd for $C_{16}H_{18}BrN_2O$ $[M + H]^+$ 333.0597, found 333.0602.

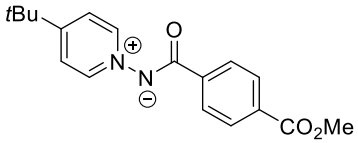


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(3-chlorobenzoyl)amide (SM18). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 3-chlorobenzoic acid (0.63 g, 4 mmol).

Yield: 0.90 g, 78%; appearance: white solid; mp 208−210 °C (EtOAc/MeOH =10:1); R_f = 0.40 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, J = 7.2 Hz, 2H), 8.16 – 8.12 (m, 1H), 8.02 (dt, J = 7.6, 1.3 Hz, 1H), 7.63 (d, J = 7.2 Hz, 2H), 7.39 (ddd, J = 7.9, 2.1, 1.2 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.8, 163.1, 142.7, 139.6, 133.9, 130.1, 129.3, 128.3, 126.3, 123.2, 35.9, 30.4. HRMS (ESI) calcd for $C_{16}H_{18}ClN_2O$ $[M + H]^+$ 289.1102, found 289.1106.

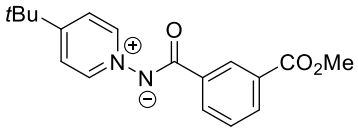


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(3-iodobenzoyl)amide (SM19). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 3-iodobenzoic acid (0.99 g, 4 mmol). Yield: 1.20 g, 79%; appearance: white solid; mp 222 − 224 °C (EtOAc/MeOH =10:1); R_f = 0.33 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 6.4 Hz, 2H), 8.50 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.61 (d, J = 6.4 Hz, 2H), 7.13 (t, J = 7.8 Hz, 1H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.5, 163.1, 142.6, 139.8, 139.0, 137.1, 129.8, 127.4, 123.2, 94.0, 35.8, 30.4. HRMS (ESI) calcd for $C_{16}H_{18}IN_2O$ $[M + H]^+$ 381.0458, found 381.0462.

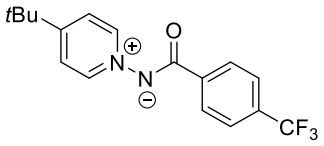


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-(methoxycarbonyl)ben-zoyl)amide (SM20). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-(methoxycarbonyl)-benzoic acid (0.72 g, 4 mmol). Yield: 0.94 g, 75%; appearance: white solid; mp 233−235 °C (EtOAc/MeOH =10:1); R_f = 0.25 (EtOAc/MeOH = 10/1); purification (gradient elution,

EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 7.1 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 7.2 Hz, 2H), 3.91 (s, 3H), 1.38 (s, 9H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.2, 167.2, 163.2, 142.6, 142.0, 131.3, 129.3, 128.0, 123.3, 52.2, 35.8, 30.4. HRMS (ESI) calcd for $C_{18}H_{21}N_2O_3$ $[M + H]^+$ 313.1547, found 313.1552.

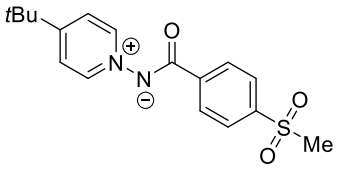


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(3-(methoxycarbonyl)ben-zoyl)amide (SM21). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 3-(methoxycarbonyl)-benzoic acid (0.72 g, 4 mmol). Yield: 0.96 g, 77%; appearance: white solid; mp 195−197 °C (EtOAc/MeOH =10:1); R_f = 0.25 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.65 (d, J = 6.7 Hz, 2H), 8.34 (d, J = 7.7 Hz, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 6.7 Hz, 2H), 7.48 (t, J = 7.7 Hz, 1H), 3.91 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 167.3, 163.1, 142.7, 138.0, 132.7, 131.2, 129.9, 129.2, 128.1, 123.2, 52.2, 35.8, 30.4. HRMS (ESI) calcd for $C_{18}H_{21}N_2O_3$ $[M + H]^+$ 313.1547, found 313.1552.

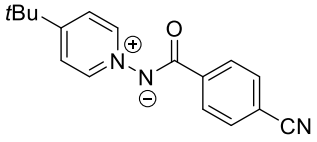


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-(trifluoromethyl)benz-oyl)amide (SM22). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-(trifluoromethyl)-benzoic acid (0.76 g, 4 mmol). Yield: .01 g, 78%; appearance: white solid; mp 278−279 °C (EtOAc/MeOH =10:1); R_f = 0.43 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 7.2 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H), 7.68 – 7.59

(m, 4H), 1.39 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.8, 163.4, 142.7, 141.1, 131.8 (q, J = 32.1 Hz), 128.4, 124.9 (q, J = 3.8 Hz), 124.4 (q, J = 272.4 Hz), 123.3, 35.9, 30.4. HRMS (ESI) calcd for $C_{17}H_{18}F_3N_2O$ $[M + H]^+$ 323.1366, found 323.1371.

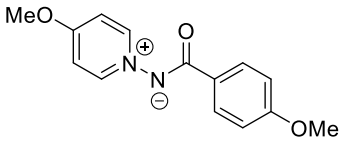


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-(methylsulfonyl)benz-oyl)amide (SM23). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-(methylsulfonyl)-benzoic acid (0.80 g, 4 mmol). Yield: 1.10 g, 83%; appearance: white solid; mp 268 – 269 °C (EtOAc/MeOH =10:1); R_f = 0.08 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 5% → 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 7.2 Hz, 2H), 8.32 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 7.2 Hz, 2H), 3.06 (s, 3H), 1.41 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 163.6, 143.0, 142.5, 141.4, 129.0, 127.1, 123.4, 44.7, 35.9, 30.4. HRMS (ESI) calcd for $C_{17}H_{21}N_2O_3S$ $[M + H]^+$ 333.1267, found 333.1273.

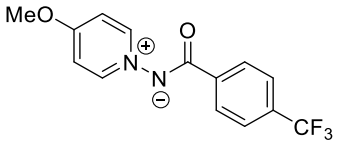


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-cyanobenzoyl)amide (SM24). General procedure was used with 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and 4-cyanobenzoic acid (0.59 g, 4 mmol). Yield: 0.76 g, 68%; appearance: white solid; mp 238 – 240 °C (EtOAc/MeOH =10:1); R_f = 0.38 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 7.2 Hz, 2H), 8.23 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 7.2 Hz, 2H), 1.40 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 163.6, 142.6, 142.1,

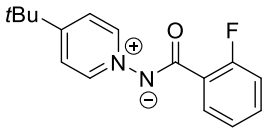
131.9, 128.7, 123.4, 119.2, 113.4, 35.9, 30.4. HRMS (ESI) calcd for $C_{17}H_{18}N_3O$ $[M + H]^+$ 280.1444, found 280.1449.



(4-Methoxybenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (SM25). General procedure was used with 4-methoxybenzoic acid (0.61 g, 4 mmol). Yield: 0.75 g, 73%; appearance: white solid; mp 149−151 °C (EtOAc/MeOH =10:1); R_f = 0.30 (EtOAc/MeOH = 4/1); purification (gradient elution, EtOAc/MeOH, 5% → 10%); ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (d, J = 7.5 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 7.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.09 (s, 3H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 174.0, 169.4, 163.2, 146.6, 130.6, 129.8, 114.2, 113.6, 58.0, 55.8. HRMS (ESI) calcd for $C_{14}H_{15}N_2O_3$ $[M + H]^+$ 259.1077, found 259.1081.



(4-Methoxypyridin-1-ium-1-yl)(4-(trifluoromethyl)benzoyl)-amide (SM26). General procedure was used with 4-(trifluoromethyl)benzoic acid (0.76 g, 4 mmol). Yield: 0.89 g, 80%; appearance: pale yellow solid; mp 176−178 °C (EtOAc/MeOH =10:1); R_f = 0.57 (EtOAc/MeOH = 4/1); purification (gradient elution, EtOAc/MeOH, 5% → 10%); ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, J = 6.4 Hz, 2H), 8.19 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 6.4 Hz, 2H), 4.09 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 172.4, 169.4, 146.3, 141.9, 133.0 (q, J = 32.1 Hz), 129.6, 125.9 (q, J = 3.8 Hz), 125.6 (q, J = 271.3 Hz), 113.6, 58.0. HRMS (ESI) calcd for $C_{14}H_{12}F_3N_2O_2$ $[M + H]^+$ 297.0845, found 297.0851.



(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(2-fluorobenzoyl)amide (SM27). General procedure was used with 2-fluorobenzoic acid (0.56 g, 4 mmol). Yield: 0.72 g, 66%; appearance: white solid; mp 175−176 °C (EtOAc/MeOH =10:1); R_f = 0.51 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 6.5 Hz, 2H), 7.89 (t, J = 7.2 Hz, 1H), 7.63 (d, J = 6.5 Hz, 2H), 7.39 – 7.30 (m, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 9.4 Hz, 1H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.8, 163.4, 160.8 (d, J = 251.3 Hz), 142.8, 130.9, 130.9 (d, J = 11.4 Hz), 126.4 (d, J = 13.3 Hz), 123.8 (d, J = 3.5 Hz),123.2, 116.4 (d, J = 23.2 Hz), 35.9, 30.4. HRMS (ESI) calcd for $C_{16}H_{18}FN_2O$ $[M + H]^+$ 273.1398, found 273.1404.

General Procedure for Copper-mediated C-H Amination with Azoles.

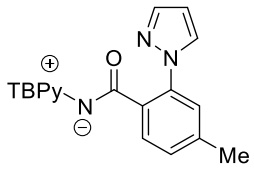
A 2-dram vial equipped with a magnetic stir bar was charged with the pyridinium ylide (0.4 mmol), copper acetate (0.8 - 1.2 mmol), azole (1.2 - 1.8 mmol) and perfluoro-*tert*-butyl alcohol (1 mL). After closing the vial with a screw cap, the mixture was vigorously stirred in a heating block at 100 - 120 °C for 48 - 72 h. After cooling the mixture, ethyl acetate was added, and the diluted mixture was poured into a saturated aqueous solution of EDTA (50 mL). The resulting mixture was stirred at 50 °C for 30 min and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

Procedure for Copper-mediated C-H Amination and Solvent Recovery.

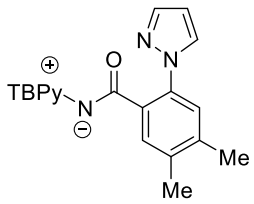
To a 25 mL round bottom pressure flask was charged with SM04 (1.2 mmol, 322 mg), $Cu(OAc)_2$ (3.6 mmol, 654 mg), pyrazole (5.4 mmol, 368 mg) and perfluoro-*tert*-butyl alcohol (3 mL). After closing the tube, the mixture was vigorously stirred in a heating block at 110 °C for 48 h. After cooling the mixture, perfluoro-*tert*-butyl alcohol was recovered by distillation (82%, 4.2 g). To the residue was added aqueous solution of EDTA (100 mL) and ethyl acetate (50 mL). The resulting mixture was stirred at 50 °C for 30 min and extracted with ethyl acetate (3 × 60 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution, EtOAc/MeOH, 0% → 10%) to give the product **13** (72%, 289 mg).[40]

Procedure for C-H Amination with Catalytic Amount of $Cu(OAc)_2$ under an Oxygen Atmosphere.

A 2-dram vial equipped with a magnetic stir bar was charged with SM04 (0.4 mmol, 107 mg), copper acetate (0.08 mmol, 15 mg), pyrazole (123 mg) and perfluoro-*tert*-butyl alcohol (1 mL). After closing the vial charged with oxygen gas, the mixture was vigorously stirred in a heating block at 110 °C for 48 h. After cooling the mixture, ethyl acetate was added, and the diluted mixture was poured into a saturated aqueous solution of EDTA (50 mL). The resulting mixture was stirred at 50 °C for 30 min and extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Yields of SM04 (37%) and the product (Table 2.2, entry 1) (34%) were determined by ^1H NMR with 1,3,5-trimethoxybenzene as the internal standard.[14]

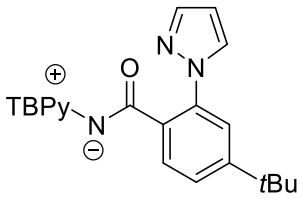


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-methyl-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 1, 1-1). SM04 (0.4 mmol, 107 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 48 h; white solid; mp 220−221 °C (EtOAc/MeOH =20:1); 74% yield (99 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.49 (EtOAc/MeOH = 7/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 7.2 Hz, 2H), 7.89 (dd, J = 2.4, 0.5 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.39 (s, 1H), 7.22 – 7.16 (m, 1H), 6.40 – 6.32 (m, 1H), 2.40 (s, 3H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.1, 163.1, 142.4, 140.2, 139.4, 138.2, 131.7, 130.7, 129.3, 128.3, 125.6, 123.2, 106.2, 35.8, 30.3, 21.3; HRMS (ESI) calcd for $C_{20}H_{23}N_4O$ [M + H]+ 335.1866, found 335.1872.

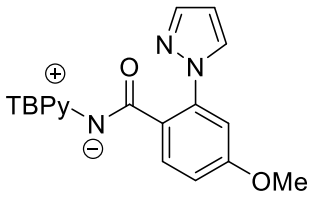


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4,5-dimethyl-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 2). SM11 (0.4 mmol, 113 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 72 h; pale yellow solid; mp 195−196 °C (EtOAc/MeOH =20:1); 60% yield (84 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.57 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 7.1 Hz, 2H), 7.84 (d, J = 2.3 Hz, 1H), 7.64 (d, J = 1.5 Hz, 1H), 7.55 − 7.46 (m, 3H), 7.32 (s, 1H), 6.32 (t, J = 2.0 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.9, 162.8, 142.3, 139.9, 137.7, 136.0,

136.0, 131.7, 130.7, 130.2, 126.0, 123.1, 105.8, 35.6, 30.2, 19.5, 19.3. HRMS (ESI) calcd for $C_{21}H_{25}N_4O$ $[M + H]^+$ 349.2023, found 349.2028.

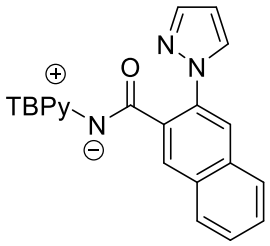


(4-(*tert*-Butyl)-2-(1H-pyrazol-1-yl)benzoyl)(4-(*tert*-butyl)-pyridin-1-ium-1-yl)amide (Table 2.2, Entry 3). SM12 (0.4 mmol, 124 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 100 °C for 72 h; white solid; mp 195−196 °C (EtOAc); 75% yield (113 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.63 (EtOAc/MeOH = 7/1);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 6.4 Hz, 2H), 7.89 (d, J = 2.2 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.58 – 7.49 (m, 3H), 7.40 (d, J = 8.1 Hz, 1H), 6.35 (t, J = 2.0 Hz, 1H), 1.31 (s, 9H), 1.30 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.0, 163.0, 152.7, 142.4, 140.1, 138.0, 131.9, 130.8, 129.0, 124.8, 123.2, 122.2, 106.1, 35.7, 34.9, 31.3, 30.3. HRMS (ESI) calcd for $C_{23}H_{29}N_4O$ $[M + H]^+$ 377.2336, found 377.2342.

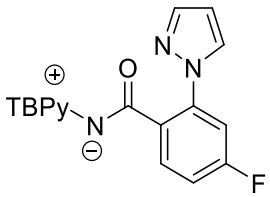


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-methoxy-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 4). SM13 (0.4 mmol, 114 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 72 h; pale yellow solid; mp 195−196 °C (EtOAc); 67% yield (94 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.10 (EtOAc/MeOH = 7/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (d, J = 7.1 Hz, 2H), 7.89 (d, J = 2.2 Hz, 1H), 7.76 – 7.66 (m, 2H), 7.56 (d, J = 7.1 Hz, 2H), 7.11 (d, J = 2.5 Hz, 1H), 6.93 (dd, J = 8.5, 2.5 Hz, 1H), 6.37 (t, J = 2.0 Hz, 1H),

3.85 (s, 3H), 1.35 (s, 9H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 171.8, 163.0, 160.3, 142.4, 140.3, 139.6, 130.9, 130.8, 127.0, 123.2, 114.0, 110.1, 106.3, 55.7, 35.8, 30.3. HRMS (ESI) calcd for $C_{20}H_{23}N_4O_2$ $[M + H]^+$ 351.1816, found 351.1821.

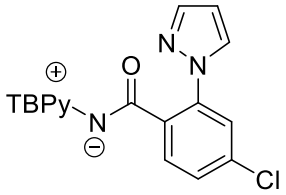


(3-(1H-Pyrazol-1-yl)-2-naphthoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (Table 2.2, Entry 5). SM14 (0.4 mmol, 122 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 72 h; pale yellow solid; mp 84−86 °C (EtOAc); 61% yield (90 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.57 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 7.1 Hz, 2H), 8.26 (s, 1H), 8.01 (s, 1H), 7.99 (d, J = 2.2 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.86 – 7.80 (m, 1H), 7.74 (d, J = 1.5 Hz, 1H), 7.56 – 7.43 (m, 4H), 6.41 (t, J = 2.0 Hz, 1H), 1.28 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.9, 163.1, 142.4, 140.4, 136.4, 133.2, 133.2, 132.2, 130.8, 129.2, 128.1, 127.8, 127.0, 126.5, 123.2, 123.2, 106.4, 35.6, 30.2. HRMS (ESI) calcd for $C_{23}H_{23}N_4O$ $[M + H]^+$ 371.1866, found 371.1878.

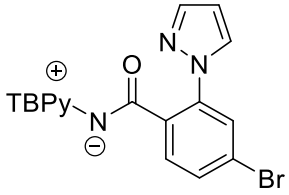


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-fluoro-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 6). SM15 (0.4 mmol, 109 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 72 h; white solid; mp 171−173 °C (EtOAc/MeOH =20:1); 64% yield (87 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.60 (EtOAc/MeOH = 7/1); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.2 Hz, 2H), 7.92 (d, J = 2.4 Hz, 1H), 7.75 – 7.71 (m, 1H), 7.70 – 7.68 (m, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.33 (dd, J = 9.6, 2.5 Hz, 1H), 7.07 (td, J = 8.3, 2.6 Hz, 1H), 6.41 – 6.33 (m, 1H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.4, 163.4, 162.5 (d, J = 248.0 Hz), 142.3, 140.8, 139.6 (d, J = 10.3 Hz), 131.2 (d, J = 9.3 Hz), 130.6, 130.3 (d, J = 3.4 Hz), 123.3, 114.3 (d, J = 21.1 Hz), 112.1 (d, J = 24.6 Hz), 106.8, 35.8, 30.3. HRMS (ESI) calcd for $C_{19}H_{20}FN_4O$ $[M + H]^+$ 339.1616, found 339.1620.

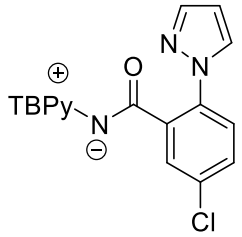


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-chloro-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 7). SM16 (0.4 mmol, 116 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 72 h; pale yellow solid; mp 179−181 °C (EtOAc); 65% yield (92 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.60 (EtOAc/MeOH = 7/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.2 Hz, 2H), 7.91 (dd, J = 2.4, 0.6 Hz, 1H), 7.70 (dd, J = 1.8, 0.5 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.35 (dd, J = 8.2, 2.1 Hz, 1H), 6.39 (dd, J = 2.4, 1.8 Hz, 1H), 1.36 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.2, 163.5, 142.3, 140.8, 139.2, 134.6, 132.8, 130.7, 130.7, 127.6, 125.1, 123.4, 106.8, 35.9, 30.3. HRMS (ESI) calcd for $C_{19}H_{20}ClN_4O$ $[M + H]^+$ 355.1320, found 355.1328.

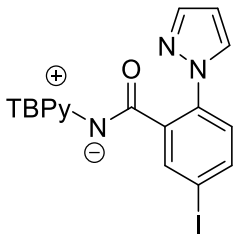


(4-Bromo-2-(1H-pyrazol-1-yl)benzoyl)(4-(*tert*-butyl)pyri-din-1-ium-1-yl)amide (Table 2.2, Entry 8). SM17 (0.4 mmol, 133 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123

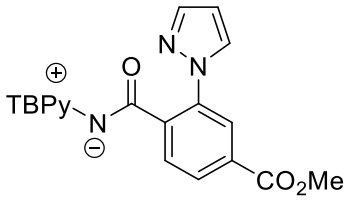
mg), 120 °C for 72 h; white solid; mp 193−195 °C (EtOAc/MeOH =20:1); 56% yield (89 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.67 (EtOAc/MeOH = 7/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 6.3 Hz, 2H), 7.90 (s, 1H), 7.76 (s, 1H), 7.69 (s, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 6.3 Hz, 2H), 7.49 (d, J = 8.2z Hz, 1H), 6.37 (s, 1H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.2, 163.5, 142.2, 140.8, 139.2, 133.2, 130.9, 130.6, 130.4, 127.9, 123.3, 122.4, 106.8, 35.8, 30.3. HRMS (ESI) calcd for $C_{19}H_{20}BrN_4O$ $[M + H]^+$ 399.0815, found 339.0820.



(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(5-chloro-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 9). SM18 (0.4 mmol, 116 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 72 h; pale yellow solid; mp 102−104 °C (EtOAc); 54% yield (77 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.72 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.1 Hz, 2H), 7.87 (d, J = 2.3 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.66 (d, J = 1.4 Hz, 1H), 7.54 (d, J = 7.1 Hz, 2H), 7.48 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 8.5, 2.4 Hz, 1H), 6.35 (t, J = 2.0 Hz, 1H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6, 163.4, 142.1, 140.5, 136.8, 135.8, 133.0, 130.5, 129.4, 129.0, 126.2, 123.3, 106.6, 35.7, 30.2. HRMS (ESI) calcd for $C_{19}H_{20}ClN_4O$ $[M + H]^+$ 355.1320, found 355.1324.

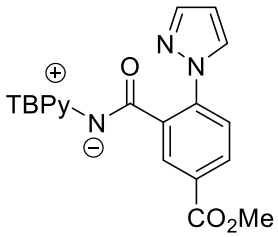


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(5-iodo-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 10). SM19 (0.4 mmol, 152 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 72 h; white solid; mp 144−146 °C (EtOAc); 47% yield (84 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.63 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.0 Hz, 2H), 8.05 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.4, 2.0 Hz, 1H), 7.69 (s, 1H), 7.57 (d, J = 7.1 Hz, 2H), 7.31 (d, J = 8.4 Hz, 1H), 6.37 (s, 1H), 1.35 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.5, 163.6, 142.2, 140.7, 138.2, 138.1, 138.0, 136.2, 130.5, 126.6, 123.3, 106.8, 92.4, 35.8, 30.3. HRMS (ESI) calcd for $C_{19}H_{20}IN_4O$ [M + H]$^+$ 447.0676, found 447.0680.

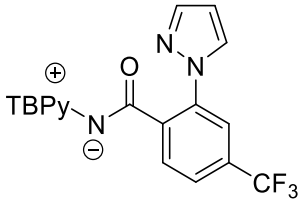


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-(methoxycarbonyl)-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 11). SM20 (0.4 mmol, 125 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 120 °C for 72 h; pale yellow solid; mp 166−167 °C (EtOAc); 47% yield (71 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.54 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.0 Hz, 2H), 8.22 (d, J = 1.5 Hz, 1H), 8.04 (dd, J = 7.9, 1.5 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.58 (d, J = 7.1 Hz, 2H), 6.39 (t, J = 2.0 Hz, 1H), 3.91 (s, 3H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$)

δ 171.3, 166.2, 163.6, 142.3, 140.8, 138.7, 138.4, 130.9, 130.6, 129.7, 128.6, 126.0, 123.4, 106.8, 52.4, 35.9, 30.3. HRMS (ESI) calcd for $C_{21}H_{23}N_4O_3$ $[M + H]^+$ 379.1765, found 379.1768.

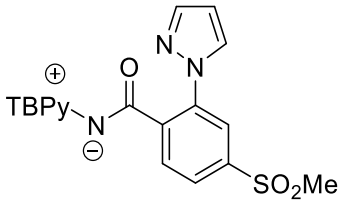


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(5-(methoxycarbonyl)-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 12). SM21 (0.4 mmol, 125 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 110 °C for 72 h; pale yellow sticky solid; 46% yield (70 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.60 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 7.1 Hz, 2H), 8.42 (d, J = 1.8 Hz, 1H), 8.10 (dd, J = 8.4, 1.9 Hz, 1H), 8.01 (d, J = 2.3 Hz, 1H), 7.73 (d, J = 1.3 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.0 Hz, 2H), 6.45 – 6.35 (m, 1H), 3.92 (s, 3H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.5, 166.3, 163.6, 142.3, 141.5, 141.1, 133.9, 131.3, 130.6, 130.4, 128.7, 124.4, 123.4, 107.1, 52.3, 35.9, 30.3. HRMS (ESI) calcd for $C_{21}H_{23}N_4O_3$ $[M + H]^+$ 379.1765, found 379.1768.

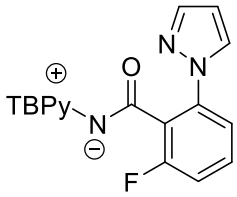


(2-(1H-Pyrazol-1-yl)-4-(trifluoromethyl)benzoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (Table 2.2, Entry 13). SM22 (0.4 mmol, 113 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 120 °C for 72 h; pale yellow solid; mp 146−148 °C (EtOAc); 67% yield (104 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.69 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 7.2 Hz, 2H), 7.97 (d, J = 2.0 Hz, 1H), 7.91 – 7.87 (m, 1H),

7.84 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 1.3 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.59 (d, *J* = 7.2 Hz, 2H), 6.43 – 6.37 (m, 1H), 1.35 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) *δ* 170.9, 163.7, 142.2, 141.0, 138.4, 137.6, 131.2 (q, *J* = 32.8 Hz), 130.6, 130.1, 124.0 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.4 Hz), 123.4, 121.9 (q, *J* = 3.9 Hz), 107.0, 35.8, 30.2. HRMS (ESI) calcd for $C_{20}H_{20}F_3N_4O$ $[M + H]^+$ 389.1584, found 389.1589.

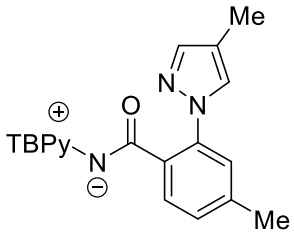


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-(methylsulfonyl)-2-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 14). SM23 (0.4 mmol, 133 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 120 °C for 72 h; pale orange solid; mp 93−95 °C (EtOAc); 36% yield (57 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.25 (EtOAc/MeOH = 1/7); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.45 (d, *J* = 6.9 Hz, 2H), 8.16 (s, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.97 – 7.85 (m, 2H), 7.72 (s, 1H), 7.61 (d, *J* = 6.9 Hz, 2H), 6.41 (s, 1H), 3.06 (s, 3H), 1.35 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) *δ* 170.6, 164.1, 142.2, 141.4, 141.0, 139.3, 138.9, 130.8, 130.7, 126.0, 123.9, 123.5, 107.4, 44.7, 35.9, 30.3. HRMS (ESI) calcd for $C_{20}H_{23}N_4O_3S$ $[M + H]^+$ 399.1485, found 399.1492.

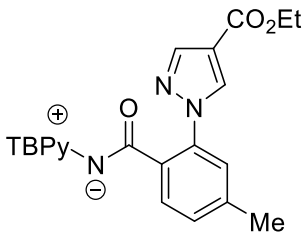


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(2-fluoro-6-(1H-pyrazol-1-yl)benzoyl)amide (Table 2.2, Entry 15). SM27 (0.4 mmol, 109 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), pyrazole (1.8 mmol, 123 mg), 120 °C for 72 h; pale yellow solid; mp 142−144 °C (EtOAc); 53% yield (72 mg); purification

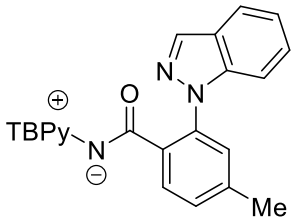
(gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.46 (EtOAc/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 6.2 Hz, 2H), 8.07 (s, 1H), 7.69 (s, 1H), 7.58 (d, J = 6.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.09 (t, J = 8.3 Hz, 1H), 6.37 (s, 1H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.7, 160.2 (d, J = 246.7 Hz), 163.9, 142.3, 140.8, 139.2 (d, J = 6.7 Hz), 130.5, 129.3 (d, J = 9.3 Hz), 123.4, 123.0 (d, J = 22.8 Hz), 119.9 (d, J = 3.2 Hz), 114.6 (d, J = 22.4 Hz), 106.8, 35.8, 30.3. HRMS (ESI) calcd for $C_{19}H_{20}FN_4O$ [M + H]$^+$ 339.1616, found 339.1622.



(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-methyl-2-(4-methyl-1H-pyrazol-1-yl)benzoyl)amide (Table 2.3, Entry 1). SM04 (0.4 mmol, 107 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), 4-methylpyrazole (1.8 mmol, 148 mg), 110 °C for 48 h; white solid; mp 206−207 °C (EtOAc/MeOH =20:1); 74% yield (103 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.57 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 7.0 Hz, 2H), 7.66 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.0 H, 2H), 7.49 (s, 1H), 7.35 (s, 1H), 7.16 (d, J = 7.8 Hz, 1H), 2.38 (s, 3H), 2.11 (s, 3H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.4, 163.1, 142.5, 141.0, 139.3, 138.3, 131.3, 129.3, 129.2, 127.9, 125.2, 123.2, 116.6, 35.8, 30.3, 21.3, 9.2. HRMS (ESI) calcd for $C_{21}H_{25}N_4O$ [M + H]$^+$ 349.2023, found 349.2023.

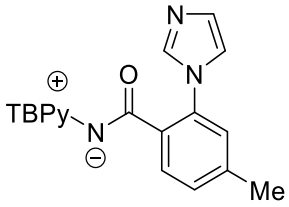


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(2-(4-(ethoxycarbonyl)-1H-pyrazol-1-yl)-4-methylbenzoyl)amide (Table 2.3, Entry 2). SM04 (0.4 mmol, 107 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), ethyl 4-pyrazolecarboxylate (1.8 mmol, 252 mg), 110 °C for 48 h; white solid; mp 175−176 °C (EtOAc); 54% yield (88 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.68 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 7.2 Hz, 2H), 8.39 – 8.32 (m, 1H), 8.09 – 8.01 (m, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.35 (s, 1H), 7.25 – 7.17 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.33 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.5, 163.4, 163.3, 142.4, 141.5, 139.8, 137.4, 134.1, 131.8, 129.7, 129.2, 125.6, 123.3, 115.7, 60.2, 35.8, 30.3, 21.2, 14.6. HRMS (ESI) calcd for $C_{23}H_{27}N_4O_3$ $[M + H]^+$ 407.2078, found 407.2084.

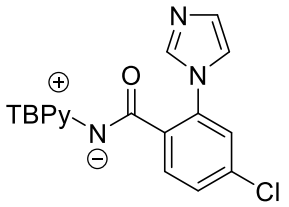


(2-(1H-Indazol-1-yl)-4-methylbenzoyl)(4-(*tert*-butyl)pyr-idin-1-ium-1-yl)amide (Table 2.3, Entry 3). SM04 (0.4 mmol, 107 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), indazole (1.8 mmol, 213 mg), 110 °C for 48 h; white solid; mp 177−178 °C (EtOAc); 67% yield (103 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.66 (EtOAc/MeOH = 7/1); ^{1}H NMR (600 MHz,$CDCl_3$) δ 8.21 – 8.16 (m, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.36 (d, J = 7.2 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.16 (t, J = 7.4 Hz, 1H), 2.45 (s, 3H), 1.28 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.3, 162.8, 142.4, 140.8, 140.2, 137.2, 134.3, 132.8, 130.3, 129.0, 127.8, 126.4, 124.3, 123.0, 120.9,

120.7, 110.8, 35.7, 30.3, 21.3. HRMS (ESI) calcd for $C_{24}H_{25}N_4O$ $[M + H]^+$ 385.2023, found 385.2026.

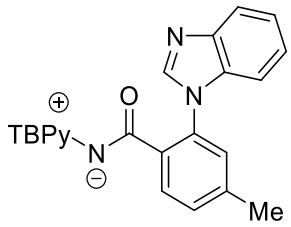


(2-(1H-Imidazol-1-yl)-4-methylbenzoyl)(4-(*tert*-butyl)pyrid-in-1-ium-1-yl)amide (Table 2.3, Entry 4). SM04 (0.4 mmol, 107 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), imidazole (1.8 mmol, 123 mg), 120 °C for 48 h; pale yellow solid; mp 180−181 °C (EtOAc); 23% yield (31 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.23 (EtOAc/MeOH = 7/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 7.2 Hz, 2H), 7.79 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.29 – 7.22 (m, 2H), 7.19 – 7.05 (m, 2H), 2.40 (s, 3H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.3, 163.4, 142.5, 139.7, 138.3 (br), 135.0, 133.4, 129.5, 129.2, 128.7 (br), 126.3, 123.3, 121.3 (br), 35.8, 30.3, 21.3. HRMS (ESI) calcd for $C_{20}H_{23}N_4O$ $[M + H]^+$ 335.1866, found 335.1875.



(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-chloro-2-(1H-imidazol-1-yl)benzoyl)amide (Table 2.3, Entry 5). SM16 (0.4 mmol, 116 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), imidazole (1.8 mmol, 123 mg), 120 °C for 48 h; pale yellow solid; mp 171−173 °C (EtOAc); 41% yield (58 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.69 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 6.0 Hz, 2H), 7.80 (s, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 6.0

Hz, 2H), 7.42 (d, J = 8.3 Hz, 1H), 7.34 (s, 1H), 7.24 (s, 1H), 7.14 (s, 1H), 1.34 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.3, 163.8, 142.3, 136.1, 134.8, 134.8, 130.9, 129.2, 128.6, 125.8, 123.4, 121.0, 35.9, 30.3. One carbonsignal could not be located. HRMS (ESI) calcd for $C_{19}H_{20}ClN_4O$ $[M + H]^+$ 355.1320, found 355.1325.

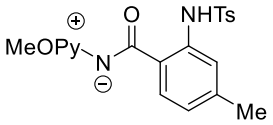


(2-(1H-Benzo[d]imidazol-1-yl)-4-methylbenzoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (Table 2.3, Entry 6). SM04 (0.4 mmol, 107 mg), $Cu(OAc)_2$ (1.2 mmol, 218 mg), benzimidazole (1.8 mmol, 213 mg), 120 °C for 72 h; pale yellow solid; mp 139−141 °C (EtOAc); 45% yield (69 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.43 (EtOAc/MeOH = 7/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.79 (d, J = 7.2 Hz, 2H), 7.47 – 7.35 (m, 4H), 7.34 – 7.24 (m, 3H), 2.47 (s, 3H), 1.30 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.7, 163.2, 144.3 (br), 143.2 (br), 142.3, 140.4, 135.7 (br), 133.9, 133.4, 130.6, 129.7, 127.5, 123.3, 123.2, 122.1, 120.0, 111.1, 35.7, 30.3, 21.3. HRMS (ESI) calcd for $C_{24}H_{25}N_4O$ $[M + H]^+$ 385.2023, found 385.2029.

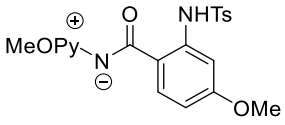
General Procedure for Copper-mediated C-H Amination with Sulfonamides.

A 2-dram vial equipped with a magnetic stir bar was charged with pyridinium ylide (0.4 mmol), copper acetate (0.52 mmol), sulfonamide (0.8 mmol), and 2,2,2-trifluoroethanol (1 mL). After closing the vial with a screw cap, the mixture was vigorously stirred in a heating block at 100 °C for 48 h. After cooling the mixture, ethyl acetate was added (40 mL) and the diluted mixture was

poured into a saturated aqueous solution of EDTA (50 mL). The resulting mixture was stirred at 60 °C for 30 min. After cooling the mixture, the product was extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

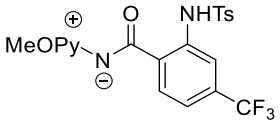


(4-Methoxypyridin-1-ium-1-yl)(4-methyl-2-((4-methylphen-yl)sulfonamido)benzoyl) amide (Table 2.5, Entry 1). SM02 (0.4 mmol, 97 mg), $Cu(OAc)_2$ (0.52 mmol, 94 mg), *p*-toluenesulfonamide (0.8 mmol, 137 mg), 100 °C for 48 h; white solid; mp 211−212 °C (EtOAc/MeOH =20:1); 60% yield (99 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.21 (EtOAc/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 7.6 Hz, 2H), 7.97 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.43 (t, J = 1.2 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.5 Hz, 2H), 6.82 (d, J = 7.6 Hz, 1H), 4.02 (s, 3H), 2.33 (s, 3H), 2.30 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.6, 166.7, 145.0, 143.2, 141.7, 138.9, 137.4, 130.0, 129.5, 127.3, 123.8, 120.7, 119.6, 111.8, 57.2, 21.8, 21.6. HRMS (ESI) calcd for $C_{21}H_{22}N_3O_4S$ $[M + H]^+$ 412.1326, found 412.1332.

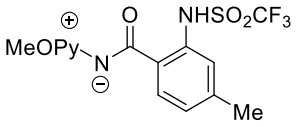


(4-Methoxy-2-((4-methylphenyl)sulfonamido)benzoyl)(4-methoxypyridin-1-ium-1-yl)amide (Table 2.5, Entry 2). SM25 (0.4 mmol, 103 mg), $Cu(OAc)_2$ (0.52 mmol, 94 mg), *p*-toluenesulfonamide (0.8 mmol, 137 mg), 100 °C for 48 h; pale yellow solid; mp 124−126 °C (EtOAc/MeOH =20:1); 56% yield (96 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.19 (EtOAc/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 7.2 Hz, 2H),

8.03 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.21 – 7.13 (m, 3H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.53 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.99 (s, 3H), 3.77 (s, 3H), 2.32 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.4, 166.7, 161.8, 145.0, 143.3, 140.6, 137.3, 131.6, 129.5, 127.3, 115.7, 111.8, 109.0, 103.5, 57.2, 55.4, 21.6. HRMS (ESI) calcd for $C_{21}H_{22}N_3O_5S$ $[M + H]^+$ 428.1275, found 428.1280.

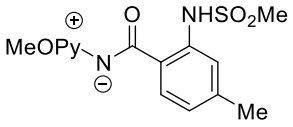


(4-Methoxypyridin-1-ium-1-yl)(2-((4-methylphenyl)sulfon-amido)-4-(trifluoromethyl) benzoyl)amide (Table 2.5, Entry 3). SM26 (0.4 mmol, 118 mg), $Cu(OAc)_2$ (0.52 mmol, 94 mg), *p*-toluenesulfonamide (0.8 mmol, 137 mg), 100 °C for 48 h; white solid; mp 207−209 °C (EtOAc/MeOH =20:1); 44% yield (82 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.28 (EtOAc/MeOH = 10/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.2 Hz, 2H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.89 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.4 Hz, 2H), 4.03 (s, 3H), 2.32 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.4, 167.1, 144.8, 143.8, 139.4, 136.8, 132.7 (q, *J* = 32.6 Hz), 130.9, 129.7, 127.3, 126.3, 123.8 (q, *J* = 272.6 Hz), 119.0 (q, *J* = 3.6 Hz), 115.6 (q, *J* = 4.1 Hz), 112.0, 57.3, 21.6. HRMS (ESI) calcd for $C_{21}H_{19}F_3N_3O_4S$ $[M + H]^+$ 466.1043, found 466.1052.

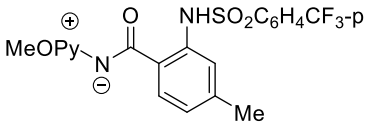


(4-Methoxypyridin-1-ium-1-yl)(4-methyl-2-((trifluorometh-yl)sulfonamido)benzoyl) amide (Table 2.5, Entry 4). SM02 (0.4 mmol, 97 mg), $Cu(OAc)_2$ (0.52 mmol, 94 mg), Trifluoromethanesulfonamide (0.8 mmol, 119 mg), 100 °C for 48 h; pale yellow solid; mp 113−115 °C (EtOAc); 53% yield (83 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.34 (EtOAc/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.6 Hz, 2H),

8.09 (d, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 7.3 Hz, 1H), 4.03 (s, 3H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.3, 167.3, 145.0, 142.6, 138.4, 129.8, 124.8, 120.3 (q, *J* = 323.8 Hz), 119.8, 119.3, 112.0, 57.3, 21.9. HRMS (ESI) calcd for $C_{15}H_{15}F_3N_3O_4S$ $[M + H]^+$ 390.0730, found 390.0736.

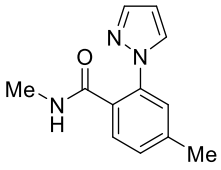


(4-Methoxypyridin-1-ium-1-yl)(4-methyl-2-(methylsulfon-amido)benzoyl)amide (Table 2.5, Entry 5). SM02 (0.4 mmol, 97 mg), $Cu(OAc)_2$ (0.52 mmol, 94 mg), methanesulfonamide (0.8 mmol, 76 mg), 110 °C for 48 h; pale greenish solid; mp 198−199 °C (EtOAc); 38% yield (51 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.12 (EtOAc/MeOH = 10/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.33 (s, 1H), 8.43 (d, *J* = 7.6 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 3H), 2.98 (s, 3H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 171.6, 166.7, 145.0, 142.2, 139.2, 130.4, 124.0, 120.5, 119.0, 111.8, 57.2, 39.3, 21.8. HRMS (ESI) calcd for $C_{15}H_{18}N_3O_4S$ $[M + H]^+$ 336.1013, found 336.1017.

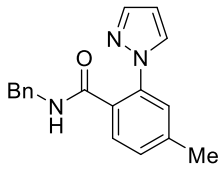


(4-Methoxypyridin-1-ium-1-yl)(4-methyl-2-((4-(trifluoro-methyl)phenyl)sulfonamido) benzoyl)amide (Table 2.5, Entry 6). SM02 (0.4 mmol, 97 mg), $Cu(OAc)_2$ (0.52 mmol, 94 mg), 4-(trifluoromethyl)benzenesulfonamide (0.8 mmol, 180 mg), 110 ℃ for 48 h; pale greenish solid; mp 212−213 °C (EtOAc/MeOH =10:1); 52% yield (97 mg); purification (gradient elution, EtOAc/MeOH, 0% → 10%); R_f = 0.37 (EtOAc/MeOH = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 6.6 Hz, 2H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.44 (s, 1H), 7.11 (d, *J* = 6.7 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.03 (s, 3H), 2.32 (s, 3H).

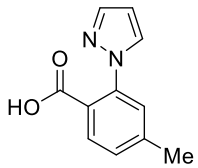
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.7, 166.8, 144.9, 144.0, 142.0, 138.6, 134.0 (q, J = 33.2 Hz), 130.0, 127.8, 126.0 (q, J = 3.7 Hz), 124.3, 123.4 (q, J = 272.5 Hz), 120.6, 119.7, 111.8, 57.2, 21.8. HRMS (ESI) calcd for $C_{21}H_{19}F_3N_3O_4S$ $[M + H]^+$ 466.1043, found 466.1052.



***N*,4-Dimethyl-2-(1H-pyrazol-1-yl)benzamide (2-2).** To a 25 mL round bottomed flask was added **2-1** (100 mg, 0.3 mmol), acetone (10 mL), and methyl iodide (0.19 mL, 3 mmol). The mixture was refluxed for 16 h. After cooling, volatile materials were removed under vacuum. To the residue was added acetic acid (2 mL) and zinc dust (196 mg, 3 mmol) and mixture was stirred at 60 °C for 3 h. After completion, the mixture was filtered through Celite® and residue was washed with EtOAc. Organic filtrates were combined and evaporated to dryness. Sodium bicarbonate (20 mL of a saturated aqueous solution) was added to the residue and mixture extracted with EtOAc (3 × 20 mL). The extracts were dried over $MgSO_4$, filtered, evaporated, and residue was purified by column chromatography (gradient elution, hexanes/EtOAc, 50% → 80%) to give the product (49 mg, 76%); pale yellow solid; mp 99−100 °C (diethyl ether); R_f = 0.20 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 6.48 – 6.38 (m, 1H), 6.28 (s, 1H), 2.74 (d, J = 4.8 Hz, 3H), 2.41 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 167.6, 141.6, 141.1, 137.4, 131.7, 129.9, 129.8, 129.6, 127.0, 107.3, 26.8, 21.3. HRMS (ESI) calcd for $C_{12}H_{13}N_3ONa$ $[M + Na]^+$ 238.0951, found 238.0956.



***N*-Benzyl-4-methyl-2-(1H-pyrazol-1-yl)benzamide (2-3).** To a 25 mL round bottomed flask was added **2-1** (100 mg, 0.3 mmol), acetone (10 mL), and benzyl bromide (0.11 mL, 0.9 mmol). The mixture was refluxed for 16 h. After cooling, volatile materials were removed under vacuum. To the residue was added acetic acid (2 mL) and zinc dust (196 mg, 3 mmol) and mixture was stirred at 60 °C for 3 h. After completion, the mixture was filtered through Celite® and residue was washed with EtOAc. Organic filtrates were combined and evaporated to dryness. Sodium bicarbonate (20 mL of a saturated aqueous solution) was added to the residue and the mixture was extracted with EtOAc (3 × 20 mL). The extracts were dried over $MgSO_4$, filtered, evaporated, and residue was purified by column chromatography (gradient elution, hexanes/EtOAc, 10% → 30%) to give the product (66 mg, 75%); pale yellow solid; mp 89−90 °C (diethyl ether); R_f = 0.20 (hexanes/EtOAc = 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.30 – 7.21 (m, 4H), 7.18 (s, 1H), 7.10 (d, J = 6.9 Hz, 2H), 6.63 (s, 1H), 6.34 (s, 1H), 4.38 (d, J = 5.4 Hz, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.7, 141.8, 141.1, 137.7, 137.4, 131.7, 130.1, 129.8, 129.6, 128.6, 128.0, 127.5, 127.2, 107.3, 44.2, 21.2. HRMS (ESI) calcd for $C_{18}H_{18}N_3O$ $[M + H]^+$ 292.1444, found 292.1453.

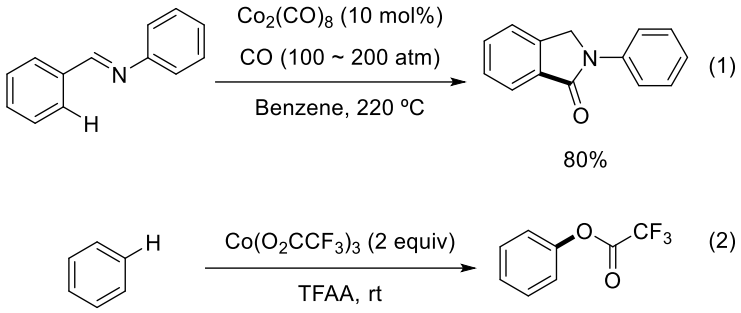


4-Methyl-2-(1H-pyrazol-1-yl)benzoic acid (2-4). To a 25 mL round bottomed flask was added **2-1** (100 mg, 0.3 mmol), acetone (10 mL), and methyl iodide (0.19 mL, 3 mmol). The mixture was

refluxed for 16 h. After cooling, volatile materials were removed under vacuum. The residue was dissolved in THF (5 mL) and water (5 mL), and LiOH (72 mg, 3 mmol) was added to the solution. The mixture was refluxed at 90 °C for 5 h. After cooling the mixture, water (10 mL) and 6 N HCl(aq) (0.8 mL) were added and the mixture was extracted with EtOAc (2 × 20 mL). The extracts were dried over $MgSO_4$, filtered, evaporated, and the solid was washed with a mixture of diethyl ether and hexanes (1:5, 2 mL) to afford the product (45 mg, 74%). pale orange solid; mp 163−164 °C (DCM); R_f = 0.20 (EtOAc/AcOH = 100/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (br, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.75 (s, 1H), 7.74 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 6.47 (s, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.2, 144.2, 140.9, 139.0, 132.6, 131.4, 129.1, 126.8, 123.9, 107.5, 21.5. HRMS (ESI) calcd for $C_{11}H_{11}N_2O_2$ $[M + H]^+$ 203.0815, found 203.0815.

CHAPTER 3: *N*-Iminopyridinium Ylide-Directed, Cobalt-Catalyzed Coupling of sp^2 C–H Bonds with Alkynes

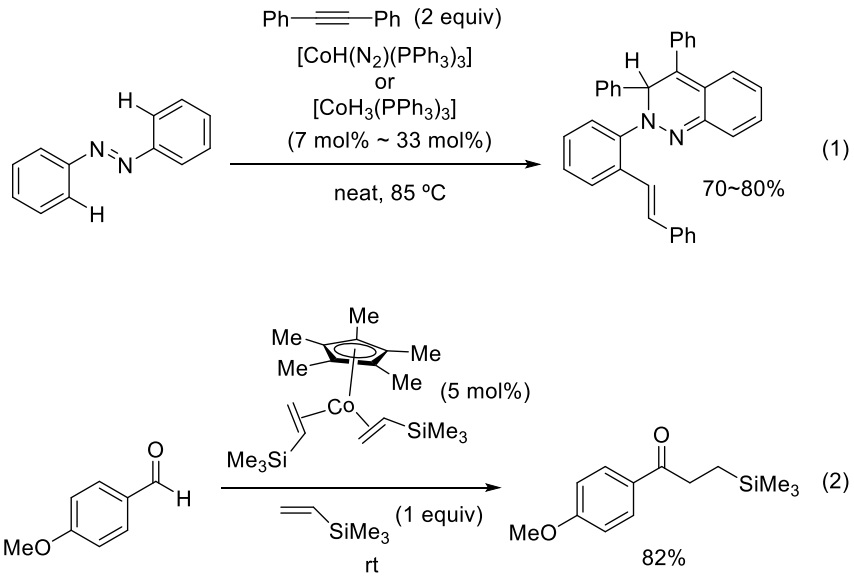
First-row transition-metal, and more specifically, cobalt-catalyzed carbon-hydrogen bond functionalization has received substantial attention in recent years.[29a, 41] Compared to their 4d and 5d analogues, non-noble transition metals are more abundant, cheap and less toxic. Additionally, the reaction manifolds accessible by 3d transition metals sometimes differ from those catalyzed by their 4d and 5d counterparts.[29a]



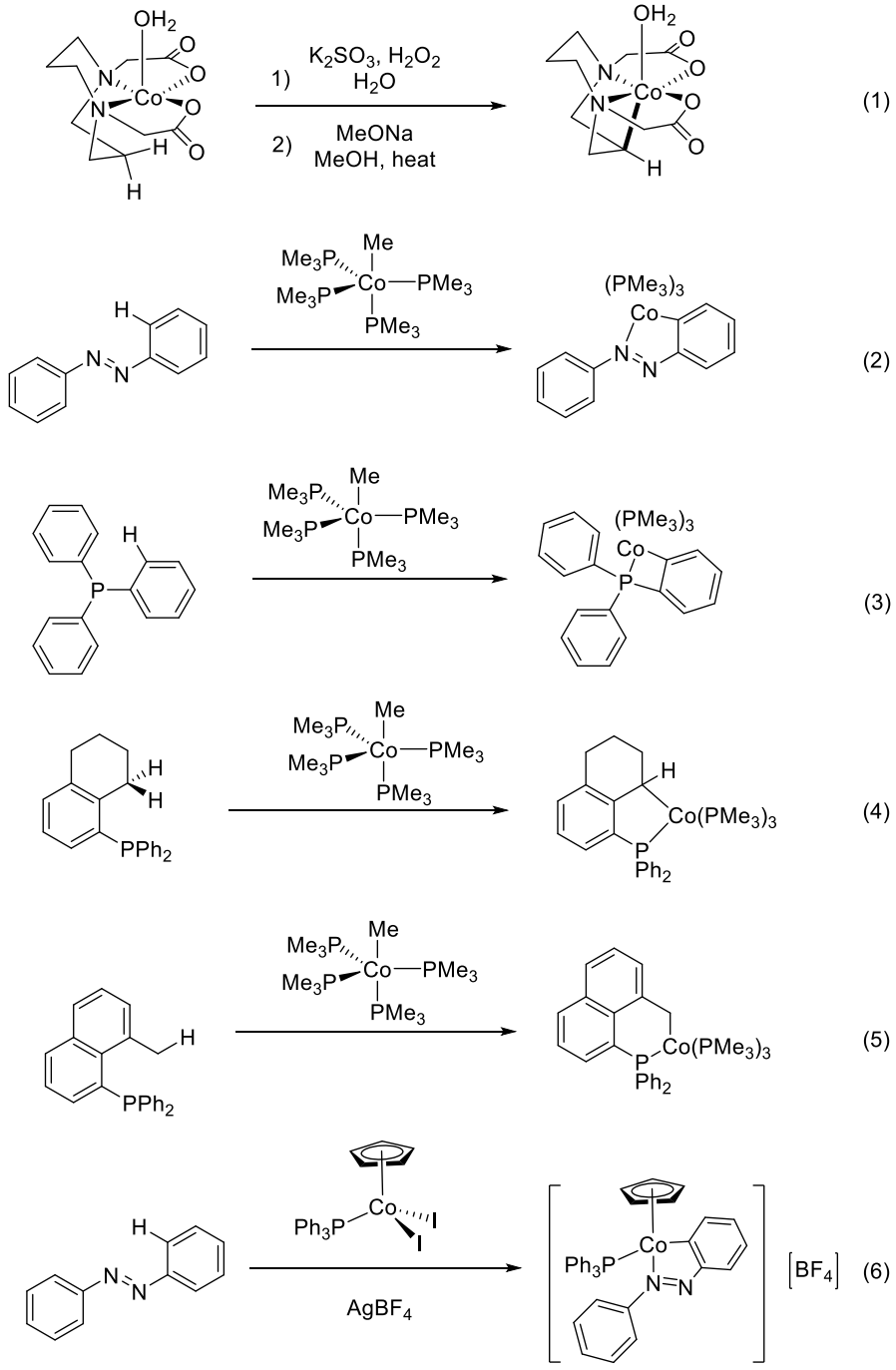
Scheme 3.1 First reports on cobalt C−H functionalization

In 1955, first transition metal catalyzed directed C−H functionalization was reported for carbonylation using limited imine substrates under harsh conditions with $CO_2(CO)_8$ (Scheme 3.1, Eq 1).[42] While mechanism for the reaction was not explored, it is reasonable to postulate that cobaltacycle formed via *ortho* C−H activation would undergo insertion reaction with carbon monoxide based on precedented mechanisms.[43] About two decades later, cobalt mediated direct C−H functionalization for C−O bond formation of arenes was achieved with $Co(OTf)_3$ (Scheme 3.1, Eq 2). Studies on the reaction mechanism for oxidation of arenes revealed that the reaction proceeds via a single electron transfer process (SET).[44] Since those early results, C−H functionalization using cobalt was dormant until hydroarylation of azobenzenes catalyzed by $CoH(N_2)(PPh_3)_3$ or $CoH_3(PPh_3)_3$ (Scheme 3.2, Eq 1) was reported.[45] Later, a cobalt (I) complex was utilized for hydroacylation of vinylsilanes with aromatic and aliphatic aldehydes (Scheme 3.2,

Eq 2).[46] Furthermore, stoichiometric reactions for the preparation of cobaltacycles via chelation assisted sp^2 and sp^3 C−H activation were studied using Co(I), Co(II) and Co(III) complexes (Scheme 3.3). The first sp^3 C−H activation with a Co(II) complex was reported in 1986 (Eq 1).[47] It was suggested that agostic cobalt−H−C interaction promotes the C−H activation. $CoMe(PPh_3)_4$ showed ability to activate both sp^2 and sp^3 C−H bonds giving 4, 5, and 6 membered cobaltacycles (Eq 2−5).[48] In 2001, the first example of C−H activation using Co(III) complex possessing Cp ligand was achieved with silver salt additive, giving a cationic cobalt (III) complex (Eq 6).[49]



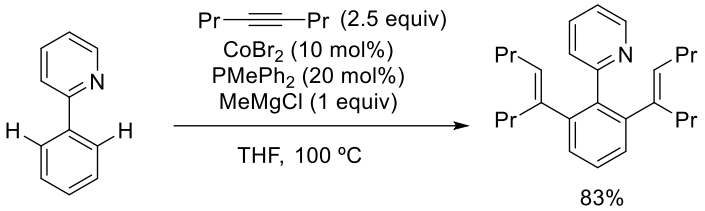
Scheme 3.2 Cobalt(I) catalyzed C−H functionalization



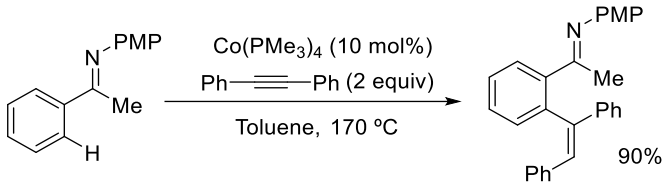
Scheme 3.3 Preparation of cobaltacycles via C−H activation

Instead of using well-defined low valent precatalysts, new protocols employing low valent cobalt species were developed. These species were generated in situ from readily available cobalt (II) or

(III) salts with reducing agents such as Grignard reagents, zinc dust, indium, or magnesium in the presence of ligands such as phosphines, *N*-heterocyclic carbenes, or *N*,*N*′-dimethylpropylene urea (Scheme 3.4).[50] In contrast to the reactions requiring sensitive Grignard reagents or other reductants that could react electrophilic functional groups, simple method using only well-defined cobalt (0) complex, $Co(PMe_3)_4$, to avoid any reducing agents was developed for alkenylation and cyclization reaction (Scheme 3.5).[51]



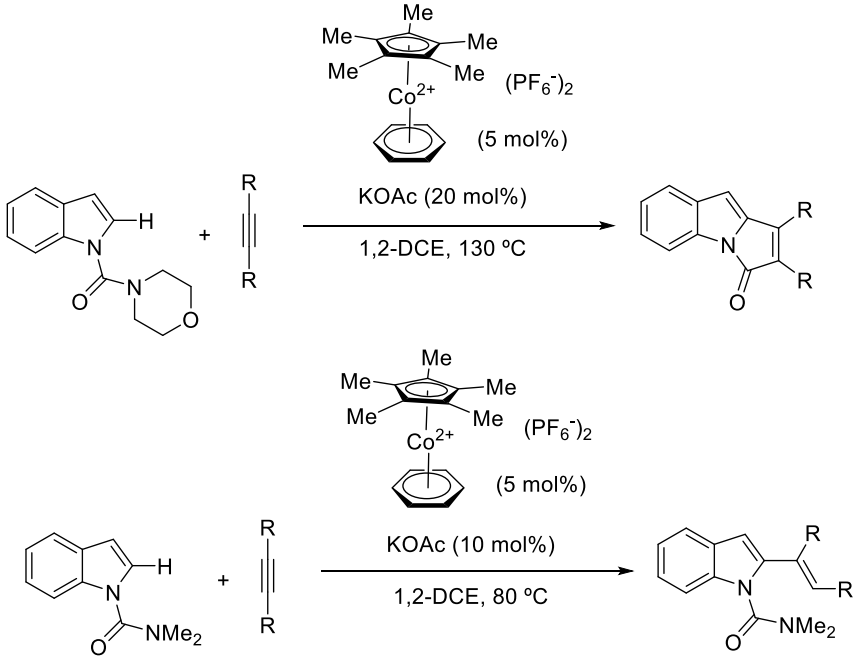
Scheme 3.4 First example using in situ generated low valent cobalt species



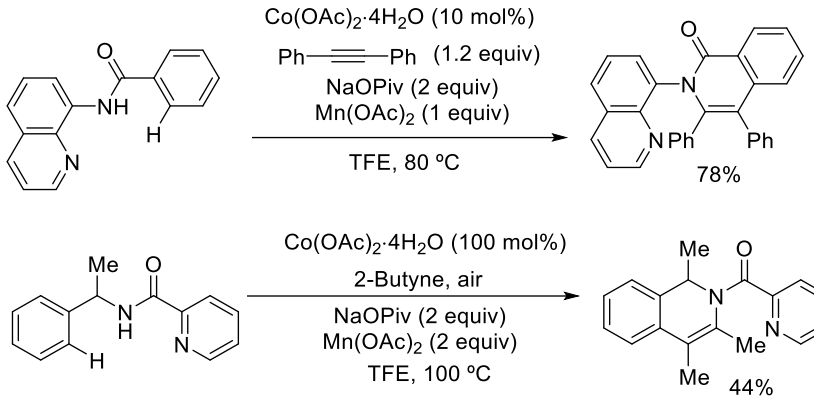
Scheme 3.5 C−H Alkenylation using Co(0) complex

Following the low valent systems, high valent cobalt catalyzed C−H functionalization using Cp*Co(III) complexes or Co(II) salts with oxidants was explored by two research groups. A pioneering report by Matsunaga and Kanai in 2014 described Cp*Co(III)-catalyzed coupling of alkynes with aromatic C−H bonds (Scheme 3.6).[52] Our group reported a method for cobalt-catalyzed, aminoquinoline- and picolinamide-directed coupling of alkynes with C(sp^2) −H bonds (Scheme 3.7).[53] The reaction employs a simple $Co(OAc)_2$ hydrate catalyst, and oxygen from air as a terminal oxidant. Subsequently, many similar high-valent cobalt catalyzed transformations have

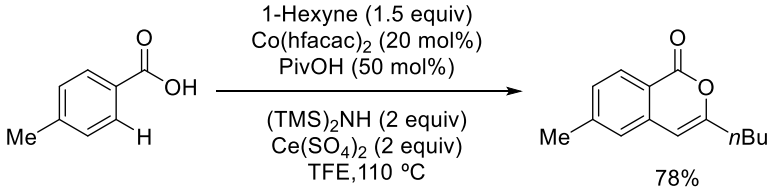
been reported.[54] The simple cobalt salt promoted transformations typically possess high regioselectivity for reactions with unsymmetrical alkynes and requires a bidentate directing group. Only in rare cases, simple directing groups can be used (Scheme 3.8).[53b] Reactions that are catalyzed by various cyclopentadienylcobalt(III) complexes can be performed by employing simpler, monodentate, directing groups, but the regioselectivity observed for unsymmetric alkynes may be lower.[54j-v] Other metals have been employed as well.[51, 55] Among cobalt-catalyzed transformations that result in formation of isoquinolones, few papers report use of monodentate directing groups (Scheme 3.9).[54n, 54r] The compatibility of these methodologies with heterocyclic substrates is underexplored.



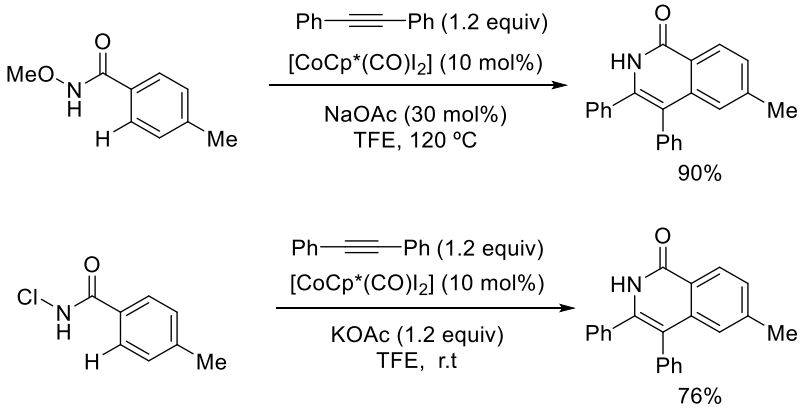
Scheme 3.6 C−H Alkenylation using a Cp*Co(III) complex



Scheme 3.7 Cobalt(II) catalyzed C−H annulation using bidentate directing groups



Scheme 3.8 Cobalt(III) Catalyzed Coupling of BenzoicAcid C−H Bonds with Alkynes

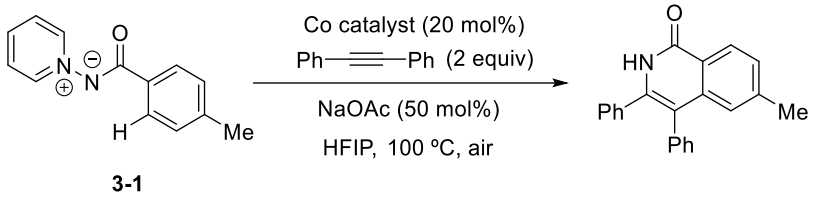


Scheme 3.9 Cobalt(III) catalyzed C−H annulation using monodentate directing groups

3.2 Results and discussion

We begin our optimization study using (4-methylbenzoyl)(pyridin-1-ium-1-yl)amide **3-1** as a model substrate (Table 3.1). Use of simple cobalt salts such as $Co(OAc)_2$ and $Co(acac)_2$ with oxidants did not afford any product (entries 1-4) while $Cp^*CoI_2(CO)$ gave the desired product in a low yield (entry 5).

Table 3.1. Optimization of reaction conditions with ylide 1[a]



3-1

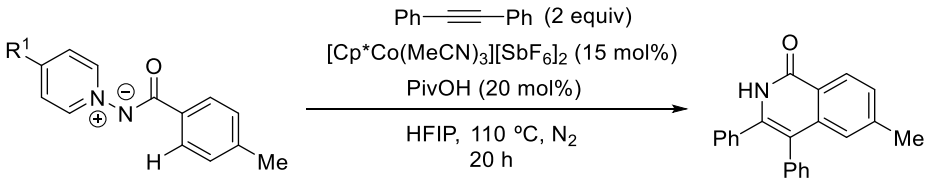
Entry	[Co]	Additive	Yield (%)[b]
1	$Co(OAc)_2{\cdot}4H_2O$	AgOAc (1 equiv)	-
2	$Co(OAc)_2{\cdot}4H_2O$	$Mn(OAc)_2$ (1 equiv)	-
3	$Co(OAc)_2{\cdot}4H_2O$	$Mn(OAc)_3$ (1 equiv)	-
4	$Co(acac)_2$	$Mn(OAc)_3$ (1 equiv)	-
5	$Cp^*CoI_{2(}CO)$	$AgSbF_6$ (40 mol%)	10 %

[a] Scale: 0.2 mmol, time: 24 h, solvent: 1 mL. [b] Yields are isolated yields. Abbreviation: HFIP = hexafluoroisopropanol.

After screening of a number of solvents, cobalt complexes, and additives, we found that the best results were obtained by using $Cp^*Co(MeCN)_3][SbF_6]_2$ catalyst in HFIP solvent with added pivalic acid (Table 3.2). Subsequently, modification of ylide moiety was undertaken (entries 1-3). Relatively low yield was obtained by employing ylide derived from commercially available 1-aminopyridinium iodide and *p*-toluoyl chloride (entry 1). Switching to 4-methoxypyridinium derivative **3-2** and 4-*tert*-butylpyridinium ylide **3-3**, previously utilized for copper promoted C−H amination, allowed to increase the reaction yields to 81-82% (entries 2–3). Pivalic acid additive was found to be optimal for the reaction (entries 4-5).[56] The best catalytic performance was

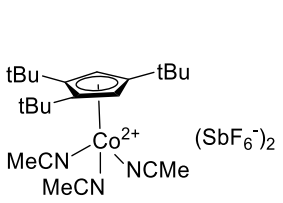
observed for $[Cp^*Co(MeCN)_3][SbF_6]_2$, while in situ generated active species gave a lower yield (entry 6). Other cationic complexes having Cp or Cp^{ttt} (1,2,4-*t*$Bu_3C_5H_2$) in place of Cp* were examined but poor results were obtained (entries 7 and 8). The cationic Co(III) complex prepared in 3,5-bis(trifluoromethyl)benzonitrile instead of acetonitrile afforded the product in a comparable yield (entry 9).

Table 3.2. Optimization of reaction conditions with Cobalt (III)[a]

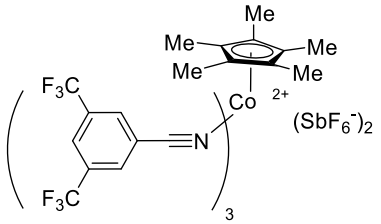


Entry	Deviation from standard conditions	Yield (%)[b]
1	R^1 = H, **3-1**	24
2	R^1 = OMe, **3-2**	82
3	R^1 = *t*Bu, **3-3**	81
4	1-$AdCO_2H$ instead PivOH	77
5	Without PivOH	55
6	$Cp^*CoI_2(CO)$ (20 mol%) $AgSbF_6$ (40 mol%) 1-$AdCO_2H$ (50 mol%)	60
7	$[CpCo(MeCN)_3][SbF_6]_2$	7
8	$[CoCp^{ttt}(MeCN)_3][SbF_6]_2$[c]	25
9	[CoCp*(3,5-bis(trifluoromethyl)benzonitrile)$_3$][SbF_6]$_2$[d]	70

[a] Scale: 0.2 mmol, HFIP: 1 mL. [b] Yields are isolated yields.



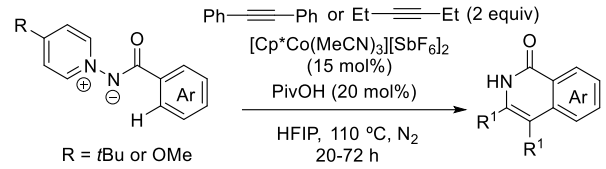
c [CoCp^{ttt}(MeCN)$_3$][SbF$_6$]$_2$

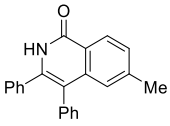
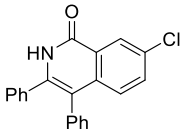
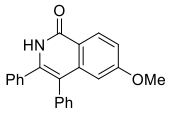
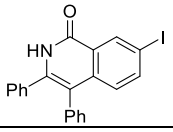
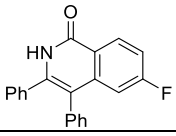
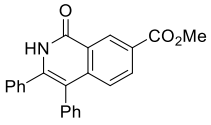
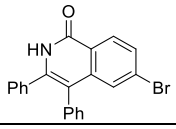
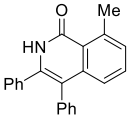
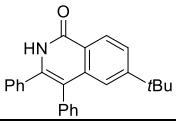
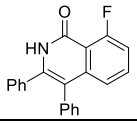
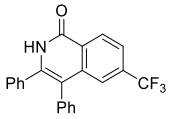
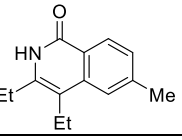
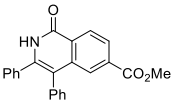
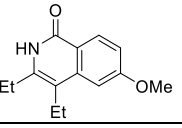
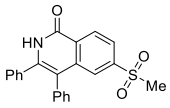
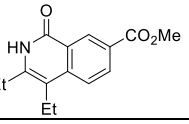
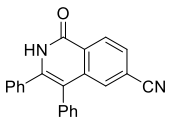


d [CoCp*(3,5-bis(trifluoromethyl)benzonitrile)$_3$][SbF$_6$]$_2$

After identification of optimal reaction conditions, we evaluated the generality of the directed C−H annulation of aryl ylides with symmetric alkynes such as diphenylacethylene and 3-hexyne (Table 3.3). Various functional groups such as alkoxy (entry 2), halides (entries 3,4, 10, 11, and 14), ester (entries 7 and 12), nitrile (entry 9), trifluoromethyl (entry 6), and sulfone (entry 8) on the aryl rings are well tolerated furnishing good to excellent yields of isoquinolones regardless of substituent electronic properties and position on the arene. The annulation of substrates with substituents at meta position of aryl group occurred only at the less hindered site to give the product regioselectively (entries 10–12). Compared to *meta* and *para* substituted compounds, *ortho* substituted substrates gave products in somewhat lower yields (entry 13). In addition to diphenylacetylene, 3-hexyne could be employed as substrate for the annulation to generate the corresponding products (entries 15–17). Comparison of *t*-butyl pyridinium ylides with the corresponding methoxy pyridinium derivatives is instructive. In some cases, performance is nearly identical (entry 1). For most other substrates, the methoxy derivative performs substantially better (entries 11, 13 and 14) even with shorter reaction times.

Table 3.3 Reaction scope with respect to ylides[a]

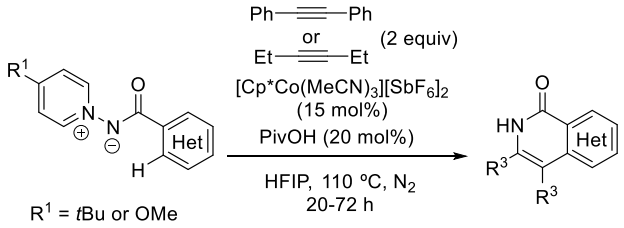


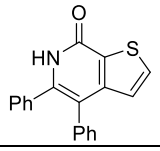
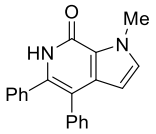
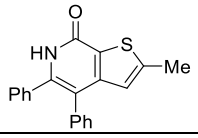
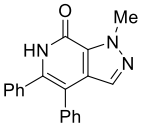
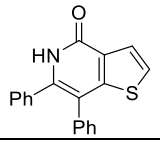
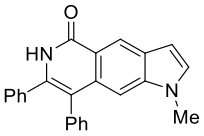
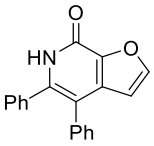
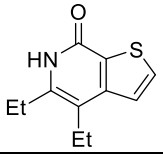
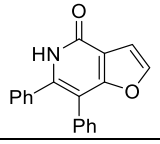
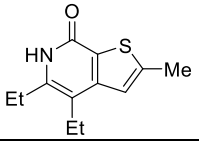
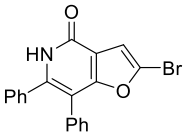
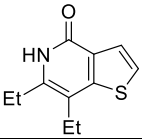
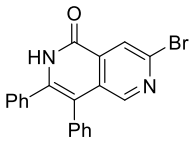
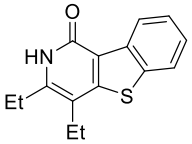
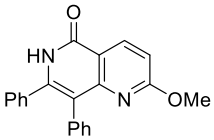
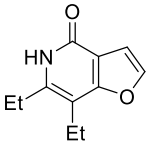
Entry	R	Product	Yield (%)	Entry	R	Product	Yield (%)
1	*t*Bu		81[b]	10	*t*Bu		54[d]
	OMe		82[b]		OMe		63[b]
2	*t*Bu		64[c]	11	*t*Bu		48[c]
	OMe		76[c]		OMe		63[b]
3	*t*Bu		63[c]	12	*t*Bu		66[e]
	OMe		78[c]				
4	*t*Bu		76[d]	13	*t*Bu		38[e]
					OMe		54[c]
5	*t*Bu		64[c]	14	*t*Bu		51[f]
					OMe		71[c]
6	*t*Bu		70[e]	15	*t*Bu		70[b]
7	*t*Bu		75[d]	16	*t*Bu		69[b]
8	*t*Bu		72[c]	17	*t*Bu		52[d]
					OMe		66[c]
9	*t*Bu		51[e]				
	OMe		62[c]				

[a] Reaction scale: 0.2 mmol, HFIP 1 mL. [b] Time: 20 h. [c] Time: 48 h. [d] Catalyst: $[Cp^*Co(MeCN)_3][SbF_6]_2$ (20 mol%), PivOH (30 mol%), 48 h. [e] Time: 72h. [f] Catalyst: $[Cp^*Co(MeCN)_3][SbF_6]_2$ (20 mol%), PivOH additive (30 mol%), 72 h. Isolated yields are reported.

The annulation protocol was investigated with respect to heteroaryl substrates (Table 3.4). Thiophene derivatives gave the expected products in good yields, irrespective of the substitution pattern (entries 1−3). Best results were obtained with 3-substituted thiophene derivative which afforded the cyclized product (entry 3) regioselectively and reacted faster than other substrates. Furan derivatives are competent substrates (entries 4−6) but if ylide derived from furan-2-carboxylic acid was employed, the product was isolated in a low yield (entry 4). Notably, brominated furan derivative is reactive (entry 6). Furthermore, nitrogen-containing heteroarene substrates participate in the transformation. Pyridine (entries 7 and 8), pyrrole (entry 9), pyrazole (entry 10), and indole moieties (entry 11) are all compatible with the reaction conditions, irrespective of the potentially strong coordinating ability of the heteroatom which may interfere with the C−H functionalization step of the annulation reaction.[33c, 37a, 57] In all cases except that for 6-methoxypyridinium substrate (entry 7), formation of only one product isomer was observed. For bromopyridinium substrate (entry 8), two isomers (C2:C4 = 5.9:1) were obtained. Next, the annulation of heterocycles with 3-hexyne was investigated. Thiophenes and benzo[*b*]thiophene are compatible and gave products in good yields (entries 12−15). However, the furan-containing substrate afforded the product (entry 16) in a modest yield. In most cases the methoxy-substituted pyridine ylide derivative performs substantially better compared with ylide derived from *t*-butylpyridine.

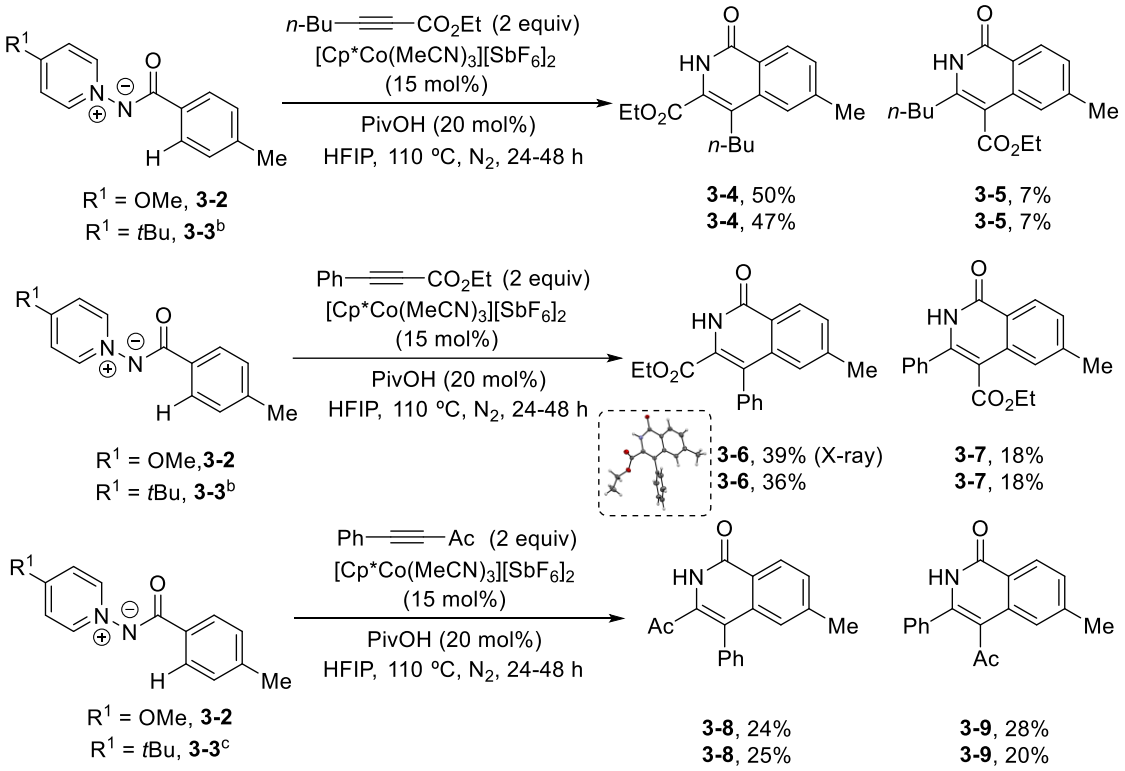
Table 3.4. Reaction scope with respect to heteroaryl ylides[a]



Entry	R	Product	Yield (%)	Entry	R	Product	Yield (%)
1	*t*Bu		82[b]	9	*t*Bu		68[d]
2	*t*Bu		79[b]	10	*t*Bu		35[d]
					OMe		71[e]
3	*t*Bu		63[c]	11	*t*Bu		51[d]
	OMe		78[c]		OMe		58[d]
4	*t*Bu		24[d]	12	*t*Bu		72[b]
	OMe		23[d]				
5	*t*Bu		65[d]	13	*t*Bu		68[b]
	OMe		56[d]				
6	*t*Bu		70[d]	14	*t*Bu		72[c]
7	*t*Bu		30[e]	15	*t*Bu		87[c]
	OMe		70[e]				
8	*t*Bu		58[e,f]	16	*t*Bu		18[d]
	OMe		53[e,f]		OMe		30[d]

[a] Reaction scale: 0.2 mmol, HFIP 1 mL. [b] Time: 48 h. [c] Time: 20 h. [d] Catalyst: $[Cp^*Co(MeCN)_3][SbF_6]_2$ (20 mol%), PivOH additive (30 mol%), 48 h. [e] Catalyst: $[Cp^*Co(MeCN)_3][SbF_6]_2$ (20 mol%), PivOH additive (30 mol%), 72 h. [f] Major isomer is shown (5.9:1). Isolated yields are reported. Please see Supporting Information for details.

Regioselectivity of reactions with unsymmetrical alkynes was investigated next (Scheme 3.10). The annulation with ethyl hept-2-ynoate exhibited good selectivity (**3-4** and **3-5**). The use of ethyl 3-phenylpropiolate resulted in about 2:1 ratio of isomeric products **3-6** and **3-7**. Poor selectivity was observed in reaction with 4-phenylbut-3-yn-2-one (**3-8** and **3-9**). The structure of the isomers was confirmed by comparing to NMR spectrum of known compounds and X-ray crystallography. The selectivities are consistent with those observed for cyclopentadienylcobalt(III)-catalyzed annulation reactions with alkynes.[54j-v]

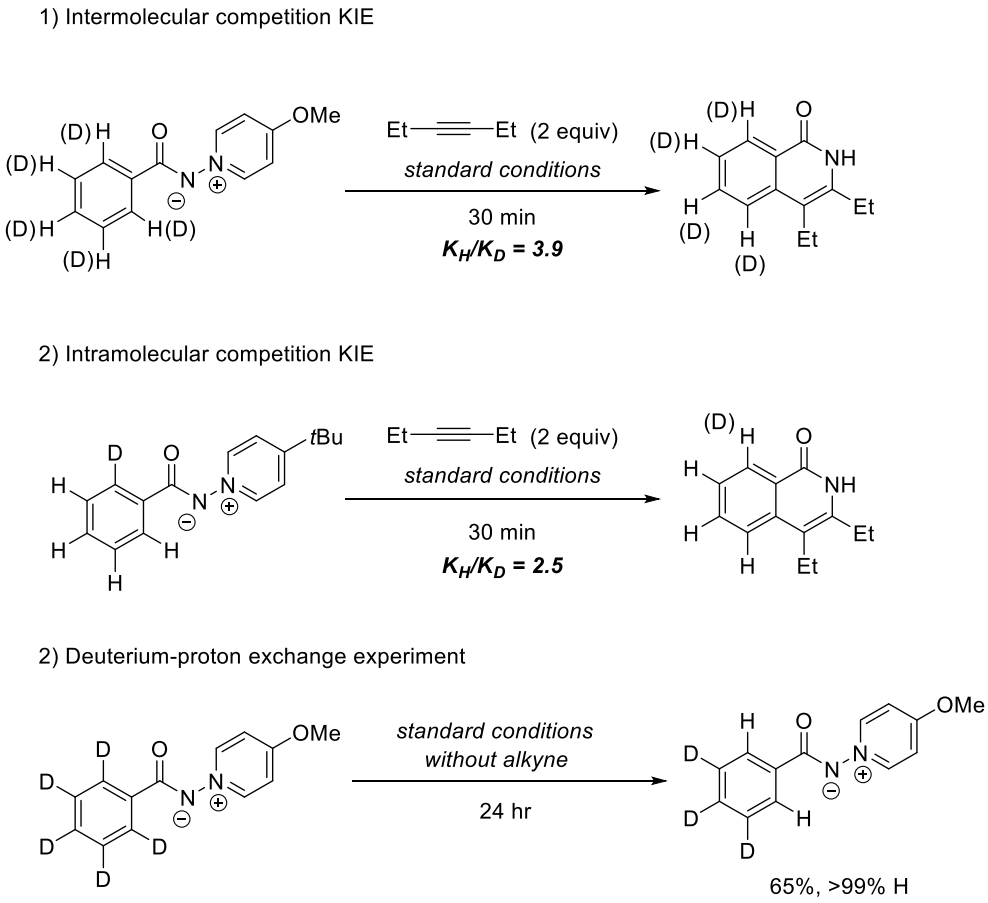


[a] Reaction scale: 0.2 mmol, HFIP 1 mL. [b] $[Cp^*Co(MeCN)_3][SbF_6]_2$ (20 mol%), PivOH (30 mol%), 48 h.[c] $[Cp^*Co(MeCN)_3][SbF_6]_2$ (15 mol%), PivOH (20 mol%), 48 h.

Scheme 3.10 Reactions with unsymmetrical alkynes[a]

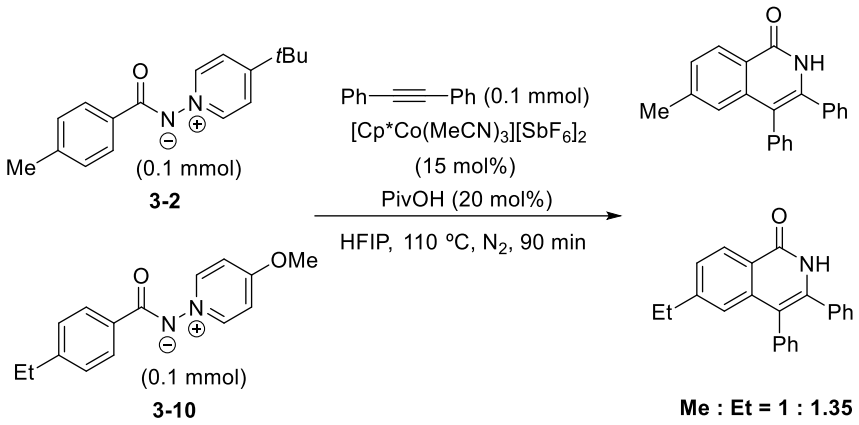
We carried out preliminary mechanistic experiments to delineate the proposed mechanism. Kinetic isotope effects (KIE) were measured by both parallel ($k_H/k_D \approx 3.9$) and competition

experiments ($k_H/k_D \approx 2.5$) (Scheme 3.11, Eq 1 and 2). While substantial KIE values were observed, C−H bond activation would not be a rate determining step because D/H exchange occurred (Eq 3)

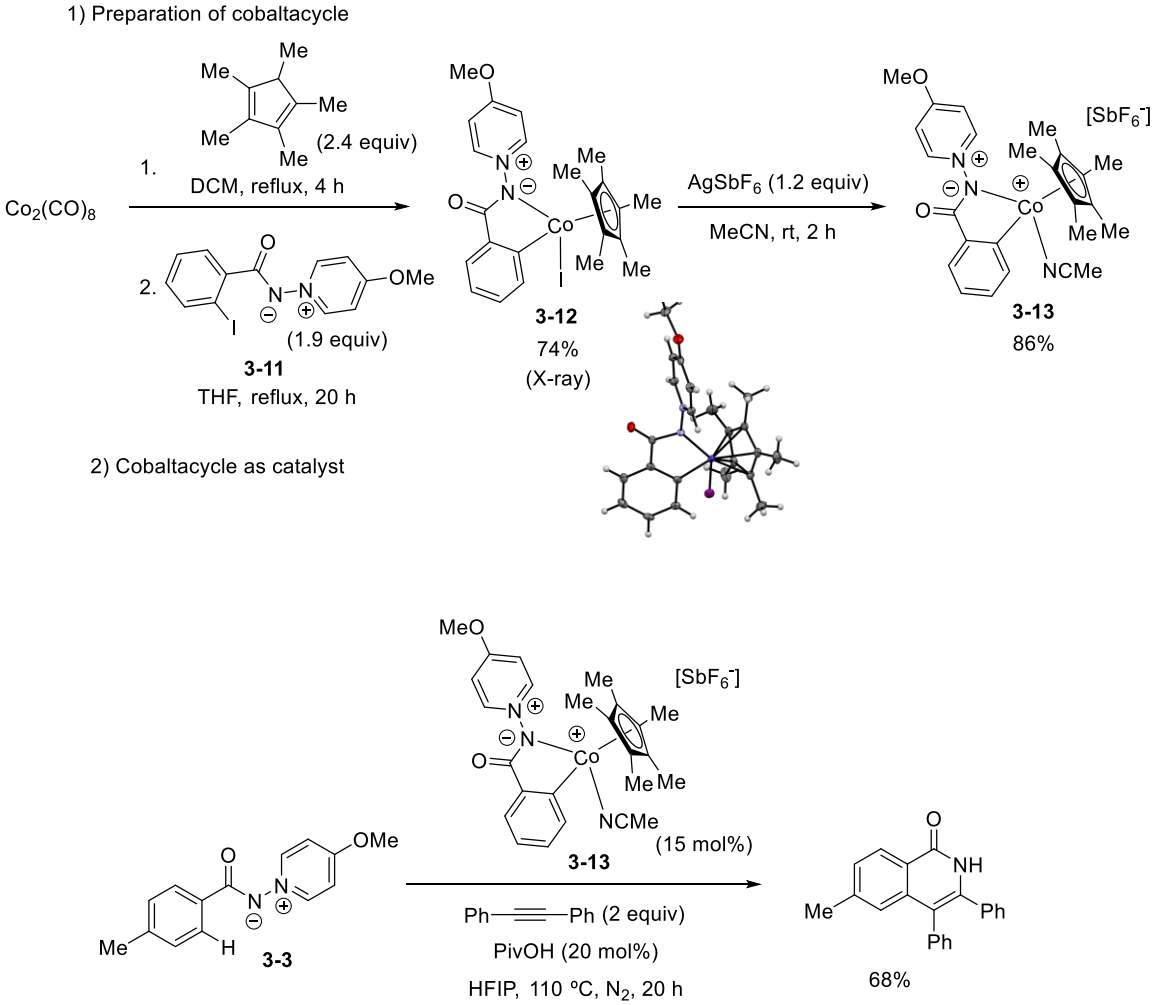


Scheme 3.11 Deuterium labelling experiments

In a competitive annulation using a 1:1 molar mixture of *tert*-butyl pyridinium ylide (**3-2**) and methoxy pyridinium ylide (**3-10**), a 1:1.35 mixture of 6-methyl-isoquinoline and 6-ethyl-isoquinoline was obtained (Scheme 3.12). A little higher reaction rate from methoxy pyridinium ylide would reflect that electron-rich ylide would be either more efficient for coordination to the cobalt catalyst or stabilizes intermediates to suppress side reactions, resulting in better yields.

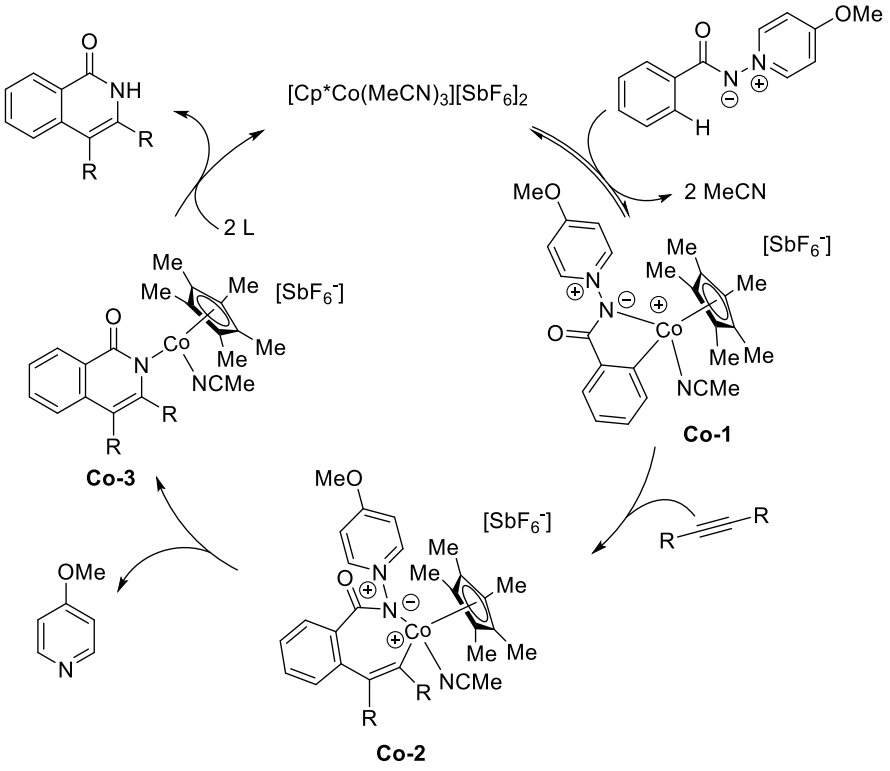


Scheme 3.12 Competition reaction between methoxy- and *tert*-butyl pyridinium ylides



Scheme 3.13 C−H annulation using Cp*Co(III)-pyridinium ylide complex

Since C−H cyclometallation would be expected to be a key step for the annulation, we attempted to prepare the cyclometalated complex via *ortho* C−H activation of the pyridinium ylide with a stoichiometric amount of $[Cp^*Co(MeCN)_3][SbF_6]_2$, but we could not obtain the desired cobaltacycle. Reversible C−H cobaltation process may contribute to the failure to isolate the complex. Alternatively, the Cp*Co(III)-pyridinium ylide complex (**3-12**) was prepared by the chelation-assisted reaction of the Ar−I bond of the pyridinium ylide (**3-11**) with Cp*Co(CO) fragment, generated in situ from cobalt carbonyl (Scheme 3.13, Eq 1).[58] The complex was characterized by single crystal X-ray diffraction and NMR spectroscopy. Iodide anion abstraction by treatment of silver hexafluorantimonate in acetonitrile afforded the cationic cobalt complex (**3-13**) bearing acetonitrile as the ligand. The cationic cobalt (III) metallacycle (**3-13**) was used as catalyst towards the annulation product in 68% (Eq 2).



Scheme 3.14. Proposed catalytic cycle

Based on the mechanistic studies and the reported mechanism for high valent cobalt catalyzed annulation with alkynes in the literature, we can propose the catalytic cycle in Scheme 3.14. The reaction starts with ligand exchange followed by subsequent chelation assisted C−H activation to give the cobaltacycle **Co-1**. Alkyne insertion to the Cobalt−C_{aryl} bond of **Co-1** forms the seven-membered cobaltacycle **Co-2**. Next, redox-neutral intramolecular amination furnishes intermediate **Co-3** and releases the pyridine. Upon proto-demetallation, the cobalt (III) catalyst is generated and gives the isoquinoline.

3.3 Conclusion

In conclusion, we have shown that *N*-aminopyridinium ylides act as competent monodentate directing groups for cobalt-catalysed annulation of sp^2 C−H bonds with internal alkynes. Coupling reactions proceed in hexafluoroisopropanol solvent at elevated temperatures and are catalyzed by $[Cp^*Co(MeCN)_3][SbF_6]_2$ complex. The pyridine moiety in ylide is cleaved during the reaction, serving as an internal oxidant. The annulation reactions possess excellent compatibility with heterocyclic substrates, tolerating furan, thiophene, pyridine, pyrrole, pyrazole, and indole functionalities.

3.4 Experimental Section

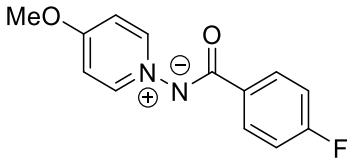
General Information.

The ^1H, ^{13}C NMR spectra were recorded on JEOL EC-400, EC-500 and EC-600 spectrometers using either residual tetramethylsilane or residual solvent peaks as a reference. Compounds for HRMS were analyzed by positive mode electrospray ionization (CI or ESI) using Agilent QTOF mass spectrometer in the Mass Spectrometry Facility (MSF) of the Department of Chemistry and Biochemistry of University of Texas-Austin. Column chromatography was performed using a

Biotage Isolera instrument with 60Å silica gel. Reagents and starting materials were purchased from commercial vendors and used without further purification. Complexes [Cp*Co(CO)I_2], [Cp*Co(MeCN)$_3$][SbF_6]$_2$, [CpCo(MeCN)$_3$[SbF_6]$_2$, [Cp^{ttt}Co(MeCN)$_3$[SbF_6]$_2$ and [Cp*Co(3,5-bis(trifluoromethyl)benzonitrile)$_3$][SbF_6]$_2$ were prepared according to the reported procedure.[59]

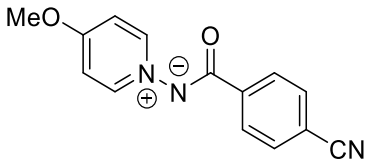
Preparation and Characterization of Pyridinium Ylides.

Pyridinium ylides were prepared according to the literature procedures.[60] Procedures and characterization data for unknown pyridinium ylides are described below.

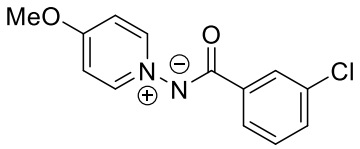


(4-Fluorobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (Method A). To a 100 mL round bottomed flask were added 4-methoxypyridine (0.41 mL, 4 mmol) and CH_2Cl_2 (20 mL). *O*-(2,4,6-Trimethylbenzenesulfonyl)hydroxylamine (1.03 g, 4.8 mmol) was added to the solution, and the mixture was stirred for 2 h. This step prepares a substituted 1-aminopyridine. To another 100 mL round bottomed flask were added 4-fluorobenzoic acid (0.56 g, 4 mmol) and CH_2Cl_2 (20 mL), and the mixture was cooled to 0 °C. Ethyl chloroformate (0.42 mL, 4.4 mmol) was added to the mixture followed by the addition of triethylamine (1.67 mL, 12 mmol). The mixture was stirred for 30 min at room temperature. To this mixture were added the 1-aminopyridinium solution prepared above dropwise and solid K_2CO_3 (1.66 g, 12 mmol). After stirring the mixture for 24 h, NaOH (50 mL of a 1 N aqueous solution) was poured in and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The extracts were dried over $MgSO_4$, and the residue was purified by column chromatography (gradient elution, EtOAc/MeOH, 0% → 15%) to give the product (0.44 g, 45%). Appearance: white solid; mp 212− 213 °C (EtOAc/MeOH = 10:1); R_f = 0.33 (EtOAc/MeOH = 5/1); ^{1}H NMR

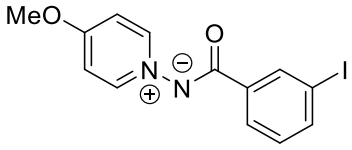
(400 MHz, MeOD) δ 8.46 (d, J = 7.0 Hz, 2H), 8.10 – 8.00 (m, 2H), 7.43 (d, J = 7.0 Hz, 2H), 7.19 – 7.03 (m, 2H), 4.10 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 173.1, 169.4, 165.8 (d, J = 248.2 Hz), 146.4, 134.1 (d, J = 3.1 Hz), 131.3 (d, J = 8.7 Hz), 115.7 (d, J = 21.8 Hz), 113.6, 58.0. HRMS (ESI) calcd for $C_{13}H_{11}FN_2O_2$ $[M + Na]^+$ 269.0697, found 269.0697.



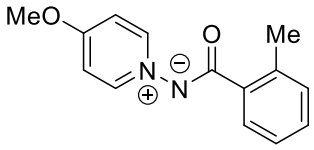
(4-Cyanobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with 4-cyanobenzoic acid (0.59 g, 4 mmol). Yield: 0.42 g, 41%; Appearance: light yellow solid; mp 221−222 °C (EtOAc/MeOH = 10:1); R_f = 0.31 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 6.8 Hz, 2H), 8.23 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 6.8 Hz, 2H), 4.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 166.4, 144.8, 142.1, 131.8, 128.6, 119.2, 113.3, 111.7, 57.1. HRMS (ESI) calcd for $C_{14}H_{11}N_3O_2$ $[M + Na]^+$ 276.0743, found 276.0750.



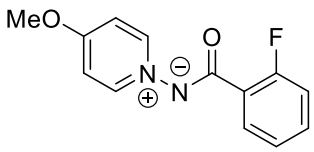
(3-Chlorobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with 3-chlorobenzoic acid (0.63 g, 4 mmol). Yield: 0.78 g, 74%; Appearance: white solid; mp 154−155 °C (EtOAc/MeOH = 10:1); R_f = 0.38 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, MeOD) δ 8.47 (d, J = 6.2 Hz, 2H), 8.01 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.51 – 7.35 (m, 4H), 4.10 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.5, 169.4, 146.3, 140.1, 135.0, 131.4, 130.6, 129.0, 127.3, 113.6, 58.0. HRMS (ESI) calcd for $C_{13}H_{11}N_2O_2Cl$ $[M + Na]^+$ 285.0401, found 285.0403.



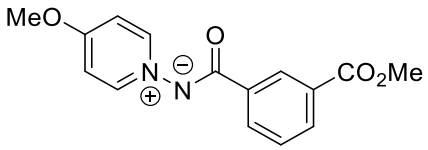
(3-Iodobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with 3-iodobenzoic acid (0.99 g, 4 mmol). Yield: 0.89 g, 63%; Appearance: white solid; mp 135−136 °C (EtOAc/MeOH = 10:1); R_f = 0.40 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.46 (m, 3H), 8.09 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.4 Hz, 2H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 166.2, 145.0, 139.7, 138.9, 137.0, 129.8, 127.3, 111.6, 93.9, 57.0. HRMS (ESI) calcd for $C_{13}H_{11}N_2O_2I$ $[M + Na]^+$ 376.9757, found 376.9753.



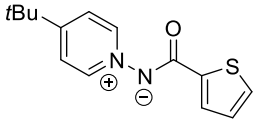
(4-Methoxypyridin-1-ium-1-yl)(2-methylbenzoyl)amide. Method A was employed, with 2-methylbenzoic acid (0.54 g, 4 mmol). Yield: 0.53 g, 55%; Appearance: white solid; mp 163−164 °C (EtOAc/MeOH = 10:1); R_f = 0.22 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 7.4 Hz, 2H), 7.67 (d, J = 7.0 Hz, 1H), 7.26 – 7.14 (m, 3H), 7.04 (d, J = 7.4 Hz, 2H), 3.96 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 166.0, 144.9, 138.7, 136.4, 130.6, 128.4, 128.2, 125.4, 111.5, 56.9, 20.5. HRMS (ESI) calcd for $C_{14}H_{14}N_2O_2$ $[M + Na]^+$ 265.0947, found 265.0943.



(2-Fluorobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with 2-fluorobenzoic acid (0.56 g, 4 mmol). Yield: 0.67 g, 68%; Appearance: white solid; mp 141−142 °C (EtOAc/MeOH = 10:1); R_f = 0.24 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 7.6 Hz, 2H), 7.89 (td, J = 7.5, 1.7 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.16 (td, J = 7.5, 0.9 Hz, 1H), 7.13 – 7.03 (m, 3H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 166.3, 160.7 (d, J = 251.2 Hz), 145.0, 130.9 (d, J = 3.2 Hz), 130.7 (d, J = 8.4 Hz), 126.4 (d, J = 13.2 Hz), 123.7 (d, J = 3.7 Hz), 116.3 (d, J = 23.2 Hz), 111.5, 57.0. HRMS (ESI) calcd for $C_{13}H_{11}N_2O_2F$ $[M + Na]^+$ 269.0697, found 269.0700.

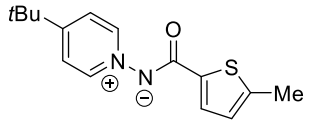


(3-(Methoxycarbonyl)benzoyl)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with 3-(methoxycarbonyl)benzoic acid (0.72 g, 4 mmol). Yield: 0.84 g, 73%; Appearance: white solid; mp 170−171 °C (EtOAc/MeOH = 10:1); R_f = 0.29 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, MeOD) δ 8.69 (s, 1H), 8.49 (d, J = 6.4 Hz, 2H), 8.25 (d, J = 7.7 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 6.5 Hz, 2H), 4.10 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.9, 169.4, 168.2, 146.4, 138.5, 133.5, 132.3, 131.2, 130.1, 129.4, 113.6, 58.0, 52.7. HRMS (ESI) calcd for $C_{15}H_{14}N_2O_4$ $[M + Na]^+$ 309.0846, found 309.0848.

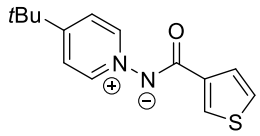


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(thiophene-2-carbonyl)amide. Method A was employed, with 2-thiophenecarboxylic acid (0.51 g, 4 mmol). Yield: 0.53 g, 51%; Appearance: white solid;

mp 225− 226 °C (EtOAc/MeOH = 10:1); R_f = 0.52 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 7.2 Hz, 2H), 7.76 (dd, J = 3.6, 1.3 Hz, 1H), 7.60 (d, J = 7.1 Hz, 2H), 7.36 (dd, J = 5.0, 1.3 Hz, 1H), 7.07 (dd, J = 5.0, 3.6 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 163.0, 142.6, 141.8, 129.0, 128.1, 127.2, 123.1, 35.8, 30.3. HRMS (ESI) calcd for $C_{14}H_{16}N_2OS$ [M + H]$^+$ 261.1056, found 261.1053.

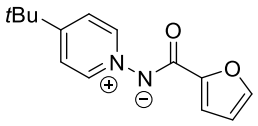


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(5-methylthiophene-2-carbonyl)amide. Method A was employed, with 5-methylthiophene-2-carboxylic acid (0.57 g, 4 mmol). Yield: 0.75 g, 68%; appearance: white solid; mp 194−195 °C (EtOAc/MeOH = 10:1); R_f = 0.52 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 7.1 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H), 7.55 (d, J = 3.6 Hz, 1H), 6.73 (d, J = 3.5 Hz, 1H), 2.50 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 162.7, 142.9, 142.6, 139.2, 129.2, 125.6, 123.0, 35.8, 30.3, 15.8. HRMS (ESI) calcd for $C_{15}H_{18}N_2OS$ [M + H]$^+$ 275.1213, found 275.1209.

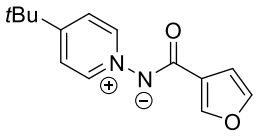


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(thiophene-3-carbonyl)amide. Method A was employed, with thiophene-3-carboxylic acid (0.51 g, 4 mmol). Yield: 0.79 g, 76%; appearance: white solid; mp 244−245 °C (EtOAc/MeOH = 10:1); R_f = 0.38 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 7.2 Hz, 2H), 8.01 (dd, J = 3.1, 1.2 Hz, 1H), 7.63 (dd, J = 5.0, 1.2 Hz, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.28 (dd, J = 4.9,

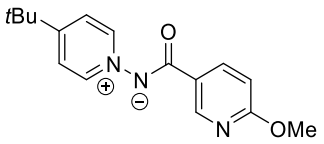
3.2 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 162.8, 142.7, 141.0, 127.7, 127.4, 124.9, 123.1, 35.8, 30.3. HRMS (ESI) calcd for $C_{14}H_{16}N_2OS$ $[M + H]^+$ 261.1056, found 261.1054.



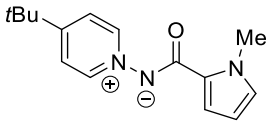
(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(furan-2-carbonyl)amide. Method A was employed, with furan-2-carboxylic acid (0.45 g, 4 mmol), Yield: 0.79 g, 81%; appearance: white solid; mp 220−221 °C (EtOAc/MeOH = 10:1); R_f = 0.29 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 7.2 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H), 7.50 (d, J = 0.8 Hz, 1H), 7.07 (dd, J = 3.4, 0.9 Hz, 1H), 6.47 (dd, J = 3.4, 1.8 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 163.0, 151.4, 143.4, 142.6, 123.2, 112.7, 111.2, 35.8, 30.3. HRMS (ESI) calcd for $C_{14}H_{16}N_2O_2$ $[M + H]^+$ 245.1285, found 245.1280.



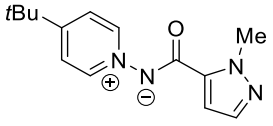
(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(furan-3-carbonyl)amide. Method A was employed, with furan-3-carboxylic acid (0.45 g, 4 mmol), Yield: 0.57 g, 58%; appearance: white solid; mp 242−243 °C (EtOAc/MeOH = 10:1); R_f = 0.36 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 7.1 Hz, 2H), 8.00 (d, J = 1.6 Hz, 1H), 7.61 (d, J = 7.1 Hz, 2H), 7.42 (s, 1H), 6.82 (d, J = 1.8 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 162.9, 144.5, 142.8, 142.7, 125.3, 123.1, 109.9, 35.7, 30.3. HRMS (ESI) calcd for $C_{14}H_{16}N_2O_2$ $[M + H]^+$ 245.1285, found 245.1281.



(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(6-methoxynicotinoyl)amide. Method A was employed, with 6-methoxynicotinic acid (4 mmol, 0.61 g), Yield: 0.78 g, 68%; appearance: white solid; mp 180−181 °C (EtOAc/MeOH = 10:1); R_f = 0.33 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 2.3 Hz, 1H), 8.64 (d, J = 7.2 Hz, 2H), 8.30 (dd, J = 8.6, 2.3 Hz, 1H), 7.62 (d, J = 7.1 Hz, 2H), 6.75 (d, J = 8.6 Hz, 1H), 3.99 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 165.3, 162.9, 147.8, 142.7, 138.6, 126.4, 123.1, 109.7, 53.7, 35.8, 30.3. HRMS (ESI) calcd for $C_{16}H_{19}N_3O_2$ $[M + H]^+$ 286.1550, found 286.1548.

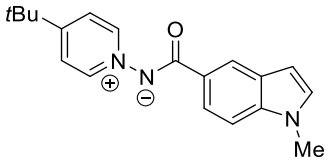


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(1-methyl-1H-pyrrole-2-carbonyl)amide. Method A was employed, with 1-methyl-1H-pyrrole-2-carboxylic acid (4 mmol, 0.50 g), Yield: 0.45 g, 44%; appearance: white solid; mp 214−215 °C (EtOAc/MeOH = 10:1); R_f = 0.36 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 7.1 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H), 6.84 (dd, J = 3.8, 1.9 Hz, 1H), 6.73 – 6.63 (m, 1H), 6.11 (dd, J = 3.8, 2.5 Hz, 1H), 3.99 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 162.4, 142.9, 128.8, 126.3, 123.0, 112.3, 106.9, 36.9, 35.6, 30.3. HRMS (ESI) calcd for $C_{15}H_{19}N_3O$ $[M + H]^+$ 258.1601, found 258.1594.

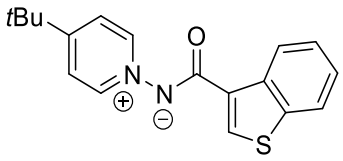


(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(1-methyl-1H-pyrazole-5-carbonyl)amide. Method A was employed, with 1-methyl-1H-pyrazole-5-carboxylic acid (4 mmol, 0.50 g), Yield: 0.66 g, 64%; appearance: white solid; mp 177−178 °C (EtOAc/MeOH = 10:1); R_f = 0.24 (EtOAc/MeOH = 10/1);

purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 7.0 Hz, 2H), 7.64 (d, J = 6.9 Hz, 2H), 7.44 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 4.24 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 163.6, 142.6, 138.8, 137.5, 123.3, 107.5, 39.4, 35.9, 30.3. HRMS (ESI) calcd for $C_{14}H_{18}N_4O$ $[M + H]^+$ 259.1553, found 259.1551



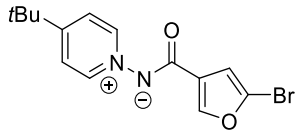
(4-(*tert*-Butyl)pyridin-1-ium-1-yl)(1-methyl-1H-indole-5-carbonyl)amide. Method A was employed, with 1-methyl-1H-indole-5-carboxylic acid (4 mmol, 0.70 g). Yield: 0.98 g, 80%; appearance: pale yellow solid; mp 218−219 °C (EtOAc/MeOH = 10:1); R_f = 0.38 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 6.7 Hz, 2H), 8.51 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 6.7 Hz, 2H), 7.32 (d, J = 8.6 Hz, 1H), 7.05 (d, J = 3.3 Hz, 1H), 6.55 (*d*, J = 3.2 Hz, 1H), 3.79 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 162.3, 143.0, 138.1, 129.3, 128.6, 128.1, 123.0, 122.1, 121.5, 108.4, 102.1, 35.6, 33.0, 30.3. HRMS (ESI) calcd for $C_{19}H_{21}N_3O$ $[M + H]^+$ 308.1757, found 308.1758



(Benzo[*b*]thiophene-3-carbonyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide. Method A was employed, with benzo[b]thiophene-3-carboxylic acid (4 mmol, 0.71 g) Yield: 0.92 g, 74%; appearance: white solid; mp 179−180 °C (EtOAc/MeOH = 10:1); R_f = 0.52 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 8.2 Hz, 1H), 8.68 (d, J = 6.5 Hz, 2H), 8.26 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 6.5

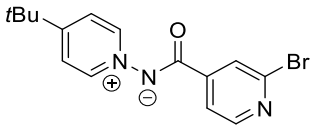
Hz, 2H), 7.47 – 7.37 (m, 1H), 7.38 – 7.30 (m, 1H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 162.9, 142.8, 140.7, 137.7, 134.6, 130.4, 125.9, 124.4, 124.1, 123.1, 122.4, 35.7, 30.3. HRMS (ESI) calcd for $C_{18}H_{18}N_2OS$ $[M + H]^+$ 311.1213, found 311.1214

Preparation of pyridinium ylides (Method B)

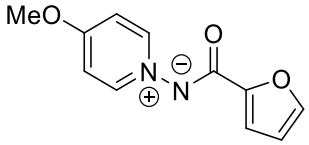


(5-Bromofuran-3-carbonyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide. To a 100 mL round bottomed flask were added 4-*tert*-butylpyridine (0.59 mL, 4 mmol) and CH_2Cl_2 (20 mL). *O*-(2,4,6-Trimethylbenzenesulfonyl)hydroxylamine (1.03 g, 4.8 mmol) was added to the solution, and the mixture was stirred for 2 h. This step prepares a substituted 1-aminopyridine. To another 100 mL round bottomed flask were added 5-bromofuran-3-carboxylic acid (0.76 g, 4 mmol), CH_2Cl_2 (20 mL), oxalyl chloride (8 mmol, 0.69 mL), and DMF (4 drops). The mixture was refluxed for two hours and cooled to room temperature. After removal of excess of oxalyl chloride and CH_2Cl_2, the residue was dissolved in CH_2Cl_2 (20 mL). To this solution were added the aminopyridinium solution prepared above and triethylamine (1.67 mL, 12 mmol) at room temperature. After stirring the mixture for 24 h, NaOH (50 mL of a 1 N aqueous solution) was poured in and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The extracts were dried over $MgSO_4$, and the residue was purified by column chromatography (gradient elution, EtOAc/MeOH, 0% → 10%) to give the product (0.52 g, 40%). Appearance: white solid; mp 206− 207 °C (EtOAc/MeOH = 10:1); R_f = 0.48 (EtOAc/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 7.0 Hz, 2H), 7.94 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 6.73 (s, 1H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 163.2,

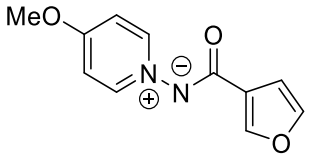
145.7, 142.6, 128.0, 123.2, 122.1, 111.6, 35.8, 30.3. HRMS (ESI) calcd for $C_{14}H_{15}BrN_2O_2$ [M + H]$^+$ 323.0390, found 323.0388.



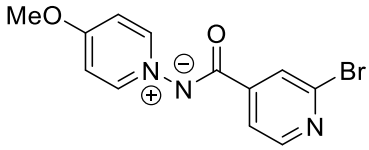
(2-Bromoisonicotinoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide. Method B was employed, with 2-bromoisonicotinic acid (4 mmol, 0.81 g). Yield : 0.68 g, 51%; appearance : white solid; mp 176−177 °C (EtOAc/MeOH = 10:1); R_f = 0.48 (EtOAc/MeOH = 10/1); purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 7.2 Hz, 2H), 8.42 (d, J = 5.3 Hz, 1H), 8.21 – 8.13 (m, 1H), 7.93 (dd, J = 5.1, 1.4 Hz, 1H), 7.68 (d, J = 7.1 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 163.9, 150.2, 148.3, 142.4, 142.3, 126.9, 123.4, 121.6, 35.9, 30.3. HRMS (ESI) calcd for $C_{15}H_{16}BrN_3O$ [M + H]$^+$ 334.0550, found 334.0550.



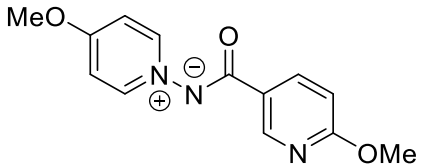
(Furan-2-carbonyl)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with furan-2-carboxylic acid (0.45 g, 4 mmol). Yield: 0.47 g, 54%; Appearance: white solid; mp 187−188 °C (EtOAc/MeOH = 10:1); R_f = 0.12 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 7.6 Hz, 2H), 7.51 – 7.42 (m, 1H), 7.10 (d, J = 7.6 Hz, 2H), 7.03 (d, J = 3.3 Hz, 1H), 6.46 (dd, J = 3.3, 1.7 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 164.3, 151.5, 144.9, 143.3, 112.4, 111.5, 111.1, 57.0. HRMS (ESI) calcd for $C_{11}H_{10}N_2O_3$ [M + Na]$^+$ 241.0584, found 241.0590.



(Furan-3-carbonyl)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with furan-3-carboxylic acid (0.45 g, 4 mmol). Yield: 0.43 g, 49%; Appearance: pale yellow solid; mp 127−128 °C (EtOAc/MeOH = 10:1); R_f = 0.21 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 7.4 Hz, 2H), 7.98 (s, 1H), 7.41 (s, 1H), 7.08 (d, J = 7.3 Hz, 2H), 6.80 (s, 1H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 166.1, 145.1, 144.5, 142.8, 125.2, 111.5, 109.8, 57.0. HRMS (ESI) calcd for $C_{11}H_{10}N_2O_3$ $[M + Na]^+$ 241.0584, found 241.0585.

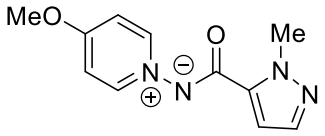


(2-Bromoisonicotinoyl)(4-methoxypyridin-1-ium-1-yl)amide. Method B was employed, with 2-bromoisonicotinic acid (0.81 g, 4 mmol). Yield: 0.55 g, 45%; Appearance: white solid; mp 192−193 °C (EtOAc/MeOH = 10:1); R_f = 0.21 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 7.2 Hz, 2H), 8.41 (d, J = 5.0 Hz, 1H), 8.16 (s, 1H), 7.92 (d, J = 4.9 Hz, 1H), 7.14 (d, J = 7.2 Hz, 2H), 4.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 166.5, 150.1, 148.4, 144.6, 142.4, 126.9, 121.5, 111.7, 57.1. HRMS (ESI) calcd for $C_{12}H_{10}N_3O_2Br$ $[M + Na]^+$ 329.9849, found 329.9849.

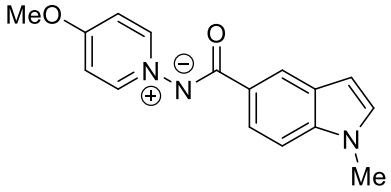


(6-Methoxynicotinoyl)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with 6-

methoxynicotinic acid (0.61 g, 4 mmol). Yield: 0.47 g, 45%; Appearance: white solid; mp 176−177 °C (EtOAc/MeOH = 10:1); R_f = 0.18 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 1.8 Hz, 1H), 8.53 (d, J = 7.4 Hz, 2H), 8.28 (dd, J = 8.6, 2.1 Hz, 1H), 7.09 (d, J = 7.4 Hz, 2H), 6.73 (d, J = 8.6 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 166.1, 165.3, 147.7, 145.1, 138.5, 126.4, 111.5, 109.8, 57.0, 53.7. HRMS (ESI) calcd for $C_{13}H_{13}N_3O_3$ $[M + Na]^+$ 282.0849, found 282.0847.



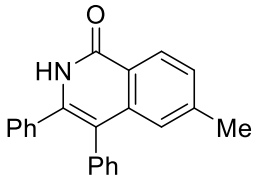
(4-Methoxypyridin-1-ium-1-yl)(1-methyl-1H-pyrazole-5-carbonyl)amide. Method A was employed, with 1-methyl-1H-pyrazole-5-carboxylic acid (0.50 g, 4 mmol). Yield: 0.55 g, 59%; Appearance: white solid; mp 148− 149 °C (EtOAc/MeOH = 10:1); R_f = 0.15 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 1.8 Hz, 1H), 7.10 (d, J = 7.6 Hz, 2H), 6.73 (d, J = 1.8 Hz, 1H), 4.23 (s, 3H), 4.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 165.8, 145.0, 138.7, 137.5, 111.6, 107.4, 57.1, 39.4. HRMS (ESI) calcd for $C_{11}H_{12}N_4O_2$ $[M + Na]^+$ 255.0852, found 255.0858.



(4-Methoxypyridin-1-ium-1-yl)(1-methyl-1H-indole-5-carbonyl)amide. Method A was employed, with 1-methyl-1H-indole-5-carboxylic acid (0.70 g, 4 mmol). Yield: 0.75 g, 67%; Appearance: white solid; mp 219− 220 °C (EtOAc/MeOH = 10:1); R_f = 0.21 (EtOAc/MeOH =

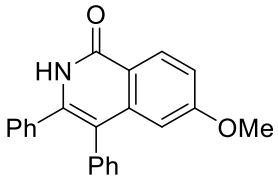
5/1); purification (gradient elution, EtOAc/MeOH, 0% → 20%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 6.1 Hz, 2H), 8.25 (s, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.47 – 7.26 (m, 4H), 6.47 (s, 1H), 4.01 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.1, 165.4, 145.1, 137.3, 129.9, 129.1, 127.3, 121.4, 120.3, 111.8, 108.2, 101.2, 57.1, 32.6. HRMS (ESI) calcd for $C_{16}H_{15}N_3O_2$ [M + Na]$^+$ 304.1056, found 304.1056.

General Procedure for Cobalt-Catalyzed C−H Annulation. A 2-dram vial equipped with a magnetic stir bar was charged with the pyridinium ylide (0.2 mmol), [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ (0.03 or 0.04 mmol), pivalic acid (0.04 or 0.06 mmol), HFIP (1 mL), and alkyne (0.4 mmol). The vial was closed with a screw cap after flushing with nitrogen. The mixture was stirred in a heating block at 110 °C for 20−72 h. After the mixture was cooled, ethyl acetate was added, and the diluted mixture was poured into a round bottom flask. The mixture was absorbed on 3 g of silica gel and purified by column chromatography on silica gel.

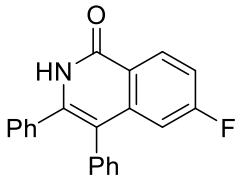


6-Methyl-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 1). Ylide **3** (0.2 mmol, 54 mg), [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 20 h; white solid; 81% yield (50 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%); R_f = 0.50 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.35 (d, J = 8.1 Hz, 1H), 7.35 – 7.28 (m, 4H), 7.26 – 7.21 (m, 5H), 7.21 – 7.21 (m, 2H), 7.12 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 143.4, 138.9, 137.4, 136.1, 135.3, 132.0, 129.5, 128.6, 128.5, 128.4, 128.3, 127.6, 127.3, 125.4, 123.1, 117.1, 22.2. This compound is known.[54n]

Ylide **2** (0.2 mmol, 48 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg). 20 h; 82% yield (51 mg).



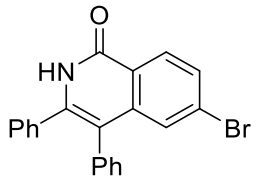
6-Methoxy-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 2). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-methoxybenzoyl)-amide (0.2 mmol, 54 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; 64% yield (42 mg); purification (gradient elution, hexanes/EtOAc, 40% → 100%); R_f = 0.30 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.38 (s, 1H), 8.25 (d, J = 8.8 Hz, 1H), 7.36 – 7.18 (m, 8H), 7.18 – 7.09 (m, 3H), 6.51 (d, J = 2.4 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.3, 161.4, 140.2, 139.3, 135.9, 134.6, 131.7, 129.8, 129.2, 128.3, 128.2, 127.7, 127.1, 118.9, 115.1, 114.6, 107.2, 55.2. This compound is known.[54r] (4-Methoxybenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 52 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 20 h; 76% yield (50 mg).



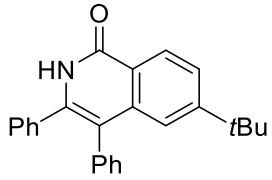
6-Fluoro-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 3). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-fluorobenzoyl)amide (0.2 mmol, 57 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; 63% yield (40 mg); purification (gradient elution, hexanes/EtOAc, 30% → 50%);

R_f = 0.53 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.45 (dd, J = 8.9, 6.0 Hz, 1H), 7.37 – 7.22 (m, 8H), 7.21 – 7.14 (m, 3H), 6.98 (dd, J = 10.7, 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (d, J = 252.2 Hz), 162.4, 141.4 (d, J = 10.0 Hz), 138.8, 135.4, 134.8, 131.8, 130.8 (d, J = 10.0 Hz), 129.4, 129.0, 128.7, 128.5, 127.7, 121.9 (d, J = 1.6 Hz), 116.9 (d, J = 3.3 Hz), 115.3 (d, J = 23.6 Hz), 111.0 (d, J = 23.4 Hz). This compound is known.[54n]

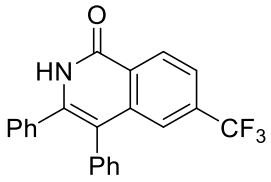
(4-Fluorobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 49 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 20 h; 78% yield (49 mg).



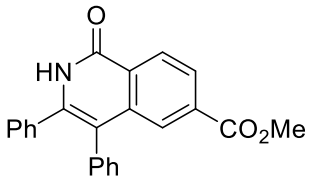
6-Bromo-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 4). (4-Bromobenzoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (0.2 mmol, 67 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; 76% yield (57 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%); R_f = 0.67 (hexanes/EtOAc = 1/1); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.68 (dd, J = 8.5, 1.8 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.26 – 7.19 (m, 6H), 7.18 – 7.13 (m, 2H). ^{13}C NMR (151 MHz, DMSO-D_6) δ 161.3, 140.3, 139.9, 135.2, 134.2, 131.7, 129.8, 129.4, 129.30, 128.5, 127.8, 127.5, 127.0, 126.9, 123.9, 114.5. One carbon signal could not be located. This compound is known.[54n]



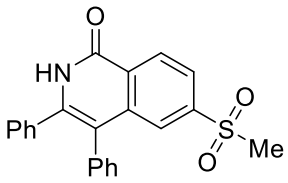
6-(*tert*-Butyl)-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 5). (4-(*tert*-Butyl)benzoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (0.2 mmol, 62 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; 64% yield (45 mg); purification (gradient elution, hexanes/EtOAc, 20% → 50%); R_f = 0.63 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.39 – 7.13 (m, 11H), 1.25 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 156.3, 138.7, 137.1, 136.0, 135.4, 132.0, 129.4, 128.7, 128.5, 128.4, 127.4, 124.9, 123.0, 121.9, 117.7, 35.4, 31.1. One carbon signal could not be located. This compound is known.[61]



3,4-Diphenyl-6-(trifluoromethyl)isoquinolin-1(2H)-one (Table 3.3, Entry 6). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-(trifluoro-methyl)benzoyl)amide (0.2 mmol, 64 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; white solid; 70% yield (51 mg); purification (gradient elution, hexanes/EtOAc, 20% → 40%); R_f = 0.73 (hexanes/EtOAc = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.53 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.39 – 7.22 (m, 8H), 7.17 (d, J = 5.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 139.1, 138.9, 134.9, 134.6, 134.4 (q, J = 32.4 Hz), 131.8, 129.5, 129.1, 128.8, 128.7, 128.5, 127.9, 127.3, 123.8 (q, J = 272.9 Hz), 123.0 (q, J = 4.0 Hz), 122.6 (q, J = 3.4 Hz), 117.2. This compound is known.[54n]

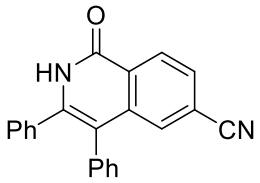


Methyl 1-oxo-3,4-diphenyl-1,2-dihydroisoquinoline-6-carboxylate (Table 3.3, Entry 7). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-(methoxycarbonyl)benzoyl)amide (0.2 mmol, 62 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; pale yellow solid; 75% yield (53 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%); R_f = 0.53 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.42 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 7.36 – 7.27 (m, 3H), 7.27 – 7.20 (m, 5H), 7.19 – 7.13 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.7, 161.2, 139.8, 138.1, 135.3, 134.3, 132.8, 131.7, 129.8, 128.4, 127.8, 127.7, 127.7, 127.4, 126.3, 125.8, 115.5, 52.6. One carbon signal could not be located. This compound is known.[61]



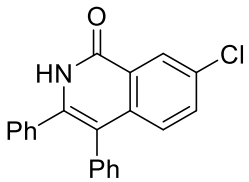
6-(Methylsulfonyl)-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 8). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-(methyl-sulfonyl)benzoyl)amide (0.2 mmol, 66 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; mp 326−327 °C (CH_2Cl_2); 72% yield (54 mg); purification (gradient elution, hexanes/EtOAc, 30% → 100%); R_f = 0.25 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.70 (s, 1H), 7.38 – 7.29 (m, 3H), 7.28 – 7.22 (m, 5H), 7.22 – 7.15 (m, 2H), 3.23 (s, 3H).

^{13}C NMR (126 MHz, DMSO-D_6) δ 161.0, 144.1, 140.8, 138.3, 134.9, 134.1, 131.8, 129.9, 128.8, 128.6, 128.5, 127.8, 127.6, 123.8, 123.6, 115.4, 43.2. One carbon signal could not be located. HRMS (ESI) calcd for $C_{22}H_{17}NO_3S$ [M + H]$^+$ 376.1002, found 376.1001.



1-Oxo-3,4-diphenyl-1,2-dihydroisoquinoline-6-carbonitrile (Table 3.3, Entry 9). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(4-cyano-benzoyl)amide (0.2 mmol, 56 mg), [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; pale orange solid; 51% yield (33 mg); purification (gradient elution, hexanes/EtOAc, 30% → 100%); R_f = 0.56 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.43 (d, J = 8.3 Hz, 1H), 7.87 (dd, J = 8.2, 1.5 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.37 – 7.20 (m, 8H), 7.19 – 7.11 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.9, 140.8, 138.2, 134.7, 134.0, 131.7, 129.9, 129.5, 128.7, 128.6, 128.3, 128.1, 127.8, 127.6, 127.5, 118.4, 115.0, 114.6. This compound is known.[54n]

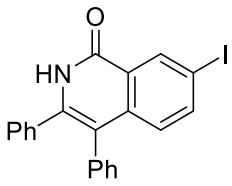
(4-Cyanobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 51 mg), [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; 76% yield (40 mg).



7-Chloro-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 10). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(3-chlorobenzoyl)amide (0.2 mmol, 58 mg), [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ (0.04 mmol, 32

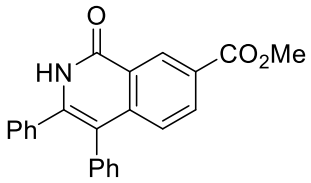
mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; pale yellow solid; 54% yield (36 mg); purification (gradient elution, hexanes/EtOAc, 30% → 70%); R_f = 0.75 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.24 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 8.8, 2.3 Hz, 1H), 7.35 – 7.20 (m, 8H), 7.19 – 7.12 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.7, 149.5, 139.2, 136.8, 135.4, 134.2, 132.7, 131.7, 131.0, 129.8, 128.4, 127.7, 127.4, 127.3, 126.2, 125.8, 115.1. One carbon signal could not be located. This compound is known.[54n]

(3-Chlorobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 53 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 20 h; 63% yield (42 mg).

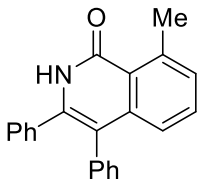


7-Iodo-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 11). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(3-iodobenzoyl)amide (0.2 mmol, 76 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; pale yellow solid; mp 266−267 °C (CH_2Cl_2); 48% yield (41 mg); purification (gradient elution, hexanes/EtOAc, 30% → 70%); R_f = 0.75 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.59 (d, J = 1.9 Hz, 1H), 7.95 (dd, J = 8.6, 2.0 Hz, 1H), 7.35 – 7.19 (m, 8H), 7.16 – 7.09 (m, 2H), 6.93 (d, J = 8.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.4, 140.8, 139.4, 137.3, 135.3, 135.1, 134.3, 131.7, 129.8, 128.5, 128.4, 127.7, 127.2, 127.2, 126.6, 115.2, 91.8. HRMS (ESI) calcd for $C_{21}H_{14}INO$ $[M + H]^+$ 424.0193, found 424.0194.

(3-Iodobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 71 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 20 h; 63% yield (53 mg).



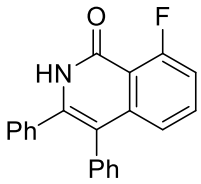
Methyl 1-oxo-3,4-diphenyl-1,2-dihydroisoquinoline-7-carboxylate (Table 3.3, Entry 12). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(3-(methoxycarbonyl)benzoyl)amide (0.2 mmol, 62 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; white solid; mp 254−255 °C (CH_2Cl_2); 66% yield (47 mg); purification (gradient elution, hexanes/EtOAc, 30% → 90%); R_f = 0.63 (hexanes/EtOAc = 1/1); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.88 (s, 1H), 8.20 – 8.02 (m, 1H), 7.35 – 7.20 (m, 9H), 7.19 – 7.12 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.7, 161.5, 141.5, 135.4, 134.2, 132.1, 131.7, 129.8, 128.7, 128.6, 128.4, 127.8, 127.3, 126.8, 125.6, 124.7, 115.4, 52.4. HRMS (ESI) calcd for $C_{23}H_{17}NO_3$ $[M + H]^+$ 356.1281, found 356.1284.



8-Methyl-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 13). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(2-methylbenzoyl)-amide (0.2 mmol, 54 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg). 48 h; white solid; 38% yield (24 mg); purification (gradient elution, hexanes/EtOAc, 20% → 50%); R_f = 0.87 (hexanes/EtOAc = 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.41 – 7.35 (m,

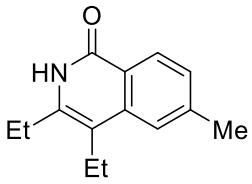
1H), 7.33 – 7.19 (m, 9H), 7.18 – 7.14 (m, 3H), 2.89 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2, 142.0, 140.6, 137.5, 136.7, 135.1, 132.1, 131.8, 129.7, 129.5, 128.5, 128.5, 128.3, 127.3, 124.0, 123.7, 117.3, 24.0. This compound is known.[54n]

(4-Methoxypyridin-1-ium-1-yl)(2-methylbenzoyl)amide (0.2 mmol, 48 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; 54% yield (34 mg).

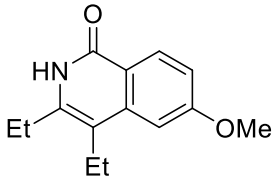


8-Fluoro-3,4-diphenylisoquinolin-1(2H)-one (Table 3.3, Entry 14). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(2-fluorobenzoyl)amide (0.2 mmol, 54 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; white solid; 51% yield (32 mg); purification (gradient elution, hexanes/EtOAc, 20% → 50%); R_f = 0.66 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.48 (td, J = 8.1, 5.1 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.27 – 7.21 (m, 5H), 7.20 – 7.15 (m, 2H), 7.14 – 7.07 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (d, J = 264.0 Hz), 160.5, 141.7, 138.6, 135.8, 134.6, 133.4 (d, J = 10.2 Hz), 132.0, 129.3, 129.0, 128.6, 128.5, 127.6, 121.7 (d, J = 4.4 Hz), 116.5, 114.5 (d, J = 6.1 Hz), 113.5 (d, J = 21.6 Hz). This compound is known.[54r]

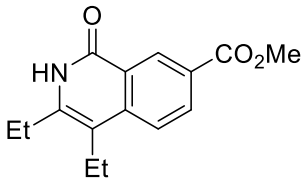
(2-Fluorobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 49 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; 71% yield (45 mg).



3,4-Diethyl-6-methylisoquinolin-1(2H)-one (Table 3.3, Entry 15). Ylide **3** (0.2 mmol, 54 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL), 20 h; white solid; mp 212−213 °C (CH_2Cl_2); 70% yield (30 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%); R_f = 0.55 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.35 (d, J = 8.2 Hz, 1H), 7.46 (s, 1H), 7.36 – 7.16 (m, 1H), 2.83 – 2.63 (m, 4H), 1.33 (t, J = 7.6 Hz, 3H), 1.21 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 142.9, 139.3, 138.5, 127.9, 127.0, 123.1, 122.8, 113.7, 24.4, 22.4, 19.6, 15.1, 14.1.

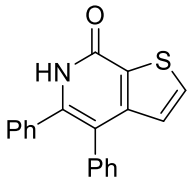


3,4-Diethyl-6-methoxyisoquinolin-1(2H)-one (Table 3.3, Entry 16). *(4-*(*tert*-Butyl)pyridin-1-ium-1-yl)(4-methoxybenzoyl)-amide (0.2 mmol, 57 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL). 48 h; light tan solid; mp 167−168 °C (CH_2Cl_2); 69% yield (32 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%); R_f = 0.39 (hexanes/EtOAc = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.99 (s, 1H), 8.37 (d, J = 8.5 Hz, 1H), 7.10 – 6.94 (m, 2H), 3.93 (s, 3H), 2.76 – 2.62 (m, 4H), 1.30 (t, J = 7.4 Hz, 3H), 1.20 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6, 163.0, 140.4, 140.0, 129.9, 119.1, 114.1, 113.6, 104.9, 55.5, 24.5, 19.8, 14.8, 14.1. HRMS (ESI) calcd for $C_{14}H_{17}NO_2$ $[M + H]^+$ 232.1332, found 232.1334.



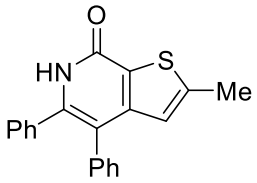
Methyl 3,4-diethyl-1-oxo-1,2-dihydroisoquinoline-7-carboxylate (Table 3.3, Entry 16). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(3-(methoxycarbonyl)benzoyl)amide (0.2 mmol, 62 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL), 72 h; light tan solid; mp 211−212 °C (CH_2Cl_2); 52% yield (27 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%); R_f = 0.50 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.72 (s, 1H), 9.12 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 8.7 Hz, 1H), 3.99 (s, 3H), 2.79 (q, J = 7.2 Hz, 4H), 1.39 (t, J = 7.5 Hz, 3H), 1.22 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 164.0, 142.6, 141.7, 132.6, 130.2, 126.8, 124.8, 123.2, 114.1, 52.4, 24.6, 19.7, 15.0, 14.2. HRMS (ESI) calcd for $C_{15}H_{17}NO_3$ $[M + H]^+$ 260.1281, found 260.1279.

(3-(Methoxycarbonyl)benzoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 57 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL), 48 h; 66% yield (34 mg).

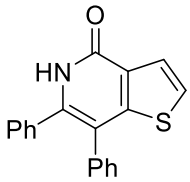


4,5-Diphenylthieno[2,3-c]pyridin-7(6H)-one (Table 3.4, Entry 1). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(thiophene-2-carbonyl)-amide (0.2 mmol, 52 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; 82% yield (50 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%);

R_f = 0.59 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.68 (d, J = 5.2 Hz, 1H), 7.37 – 7.22 (m, 8H), 7.21 – 7.15 (m, 2H), 7.07 (d, J = 5.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.1, 146.8, 139.9, 136.4, 134.2, 134.0, 130.8, 130.1, 128.4, 128.3, 128.1, 127.9, 127.0, 124.6, 114.8. This compound is known.[62]

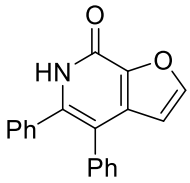


2-Methyl-4,5-diphenylthieno[2,3-c]pyridin-7(6H)-one (Table 3.4, Entry 2). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(5-methylthio-phene-2-carbonyl)amide (0.2 mmol, 55 mg), [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; mp 287−288 °C (CH_2Cl_2); 79% yield (50 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%); R_f = 0.54 (hexanes/EtOAc = 1/1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.30 – 7.17 (m, 8H), 7.15 – 7.07 (m, 2H), 6.64 (s, 1H), 2.51 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.7, 148.2, 147.3, 140.0, 136.5, 134.0, 130.8, 130.1, 128.4, 128.3, 127.8, 127.0, 126.5, 123.0, 114.5, 15.9. HRMS (ESI) calcd for $C_{20}H_{15}NOS$ $[M + H]^+$ 318.0947, found 318.0948.



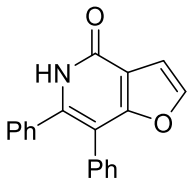
6,7-Diphenylthieno[3,2-c]pyridin-4(5H)-one (Table 3.4, Entry 3). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(thiophene-3-carbonyl)-amide (0.2 mmol, 55 mg), [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 20 h; white solid; 82% yield (50 mg); purification (gradient elution, hexanes/EtOAc, 30% → 80%);

R_f = 0.44 (hexanes/EtOAc = 1/1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.68 – 7.49 (m, 2H), 7.37 – 7.13 (m, 10H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.1, 151.8, 139.2, 137.0, 134.0, 130.7, 130.5, 129.8, 129.1, 128.4, 128.2, 126.4, 125.1, 114.2. One carbon signal could not be located. This compound is known.[63]



4,5-Diphenylfuro[2,3-c]pyridin-7(6H)-one (Table 3.4, Entry 4). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(furan-2-carbonyl)amide (0.2 mmol, 49 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; pale brown solid; 24% yield (14 mg); purification (gradient elution, hexanes/EtOAc, 30% → 80%); R_f = 0.29 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.59 (d, J = 1.8 Hz, 1H), 7.29 – 7.20 (m, 3H), 7.19 – 7.08 (m, 5H), 7.07 – 6.99 (m, 2H), 6.50 (d, J = 1.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 149.1, 141.9, 138.3, 136.4, 135.3, 134.0, 130.3, 129.6, 128.9, 128.6, 128.4, 127.5, 114.4, 107.5. This compound is known.[64]

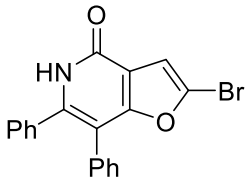
(Furan-2-carbonyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 44 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; 23% yield (13 mg).



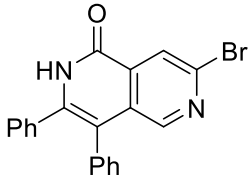
6,7-Diphenylfuro[3,2-c]pyridin-4(5H)-one (Table 3.4, Entry 5). (4-(*tert*-butyl)pyridin-1-ium-1-yl)(furan-3-carbonyl)amide (0.2 mmol, 49 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg),

pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; 65% yield (37 mg); purification (gradient elution, hexanes/EtOAc, 30% → 80%); R_f = 0.27 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.89 (s, 1H), 7.38 – 7.22 (m, 8H), 7.21 – 7.14 (m, 2H), 7.04 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.1, 158.8, 144.6, 140.8, 133.3, 132.4, 130.8, 130.1, 128.8, 128.2, 128.0, 127.2, 114.5, 108.0, 107.1. This compound is known.[63]

(Furan-3-carbonyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 44 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; 56% yield (32 mg).

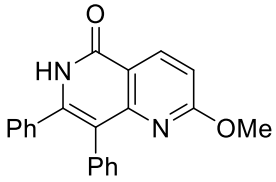


2-Bromo-6,7-diphenylfuro[3,2-c]pyridin-4(5H)-one (Table 3.4, Entry 6). (5-Bromofuran-3-carbonyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (0.2 mmol, 65 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; mp 287−288 °C (CH_2Cl_2); 70% yield (51 mg); purification (gradient elution, hexanes/EtOAc, 30% → 70%); R_f = 0.34 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (d, J = 4.3 Hz, 1H), 7.38 – 7.01 (m, 11H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.1, 157.5, 141.4, 133.0, 131.8, 130.8, 130.0, 128.9, 128.3, 128.0, 127.5, 125.0, 116.1, 109.0, 107.5. HRMS (ESI) calcd for $C_{19}H_{12}BrNO_2$ $[M + H]^+$ 366.0124, found 366.0126.



7-Bromo-3,4-diphenyl-2,6-naphthyridin-1(2H)-one (Table 3.4, Entry 7). (2-Bromoisonicotinoyl)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (0.2 mmol, 49 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; pale yellow solid; mp 261−262 °C (CH_2Cl_2); 30% yield (23 mg); purification (gradient elution, hexanes/EtOAc, 20% → 60%); R_f = 0.78 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.53 (s, 1H), 8.30 (s, 1H), 7.39 – 7.23 (m, 8H), 7.22 – 7.12 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 150.2, 139.5, 138.4, 133.9, 133.6, 132.1, 132.0, 131.6, 129.4, 129.4, 128.9, 128.6, 128.2, 123.8, 115.3. HRMS (ESI) calcd for $C_{20}H_{13}BrN_2O$ $[M + H]^+$ 377.0284, found 377.0283.

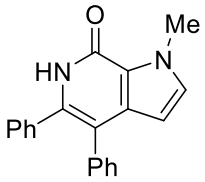
(2-Bromoisonicotinoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 62 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; 70% yield (53 mg).



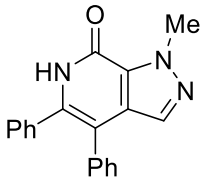
2-Methoxy-7,8-diphenyl-1,6-naphthyridin-5(6H)-one (Table 3.4, Entry 8). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(6-methoxy-nicotinoyl)amide (0.2 mmol, 57 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.04 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; white solid; mp 264−265 °C (CH_2Cl_2); 58% yield (38 mg); purification (gradient elution, hexanes/EtOAc, 30% → 70%); R_f = 0.56 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.46 (d, J = 8.7 Hz, 1H), 7.35 – 7.17 (m, 10H), 6.80 (d, J = 8.7 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 162.8, 153.6, 142.0,

138.2, 135.1, 134.9, 132.4, 129.7, 129.1, 128.5, 127.4, 126.7, 118.4, 115.8, 111.0, 53.8. HRMS (ESI) calcd for $C_{21}H_{16}N_2O_2$ $[M + H]^+$ 329.1285, found 329.1286.

(6-Methoxynicotinoyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 52 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; 53% yield (35 mg).



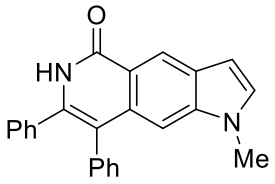
1-Methyl-4,5-diphenyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one (Table 3.4, Entry 9). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(1-methyl-1H-pyrrole-2-carbonyl)amide (0.2 mmol, 51 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; light tan solid; mp 277−278 °C (CH_2Cl_2); 68% yield (41 mg); purification (gradient elution, hexanes/EtOAc, 30% → 80%); R_f = 0.32 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.27 – 7.13 (m, 8H), 7.12 – 7.05 (m, 2H), 5.96 (d, J = 2.7 Hz, 1H), 4.11 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.4, 136.8, 134.7, 134.2, 132.6, 132.1, 130.4, 130.2, 128.1, 127.8, 126.5, 121.6, 113.2, 101.6, 35.3. HRMS (ESI) calcd for $C_{20}H_{16}N_2O$ $[M + H]^+$ 301.1335, found 301.1340.



1-Methyl-4,5-diphenyl-1,6-dihydro-7H-pyrazolo[3,4-c]pyridin-7-one (Table 3.4, Entry 10). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(1-methyl-1H-pyrazole-5-carbonyl)amide (0.2 mmol, 52 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and

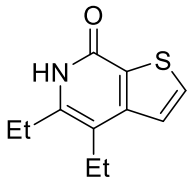
diphenylacethylene (0.4 mmol, 71 mg), 48 h; white solid; mp 243−244 °C (CH_2Cl_2); 35% yield (21 mg); purification (gradient elution, hexanes/EtOAc, 30% → 70%); R_f = 0.56 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.64 (s, 1H), 7.35 – 7.23 (m, 8H), 7.22 – 7.14 (m, 2H), 4.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 135.7, 134.5, 134.5, 133.5, 130.4, 129.8, 129.4, 128.9, 128.7, 128.6, 128.5, 127.4, 113.1, 38.5. HRMS (ESI) calcd for $C_{19}H_{15}N_3O$ [M + H]$^+$ 302.1288, found 302.1292.

(4-Methoxypyridin-1-ium-1-yl)(1-methyl-1H-pyrazole-5-carbonyl)amide (0.2 mmol, 46 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 72 h; 71% yield (43 mg).

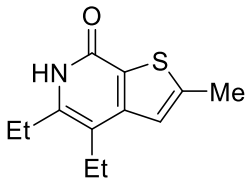


1-Methyl-7,8-diphenyl-1,6-dihydro-5H-pyrrolo[2,3-g]isoquinolin-5-one (Table 3.4, Entry 11). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(1-methyl-1H-indole-5-carbonyl)amide (0.2 mmol, 61 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; pale yellow solid; mp 332−333 °C (CH_2Cl_2); 51% yield (36 mg); purification (gradient elution, hexanes/EtOAc, 20% → 60%); R_f = 0.42 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.62 (s, 1H), 7.54 (d, J = 3.1 Hz, 1H), 7.37 – 7.26 (m, 3H), 7.25 – 7.14 (m, 7H), 7.00 (s, 1H), 6.67 (d, J = 3.1 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.7, 139.4, 136.8, 135.5, 135.3, 133.4, 132.6, 131.9, 129.9, 128.3, 128.0, 127.6, 127.6, 127.0, 119.7, 118.6, 116.0, 103.6, 101.3, 32.6. HRMS (ESI) calcd for $C_{24}H_{18}N_2O$ [M + H]$^+$ 351.1492, found 351.1499.

(4-Methoxypyridin-1-ium-1-yl)(1-methyl-1H-indole-5-carbonyl)amide (0.2 mmol, 56 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; 58% yield (33 mg).

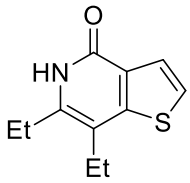


4,5-Diethylthieno[2,3-c]pyridin-7(6H)-one (Table 3.4, Entry 12). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(thiophene-2-carbonyl)amide amide (0.2 mmol, 52 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL), 48 h; pale brown solid; 72% yield (30 mg); purification (gradient elution, hexanes/EtOAc, 20% → 60%); R_f = 0.39 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 7.71 (d, J = 4.8 Hz, 1H), 7.45 – 7.21 (m, 1H), 2.93 – 2.53 (m, 4H), 1.33 (t, J = 7.0 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 148.2, 141.3, 133.2, 127.4, 123.0, 114.6, 23.7, 21.5, 15.5, 14.7. This compound is known.[62]

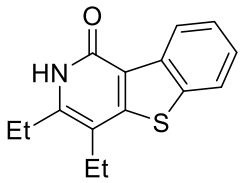


4,5-Diethyl-2-methylthieno[2,3-c]pyridin-7(6H)-one (33). (Table 3.4, Entry 13). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(5-methylthio-phene-2-carbonyl)amide (0.2 mmol, 55 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL), 48 h; pale brown solid; mp 213−214 °C (CH_2Cl_2); 68% yield (30 mg); purification (gradient elution, hexanes/EtOAc, 20% → 60%); R_f = 0.37 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 6.93 (s, 1H), 2.74 – 2.62 (m, 4H), 2.61 (s, 3H),

1.28 (t, J = 7.5 Hz, 3H), 1.17 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 148.9, 148.6, 141.2, 126.0, 121.3, 114.3, 23.7, 21.4, 16.6, 15.4, 14.6. HRMS (ESI) calcd for $C_{12}H_{15}NOS$ $[M + H]^+$ 222.0947, found 222.0949.

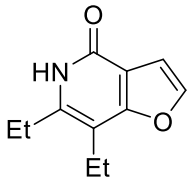


6,7-Diethylthieno[3,2-c]pyridin-4(5H)-one (34). (Table 3.4, Entry 14). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(thiophene-3-carbonyl)amide (0.2 mmol, 52 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL), 20 h; white solid; 72% yield (30 mg); purification (gradient elution, hexanes/EtOAc, 20% → 80%); R_f = 0.24 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 7.65 (d, J = 5.4 Hz, 1H), 7.27 – 7.20 (m, 1H), 2.77 – 2.60 (m, 4H), 1.32 (t, J = 7.6 Hz, 3H), 1.25 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 152.4, 140.3, 128.5, 125.1, 123.2, 113.9, 23.7, 23.1, 14.3, 14.3. This compound is known.[62]



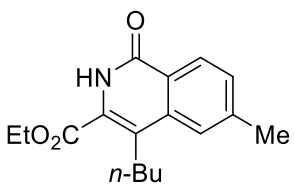
3,4-Diethylbenzo[4,5]thieno[3,2-c]pyridin-1(2H)-one (Table 3.4, Entry 15). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(thiophene-3-carbonyl)amide (0.2 mmol, 62 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL), 20 h; white solid; mp 229−230 °C (CH_2Cl_2); 87% yield (45 mg); purification (gradient elution, hexanes/EtOAc, 20% → 70%); R_f = 0.45 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.5

Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 2.86 (q, *J* = 7.6 Hz, 2H), 2.73 (q, *J* = 7.5 Hz, 2H), 1.45 (t, *J* = 7.6 Hz, 3H), 1.28 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 154.0, 143.4, 137.5, 137.3, 125.3, 125.3, 124.7, 121.9, 121.2, 114.1, 23.9, 23.1, 14.4, 14.4. HRMS (ESI) calcd for $C_{15}H_{15}NOS$ $[M + H]^+$ 258.0947, found 258.0948.

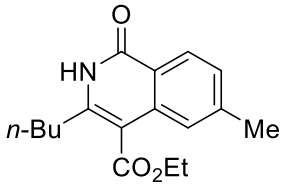


6,7-Diethylfuro[3,2-c]pyridin-4(5H)-one (Table 3.4, Entry 16). (4-(*tert*-Butyl)pyridin-1-ium-1-yl)(furan-3-carbonyl)amide (0.2 mmol, 49 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL), 48 h; white solid; mp 150−151 °C (CH_2Cl_2); 18% yield (7 mg); purification (gradient elution, hexanes/EtOAc, 20% → 80%); R_f = 0.21 (hexanes/EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 7.48 (s, 1H), 6.95 (s, 1H), 2.77 – 2.60 (m, 4H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 160.9, 142.9, 142.4, 113.7, 108.6, 107.0, 23.6, 18.2, 15.0, 14.5. HRMS (ESI) calcd for $C_{11}H_{13}NO_2$ $[M + H]^+$ 192.1019, found 192.1017.

(Furan-3-carbonyl)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 44 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg), 48 h; 30% yield (11 mg).



and

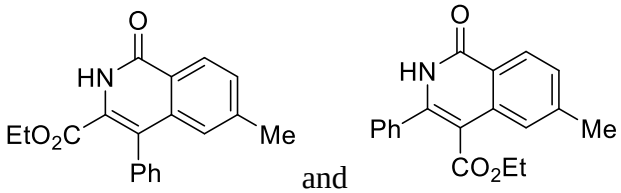


Ethyl 4-butyl-6-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylate (3-4) and ethyl 3-butyl-6-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3-5). Ylide **3-2** (0.2 mmol, 48 mg),

$[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and ethyl hept-2-ynoate (0.4 mmol, 62 mg), 24 h; white solid; mp 141−142 °C (CH_2Cl_2); 50% yield (29 mg); purification (gradient elution, hexanes/EtOAc, 20% → 40%); R_f = 0.42 (hexanes/EtOAc = 1/3); **3-4:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 4.45 (q, J = 6.9 Hz, 2H), 3.19 (d, J = 7.5 Hz, 2H), 2.56 (s, 3H), 1.66 – 1.57 (m, 2H), 1.57 – 1.49 (m, 2H), 1.45 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 161.0, 143.6, 137.3, 130.6, 128.2, 126.2, 125.5, 125.1, 124.3, 62.6, 32.8, 26.6, 23.3, 22.4, 14.4, 14.1. HRMS (ESI) calcd for $C_{17}H_{21}NO_3$ $[M + H]^+$ 288.1594, found 288.1596.

3-5: White solid; mp 209−210 °C (CH_2Cl_2); 7% yield (4 mg); R_f = 0.55 (hexanes/EtOAc = 1/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (s, 1H), 8.28 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.30 (d, J = 8.1 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 2.85 – 2.71 (m, 2H), 2.49 (s, 3H), 1.82 – 1.69 (m, 2H), 1.52 – 1.37 (m, 5H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5, 164.1, 144.6, 144.0, 135.9, 128.2, 127.4, 124.2, 122.0, 109.2, 61.4, 32.5, 31.6, 22.8, 22.4, 14.5, 13.9. HRMS (ESI) calcd for $C_{17}H_{21}NO_3$ $[M + H]^+$ 288.1594, found 288.1596.

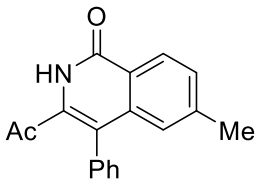
Ylide **3-3** (0.2 mmol, 54 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL) and ethyl hept-2-ynoate (0.4 mmol, 62 mg), 48 h; **3-4**: 47% yield (27 mg) and **3-5**: 7% yield (4 mg).

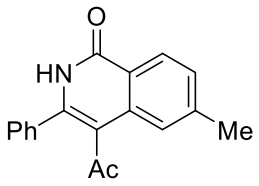


Ethyl 6-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylate (3-6) and ethyl 6-methyl-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carboxylate (3-7). Ylide **3-2** (0.2 mmol, 48 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1

mL), and ethyl 3-phenylpropiolate (0.4 mmol, 70 mg). 24 h; white solid; mp 181−182 °C (CH_2Cl_2); 38% yield (23 mg); purification (gradient elution, hexanes/EtOAc, 20% → 50%); R_f = 0.35 (hexanes/acetone = 1/3); **3-6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.41 (d, J = 8.1 Hz, 1H), 7.52 – 7.41 (m, 4H), 7.29 – 7.19 (m, 2H), 6.97 (s, 1H), 4.07 (q, J = 7.2 Hz, 2H), 2.36 (s, 3H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 161.3, 143.6, 138.2, 135.9, 130.7, 130.0, 128.3, 127.8, 127.7, 125.6, 125.0, 124.9, 62.2, 22.1, 13.4. One carbon signal could not be located. HRMS (ESI) calcd for $C_{19}H_{17}NO_3$ $[M + H]^+$ 308.1281, found 308.1283. Structure of this compound was verified by X-ray crystallographic analysis after recrystallization from diethyl ether. **3-7**: White solid; mp 197−198 °C (CH_2Cl_2); 18% yield (11 mg); R_f = 0.30 (hexanes/acetone = 1/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 7.71 (s, 1H), 7.50 (q, J = 3.5, 2.4 Hz, 5H), 7.35 (d, J = 8.2 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 162.7, 144.4, 141.8, 135.4, 135.0, 130.0, 129.0, 128.1, 127.8, 124.4, 122.5, 110.2, 61.3, 22.3, 13.6. One carbon signal could not be located. HRMS (ESI) calcd for $C_{19}H_{17}NO_3$ [M + H]+ 308.1281, found 308.1284.

Ylide **3-3** (0.2 mmol, 54 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.04 mmol, 32 mg), pivalic acid (0.06 mmol, 6 mg), HFIP (1 mL), and ethyl hept-2-ynoate (0.4 mmol, 62 mg), 48 h; **3-6**: 39% yield (24 mg) and **3-7**: 18% yield (11 mg).



and


3-Acetyl-6-methyl-4-phenylisoquinolin-1(2H)-one (3-8) and 4-acetyl-6-methyl-3-phenylisoquinolin-1(2H)-one (3-9). Ylide **3-2** (0.2 mmol, 48 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 4-phenylbut-3-yn-2-one (0.4

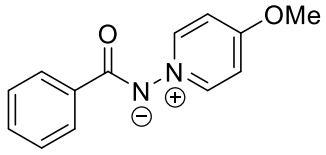
mmol, 58 mg). 24 h; **3-8**: white solid; mp 254−255 °C (CH_2Cl_2); 24% yield (13 mg); purification (gradient elution, hexanes/EtOAc, 20% → 60%); R_f = 0.14 (hexanes/EtOAc = 1/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.29 (d, J = 8.1 Hz, 1H), 7.65 – 7.49 (m, 6H), 7.36 (d, J = 8.1 Hz, 1H), 2.49 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7, 162.9, 144.5, 139.4, 134.9, 134.1, 130.8, 129.5, 129.0, 128.9, 127.9, 124.1, 122.7, 118.6, 32.9, 22.3. HRMS (ESI) calcd for $C_{18}H_{15}NO_2$ $[M + H]^+$ 278.1176, found 278.1176.

3-9: White solid; mp 191−192 °C (CH_2Cl_2); 28% yield (16 mg); R_f = 0.23 (hexanes/EtOAc = 1/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.41 (d, J = 8.1 Hz, 1H), 7.65 – 7.52 (m, 3H), 7.45 (d, J = 8.1 Hz, 1H), 7.40 – 7.30 (m, 2H), 6.93 (s, 1H), 2.37 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 161.0, 143.6, 138.2, 135.6, 131.7, 131.1, 130.8, 129.4, 129.2, 128.0, 127.8, 126.0, 125.2, 29.9, 22.1. HRMS (ESI) calcd for $C_{18}H_{15}NO_2$ [M + H]+ 278.1180, found 278.1176.

Ylide **3** (0.2 mmol, 54 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and ethyl hept-2-ynoate (0.4 mmol, 62 mg), 48 h; **3-8**: 25% yield (14 mg) and **3-9**: 20% yield (11 mg).

Deuterium labeling study experiments and mechanistic investigations.

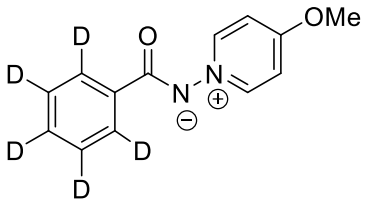
Preparation of non-deuterated substrates and deuterated substrates.



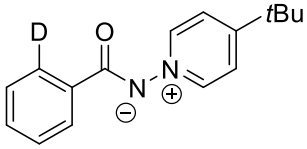
Benzoyl(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with benzoic acid (0.49 g, 4 mmol). Yield: 0.56 g, 61%; appearance: white solid; purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 6.5 Hz, 2H), 8.12 (d, J =

5.7 Hz, 2H), 7.48 – 7.33 (m, 3H), 7.05 (d, J = 6.5 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 166.0, 145.1, 137.4, 130.1, 128.0, 127.9, 111.5, 56.9.

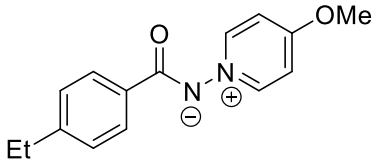
This compound is known.[65]



(Benzoyl-2,3,4,5,6-d$_5$)(4-methoxypyridin-1-ium-1-yl)amide. Method A was employed, with benzoic-2,3,4,5,6-d_5 acid (0.25 g, 2 mmol). Yield: 0.30 g, 64%; appearance: white solid; ^{1}H NMR (400 MHz, $CDCl_0$) δ 8.52 (d, J = 4.4 Hz, 2H), 7.05 (d, J = 4.4 Hz, 2H), 3.97 (s, 3H).

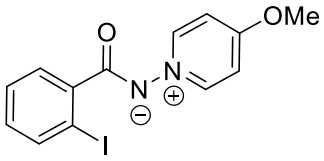


(Benzoyl-2-d)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide. Method A was employed, with benzoic-2-*d* acid[66] (0.25 g, 2 mmol). Yield: 0.42 g, 82%; appearance: white solid; purification (gradient elution, EtOAc/MeOH, 0% → 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 6.9 Hz, 2H), 8.14 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 6.9 Hz, 2H), 7.46 – 7.36 (m, 3H), 1.38 (s, 9H).



(4-Ethylbenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (3-10). Method A was employed, with 4-ethylbenzoic acid (0.60 g, 4 mmol). Yield: 0.62 g, 60%; Appearance: white solid; mp 179−180 °C (EtOAc/MeOH = 10:1); R_f = 0.37 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 5.8 Hz, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.05 (d, J = 6.0 Hz, 1H), 3.96 (s, 1H), 2.67 (q, J =

7.1 Hz, 1H), 1.24 (t, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 166.0, 146.4, 145.2, 134.8, 128.0, 127.5, 111.4, 56.9, 28.9, 15.6.

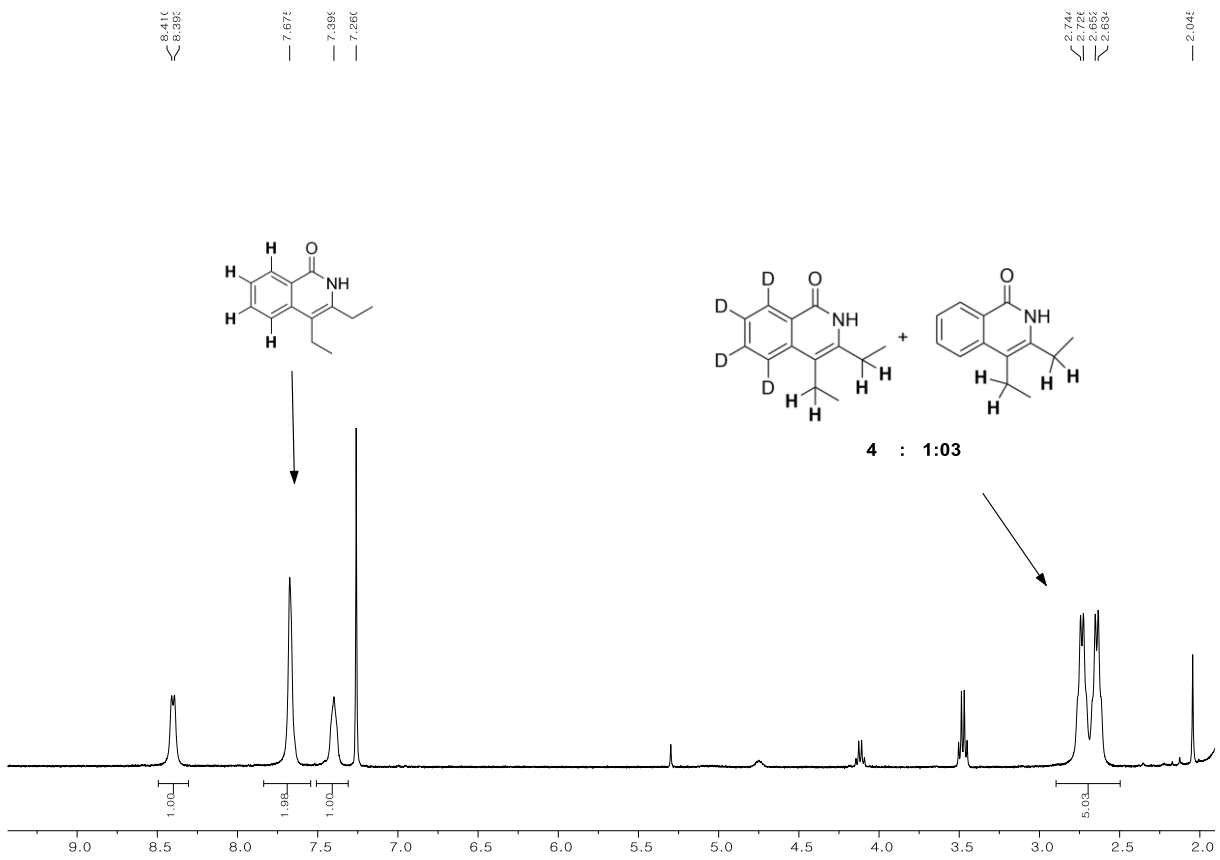


(2-Iodobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide (3-11). Method A was employed, with 2-iodobenzoic acid (0.99 g, 4 mmol). Yield: 0.92 g, 65%; appearance: white solid; mp 195−196 °C (EtOAc/MeOH = 10:1); R_f = 0.37 (EtOAc/MeOH = 5/1); purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 6.5 Hz, 2H), 7.83 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.15 – 7.05 (m, 2H), 6.99 (t, J = 7.6 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 166.4, 144.7, 144.4, 139.4, 129.6, 128.6, 128.0, 111.7, 94.8, 57.0.

Intermolecular competition KIE

A 2-dram vial equipped with a magnetic stir bar was charged with benzoyl(4-methoxypyridin-1-ium-1-yl)amide (0.1 mmol, 23 mg), (benzoyl-2,3,4,5,6-d_5)(4-methoxypyridin-1-ium-1-yl)amide (0.1 mmol, 23 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL). The vial was closed with a screw cap after flushing with nitrogen. The mixture was stirred in a heating block at 110 °C for 30 min. After the mixture was cooled, ethyl acetate was added, and the diluted mixture was poured into a round bottom flask. The mixture was absorbed on 3 g of silica gel and purified by column chromatography on silica gel. The purified mixture was used to check the ratio of products by ^{1}H-NMR spectroscopy signal.

Figure 3.1. ^{1}H NMR spectrum of intermolecular competition KIE

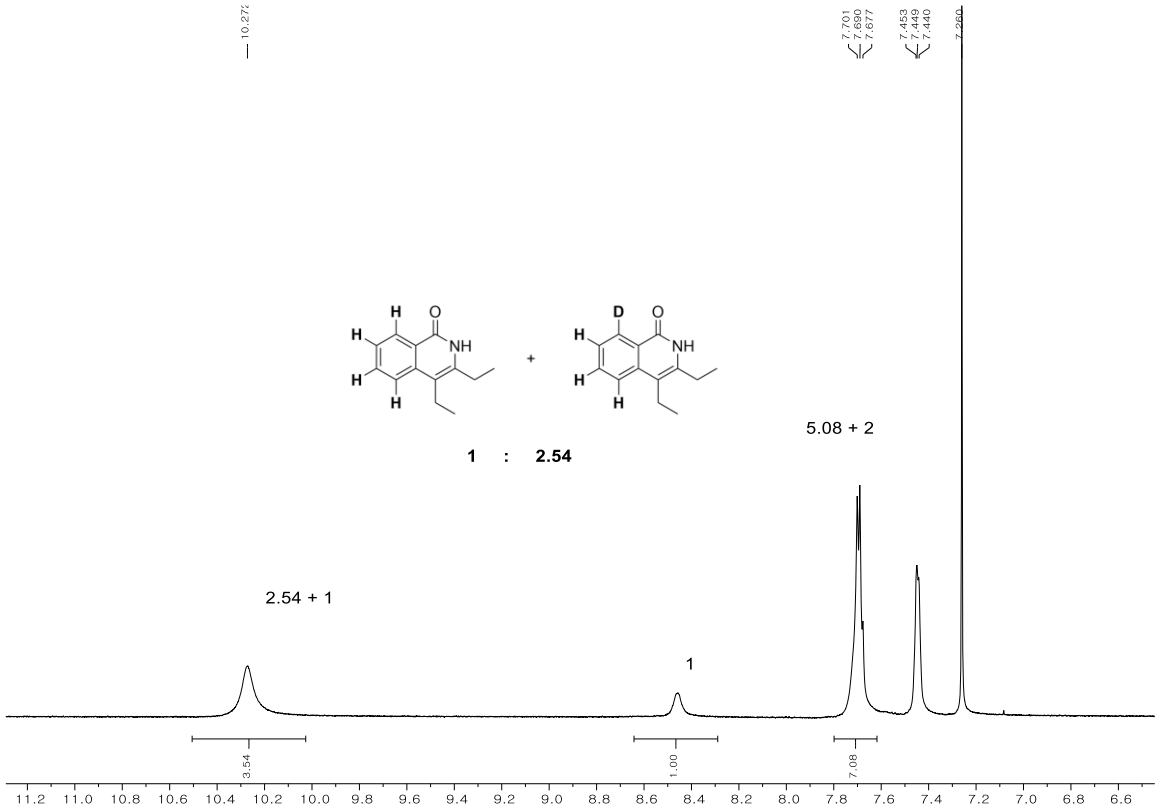


Intramolecular competition KIE

A 2-dram vial equipped with a magnetic stir bar was charged with (benzoyl-2-*d*)(4-(*tert*-butyl)pyridin-1-ium-1-yl)amide (0.2 mmol, 51 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and 3-hexyne (0.4 mmol, 45 μL). The vial was closed with a screw cap after flushing with nitrogen. The mixture was stirred in a heating block at 110 °C for 30 min. After the mixture was cooled, ethyl acetate was added, and the diluted mixture

was poured into a round bottom flask. The mixture was absorbed on 3 g of silica gel and purified by column chromatography on silica gel. The purified mixture was used to check the ratio of products by ^{1}H-NMR spectroscopy.

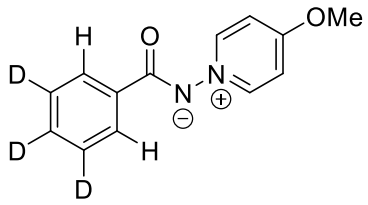
Figure 3.2. ^{1}H NMR spectrum of intramolecular competition KIE



Deuterium-proton exchange experiment

A 2-dram vial equipped with a magnetic stir bar was charged with (benzoyl-2,3,4,5,6-d_5)(4-methoxypyridin-1-ium-1-yl)amide (0.2 mmol, 46 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL). The vial was closed with a screw cap after flushing with nitrogen. The mixture was stirred in a heating block at 110 °C for 24 h. After the mixture was cooled, ethyl acetate was added, and the diluted mixture was poured into a round

bottom flask. The mixture was absorbed on 3 g of silica gel and purified by column chromatography on silica gel.

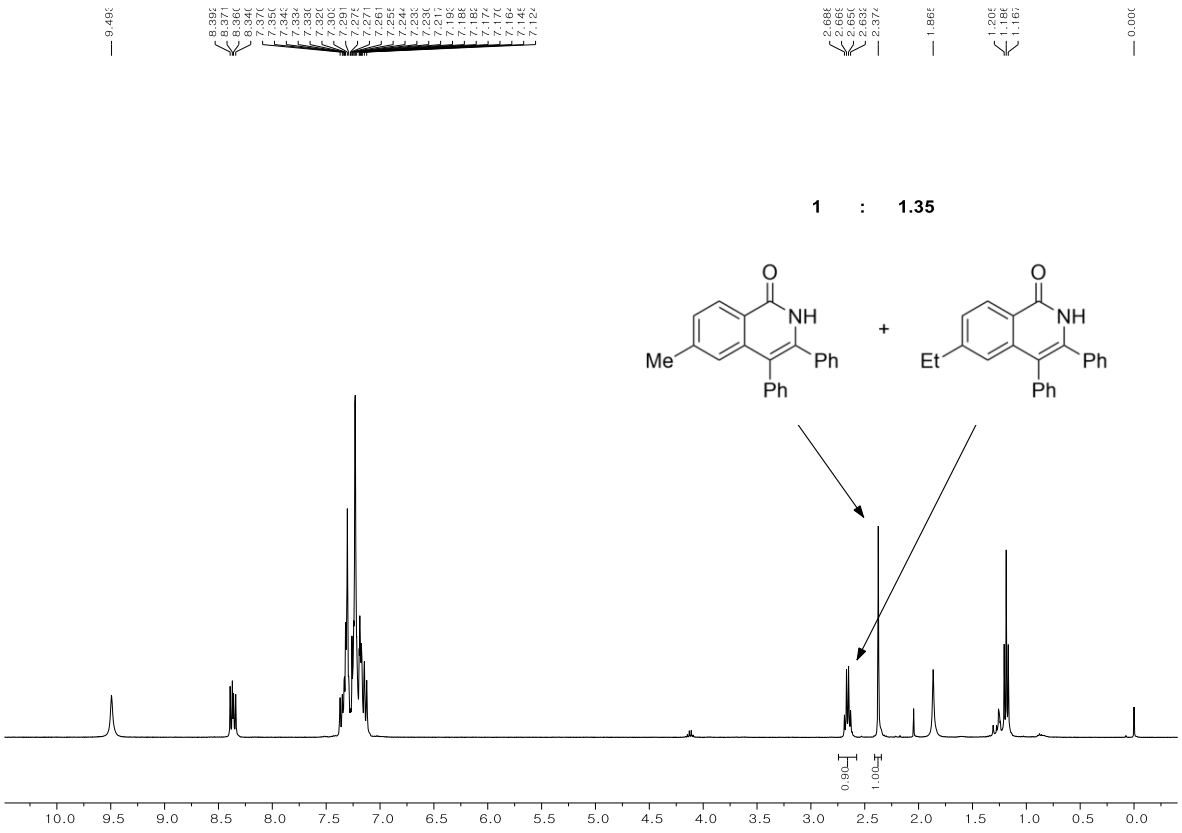


(Benzoyl-3,4,5-d3)(4-methoxypyridin-1-ium-1-yl)amide. Yield: 30 mg, 65%; Appearance: white solid; purification (gradient elution, EtOAc/MeOH, 0% → 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 6.0 Hz, 2H), 8.13 (s, 2H), 7.07 (d, J = 5.5 Hz, 2H), 3.99 (s, 3H).

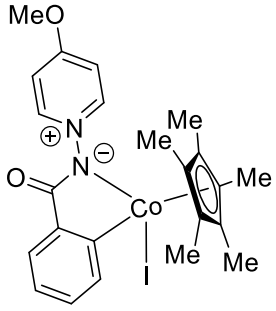
Intermolecular competition experiment between (4-(*tert*-butyl)pyridin-1-ium-1-yl)(4-methylbenzoyl)amide and (4-ethylbenzoyl)(4-methoxypyridin-1-ium-1-yl)amide.

A 2-dram vial equipped with a magnetic stir bar was charged with (4-(*tert*-butyl)pyridin-1-ium-1-yl)(4-methylbenzoyl)amide **3-2** (0.1 mmol, 27 mg), (4-ethylbenzoyl)(4-methoxypyridin-1-ium-1-yl)amide **3-10** (0.1 mmol, 26 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.03 mmol, 24 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.1 mmol, 18 mg). The vial was closed with a screw cap after flushing with nitrogen. The mixture was stirred in a heating block at 110 °C for 90 min. After the mixture was cooled, ethyl acetate was added, and the diluted mixture was poured into a round bottom flask. The mixture was absorbed on 3 g of silica gel and purified by column chromatography on silica gel. The purified mixture was used to check the ratio of products by ^{1}H-NMR spectroscopy.

Figure 3.3. ^{1}H NMR spectrum of competition reaction



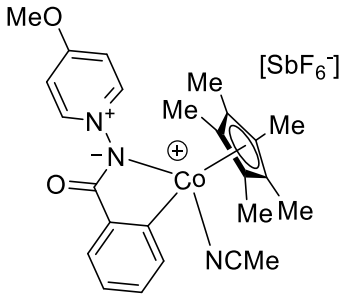
Preparation of cobaltacycles



(3-12)

The oven dried flask was charged with $Co_2(CO)_8$ (0.5 mmol, 0.17 g), CH_2Cl_2 (50 mL), and 1,2,3,4,5-pentamethylcyclopentadiene (1.2 mmol, 188 μL). The mixture was refluxed under a

nitrogen atmosphere for 4 h and cooled to room temperature. The solvent was removed under vacuum. The residue was dissolved in THF (10 mL). (2-Iodobenzoyl)(4-methoxypyridin-1-ium-1-yl)amide **3-11** (0.95 mmol, 0.34 g) as a solution in THF (30 mL) was added to the solution at room temperature and refluxed for 20 h under a nitrogen atmosphere. After removal of the solvent, the resulting residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 1:1 to CH_2Cl_2/EtOAc/MeOH 5:5:1) to provide the complex **3-12** (0.39 g, 74%). Structure of this compound was verified by X-ray crystallographic analysis after recrystallization from CH_2Cl_2 and diethyl ether at room temperature. appearance: black olive solid; R_f = 0.50 (CH_2Cl_2/EtOAc/MeOH = 5/5/1); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.34 (s, 2H), 8.36 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.1 Hz, 2H), 7.25 – 7.10 (m, 2H), 7.03 (t, J = 7.3 Hz, 1H), 3.98 (s, 3H), 1.33 (s, 15H). ^{13}C NMR (151 MHz, CD_2Cl_2) δ 177.3, 173.7, 168.3, 148.2, 142.7, 139.4, 130.6, 126.3, 122.5, 112.0, 91.8, 58.1, 10.4.



(3-13)

To a flask was added pyidinium ylide cobaltacycle **3-12** (0.11 g, 0.2 mmol) and CH_3CN (3 mL). To the solution was added the solution of $AgSbF_6$ (0.08 g, 0.24 mmol) in CH_3CN (5 mL) dropwise at room temperature. The suspension was stirred for 2 h at room temperature under a nitrogen atmosphere. Then the suspension was filtered through celite and washed with CH_3CN (5 mL). After removal of the solvent, the resulting solid **3-13** was used without further purification. Yield: 120 mg, 86%; appearance: dark purple solid; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.63 (d, J = 6.7 Hz, 2H), 8.17 (d, J = 7.7 Hz, 1H), 7.63 – 7.41 (m, 4H), 7.23 – 7.07 (m, 1H), 4.13 (s, 3H), 2.25 (s, 3H),

1.24 (s, 15H). ^{13}C NMR (151 MHz, CD_2Cl2) δ 169.6, 169.3, 147.5, 139.7, 138.7, 138.5, 132.1, 127.3, 124.5, 113.2, 95.4, 58.4, 58.4, 9.4, 4.5.

The use of cationic cobaltacycle as a catalyst.

A 2-dram vial equipped with a magnetic stir bar was charged with (4-methoxypyridin-1-ium-1-yl)(4-methylbenzoyl)amide (0.2 mmol, 48 mg), pyridinium ylide cationic cobaltacycle **3-13** (0.03 mmol, 21 mg), pivalic acid (0.04 mmol, 4 mg), HFIP (1 mL), and diphenylacethylene (0.4 mmol, 71 mg). The vial was closed with a screw cap after flushing with nitrogen. The mixture was stirred in a heating block at 110 °C for 20 h. After the mixture was cooled, ethyl acetate was added, and the diluted mixture was poured into a round bottom flask. The mixture was absorbed on 3 g of silica gel and purified by column chromatography on silica gel. The purified mixture was used to check the yield (68%) using 1,3,5-trimethoxybenzene as an internal standard.

Bibliography

1. (a) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-catalyzed cross-coupling: a historical contextual perspective to the 2010 nobel prize. *Angew. Chem. Int. Ed.* **2012,** *51*, 5062-5085; (b) Gildner, P. G.; Colacot, T. J. Reactions of the 21st century: two decades of innovative catalyst design for palladium-catalyzed cross-couplings. *Organometallics* **2015,** *34*, 5497-5508; (c) Campeau, L. C.; Hazari, N. Cross-coupling and related reactions: connecting past success to the development of new reactions for the future. *Organometallics* **2019,** *38*, 3-35.

2. (a) Rej, S.; Ano, Y.; Chatani, N. Bidentate directing groups: an efficient tool in C–H bond functionalization chemistry for the expedient construction of C–C bonds. *Chem. Rev.* **2020,** *120*, 1788-1887; (b) Xu, X.; Luo, J. Transition metal-catalyzed directing-group-assisted C−H activation of phenols. *ChemSusChem* **2019,** *12*, 4601-4616; (c) Sambiagio, C.; Schonbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnurch, M. A comprehensive overview of directing groups applied in metal-catalysed C−H functionalisation chemistry. *Chem. Soc. Rev.* **2018,** *47*, 6603-6743; (d) Rouquet, G.; Chatani, N. Catalytic functionalization of C(sp^2)-H and C(sp^3)-H bonds by using bidentate directing groups. *Angew. Chem. Int. Ed.* **2013,** *52*, 11726-11743; (e) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. Recent advances in directed C–H functionalizations using monodentate nitrogen-based directing groups. *Org. Chem. Front.* **2014,** *1*, 843-895.

3. Sambiagio, C.; Schonbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnurch, M. A comprehensive overview of directing groups applied in metal-catalysed C−H functionalisation chemistry. *Chem. Soc. Rev.* **2018,** *47*, 6603-6743.

4. Lim, Y.-G.; Kim, Y. H.; Kang, J.-B. Rhodium-catalysed regioselective alkylation of the phenyl ring of 2-phenylpyridines with olefins. *J. Chem. Soc., Chem. Commun.* **1994**, 2267.

5. Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. $Ru_3(CO)_{12}$-catalyzed reaction of pyridylbenzenes with carbon monoxide and olefins. carbonylation at a C−H bond in the benzene ring. *J. Org. Chem.* **1997,** *62*, 2604-2610.

6. Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. $Ru_3(CO)_{12}$-catalyzed coupling reaction of sp^3 C−H bonds adjacent to a nitrogen atom in alkylamines with alkenes. *J. Am. Chem. Soc.* **2001,** *123*, 10935-10941.

7. (a) Shabashov, D.; Daugulis, O. Catalytic coupling of C-H and C-I bonds using pyridine as a directing group. *Org. Lett.* **2005,** *7*, 3657-3659; (b) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. Expedient C–H amidations of heteroaryl arenes catalyzed by versatile ruthenium(II) catalysts. *Org. Lett.* **2013,** *15*, 3286-3289; (c) Hofmann, N.; Ackermann, L. *meta*-Selective C–H bond alkylation with secondary alkyl halides. *J. Am. Chem. Soc.* **2013,** *135*, 5877-5884; (d) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. Ruthenium-catalyzed carbonylative C–C coupling in water by directed C–H bond activation. *Angew. Chem. Int. Ed.* **2013,** *52*, 6293-6297; (e) Batchu, H.; Bhattacharyya, S.; Kant, R.; Batra, S. Palladium-catalyzed chelation-assisted regioselective oxidative dehydrogenative homocoupling/*ortho*-hydroxylation in *N*-phenylpyrazoles. *J. Org. Chem.* **2015,** *80*, 7360-7374; (f) Moselage, M.; Li, J.; Kramm, F.; Ackermann, L. Ruthenium(II)-catalyzed C-C arylations and alkylations: decarbamoylative C-C functionalizations. *Angew. Chem. Int. Ed.* **2017,** *56*, 5341-5344; (g) Dongbang, S.; Shen, Z.; Ellman, J. A. Synthesis of homoallylic alcohols with acyclic quaternary centers through Co^{III}-catalyzed three-component C−H bond addition to Internally substituted dienes and carbonyls. *Angew. Chem. Int. Ed.* **2019,** *58*, 12590-12594; (h) Zhang, Z.; Tang, M.; Han, S.; Ackermann, L.;

Li, J. Carboxylate-enhanced rhodium(III)-catalyzed aryl C–H alkylation with conjugated alkenes under mild conditions. *J. Org. Chem.* **2017,** *82*, 664-672.

8. (a) Yu, D. G.; Gensch, T.; de Azambuja, F.; Vasquez-Cespedes, S.; Glorius, F. Co(III)-catalyzed C–H activation/formal SN-type reactions: selective and efficient cyanation, halogenation, and allylation. *J. Am. Chem. Soc.* **2014,** *136*, 17722-17725; (b) Gensch, T.; Vasquez-Cespedes, S.; Yu, D. G.; Glorius, F. Cobalt(III)-catalyzed directed C–H allylation. *Org. Lett.* **2015,** *17*, 3714-3717; (c) De, P. B.; Pradhan, S.; Banerjee, S.; Punniyamurthy, T. Expedient cobalt(II)-catalyzed site-selective C7-arylation of indolines with arylboronic acids. *Chem. Commun.* **2018,** *54*, 2494-2497; (d) Wang, C. M.; Rueping, M. Rhenium- and manganese-catalyzed selective alkenylation of indoles. *Chemcatchem* **2018,** *10*, 2681-2685; (e) Kurihara, T.; Kojima, M.; Yoshino, T.; Matsunaga, S. Cp*Co^{III}/chiral carboxylic acid-catalyzed enantioselective 1,4-addition reactions of indoles to maleimides. *Asian J. Org. Chem.* **2019,** *9*, 368-371; (f) Li, S.; Shi, P.; Liu, R. H.; Hu, X. H.; Loh, T. P. Cobalt-catalyzed N-O and C-C bond cleavage in 1,2-oxazetidines: solvent-controlled C–H aminomethylation and hydroxymethylation of heteroarenes. *Org. Lett.* **2019,** *21*, 1602-1606; (g) Zhou, Y.; Li, C.; Yuan, X.; Zhang, F.; Liu, X.; Liu, P. Cobalt-catalyzed C2α-acyloxylation of 2-substituted indoles with *tert*-butyl peresters. *Org Biomol Chem* **2019,** *17*, 3343-3347.

9. (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. A Highly selective catalytic method for the oxidative functionalization of C−H bonds. *J. Am. Chem. Soc.* **2004,** *126*, 2300-2301; (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. Oxidative C−H activation/C−C bond forming reactions: synthetic scope and mechanistic insights. *J. Am. Chem. Soc.* **2005,** *127*, 7330-7331; (c) Chen, X.; Goodhue, C. E.; Yu, J.-Q. Palladium-catalyzed alkylation of sp^2 and sp^3 C−H bonds with

methylboroxine and alkylboronic acids: two distinct C−H activation pathways. *J. Am. Chem. Soc.* **2006,** *128*, 12634-12635.

10. (a) Maiden, T. M. M.; Swanson, S.; Procopiou, P. A.; Harrity, J. P. A. A mild and regioselective route to functionalized quinazolines. *Chem. Eur. J.* **2015,** *21*, 14342-14346; (b) Mei, R.; Loup, J.; Ackermann, L. Oxazolinyl-assisted C–H amidation by cobalt(III) catalysis. *ACS Catal.* **2016,** *6*, 793-797.

11. Peng, Z.; Yu, Z.; Li, T.; Li, N.; Wang, Y.; Song, L.; Jiang, C. Catalytic Regioselective C–H Acetoxylation of Arenes Using 4,6-Dimethoxy-1,3,5-triazin-2-yloxy as a Removable/Modifiable Directing Group. *Organometallics* **2017,** *36*, 2826-2831.

12. Pawar, A. B.; Chang, S. Cobalt-catalyzed C–H cyanation of (hetero)arenes and 6-arylpurines with *N*-cyanosuccinimide as a new cyanating agent. *Org. Lett.* **2015,** *17*, 660-663.

13. (a) Liu, B.; Li, R.; Zhan, W.; Wang, X.; Ge, Z.; Li, R. Rh(III)-catalyzed C–H oxidative ortho-olefination of arenes using 7-azaindole as a directing group and utilization in the construction of new tetracyclic heterocycles containing a 7-azaindole skeleton. *RSC Advances* **2016,** *6*, 48205-48211; (b) Pipaliya, B. V.; Chakraborti, A. K. Ligand-assisted heteroaryl C(sp^2)−H bond activation by a cationic ruthenium(II) complex for alkenylation of heteroarenes with alkynes directed by biorelevant heterocycles. *ChemCatChem* **2017,** *9*, 4191-4198; (c) Pipaliya, B. V.; Chakraborti, A. K. Cross-dehydrogenative coupling of heterocyclic scaffolds with unfunctionalized aroyl surrogates by palladium(II) catalyzed C(sp^2)–H aroylation through organocatalytic dioxygen activation. *J. Org. Chem.* **2017,** *82*, 3767-3780.

14. (a) Ackermann, L.; Diers, E.; Manvar, A. Ruthenium-catalyzed C–H bond arylations of arenes bearing removable directing groups via six-membered ruthenacycles. *Org. Lett.* **2012,** *14*, 1154-1157; (b) Smout, V.; Peschiulli, A.; Verbeeck, S.; Mitchell, E. A.; Herrebout, W.; Bultinck, P.;

Vande Velde, C. M.; Berthelot, D.; Meerpoel, L.; Maes, B. U. Removal of the pyridine directing group from alpha-substituted *N*-(pyridin-2-yl)piperidines obtained via directed Ru-catalyzed sp^3 C–H functionalization. *J. Org. Chem.* **2013,** *78*, 9803-9814.

15. Ackermann, L.; Lygin, A. V. Ruthenium-catalyzed direct C–H bond arylations of heteroarenes. *Org. Lett.* **2011,** *13*, 3332-3335.

16. Kashima, C.; Hibi, S.; Maruyama, T.; Harada, K.; Omote, Y. Ozonolysis of five-membered heterocycles. *J. Heterocycl. Chem.* **1987,** *24*, 637-639.

17. (a) Gulia, N.; Daugulis, O. Palladium-catalyzed pyrazole-directed sp^3 C–H bond arylation for the synthesis of beta-phenethylamines. *Angew. Chem. Int. Ed.* **2017,** *56*, 3630-3634; (b) Moselage, M.; Li, J.; Kramm, F.; Ackermann, L. Ruthenium(II)-catalyzed C-C arylations and alkylations: decarbamoylative C-C functionalizations. *Angew. Chem. Int. Ed.* **2017,** *56*, 5341-5344.

18. (a) Johnson, L. K.; Killian, C. M.; Brookhart, M. New Pd(II)- and Ni(II)-based catalysts for polymerization of ethylene and .alpha.-olefins. *J. Am. Chem. Soc.* **1995,** *117*, 6414-6415; (b) Ittel, S. D.; Johnson, L. K.; Brookhart, M. Late-metal catalysts for ethylene homo- and copolymerization. *Chem. Rev.* **2000,** *100*, 1169-1204; (c) Meinhard, D.; Wegner, M.; Kipiani, G.; Hearley, A.; Reuter, P.; Fischer, S.; Marti, O.; Rieger, B. New nickel(II) diimine complexes and the control of polyethylene microstructure by catalyst design. *J. Am. Chem. Soc.* **2007,** *129*, 9182-9191.

19. (a) Haridharan, R.; Muralirajan, K.; Cheng, C.-H. Rhodium(III)-catalyzed ortho-arylation of anilides with aryl halides. *Adv. Synth. Catal.* **2015,** *357*, 366-370; (b) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, monoanionic auxiliary-directed functionalization of carbon-hydrogen bonds. *Acc. Chem. Res.* **2015,** *48*, 1053-1064; (c) Li, D.; Xu, N.; Zhang, Y.; Wang, L. A highly efficient Pd-catalyzed decarboxylative ortho-arylation of amides with aryl acylperoxides. *Chem. Commun.* **2014,** *50*, 14862-14865; (d) Engle, K. M.; Mei, T. S.; Wang, X.; Yu, J. Q. Bystanding F^+ oxidants

enable selective reductive elimination from high-valent metal centers in catalysis. *Angew. Chem. Int. Ed.* **2011,** *50*, 1478-1491; (e) Ackermann, L. Carboxylate-assisted transition-metal-catalyzed C-H bond functionalizations: mechanism and scope. *Chem. Rev.* **2011,** *111*, 1315-45; (f) Yeung, C. S.; Zhao, X. D.; Borduas, N.; Dong, V. M. Pd-catalyzed ortho-arylation of phenylacetamides, benzamides, and anilides with simple arenes using sodium persulfate. *Chem. Sci.* **2010,** *1*, 331-336; (g) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-catalyzed C−C bond formation via heteroatom-directed C−H bond activation. *Chem. Rev.* **2010,** *110*, 624-655; (h) Li, B. J.; Tian, S. L.; Fang, Z.; Shi, Z. J. Multiple C−H activations to construct biologically active molecules in a process completely free of organohalogen and organometallic components. *Angew. Chem. Int. Ed.* **2008,** *47*, 1115-1118; (i) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. Oxidative C−H activation/C−C bond forming reactions: synthetic scope and mechanistic insights. *J. Am. Chem. Soc.* **2005,** *127*, 7330-7331.

20. (a) Zhang, D.; Nadres, E. T.; Brookhart, M.; Daugulis, O. Synthesis of highly branched polyethylene using "sandwich" (8-*p*-tolyl naphthyl α-diimine)nickel(II) catalysts. *Organometallics* **2013,** *32*, 5136-5143; (b) Chen, Z.; Liu, W.; Daugulis, O.; Brookhart, M. Mechanistic studies of Pd(II)-catalyzed copolymerization of ethylene and vinylalkoxysilanes: evidence for a beta-silyl elimination chain transfer mechanism. *J. Am. Chem. Soc.* **2016,** *138*, 16120-16129.

21. (a) Shabashov, D.; Daugulis, O. Palladium-catalyzed anilide *ortho*-arylation and subsequent one-pot cyclization to phenanthridines. *J. Org. Chem.* **2007,** *72*, 7720-7725; (b) Daugulis, O.; Zaitsev, V. G. Anilide *ortho*-arylation by using C–H activation methodology. *Angew. Chem. Int. Ed.* **2005,** *44*, 4046-4048.

22. (a) Reddy, G. M.; Rao, N. S. S.; Satyanarayana, P.; Maheswaran, H. PhI($OCOCF_3$)$_2$-mediated ruthenium catalyzed highly site-selective direct *ortho*-C–H monoarylation of 2-phenylpyridine and 1-phenyl-1*H*-pyrazole and their derivatives by arylboronic acids. *RSC Advances* **2015,** *5*, 105347-105352; (b) Ackermann, L.; Pospech, J.; Potukuchi, H. K. Well-defined ruthenium(II) carboxylate as catalyst for direct C-H/C-O bond arylations with phenols in water. *Org. Lett.* **2012,** *14*, 2146-2149; (c) Luo, N.; Yu, Z. $RuCl_3$·x H_2O-catalyzed direct arylation of arenes with aryl chlorides in the presence of triphenylphosphine. *Chem. Eur. J.* **2010,** *16*, 787-791; (d) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. C-H bond functionalization in water catalyzed by carboxylato ruthenium(II) systems. *Angew. Chem. Int. Ed.* **2010,** *49*, 6629-6632; (e) Kim, M.; Kwak, J.; Chang, S. Rhodium/*N*-heterocyclic carbene catalyzed direct intermolecular arylation of sp^2 and sp^3 C−H bonds with chelation assistance. *Angew. Chem. Int. Ed.* **2009,** *48*, 8935-8939; (f) Oi, S.; Sasamoto, H.; Funayama, R.; Inoue, Y. Ortho-selective arylation of arylazoles with rayl bromides actalyzed by ruthenium complexes. *Chem. Lett.* **2008,** *37*, 994-995; (g) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. Iron-catalyzed direct arylation through directed C−H bond activation. *J. Am. Chem. Soc.* **2008,** *130*, 5858-5859; (h) Ackermann, L.; Althammer, A.; Born, R. Catalytic arylation reactions by C−H bond activation with aryl tosylates. *Angew. Chem. Int. Ed.* **2006,** *45*, 2619-2622; (i) Kantchev, E.; Kwong, F.-Y.; Li, Y.-G.; Wang, Z.-Y.; Zou, Y.-L.; So, C.-M.; Qin, H.-L. Bulky phosphane ligand for monoselective ruthenium-catalyzed, directed *o*-C–H arylation with challenging aryl chlorides. *Synlett* **2016**, 499-503.

23. Teskey, C. J.; Sohel, S. M. A.; Bunting, D. L.; Modha, S. G.; Greaney, M. F. Domino *N*-/*C*-arylation via in situ generation of a directing group: atom-efficient arylation using diaryliodonium salts. *Angew. Chem. Int. Ed.* **2017,** *56*, 5263-5266.

24. Cristau, H.-J.; Cellier, Pascal P.; Spindler, J.-F.; Taillefer, M. Mild conditions for copper-catalysed *N*-arylation of pyrazoles. *Eur. J. Org. Chem.* **2004**, 695-709.

25. Chen, X.; She, J.; Shang, Z.-C.; Wu, J.; Zhang, P. Room-temperature synthesis of pyrazoles, diazepines, β-enaminones, and β-enamino esters using silica-supported sulfuric acid as a reusable catalyst under solvent-free conditions. *Synth. Commun.* **2009,** *39*, 947-957.

26. Lill, A.; Scholich, K.; Stark, H. Synthesis of novel dansyl-labeled Celecoxib derivatives. *Tetrahedron Lett.* **2013,** *54*, 6682-6686.

27. (a) Kunz, K.; Scholz, U.; Ganzer, D. Renaissance of ullmann and goldberg reactions - progress in copper catalyzed C−N-, C−O- and C−S-coupling. *Synlett* **2003**, 2428-2439; (b) Ley, S. V.; Thomas, A. W. Modern synthetic methods for copper-mediated C(aryl)−O, C(aryl)−N, and C(aryl)−S bond formation. *Angew. Chem. Int. Ed.* **2003,** *42*, 5400-5449; (c) Monnier, F.; Taillefer, M. Catalytic C−C, C−N, and C−O Ullmann-type coupling reactions. *Angew. Chem. Int. Ed.* **2009,** *48*, 6954-6971.

28. (a) Fischer, C.; Koenig, B. Palladium- and copper-mediated *N*-aryl bond formation reactions for the synthesis of biological active compounds. *Beilstein J. Org. Chem.* **2011,** *7*, 59-74; (b) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald-Hartwig amination after 25 years. *Angew. Chem. Int. Ed.* **2019,** *58*, 17118-17129.

29. (a) Gandeepan, P.; Muller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition metals for C−H activation. *Chem. Rev.* **2019,** *119*, 2192-2452; (b) Park, Y.; Kim, Y.; Chang, S. Transition metal-catalyzed C−H amination: scope, mechanism, and applications. *Chem. Rev.* **2017,** *117*, 9247-9301; (c) Zhou, Y.; Yuan, J.; Yang, Q.; Xiao, Q.; Peng, Y. Directing-group-assisted transition-metal-catalyzed direct intermolecular C−H amidation and amination of arenes. *ChemCatChem* **2016,** *8*, 2178-2192; (d) Dai, H.-X.; Shang, M.; Sun, S.-Z.; Wang, H.-L.; Wang,

M.-M. Recent progress on copper-mediated directing-group-assisted C(sp^2)−H activation. *Synthesis* **2016,** *48*, 4381-4399; (e) Louillat, M. L.; Patureau, F. W. Oxidative C−H amination reactions. *Chem. Soc. Rev.* **2014,** *43*, 901-910.

30. (a) Rousseau, G.; Breit, B. Removable directing groups in organic synthesis and catalysis. *Angew. Chem. Int. Ed.* **2011,** *50*, 2450-2494; (b) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition metal-catalyzed C–H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* **2015,** *2*, 1107-1295; (c) Gandeepan, P.; Ackermann, L., Organometallic chelation-assisted C−H functionalization. In *non-noble metal catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2018; pp 391-423; (d) Motati, D. R.; Uredi, D.; Watkins, E. B., Metal-catalyzed, bidentate directing group-assisted C−H functionalization: Application to the synthesis of complex natural products. In *Stud. Nat. Prod. Chem.*, 1 ed.; Elsevier Inc.: 2019; Vol. 63, pp 81-112.

31. Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. Cu(II)-catalyzed functionalizations of aryl C−H bonds using O_2 as an oxidant. *J. Am. Chem. Soc.* **2006,** *128*, 6790-6791.

32. (a) Uemura, T.; Imoto, S.; Chatani, N. Amination of the ortho C–H bonds by the $Cu(OAc)_2$-mediated reaction of 2-phenylpyridines with anilines. *Chem. Lett.* **2006,** *35*, 842-843; (b) John, A.; Nicholas, K. M. Copper-catalyzed amidation of 2-phenylpyridine with oxygen as the terminal oxidant. *J. Org. Chem.* **2011,** *76*, 4158-4162; (c) Song, C.; Wang, T.; Yu, T.; Cui, D. M.; Zhang, C. 2,4-Diamino-1,3,5-triazine-enabled Cu-catalyzed direct sulfonamidation of aromatic C−H bonds. *Org. Biomol. Chem.* **2017,** *15*, 7212-7217.

33. (a) Tran, L. D.; Roane, J.; Daugulis, O. Directed amination of non-acidic arene C−H bonds by a copper-silver catalytic system. *Angew. Chem. Int. Ed.* **2013,** *52*, 6043-6046; (b) Li, Q.; Zhang, S. Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. Copper-catalyzed carboxamide-directed *ortho*

amination of anilines with alkylamines at room temperature. *Org. Lett.* **2014,** *16*, 1764-1767; (c) Shang, M.; Sun, S. Z.; Dai, H. X.; Yu, J. Q. Cu(II)-mediated C−H amidation and amination of arenes: exceptional compatibility with heterocycles. *J. Am. Chem. Soc.* **2014,** *136*, 3354-3357; (d) Lee, W. C.; Shen, Y.; Gutierrez, D. A.; Li, J. J. 2-Aminophenyl-1*H*-pyrazole as a removable directing group for copper-mediated C−H amidation and sulfonamidation. *Org. Lett.* **2016,** *18*, 2660-2663; (e) Liu, Y.; Zhang, Q.; Guo, Q. H.; Wang, M. X. Synthesis of functionalized azacalix[1]arene[3]pyridine macrocycles from Cu(II)-mediated direct amination reactions of arene through high valent arylcopper(III) intermediates. *J. Org. Chem.* **2016,** *81*, 10404-10410; (f) Roane, J.; Daugulis, O. A General method for aminoquinoline-directed, copper-catalyzed sp^2 C−H bond amination. *J. Am. Chem. Soc.* **2016,** *138*, 4601-4607; (g) Singh, B. K.; Polley, A.; Jana, R. Copper(II)-mediated intermolecular C(sp^2)−H amination of benzamides with electron-rich anilines. *J. Org. Chem.* **2016,** *81*, 4295-4303; (h) Li, Z.; Yu, H.; Bolm, C. Dibenzothiophene sulfoximine as an NH_3 surrogate in the synthesis of primary amines by copper-catalyzed C−X and C−H bond amination. *Angew. Chem. Int. Ed.* **2017,** *56*, 9532-9535; (i) Pradhan, S.; De, P. B.; Punniyamurthy, T. Copper(II)-mediated chelation-assisted regioselective *N*-naphthylation of indoles, pyrazoles and pyrrole through dehydrogenative cross-coupling. *J. Org. Chem.* **2017,** *82*, 4883-4890; (j) Kim, H.; Heo, J.; Kim, J.; Baik, M. H.; Chang, S. Copper-mediated amination of aryl C−H bonds with the direct use of aqueous ammonia via a disproportionation pathway. *J. Am. Chem. Soc.* **2018,** *140*, 14350-14356.

34. (a) Du, C.; Li, P.-X.; Zhu, X.; Han, J.-N.; Niu, J.-L.; Song, M.-P. Cobalt-catalyzed oxidative C–H/N–H cross-coupling: selective and facile access to triarylamines. *ACS Catal.* **2017,** *7*, 2810-2814; (b) Zhang, S. K.; Samanta, R. C.; Sauermann, N.; Ackermann, L. Nickel-catalyzed electrooxidative C-H amination: support for nickel(IV). *Chem. Eur. J.* **2018,** *24*, 19166-19170.

35. Shang, M.; Shao, Q.; Sun, S. Z.; Chen, Y. Q.; Xu, H.; Dai, H. X.; Yu, J. Q. Identification of monodentate oxazoline as a ligand for copper-promoted *ortho*-C−H hydroxylation and amination. *Chem. Sci.* **2017,** *8*, 1469-1473.

36. Le, K. K. A.; Nguyen, H.; Daugulis, O. 1-Aminopyridinium ylides as monodentate directing groups for sp^3 C−H bond functionalization. *J. Am. Chem. Soc.* **2019,** *141*, 14728-14735.

37. (a) Shang, M.; Wang, M. M.; Saint-Denis, T. G.; Li, M. H.; Dai, H. X.; Yu, J. Q. Copper-mediated late-stage functionalization of heterocycle-containing molecules. *Angew. Chem. Int. Ed.* **2017,** *56*, 5317-5321; (b) Wang, M.; Hu, Y.; Jiang, Z.; Shen, H. C.; Sun, X. Divergent copper-mediated dimerization and hydroxylation of benzamides involving C−H bond functionalization. *Org. Biomol. Chem.* **2016,** *14*, 4239-4246.

38. (a) Mousseau, J. J.; Bull, J. A.; Charette, A. B. Copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides. *Angew. Chem. Int. Ed.* **2010,** *49*, 1115-1118; (b) Larivee, A.; Mousseau, J. J.; Charette, A. B. Palladium-catalyzed direct C−H arylation of *N*-iminopyridinium ylides: application to the synthesis of (+/-)-anabasine. *J. Am. Chem. Soc.* **2008,** *130*, 52-54.

39. Yeung, J. M.; Corleto, L. A.; Knaus, E. E. Synthesis of *N*-[[(substituted-phenyl)carbonyl]amino]-1,2,3,6-tetrahydropyridines with analgesic and hyperglycemic activity. *J. Med. Chem.* **1982,** *25*, 720-723.

40. Since perfluoro-*tert*-butanol is somewhat expensive ($2.16/g from Oakwood Chemical), recovery of the solvent was attempted.

41. (a) Kulkarni, A. A.; Daugulis, O. Direct conversion of carbon−hydrogen into carbon−carbon bonds by first-row transition-metal catalysis. *Synthesis* **2009**, 4087-4109; (b) Moselage, M.; Li, J.; Ackermann, L. Cobalt-catalyzed C–H activation. *ACS Catal.* **2015,** *6*, 498-525; (c) Baccalini, A.;

Vergura, S.; Dolui, P.; Zanoni, G.; Maiti, D. Recent advances in cobalt-catalysed C−H functionalizations. *Org. Biomol. Chem.* **2019,** *17*, 10119-10141.

42. Murahashi, S. Synthesis of phthalimidines from schiff bases and carbon monoxide. *J. Am. Chem. Soc.* **1955,** *77*, 6403-6404.

43. Planas, O. C., P. G.; Whiteoak, C. J.; Ribas, X. Current mechanistic understanding of cobalt-catalyzed C–H functionalization. *Adv. Organomet. Chem.* **2018,** *69*, 209-282.

44. (a) Kochi, J. K.; Tang, R. T.; Bernath, T. Mechanisms of aromatic substitution. role of cation-radicals in the oxidative substitution of arenes by cobalt(III). *J. Am. Chem. Soc.* **1973,** *95*, 7114-7123; (b) Tang, R.; Kochi, J. K. Cobalt(III) trifluoroacetate: an electron transfer oxidant. *J. Inorg. Nucl. Chem.* **1973,** *35*, 3845-3856.

45. Halbritter, G.; Knoch, F.; Wolski, A.; Kisch, H. Functionalization of aromatic azo compounds by the cobalt-catalyzed, regioselective double addition of tolane: 2,6-distilbenylazobenzenes and 2,3-dihydrocinnolines. *Angew. Chem. Int. Ed.* **1994,** *33*, 1603-1605.

46. (a) Lenges, C. P.; Brookhart, M. Co(I)-catalyzed inter- and intramolecular hydroacylation of olefins with aromatic aldehydes. *J. Am. Chem. Soc.* **1997,** *119*, 3165-3166; (b) Lenges, C. P.; White, P. S.; Brookhart, M. Mechanistic and synthetic studies of the addition of alkyl aldehydes to vinylsilanes catalyzed by Co(I) complexes. *J. Am. Chem. Soc.* **1998,** *120*, 6965-6979.

47. (a) Kanamori, K.; Broderick, W. E.; Jordan, R. F.; Willett, R. D.; Legg, J. I. Intramolecular carbon-hydrogen bond activation in aqueous solution: preparation of a unique cobalt(III)-alkyl complex by deprotonation of an agostic intermediate. crystal structure of [Co(III)(dacoda-C(2))(H_2O)].cntdot.2H_2O. *J. Am. Chem. Soc.* **1986,** *108*, 7122-7124; (b) Broderick, W. E.; Kanamori, K.; Willett, R. D.; Legg, J. I. Intramolecular carbon-hydrogen bond activation: preparation, structure, and properties of a unique cobalt(III) complex,

K[Co(III)(dacoda)(SO_3).cntdot.5H_2O, containing a weak agostic interaction in aqueous solution. *Inorg. Chem.* **1991,** *30*, 3875-3881.

48. (a) Klein, H.-F.; Helwig, M.; Koch, U.; Flörke, U.; Haupt, H.-J. Coordination and reactions of diazenes in trimethylphosphinecobalt(I). complexes - syntheses and structures of complexes containing μ^2-(N,N′)-benzo[c]cinnoline and η^2-azobenzene ligands. *Z. Naturforsch. B* **1993,** *48*, 778-784; (b) Klein, H. F.; Schneider, S.; He, M. Z.; Floerke, U.; Haupt, H. J. *ortho*-metalation of triarylphosphane at cobalt and template synthesis of chelating 2-(diarylphosphanyl)aroyl ligands. *Eur. J. Inorg. Chem.* **2000**, 2295-2301; (c) Klein, H. F.; Beck, R.; Florke, U.; Haupt, H. J. Five- and six-membered cobaltocycles with C,P-chelating ligands through regiospecific cyclometalation of mono(2-substituted) triphenylphosphane. *Eur. J. Inorg. Chem.* **2003**, 1380-1387; (d) Klein, H. F.; Camadanli, S.; Beck, R.; Leukel, D.; Florke, U. Cyclometalation of substrates containing imine and pyridyl anchoring groups by iron and cobalt complexes. *Angew. Chem. Int. Ed.* **2005,** *44*, 975-977.

49. Avilés, T.; Dinis, A.; Calhorda, M. J.; Pinto, P. c.; Félix, V.; Drew, M. G. B. Synthesis, X-ray structure, and theoretical studies of novel cationic mono-cyclopentadienyl complexes of Co(III): the orthometalation of trans-azobenzene. *J. Organomet. Chem.* **2001,** *625*, 186-194.

50. (a) Gao, K.; Lee, P. S.; Fujita, T.; Yoshikai, N. Cobalt-catalyzed hydroarylation of alkynes through chelation-assisted C−H bond activation. *J. Am. Chem. Soc.* **2010,** *132*, 12249-12251; (b) Lee, P. S.; Fujita, T.; Yoshikai, N. Cobalt-catalyzed, room-temperature addition of aromatic imines to alkynes via directed C−H bond activation. *J. Am. Chem. Soc.* **2011,** *133*, 17283-17295; (c) Chen, Q. A.; Kim, D. K.; Dong, V. M. Regioselective hydroacylation of 1,3-dienes by cobalt catalysis. *J. Am. Chem. Soc.* **2014,** *136*, 3772-3775; (d) Gao, K.; Paira, R.; Yoshikai, N. Cobalt-catalyzed *ortho*-C−H alkylation of 2-arylpyridines via ring-opening of aziridines. *Adv. Synth. Catal.* **2014,**

356, 1486-1490; (e) Moselage, M.; Sauermann, N.; Richter, S. C.; Ackermann, L. C−H alkenylations with alkenyl acetates, phosphates, carbonates, and carbamates by cobalt catalysis at 23 °C. *Angew. Chem. Int. Ed.* **2015,** *54*, 6352-6355.

51. (a) Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Petit, M. C−H activation/functionalization catalyzed by simple, well-defined low-valent cobalt complexes. *J. Am. Chem. Soc.* **2015,** *137*, 2448-2451; (b) Fallon, B. J.; Garsi, J.-B.; Derat, E.; Amatore, M.; Aubert, C.; Petit, M. Synthesis of 1,2-dihydropyridines catalyzed by well-defined low-valent cobalt complexes: C–H activation made simple. *ACS Catal.* **2015,** *5*, 7493-7497.

52. Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. Pyrroloindolone synthesis via a Cp*Co(III)-catalyzed redox-neutral directed C−H alkenylation/annulation sequence. *J. Am. Chem. Soc.* **2014,** *136*, 5424-5431.

53. (a) Grigorjeva, L.; Daugulis, O. Cobalt-catalyzed, aminoquinoline-directed C(sp^2)−H bond alkenylation by alkynes. *Angew. Chem. Int. Ed.* **2014,** *53*, 10209-10212; (b) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. Cobalt-catalyzed coupling of benzoic acid C−H bonds with alkynes, styrenes, and 1,3-dienes. *Angew. Chem. Int. Ed.* **2018,** *57*, 1688-1691.

54. (a) Zhai, S.; Qiu, S.; Chen, X.; Wu, J.; Zhao, H.; Tao, C.; Li, Y.; Cheng, B.; Wang, H.; Zhai, H. 2-(1-Methylhydrazinyl)pyridine as a reductively removable directing group in a cobalt-catalyzed C(sp^2)−H bond alkenylation/annulation cascade. *Chem. Commun.* **2017,** *54*, 98-101; (b) Kalsi, D.; Sundararaju, B. Cobalt catalyzed C−H and N−H bond annulation of sulfonamide with terminal and internal alkynes. *Org. Lett.* **2015,** *17*, 6118-6121; (c) Zhang, L. B.; Hao, X. Q.; Liu, Z. J.; Zheng, X. X.; Zhang, S. K.; Niu, J. L.; Song, M. P. Cobalt(II)-catalyzed C(sp^2)−H alkynylation/annulation with terminal alkynes: selective access to 3-methyleneisoindolin-1-one. *Angew. Chem. Int. Ed.* **2015,** *54*, 10012-10015; (d) Mei, R.; Ma, W.; Zhang, Y.; Guo, X.;

Ackermann, L. Cobaltaelectro-catalyzed oxidative C−H/N−H activation with 1,3-diynes by electro-removable hydrazides. *Org. Lett.* **2019,** *21*, 6534-6538; (e) Landge, V. G.; Jaiswal, G.; Balaraman, E. Cobalt-catalyzed bis-alkynylation of amides via double C−H bond activation. *Org. Lett.* **2016,** *18*, 812-815; (f) Martinez, A. M.; Rodriguez, N.; Gomez-Arrayas, R.; Carretero, J. C. Cobalt-catalyzed *ortho*-C−H functionalization/alkyne annulation of benzylamine derivatives: access to dihydroisoquinolines. *Chem. Eur. J.* **2017,** *23*, 11669-11676; (g) Kuai, C.; Wang, L.; Li, B.; Yang, Z.; Cui, X. Cobalt-catalyzed selective synthesis of isoquinolines using picolinamide as a traceless directing group. *Org. Lett.* **2017,** *19*, 2102-2105; (h) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. Cobalt-catalyzed, aminoquinoline-directed functionalization of phosphinic amide sp^2 C−H bonds. *ACS Catal.* **2016,** *6*, 551-554; (i) Mei, R.; Sauermann, N.; Oliveira, J. C. A.; Ackermann, L. Electroremovable traceless hydrazides for cobalt-catalyzed electro-oxidative C−H/N−H activation with internal alkynes. *J. Am. Chem. Soc.* **2018,** *140*, 7913-7921; (j) Dutta, P. K.; Sen, S. (Benz)imidazole-directed cobalt(III)-catalyzed C−H activation of arenes: a facile strategy to access polyheteroarenes by oxidative annulation. *Eur. J. Org. Chem.* **2018**, 5512-5519; (k) Liang, Y.; Jiao, N. Cationic cobalt(III) catalyzed indole synthesis: the regioselective intermolecular cyclization of *N*-nitrosoanilines and alkynes. *Angew. Chem. Int. Ed.* **2016,** *55*, 4035-4039; (l) Barsu, N.; Sen, M.; Premkumar, J. R.; Sundararaju, B. Cobalt(III) catalyzed C-8 selective C−H and C−O coupling of quinoline *N*-oxide with internal alkynes via C−H activation and oxygen atom transfer. *Chem. Commun.* **2016,** *52*, 1338-1341; (m) Kong, L.; Yang, X.; Zhou, X.; Yu, S.; Li, X. Cobalt(III)-catalyzed efficient synthesis of indenones through carboannulation of benzoates and alkynes. *Org. Chem. Front.* **2016,** *3*, 813-816; (n) Sivakumar, G.; Vijeta, A.; Jeganmohan, M. Cobalt-catalyzed cyclization of *N*-methoxy benzamides with alkynes using an internal oxidant through C−H/N−O bond activation. *Chem. Eur. J.* **2016,** *22*, 5899-903; (o) Kubo,

H.; Hirose, T.; Matsuda, K. Control over the emission properties of [5]helicenes based on the symmetry and energy levels of their molecular orbitals. *Org. Lett.* **2017,** *19*, 1776-1779; (p) Mandal, R.; Sundararaju, B. Cp*Co(III)-catalyzed annulation of carboxylic acids with alkynes. *Org. Lett.* **2017,** *19*, 2544-2547; (q) Bera, S. S.; Debbarma, S.; Ghosh, A. K.; Chand, S.; Maji, M. S. Cp*Co(III)-catalyzed syn-selective C−H hydroarylation of alkynes using benzamides: an approach toward highly conjugated organic frameworks. *J. Org. Chem.* **2017,** *82*, 420-430; (r) Yu, X.; Chen, K.; Guo, S.; Shi, P.; Song, C.; Zhu, J. Direct access to cobaltacycles via C−H activation: *N*-chloroamide-enabled room-temperature synthesis of heterocycles. *Org. Lett.* **2017,** *19*, 5348-5351; (s) Xu, X.; Yang, Y.; Zhang, X.; Yi, W. Direct synthesis of quinolines via Co(III)-catalyzed and DMSO-involved C−H activation/cyclization of anilines with alkynes. *Org. Lett.* **2018,** *20*, 566-569; (t) Kong, L.; Yu, S.; Zhou, X.; Li, X. Redox-neutral couplings between amides and alkynes via cobalt(III)-catalyzed C−H activation. *Org. Lett.* **2016,** *18*, 588-591; (u) Wang, H.; Moselage, M.; González, M. J.; Ackermann, L. Selective synthesis of indoles by cobalt(III)-catalyzed C–H/N–O functionalization with nitrones. *ACS Catal.* **2016,** *6*, 2705-2709; (v) Tanaka, R.; Ikemoto, H.; Kanai, M.; Yoshino, T.; Matsunaga, S. Site- and regioselective monoalkenylation of pyrroles with alkynes via Cp*Co(III) catalysis. *Org. Lett.* **2016,** *18*, 5732-5735.

55. (a) Matsubara, T.; Ilies, L.; Nakamura, E. Oxidative C-H activation approach to pyridone and isoquinolone through an iron-catalyzed coupling of amides with alkynes. *Chem. Asian. J.* **2016,** *11*, 380-384; (b) Misal Castro, L. C.; Obata, A.; Aihara, Y.; Chatani, N. Chelation-assisted nickel-catalyzed oxidative annulation via double C−H activation/alkyne insertion reaction. *Chem. Eur. J.* **2016,** *22*, 1362-1367; (c) Yang, J.; Yoshikai, N. Cobalt-catalyzed annulation of salicylaldehydes and alkynes to form chromones and 4-chromanones. *Angew. Chem. Int. Ed.* **2016,** *55*, 2870-2874; (d) Zheng, X. X.; Du, C.; Zhao, X. M.; Zhu, X.; Suo, J. F.; Hao, X. Q.; Niu, J. L.; Song, M. P.

Ni(II)-catalyzed C(sp^2)−H alkynylation/annulation with terminal alkynes under an oxygen atmosphere: a one-pot approach to 3-methyleneisoindolin-1-one. *J. Org. Chem.* **2016,** *81*, 4002-4011; (e) Cera, G.; Haven, T.; Ackermann, L. Iron-catalyzed C−H/N−H activation by triazole guidance: versatile alkyne annulation. *Chem. Commun.* **2017,** *53*, 6460-6463.

56. Ackermann, L. Carboxylate-assisted transition-metal-catalyzed C–H bond functionalizations: mechanism and scope. *Chem. Rev.* **2011,** *111*, 1315-1345.

57. (a) Desai, L. V.; Stowers, K. J.; Sanford, M. S. Insights into directing group ability in palladium-catalyzed C−H bond functionalization. *J. Am. Chem. Soc.* **2008,** *130*, 13285-13293; (b) Liu, Y. J.; Xu, H.; Kong, W. J.; Shang, M.; Dai, H. X.; Yu, J. Q. Overcoming the limitations of directed C−H functionalizations of heterocycles. *Nature* **2014,** *515*, 389-393; (c) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016,** *45*, 546-576.

58. (a) Martinez de Salinas, S.; Sanjose-Orduna, J.; Odena, C.; Barranco, S.; Benet-Buchholz, J.; Perez-Temprano, M. H. Weakly coordinated cobaltacycles: trapping catalytically competent intermediates in Cp*Co(III) catalysis. *Angew. Chem. Int. Ed.* **2020,** *59*, 6239-6243; (b) Sanjose-Orduna, J.; Gallego, D.; Garcia-Roca, A.; Martin, E.; Benet-Buchholz, J.; Perez-Temprano, M. H. Capturing elusive cobaltacycle intermediates: a real-time snapshot of the Cp*Co(III)-catalyzed oxidative alkyne annulation. *Angew. Chem. Int. Ed.* **2017,** *56*, 12137-12141.

59. (a) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. Air-stable carbonyl(pentamethylcyclopentadienyl)cobalt diiodide complex as a precursor for cationic (pentamethylcyclopentadienyl)cobalt(III) catalysis: application for directed C-2 selective C−H amidation of indoles. *Adv. Synth. Catal.* **2014,** *356*, 1491-1495; (b) Yu, D. G.; Gensch, T.; de Azambuja, F.; Vasquez-Cespedes, S.; Glorius, F. Co(III)-catalyzed C−H activation/formal SN-

type reactions: selective and efficient cyanation, halogenation, and allylation. *J. Am. Chem. Soc.* **2014,** *136*, 17722-17725.

60. Kwak, S. H.; Daugulis, O. *N*-Aminopyridinium ylide-directed, copper-promoted amination of sp^2 C−H bonds. *J. Org. Chem.* **2019,** *84*, 13022-13032.

61. Li, B.; Feng, H.; Xu, S.; Wang, B. Ruthenium-catalyzed isoquinolone synthesis through C−H activation using an oxidizing directing group. *Chem. Eur. J.* **2011,** *17*, 12573-12577.

62. Zhu, H.; Zhuang, R.; Zheng, W.; Fu, L.; Zhao, Y.; Tu, L.; Chai, Y.; Zeng, L.; Zhang, C.; Zhang, J. Synthesis of isoquinolone via rhodium(III)-catalyzed C−H activation with 1,4,2-dioxazol-5-ones as oxidizing directing group. *Tetrahedron* **2019,** *75*, 3108-3112.

63. Reddy, M. C.; Manikandan, R.; Jeganmohan, M. Ruthenium-catalyzed aerobic oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes: a new route to isoquinolones. *Chem. Commun.* **2013,** *49*, 6060-6062.

64. Lu, S.; Lin, Y.; Zhong, H.; Zhao, K.; Huang, J. A practical one-pot procedure for the synthesis of N–H isoquinolones. *Tetrahedron Lett.* **2013,** *54*, 2001-2005.

65. Yeung, J. M.; Knaus, E. E. Synthesis of *N*-(3,6-dihydro-1(2H)-pyridinyl)benzamides with hyperglycemic-hypoglycemic activity. *J. Med. Chem.* **1987,** *30*, 104-108.

66. Chiong, H. A.; Pham, Q. N.; Daugulis, O. Two methods for direct *ortho*-arylation of benzoic acids. *J. Am. Chem. Soc.* **2007,** *129*, 9879-9884.