Doctoral Dissertation

Studies on Rhodium-Catalyzed Transformation of Aromatic Carbamates and *N*-Heterocyclic Carbene-Catalyzed Nucleophilic Aromatic Substitution

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Preface and Acknowledgement

The researches presented in this thesis were carried out under the direction of Professor Mamoru Tobisu and Professor Naoto Chatani of the Department of Applied Chemistry, Faculty of Engineering, Osaka University. I belonged to Chatani's laboratory from April 2014 to March 2017 and move to Tobisu's laboratory with his promotion to full professor, and spent a life as a Ph.D. student from April 2017 to March 2020. The thesis is concerned with the rhodium-catalyzed transformation of aromatic carbamates and *N*-heterocyclic carbene-catalyzed nucleophilic aromatic substitution.

This thesis has not been able to be achievable without the support of numerous people. Here, I wish to express my sincerest appreciation to all those people.

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Kosuke Yasui

Contents

General Introduction

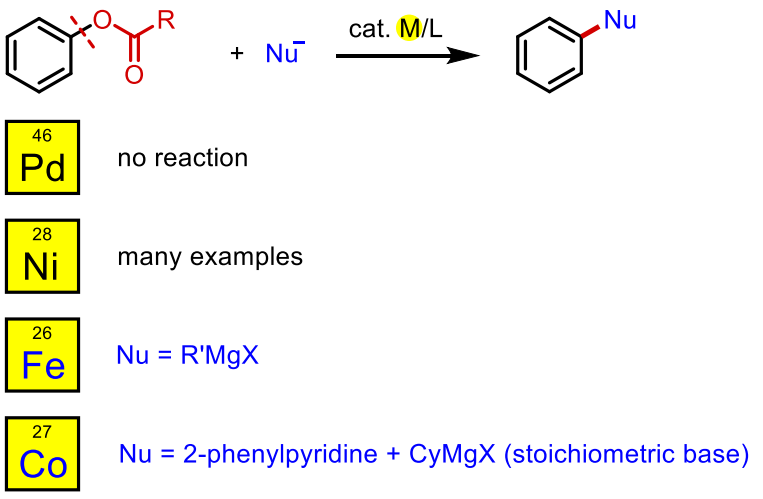
Aromatic compounds are one of the more important scaffolds in organic chemistry and are frequently found as components in millions of pharmaceutical molecules and organic materials.[1] Therefore, developing new reactions involving the transformation of aromatic compounds is recognized as one of the most important research topics in organic chemistry and has the potential to create new synthetic strategies and for preparing exotic compounds that are unknown today.

Among the various transformations of aromatic compounds, this doctoral thesis focuses on two primary strategies, *i. e.* transition metal-catalyzed cross-coupling reactions[2] and nucleophilic aromatic substitution.[3] Although these two promising reactions have been used to prepare a wide variety of pharmaceuticals and organic materials, they have some problems that should be solved.

A problem with the cross-coupling reactions is that they require the use of organic electrophiles and organometallic reagents, which have a high environmental load. What is worse, these two reagents result in the formation of stoichiometric amounts of metal-based byproducts, which can cause problems related to the purification of the desired product. To avoid the use of these two reagents, some compounds have emerged as alternatives to aryl halides and organometallic reagents.

Phenol derivatives, which are inexpensive and naturally abundant compounds, are often recognized as an environmentally benign alternative to aryl halides.[4] Although reaction using the ideal substrates, the C-O bond in these compounds is too strong to allow the application of oxidative addition reactions.

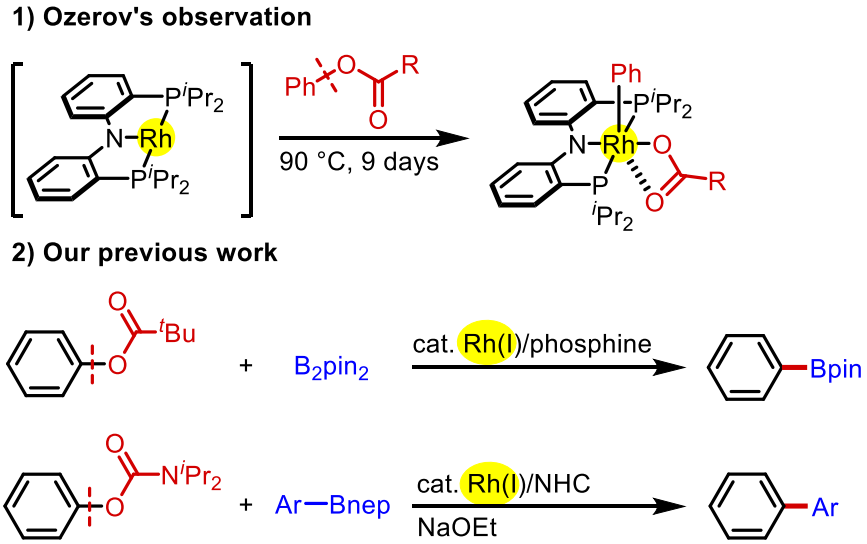
The cleavage of the C-O bond in inert phenol derivatives is often promoted by nickel catalyst, which allows various reactions to be conducted using phenol derivatives as a starting material.[4] On the other hand, a palladium catalyst, which is often used in a typical cross-coupling reaction using aryl halides, cannot be used to cleave inert C-O bonds in phenol derivatives. Nevertheless, the cleavage of an inert C-O bond with other transition metals would be expected to expand the variety of transformations using inert phenol derivatives. Iron[5] and cobalt[6] can also be used to catalyze reactions using inert phenol derivatives. However, in these cases, a stoichiometric amount of the Grignard reagent is required, which limits the widespread use of these reactions, in terms of functional group



Scheme 1. C-O Bond Activation reactions by Transition-Metal Catayst

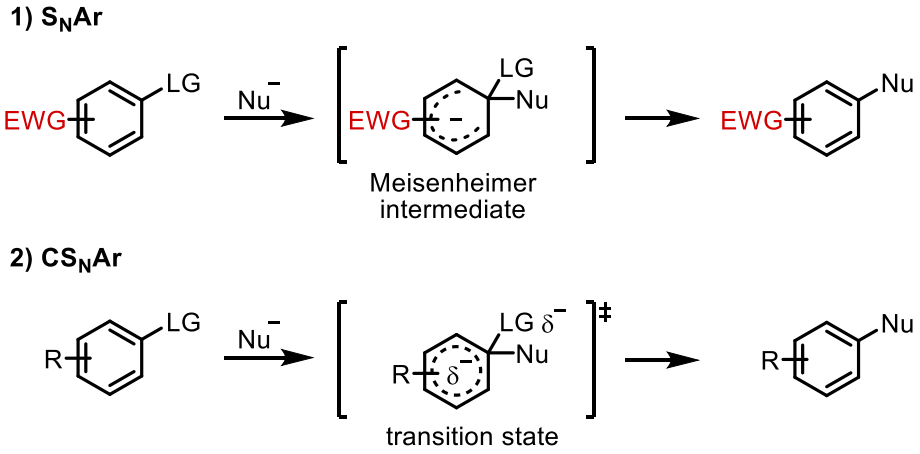
compatibility.

Our group reported the first example of rhodium-catalyzed C-O bond transformation reactions.[7] Although Ozerov reported the first observation of the oxidative addition of a C-O bond in an inert phenyl ester to a rhodium center[8], the rhodium bearing a PNP pincer ligand is not valid for catalytic applications. Our group developed rhodium-catalyzed C-O bond borylation[7(a)] and Suzuki Miyaura type cross-coupling reactions in which aryl boron reagents were used[7(b)]. Even though we were delighted to develop rhodium-catalyzed reactions, these two reactions can be catalyzed by less expensive nickel catalyst and there is no clear advantage of using rhodium catalysts. Therefore, I turned my attention to the development of rhodium-catalyzed reactions that are not possible with a nickel catalyst.



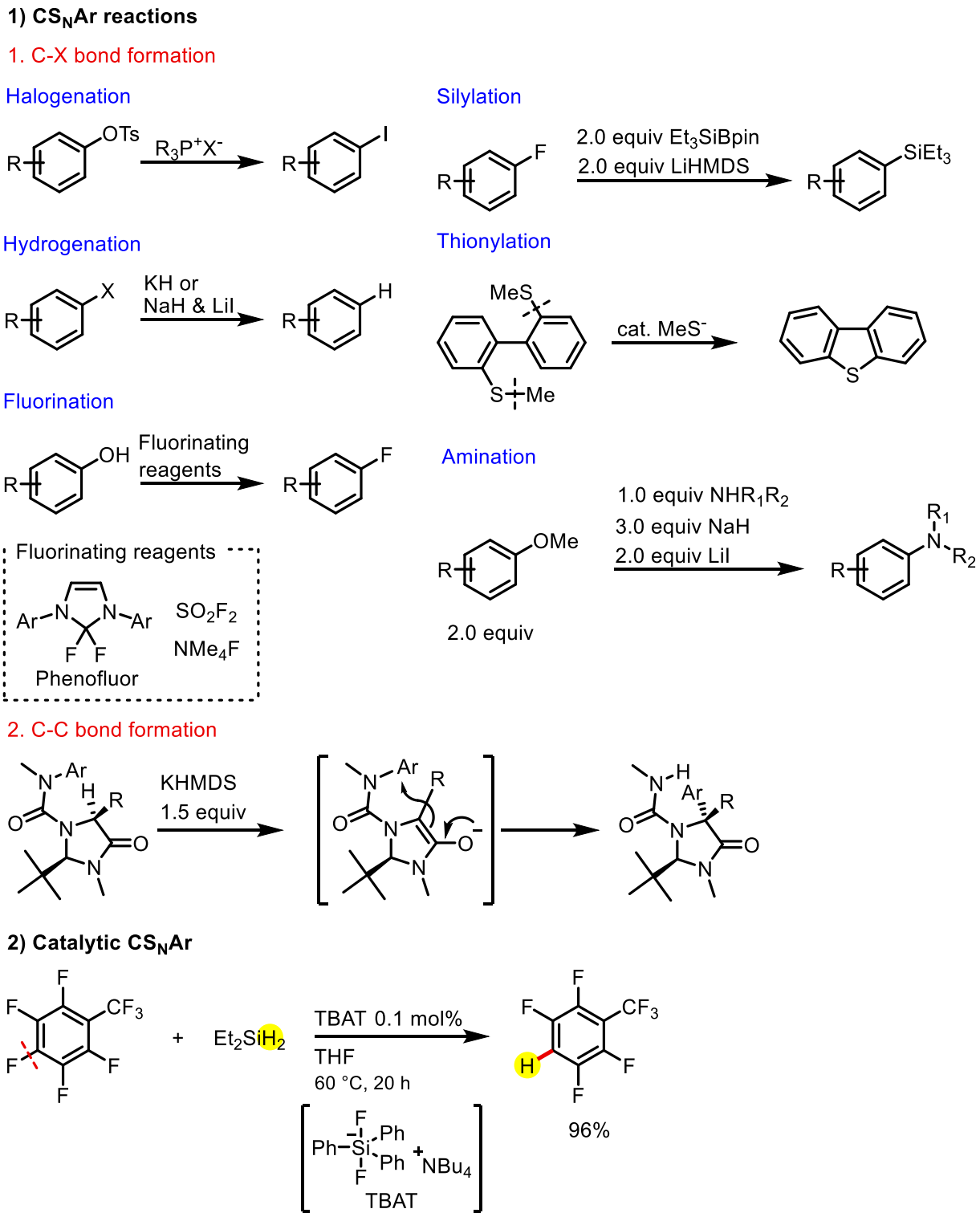
Scheme 2. Rhodium-Catalyzed C-O Bond Transformations

Nucleophilic aromatic substitution is the classical textbook reaction of aromatic compounds. [3] Although this type of reaction has been used to elaborate a number of functionalized aromatic compounds related to pharmaceutical and organic materials, an electron-withdrawing group in the substrate is essential in terms of stabilizing a Meisenheimer intermediate.[9] This limitation reduces the synthetic utility of this reaction.



Scheme 2. S_NAr and CS_NAr

Several reports recently revealed that the S_NAr reaction can proceed, not in a stepwise, but rather in a concerted manner (CS_NAr,). The CS_NAr pathway generally has a lower activation energy (13–25 kcal/mol) intermediate since part of the aromaticity of the substrate can be retained. [7] In addition, the negative charge in the transition state can be dispersed not only on an aromatic ring but also on a leaving group, thereby making the CS_NAr reaction less sensitive to the electronic nature of the substrate.



Scheme 4. Reported CS_NAr Reactions

Although many CS_NAr reactions have been reported so far, as shown in Scheme 4, CS_NAr reactions have two significant problems associated with them that should be solved. One is that all of the CS_NAr reactions reported thus far require stoichiometric activating reagents and bases apart from the TBAT catalyzed reductive cleavage of C-F bonds reported by Ogoshi.[11] Although this reaction represents a critical advance in a catalytic CS_NAr reaction, the scope of substrates is limited to electron-deficient arene substrates that can be activated by a number of fluorine groups, making it difficult to apply to reactions involving electron- rich substrates. The other problem is that the scope of CS_NAr reactions is currently limited to the formation of carbon-heteroatom bonds[10(a)-(m)] and applications to carbon-carbon bond-forming processes remain underdeveloped, except for this aryl migration reaction using a stoichiometric base.[12]

To solve the problems related to cross-coupling reactions and CS_NAr reactions as mentioned above, this study focuses on the development of some catalytic reactions.

References

(1) (a) Ackermann, L. Modern Arylation Methods; Wiley: Weinheim, Germany, 2009. (b) Cepanec, I. Synthesis of Biaryls; Elsevier: New York, 2004. (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (d) Boldi, A. M. *Curr. Opin. Chem. Biol.* **2004**, *8*, 281. (e) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (f) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (g) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. (h) Wu, J.-S.; Cheng, S.-W.; Cheng, Y.-J.; Hsu, C.-S. *Chem. Soc. Rev.* **2015**, *44*, 1113.

(2) Reviews on cross-coupling: (a) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N. Ed.; Springer: Berlin, Germany, 2002. (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, NY, 2004. A recent themed issue on cross-coupling: (c) Suzuki, A.; Yamamoto, Y. *Chem. Lett.* **2011**, *40*, 894.

(3) Brgckner, R. *In Organic Mechanisms: Reactions, Stereochemistry and Synthesis*; Harmata, M., Eds.; Springer: Berlin, 2010; chap. 2 and chap. 5.

(4) Reviews on cross-coupling using inert phenol derivatives: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (b) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.–Eur. J.* **2011**, *17*, 1728. (c) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, *2013*, 19. (d) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081. (e) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717.

(5) (a) Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656. (b) Silberstein, A. L.; Ramgren, S. D.; Garg, N. K.*Org. Lett.* 2012, 14, 3796.

(6) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251.

(7) (a) Kinuta, H.; Hasegawa, J.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 366. (b) Nakamura, K.; Yasui, K.; Tobisu, M.; Chatani, N. *Tetrahedron* **2015**, *71*, 4484.

(8) Zhu, Y.; Smith, D. A.; Herbert, D. E.; Gatard, S.; Ozerov, O. V. *Chem. Commun.* **2012**, *48*, 218.

(9) (a) Terrier, F. *Chem. Rev.* **1982**, *82*, 77. (b) Terrier, F. *Modern Nucleophilic Aromatic Substitution*; Wiley: New York, 2013; pp 1-94.

(10) (a) Rohrbach, S.; Smith, A. J.; Pang, J. H.; Poole, D. L.; Tuttle, T.; Chiba, S.; Murphy, J. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 16368. (b) Handel, H.; Pasquini, M. A.; Pierre, J. L. *Tetrahedron* **1980**, *36*, 3205. (c)

Fry, S. E.; Pienta, N. J. *J. Am. Chem. Soc.* **1985**, *107*, 6399. (d) Handel, H.; Pasquini, M. A.; Pierre, J. L. *Tetrahedron* **1980**, *36*, 3205. (e) Ong, D. Y.; Tejo, C.; Xu K.; Hirao, H.; Chiba, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 1840. (f) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482. (g) Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369. (h) Neumann, C. N.; Ritter, T. *Acc. Chem. Res.* **2017**, *50*, 2822. (i) Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 1452. (j) Schimler, S. D.; Froese, R. D. J.; Bland, D. C.; Sanford, M. S. *J. Org. Chem.* **2018**, *83*, 11178. (k) Kaga, A.; Hayashi, H.; Hakamata, H.; Oi, M.; Uchiyama, M.; Takita, R.; Chiba, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 11807. (l) Liu, X.-W.; Zarate, C.; Martin, R. *Angew. Chem. Int. Ed.* **2019**, *58*, 2064. (m) Mauya, Y.; Kawashima, Y.; Kodama, T.; Chatani, N.; Tobisu, M. *Synlett* **2019**, *15*, 1995.

(11) Kikushima, K.; Grellier, M.; Ohashi, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 16191.

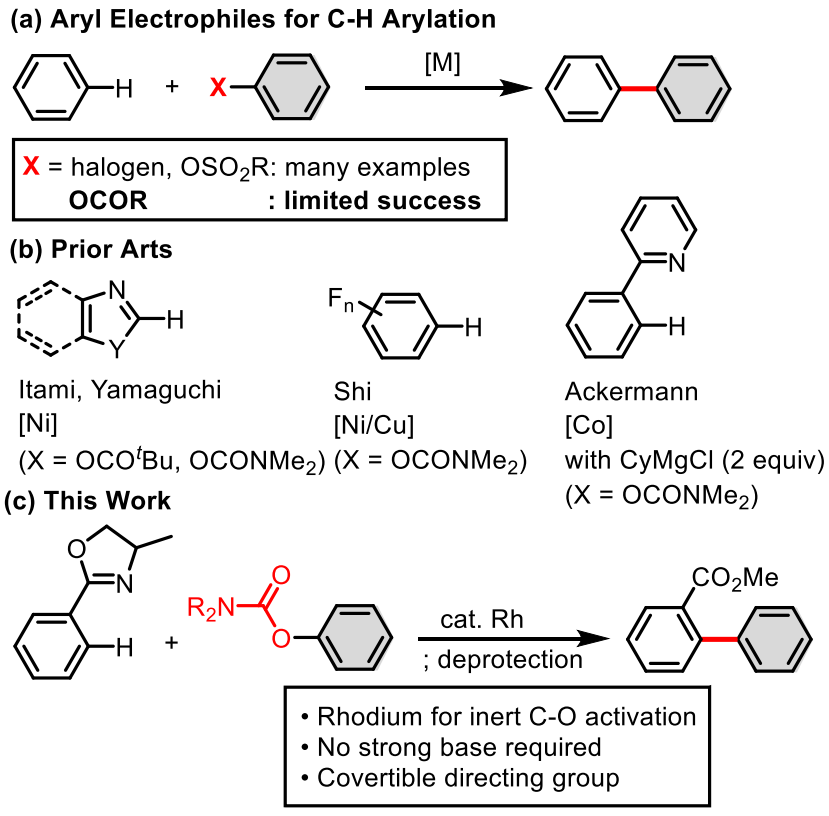
(12) (a) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. (b) Leonard, D. J.; Ward, J. W.; Clayden, J. *Nature* **2018**, *562*, 105.

Chapter 1

Rhodium-Catalyzed Directed C-H bonds Arylation with Aryl Carbamates

1.1 Introduction

Metal-catalyzed cross-coupling of organometallic nucleophiles with aryl halides has been established as the predominant method for functionalization of aromatic compounds.[1] Recently, phenol and its unactivated derivatives, such as ethers and esters, have emerged as less expensive and more environmentally-benign alternatives to aryl halides and triflates.[2] An even more important advantage of using these phenol derivatives is that their metal-coordinating ability and robustness allows new synthetic strategies, including late-stage functionalization and directing group manipulation. Nickel is the best catalyst to activate C(aryl)-O bonds, and it mediates a range of cross-coupling reactions using inert phenol derivatives.[2] Considering that C–H cross-coupling reactions have become increasingly popular methods,[3] it is natural to expect that C–H arylation with inert phenol derivatives should enable a dramatic increase in the scope and application of C–O cross-coupling reactions of inert phenol derivatives (Scheme 1a). However, C–H cross-coupling using inert phenol derivatives has had limited success. Itami and Yamaguchi first reported this type of reaction by developing nickel-catalyzed cross-coupling of aryl pivalates with azoles.[4] Shi recently reported that a C–H bond in perfluorinated arenes can be arylated by nickel/copper dual catalysis using aryl carbamates.[5] Although these two reactions provide valuable products related to pharmaceuticals and organic materials, the substrates are limited to those bearing a relatively acidic C–H bond.[6] Ackermann achieved cross-coupling of non-acidic unactivated C–H bonds with aryl carbamates using a cobalt catalyst.[7] Although this reaction represents an important advancement, the requirement for the use of excess Grignard reagent leaves several

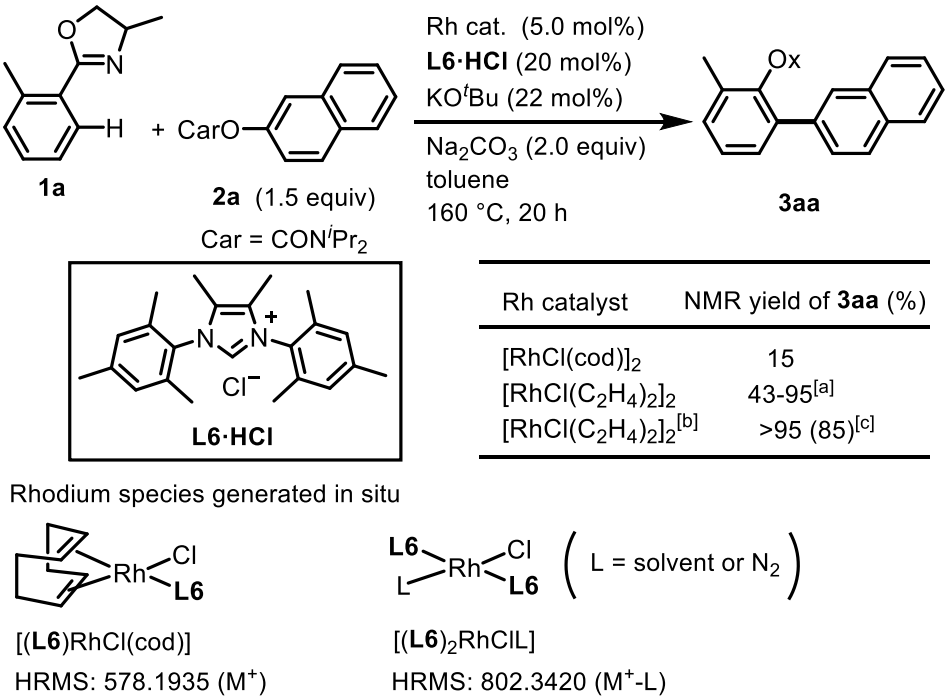


Scheme 1. C-H/C-O Cross-Coupling

issues to be addressed: (1) electrophilic functional groups, such as ketones and nitriles, are not compatible; and (2) an applicable directing group is limited to a robust but synthetically less attractive pyridine ring. With these considerations in mind, my research focuses on developing a rhodium-catalyzed cross-coupling of arenes bearing a convertible directing group with aryl carbamates in the absence of a strong base.

1.2 Results and Discussion

To realize cross-coupling of unactivated C–H bonds with inert phenol derivatives, the catalyst needs to efficiently mediate activation of both C–H and C–O bonds. Based on its remarkable activity in C–H activation,[8] I decided to use a rhodium catalyst, even though rhodium complexes are rarely used for C–O bond activation processes.[9] Reported rhodium complexes that can activate the C(aryl)–O bond require the use of a pincer-type ligand[9a,b] or boron-based reagents,[9c-e] both of which cannot be directly applied to our target C–H/C–O cross-coupling reactions. This research commenced with examining the reaction between *ortho* arylation of **1a**[10] and aryl carbamate **2a** as a model reaction for catalyst development. It should be noted that the oxazoline substrates are readily accessible from the corresponding carboxylic acids by condensation with 2-aminopropan-1-ol. Initial ligand screen led me to identify an NHC-based ligand **L6** as a potential lead for further optimization.[11,12] Interestingly, the use of $[RhCl(C_2H_4)_2]_2$ instead of $[RhCl(cod)]_2$ as the catalyst precursor along with **L6** considerably improved the yield of **3aa**, although the yields were variable among the experiments (Scheme 2). It was found that a consistently high yield of **3aa** can be obtained using the catalyst generated by preheating (60 °C, 1 h) a mixture of $[RhCl(C_2H_4)_2]_2$ and **L6**. FAB-MS and ^{13}C NMR analysis of the preheated solution of $[RhCl(C_2H_4)_2]_2$ and **L6** suggested exclusive generation of the bis-NHC species[13] $[(\mathbf{L6})_2RhCl^+$: 802.3420; ^{13}C NMR of C2: δ 190.2 (d, $J_{Rh\text{-}C}$ = 40 Hz)], whereas only the mono-NHC species $[(\mathbf{L6})RhCl(cod)^+$: 578.1935; ^{13}C NMR of C2: δ 185.1 (d, $J_{Rh\text{-}C}$ = 52 Hz)] was generated

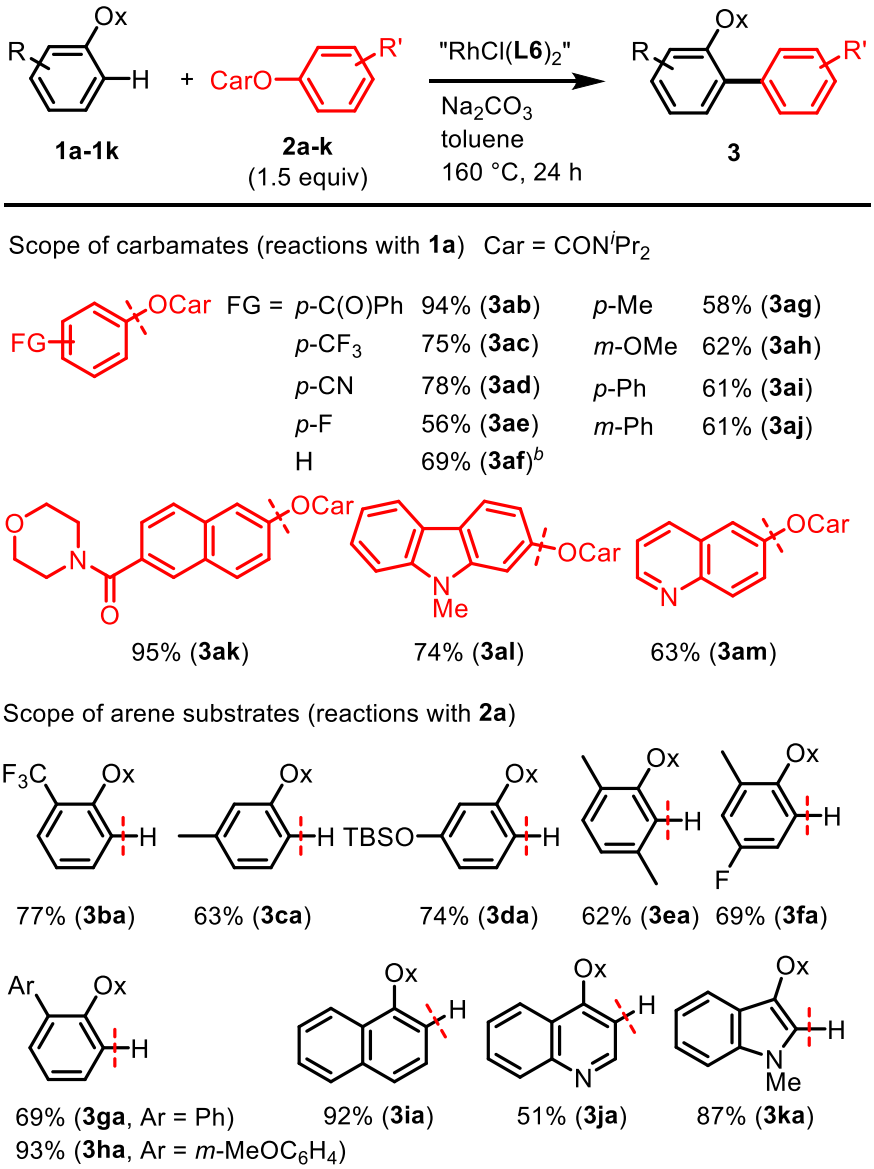


Scheme 2. Optimization of Rhodium-Catalyzed Cross-Coupling of Arene **1a** with Aryl Carbamate **2a** [a] Results of six independent experiments. [b] $RhCl(C_2H_4)]_2$, **L6·HCl** and KO^{t}Bu were stirred at 60 °C for 1 h prior to being used for the catalytic reaction. [c] Isolated yield.

from the preheated solution of $[RhCl(cod)]_2$ and **L6**.

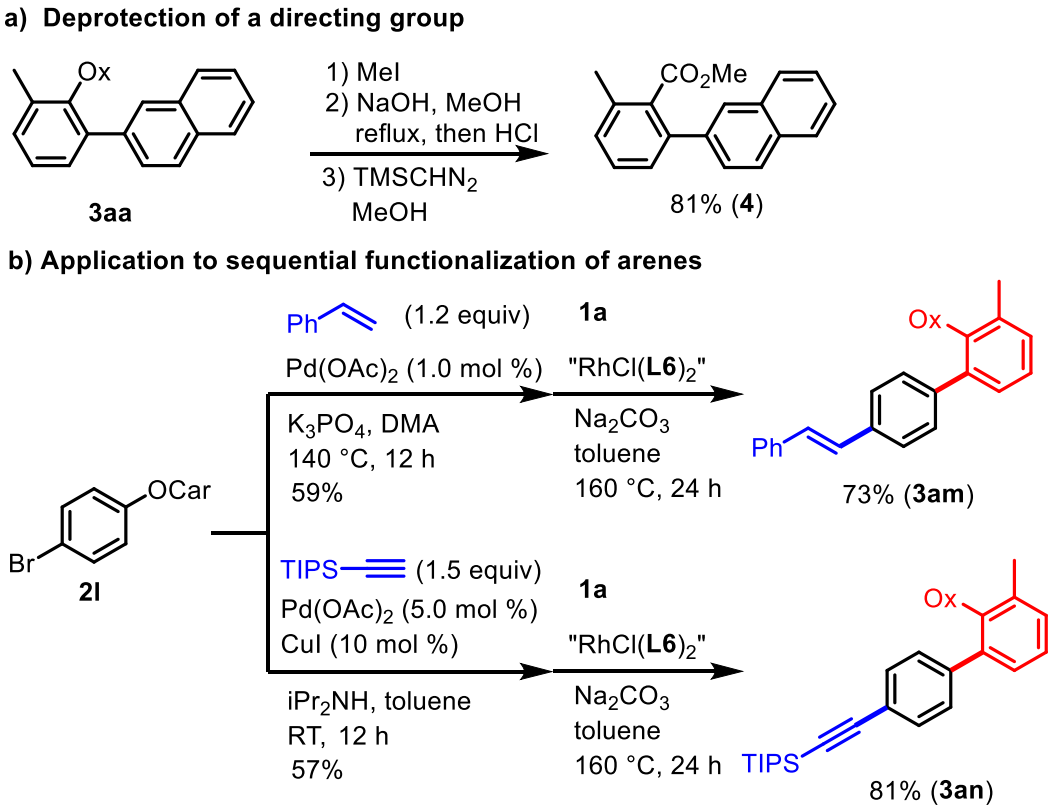
With the protocol to generate an active catalyst in hand, the scope of C-H/C-O cross-coupling with respect to the aryl carbamate component was examined. As shown in Scheme 3, this transformation is applicable to aryl carbamates bearing a range of functional groups, including ketones (**3ab**), nitriles (**3ad**), fluorides (**3ac** and **3ae**) and amides (**3ak**). Moreover, heteroaromatic carbamates (**3al** and **3am**) can also be successfully coupled with **1a**. The scope of the arene substrate was next evaluated. When meta-substituted arenes were reacted with **2a**, arylation exclusively occurred at the less hindered C-H bond, as in **3ca** and **3da**. However, a sterically congested C-H bond can also be arylated when it is the only reactive site, as evidenced by formation of **3ea**. This arylation is applicable to fused arenes (**3ia**) and heteroarenes (**3ja** and **3ka**).

The 4-methyl-4,5-dihydrooxazol-2-yl group used as the directing group in the present study can be readily



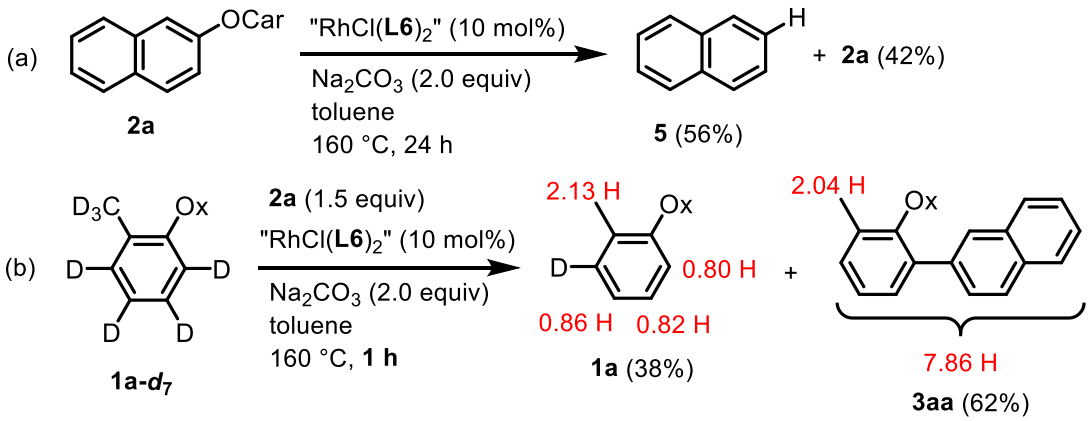
Scheme 3. Reaction Scope [a] $RhCl(\mathbf{L6})_2$ was prepared by stirring a mixture of $[RhCl(C_2H_4)]_2$ (0.015 mmol), **L6·HCl** (0.060 mmol) and KO^{t}Bu (0.066 mmol) at 60 °C for 1 h. Reaction conditions: **1** (0.30 mmol), **2** (0.45 mmol), catalyst, and Na_2CO_3 (0.60 mmol) in toluene (1.0 mL) for 24 h. The yield refers to the isolated yield. [b] $[RhCl(C_2H_4)]_2$ (0.023 mmol), **L6·HCl** (0.090 mmol) and KO^{t}Bu (0.099 mmol) were used.

converted to the corresponding carboxylic acid derivative, allowing further synthetic elaboration of the C-H/C-O coupling products (Scheme 4a). Because the carbamate group is completely stable under the conditions used for standard palladium-catalyzed cross-coupling of aryl halides, such as the Mizoroki-Heck and Sonogashira reactions, sequential functionalization of C-X and C-O bonds is possible (Scheme 4b).



Scheme 4. Synthetic Applications

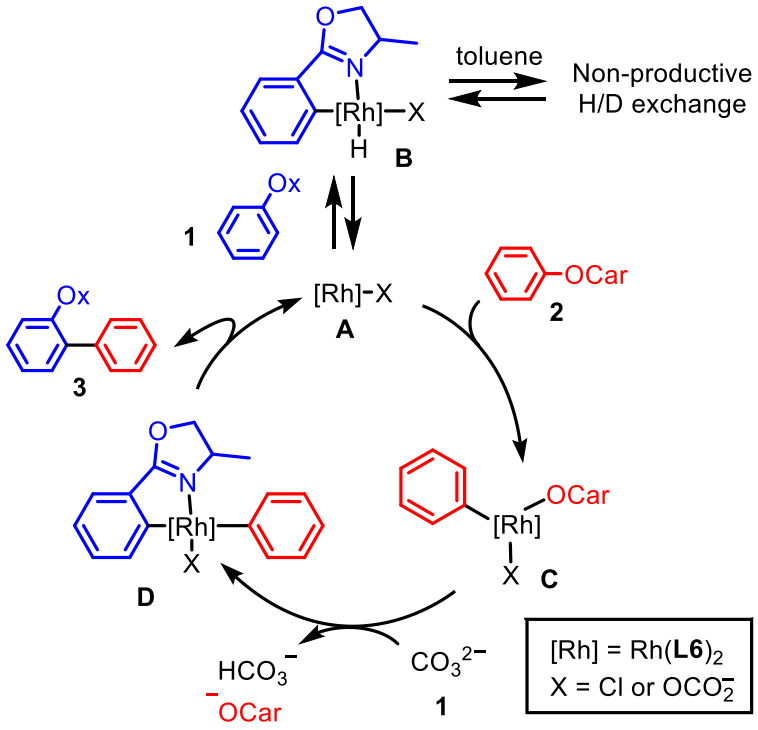
To obtain insight into the mechanism, several experiments were performed. When aryl carbamate **2a** was subjected to the rhodium-catalyzed conditions in the absence of an arene substrate, naphthalene (**5**) was formed in 56% yield (Scheme 5a). This observation indicates that Rh^{I}(**L6**)$_2$ can activate the C-O bond of **2a**, presumably by oxidative addition,[9] and the resulting arylrhodium(III) species undergoes protonation to form **5**. Labeling studies



Scheme 5. Mechanistic Studies

revealed that Rh^{I}(**L6**)$_2$ can also activate a C-H bond (Scheme 5b). When deuterated arene **1a-*d*$_7$** was reacted with **2a** in the presence of a Rh^{I}(**L6**)$_2$ catalyst for 1 h (62% conversion), deuterium content of the recovered **1a** was significantly decreased. Interestingly, the H/D exchange took place not only at the ortho position of **1a** but also at the meta, para and even benzylic positions. Therefore, non-selective C-H activation by Rh^{I}(**L6**)$_2$ can occur under these conditions.[9e,14] The decrease in the deuterium content of **1a** was less when the rhodium-catalyzed reaction of **1a-*d*$_7$** with **2a** was performed in deuterated solvent, indicating that the solvent toluene was the main source of hydrogen incorporated in the recovered **1a** (see Supporting Information).

A possible mechanism is shown in Scheme 6. Although Rh^{I}(**L6**)$_2$ species **A** can activate both C-H and C-O bonds, the initial C-H activation only leads to non-productive H/D exchange via intermediate **B**. The catalytic cycle that gives arylated product **3** begins with oxidative addition of the C-O bond in carbamate **2** to form arylrhodium(III) intermediate **C**. The subsequent ortho C-H activation by rhodium(III) species **C**, presumably through concerted metalation/deprotonation pathway,[15] gives diarylrhodium **D**, which finally gives arylated product **3** with concurrent regeneration of **A**.



Scheme 6. Possible mechanism.

1.3 Conclusion

In summary, I have developed rhodium-catalyzed aryla-tion of non-acidic C(sp^2)-H bonds using aryl carbamates as the arylating reagent. The key to success is the use of a bis(NHC) complex of rhodium(I) as the catalyst, which facilitates activation of inert C(sp^2)-O bonds in aryl carbamates. This readily generated rhodium species enabled activation of inert C(sp^2)-O bonds in the absence of a strong base, allowing for the use of a synthetically useful directing group in C-H/C-O coupling.

1.4 Experimental Section

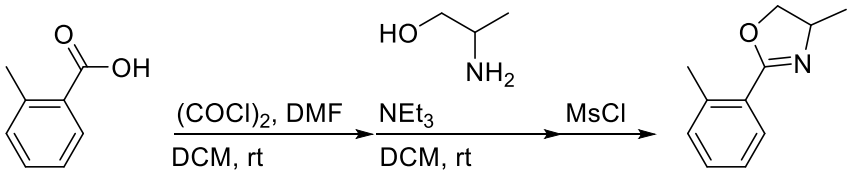
I. General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The data is reported as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad peak, and m = multiplet), coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer. Absorption is reported in reciprocal centimeters (cm^{-1}) with the following relative intensities: s (strong), m (medium), or w (weak). High resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SilicaFlash F60 (230-400 mesh)).

II. Materials

L2·HCl were purchased from Strem Chemicals and used as received. **L4·HCl**, **L5·HCl**, KO^{t}Bu, and diisopropylcarbamoyl chloride were purchased from TCI and used as received. Toluene (for Organic Synthesis) and $[RhCl(cod)]_2$ were purchased from Wako Chemicals and used as received. Na_2CO_3 and NaH was purchased from nacalai tesque and used as received. **L1·HCl**,[16] **L3·HCl**,[9(d)] $[RhCl(C_2H_4)_2]_2$,[17] and **L6·HCl**[9(e)] were prepared according to literature procedures. Compuonds **1a** (503544-61-4), **1b**, **1c** (928150-56-5), **1e**, **1f**, **1g** (220398-99-2), **1h** (132912-28-8), **1i**, and **1j** (497866-94-1) were prepared according to the general procedures shown below. Compounds **2a** (61912-15-0), **2b** (1684447-70-8), **2c**(1684447-67-3), **2d**, **2e** (1126310-52-8), **2f** (142075-48-7), **2g** (913621-13-3), **2h** (1684447-65-1), **2i** (885012-28-2), **2j** (1684447-74-2), **2k** (1684447-73-1) and **2l** (1684447-77-5) were prepared according to the literature procedure.[9(d)]

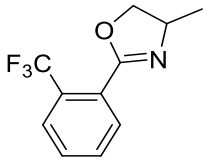
III. Synthesis of Starting Materials



General procedure for the preparation of 2-aryl-4-methyl-4,5-dihydrooxazole. To an oven-dried 100 mL three-necked flask, 2-methylbenzoic acid (1.5 g, 10 mmol), DMF (5 drops) and DCM (20 mL) were added under a N_2 atmosphere. Oxalyl chloride (1.0 mL, 12 mmol, 1.2 equiv) was added dropwise at 0 °C resulting in vigorous bubbling. The mixture was stirred for 1 h at rt, and the solvent was then removed *in vacuo*. The resulting acid chloride was used immediately without further purification. To a solution of acid chloride in DCM (30 mL), the solution of 2-aminopropan-1-ol (0.75 g, 10 mmol, 1.0 equiv), Et_3N (15 mL, 144 mmol, 14 equiv) in DCM (15 mL) were added dropwise to the solution at 0 °C, and the solution was then warmed to rt. After stirring the mixture for 1 h, methanesulfonyl chloride (1.5 mL, 20 mmol, 2.0 equiv) was added dropwise at rt. After stirring overnight, the resulting mixture was quenched with sat. aq. $NaHCO_3$ (30 mL) and the organic layer was separated. The aqueous layer was extracted with ether (2 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The resulting crude mixture was purified by column

chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to afford the desired oxazoline as a colorless oil (1.2 g, 69%).

4-Methyl-2-(2-(trifluoromethyl)phenyl)-4,5-dihydrooxazole (1b).



Rf 0.34 (hexane/EtOAc = 5/1). Colorless oil (1.92 g, 84%).

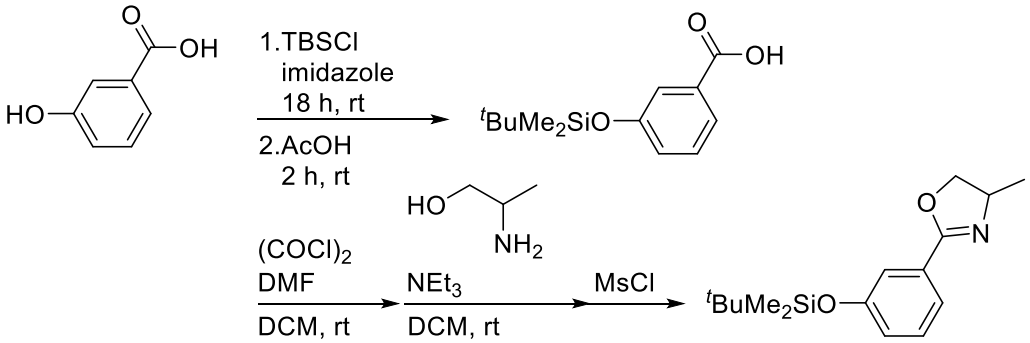
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39 (d, *J* = 6.4 Hz, 3H), 4.01 (t, *J* = 7.8 Hz, 1H), 4.01 (m, 1H), 4.55 (t, *J* = 8.2 Hz, 1H), 7.54-7.60 (m, 2H), 7.71-7.77 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 62.3, 75.0, 126.2 (q, *J* = 278.4 Hz), 126.5 (q, *J* = 5.7 Hz), 127.6, 129.1 (q, *J* = 31.5 Hz), 130.4, 131.0, 131.6, 162.9.

IR (ATR): 2973 w, 2899 w, 1663 m, 1606 w, 1579 w, 1496 w, 1451 w, 1356 w, 1340 w, 1312 s, 1273 w, 1251 w, 1167 s, 1136 s, 1112 s, 1083 m, 1034 s, 963 m, 935 w, 893 w, 848 w, 770 m, 690 w.

HRMS (EI): Calcd for $C_{11}H_{10}F_3NO$ 229.0714, Found 229.0716.

2-(3-((tert-Butyldimethylsilyl)oxy)phenyl)-4-methyl-4,5-dihydrooxazole (1d).



3-((tert-Butyldimethylsilyl)oxy)benzoic acid was synthesized according to Koch's procedure.[18]

A solution of 3-hydroxybenzoic acid (3.0 g, 21 mmol), TBSCl (7.2 g, 48 mmol) and imidazole (3.3 g, 48 mmol) in dry DMF (30 mL) was stirred at rt for 18 h. Acetone (150 mL) was added to the reaction mixture, filtered and the filtrate was evaporated. The residue was taken up in EtOAc (50 mL), washed with water (3x 40 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield *tert*-butyldimethylsilyl 3-[(*tert*butyldimethylsilyl)oxy]benzoate as a colorless liquid. This crude product was treated with a mixture of AcOH (45 mL), THF (15 mL) and water (15 mL) and stirred at rt for 2 h. EtOAc (50 mL) and water (50 mL) were added and the organic phase was extracted, washed with sat. aq. $NaHCO_3$ sol. (3 × 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was dried under high vacuum to give the 3-(*tert*butyldimethylsilyl)oxybenzoic acid as a white solid (4.19 g, 76%). The obtained benzoic acid was derivatized to **3d** according to the general procedure (10 mmol scale, 2.4 g, 90%).

Rf 0.30 (hexane/EtOAc = 5/1). Colorless oil (1.4 g, 74%).

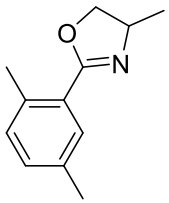
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.20 (s, 6H), 0.99 (s, 9H), 1.36 (d, *J* = 6.4 Hz, 3H), 3.94 (t, *J* = 7.8 Hz, 1H), 4.32-4.41 (m, 1H), 4.50 (dd, *J* = 9.4, 8.0 Hz, 1H), 6.94 (dq, *J* = 8.1, 1.1 Hz, 1H), 7.23-7.27 (m, 1H), 7.41 (t, *J* = 1.8 Hz, 1H), 7.55 (dt, *J* = 7.8, 1.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ -4.5, 18.1, 21.4, 25.6, 62.0, 74.0, 119.9, 121.3, 123.0, 129.2, 129.3, 155.5, 163.2.

IR (ATR): 2968 w, 2927 w, 2896 w, 1665 s, 1607 w, 1587 m, 1447 w, 1374 w, 1157 w, 1116 m, 1037 s, 1011 w, 978 w, 950 m, 865 m, 822 m, 743 m, 731 w, 679 w.

HRMS (EI): Calcd for $C_{16}H_{25}NO_2Si$ 291.1655, Found 291.1656.

2-(2,5-Dimethylphenyl)-4-methyl-4,5-dihydrooxazole (1e).



Rf 0.21 (hexane/EtOAc = 5/1). Colorless oil (1.68 g, 89%).

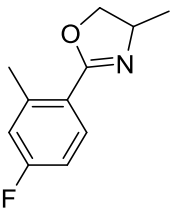
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (d, *J* = 6.4 Hz, 3H), 2.31 (s, 3H), 2.52 (s, 3H), 3.90 (t, *J* = 7.3 Hz, 1H), 4.33-4.47 (m, 2H), 7.08-7.13 (m, 2H), 7.60 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.6, 21.0, 21.6, 62.1, 73.3, 127.0, 130.2, 131.0, 131.1, 134.9, 135.3, 164.1.

IR (ATR): 2967 w, 2896 w, 2361 w, 2294 w, 1644 s, 1570 w, 1544 m, 1476 w, 1451 w, 1401 m, 1373 w, 1332 m, 1289 m, 1141 w, 1106 w, 1075 w, 1048 w, 1075 w, 1048 s, 1029 s, 970 s, 931 w, 890 w, 844 w, 816 m, 743 w, 706 w.

HRMS (EI): Calcd for $C_{12}H_{15}NO$ 189.1154, Found189.1156.

2-(4-Fluoro-2-methylphenyl)-4-methyl-4,5-dihydrooxazole (1f).



Rf 0.30 (hexane/EtOAc = 5/1). Colorless oil (1.4 g, 74%).

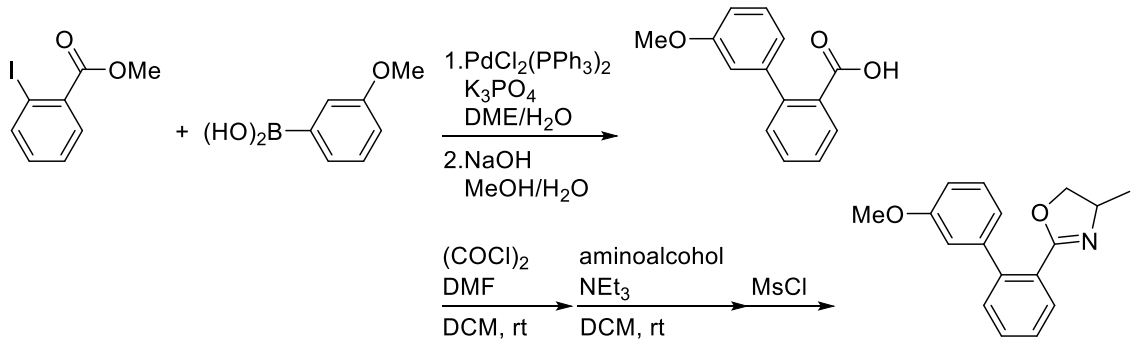
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (d, *J* = 6.4 Hz, 3H), 2.58 (s, 3H), 3.86-4.09 (m, 1H), 4.34-4.48 (m, 2H), 6.87-6.95 (m, 2H), 7.78 (dd, *J* = 8.6, 6.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 21.7, 62.3, 73.2, 112.4 (d, *J* = 21.0 Hz), 117.7 (d, *J* = 20.9 Hz), 123.4 (d, *J* = 2.9 Hz), 131.9 (d, *J* = 8.6 Hz), 141.7 (d, *J* = 8.5 Hz), 162.9, 163.5 (d, *J* = 249.8 Hz).

IR (ATR): 2968 w, 2927 w, 2896 w, 1665 s, 1607 w, 1587 m, 1447 w, 1374 w, 1157 w, 1116 m, 1037 s, 1011 w, 978 w, 950 m, 865 m, 822 m, 743 m, 731 w, 679 w.

HRMS (EI): Calcd for $C_{11}H_{12}FNO$ 193.0903, Found 193.0900.

2-(3'-Methoxy-[1,1'-biphenyl]-2-yl)-4-methyl-4,5-dihydrooxazole (1h).



A solution of methyl 2-iodobenzoate (2.61 g, 10 mmol), (3-methoxyphenyl)boronic acid (1.97 g, 12 mmol), K_3PO_4 (9.6 g, 45 mmol), and $PdCl(PPh_3)_2$ (60 mg, 1 mol%) in DME (8 mL) / H_2O (8 mL) was stirred for 15 min at 180 °C in a microwave reactor. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. This material was used in the subsequent step without further purification. An aqueous solution of NaOH (8 mL, 1 M) was added to a stirred mixture of the obtained compound in MeOH (8 mL). The reaction mixture was heated for 5 min at 150 °C in a microwave reactor. The reaction mixture was concentrated under reduced pressure. The residue was quenched with 6 M HCl until pH < 3 and was extracted with EtOAc (3 × 20 mL). The combined layers were washed with brine (1 × 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford 3'-methoxy-[1,1'-biphenyl]-2-carboxylic acid. Yield: 2.3 g (100%), colorless oil. The obtained benzoic acid was derivatized to oxazoline **1h** according to the general procedure (10 mmol scale, 2.3 g, 85%).
Rf 0.06 (hexane/EtOAc = 5/1). Colorless oil (2.3 g, 85%).

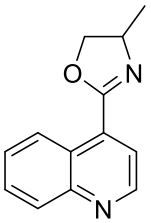
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (d, *J* = 6.4 Hz, 3H), 3.62-3.70 (m, 1H), 3.81 (s, 3H), 4.19-4.29 (m, 2H), 6.88 (dt, *J* = 8.2, 1.4 Hz, 1H), 6.94-6.99 (m, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.35-7.40 (m, 2H), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H), 7.73 (dd, *J* = 7.6, 1.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 55.1, 61.9, 74.3, 112.8, 113.7, 120.8, 127.1, 127.7, 128.9, 129.98, 130.03, 130.4, 141.5, 142.5, 159.2, 164.9.

IR (ATR): 2965 w, 2835 w, 2360 w, 1651 m, 1600 m, 1582 m, 1471 m, 1423 w, 1374 w, 1353 w, 1338 w, 1302 m, 1268 m, 1239 m, 1212 s, 1176 w, 1108 w, 1070 w, 1048 s, 1034 s, 994 w, 964 s, 933 w, 890 w, 860 m, 758 s, 725 m, 696 s, 668 w.

HRMS Calcd for $C_{17}H_{18}NO_2^+$ (APCI, $[M+H]^+$): 268.1338, Found 268.1332.

4-Methyl-2-(quinolin-4-yl)-4,5-dihydrooxazole (1j).



Rf 0.03 (hexane/EtOAc = 5/1). White solid (1.0 g, 84%). Mp = 70 °C

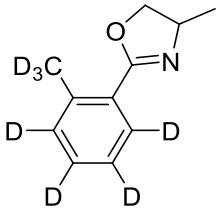
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.47 (d, *J* = 6.4 Hz, 3H), 4.07-4.00 (m, 1H), 4.61-4.54 (m, 2H), 7.65 (ddd, *J* = 1.4 Hz, 6.9 Hz, 8.6 Hz, 1H), 7.76 (ddd, *J* = 1.4 Hz, 6.9 Hz, 8.6 Hz, 1H), 7.88 (d, *J* = 4.4 Hz, 1H), 8.15 (dd, *J* = 8.5 Hz, 0.7 Hz, 1H), 8.99 (d, *J* = 4.4 Hz, 1H), 9.09 (dd, *J* = 8.7 Hz, 0.9 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 63.1, 73.4, 121.7, 125.3, 126.4, 127.7, 129.6, 129.9, 132.5, 148.9, 149.7, 161.6.

IR (ATR): 2960 w, 2875 w, 1644 w, 1576 w, 1509 m, 1455 w, 1414 w, 1401 m, 1351 w, 1330 m, 1294 m, 1245 w, 1212 w, 1182 w, 1145 m, 1100 m, 1071 m, 1039 s, 996 s, 962 m, 855 m, 770 m, 743 m, 698 m, 657 w.

HRMS (EI): Calcd for $C_{13}H_{12}N_2O$ 212.0950, Found 212.0948.

4-Methyl-2-(2-(methyl-*d*$_3$)phenyl-3,4,5,6-*d*$_4$)-4,5-dihydrooxazole (1a-*d*$_7$).



Rf 0.21 (hexane/EtOAc = 5/1). Colorless oil (1.0 g, 91%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (d, *J* = 6.4 Hz, 3H), 3.91 (t, *J* = 6.9 Hz, 1H), 4.34-4.47 (m, 2H).

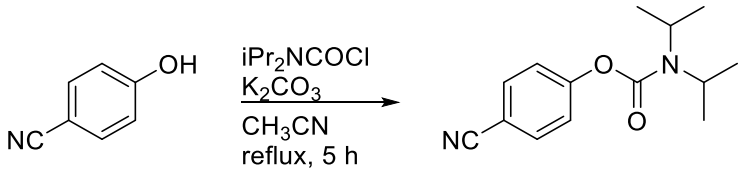
^{2}H NMR ($(CH_3)_2CO$, 400 MHz): δ 2.54 (s, 3H), 7.31 (s, 1H), 7.40 (s, 1H), 7.82 (s, 1H), 8.00 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7 (t, *J* = 20.0 Hz), 21.6, 62.3, 73.3, 125.0 (t, *J* = 24.8 Hz), 127.3, 129.3 (t, *J* = 24.8 Hz), 129.9 (t, *J* = 24.8 Hz), 130.6 (t, *J* = 24.8 Hz), 138.4, 163.9.

IR (ATR): 2968 w, 2893 w, 1640 s, 1410 m, 1371 w, 1352 w, 1295 m, 1227 s, 1168 w, 1106 w, 1075 w, 1039 s, 1017 s, 970 m, 930 w, 894 w, 869 w, 840 w, 744 w, 685 w.

HRMS (EI): Calcd for $C_{11}H_6D_7NO$ 182.1437, Found.182.1438.

4-Cyanophenyl diisopropylcarbamate (2d).



A mixture of 4-hydroxybenzonitrile (1.19 g, 10.0 mmol), ^{i}Pr$_2$NCOCl (2.45 g, 15.0 mmol) and K_2CO_3 (2.07 g, 14.9 mmol) in CH_3CN (25 mL) was refluxed for 5 h. The reaction mixture was cooled to rt and concentrated under vacuum. The residue was dissolved in H_2O (ca. 50 mL) and extracted with Et_2O (ca. 2 × 20 mL). The organic fractions were combined and then washed successively with KOH aq. (1M, ca. 25 mL) and water. Finally the organic layer was separated, dried over $MgSO_4$, and concentrated under vacuum to yield **2d** (1.92 g, 73%).

Rf 0.30 (hexane/EtOAc = 5/1). White solid. (1.91 g, 73%). Mp = 94 °C

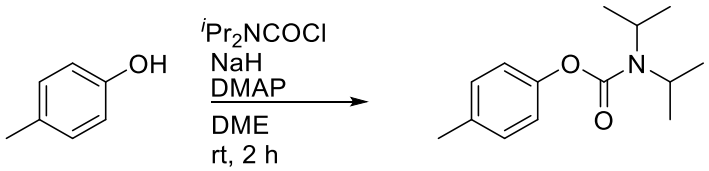
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (m, 12H), 3.98 (m, 1H), 4.06 (m, 1H), 7.26 (dt, *J* = 9.2, 2.2 Hz, 2H), 7.66 (dt, *J* = 9.2, 2.2 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3, 21.5, 46.5, 47.1, 108.5, 118.6, 125.7, 133.4, 152.4, 154.8.

IR (ATR): 2968 w, 2927 w, 2896 w, 1665 s, 1607 w, 1587 m, 1447 w, 1374 w, 1157 w, 1116 m, 1037 s, 1011 w, 978 w, 950 m, 865 m, 822 m, 743 m, 731 w, 679 w.

HRMS calcd for $C_{14}H_{19}N_2O_2^+$ (CI, $[M+H]^+$): 247.1447, Found 247.1450.

***p*-Tolyl diisopropylcarbamate (2g).**



To a mixture of *p*-cresol (1.2 g, 10.0 mmol) and NaH (0.50 g, 10 mmol) in DME (20 mL), $^{i}Pr_2NCOCl$ (2.0 g, 12.0 mmol) and N,N-dimethylpyridin-4-amine (DMAP) (36 mg, 3 mol%) were added and stirred for 2 h at rt. The residue was dissolved in H_2O (50 mL) and extracted with Et_2O (2 × 20 mL). The organic fractions were combined and then washed successively with an aqueous solution of Na_2CO_3 (1 M, 25 mL) and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a vacuum to yield **2g** as a colorless oil (2.2 g, 95%).

Rf 0.35 (hexane/EtOAc = 5/1). Colorless oil. (1.91 g, 73%).

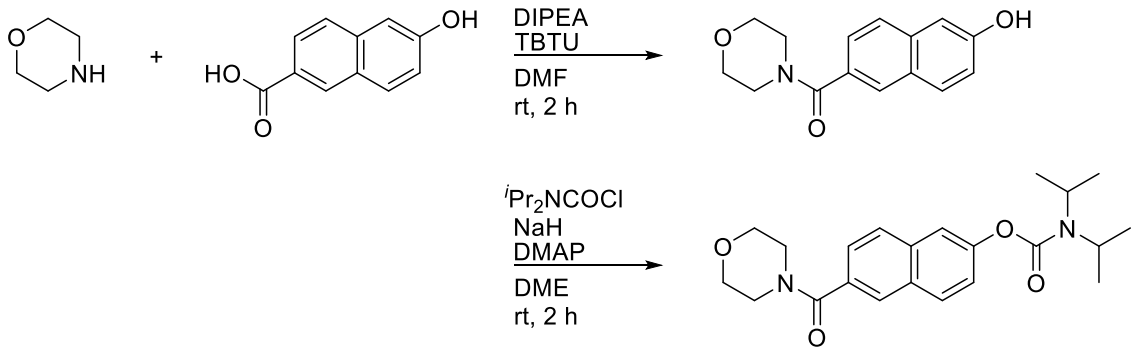
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (m, 12H), 2.32 (s, 3H), 3.93 (m, 1H), 4.10 (m, 1H), 6.96-7.01 (m, 2H), 7.14 (d, *J* = 7.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.4, 20.8, 21.5, 121.5, 129.6, 134.4, 149.1, 154.1.

IR (ATR): 2967 w, 2923 w, 2360 w, 1927 w, 1664 s, 1589 w, 1515 w, 1461 m, 1374 w, 1333 w, 1296 w, 1250 w, 1236 w, 1114 w, 1037 s, 963 m, 888 w, 823 s, 786 s, 757 w, 730 w.

HRMS calcd for $C_{14}H_{22}NO_2^+$ (FAB+, $[M+H]^+$): 236.1651, Found 236.1654.

6-(Morpholine-4-carbonyl)naphthalen-2-yl diisopropylcarbamate (2k).



To a mixture of morpholine (1.04 g, 12 mmol) and 6-hydroxy-2-naphthoic acid (1.88 g, 10 mmol) in THF (20 mL), TBTU (6.4 g, 20 mmol) and DIPEA (2.6 g, 20 mmol) were added. The suspension was stirred at rt for 18 h. 1M HCl was then added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with $NaHCO_3$ aq and brine and dried over $MgSO_4$, and concentrated under a vacuum to yield (6-hydroxynaphthalen-2-yl)(morpholino)methanone (1.0 g, 40%). This material was used in the subsequent step without further purification. To a mixture of the obtained amide and NaH (0.25 g, 5 mmol) in DME (20 mL), $^{i}Pr_2NCOCl$ (1.0 g, 6.0 mmol) and DMAP (18 mg, 3 mol%) were added and stirred at rt for 2 h. The residue was dissolved in H_2O (50 mL) and extracted with Et_2O (2 × 20 mL). The organic extracts were combined and then washed successively with 1 M Na_2CO_3 (25 mL) and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a vacuum to yield **2k** as a white solid (0.9 g, 61%).

Rf 0.05 (hexane/EtOAc = 1/1). White solid. (0.9 g, 24%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32-1.39 (m, 12H), 3.53-4.15 (m, 10H), 7.35 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.48 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 7.82-7.90 (m, 3H).

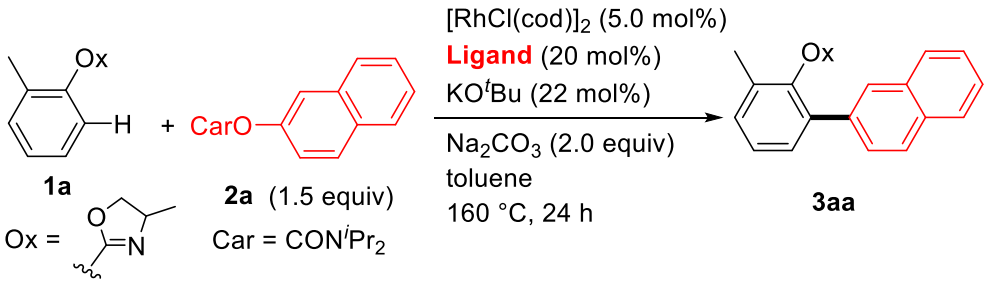
^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.4, 21.6, 66.9 (two overlapping peaks), 118.4, 122.8, 124.7, 126.9, 128.0, 129.6, 130.2, 131.9, 134.3, 150.1, 153.7, 170.4.

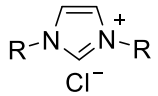
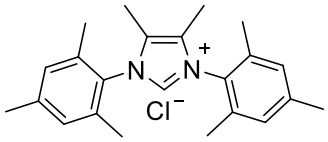
IR (ATR): 2967 w, 2923 w, 2360 w, 1927 w, 1664 s, 1589 w, 1515 w, 1461 m, 1374 w, 1333 w, 1296 w, 1250 w, 1236 w, 1114 w, 1037 s, 963 m, 888 w, 823 s, 786 s, 757 w, 730 w.

HRMS calcd for $C_{22}H_{29}N_2O_4^+$ (APCI, $[M+H]^+$): 385.2122, Found 385.2127.

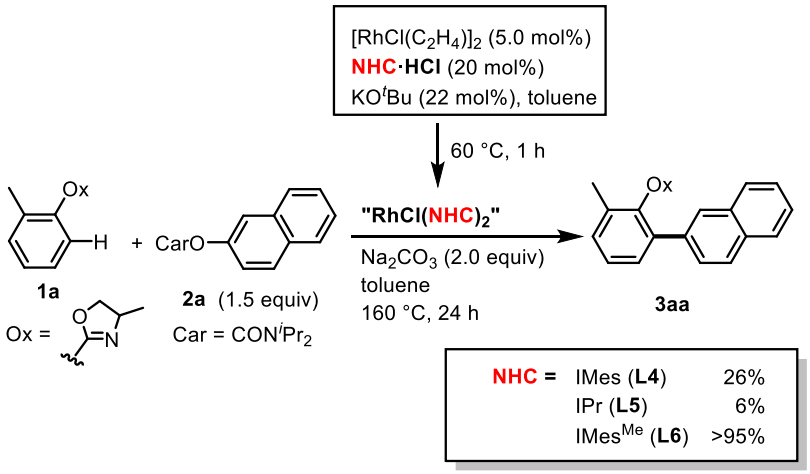
IV. Optimization Studies

Effect of Ligands.

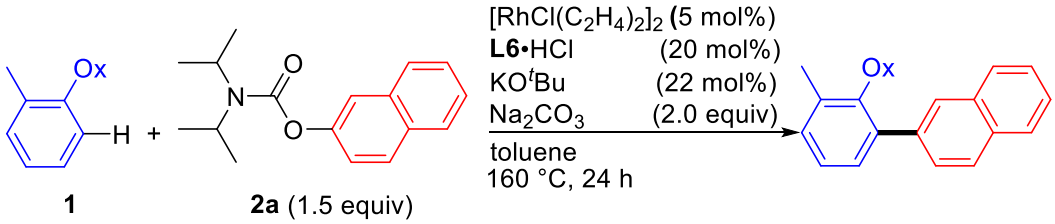


Ligand		GC yield of **3aa** (%)
	R = cyclohexyl (**L1·HCl**)	0
	R = 1-adamantyl (**L2·HCl**)	0
	R = 2-adamantyl (**L3·HCl**)	0
	R = 2,4,6-$Me_3C_6H_2$ (**L4·HCl**)	0
	R = 2,6-$^i Pr_2C_6H_3$ (**L5·HCl**)	15
	IMes^{Me}•HCl (**L6·HCl**)	15

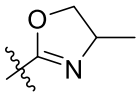
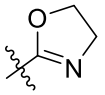
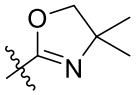
Effect of Ligands under Preheating Conditions. The use of **L4** and **L5** were not effective under these preheated conditions (26% and 6%, respectively), indicating that the use of **L6** is essential for an efficient reaction.



Effect of the Oxazoline Directing Group.

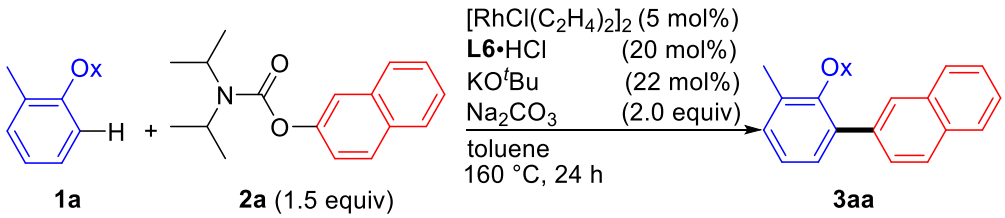


1 **2a** (1.5 equiv)

Entry	Ox		Isolated yield (%)
1		**1a**	85
2		**1a'**	46
3		**1a"**	21

$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L6·HCl** (22.3 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), Na_2CO_3 (63.6 mg, 0.60 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. After 1 h, **2a** (122 mg, 0.45 mmol), **1** (0.30 mmol) and toluene (0.60 mL) were added to the vial in the glove box. The vessel was stirred at 160 °C for 24 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (eluting with hexane/EtOAc = 10/1) to give **3** as a pale yellow oil [**3aa** (77 mg, 85%), **3a′a** (40.0 mg, 46%), **3a″a** (20.3 mg, 21%)].

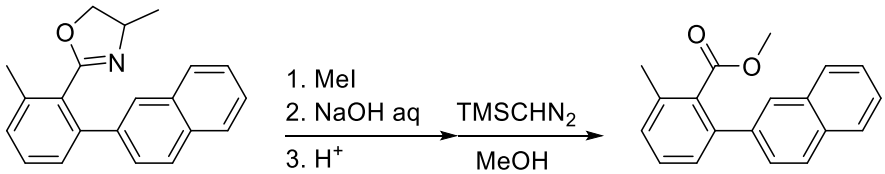
V. Typical Procedure for Rh-Catalyzed Directed C-H Bond Arylation with Aryl Carbamates



1a **2a** (1.5 equiv) **3aa**

$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L6·HCl** (22.3 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), Na_2CO_3 (63.6 mg, 0.60 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. After 1 h, **2a** (122 mg, 0.45 mmol), **1a** (52.5 mg, 0.30 mmol), and toluene (0.60 mL) were added to the vial in the glove box. The vessel was stirred at 160 °C for 24 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (eluting with hexane/EtOAc = 10/1) to give **3a** as a pale yellow oil (77 mg, 85%).

VI. Procedure for Deprotection of Oxazoline



3aa **4**

The oxazolinyl group was deprotected according to Cram's procedure.[1] A solution of **3aa** (70.1 mg, 0.23 mmol) in CH_3I (3.0 mL) was stirred overnight under N_2. The excess CH_3I was removed by evaporation under a stream of N_2, and the residue was dissolved in MeOH (1.5 mL). An aqueous solution NaOH (20%, 1.5 mL) was added, and the suspension was refluxed under N_2 overnight. The cooled solution was slowly poured into an aqueous solution of HCl (6 M). The residue was taken up in EtOAc (50 mL), washed with water (3 × 40 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo gave a white solid. The solid was dissolved in MeOH (1 mL) and $TMSCHN_2$ (10% in hexane, 1.2 mL, 0.69 mmol) was added, and the resulting mixture was stirred at rt for 30 min. The reaction mixture was then concentrated in vacuo. The residue was dissolved in H_2O (ca. 20 mL) and extracted with Et_2O (ca. 2 × 20 mL). The organic fractions were combined and then successively washed with brine. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo to give the corresponding ester **4** as a white solid (67.1 mg, 81%).

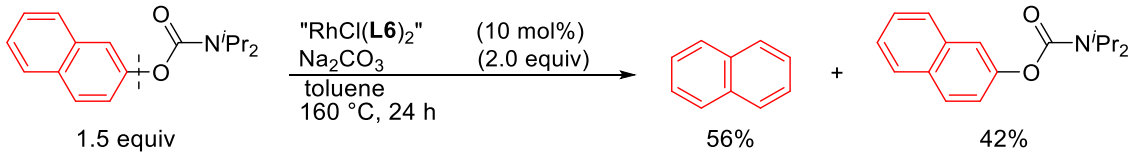
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.43 (s, 3H), 3.53 (s, 3H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.46-7.51 (m, 3H), 7.84-7.86 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 51.9, 126.0, 126.3, 126.5, 127.0, 127.5, 127.6, 127.9, 128.1, 129.2, 129.5, 132.5, 133.3 (two overlapping peaks), 135.6, 138.4, 140.0, 170.3.

HRMS (EI): Calcd for $C_{19}H_{16}O_2$ 276.1150, Found.276.1150.

VII. Mechanistic Studies

1. C-O Activation by RhCl(L6)$_2$ (Scheme 3a)



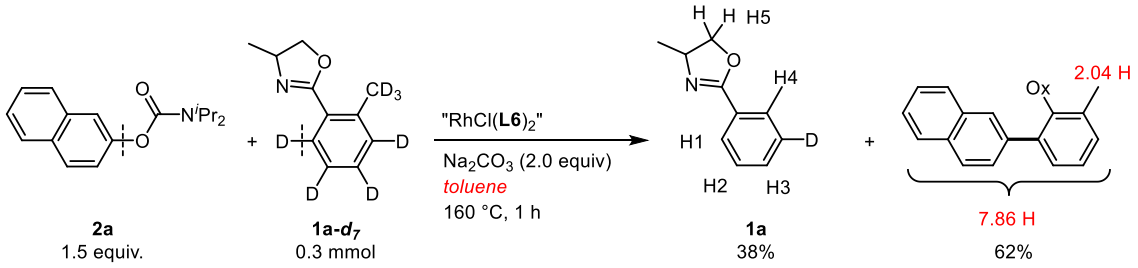
1.5 equiv 56% 42%

[RhCl(C_2H_4)$_2$]$_2$ (5.8 mg, 0.015 mmol), **L6·HCl** (22.3 mg, 0.06 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), Na_2CO_3 (63.6 mg, 0.6 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. After 1 h, **2a** (81.3 mg, 0.30 mmol) and toluene (0.60 mL) were added to the vial in the glove box. The vessel was stirred at 160 °C for 24 h followed by cooling to rt. After the reaction, naphthalene was observed by GC analysis of the crude reaction mixture.

[1] Wilson, J. M.; Cram, J. D. *J. Org. Chem.* **1984**, *49*, 4930.

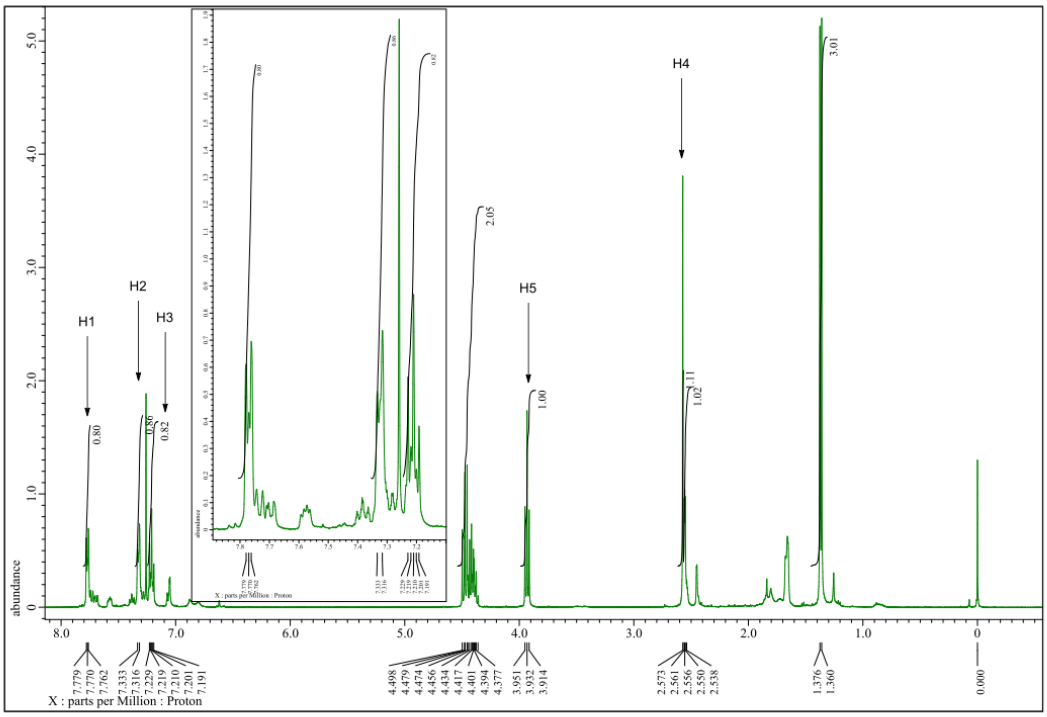
2. Labeling Experiments

The reaction of 1a-d_7 with 2a in toluene (Scheme 3b).



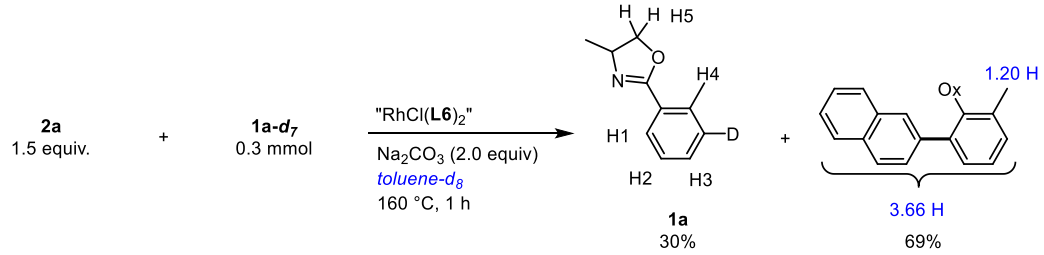
$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L6·HCl** (22.3 mg, 0.06 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), Na_2CO_3 (63.6 mg, 0.60 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. After 1 h, **2a** (122 mg, 0.45 mmol), **1a-d_7** (54.6 mg, 0.30 mmol), and toluene (0.60 mL) were added to the vial in the glove box. The vessel was stirred at 160 °C for 1 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (eluting with hexane/EtOAc = 10/1) to give **3a** as a pale yellow oil (56.5 mg, 63%) and **1a** as a colorless oil (20.9 mg, 38%).

NMR spectrum of reaction (b)



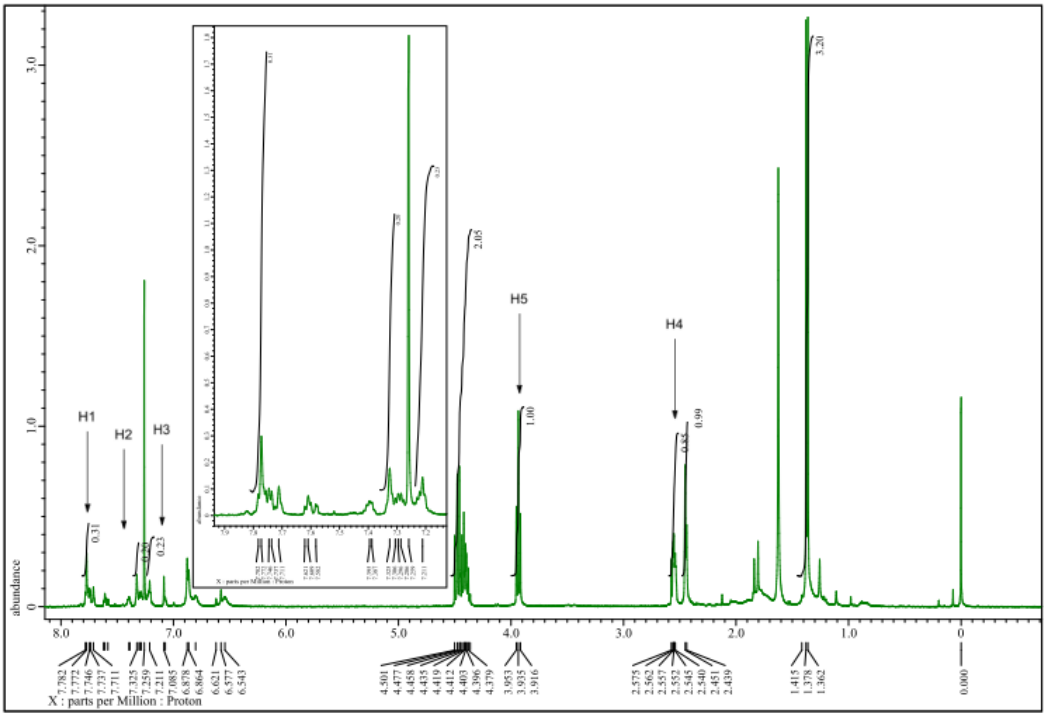
H	chemical shift (ppm)	integration value
H1	7.77	0.801
H2	7.32	0.822
H3	7.21	0.858
H4	2.54-2.57	2.131
H5	3.93	1.000

The reaction of 1a-d_7 with 2a in toluene-d_8 (Scheme 3c).



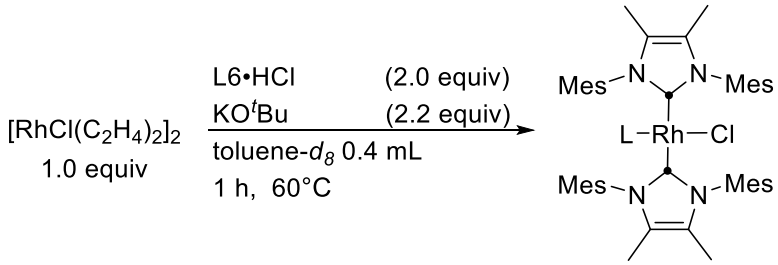
$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L6·HCl** (22.3 mg, 0.06 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), Na_2CO_3 (63.6 mg, 0.6 mmol), and toluene-d_8 (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. After 1 h, **2a** (122 mg, 0.45 mmol), **1a-d_7** (54.6 mg, 0.30 mmol), and toluene-d_8 (0.60 mL) were added to the vial in the glove box. The vessel was stirred at 160 °C for 1 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (eluting with hexane/EtOAc = 10/1) to give **3a** as a pale yellow oil (63 mg, 69%) and **1a** as a colorless oil (16.5 mg, 30%).

NMR spectrum of reaction (c)



H	chemical shift (ppm)	integration value
H1	7.77	0.310
H2	7.33	0.200
H3	7.21	0.230
H4	2.54-2.58	0.850
H5	3.93	1.000

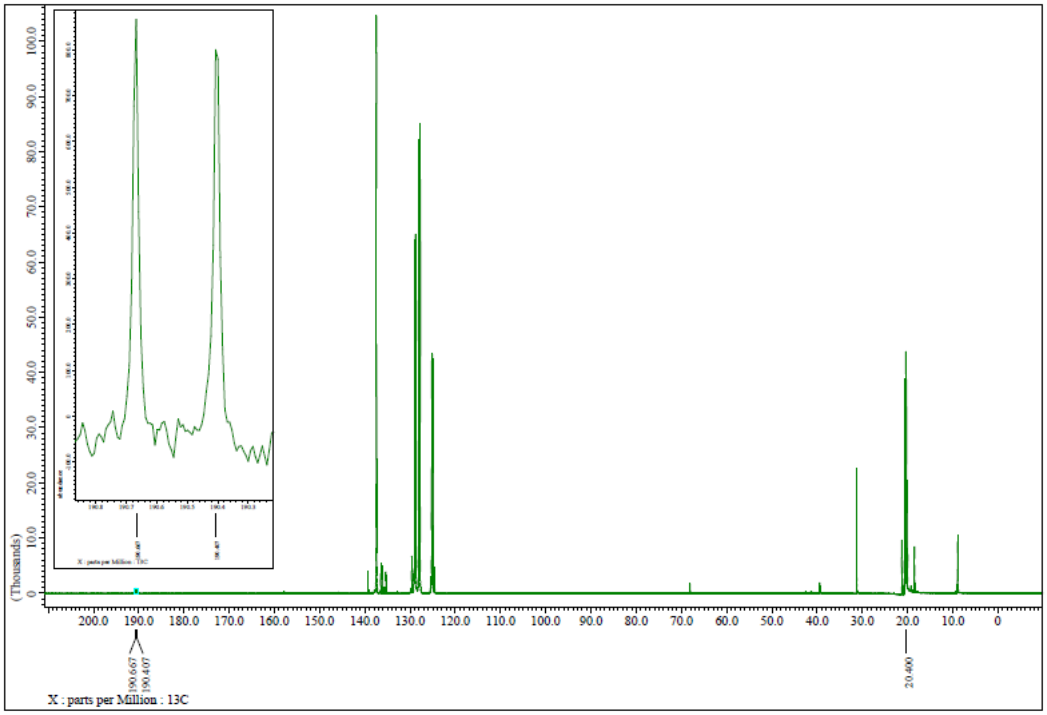
VIII. Observation of the Rhodium Complexes Generated in Situ

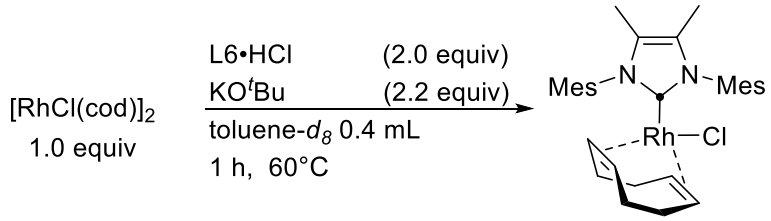


$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L6·HCl** (22.3 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), and toluene-d_8 (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. The mixture was analyzed by ^{13}C NMR and HRMS.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.5 (d, ^1J(Rh,C) = 32.5 Hz, *C*-carbene).

HRMS calcd for $C_{46}H_{56}ClN_4Rh^+$ (FAB, $[M\text{-}L]^+$): 802.3249, found: 802.3240.

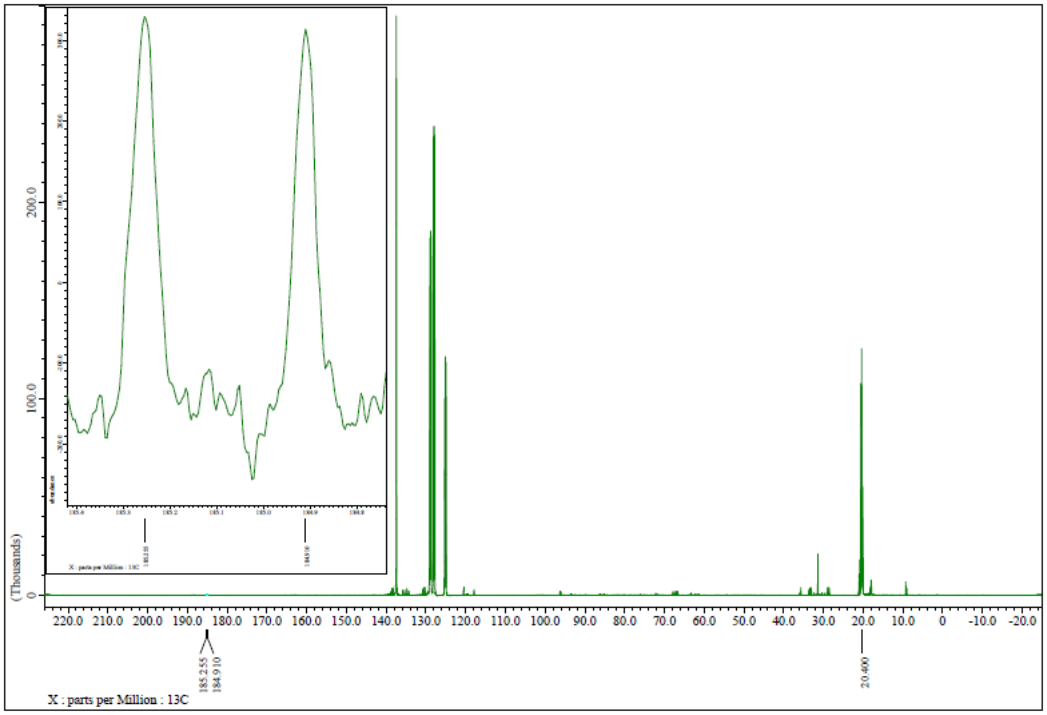


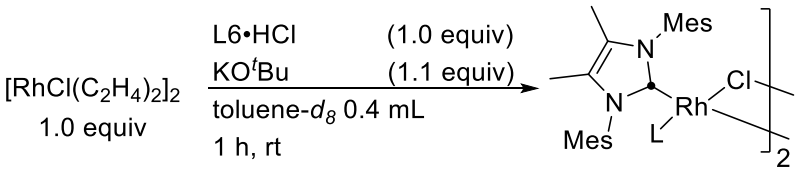


[RhCl(cod)]$_2$ (7.4 mg, 0.015 mmol), **L6·HCl** (22.3 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), and toluene-d_8 (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. The mixture was analyzed by ^{13}C NMR and HRMS.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 185.1 (d, ^1J(Rh,C) = 43.1 Hz, *C*-carbene),.

HRMS calcd for $C_{31}H_{40}ClN_2Rh^+$ (FAB, $[M]^+$): 578.1924, found: 578.1935.

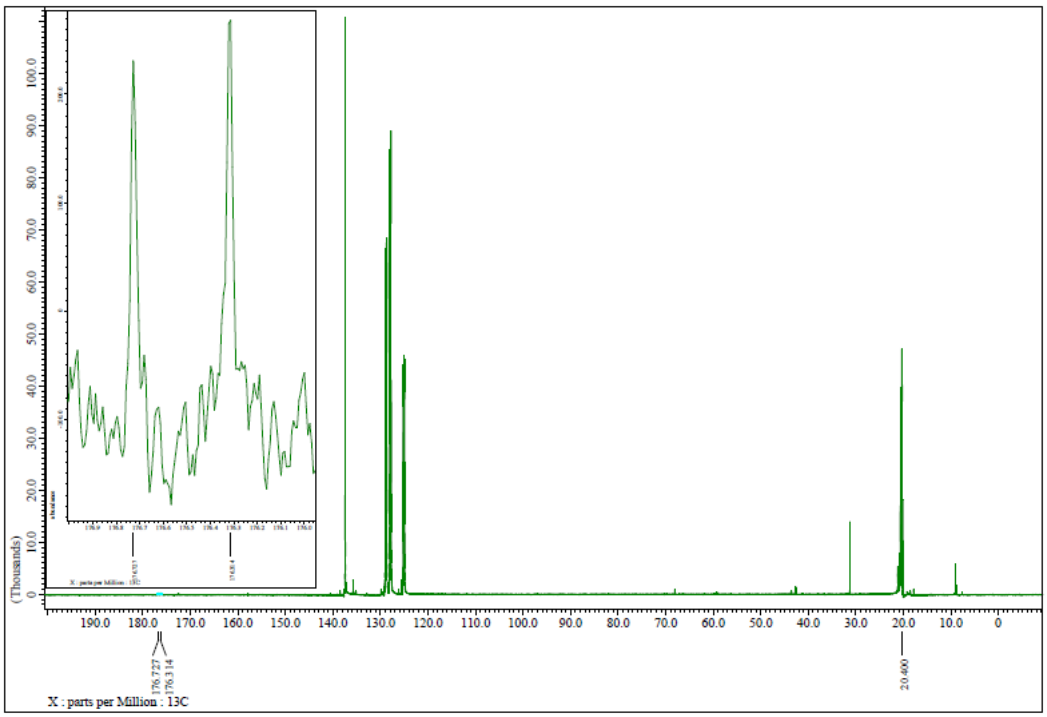




This complex was prepared according to Crudden's procedure.[13] $[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L6·HCl** (11.2 mg, 0.030 mmol), KO^{t}Bu (3.7 mg, 0.033 mmol), and toluene-d_8 (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at rt for 1 h. The mixture was analyzed by ^{13}C NMR and HRMS.

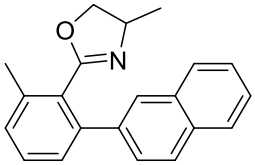
^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.5 (d, ^1J(Rh,C) = 51.6 Hz, *C*-carbene),.

HRMS calcd for $C_{46}H_{56}Cl_2N_4Rh_2^+$ (FAB, $[M\text{-}2L]^+$): 940.1970, found: 940.1963.



IX. Spectroscopic Data of Products

4-Methyl-2-(2-methyl-6-(naphthalen-2-yl)phenyl)-4,5-dihydrooxazole (3aa).



Rf 0.09 (hexane/EtOAc = 5/1). Pale yellow oil (77 mg, 85%).

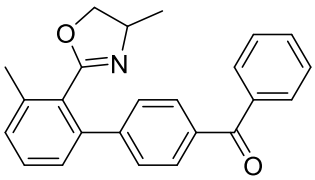
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (d, *J* = 6.0 Hz, 3H) 2.45 (s, 3H), 3.57-3.63 (m, 1H), 4.11-4.21 (m, 2H), 7.25 (d, *J* = 5.0 Hz, 1H), 7.25 (d, *J* = 5.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.47-7.50 (m, 2H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.83-7.86 (m, 3H), 7.91 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9, 21.2, 61.9, 74.4, 125.8, 126.1, 126.8, 127.0, 127.3, 127.6, 128.1, 130.5, 130.8, 131.4, 132.4, 133.3, 137.1 (two overlapping peaks), 138.8 (two overlapping peaks), 165.3.

IR (ATR): 3054 w, 2965 m, 2925 m, 2360 m, 1734 w, 1665 s, 1587 w, 1505 w, 1457 m, 1328 w, 1296 w, 1237 w, 1167 w, 1114 w, 1036 s, 962 m, 913 w, 859 w, 822 w, 789 s, 746 s.

HRMS calcd for $C_{21}H_{20}NO^+$ (CI, $[M+H]^+$): 302.1545, found: 302.1548.

(3'-Methyl-2'-(4-methyl-4,5-dihydrooxazol-2-yl)-[1,1'-biphenyl]-4-yl)(phenyl)methanone (3ab).



Rf 0.06 (hexane/EtOAc = 5/1). Colorless oil (99.6 mg, 94%).

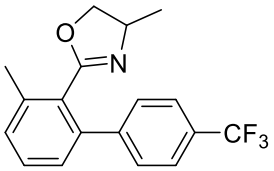
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.18 (d, *J* = 6.4 Hz, 3H), 2.44 (s, 3H), 3.72 (t, *J* = 6.9 Hz, 1H), 4.18-4.29 (m, 2H), 7.23-7.28 (m, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.48-7.81 (m, 5H), 7.81-7.84 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.9, 62.2, 73.8, 127.0, 128.1, 128.3, 128.5, 129.56, 129.6, 129.9, 130.0, 132.3, 136.1, 137.71, 137.74, 140.8, 145.5, 162.9, 196.5.

IR (ATR): 3060 w, 2966 w, 2925 w, 2361 w, 1658 s, 1604 m, 1447 m, 1401 w, 1374 w, 1313 m, 1277 s, 1178 w, 1149 w, 1115 w, 1075 w, 1038 s, 1000 w, 961 m, 925 m, 888 w, 853 w, 787 m, 745 m, 702 s.

HRMS calcd for $C_{24}H_{22}NO_2^+$ (CI, $[M+H]^+$): 356.1651, found: 356.1654.

4-Methyl-2-(3-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (3ac).



Rf 0.09 (hexane/EtOAc = 5/1). Pale yellow oil (72 mg, 75%).

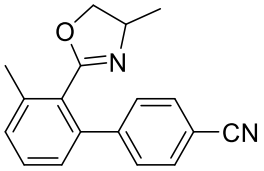
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.14 (d, *J* = 6.4 Hz, 3H), 2.43 (s, 3H), 3.69 (t, *J* = 7.3 Hz, 1H), 4.15-4.27 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.9, 62.2, 73.7, 125.0 (q, *J* = 3.8 Hz), 126.9 (q, *J* = 259.3 Hz), 127.0, 128.9 (two overlapping peaks), 129.3 (q, *J* = 32.5 Hz), 129.6, 129.7, 137.7, 140.5, 144.8, 162.8.

IR (ATR): 2968 w, 2927 w, 2361 w, 1665 w, 1618 w, 1588 w, 1461 w, 1404 w, 1376 w, 1324 s, 1239 w, 1164 m, 1122 s, 1084 w, 1064 m, 1038 m, 1019 w, 963 w, 932 w, 888 w, 871 w, 845 w, 790 w, 757 w, 664 w.

HRMS calcd for $C_{18}H_{17}F_3NO^+$ (CI, $[M+H]^+$): 320.1262, found: 320.1258.

3'-Methyl-2'-(4-methyl-4,5-dihydrooxazol-2-yl)-[1,1'-biphenyl]-4-carbonitrile (3ad).



Rf 0.05 (hexane/EtOAc = 5/1). Orange oil (65 mg, 78%).

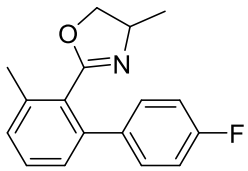
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16 (d, *J* = 6.4 Hz, 3H), 2.47 (s, 3H), 3.70 (t, *J* = 7.3 Hz, 1H), 4.18-4.28 (m, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.6, 20.9, 62.2, 73.7, 110.9, 118.9, 126.8, 128.0, 129.3, 129.6, 130.0, 131.7, 137.9, 140.0, 145.9, 162.6.

IR (ATR): 2964 w, 2925 w, 2362 w, 2227 w, 1927 w, 1663 s, 1607 w, 1504 w, 1462 m, 1376 w, 1332 w, 1297 w, 1246 m, 1206 w, 1176 w, 1114 w, 1037 s, 960 m, 888 w, 843 s, 789 s, 757 m, 735 m.

HRMS calcd for $C_{18}H_{17}N_2O^+$ (CI, $[M+H]^+$): 277.1341, found: 277.1336.

2-(4'-Fluoro-3-methyl-[1,1'-biphenyl]-2-yl)-4-methyl-4,5-dihydrooxazole (3ae).



Rf 0.07 (hexane/EtOAc = 5/1). Pale yellow oil (45 mg, 56%).

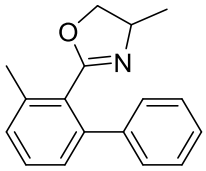
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16 (d, *J* = 6.4 Hz, 3H), 2.41 (s, 3H), 3.69 (t, *J* = 6.9 Hz, 1H), 4.16-4.27 (m, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.32-7.40 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): 19.6, 21.0, 62.1, 73.7, 114.7 (d, *J* = 20.9), 127.1, 128.3, 129.0, 129.4, 130. 2 (d, *J* = 8.6 Hz), 137.1 (d, *J* = 2.9 Hz), 137.4, 140.9, 163.0, 162.2 (d, *J* = 245.0 Hz).

IR (ATR): 2967 w, 2925 w, 2360 w, 1664 s, 1603 w, 1511 s, 1462 m, 1374 w, 1334 w, 1297 w, 1223 s, 1160 w, 1116 w, 1037 s, 963 m, 932 w, 887 w, 839 s, 790 s, 755 m.

HRMS calcd for $C_{17}H_{17}FNO^+$ (CI, $[M+H]^+$): 270.1294, found: 270.1291.

4-Methyl-2-(3-methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (3af).



Rf 0.06 (hexane/EtOAc = 5/1). Pale yellow oil (35 mg, 53%).

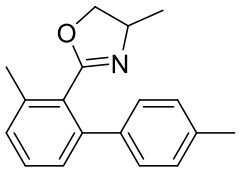
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (d, *J* = 6.4 Hz, 3H), 2.42 (s, 3H), 3.66 (t, *J* = 7.4 Hz, 1H), 4.15-4.25 (m, 2H), 7.19-7.22 (m, 2H), 7.29-7.43 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.9, 62.1, 73.6, 127.06, 127.1, 127.9, 128.2, 128.6, 128.9, 129.3, 137.3, 141.1, 142.0, 163.2.

IR (ATR): 3058 w, 2967 w, 2925 w, 1664 s, 1588 w, 1462 m, 1375 w, 1333 w, 1296 w, 1236 m, 1173 w, 1116 w, 1071 w, 1037 s, 963 m, 931 w, 887 w, 795 w, 761 s, 701 s.

HRMS calcd for $C_{17}H_{18}NO^+$ (CI, $[M+H]^+$): 252.1388, found: 252.1391.

2-(3,4'-Dimethyl-[1,1'-biphenyl]-2-yl)-4-methyl-4,5-dihydrooxazole (3ag).



Rf 0.06 (hexane/EtOAc = 5/1). Colorless oil (46 mg, 58%).

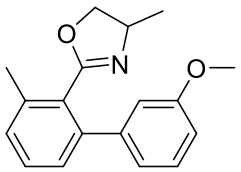
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.18 (d, *J* = 6.4 Hz, 3H), 2.37 (s, 3H), 2.41 (s, 3H), 3.69 (t, *J* = 7.1 Hz, 1H), 4.15-4.30 (m, 2H), 7.18 (t, *J* = 8.2 Hz, 4H), 7.32 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.9, 21.1, 62.1, 73.6, 127.2, 128.1, 128.4, 128.6, 128.7, 129.3, 136.7, 137.3, 138.2, 141.8, 163.3.

IR (ATR): 2967 w, 2875 w, 2360 w, 1708 s, 1650 w, 1594 w, 1511 w, 1430 m, 1371 w, 1314 m, 1293 m, 1201 s, 1150 m, 1043 w, 1018 w, 991 w, 895 w, 850 w, 782 w, 757 w, 733 w.

HRMS Calcd for $C_{18}H_{20}NO^+$ (FAB+, $[M+H]^+$): 266.1545, Found 266.1542.

2-(3'-Methoxy-3-methyl-[1,1'-biphenyl]-2-yl)-4-methyl-4,5-dihydrooxazole (3ah).



Rf 0.06 (hexane/EtOAc = 5/1). Pale yellow oil (52 mg, 62%).

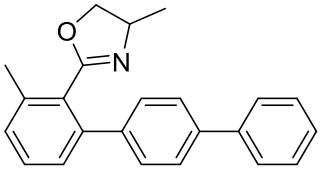
^{1}H NMR ($CDCl_3$, 400 MHz):. δ 1.16 (d, *J* = 6.4 Hz, 3H), 2.41 (s, 3H), 3.70 (t, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 4.15-4.27 (m, 2H), 6.86 (dd, *J* = 2.3, 7.8 Hz, 1H), 6.97-7.02 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.25-7.28 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.6, 20.9, 55.2, 62.1, 73.7, 113.0, 113.9, 121.1, 127.0, 128.1, 128.9, 129.0, 129.3, 137.3, 141.8, 142.4, 159.1, 162.2.

IR (ATR): 2964 w, 2925 w, 2359 w, 1726 w, 1665 s, 1577 m, 1466 s, 1375 w, 1318 m, 1297 m, 1227 s, 1169 w, 1115 w, 1038 s, 962 m, 931 w, 886 w, 779 s, 732 m, 699 s.

HRMS calcd for $C_{18}H_{20}NO_2^+$ (CI, $[M+H]^+$): 282.1494, found: 282.1488.

4-Methyl-2-(3-methyl-[1,1':4',1''-terphenyl]-2-yl)-4,5-dihydrooxazole (3ai).



Rf 0.06 (hexane/EtOAc = 5/1). Pale yellow oil (60 mg, 61%).

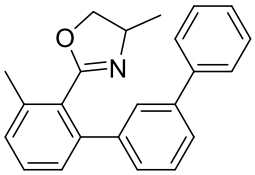
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (d, *J* = 6.4 Hz, 3H), 2.43 (s, 3H), 3.70 (t, *J* = 7.4 Hz, 1H), 4.17-4.28 (m, 2H), 7.21-7.24 (m, 2H), 7.33-7.38 (m, 2H), 7.43-7.46 (m, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.60-7.64 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.9, 62.1, 73.7, 126.6, 127.0, 127.1, 127.3, 128.2, 128.8, 129.0 (two overlapping peaks), 129.4, 137.4, 139.9, 140.1, 140.8, 141.5, 163.2.

IR (ATR): 3052 w, 2966 m, 2924 w, 1664 s, 1453 w, 1377 w, 1377 w, 1333 w, 1298 w, 1254 w, 1227 s, 1174 w, 1139 w, 1124 w, 1061 w, 998 w, 966 m, 936 w, 859 w, 820 s, 746 m.

HRMS calcd for $C_{23}H_{22}NO^+$ (CI, $[M+H]^+$): 328.1701, found: 328.1706.

4-Methyl-2-(3-methyl-[1,1':3',1''-terphenyl]-2-yl)-4,5-dihydrooxazole (3aj).



Rf 0.14 (hexane/EtOAc = 5/1). Pale yellow oil (60 mg, 61%).

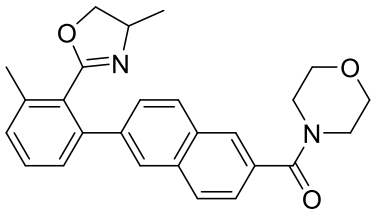
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.07 (d, *J* = 6.4 Hz, 3H), 2.44 (s, 3H), 3.64 (t, *J* = 6.9 Hz, 1H), 4.14-4.23 (m, 2H), 7.25 (t, *J* = 9.2 Hz, 2H), 7.32-7.46 (m, 6H), 7.56-7.58 (m, 1H), 7.63 (d, *J* = 6.8 Hz, 2H), 7.69 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.8, 62.1, 73.7, 125.7, 127.0, 127.1, 127.3, 127.47, 127.5, 128.3, 128.4, 128.7, 129.0, 129.4, 137.4, 140.6, 140.8, 141.5, 141.9, 163.2.

IR (ATR): 3059 w, 2966 w, 2925 w, 1664 m, 1597 w, 1463 m, 1406 w, 1375 w, 1332 w, 1296 w, 1238 w, 1170 w, 1117 w, 1075 w, 1037 w, 962 m, 931 w, 887 w, 857 w, 791 m, 758 m, 702 s.

HRMS calcd for $C_{23}H_{22}NO^+$ (CI, $[M+H]^+$): 328.1701, found: 328.1702.

(6-(3-Methyl-2-(4-methyl-4,5-dihydrooxazol-2-yl)phenyl)naphthalen-2-yl)(morpholino)methanone (3ak).



Rf 0.01 (hexane/EtOAc = 1/1). White solid (119.3 mg, 96%).

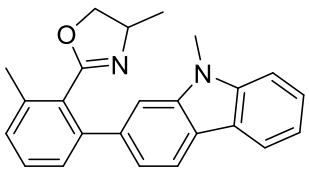
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (d, *J* = 6.4 Hz, 3H), 2.45 (s, 3H), 3.55-3.79 (m, 9H), 4.08-4.21 (m, 2H), 7.28 (t, *J* = 9.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.49-7.51 (m, 1H), 7.62 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.93 (s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.9, 62.0 (two overlapping peaks), 66.8, 73.6, 124.4, 126.7, 127.1, 127.2, 127.9, 127.9, 128.2, 128.5, 129.2, 129.4, 131.6, 132.4, 133.3, 137.5, 140.0, 141.2, 163.0, 170.3.

IR (ATR): 2967 w, 2922 w, 2857 w, 2241 w, 1628 s, 1492 w, 1461 w, 1428 m, 1361 w, 1333 w, 1299 w, 1281 m, 1256 w, 1230 w, 1183 w, 1114 m, 1069 w, 1026 m, 962 w, 908 m, 849 w, 822 w, 784 w, 727 s, 671 w.

HRMS Calcd for $C_{26}H_{27}N_2O_3^+$ (APCI, $[M+H]^+$): 415.2016, Found 415.2019.

4-Methyl-2-(2-methyl-6-(9-methyl-9H-carbazol-2-yl)phenyl)-4,5-dihydrooxazole (3al).



Rf 0.06 (hexane/EtOAc = 5/1). Yellow oil (78 mg, 74%).

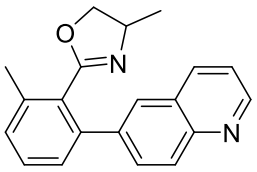
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (d, *J* = 6.4 Hz, 3H), 2.45 (s, 3H), 3.59-3.62 (m, 1), 3.83 (s, 3 H), 4.12-4.20 (m, 2H), 7.22-7.25 (m, 2H), 7.29-7.40 (m, 4H), 7.45-7.49 (m, 2H), 8.06 (d, *J* = 7.8 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.8, 21.0, 29.0, 62.1, 73.7, 108.4, 108.7, 118.9, 119.7, 119.9, 120.3, 121.7, 122.6, 125.6, 127.6, 128. 4, 128.8, 129.3, 137.3, 138.9, 140.8, 141.3, 142.8, 163.4.

IR (ATR): 3055 w, 2969 w, 2925 w, 2210 w, 1662 m, 1628 w, 1601 w, 1473 w, 1452 m, 1420 w, 1356 w, 1323 m, 1296 w, 1247 m, 1157 w, 1125 w, 1038 m, 1000 w, 962 w, 928 w, 909 m, 888 w, 844 w, 822 w, 790 m, 768 m, 726 s.

HRMS calcd for $C_{24}H_{23}N_2O^+$ (CI, $[M+H]^+$): 355.1810, found: 355.1808.

4-Methyl-2-(2-methyl-6-(quinolin-6-yl)phenyl)-4,5-dihydrooxazole (3am).



Rf 0.01 (hexane/EtOAc = 5/1). Orange oil (57 mg, 63%).

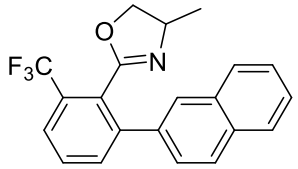
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (d, *J* = 6.4 Hz, 3H), 2.46 (s, 3H), 3.62 (t, *J* = 7.4 Hz, 1H), 4.12-4.23 (m, 2H), 7.30 (d, *J* = 10.6 Hz, 2H), 7.38-7.44 (m, 2H), 7.82 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.87 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.92 (d, *J* = 4.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.9, 62.1, 73.7, 121.4, 127.2, 127.3, 127.9, 128.4, 128.9, 129.4, 129.5, 130.7, 136.1, 137.6, 139.5, 141.0, 147.5, 150.4, 163.0.

IR (ATR): 2966 w, 2925 w, 2360 w, 1712 w, 1664 s, 1591 w, 1499 m, 1472 m, 1374 w, 1350 w, 1330 w, 1294 m, 1237 m, 1143 w, 1113 m, 1036 s, 961 m, 932 w, 912 w, 888 w, 842 s, 820 w, 792 s, 754 m, 730 w, 661 w.

HRMS calcd for $C_{20}H_{19}N_2O^+$ (CI, $[M+H]^+$): 303.1497, found: 303.1497.

4-Methyl-2-(2-(naphthalen-2-yl)-6-(trifluoromethyl)phenyl)-4,5-dihydrooxazole (3ba).



Rf 0.29 (hexane/EtOAc = 5/1). Orange oil (82 mg, 77%).

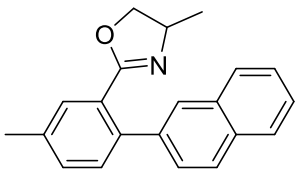
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04 (d, *J* = 6.4 Hz, 3H), 3.60 (t, *J* = 7.8 Hz, 1H), 4.06-4.20 (m, 2H), 7.49-7.56 (m, 3H), 7.59-7.67 (m, 2H), 7.75 (d, *J* = 7.3 Hz, 1H), 7.82-7.89 (m, 3H), 7.91 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.2, 62.4, 74.3, 125.2 (q, *J* = 4.7 Hz), 126.1 (d, *J* = 272.6 Hz), 126.3, 126.4, 126.8, 127.1 (d, *J* = 1.9 Hz), 127.6, 127.7, 127.9, 128.1, 129.7, 129.8 (q, *J* = 31.4 Hz), 132.6, 132.9, 133.5, 136.8, 143.6, 160.7.

IR (ATR): 2971 w, 1670 m, 1595 w, 1506 w, 1477 w, 1453 w, 1321 s, 1290 m, 1248 w, 1200 w, 1168 w, 1129 s, 1093 m, 1039 s, 960 m, 930 w, 908 w, 860 w, 811 s, 747 s, 731 s, 688 m, 667 w.

HRMS (EI): Calcd for $C_{21}H_{16}F_3NO$ 355.1184, found: 355.1183.

4-Methyl-2-(5-methyl-2-(naphthalen-2-yl)phenyl)-4,5-dihydrooxazole (3ca).



Rf 0.06 (hexane/EtOAc = 5/1). Pale yellow oil (57 mg, 63%).

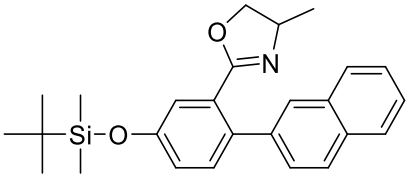
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (d, *J* = 6.4 Hz, 3H), 2.42 (s, 3H), 3.57 (t, *J* = 7.8 Hz, 1H), 4.13-4.26 (m, 2H), 7.32-7.35 (m, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.47-7.51 (m, 3H), 7. 36 (s, 1H), 7.82-7.86 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9, 21.2, 61.9, 74.4, 126.1 (two overlapping peaks), 125.8, 126.8, 127.0, 127.3, 127.6, 128.1, 130.5, 130.8, 131.3, 132.4, 133.3, 137.1, 138.8 (two overlapping peaks), 165.3.

IR (ATR): 3053 w, 2925 m, 2859 w, 2361 w, 1652 m, 1571 w, 1497 w, 1454 m, 1375 w, 1325 s, 1272 w, 1241 w, 1195 w, 1165 m, 1120 s, 1064 m, 1040 m, 968 m, 913 w, 853 w, 816 s, 790 w, 746 s, 664 w.

HRMS calcd for $C_{21}H_{20}NO^+$ (CI, $[M+H]^+$): 302.1545, found: 302.1544.

2-(5-((tert-Butyldimethylsilyl)oxy)-2-(naphthalen-2-yl)phenyl)-4-methyl-4,5-dihydrooxazole (3da).



Rf 0.29 (hexane/EtOAc = 5/1). Orange oil (93 mg, 74%).

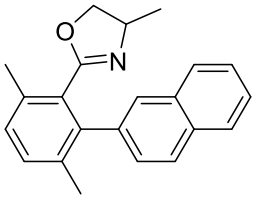
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.25 (s, 6H), 1.01 (s, 9H), 1.24 (d, *J* = 6.4 Hz, 3H), 3.56 (t, *J* = 7.4 Hz, 1H), 4.14-4.26 (m, 2H), 6.99 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.26 (d, *J* = 2.3, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.44-7.50 (m, 3H), 7.80-7.85 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ -4.37, 18.2, 21.1, 25.6, 62.0, 74.3, 121.6, 122.1, 125.7, 126.0, 126.7, 127.15, 127.2, 127.6, 128.0, 128.9, 131.7, 132.3, 133.3, 134.7, 138.6, 154.8, 164.7.

IR (ATR): 3054 w, 2955 w, 2930 w, 2859 w, 1651 w, 1603 m, 1559 w, 1494 m, 1464 m, 1417 w, 1334 w, 1306 m, 1278 m, 1258 m, 1213 m, 1130 w, 1103 w, 1066 w, 1046 w, 1014 w, 978 s, 950 s, 883 s, 837 w, 815 s, 781 s, 747 m, 677 w.

HRMS (EI): Calcd for $C_{26}H_{31}NO_2Si$ 417.2124, found: 417.2118.

2-(3,6-Dimethyl-2-(naphthalen-2-yl)phenyl)-4-methyl-4,5-dihydrooxazole (3ea).



This compound was isolated as a 1:1 mixture of rotamers.

Rf 0.09 (hexane/EtOAc = 5/1). Colorless oil (49 mg, 51%).

Conformer A

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75 (d, *J* = 6.0 Hz, 3H) , 2.09 (s, 3H) (overlapped with Conformer B), 2.37 (s, 3H) (overlapped with Conformer B), 3.22-3.29 (m, 1H), 3.92-4.01 (m, 2H) (overlapped with Conformer B), 7.15 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 8.7 Hz, 2H), 7.47-7.49 (m, 2H) (overlapped with Conformer B), 7.79-7.89 (m, 3H) (overlapped with Conformer B).

Conformer B

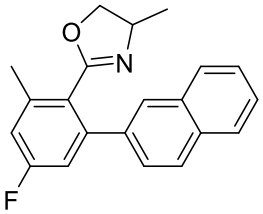
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (d, *J* = 6.4 Hz, 3H), 2.09 (s, 3H) (overlapped with Conformer A), 2.37 (s, 3H) (overlapped with Conformer A), 3.39-3.45 (m, 1H), 3.92-4.01 (m, 2H) (overlapped with Conformer A), 7.23 (d, *J* = 7.8 Hz, 2H), 7.47-7.49 (m, 2H) (overlapped with Conformer A), 7.70 (d, 2H), 7.79-7.89 (m, 3H) (overlapped with Conformer A).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2, 19.3, 20.2, 20.7, 20.8, 61.8, 73.4, 73.5, 125.7, 125.87, 125.90, 126.99, 127.05, 127.6, 128.0, 128.1, 128.87, 128.92, 129.41, 129.45, 131.0, 132.3, 132.4, 132.96, 133.04., 133.5, 134.1, 137.3, 137.4, 141.0, 141.1, 163.17, 163.24.

IR (ATR): 3052 w, 2966 m, 2924 w, 1664 s, 1453 w, 1377 w, 1377 w, 1333 w, 1298 w, 1254 w, 1227 s, 1174 w, 1139 w, 1124 w, 1061 w, 998 w, 966 m, 936 w, 859 w, 820 s, 746 m.

HRMS (EI): Calcd for $C_{22}H_{21}NO$ 315.1623, found: 315.1620.

2-(4-Fluoro-2-methyl-6-(naphthalen-2-yl)phenyl)-4-methyl-4,5-dihydrooxazole (3fa).



Rf 0.06 (hexane/EtOAc = 5/1). Pale yellow oil (66 mg, 69%).

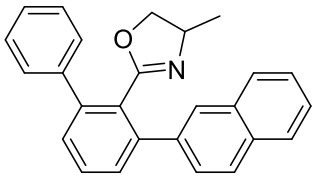
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (d, *J* = 6.4 Hz, 3H), 2.44 (s, 3H), 3.56 (m, 1H), 4.11-4.19 (m, 2H), 6.96 (dd, *J* = 2.3, 9.2 Hz, 1H), 7.02 (dd, *J* = 2.3, 9.6 Hz, 1H), 7.47-7.55 (m, 3H), 7.84 (dd, *J* = 3.7, 11.9 Hz, 3H), 7.89 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.9, 20.9, 62.1, 73.7, 114.3 (d, *J* = 21.9 Hz), 115.7 (d, *J* = 20.9 Hz), 124.5 (d, *J* = 2.8 Hz), 126.1, 126.2, 126.5, 127.3, 127.58, 127.63, 128.1, 132.6, 133.0, 137.5, 140.4 (d, *J* = 8.6 Hz), 144.2 (d, *J* = 8.5 Hz), 162.62, 162.7 (d, *J* = 247.0 Hz).

IR (ATR): 3055 w, 2966 w, 2925 w, 2360 w, 1664 s, 1592 s, 1505 w, 1461 m, 1348 m, 1319 m, 1295 w, 1245 m, 1199 w, 1156 m, 1130 m, 1108 w, 1042 m, 984 w, 961 s, 908 m, 858 s, 821 s, 788 w, 748 s, 730 s, 661 w.

HRMS (EI): Calcd for $C_{21}H_{18}FNO$ 319.1372, found: 319.1367.

4-Methyl-2-(3-(naphthalen-2-yl)-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (3ga).



Rf 0.17 (hexane/EtOAc = 5/1). Pale yellow oil (58 mg, 69%).

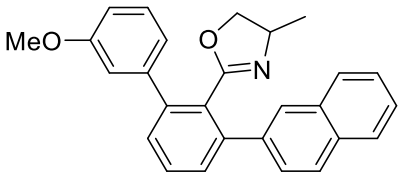
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (d, *J* = 6.4 Hz, 3H), 3.38 (t, *J* = 7.8 Hz, 1H), 3.83-3.90 (m, 1H), 3.94-3.98 (m, 1H), 7.32-7.42 (m, 4H), 7.48-7.50 (m, 5H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.60 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.81-7.87 (m, 3H), 7.96 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.1, 29. 7, 62.0, 73.8, 125.9, 126.1, 127.1, 127.3, 127.5, 127.6, 127.85, 127.91, 128.1, 128.7, 128.8, 129.0, 129.5, 132.5, 133.1, 138.3, 140. 8, 142.1, 142.4, 162.8.

IR (ATR): 3056 w, 2924 w, 2853 w, 2361 w, 1667 m, 1574 w, 1508 w, 1436 w, 1376 w, 1345 w, 1294 w, 1241 w, 1179 w, 1136 w, 1110 w, 1072 w, 1036 m, 963 m, 910 m, 860 m, 809 s, 761 s, 735 s, 700 s, 664 w.

HRMS (EI): Calcd for $C_{26}H_{21}NO$ 363.1623, found: 363.1626.

2-(3'-Methoxy-3-(naphthalen-2-yl)-[1,1'-biphenyl]-2-yl)-4-methyl-4,5-dihydrooxazole (3ha)



Rf 0.14 (hexane/EtOAc = 5/1). White solid (110.0 mg, 93%).

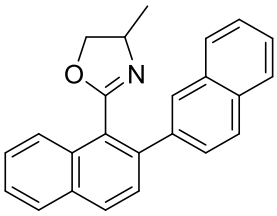
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (d, *J* = 6.4 Hz, 3H), 3.41 (t, *J* = 7.8 Hz, 1H), 3.81 (s, 3H), 3.84-3.93 (m, 1H), 3.99 (t, *J* = 8.5 Hz, 1H), 6.89 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.04-7.08 (m, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.41-7.56 (m, 5H), 7.60 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.82-7.87 (m, 3H), 7.96 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.1, 55.2, 62.0, 73.8, 113.4, 113.9, 121.2, 125.9, 126.2, 127.0, 127.5, 127.5, 127.6, 127.7, 128.1, 128.7, 129.0, 129.1, 129.5, 132.4, 133.1, 138.2, 142.05, 142.10, 142.2, 159.1, 162.8.

IR (ATR): 3055 w, 2966 w, 2834 w, 2211 w, 1665 m, 1601 m, 1577 m, 1491 w, 1461 m, 1419 w, 1374 w, 1349 w, 1322 m, 1288 m, 1226 s, 1173 w, 1134 w, 1112 w, 1035 s, 962 m, 907 m, 860 m, 823 w, 806 m, 786 m, 730 s, 699 s, 664 w.

HRMS Calcd for $C_{27}H_{24}NO_2^+$ (APCI, $[M+H]^+$): 394.1807, Found 394.1802.

2-([2,2'-Binaphthalen]-1-yl)-4-methyl-4,5-dihydrooxazole (3ia).



Rf 0.09 (hexane/EtOAc = 5/1). Yellow oil (102 mg, 92%).

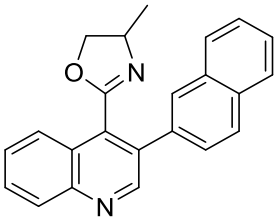
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22 (d, *J* = 6.0 Hz, 3H), 3.68-3.72 (m, 1H), 4.27-4.35 (m, 2H), 7.43-7.63 (m, 5H), 7.68 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.85-7.90 (m, 4H), 7.97 (d, *J* = 8.2 Hz, 1H), 8.02 (s, 1H), 8.13 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 62.4, 73.9, 125.2, 125.3, 126.0, 126.18, 126.20, 127.0, 127.2, 127.6, 127.7, 127.67, 127.70, 128.01, 128.1, 130.0, 131.6, 132.3, 132.5, 133.2, 138.6, 139.7, 162.8.

IR (ATR): 3055 w, 2966 w, 2924 w, 1658 m, 1503 w, 1220 m, 1130 m, 999 s, 958 m, 907 s, 860 m, 817 s, 790 w, 730 s, 686 w.

HRMS (EI): Calcd for $C_{24}H_{19}NO$ 337.1467, found: 337.1464.

4-Methyl-2-(3-(naphthalen-2-yl)quinolin-4-yl)-4,5-dihydrooxazole (3ja).



Rf 0.03 (hexane/EtOAc = 5/1). Yellow oil (52 mg, 51%).

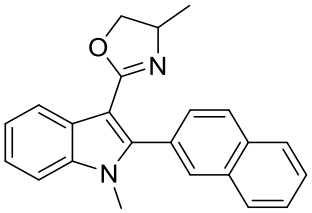
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29 (d, *J* = 3.2 Hz, 3H), 3.77-3.82(m, 1H), 4.34-4.45 (m, 2H), 7.53-7.57 (m, 2H), 7.64-7.69 (m, 2H), 7.76-7.80 (m, 1H), 7.90-7.96 (m, 3H), 8.05 (d, *J* = 1.4 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 9.11 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 62.8, 74.4, 125.3, 125.6, 126.6, 126.7, 126.8, 127.8, 127.9, 128.0, 128.2, 128.3, 129.7, 129.8, 130.0, 132.9, 133.2, 133.8, 134.9, 147.1, 151.4, 160.7.

IR (ATR): 2961 w, 1712 w, 1666 w, 1568 w, 1498 w, 1455 w, 1366 w, 1324 w, 1281 w, 1245 w, 1199 w, 1152 m, 1042 m, 1005 s, 959 m, 911 w, 858 m, 822 m, 746 s, 699 w.

HRMS calcd for $C_{23}H_{19}N_2O^+$ (CI, $[M+H]^+$): 339.1497, found: 339.1499.

4-Methyl-2-(1-methyl-2-(naphthalen-2-yl)-1H-indol-3-yl)-4,5-dihydrooxazole (3ka).



Rf 0.01 (hexane/EtOAc = 5/1). Yellow solid (89.2 mg, 87%).

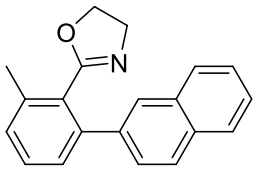
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (d, *J* = 6.4 Hz, 3H), 3.55-3.60 (m, 4H), 4.11 (d, *J* = 7.8 Hz, 1H), 4.20-4.29 (m, 1H), 7.27-7.36 (m, 3H), 7.49-7.55 (m, 3H), 7.86-7.91 (m, 4H), 8.37 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7, 30.9, 61.4, 72.7, 102.7, 109.4, 121.4, 121.9, 122.7, 126.3, 126.6, 126.7, 127.3, 127.7, 128.2, 128.3, 129.2, 130.0, 132.7, 133.1, 137.2, 142.9, 160.7.

IR (ATR): 3053 w, 2963 w, 2924 w, 2360 w, 1638 s, 1575 w, 1542 w, 1501 w, 1168 s, 1432 m, 1415 m, 1376 m, 1336 w, 1288 w, 1249 w, 1155 w, 1093 m, 991 s, 959 m, 907 s, 861 w, 822 m, 745 s, 729 s, 684 w.

HRMS (EI): Calcd for $C_{23}H_{20}N_2O$ 340.1576, found: 340.1574.

2-(2-Methyl-6-(naphthalen-2-yl)phenyl)-4,5-dihydrooxazole (3a′a, 1078710-25-4).



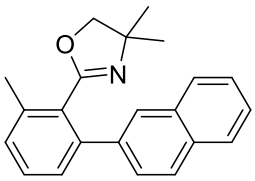
Rf 0.06 (hexane/EtOAc = 5/1). Pale yellow oil. (40 mg, 46%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.44 (s, 3H), 3.81 (t, *J* = 9.6 Hz, 2H), 4.08 (t, *J* = 9.6 Hz, 2H), 7.24 (d, *J* = 6.9 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.46-7.48 (m, 2H), 7.55 (dd, *J* = 1.8, 8.2 Hz, 1H), 7.82-7.85 (m, 3H), 7.89 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.8, 55.1, 67.2, 125.8, 126.1, 126.8, 127.2, 127.4, 127.6, 128.1, 129.0, 129.5, 132.4, 133.3, 137.6, 138.0, 138.7, 141.9, 164.4.

HRMS calcd for $C_{20}H_{18}NO^+$ (CI, $[M+H]^+$): 288.1388, found: 288.1391.

4,4-Dimethyl-2-(2-methyl-6-(naphthalen-2-yl)phenyl)-4,5-dihydrooxazole (3a″a).



Rf 0.14 (hexane/EtOAc = 5/1). Pale yellow oil (20 mg, 21%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (s, 6H), 2.46 (s, 3H), 3.75 (s, 2H), 7.23-7.31 (m, 2H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.47-7.49 (m, 2H), 7.58 (dd, 1.8, 8.2 Hz, 1H), 7.81-7.86 (m, 3H), 7.91 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.6, 28.0, 67.8, 78.9, 125.8, 126.1, 126.8, 127.2, 127.38, 127.4, 127.6, 128.0, 128.5, 129.0, 129.4, 132.4, 133.1, 137.4, 138.6, 141.8, 161.9.

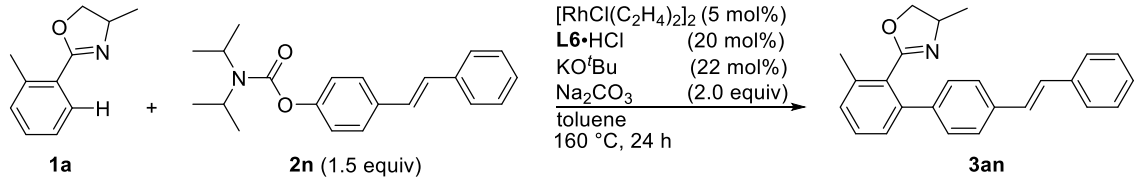
IR (ATR): 3056 w, 2966 m, 2926 m, 2361 w, 1929 w, 1661 s, 1587 m, 1510 m, 1458 m, 1364 m, 1293 s, 1246 s, 1211 m, 1176 m, 1105 w, 1076 m, 1039 s, 960 m, 915 m, 861 m, 823 m, 789 s, 747 s, 659 w.

HRMS calcd for $C_{22}H_{22}NO^+$ (CI, $[M+H]^+$): 316.1701, found: 316.1697.

X. Application to Sequential Functionalization of Arenes

Compounds **2m** and **2n** were prepared according to the literature procedure.[9(d)]

(E)-4-Methyl-2-(3-methyl-4'-styryl-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (3an).



Typical procedure was followed except that **2n** was used instead of **2a**.

Rf 0.06 (hexane/EtOAc = 5/1). Yellow oil (77 mg, 73%).

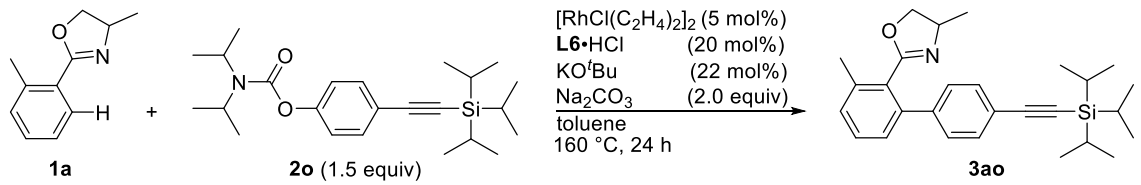
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (d, *J* = 6.4 Hz, 3H), 2.42 (s, 3H), 3.69 (t, *J* = 6.9 Hz, 1H), 4.19-4.27 (m, 2H), 7.13-7.17 (m, 2H), 7.20-7.25 (m, 3H), 7.32-7.37 (m, 3H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.50-7.52 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7, 20.9, 62.1, 73.3, 126.1, 126.4, 127.0, 127.6, 128.1, 128.3, 128.57, 128.62, 128.86, 128.94, 129.4, 136.1, 137.2, 137.4, 140.4, 141.5, 163.2.

IR (ATR): 3026 w, 2926 w, 2925 w, 2359 w, 1663 s, 1592 w, 1512 w, 1462 m, 1375 w, 1332 w, 1297 w, 1236 w, 1114 w, 1073 w, 1035 s, 963 s, 911 w, 887 w, 864 w, 823 w, 787 s, 752 s, 731 s, 692 s.

HRMS calcd for $C_{25}H_{24}NO^+$ (CI, $[M+H]^+$): 354.1858, found: 354.1856.

4-Methyl-2-(3-methyl-4'-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (3ao).



Typical procedure was followed except that **2o** was used instead of **2a**.

Rf 0.17 (hexane/EtOAc = 5/1). Yellow oil (105 mg, 81%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10-1.17 (m, 21H), 1.21 (d, *J* = 6.4 Hz, 3H), 2.41 (s, 3H), 3.70 (t, *J* = 6.9 Hz, 1H), 4.17-4.27 (m, 2H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.3, 18.6, 19.7, 21.0, 62.2, 73.7, 90.8, 107.0, 122.2, 127.0, 128.0, 128.4, 128.7, 129.2, 129.4, 131.6, 137.5, 141.2, 163.0.

IR (ATR): 2942 m, 2891 w, 2864 m, 2153 w, 1664 m, 1508 w, 1461 m, 1235 w, 1036 m, 995 w, 964 w, 920 w, 883 m, 840 m, 788 m, 757 w, 735 m, 664 s.

HRMS calcd for $C_{28}H_{38}NOSi^+$ (CI, $[M+H]^+$): 432.2723, found: 432.2720.

1.5 References

(1) Reviews on cross-coupling: (a) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N. Ed.; Springer: Berlin, Germany, 2002. (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, NY, 2004. A recent themed issue on cross-coupling: (c) *Chem. Lett.* **2011**, *40*, 894.

(2) Reviews on cross-coupling using inert phenol derivatives: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (b) Li, B.-J.; Yu, D.-G.; Sun, C.-L. ; Shi, Z.-J. *Chem.–Eur. J.* **2011**, *17*, 1728. (c) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, *2013*, 19. (d) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081. (e) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717.

(3) Selected reviews on catalytic C-H functionalization: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (d) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (e) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (f) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751. (g) Kakiuchi, F.; Kochi, T.; Murai, S. *Synlett* **2014**, *25*, 2390. (h) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (i) Su, B.; Cao, Z.-C.; Shi, Z.-J. *Acc. Chem. Res.* **2015**, *48*, 886. (j) Castro, L. C. M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410.

(4) (a) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. (b) Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384. (c) Xu, H.; Muto, K.; Yamaguchi, J.; Zhao, C.; Itami, K.; Musaev, D. G. *J. Am. Chem. Soc.* **2014**, *136*, 14834. (d) Muto, K.; Hatakeyama, T.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2015**, *6*, 6792.

(5) Wang, Y.; Wu, S.-B.; Shi, W.-J.; Shi, Z.-J. *Org. Lett.* **2016**, *18*, 2548.

(6) Intramolecular C-H/C-O coupling was reported: Wang, J.; Ferguson, D. M.; Kalyani, D. *Tetrahedron* **2013**, *69*, 5780.

(7) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251.

(8) Reviews on rhodium-catalyzed C-H functionalization: (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (b) Colby, D. A.; Tsai, A. S.; Bergman, R.G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (c) Lewis, J. C.; Bergman, R. G.; Ellman; J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

(9) (a) Zhu, Y.; Smith, D. A.; Herbert, D. E.; Gatard, S.; Ozerov, O. V. *Chem. Commun.* **2012**, *48*, 218. (b) Edouard, G. A.; Kelley, P.; Herbert, D. E.; Agapie, T. *Organometallics* **2015**, *34*, 5254. (c) Kinuta, H.;

Hasegawa, J.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 366. (d) Nakamura, K.; Yasui, K.; Tobisu, M.; Chatani, N. *Tetrahedron* **2015**, *71*, 4484. (e) Kinuta, H.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 1593.

(10) 4,5-Dihydrooxazol-2-yl and 4,4-dimethyl-4,5-dihydrooxazol-2-yl groups were found to be less effective directing groups. See SI for details.

(11) See the Supporting Information for the results using other NHC ligands.

(12) Our works on inert C-O bond activation using NHC ligands: (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett.* **2009**, *38*, 710. (b) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 2929. (c) Tobisu, M.; Yasutome, A.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Tetrahedron* **2012**, *68*, 5157. (d) Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5572. (e) Tobisu, M.; Takahira, T.; Ohtsuki, A.; Chatani, N. *Org. Lett.* **2015**, *17*, 680. (f) Tobisu, M.; Takahira, T.; Chatani, N. *Org. Lett.* **2015**, *17*, 4352. (g) Tobisu, M.; Morioka, T.; Ohtsuki, A.; Chatani, N. *Chem. Sci.* **2015**, *6*, 3410. (h) Morioka, T.; Nishizawa, A.; Nakamura, K.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 1729. (i) Nakamura, K.; Tobisu, M.; Chatani, N. *Org. Lett.* **2015**, *17*, 6142.

(13) A related $RhCl(SIPr)_2(N_2)$ complex: Zenkina, O. V.; Keske, E. C.; Wang, R.; Crudden, C. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8100.

(14) Nonselective C-H activation of arenes by a rhodium complex: (a) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999,** *121,* 6616. (b) Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485.

(15) Rhodium(III)-mediated C-H bond activation through concerted metalation/deprotonation: (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (b) Walsh, A. P.; Jones, W. D. *Organometallics* **2015**, *34*, 3400.

(16) Mistryukov, E. A. *Mendeleev Commun.* **2006**, *16*, 258.

(17) Cramer, R. *Inorg. Chem.* **1962**, *1*, 722.

(18) Jung, M. E.; Koch, P. *Tetrahedron Lett.*, **2011**, *52*, 6051.

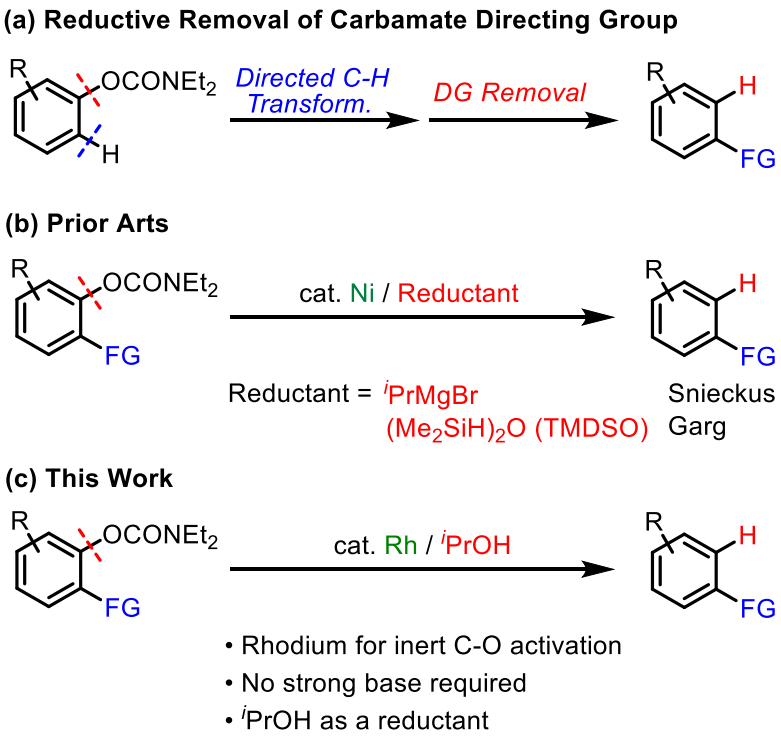
Chapter 2

Rhodium-Catalyzed C-O Bond Transformations with Isopropylalcohol and Propargyl Alcohol

2-1 Rhodium-Catalyzed Reductive Cleavage of C-O Bond of Aromatic Carbamates with ^{i}PrOH

2-1.1 Introduction

Transition-metal catalyzed C-O bond functionalization of inert phenol derivatives has emerged as an attractive methodology because this transformation enables the use of naturally abundant and more environmentally benign phenol derivatives instead of aryl halides.[1] Among the inert phenol derivatives, carbamates are frequently used not only as a protected form of phenols but also as a substrate in directed *ortho* C-H bond functionalization reactions. In particular, directed *ortho* metalation (D*o*M) reaction is one of the most powerful methods for regioselective transformation of arenes.[2] Catalytic C-H bond functionalization reactions directed by a carbamate group have also been reported.[3] Although these methods allow access to elaborate aromatic compounds from simple phenol derivatives, post-synthetic manipulation of the carbamate directing group is essential to produce target products. Therefore, the synthetic utility of C-H bond functionalization would be enhanced if the carbamate moiety could be reductively removed after *ortho* C-H bond functionalization (Scheme 1a). In 1992, Snieckus reported nickel-catalyzed reductive cleavage of aryl carbamates using ^{i}PrMgX as a



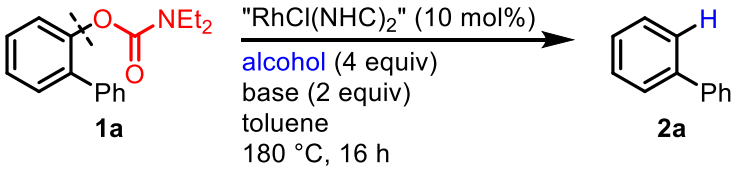
Scheme 1. Reductive removal of carbamate directing group

reducing agent (Scheme 1b).[4a,b] Garg reported that tetramethyldisiloxane (TMDSO) can be used as a milder reductant for the nickel-catalyzed reaction of aryl carbmates.[4c] Although these reactions allow carbamates to be used as a temporary directing group in *ortho* C-H bond functionalization, functional groups that react with ^{i}PrMgX or hydrosilane, such as ketones and unsaturated bonds, are inapplicable. Our group have developed a series of reactions by C-O bond cleavage of inert phenol derivatives catalyzed by nickel[5] and rhodium.[6] Our group recently reported rhodium-catalyzed directed C-H bond arylation with aryl carbamates by C-O bond cleavage.[6d] Based on this finding, it is envisioned that a rhodium catalyst could be applied to reductive cleavage of aryl carbamates when an appropriate reductant is added. Herein, this research focuses on rhodium-catalyzed reductive removal of the carbamate group using ^{i}PrOH as a reductant (Scheme 1c).

2-1.2 Results and Discussion

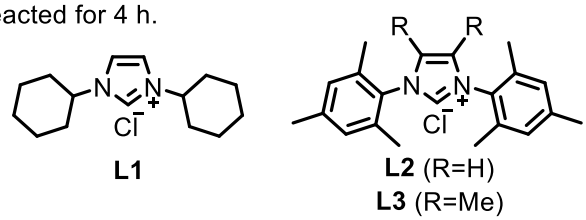
First, I investigated reductive cleavage of *ortho*-substituted phenyl carbamate **1a** in the presence of a rhodium bis(NHC) catalyst[6d] using ^{i}PrOH as a reducing agent.[7] Among the NHC ligands tested, **L2** was optimal and provided **2a** in 40% yield (Table 1, entries 1-3). The yield of **2a** increased by changing the base, with K_3PO_4 being the most effective base to give **2a** in 75% yield (entry 7).[8] For the reductant, both primary (entries 8 and 9) and tertiary (entry 10) alcohols were totally ineffective.[9] The reaction was complete within 4 h using 1 equiv of ^{i}PrOH (entry 11).

With the optimal reaction conditions in hand, we next investigated the scope of aryl carbamates (Scheme 3).[10] Substrates bearing electron-withdrawing (**1b**) and electron-donating (**1c**) groups both underwent the reaction to give the corresponding reduced products in 64% and 72% yields, respectively. Carbamates with a variety of *ortho* functional groups, such as trimethylsilyl (**1d**), benzoyl (**1e**) and methoxy (**1f**), are applicable, demonstrating the utility of this method in carbamate-directed *ortho* C-H functionalization reactions. Importantly, the ketone group in substrates **1e** and **1f** remained intact under these conditions without accompanying reduction of the carbonyl group. Moreover, heteroaromatic carbamates with basic nitrogen (i.e., **1h**) and an acidic proton (i.e., **1i**) were also tolerated. It should be noted that these four substrates (i.e., **1e**, **1f**, **1g**, **1i**) did not form any of the corresponding reductive cleavage product when the Ni/TMDSO system[4c] was used.



entry	NHC	alcohol	base	GC yield of 2a
1	**L1**	^{i}PrOH	Na_2CO_3	12%
2	**L2**	^{i}PrOH	Na_2CO_3	40%
3	**L3**	^{i}PrOH	Na_2CO_3	20%
4	**L2**	^{i}PrOH	K_2CO_3	67%
5	**L2**	^{i}PrOH	KOAc	27%
6	**L2**	^{i}PrOH	KOPiv	16%
7	**L2**	^{i}PrOH	K_3PO_4	75%
8	**L2**	MeOH	K_3PO_4	0%
9	**L2**	EtOH	K_3PO_4	trace
10	**L2**	^{t}BuOH	K_3PO_4	trace
11	**L2**	^{i}PrOH	K_3PO_4	75%[a]

[a] Reacted for 4 h.

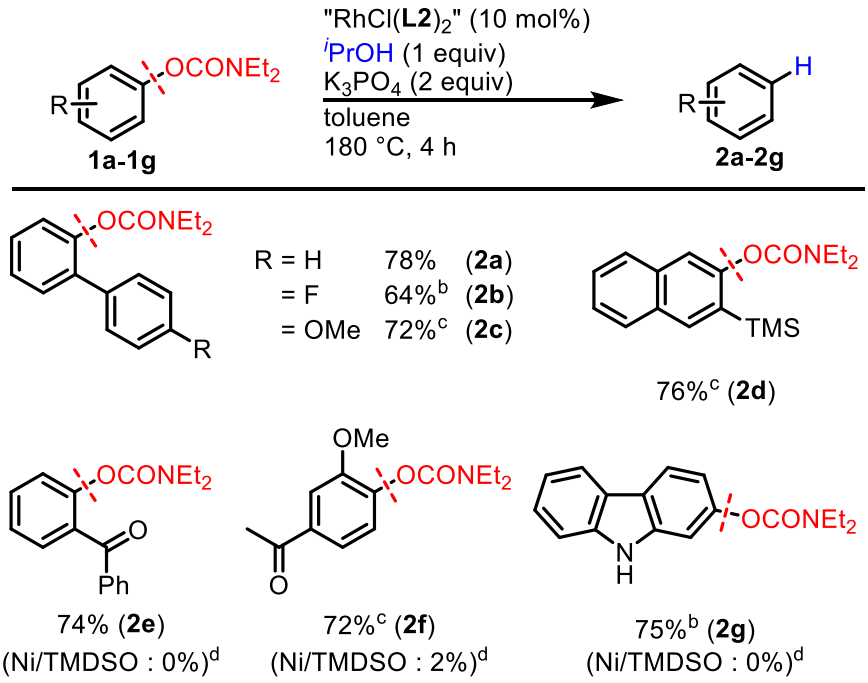


Scheme 2. RhCl(**L2**)$_2$ catalyzed reductive cleavage of aryl carbamates

[a] Reaction conditions: **3a** or **3b** (0.50 mmol), **4** (1.0 mmol), $Pd(OAc)_2$ (0.050 mmol), ligand (0.10 mmol), Et_3N (2.5 mmol), additive (0.25 mmol) in THF (2 mL) at 65 °C for 15 h. [b] Isolated yields are shown.

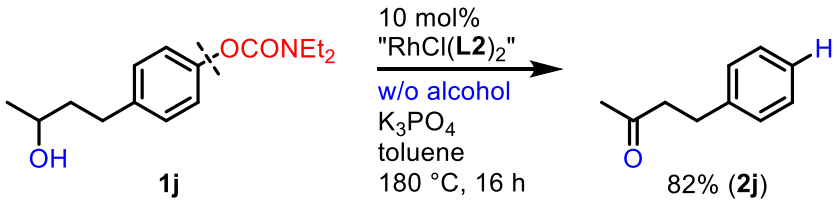
Next, carbamates bearing an alcohol moiety **1j** was investigated, with the expectation that intramolecular hydride transfer would occur (Scheme 4). The desired reaction proceeded without adding ^{i}PrOH to form reduced product **2j**, with the pendant alcohol moiety oxidized to the corresponding ketone, as expected.

This reductive cleavage method broadens the utility of the carbamate group in the synthesis of multi-functionalized arenes (Scheme 4). For example, palladium-catalyzed cross-coupling of **1k** proceeded without affecting the carbamate moiety. Subsequent *ortho* acylation by the D*o*M strategy followed by rhodium-catalyzed C-O bond cleavage delivered 2l in 75% yield.[12] Again, the final reductive cleavage reaction did not proceed when the Ni/TMDSO system[4c] was used, further demonstrating the robustness of the rhodium system.



Scheme 2. RhCl(**L2**)$_2$ catalyzed reductive cleavage of aryl carbamates

[a] RhCl(**L2**)$_2$ (0.030mol), K_3PO_4 (0.60 mmol), **1** (0.30 mmol), 2-propanol (0.30 mmol), toluene (1.0 mL), 180 °C, 4 h. [b] "RhCl(**L2**)$_2$" (20 mol%) was used. [c] Reacted for 16 h. [d] Yield when the method reported in ref 4c was used.

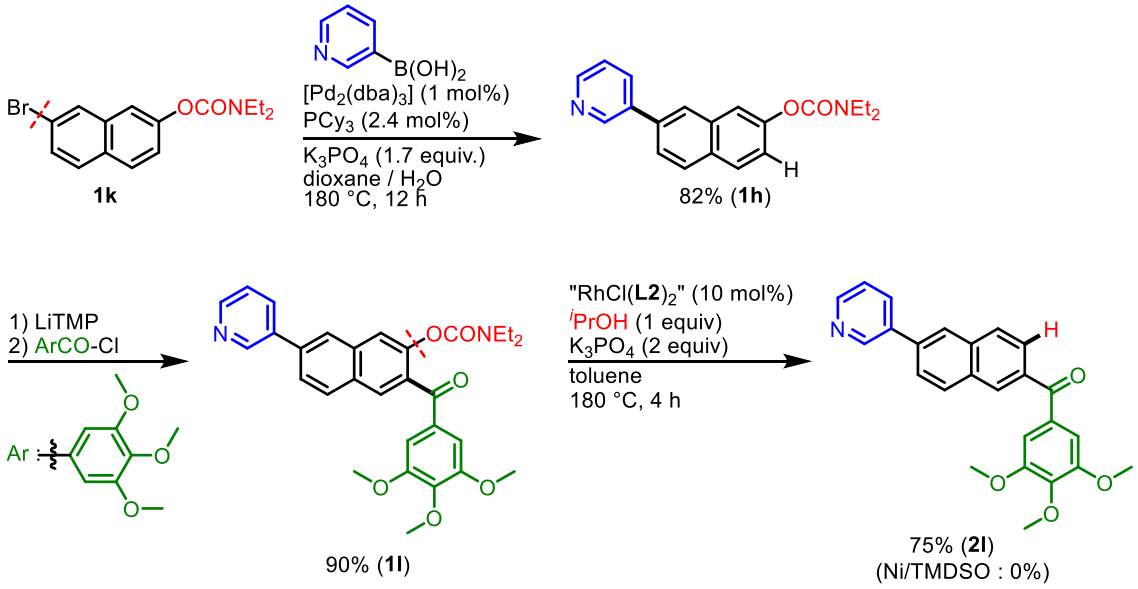


Scheme 3. Rh-catalyzed reductive cleavage of aryl carbamates using an internal alcohol group as the reductant

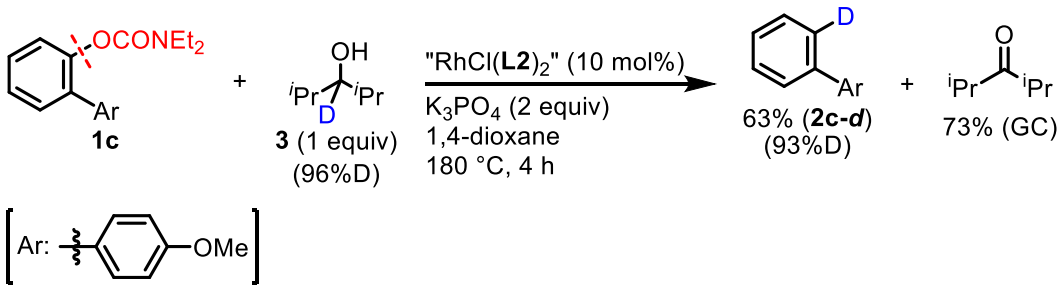
Finally, a deuterium labeling experiment was performed to obtain insight into the hydrogen source (Scheme 5). The reductive cleavage reaction with alcohol **3** bearing a deuterium atom at the 3-position instead of ^{i}PrOH revealed that the deuterium atom was incorporated into the reduced product and the corresponding ketone was produced. This experiment indicates that the hydrogen in the product is derived from the hydrogen adjacent to the hydroxyl group of the added alcohol.

The proposed mechanism is shown in Scheme 6. Rhodium(I) bis(NHC) complex A generated in situ initially reacts with ^{i}PrOH to produce alkoxorhodium(I) complex B, and subsequent β-hydrogen elimination gives rhodium(I) hydride C.[7] Complex C mediates oxidative addition of the C-O bond in

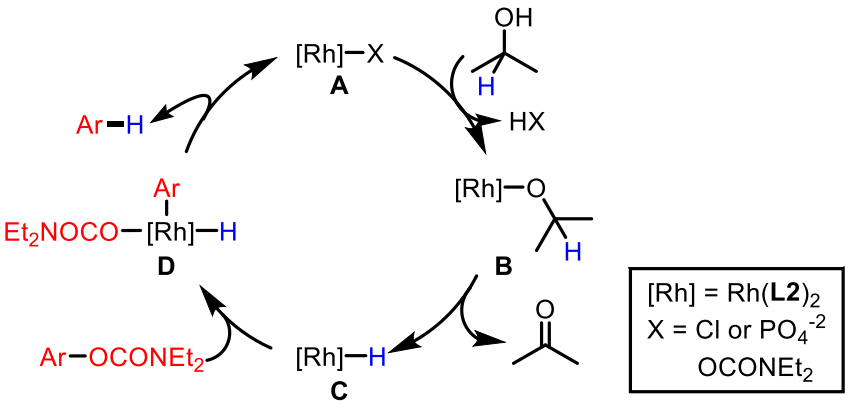
the aryl carbamate to form arylrhodium(III) intermediate D. Subsequent reductive elimination gives



Scheme 4. Synthetic application



Scheme 5. Mechanistic study



Scheme 6. Plausible Mechanism

the reductive cleavage product, and complex A is regenerated.

2-1.3 Conclusion

In summary, I have developed rhodium-catalyzed reductive cleavage of aryl carbamates using ^{i}PrOH as a reductant. Unlike previously reported methods using ^{i}PrMgX and TMDSO,[4] this reaction tolerates carbonyl groups, alkenes and heteroaromatic rings, such as carbazole and pyridine.

2-1.4 Experimental Section

I. General Information

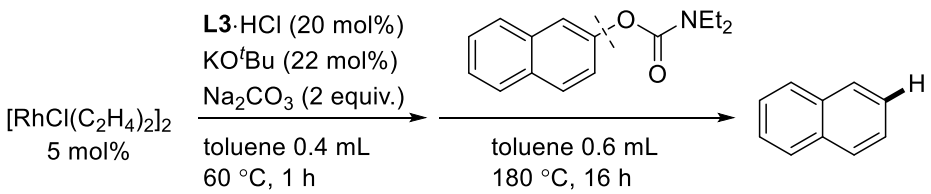
^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The data is reported as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer. Absorption is reported in reciprocal centimeters (cm^{-1}) with the following relative intensities: s (strong), m (medium), or w (weak). High resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SilicaFlash F60 (230-400 mesh) or Silica Gel 60 (spherical) NH_2).

II. Materials

IMes•HCl, KO^{t}Bu, Na_2CO_3, K_2CO_3, KOAc, KOPiv, K_3PO_4 and $ClCONEt_2$ were purchased from TCI and used as received. Toluene (for Organic Synthesis), acetonitrile and isopropanol were purchased from Wako Chemicals and used as received. NaH was purchased from nacalai tesque and used as received. ICy·HCl,[11] $[RhCl(C_2H_4)_2]_2$,[12] and IMes^{Me}•HCl[6(c)] were prepared according to literature procedure. Carbamates **1a** (132939-03-8)[13], **1b** (858647-65-1)[14], **1c** (776296-18-5)[15], **1d** (1449272-80-3)[16], and **1g** (952234-35-4)[6(b)] were known compounds and prepared by the reaction of the corresponding phenol and $ClCONEt_2$ using NaH as a base.

III. Optimization Studies

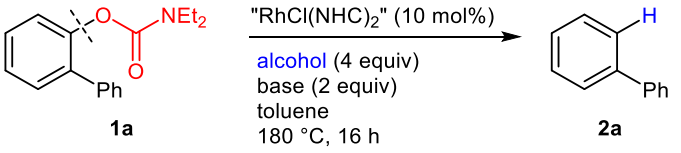
$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L3**·HCl (22 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), Na_2CO_3 (64 mg, 0.60 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. naphthalen-2-yl diethylcarbamate (73 mg, 0.30 mmol), reductant (1.2 mmol) and toluene (0.60 mL) were added to the vial in the glove box. The vessel was stirred at 180 °C for 16 h followed by cooling to rt. The mixture was analyzed by GC.



entry	reductant	product (%)
1	none	13
2	**isopropanol**	**87**
3	$SiH(OEt)_3$	17
4	cyclohexadiene	49
5[a]	isopropanol	29
6[b]	isopropanol	28

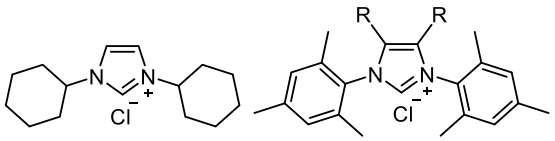
a: without base
b: without preheating

As a result of this initial screening of the reductant, we identified isopropanol as the most suitable reductant among examined under these rhodium-catalyzed conditions. Therefore, we next optimized the base and ligand using isopropanol as a reductant. At this stage, we employed less reactive substrate **1a** as our model compound for use in D*o*M chemistry. As detailed in the Table below, **L2** was found to be an optimal ligand among tested (entry 2). The nature of the base used has a significant impact with K_3PO_4 giving the highest yield of **2a** (entry 7). Regarding the alcohol reductant, neither primary nor tertiary alcohols cannot be used under these conditions (entries 8-10). The amount of isopropanol can be reduced to 1 equiv and the reaction time can be shortened to 4 h.



1a **2a**

entry	NHC	alcohol	base	GC yield of **2a**
1	**L1**	^{i}PrOH	Na_2CO_3	12%
2	**L2**	^{i}PrOH	Na_2CO_3	40%
3	**L3**	^{i}PrOH	Na_2CO_3	20%
4	**L2**	^{i}PrOH	K_2CO_3	67%
5	**L2**	^{i}PrOH	KOAc	27%
6	**L2**	^{i}PrOH	KOPiv	16%
7	**L2**	^{i}PrOH	K_3PO_4	75%
8	**L2**	MeOH	K_3PO_4	0%
9	**L2**	EtOH	K_3PO_4	trace
10	**L2**	^{t}BuOH	K_3PO_4	trace
11[b]	**L2**	^{i}PrOH	K_3PO_4	75%(12%)[c]



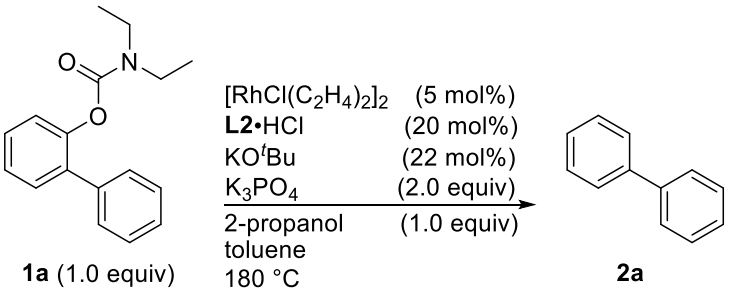
L1 **L2** (R=H)
L3 (R=Me)

[a] Reaction conditions: $[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), NHC·HCl (0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), base (0.60 mmol), and toluene (0.40 mL) at 60 °C for 1 h; **1a** (53 mg, 0.30 mmol), ^{i}PrOH (72 mg, 1.2 mmol) and toluene (0.60 mL) at 180 °C for 16 h.

[b] 1.0 equiv. of ^{i}PrOH was used and reacted for 4 h.

[c] The number in parentheses is the amount of recovered **1a**.

IV. General Procedure for Rh-Catalyzed C-O Bond Reduction of Aryl Carbamates

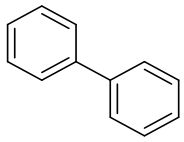


1a (1.0 equiv) **2a**

$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L2**·HCl (21 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), K_3PO_4 (127 mg, 0.60 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. Carbamate **1a** (53 mg, 0.30 mmol), 2-propanol (18 mg, 0.30 mmol) and toluene (0.60 mL) were added to the vial

in the glove box. The vessel was stirred at 180 °C for 4 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (eluting with hexane/EtOAc = 100/1) to give **2a** as a white solid (36 mg, 78%).

1,1'-Biphenyl (2a) [CAS: 92-52-4].



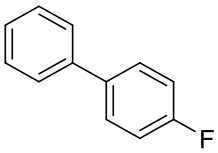
Rf 0.78 (hexane/EtOAc = 5/1). White solid (36 mg, 78%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59-7.62 (m, 4H), 7.43-7.47 (m, 4H), 7.33-7.37 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.2, 128.7, 127.2, 127.2.

HRMS (EI): Calcd for $C_{12}H_{10}$ 154.0783, Found 154.0784.

4-Fluoro-1,1'-biphenyl (2b) [CAS: 324-74-3].



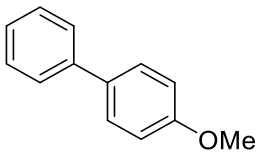
Rf 0.78 (hexane/EtOAc = 5/1). White solid (33 mg, 64%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.57 (m, 4H), 7.41-7.46 (m, 2H), 7.32-7.37 (m, 1H), 7.10-7.16 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4 (d, J = 245.8 Hz), 140.2, 137.3 (d, J = 3.0 Hz), 128.8, 128.7 (d, J = 7.0 Hz), 127.24 127.0, 115.6 (d, J = 22.0 Hz).

HRMS (EI): Calcd for $C_{12}H_9F$ 172.0688, Found 172.0687.

4-Methoxy-1,1'-biphenyl (2c) [CAS: 613-37-6].



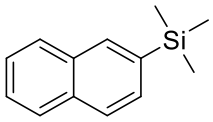
Rf 0.68 (hexane/EtOAc = 5/1). White solid (40 mg, 72%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.57 (m, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 6.98 (d, J = 7.8 Hz, 2H), 3.85 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.3.

HRMS (EI): Calcd for $C_{13}H_{12}O$ 184.0888, Found 184.0887.

Trimethyl(naphthalen-2-yl)silane (2d) [CAS: 18052-85-2].



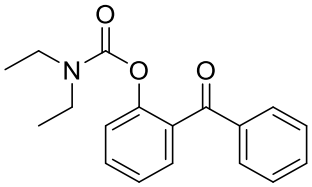
Rf 0.57 (hexane/EtOAc = 5/1). Colorless oil (45 mg, 76%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 1H), 7.79-7.85 (m, 3H), 7.59 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.45-7.49 (m, 2H), 0.34 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): 137.9, 133.7, 133.6, 132.9, 129. 8, 128.0, 127.7, 126. 9, 126.2, 125.9, -1.1.

HRMS (EI): Calcd for $C_{13}H_{16}Si$ 200.1021, Found 200.1024.

2-Benzoylphenyl diethylcarbamate (1e).



A mixture of 2-benzoylphenol (5.9 g, 20 mmol) and $ClCONEt_2$ (4.1 g, 30 mmol) and K_2CO_3 (5.5 g, 30 mmol) in CH_3CN (50 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature and concentrated under a vacuum. The residue was dissolved in H_2O (ca. 50 mL) and extracted with Et_2O (ca. 2 × 20 mL). The organic extracts were combined and then washed successively with saturated aqueous solution of $NaHCO_3$ (ca. 25 mL) and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a vacuum to yield **1e** as a colorless oil (2.2 g, 76%).

Rf 0.19 (hexane/EtOAc = 5/1). Colorless oil (2.2 g, 76%).

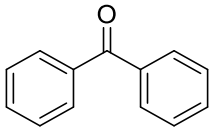
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.84 (m, 2H), 7.49-7.57 (m, 3H), 7.41-7.45 (m, 2H), 7.26-7.31 (m, 2H), 3.18 (q, *J* = 7.1 Hz, 2H), 3.01 (q, *J* = 7.1 Hz, 2H), 1.00 (t, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.2, 153.1, 149.3, 137.6, 132.8, 132.0, 131.8, 130.0, 129.8, 128.3, 124.9, 123.3, 42.1, 41.5, 13. 8, 13.1.

IR (ATR): 3350 w, 2972 w, 2873 w, 1719 s, 1666 s, 1601 w, 1580 w, 1522 m, 1471 m, 1450 m, 1418 s, 1382 m, 1316 m, 1293 m, 1272 s, 1206 s, 1152 s, 1100 w, 1044 w, 961 w, 926 w, 827 w, 788 w, 758 m, 740 m, 699 s.

HRMS (EI): Calcd for $C_{18}H_{19}NO_3$ 297.1365, Found 297.1366.

Benzophenone (2e) [CAS: 119-61-9].



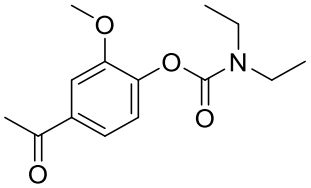
Rf 0.62 (hexane/EtOAc = 5/1). White solid (40 mg, 74%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.82 (m, 4H), 7.58-7.62 (m, 2H), 7.47-7.51 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.8, 137.5, 132.4, 130.1, 128.3.

HRMS (EI): Calcd for $C_{13}H_{10}O$ 182.0732, Found 182.0732.

4-Acetyl-2-methoxyphenyl diethylcarbamate (1f).



This compound was prepared according to the procedure for **1e**, except that 4'-hydroxy-3'-methoxyacetophenone was used instead of 2-benzoylphenol.

Rf 0.18 (hexane/EtOAc = 2/1). Colorless oil (1.7 g, 32%).

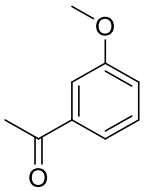
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, J = 1.8 Hz, 1H), 7.54 (dd, J = 8.2, 1.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 3.88 (s, 3H), 3.43 (m, 4H), 2.59 (s, 3H), 1.19-1.29 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.0, 153.4, 151. 9, 144.9, 135.2, 123.1, 122.0, 111.3, 56.0, 42.3, 42.1, 26.5, 14.0, 13.3.

IR (ATR): 2975 w, 1718 s, 1680 s, 1600 w, 1508 w, 1460 w, 1415 s, 1359 w, 1281 s, 1261 s, 1202 s, 1174 m, 1150 s, 1032 m, 958 w, 881 w, 780 w, 750 w, 690 w.

HRMS (EI): Calcd for $C_{14}H_{19}NO_4$ 265.1314, Found 265.1315.

1-(3-Methoxyphenyl)ethan-1-one (2f) [CAS: 586-37-8].



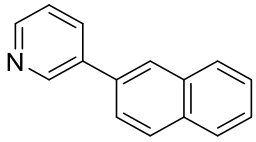
Rf 0.36 (hexane/EtOAc = 5/1). White solid (32 mg, 72%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53-7.56 (m, 1H), 7.49 (q, J = 1.4 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.12 (dt, J = 8.2, 1.4 Hz, 1H), 3.86 (s, 3H), 2.61 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 159.7, 138.4, 129.6, 121.1, 119.7 112.2, 55.4, 26.8.

HRMS (EI): Calcd for $C_{13}H_{12}O$ 150.0681, Found 150.0683.

3-(Naphthalen-2-yl)pyridine (2h) [CAS: 92497-48-8].



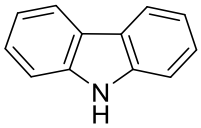
Rf 0.17 (hexane/EtOAc = 2/1). White solid (49 mg, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.62 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.04 (d, *J* = 1.6 Hz, 1H), 7.99 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.87-7.96 (m, 3H), 7.71 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.49-7.56 (m, 2H), 7.40 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.6, 148.5, 136.6, 135.2, 134.5, 133.6, 132.9, 128.9, 128.2, 127.7, 126.6, 126.4, 126.2, 125.0, 123.6.

HRMS (EI): Calcd for $C_{15}H_{11}N$ 205.0891, Found 205.0890.

9*H*-Carbazole (2i) [CAS: 86-74-8].



Rf 0.41 (hexane/EtOAc = 5/1). White solid (38 mg, 75%).

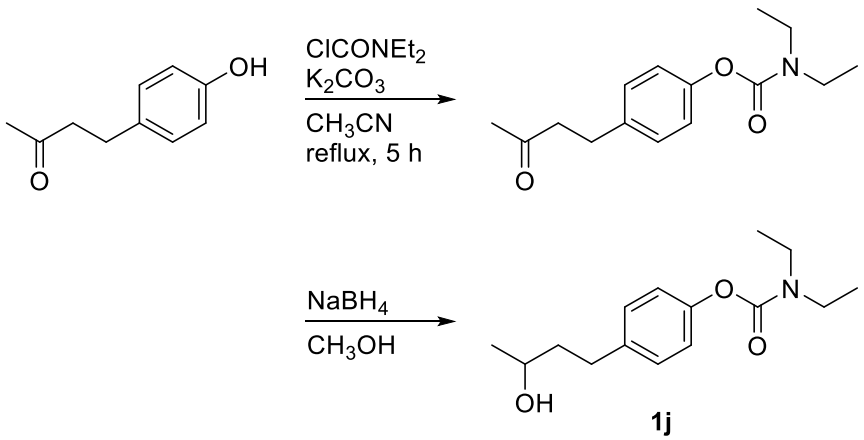
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05-8.10 (m, 3H), 7.42-7.45 (m, 4H), 7.22-7.26 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.4, 125.8, 123.3, 120.3, 119.4, 110.5.

HRMS (EI): Calcd for $C_{12}H_9N$ 167.0735, Found167.0733.

V. Rh-Catalyzed Reductive Cleavage of Aryl Carbamates Using an Internal Alcohol Group as the Reductant

4-(1-Hydroxyethyl)-2-methoxyphenyl diethylcarbamate (1j).



1j

A mixture of 4-(4-hydroxyphenyl)butan-2-one (3.3 g, 20 mmol) and $ClCONEt_2$ (4.1 g, 30.0 mmol) and K_2CO_3 (5.5 g, 30 mmol) in 50 mL of CH_3CN was refluxed for 5 h. The reaction mixture was

cooled to room temperature and concentrated under a vacuum. The residue was dissolved in H_2O (ca. 50 mL) and extracted with Et_2O (ca. 2 × 20 mL). The organic extracts were combined and then washed successively with saturated aqueous solution of $NaHCO_3$ (ca. 25 mL) and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under a vacuum to yield 4-(3-oxobutyl)phenyl diethylcarbamate (2.1 g, 41%). A mixture of 4-(3-oxobutyl)phenyl diethylcarbamate (1.3 g, 5.0 mmol) and $NaBH_4$ (380 mg, 10 mmol) in anhydrous MeOH (30 mL) was stirred at rt for 25 min. Saturated aqueous solution of $NaHCO_3$ (20 mL) and $CHCl_3$ (30 mL) were added, and the mixture was stirred at 0 °C for 5 min. The organic layer was seperated and the aqueous layer was extracted with $CHCl_3$ (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give 1.3 g (95%) of **1j** as a colorless oil.

Rf 0.12 (hexane/EtOAc = 2/1). Colorless oil (1.34 g, 95%).

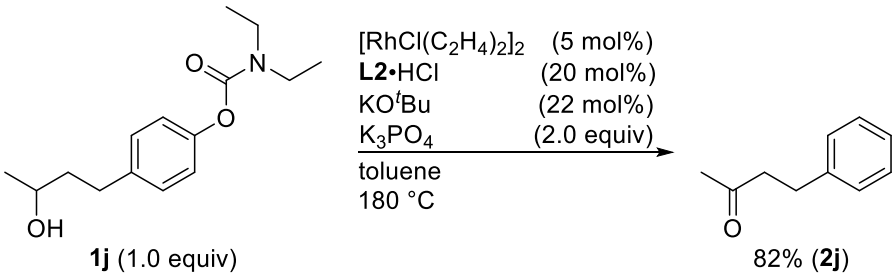
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12-7.22 (m, 2H), 6.98-7.07 (m, 2H), 3.77-3.86 (m, 1H), 3.40 (d, *J* = 7.8 Hz, 4H), 2.62-2.78 (m, 2H), 1.68-1.82 (m, 2H), 1.32 (d, *J* = 5.0 Hz, 1H), 1.22 (m, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.4, 149.6, 138.7, 129.1, 121.6, 67.3, 42.2, 41.8, 40.8, 31.4, 23.6, 14.2, 13.4.

IR (ATR): 3438 w, 2970 w, 2932 w, 1699 s, 1510 w, 1473 w, 1457 w, 1419 s, 1380 w, 1315 w, 1274 s, 1207 s, 1169 m, 1155 m, 961 w.

HRMS (EI): Calcd for $C_{15}H_{23}NO_3$ 265.1678, Found 265.1677.

4-Phenylbutan-2-one (2j) [CAS: 2550-26-7].



1j (1.0 equiv) 82% (**2j**)

$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L2**·HCl (21 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), K_3PO_4 (127 mg, 0.60 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. Carbamate **1i** (80 mg, 0.30 mmol) and toluene (0.60 mL) were added to the vial in the glove box. The vessel was stirred at 180 °C for 16 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (eluting with hexane/EtOAc = 10/1) to give **2j** as a colorless oil (36 mg, 82%).

Rf 0.48 (hexane/EtOAc = 5/1). White solid (36 mg, 82%).

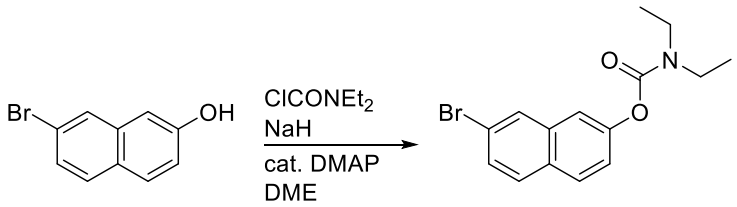
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.30 (m, 2H), 7.17-7.21 (m, 3H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.13 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.9, 141.0, 128.5, 128.3, 126.1, 45.1, 30.0, 29.7.

HRMS (EI): Calcd for $C_{10}H_{12}O$ 148.0888, Found 148.0888.

VI. Synthetic Application

7-Bromonaphthalen-2-yl diethylcarbamate (1k).



A solution of 7-bromonaphthalen-2-ol (4.43 g, 20 mmol) in DME (30 mmol) was added dropwise to a suspension of NaH (60% oil dispersion, 1.4 g, 30 mmol) in DME (15 mL) at 0 °C, and the mixture was stirred at room temperature for 10 min. Et_2NCOCl (4.1 g, 30 mmol) and DMAP (24 mg, 1 mol%) was then added to the reaction mixture and stirred at room temperature for 2 h. The solvent was removed in vacuo to give a residue, which was dissolved in EtOAc and filtered through a pad of silica gel. The filtrate was then concentrated in vacuo to give the crude product, which was purified by flash column chromatography over silica gel (eluent: hexane/EtOAc = 10/1) to give **1k** (6.3 g, 98%) as a colorless oil.

Rf 0.39 (hexane/EtOAc = 5/1). Colorless oil (6.3 g, 98%).

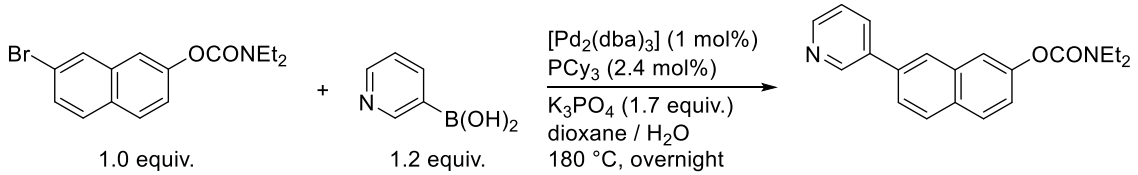
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, J = 1.8 Hz, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.50 (dd, J = 8.9, 2.1 Hz, 2H), 7.30 (dd, J = 8.7, 2.3 Hz, 1H), 3.45 (m, 4H), 1.26 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1, 150.0, 135.0, 129.50, 129.47, 129.3, 129.1, 128.7, 122.2, 120.5, 117.6, 42.3, 42.0, 14.3, 13.4.

IR (ATR): 2974 w, 2930 w, 1716 s, 1629 w, 1504 w, 1473 w, 1415 m, 1381 w, 1358 w, 1272 m, 1237 m, 1199 s, 1160 s, 1097 w, 1065 w, 973 w, 913 m, 838 w, 745 m.

HRMS (EI): Calcd for $C_{15}H_{16}BrNO_2$ 321.0364, Found 321.0362.

7-(Pyridin-3-yl)naphthalen-2-yl diethylcarbamate (1h).



Carbamate **1h** was synthesized according to Fu's procedure.[17] Pyridin-3-ylboronic acid (740 mg, 6.0 mmol), $[Pd_2(dba)_3]$ (46 mg, 0.050 mmol), and PCy_3 (33 mg, 0.12 mmol) were added to a 25-mL Schlenk flask equipped with a stir bar in air. The flask was evacuated and refilled with nitrogen five times. Dioxane (9 mL), **1k** (1.6 g, 5.0 mmol), and aqueous solution of K_3PO_4 (1.3 M, 3.0 mL, 8.5

mmol) were added by syringe. The Schlenk flask was sealed and heated in an oil bath at 100 °C for 18 h with vigorous stirring. The mixture was then filtered through a pad of NH silica gel (washing with EtOAc), the filtrate concentrated under reduced pressure, and the aqueous residue extracted three times with Et_2O. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was then purified by column chromatography on NH silica gel eluting with hexane/EtOAc = 10/1) to give **1h** as a pale-yellow oil (1.3 g, 82%).
Rf 0.06 (hexane/EtOAc = 2/1). Pale yellow oil (1.3 g, 82%).

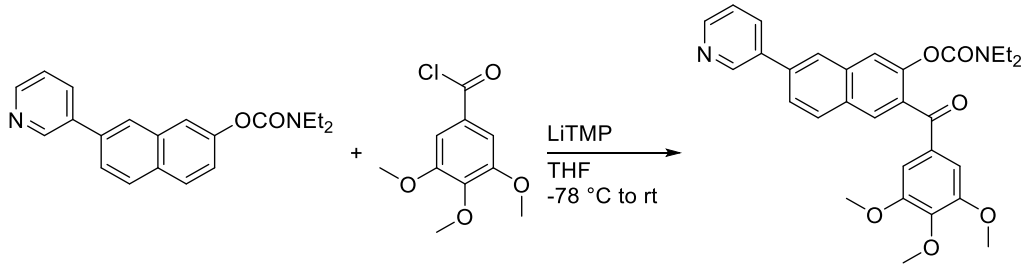
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.96 (d, *J* = 1.8 Hz, 1H), 8.62 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.92-7.99 (m, 3H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.66 (dt, *J* = 6.3, 1.9 Hz, 2H), 7.38-7.42 (m, 1H), 7.32 (dd, *J* = 9.2, 2.3 Hz, 1H), 3.47 (m, 4H), 1.28 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.2, 149.8, 148.6, 136.5, 135. 7, 134.6, 134.1, 130.6, 128.9, 128.7, 125.8, 124.5, 123.6, 122.3, 118.7, 65.8, 42.3, 42.0, 14.3, 13.4.

IR (ATR): 2974 w, 2359 w, 1714 s, 1474 w, 1457 w, 1418 m, 1373 w, 1275 m, 1234 w, 1202 s, 1165 s, 971 w, 913 w, 811 w, 746 w, 713 w.

HRMS (EI): Calcd for $C_{20}H_{20}N_2O_2$ 320.1525, Found 320.1523.

7-(Pyridin-3-yl)-3-(3,4,5-trimethoxybenzoyl)naphthalen-2-yl diethylcarbamate (1l) .



Carbamate **1l** was synthesized according to Snieckus' procedure.[16] Under an nitrogen atmosphere, 3.0 equivalents of ^{n}BuLi (2.4 M in hexanes, 2.5 mL) were added to a pre-cooled solution (0 ˚C) of TMP (7.4 mL, 6.0 mmol) in THF (10 mL), and the resulting mixture was stirred for 15 min. The LiTMP solution was slowly added to a solution of **1h** (640 mg, 2.0 mmol) in THF (10 mL) at –78 °C, whilst keeping the internal temperature of the solution below –73 °C. After 1.5 h, 3,4,5-trimethoxybenzoyl chloride (1.4 g, 6.0 mmol) was added quickly. The resulting mixture was stirred at –78 °C for 2 h and for additional 12 h at room temperature. After that time the reaction mixture was quenched with a saturated NH_4Cl solution, and extracted with Et_2O, affording the crude product. Flash column chromatography (NH silica gel) using hexane/EtOAc as eluent systems afforded **1l** as a pale yellow solid (925 mg, 90%).
Rf 0.30 (EtOAc). Pale yellow solid (930 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (d, *J* = 2.3 Hz, 1H), 8.66 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.06 (d, *J* = 4.6 Hz, 2H), 7.99-8.02 (m, 2H), 7.79 (s, 1H), 7.74 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.44 (dd, *J* = 8.0, 4.8

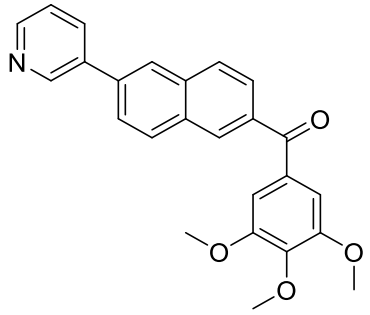
Hz, 1H), 7.14 (s, 2H), 3.93 (s, 3H), 3.85 (s, 6H), 3.25 (q, J = 7.2 Hz, 2H), 3.16 (q, J = 7.2 Hz, 2H), 1.01-1.08 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.8, 153.3, 153.0, 149.0, 148.6, 146.8, 142.5, 137.3, 136.1, 135.0, 134.6, 132.7, 132.4, 130.3, 129.7, 129.5, 125.7, 125.5, 123.7, 120.8, 107.3, 60.9, 56.2, 42.3, 41.7, 13.9, 13.2.

IR (ATR): 2976 w, 2360 w, 2335 w, 1716 s, 1659 w, 1583 m, 1503 m, 1464 m, 1415 s, 1380 w, 1333s, 1273 m, 1232 m, 1172 m, 1155 m, 1127 s, 1002 w, 913 m, 804 w, 747 m, 717 w.

HRMS (EI): Calcd for $C_{30}H_{30}N_2O_6$ 514.2104, Found 514.2110.

(6-(Pyridin-3-yl)naphthalen-2-yl)(3,4,5-trimethoxyphenyl)methanone (2l) .



Rf 0.33 (EtOAc). Pale orange oil (90 mg, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.02 (bs, 1H), 8.68 (bs, 1H), 8.33 (s, 1H), 8.13 (s, 1H), 7.96-8.07 (m, 4H), 7.81 (d, J = 8.2 Hz, 1H), 7.46 (bs, 1H), 7.14 (s, 2H), 3.97 (s, 3H), 3.89 (s, 6H).

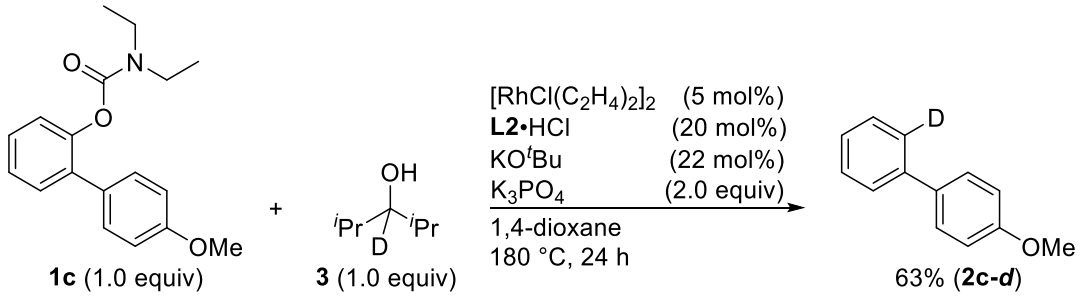
^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5, 152.9, 149.0, 148.6, 142.2, 137.6, 136.0, 135.5, 135.3, 134.6, 132.7, 131.7, 131.1, 130.3, 128.5, 126.6, 126.1, 126.0, 123.7, 107.8, 61.0, 56. 3.

IR (ATR): 2939 w, 1715 w, 1652 w, 1626 w, 1581 m, 1503 m, 1464 m, 1413 m, 1378 w, 1328 s, 1275 w, 1234 m, 1215 m, 1171 m, 1124 s, 1001 m, 912 m, 823 w, 801 w, 750 m, 726 s, 645 w.

HRMS (EI): Calcd for $C_{25}H_{21}NO_4$ 399.1471, Found 399.1470.

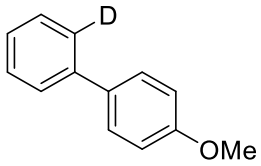
VII. Procedure of Deuterium Labelling Experiment

Alcohol **3** was synthesized according to the literature procedure. The deuterium content was determined to be 96% by ^{1}H-NMR analysis.



$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L2**·HCl (21 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), K_3PO_4 (127 mg, 0.60 mmol), and 1,4-dioxane (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 60 °C for 1 h. Carbamate **1c** (90 mg, 0.30 mmol), **3** (35 mg, 0.30 mmol) and 1,4-dioxane (0.60 mL) were added to the vial in the glove box. The vessel was stirred at 180 °C for 24 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (eluting with hexane/EtOAc = 100/1) to give **2c-*d*** as a white solid (35 mg, 63%).

4-Methoxy-1,1'-biphenyl-2'-d (2c-*d*).



Rf 0.68 (hexane/EtOAc = 5/1). White solid (35 mg, 63%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.57 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 140.8, 133.7, 128.7, 128.6, 128.1, 126.7, 126.6, 114.1, 114.0, 55.3.

^{2}H NMR ($CHCl_3$, 400 MHz): 7.61.

IR (ATR): 3004 w, 2961 w, 1737 w, 1604 s, 1581 w, 1520 s, 1480 s, 1465 w, 1440 m, 1036 s, 835 s, 761 s, 731 s, 716 s, 691 m, 628 m.

HRMS (EI): Calcd for $C_{13}H_{11}DO$ 185.0951, Found 185.0950.

2-1.5 References

(1) Reviews on cross-coupling using inert phenol derivatives: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (b) Li, B.-J.; Yu, D.-G.; Sun, C.-L. ; Shi, Z.-J. *Chem.–Eur. J.* **2011**, *17*, 1728. (c) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, *2013*, 19. (d) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081. (e) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717.

(2) Reviews on *DoM* strategy: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Snieckus, V. *Beilstein J. Org. Chem.* **2011**, 1215.

(3) (a) Bedford, R. B.; Webster, R. L.; Mitchell, C. J. *Org. Biomol. Chem.* **2009**, *7*, 4853. (b) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 468. (c) Bedford, R. B.; Mitchell, C. J.; Webster, R. L. *Chem. Commun.* **2010**, *46*, 3095. (d) Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. *Org. Lett.*

2011, *13*, 3235. (e) John, A.; Nicholas, K. M. *J. Org. Chem.* **2012**, 77, 5600. (f) Li, J.; Kornhaass, C.; Ackermann, L. *Chem. Commun.* **2012**, *48*, 11343. (g) Li, B.; Ma, J.; Liang, Y.; Wang, N.; Xu, S.; Song, H.; Wang, B. *Eur. J. Org. Chem.* **2013**, 1950. (h) Bedford, R. B.; Brenner, P. B.; Durrant, S. J.; Gallagher, T.; Mendez-G., C.; Montgomery, M. *J. Org. Chem.* **2016**, *81*, 3473.

(4) (a) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 406. (b) Mesganaw, T.; Fine N., N. F.; Garg, N. K. *Org. Lett.* **2012**, *14*, 2918.

(5) (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4866. (b) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett.* **2009**, *38*, 710. (c) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 2929. (d) Tobisu, M.; Yasutome, A.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Tetrahedron* **2012**, *68*, 5157. (e) Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5572. (f) Tobisu, M.; Takahira, T.; Ohtsuki, A.; Chatani, N. *Org. Lett.* **2015**, *17*, 680. (g) Tobisu, M.; Takahira, T.; Chatani, N. *Org. Lett.* **2015**, *17*, 4352. (h) Tobisu, M.; Morioka, T.; Ohtsuki, A.; Chatani, N. *Chem. Sci.* **2015**, *6*, 3410. (i) Morioka, T.; Nishizawa, A.; Nakamura, K.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 1729. (j) Nakamura, K.; Tobisu, M.; Chatani, N. *Org. Lett.* **2015**, *17*, 6142.

(6) (a) Kinuta, H.; Hasegawa, J.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 366. (b) Nakamura, K.; Yasui, K.; Tobisu, M.; Chatani, N. *Tetrahedron* **2015**, *71*, 4484. (c) Kinuta, H.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 1593. (d) Tobisu, M.; Yasui, K.; Aihara, Y.; Chatani, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 1877.

(7) Spogliarich, R.; Zassinovich, G.; Mestroni, G.; Graziani, M. *J. Organomet. Chem.* **1980**, *198*, 81.

(8) Addition of stoichiometric base is essential for this reaction to proceed. See SI for details.

(9) Non-alcoholic reducing agents, such as 1,4-cyclohexadiene and hydrosilane were ineffective. See SI for details.

(10) The catalyst generated in situ by the reaction of $[RhCl(C_2H_4)_2]_2$, **L2**·HCl and KO^{t}Bu at 60 °C for 1 h in toluene is described as "RhCl(**L2**)$_2$" throughout this section.

(11) Mistryukov, E. A. *Mendeleev Commun.* **2006**, *16*, 258.

(12) Cramer, R. *Inorg. Chem.* **1962**, *1*, 722.

(13) Lo, H.-J.; Lin, C.-Y.; Tseng, M.-C.; Chein, R.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 9026.

(14) Zhao, Z.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2523.

(15) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 6790.

(16) Groom, K.; Hussain, S. M. S.; Morin, J.; Nilewski, C.; Rantanen, T.; Snieckus, V. *Org. Lett.* **2014**, *16*, 2378.

(17) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1282.

(18) Karabotsos, G. J. *J. Org. Chem.* **1960**, *25*, 1409.

2-2 Rhodium-Catalyzed Alkynylation of C-O Bond of Aromatic Carbamates with Propargyl Alcohol

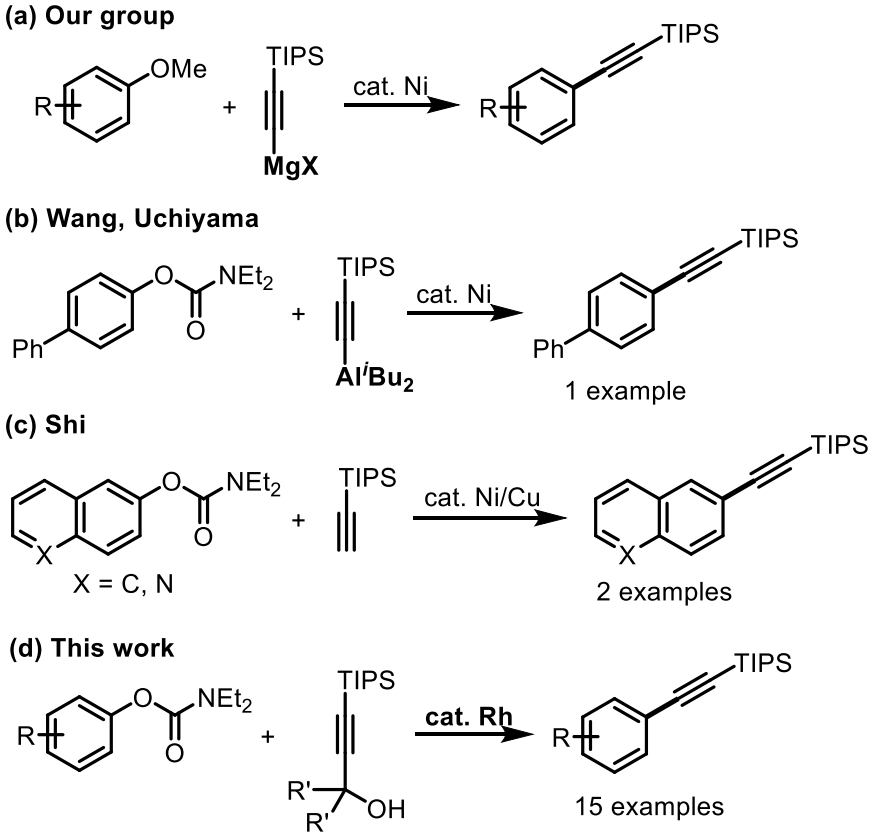
2-2.1 Introduction

Given the widespread use of aromatic alkynes in organic chemistry, developing methods to synthesize these compounds continues to be a subject of great interest.[1] The Sonogashira-type cross-coupling reaction is among the most powerful methods for the construction of a C(sp)-C(sp2) bond using aryl halides and terminal alkynes.[2] Considering that phenols are abundant chemical feedstock,[3] it is of great synthetic value to develop catalytic systems that use phenol and its derivatives instead of aryl halides. A classical way to use phenols in cross-coupling reactions is to convert them to aryl triflates, thereby activating the C(aryl)-O bond toward oxidative addition. Despite the synthetic utility of aryl triflates, these reactions can be costly and generate harmful waste derived from the fluorine-based leaving group. Non-fluorinated phenol derivatives such as ethers, esters and carbamates have recently emerged as a less expensive and more environmentally benign alternative to aryl halides and triflates. [4,5,6,7]

Although significant progress has been made in the catalytic transformation of inert phenol derivatives, the use of Sonogashira type cross-coupling has had limited success. [5h,8,9] We have previously described a nickel-catalyzed cross-coupling of anisoles with alkynyl Grignard reagents (Scheme 1a),[5h] while Uchiyama developed a nickel-catalyzed alkynylation of aryl carbamates using alkynylaluminum reagents (Scheme 1b).[8] Although these two methods pioneered the Sonogashira-type reaction of inert phenol derivatives, the use of strong organometallic nucleophiles limits functional group compatibility. Shi reported a unique Ni/Cu co-catalytic system that allows the direct use of terminal alkynes in the alkynylation of aryl carbamates, although only two specific substrates were examined, and a detailed investigation was not carried out.[9] In the field of C(aryl)-O bond activation of inert phenol derivatives, the vast majority of the reported reactions use nickel as the catalyst.[4,6]

In contrast, we have developed several rhodium catalysts that can activate inert C(aryl)-O bonds.[7] Importantly, the use of rhodium enabled transformations that were not possible with nickel catalysts. For example, the use of rhodium allows cross-coupling with non-organometallic reagents, such as arenes bearing a directing group,[7d] and isopropanol as a hydride equivalent.[7e]

Mechanistic investigation of the latter reaction revealed that the hydride incorporated at the ipso position of aryl carbamates is derived from the β–hydrogen of the isopropanol and is transferred through β–hydrogen elimination. We envisioned that aryl carbamates would undergo C-O bond alkynylation in the presence of our rhodium catalyst, as propargyl alcohols serve as alkynylating reagents under rhodium(I) catalysis via β–carbon elimination.[10,11] We also expected that a broad range of aryl carbamates could be used by avoiding the use of organometallic alkynylating reagents.

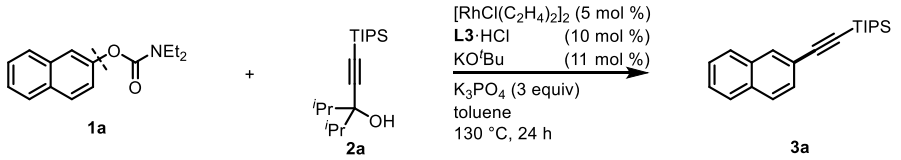


Scheme 1. Alkynylation of Inert Phenol Derivatives

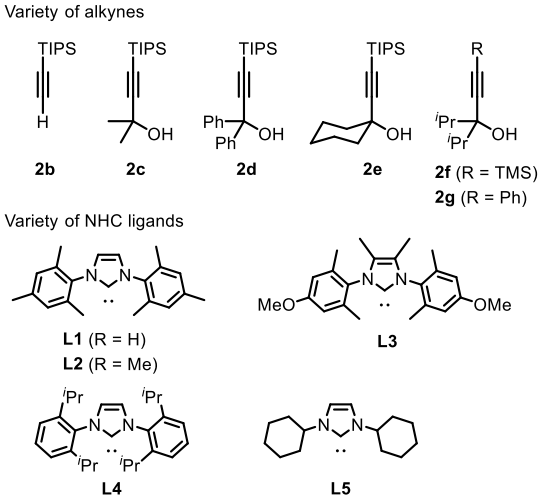
2-1.2 Results and Discussion

This study began by optimizing the conditions for the reaction between 2-napthyl carbamate **1a** and alkynylating reagents **2a**-**2e** in the presence of a rhodium/NHC catalyst. After systematic screening, the target alkynylation product **3a** was formed in 74% isolated yield when **2a** was used as an alkynylating reagent, with **L3** as the ligand and K_3PO_4 as the stoichiometric base (Table 1, entry 1). The use of terminal alkyne **2b** significantly decreased the yield of **3a** due to the formation of enyne byproducts, which are generated through dimerization of **2b** (entry 2).[12] Propargyl alcohols **2c**, **2d** and **2e** failed to give **3a** efficiently, again due to the formation of the enyne byproducts (entries 3-5). The use of **2a** completely suppressed the formation of the enyne byproduct, presumably as its bulkiness prevented **2a** from reacting with an alkynylrhodium intermediate. A TIPS protecting group is critical, as evidenced by the lack of a product formed with TMS- and phenyl-substituted derivative **2f** and **2g**, respectively, presumably due to oligomerization of **2f** and **2g** (entries 6 and 7). Despite the limited scope of the propargyl alcohols, the TIPS group can be easily removed from the alkynylated products to give corresponding terminal alkynes, which are amenable to further elaboration. (see Scheme 3) Several other bases, such as KOAc, K_2CO_3, and K_2HPO_4 gave inferior yields to that obtained with K_3PO_4 (entries 8-10). NHC ligands with an N-mesityl structure (such as **L1** and **L2**) promoted the

reaction, with **L3** exhibiting the best activity (entries 11 and 12). Both methyl groups on the imidazole ring and the methoxy groups of **L3** are important for enhancing the catalytic activity. The use of **L4** or **L5**, however, led to a significant reduction in yield of **3a** (entries 13 and 14). Increasing the ratio of the NHC ligand to rhodium to 2:1 did not improve the yield of **3a** (entry 15), which indicated that the catalytically active species generated in situ is the rhodium complex bearing one NHC ligand. The $[RhCl(C_2H_4)(\mathbf{L3})]_2$ species could be observed in the catalyst solution by using ^{13}C NMR and HRMS (see Supporting Information (SI) for details).[13]



entry	variation from above	GC yields [%]		
		3a	**1a**	**2**
1	none	75 (74)	0	0
2	**2b** instead of **2a**	18	12	trace
3	**2c** instead of **2a**	35	15	0
4	**2d** instead of **2a**	25	9	trace
5	**2e** instead of **2a**	22	7	0
6	**2f** instead of **2a**	0	64	0
7	**2g** instead of **2a**	0	>95	0
8	KOAc instead of K_3PO_4	23	39	0
9	K_2CO_3 instead of K_3PO_4	47	trace	0
10	K_2HPO_4 instead of K_3PO_4	28	trace	0
11	**L1** instead of **L3**	20	3	0
12	**L2** instead of **L3**	53	2	0
13	**L4** instead of **L3**	trace	68	0
14	**L5** instead of **L3**	12	47	trace
15	2.0 equiv of **L3**	73	0	0
16	$[RhCl(cod)]_2$ instead of $[RhCl(C_2H_4)_2]_2$	trace	>95	>95

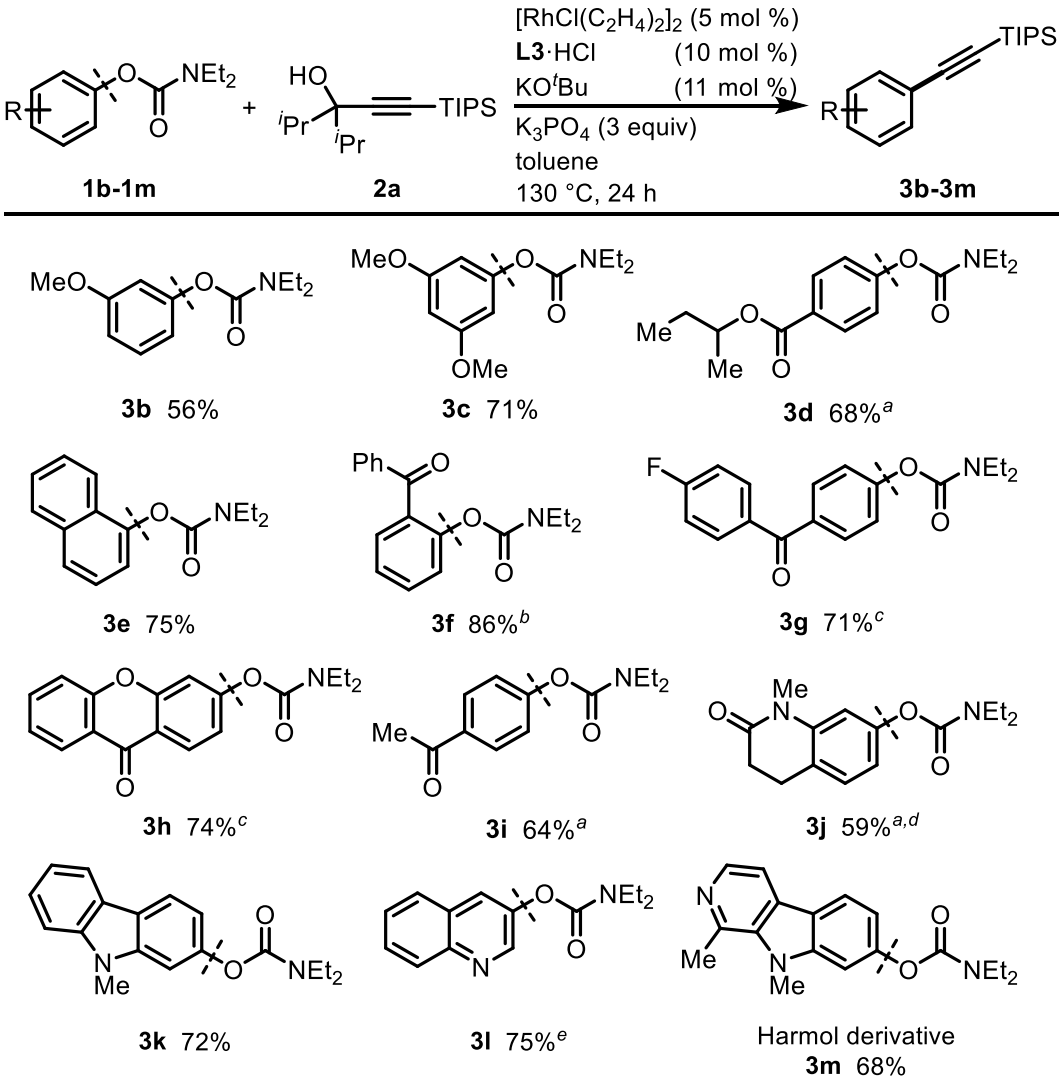


Scheme 2. Alkynylation of Inert Phenol Derivatives

Conditions: $[RhCl(C_2H_4)_2]_2$ (0.015 mmol), **L**·HCl (0.030 mmol), KO^{t}Bu (0.033 mmol), base (0.90 mmol), **1** (0.30 mmol) and **2** (0.45 mmol) in toluene (1.0 mL) at 130 °C for 24 h. Yield in parenthesis is isolated yield.

With the optimized reaction conditions in hand, the scope of the aryl carbamates was evaluated next (Scheme 2). Aryl carbamates **1b** and **1c** underwent alkynylation without affecting the methoxy group, which can be reactive with nickel catalysts. [5g] The use of **2a** as an alkynylating reagent allows the use of aryl carbamates bearing a carbonyl functional group, such as esters (**1d**), ketones (**1f-1i**) and amides (**1j**), which are incompatible with organometallic alkynylating reagents. Although nickel-catalyzed α–arylations of ketones and amides using aryl esters as an aryl donor have been reported,[14] this rhodium system did not produce such an α–arylation product, even when aryl carbamates bearing enolizable ketone (**1i**) and amide (**1j**) were used. Sterically hindered 1-naphthyl carbamate **1e** provided

the corresponding alkynylated product in 75% yield. In addition, the use of more sterically congested *ortho* benzoyl carbamate **1f** was also possible by using smaller ligand **L5**.[15] In this transformation, a carbamate bearing a fluorine (**1g**) is also compatible, whereas C-F bonds often react in nickel-catalyzed cross-couplings of inert phenol derivatives.[5h,16] Moreover, heteroaromatic carbamates, such as carbazole **1k** and quinoline **1l,** successfully afforded the corresponding alkynylated products. This

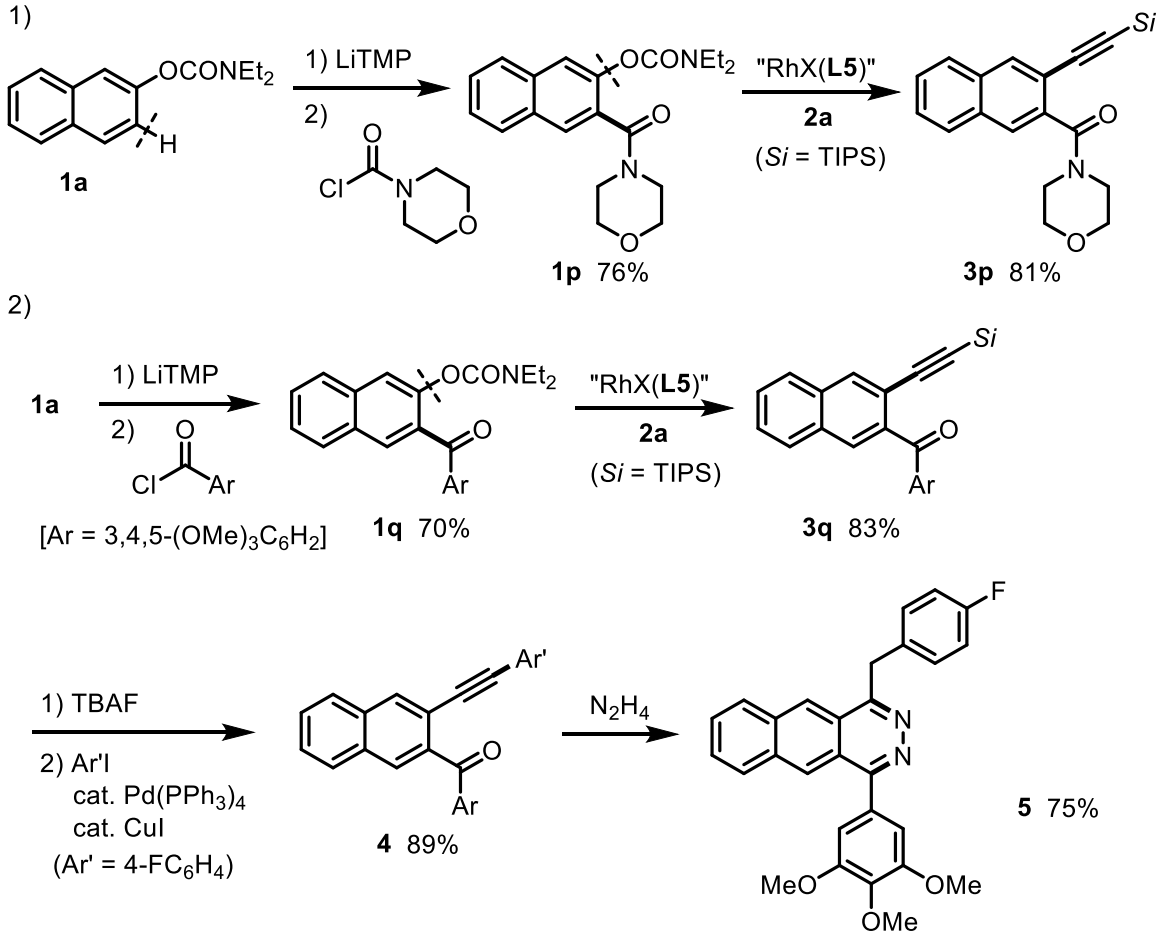


Scheme 3. Alkynylation of Inert Phenol Derivatives

Conditions: $[RhCl(C_2H_4)_2]_2$ (0.015 mmol), **L3**·HCl (0.030 mmol), KO^{t}Bu (0.033 mmol), K_3PO_4 (0.90 mmol), **1** (0.30 mmol) and **2c** (0.45 mmol) in toluene (1.0 mL) at 130 °C for 24 h. Isolated yields of alkynylated products are shown. [a]Reacted at 120 °C. [b]**L5**·HCl (0.030 mmol) was used instead of **L3**·HCl. [c]At 110 °C. [d] $[RhCl(C_2H_4)_2]_2$ (0.023 mmol), **L3**·HCl (0.045 mmol), and KO^{t}Bu (0.050 mmol) were used. [e]At 140 °C.

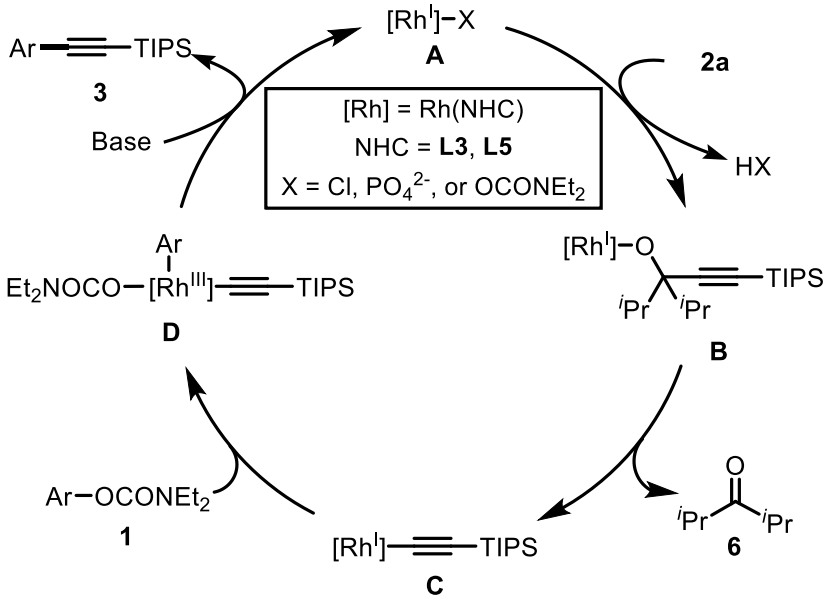
catalytic system could be used for the derivatization of biologically active phenol compounds, as exemplified by the synthesis of alkynylated Harmol **3m**.[17,18]

Because a carbamoyl group is known to be a powerful *ortho* directing group in arene functionalization reactions,[19] *ortho*-substituted aryl alkynes can readily be accessed via an *ortho* C-H functionalization/*ipso* alkynylation sequence of simple aryl carbamates. For example, *ortho* lithiation of **1a** by LiTMP, followed by reaction with carbamoyl chloride forms carbamate **1p**, which can be converted into alkyne **3p** (Scheme 3). Similarly, *ortho*-acylated aromatic alkyne **3q** was successfully synthesized in a straightforward manner. Although our method requires the use of TIPS-protected propargyl alcohols, the TIPS group in the product can be easily removed and replaced with a different group via the established methods. For example, deprotection of **3q**, followed by arylation under Sonogashira conditions afforded diaryl alkyne **4**. It should also be noted that the resulting *ortho* acylated aromatic alkynes are valuable precursors of a range of heterocycles.[19] For example, the reaction of **4** with hydrazine led to the construction of a phthalazine skeleton,[21] which can further serve as a diene component in aza Diels-Alder reactions.[22]



Scheme 4. Synthetic Applications

A plausible mechanism for this transformation is shown in Scheme 4. Initially, rhodium complex **A** is generated *in situ*, and reacts with propargyl alcohol **2** to form rhodium alkoxide **B**. β–Carbon elimination of **B** then forms alkynylrhodium **C**, releasing ketone **6**. The formation of intermediate **C** is supported by the isolation and X-ray analysis of analogous alkynylrhodium complexes. [11g,23] Intermediate **C** mediates the oxidative addition of the C-O bond in aryl carbamate **1** to form rhodium(III) intermediate **D**, which provides the alkynylated product **3** via reductive elimination with regeneration of the catalyst.



Scheme 5. Plausible Mechanism

2-2.3 Conclusion

In summary, we have developed a rhodium-catalyzed alkynylation of aryl carbamates using propargyl alcohols as the alkynylating agents. The use of propargyl alcohols allows this inert C-O bond alkynylation to be compatible with a range of functional groups, such as ketones, esters and amides, which are incompatible with previously reported cross-couplings using organometallic nucleophiles. This alkynylation method enables the use of a carbamate directing group as a handle for the synthesis of functionalized aromatic alkynes, which serve as useful building blocks in organic synthesis.

2-2.4 Experimental Section

I. General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The data is reported as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, and m = multiplet), coupling

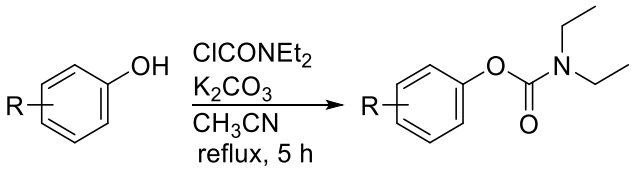
constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer. Absorption is reported in reciprocal centimeters (cm^{-1}) with the following relative intensities: s (strong), m (medium), or w (weak). High resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SilicaFlash F60 (230-400 mesh) or Silica Gel 60 (spherical) NH_2).

II. Materials

L1•HCl, **L4**•HCl, KO^{t}Bu, K_2CO_3, K_2HPO_4, KOAc, K_3PO_4, $ClCONEt_2$, ethynyltriisopropylsilane, ethynylbenzene, 2,4-dimethylpentan-3-one, dibenzophenone, 1-fluoro-4-iodobenzene and all phenols used in the preparation of starting materials were purchased from TCI and used as received. Toluene (for Organic Synthesis) and acetonitrile were purchased from Wako Chemicals and used as received. NaH was purchased from nacalai tesque and used as received. $[RhCl(C_2H_4)_2]_2$,[24] **L2**·HCl, **L3**·HCl,[7(c)] and **L5**·HCl[25] were prepared according to literature procedure. Carbamates **1a** (61912-14-9), **1b** (85630-17-7),[26] **1c** (1025324-83-7),[27] **1e** (85630-39-3),[2(a)] **1f** (2129155-68-4),[7(e)] **1i** (73747-43-0),[28] **1k** (1379516-36-5),[29] **1l** (117902-24-6),[30] **2c** (1174908-08-7),[32] and **2d** (948300-01-4)[32] are known compounds.

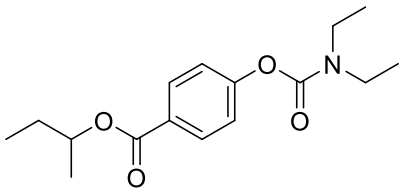
III. Preparation of Starting Materials

General procedure for the preparation of aryl carbamates.



A mixture of corresponding phenol (10.0 mmol), $ClCONEt_2$ (1.62 g, 12.0 mmol) and K_2CO_3 (2.07 g, 14.9 mmol) in CH_3CN (25 mL) was refluxed for 5 h. The reaction mixture was cooled to rt and concentrated under vacuum. The residue was dissolved in H_2O (ca. 50 mL) and extracted with Et_2O (ca. 2 × 20 mL). The organic fractions were combined and then washed successively with aqueous solution of $NaHCO_3$ (1M, ca. 25 mL) and water. The organic layer was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using hexane/EtOAc as a eluent.

***Sec*-Butyl 4-[(diethylcarbamoyl)oxy]benzoate (1d).**



Rf 0.36 (hexane/EtOAc = 5/1). Colorless oil (2.7 g, 92%).

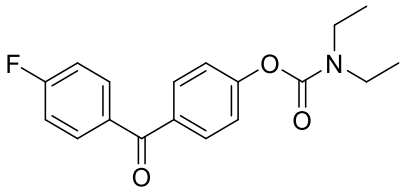
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (dt, *J* = 9.0, 2.3 Hz, 2H), 7.19 (dt, *J* = 9.0, 2.3 Hz, 2H), 5.08 (td, *J* = 12.6, 6.3 Hz, 1H), 3.37-3.47 (m, 4H), 1.61-1.80 (m, 2H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.24 (m, 6H), 0.97 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 155.1, 153.5, 130.9, 127.6, 121.5, 72.8, 42.3, 41.9, 28.9, 19.6, 14.2, 13.3, 9.7.

IR (ATR): 2974 w, 1714 s, 1458 w, 1416 m, 1268 s, 1209 s, 1154 s, 1094 s, 959 w, 760 m.

HRMS (EI): Calcd for $C_{16}H_{23}NO_4$ 293.1627, Found 293.1624.

4-(4-Fluorobenzoyl)phenyl diethylcarbamate (1g).



Rf 0.23 (hexane/EtOAc = 5/1). Colorless solid (2.6 g, 84%).

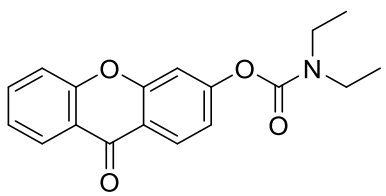
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.86 (m, 4H), 7.24-7.28 (m, 2H), 7.13-7.18 (m, 2H), 3.39-3.49 (m, 4H), 1.21-1.29 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.2, 166. 3 (d, *J* = 252.6 Hz), 155.0, 153.4, 134.1, 133.8 (d, *J* = 2.9 Hz), 132.5 (d, *J* = 9.0 Hz), 131.4, 121.6, 115.4 (d, *J* = 21.9 Hz), 42.4, 42.0, 14.2, 13.3.

IR (ATR): 2942 w, 2864 w, 1722 s, 1648 m, 1599 m, 1469 w, 1420 m, 1273 s, 1227 m, 1210 s, 1152 s, 1115 m, 929 m, 760 m, 668 s.

HRMS (FAB+): Calcd for $C_{18}H_{18}FNO_3$ 315.1272, Found 315.1273.

9-Oxo-9*H*-xanthen-3-yl diethylcarbamate (1h).



Rf 0.14 (hexane/EtOAc = 5/1). White solid (1.3 g, 89%).

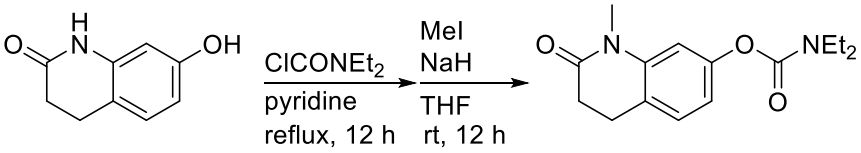
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33-8.35 (m, 2H), 7.72 (ddd, *J* = 8.8, 6.8, 1.2 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.37-7.41 (m, 1H), 7.36 (d, *J* = 1.8 Hz, 1H), 7.17 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.40-3.50 (m, 4H), 1.22-1.31 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.5, 156.9, 156.6, 156.3, 153.0, 134.7, 127.9, 126.7, 124.0, 121.8, 119.0, 118.3, 117. 9, 110.5, 42.5, 42.1, 14.3, 13.3.

IR (ATR): 2940 w, 2866 w, 2360 m, 2340 w, 1723 s, 1663 s, 1608 s, 1463 s, 1418 s, 1318 m, 1270 m, 1245 m, 1227 m, 1152 s, 1102 m, 982 w, 758 m, 667 m.

HRMS (EI): Calcd for $C_{18}H_{17}NO_4$ 311.1158, Found 311.1156.

1-Methyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl diethylcarbamate (1j)



A mixture of 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (1.63 g, 10.0 mmol), $ClCONEt_2$ (1.62 g, 12.0 mmol) in pyridine (20 mL) was refluxed for 12 h. After cooling to rt, 4M HCl was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to yield the corresponding 2-oxo-1,2,3,4-tetrahydroquinolin-7-yl diethylcarbamate (2.1 g, 80%). To a suspension of NaH (60% dispersion in Paraffin liquid, 220 mg, 5.5 mmol) in dry THF (15 mL), a solution of 2-oxo-1,2,3,4-tetrahydroquinolin-7-yl diethylcarbamate (1.31 g, 5.0 mmol) in dry THF (15 mmol) was added dropwise at 0°C and the resulting mixture was stirred for 30 min at rt. MeI (1.7 mL, 5.5 mmol) was then added dropwise to the solution and stirred for 12 h. The volatile components were removed in vacuo and an aqueous solution of $NaHCO_3$ (20 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual solid was purified by column chromatography using hexane/EtOAc = 10/1 to give **1j** (1.1 g, 76%).

Rf 0.03 (hexane/EtOAc = 5/1). White solid (1.1 g, 76%).

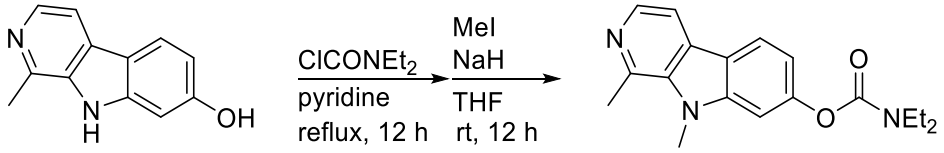
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (d, *J* = 8.7 Hz, 1H), 6.75-6.77 (m, 2H), 3.33 (s, 3H), 3.38-3.47 (m, 4H), 2.88 (t, *J* = 8.0 Hz, 2H), 2.64 (d, *J* = 8.0 Hz, 2H), 1.19-1.28 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 154.0, 150.8, 141.2, 127.9, 122.7, 115.6, 108.9, 42.1, 41.8, 31.6, 29. 5, 24.8, 14.1, 13.3.

IR (ATR): 2973 w, 1713 s, 1675 s, 1611 m, 1471 m, 1415 s, 1354 s, 1258 s, 1207 m, 1185 m, 1153 s, 1127 s, 974 m.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{15}H_{21}N_2O_3$ 277.1547, Found 277.1549.

1,9-Dimethyl-9*H*-pyrido[3,4-b]indol-7-yl diethylcarbamate (1m).



A mixture of Harmol (1.0 g, 5.0 mmol), $ClCONEt_2$ (1.56 g, 10.0 mmol) in pyridine (20 mL) was refluxed for 12 h. After cooling to rt, 4M HCl was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated under vacuum to yield 1-methyl-9*H*-pyrido[3,4-b]indol-7-yl diethylcarbamate (540 mg, 36%). To a suspension of NaH (60% dispersion in Paraffin liquid, 90 mg, 2.25 mmol) in dry THF (15 mL), a solution of 1-methyl-9*H*-pyrido[3,4-b]indol-7-yl diethylcarbamate (446 mg, 1.5 mmol) in dry THF (15 mmol) was added dropwise at 0°C and the resulting mixture was stirred for 30 min at rt. MeI (0.5 mL, 7.5 mmol) was added dropwise to the solution and stirred for 12 h. The volatile components were removed in vacuo and an aqueous solution of $NaHCO_3$ aq. (20 mL) was added to the residue. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual solid was purified by column chromatography using CH_2Cl_2/MeOH = 10/1 to give **1m** (312 mg, 67%).

Rf 0.40 (CH_2Cl_2/MeOH = 5/1). White solid (312 mg, 24%).

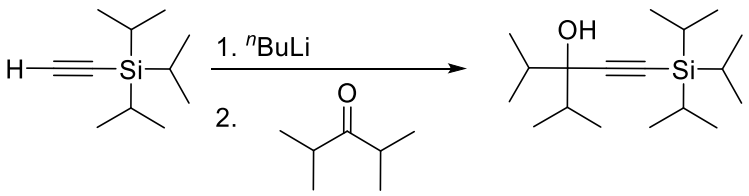
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 5.0 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 5.0 Hz, 1H), 7.24 (d, *J* = 1.8 Hz, 1H), 7.02 (dd, *J* = 8.7, 1.8 Hz, 1H), 4.08 (s, 3H), 3.47 (m, 4H), 3.07 (s, 3H), 1.28 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.3, 152.0, 142.6, 141.5, 138.3, 136.3, 128.6, 121.8, 118.4, 114.2, 112.7, 102.9, 42.3, 41.9, 32.4, 23.6, 14.3, 13.4.

IR (ATR): 2973 w, 1713 s, 1627 w, 1451 m, 1418 m, 1377 w, 1270 m, 1235 m, 1193 s, 1155 s, 1135 m, 970 m.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{18}H_{22}N_3O_2$ 312.1710, Found 312.1713.

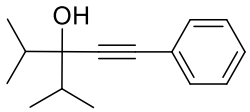
Synthesis of 3-isopropyl-4-methyl-1-(triisopropylsilyl)pent-1-yn-3-ol (2a).



The title compound was synthesized according to Hayashi's procedure.[32] To a solution of (triisopropylsilyl)acetylene (**2b**, 1.82 g, 10.0 mmol) in THF (15.0 mL), ^{n}BuLi (10.0 mmol, 6.25 mL, 1.6 M in hexane) was added dropwise at -78 °C, and the mixture was stirred at -78 °C for 1 h. To the

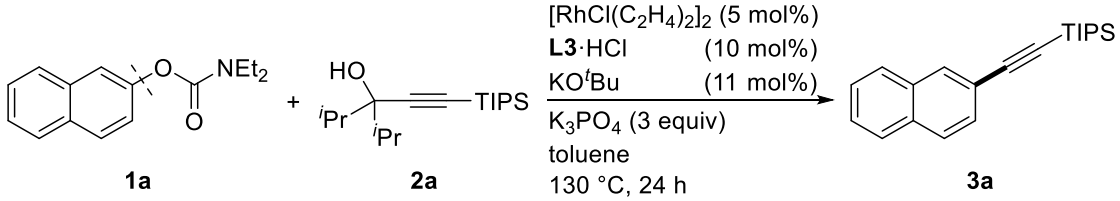
mixture, 2,4-dimethylpentan-3-one (1.14 g, 10.0 mmol) was added dropwise, and the mixture was warmed to room temperature and stirred for 12 h. An aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent followed by flash column chromatography on silica gel (hexane/ether = 100/1) gave **2a** as a colorless oil (2.8 g, 96% yield).
Rf 0.50 (hexane/EtOAc = 5/1). Colorless oil (2.8 g, 96%).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.95 (h, *J* = 6.9 Hz, 2H), 1.71 (s, 1H), 1.08 (m, 21H), 1.05 (d, *J* = 6.9 Hz, 6H), 1.00 (d, *J* = 6.4 Hz, 6H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 109.09, 85.58, 34.26, 18.62, 18.07, 16.26, 11.20.
IR (ATR): 2963 s, 2943 s, 2867 s, 1756 w, 1464 m, 1382 w, 1244 w, 995 s, 954 w, 954 w, 916 w, 883 m, 748 m, 676 s, 661 m.
HRMS (EI): Calcd for $C_{18}H_{36}OSi$ 296.2535, Found 296.2531.

3-Isopropyl-4-methyl-1-phenylpent-1-yn-3-ol (2e).



A procedure for the synthesis of **2a** was followed, except that phenylacetylene was used instead of (triisopropylsilyl)acetylene.
Rf 0.49 (hexane/EtOAc = 5/1). White solid (2.1 g, 98%).
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.45 (m, 2H), 7.28-7.32 (m, 3H), 2.04 (h, *J* = 6.9 Hz, 2H), 1.82 (s, 1H), 1.10 (d, *J* = 6.9 Hz, 6H), 1.05 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ131.7, 128.2, 128.1, 123.0, 90.6, 85.5, 34.5, 18.2, 16.3.
IR (ATR): 2968 m, 1490 w, 1468 w, 1382 w, 1344 w, 1307 w, 1147 w, 976 s, 954 m, 755 s, 690 s.
HRMS (EI, [M+Na^+]): $C_{15}H_{20}ONa$ 239.1412, Found 239.1416.

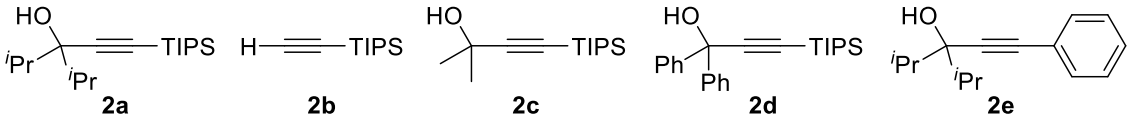
IV. Optimization Studies



1a **2a** **3a**

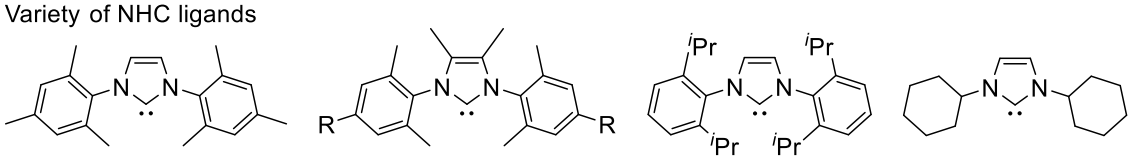
Entry	Variation from above	GC Yields [%]		
		3a	**1a**	**2**
1	none	75 (74)	0	0
2	**2b** instead of **2a**	18	12	trace
3	**2c** instead of **2a**	35	15	0
4	**2d** instead of **2a**	25	9	trace
5	**2e** instead of **2a**	0	>95	0
6	KOAc instead of K_3PO_4	23	39	0
7	K_2CO_3 instead of K_3PO_4	47	trace	0
8	K_2HPO_4 instead of K_3PO_4	28	trace	0
9	**L1** instead of **L3**	20	3	0
10	**L2** instead of **L3**	53	2	0
11	**L4** instead of **L3**	trace	68	0
12	**L5** instead of **L3**	12	47	trace
13	2.0 equiv. of **L3**	73	0	0
14	$[RhCl(cod)]_2$ instead of $[RhCl(C_2H_4)_2]_2$	trace	>95	>95

Variety of Alkynes



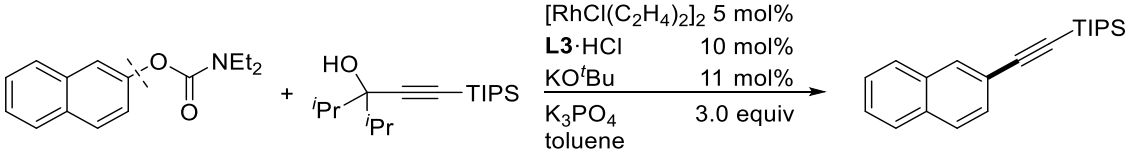
2a **2b** **2c** **2d** **2e**

Variety of NHC ligands



L1 R = Me **L2** R = OMe **L3** **L4** **L5**

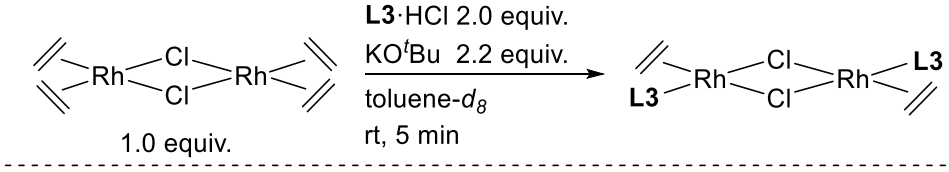
V. Typical Procedure for Rh-Catalyzed C-O Bond Alkynylation Using a Propargyl Alcohol



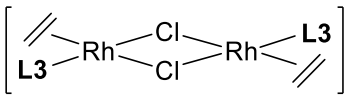
1a **2a** **3a**

$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L3**·HCl (12.0 mg, 0.030 mmol), KO^{t}Bu (3.7 mg, 0.033 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at rt for 5 min. K_3PO_4 (190 mg, 0.90 mmol), **1a** (73 mg, 0.30 mmol), **2c** (133.3 mg, 0.45 mmol), and toluene (0.60 mL) were added to the vial. The vessel was stirred at 130 °C for 24 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (hexane/EtOAc = 100/1) to give **3a** as a colorless oil (68 mg, 74%).

VI. Observation of Rhodium Complex Generated in Situ



Rhodium species generated in situ and characteristic spectrum

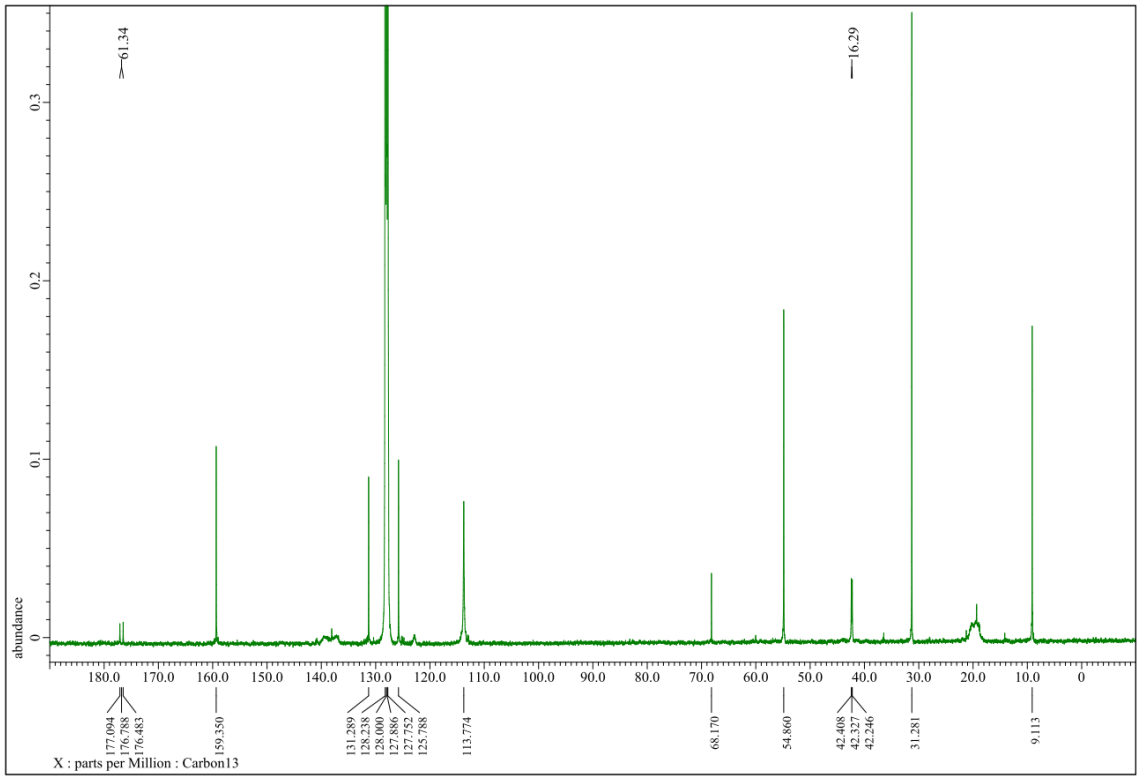


HRMS : 1004.1920, Found: 1004.1926.
(loss of two ethylene molecules)
^{13}C NMR : 159.7 (d, *J* (Rh,C)= 63.3 Hz, *C*-carbene)
42.4 (d, *J* (Rh,C)= 16.2 Hz, η^2-*C*H=*C*H)

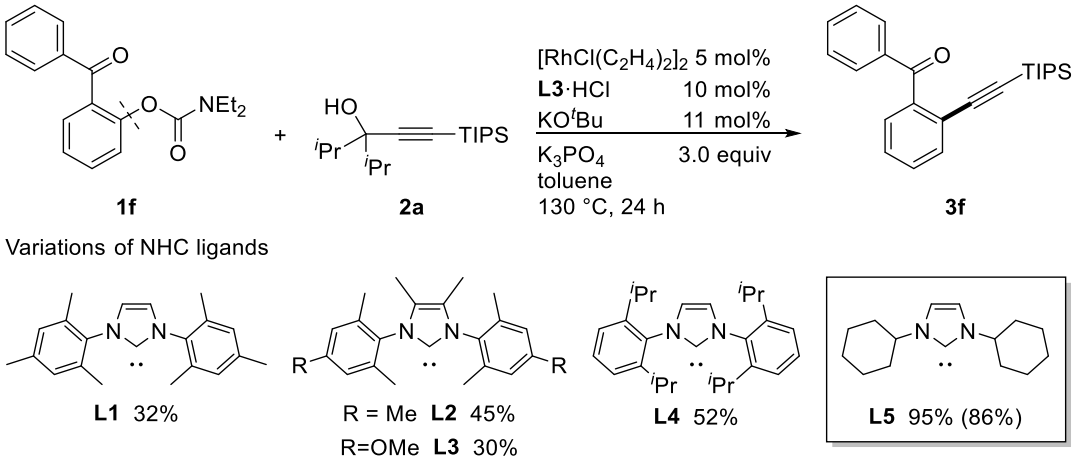
$[RhCl(C_2H_4)_2]_2$ (11.6 mg, 0.030 mmol), **L3**·HCl (24.0 mg, 0.060 mmol), KO^{t}Bu (7.4 mg, 0.066 mmol), and C_6D_6 (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at rt for 5 min. After stirring, the obtained solution was used for NMR analysis and HRMS. The spectra of this solution are analogous to those of related complexes.[13]

^{13}C NMR (C_6D_6, 100 MHz): δ 176.8 (d, $J_{Rh,C}$ = 61.3 Hz), 159.4, 131.3, 125.8, 113.8, 68.2, 54.9, 42.3 (d, $J_{Rh,C}$ = 16.3 Hz), 31.3, 9.1.

HRMS (FAB+): Calcd for $C_{47}H_{58}Cl_2N_4O_4Rh_2$ 1004.1920, Found 1004.1926.



VII. Optimization for *ortho* Functionalized Aryl Carbamates



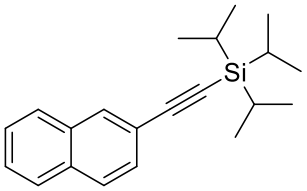
Alkynylation of **1f** with **2a** proceeded to form **3f** in only 30% yield under our optimal conditions using **L3** as a ligand. We therefore reoptimized the conditions for this specific substrate. After a brief screening of the ligand, **L5** proved to be the best ligand to provide **3f** in 86% isolated yield. These conditions were found to be effective for the alkynylation of other sterically hindered substrates. A typical procedure is as follows:

$[RhCl(C_2H_4)_2]_2$ (5.8 mg, 0.015 mmol), **L5**·HCl (0.030 mmol, 7.9 mg), KO^{t}Bu (3.7 mg, 0.033 mmol), and toluene (0.40 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at rt for 5 min. After the period, K_3PO_4 (190 mg, 0.90 mmol), **1f** (73

mg, 0.30 mmol), **2c** (133.3 mg, 0.45 mmol), and toluene (0.60 mL) were added to the vial. The vessel was stirred at 130 °C for 24 h followed by cooling to rt. The mixture was purified by flash column chromatography over silica gel (hexane/EtOAc = 100/1) to give **3f** as a colorless oil (94 mg, 86%).

VIII. Spectroscopic Data of Products

Triisopropyl(naphthalen-2-ylethynyl)silane (3a) [CAS: 1644532-86-4].



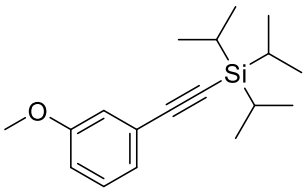
Rf 0.58 (hexane/EtOAc = 5/1). Colorless oil (68 mg, 74%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 1H), 7.75-7.81 (m, 3H), 7.45-7.53 (m, 3H), 1.16 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 133.0, 132.9, 131.9, 128.9, 127. 9, 127.81, 127.80, 126.7, 126.6, 120.9, 107.5, 91.0, 18.8, 11.5.

HRMS (EI): Calcd for $C_{21}H_{28}Si$ 308.1960, Found 308.1962.

Triisopropyl[(3-methoxyphenyl)ethynylsilane] (3b) [CAS: 889361-55-1].



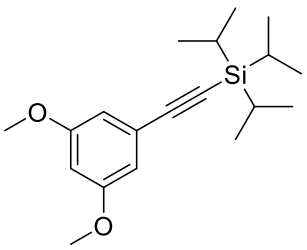
Rf 0.63 (hexane/EtOAc = 5/1). Colorless oil (48 mg, 56%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (t, *J* = 7.9 Hz, 1H), 7.08 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.99 (q, *J* = 1.3 Hz, 1H), 6.87 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 3.81 (s, 3H), 1.13 (s, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 129.2, 124.7, 116. 8, 114. 9, 107.0, 99.9, 90.3, 55.3, 18.7, 11.3.

HRMS (EI): Calcd for $C_{18}H_{28}OSi$ 288.1909, Found 288.1913.

[(3,5-Dimethoxyphenyl)ethynyl]triisopropylsilane (3c) [CAS: 909730-04-7].



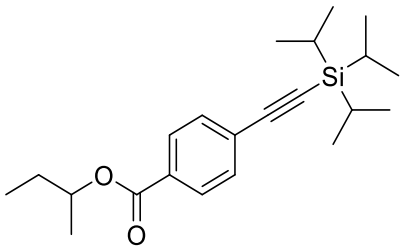
Rf 0.54 (hexane/EtOAc = 5/1). Colorless oil (69 mg, 71%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.62 (d, *J* = 2.3 Hz, 2H), 6.43 (t, *J* = 2.3 Hz, 1H), 3.77 (s, 6H), 1.13 (s, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.4, 124.8, 109.8, 107.0, 101.8, 90.1, 55.4, 18.7, 11.3.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{19}H_{31}O_2Si$ 319.2088, Found 319.2088.

***sec*-Butyl 4-[(triisopropylsilyl)ethynyl]benzoate (3d).**



Rf 0.69 (hexane/EtOAc = 5/1). Colorless oil (73 mg, 68%).

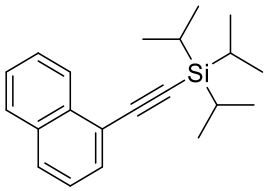
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.51 (dt, *J* = 8.3, 1.7 Hz, 2H), 5.09 (td, *J* = 12.5, 6.2 Hz, 1H), 1.62-1.80 (m, 2H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.10-1.17 (m, 21H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7, 131.8, 130.3, 129.3, 127.9, 106.2, 94.1, 73.1, 28.9, 19.5, 18.6, 11.7, 9.7.

IR (ATR): 2942 w, 2866 w, 1717 s, 1604 w, 1462 w, 1270 s, 1173 w, 1093 m, 1017 w, 995 w, 883 m, 858 m, 769 m, 676 s.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{22}H_{35}O_2Si$ 359.2401, Found 359.2401.

Triisopropyl(naphthalen-1-ylethynyl)silane (3e) [CAS: 864227-70-3].



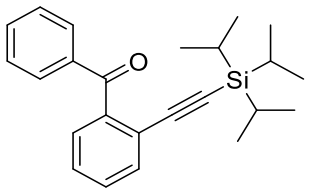
Rf 0.58 (hexane/EtOAc = 5/1). Colorless oil (69 mg, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.39 (d, *J* = 8.7 Hz, 1H), 7.82 (t, *J* = 8.9 Hz, 2H), 7.72 (dd, *J* = 7.1, 1.1 Hz, 1H), 7.57 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.50 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.40 (dd, *J* = 8.2, 7.3 Hz, 1H), 1.19-1.20 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 133.5, 133. 1, 131. 0, 128.7, 128.2, 126.8, 126.32, 126.27, 125.1, 121.2, 104.9, 95.8, 18.8, 11.4.

HRMS (EI): Calcd for $C_{21}H_{28}Si$ 308.1960, Found 308.1958.

Phenyl(2-((triisopropylsilyl)ethynyl)phenyl)methanone (3f) [CAS: 2107429-99-0].



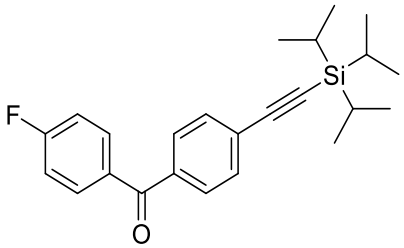
Rf 0.59 (hexane/EtOAc = 5/1). Colorless oil (94 mg, 86%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.84 (m, 2H), 7.56 (dt, *J* = 6.9, 2.4 Hz, 1H), 7.53 (dt, *J* = 7.3, 1.6 Hz, 1H), 7.40-7.46 (m, 5H), 0.88-0.91 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.0, 142.4, 136.8, 133.2, 133. 1, 130.3, 129.6, 128.3, 128.3, 127.6, 121.5, 104.0, 97.1, 18.4, 11.02.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{24}H_{31}OSi$ 363.2139, Found 363.2145.

(4-Fluorophenyl){4-[(triisopropylsilyl)ethynyl]phenyl}methanone (3g).



Rf 0.53 (hexane/EtOAc = 5/1). Colorless oil (81 mg, 71%).

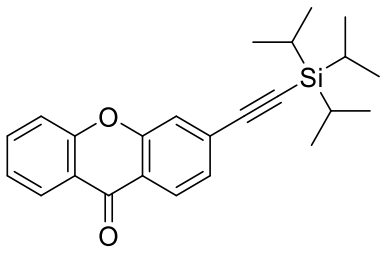
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.84 (m, 2H), 7.71 (dt, *J* = 8.2, 1.7 Hz, 2H), 7.58 (dt, *J* = 8.2, 1.7 Hz, 2H), 7.13-7.19 (m, 2H), 1.14-1.15 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.5, 166.4 (d, *J* = 253.1 Hz), 136.7, 133.6 (d, *J* = 3.4 Hz), 132.6 (d, *J* = 9.1 Hz), 131.9, 129.7, 127.8, 115.5 (d, *J* = 21.4 Hz), 106.0, 94.7, 18.6, 11.3.

IR (ATR): 2943 m, 2666 m, 1661 s, 1600 s, 1463 w, 1306 m, 1274 s, 1236 m, 1156 w, 928 m, 858 w, 768 m, 677 m.

HRMS (EI): Calcd for $C_{24}H_{29}FOSi$ 380.1972, Found 380.1968.

3-[(Triisopropylsilyl)ethynyl]-9*H*-xanthen-9-one (3h).



Rf 0.52 (hexane/EtOAc = 5/1). Colorless oil (84 mg, 74%).

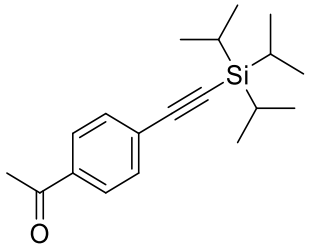
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.73 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.60 (d, *J* = 1.1 Hz, 1H), 7.48 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.44 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.39 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 1.15-1.17 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.6, 156.2, 155.8, 135.0, 130.0, 127.4, 126.7, 126.6, 124.1, 121.9, 121.3, 121.3, 118.0, 105.4, 96.1, 18.6, 11.2.

IR (ATR): 2943 w, 2865 w, 2360 w, 1666 s, 1607 s, 1464 s, 1418 s, 1316 w, 971 w, 881 w, 759 m, 668 s.

HRMS (FAB-, [M^-]): Calcd for $C_{24}H_{28}O_2Si$ 376.1859, Found 376.1855.

1-{4-[(Triisopropylsilyl)ethynyl]phenyl}ethan-1-one (3i) [CAS: 480423-11-8].



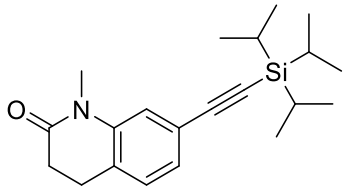
Rf 0.56 (hexane/EtOAc = 5/1). Colorless oil (58 mg, 64%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (dt, *J* = 8.2, 1.8 Hz, 2H), 7.55 (dt, *J* = 8.2, 1.8 Hz, 2H), 2.60 (s, 3H), 1.13-1.14 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.2, 136.2, 132.1, 128.3, 128.1, 106.0, 94.7, 26.6, 18.6, 11.2.

HRMS (EI): Calcd for $C_{19}H_{28}OSi$ 300.1909, Found 300.1905.

1-Methyl-7-[(triisopropylsilyl)ethynyl]-3,4-dihydroquinolin-2(1H)-one (3j).



Rf 0.19 (hexane/EtOAc = 5/1). Colorless oil (60 mg, 59%).

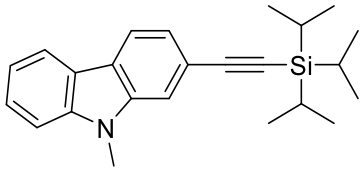
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 0.9 Hz, 1H), 3.36 (s, 3H), 2.88-2.92 (m, 2H), 2.61-2.66 (m, 2H), 1.13 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 140.5, 127.6, 126.7 (two overlapping peaks), 122.7, 117.8, 106.6, 90.7, 31.5, 29.6, 25.4, 18.7, 11.3.

IR (ATR): 2942 m, 2864 w, 1682 s, 1605 m, 1567 w, 1510 w, 1463 m, 1420 m, 1354 m, 1332 m, 1268 w, 1202 w, 1129 m, 993 w, 882 w, 676 m, 660 m.

HRMS (FAB-, [M^-]): Calcd for $C_{21}H_{30}NOSi$ 340.2097, Found 340.2098.

9-Methyl-2-[(triisopropylsilyl)ethynyl]-9*H*-carbazole (3k) [CAS: 1644533-06-1].



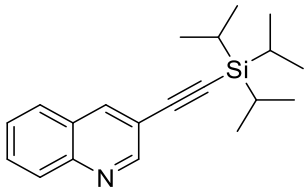
Rf 0.24 (hexane/EtOAc = 20/1). Colorless oil (78 mg, 72%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.47-7.53 (m, 2H), 7.35-7.41 (m, 2H), 7.23 (m, 1H), 3.86 (s, 3H), 1.17 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.7, 140. 6, 126.3, 123.3, 123.0, 122.6, 120.7, 120.4, 120.15, 119.3, 112.2, 108.7, 108.6, 89.8, 29.3, 18.9, 11.5.

HRMS (EI): Calcd for $C_{24}H_{31}NSi$ 361.2226, Found 361.2232.

3-[(Triisopropylsilyl)ethynyl]quinoline (3l) [CAS: 2107430-12-4].



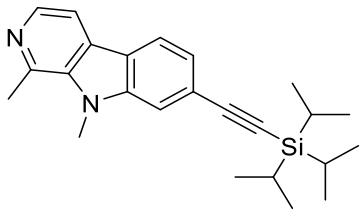
Rf 0.52 (EtOAc). Colorless oil (70 mg, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.92 (d, *J* = 2.3 Hz, 1H), 8.26 (d, *J* = 1.6 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.78 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.713 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.56 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 1.17 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 13C-NMR (101 MHz, CHLOROFORM-D) δ 152.5, 146.8, 138.8, 130.0, 129.4, 127.5, 127.2, 127.1, 117.6, 104.0, 94.8, 18.7, 11.3.

HRMS (EI): Calcd for $C_{20}H_{27}NSi$ 309.1913, Found 309.1914.

1,9-Dimethyl-7-[(triisopropylsilyl)ethynyl]-9*H*-pyrido[3,4-b]indole (3m).



Rf 0.29 (CH_2Cl_2/MeOH = 10/1). White solid (77 mg, 68%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (d, *J* = 5.0 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 5.0 Hz, 1H), 7.53 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 4.09 (s, 3H), 3.07 (s, 3H), 1.15-1.22 (m, 21H).

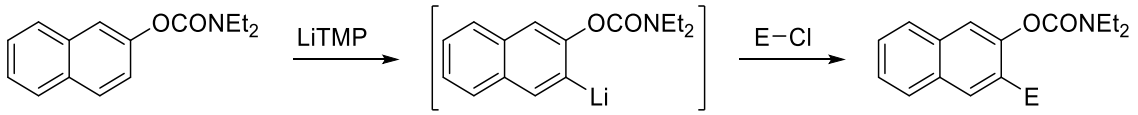
^{13}C NMR ($CDCl_3$, 150 MHz): δ 141.9, 141.5, 138.3, 136.4, 128.3, 123.6, 122.8, 121.1, 121.0, 113.0, 112.9, 107.8, 91.1, 32.2, 23.7, 18.7, 11.4.

IR (ATR): 2942 m, 2864 m, 2360 w, 2156 w, 1620 w, 1567 w, 1451 s, 1400 w, 1290 w, 1236 m, 943 m, 882 m, 808 s, 745 m, 677 s, 658 s.

HRMS (EI): Calcd for $C_{24}H_{32}N_2Si$ 376.2335, Found 367.2330.

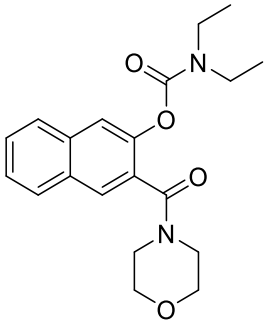
XI. Synthetic Application

General procedure for *orhto* functionalized carbamates 1n-1p.



Carbamates **1n-1p** were synthesized according to the Snieckus' procedure.[33] Under a nitrogen atmosphere, 3.0 equivalents of ^{n}BuLi (1.5 M in hexanes, 10 mL) were added to a pre-cooled solutin (0 °C) of TMP (18.5 mL, 15.0 mmol) in THF (25 mL), and the resulting mixture was stirred for 15 min. The solution of LiTMP was slowly added via cannula to a solution of **1a** (1.2 g, 5.0 mmol) in THF (25 mL) at –78 °C, whilst keeping the internal temperature of the solution below –73 °C. After stirring at –73 °C for 1.5 h, the corresponding electrophile (15.0 mmol) was added quickly. The resulting mixture was stirred at –78 °C for 2 h and for additional 12 h at room temperature. The reaction mixture was then quenched with a saturated NH_4Cl solution and extracted with Et_2O (3 × 20 mL), affording the crude product. The mixture was purified by flash column chromatography over silica gel (hexane/EtOAc) to give **1p** or **1q**.

3-(Morpholine-4-carbonyl)naphthalen-2-yl diethylcarbamate (1p).



Morpholine-4-carbonyl chloride (2.1 g, 15.0 mmol) was used as the electrophile in the typical procedure.

Rf 0.4 (EtOAc). Colorless oil (1.4 g, 76%).

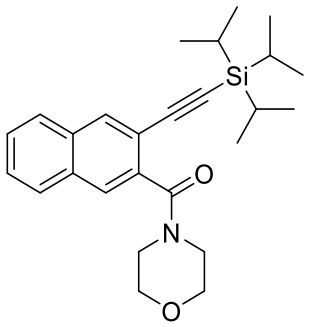
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (t, *J* = 8.9 Hz, 2H), 7.75 (s, 1H), 7.68 (s, 1H), 7.46-7.54 (m, 2H), 3.72-3.86 (m, 4H), 3.60 (t, *J* = 4.8 Hz, 2H), 3.39-3.50 (m, 6H), 1.26 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.0, 153.8, 145.4, 134.0, 130.5, 128.8, 127.8, 127.5, 127.3, 127.0, 126.1, 120.4, 66. 9, 66.8, 47. 8, 42.4, 42.15, 42.11, 14.2, 13.5.

IR (ATR): 2968 w, 1715 s, 1614 m, 1474 w, 1420 s, 1381 w, 1276 s, 1237 m, 1214 s, 1167 m, 1152 m, 1116 m, 749 s.

HRMS FAB+, [M+H$^+$]): Calcd for $C_{20}H_{25}N_2O_4$ 357.1814, Found 357.1820.

Morpholino{3-[(triisopropylsilyl)ethynyl]naphthalen-2-yl}methanone (3p).



A procedure for alkynylation of **1f** using **L5** was followed.

Rf 0.13 (hexane/EtOAc = 5/1). Colorless oil (102 g, 81%).

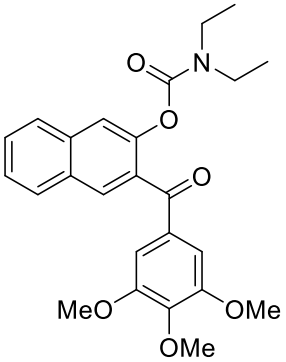
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (s, 1H), 7.79-7.83 (m, 2H), 7.77 (s, 1H), 7.50-7.55 (m, 2H), 4.12 (m, 1H), 3.20-3.88 (m, 7H), 1.15 (s, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 135.4, 133.4, 132.7, 132.4, 128.0, 127.53, 127.50, 127.4, 126.0, 117.7, 104.1, 94.5, 66.9, 66.8, 47.3, 42.1, 18.7, 11.3.

IR (ATR): 2942 m, 2863 m, 2151 w, 1642 s, 1467 m, 1423 m, 1277 m, 1255 m, 1211 w, 1117 s, 1068 w, 1007 m, 883 m, 733 s, 676 s.

HRMS (EI): Calcd for $C_{26}H_{35}NO_2Si$ 421.2437, Found 421.2430.

3-(3,4,5-Trimethoxybenzoyl)naphthalen-2-yl diethylcarbamate (1q).



3,4,5-Trimethoxybenzoyl chloride (3.5 g, 15 mmol) was used as the electrophile in the typical procedure.

Rf 0.06 (hexane/EtOAc = 5/1). Colorless oil (1.5 g, 70%).

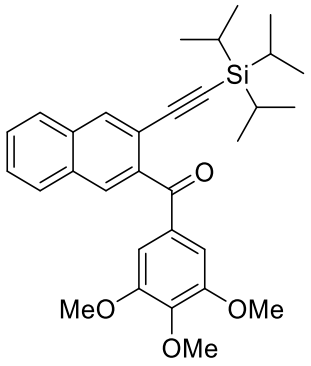
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.58 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.51 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.13 (s, 2H), 3.92 (s, 3H), 3.84 (s, 6H), 3.24 (q, *J* = 7.2 Hz, 2H), 3.15 (q, *J* = 7.2 Hz, 2H), 1.04-1.07 (m, 3H), 1.01-1.03 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.0, 153.4, 152.9, 146.1, 142.3, 134.8, 132.9, 131.8, 130.6, 130.3, 128.5, 127.9, 127.5, 126.2, 120.5, 107.2, 60.9, 56.2, 42.2, 41.7, 13.9, 13.2.

IR (ATR): 2938 w, 1925 w, 1716 s, 1661 w, 1582 m, 1501 w, 1459 m, 1414 s, 1334 s, 1273 m, 1233 m, 1200 m, 1163 s, 1134 s, 1100 w, 750 m.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{25}H_{28}NO_6$ 438.1917, Found 438.1925.

{3-[(Triisopropylsilyl)ethynyl]naphthalen-2-yl}(3,4,5-trimethoxyphenyl)methanone (3q).



A procedure for alkynylation of **1f** using **L5** was followed.

Rf 0.20 (hexane/EtOAc = 5/1). Colorless oil (125 mg, 83%).

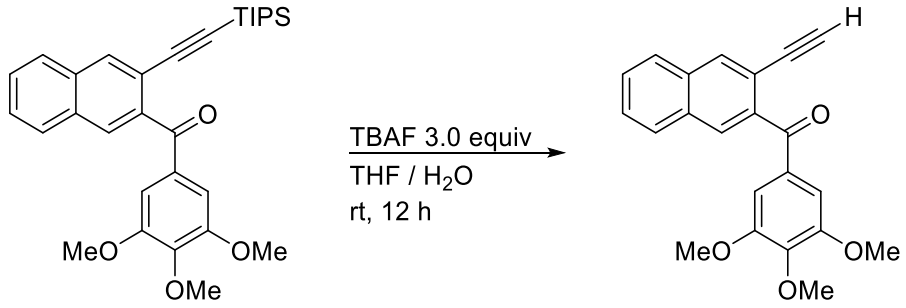
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H), 7.91 (s, 1H), 7.86-7.89 (m, 2H), 7.54-7.61 (m, 2H), 7.12 (s, 2H), 3.91 (s, 3H), 3.81 (s, 6H), 0.91-0.97 (m, 21H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.8, 152.9, 142.8, 139.2, 133.29, 133.27, 132.3, 132.2, 128.4, 127.80, 127.77, 127.59, 127.55, 118.5, 107.9, 104.4, 96.4, 60.8, 56.2, 18.5, 11.1.

IR (ATR): 2941 w, 2864 w, 1665 w, 1582 m, 1502 w, 1461 m, 1414 m, 1332 s, 1233 w, 1128 s, 1004 w, 747 m.

HRMS (EI): Calcd for $C_{31}H_{38}O_4Si$ 502.2539, Found 502.2541.

(3-Ethynylnaphthalen-2-yl)(3,4,5-trimethoxyphenyl)methanone (3q').



THF (20 mL) and water (1.0 mL) were added to **3q** (530 mg, 1.1 mmol) and TBAF (381 mg, 3.2 mmol), and the mixture was stirred at room temperature for 12 h. After all volatiles were removed in vacuo, the resulting mixture was partitioned between CH_2Cl_2 and water. The organic layer was washed with brine and water, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to give **3q'** as a white solid (337 mg, 97%).

Rf 0.17 (hexane/EtOAc = 4/1). Colorless oil (337 mg, 97%).

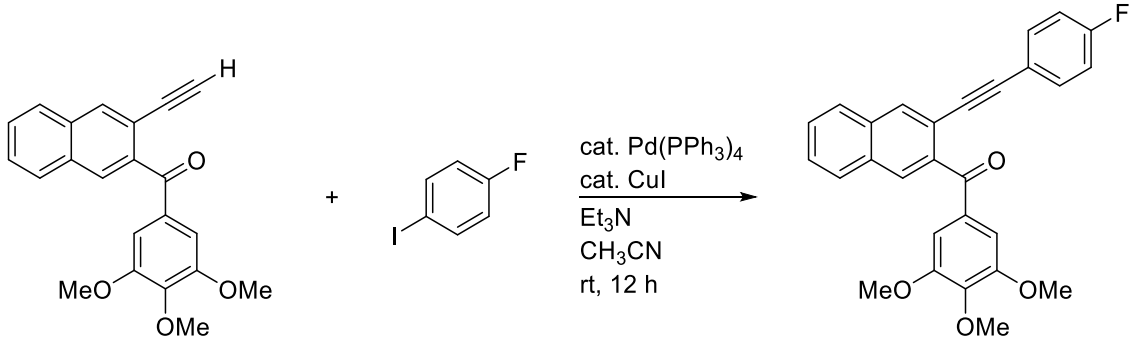
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 1H), 7.94 (s, 1H), 7.86-7.89 (m, 2H), 7.56-7.64 (m, 2H), 7.14 (s, 2H), 3.95 (s, 3H), 3.84 (s, 6H), 3.14 (s, 1H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.0, 152.9, 142.9, 138.2, 134.3, 133.4, 132.3, 131.8, 128.8, 128.5, 128.2, 127.9, 127.7, 117.7, 108.0, 81.5, 61.0, 56.3.

IR (ATR): 1662 w, 1581 w, 1502 w, 1460 w, 1413 w, 1332 s, 1231 m, 1226 s, 1001 w, 749 w.

HRMS (EI): Calcd for $C_{22}H_{18}O_4$ 346.1205, Found 346.1207.

{3-[(4-Fluorophenyl)ethynyl]naphthalen-2-yl}(3,4,5-trimethoxyphenyl)methanone (4).



Alkyne **3q'** (173 mg, 0.5 mmol), 1-fluoro-4-iodobenzene (133 mg, 0.6 mmol), $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol), and CuI (3.0 mg, 0.015 mmol) were dissolved in a degassed solution of CH_3CN (5.0 mL) and Et_3N (0.2 mL), and the mixture was stirred at rt for 12 h under an atmosphere of nitrogen. After removal of the solvent in vacuo, the residue was filtered through a Celite pad. The filtrate was concentrated to give a residue, which was purified by flash chromatography on silica gel (hexane/EtOAc = 4/1) to give **4** (202 g, 92%) as a white solid.

Rf 0.17 (hexane/EtOAc = 5/1). White solid (202 mg, 92%).

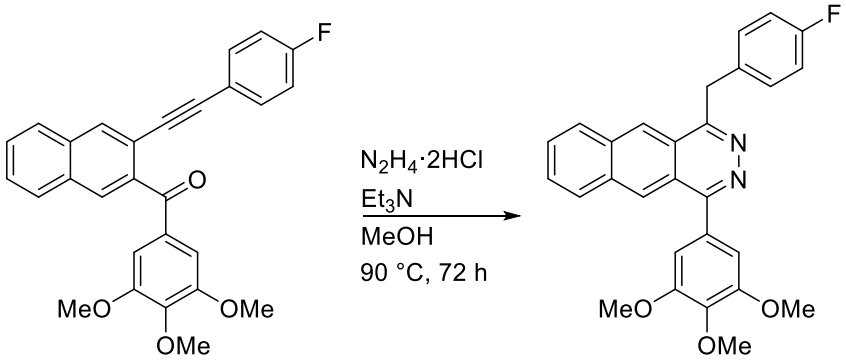
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (s, 1H), 8.03 (s, 1H), 7.89-7.91 (m, 2H), 7.56-7.63 (m, 2H), 7.18 (m, 4H), 6.95 (t, *J* = 8.7 Hz, 2H), 3.91 (s, 3H), 3.83 (s, 6H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.5, 162.6 (d, *J* = 250.2 Hz), 161.7, 153.0, 142.7, 138.2, 133.5 (d, *J* = 8.1 Hz), 133.3, 132.76, 132.74, 131.88, 129.23, 128.64, 128.20, 127.63, 118.9 (d, *J* = 3.0 Hz), 118.60, 115.5 (d, *J* = 22.0 Hz), 107.95, 93.17, 87.55, 60.95, 56.37.

IR (ATR): 1658 w, 1582 w, 1505 m, 1459 s, 1413 m, 1332 s, 1231 m, 1126 s, 1002 w, 912 m, 837 w, 744 m.

HRMS (EI): Calcd for $C_{28}H_{21}FO_4$ 440.1424, Found 440.1421.

1-(4-Fluorobenzyl)-4-(3,4,5-trimethoxyphenyl)benzo[g]phthalazine (5).



Phthalazine **5** was synthesized according to Dong's procedure.[21] Et_3N (3.0 mmol, 0.4 mL) was added to a solution of **4** (0.15 mmol, 66 mg) and hydrazine hydrochloride (5 equiv, 0.75 mmol, 79 mg) in methanol (2 mL). The resulting mixture was then stirred under 90 °C for 72 h. After cooling to room temperature, water was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated to give a yellow residue, which was further purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 10/1) to afford **5** (51 mg, 75%) as a white solid.

Rf 0.31 (CH_2Cl_2/MeOH = 10/1). Colorless oil (51 mg, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.71 (s, 1H), 8.68 (s, 1H), 8.04-8.10 (m, 2H), 7.63-7.70 (m, 2H), 7.44 (m, 2H), 7.08 (s, 2H), 6.96-7.02 (m, 2H), 4.84 (s, 2H), 3.99 (s, 3H), 3.93 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.7 (d, *J* = 244.9 Hz), 159.7, 158.2, 153.4, 139.2, 134.6, 134.5, 134.1 (d, *J* = 2.4 Hz), 132.0, 130.2 (d, *J* = 7.7 Hz), 129.1, 128.9, 128.4 (d, *J* = 20.1 Hz), 127.7, 125.0, 122.8, 122.7, 115.6, 115.4, 107.6, 61.0, 56.4, 39.5.

IR (ATR): 2934 w, 1585 m, 1507 s, 1412 m, 1414 m, 1379 m, 1233 m, 1127 s, 1009 w, 838 w, 756 m.

HRMS (EI): Calcd for $C_{28}H_{23}FN_2O_3$ 454.1693, Found 454.1693.

2-2.5 References

(1) (a) *Acetylene Chemistry*; Diederich, F.; Stang, P. J.; Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005. A themed issue on click chemistry: (b) Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1231 and articles therein. A review on alkyne metathesis: (c) Zhang, W.; Moore, J. S. *Adv. Synth. Catal.* **2007**, *349*, 93. A review on cycloisomerization using alkynes: d) Lee, S. I.; Chatani, N. *Chem. Comm.* **2009**, *45*, 371.

(2) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16* 4467. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (c) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954. (d) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

(3) (a) *Synthetic and Natural Phenols*; Tyman, J. H. P., Ed.; Elsevier: Amsterdam, 1996; b) *The Chemistry of Phenols*; Rappoport, Z.; Ed.; Wiley: Chichester, 2003.

(4) Reviews on cross-coupling with inert phenol derivatives: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (b) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem. Eur. J.* **2011**, *17*, 1728. (c) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19. (d) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081. (e) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717.

(5) Our works on inert C-O bond activation using a nickel catalyst: (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4866. (b) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett.* **2009**, *38*, 710. (c) Shimasaki, T.; Konno, Y.; Tobisu, M.; Chatani, N.*Org*. *Lett.* **2009**, *11*, 4890. (d) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 2929. (e) Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Chem. Commun.* **2011**, *47*, 2946 (f) Tobisu, M.; Yasutome, A.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Tetrahedron* **2012**, *68*, 5157. (g) Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N *Org. Lett.* **2014**, *16*, 5572. (h) Tobisu, M.; Takahira, T.; Ohtsuki, A.; Chatani, N. *Org. Lett.* **2015**, *17*, 680. (i) Tobisu, M.; Takahira, T.; Chatani, N. *Org. Lett.* **2015**, *17*, 4352. (j) Tobisu, M.; Morioka, T.; Ohtsuki, A.; Chatani, N. *Chem. Sci.* **2015**, *6*, 3410. (k) Morioka, T.; Nishizawa, A.; Nakamura, K.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 1729. (l) Nakamura, K.; Tobisu, M.; Chatani, N. *Org. Lett.* **2015**, *17*, 6142. (m) Tobisu, M.; Takahira, T.; Morioka, T.; Chatani N. *J. Am. Chem. Soc.* **2016**, *138*, 6711. (n) Ohtsuki, A.; Sakurai, S.; Tobisu, M.; Chatani, N. *Chem*. *Lett.* **2016**, *45*, 1277. (o) Ohtsuki, A.; Yanagisawa, K.; Furukawa, T.; Tobisu, M.; Chatani, N. *J. Org. Chem.* **2016**, *81*, 9409. (p) Schwarzer, M.; Konno, R.; Hojo, T.; Ohtsuki, A.; Nakamura, K.; Yasutome, A.; Takahashi, H.; Shimasaki, T.; Tobisu, M.; Chatani, N.; Mori S. *J. Am. Chem. Soc.* **2017**, *139*, 10347.

(6) Notable exceptions: [Fe catalyst] (a) Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.;

Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656. (b) Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2012**, *14*, 3796. [Co catalyst] (c) Song, W.; Ackermann, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8251.

(7) Our works on inert C-O bond activation using a rhodium catalyst: (a) Kinuta, H.; Hasegawa, J.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 366. (b) Nakamura, K.; Yasui, K.; Tobisu, M.; Chatani, N. *Tetrahedron* **2015**, *71*, 4484. (c) Kinuta, H.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 1593. (d) Tobisu, M.; Yasui, K.; Aihara, Y.; Chatani, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 1877. (e) Yasui, K.; Higashino, M.; Chatani, N.; Tobisu, M. *Synlett* **2017**, *28*, 2569.

(8) Ogawa, H.; Yang, Z.-K.; Minami, H.; Kojima, K.; Saito, T.; Wang, C.; Uchiyama, M. *ACS Catal.* **2017**, *7*, 3988.

(9) Wang, Y.; Wu, S.-B.; Shi, W.-J.; Shi, Z.-J. *Org. Lett.* **2016**, *18*, 2548.

(10) Palladium-catalyzed alkynylation of aryl *halides* using propargyl alcohols: (a) Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910. (b) Hu, H.; Yang, F.; Wu, Y. *J. Org. Chem.* **2013**, *78*, 10506.

(11) Selected examples of generation of alkynylrhodium complexes via □-carbon elimination of propargyl alcohols: (a) Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2005**, *127*, 15354. (b) Horita, A.; Tsurugi, H.; Funayama, A.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 2231. (c) Nishimura, T.; Guo, X.-X.; Ohnishi, K.; Hayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 2669. (d) Nishimura, T.; Katoh, T.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14158. (e) Shintani, R.; Takatsu, K.; Katoh, T.; Nishimura, T.; Hayashi, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 1447. (f) Xia, Y.: Feng, S.; Liu, Z.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 7891. (g) Dou, X.; Huang, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 1133.

(12) Rubio-Perez, L.; Azpiroz, R.; Di Giuseppe, A.; Polo, V.; Castarlenas, R.; Perez-Torrente, J. J.; Oro, L. A. *Chem. Eur. J.* **2013**, *19*, 15304.

(13) Related $[RhCl(NHC)(C_2H_4)]_2$ complexes: (a) Zenkina, O. V.; Keske, E. C.; Wang, R.; Crudden, C. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8100. (b) Zenkina, O. V.; Keske, E. C.; Wang, R.; Crudden, C. M. *Organometallics* **2011**, *30*, 6423.

(14) (a) Takise, R.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2014**, *53*, 6791. (b) Cornella, J.; Jackson, E. P.; Martin R. *Angew. Chem. Int. Ed.* **2015**, *54*, 4075. (c) Koch, E.; Takise, R.; Studer, A.; Yamaguchi, J.; Itami K. *Chem. Commun.*, **2015**, *51*, 855.

(15) Kerr, W. J.; Reid, M.; Tuttle, T. *ACS Catal.* **2015**, *5*, 402.

(16) Selected examples: (a) Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 17978. (b) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, *44*, 1437. (c) Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan,

B.-T.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 10124. (d) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J.Am.Chem.Soc.* **2011**, *133*, 19505.

(17) Bálint, B.; Wéber, C.; Cruzalegui, F.; Burbridge, M.; Kotschy, A. *ChemMedChem* **2017**, *12*, 932. (b) Bain, J.; Plater, L.; Elliott, M.; Shpiro, N.; Hastie, C. J.; McLauchlan, H.; Klevernic, I.; Arthur, J. S.; Alessi, D. R.; Cohen, P. *J. Biochem.* **2007**, *408*, 297. (c) Miralles, A.; Esteban, S.; Sastre-Coll, A.; Moranta, D.; Asensio, V. J.; Garcia-Sevilla, J. A. *Eur. J. Pharmacol.* **2005**, *518*, 234.

(18) (a) 2-Napthyl pivalate also underwent this alkynylation to form **3a** in 68% yield under the typical conditions shown in Scheme 2. (b) Alkynylation of phenyl carbamate did not proceed efficiently (ca.10% yield). (c) Although we routinely generate **L3** by pretreatment of **L3·HCl** with KO^{t}Bu, a similar result can be obtained when the reaction was performed in the absence of KO^{t}Bu.

(19) A selected review: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(20) Selected reviews on the synthesis of heterocycles from aromatic alkynes: (a) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen L. J. *Chem. Rev.* **2015**, *115*, 2596. (b) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.

(21) Dong, C.; Liao, Z.; Xu, X.; Zhou, H. *J. Heterocyclic Chem.* **2014**, *51*, 1282.

(22) Selected examples: (a) Rastogi, S. K.; Medellin, D. C.; Kornienko, A. *Org. Biomol. Chem.* **2014***, 12*, 410. (b) Sumaria, C. S.; Türkmen, Y. E.; Rawal, V. H. *Org. Lett.* **2014**, *16*, 3236. (c) Türkmen, Y. E.; Montavon, T. J.; Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 9062. Kessler, S. N. (d) Neuburger, M.; Wegner, H. A. *Eur. J. Org. Chem.* **2011**, 3238. (e) Kessler, S. N.; Wegner, H. A. *Org. Lett.* **2010**, *12*, 4062.

(23) Ogata, K.; Ohashi, I.; Fukuzawa, S.-I. *Org. Lett.* **2012**, *14*, 4214.

(24) Cramer, R. *Inorg. Chem.* **1962**, *1*, 722.

(25) Mistryukov, E. A. *Mendeleev Commun.* **2006**, *16*, 258.

(26) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 6790.

(27) Macklin, T. K.; Reed, M. A.; Snieckus, V. *Eur. J. Org. Chem.* **2008**, 1507.

(28) Varjosaari, S. E.; Suating, P.; Adler, M. J. *Synlett* **2016**, *48*, 43.

(29) (a) Liu, L.; Carroll, P. J.; Kozlowski, M. C. *Org. Lett.* **2015**, *17*, 508. (b) Mesganaw, T.; Fine N., N. F.; Garg, N. K *Org. Lett.* **2012**, *11*, 2918.

(30) Varjosaari, S. E.; Suating, P.; Adler, M. J. *Synlett* **2016**, *48*, 43.

(31) Jacquelin, J. M.; Robin, Y.; Godard, A.; Queguiner, G. *Can. J. Chem*. **1988**, 66, 1135.

(32) Dou, X.; Huang, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 1133.

(33) Groom, K.; Hussain, S. M. S.; Morin, J.; Nilewski, C.; Rantanen, T.; Snieckus, V. *Org. Lett.* **2014**, *16*, 2378.

Chapter 3

N-Heterocyclic Carbene Catalyzed Concerted Nucleophilic Aromatic Substitution of α, β-Unsaturated Amide with an Ortho Fluorine Leaving Group

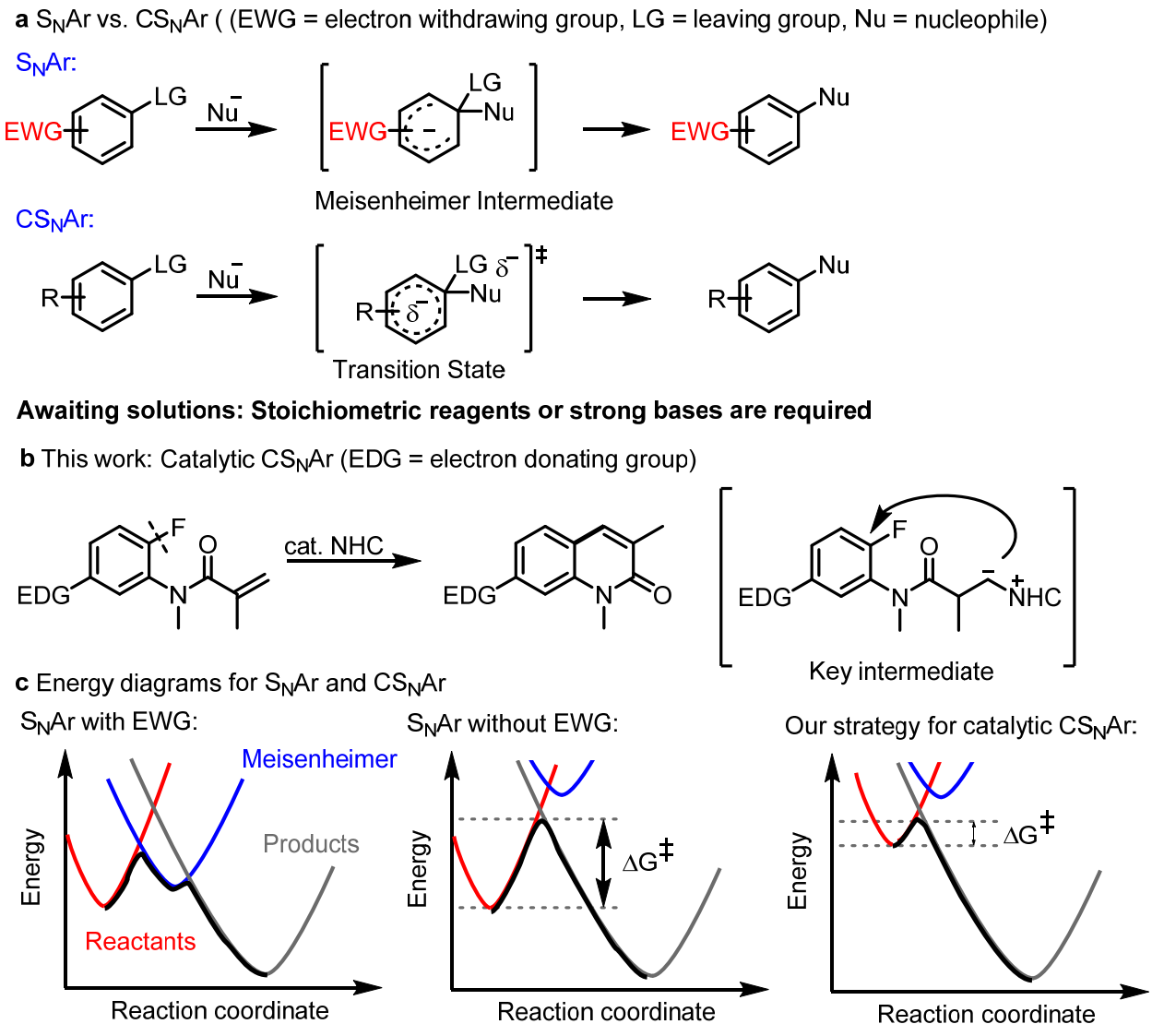
3.1 Introduction

Nucleophilic aromatic substitution (S_NAr) is a classical type of reaction, and has been used to elaborate a number of functionalized aromatic compounds related to pharmaceutical and organic materials.[1] In fact, analysis in 2016 revealed that S_NAr is the second most frequently used reaction in medicinal chemistry research.[2] In S_NAr reactions, a nucleophile attacks the aromatic ring at the ipso position of a leaving group to form a so-called Meisenheimer intermediate (Scheme 1a, top).[3,4] This intermediate is formed via the complete loss of aromaticity, which requires a high activation energy of around 30 kcal/mol.[5] To make the process energetically feasible, a strong electron-withdrawing group is essential to stabilize a discrete negative charge that develops in the Meisenheimer intermediate, thereby decreasing the activation barrier. This mechanistic feature limits the scope of aromatic substrates to highly electron-deficient (hetero)arenes, which is an obvious disadvantage of classical S_NAr reactions when applied to organic synthesis.

Several reports recently revealed that the S_NAr reaction can proceed, not in a stepwise, but, rather, in a concerted manner (CS_NAr, Scheme 1a, bottom).[6] The CS_NAr pathway generally has a lower activation energy (13~25 kcal/mol)[6] than what is required for the formation of the Meisenheimer intermediate since part of the aromaticity of the substrate can be retained.[7] In addition, the negative charge in the transition state can be dispersed not only on an aromatic ring but also on a leaving group, thereby making the CS_NAr reaction less sensitive to the electronic nature of the substrate. In fact, several reports dealing with nucleophilic aromatic substitution reactions of electron-neutral and electron-rich substrates have now been documented, including iodination,[8] hydride reduction,[9,10] fluorination,[11-15] amination,[16] silylation,[17] thionylation,[18] and aryl migration[19,20] reactions. Although these examples significantly advanced the scope of CS_NAr reactions, all of these reactions require stoichiometric amounts of activating reagents and/or strong bases, such as NaH or MHMDS (M = Li, K) to generate the key reactive species.

To further expand the synthetic utility of CS_NAr reactions, we hypothesized that a catalytic variant that would permit the use of stoichiometric strong bases or reagents to be avoided would be highly desirable. Moreover, the scope of CS_NAr reactions is currently limited to the formation of carbon-heteroatom bonds, except for aryl migration,[19,20] and applications to carbon-carbon bond-forming processes remain underdeveloped. The use of carbon nucleophiles in aromatic substitution reactions has been considered to be intrinsically more difficult than heteroatom-based nucleophiles, since the latter can provide extra stabilization for the transition state through the interaction between the lone pair of electrons and a π^* orbital and assist in the bond-breaking process.[21] To realize catalytic C–C bond-forming CS_NAr reactions, we envisioned the use of N-heterocyclic carbene (NHC) catalysts, which can be used to generate a nucleophile from a carbonyl compound or an alkyl halide in a catalytic manner.[22-24] Among the several precursors that can be activated by an NHC catalyst, we opted to use α, β- unsaturated carbonyl compounds, which are known to serve as a latent β-carbanion via umpolung. Although the generation of this type of nucleophile has been utilized in several NHC-catalyzed reactions[25] since the first report by Fu,[26] its use in catalytic aromatic substitution reactions has not been accomplished.[27,28] We used an aromatic fluoride bearing an α, β-unsaturated amide, which would undergo an aromatic substitution reaction by a catalytically generated β-carbanion (Scheme 1b). This reaction allows readily available anilides to be converted into quinolin-2-one derivatives, which

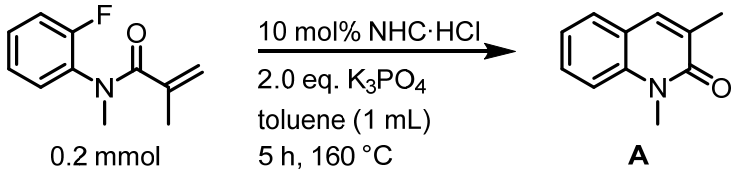
are structures contained in a number of natural products and pharmaceuticals.[29,30] According to Jacobsen's analysis of S_NAr reactions based on the Marcus theory,[31] the Meisenheimer intermediate is highly stabilized by a strong electron-withdrawing group, leading to a minimum along the reaction coordinate (Scheme 1c, left). In contrast, the energy surface of the Meisenheimer intermediate does not have intersections between those of a reactant and a product when the substrate does not contain a strong electron-withdrawing group, which results in a transition state with an insurmountable barrier (Scheme 1c, middle). I envisioned that increasing the nucleophilicity of the carbanion intermediate should destabilize the reactant, thereby decreasing the activation energy required for a CS_NAr reaction (Scheme 1c, right). Here I report the realization of the NHC-catalyzed cyclization of aryl fluorides via a CS_NAr pathway (Scheme 1b).



Scheme 1. Plausible Mechanism

A close look at the structure of the key intermediate shown in Scheme 1b led us to hypothesize that the nucleophilicity of this carbanion intermediate should depend on the electron-donating ability of an NHC catalyst, which is adjacent to the β anion in the transition state. Based on these hypotheses, I examined the catalytic activity of an array of NHCs for the cyclization of **1a**, which does not normally undergo aromatic substitution reactions,

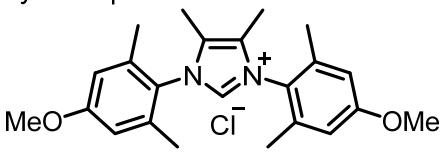
since no electron-withdrawing group is present. Intensive optimization studies (Scheme 2) led us to determine that **L** as an optimal NHC catalyst and CsF as an optimal base in the cyclization of **1a**. Thus, the reaction of **1a** in the presence of **L**·HCl (20 mol%) and CsF (2.0 equiv) in toluene at 160 °C for 5 h gave the cyclized product **2a** in



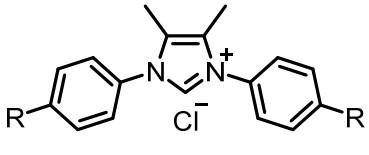
0.2 mmol **A**

Entry	NHC	**A** (GC yield)	SM (GC yield)	note
1	$IMXy^{Me}$	32%	67%	
2	$IOMe^{Me}$ (**L**)	68%	28%	
3	$INMe_2^{Me}$	33%	51%	
4	$IOMe^{NMe2}$	0%	>95%	
5	IXy^{Me}	0%	>95%	
6	ICy	33%	58%	
7	I-2Ad	10%	67%	
8	IMes	0%	>95%	
9	$IMes^{Me}$	0%	>95%	
10	IPr	0%	>95%	
11	TPT	6%	77%	
12	IOMe	25%	71%	
13	**L**	>95% (100%)	0%	with CsF instead of K_3PO_4
14	**L**	20%	48%	with CsOAc instead of K_3PO_4
15	**L**	51%	22%	with Cs_2CO_3 instead of K_3PO_4
16	**L**	59%	0%	with K_2CO_3 instead of K_3PO_4
17	**L**	0%	73%	with NaOAc instead of K_3PO_4
18	**L**	27%	30%	with DBU instead of K_3PO_4

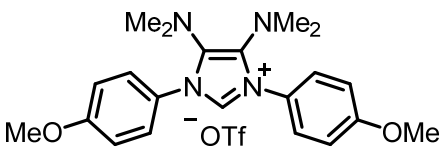
* The yield in parentheses refers to an isolated yield.



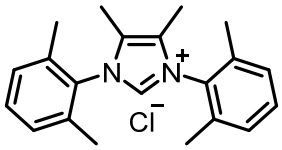
$IMXy^{Me}$



$IOMe^{Me}$ **L**: R = OMe
$INMe_2^{Me}$: R = NMe_2



$IOMe^{NMe2}$



IXy^{Me}

Scheme 2. Optimization Study

quantitative isolated yield (Scheme 2a). It should be noted that this cyclization can proceed at a lower temperature of 120 °C (96%).

With the optimized reaction conditions in hand, I next examined the scope of substrates (Scheme 2). Not surprisingly, electron-deficient substrates bearing CF_3 (**2b**), methyl ester (**2c**), or cyano (**2d**) groups smoothly participated in this catalytic cyclization to produce the corresponding functionalized quinolin-2-one derivatives. Our NHC-catalyzed protocol can be used for the synthesis of quinoline-2-one derivatives bearing chloro (**2e**), bromo (**2f**) and even iodo (**2g**) groups without their loss, which can serve as handles for further structural elaboration. Whereas pyridines bearing a leaving group at the C2 or C4 position are suitable substrates for nucleophilic aromatic substitution, pyridines bearing a leaving group at the C3 position are known to be much less reactive.[32] Nevertheless, this catalytic cyclization could be applied successfully to a 3-fluoropyridine derivative **1j** to form the aza-quinoine-2-one skeleton **2j**. The tricyclic skeleton **2k**, a common structural motif of drugs for Cushing's syndrome and the metabolic syndrome,[33] are also accessible.

This method is applicable to substrates with a cyclic alkene moiety, which allows for the rapid access to an array of fused ring systems containing a quinolin-2-one core, such as **2m, 2n**, and **2o** (Scheme 2b). One might expect that these ring systems can be accessed by the Mizoroki-Heck reaction of the bromide analogue of **1**. However, such an approach was reported to favor the formation of a five-membered ring via a 5-exo cyclization mode, which is complementary to our 6-membered ring formation.[34]

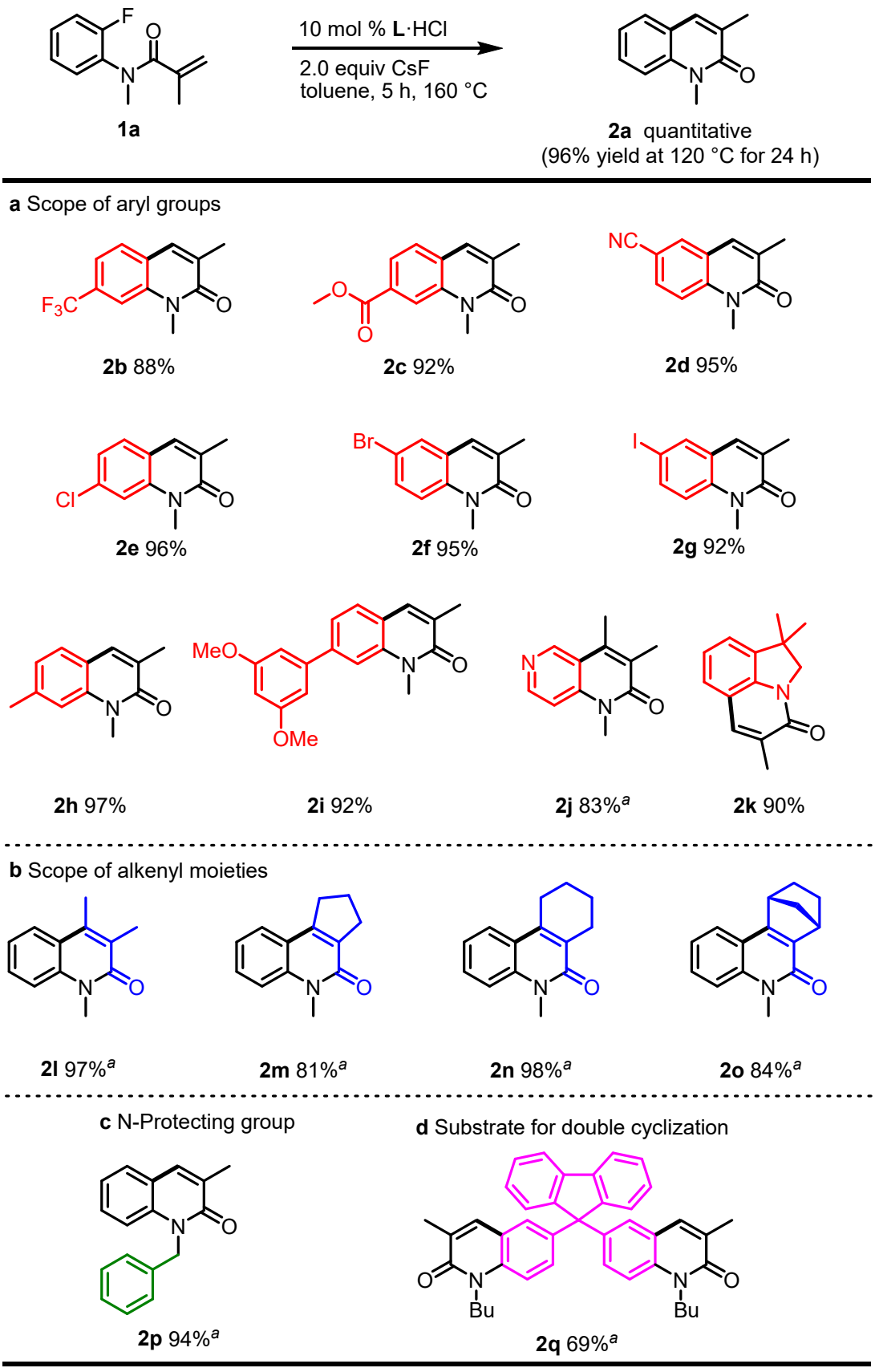
Although our protocol failed to cyclize a secondary amide substrate, an N-benzyl group **2p** was well-tolerated, allowing for the modification of the N-substituent of quinolin-2-one products after debenzylation (Scheme 2c). The substrate derived from 9,9-bis(4-amino-3-fluorophenyl)fluorene **1q**, a promising scaffold for the synthesis of organic electroluminescence materials, could also deliver the corresponding double cyclized product **2q** (Scheme 2d).

The unambiguous advantage of this catalytic cyclization is that electron-rich substrates can participate in the reaction, as shown Figure 2e. Although more forcing conditions were needed (30 mol% of **L6**, 72 h), substrates bearing indoline **2r**, NMe_2 **2s**, or OMe **2t** groups, the most challenging class of substrates for nucleophilic aromatic substitution, participated in the catalytic cyclization to deliver the corresponding products (Scheme 3).

Because stoichiometric strong bases are not required in this reaction, this nucleophilic aromatic substitution method can be used for the late-stage functionalization of intricate molecules. For example, Diflufenican, a herbicide bearing an ortho-fluoroaniline moiety, can be readily elaborated into quinolin-2-one analogue **2u** in three steps (Scheme 4).

To demonstrate the scalability of this reaction, the cyclization of **1a** was conducted on a 1.5 g scale, resulting in the complete consumption of starting materials and the formation of the desired product in 92% (1.25 g) isolated yield without any difficulty (Scheme 5).

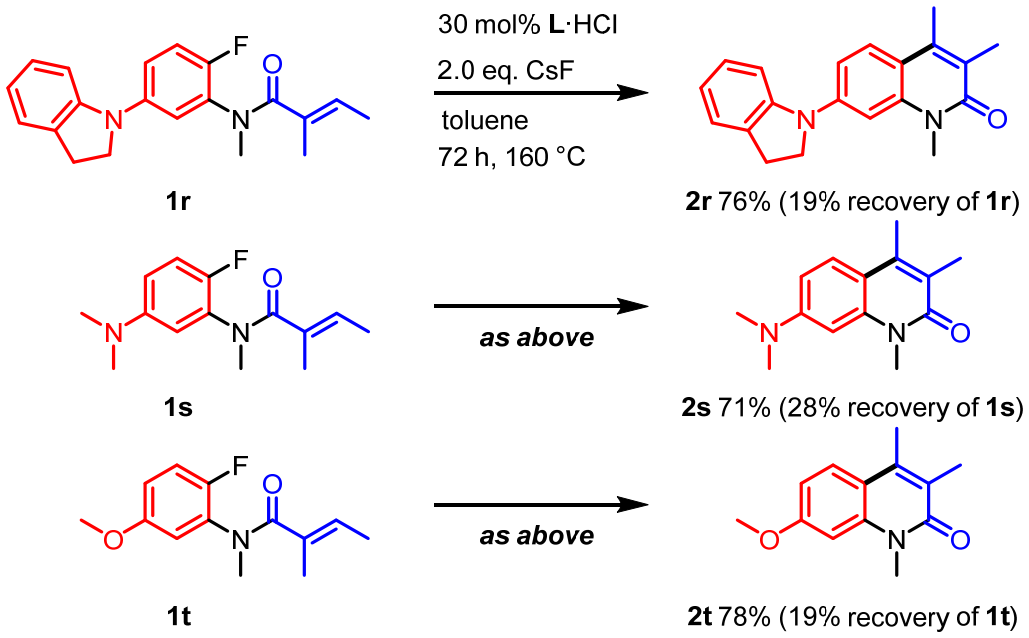
To elucidate whether this reaction proceeds through the classical S_NAr or CS_NAr reactions, I investigated the reaction pathway using DFT calculations. The energy changes at the M06-2X/def2-TZVPP level of theory [SCRF (pcm, solvent = toluene)] are shown in kcal/mol (Scheme 3a). Because the reaction route from an α,β-unsaturated ester and an NHC catalyst to the ylide intermediate similar to **Int 1** was previously calculated,[35] our calculations were focused on the key intramolecular nucleophilic substitution process. This catalytic cyclization was found to proceed through a single transition state, in which both a nucleophilic attack of the β carbon and the dissociation of the fluorine leaving group proceeded in a synchronized fashion. Approaching the **TS** requires a barrier of 26.2



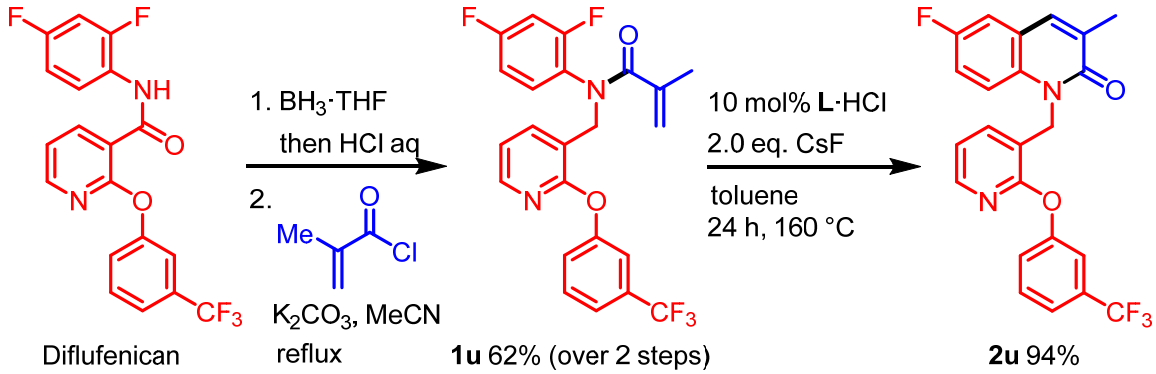
Scheme 2. Scope of Substrates

Conditions: Conditions: **1** (0.20 mmol), **L**·HCl (0.030 mmol), CsF (0.60 mmol), in toluene (1.0 mL) at 160 °C for 5 h. Isolated yields of the cyclized products are shown. [a] Reacted for 24 h. The reaction temperature is a preset temperature on aluminum block for constant temperature.

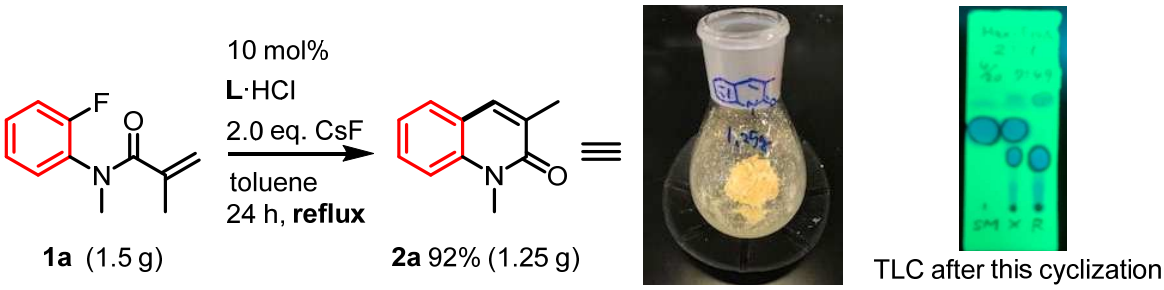
kcal/mol, which lies within the range of that reported for other CS_NAr reactions,[6] following the formation of thermodynamically stable **Int 2**. It should be noted that the intrinsic reaction coordinate (IRC) analysis for **TS** led



Scheme 3. Scope of Substrates

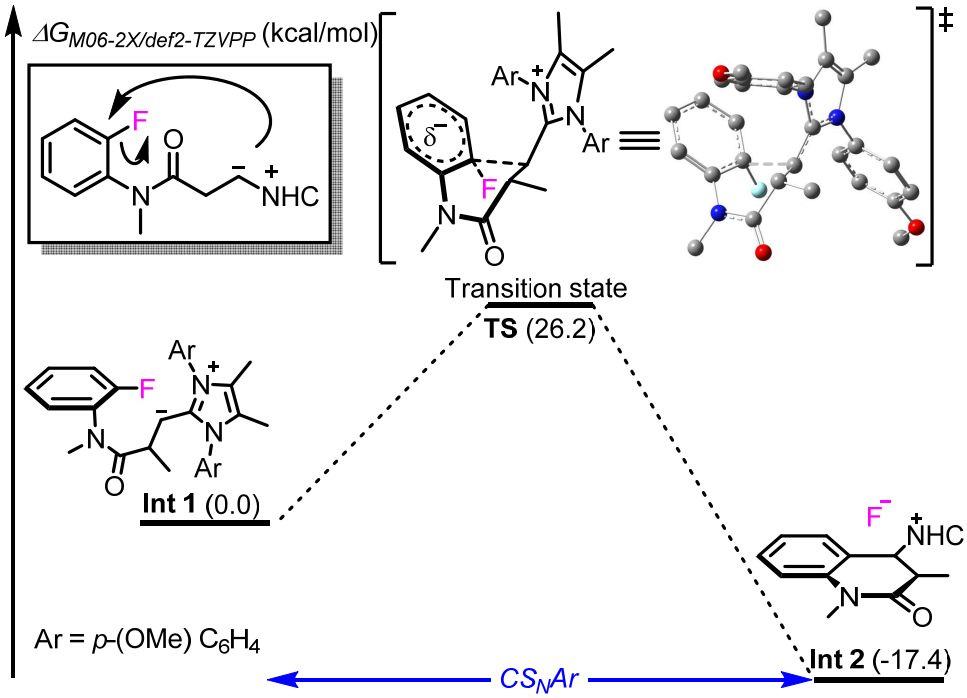


Scheme 4. Scope of Substrates



Scheme 5. Scope of Substrates

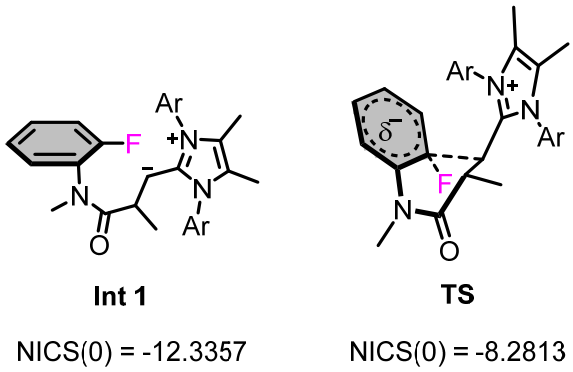
us to identify no additional intermediates along the pathway from **Int1** to **Int2**, excluding the intermediacy of a Meisenheimer type intermediate in this catalytic cyclization reaction. In addition, all our attempts to find the Meisenheimer type intermediate did not provide any stable intermediates, which suggests that the intermediate lies



Scheme 6. Scope of Substrates

on much more higher energy curve as reported.[5]

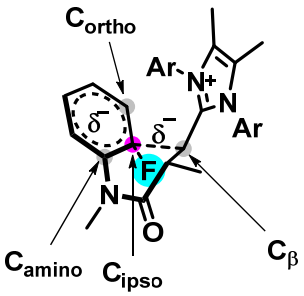
The Meisenheimer intermediate involved in S_NAr reactions is known to possess no aromaticity.[3-5] In contrast, the transition state in CS_NAr was reported to retain partial aromaticity,[7] which is likely to be critical to lowering the activation energy for CS_NAr. To investigate the aromaticity of the **TS** in our reaction, the NICS values[36] of the **TS** and **Int1** were calculated (HF/6-31+G*). Although the NICS value of **TS** (-8.28) increased compared with that for **Int1** (-12.3), it is still largely negative, which indicates that the **TS** possesses an aromatic character (Scheme 3b). These results suggest that this NHC-catalyzed CS_NAr reaction can proceed with a lower energy barrier because complete dearomatization is not required in the **TS**, unlike classical S_NAr reactions involving the Meisenheimer intermediate.



Scheme 7. Scope of Substrates

The aromaticity in TS made me curious about the hybrid orbital of the ipso carbon of the fluorine leaving group because the carbon looks like an sp^3 carbon despite its aromaticity. To get insight into the hybrid orbitals, I conducted an NBO analysis. As a result, $sp^{1.90}$ and $sp^{2.03}$ orbitals respectively contribute to the formation of C_{ipso}-C_{amino} and C_{ipso}-C_{ortho}, which constitute the aromatic ring. Therefore, C_{ipso}-C_{amino} and C_{ipso}-C_{ortho} in TS can still keep the planer

aromatic ring, which shows the aromaticity based on the NICS value. On the other hand, $sp^{9.06}$ orbital interacts with the anion on the carbon at the β position, which results in the desired bond formation. Besides, the orbital of C_{ipso}-F is $sp^{4.10}$, and the C_{ipso}-F is getting weaker than typical C_{ipso}-F and cleaved.

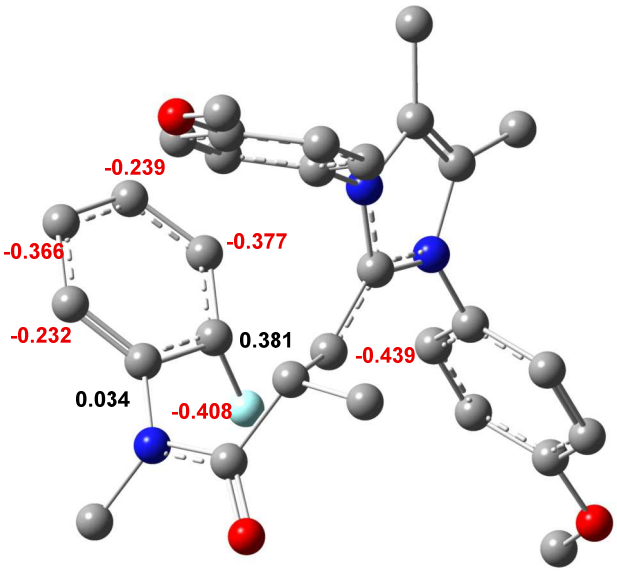


	hybrid orbital of C_{ipso}
C_{ipso}—C_{amino}	$sp^{1.90}$
C_{ipso}—C_{ortho}	$sp^{2.03}$
C_{ipso}—C_{β}	$sp^{9.06}$
C_{ipso}—F	$sp^{4.10}$

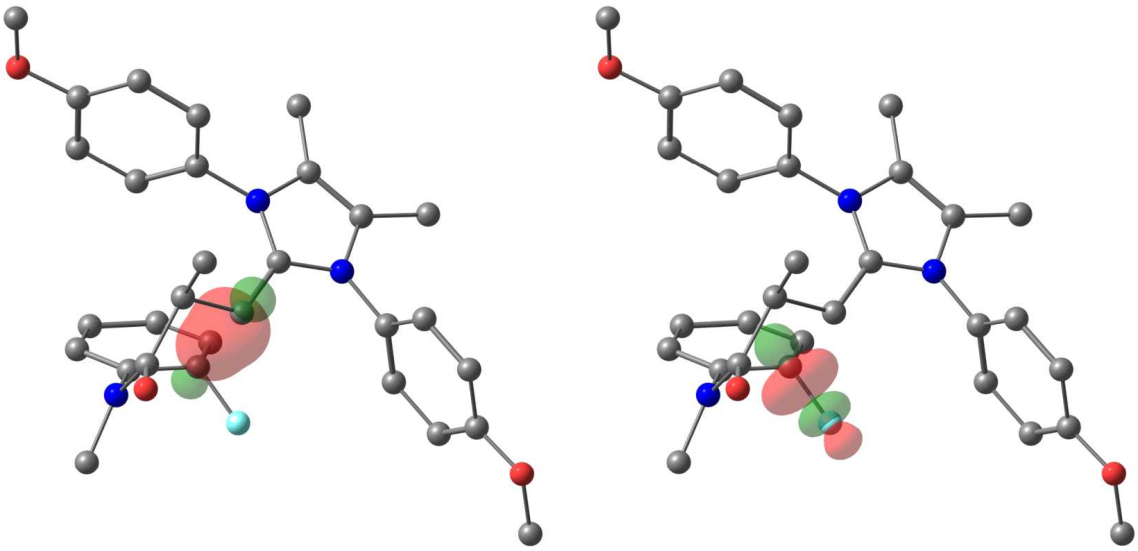
Scheme 8. Scope of Substrates

I next conducted a natural bond orbital (NBO) analysis to obtain insights into the charge distribution in the transition state (M062X/6-31+G*) (Scheme 3c). The negative charges were found to be distributed, not only on an aromatic ring (C3: -0.377, C4:-0.239, C5: -0.366, C6: -0.232), but also on the fluorine leaving group (F: -0.408) and the nucleophilic β carbon (-0.439), which is a characteristic charge distribution for CS_NAr.[13] These results are in agreement with the experimental observation that electron-rich aryl fluorides were compatible with this catalytic cyclization (Scheme 2f).

An NBO analysis also revealed the essential orbital interactions in the **TS**.[37] A noncovalent stereoelectronic interaction between the σ (C_{ipso}-C_{β}) bond orbital (Scheme 3d) and the σ* (C_{ipso}-F) antibonding orbital (Scheme 3e) was observed with an NBO interaction energy of 2.96 kcal/mol, which contributes to stabilizing the **TS**. It must also be noted that this weak but significant stereoelectronic interaction explains the concerted nature of this substitution reaction well. Although the π* orbital at the ipso carbon of the leaving group is reported to be involved in CS_NAr reactions [4,12], our calculations revealed that the σ* (C_{ipso}-F) orbital lying on the C-F bond (Scheme 3f) serves as an acceptor orbital for σ (C_{ipso}-C_{β}) bond in the transition state during the CS_NAr process.



Scheme 9. Scope of Substrates



$\sigma(C_{ipso}\text{-}C_{\beta}) \rightarrow \sigma^{*}(C\text{-}F) = 2.96$ kcal/mol

Scheme 10. Scope of Substrates

3.3 Conclusion

In summary, I report on the first catalytic concerted nucleophilic aromatic substitution forming C-C bond, in which a catalytically generated carbanion displaces the fluorine group on the aromatic ring. The concerted nature of the transition state allows electron-rich aryl fluorides to be cyclized in a catalytic manner. Since this method does not rely on the use of strong bases or transition metals, it is possible to synthesize quinolin-2-one derivatives bearing a diverse range of functional groups including iodides and bromides. DFT calculations confirmed that this catalytic cyclization proceeds in a concerted manner. In addition, the formation of a C_{ipso}-C_{β} bond in the transition state results in a significant stereoelectronic interaction with the antibonding orbital of the C_{ipso}-F bond, which stabilizes the transition state for this concerted cyclization process.

3.4 Experimental Section

I. General Information

^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The data is reported as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, and m = multiplet), coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer. Absorption is reported in reciprocal centimeters (cm^{-1}) with the following relative intensities: s (strong), m (medium), or w (weak). High resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Column chromatography was performed with SiO_2 (Silicycle SilicaFlash F60 (230-400 mesh) or Silica Gel 60 (spherical) NH_2).

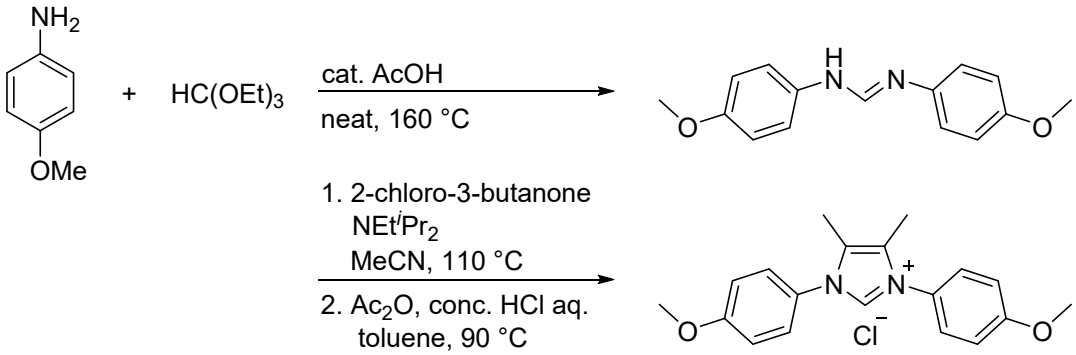
II. Materials

ICy•HCl, IMes•HCl, IPr•HCl, K_3PO_4, CsF, methacryloyl chloride, and 2-fluoroaniline used in the preparation of starting materials were purchased from TCI and used as received. Toluene (for Organic Synthesis), THF, and triethylamine were purchased from Wako Chemicals and used as received. NaH was purchased from nacalai

tesque and used as received. TTP•HCl[44] (136152-26-6) and IOMe•HCl[45] (1271734-36-1) were prepared according to literature procedures.

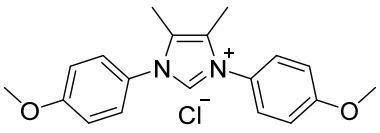
III. Preparation of Catalysts

Procedure for the preparation of L6.



L6•HCl was synthesized according to the literature procedure[46] with the use of 4-methoxyaniline instead of 4-methoxy-2,6-dimethylaniline. A mixture of 4-methoxyaniline (5.0 g, 40 mmol), triethyl orthoformate (3.3 mL, 20 mmol), and acetic acid (30 mg, 0.50 mmol) was heated at 160 °C for 3 h. The resulting solid was triturated and washed with cold hexane. The obtained solid was dried in vacuo to give (2E,3E)-N^2,N^3-bis(4-methoxyphenyl)butane-2,3-diimine as an off-white solid (4.1 g, 80%). This material was used for the subsequent step without further purification. To a suspension of (E)-N,N'-bis(4-methoxyphenyl)formimidamide (4.1 g, 16 mmol) in acetonitrile (30 mL), NEt^iPr_2 (3.3 mL, 19 mmol) and 3-chloro-2-butanone (3.2 mL, 32 mmol) were added, and the suspension was heated at 110 °C for 24 h. The volatile components were removed in vacuo, and then toluene (50 mL), 37% HCl (aq) (3.0 mL), and acetic anhydride (6.4 mL, 48 mmol) were added to the residue. After heating at 90 °C for 15 h, H_2O (10 mL) was added and the solution was stirred for 10 min. After separating the two layers, the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic extracts were washed with 1 M HCl (aq), dried over Na_2SO_4, and concentrated in vacuo. The residual solid was washed with EtOAc and then recrystallization from Et_2O/CH_2Cl_2 (10:1) to give the title compound as a white solid (2.0 g, 40%).

1,3-Bis(4-methoxyphenyl)-4,5-dimethyl-1H-imidazol-3-ium chloride (L6).



Rf 0.22 (CH_2Cl_2/MeOH = 10/1). White solid (1.97 g, 40%). Mp = 237 °C.

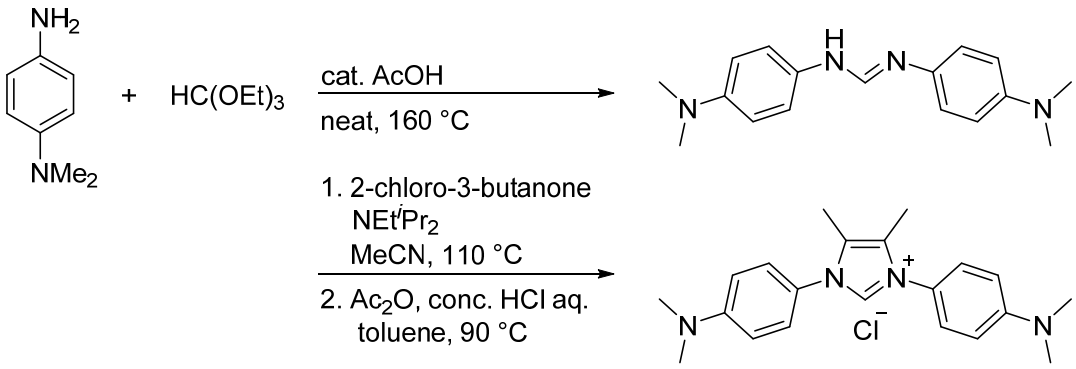
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.60 (s, 1H), 7.81 (ddd, *J* = 6.2, 3.0, 2.4 Hz, 4H), 7.07 (ddd, *J* = 6.2, 3.0, 2.4 Hz, 4H), 3.87 (s, 6H), 2.22 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.9, 135.9, 127.7, 127.3, 125.7, 115.1, 55.6, 9.4.

IR (ATR): 3396 w, 1548 m, 1502 s, 1252 s, 841 w.

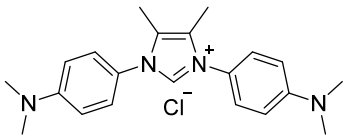
HRMS (FAB+, [M+H^+]): Calcd for $C_{19}H_{21}N_2O_2^+$ 309.1598, Found 309.1609.

Procedure for the preparation of L7.



L7•HCl was synthesized according to the literature procedure[46] with the use of N^1,N^1-dimethylbenzene-1,4-diamine instead of 4-methoxy-2,6-dimethylaniline. A mixture of N^1,N^1-dimethylbenzene-1,4-diamine (2.7 g, 20 mmol), triethylorthoformate (1.7 mL, 10 mmol), and acetic acid (30 mg, 0.5 mmol) was heated at 160 °C for 3 h. The resulting solid was triturated and washed with cold hexane. The obtained solid was dried in vacuo to give 4,4'-(((2E,3E)-butane-2,3-diylidene)bis(azaneylylidene))bis(N,N-dimethylaniline) as an off-white solid (3.2 g, 100%). This material was used for the subsequent step without further purification. To a suspension of (E)-N,N'-bis(4-(dimethylamino)phenyl)formimidamide (3.2 g, 10 mmol) in acetonitrile (30 mL), NEt^iPr_2 (3.3 mL, 19 mmol) and 3-chloro-2-butanone (3.2 mL, 32 mmol) were added, and the suspension was heated at 110 °C for 24 h. The volatile components were removed in vacuo, and then toluene (50 mL), 37% HCl (aq) (3.0 mL), and acetic anhydride (6.4 mL, 48 mmol) were added to the residue. After heating at 90 °C for 15 h, H_2O (10 mL) was added and the solution was stirred for 10 min. After separating the two layers, the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic extracts were washed with conc. $NaHCO_3$ (aq), dried over Na_2SO_4, and concentrated in vacuo. The residual solid was washed with EtOAc and then recrystallization from Et_2O/CH_2Cl_2 (10:1) to give the title compound as a white solid (1.2 g, 37%).

1,3-Bis(4-(dimethylamino)phenyl)-4,5-dimethyl-1H-imidazol-3-ium chloride (L7).



Rf 0.15 (CH_2Cl_2/MeOH = 10/1). White solid (1.2 g, 37%). Mp = 230 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.38 (s, 1H), 7.57-7.61 (m, 4H), 6.77-6.81 (m, 4H), 3.03 (s, 12H), 2.22 (s, 6H).

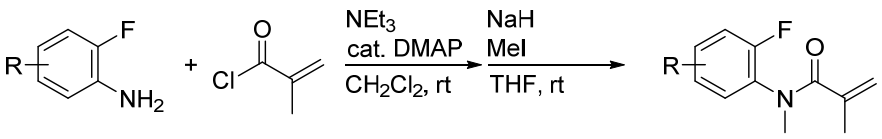
^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.3, 135.3, 127.5, 126.9, 121.3, 112.2, 40.3, 9.4.

IR (ATR): 1609 m, 1546 m, 1519 s, 1360 w, 825 w, 744 w.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{21}H_{27}N_4^+$ 335.2230, Found 335.2238.

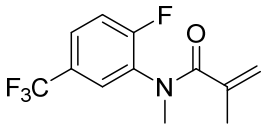
IV. Preparation of Starting Materials

General procedure for the preparation of N-(2-fluorophenyl)-N-methylacrylamides.



To a mixture of 2-fluoroaniline (5.0 mmol), NEt_3 (900 μL, 10 mmol) and DMAP (30 mg, 250 μmol) in CH_2Cl_2 (20 mL), methacryloyl chloride (600 μL, 6.0 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to rt and stirred until the aniline was completely consumed (1~3 h). H_2O (ca. 20 mL) was then added and extracted with CH_2Cl_2 (ca. 20 mL × 2). The organic fractions were combined and dried over Na_2SO_4. After filtration through a Celite pad to remove Na_2SO_4, all volatiles were removed in vacuo. The obtained crude materials were used for the subsequent N-methylation without further purification. To a suspension of NaH (60% dispersion in paraffin liquid, 240 mg, 6.0 mmol) in dry THF (10 mL), a solution of the crude materials in dry THF (10 mmol) was added dropwise at 0°C and the resulting mixture was stirred for 30 min at rt. MeI (1.7 mL, 5.5 mmol) was then added dropwise to the solution at 0 °C and stirred for 4 h. An aqueous solution of $NaHCO_3$ (20 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 (30 mL × 3) and the combined organic extracts were dried over Na_2SO_4, and concentrated in vacuo. The residual materials were purified by column chromatography using hexane/EtOAc = 12~96% gradient to give desired N-(2-fluorophenyl)-N-methylacrylamide.

N-(2-Fluoro-5-(trifluoromethyl)phenyl)-N-methylmethacrylamide (1b).



Rf 0.35 (hexane/EtOAc = 2/1). White solid (240 mg, 16%). Mp = 93 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.01 (dd, J = 7.1, 2.1 Hz, 1H), 7.74-7.78 (m, 1H), 7.56 (t, J = 9.4 Hz, 1H), 5.10 (s, 1H), 4.85 (s, 1H), 3.23 (s, 3H), 1.79 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 142.2, 140.3, 137.0, 133. 6, 132.4, 129.6, 128.6, 128.5, 128.3, 126.8, 118.4, 36.4, 20.4.

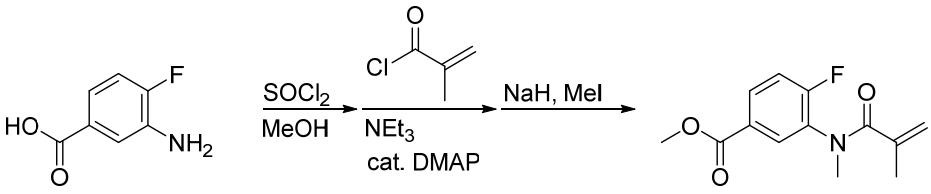
^{19}F NMR ($CDCl_3$, 375 MHz): δ -63.4, -116.8.

[Perfluorobenzene (-163.0 ppm) was used as an internal standard.]

IR (ATR): 1632 s, 1052 s, 1024 s, 1005 s, 821 m, 758 m.

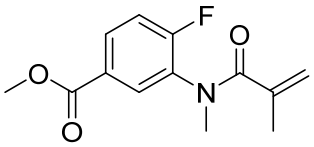
HRMS (FAB+, [M+H$^+$]): Calcd for $C_{12}H_{12}F_4NO$ 262.0777, Found 262.0860.

Procedure for the preparation of 1c.



To a mixture of 3-amino-4-fluorobenzoic acid (5.0 g, 32 mmol) in MeOH (60 mL) was added thionyl chloride (2.8 mL, 38.4 mmol) dropwise at 0°C. The reaction mixture was warmed to 70 °C and stirred for 12 h. All volatiles were removed *in vacuo* to give a methyl ester product. The obtained crude material was used for the subsequent step without further purification. The general procedure was followed to convert the methyl ester to **1c**.

Methyl 4-fluoro-3-(N-methylmethacrylamido)benzoate (1c).



Rf 0.48 (hexane/EtOAc = 1/1). White solid (2.5 g, 31%). Mp = 104 °C.

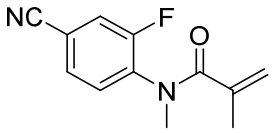
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.99 (m, 1H), 7.91 (dd, *J* = 7.8, 2.3 Hz, 1H), 7.18 (dd, *J* = 9.2 Hz, 1H), 5.04 (s, 1H), 4.92 (s, 1H), 3.93 (s, 3H), 3.32 (s, 3H), 1.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz):δ 172.1, 165.3, 160.5 (d, *J* = 254.5 Hz), 139.8, 132.5, 130.57 (d, *J* = 1.9 Hz), 130.55 (d, *J* = 8.6 Hz), 127.2 (d, *J* = 3.8 Hz), 118.86, 116.8 (d, *J* = 21.9 Hz), 52.5, 36.9, 19.9.

IR (ATR): 1719 s, 1650 s, 1628 m, 1605 m, 1440 m, 1263 s, 1226 s, 755 m.

HRMS (EI): Calcd for $C_{13}H_{14}FNO_3$ 251.0958, Found 251.0959.

N-(4-Cyano-2-fluorophenyl)-N-methylmethacrylamide (1d).



Rf 0.65 (hexane/EtOAc = 3/1). White solid (1.0 g, 63%). Mp = 96°C

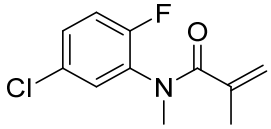
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.49 (m, 2H), 7.32 (dd, *J* = 7.8 Hz, 1H), 5.12 (s, 1H), 4.92 (s, 1H), 3.33 (s, 3H), 1.89 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7, 156.9 (d, *J* = 250.8 Hz), 139.6, 137.4 (d, *J* = 12.4 Hz), 129.5, 129.0 (d, *J* = 4.8 Hz), 120.6 (d, *J* = 23.8 Hz), 119.7, 116.9, 112.0 (d, *J* = 9.6 Hz), 36.9, 19.7.

IR (ATR): 2362 m, 2343 m, 1661 s, 1631 m, 1612 s, 1509 s, 1361 s, 914 s, 744 s.

HRMS (FAB+, [M+H^+]): Calcd for $C_{12}H_{12}FN_2O$ 219.0855, Found 219.0932.

N-(5-Chloro-2-fluorophenyl)-N-methylmethacrylamide (1e).



Rf 0.78 (hexane/EtOAc = 1/1). Colorless oil (530 mg, 34%).

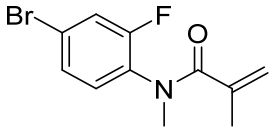
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.26 (m, 1H), 7.19 (dd, *J* = 6.6, 2.5 Hz, 1H), 7.07 (dd, *J* = 9.2 Hz, 1H), 5.08 (s, 1H), 4.95 (s, 1H), 3.29 (s, 3H), 1.86 (s, 3H)

^{13}C NMR ($CDCl_3$, 150 MHz): δ 171.9, 156.2 (d, *J* = 247.7 Hz), 139.8, 133.4 (d, *J* = 14.4 Hz), 129.4 (d, *J* = 3.5 Hz), 128.79, 128.75 (d, *J* = 9.8 Hz), 118.9, 117.6 (d, *J* = 21.8 Hz), 36.9, 19.8.

IR (ATR): 1658 s, 1629 m, 1603 m, 1496 s, 1356 s, 1228 s, 1105 m, 648 m.

HRMS (FAB+, [M+H^+]): Calcd for $C_{11}H_{13}ClFNO$ 228.0513, Found 228.0595.

N-(4-Bromo-2-fluorophenyl)-N-methylmethacrylamide (1f).



Rf .025 (hexane/EtOAc = 3/1). Pale brown solid (1.8 g, 67%). Mp = 119 °C.

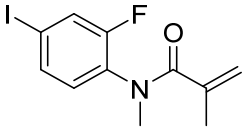
^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.29-7.33 (m, 2H), 7.07-7.11 (m, 1H), 5.04 (s, 1H), 4.89 (s, 1H), 3.23 (s, 3H), 1.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.0, 157.4 (d, *J* = 252.3 Hz), 139.9, 131.7, 129.9, 128.1 (d, *J* = 3.9 Hz), 121.1 (d, *J* = 8.7 Hz), 120.4 (d, *J* = 8.7 Hz), 118.8, 36.8, 19.9.

IR (ATR):1657 s, 1628 s, 1494 s,1361 s, 1105 m, 914 m, 889 m, 853 m.

HRMS (EI): Calcd for $C_{11}H_{11}BrFNO$ 271.0068, Found 271.0011.

N-(2-Fluoro-4-iodophenyl)-N-methylmethacrylamide (1g).



Rf 0.0.51 (hexane/EtOAc = 2/1). Pale brown solid (830 mg, 52%). Mp = 122 °C.

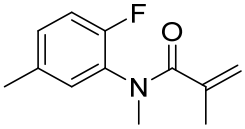
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.49 (m, 2H), 6.91 (dd, *J* = 8.2 Hz, 1H), 5.06 (s, 1H), 4.94 (s, 1H), 3.27 (s, 3H), 1.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0, 157.1 (d, *J* = 253.1 Hz), 139.8, 134.1 (d, *J* = 3.3 Hz), 132.4 (d, *J* = 12.8 Hz), 130.2, 126.0 (d, *J* = 22.4 Hz), 118.9, 91.6 (d, *J* = 7.1 Hz), 36.8, 19.9.

IR (ATR): 1654 s, 1625 s, 1490 s, 1359 s, 1104 s, 842 s, 589 m.

HRMS (EI): Calcd for $C_{11}H_{11}FINO$ 318.9869, Found 318.9866.

N-(2-Fluoro-5-methylphenyl)-N-methylmethacrylamide (1h).



Rf 0.65 (hexane/EtOAc = 3/1). Colorless oil (1.1 g, 64%).

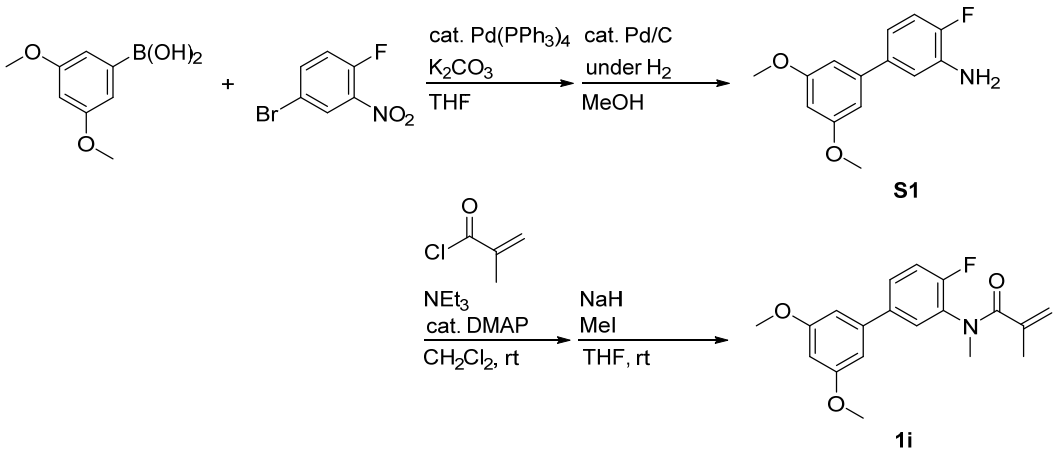
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.96-7.07 (m, 3H), 5.01 (s, 1H), 4.95 (s, 1H), 3.28 (s, 3H), 2.32 (s, 3H), 1.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 155.7 (d, *J* = 245.1 Hz), 140.13, 134.4 (d, *J* = 3.9 Hz), 131.7, 129.3 (d, *J* = 6.7 Hz), 129.2, 118.3, 116.1 (d, *J* = 20.0 Hz), 36.9, 20.6, 20.0.

IR (ATR):1655 s, 1629 s, 1609 m, 1452 m, 1422 m, 1358 s, 1241 m, 1233 m, 1101 m, 813 m, 757 m.

HRMS (EI): Calcd for $C_{12}H_{14}FNO$ 207.1059, Found 207.1062.

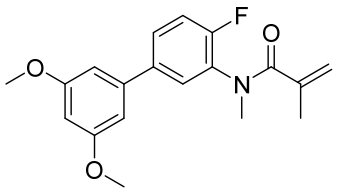
Procedure for the preparation of 1i.



To a mixture of 4-bromo-1-fluoro-2-nitrobenzene (1.1 g, 5.0 mmol) and (3,5-dimethoxyphenyl)boronic acid (1.1 g, 6.0 mmol) in THF (10 mL), $Pd(PPh_3)_4$ (170 mg, 150 μmol) and K_2CO_3 (3.5 g, 5 mmol) were added. This mixture was refluxed for 12 h under N_2. After addition of H_2O (10 mL), the organic layer was extracted with CH_2Cl_2 (20 mL × 3) and dried over Na_2SO_4. This organic layer was concentrated in vacuo to give crude materials. This crude material was used in the following reduction after filtration through a silica pad.

To the mixture of the crude materials in MeOH (10 mL), 10% palladium on carbon (150 mg, 1.5 mmol) was added and stirred for 12 h under hydrogen atmosphere. After filration through a celite pad, the organic solvent was removed in vacuo to give the corresponding aniline **S1**, which was used for the subsequent acylation without further purification according to the general procedure to give **1j** (300 mg, 18%).

N-(4-Fluoro-3',5'-dimethoxy-[1,1'-biphenyl]-3-yl)-N-methylmethacrylamide (1i).



Rf 0.47 (hexane/EtOAc = 2/1). Pale orange solid (300 mg, 18%). Mp = 89 °C

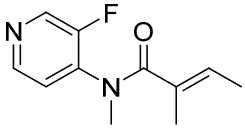
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.48 (m, 1H), 7.36 (dd, *J* = 7.8, 2.3 Hz, 1H), 7.16 (t, *J* = 9.2 Hz, 1H), 6.62 (d, *J* = 2.3 Hz, 2H), 6.48 (t, *J* = 2.1 Hz, 1H), 5.06 (s, 1H), 5.01 (s, 1H), 3.85 (s, 6H), 3.34 (s, 3H), 1.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 161.2, 157.1 (d, *J* = 248.9 Hz), 141.3, 140.1, 138.1 (d, *J* = 3.8 Hz), 132.4 (d, *J* = 9.5 Hz), 127.6, 127.49 (d, *J* = 8.6 Hz), 118.7, 116.9 (d, *J* = 2.1 Hz), 105.3, 99.3, 55.4, 36.9, 20.0.

IR (ATR):1655 m, 1588 s, 1509 m, 1204 s, 1155 s

HRMS (EI): Calcd for $C_{19}H_{20}FNO_3$ 329.1425, Found 329.1425.

(E)-N-(3-Fluoropyridin-4-yl)-N,2-dimethylbut-2-enamide (1j).



Rf 0.40 (hexane/EtOAc = 3/1). Colorless oil (690 mg, 59%).

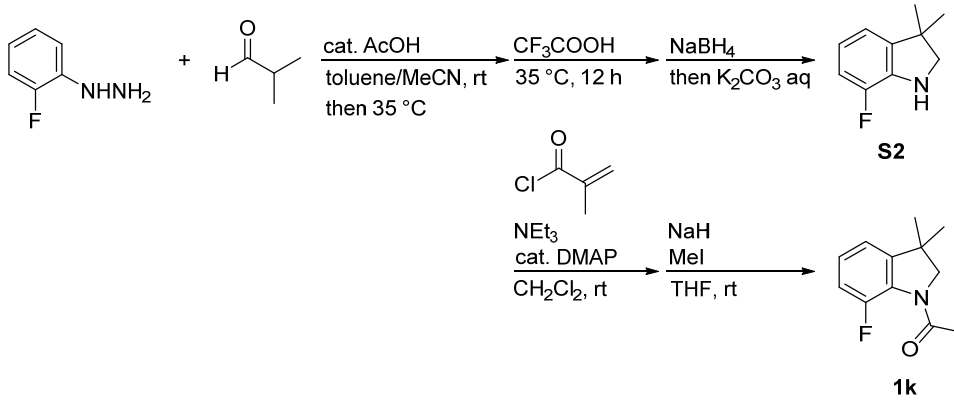
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 (d, *J* = 2.4 Hz, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 7.10 (dd, *J* = 6.6, 5.2 Hz, 1H), 5.65 (qq, *J* = 6.9, 1.5 Hz, 1H), 3.33 (s, 3H), 1.76-1.77 (m, 3H), 1.51 (dq, *J* = 6.9, 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 153.7 (d, *J* = 257.5 Hz), 146.6 (d, *J* = 5.7 Hz), 140.3 (d, *J* = 9.5 Hz), 139.5 (d, *J* = 22.9 Hz), 131.5, 122.6, 121.9, 36.58, 13.50, 13.47.

IR (ATR):1665 s, 1644 m, 1595 s, 1500 m, 1416 m, 1354 m, 743 w.

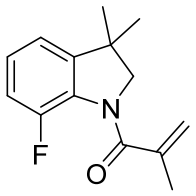
HRMS (EI): Calcd for $C_{11}H_{13}FN_2O$ 208.1012, Found 208.1011.

Procedure for the preparation of 1k.



To the mixture of (2-fluorophenyl)hydrazine (500 mg, 3.0 mmol) in toluene/MeCN (15/1.5 mL) was added isobutyraldehyde (270 μL, 4.7 mmol) and 5 drops of AcOH and stirred for 1 h at rt. To the mixture, CF_3COOH (660 μL, 3.9 mmol) was added and the resulting mixture was stirred for 12 h at rt. After cooled to 0°C, $NaBH_4$ (140 mg, 3.7 mmol) was added and stirred for 3 h. After consumption of starting material, all volatiles were removed in vacuo and added conc. K_2CO_3 aq (10 mL). The organic layer was extracted with EtOAc (20 mL × 3) and dried over Na_2SO_4. All volatiles were removed in vacuo to give indoline **S2**, which was used for the subsequent acylation without further purification according to the general procedure to give **1k** (160 mg, 16%).

1-(7-Fluoro-3,3-dimethylindolin-1-yl)-2-methylprop-2-en-1-one (1k).



Rf 0.35 (hexane/EtOAc = 1/1). Orange oil (160 mg, 16%, over 2 steps)

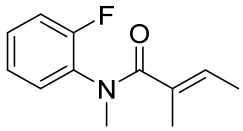
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (m, 1H), 6.89-6.95 (m, 2H), 5.34 (s, 1H), 5.27 (s, 1H), 3.88 (s, 2H), 2.065-2.069 (m, 3H), 1.32 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.4, 151.4 (d, *J* = 250.7 Hz), 145.9, 140.8, 128.7 (d, *J* = 9.5 Hz), 125.7 (d, *J* = 4.8 Hz), 118.3 , 117.5, 116.8 (d, *J* = 20.1 Hz), 115.4 (d, *J* = 20.1 Hz), 65.3, 41.5, 26.5, 19.3.

IR (ATR): 2359 m, 2342 m, 2159 m, 1770 m, 1651 m, 1625 m, 1484 m, 1366 m, 1246 s.

HRMS (EI): Calcd for $C_{14}H_{16}FNO$ 233.1216, Found 233.1215.

(E)-N-(2-Fluorophenyl)-N,2-dimethylbut-2-enamide (1l).



Rf 0.64 (hexane/EtOAc = 1/1). Colorless oil (1.2 g, 55%).

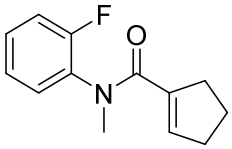
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.26 (m, 1H), 7.08-7.15 (m, 3H), 5.67 (qq, *J* = 6.9, 1.4 Hz, 1H), 3.28 (s, 3H), 1.64 (s, 3H), 1.46 (dq, *J* = 6.9, 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 173.5, 157.4 (d, *J* = 247.5 Hz), 132.7 (d, *J* = 12.0 Hz), 132.0 , 129.5, 129.0, 128.5 (d, *J* = 8.1 Hz), 124.5 (d, *J* = 4.1 Hz), 116.4 (d, *J* = 20.1 Hz), 36.9, 13.5, 13.2.

IR (ATR): 1655 s, 1588 s, 1509 s, 1456 s, 1354 s, 1204 s, 1155 s.

HRMS (EI): Calcd for $C_{12}H_{14}FNO$ 207.1059, Found 207.1062.

N-(2-Fluorophenyl)-N-methylcyclopent-1-ene-1-carboxamide (1m).



Rf 0.62 (hexane/EtOAc = 1/1). Colorless oil (350 mg, 42%).

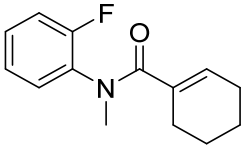
^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.25-7.31 (m, 1H), 7.21 (m, 1H), 7.09-7.16 (m, 2H), 5.68 (s, 1H), 3.25 (s, 3H), 2.31 (bs, 2H), 2.20 (bs, 2H), 1.67-1.75 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 168.8, 157.8 (d, *J* = 248.3 Hz), 138.8, 137.2, 132.3 (d, *J* = 12.2 Hz), 129.3, 129.0 (d, *J* = 8.1 Hz), 124.6 (d, *J* = 3.5 Hz), 116.5 (d, *J* = 20.1 Hz), 36.9, 33.4, 33.1, 23.1.

IR (ATR):1649 s, 1605 m, 1501 s, 1368 s, 1311 m, 760 s, 734 m.

HRMS (EI): Calcd for $C_{13}H_{14}FNO$ 219.1059, Found 219.1062.

N-(2-Fluorophenyl)-N-methylcyclohex-1-ene-1-carboxamide (1n).



Rf 0.47 (hexane/EtOAc = 3/1). Colorless oil (870 mg, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17-7.22 (m, 1H), 7.03-7.13 (m, 3H), 5.72-5.74 (m, 1H), 3.23 (s, 3H), 2.01-2.02 (m, 2H), 1.78-1.81 (m, 2H), 1.40-1.45 (m, 2H), 1.32-1.38 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8, 157.3 (d, *J* = 247.9 Hz), 133.9, 132.6 (d, *J* = 12.4 Hz), 131.5, 128.9, 128.5 (d, *J* = 8.6 Hz), 124.4 (d, *J* = 3.8 Hz), 116.3 (d, *J* = 20.9 Hz), 36.7, 25.4, 24.7, 21.8, 21.3.

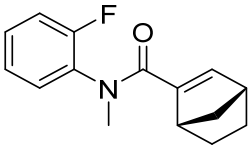
IR (ATR):1657 s, 1635 s, 1607 m, 1500 s, 1375 m, 1354 m, 1307 m, 1262 m, 760 s, 746 m.

HRMS (EI): Calcd for $C_{14}H_{16}FNO$ 233.1216, Found 233.1214.

Procedure for the preparation of 1o.

Methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate was prepared according to Yu's procedure[47] and the obtained methyl ester was converted into corresponding carboxylic acid according to Dong's procedure.[48] The acid chloride from the acid was used for the acylation based on the typical procedure to produce **1o** in 58% (710 mg, over 6 steps).

N-(2-Fluorophenyl)-N-methylbicyclo[2.2.1]hept-2-ene-2-carboxamide (1o).



Rf 0.48 (hexane/EtOAc = 3/1). Colorless oil (710mg, 58%).

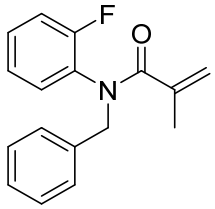
^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.20-7.31 (m, 2 H), 7.09-7.17 (m, 2H), 5.62 (bs, 1H), 3.23 (s, 3H), 3.03 (s, 1H), 2.70 (s, 1H), 1.61-1.62 (m, 2H), 1.09-1.17 (m, 2H), 1.00 (d, *J* = 8.2 Hz, 1H), 0.88-0.94 (m, 1H).

^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.5, 158.6 (d, *J* = 239.1 Hz), 142.7, 140.8, 132.7 (d, *J* = 11.6 Hz), 129.0 (two overlapping peaks), 124.5 (d, *J* = 3.5 Hz), 116.6 (d, *J* = 20.1 Hz), 47.3, 44.3, 43.4, 36.9, 24.8 (two overlapping peaks).

IR (ATR): 2360 m, 2159 s, 1738 s, 1503 m, 1366 s, 1216 m, 913 m, 744 m.

HRMS (EI): Calcd for $C_{15}H_{16}FNO$ 245.1216, Found 245.1212.

N-Benzyl-N-(2-fluorophenyl)methacrylamide (1p).



Rf 0.48 (hexane/EtOAc = 3/1). White solid (160 mg, 59%). Mp = 109 °C.

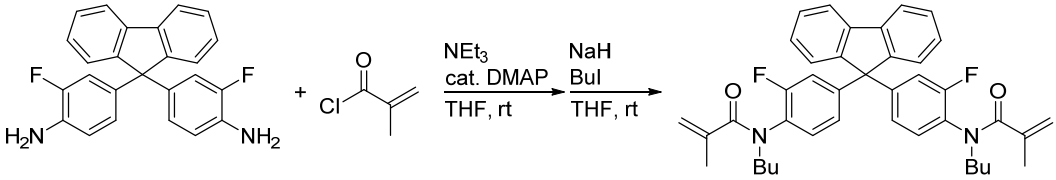
^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.19-7.29 (m, 6H), 6.97-7.07 (m, 3H), 5.10 (bs, 1H), 4.93-5.00 (m, 2H), 4.72 (bs, 1H), 1.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0, 157.7 (d, *J* = 247.9 Hz), 140.0, 136.8, 130.5 (d, *J* = 10.5 Hz), 129.6, 128.9 (d, *J* = 8.6 Hz), 128.4 (d, *J* = 28.6 Hz), 127.5, 127.3, 124.3 (d, *J* = 2.9 Hz), 118.4, 116.3 (d, *J* = 20.0 Hz), 52.1, 19.9.

IR (ATR): 1736 s, 1373 m, 1235 s, 1044 s, 633 w, 607 w

HRMS (EI): Calcd for $C_{17}H_{16}FNO$ 269.1216, Found 269.1211.

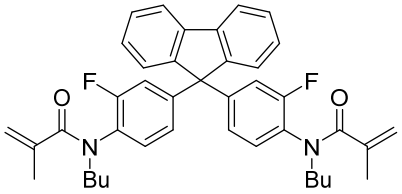
A procedure for the preparation of 1q.



To a mixture of 4,4'-(9H-fluorene-9,9-diyl)bis(2-fluoroaniline) (2.0 g, 5.2 mmol), NEt_3(1.5 mL, 16.6 mmol) and DMAP (30 mg, 250 μmol) in THF (20 mL), methacryloyl chloride (1.36 g, 13 mmol) was added dropwise at 0°C.

The reaction mixture was warmed to rt and stirred for 12 h. H_2O (ca. 20 mL) was added, and the mixture was extracted with CH_2Cl_2 (ca. 2 × 20 mL). The organic fractions were combined and dried over Na_2SO_4. After filtration through a Celite pad, all volatiles were removed in vacuo. The obtained crude materials were used without further purification. To a suspension of NaH (60% dispersion in Paraffin liquid, 800 mg, 20 mmol) in dry THF (10 mL), a solution of the crude materials in dry THF (10 mmol) was added dropwise at 0°C and the resulting mixture was stirred for 30 min at rt. Butyl iodide (2.28 mL, 20 mmol) was then added dropwise to the solution at 0°C and stirred for 4 h. An aqueous solution of $NaHCO_3$ (20 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residual materials were purified by column chromatography using hexane/EtOAc = 12~96% gradient to give **1q** as a white solid (2.2 g, 67%).

N,N'-((9H-Fluorene-9,9-diyl)bis(2-fluoro-4,1-phenylene))bis(N-butyl-2-methylacrylamide) (1q).



Rf 0.20 (hexane/EtOAc = 3/1). White solid (2.2 g, 67%). Mp = 81 °C.

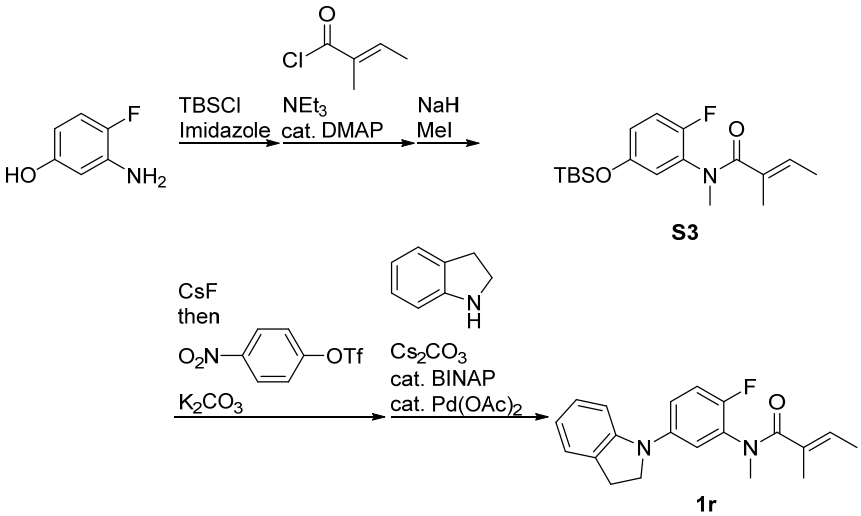
^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.80 (d, *J* = 7.3 Hz, 2H), 7.30-7.45 (m, 6H), 6.87-7.06 (m, 6H), 4.88 (bs, 2H), 4.98 (bs, 2H), 3.66 (t, *J* = 7.8 Hz, 4H), 1.79 (bs, 4H), 1.44-1.50 (m, 4H), 1.26-1.34 (m, 6H), 0.86-0.90 (m, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8, 158.8 (d, *J* = 247.0 Hz), 149.4 , 146.5 (d, *J* = 6.6 Hz), 140.3, 140.0, 129.3 (d, *J* = 11.5 Hz), 128.3, 128.1, 128.0, 125.8, 124.1 (d, *J* = 1.9 Hz), 120.5 (d, *J* = 7.6 Hz), 118.3, 116.1 (d, *J* = 22.9 Hz), 64.4, 49.0, 29.7, 20.0, 18.6, 13.8.

IR (ATR): 1655 s, 1629 s, 1507 s, 1449 m, 1392 m, 746 s.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{41}H_{42}F_2N_2O_2$ 633.3214, Found 633.3286.

Procedure for the preparation of 1r.



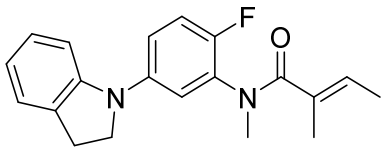
To a mixture of 3-amino-4-fluorophenol (2.5 g, 20 mmol) in DMF (30 mL), TBSCl (3.6 g, 24 mmol) and imidazole (2.0 g. 30 mmol) were added. The reaction mixture was stirred for 12 h at rt. The organic layer was extracted with Hex/EtOAc = 5/1 (50 mL × 5) and dried over Na_2SO_4. All volatiles were removed in vacuo. The obtained crude

materials were used without further purification. Acylation and methylation were followed based on the general procedure to give **S3 (**4.2 g, 62%).

To a mixture of **S3** in DMF (60 mL), CsF (9.0 g, 60 mmol) was added and the mixture was stirred for 1 h at rt. Then, 4-nitrophenyl trifluoromethane sulfonate (25 mmol, 4.0 g) and K_2CO_3 (3.2 g, 25 mmol) were added to the mixture and stirred for 12 h at rt. H_2O (ca. 20 mL) was then added, and the organic layer was extracted with Hex/EtOAc = 5/1 (50 mL × 5) and the combined organic extracts were dried over Na_2SO_4. After filtration through a silica pad, all volatiles were removed in vacuo to give the corresponding triflate.

To a mixture of the triflate (355 mg, 1.0 mmol) in toluene (5 mL) indoline (143 mg, 1.2 mmol), $Pd(OAc)_2$ (11.2 mg, 50 μmol), Cs_2CO_3 (650 mg, 2.0 mmol), and BINAP (47 mg, 75 μmol) were added and the mixture was refluxed for 12 h. The organic layer was extracted by CH_2Cl_2 (10 mL × 3) and dried over Na_2SO_4. All volatiles were removed in vacuo. The crude materials were purified by column chlomatography (hexane/EtOAc = 88:12~4:96) to give **1r** (230 mg, 72%).

(E)-N-(2-Fluoro-5-(indolin-1-yl)phenyl)-N,2-dimethylbut-2-enamide (1r).



Rf 0.56 (hexane/EtOAc = 1/1). Pale orange oil (230 mg, 72%).

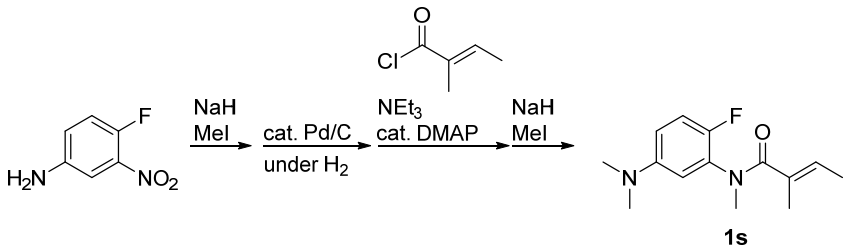
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, *J* = 6.4 Hz, 1-H), 7.02-7.14 (m, 3H), 6.96-6.98 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.78-6.81 (m, 1H), 5.84 (qq, *J* = 7.0, 1.6 Hz, 1H), 3.89 (t, *J* = 8.0 Hz, 2H), 3.31 (s, 3H), 3.15 (t, *J* = 8.0 Hz, 2H), 1.68 (s, 3H), 1.56 (dq, *J* = 6.9, 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5, 151.8 (d, *J* = 242.2 Hz), 146.8, 140.7, 132.8 (d, *J* = 13.4 Hz), 132.3, 131.0, 130.1, 127.1, 125.2, 119.3, 118.3, 117.6 (d, *J* = 7.2 Hz), 116.8 (d, *J* = 21.0 Hz), 107.4, 52.4, 36.9, 28.1, 13.7, 13.5.

IR (ATR): 1642 w, 1602 w, 1508m, 913 m, 771 m, 744 s.

HRMS (EI): Calcd for $C_{20}H_{21}FN_2O$ 324.1638, Found 324.1642.

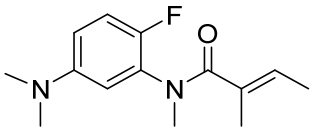
Procedure for the preparation of 1s.



To a suspension of NaH (60% dispersion in Paraffin liquid, 2.7 g, 68 mmol) in dry DMF (80 mL), a solution of 4-fluoro-3-nitroaniline (4.7 g, 30 mmol) in dry DMF (20 mL) was added dropwise at 0°C and the resulting mixture was stirred for 30 min at rt. MeI (5.7 mL, 68 mmol) was then added dropwise to the solution at 0 °C and stirred for 4 h. After addition of H_2O (40 mL) to quench the reaction, the organic layer was extracted with Hex:EtOAc = 4:1 (50 mL × 5) and dried over Na_2SO_4. All volatiles were removed in vacuo to give dimethylated product quantitatively. This material was used without further purification.

To the mixture of 4-fluoro-N,N-dimethyl-3-nitroaniline in MeOH (50 mL), 10% palladium on carbon (300 mg, 2.8 mmol) was added and stirred at room temperature for 12 h under hydrogen atmosphere (1 atm). After filtration to remove the palladium, the reaction mixture was concentrated in vacuo to give 4-fluoro-N1,N1-dimethylbenzene-1,3-diamine quantitatively. The obtained aniline was functionalized based on the typical reaction conditions to give **1s** (950mg, 13% over 4 steps).

(E)-N-(5-(Dimethylamino)-2-fluorophenyl)-N,2-dimethylbut-2-enamide (1s).



Rf 0.40 (hexane/EtOAc = 1/1). Pale orange oil (950 mg, 13%).

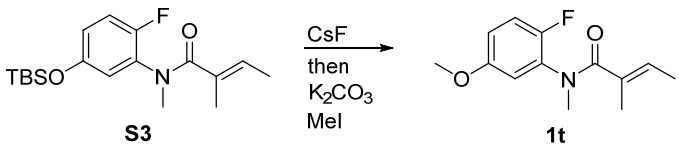
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.95 (dd, *J* = 9.4 Hz, 1H), 6.53-6.57 (m, 1H), 6.40 (dd, *J* = 3.2 Hz, 1H), 5.74 (qq, *J* = 6.9, 1.7 Hz, 1H), 3.27 (s, 3H), 2.89 (s, 6H), 1.64 (s, 3H), 1.49 (dq, *J* = 6.9, 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 173.67, 150.57 (d, *J* = 237.2 Hz), 147.55, 132.5 (d, *J* = 13.2 Hz), 132.4, 129.0, 116.4 (d, *J* = 21.3 Hz), 112.64, 112.1 (d, *J* = 6.3 Hz), 40.98, 36.86, 13.62, 13.28.

IR (ATR): 1638 m, 1607 m, 1514 s, 1350 m, 1227 m, 741 m

HRMS (EI): Calcd for $C_{14}H_{19}FN_2O$ 250.1481, Found 250.1481.

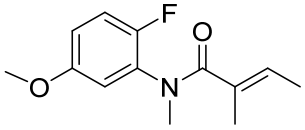
Procedure for the preparation of 1t



S3 **1t**

S3 can be obtained according to the procedure for **1r**. To the mixture of **S3** (340 mg, 1.0 mmol) DMF (10 mL), CsF (450 mg, 3.0 mmol) was added and the mixture was stirred for 1 h at rt. Then K_2CO_3 (380 mg, 3.0 mmol) and MeI (250 μmmol, 3.0 mmol) was added and stirred for 3 h at rt. After addition of H_2O (20 mL), the organic layer was extracted with Hex:EtOAc = 4:1 (20 mL × 4) and dried over Na_2SO_4. The solution was concentrated in vacuo. The obtained crude materials were purified by column chlomatography (hexane/EtOAc = 88:12~4:96) to give **1t** (223 mg, 94%).

(E)-N-(2-Fuoro-5-methoxyphenyl)-N,2-dimethylbut-2-enamide (1t).



Rf 0.51 (hexane/EtOAc = 1/1). Colorless oil (223 mg, 94%).

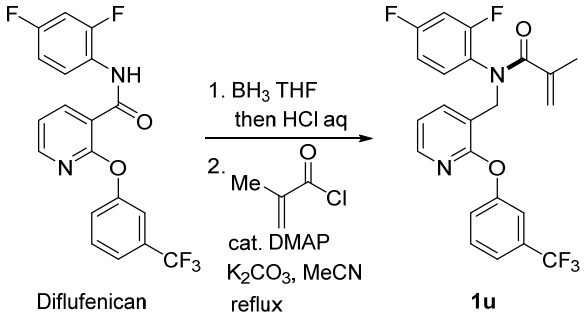
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01 (dd, *J* = 9.4 Hz, 1H), 6.73-6.77 (m, 1H), 6.64 (dd, *J* = 3.1 Hz, 1H), 5.70 (qq, *J* = 6.9, 1.4 Hz, 1H), 3.76 (s, 3H), 3.27 (s, 3H), 1.66 (s, 3H), 1.49 (dq, *J* = 6.9, 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.6, 155.7 (d, *J* = 1.9 Hz), 151.8 (d, *J* = 239.3 Hz), 133.1 (d, *J* = 13.4 Hz), 132.1, 129.6, 116.6 (d, *J* = 22.0 Hz), 114.0, 113.3 (d, *J* = 7.7 Hz) , 55.8, 36.9, 13.6, 13.4.

IR (ATR): 1663 m, 1639 m, 1605 m, 1507 s, 1211 m, 1032 m.

HRMS (EI): Calcd for $C_{13}H_{16}FNO_2$ 237.1165, Found 237.1167.

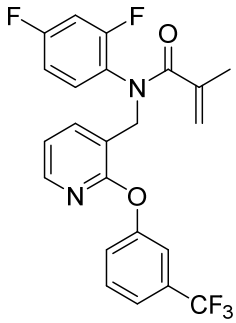
Procedure for the preparation of 1u



To a solution of Diflufenican (789 mg, 2.0 mmol) in THF (50 mL), BH_3•THF (6.0 mL, 6.0 mmol) was added and the mixture was stirred at 60 °C for 16 h. HCl aq. (4 M, 20 mL) was then added and the mixture was stirred at 60 °C for 12 h. After neutralization with NH_4OH aq., the organic layer was extracted with CH_2Cl_2 (30 mL × 5) and dried over Na_2SO_4. After filtration through a silica pad, the filtrate was concentrated in vacuo. This crude material was used for the subsequent step without further purification.

To the mixture of the crude material (300 mg) in CH_2Cl_2 (20 mL), K_2CO_3 (150 mg, 1.2 mmol), DMAP (30 mg, 250 μmmol), and methacryloyl chloride (120 μL, 1.2 mmol) were added and the mixture was refluxed for 12 h. All volatiles were removed in vacuo. The obtained crude materials were purified by column chlomatography (hexane/EtOAc = 92:8~36:64) to give **1u** as a white solid (223 mg, 62%).

N-(2,4-Dfluorophenyl)-N-((2-(3-(trifluoromethyl)phenoxy)pyridin-3-yl)methyl)yl)methyl) methacrylamide (1u).



Rf 0.15 (hexane/EtOAc = 4/1). White solid (223 mg, 62%). Mp = 163 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (dd, *J* = 2.1 Hz, 1H), 7.92 (d, *J* = 6.9 Hz, 1H), 7.40-7.47 (m, 2H), 6.98-7.10 (m, 8H), 6.76-6.80 (m, 2H), 4.97-5.11 (m, 4H), 1.84 (s, 3H).

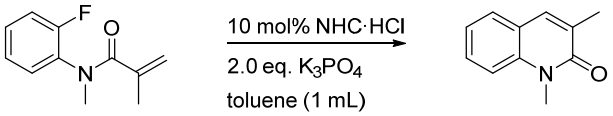
^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 160.5, 153.7, 146.7, 140.6, 139.7, 130.3, 130.2, 129.9, 124.3, 121.2, 120.4, 119.5, 119.1, 117.8, 111.9, 111.6, 105.2, 105.0, 104.7, 46.6, 20.0.

^{19}F NMR ($CDCl_3$, 375 MHz): δ -63.4, -116.8. [Perfluorobenzene (-163.0 ppm) was used as an internal standard.]

IR (ATR): 1509 m, 1425 m, 1325 s, 1243 m, 1167 m, 1127 m

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{23}H_{18}F_5N_2O_2$ 449.1210, Found 449.1292.

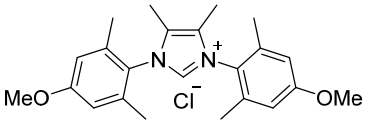
V. Optimization Studies



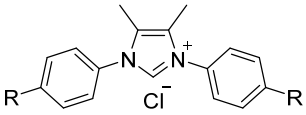
0.2 mmol — **A**

Entry	NHC	**A** (GC yield)	SM (GC yield)	note
1	$IMXy^{Me}$	32%	67%	
2	$IOMe^{Me}$	68%	28%	
3	$INMe_2^{Me}$	33%	51%	
4	$IOMe^{NMe2}$	0%	>95%	
5	IXy^{Me}	0%	>95%	
6	ICy	33%	58%	
7	I-2Ad	10%	67%	
8	IMes	0%	>95%	
9	$IMes^{Me}$	0%	>95%	
10	IPr	0%	>95%	
11	TPT	6%	77%	
12	IOMe	25%	71%	
13	$IOMe^{Me}$	>95% (100%)	0%	with CsF instead of K_3PO_4
14	$IOMe^{Me}$	20%	48%	with CsOAc instead of K_3PO_4
15	$IOMe^{Me}$	51%	22%	with Cs_2CO_3 instead of K_3PO_4
16	$IOMe^{Me}$	59%	0%	with K_2CO_3 instead of K_3PO_4
17	$IOMe^{Me}$	0%	73%	with NaOAc instead of K_3PO_4
18	$IOMe^{Me}$	27%	30%	with DBU instead of K_3PO_4

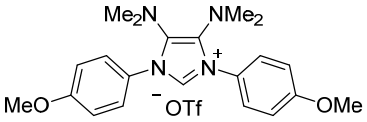
* The yield in parentheses refers to an isolated yield.



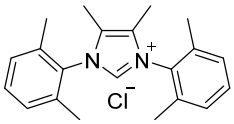
$IMXy^{Me}$



$IOMe^{Me}$: R = OMe
$INMe_2^{Me}$: R = NMe_2

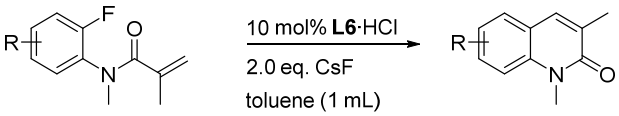


$IOMe^{NMe2}$



IXy^{Me}

VI. Typical Procedure for N-Heterocyclic Carbene-Catalyzed Concerted Nucleophilic Aromatic Substitution of Aryl Fluorides Bearing *α,β*-Unsaturated Amides

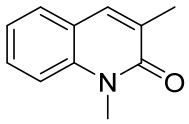


1 — **2**

1 (0.20 mmol), **L6**•HCl (6.8 mg, 0.020 mmol), CsF (65.0 mg, 0.4 mmol) and toluene (1.00 mL) were added to a 5 mL screw-capped vial in a glovebox filled with nitrogen, and the resulting mixture was stirred at 160 °C for 5 h

followed by cooling to rt. The mixture was purified by column chlomatography (hexane/EtOAc = 93:7→44:56) to give **2**.

1,3-Dimethylquinolin-2(1H)-one (2a) [CAS: 55539-83-8].



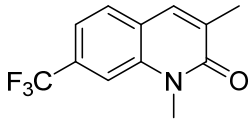
Rf 0.29 (hexane/EtOAc = 2/1). White solid (34.5 mg, 100%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (s, 1H), 7.49-7.53 (m, 2H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.19-7.23 (m, 1H), 3.75 (s, 3H), 2.27 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 139.0, 135.6, 130.0, 129.2, 127.8, 121.9, 120.7, 113.9, 29.7, 17.8.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{17}H_{12}NO$ 174.0841, Found 174.0919

1,3-Dimethyl-7-(trifluoromethyl)quinolin-2(1H)-one (2b).



Rf 0.12 (hexane/EtOAc = 2/1). White solid (42.2 mg, 88%). Mp = 159 °C.

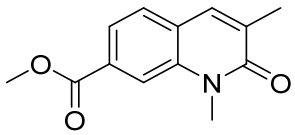
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57-7.62 (m, 3H), 7.45 (dd, *J* = 8.0, 1.1 Hz, 1H), 3.79 (s, 3H), 2.30 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 138.7, 134.7, 132.9, 131.1 (d, *J* = 32.4 Hz), 128.4, 123.9 (d, *J* = 271.2 Hz), 123.0, 118.4 (q, *J* = 3.4 Hz), 111.0 (q, *J* = 3.8 Hz), 29.9, 17.9.

IR (ATR): 1646 s, 1632 s, 1607 s, 1296 m, 1232 s, 1163 s, 1106 s, 1082 s, 988 s.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{12}H_{11}F_3NO$ 242.0714, Found 242.0794.

Methyl 1,3-dimethyl-2-oxo-1,2-dihydroquinoline-7-carboxylate (2c) [CAS: 813425-16-0].



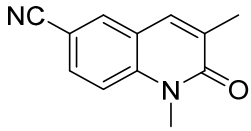
Rf 0.48 (hexane/EtOAc = 1/1). White solid (42.6 mg, 92%). Mp = 168 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (s, 1H), 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (t, *J* = 8.5 Hz, 2H), 3.98 (s, 3H), 3.80 (s, 3H), 2.29 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 162.7, 138.7, 134.8, 132.9, 130.3, 127.7, 124.0, 122.6, 115.4, 52.5, 29.9, 18.0.

HRMS (EI): Calcd for $C_{13}H_{13}NO_3$ 231.0893, Found 231.0891.

1,3-Dimethyl-2-oxo-1,2-dihydroquinoline-6-carbonitrile (2d).



Rf 0.50 (hexane/EtOAc = 3/1). White solid (37.7 mg, 95%). Mp = 192 °C.

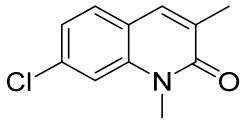
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.55 (s, 1H), 7.40 (d, *J* = 8.7 Hz, 1H), 3.76 (s, 3H), 2.29 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 141.6, 134.4, 132.5, 132.1, 131.9, 120.7, 118.5, 114.8, 105.4, 30.0, 17.8.

IR (ATR):2359 m, 2341 m, 1757 m, 1372 m, 1240 s, 1049 m, 914 m, 746 m.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{12}H_{11}N_2O$ 199.0793, Found 199.0868.

7-Chloro-1,3-dimethylquinolin-2(1H)-one (2e).



Rf 0.28 (hexane/EtOAc = 5/1). White solid (39.8 mg, 96%). Mp = 176 °C.

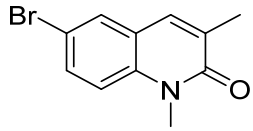
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.18 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.71 (s, 3H), 2.25 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 139.8, 135. 2, 135.0, 130.3, 128.8, 122.4, 119.1, 114.0, 29.8, 17.8.

IR (ATR): 1650 s, 1590 s, 1499 m, 1366 m, 1228 m, 1092 m, 763 m.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{11}H_{11}ClNO$ 208.0451, Found 208.0525.

6-Bromo-1,3-dimethylquinolin-2(1H)-one (2f).



Rf 0.19 (hexane/EtOAc = 3/1). White solid (56.4 mg, 95%). Mp = 165 °C.

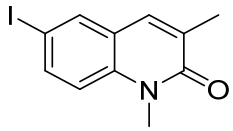
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, *J* = 1.8 Hz, 1H), 7.58 (dd, *J* = 9.2, 1.8 Hz, 1H), 7.46 (s, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 3.72 (s, 3H), 2.27 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 138.0, 134.3, 131.9, 131.6, 129.9, 122.2, 115.6, 114.7, 29.8, 17.8.

IR (ATR): 2362 w, 1649 s, 1628 m, 1216 w, 806 w.

HRMS (EI): Calcd for $C_{11}H_{10}BrNO$ 250.9946, Found 250.9944.

6-Iodo-1,3-dimethylquinolin-2(1H)-one (2g).



Rf 0.30 (hexane/EtOAc = 3/1). White solid (55.0 mg, 92%). Mp = 165 °C.

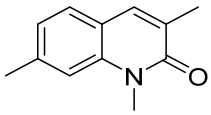
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.44 (s, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 3.71 (s, 3H), 2.26 (d, *J* = 0.9 Hz, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 138.6, 137.6, 136.0, 134.2, 131.4, 122.7, 115.9, 84.8, 29.7, 17.8.

IR (ATR):1644 s, 1619 s, 1582 s, 1407 m, 1214 m, 1102 m, 905 m, 817 m.

HRMS (EI): Calcd for $C_{11}H_{10}INO$ 298.9807, Found 298.9808.

1,3,7-Trimethylquinolin-2(1H)-one (2h).



Rf 0.29 (hexane/EtOAc = 2/1). White solid (36.3 mg, 97%). Mp = 127 °C.

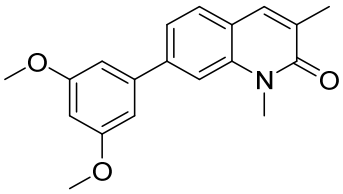
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.13 (s, 1H), 7.04 (dd, *J* = 7.8, 0.9 Hz, 1H), 3.73 (s, 3H), 2.49 (s, 3H), 2.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 139.7, 139.1, 135.5, 128.7, 127.6, 123.3, 118.5, 114.1, 29.6, 22.1, 17.7.

IR (ATR):1643 s, 1599 s, 1561 w, 1371 w, 1233 w.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{12}H_{14}NO$ 188.0997, Found 188.0995.

7-(3,5-Dimethoxyphenyl)-1,3-dimethylquinolin-2(1H)-one (2i).



Rf 0.19 (hexane/EtOAc = 3/1). White solid (56.9 mg, 92%). Mp = 188 °C.

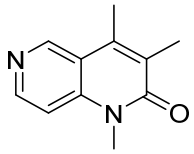
^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.52-7.55 (m, 2H), 7.45 (s, 1H), 7.40 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.76 (d, *J* = 2.1 Hz, 2H), 6.50 (t, *J* = 2.1 Hz, 1H), 3.86 (s, 6H), 3.77 (s, 3H), 2.26 (d, *J* = 0.9 Hz, 3H)

^{3}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 161.1, 142.8, 142.3, 139.3, 135.2, 130., 128.0, 121.2, 120.0, 112.4, 105.8, 99.4, 55.4, 29.7, 17.8.

IR (ATR): 1644 m, 1588 s, 1559 m, 1455 m, 1418 m, 1203 m, 1154 s.

HRMS (EI): Calcd for $C_{19}H_{19}NO_3$ 309.1365, Found 309.1360.

1,3,4-Trimethyl-1,6-naphthyridin-2(1H)-one (2j).



Rf 0.31 (hexane/EtOAc = 1/1). White solid (31.2 mg, 83%). Mp = 148 °C.

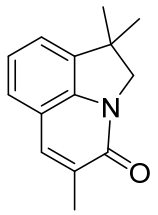
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.98 (s, 1H), 8.58 (d, *J* = 6 .0 Hz, 1H), 7.18 (d, *J* = 6.0 Hz, 1H), 3.70 (s, 3H), 2.53 (s, 3H), 2.29 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 148.7, 147.2, 143.2, 140.0, 128.7, 117.3, 108.0, 29.5, 14.6, 13.6.

IR (ATR):2362 w, 1639 s, 1617 m, 1586 s, 1363 w, 763 w.

HRMS (EI): Calcd for $C_{11}H_{12}N_2O$ 188.0950, Found 188.0952.

1,1,5-Trimethyl-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one (2k).



Rf 0.29 (hexane/EtOAc = 1/1). White solid (38.5 mg, 90%). Mp = 199 °C.

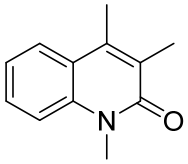
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, *J* = 0.9 Hz, 1H), 7.34 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.22 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 4.20 (s, 2H), 2.29 (d, *J* = 1.4 Hz, 3H), 1.46 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 140.1, 139.3, 133.8, 132.5, 123.1, 122.9, 121.2, 117.7, 61.7, 41.5, 29.2, 17.5.

IR (ATR): 1642 s, 1606 s, 1574 m, 1479 m, 1024 s, 998 s, 762 s.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{14}H_{16}NO$ 214.1154, Found 214.1156.

1,3,4-Trimethylquinolin-2(1H)-one (2l) [CAS: 105906-45-4].



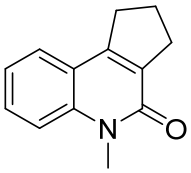
Rf 0.48 (hexane/EtOAc = 3/1). White solid (160 mg, 97%). Mp = 108 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.49-7.54 (m, 1H), 7.34 -7.37 (m, 1H), 7.25 (td, *J* = 7.6, 1.2 Hz, 1H), 3.75 (s, 3H), 2.47 (s, 3H), 2.30 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 140.8, 138.2, 129.1, 127.1, 124.8, 121.8, 121.5, 114.1, 29.8, 15.3, 13.9.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{12}H_{13}NO$ 188.0997, Found 188.0993.

5-Methyl-1,2,3,5-tetrahydro-4H-cyclopenta[c]quinolin-4-one (2m) [CAS: 28924-39-2].



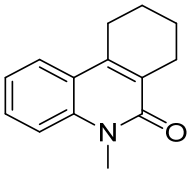
Rf 0.24 (hexane/EtOAc = 2/1). White solid (32.7 mg, 81%). Mp = 121 °C.

^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.51-7.56 (m, 2H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.22-7.26 (m, 1H), 3.69 (s, 3H), 3.14 (t, *J* = 7.6 Hz, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.18 (quint, *J* = 7.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.1, 150.0, 139.9, 133.2, 129.5, 125.4, 121.8, 119.6, 114.4, 32.2, 31.3, 29.2, 22.6.

HRMS (EI): Calcd for $C_{13}H_{13}NO$ 199.0997, Found 199.0998.

5-Methyl-7,8,9,10-tetrahydrophenanthridin-6(5H)-one (2n) [CAS: 52850-98-3].



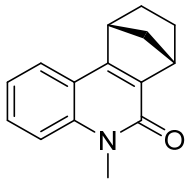
Rf 0.28 (hexane/EtOAc = 2/1). White solid (41.7 mg, 98%). Mp = 103 °C.

^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.48-7.53 (m, 1H), 7.36 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.23 (td, *J* = 7.7, 1.1 Hz, 1H), 3.69 (s, 3H), 2.84-2.87 (m, 2H), 2.58-2.62 (m, 2H), 1.76-1.89 (m, 4H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 162.2, 141.7, 138.2, 129.0, 128.6, 123.6, 121.7, 121.3, 114.1, 29.5, 25.5, 24.7, 22.02, 22.00.

HRMS (EI): Calcd for $C_{14}H_{15}NO$ 213.1154, Found 213.1155.

5-Methyl-7,8,9,10-tetrahydro-7,10-methanophenanthridin-6(5H)-one (2o).



Rf 0.35 (hexane/EtOAc = 1/1). White solid (160 mg, 84%). Mp = 137 °C.

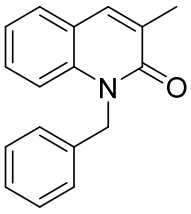
^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.70 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.49-7.54 (m, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.22-7.26 (m, 1H), 3.78 (d, *J* = 1.8 Hz, 1H), 3.68 (s, 3H), 3.62 (q, *J* = 1.4 Hz, 1H), 1.93-2.03 (m, 2H), 1.73 (dt, *J* = 6.3, 2.2 Hz, 1H), 1.52 (dt, *J* = 8.9, 1.6 Hz, 1H), 1.09-1.30 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 154.3, 140.0, 135.7, 129.5, 124.6, 121.7, 117.6, 114.8, 48.6, 42.0, 41.1, 29.3, 26.5, 25.6.

IR (ATR):1638 s, 1583 m, 1501 s, 1366 m, 1302 m, 760 s, 742 s.

HRMS (EI): Calcd for $C_{15}H_{15}NO$ 225.1154, Found 225.1150.

1-Benzyl-3-methylquinolin-2(1H)-one (2p).



Rf 0.28 (hexane/EtOAc = 3/1). White solid (47.0 mg, 94%). Mp = 92 °C.

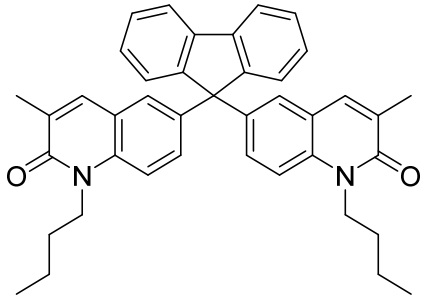
^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.64 (s, 1H), 7.53 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.15-7.39 (m, 8H), 5.55 (s, 2H), 2.27 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 138.5, 136.5, 136.3, 130.0, 129.3, 128.7, 127.9, 127.2, 126.6, 122.1, 121.0, 114.8, 46.3, 17.8.

IR (ATR): 2362 w, 1647 s, 1596 s, 1454 w, 1229 w, 913 w, 749 m, 729 w.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{17}H_{16}NO$ 250.1232, Found 250.1234.

6,6'-(9H-Fluorene-9,9-diyl)bis(1-butyl-3-methylquinolin-2(1H)-one) (2q).



Rf 0.42 (hexane/EtOAc = 1/1). White solid (81.3 mg, 69%). Mp = 140 °C.

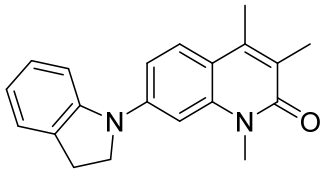
^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.81 (d, *J* = 7.3 Hz, 2H), 7.35-7.43 (m, 8H), 7.30 (td, *J* = 7.4, 1.4 Hz, 4H), 7.22 (d, *J* = 9.2 Hz, 2H), 4.24 (t, *J* = 8.0 Hz, 4H), 2.19 (d, *J* = 0.9 Hz, 6H), 1.66-1.73 (m, 4H), 1.41-1.50 (m, 4H), 0.97 (t, *J* = 7.6 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 150.8, 140.0, 139.0, 137.2, 135.7, 130.2, 129.4, 127.9, 127.9, 126.9, 125.9, 120.8, 120.5, 114.2, 64.1, 42.5, 29.6, 20.3, 17.6, 13.8.

IR (ATR): 1648 s, 1627 m, 1599 m, 1567 m, 913 m, 740 s.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{41}H_{41}N_2O_2$ 593.3168, Found 593.3177.

7-(Indolin-1-yl)-1,3,4-trimethylquinolin-2(1H)-one (2r).



Rf 0.17 (hexane/EtOAc = 2/1). White solid (46.2 mg, 76%). Mp = 164 °C.

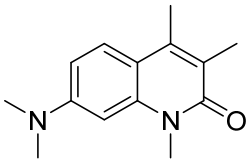
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.23 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.12-7.16 (m, 2H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.84 (td, *J* = 7.3, 0.9 Hz, 1H), 4.08 (t, *J* = 8.2 Hz, 2H), 3.73 (s, 3H), 3.19 (t, *J* = 8.2 Hz, 2H), 2.44 (s, 3H), 2.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 145.9, 144.8, 140.8, 139.6, 131.7, 127.2, 125.7, 125.3, 123.8, 119.9, 115.4, 111.7, 108.7, 100.9, 52.1, 29.8, 28.1, 15.2, 13.6.

IR (ATR): 1644 m, 1588 s, 1559 m, 1455 m, 1418 m, 1203 m, 1154 s.

HRMS (EI): Calcd for $C_{20}H_{20}N_2O$ 304.1576, Found 304.1574.

7-(Dimethylamino)-1,3,4-trimethylquinolin-2(1H)-one (2s).



Rf 0.33 (CH_2Cl_2/EtOAc = 4/1). White solid (32.7 mg, 71%). Mp = 125 °C.

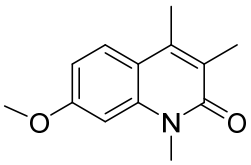
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, *J* = 9.2 Hz, 1H), 6.68 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.41 (d, *J* = 2.7 Hz, 1H), 3.72 (s, 3H), 3.08 (s, 6H), 2.40 (s, 3H), 2.24 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 150.9, 141.1, 139.9, 125.7, 121.6, 112.3, 107.8, 95.5, 40.4, 29.7, 15.2, 13.5.

IR (ATR): 1735 m, 1648 m, 1591 s, 1372 m, 1238 s, 1205 m, 1156 m, 1043 m.

HRMS (EI): Calcd for $C_{14}H_{18}N_2O$ 230.1419, Found 230.1418.

7-Methoxy-1,3,4-trimethylquinolin-2(1H)-one (2t).



Rf 0.28 (hexane/EtOAc = 3/1). White solid (33.8 mg, 78%). Mp = 118 °C.

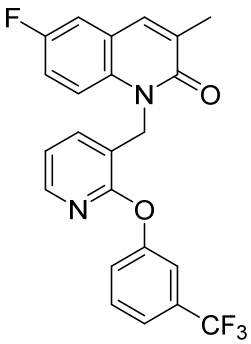
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, *J* = 8.7 Hz, 1H), 6.84 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.79 (d, *J* = 2.3 Hz, 1H), 3.92 (s, 3H), 3.72 (s, 3H), 2.43 (s, 3H), 2.26 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 160.4, 140.8, 139.8, 126.2, 124.1, 115.7, 108.9, 98.6, 55.5, 29.9, 15.4, 13.6.

IR (ATR): 1631 s, 1591 s, 1451 w, 1319 m, 1238 s, 742 m.

HRMS (EI): Calcd for $C_{13}H_{15}NO_2$ 217.1103, Found 217.1104.

6-Fluoro-3-methyl-1-((2-(3-(trifluoromethyl)phenoxy)pyridin-3-yl)methyl)quinolin-2(1H)-one (2u).



Rf 0.35 (hexane/EtOAc = 2/1). White solid (80.4 mg, 94%). Mp = 171 °C.

^{1}H NMR (CD_2Cl_2, 400 MHz): δ 8.01 (q, *J* = 2.1 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.20-7.27 (m, 3H), 7.15 (td, *J* = 8.7, 2.7 Hz, 1H), 6.92 (dd, *J* = 7.6, 4.8 Hz, 1H), 5.65 (s, 2H), 2.29 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 159.9, 159.1, 156.7, 153.8, 146.1, 137.2, 135.51, 135.48, 134.65, 134.64, 132.6, 132.2, 131.9, 131.6, 130.2, 127.7, 125.0, 124.8, 122.3, 121.9, 121.8, 121.7, 121.61, 121.57, 121.54, 119.9, 119.6, 118.6, 118.52, 118.48, 118.45, 117.4, 117.2, 115.9, 115.8, 113.2, 113.0, 41.0, 17.8.

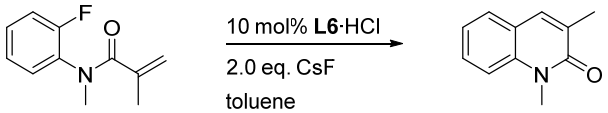
^{19}F NMR ($CDCl_3$, 375 MHz): δ -63.6, -122.1.

Perfluorobenzene (-163.0 ppm) was used as an internal standard.

IR (ATR):1652 m, 1425 s, 1324 s, 1240 s, 1165 m, 1126 m.

HRMS (FAB+, [M+H$^+$]): Calcd for $C_{23}H_{17}F_4N_2O_2$ 429.1148, Found 429.1227.

VIII. Procedure for a Gram Scale Reaction



1a 7.8 mmol (1.5 g) **2a** 92% (1.25 g)

1a (1.5 g, 7.8 mmol), **L6**•HCl (530 mg, 780 μmol), CsF (2.5 g, 15.6 mmol) and toluene (40 mL) were added to a 100 mL two-necked round bottom flask with a reflux condenser under nitrogen, and the resulting mixture was refluxed for 24 h followed by cooling to rt. After addition of H_2O (20 mL), the mixture was extracted with CH_2Cl_2 (20 mL × 3) and dried over Na_2SO_4. The mixture was purified by column chromatography (hexane/EtOAc = 93:7→44:56) to give **2a** as a pale yellow solid (1.25 g, 92%).

VIII. Computational details

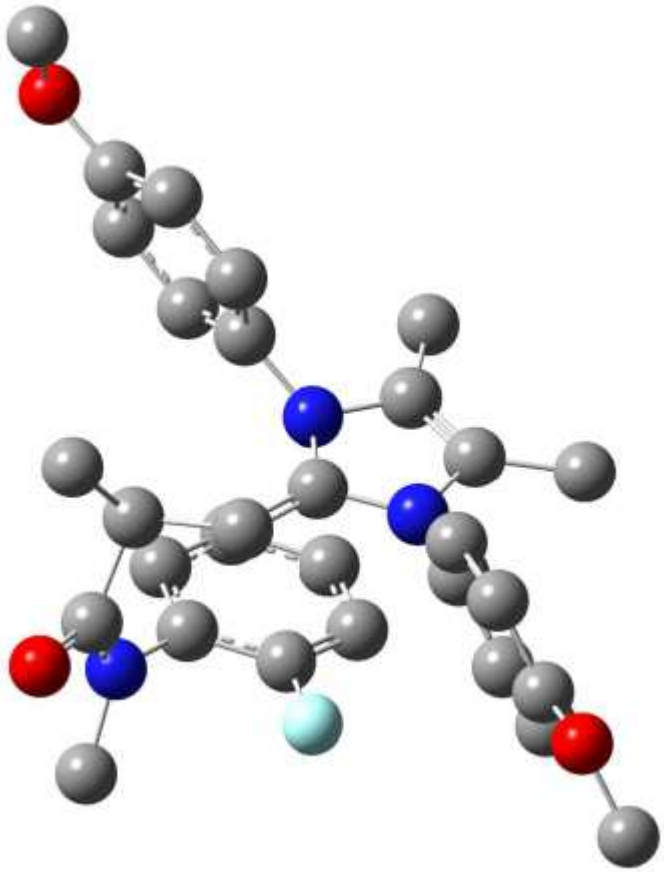
Calculations were performed with the Gaussian 09 (G09) program.[49] Geometry optimizations and frequency calculations for all reported structures were performed using M06-2X with the 6-31+G* basis set for C, H, O, N, and F. PCM[50-52] solvent effects were incorporated for all calculations with toluene as the solvent. Each reported minimum has zero imaginary frequency and each transition state (TS) structure has only one imaginary frequency. From TSs, reaction paths were traced by the intrinsic reaction coordinate (IRC) method[52, 53] to obtain the energy-minimum geometries. Energy changes were shown by the use of Gibbs free energies (T = 298.15 K and P = 1 atm). Electronic structures and properties were analyzed by the Natural Bond Orbitals (NBO)[54] version 3.1[55] method at the M06-2X level of theory.

VIII-II. M0-2X/6-31+G* optimized energies for calculated structures in Figure 4a

structure	E (a.u.)	H (a.u.)	G^o (a.u.)	Im. Freq.
Int 1	-1650.965922	-1650.964978	-1651.068879	-
TS	-1650.932258	-1650.931314	-1651.033331	426.38i
Int 2	-1650.987685	-1650.986741	-1651.087796	-

VIII-III. Cartesian coordinates of the M0-2X/6-31+G* optimized geometries

・Int1

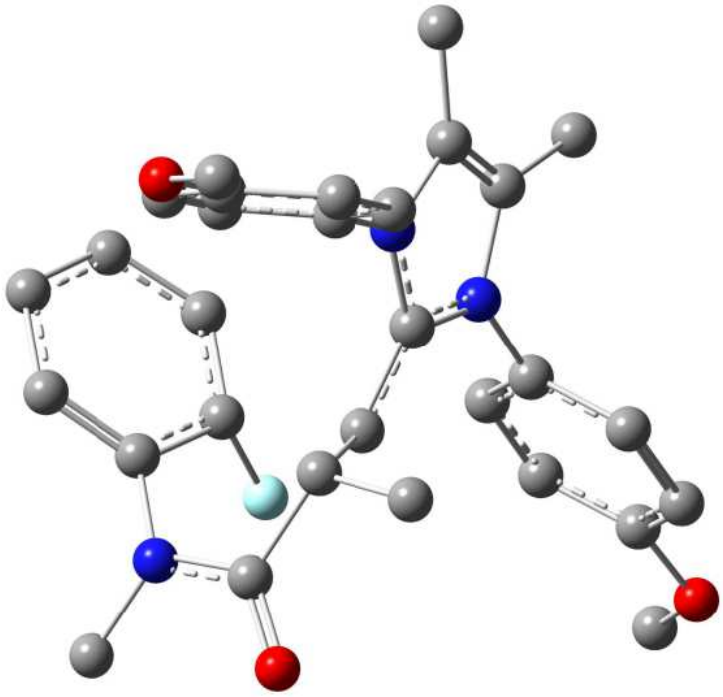


C	0.24328800	-0.45800500	0.08914400
N	1.31300700	-0.91029300	0.86033100
C	0.85186200	-1.32150000	2.12597400
C	-0.47827200	-1.14409300	2.16211000
N	-0.88881600	-0.60276500	0.90709800
C	2.63436600	-1.09525600	0.37384400
C	-2.15004900	-0.98846600	0.35222400
C	-3.33079300	-0.42515400	0.83704800
C	-4.55778500	-0.82890400	0.33848000
C	-4.62355600	-1.79464600	-0.66933200
C	-3.44750900	-2.35980200	-1.16155700
C	-2.22006500	-1.95836300	-0.63937700
C	3.43235800	-0.00331400	0.05876600
C	4.72812500	-0.18434000	-0.41979000
C	5.23384600	-1.47612200	-0.56756700
C	4.43552900	-2.57714600	-0.24578200
C	3.14134900	-2.38575300	0.20668500
O	-5.87002100	-2.11814400	-1.10362600

C	-5.97724400	-3.09260000	-2.12538800
O	6.48047200	-1.76173700	-1.02378800
C	7.32158800	-0.67391300	-1.36381500
C	0.31376500	0.03158800	-1.17047500
C	-0.78926300	0.78471700	-1.87311400
C	-1.24851200	0.14175600	-3.18224800
C	-0.20377900	2.17163600	-2.15260100
O	0.33852900	2.43665900	-3.21231100
N	-0.24521000	3.09660400	-1.13433600
C	0.44329300	4.37412400	-1.30560300
C	-0.75057800	2.83180500	0.16773600
C	-2.09830400	2.99984800	0.47963500
C	-2.55433700	2.82147200	1.78043500
C	-1.66280700	2.46127900	2.78825700
C	-0.31368300	2.29058800	2.50049600
C	0.11690600	2.49042600	1.20113300
F	1.42785900	2.37661000	0.93008000
H	-3.27156100	0.33492600	1.60559200
H	-5.48222700	-0.40345400	0.70980900
H	-3.46945000	-3.11165600	-1.93906300
H	-1.30266800	-2.38934400	-1.02454400
H	3.02782100	0.99360300	0.17900100
H	5.32482800	0.68332200	-0.66599100
H	4.84712900	-3.57120800	-0.37176300
H	2.51036500	-3.23662800	0.44008600
H	-5.45455300	-2.77193800	-3.03125700
H	-7.03943300	-3.19321300	-2.33522700
H	-5.57800100	-4.05535000	-1.79287300
H	7.51764100	-0.04262100	-0.49215100
H	6.88030400	-0.07050000	-2.16214800
H	8.25373500	-1.11148000	-1.71314800
H	1.28183600	0.01316200	-1.65635100
H	-1.64392000	0.89016700	-1.20309400
H	-0.40271900	0.03844800	-3.86294800
H	-2.00983400	0.75184200	-3.67511700
H	-1.66510800	-0.84561600	-2.97815100
H	1.46368800	4.32500600	-0.91234100
H	0.48545700	4.60796600	-2.36671200
H	-0.10936400	5.14975600	-0.77523600
H	-2.77710000	3.27770400	-0.31915800

H	-3.60544300	2.95611200	2.00574300
H	-2.01449800	2.32384200	3.80406800
H	0.40863000	2.01724000	3.26003100
C	1.81490900	-1.74109700	3.18188200
H	2.32391700	-2.67192100	2.91986800
H	2.58472600	-0.97665100	3.32169800
H	1.29508300	-1.89012200	4.12743100
C	-1.45953100	-1.34880700	3.26147000
H	-1.93012100	-0.40153800	3.54495900
H	-2.25580800	-2.03723700	2.96579100
H	-0.95951100	-1.76290100	4.13660600

・TS



C	0.25564200	-0.79691800	-0.13069800
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C	-0.31733900	-2.78286100	0.81833300
N	-0.78966000	-1.58252000	0.25550700
C	2.71192900	-1.12261900	-0.14088100
C	-2.17864300	-1.33499200	0.00595200
C	-2.90785400	-0.51422800	0.86543400
C	-4.24682900	-0.26792000	0.60759700
C	-4.87034600	-0.85415900	-0.50294700
C	-4.14346700	-1.69636200	-1.35084100
C	-2.79392800	-1.93166000	-1.08727700
C	3.54299100	-0.48309600	0.76718600
C	4.85283600	-0.15521700	0.41322000
C	5.31938800	-0.47194000	-0.86481000
C	4.47443400	-1.11140100	-1.78382900
C	3.17768100	-1.43442700	-1.42161300
O	-6.17992500	-0.55064700	-0.67414800
C	-6.84521600	-1.09037400	-1.80280500
O	6.57155600	-0.20262100	-1.30753200
C	7.45639100	0.46924300	-0.42765800
C	0.27491600	0.54803300	-0.56421000
C	-0.86057500	1.19014500	-1.34723700
C	-0.98820400	0.64513500	-2.76878700

C	-0.61456900	2.70471100	-1.38230800
O	-0.37594800	3.31113900	-2.42305100
N	-0.68986800	3.33627400	-0.17639700
C	-0.34042700	4.75044000	-0.10601000
C	-0.74589500	2.55672100	1.02050900
C	-1.78845300	2.68071600	1.92265700
C	-1.82782300	1.92499900	3.10227200
C	-0.80549500	0.99516200	3.32035200
C	0.23277900	0.82708400	2.41332000
C	0.29967200	1.60424600	1.22111700
F	1.59352300	2.05962700	0.91046000
H	-2.41273200	-0.05019700	1.71320600
H	-4.82937000	0.38409800	1.25143000
H	-4.60566900	-2.16276500	-2.21271300
H	-2.21360300	-2.57417600	-1.74506100
H	3.16760000	-0.22575100	1.75284400
H	5.48410900	0.34960600	1.13464300
H	4.85876800	-1.34055500	-2.77262100
H	2.51210100	-1.92669700	-2.12605700
H	-6.37119200	-0.75756900	-2.73321100
H	-7.86553500	-0.71184300	-1.75709900
H	-6.85807500	-2.18561600	-1.76454400
H	7.63753400	-0.12425000	0.47586900
H	7.06149700	1.45327600	-0.15140000
H	8.38922300	0.59032200	-0.97695400
H	1.25544600	0.82211700	-0.95021000
H	-1.80609400	1.04735900	-0.81046200
H	-0.06786200	0.82884000	-3.33083200
H	-1.81193600	1.12655200	-3.30500500
H	-1.17082100	-0.43352200	-2.73874900
H	0.74640100	4.88788000	-0.16011100
H	-0.80497200	5.28037400	-0.93900800
H	-0.70803200	5.15160500	0.83927900
H	-2.57553900	3.39833200	1.69664300
H	-2.62871100	2.05797300	3.82145600
H	-0.80406000	0.39661200	4.22880300
H	1.03977000	0.12826500	2.62062400
C	2.07708300	-3.67756600	1.26853100
H	2.74943900	-3.96395200	0.45293500

H	2.68848800	-3.23319900	2.06152800
H	1.60867600	-4.58204900	1.66136500
C	-1.25590800	-3.81379500	1.34345400
H	-1.92341500	-3.38617600	2.09953400
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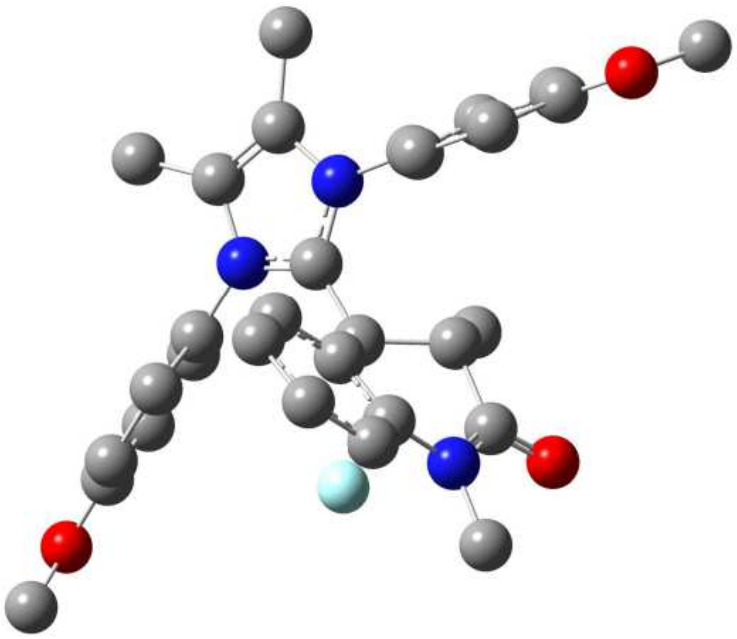
H	-0.69289600	-4.62831000	1.80384600

- Int 2



C	0.08654000	-0.96447500	0.03129700
N	1.17150200	-1.74846500	0.14448400
C	0.79480100	-3.05369800	0.45797600
C	-0.56508700	-3.05801800	0.53277600
N	-0.98059400	-1.75352400	0.26905100
C	2.53564900	-1.32828500	-0.04300900
C	-2.35821200	-1.34589800	0.21036600
C	-2.91658900	-0.58738800	1.24001400
C	-4.23471400	-0.17232000	1.14140100
C	-5.00467000	-0.52013600	0.02199000
C	-4.44646900	-1.30191600	-0.99550100
C	-3.11890200	-1.71238100	-0.89224200
C	3.12561500	-0.45700100	0.85812500
C	4.44693600	-0.05740500	0.67209400
C	5.16686600	-0.54698300	-0.41951000
C	4.56398500	-1.43750600	-1.31901900
C	3.24712400	-1.81907400	-1.13717000

O	-6.27505700	-0.05984300	0.01634100
C	-7.07823800	-0.32968800	-1.12167400
O	6.45214000	-0.21949000	-0.69201800
C	7.07023900	0.76686600	0.11662600
C	0.11563700	0.49475400	-0.24756600
C	-0.86024600	0.94464900	-1.34845300
C	-0.62371200	0.17339100	-2.64227900
C	-0.66765000	2.43673700	-1.59756200
O	-0.86555300	2.93223000	-2.69502400
N	-0.35735800	3.21639700	-0.50170200
C	-0.15613100	4.64171900	-0.71747300
C	-0.28207000	2.69896400	0.80239900
C	-0.40583800	3.54054700	1.91338900
C	-0.30075900	3.02865100	3.20631100
C	-0.07519100	1.67101800	3.40627400
C	0.04076300	0.83205900	2.29659800
C	-0.06043700	1.32213700	0.99681000
F	2.12214400	1.50807300	-1.67567000
H	-2.31697600	-0.30529700	2.09932000
H	-4.69060500	0.43112400	1.91958000
H	-5.02138800	-1.58505800	-1.86885300
H	-2.66928600	-2.30143100	-1.68710600
H	2.55513000	-0.06657700	1.69592400
H	4.88652800	0.64528600	1.36912200
H	5.13846100	-1.78533500	-2.17108200
H	2.75970100	-2.47532500	-1.85296000
H	-6.62668300	0.09207600	-2.02631100
H	-8.03572700	0.15287400	-0.93126800
H	-7.22954000	-1.40759700	-1.24755800
H	7.16702700	0.42098800	1.15246400
H	6.50371000	1.70366900	0.08785800
H	8.06073800	0.92292000	-0.30912100
H	1.12736000	0.76998800	-0.70991500
H	-1.90743600	0.84346400	-1.02303400
H	0.41701300	0.32594600	-2.94788500
H	-1.28739400	0.52801600	-3.43335000
H	-0.80363700	-0.89829600	-2.49184900
H	0.69256300	4.97819700	-0.11753100
H	0.06244900	4.79215000	-1.77262300
H	-1.04808000	5.22117700	-0.45126900

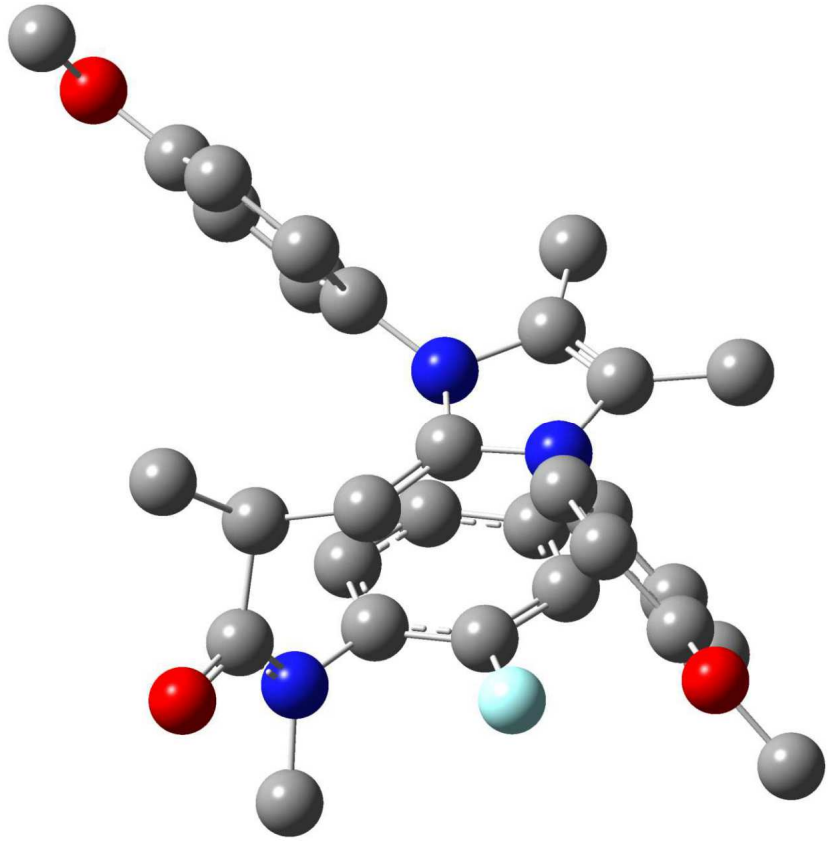
H	-0.58855700	4.60024500	1.77324100
H	-0.39701000	3.70084500	4.05387300
H	0.01247900	1.26449300	4.40925200
H	0.21671800	-0.23226800	2.45470600
C	1.79207300	-4.13993200	0.67683000
H	2.27680800	-4.43950200	-0.25699800
H	2.57417200	-3.81239500	1.36831400
H	1.29653200	-5.01559800	1.10041400
C	-1.53253900	-4.14754500	0.84727400
H	-2.23510100	-3.83179000	1.62454300
H	-2.11450200	-4.43705200	-0.03323600
H	-0.99448800	-5.02770200	1.20460700

VIII-IV. M0-2X/def2-TZVPP optimized energies for calculated structures in Figure 4a

structure	*E* (a.u.)	*H* (a.u.)	G^o (a.u.)	Im. Freq.
Int 1	-1651.576870	-1651.575926	-1651.678936	-
TS	-1651.542380	-1651.541436	-1651.637218	437.43i
Int 2	-1651.604942	-1651.603998	-1651.706712	-

VIII-V. Cartesian coordinates of the M0-2X/def2-TZVPP optimized geometries

・Int1



C	0.09222400	-0.46933400	0.00547300
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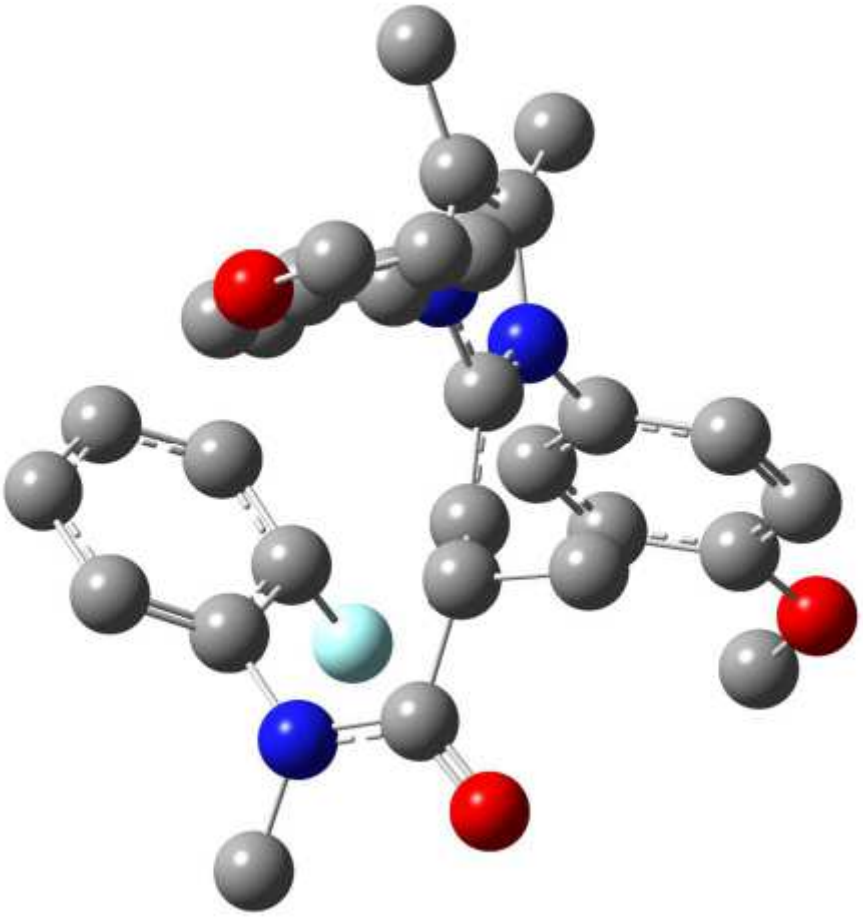
C	0.76596500	-1.47506400	1.95179200
C	-0.54970400	-1.25773300	2.06298000
N	-0.99765000	-0.62654800	0.87029900
C	2.47183300	-1.16464700	0.13867000
C	-2.31769400	-0.87883400	0.38875600
C	-3.41174700	-0.23244700	0.95886800
C	-4.69405400	-0.51137800	0.52704900
C	-4.90602400	-1.43485600	-0.49660800
C	-3.81764500	-2.08370600	-1.07177800
C	-2.53415400	-1.80585200	-0.61806300
C	3.57358100	-0.53029000	0.68630500
C	4.84727300	-0.72999100	0.16335200

C	5.01253700	-1.55850600	-0.94052300
C	3.90110200	-2.18474800	-1.50917900
C	2.64681200	-1.99302800	-0.97021100
O	-6.19624100	-1.63446100	-0.86308900
C	-6.44821800	-2.55524000	-1.90445100
O	6.20500400	-1.81313600	-1.53251200
C	7.34894600	-1.17232200	-1.00770200
C	0.12444000	0.11988400	-1.21025900
C	-0.97322100	0.97009900	-1.79507700
C	-1.54310400	0.42287300	-3.10128200
C	-0.38276700	2.35887300	-2.04683100
O	-0.08576100	2.73995800	-3.16441900
N	-0.16814800	3.17154400	-0.96047900
C	0.53188500	4.43256700	-1.18506700
C	-0.30939700	2.75333900	0.38923300
C	-1.51555800	2.85249900	1.06780500
C	-1.60694800	2.50301900	2.41046800
C	-0.48751100	2.04335200	3.08650000
C	0.73043200	1.93727900	2.42656900
C	0.79893700	2.30045000	1.09923300
F	1.97226400	2.21257300	0.45961400
H	-3.24473600	0.49488800	1.74122000
H	-5.55100900	-0.01709500	0.96381100
H	-3.95191100	-2.80541700	-1.86350400
H	-1.68528300	-2.30559300	-1.06700300
H	3.43574500	0.13939800	1.52450200
H	5.68815600	-0.22507500	0.61399200
H	4.05034000	-2.82191200	-2.37009600
H	1.78296500	-2.47611700	-1.40844100
H	-5.95659600	-2.24670900	-2.82992000
H	-7.52401900	-2.56186800	-2.05136600
H	-6.11221300	-3.55845500	-1.63278600
H	7.52266700	-1.46419800	0.03061400
H	7.25251500	-0.08592900	-1.06756500
H	8.18659800	-1.49492700	-1.61863100
H	1.06946800	0.11461800	-1.73738700
H	-1.77692500	1.07888400	-1.06528200
H	-0.74780700	0.30767900	-3.83597300
H	-2.29121500	1.09623200	-3.52096200
H	-2.00189000	-0.54810000	-2.92289500

H	1.60839500	4.27709400	-1.28043700
H	0.16329300	4.88292300	-2.10220200
H	0.33415600	5.09441500	-0.34502000
H	-2.38113700	3.21302800	0.52642800
H	-2.55308100	2.59755700	2.92656400
H	-0.55378400	1.76828500	4.13058000
H	1.62089900	1.57728300	2.92395000
C	1.73708300	-2.06774900	2.90606300
H	2.31705400	-2.85777300	2.42578700
H	2.44708800	-1.32549900	3.27771600
H	1.21221000	-2.49477800	3.75722200
C	-1.48747300	-1.53483700	3.17955900
H	-1.92310800	-0.60853100	3.56329800
H	-2.31171200	-2.17629200	2.86226400
H	-0.96267700	-2.02915900	3.99401900

・TS

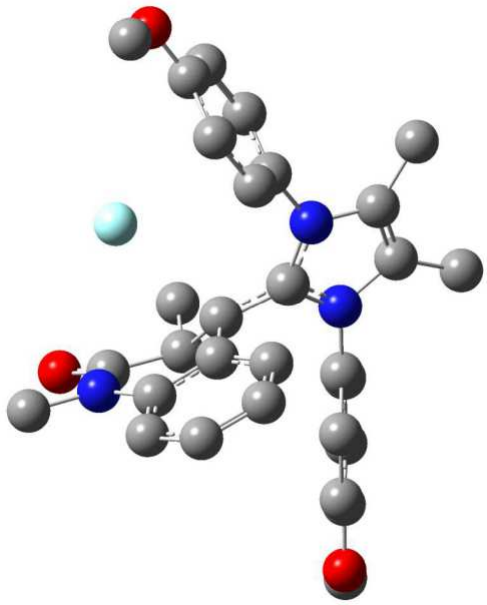


C	0.25575300	-0.79665300	-0.12833400
N	1.37867100	-1.49245200	0.22866900
C	1.03235700	-2.72424900	0.80146600

C	-0.31851900	-2.78143100	0.82237500
N	-0.79010900	-1.58150700	0.25795600
C	2.71173900	-1.12370800	-0.13769300
C	-2.17887900	-1.33418200	0.00699300
C	-2.90813000	-0.51063900	0.86373000
C	-4.24702000	-0.26489200	0.60496000
C	-4.87052300	-0.85467500	-0.50369200
C	-4.14365500	-1.69976000	-1.34874500
C	-2.79413700	-1.93429600	-1.08438000
C	3.54249200	-0.48071500	0.76818500
C	4.85236300	-0.15391500	0.41325400
C	5.31927500	-0.47538400	-0.86345800
C	4.47461200	-1.11834600	-1.78028900
C	3.17781900	-1.44012500	-1.41718300
O	-6.18011200	-0.55171400	-0.67583400
C	-6.84533000	-1.09452800	-1.80305400
O	6.57155700	-0.20778300	-1.30683800
C	7.45660000	0.46619900	-0.42881900
C	0.27616100	0.54754900	-0.56396300
C	-0.85811700	1.18936400	-1.34881100
C	-0.98703000	0.64046100	-2.76873800
C	-0.60793900	2.70346200	-1.38839200
O	-0.36202000	3.30281300	-2.43132800
N	-0.69026600	3.33787800	-0.18356500
C	-0.33728500	4.74996400	-0.10078500
C	-0.74840000	2.55930200	1.01424200
C	-1.79229600	2.68444500	1.91468500
C	-1.83256300	1.93149400	3.09597400
C	-0.80936900	1.00350200	3.31802500
C	0.23039400	0.83435400	2.41295900
C	0.29796900	1.60852300	1.21893300
F	1.59179400	2.06405000	0.90846900
H	-2.41315000	-0.04427100	1.71024300
H	-4.82953600	0.38917600	1.24674000
H	-4.60589700	-2.16896800	-2.20907200
H	-2.21382100	-2.57894200	-1.74009100
H	3.16686800	-0.21975800	1.75280100
H	5.48336600	0.35379700	1.13288500
H	4.85915300	-1.35117800	-2.76814000

H	2.51243800	-1.93501500	-2.11998800
H	-6.37093600	-0.76466200	-2.73431700
H	-7.86551900	-0.71548300	-1.75871000
H	-6.85863800	-2.18964600	-1.76156300
H	7.63642700	-0.12419300	0.47700000
H	7.06276900	1.45174700	-0.15644900
H	8.38993300	0.58409100	-0.97795500
H	1.25730500	0.82029100	-0.94938600
H	-1.80381400	1.05008500	-0.81149200
H	-0.06653300	0.82085900	-3.33154600
H	-1.81008400	1.12175100	-3.30614700
H	-1.17171800	-0.43774600	-2.73539300
H	0.74846700	4.87571100	-0.00839700
H	-0.67982200	5.25680300	-1.00356800
H	-0.82346300	5.18308000	0.77505200
H	-2.58013200	3.40038900	1.68596600
H	-2.63471300	2.06520700	3.81361100
H	-0.80860200	0.40721500	4.22796000
H	1.03783700	0.13685300	2.62296700
C	2.07530600	-3.67639800	1.27525000
H	2.74742000	-3.96490600	0.46020100
H	2.68706800	-3.23084300	2.06730200
H	1.60629700	-4.57976900	1.66992100
C	-1.25773100	-3.81148500	1.34807200
H	-1.92682400	-3.38232700	2.10186100
H	-1.88196800	-4.23447700	0.55399100
H	-0.69531200	-4.62470800	1.81145600

・Int2



C	-0.06224200	-0.92856700	0.03846900
N	0.99390300	-1.75447500	0.23603500
C	0.56177800	-3.05894400	0.46492000
C	-0.78893300	-3.04290800	0.39759800
N	-1.15649800	-1.72065800	0.14622300
C	2.36892200	-1.41282400	0.01709700
C	-2.50189400	-1.24013000	0.17025300
C	-2.89428300	-0.34464300	1.16052600
C	-4.18722100	0.13358600	1.17467400
C	-5.10488900	-0.28670300	0.20787200
C	-4.71182400	-1.18982000	-0.77556800
C	-3.40372700	-1.65834700	-0.78980200
C	3.07925000	-0.66252800	0.93125100
C	4.41152800	-0.34892000	0.68917000
C	5.02530500	-0.80136300	-0.47374200
C	4.30323300	-1.56969700	-1.38967000
C	2.98124100	-1.86760800	-1.14666700
O	-6.34627600	0.23523300	0.30627900
C	-7.30106000	-0.13487900	-0.66943000
O	6.31170700	-0.54740700	-0.80227900
C	7.06354900	0.27953200	0.06358300
C	-0.00855700	0.48719200	-0.22888700
C	-0.97382300	1.04472400	-1.26635600
C	-0.99169300	0.22931700	-2.55524500
C	-0.58957600	2.48216200	-1.60238200
O	-0.80596700	2.95471300	-2.70371000
N	-0.03190800	3.23166100	-0.59926500

C	0.32770200	4.60730500	-0.89697200
C	0.14649700	2.74886900	0.71344900
C	0.31990800	3.62997400	1.77287300
C	0.53891100	3.16166100	3.06482600
C	0.56459100	1.79679300	3.29679200
C	0.37499300	0.91356800	2.24227600
C	0.18397800	1.35215700	0.92586700
F	2.18966600	1.20744600	-1.67323500
H	-2.17534300	-0.00961900	1.89744400
H	-4.51345800	0.83886100	1.92619200
H	-5.40051600	-1.52437200	-1.53586100
H	-3.08471500	-2.34097200	-1.56662400
H	2.59847300	-0.30313100	1.82954700
H	4.94812900	0.25166100	1.40713100
H	4.79574700	-1.89886500	-2.29381100
H	2.40580200	-2.43745800	-1.86502400
H	-6.97164300	0.15532800	-1.66914800
H	-8.21197200	0.39963800	-0.41886500
H	-7.49080800	-1.21001100	-0.64459000
H	7.17386200	-0.17979100	1.04840700
H	6.59720800	1.26090400	0.16936400
H	8.04132100	0.38977400	-0.39538000
H	1.46290900	0.86918200	-1.10645600
H	-2.00797600	1.12442000	-0.89011200
H	-0.00005200	0.23292200	-3.00997200
H	-1.69813200	0.64780500	-3.26799700
H	-1.27448500	-0.80397800	-2.35300600
H	1.29783500	4.82786300	-0.45476100
H	0.37909800	4.71682600	-1.97392600
H	-0.41188600	5.30891600	-0.50524700
H	0.28628900	4.69520400	1.59638400
H	0.67607300	3.86490800	3.87441100
H	0.71702800	1.41308700	4.29732400
H	0.37346500	-0.15252300	2.44446500
C	1.51128600	-4.16876300	0.74037700
H	2.09935400	-4.42558300	-0.14103400
H	2.20855300	-3.88810800	1.53030700
H	0.96477400	-5.05377000	1.05726500
C	-1.78786900	-4.12490900	0.59576100

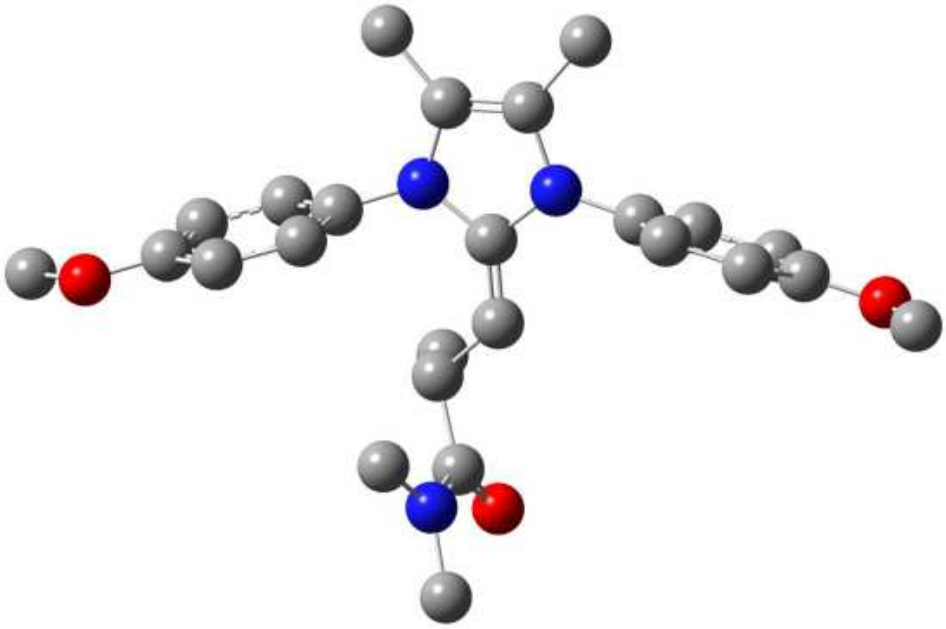
H	-2.54595800	-3.82468000	1.32000400
H	-2.29921000	-4.38008400	-0.33262100
H	-1.29144800	-5.01908100	0.96456000

VIII-VI. M0-2X/6-31+G* optimized energies for calculated structures in Figure 4b

structure	*E* (a.u.)	*H* (a.u.)	G^o (a.u.)	HOMO
Int 3_L6	-1360.702250	-1360.701306	-1360.802041	-0.14781
Int 3_L8	-1131.720573	-1131.719629	-1131.806679	-0.15614
Int 3_L5	-1282.122082	-1282.121138	-1282.214857	-0.15691
Int 3_L9	-1053.140711	-1053.139767	-1053.220287	-0.16487

VIII-VII. Cartesian coordinates of the optimized geometries and energies in Figure 4b

・Int 3_L6

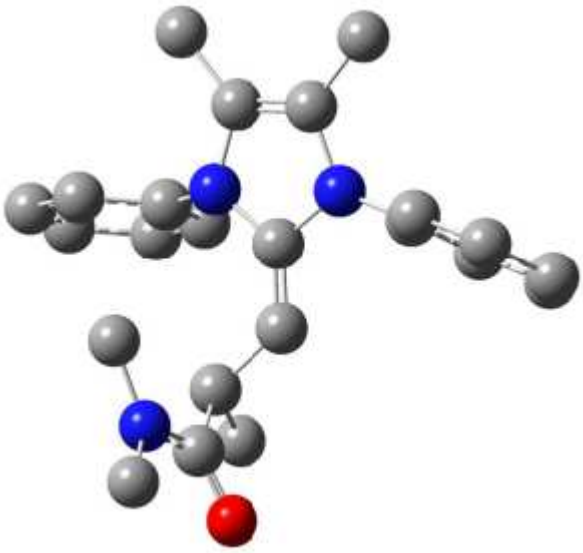


C	-0.85264700	1.65365200	1.01867000
C	0.25307800	0.75341300	0.49401100
C	-1.05880200	1.50530000	2.54049400
C	-0.50920300	3.12413600	0.69755000
C	0.21949800	-0.60215500	0.34157900
N	-0.86252400	-1.50559900	0.39794800
C	-0.38496200	-2.82827400	0.13791100
C	0.95422700	-2.76533700	-0.02192100
N	1.34253400	-1.41150000	0.10207200
C	2.68213300	-0.92887900	0.06963000
C	-2.20836200	-1.14051700	0.06598500
C	-2.55297200	-0.80949000	-1.25440800
C	-3.86522500	-0.49677100	-1.58689400

C	-4.86564300	-0.51684600	-0.60015600
C	-4.53443400	-0.85796900	0.71692700
C	-3.20710400	-1.16698000	1.03777600
C	3.33757800	-0.73894000	-1.14752900
C	4.66285000	-0.28940700	-1.19031400
C	5.33473000	-0.00983300	0.00615800
C	4.67589900	-0.18615700	1.23468400
C	3.36414400	-0.64194700	1.26340900
N	-0.71103700	3.57285500	-0.58781500
O	-0.05541000	3.87011100	1.56827100
C	-1.25750800	2.77141900	-1.67158500
C	-0.46244000	4.97265000	-0.90319300
C	-1.31501300	-3.99497900	0.14641600
C	1.96640600	-3.84394400	-0.22326800
O	6.62324800	0.43614700	0.08480700
C	7.34028600	0.66629100	-1.12108100
O	-6.12270000	-0.19342900	-1.02486800
C	-7.18190400	-0.18769200	-0.07542400
H	-1.80934500	1.41902600	0.53588700
H	1.23719600	1.20447900	0.41280000
H	-1.88066700	2.13954200	2.89658900
H	-1.29323300	0.46220800	2.77845500
H	-0.15337900	1.79408200	3.08012600
H	-1.77984100	-0.80146900	-2.01825600
H	-4.14264000	-0.23934600	-2.60498300
H	-5.28699300	-0.88237500	1.49703700
H	-2.94477100	-1.42615400	2.05935100
H	2.80736600	-0.94336700	-2.07392300
H	5.14765700	-0.15793100	-2.15115100
H	5.21267200	0.04025400	2.15107700
H	2.85153700	-0.77298100	2.21213700
H	-1.07719700	1.71163300	-1.49582900
H	-2.33661200	2.94420100	-1.80377000
H	-0.75284800	3.04638200	-2.60627800
H	-0.10183400	5.47663800	-0.00705300
H	0.29069900	5.05853500	-1.69858800
H	-1.38615900	5.45828000	-1.24923300
H	-1.82257100	-4.10203600	1.11514600
H	-2.09799800	-3.90624600	-0.61789700
H	-0.76398000	-4.91971800	-0.04700000

H	1.47898500	-4.82219100	-0.25177100
H	2.52039700	-3.71575900	-1.16210800
H	2.70825700	-3.85831300	0.58617400
H	8.32466600	1.02513000	-0.81595900
H	7.45298900	-0.25884200	-1.70175300
H	6.84798900	1.42971000	-1.73760700
H	-8.07561500	0.10024400	-0.63141500
H	-7.32933600	-1.18339000	0.36292400
H	-6.99698300	0.54239000	0.72319300

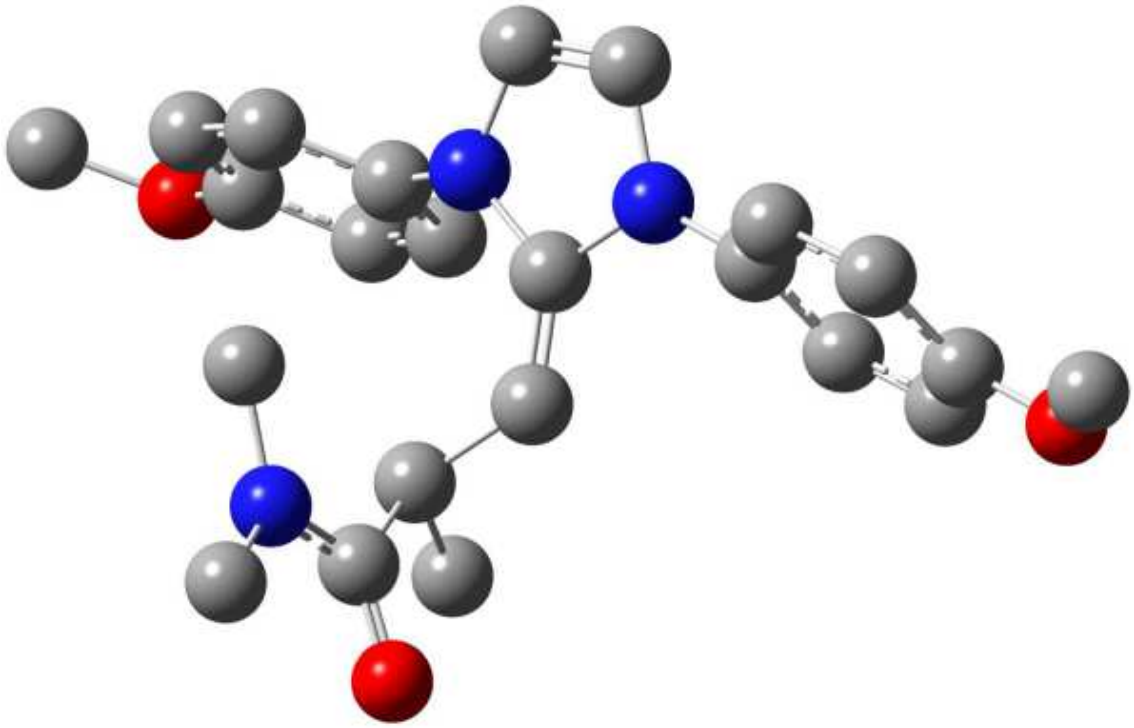
・Int 3_L8



C	0.96364300	1.82757300	-0.75335300
C	-0.18063300	0.83824700	-0.69578100
C	1.40787600	2.13454500	-2.19652400
C	0.50051500	3.13962700	-0.07905700
C	-0.18973700	-0.40955200	-0.15653100
N	0.86812000	-1.14511400	0.43043800
C	0.33721000	-2.36271200	0.97220900
C	-0.99099800	-2.38659500	0.73438300
N	-1.33143500	-1.22096200	0.00821500
C	-2.65701600	-0.79309700	-0.28027100
C	2.20784200	-1.11701500	-0.08207600
C	2.45772100	-1.33166000	-1.44410500
C	3.76919300	-1.34855400	-1.92115200
C	4.84232300	-1.16316600	-1.04304200
C	4.59464400	-0.95679900	0.31651800
C	3.28199600	-0.92831900	0.79558300
C	-3.08741300	-0.69991000	-1.61060300

C	-4.38761800	-0.28151200	-1.89831900
C	-5.27038000	0.03686500	-0.86093000
C	-4.84263800	-0.05385900	0.46625100
C	-3.53682300	-0.45690200	0.75749500
N	0.57318300	3.24181500	1.29460600
O	0.07635500	4.07512400	-0.76038600
C	0.05532300	4.44954000	1.92586700
C	0.80602400	2.13666800	2.21055900
C	1.21563500	-3.35687200	1.65478200
C	-2.01692400	-3.41802800	1.07239500
H	1.83102300	1.43724000	-0.21375200
H	-1.12202200	1.19721300	-1.10096500
H	2.21544800	2.87624900	-2.21442800
H	1.76433600	1.21655800	-2.67467700
H	0.57431800	2.53782700	-2.77774500
H	1.62114300	-1.47854000	-2.12104800
H	3.95352900	-1.51289400	-2.97990100
H	5.86268800	-1.17712500	-1.41683900
H	5.42169900	-0.80797800	1.00603000
H	3.08264700	-0.75602400	1.84956800
H	-2.39654700	-0.95551600	-2.40900100
H	-4.71361000	-0.21067300	-2.93282300
H	-6.28378300	0.35812200	-1.08665700
H	-5.52075500	0.20106700	1.27673800
H	-3.19031800	-0.50472200	1.78620800
H	0.70283600	4.72855500	2.76590300
H	0.03118700	5.25488700	1.19268300
H	-0.96413100	4.29103100	2.31008500
H	1.48379700	2.46140400	3.01107000
H	-0.13646000	1.80445100	2.67234900
H	1.24993400	1.28071000	1.70829200
H	0.62863700	-4.22404100	1.96966600
H	2.02017300	-3.71644300	1.00078100
H	1.69307800	-2.93495900	2.54997500
H	-1.54016700	-4.29775400	1.51254100
H	-2.76612300	-3.05044900	1.78504700
H	-2.56106400	-3.74043000	0.17539800

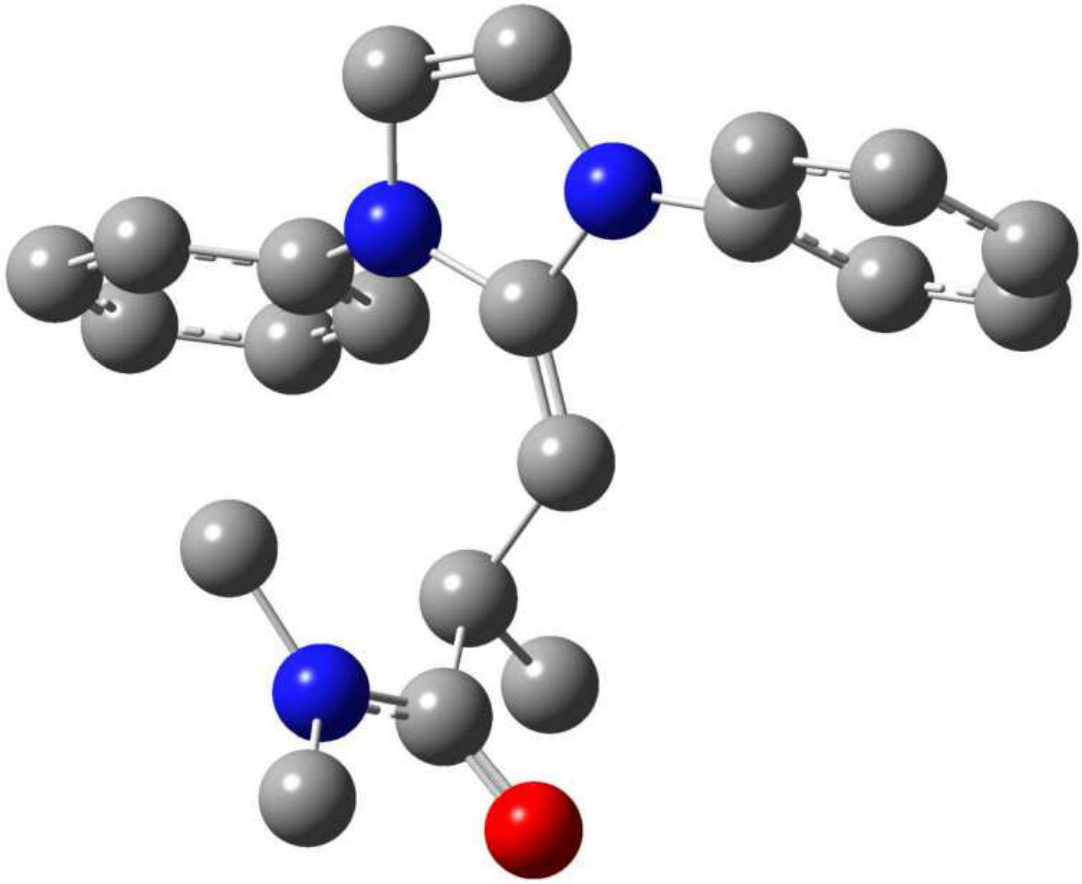
- Int 3_L5



C	-0.85324200	1.59275500	0.89756400
C	0.23751900	0.57908900	0.62106700
C	-1.22072700	1.67123600	2.39192600
C	-0.34632000	2.97737500	0.43171600
C	0.17323900	-0.54314000	-0.14479000
N	-0.93364600	-1.11245700	-0.82137100
C	-0.47599100	-2.18321200	-1.62628300
C	0.85014600	-2.30975800	-1.45260800
N	1.27361900	-1.35206300	-0.52184100
C	2.62991500	-1.13978200	-0.16676200
C	-2.28730700	-1.08675500	-0.36372700
C	-2.61088600	-1.39832100	0.96661500
C	-3.93561300	-1.42452800	1.38143200
C	-4.97064700	-1.15969500	0.46896000
C	-4.65810000	-0.86633600	-0.86367600
C	-3.31787800	-0.82501400	-1.26764700
C	3.02488200	-1.11648400	1.18197800
C	4.35960000	-0.94429400	1.52291000
C	5.33660800	-0.80811400	0.52282900
C	4.95483600	-0.83856500	-0.82326100
C	3.60400300	-0.99095400	-1.15764500
N	-0.48314400	3.32429000	-0.89625700
O	0.16995800	3.75441200	1.23728500

C	0.08105600	4.59373700	-1.33900700
C	-0.82925400	2.41105100	-1.97364800
O	6.62109400	-0.65396100	0.96382100
C	7.65490500	-0.49230300	0.00207600
O	-6.23793700	-1.21459500	0.97653300
C	-7.33092100	-0.94238200	0.10929800
H	-1.76030200	1.33752100	0.34296400
H	1.20770000	0.82413500	1.04160500
H	-1.98609300	2.43524000	2.57405100
H	-1.60590200	0.70359800	2.72907600
H	-0.34315500	1.93135600	2.98975900
H	-1.16823400	-2.76741400	-2.21171200
H	1.54769200	-3.01490100	-1.87780900
H	-1.81368100	-1.61250000	1.67176800
H	-4.19496900	-1.65873900	2.40971100
H	-5.43507200	-0.65835400	-1.59067400
H	-3.07516100	-0.58379500	-2.29936200
H	2.27794000	-1.23947900	1.96025900
H	4.67185400	-0.92341300	2.56275500
H	5.68520700	-0.73055300	-1.61730900
H	3.30887900	-0.99010400	-2.20351600
H	0.18576600	5.25785700	-0.48187800
H	1.07161700	4.44973100	-1.79730800
H	-0.58349200	5.04733700	-2.08407600
H	-1.31658200	1.51365200	-1.60093600
H	-1.51246100	2.91231800	-2.67170900
H	0.06752500	2.10226500	-2.53238300
H	8.57754200	-0.38271200	0.57450100
H	7.73324300	-1.37126500	-0.65164600
H	7.49498700	0.40640200	-0.60811700
H	-8.22727500	-1.03461600	0.72480200
H	-7.27161000	0.07494700	-0.29943000
H	-7.37761100	-1.66740400	-0.71412700

- Int 3_L9



C	-0.90385300	1.46440400	0.92403300
C	0.24008200	0.49367100	0.71555100
C	-1.23930000	1.66817500	2.41422300
C	-0.47803600	2.82391800	0.31929300
C	0.24617500	-0.68107600	0.03179300
N	-0.82486900	-1.36297900	-0.59787300
C	-0.29798700	-2.40266000	-1.39811600
C	1.03491000	-2.42908000	-1.23826300
N	1.40031700	-1.42997800	-0.32553200
C	2.74296500	-1.10697400	-0.01876100
C	-2.18003300	-1.39952300	-0.16481000
C	-2.50851200	-1.47865400	1.19554800
C	-3.84520700	-1.56241300	1.58574300
C	-4.86530400	-1.58900200	0.62888500
C	-4.53603000	-1.52820500	-0.72785300
C	-3.20114200	-1.42671400	-1.12597600
C	3.13756500	-0.85981300	1.30533900
C	4.47106000	-0.57001600	1.59422400
C	5.42932400	-0.53907800	0.57585800
C	5.03920000	-0.79514700	-0.74105600
C	3.70327400	-1.06789400	-1.04216200

N	-0.67536400	3.04499300	-1.02673900
O	0.02986600	3.68850700	1.03581400
C	-0.17389200	4.28971000	-1.59907200
C	-1.01010700	2.02200500	-2.00560100
H	-1.80657300	1.11130200	0.41967300
H	1.19520000	0.83491200	1.10049200
H	-2.04767900	2.39783300	2.54187300
H	-1.55290900	0.71947600	2.86097800
H	-0.36617600	2.04258000	2.95481400
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H	-4.08924000	-1.61931600	2.64357600
H	-5.90464200	-1.65715400	0.93816500
H	-5.31906500	-1.54626900	-1.48159400
H	-2.94596900	-1.35825100	-2.18031300
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H	4.76346500	-0.37887700	2.62353500
H	6.46738300	-0.31643700	0.80695800
H	5.77235900	-0.76759200	-1.54321100
H	3.39843200	-1.23661500	-2.07115100
H	-0.87222900	4.64377100	-2.36633300
H	-0.08017700	5.03493100	-0.81013100
H	0.81255800	4.14369000	-2.06512300
H	-1.50548100	1.17001100	-1.54576400
H	-1.68768200	2.44833600	-2.75579800
H	-0.10952600	1.65613500	-2.52183600

3-1.5 References

(1) Brgckner, R. *In Organic Mechanisms: Reactions, Stereochemistry and Synthesis*; Harmata, M., Eds.; Springer: Berlin, 2010; chap. 2 and chap. 5.

(2) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443.

(3) Terrier, F. *Chem. Rev.* **1982**, *82*, 77.

(4) Terrier, F. *Modern Nucleophilic Aromatic Substitution*; Wiley: New York, 2013; pp 1-94.

(5) Jones, G. O.; Al Somaa, A.; O'Brien, J. M.; Albishi, H.; Al-Megren, H. A.; Alabdulrahman, A. M.; Alsewailem, F. D.; Hedrick, J. L.; Rice, J. E.; Horn, H. W. *J. Org. Chem.* **2013**, *78*, 5436.

(6) Rohrbach, S.; Smith, A. J.; Pang, J. H.; Poole, D. L.; Tuttle, T.; Chiba, S.; Murphy, J. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 16368.

(7) Glukhovtsev, M. N.; Bach, R. D.; Laiter, S. *J. Org. Chem.* **1997**, *62*, 4036.

(8) Fry, S. E.; Pienta, N. J. *J. Am. Chem. Soc.* **1985**, *107*, 6399.

(9) Handel, H.; Pasquini, M. A.; Pierre, J. L. *Tetrahedron* **1980**, *36*, 3205.
(10) Ong, D. Y.; Tejo, C.; Xu K.; Hirao, H.; Chiba, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 1840.
(11) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.
(12) Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369.
(13) Neumann, C. N.; Ritter, T. *Acc. Chem. Res.* **2017**, *50*, 2822.
(14) Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 1452
(15) Schimler, S. D.; Froese, R. D. J.; Bland, D. C.; Sanford, M. S. *J. Org. Chem.* **2018**, *83*, 11178.
(16) Kaga, A.; Hayashi, H.; Hakamata, H.; Oi, M.; Uchiyama, M.; Takita, R.; Chiba, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 11807.
(17) Liu, X.-W.; Zarate, C.; Martin, R. *Angew. Chem. Int. Ed.* **2019**, *58*, 2064.
(18) Mauya, Y.; Kawashima, Y.; Kodama, T.; Chatani, N.; Tobisu, M. *Synlett* **2019**, *30*, 1995.
(19) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488.
(20) Leonard, D. J.; Ward, J. W.; Clayden, J. *Nature* **2018**, *562*, 105.
(21) Kwan, E. E.; Zeng, Y.; Besser, H. A.; Jacobsen, E. N. *Nat. Chem.* **2018**, *10*, 917.
(22) Kirby, A. J. *Stereoelectronic Effects*; Oxford Chemistry Primers: Oxford, 1996, pp 68-69.
(23) Flanigan, D. M.; Romanov-M., F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.
(24) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485.
(25) Zhang, C.; Hooper, J. F.; Lupton, D. W. *ACS Catal.* **2017**, *7*, 2583.
(26) Matsuoka, S.-I.; Ota, Y.; Washio, A.; Katada, A.; Ichioka, K.; Takagi, K.; Suzuki, M. *Org. Lett.* **2011**, *13*, 3722.
(27) Biju, A.T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8412.
(28) Schedler, M.; Wurz, N. E.; Daniliuc, C. G.; Glorius, F. *Org. Lett.* **2014**, *16*, 3134.
(29) Rajachan, O.; Paul, M.; Yatham, V. R.; Neudorfl, J.-M.; Kanokmedhakul, K.; Kanokmedhakul, S.; Berkessel, A. *Tetrahedron Lett.* **2015**, *56*, 6537.
(30) Nakano, Y.; Lupton, D. W. Enantioselective *Angew. Chem. Int. Ed.* **2016**, *55*, 3135.
(31) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472.
(32) Suzuki, Y.; Toyota, T.; Imada, F.; Sato, M.; Miyashita, A. *Chem. Commun.* **2003**, *39*, 1314.
(33) Janssen-Mueller, D.; Singha, S.; Lied, F.; Gottschalk, K.; Glorius, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 6276.
(34) Simonetti, S. O.; Larghi, E. L.; Kaufman, T. S. *Nat. Prod. Rep.* **2016**, *33*, 1425.
(35) Poulie, C. B. M.; Bunch, L. *ChemMedChem* **2013**, *8*, 205.
(36) Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6915.
(37) Nelson, D. J.; Nolan, S. P. *Chem. Soc. Rev.* **2013**, *42*, 6723.
(38) Schlosser, M.; Ruzziconi, R. *Synthesis* **2010**, *13*, 2111.
(39) Xudong, C.; Yifang, Z.; Yin, C.; Yinli, Q.; Minquan, Y.; Xiangqing, X.; Xin, L.; Bi-Feng, L.; Liangren, Z.; Guisen, Z. *J. Med. Chem.* **2018**, *61*, 10017.
(40) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.
(41) Zhao, L.; Chen, X. Yu.; Ye, S.; Wang, Z.-X. *J. Org. Chem.* **2011**, *76*, 2733.
(42) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. R. *Chem. Rev.* **2005**, *105*, 3842.

(43) Foster, J. P. & Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211.

(44) Beillard, A.; Bantreil, X.; Metro, T.-X.; Martinez, J.; Lamaty, F. *Dalton Trans.*, **2016**, *45*, 17859.

(45) Higgins, E. M.; Sherwood, J. A.; Lindsay, A. G.; Armstrong, J.; Massey, R. S.; Alder, R. W.; O'Donoghue, A. C. *Chem. Commun.*, **2011**, *47*, 1559.

(46) Kinuta, H.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 1593.

(47) Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 11574.

(48) Li, R.; Dong, G. *Angew. Chem. Int. Ed.* **2016**, *55*, 1133.

(49) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö .; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013.

(50) Cances, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032.

(51) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253.

(52) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.
Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161.

(53) Vonszentpaly, L.; Fuentealba, P.; Preuss, H; Stoll, H. *Chem. Phys. Lett.* **1982**, *93*, 555.

(54) (a) Weinhold, F.; Landis, C. R.; Glendening, E. D. *International Reviews in Physical Chemistry* **2016**, *35*, 1. (b) Reed, A. E.; Weinhold, F. *J. Chem. Phys.*, **1985**, *83*, 1736. (c) Reed, A. E.; Weinhold, F. *Isr. J. Chem.*, **1991**, *31*, 277. (d) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.*, **1988**, *88*, 899. (e) Weinhold F. in Schleyer P.v.R. Encyclopedia of Computational Chemistry: *Wiley: New-York*, **1998**, *3*, 1792.

(55) NBO Version 3.1, E. D. Glendening, A. E. Reed, J. E. Carpenter, and F. Weinhold.

Chapter 3

The research reported in this thesis focused on the development new reactions using new rhodium catalysts or a new NHC catalyst to solve several problems related to cross-coupling rections and nucleophilic aromatic substitution reactions.

In Chapter 1, rhodium-catalyzed aryla-tion of non-acidic C(sp2)-H bonds using aryl carbamates as the arylating reagent was described. The key to success is the use of a bis(NHC) complex of rhodium(I) as the catalyst, which facilitates activation of inert C(sp2)-O bonds in aryl carbamates. This readily generated rhodium species enabled activation of inert C(sp2)-O bonds in the absence of a strong base, allowing for the use of a synthetically useful directing group in C-H/C-O coupling.

In Chapter 2, rhodium-catalyzed two transformations of aryl carbamates using alcohol were described. One is the reductive cleavage of the C-O bond using ^{i}PrOH as a reductant. The other is the alkynylation reaction of aryl carbamates using propargyl alcohol as an alkynylating reagent. Unlike previously reported methods using ^{i}PrMgX and TMDSO, the rhodium-catalyzed reductive cleavage tolerates carbonyl groups, alkenes and heteroaromatic rings, such as carbazole and pyridine. Similarly, the use of propargyl alcohols allows the inert C-O bond alkynylation to be compatible with a range of functional groups, such as ketones, esters and amides, which are incompatible with previously reported cross-couplings using organometallic nucleophiles. This alkynylation method enables the use of a carbamate directing group as a handle for the synthesis of functionalized aromatic alkynes, which serve as useful building blocks in organic synthesis.

In Chapter 3, the first catalytic concerted nucleophilic aromatic substitution forming C-C bond, in which a catalytically generated carbanion displaces the fluorine group on the aromatic ring, was described. The concerted nature of the transition state allows electron-rich aryl fluorides to be cyclized in a catalytic manner. Since this method does not rely on the use of strong bases or transition metals, it is possible to synthesize quinolin-2-one derivatives bearing a diverse range of functional groups including iodides and bromides. DFT calculations confirmed that this catalytic cyclization proceeds in a concerted manner. In addition, the formation of a C_{ipso}-C_{β} bond in the transition state results in a significant stereoelectronic interaction with the antibonding orbital of the C_{ipso}-F bond, which stabilizes the transition state for this concerted cyclization process.

List of Publications

(1) C-O Activation by a Rhodium Bis(N-Heterocyclic Carbene) Catalyst: Aryl Carbamates as Arylating Reagents in Directed C-H Arylation
Mamoru Tobisu, Kosuke Yasui, Yoshinori Aihara and Naoto Chatani
Angew. Chem. Int. Ed. **2017**, *56*, 1877-1880.
(2) Rhodium-Catalyzed Reductive Cleavage of Aryl Carbamates Using Isopropanol as a Reductant
Kosuke Yasui, Masaya Higashino, Naoto Chatani, Mamoru Tobisu
Synlett **2017**, *28*, 2569-2572.
(3) Rhodium-Catalyzed C-O Bond Alkynylation of Aryl Carbamates with Propargyl Alcohols
Kosuke Yasui, Naoto Chatani and Mamoru Tobisu
Org. Lett. **2018**, *20*, 2108-2111.
(4) N-Heterocyclic Carbene-Catalyzed Concerted Nucleophilic Aromatic Substitution of Aryl Fluorides Bearing α, β-Unsaturated Amides
Kosuke Yasui, Miharu Kamitani, Mamoru Tobisu
Angew. Chem. Int. Ed. **2019**, *58*, 14157-14161.

Supplementary List of Publications
(1) Rhodium-catalyzed Cross-coupling of Aryl Carbamates with Arylboron Reagents
Keisuke Nakamura, Kosuke Yasui, Mamoru Tobisu, Naoto Chatani
Tetrahedron **2015**, *71*, 4484-4489.
(2) 11-Step Total Synthesis of Teleocidins B-1–B-4
Hugh Nakamura, Kosuke Yasui, Yuzuru Kanda, Phil S. Baran
J. Am. Chem. Soc. **2019**, *141*, 1494-1497.
(3) Nickel-Catalyzed Decarboxylation of Aryl Carbamates for Converting Phenols into Aromatic Amines
Akihiro Nishizawa, Tsuyoshi Takahira, Kosuke Yasui, Hayato Fujimoto, Tomohiro Iwai, Masaya Sawamura, Naoto Chatani, Mamoru Tobisu
J. Am. Chem. Soc. **2019**, *141*, 4177-4181.