NANYANG TECHNOLOGICAL UNIVERSITY

TRANSITION METAL CATALYZED OLEFIN FUNCTIONALIZATION

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TRANSITION METAL CATALYZED OLEFIN FUNCTIONALIZATION

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LIST OF ABBREVIATIONS

δ	chemical shift
°C	degree centigrade
Ac	acetyl
Ad	adamantyl
Ar	aryl
BHT	2,6-*di*-*t*-butyl-*p*-cresol
BIPHEP	2,2'-bis(diphenylphosphino)biphenyl
Bn	benzyl
BQ	1,4-benzoquinone
Bz	benzoyl
calcd	calculated
CH_2Cl_2	dichoromethane
$CDCl_3$	deuterated chloroform
cm^{-1}	inverse centimeter
CSA	camphorsufonic acid
d	doublet
DIBAL-H	diisobutylaluminium hydride
d-*i*-Prpf	1,1′-bis(diisopropylphosphino)ferrocene
dd	doublet of doublets
DCE	1,2-dichloroethane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide

DMSO	dimethyl sulfoxide
dt	doublet of triplets
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FG	functional group
FTIR	fourier transform infrared spectrometry
g	gram
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
m	multiplet
m/z	mass per charge ratio
M^+	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol%	mole percent
MS	mass spectrometry

n-Bu	*n*-butyl
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
NMP	*N*-methyl pyrrolidone
Ns	2-nitrobenzenesulfonyl
OTf	trifluoromethanesulfonate
$Pcyp_3$	tricyclopentylphosphine
Ph	phenyl
Phth	phthaloyl
PivOH	pivalicacid
PMB	*P*-methoxybenzyl
PMP	4-methoxyphenyl
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
Py	pyridine
q	quartet
R_f	retention factor
R.E.	reductive elimination
rt	room temperature
t-AmOH	2-methyl-2-butanol
TFA	trifluoroacetic acid
TMS	trimethylsilyl

ABSTRACT

This thesis describes transition metal (Pd, Rh, Cu) catalyzed olefin functionalization for the creation of new C-C bonds.

Chapter 1

In chapter 1, the palladium-catalyzed bisolefination of alkynes are described. It not only offers a new synthetic pathway for the access of functionalized naphthalenes but also provide an instance of uncommon *trans*-carbopalladation for the reaction initiation.

Chapter 2

In chapter 2, the cationic rhodium complex catalyzed olefination of phenol derivatives for the direct introdution of an α,β-unsaturated ester appendage is described. Deuterium labelling and kinetic isotope effect studies were performed to probe the reaction mechanism.

Chapter 3

In chapter 3, rhodium-catalyzed hydroarylation of internal alkynes via C-H bond activation was described using *N*,*N*-dimethylaminocarbonyl as directing group. This protocol exhibits a wide spectrum of functionality

compatibility because of the mild reaction condition employed and provides a highly effective synthetic method in the realm of C-H olefination.

Chapter 4

In chapter 4, copper catalyzed olefinic trifluoromethylation and oxytrifluoromethylation of enamides were reported. The direct olefinic C-H trifluoromethylation constitutes an efficient method for the stereoselective synthesis of β-trifluoromethyl substituted enamides.

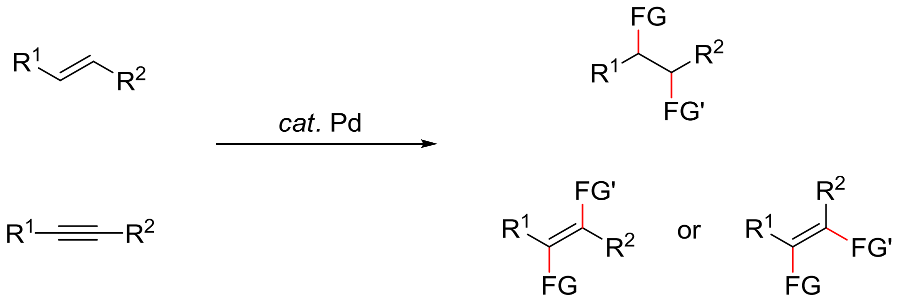
Chapter 5

In chapter 5, palladium-catalyzed intermolecular C-H olefination of benzylamine derivatives employing bidentate system was described. Not only acrylate derivatives but also electron-neutral olefins could be employed, which further broaden the scope of palladium-catalyzed coupling reactions.

Palladium Catalyzed Bis-Olefination of C-C Triple Bonds: Facile Method for the Synthesis of Naphthalene Derivatives

1.1 Introduction

In the past two decades, palladium-catalyzed transformations have found widespread application in organic synthesis.[1] In particular, the difunctionalization of unsaturated systems (Scheme 1.1), which allows for the introduction of two functionalized groups to the vicinal position, continues to be a hot and fantastic arena, because of its conciseness and high efficiency in constructing multiple new chemical bonds, thus leading to various synthetically useful structures in one step.



Scheme 1.1 Palladium-catalyzed difunctionalization

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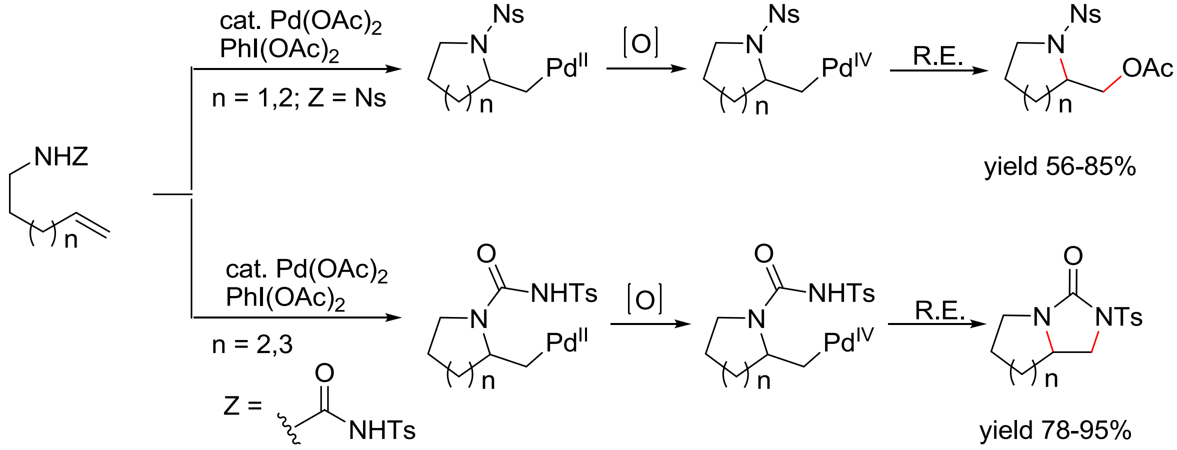
[1] (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev*. **2007**, *107*, 5318. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

1.1.2 Difunctionalization of alkenes

In 2005, Sorensen[2] and Muniz[3] independently reported aminoacetoxylation and intramolecular diamination of alkenes (Scheme 1.2). The key to the success of these reactions relies on the employment of $PhI(OAc)_2$ as a highly selective and effective oxidant, which could smmothly oxidize initially formed alkyl Pd^{II} intermediate to alkyl Pd^{IV} species.[4] Because of the high oxidation state of alkyl Pd^{IV} intermediate, it tends to undergo reductive elimination much more easily as compared to the potential *β*-hydride elimination (fundamental reaction concerning alkyl Pd^{II} intermediate), thus guaranteing the overall difunctionalization of alkenes.



Scheme 1.2 Aminoacetoxylation and intramolecular diamination of alkenes

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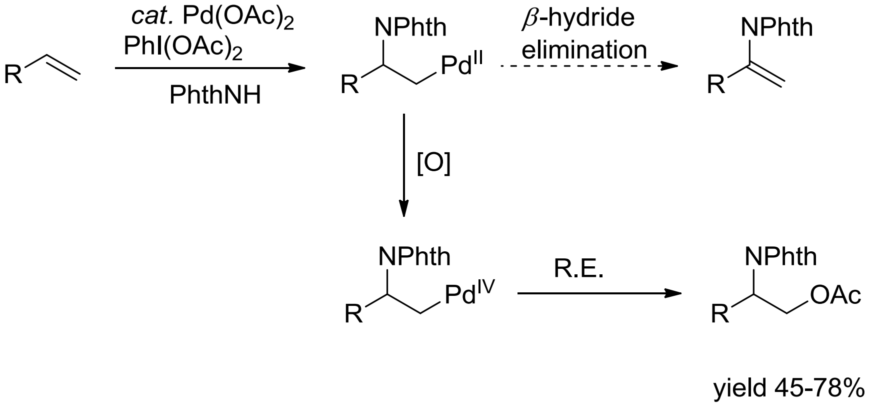
[2] Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690

[3] Streuff, J.; Hovelmann, C. H.; Nieger, M.; Muniz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586.

[4] (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542-9543. (c) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (d) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46* (6), 1924.

Using phthalimide as nucleophile, Stahl successfully realized the intermolecular type of aminoacetoxylation of alkenes in 2006 (Scheme 1.3).[5] In stark contrast with aforementioned examples, it was proved that this reaction proceed through *cis*-amino palladation and S_N2 type reductive elimination.



Scheme 1.3 Intermolecular aminoacetoxylation of alkenes

Owing to the importance and prevalence of 1,2-dioxygenated skeleton in biologically active compounds, the Sharpless dihydroxylation of alkenes, since its discovering in 1988, continues to be the most popular and reliable method for the access of such motifs. However, the synthetic value of such transformation was more or less compromised because of the highly toxic of Os complexes used, especially when carrying out large scale recations. The palladium-catalyzed dioxygenation of olefin, which offers an

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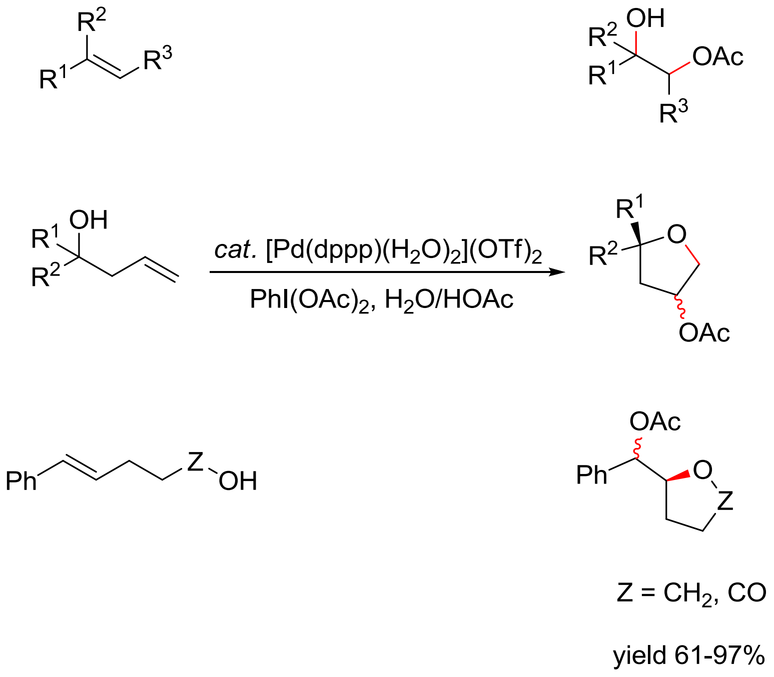
[5] Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.

alternative pathway to Sharpless dihydroxylation, was discovered by Dong in 2008 (Scheme 1.4).[6]



Scheme 1.4 Palladium-catalyzed dioxygenation of alkenes

In 2009, Jiang made breakthrough in alkene diacetoxylation using oxygene as the sole oxidant (Scheme 1.5).[7] Two features of this reaction make it quite distinctive as compared with other related precedents: 1. the inorganic salt KI was found to be indispensable for the transformation; 2. molecular oxygene was proved to be competent in oxidizing Pd^{II} to Pd^{IV}, which is always carried out using strong oxidant such as $PhI(OAc)_2$, K_2SO_8, NFSI, Selectfluor.

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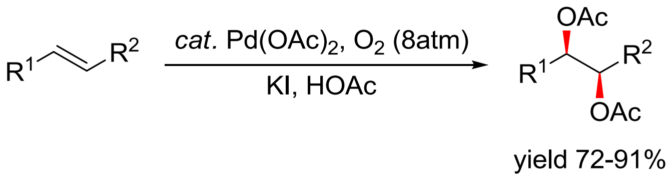
[6] Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962.
[7] Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846.



Scheme 1.5 Palladium-catalyzed diacetoxylation of alkenes with O_2 as oxidant

1.1.1 Difunctionalization of alkynes

Similar with the reaction manner of alkene, alkyne difunctionalizations are always initiated by nucleopalladation of alkynes, either through *cis* or *trans* insertion pathway, resulting sp^2 carbon bonded palladium intermediate, which could be further elaborated through Pd^0/Pd^{II} catalytic cycle with no warry about β-hydride elimination that otherwise may be faced by alkene difunctionalization.

Initiated by halopalladation or acetopalladation Lu successfully developed difunctionalization of alkene tethered alkynoate and alkynamide (Scheme 1.6).[8] Assisted by chiral oxazoline ligand the author realized excellent enatioselective cyclization of alkynoate with ee up to 92%. In these two cases, the initial heteroatompalladation of alkyne was found to proceed through anti insertion fashion.

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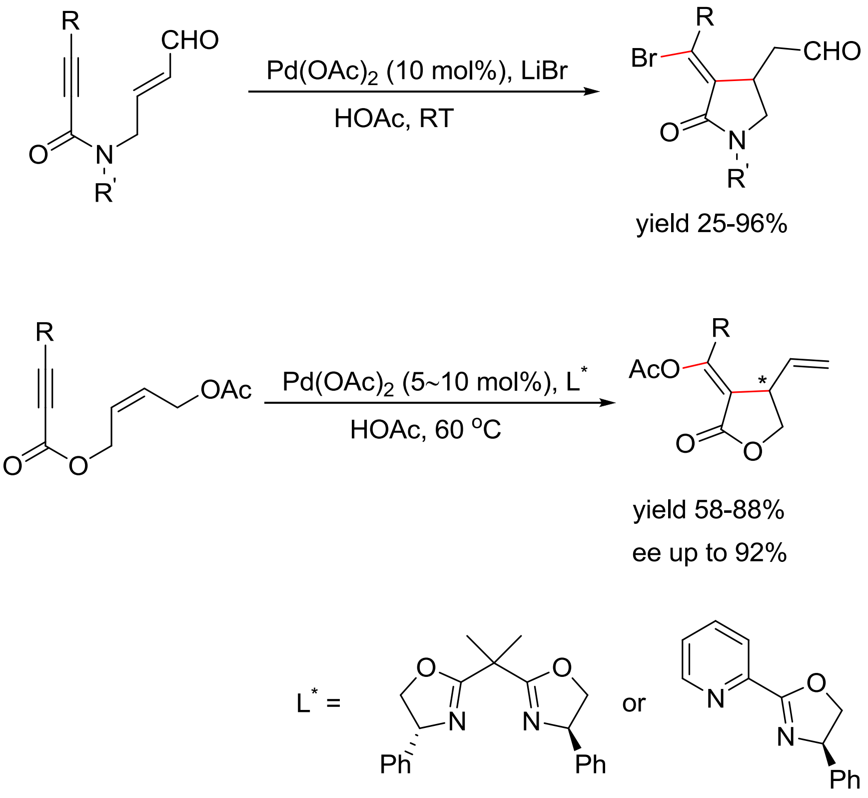
[8] (a) Xie, X.; Lu, X. *Synlett* **2000**, *5*, 707. (b) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604.



Scheme 1.6 Palladium-catalyzed difunctionalization of alkyne with halide or acetate as nucleophile

In 2003, Tobe reported palladium-catalyzed intramolecular diarylation of internal alkynes, which proceeded through arylpalladation/C-H activation cascade to afford biindenylidene derivatives in low to moderate yield (Scheme 1.7).[9]

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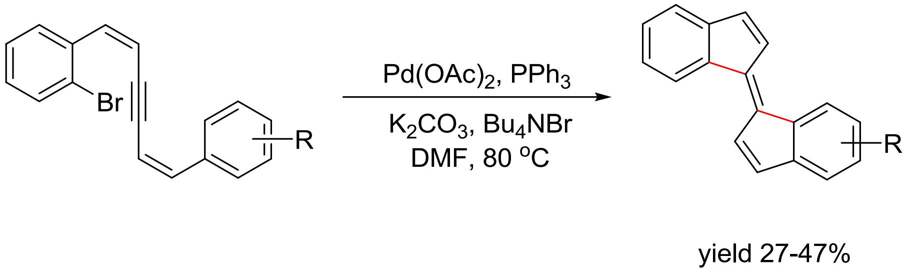
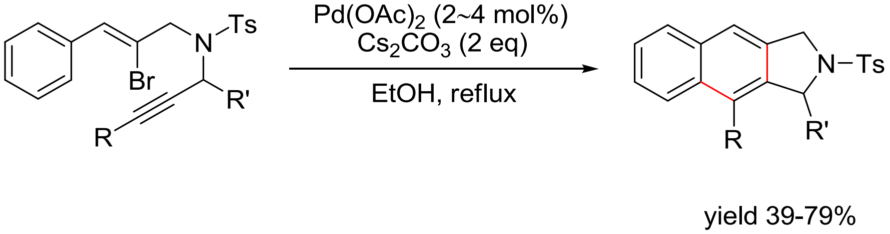
[9] Rahman, S. M. A.; Sonoda, M.; Itahashi, K.; Tobe, Y. *Org. Lett.* **2003**, *5*, 3411.



Scheme 1.7 Intramolecular diarylation of alkyne through arylpalladation/C-H activation cascade

In 2005, Tanaka reported a cascade cyclization using bromoenynes as starting material (Scheme 1.8).[10] Similar with Tobe's work, this reaction undergoes carbopalladation/C-H activation cascade and the only difference between these two cases is that in Tobe's reaction the alkyne undergoes *trans*-difunctionalization while in Tanaka's reaction the *cis*-difunctionalization happens.



Scheme 1.8 *Cis*-difunctionalization of alkynes through tandem cyclization

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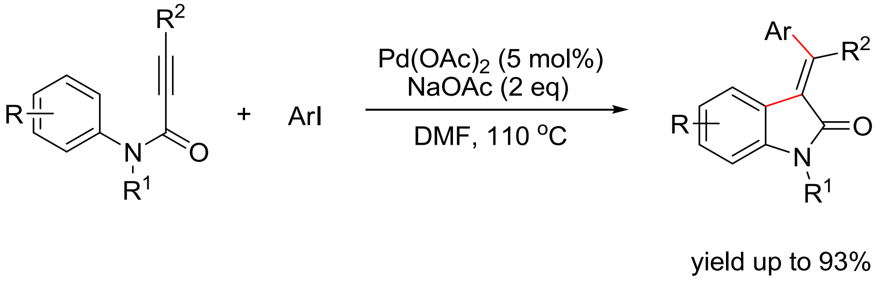
[10] Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 5103.

In 2006, a cascade transformation comprises intermolecular arylpalladation followed by intramolecular C-H activation was devised by Zhu (Scheme 1.9).[11] With $Pd(OAc)_2$/NaOAc/DMF reaction system, aryl iodide reacted efficiently with alkynamide and the 3-(diarylmethylenyl)indolinone products were produced in high to excellent yield.



Scheme 1.9 *Cis*-diarylation of alkynes

While much effort has been devoted to this area, however, to the best of our knowledge, there is still no report on the bis-olefination of C-C triple bond in palladium chemistry. In this aspect we came to an idea using alkene as the initiator for nucleopalladation of alkyne followed by coupling with another alkene for the concise construction of triene derivatives.[12] If feasible, this will lead to an ideal method for the synthesis of triene derivatives, in view that no prefunctionalized coupling partners such as organohalides and/or organometallics are required, which makes them environmentally friendly and cost

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[11] Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927.

[12] For Outer-sphere cabbopalladation of unsaturated systems with C=C as nucleophiles see: (a) Castano, A. M.; Backvall, J. E. *J. Am. Chem. Soc*. **1995**, *117*, 560. (b) Dorange, I.; Narhi, K.; Franzen, J.; Backwall, J. E. *Chem. Eur. J.* **2003**, *9*, 3445. (c) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2004**, *126*, 10250. (d) Liu, C.; Widenhoefer, R. A. *Chem. Eur. J.* **2006**, *12*, 2371.

effective.[13] In connection with our interest in the search of new coupling reactions for the synthesis of naphthalene derivatives, we present a palladium-catalyzed sequential intra- and intermolecular coupling reaction with molecular oxygen as the sole oxidant to construct naphthalene derivatives in high regioselectivity**.**

1.2 Results and discussion

With the idea that the initial vinylpalladation of alkyne moiety to be the key step for the successful implementation of thus assumed bis-olefination of internal alkynes, 1-(phenylethynyl)-2-vinylbenzene was first selected as the model substrate to react with butyl acrylate for the ease of the reaction initiation in intramolecular pathway. However, under various conditions, all attempts gave intractable mixtures, with neither indene derivatives, which should be formed through the cis-vinylpalladation of enyne, nor naphthalene derivatives, which should be formed in the trans-vinylpalladation pathway, could be detected. Considering that this may be due to the low nucleophilicity of the 2-vinyl pedant, we installed a methyl group at the α-position of the styrene derivative. Fortunately, the reaction proceeded to form the naphthalene derivative, albeit in low yield.

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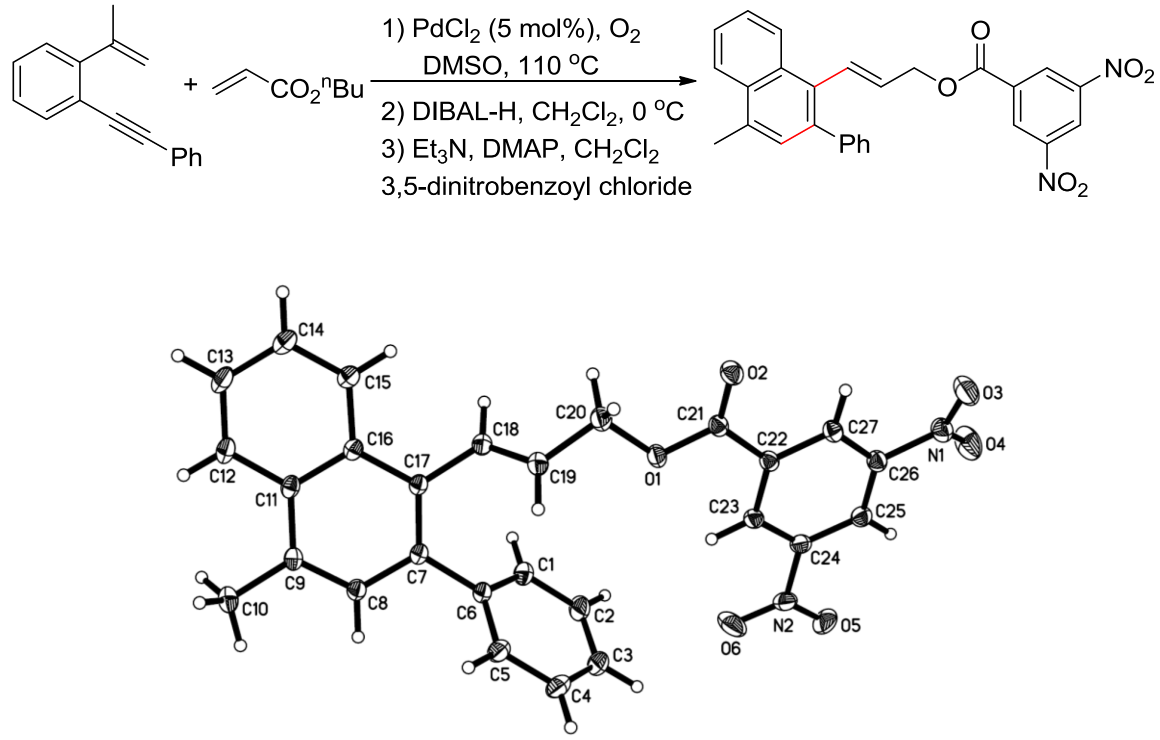
[13] For related coupling reaction employing unprefunctionalized coupling partners see: (a) Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Chem. Soc*. **2009**, *131*, 1372. (b) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett*. **2004**, *6*, 4623. (c) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc*. **2002**, *124*, 12420. (d) Trost, B. M.; Machacek, M.; Schnaderbeck, M. J. *Org. Lett.* **2000**, *2*, 1761. (e) Reichard, H. A.; Micalizio, G. C. *Angew. Chem. Int. Ed*. **2007**, *46*, 1440. (f) Shimamoto, T.; Chimori, M.; Sogawa, H.; Yamamoto, K. *J. Am. Chem. Soc*. **2005**, *127*, 16410. (g) Chang, H. T.; Jayanth, T. T.; Wang, C. C.; Cheng, C. H. *J. Am. Chem. Soc*. **2007**, *129*, 12032.

In order to determine the exact structure of the product, further derivatizations were adopted as shown in Scheme 1.10. From the crystal structure, we could clearly see that this substrate underwent 6-endo-dig cyclization to deliver the naphthalene derivative.

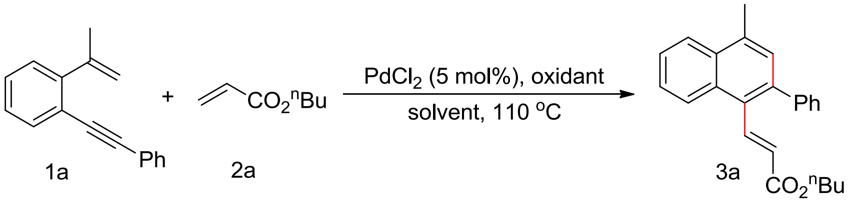


Scheme 1.10 Structure determination

With the promising preliminary result in hand, different catalysts, solvents, and oxidants were screened and the results are summarized in Table 1.1. As shown in Table 1.1, our attempts to use $Pd(OAc)_2$ as catalyst were not successful (Table 1.1, entries 1-6). When the catalyst was changed to $Pd(OCOCF_3)_2$ with $Cu(OAc)_2$/air as the oxidant, there was still no improvement in the yield of the product. Surprisingly, the yield was dramatically increased to 64% when $Cu(OTf)_2$/air was used as oxidants (Table 1.1, entry 8). After many attempts, it was found that the reaction proceeded well in DMSO (Table

1.1, entries 8-11). As expected, there was no reaction in the absence of palladium catalyst (Table 1.1, entry 12). With this optimum oxidant system of $Cu(OTf)_2$/air in hand, various palladium catalysts were screened to ascertain their efficiency in the reaction (Table 1.1, entries 13-16). These results showed that many types of palladium catalysts could catalyze this reaction while the use of palladium chloride as catalyst gave the best result (78% yield, entry 16). Further examination of several oxidant systems using palladium chloride as catalyst proved that BQ/air and molecular oxygen were also suitable for this reaction (Table 1.1, entries 18-19), providing comparable yield to the $Cu(OTf)_2$/air system. From an economical point of consideration, the optimized reaction conditions were affirmed as follows: 5 mol% $PdCl_2$ as catalyst, molecular oxygen as oxidant in DMSO at 110 ^{o}C for 24 hours.

Table 1.1 Reaction Conditions Optimization.^{a}



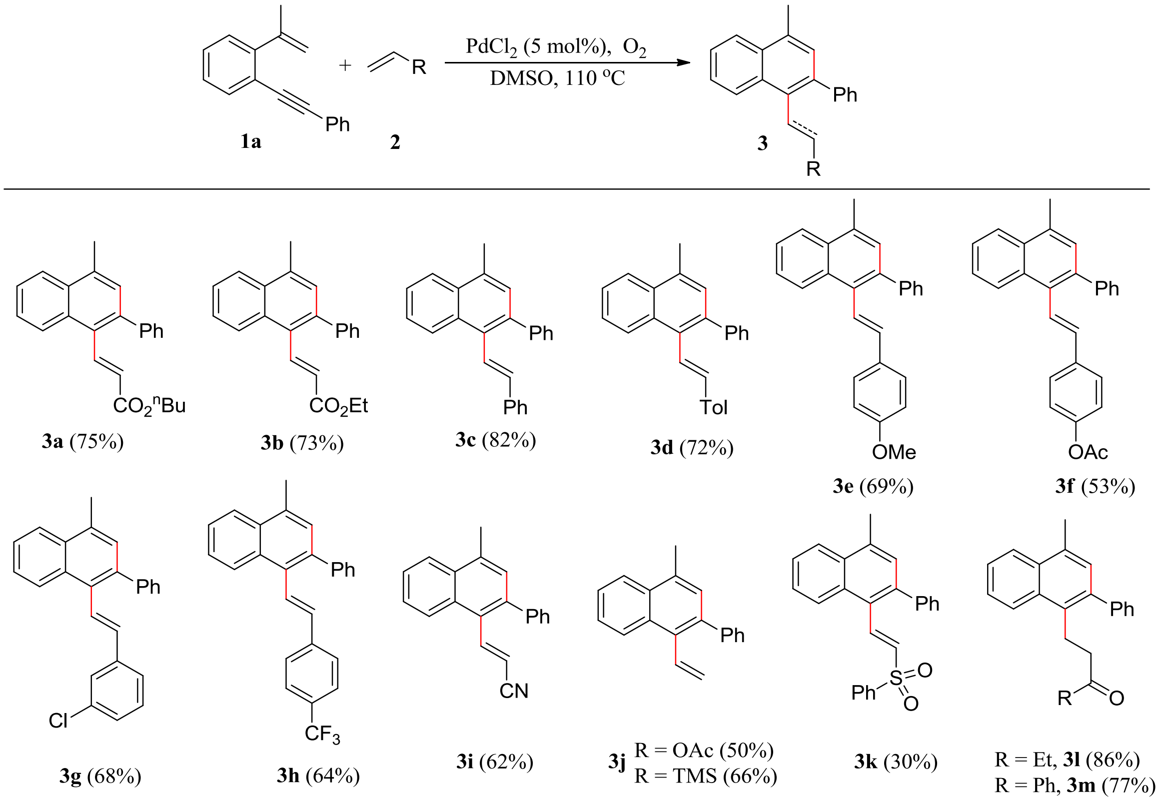
Entry	Catalyst	Oxidant	Solvent	Yield (%)^{b}
1	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	DMSO	15
2	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	toluene	NR
3	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	DMF	trace
4	$Pd(OAc)_2$	AgOAc/air	DMSO	trace
5	$Pd(OAc)_2$	$Cu(OAc)_2$/air	DMA	trace
6	$Pd(OAc)_2$	O_2	DMSO	20
7	$Pd(OCOCF_3)_2$	$Cu(OAc)_2$/air	DMSO	20
8	$Pd(OCOCF_3)_2$	$Cu(OTf)_2$/air	DMSO	64

9	$Pd(OCOCF_3)_2$	$Cu(OTf)_2$/air	toluene	trace
10	$Pd(OCOCF_3)_2$	$Cu(OTf)_2$/air	dioxane	trace
11	$Pd(OCOCF_3)_2$	$Cu(OTf)_2$/air	DCE	trace
12	none	$Cu(OTf)_2$/air	DMSO	0[c]
13	$Pd(acac)_2$	$Cu(OTf)_2$/air	DMSO	54
14	$Pd(PPh_3)_4$	$Cu(OTf)_2$/air	DMSO	60
15	$Pd(MeCN)_2Cl_2$	$Cu(OTf)_2$/air	DMSO	70
16	$PdCl_2$	$Cu(OTf)_2$/air	DMSO	78
17	$PdCl_2$	Ag_2O/air	DMSO	trace
18	$PdCl_2$	BQ/air	DMSO	77[d]
19	$PdCl_2$	O_2	DMSO	75
20	$PdCl_2$	O_2	DMSO	72[e]

[a] Unless otherwise noted, the reactions were carried out at 110 °C using **1a** (0.1 mmol), **2a** (0.3 mmol), catalyst (0.005 mmol), oxidant (0.02 mmol), DMSO (0.4 mL) for 24 h under air or oxygen atmosphere. [b] Isolated yields. [c] Quantitative amount of **1a** was recovered. [d] BQ = 1,4-benzoquinone. [e] 4A molecular sieve was add.

With the optimized reaction conditions in hand, we next investigated the scope of the reaction using different types of external olefins. As shown in Table 1.2, both acrylate and styrene derivatives reacted efficiently to afford the desired products in good to excellent yields. It is noteworthy that styrene derivatives with both electron-donating and electron-withdrawing substituents could be smoothly transformed into the desired products in good yields (**3c-3h**). Vinyl cyanide also worked well for this transformation (**3i**). Interestingly, when using trimethylsilyl substituted ethylene and vinyl acetate as the terminating coupling reagents, product **3j** was obtained, suggesting the involvement of a β-heteroatom elimination process in the reaction.[10] In order to prove the involvement of β-heteroatom elimination step, these experiments were performed in argon atmosphere and afforded the desired product in comparable chemical yield. Vinyl phenyl sulfone was not a good coupling partner since it afforded the target product in low yield (**3k**).

Table 1.2: Sequential Coupling between **1a** and Olefins **2**.[a, b]



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

3a (75%) **3b** (73%) **3c** (82%) **3d** (72%) **3e** (69%) **3f** (53%)

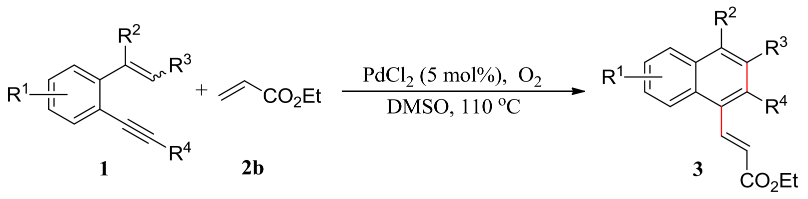
3g (68%) **3h** (64%) **3i** (62%) **3j** R = OAc (50%), R = TMS (66%) **3k** (30%) R = Et, **3l** (86%); R = Ph, **3m** (77%)

[a] Unless otherwise noted, the reactions were carried out at 110 °C using **1a** (0.1 mmol), **2** (0.3 mmol), PdCl$_2$ (0.005 mmol), DMSO (0.4 mL) for 24 h under oxygen atmosphere. [b] Isolated yields.

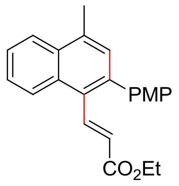
Intriguingly, when vinyl ketone was used as the external coupling partner, reductive products with alkyl chain were obtained (**3l**, **3m**). This result indicated that the final protonation step of the catalytic cycle proceeded much faster than *β*-hydride elimination in such cases. What need to be pointed out is that simple aliphatic alkenes and internal alkenes are not effective coupling partners to be used for this bis-olefination of alkynes.

To investigate the scope of the internal enyne, ethyl acrylate was chosen as the intermolecular coupling partner. The results are summarized in Table 1.3. Substrate **1n** with methoxy substituent on the *para* position of the tethered phenyl group gave the product in low yield. This might be due to competitive complexation of palladium between the alkyne and methoxy group. In comparison, substrate **1o** with methoxy substituent adjacent to the alkyne group was smoothly transformed into the desired product with good yield, which further proved the involvement of a competitive complexation in the reaction with **1n**. Moreover, alkyl and alkenyl tethered substrates were also efficiently converted into the corresponding products with moderate to good yields (**3p**-**3r**). Substrate **3s** which has a methyl group *ortho* to the alkenyl moiety resulted in moderate yield mainly owing to repulsion between the two adjacent methyl groups. Substrates possessing alkoxy substituents on the aromatic ring of styrene derivatives could also be successfully transformed into the corresponding products albeit in low yield (**3t**, **3u**). In addition, halogen atom on the aromatic ring was inert in such reaction, which could be used for further transformation (**3v**). Furthermore, a variety of substituents on the alkenyl moiety can be used in this reaction. For instance, both *tert*-butyl and phenyl group at the *α*-position of the styrene derivatives were transformed into the corresponding product in excellent yield (**3w**, **3x**).

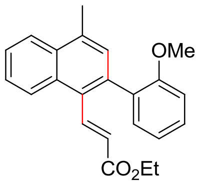
Table 1.3: Sequential Coupling between Enynes **1** and **2b**.[a, b]



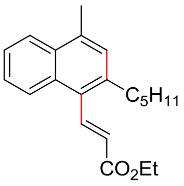
1 **2b** **3**



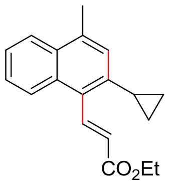
3n (32%)



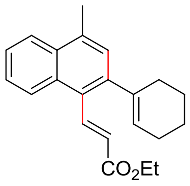
3o (69%)



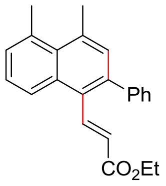
3p (71%)



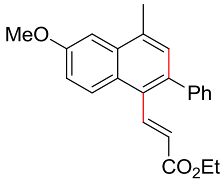
3q (57%)



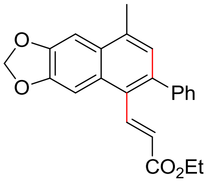
3r (59%)



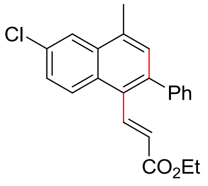
3s (45%)



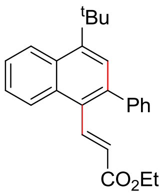
3t (55%)



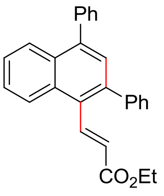
3u (33%)



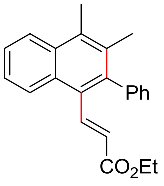
3v (66%)



3w (92%)



3x (88%)

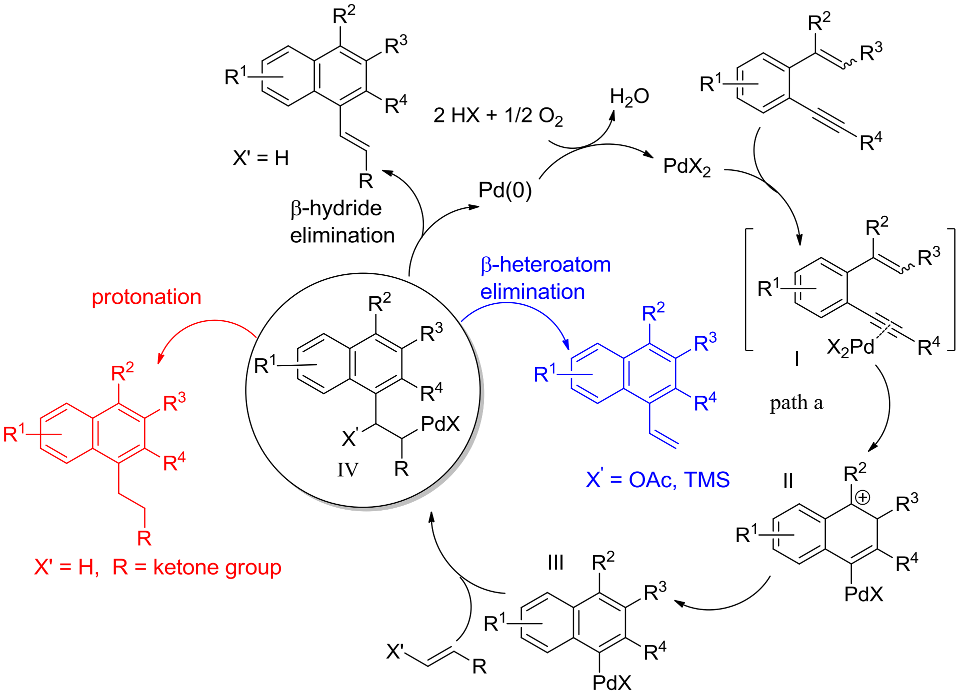


3y (61%)

[a] Unless otherwise noted, the reactions were carried out at 110 °C using **1** (0.1 mmol), **2b** (0.3 mmol), PdCl$_2$ (0.005 mmol), DMSO (0.4 mL) for 24 h under oxygen atmosphere. [b] Isolated yields.

It is important to note that this strategy was also applicable to the annulation of *α,β*-disubstituted substrate regardless of the configuration of the double bond. For example, the reaction of *E*, *Z* mixture of *α,β*-dimethyl styrene derivative **1y** proceeded selectively to give the desired *(E)*-configuration product **3y** in good yield.

A proposed mechanism is illustrated in Scheme 1.11. Initially, Pd^{II} coordinates with the triple bond forming the π-complex **I**. This initial step makes the alkynyl group electron deficient and instantaneously triggers the intramolecular carbopalladation to afford intermediate **II**. From intermediate **II** shown here, we may understand why the R^2 substituent is so crucial for this reaction, mainly due to its role in stabilization of the carbocation generated. Subsequently, deprotonation and external olefin insertion occur to produce intermediate **IV**. The regioselectivity of external olefin insertion is controlled by the electronic property of the olefin substrates, for example, when using electron deficient olefin as terminating reagent, the potentially negatively charged naphthyl group migrates to the potentially positively charged *β* carbon of the olefin. Intermediate **IV** further undergoes *β*-hydride elimination and generates the desired product as well as Pd^0 that could be reoxidized to the Pd^{II} species by molecular oxygen. We believe that the success of this transformation relies on the dual roles of the palladium catalyst, namely its Lewis acidity and late transition metal character.



Scheme 1.11 Proposed reaction mechanism

1.3 Conclusion

In conclusion, we have demonstrated the first palladium-catalyzed bis-olefination of C-C triple bonds, which represented as a rare example of anti carbopalladation using a soft nucleophile. This transformation is believed to be an efficient and sustainable process in which molecular oxygen is the exclusive oxidant with water as the only byproduct generated. Additionally, this reaction provides a facile method for the synthesis of naphthalene derivatives that are of tremendous importance in medicinal chemistry. Further studies to extend the bis-olefination of C-C triple bonds to intermolecular three-components reaction are in progress.

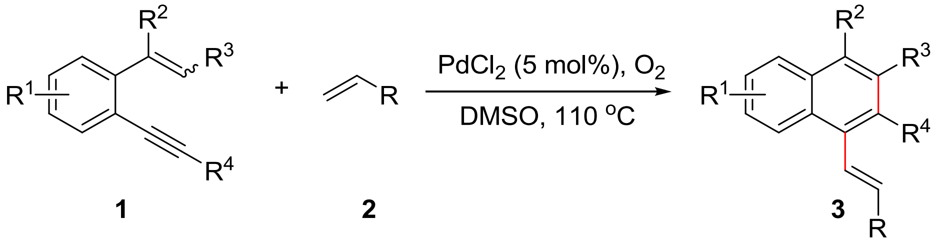
1.4 Experimental Section

$PdCl_2$ (99.9% purity) and DMSO were purchased from Aldrich without further purification. Various enynes were synthesized using reported method.[1,2] Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with acidic solution of ceric molybdate or iodine.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions. High Resolution Mass (HRMS) spectra were obtained using Waters Q-Tof Permies Mass Spectrometer. ^1H

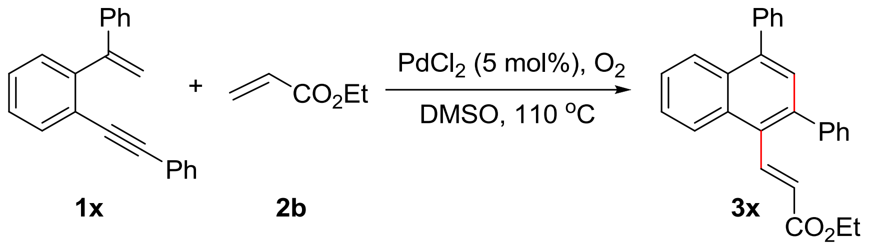
NMR (300MHz), (400 MHz) and ^{13}C (75 MHz), (100 MHz) were registered on Bruker spectrometers with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in units (ppm) by assigning TMS resonance in the ^1H spectrum as 0.00 ppm and $CDCl_3$ resonance in the ^{13}C spectrum as 77.0 ppm. All coupling constants (*J* values) were reported in Hertz (Hz). Multiplicities were given as: s (singlet); d (doublet); dd (doublets of doublet); t (triplet); q (quartet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH.

1.4.1 General Procedure for the Bis-olefination of C-C Bonds



General Procedure: An oven-dried 8 mL sample vial was charged with **1** (0.1 mmol), **2** (0.3 mmol), palladium chloride (0.005 mmol), and DMSO (0.4 mL) sequentially. After purging with oxygen the sample vial was closed tightly and heated at 110 °C with stirring for 24 hours. After reaction, the mixture was diluted with dichloromethane, and filtered through a short pad of celite. Removal of the solvent in vacuo and purification of the residue by silica gel column chromatography afforded the desired product.

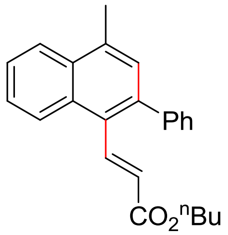
1.4.2 Gram Scale for the Synthesis of 3x



Procedure: An oven-dried 100 mL RBF was connected with freezing water cooling condenser equipped with an oxygen filled balloon. **1x** (4 mmol), **2b** (12 mmol), palladium chloride (0.2 mmol), and DMSO (16 mL) (which was pre-bubbled with oxygen for 20 minitues) were added sequentially. The resulting mixture was heated at 110 ^{o}C and monitored by TLC analysis. After disappearance of the starting material, the resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Purification of the residue by silica gel column chromatography afforded the desired product (**3x**, 1.28g) in 85%.

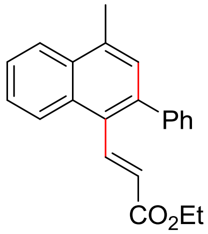
1.4.3 Characterization of Products

(*E*)-Butyl 3-(4-methyl-2-phenylnaphthalen-1-yl)acrylate



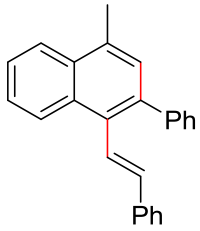
Colorless oil; **FTIR (NaCl, neat):** *ν* 1714, 1634 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 0.93 (t, *J* = 7.4 Hz, 3H), 1.34-1.41 (m, 2H), 1.59-1.67 (m, 2H), 2.73 (s, 3H), 4.16 (t, *J* = 6.6 Hz, 2H), 6.08 (d, *J* = 16.3 Hz, 1H), 7.33-7.43 (m, 6H), 7.55-7.57 (m, 2H), 7.99-8.06 (m, 2H), 8.26-8.28 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 13.7, 19.1, 19.6, 30.7, 64.3, 124.5, 125.5, 125.8, 125.9, 126.6, 127.2, 128.1, 128.6, 129.2, 130.0, 131.3, 132.0, 135.4, 139.2, 141.2, 142.9, 166.7 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{24}H_{25}O_2$: 345.1855, found $[M+H]^+$: 345.1865.

(*E*)-Ethyl 3-(4-methyl-2-phenylnaphthalen-1-yl)acrylate



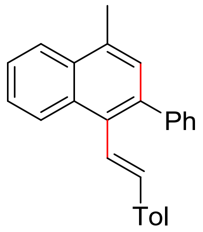
Colorless oil; **FTIR (NaCl, neat):** *ν* 1713, 1634 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 1.29 (t, *J* = 7.1 Hz, 3H), 2.73 (s, 3H), 4.22(q, *J* = 7.1 Hz, 2H), 6.07 (d, *J* = 16.3 Hz, 1H), 7.35-7.41 (m, 6H), 7.55-7.58 (m, 2H), 8.01-8.06 (m, 2H), 8.25-8.28 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 14.3, 19.6, 60.4, 124.5, 125.5, 125.8, 125.9, 126.6, 127.2, 128.1, 128.6, 129.2, 130.0, 131.3, 132.0, 135.4, 139.1, 141.2, 143.0, 166.6 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{21}O_2$: 317.1542, found $[M+H]^+$: 317.1535.

(*E*)-4-Methyl-2-phenyl-1-styrylnaphthalene



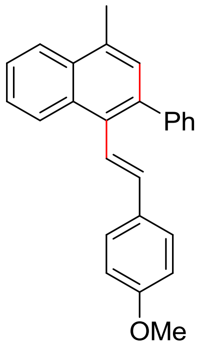
Colorless oil; **FTIR (NaCl, neat):** *ν* 1597, 1494 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.73 (s, 3H), 6.67 (d, *J* = 16.6 Hz, 1H), 7.21-7.27 (m, 2H), 7.30-7.33 (m, 3H), 7.36-7.39 (m, 5H), 7.44-7.46 (m, 2H), 7.52-7.55 (m, 2H), 8.04-8.06 (m, 1H), 8.40-8.42 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 19.5, 124.4, 125.6, 126.0, 126.3, 126.3, 126.6, 126.7, 127.5, 128.0, 128.6, 129.2, 130.2, 131.4, 131.9, 132.3, 133.5, 135.9, 137.7, 137.7, 142.1 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{25}H_{21}$: 321.1643, found $[M+H]^+$: 321.1649.

(*E*)-4-Methyl-1-(4-methylstyryl)-2-phenylnaphthalene



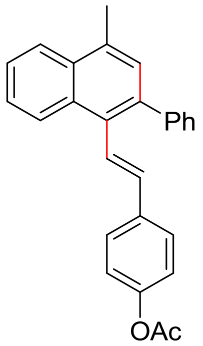
Colorless oil; **FTIR (NaCl, neat):** *ν* 1630, 1597, 1510 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.34 (s, 3H), 2.73 (s, 3H), 6.64 (d, *J* = 16.7 Hz, 1H), 7.11-7.13 (m, 2H), 7.26-7.31 (m, 4H), 7.36-7.39 (m, 3H), 7.44-7.45 (m, 2H), 7.49-7.56 (m, 2H), 8.03-8.05 (m, 1H), 8.39-8.42 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 19.5, 21.2, 124.3, 125.3, 125.6, 125.9, 126.2, 126.6, 126.7, 127.9, 129.2, 129.3, 130.2, 131.6, 132.0, 132.3, 133.3, 134.9, 135.8, 137.3, 137.6, 142.2 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{26}H_{23}$: 335.1800, found [M+H]$^+$: 335.1797.

(*E*)-1-(4-Methoxystyryl)-4-methyl-2-phenylnaphthalene



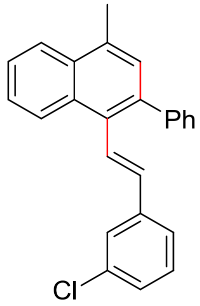
Colorless oil; **FTIR (NaCl, neat):** *ν* 1605, 1510 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.73 (s, 3H), 3.80 (s, 3H), 6.61 (d, *J* = 16.6 Hz, 1H), 6.85-6.87 (m, 2H), 7.14 (d, *J* = 16.6 Hz, 1H), 7.28-7.32 (m, 3H), 7.36-7.40 (m, 3H), 7.44-7.46 (m, 2H), 7.50-7.56 (m, 2H), 8.03-8.05 (m, 1H), 8.40-8.42 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 19.5, 55.3, 114.0, 124.2, 124.3, 125.6, 125.9, 126.6, 126.7, 127.5, 127.9, 129.2, 130.2, 130.6, 131.7, 132.0, 132.3, 133.2, 135.3, 137.6, 142.2, 159.2 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{26}H_{23}O$: 351.1749, found [M+H]$^+$: 351.1742.

(*E*)-4-(2-(4-Methyl-2-phenylnaphthalen-1-yl)vinyl)phenyl acetate



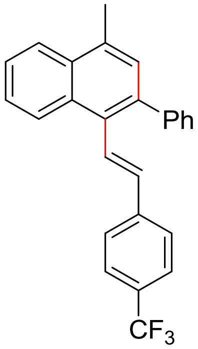
Colorless oil; **FTIR (NaCl, neat):** *v* 1761, 1597, 1504 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.30 (s, 3H), 2.73 (s, 3H), 6.64 (d, *J* = 16.6 Hz, 1H), 7.02-7.05 (m, 2H), 7.22-7.24 (m, 1H), 7.31-7.32 (m, 1H), 7.36-7.38 (m, 4H), 7.40-7.44 (m, 3H), 7.52-7.55 (m, 2H), 8.04-8.06 (m, 1H), 8.36-8.38 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 19.5, 21.1, 121.7, 124.4, 125.6, 126.0, 126.5, 126.6, 126.8, 127.2, 128.0, 129.2, 130.2, 131.2, 131.9, 132.3, 133.5, 134.9, 135.5, 137.8, 142.0, 149.9, 169.5 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{27}H_{23}O_2$: 379.1698, found [M+H]$^+$: 379.1699.

(*E*)-1-(3-Chlorostyryl)-4-methyl-2-phenylnaphthalene



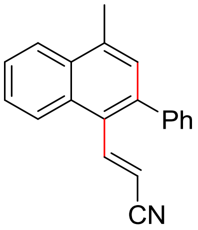
Colorless oil; **FTIR (NaCl, neat):** *v* 1636, 1593 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.73 (s, 3H), 6.58 (d, *J* = 16.6 Hz, 1H), 7.18-7.23 (m, 3H), 7.28-7.44 (m, 8H), 7.53-7.56 (m, 2H), 8.04-8.07 (m, 1H), 8.33-8.36 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 19.5, 124.4, 124.4, 125.7, 126.1, 126.2, 126.3, 126.8, 127.3, 127.8, 128.0, 129.2, 129.8, 130.2, 130.9, 131.8, 132.2, 133.8, 134.5, 134.6, 138.0, 139.5, 142.0 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{25}H_{20}Cl$: 355.1254, found [M+H]$^+$: 355.1259.

(*E*)-4-Methyl-2-phenyl-1-(4-(trifluoromethyl)styryl)naphthalene



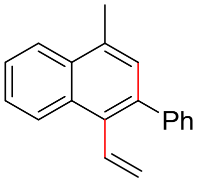
Colorless oil; **FTIR (NaCl, neat):** *ν* 1614, 1497 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.74 (s, 3H), 6.68 (d, *J* = 16.7 Hz, 1H), 7.32-7.44 (m, 9H), 7.55-7.57 (m, 4H), 8.05-8.08 (m, 1H), 8.34-8.36 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 19.6, 124.5, 125.5, 125.6, 125.7, 126.2, 126.2, 126.3, 126.9, 128.0, 129.0, 129.2, 130.2, 130.7, 131.8, 132.3, 134.0, 134.4, 138.1, 141.0, 141.9 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{26}H_{20}F_3$: 389.1517, found [M+H]$^+$: 389.1511.

(*E*)-3-(4-Methyl-2-phenylnaphthalen-1-yl)acrylonitrile



Colorless oil; **FTIR (NaCl, neat):** *ν* 2216, 1643, 1634 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.80 (s, 3H), 5.50 (d, *J* = 17.0 Hz, 1H), 7.32-7.34 (m, 3H), 7.40-7.47 (m, 3H), 7.59-7.61 (m, 2H), 7.78 (d, *J* = 17.0 Hz, 1H), 8.06-8.09 (m, 1H), 8.14-8.16 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 19.7, 103.7, 117.9, 124.8, 124.9, 126.2, 127.2, 127.3, 127.7, 128.5, 129.2, 129.8, 130.9, 132.0, 136.6 139.5, 140.6, 149.1 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{20}H_{16}N$: 270.1283, found [M+H]$^+$: 270.1279.

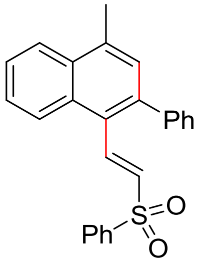
4-Methyl-2-phenyl-1-vinylnaphthalene



Colorless oil; **FTIR (NaCl, neat):** *ν* 1595 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.71 (s, 3H), 5.31 (d, *J* = 17.9 Hz, 1H), 5.56 (d, *J* = 11.4 Hz, 1H), 6.92 (dd, J_1 = 17.9 Hz, J_2 = 11.5 Hz, 1H), 7.31-7.34 (m, 2H), 7.38-7.41 (m, 4H), 7.52-7.56 (m, 2H), 8.02-8.04 (m, 1H), 8.32-8.35 (m, 1H) ppm; **^{13}C NMR**

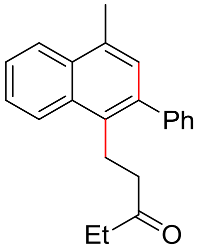
(100 MHz, CDCl$_3$): *δ* 19.5, 121.7, 124.3, 125.5, 125.9, 126.5, 126.6, 127.8, 129.1, 130.2, 131.7, 132.1, 132.3, 133.3, 134.4, 137.5, 142.3 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{19}H_{17}$: 245.1330, found $[M+H]^+$: 245.1335.

(*E*)-4-Methyl-2-phenyl-1-(2-(phenylsulfonyl)vinyl)naphthalene



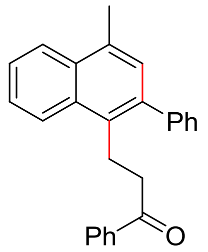
Colorless oil; **FTIR (NaCl, neat):** *v* 1595, 1447 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.72 (s, 3H), 6.35 (d, *J* = 15.7 Hz, 1H), 7.15-7.25 (m, 6H), 7.49-7.53 (m, 2H), 7.58-7.62 (m, 3H), 7.75-7.77 (m, 2H), 8.04-8.08 (m, 2H), 8.16-8.18 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 19.6, 124.6, 125.1, 126.2, 126.2, 127.1, 127.2, 127.6, 128.2, 129.0, 129.2, 129.7, 131.1, 131.9, 133.2, 133.9, 136.4, 139.6, 140.3, 140.6, 140.7 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{25}H_{21}O_2S$: 385.1262, found $[M+H]^+$: 385.1260.

1-(4-Methyl-2-phenylnaphthalen-1-yl)pentan-3-one



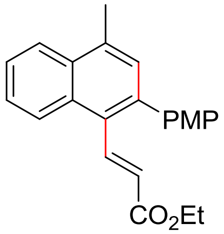
Colorless oil; **FTIR (NaCl, neat):** *v* 1713, 1597 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 0.98 (t, *J* = 7.3 Hz, 3H), 2.29 (q, *J* = 7.3 Hz, 2H), 2.64 (t, *J* = 8.1 Hz, 2H), 2.68 (s, 3H), 3.26 (t, *J* = 8.1 Hz, 2H), 7.20 (s, 1H), 7.31-7.33 (m, 2H), 7.35-7.38 (m, 1H), 7.41-7.45 (m, 2H), 7.53-7.57 (m, 2H), 8.04-8.06 (m, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 7.8, 19.3, 23.2, 35.7, 43.6, 124.5, 124.9, 125.4, 126.2, 127.0, 128.2, 129.1, 130.0, 131.7, 132.1, 132.3, 132.4, 139.1, 142.5, 210.6 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{23}O$: 303.1749, found $[M+H]^+$: 303.1747.

3-(4-Methyl-2-phenylnaphthalen-1-yl)-1-phenylpropan-1-one



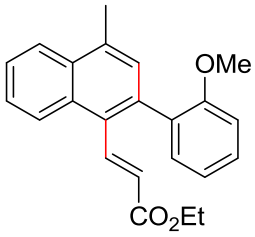
Colorless oil; **FTIR (NaCl, neat):** *ν* 1682, 1597 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.70 (s, 3H), 3.17(t, *J* = 8.3 Hz, 2H), 3.44 (t, *J* = 8.3 Hz, 2H), 7.33-7.38 (m, 5H), 7.40-7.51 (m, 4H), 7.55-7.58 (m, 2H), 7.72-7.74 (m, 2H), 8.06-8.08 (m, 1H), 8.11-8.14 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 19.3, 24.0, 40.2, 124.6, 124.9, 125.4, 126.4, 127.0, 128.0, 128.3, 128.4, 128.5, 129.1, 129.2, 131.7, 132.1, 132.4, 133.0, 136.4, 139.3, 142.5, 199.3 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{25}H_{23}O$: 339.1749, found $[M+H]^+$: 339.1754.

(*E*)-Ethyl 3-(2-(4-methoxyphenyl)-4-methylnaphthalen-1-yl)acrylate



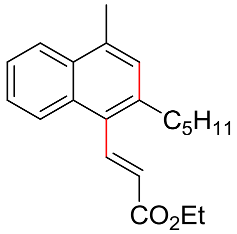
Colorless oil; **FTIR (NaCl, neat):** *ν* 1713, 1634, 1608 1512 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** *δ* 1.31 (t, *J* = 7.1 Hz, 3H), 2.73 (s, 3H), 3.86 (s, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.12 (d, *J* = 16.3 Hz, 1H), 6.94-6.97 (m, 2H), 7.27-7.33 (m, 3H), 7.54-7.58 (m, 2H), 7.99-8.06 (m, 2H), 8.26-8.29 (m, 1H) ppm; **^{13}C NMR (75 MHz, CDCl$_3$):** *δ* 14.3, 19.6, 55.3, 60.4, 113.6, 124.5, 125.2, 125.7, 125.8, 126.5, 128.4, 129.4, 131.2, 131.9, 133.5, 135.3, 138.8, 143.3, 158.9, 166.7 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{23}H_{23}O_3$: 347.1647, found $[M+H]^+$: 347.1643.

(*E*)-Ethyl 3-(2-(2-methoxyphenyl)-4-methylnaphthalen-1-yl)acrylate



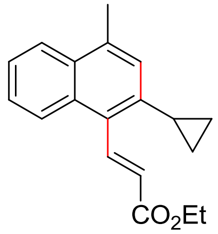
Colorless oil; **FTIR (NaCl, neat):** *ν* 1713, 1634, 1601 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** *δ* 1.26 (t, *J* =7.1 Hz, 3H), 2.71 (s, 3H), 3.73 (s, 3H), 4.18 (q, *J* =7.1 Hz, 2H), 5.93 (d, *J* =16.2 Hz, 1H), 6.93-7.04 (m, 2H), 7.18-7.23 (m, 1H), 7.28-7.37 (m, 2H), 7.52-7.56 (m, 2H), 8.00-8.06 (m, 2H), 8.17-8.20 (m, 1H) ppm; **^{13}C NMR (75 MHz, CDCl$_3$):** δ 14.3, 19.6, 55.4, 60.2, 111.0, 120.6, 124.0, 124.5, 125.7, 126.3, 129.0, 129.5, 129.7, 130.1, 131.3, 131.4, 132.0, 135.0, 135.6, 143.1, 156.1, 166.7 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{23}H_{23}O_3$: 347.1647, found [M+H]$^+$: 347.1652.

(*E*)-Ethyl 3-(4-methyl-2-pentylnaphthalen-1-yl)acrylate



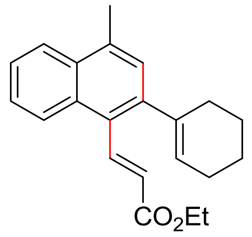
Colorless oil; **FTIR (NaCl, neat):** ν 1715, 1638, 1599 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.33-1.40 (m, 7H), 1.60-1.65 (m, 2H), 2.68 (s, 3H), 2.76 (t, *J* = 7.7 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 6.20 (d, *J* = 16.3 Hz, 1H), 7.20 (s, 1H), 7.46-7.51 (m, 2H), 7.95-7.98 (m, 1H), 8.04-8.08 (m, 1H), 8.19 (d, *J* = 16.3, 1H) ppm; **^{13}C NMR (75 MHz, CDCl$_3$):** δ 14.0, 14.3, 19.5, 22.5, 31.1, 31.7, 33.8, 60.6, 124.3, 125.1, 125.3, 125.5, 126.1, 128.8, 128.9, 131.3, 131.5, 134.9, 138.6, 142.9, 166.6 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{21}H_{27}O_2$: 311.2011, found [M+H]$^+$: 311.2014.

(*E*)-Ethyl 3-(2-cyclopropyl-4-methylnaphthalen-1-yl)acrylate



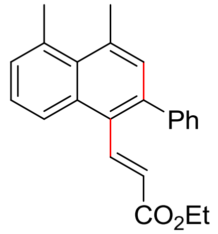
Colorless oil; **FTIR (NaCl, neat):** ν 1715, 1636, 1599 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 0.79-0.83 (m, 2H), 1.03-1.08 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 2.15-2.21 (m, 1H), 2.67 (s, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 6.33 (d, *J* = 16.3 Hz, 1H), 6.93 (s, 1H), 7.48-7.52 (m, 2H), 7.96-7.98 (m, 1H), 8.07-8.09 (m, 1H), 8.37 (d, *J* = 16.3 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 8.9, 14.0, 14.3, 19.7, 60.6, 124.0, 124.3, 125.1, 125.2, 125.4, 126.2, 130.0, 131.0, 131.4, 135.3, 138.5, 142.8, 166.8 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{19}H_{21}O_2$: 281.1542, found $[M+H]^+$: 281.1543.

(*E*)-Ethyl 3-(2-cyclohexenyl-4-methylnaphthalen-1-yl)acrylate



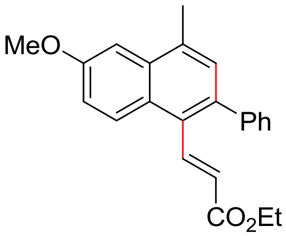
Colorless oil; **FTIR (NaCl, neat):** *ν* 1715, 1634, 1595 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 1.36 (t, *J* = 7.1 Hz, 3H), 1.71-1.76 (m, 4H), 2.21-2.25 (m, 4H), 2.68 (s, 3H), 4.30 (q, *J* = 7.1 Hz, 2H), 5.67 (s, 1H), 6.34 (d, *J* = 16.3 Hz, 1H), 7.17 (s, 1H), 7.49-7.52 (m, 2H), 7.97-8.00 (m, 1H), 8.17-8.21 (m, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 14.4, 19.6, 22.0, 23.1, 25.6, 30.3, 60.4, 123.7, 124.4, 125.4, 125.6, 126.3, 127.4, 128.1, 128.7, 131.4, 131.7, 135.2, 138.4, 142.3, 143.1, 167.0 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{25}O_2$: 321.1855, found $[M+H]^+$: 321.1853.

(*E*)-Ethyl 3-(4,5-dimethyl-2-phenylnaphthalen-1-yl)acrylate



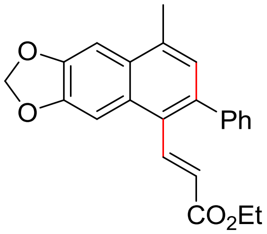
Colorless oil; **FTIR (NaCl, neat):** *ν* 1713, 1634 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** *δ* 1.22 (t, *J* = 7.1 Hz, 3H), 2.71 (s, 6H), 4.14 (q, *J* = 7.1 Hz, 2H), 5.46 (d, *J* = 16.1 Hz, 1H), 7.28-7.46 (m, 8H), 7.91-7.93 (m, 1H), 8.33 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (75 MHz, CDCl$_3$):** *δ* 14.2, 20.3, 27.2, 60.2, 122.9, 124.5, 125.6, 126.8, 128.0, 129.0, 129.8, 130.2, 130.4, 131.9, 133.1, 135.2, 135.7, 139.8, 142.1, 147.9, 166.4 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{23}H_{23}O_2$: 331.1698, found $[M+H]^+$: 331.1692.

(*E*)-Ethyl 3-(6-methoxy-4-methyl-2-phenylnaphthalen-1-yl)acrylate



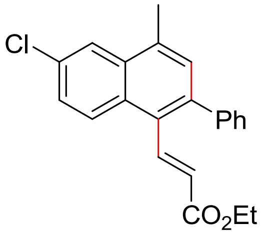
Colorless oil; **FTIR (NaCl, neat):** *v* 1714, 1620, 1597 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 1.29 (t, *J* = 7.1 Hz, 3H), 2.68 (s, 3H), 3.97 (s, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 6.06 (d, *J* = 16.3 Hz, 1H), 7.24-7.28 (m, 2H), 7.32-7.42 (m, 6H), 8.00 (d, *J* = 16.3 Hz, 1H), 8.17-8.20 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 14.3, 19.8, 55.3, 60.4, 103.3, 118.5, 125.3, 126.5, 127.1, 127.5, 128.1, 128.5, 129.7, 130.0, 133.4, 134.0, 136.9, 141.2, 143.2, 157.5, 166.6 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{23}H_{23}O_3$: 347.1647, found [M+H]$^+$: 347.1642.

(*E*)-Ethyl 3-(8-methyl-6-phenylnaphtho[2,3-*d*][1,3]dioxol-5-yl)acrylate



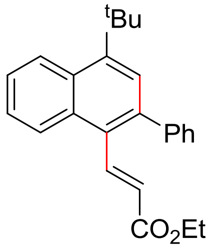
Colorless oil; **FTIR (NaCl, neat):** *v* 1714, 1634 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** *δ* 1.28 (t, *J* = 7.1 Hz, 3H), 2.63 (s, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 6.01 (d, *J* = 16.3 Hz, 1H), 6.08 (s, 2H), 7.20 (s, 1H), 7.32-7.42 (m, 6H), 7.57 (s, 1H), 7.94 (d, *J* = 16.3 Hz, 1H) ppm; **^{13}C NMR (75 MHz, CDCl$_3$):** *δ* 14.3, 20.1, 60.4, 101.0, 101.3, 102.5, 125.2, 127.1, 128.0, 128.0, 128.1, 128.5, 129.2, 130.0, 134.2, 137.8, 141.3, 143.4, 147.5, 148.2, 166.5 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{23}H_{21}O_4$: 361.1440, found [M+H]$^+$: 361.1445.

(*E*)-Ethyl 3-(6-chloro-4-methyl-2-phenylnaphthalen-1-yl)acrylate



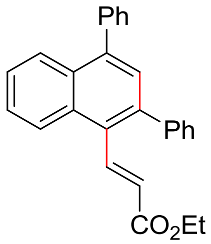
Colorless oil; **FTIR (NaCl, neat):** *v* 1714, 1634, 1595 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** *δ* 1.29 (t, *J* = 7.1 Hz, 3H), 2.69 (s, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 6.05 (d, *J* = 16.3 Hz, 1H), 7.33-7.50 (m, 7H), 7.96 (d, *J* = 16.3 Hz, 1H), 8.00-8.01 (m, 1H), 8.17-8.20 (m, 1H) ppm; **^{13}C NMR (75 MHz, CDCl$_3$):** *δ* 14.3, 19.5, 60.5, 123.6, 125.9, 127.2, 127.4, 127.6, 128.2, 128.7, 129.7, 129.9, 130.3, 132.0, 133.0, 134.5, 139.3, 140.7, 142.5, 166.3 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{20}O_2Cl$: 351.1152, found $[M+H]^+$: 351.1154.

(*E*)-Ethyl 3-(4-*tert*-butyl-2-phenylnaphthalen-1-yl)acrylate



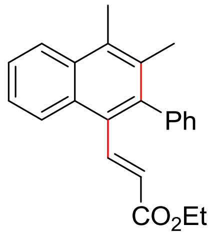
Colorless oil; **FTIR (NaCl, neat):** *v* 1714, 1634 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 1.28 (t, *J* = 7.1 Hz, 3H), 1.65 (s, 9H), 4.21 (q, *J* = 7.1 Hz, 2H), 6.01 (d, *J* = 16.3 Hz, 1H), 7.35-7.42 (m, 4H), 7.50-7.53 (m, 4H), 8.06 (d, *J* = 16.3 Hz, 1H), 8.26-8.28 (m, 1H), 8.52-8.54 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 14.2, 31.9, 36.1, 60.4, 124.7, 125.6, 125.9, 126.1, 126.6, 127.1, 128.1, 129.2, 130.1, 130.9, 132.8, 138.5, 141.7, 143.2, 146.9, 166.5 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{25}H_{27}O_2$: 359.2011, found $[M+H]^+$: 359.2005.

(*E*)-Ethyl 3-(2,4-diphenylnaphthalen-1-yl)acrylate



Colorless oil; **FTIR (NaCl, neat):** *v* 1714, 1634 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 1.30 (t, *J* = 7.1 Hz, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.14 (d, *J* = 16.4 Hz, 1H), 7.35-7.37 (m, 1H), 7.40-7.56 (m, 12H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 16.4 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 14.3, 60.5, 125.6, 126.0, 126.1, 126.8, 127.3, 127.5, 128.2, 128.3, 129.4, 129.7, 130.0, 130.1, 131.1, 131.7, 138.9, 140.1, 140.9, 141.0, 142.8, 166.5 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{27}H_{23}O_2$: 379.1698, found $[M+H]^+$: 379.1700.

(*E*)-Ethyl 3-(3,4-dimethyl-2-phenylnaphthalen-1-yl)acrylate



Colorless oil; **FTIR (NaCl, neat):** *ν* 1714, 1634 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 1.24 (t, *J* = 7.1 Hz, 3H), 2.16 (s, 3H), 2,68 (s, 3H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.95 (d, *J* = 16.3 Hz, 1H), 7.13-7.14 (m, 2H), 7.30-7.56 (m, 5H), 7.72 (d, *J* = 16.3 Hz, 1H), 8.11-8.19 (m, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 14.2, 15.6, 18.5, 60.3, 124.2, 124.8, 125.5, 125.8, 125.9, 127.1, 128.3, 129.4, 129.4, 129.7, 132.1, 132.3, 132.9, 140.7, 140.8, 143.6, 166.5 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{23}H_{23}O_2$: 331.1698, found $[M+H]^+$: 331.1703.

Rhodium-Catalyzed Direct *ortho* C-H Olefination of Phenol Derivatives

2.1 Introduction

In the past decade, the transition-metal-catalyzed C-H bond olefination has evolved into an efficient and reliable complementary synthetic method to the traditional cross coupling strategy for the installation of alkenyl functionality.[1] The obviation of preactivation of the substrates, compared with using carbon-halogen or carbon-metal counterparts, dramatically improved the overall efficiency. Thus, a large number of olefination studies have been reported concerning a variety of substrates with different type of transition-metals.[2]

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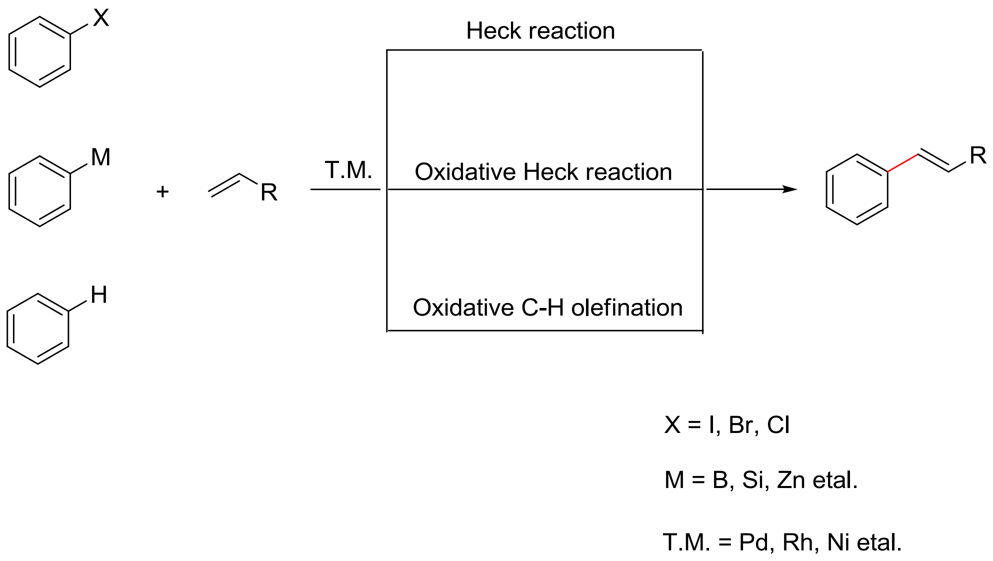
1 (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731. b) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633. d) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem*. **2004**, *69,* 1221.

[2] For palladium-catalyzed C-H olefination, see: (a) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 4156. (b) Nishikata, T.; Lipshutz, B. H. *Org. Lett*. **2010**, *12*, 1972. (c) Yokota, T.; Tani, M.; Sakaguchi, S. Ishii, Y. *J. Am. Chem. Soc*. **2003**, *125*, 1476. (d) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc*. **2008**, *130*, 10066. (e) Cai, G.; Fu, Y.; Li, Y.; Wan, X. Shi, Z. *J. Am. Chem. Soc*. **2007**, *129*, 7666. (f) Wang, D-H.; Engle, K. M.; Shi, B-F.; Yu, J-Q. *Science* **2010**, *327*, 315. (g) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc*. **2006**, *128*, 2528. (h) Zhu, C.; Falck, J. R. *Org. Lett*. **2011**, *13*, 1214. (i) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211. (j) Garcia-Rubia, A. Arrayas, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 6511. (k) Jiang, H.; Feng, Z.; Wang, A.; Liu, X.; Chen, Z. *Eur. J. Org. Chem*. **2010**, 1227. (l) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc*. **2008**, *130*, 9254. (m) Obora, Y.; Ishii, Y. *Molecules* **2010**, *15*, 1487. (n) Shi, B-F.; Zhang, Y-H.; Lam, J. K.; Wang, D-H.; Yu, J-Q. *J. Am. Chem. Soc*. **2010**, *132*, 460. (o) Lu, Y.; Wang, D-H.; Engle, K. M.; Yu, J-Q. *J. Am. Chem. Soc*. **2010**, *132*, 5916. (p) Li, J-J.; Mei, T-S.; Yu, J-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452. (q) Dams, M. D.; Vos, D. E. D.; Celen, S.; Jacobs, P. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3512. (r) Wasa, M.; Engle, K. M.; Yu, J-Q. *J. Am. Chem. Soc*. **2010**, *132*, 3680. (s) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc*. **2011**, *133*, 6541. For Ruthenium-catalyzed C-H olefination, see: Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett*. **2011**, *13*, 706. For Copper-catalyzed C-H olefination, see: Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1115.



Scheme 2.1 Transition metal-catalyzed (oxidative) Heck and C-H olefination

In this regard, the Rh-catalyzed C-H activation has witnessed substantial advancement during recent years.[3] The pioneering work of Fagnou,[4] Glorius,[5] Ellman,[6]

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[3] (a) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*. **2011**, *133*, 1248. (b) Li, Y.; Li, B-J.; Wang, W-H.; Huang, W-P.; Zhang, X-S.; Chen, K.; Shi, Z-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 2115. (c) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc*. **2008**, *130*, 16474. (d) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc*. **2009**, *131*, 12050. (e) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc*. **2011**, *133*, 6449. (f) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc*. **2010**, *132*, 6908. (g) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou,K. *J. Am. Chem. Soc*. **2010**, *132*, 18326. (h) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc*. **2011**, *133*, 2154. (i) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc*. **2010**, *132*, 9585. (j) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett*. **2010**, *12*, 5462. (k) Song, G.; Chen, D.; Pan, C-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487. (l) Wang, F.; Song, G.; Du, Z.; Li, X. *J. Org. Chem.* **2011**, *76*, 2926. (m) Too, P. C.; Wang, Y-F.; Chiba, S. *Org. Lett*. **2010**, *12*, 5688.

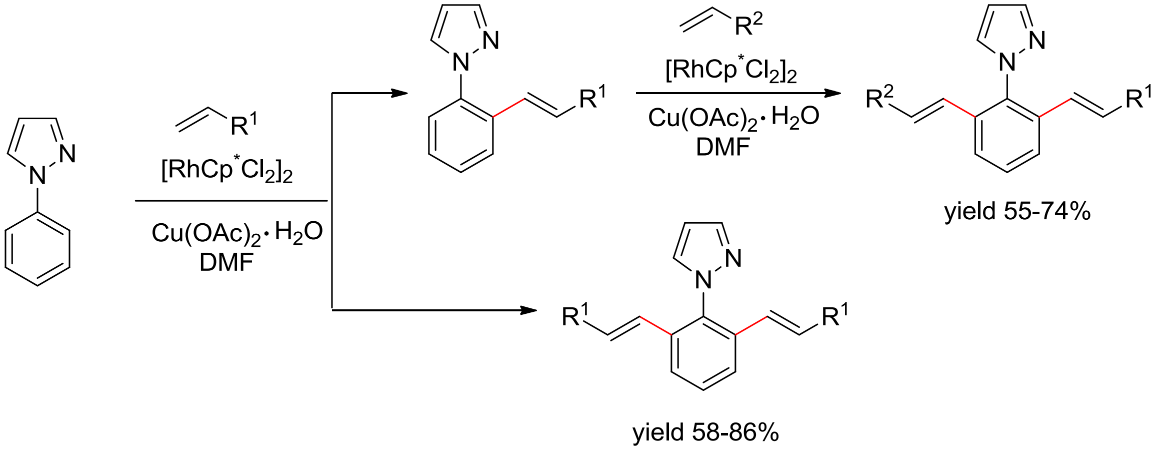
[4] (a) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc*. **2010**, *132*, 6910. (b) Fagnou, K.; Lautens, M. *Chem. Rev*. **2003,** *103*, 169.

[5] (a) Rakshit, s.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc*. **2011**, *133*, 2350. (b) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc*. **2010**, *132*, 9982. (c)) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1064. (d) Willwacher, J.; Rakshit, S.; Glorius, F. *Org. Biomol. Chem.* **2011**, *9*, 4736. (e) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem. Eur. J.* **2011**, *17*, 7167.

[6] Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett*. **2010**, *12*, 540.

Miura[7] and others,[8] to some extent, further demonstrated the competency and efficiency of Rh in the C-H olefination reactions.

In 2009, Miura reported Rh(III)-catalyzed C-H olefination of arenes employing pyrazole as directing group with copper acetate as oxidant DMF as solvent (Scheme 2.2).[7a] By modifying relative stoichiometry and reaction temperature the author demonstrated that this catalytic system allows selective 2-mono or 2,6-diolefination. In addition, the introduction of two different olefin moieties in a one-pot manner was proved to be feasible.



Scheme 2.2 Rh^{III}-catalyzed oxidative C-H olefination of 1-phenylpyrazoles and relatived compounds

In 2010, Glorious reported the first example of cationic Rh^{III}-catalyzed oxidative C-H olefination of unactivated acetanilides, which opens a new window for the

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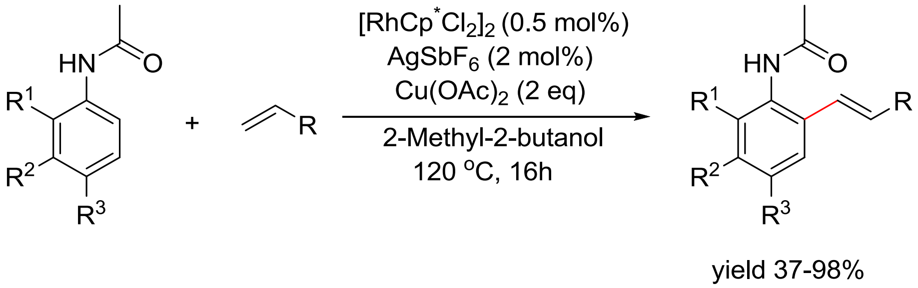
[7] (a) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2009**, *74,* 7094. (b) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett*. **2010**, *12*, 5776. (c) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2011**, *76*, 3024.

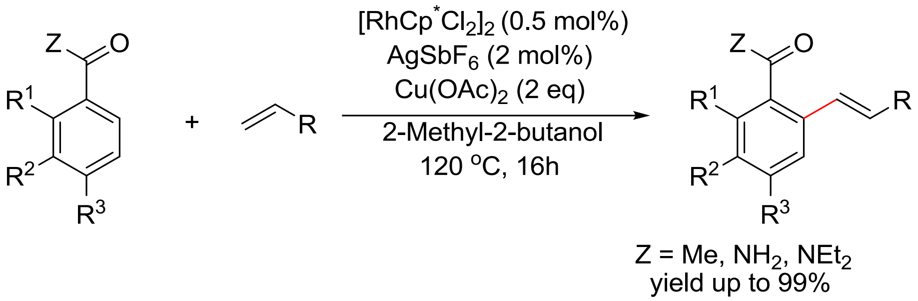
[8] (a) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett*. **2011**, *13*, 2372. (b) Wang, F.; Song, G.; Li, X. *Org. Lett*. **2010**, *12*, 5430. (c) Chen, J.; Song, G.; Pan, C-L.; Li. X. *Org. Lett.*, **2010**, *12*, 5426.

realization of olefine introduction (Scheme 2.3).[5b] Compared with relative palladium-catalyzed protocol, this method carries more advantages: 1. It requires only 0.5 mol% of catalyst loading while giving rise to the desired olefination product in high up to 98%; 2. In addition to acrylates, non-activated olefines such as styrene derivatives and ethylene, which proved to be unreactive in palladium-catalyzed olefination, were nicely reacted.



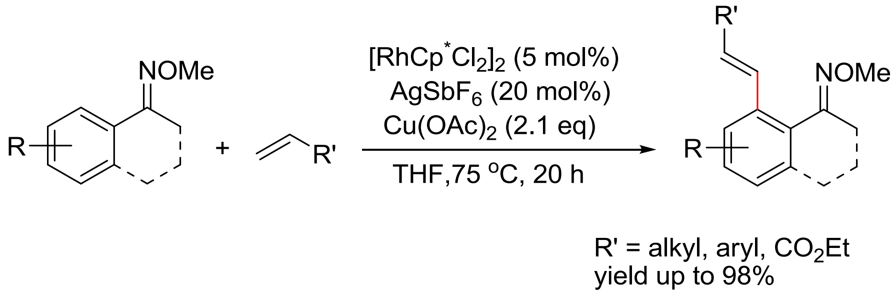
Scheme 2.3 Rh^{III}-catalyzed oxidative C-H olefination of acetanilides

Because of the high reactivity of [RhCp*Cl$_2$]$_2$/AgSbF$_6$ catalytic system, Glorious found electron-deficient arenes such acetophenone and benzamide, which always proved to be challenge with palladium catalysis, could be employed as competent subatrates in the oxidative olefination, delivering the product in high to excellent yield (Scheme 2.4).[5c]



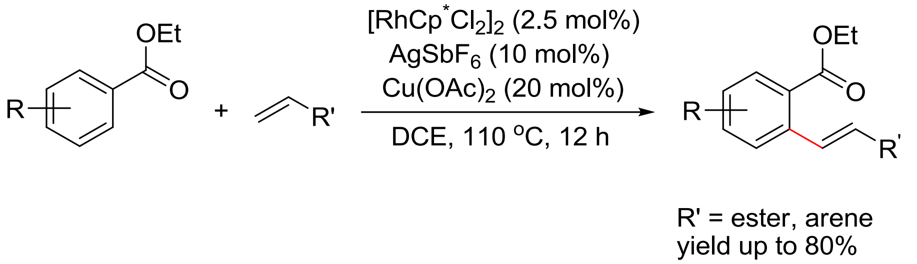
Scheme 2.4 Rh^{III}-catalyzed oxidative C-H olefination of acetophenone and benzamide derivatives

In 2011, Ellman reported the Rh(III)-catalyzed oxidative coupling of unactivated alkenes, especially the aliphatic olefin, with oxime as directing group (Scheme 2.5).[6] It was demonstrated that electron-donating substituents displayed positive effect on the reaction efficiency while electron-withdrawing one retarded the reaction and when cyano-containing subsrate was used, the desired olefination product was formed in less than 10% yield. In addition, in the case of acylic oxime substrates the location of substituent was found to be highlt important. While *meta*- and *para*-substitutents were nicely tolerated, the coupling reaction was found to hardly proceed in the case of *orth*-substitued one, which is due to the steric repulsion.



Scheme 2.5 RhIII-catalyzed oxidative C-H olefination using oxime as directing group

In the same year, Chang realized the oxidative olefination using ester as directing group and the copper acetate could be reduced to catalytic amount with air as the ultimate oxidant (Scheme 2.6).[8a]



Scheme 2.6 RhIII-catalyzed oxidative C-H olefination of benzoester

While many aniline-centered derivatives, such as *N*-acetyl, *N*-pivalyl and *N*-tosyl substrates have been widely employed in C-H bond activation, the phenol counterpart however, was far less explored.[9] This consequence is, to some degree, due to the more flexible conformation of the transition-metal complex of phenol derivatives compared with that of aniline derivatives, which could hinder the initiation of C-H bond activation. We assumed to use o-protected phenol as substrate in the directing group assisted *ortho* C-H bond olefination not only because of the directing ability of acyoxyl group but also its latent leaving ability, which allows further elaboration in the subsequent nickel-catalyzed cross-coupling reactions (Scheme 2.7).[10]

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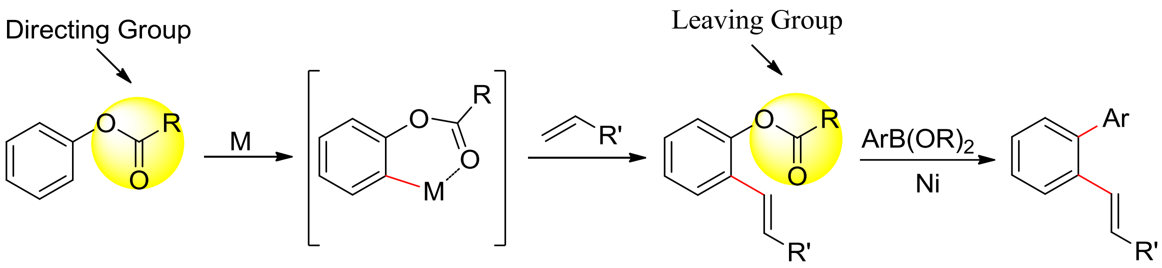
[9] (a) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416. (b) Boele, M. D. K.; Strijdonck, G. P. F.; Vries, A. H. M.; Kamer, P. C. J.; Vries, J. G.; Leeuwen, P. W. N. M. *J. Am. Chem.* Soc. **2002**, *124*, 1586. (c) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem.* Soc. **2005**, *127*, 4156; (d) Wang, J-R.; Yang, C-T.; Liu, L.; Guo, Q-X. *Tetrahedron Lett*. **2007**, *48*, 5449. (e) Nishikata, T.; Lipshutz, B. H. *Org. Lett*. **2010**, *12*, 1972. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147.

[10] (a) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem.* Soc. **2008**, *130*, 14468. (b) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem.* Soc. **2009**, *131*, 17750.



Scheme 2.7 Oxidative C-H olefination of phenol derivatives

In the course of our continuing efforts in direct C-H bond olefination, we would like to report herein the rhodium-catalyzed direct oxidative olefination of phenol carbamate.[11]

2.2 Results and discussion

At the outset, the reaction condition was optimized employing 1-naphthol *N*,*N*-dimethyl carbamate (**1a**) and ethyl acrylate as the model substrates. Treatment of **1a** with ethyl acrylate using $[Cp^{*}RhCl_2]_2$ as catalyst, $AgSbF_6$ as halide scavenger and $Cu(OAc)_2$ as oxidant in DCE solvent gave the desired olefination product **2a** in a promising 56% yield. With this exciting preliminary result in hand, a systematic solvent screening was carried out (Table 2.1, entries 2-8). The reaction displayed tremendous solvent dependence characteristic, while 1,4-dioxane, toluene, *t*-AmOH and chlorobenzene provided inferior result compared to DCE, solvents which possess coordinating ability, such as DMF and MeCN completely impeded the reaction. This is mainly because such solvent could form relatively stable complexes with the active catalyst, which in turn, would reduce the electrophilicity of the catalyst. Much to our

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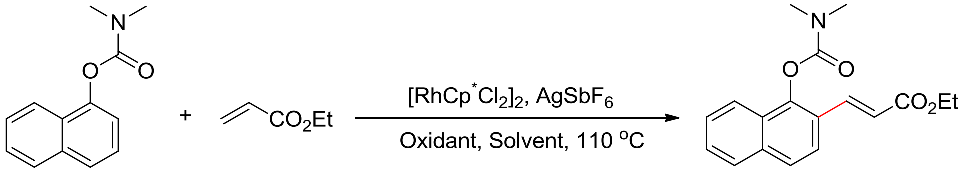
[11] For the alkene scope, refer to a similar work by Liu: Gong, T-J.; Xiao, B.; Liu, Z-J.; Wan, J.; Xu, J.; Luo, D-F.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 3235.

delight, the reaction efficiency was dramatically improved and almost quantitative isolated yield was obtained when the reaction solvent was simply changed to DME (Table 2.1, entry 8). The substantial difference between using DME and DCE as solvent may be in part, due to the relatively higher solubility of $Cu(OAc)_2$ in DME. The substitution of $Cu(OAc)_2$ with other oxidants was next carried out using DME as solvent, although all modifications resulted in either a reduced yield or no desired product (Table 2.1, entries 9-11). Only trace amount of the coupling product could be detected if no $AgSbF_6$ was added, which implied that a somewhat cationic characteristic of the catalyst is of vital importance in this reaction (Table 2.1, entry 12). As expected, there is no reaction in the absence of $[Cp^*RhCl_2]_2$ and also, palladium catalyst proved to be ineffective in this reaction (Table 2.1, entries 13, 14).

Table 2.1 Reaction Conditions Optimization.[a]



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

Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DCE	56
2	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	Dioxane	21
3	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DMF	NR
4	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	Toluene	15
5	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	*t*-AmOH	12
6	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	PhCl	34
7	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	MeCN	NR
8	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DME	97

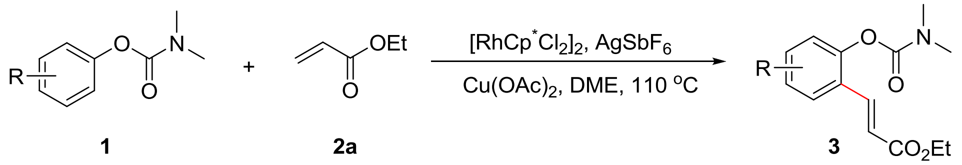
9	$[Cp^*RhCl_2]_2$	$Cu(OTf)_2$	DME	trace
10	$[Cp^*RhCl_2]_2$	$K_2S_2O_8$	DME	32
11	$[Cp^*RhCl_2]_2$	$PhI(OAc)_2$	DME	45
12	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DME	trace[c]
13	-	$Cu(OAc)_2$	DME	NR
14	$Pd(MeCN)_2Cl_2$	$Cu(OAc)_2$	DME	NR

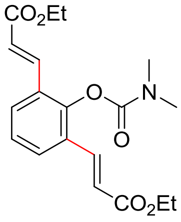
[a] unless otherwise noted the reactions were carried out at 110 °C using **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (0.0025 mmol), $AgSbF_6$ (0.01mmol), oxidant (0.2 mmol) in solvent (0.5 mL) stirred for 24 h. [b] Isolated yields. [c] $AgSbF_6$ was omitted. DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane.

With the optimized reaction condition in hand, the reaction scope with respect to the aryl carbamate was investigated using ethyl acrylate as the standard coupling partner. When phenol *N*,*N*-dimethyl carbamate (**2b**) was employed, the reaction could selectively form mono- or bis-olefinated product in excellent yield depending on the relative stoichiometry of the two coupling partners.

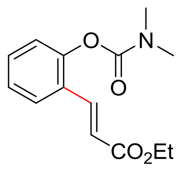
It is evident that electron-releasing functional groups, such as methyl, methoxyl, cyclic alkyl together with cyclic alkenyl all have beneficial effect on the oxidative coupling, affording the desired product in excellent yield (Table 2.2, **3d**-**3j**). However, **1k**, which possesses a 1-adamantyl group at the *ortho*-position, displayed slightly low efficiency compared to the nonsubstituted version, which is probably due to the huge steric hinderance (Table 2.2, **3k**). Intriguingly, when substrates contain *meta*-substituents was used, the reaction pattern depended upon the dominance between the steric- and electronic-factors. For example, **1e**, which has a methyl group at 3-position of phenol carbamate tended to afford olefination at the sterically more accessible position, due to the predominance of the steric effect in this case (see also Table 2.2, **3f**, **3v** and **3w**). However, the reaction was inclined to provide mono- and bis-olefinated products, when 3-methoxyl substituted carbamate was employed, suggesting the predominance of electronic effect. This dilemma could be easily resolved simply through using two-fold of catalyst and olefin, which allowed the formation of bis-olefination product in excellent yield (Table 2.2, **3g**). The ester functionality is also tolerated under this mild reaction condition, despite its exertion to some degree of electronic erosion, thus providing the desired product in moderate yield (Table 2.2, **3l**, **3u**). Moreover, the present reaction also worked efficiently with biphenyl derivatives, where substrates containing electron-donating group afforded better yield than those with electron-withdrawing one, which is in accordance with the aforementioned electronic effect on the reaction efficiency (Table 2.2, **3m**-**3p**). Notably, the hetero-atom containing biaryl system was also a viable coupling partner albeit affording the product in moderate yield (Table 2.2, **3q**). It also need to be pointed out that the halide functionalities were compatible under this reaction condition, which could provide handle for the further elaboration (Table 2.2, **3r**, **3s**, **3w**). Last but not least, TBS functionality was also inert under this reaction condition affording the TBS-containing product **2t** in moderate yield. This could provide extra opportunity for further Hiyama-like cross-coupling and the ability to access more complex molecules.

Table 2.2 Reaction scope.[a,b]

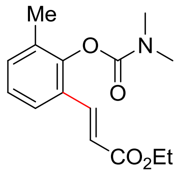




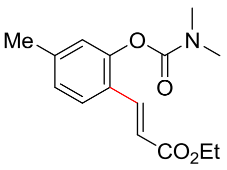
3b (92%)[c]



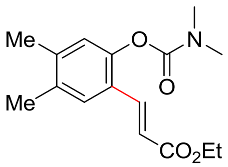
3c (81%)



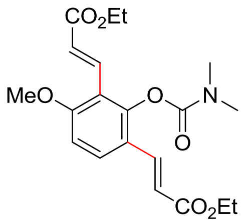
3d (94%)



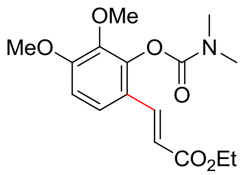
3e (92%)



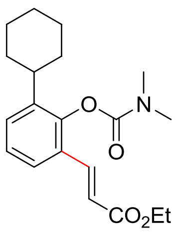
3f (96%)



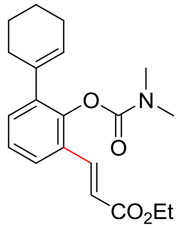
3g (90%)[c]



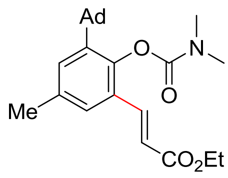
3h (97%)



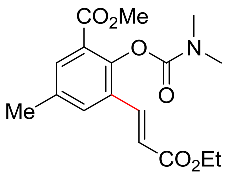
3i (98%)



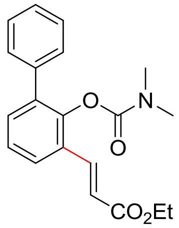
3j (97%)



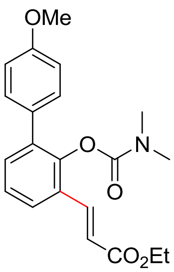
3k (73%)



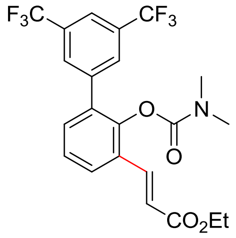
3l (76%)



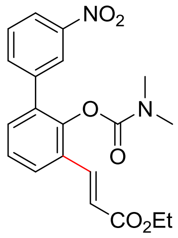
3m (95%)



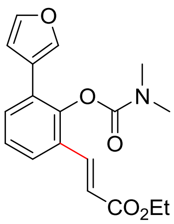
3n (99%)



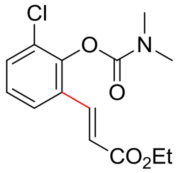
3o (64%)[c]



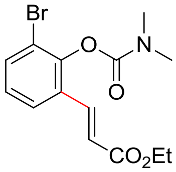
3p (79%)[c]



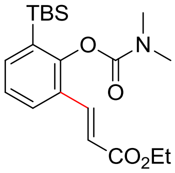
3q (63%)[c]



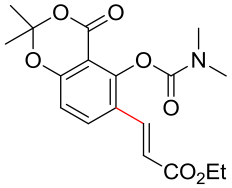
3r (95%)^c



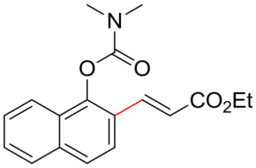
3s (62%)^c



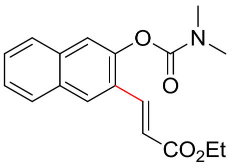
3t (68%)^{c,d}



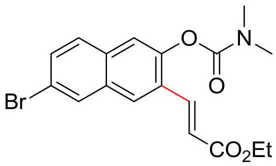
3u (80%)^c



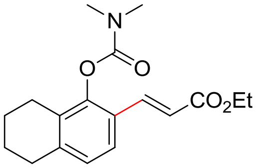
3a (97%)



3v (90%)



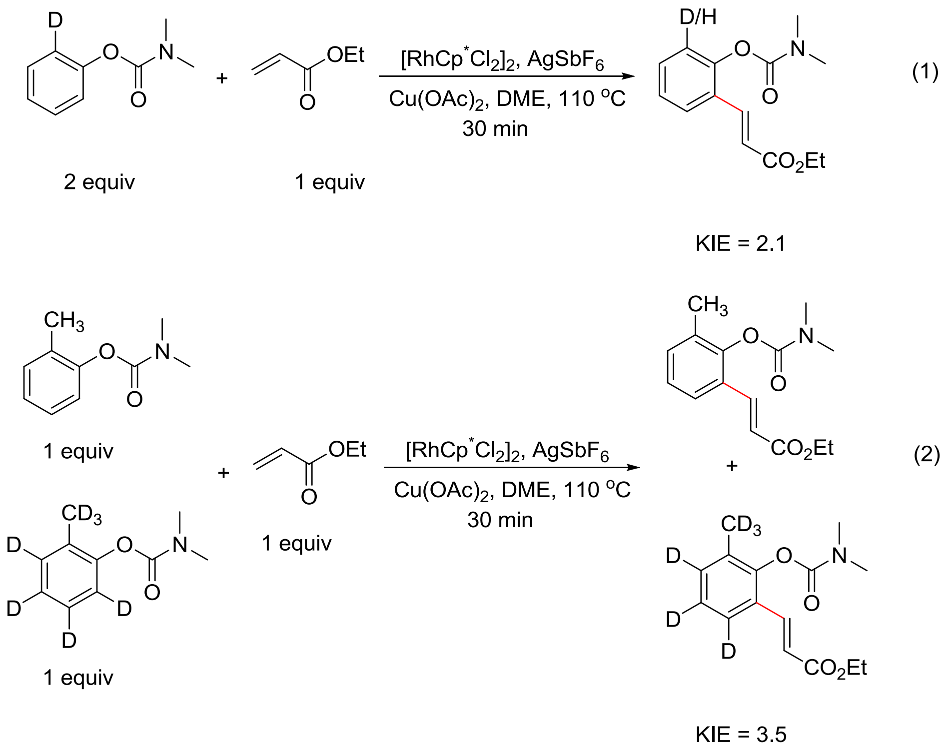
3w (85%)



3x (95%)

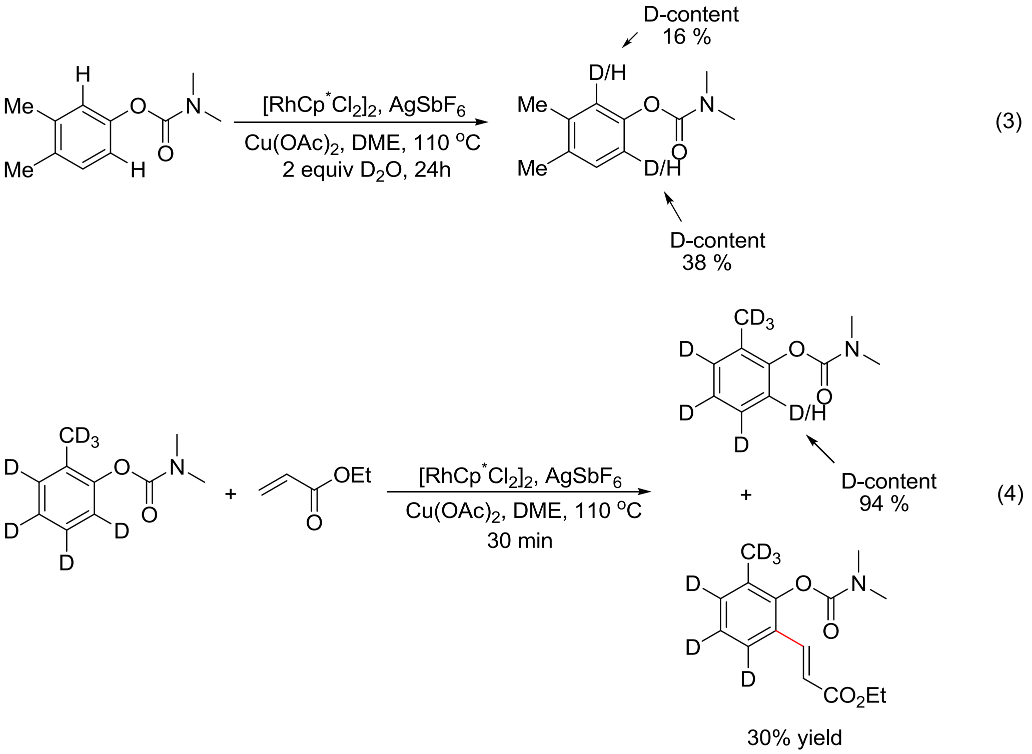
[a] unless otherwise noted the reactions were carried out at 110 °C using **1** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.0025 mmol), $AgSbF_6$ (0.01mmol), $Cu(OAc)_2$ (0.2 mmol) in DME (0.5 mL) stirred for 24 h. b Isolated yield. [c] catalyst (0.005 mmol) was used. [d] DCE was used as solvent. DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane.

In order to probe the mechanism of this oxidative olefination reaction, intra- and inter-molecular deuterium kinetic isotope effect studies were performed. The intramolecular kinetic isotope effect (KIE) study using **1b**-d_1 displayed a KIE of 2.1 (Scheme 2.8, Eq. (1)), while the intermolecular version between **1d** and **1d**-*d*7 showed a KIE of 3.5 (Scheme 2.8, Eq. (2)). These two experiments demonstrated that the C-H bond cleavage is most likely the rate-determining step of the whole process.



Scheme 2.8 Kinetic isotope effect study

To obtain further insight into the mechanism, the following experiments were performed. When **1f** was subjected to the standard reaction condition but without ethyl acrylate and at the same time adding two equivalent of D_2O, the deuterium contents at both *ortho*-position were observed as 38% and 16% favoring the more sterically accessible site (Scheme 2.9, Eq. (3)). Moreover, stopping the reaction between **1d**-*d*7 and ethyl acrylate at an early stage, the recovered **1d**-*d*7 showed a loss of 6% of deuterium content at the *ortho*-positions while delivering the coupling product in 30% yield (Scheme 2.9, Eq. (4)). These experiments indicated 1) the C-H activation is a reversible but slow process; 2) the high regioselectivity is, to large extent, controlled by the ease of olefin insertion but not by the site of C-H metallation; 3) the exchange of H and D is far slower compared to the subsequent productive processes.



Scheme 2.9 Deuterium labelling study

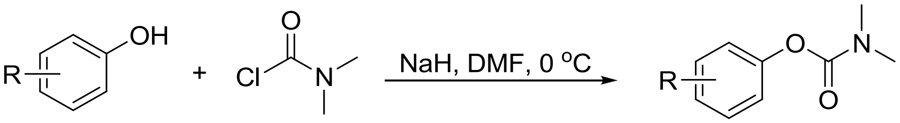
2.3 Conclusion

In conclusion, we have developed a mild and efficient rhodium-catalyzed process for direct C-H olefination of phenol derivatives. Both silver hexafluoroantimonate and rhodium catalyst prove to be essential for the success of this reaction, idicating that the C-H activation proceeded in an electrophilic metallation manner. The incompetency of palladium catalyst in this oxidative C-H olefination further highlighted the usefulness of this methodology. A large variety of functional groups are tolerated, such as alkenyl, methoxyl, trifluoromethyl, ester, halogen, nitro and so on. And the reaction mechanism was also investigated by deuterium labeling and kinetic isotope effect studies.

2.4 Experiment Section

$[RhCp^*Cl_2]_2$, $AgSbF_6$, and $Cu(OAc)_2$ were purchased from commercial suppliers and used as received unless otherwise noted. Phenol carbamates are synthesized according to the reported procedure. All reactions were carried out under air unless otherwise stated. Commercial solvents and reagents were used without further purification. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible using basic solution of potassium permanganate or acidic solution of ceric molybdate as stain, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. HRMS spectra were recorded on a Waters Q–Tof Permier Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Avance 300, 400 and 500 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.260, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); td (triplet of doublet); m (multiplets); ddt (doublet of doublet of triplet) and etc. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet).

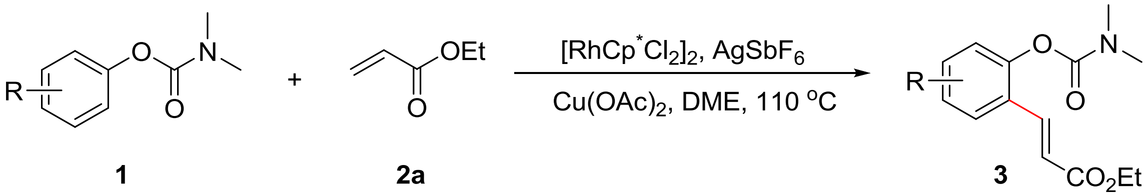
2.4.1 General procedure for the synthesis of aryl carbamate derivatives



1

General Procedure: To a 100 mL round-bottom flask was charged phenol (10 mmol) and 20 mL DMF. The resulting solution was cooled to 0 ℃ in an ice bath. Subsequently, NaH (60% oil dispersion, 520 mg, 13 mmol) was added and the reaction mixture was stirred for 0.5 h, upon which dimethylcarbamoyl chloride (10 mmol) was added. The resulting suspension was allowed to warm to room temperature over 3 h. The reaction mixture was diluted with 100 mL EtOAc and washed with 3 x 25 mL water. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and the resulting residue was purified by column chromatography to afford the aryl carbamate.

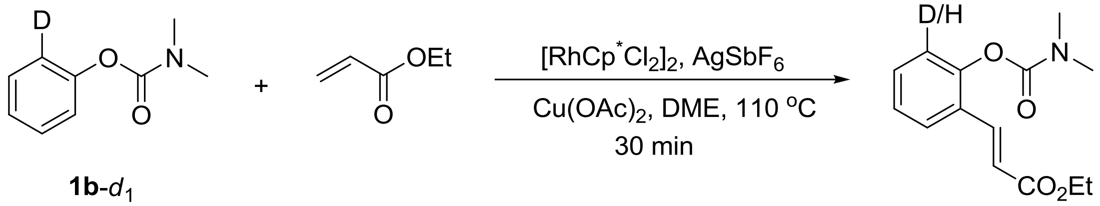
2.4.2 General procedure for the direct olefination of phenol carbamate derivatives



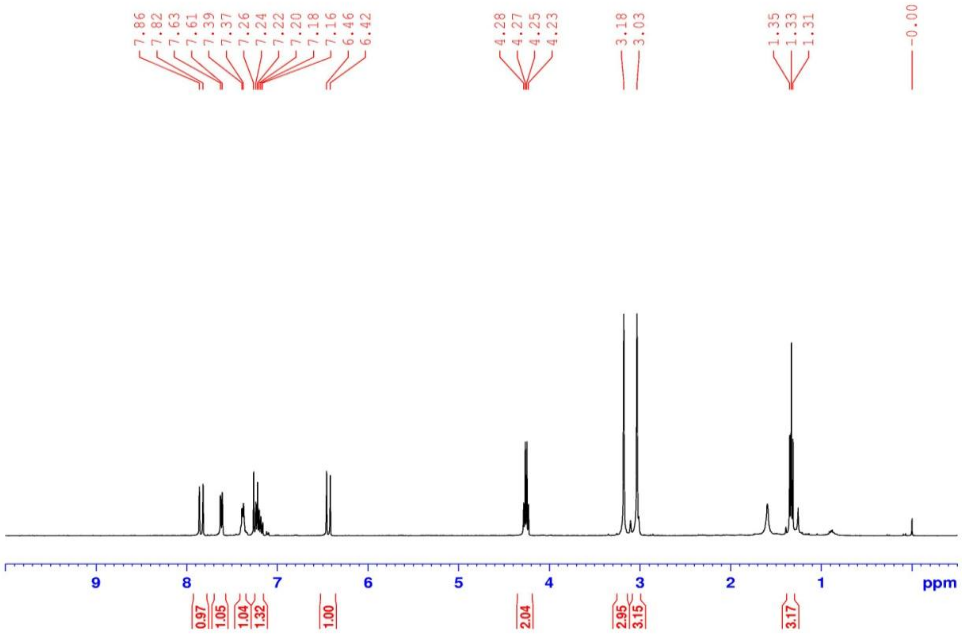
General Procedure: The phenol carbamate **1** (0.1 mmol, 1equiv), $[RhCp^{*}Cl_2]_2$ (0.0025 mmol, 0.025 equiv), $AgSbF_6$ (0.01 mmol, 0.1 equiv), $Cu(OAc)_2$ and 1,2-dimethoxyethane (0.5 mL) were placed in a glass vial under air. Ethyl acrylate **2a** (0.2 mmol, 2 equiv) was then added and the reaction was heated to 110 ℃ for 24 h. The reaction was then filtered and concentrated *in vacuo* to give a crude product **3** that was purified by column chromatography.

2.4.3 Deuterium labelling and kinetic isotope effect studies

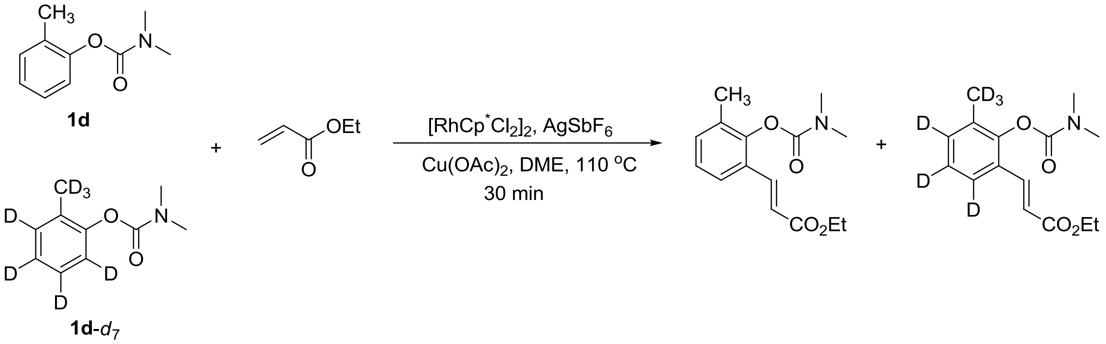
2.4.3.1 Intramolecular KIE determination



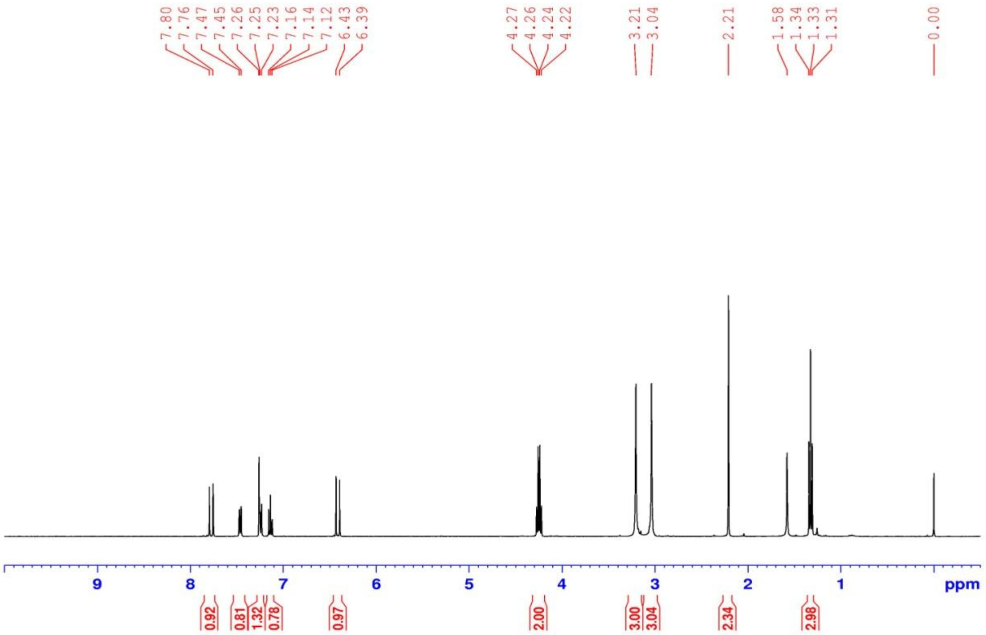
1b-*d*$_1$ (0.2 mmol, 1equiv), [RhCp*Cl$_2$]$_2$ (0.0025 mmol, 0.025 equiv), AgSbF$_6$ (0.01 mmol, 0.1 equiv), Cu(OAc)$_2$ and 1,2-dimethoxyethane (0.5 mL) were placed in a glass vial under air. Ethyl acrylate (0.1 mmol, 1 equiv) was then added and the reaction was heated to 110 ℃ for 30 min. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography.



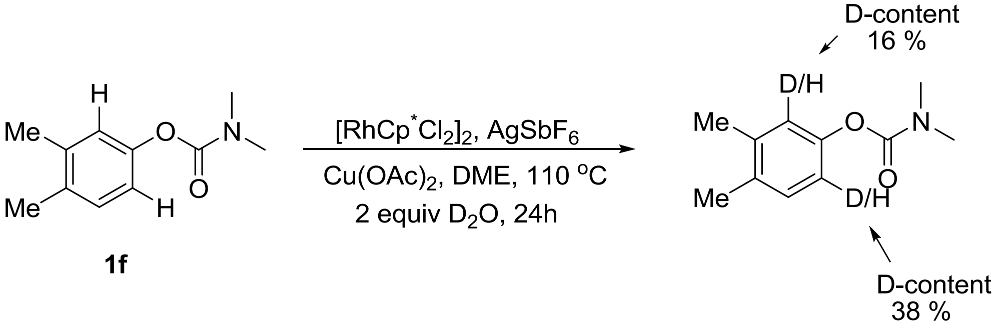
2.4.3.2 Intermolecular KIE determination



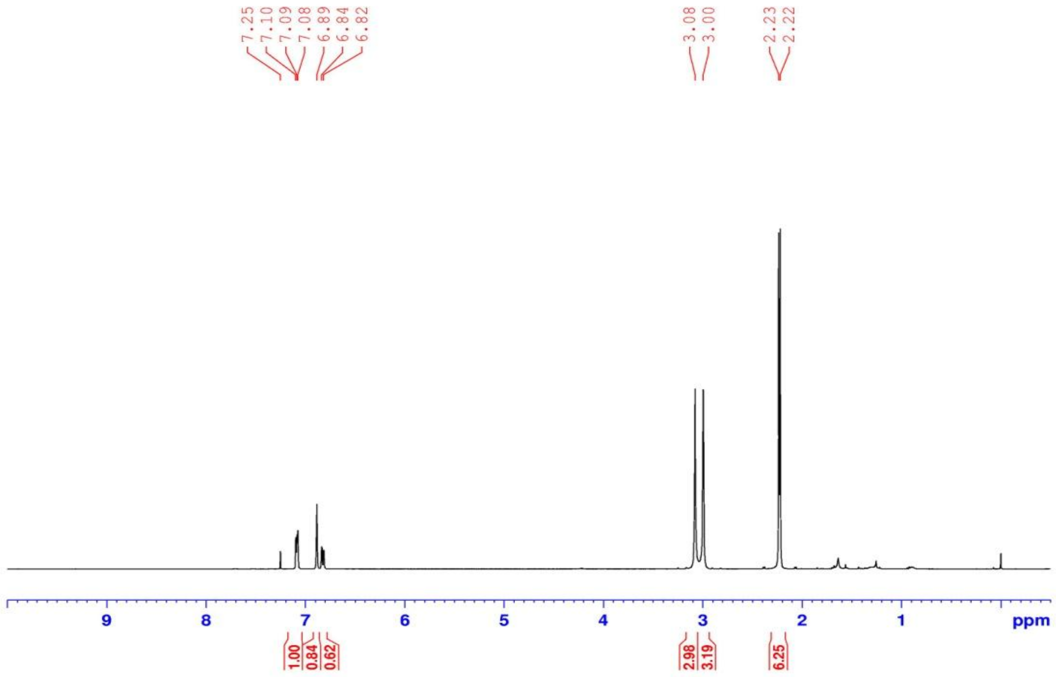
1d (0.1 mmol, 1equiv), **1d**-d_7 (0.1 mmol, 1equiv), $[RhCp^*Cl_2]_2$ (0.0025 mmol, 0.025 equiv), $AgSbF_6$ (0.01 mmol, 0.1 equiv), $Cu(OAc)_2$ and 1,2-dimethoxyethane (0.5 mL) were placed in a glass vial under air. Ethyl acrylate (0.1 mmol, 1 equiv) was then added and the reaction was heated to 110 ℃ for 30 min. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography.

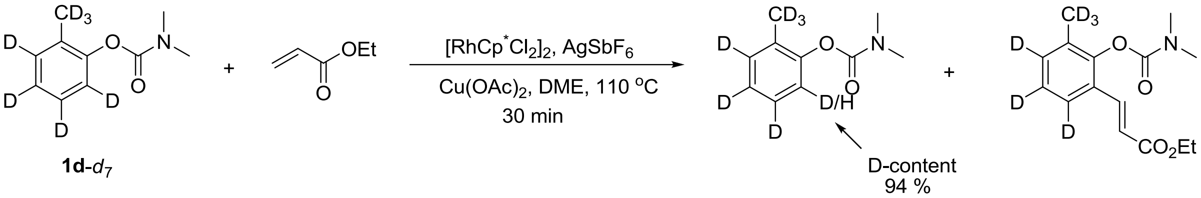


2.4.3.3 H/D exchange expriments

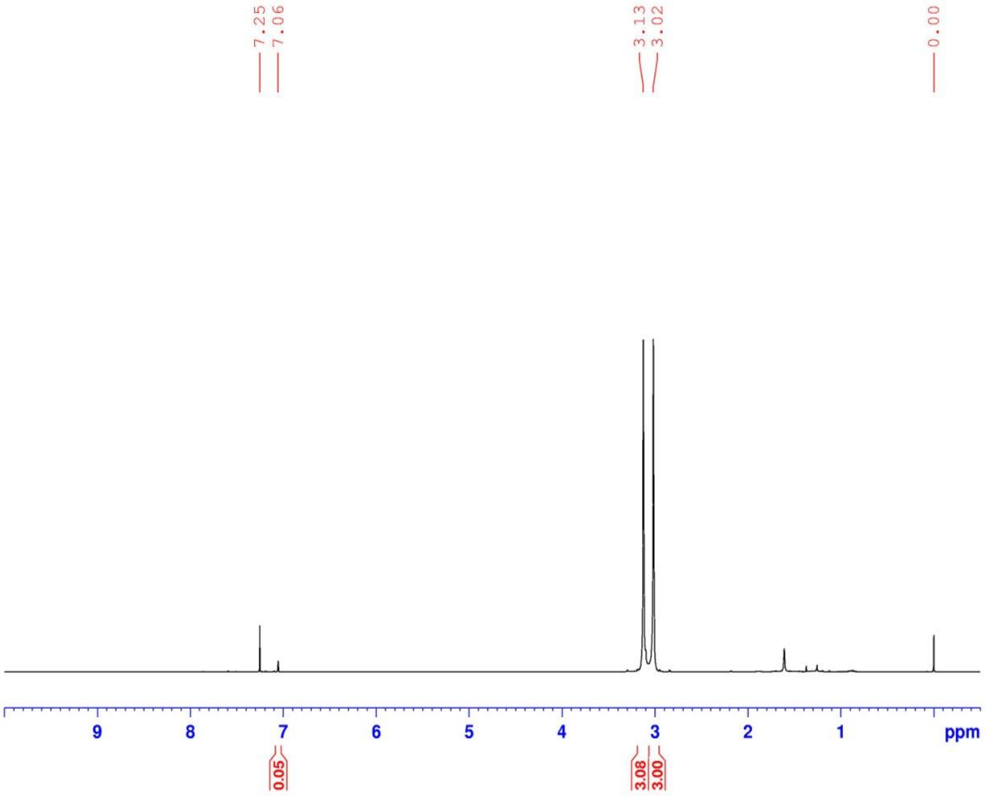


1f (0.1 mmol, 1equiv), [RhCp*Cl$_2$]$_2$ (0.0025 mmol, 0.025 equiv), AgSbF$_6$ (0.01 mmol, 0.1 equiv), Cu(OAc)$_2$, D$_2$O (0.2 mmol, 2 equiv) and 1,2-dimethoxyethane (0.5 mL) were placed in a glass vial under air. The mixture was heated to 110 ℃ for 30 min. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography.



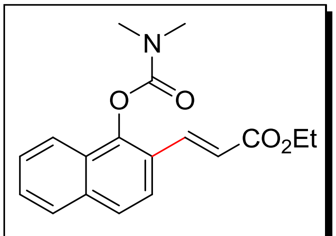


1d-*d*$_7$ (0.1 mmol, 1equiv), $[RhCp^*Cl_2]_2$ (0.0025 mmol, 0.025 equiv), $AgSbF_6$ (0.01 mmol, 0.1 equiv), $Cu(OAc)_2$, and 1,2-dimethoxyethane (0.5 mL) were placed in a glass vial under air. Ethyl acrylate (0.2 mmol, 2 equiv) was then added and the reaction was heated to 110 ℃ for 30 min. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography.



2.4.4 Characterization of Products

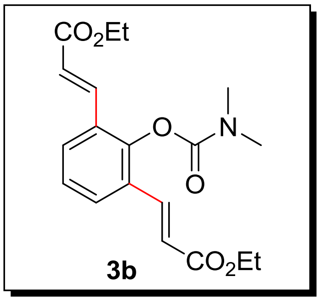
(*E*)-ethyl 3-(1-(dimethylcarbamoyloxy)naphthalen-2-yl)acrylate:



3a

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.34 (t, *J* = 7.1 Hz, 3H), 3.09 (s, 3H), 3.35 (s, 3H), 4.28 (q, *J* = 7.1, 2H), 6.54 (d, *J* = 16.1, 1H), 7.49-7.54 (m, 2H), 7.67-7.72 (m, 2H), 7.97 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.7, 37.0, 60.5, 119.9, 122.2, 122.8, 124.0, 126.1, 127.1, 127.4, 127.9, 135.3, 138.1, 146.7, 154.3, 166.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{18}H_{19}NO_4$ $[M+Na]^+$ 336.1212, found: 336.1220.

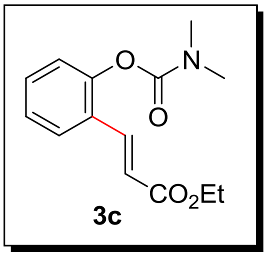
(2*E*,2'*E*)-diethyl 3,3'-(2-(dimethylcarbamoyloxy)-1,3-phenylene)diacrylate:



3b

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33 (t, *J* = 7.1 Hz, 6H), 3.04 (s, 3H), 3.26 (s, 3H), 4.26 (q, *J* = 7.1, 4H), 6.44 (d, *J* = 16.1, 1H), 7.25-7.29 (m, 1H), 7.65 (d, *J* = 7.8, 2H), 7.75 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.2, 36.6, 37.0, 60.6, 120.8, 126.2, 128.8, 129.2, 137.7, 148.7, 153.7, 166.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{19}H_{23}NO_6$ $[M+Na]^+$ 384.1423, found: 384.1435.

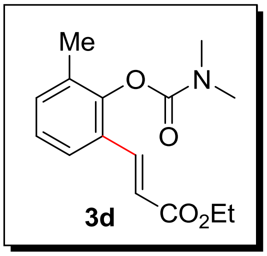
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)phenyl)acrylate:



3c

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 3.03 (s, 3H), 3.18 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.44 (d, *J* = 16.1 Hz, 1H), 7.16-7.24 (m, 2H), 7.36-7.40 (m, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.5, 36.8, 60.5, 119.8, 123.4, 125.7, 127.2, 127.3, 131.0, 138.3, 150.1, 154.3, 166.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{14}H_{17}NO_4$ $[M+Na]^+$ 286.1055, found: 286.1068.

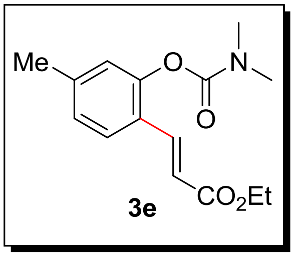
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-3-methylphenyl)acrylate:



3d

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 2.21 (s, 3H), 3.03 (s, 3H), 3.20 (s, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 6.42 (d, *J* = 16.1 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.4 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 16.2, 36.5, 36.9, 60.4, 119.8, 124.9, 125.7, 128.0, 131.9, 132.7, 138.7, 148.8, 153.8, 166.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{15}H_{19}NO_4$ $[M+Na]^+$ 300.1212, found: 300.1225.

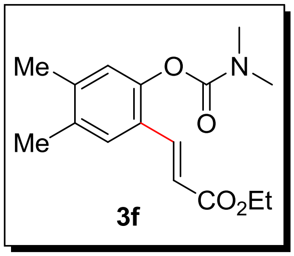
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-4-methylphenyl)acrylate:



3e

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 2.36 (s, 3H), 3.03 (s, 3H), 3.17 (s, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 6.39 (d, *J* = 16.1 Hz, 1H), 6.99 (s, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 21.3, 36.5, 36.8, 60.4, 118.6, 123.8, 124.4, 126.7, 127.0, 138.3, 141.8, 150.0, 154.4, 167.0 ppm; **HRMS (ESI, m/z):** calcd for $C_{15}H_{19}NO_4$ $[M+Na]^+$ 300.1212, found: 300.1222.

(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-4,5-dimethylphenyl)acrylate:

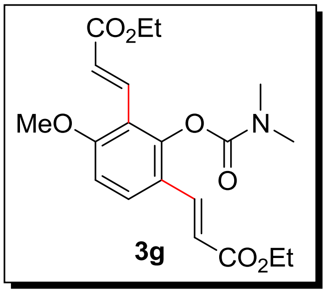


3f

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 3.02 (s, 3H), 3.16 (s, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.39 (d, *J* = 16.1 Hz, 1H), 6.93 (s, 1H), 7.37 (s, 1H), 7.77 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz,**

$CDCl_3$): δ 14.3, 19.2, 19.9, 36.5, 36.8, 60.3, 118.4, 124.2, 124.4, 128.0, 134.1, 138.4, 140.5, 148.1, 154.6, 167.1 ppm; **HRMS (ESI, m/z):** calcd for $C_{16}H_{21}NO_4$ $[M+Na]^+$ 314.1368, found: 314.1371.

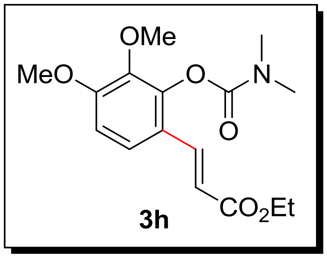
(2*E*,2'*E*)-diethyl 3,3'-(2-(dimethylcarbamoyloxy)-4-methoxy-1,3-phenylene) diacrylate:



3g

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30-1.35 (m, 6H), 3.03 (s, 3H), 3.25 (s, 3H), 3.93 (s, 3H), 4.22-4.28 (m, 4H), 6.33 (d, *J* = 16.1 Hz, 1H), 6.73 (d, *J* = 16.1 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 1H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.67-7.75 (m, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.3, 14.3, 36.5, 37.0, 56.0, 60.3, 60.4, 108.9, 118.0, 118.2, 121.5, 123.2, 128.8, 134.3, 137.9, 150.1, 153.5, 160.9, 166.9, 167.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{25}NO_7$ $[M+Na]^+$ 414.1529, found: 414.1531.

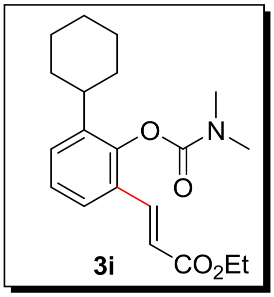
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-3,4-dimethoxyphenyl)acrylate:



3h

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 3.04 (s, 3H), 3.19 (s, 3H), 3.85(s, 3H), 3.89 (s, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.34 (d, *J* = 16.1 Hz, 1H), 6.81(d, *J* = 8.9 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.3, 36.6, 36.9, 56.0, 60.3, 60.7, 109.7, 117.7, 121.6, 122.1, 138.4, 141.8, 144.4, 154.1, 155.0, 167.1 ppm; **HRMS (ESI, m/z):** calcd for $C_{16}H_{21}NO_6$ $[M+Na]^+$ 346.1267, found: 346.1268.

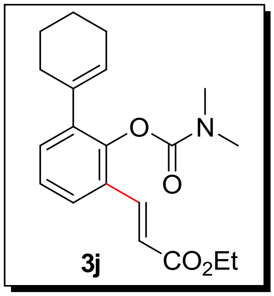
(*E*)-ethyl 3-(3-cyclohexyl-2-(dimethylcarbamoyloxy)phenyl)acrylate:



3i

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.30-1.38 (m, 8H), 1.74-1.77 (m, 1H), 1.84-1.86 (m, 4H), 2.60 (s, 1H), 3.04 (s, 3H), 3.21 (s, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.40 (d, *J* = 16.1 Hz, 1H), 7.20(t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 26.1, 26.9, 36.5, 36.9, 38.0, 60.4, 119.7, 124.6, 126.0, 128.2, 128.9, 139.0, 141.0, 147.8, 154.4, 166.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{27}NO_4$ $[M+Na]^+$ 368.1838, found: 368.1846.

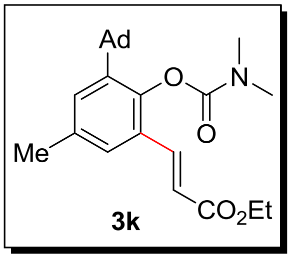
(*E*)-ethyl 3-(3-cyclohexenyl-2-(dimethylcarbamoyloxy)phenyl)acrylate:



3j

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.62-1.65 (m, 2H), 1.71-1.73 (m, 2H), 2.12 (s, 2H), 2.24 (s, 2H), 2.99 (s, 3H), 3.12 (s, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 5.71 (s, 1H), 6.42 (d, *J* = 16.1 Hz, 1H), 7.15-7.22 (m, 2H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.81 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 22.0, 23.1, 25.5, 29.1, 36.4, 36.8, 60.4, 119.7, 125.4, 125.6, 127.3, 128.3, 131.0, 134.4, 138.8, 139.0, 147.4, 154.1, 166.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{25}NO_4$ $[M+Na]^+$ 366.1681, found: 366.1685.

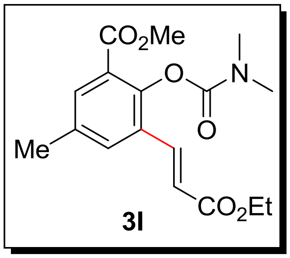
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-3-adamantyl-5-methylphenyl)acrylate:



3k

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.72-1.80 (m, 6H), 1.90-1.93 (m, 3H), 2.09-2.13 (m, 6H), 2.33 (s, 3H), 3.05 (s, 3H), 3.26 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 6.36 (d, *J* = 15.9 Hz, 1H), 7.17 (s, 1H), 7.28 (s, 1H), 7.60 (d, *J* = 15.9 Hz, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.3, 21.2, 28.9, 36.6, 36.9, 37.0, 37.0, 41.3, 60.3, 119.4, 125.6, 129.0, 130.1, 134.9, 139.4, 142.1, 147.0, 154.7, 166.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{25}H_{33}NO_4$ $[M+Na]^+$ 434.2307, found: 434.2309.

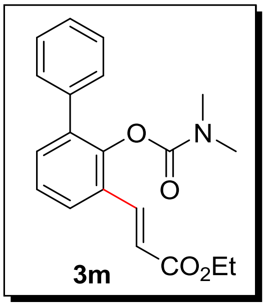
(*E*)-methyl 2-(dimethylcarbamoyloxy)-3-(3-ethoxy-3-oxoprop-1-enyl)-5-methyl benzoate:



3l

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 2.38 (s, 3H), 3.04 (s, 3H), 3.19 (s, 3H), 3.85 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.43 (d, *J* = 16.1 Hz, 1H), 7.59 (s, 1H), 7.81-7.85 (m, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.2, 20.8, 36.6, 36.9, 52.1, 60.5, 120.7, 124.3, 129.2, 131.7, 133.7, 135.1, 137.8, 147.7, 154.2, 165.0, 166.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{17}H_{21}NO_6$ $[M+Na]^+$ 358.1267, found: 358.1275.

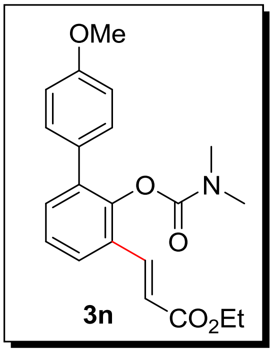
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)biphenyl-3-yl)acrylate:



3m

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 2.79 (s, 3H), 2.92 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.47 (d, *J* = 16.1 Hz, 1H), 7.25-7.42 (m, 7H), 7.62-7.64 (m, 1H), 7.83 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.3, 36.3, 36.7, 60.5, 120.2, 126.0, 126.4, 127.5, 128.0, 128.8, 128.9, 132.4, 136.6, 137.5, 138.7, 147.4, 153.8, 166.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{21}NO_4$ $[M+Na]^+$ 362.1368, found: 362.1378.

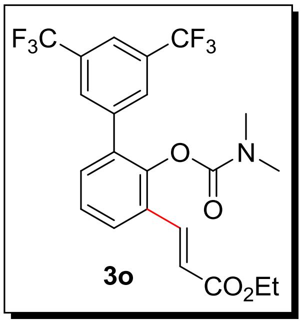
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-4'-methoxybiphenyl-3-yl)acrylate:



3n

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 2.82 (s, 3H), 2.97 (s, 3H), 3.84 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.46 (d, *J* = 16.1 Hz, 1H), 6.91-6.95 (m, 2H), 7.25-7.29 (m, 1H), 7.33-7.37 (m, 3H), 7.58-7.61 (m, 1H), 7.82 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.4, 36.7, 55.2, 60.4, 113.5, 120.1, 126.0, 126.1, 128.8, 129.8, 130.1, 132.5, 136.2, 138.7, 147.5, 153.8, 159.0, 166.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{21}H_{23}NO_5$ [M+Na]$^+$ 392.1474, found: 392.1480.

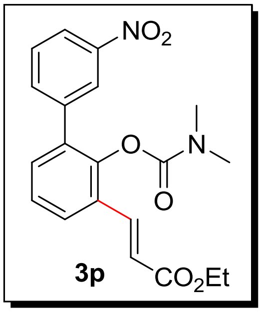
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-3',5'-bis(trifluoromethyl)biphenyl-3-yl) acrylate:



3o

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.34 (t, *J* = 7.1 Hz, 3H), 2.82 (s, 3H), 2.97 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 7.36-7.44 (m, 2H), 7.72 (dd, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.88 (s, 1H), 7.92 (s, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.1, 36.7, 60.6, 121.1, 121.2, 121.3, 121.3, 121.3, 121.4, 121.9, 124.6, 126.5, 128.0, 129.2, 129.5, 131.1, 131.4, 131.7, 131.9, 132.1, 133.5, 137.8, 139.5, 147.2, 153.2, 166.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{19}F_6NO_4$ [M+Na]$^+$ 498.1116, found: 498.1124.

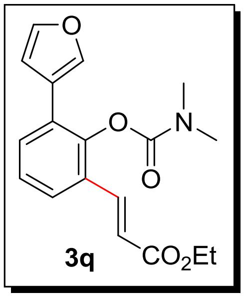
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-3'-nitrobiphenyl-3-yl)acrylate:



3p

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.34 (t, *J* = 7.1 Hz, 3H), 2.81 (s, 3H), 3.02 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 7.35-7.38 (m, 1H), 7.42-7.44 (m, 1H), 7.58-7.62 (m, 1H), 7.69-7.71 (m, 1H), 7.77-7.83 (m, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.3, 36.8, 60.6, 120.9, 122.4, 123.8, 126.4, 127.6, 129.3, 129.3, 132.0, 134.1, 135.1, 138.0, 139.1, 147.2, 148.0, 153.3, 166.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{20}N_2O_6$ $[M+Na]^+$ 407.1219, found: 407.1225.

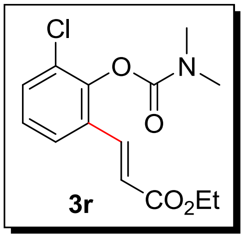
(*E*)-ethyl 3-(2-(dimethylcarbamoyloxy)-3-(furan-3-yl)phenyl)acrylate:



3q

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 2.98 (s, 3H), 3.19 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.64 (s, 1H), 7.25-7.29 (m, 1H), 7.47-7.50 (m, 2H), 7.55-7.57 (m, 1H), 7.65 (s, 1H), 7.78 (d, *J* = 16.0 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.5, 36.9, 60.5, 110.2, 120.4, 121.5, 126.1, 126.2, 127.6, 129.1, 130.9, 138.4, 140.2, 142.9, 147.2, 153.7, 166.7 ppm; **HRMS (ESI, m/z):** calcd for $C_{18}H_{19}NO_5$ $[M+Na]^+$ 352.1161, found: 352.1169.

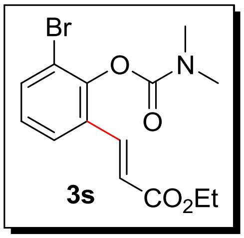
(*E*)-ethyl 3-(3-chloro-2-(dimethylcarbamoyloxy)phenyl)acrylate:



3r

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 3.05 (s, 3H), 3.21 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.44 (d, *J* = 16.1 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.43-7.45 (m, 1H), 7.51-7.53 (m, 1H), 7.76 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.2, 36.6, 37.0, 60.6, 121.2, 125.7, 126.5, 128.8, 130.3, 131.4, 137.7, 146.6, 153.1, 166.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{14}H_{16}ClNO_4$ $[M+Na]^+$ 320.0666, found: 320.0679.

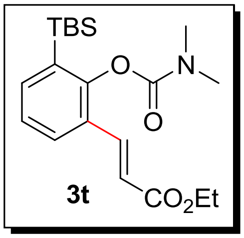
(*E*)-ethyl 3-(3-bromo-2-(dimethylcarbamoyloxy)phenyl)acrylate:



3s

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 3.05 (s, 3H), 3.22 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.43 (d, *J* = 16.1 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.55-7.61 (m, 2H), 7.75 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.7, 37.0, 60.6, 118.4, 121.2, 126.4, 127.0, 130.5, 134.5, 137.9, 147.7, 153.0, 166.4 ppm; **HRMS (ESI, m/z):** calcd for $C_{14}H_{16}BrNO_4$ $[M+Na]^+$ 364.0160, found: 364.0170.

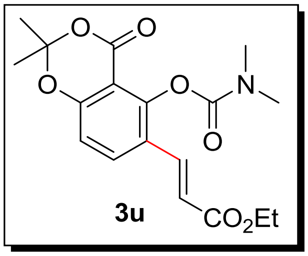
(*E*)-ethyl 3-(3-(tert-butyldimethylsilyl)-2-(dimethylcarbamoyloxy) phenyl) acrylate:



3t

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.25 (s, 3H), 0.30 (s, 3H), 0.89 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H), 3.01 (s, 3H), 3.20 (s, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 7.21-7.25 (m, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.62-7.66 (m, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ -5.4, -4.8, 14.3, 17.4, 26.7, 36.5, 36.8, 60.4, 119.8, 125.4, 127.9, 128.5, 131.2, 138.4, 138.9, 154.7, 154.8, 166.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{31}NO_4Si$ $[M+Na]^+$ 400.1920, found: 400.1927.

(*E*)-ethyl 3-(5-(dimethylcarbamoyloxy)-2,2-dimethyl-4-oxo-4H-benzo[d][1,3] dioxin-6-yl)acrylate:

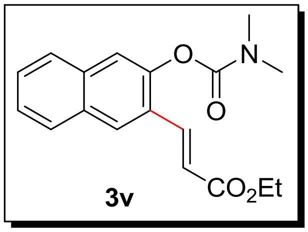


3u

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33 (t, *J* = 7.1 Hz, 3H), 1.75 (s, 6H), 3.03 (s, 3H), 3.21 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.38 (d, *J* = 16.2 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.79

(d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 16.2 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 25.6, 36.9, 60.6, 106.4, 108.5, 114.7, 119.4, 123.2, 133.7, 136.9, 150.9, 153.6, 157.9, 158.0, 166.7 ppm; **HRMS (ESI, m/z):** calcd for $C_{18}H_{21}NO_7$ $[M+Na]^+$ 386.1216, found: 386.1227.

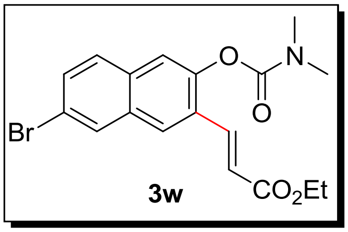
(*E*)-ethyl 3-(3-(dimethylcarbamoyloxy)naphthalen-2-yl)acrylate:



3v

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.35 (t, *J* = 7.2 Hz, 3H), 3.06 (s, 3H), 3.22 (s, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 6.58 (d, *J* = 16.1 Hz, 1H), 7.43-7.50 (m, 2H), 7.62 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* =16.1 Hz, 1H), 8.10 (s, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.6, 36.9, 60.5, 120.3, 120.3, 126.1, 127.0, 127.4, 127.4, 128.0, 128.2, 131.0, 134.4, 139.0, 147.3, 154.5, 166.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{18}H_{19}NO_4$ $[M+Na]^+$ 336.1212, found: 336.1204.

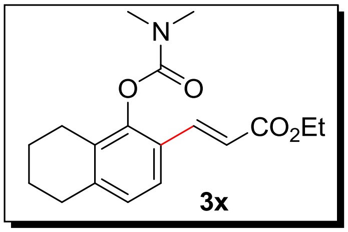
(*E*)-ethyl 3-(7-bromo-3-(dimethylcarbamoyloxy)naphthalen-2-yl)acrylate:



3w

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.35 (t, *J* = 7.1 Hz, 3H), 3.06 (s, 3H), 3.22 (s, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 6.56 (d, *J* = 16.1 Hz, 1H), 7.53-7.55 (m, 1H), 7.60-7.63 (m, 2H), 7.80 (d, *J* = 16.1 Hz, 1H), 7.98 (s, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 36.6, 36.9, 60.6, 119.9, 120.3, 121.1, 126.9, 128.2, 129.0, 130.1, 130.7, 132.0, 132.8, 138.4, 147.6, 154.2, 166.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{18}H_{18}BrNO_4$ $[M+Na]^+$ 414.0317, found: 414.0305.

(*E*)-ethyl 3-(1-(dimethylcarbamoyloxy)-5,6,7,8-tetrahydronaphthalen-2-yl) acrylate:



3x

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.77 (s, 4H), 2.59 (s, 2H), 2.77 (s, 2H), 3.03 (s, 3H), 3.19 (s, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.38 (d, *J* = 16.1 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 16.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 22.3, 22.3, 23.2, 29.6, 36.5, 36.8, 60.3, 118.5, 123.8, 125.1, 126.8, 131.0, 138.8, 141.6, 148.5, 153.9, 167.1 ppm; **HRMS (ESI, m/z):** calcd for $C_{18}H_{23}NO_4$ $[M+Na]^+$ 340.1525, found: 340.1538.

N,*N*-Dimethylaminocarbonyl Directed Rh(III)-Catalyzed Hydroarylation of Internal Alkynes Through C-H Bond Activation

3.1 Introduction

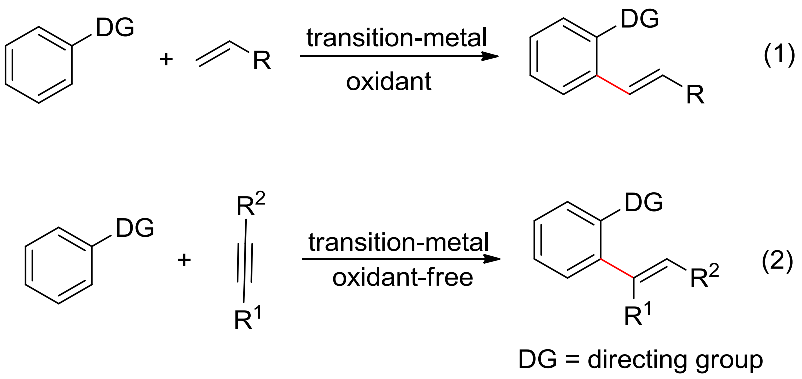
Transition-metal-catalyzed oxidative coupling of arene with alkene through C-H bond activation, which is widely known as Fujiwara-Moritani reaction, has provided an effective and efficient synthetic protocol for the direct introduction of olefin moieties (Scheme 3.1, Eq. (1)).[1] The direct manipulation of carbon-hydrogen bond as a reactive functionality instead of carbon-halogen or carbon-metal counterpart, which is usually employed in normal and oxidative Heck reaction,[2] renders this reaction much more simpler and straightforward. However, the employment of external oxidant, normally in the form of metal salt, and commonly used acidic reaction medium would inevitably result in metallic and acidic waster after reaction, diverting from the goals of modern chemistry towards environmental benignity and sustainability. In this aspect, the transition-metal-catalyzed hydroarylation of alkynes with aromatic C-H bond nicely

---

[1] (a) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (b) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, *9*, 633. (c) Moritani, S.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. (d) Jia, C.; Kitamura, T.; Fujiwara, Y.; *Acc. Chem. Res.* **2001**, *34*, 633.

[2] (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Nicolaou, K. C.; Bulger, P. G.; D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. (c) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079. (d) Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem.* Soc. **2008**, *130*, 2424. (e) Lindh, J.; Enquist, P.-A.; Pilotti, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957. (f) Werner, E. W.; Sigman, M. S. *J. Am. Chem.* Soc. **2010**, *132*, 13981. (g) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem.* Soc. **2008**, *130*, 11270.

solves the problem and provides a complementary synthetic methodology for the access to such skeletons (Scheme 3.1, Eq. (2)).[3]



Scheme 3.1 Transition-metal-catalyzed oxidative olefination and hydroarylation reaction.

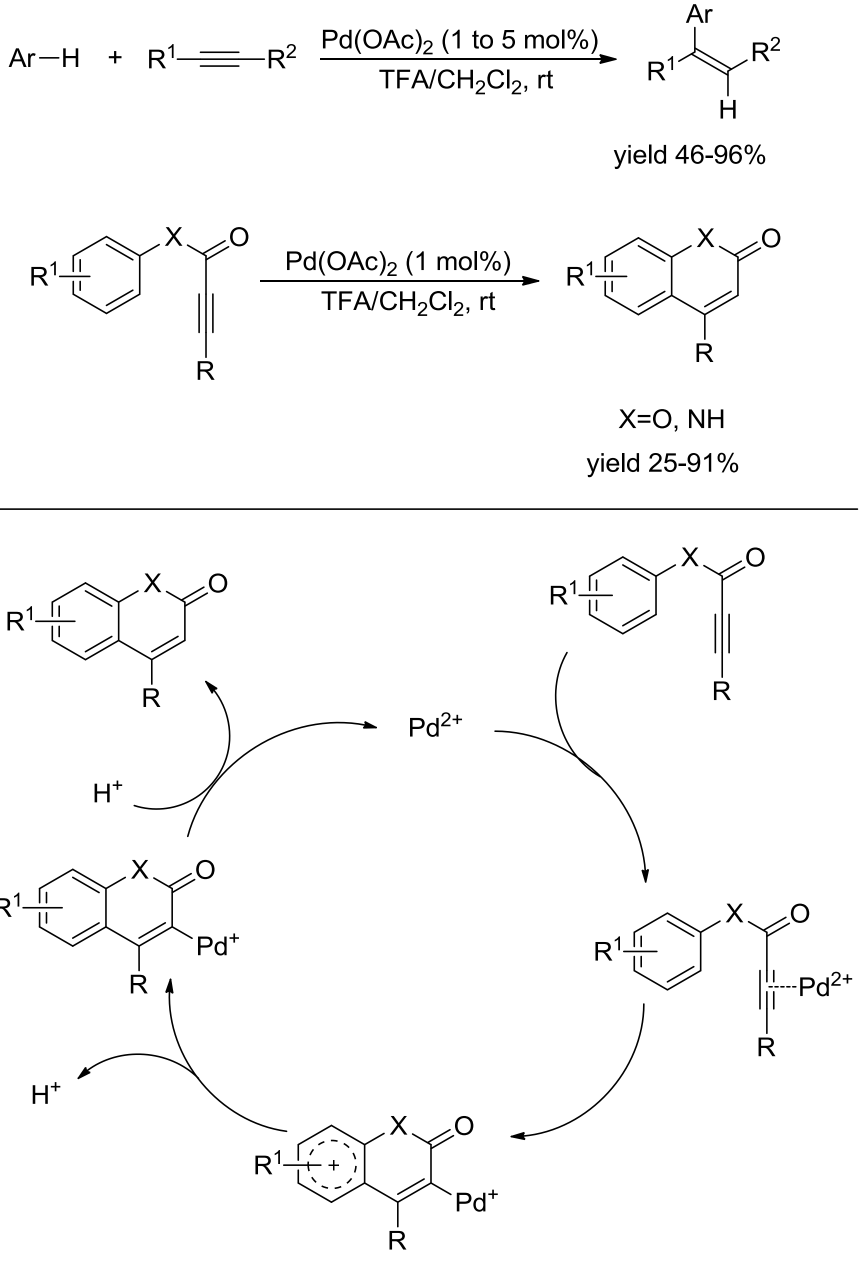
In 2000, Fujiwara reported the seminal work of highly regioselective hydroarylation of alkynes (Scheme 3.2).[4] Using palladium acetate as catalyst, TFA and CH_2Cl_2 as mixed solvent, this catalytic system allowed both terminal and internal alkynes to be as competent coupling partners, while for the arene partners it was mainly limited to electron rich ones. At that time, the author deemed that the reaction was initiated through the electronphilic activation of arene system to yield σ-arylpalladium intermediate, which underwent *trans*-insertion to alkyne followed by protonation, thus ultimately leading to the formation of cis-olefins. It was until 2005, Tunge restudied the mechanism of Fujiwara hydroarylation through kinetics studies and kinetic isotope effects and finally

---

[3] (a) Nevado, C.; Echavarren, A. M. *synthesis* **2005**, 167. (b) Kakiachi, F.; Kochi, T. *synthesis* **2008**, 3013. (c) Kitamura, T. *Eur. J. Org. Chem*. **2009**, 1111. (d) Colby, D. A.; Bergman, R. G.; Ellman,J. A. *Chem. Rev.* **2010**, *110,* 624.

[4] Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992-1995.

demonstrated that such reaction proceed through electrophilic activation of alkynes followed by electrophilic aromatic substitution.[5]



Scheme 3.2 Palladium-catalyzed inter- and intramolecular hydroarylation.

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[5] Tunge J. A.; Foresee, L. N. *Organometallics*, 2005, **24**, 6440.

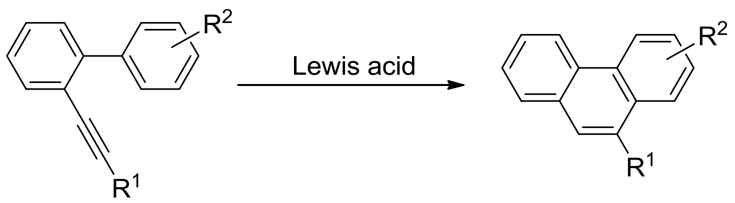
Since the seminal report by Fujiwara and coworkers in 2000,[4] much interest has been generated in the assisting group directed C-H hydroarylation of alkynes using a variety of transition-metals,[6] and it continues to fascinate chemists not only because of its high convergence and atom-economy but also its characteristic as a redox neutral process, which could render this transformation catalytic without the need of an external oxidant. The transition-metal-catalyzed addition of aromatic C-H bond across alkynes typically falls into two classes. The first initiates through direct oxidative addition of the aromatic C-H bonds to the low-valent transition metals used, which is always accompanied by the use of electron-rich and structure-specific phosphine ligands, while the other proceeds through the activation of alkynes or aromatic systems by high-valent electrophilic transition metals.

In 2004, Furstner reported a Fujiwara type hydroarylation for the synthesis of phenanthrenes and polycyclic heteroarenes (Scheme 3.3).[7] A variety of Lewis acids exhibited catalytic activity in such 6-endo-dig cyclization, which in turn provided evidences of initiation of this reaction through electrophilic activation of tethered alkyne. As expected, electron-deficient systems stood out as challenge for this reaction.

---

[6] For iridium-catalyzed cases see: a) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821. (b) Tsuchikama, K.; Kasagawa, M.; Hashimoto, Y.-K.; Endo, K.; Shibata, T. *J. Organomet. Chem.* **2008**, *693*, 3939. For ruthenium-catalyzed case see: Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett*. **2008**, *10*, 5309. For rhodium-catalyzed cases see: (a) Tanaka, K.; Otake, Y.; Wada, A.; Noguchi, K.; Hirano, M. *Org. Lett*. **2007**, *9*, 2203. (b) Tsuchikama, K.; Kuwata, Y.; Tahara, Y.; Yoshinami, Y.; Shibata, T. *Org. Lett.* **2007**, *9*, 3097. (c) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem.* Soc. **2010**, *132*, 6910. For cobalt-catalyzed cases see: (a) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem.* Soc. **2010**, *132*, 12249. (b) Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem.* Soc. **2011**, *133*, 17283.

[7] Mamane, V.; Hannen, P.; Furstner A. *Chem. Eur. J.*, **2004**, *10*,4556.



Lewis acid = $PtCl_2$, AuCl, $AuCl_3$, $GaCl_3$, $InCl_3$
R^1 = aryl, alkyl, halogen, H
R^2 = EWG, H
yield 54-95%

Scheme 3.3 Lewis acid-catalyzed Fujiwara hydroarylation

In 2008, Gevorgyan published a very interesting work dealing with intramolecular hydroarylation of tethered alkynes using $Pd(OAc)_2$/d-i-Prpf catalytic system (Scheme 3.4).[8] In sharp contrast to previously reported Fujiwara type hydroarylation, which underwent trans-hydroarylation across alkynes, this reaction exhibited highly cis-selectivity. The primary kinetic isotope effect in both intra- and intermolecular experiments provided stronge evidence that C-H bond cleavage was involved in the rate-determining step.

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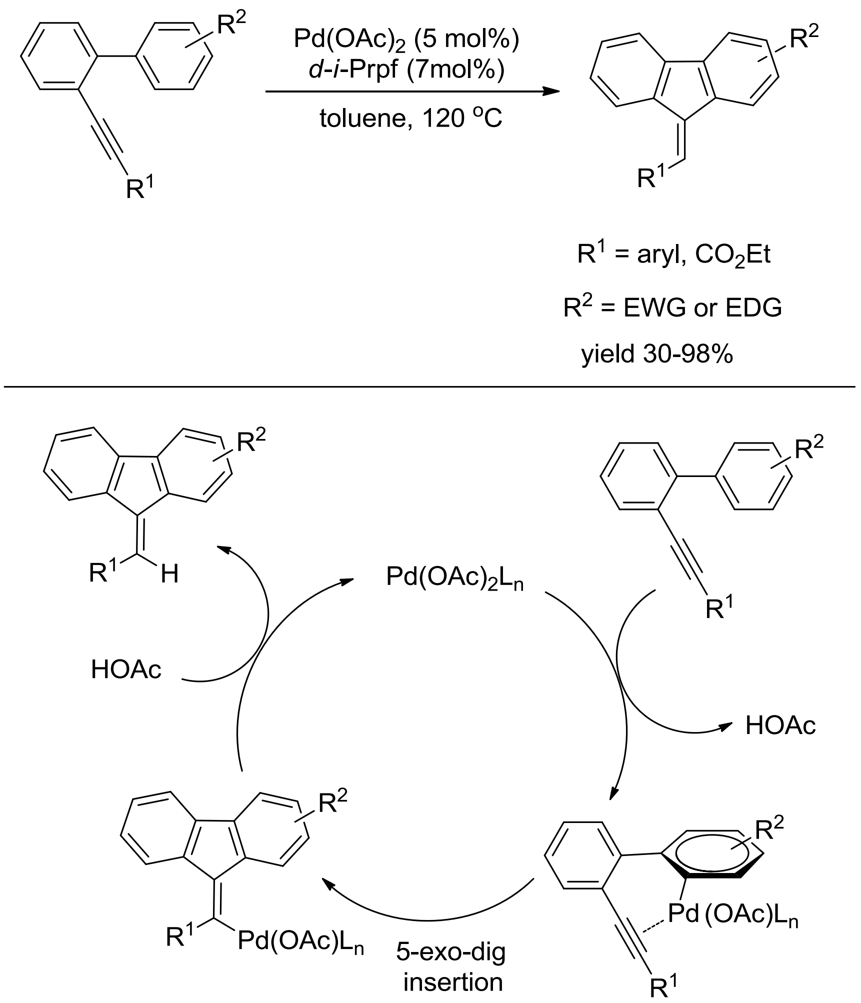
[8] Chernyak N.; Gevorgyan, V. *J. Am. Chem. Soc.*, 2008, **130**, 5636.



Scheme 3.4 Palladium-catalyzed 5-*exo-dig* hydroarylation via C-H activation

In 2006, Hiyama reported a hydroheteroarylation of internal alkyne using Ni(cod)$_2$/Pcyp$_3$ as catalyst (Scheme 3.5).[9] A diverse range of heteroarenes, for example indole, imidazole, benzofurane, benzothiophene, benzoxazole and thiazole were compatible with this reaction condition. The author proposed that this reaction starts form

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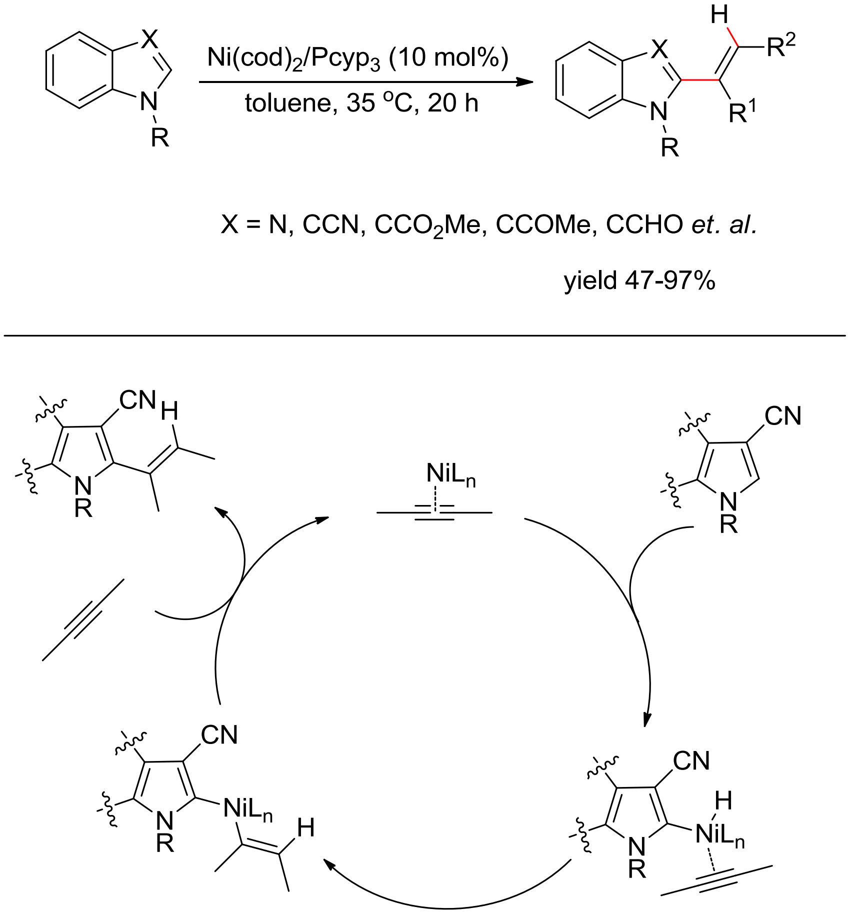
[9] Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146.

the oxidative insertion of alkyne coordinated Ni(0) into heteroaryl C-H bond, followed by migratory insertion of alkyne and reductive elimination.



Scheme 3.5 Ni(0)-catalyzed hydroheteroarylation of internal alkyne

In 2003, Jun reported a Rh(I)-catalyzed directed olefination of aromatic ketimines through hydroarylation of alkynes (Scheme 3.6).[10] With this catalytic protocol, both internal and terminal alkynes could be employed as viable coupling partners.

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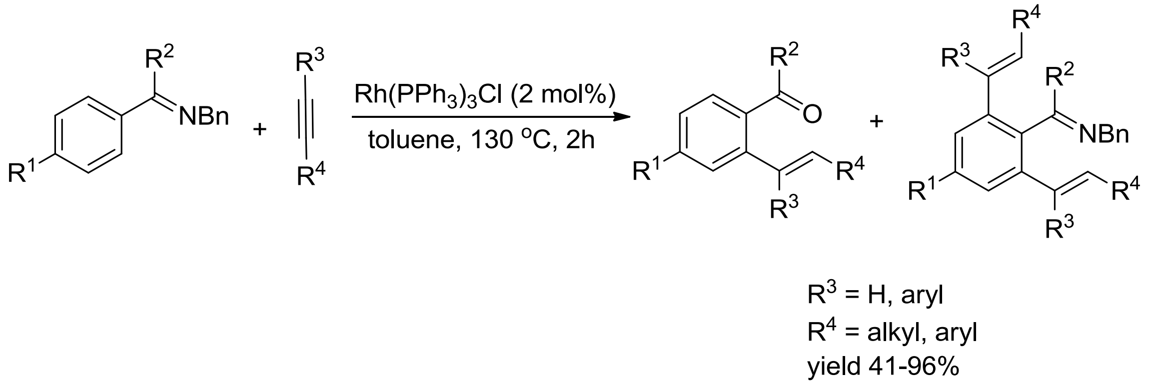
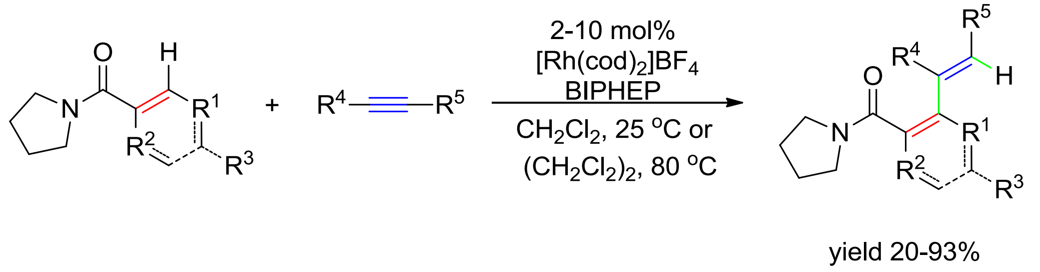
[10] Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759.



Scheme 3.6 Imine-directed Rh(I)-catalyzed hydroarylation of alkyne

In 2009, Tanaka reported an amide-directed alkenylation of sp^2 C-H bonds catalyzed by cationic Rh(I)/BIPHEP (Scheme 3.7).[11] It was demonstrated that both alkenyl and aryl carboxamides could be effectively alkenylated at the *ortho*-position with internal alkynes.



Scheme 3.7 Rh(I)-catalyzed hydroarylation via C-H activation

Although much advancement in this arena has been attained in the past few years, some problems still remain because of the requirement of sensitive phosphines as assisting ligands, harsh reaction condition adopted, low reactivity towards simple di-

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[11] Shibata, Y.; Otake, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2009**, *11*, 689.

aliphatic substituted alkynes and narrow functional group tolerance, thus limiting its applicability somewhat. In light of all these drawbacks, it is still highly desirable to establish a new protocol which could deliver the aromatic C-H olefination product in a highly efficient and straightforward manner while avoiding the use of any sensitive or waster-generating reagents that are often involved otherwise. Incited by the advancement attained in Rh(III)-catalyzed C-H functionalization over the past several years and also as part of our ongoing interest in the direct olefination of aromatic systems,[12] we would like to report herein a Rh(III)-catalyzed hydroarylation protocol under very mild reaction condition, which imported unprecedented tolerance towards a broad array of functionalities.[8]

3.2 Results and discussion

At the outset of our studies, the reaction condition was optimized using *N*,*N*-dimethylbenzamide (**1a**) and diphenylacetylene (**2a**) as the model substrates. After extensive trials, we were pleased to find that 70% yield of the *cis*-olefination product could be obtained by slight modification of the reaction condition in our recently reported C-H olefination reaction. Guided by the dramatic solvent effect observed in our recent C-H olefination reaction, a series of solvents were subsequently examined. With acetonitrile, the desired transformation was totally impeded, which is due to deactivation of the catalyst by formation of inactive complex between the solvent and catalyst used (Table 3.1, entry 2). With other solvents, such as THF, 1,4-dioxane and *t*-AmOH, results were

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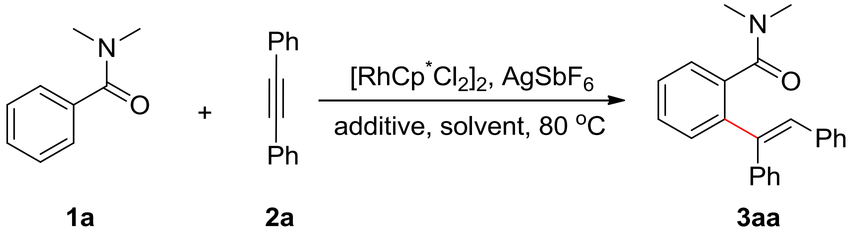
[12] (a) Feng, C.; Loh, T. P. *J. Am. Chem. Soc*. **2010**, *132*, 17710. (b) Feng, C.; Loh, T. P. *Chem. Commun*. **2011**, 10458.

inferior compared to that of using DME, while isolated yield of the desired product was increased to 78% in the case of DCE (Table 3.1, entries 3-6). In order to further optimize the reaction condition, a variety of additives were screened in hope of some positive effect on this transformation. Much to our surprise, when $CuBr_2$ was added instead of $Cu(OAc)_2$ no reaction occurred, indicating that the acetate counter anion is involved and should have important role in the catalytic cycle (Table 3.1, entry 7). Though not so effective as using $Cu(OAc)_2$, NaOAc did promote the reaction to a moderate extent (Table 3.1, entry 8). It is a pleasant surprise to find that the reaction efficiency was dramatically increased, delivering the desired olefination product in 95%, when catalytic amount of HOAc was applied (Table 3.1, entry 9). On the contrary, TFA was found to be totally inactive for the reaction, which could be attributed to the strong electron-withdrawing effect of fluorine, thus rendering it incompetent as a hydrogen abstracter (Table 3.1, entry 11). When the reaction was carried out in the absence of HOAc, only a trace amount of the desired product could be detected, whilst most of the starting material remained unchanged (Table 3.1, entry 12). In light of this phenomenon, it is evident that the HOAc indeed act as a hydrogen atom shuttle in the catalytic turnover, which not only transfers the hydrogen atom but more importantly, helps to liberate the active Rh(III) catalyst, rending this transformation a redox neutral process. It is worth mentioning that the yield remained essentially the same, when the reaction time was drastically shortened to half an hour, which in turn shed some light on its high reaction efficiency. In view of this, we have reason to believe that the reaction may exhibit high tolerance of various functionalities that would otherwise be susceptible to prolonged heating (Table 3.1, entry 10). Not surprisingly, the hydroarylation reaction could hardly proceed in the absence of either the

Rh(III) precatalyst or $AgSbF_6$, suggesting that cationic character of the Rh(III) catalyst is required in the catalytic cycle (Table 3.1, entries 13, 14). The palladium catalyst was also proved to be inactive in this reaction (Table 3.1, entry 15).

Table 3.1 Reaction Conditions Optimization.[a]

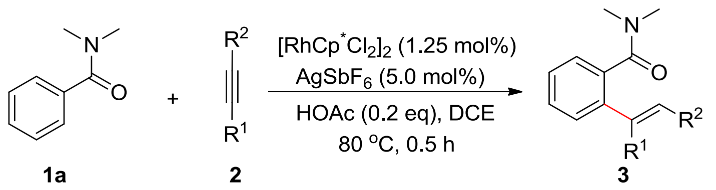


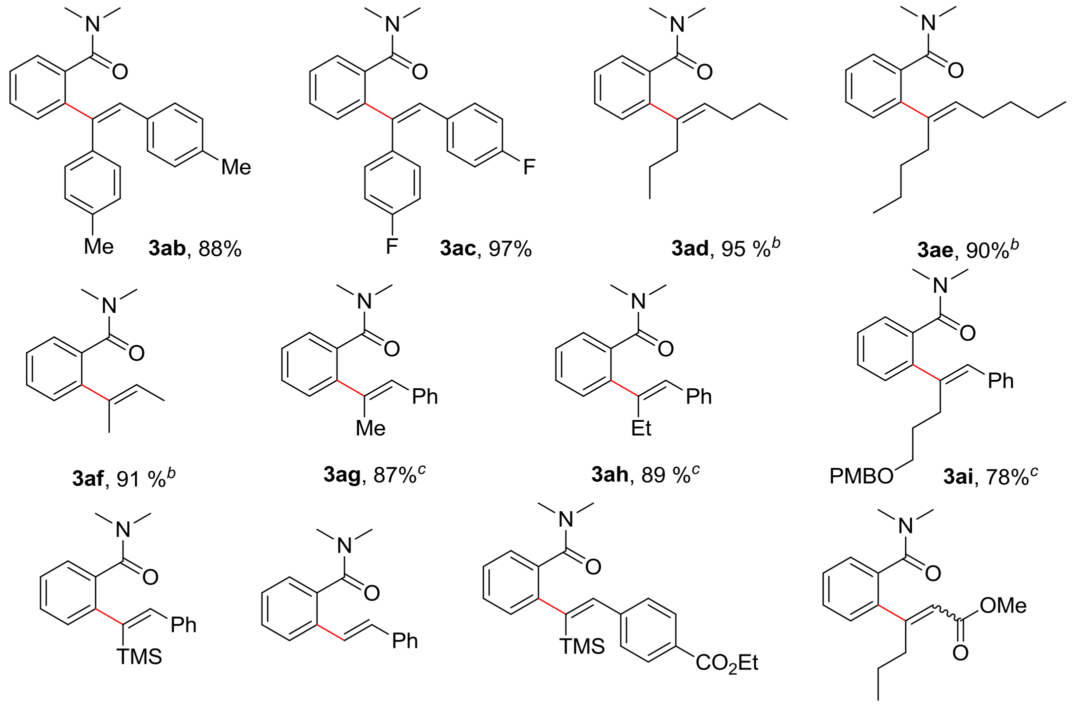
Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DME	70
2	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	MeCN	NR
3	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	43
4	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	Dioxane	52
5	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	*t*-AmOH	48
6	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DCE	78
7	$[Cp^*RhCl_2]_2$	$CuBr_2$	DCE	NR
8	$[Cp^*RhCl_2]_2$	NaOAc	DCE	46
9	$[Cp^*RhCl_2]_2$	HOAc	DCE	95
10	$[Cp^*RhCl_2]_2$	HOAc	DCE	96[c]
11	$[Cp^*RhCl_2]_2$	TFA	DCE	NR
12	$[Cp^*RhCl_2]_2$	-	DCE	trace[c]
13	$[Cp^*RhCl_2]_2$	HOAc	DCE	trace[d]
14	-	HOAc	DCE	NR
15	$Pd(MeCN)_2Cl_2$	HOAc	DCE	NR

[a] Unless otherwise noted, the reactions were carried out at 80 °C using **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (0.0025mmol), $AgSbF_6$ (0.01mmol), additive (0.04 mmol) in solvent (1 mL) for 24 h. [b] Isolated yields. [c] Reaction is stopped after 0.5h. [d] $AgSbF_6$ was omitted.

With the optimized reaction condition in hand, we turned our attention to exploration of the reaction scope of various internal alkynes with *N*,*N*-dimethylbenzamide (Table 3.2, **1a**). Expectedly, both electron-donating and electron-withdrawing functional groups containing diaryl substituted alkynes were well adapted in this reaction, affording the desired hydroarylation products in excellent yield. It is worth noting that such protocol could enable dialkyl substituted alkynes to be used as effective reaction partners, thus allowing for the concise construction of *α,β*-dialkyl substituted styrene derivatives, although stoichiometric amount of acid additive and prolonged reaction time were always necessary in these cases to achieve full conversion. When using alkyl aryl disubstituted alkynes as coupling partner, the reactions worked efficiently and regioselectively, affording the olefination products in high chemical yields.[10] It should also be mentioned that PMB protected aliphatic alcohol fragment is nicely tolerated under this reaction condition, which allows further chemical elaboration for the construction of complex molecules. Intriguingly, trimethylsilyl-protected terminal alkynes were also viable reaction partners, which after regioselective insertion delivered the corresponding alkenylsilanes in moderate to high yields (Table 3.2, **3aj**, **3al**). Desilylation can be effected by using more acid additive and lengthening the reaction time, thus affording the *trans*-stilbene derivative in high yield (Table 3.2, **3ak**). Notably, the reaction was also applicable to alkynoate, furnishing the desired product in 65% yield when methyl hex-2-ynoate was used, albeit giving *cis/trans* isomers. It should be pointed out that terminal alkynes were not suitable substrates for this hydroarylation reactions, which is probably due the acidic terminal proton.

Table 3.2 Hydroarylation between **1a** and various alkynes.[a]





3ab, 88%; **3ac**, 97%; **3ad**, 95 %[b]; **3ae**, 90%[b]

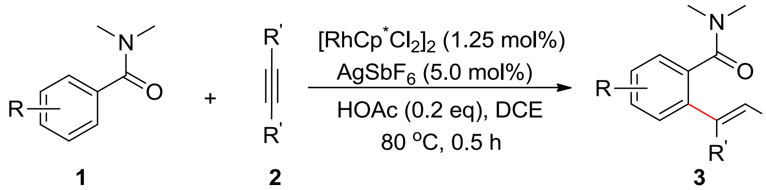
3af, 91 %[b]; **3ag**, 87%[c]; **3ah**, 89 %[c]; **3ai**, 78%[c]

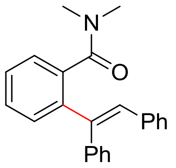
3aj, 67%; **3ak**, 80%[b]; **3al**, 70%; **3am**, 65%[b]

[a] Unless otherwise noted, the reactions were carried out at 80 °C using **1a** (0.2 mmol), **2a** (0.22 mmol), $[Cp^*RhCl_2]_2$ (0.0025 mmol), $AgSbF_6$ (0.01 mmol), HOAc (0.04 mmol) in DCE (1 mL) for 0.5 h, and the yields were isolated yields. [b] HOAc (0.5 mmol) and reaction time 24 h were employed. [c] PivOH (0.2 eq) was used instead of HOAc.

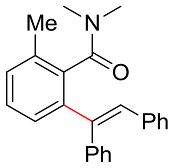
The substrate scope of the amide partner was further investigated by reaction with either diphenylacetylene or 4-octyne. As can be clearly seen from Table 3.3, this reaction showed marvelous compatibility with a vast array of different functionalities. A little to our surprise, not only neutral and electron-donating substituents (Table 3.3, **1c** to **1j**) but also electron-withdrawing ones (Table 3.3, **1k** to **1n**), and even those with highly electron-withdrawing ability, such as nitro and trifluoromethyl, were well tolerated, affording the corresponding olefination products in high to quantitative yields. The extremely high reactivity of electron-poor substrates is in sharp contrast with previously reported protocols, suggesting that direct electrophilic aromatic substitution is unlikely to be the pathway of this C-H activation process. The *ortho*-substituted benzamide also served as viable substrate (Table 3.3, **1b**), although the reaction efficiency was greatly hampered because of steric repulsion between the substituents and the dimethylamino group, which would result in the rotation of the aryl-carbonyl C-C bond. It is reasonable to assume that the aryl C-H bond would exit the interaction sphere of the metal center due to the rotation, thus rendering the C-H bond cleavage more difficult. On the other hand, reactions employing *meta*-substituted substrates were inclined to produce regio-selective olefination, favoring the strically more accessible site (Table 3.3, **1c**, **1i**, **1q**). What needs to be further mentioned is that when substrates containing additional potential directing groups, such as **1f**, **1h**, **1m** and **1n**, which were previously reported as efficient assisting groups in Rh(III)-catalyzed C-H functionalization,[11] were employed, the reaction tended to favour the regiospecific olefination *ortho* to the *N*,*N*-dimethylaminocarbonyl group, indicating its superiority as directing group. In addition, the free hydroxyl group of phenol, which is known to degrade under oxidative reaction conditions did not show any detrimental effect in this reaction and the desired product was isolated in high yield (Table 3.3, **3ga**). It should also be pointed out that halogen substituents were compatible and could be transferred into the products without any deleterious effect, making it possible for further elaboration using traditional cross-coupling methods (Table 3.3, **3oa**, **3pa**). Due to the mild reaction condition employed, silicon-bearing substrate worked perfectly in this reaction and furnished the desired product in quantitative yield (Table 3.3, **3ra**). The tolerance of silicon substituent provides further evidence for the power and compatibility of this reaction and set the stage for further transformation in the pursuit of more complex molecules through well-established silicon chemistry, such as Hiyama cross-coupling. In addition, aromatic heterocycles were also effective substrates affording the desired products in excellent yields (Table 3.3, **1s**, **1t**).

Table 3.3 Hydroarylation between **1** and **2**.[a]

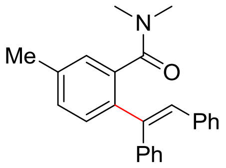




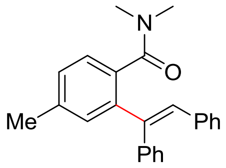
3aa, 96%



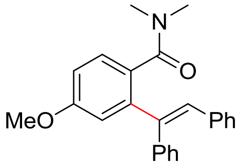
3ba, 63%



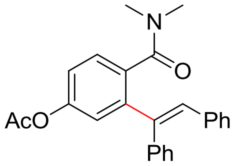
3ca, 96%



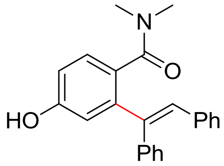
3da, 95%



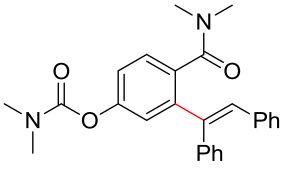
3ea, 99%



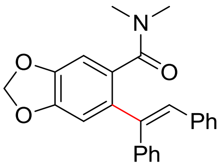
3fa, 90%



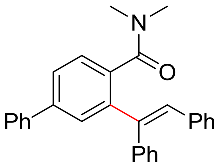
3ga, 83%



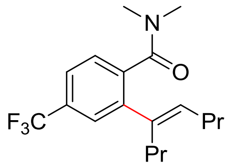
3ha, 93%



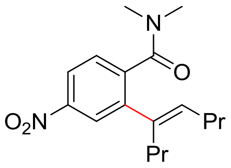
3ia, 94%



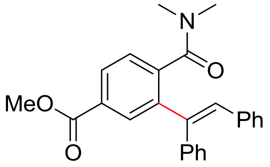
3ja, 99%



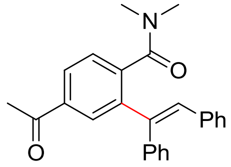
3kd, 95%[b]



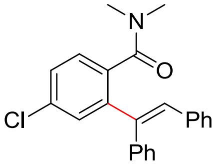
3ld, 89%[b]



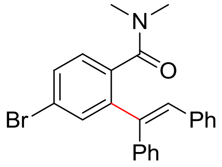
3ma, 94%



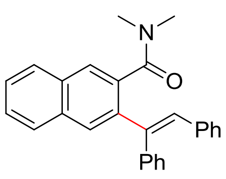
3na, 80%



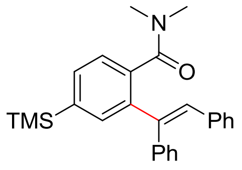
3oa, 87%



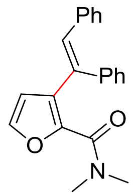
3pa, 86%



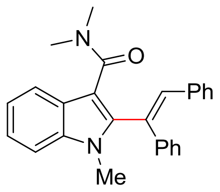
3qa, 96%



3ra, 98%



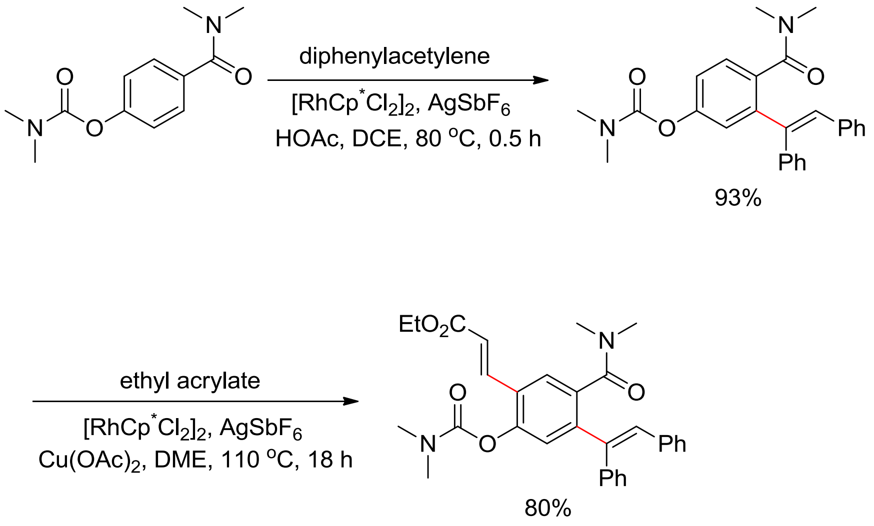
3sa, 97%[c]



3ta, 98%[d]

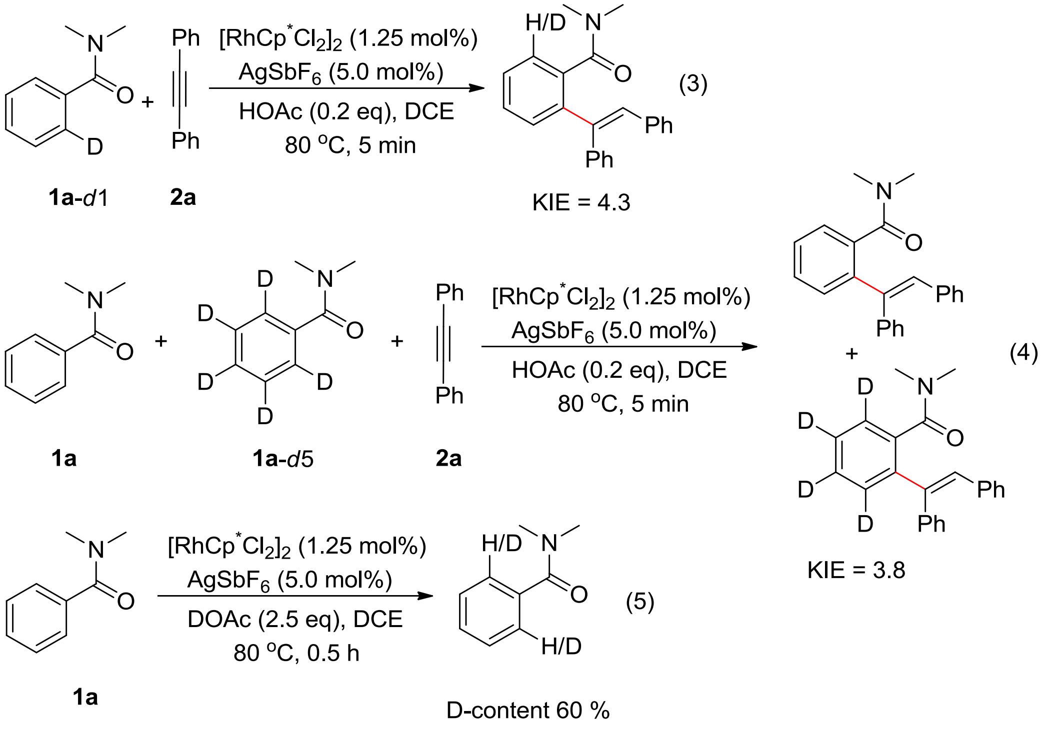
[a] Unless otherwise noted, the reactions were carried out at 80 ^{o}C using **1a** (0.2 mmol), **2a** (0.22 mmol), [Cp*RhCl$_2$]$_2$ (0.0025 mmol), AgSbF$_6$ (0.01 mmol), HOAc (0.04 mmol) in DCE (1 mL) for 0.5 h, and the yields were isolated yields. [b] HOAc (0.5 mmol) and reaction time 24 h were employed. [c] PivOH (0.2 eq) was used instead of HOAc. d Reaction time 3h.

As a demonstration of further elaboration of the hydroarylation products, a sequential C-H olefination strategy was attempted. It is clearly illustrated in scheme 3.8 that the combination of this hydroarylation and our recently reported oxidative C-H olefination methodology allowed a step-economical and concise synthesis of di-olefination product in high yield. The difference in nature and binding ability of the two directing groups employed enabled this sequential C-H olefination reaction to proceed successfully and we believe this concept could find more application in the utilization of C-H transformations.



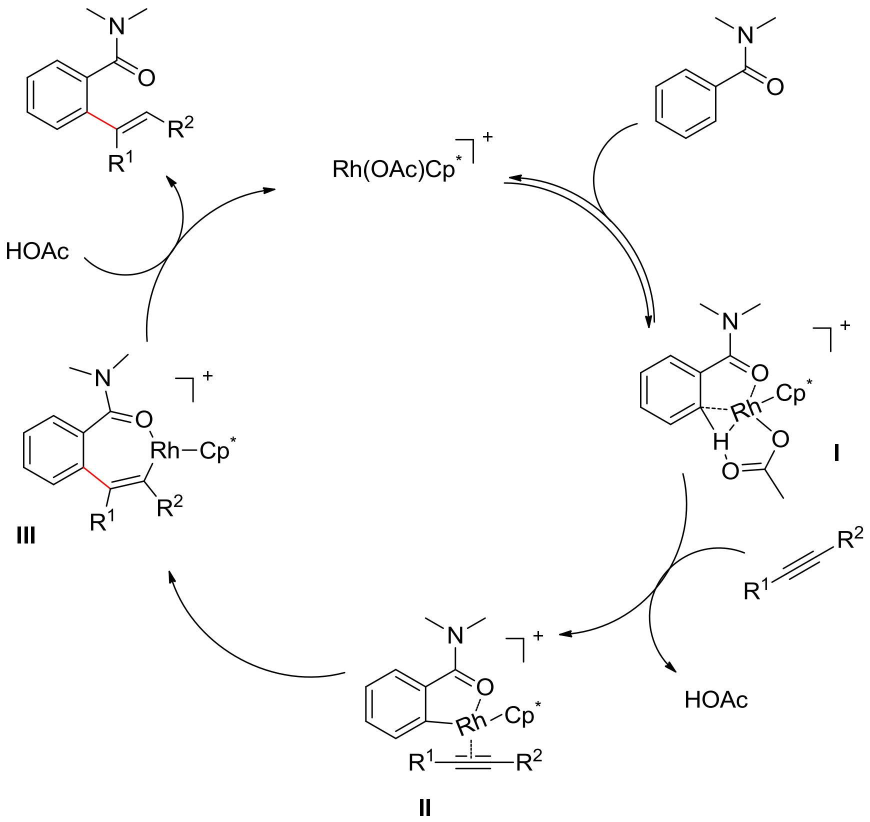
Scheme 3.8 Sequential C-H olefination

In order to obtain more detailed information about the mechanism of the present hydroarylation reaction, the following experiments were conducted as shown in scheme 3.9. Significant isotope effects were observed either in the intramolecular or intermolecular studies (eq 3, eq 4), thus indicating the rationality of C-H bond cleavage being the rate-determining step. In combination with the high reactivity of highly electron-deficient substrates and the indispensability of HOAc as additive, a concerted-metalation-deprotonation is most likely the plausible mechanistic pathway. Additionally, when **1a** was treated with DOAc under otherwise identical reaction condition, significant deuterium incorporation was observed at both *ortho* position (eq 5), which indicated the C-H bond cleavage is a reversible process.



Scheme 3.9 Kinetic isotope effects and deuterium-incorporation experiments

On the basis of our experimental results, a plausible mechanism is proposed in Scheme 3.10. Precomplexation of amide substrate with active Rh(III) catalyst would trigger *ortho* C-H activation to form the metallacycle *via* a concerted-metalation-deprotonation pathway. As can be anticipated from the structure of intermediate **I**, the strength of *ortho* C-H bond will be dramatically lessened because of the agostic interaction with the metal center, while the acetate anion on the metal sphere act as a hydrogen atom accepter to further induce complete cleavage of the C-H bond. The dissociation of acetic acid and reoccupying the vacancy by the incoming alkyne furnishes π-complex **II**, which in turn undergoes migratory insertion to deliver intermediate **III**. Transfer of hydrogen atom from previously dissociated acetic acid to the intermediate **III** provides the desired olefination product and at the same time closes the catalytic cycle by regenerating the active Rh(III) catalyst.



Scheme 3.10 Proposed Mechanism

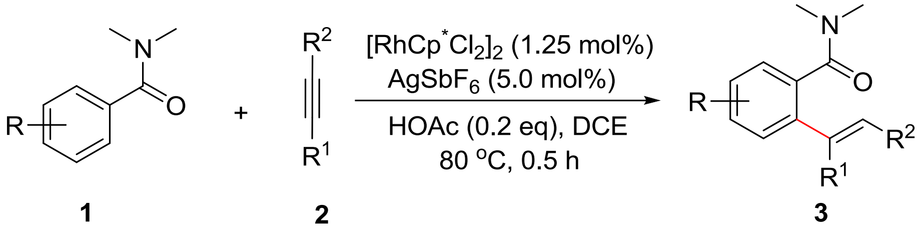
3.3 Conclusion

In conclusion, we have reported a novel cationic Rh(III)-catalyzed hydroarylation of internal alkynes, which delivers the olefination products in high to excellent yields without the need of an external oxidant. Compared with the traditional methods reported for the hydroarylation of internal alkynes using low valent transition metal, this reaction relies on the directing group assisted electrophilic metallation of arene substrates with high valent rhodium catalyst. The addition of catalytic amount of acetic acid proves to be crucial for this reaction, which implies that the C-H bond activation proceeds through concerted metallation and deprotonation pathway. Furthermore, terminal alkynes are not viable substrates for this reaction. The mild condition and highly efficiency of this reaction enables a nice tolerance of functionalities.

3.4 Experiment Section

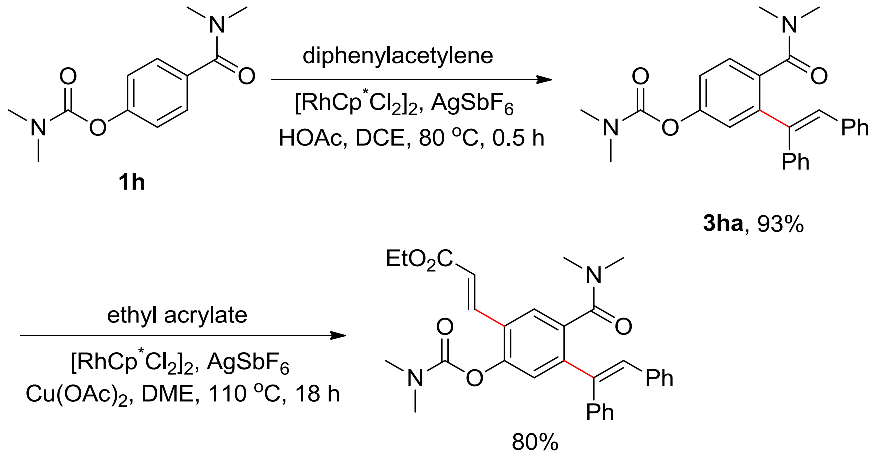
$[RhCp^*Cl_2]_2$, $AgSbF_6$, HOAc, PivOH and DCE were purchased from commercial suppliers and used as received unless otherwise noted. All reactions were carried out under air unless otherwise stated. Commercial solvents and reagents were used without further purification. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible using basic solution of potassium permanganate or acidic solution of ceric molybdate as stain, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. HRMS spectra were recorded on a Waters Q–Tof Permier Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of $SiMe_4$ (δ 0.00, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); td (triplet of doublet); m (multiplets); ddt (doublet of doublet of triplet) and etc. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet).

3.4.1 General procedure for the hydroarylation of internal alkynes



General Procedure: An oven-dried 8 mL sample vial was charged with **1** (0.2 mmol), **2** (0.22 mmol), [RhCp*Cl$_2$]$_2$ (0.0025 mmol, 0.0125 equiv), AgSbF$_6$ (0.01 mmol, 0.05 equiv), HOAc (0.04 mmol, 0.2 equiv) and DCE (1 mL) sequentially. After heating and stirring at 80 °C for 30 minutes, the mixture was cooled down to room temperature, diluted with dichloromethane, and filtered through a short pad of celite. Removal of the solvent in *vacuo* and purification of the residue by silica gel column chromatography afforded the desired product **3**.

3.4.2 Rh(III)-Catalyzed Sequential C-H olefination

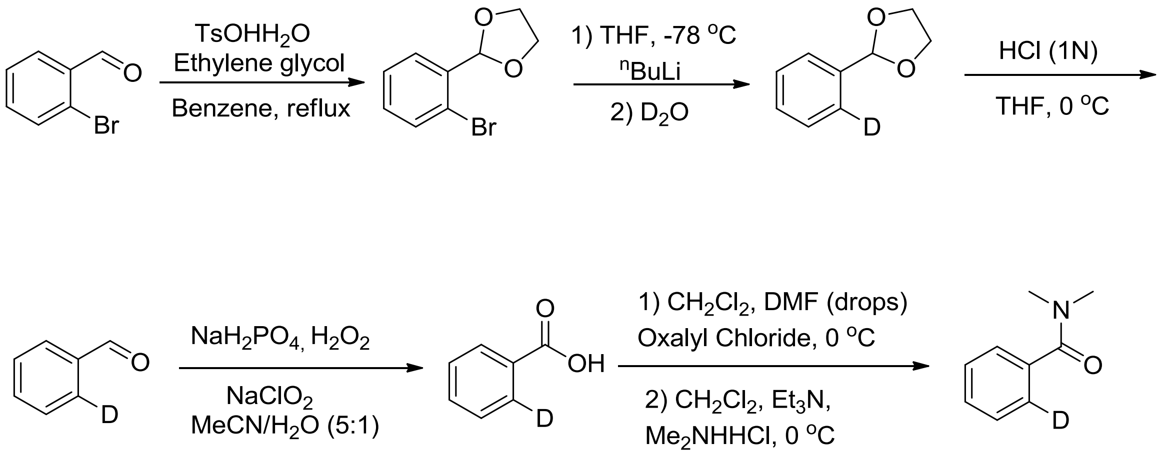


Procedure: 1. An oven-dried 8 mL sample vial was charged with **1h** (0.2 mmol), **2a** (0.22 mmol), [RhCp*Cl$_2$]$_2$ (0.0025 mmol, 0.0125 equiv), AgSbF$_6$ (0.01 mmol, 0.05 equiv), HOAc (0.04 mmol, 0.2 equiv) and DCE (1 mL) sequentially. After heating and stirring at 80 ^{o}C for 30 minutes, the mixture was cooled down to room temperature, diluted with dichloromethane, and filtered through a short pad of celite. Removal of the solvent in *vacuo* and purification of the residue by silica gel column chromatography afforded the desired product **3ha** (77 mg, 93%).

2. **3ha** (0.1 mmol, 1equiv), $[RhCp^{*}Cl_2]_2$ (0.0025 mmol, 0.025 equiv), $AgSbF_6$ (0.01 mmol, 0.1 equiv), $Cu(OAc)_2$ (0.2 mmol) and 1,2-dimethoxyethane (0.5 mL) were placed in a glass vial under air. Ethyl acrylate (0.2 mmol, 2 equiv) was then added and the reaction was heated to 110 ℃ for 24 h. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography to deliver di-olefination product (41 mg, 80%).

3.4.3 Deuterium incorporation and kinetic isotope effect studies

Synthesis of **1a**-*d*1:



a) To a 100 mL round-bottom flask equipped with a magnetic stirring bar and Dean-Stark were added 2-bromobenzaldehyde (30 mmol), ethylene glycol (40 mmol), PhH (30 mL) and *p*-toluenesulfonic acid hydrate (3 mmol). After heating under reflux overnight, the resulting solution was poured into a saturated solution of $NaHCO_3$ (20 mL) and extracted with Et_2O (3 x 30 mL). The organic layer was dried over $MgSO_4$ and filtered. Then the filtrate was concentrated under vacuum to afford the crude product which was then purified by flash column chromatography on silica gel to give the product 2-(2-bromophenyl)-1,3-dioxolane (95%).

b) *n*-BuLi (1.6 M in hexane, 11 mmol) was added dropwise to a solution of 2-(2-bromophenyl)-1,3-dioxolane (10 mmol) in dry THF (40 mL) at –78 ℃. After addition the resulting solution was stirred 30 min at –78 ℃. While keeping the temperature at –78 ℃, D_2O (2 mL) was added. The mixture was then allowed to warm to rt and stirred for additional 2 hours, at which time a saturated solution of NH_4Cl (20 mL) was added. The aqueous layer was extracted with EtOAc (3 x 50 mL), washed with brine (50 mL) and dried over $MgSO_4$. Concentration under vacuum gave the crude material which was used directly without further purification.

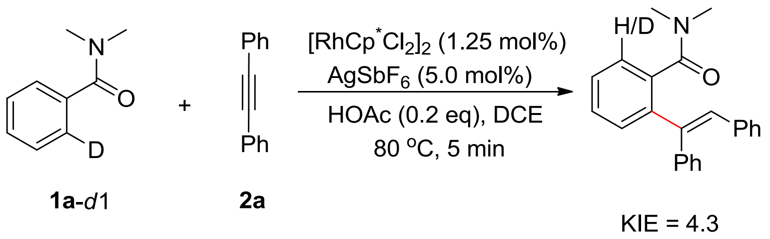
c) To the crude 2-deuteriophenyl-1,3-dioxolane in THF (30 mL) was added HCl (1N, 18 mL) at 0 ^{o}C. After addition, the mixture was allowed to warm to rt and the progress of reaction was monitored through thin layer chromatography. When the starting material disappeared, saturated solution of $NaHCO_3$ (20 mL) was added. The aqueous solution was extracted with EtOAc (3 x 30 mL) washed with brine (50 mL), dried over $MgSO_4$ and filtered. Concentration under vacuum gave the crude material which was used directly without further purification.

d) To a stirred solution of 2-deuteriobenzaldehyde, NaH_2PO_4 (4 mmol), and H_2O_2 (33%, 20 mmol) in 60 mL of MeCN/H_2O (5/1, v/v), was added a solution of $NaClO_2$ (20 mmol) in 25 mL of H_2O dropwise keeping the temperature at 10 ℃ with water cooling. The mixture was stirred at room temperature overnight, then $Na_2S_2O_3$ (3.20 mmol) was added and the mixture was stirred for a further 5 min to decompose the excess of H_2O_2. The mixture was diluted with water and HCl (2N, 5 mL) then extracted with EtOAc (3 x 30 mL). The organic extracts were separated, washed with birine and extracted with solution NaOH (1N, 2 x 30 mL). The alkaline extracts were separated, acidified with HCl (2N), and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over $MgSO_4$ and evaporated to give 2-deuteriobenzoic acid.

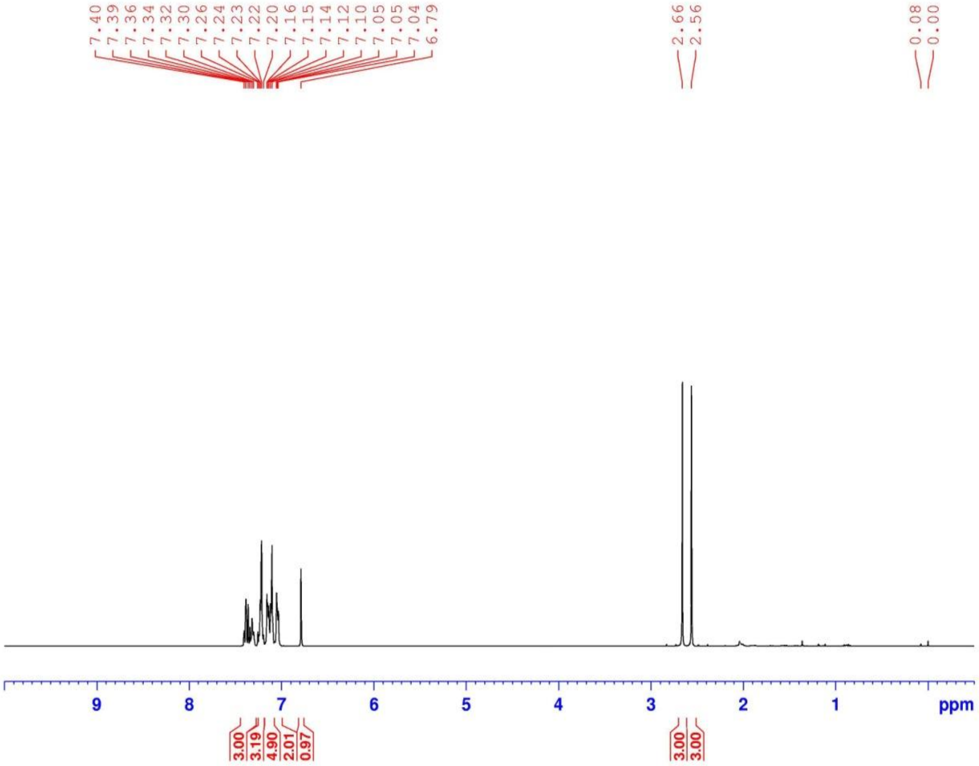
e) 1.To a solution of 2-deuteriobenzoic acid, CH_2Cl_2 (30 mL), DMF (2 drops), was added oxalyl Chloride (10 mmol) at 0 ^{o}C. After addition, the mixture was allowed to warm to rt and stirred for 3h, at which time the solution was concentrated under vacuum to afford the crude 2-deuteriobenzoyl chloride.

2. To a solution of Me_2NHHCl (15 mmol) in CH_2Cl_2 (30 mL) was added Et_3N at 0 ^{o}C, followed by adding a solution of 2-deuteriobenzoyl chloride in 10 mL of CH_2Cl_2 dropwise. After addition, the mixture was allowed to warm to rt and stirred for additional 3h. The reaction was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to give crude **1a-***d*1, which was purified by flash column chromatography on silica gel to give the pure product.

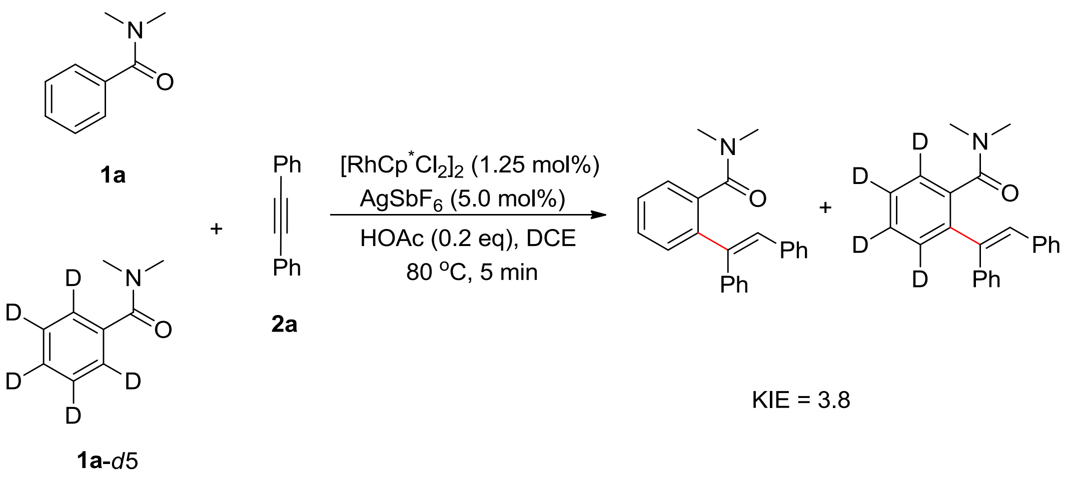
3.4.3.1 Determination of intramolecular kinetic isotope effect



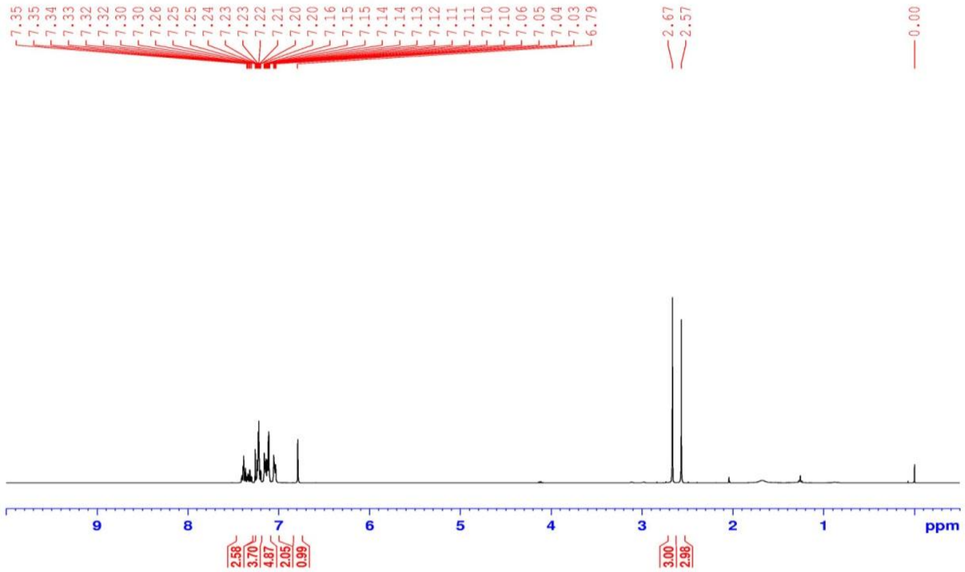
1a-*d*$_1$ (0.2 mmol, 1equiv), **2a** (0.2 mmol, 1equiv), [RhCp*Cl$_2$]$_2$ (0.0025 mmol, 0.0125 equiv), AgSbF$_6$ (0.01 mmol, 0.05 equiv), HOAc (0.04 mmol, 0.2 equiv) and DCE (1 mL) were placed in a glass vial under air. The mixture was heated to 80 ℃ for 5 min. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography.



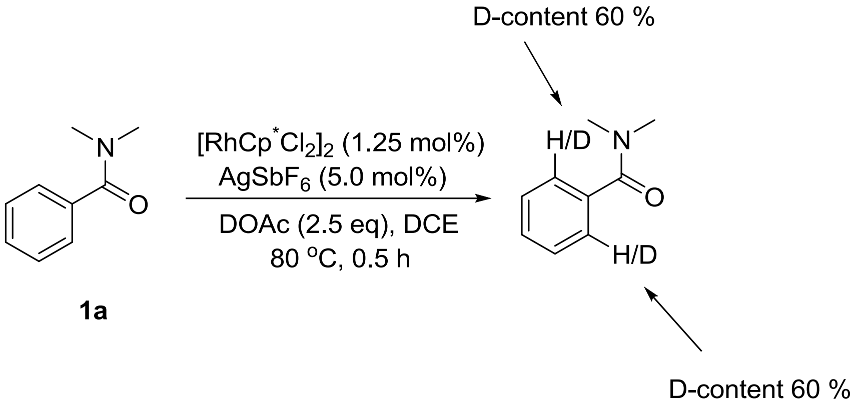
3.4.3.2 Determination of intermolecular kinetic isotope effect



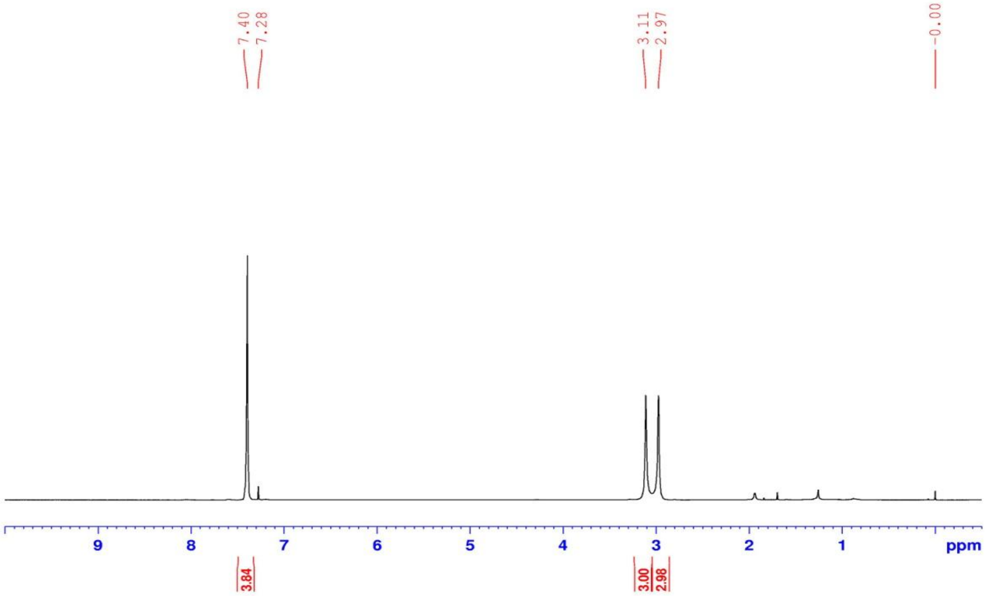
1a (0.2 mmol, 1equiv)**,** **1a**-*d*$_5$ (0.2 mmol, 1equiv), **2a** (0.2 mmol, 1equiv), $[RhCp^*Cl_2]_2$ (0.0025 mmol, 0.0125 equiv), $AgSbF_6$ (0.01 mmol, 0.05 equiv), HOAc (0.04 mmol, 0.2 equiv) and DCE (1 mL) were placed in a glass vial under air. The mixture was heated to 80 ℃ for 5 min. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography.



3.4.3.3 Deuterium incorporation experiment

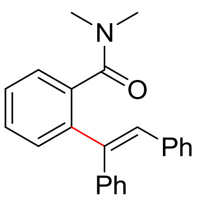


1a (0.2 mmol, 1equiv), $[RhCp^{*}Cl_2]_2$ (0.0025 mmol, 0.0125 equiv), $AgSbF_6$ (0.01 mmol, 0.05 equiv), DOAc (0.5 mmol, 2.5 equiv) and DCE (1 mL)were placed in a glass vial under air. The mixture was heated to 80 ℃ for 30 min. The reaction was then filtered and concentrated *in vacuo* to give a crude product that was purified by column chromatography.



3.4.4 Characterization of Products

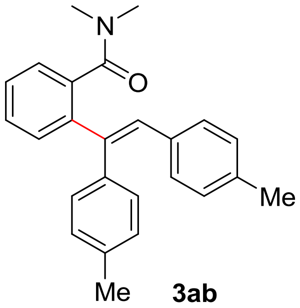
(*E*)-2-(1,2-Diphenylvinyl)-*N*,*N*-dimethylbenzamide:



3aa

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 3H), 2.66 (s, 3H), 6.79 (s, 1H), 7.03-7.05 (m, 2H), 7.09-7.16 (m, 5H), 7.19-7.25 (m, 4H), 7.29-7.41 (m, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 34.2, 38.6, 128.6, 126.9, 127.3, 127.4, 127.8, 128.0, 128.8, 129.4, 130.3, 130.3, 130.7, 136.2, 137.1, 139.4, 141.4, 141.7, 170.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{23}H_{21}NO$ $[M+H]^+$ 328.1701, found: 328.1706.

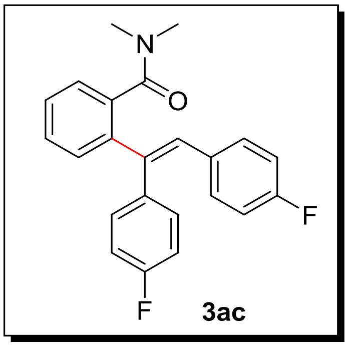
(*E*)-2-(1,2-Dip-tolylvinyl)-*N*,*N*-dimethylbenzamide:



3ab

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.32 (s, 3H), 2.61 (s, 3H), 2.68 (m, 3H), 6.71 (s, 1H), 6.92-6.97 (m, 4H), 7.04 (s, 4H), 7.20-7.22 (m, 1H), 7.28-7.34 (m, 3H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.1, 21.2, 34.2, 38.6, 127.0, 127.3, 128.6, 128.7, 129.3, 130.2, 130.2, 130.4, 134.4, 136.1, 136.5, 136.7, 136.9, 140.4, 142.0, 170.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{25}H_{25}NO$ $[M+H]^+$ 356.2014, found: 356.2023.

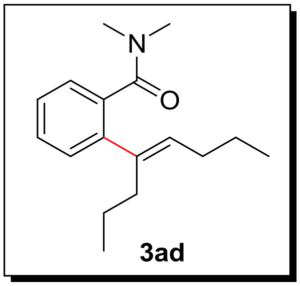
(*E*)-2-(1,2-Bis(4-fluorophenyl)vinyl)-*N*,*N*-dimethylbenzamide:



3ac

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.60 (s, 3H), 2.69 (s, 3H), 6.73(s, 1H), 6.81-6.85 (m, 2H), 6.91-6.95 (m, 2H), 6.98-7.01 (m, 2H), 7.09-7.13 (m, 2H), 7.20-7.21 (m, 1H), 7.31-7.38 (m, 3H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.2, 38.7, 114.8, 115.0, 115.1, 115.2, 127.0, 127.7, 128.9, 129.7, 130.3, 130.9, 131.0, 132.1, 132.2, 133.0 (d, *J* = 3.4 Hz), 135.2 (d, *J* = 3.4 Hz), 136.1, 140.4, 141.4, 160.6 (d, *J* = 46.3 Hz), 163.1 (d, *J* = 46.4 Hz), 170.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{23}H_{19}F_2NO$ $[M+H]^+$ 364.1513, found: 364.1523.

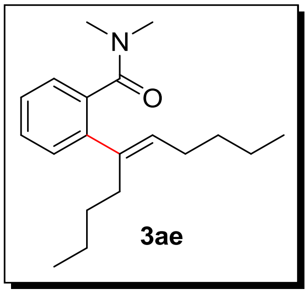
(*E*)-*N*,*N*-Dimethyl-2-(oct-4-en-4-yl)benzamide:



3ad

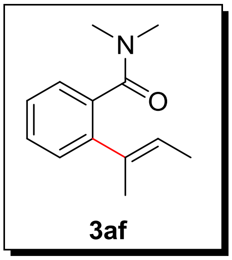
^{1}H NMR (400 MHz, CDCl$_3$): δ 0.87 (t, *J* = 7.3 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H), 1.32-1.33 (m, 2H), 1.39-1.45 (m, 2H), 2.10-2.15 (m, 2H), 2.33 (t, *J* = 7.8 Hz, 2H), 2.77 (s, 3H), 3.05 (s, 3H), 5.42 (t, *J* = 7.3 Hz, 1H), 7.18-7.32 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 13.8, 14.0, 21.9, 22.9, 30.4, 33.0, 34.6, 38.7, 126.5, 126.5, 128.5, 129.1, 130.9, 135.2, 139.9, 141.8, 171.7 ppm; **HRMS (ESI, m/z):** calcd for $C_{17}H_{25}NO$ $[M+H]^+$ 260.2014, found: 260.2005.

(*E*)-2-(Dec-5-en-5-yl)-*N*,*N*-dimethylbenzamide:


3ae

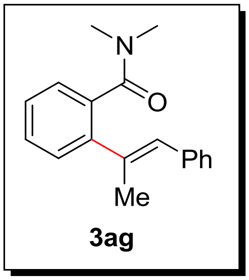
^{1}H NMR (400 MHz, CDCl$_3$): δ 0.85 (t, *J* = 6.2 Hz, 3H), 0.92 (t, *J* = 6.6 Hz 3H), 1.28-1.29 (m, 4H), 1.35-1.39 (m, 4H), 2.12-2.15 (m, 2H), 2.35 (t, *J* = 7.3 Hz, 2H), 2.76 (s, 3H), 3.04 (s, 3H), 5.40 (t, *J* = 7.3 Hz, 1H), 7.18-7.31 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 13.9, 14.0, 22.4, 22.7, 28.0, 30.7, 31.0, 32.0, 34.6, 38.7, 126.5, 126.6, 128.5, 129.1, 130.9, 135.3, 139.9, 141.8, 171.7 ppm; **HRMS (ESI, m/z):** calcd for $C_{19}H_{29}NO$ $[M+H]^+$ 288.2327, found: 288.2326.

(*E*)-2-(But-2-en-2-yl)-*N*,*N*-dimethylbenzamide:


3af

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.74 (d, *J* = 6.8 Hz, 3H), 1.97 (s, 3H), 2.76 (s, 3H), 3.05 (s, 3H), 5.59 (q, *J* = 6.8 Hz, 1H), 7.20-7.33 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.2, 16.8, 34.6, 38.5, 125.1, 126.6, 126.8, 128.0, 128.7, 134.8, 134.9, 142.5, 171.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{17}NO$ $[M+H]^+$ 204.1388, found: 204.1396.

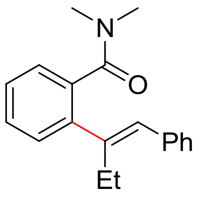
(*E*)-N,N-Dimethyl-2-(1-phenylprop-1-en-2-yl)benzamide:



3ag

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.23 (s, 3H), 2.82 (s, 3H), 3.06 (s, 3H), 6.57 (s, 1H), 7.22-7.26 (m, 1H), 7.31-7.38 (m, 8H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 19.0, 34.7, 38.6, 126.6, 27.1, 127.2, 128.0, 128.2, 128.9, 130.1, 135.1, 136.9, 137.8, 142.5, 171.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{17}NO$ $[M+H]^+$ 266.1545, found: 266.1551.

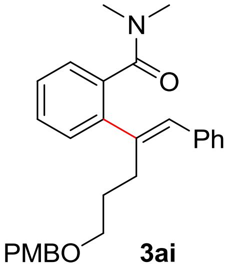
(*E*)-N,N-Dimethyl-2-(1-phenylbut-1-en-2-yl)benzamide:



3ah

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.98 (t, *J* = 7.5 Hz, 3H), 2.62 (q, *J* = 7.5 Hz, 2H), 2.84 (s, 3H), 3.05 (s, 3H), 6.48 (s, 1H), 7.25-7.37 (m, 9H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 13.3, 24.5, 34.7, 38.8, 126.6, 126.9, 127.2, 128.2, 128.6, 128.7, 129.1, 129.4, 135.4, 137.7, 140.8, 144.2, 171.4 ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{17}NO$ [M+H]$^+$ 280.1701, found: 280.1692.

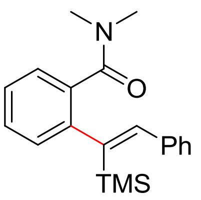
(*E*)-2-(5-(4-Methoxybenzyloxy)-1-phenylpent-1-en-2-yl)-*N,N*-dimethylbenzamide:



3ai

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.63-1.70 (m, 2H), 2.69 (s, 2H), 2.83 (s, 3H), 3.03 (s, 3H), 3.39 (d, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 4.31 (s, 2H), 6.50 (s, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.17 (t, *J* = 8.5 Hz, 2H), 7.24-7.36 (m, 9H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 28.0, 28.7, 34.7, 38.8, 55.2, 69.6, 72.3, 113.6, 126.7, 126.8, 127.2, 128.3, 128.7, 128.8, 129.1, 130.3, 130.7, 135.4, 137.6, 141.0, 142.3, 159.0, 171.4 ppm; **HRMS (ESI, m/z):** calcd for $C_{28}H_{31}NO_3$ [M+H]$^+$ 430.2382, found: 430.2387.

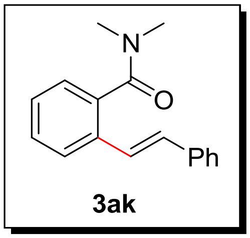
(*Z*)-*N,N*-Dimethyl-2-(2-phenyl-1-(trimethylsilyl)vinyl)benzamide:



3aj

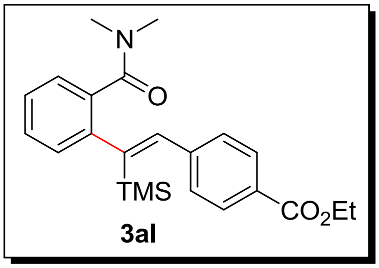
^{1}H NMR (400 MHz, CDCl$_3$): δ 0.15 (s, 9H), 3.07 (s, 3H), 3.34 (s, 3H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.44-7.57 (m, 9H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 0.7, 34.6, 38.8, 125.8, 126.6, 127.3, 127.9, 128.3, 128.4, 134.9, 139.6, 144.2, 145.3, 146.2, 171.2 ppm; **HRMS (ESI, m/z):** calcd for $C_{20}H_{25}NOSi$ [M+H]$^+$ 324.1784, found: 324.1782.

(*E*)-*N*,*N*-Dimethyl-2-styrylbenzamide:


3ak

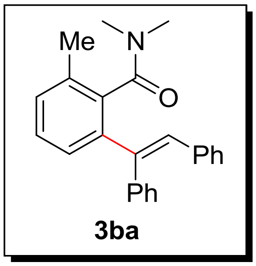
^{1}H NMR (400 MHz, CDCl$_3$): δ 2.79 (s, 3H), 3.16 (s, 3H), 7.10 (s, 2H), 7.24-7.31 (m, 3H), 7.33-7.40 (m, 3H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 7.9 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.7, 38.5, 125.1, 125.5, 126.5, 126.7, 127.6, 127.9, 128.6, 129.0, 131.1, 133.9, 135.8, 137.0, 171.1 ppm; **HRMS (ESI, m/z):** calcd for $C_{17}H_{17}NO$ [M+H]$^+$ 252.1388, found: 252.1384.

(*Z*)-Ethyl 4-(2-(2-(dimethylcarbamoyl)phenyl)-2-(trimethylsilyl)vinyl)benzoate:


3al

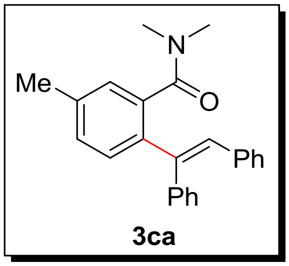
^{1}H NMR (400 MHz, CDCl$_3$): δ 0.15 (s, 9H), 1.62 (t, *J* = 7.1 Hz, 3H), 3.08 (s, 3H), 3.33 (s, 3H), 4.60 (q, *J* = 7.1 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.42-7.48 (m, 3H), 7.52-7.57 (m, 3H), 8.23 (d, *J* = 8.2 Hz, 2H), ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 0.7, 14.3, 34.7, 38.9, 61.0, 126.0, 126.6, 128.3, 128.3, 128.3, 129.3, 134.7, 143.8, 144.1, 144.3, 148.0, 166.4, 171.1 ppm; **HRMS (ESI, m/z):** calcd for $C_{23}H_{29}NO_3Si$ [M+H]$^+$ 396.1995, found: 396.1983.

(*E*)-2-(1,2-Diphenylvinyl)-*N*,*N*,6-trimethylbenzamide:


3ba

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.22 (s, 3H), 2.42 (s, 3H), 2.70 (s, 3H), 6.73 (s, 1H), 7.01-7.03 (m, 2H), 7.09-7.26 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 19.0, 33.7, 37.4, 126.7, 127.3, 127.8, 127.9, 128.0, 128.2, 129.3, 129.4, 130.2, 130.9, 134.1, 135.9, 137.2, 139.6, 141.3, 141.6, 169.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{24}H_{23}NO$ $[M+H]^+$ 342.1858, found: 342.1862.

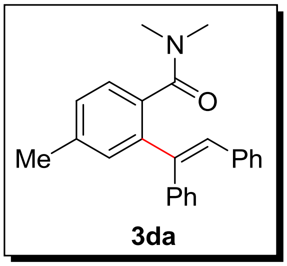
(*E*)-2-(1,2-Diphenylvinyl)-N,N,5-trimethylbenzamide:



3ca

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.35 (s, 3H), 2.60 (s, 3H), 2.66 (s, 3H), 6.77 (s, 1H), 7.02-7.04 (m, 3H), 7.08-7.17 (m, 6H), 7.20-7.27 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 20.9, 34.1, 38.6, 126.7, 127.3, 127.6, 127.8, 127.9, 129.3, 129.4, 130.2, 130.2, 130.3, 136.0, 137.2, 137.4, 138.8, 139.5, 141.3, 170.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{24}H_{23}NO$ $[M+H]^+$ 342.1858, found: 342.1861.

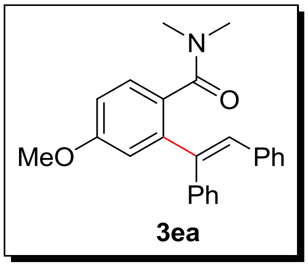
(*E*)-2-(1,2-Diphenylvinyl)-*N*,*N*,4-trimethylbenzamide:



3da

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.37 (s, 3H), 2.56 (s, 3H), 2.64 (s, 3H), 6.77 (s, 1H), 7.03-7.05 (m, 2H), 7.08-7.16 (m, 7H), 7.21-7.23 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 21.2, 34.2, 38.6, 126.7, 127.0, 127.3, 127.8, 127.9, 128.1, 129.4, 130.3, 130.5, 130.9, 133.4, 137.2, 138.6, 139.4, 141.7, 141.7, 170.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{24}H_{23}NO$ $[M+H]^+$ 342.1858, found: 342.1867.

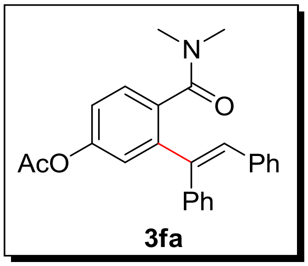
(*E*)-2-(1,2-Diphenylvinyl)-4-methoxy-*N*,*N*-dimethylbenzamide:



3ea

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.57 (s, 3H), 2.63 (s, 3H), 3.82 (s, 3H), 6.80 (s, 1H), 6.83-6.86 (m, 1H), 6.93-6.94 (m, 1H), 7.04-7.06 (m, 2H), 7.11-7.16 (m, 6H), 7.21-7.26 (m, 3H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.3, 38.7, 55.3, 112.6, 115.9, 126.8, 127.4, 127.8, 127.9, 128.4, 128.8, 129.4, 130.3, 130.6, 137.0, 139.2, 141.5, 143.5, 159.7, 170.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{24}H_{23}NO_2$ $[M+H]^+$ 358.1807, found: 358.1812.

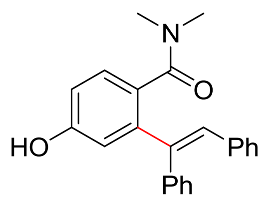
(*E*)-4-(Dimethylcarbamoyl)-3-(1,2-diphenylvinyl)phenyl acetate:



3fa

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.29 (s, 3H), 2.59 (s, 3H), 2.65 (s, 3H), 6.80 (s, 1H), 7.02-7.16 (m, 9H0, 7.21-7.24 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 21.1, 34.2, 38.7, 120.6, 123.3, 127.0, 127.5, 127.9, 128.1, 129.4, 130.4, 131.3, 133.7, 136.8, 138.9, 140.5, 143.4, 150.7, 169.0, 169.9 ppm; **HRMS (ESI, m/z):** calcd for $C_{25}H_{23}NO_3$ $[M+H]^+$ 386.1756, found: 386.1753.

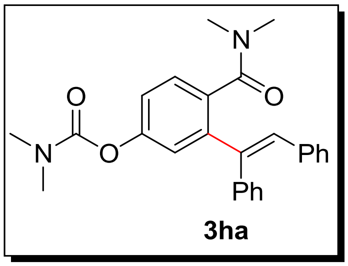
(*E*)-2-(1,2-Diphenylvinyl)-4-hydroxy-*N*,*N*-dimethylbenzamide:



3ga

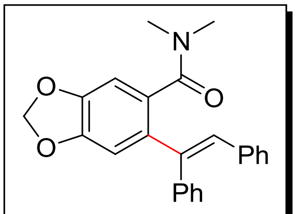
^{1}H NMR (400 MHz, CDCl$_3$): δ 2.61 (s, 3H), 2.63 (s, 3H), 6.76 (s, 1H), 6.79 (dd, J_1 = 8.3 Hz, J_2 = 2.4 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 7.02-7.06 (m, 3H), 7.09-7.11 (m, 5H), 7.24-7.26 (m, 3H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 33.5, 38.2, 113.9, 116.8, 126.6, 127.2, 127.6, 127.8, 128.3, 129.1, 130.2, 130.3, 137.1, 139.4, 141.6, 143.8, 158.2, 172.2 ppm; **HRMS (ESI, m/z):** calcd for $C_{23}H_{21}NO_2$ $[M+H]^+$ 344.1651, found: 344.1655.

(*E*)-4-(Dimethylcarbamoyl)-3-(1,2-diphenylvinyl)phenyl dimethylcarbamate:


3ha

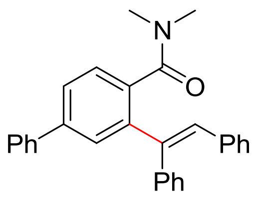
^{1}H NMR (400 MHz, CDCl$_3$): δ 2.57 (s, 3H), 2.64 (s, 3H), 3.01 (s, 3H), 3.09 (s, 3H), 6.80 (s, 1H), 7.02-7.04 (m, 2H), 7.10-7.13 (m, 4H), 7.14-7.23 (m, 7H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 34.2, 36.4, 36.6, 38.7, 120.7, 123.5, 126.9, 127.4, 127.8, 127.9, 128.0, 129.4, 130.4, 131.1, 133.1, 136.9, 139.0, 140.8, 143.2, 151.6, 154.4, 170.1 ppm; **HRMS (ESI, m/z)**: calcd for $C_{26}H_{26}N_2O_3$ $[M+H]^+$ 415.2022, found: 415.2028.

(*E*)-6-(1,2-Diphenylvinyl)-*N*,*N*-dimethylbenzo[*d*][1,3]dioxole-5-carboxamide:


3ia

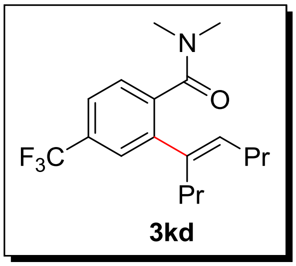
^{1}H NMR (400 MHz, CDCl$_3$): δ 2.52 (s, 3H), 2.63 (s, 3H), 5.96 (s, 2H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 2H), 6.87 (s, 1H), 7.05-7.07 (m, 2H), 7.10-7.12 (m, 3H), 7.18-7.21 (m, 5H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.3, 38.8, 101.1, 107.1, 120.6, 124.2, 126.9, 127.3, 127.8, 127.9, 129.4, 130.1, 130.6, 132.5, 134.4, 136.6, 138.8, 146.0, 147.7, 169.8 ppm; **HRMS (ESI, m/z):** calcd for $C_{24}H_{21}NO_3$ $[M+H]^+$ 372.1600, found: 372.1604.

(*E*)-3-(1,2-Diphenylvinyl)-*N*,*N*-dimethylbiphenyl-4-carboxamide:


3ja

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.59 (s, 3H), 2.66 (s, 3H), 6.87 (s, 1H), 7.05-7.08 (m, 2H), 7.10-7.13 (m, 3H), 7.18-7.20 (m, 2H), 7.21-7.24 (m, 3H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.33-7.37 (m, 1H), 7.41-7.45 (m, 2H), 7.55 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.60-7.62 (m, 1H), 7.66 (d, *J* = 1.8 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.2, 38.6, 126.1, 126.9, 127.1, 127.4, 127.5, 127.6, 127.9, 128.0, 128.8, 129.1, 129.4, 130.4, 130.9, 135.1, 137.1, 139.2, 140.1, 141.5, 141.7, 142.3, 170.4 ppm; **HRMS (ESI, m/z):** calcd for $C_{29}H_{25}NO$ [M+H]$^+$ 404.2014, found: 404.2024.

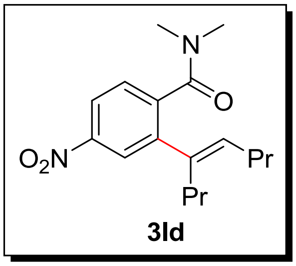
(*E*)-*N,N*-Dimethyl-2-(oct-4-en-4-yl)-4-(trifluoromethyl)benzamide:



3kd

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.88 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H), 1.32 (s, 2H), 1.39-1.48 (m, 2H), 2.12-2.17 (m, 2H), 2.35 (t, *J* = 7.8 Hz, 2H), 2.77 (s, 3H), 3.06 (s, 3H), 5.47 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.45 (s, 1H), 7.51 (d, *J* = 7.93 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 13.8, 14.0, 21.9, 22.8, 30.4, 32.9, 34.6, 38.6, 122.5, 123.5 (q, *J* = 3.66 Hz), 125.2, 126.0 (q, *J* = 3.66 Hz), 127.1, 130.7 (q, *J* = 32.25 Hz), 132.3, 138.8, 139.0, 142.6, 170.3 ppm; **HRMS (ESI, m/z):** calcd for $C_{18}H_{24}F_3NO$ [M+H]$^+$ 328.1888, found: 328.1892.

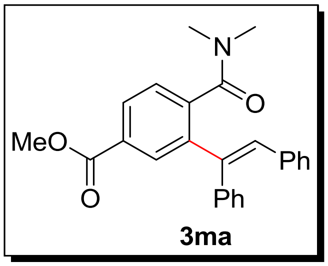
(*E*)-*N,N*-Dimethyl-4-nitro-2-(oct-4-en-4-yl)benzamide:



3ld

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.90 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H), 1.34 (s, 2H), 1.40-1.49 (m, 2H), 2.14-2.19 (m, 2H), 2.38 (t, *J* = 7.9 Hz, 2H), 2.78 (s, 3H), 3.07 (s, 3H), 5.53 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 8.12 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 13.8, 14.0, 21.9, 22.8, 30.4, 32.7, 34.6, 38.5, 121.6, 124.1, 127.8, 133.2, 138.2, 141.5, 143.5, 147.7, 169.4 ppm; **HRMS (ESI, m/z):** calcd for $C_{17}H_{24}N_2O_3$ [M+H]$^+$ 305.1865, found: 305.1863.

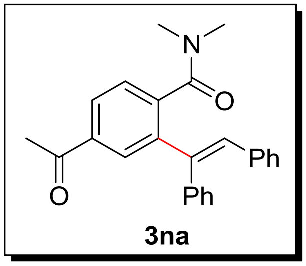
(*E*)-Methyl 4-(dimethylcarbamoyl)-3-(1,2-diphenylvinyl)benzoate:



3ma

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.49 (s, 3H), 2.64 (s, 3H), 3.93 (s, 3H), 6.83 (s, 1H), 7.03-7.06 (m, 2H), 7.12-7.15 (m, 5H), 7.22-7.28 (m, 4H), 8.00 (dd, J_1 = 7.3 Hz, J_2 = 1.7 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.1, 38.4, 52.2, 127.0, 127.1, 127.6, 127.9, 128.1, 128.5, 129.4, 130.3, 130.5, 131.4, 131.6, 136.7, 138.8, 140.4, 140.6, 142.2, 166.4, 169.5 ppm; **HRMS (ESI, m/z):** calcd for $C_{25}H_{23}NO_3$ $[M+H]^+$ 386.1756, found: 386.1772.

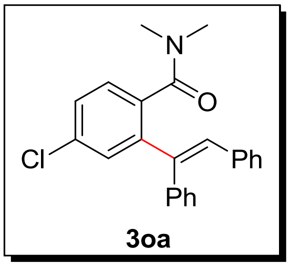
(*E*)-4-Acetyl-2-(1,2-diphenylvinyl)-*N*,*N*-dimethylbenzamide:



3na

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.50 (s, 3H), 2.63 (s, 3H), 2.65 (s, 3H), 6.83 (s, 1H), 7.04-7.06 (m, 2H), 7.12-7.16 (m, 5H), 7.24-7.25 (m, 3H), 7.30 (d, J = 7.9 Hz, 1H), 7.91 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 1H), 8.03 (d, J = 1.7 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 26.8, 34.2, 38.5, 127.2, 127.4, 127.7, 128.0, 128.2, 129.5, 130.2, 130.4, 131.7, 136.8, 137.3, 138.9, 140.7, 140.7, 142.5, 169.6, 197.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{25}H_{23}NO_2$ $[M+H]^+$ 370.1807, found: 370.1798.

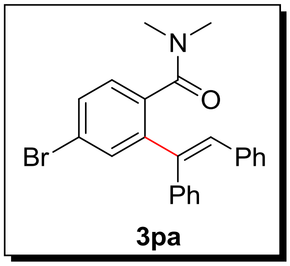
(*E*)-4-Chloro-2-(1,2-diphenylvinyl)-*N*,*N*-dimethylbenzamide:



3oa

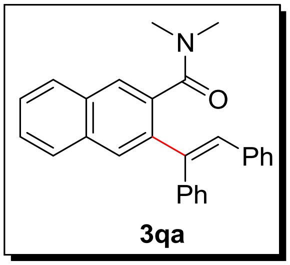
^{1}H NMR (400 MHz, CDCl$_3$): δ 2.54 (s, 3H), 2.64 (s, 3H), 6.79 (s, 1H), 7.02-7.04 (m, 2H), 7.10-7.15 (m, 6H), 7.22-7.26 (m, 3H), 7.30 (dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz, 1H), 7.42 (d, J = 2.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.2, 38.6, 127.1, 127.4, 127.7, 127.9, 128.1, 128.3, 129.4, 130.2, 130.3, 131.6, 134.6, 134.7, 136.7, 138.7, 140.2, 143.6, 169.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{23}H_{20}ClNO$ $[M+Na]^+$ 362.1312, found: 362.1308.

(*E*)-4-Bromo-2-(1,2-diphenylvinyl)-*N*,*N*-dimethylbenzamide:


3pa

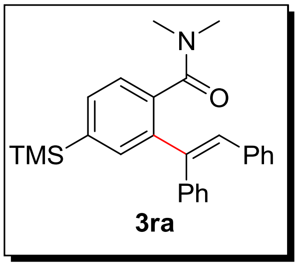
^{1}H NMR (400 MHz, CDCl$_3$): δ 2.53 (s, 3H), 2.63 (s, 3H), 6.79 (s, 1H), 7.02-7.04 (m, 2H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.10-7.15 (m, 5H), 7.23-7.26 (m, 3H), 7.46 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H), 7.58 (d, *J* = 1.9 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.2, 38.6, 122.8, 127.2, 127.7, 127.9, 128.1, 128.5, 129.4, 130.3, 130.4, 131.7, 133.1, 135.1, 136.7, 138.7, 140.2, 143.9, 169.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{23}H_{20}BrNO$ $[M+H]^+$ 406.0807, found: 406.0817.

(*E*)-3-(1,2-Diphenylvinyl)-*N*,*N*-dimethyl-2-naphthamide:


3qa

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.52 (s, 3H), 2.67 (s, 3H), 6.93 (s, 1H), 7.07-7.14 (m, 5H), 7.17-7.19 (m, 2H), 7.21-7.24 (m, 3H), 7.47-7.53 (m, 2H), 7.67 (s, 1H), 7.78-7.85 (m, 2H), 7.92 (s, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.2, 38.7, 126.5, 126.6, 126.8, 126.9, 127.4, 127.7, 127.8, 128.0, 129.3, 129.5, 130.5, 130.7, 132.0, 133.2, 134.4, 137.2, 139.3, 139.7, 141.7, 170.4 ppm; **HRMS (ESI, m/z):** calcd for $C_{27}H_{23}NO$ $[M+H]^+$ 378.1858, found: 378.1862.

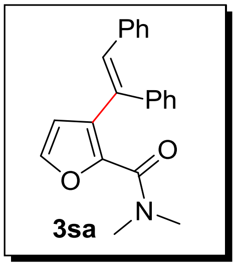
(*E*)-2-(1,2-Diphenylvinyl)-*N*,*N*-dimethyl-4-(trimethylsilyl)benzamide:



3ra

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.28 (s, 9H), 2.51 (s, 3H), 2.62 (s, 3H), 6.79 (s, 1H), 7.05-7.07 (m, 2H), 7.10-7.17 (m, 6H), 7.20-7.23 (m, 3H), 7.47 (dd, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1H), 7.56 (s, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ -1.2, 34.1, 38.6, 126.1, 126.8, 127.3, 127.9, 127.9, 129.4, 130.4, 130.5, 132.5, 135.1, 136.5, 137.2, 139.4, 140.9, 141.6, 142.0, 170.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{26}H_{29}NOSi$ $[M+H]^+$ 400.2097, found: 400.2100.

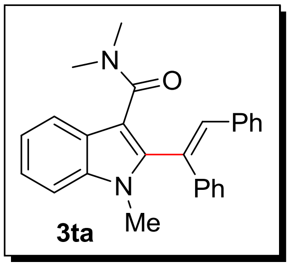
(*E*)-3-(1,2-Diphenylvinyl)-N,N-dimethylfuran-2-carboxamide:



3sa

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.68 (s, 3H), 2.88 (s, 3H), 6.41 (d, *J* = 1.7 Hz 1H), 6.88 (s, 1H), 7.02-7.04 (m, 2H), 7.10-7.12 (m, 3H), 7.21-7.24 (m, 2H), 7.26-7.28 (m, 3H),7.40 (d, *J* = 1.7 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 34.6, 38.0, 111.4, 127.0, 127.7, 127.9, 128.2, 128.5, 129.3, 129.4, 129.7, 133.0, 136.6, 138.6, 142.4, 143.5, 162.2 ppm; **HRMS (ESI, m/z):** calcd for $C_{26}H_{29}NOSi$ $[M+H]^+$ 318.1494, found: 318.1502.

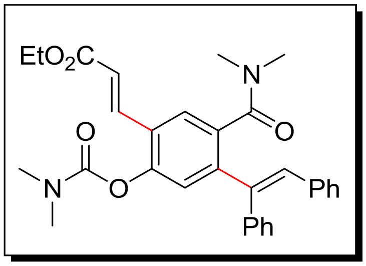
(*E*)-2-(1,2-Diphenylvinyl)-*N*,*N*,1-trimethyl-1H-indole-3-carboxamide:



3ta

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.92 (s, 6H), 3.46 (s, 3H), 6.89 (s, 1H), 7.14-7.17 (m, 6H), 7.22-7.28 (m, 7H), 7.56 (d, *J* = 7.9 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 31.1, 109.5, 112.0, 119.9, 120.5, 122.5, 125.7, 127.4, 127.7, 128.0, 128.3, 129.5, 130.0, 131.8, 133.9, 136.2, 137.1, 138.2, 141.2, 167.6 ppm; **HRMS (ESI, m/z):** calcd for $C_{26}H_{24}N_2O$ $[M+H]^+$ 381.1967, found: 381.1971.

(*E*)-Ethyl 3-(5-(dimethylcarbamoyl)-2-(dimethylcarbamoyloxy)-4-((*E*)-1,2-diphenyl vinyl)phenyl)acrylate:



^{1}H NMR (400 MHz, CDCl$_3$): δ 1.29 (t, *J* = 7.2 Hz, 3H), 2.36 (s, 3H), 2.69 (s, 3H), 3.03 (s, 3H), 3.11 (s, 3H), 4.21 (q, *J* = 7.2 Hz, 2H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.75 (s, 1H), 7.00-7.02 (m, 2H), 7.10-7.12 (m, 3H), 7.16-7.18 (m, 2H), 7.22-7.24 (m, 4H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.53 (d, *J* = 15.8 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.2, 34.0, 36.5, 36.7, 37.8, 60.5, 118.4, 121.6, 125.3, 127.0, 127.5, 127.9, 128.1, 129.4, 130.2, 131.7, 132.7, 133.6, 136.7, 138.8, 140.3, 140.5, 143.7, 151.4, 154.3, 166.2, 168.0 ppm; **HRMS (ESI, m/z):** calcd for $C_{31}H_{32}N_2O_5$ $[M+H]^+$ 513.2389, found: 513.2390.

Copper-Catalyzed Olefinic C-H Trifluoromethylation of Enamides at Room Temperature

4.1 Introduction

With substantial progress in medicinal and biochemistry, trifluoromethyl-containing skeletons had gained increasingly more attention, especially in recent decade, mainly due to its attractive electronic property, metabolic stability and lipophilicity.[1] Because of its unique characteristics, modification with the trifluoromethyl group gradually evolved to be a routine in the pharmaceutical and agrochemical industries, in pursuit of new active candidates. In this regard, enormous effort has been devoted to the exploration of new synthetic methods for the introduction of trifluoromethyl functionality into a series of useful substrates.[2] Within this arena, transition metal-catalyzed protocol is extremely appealing in view of the regioselectivity, functionality compatibility and reaction efficiency, which otherwise often proved to be problematic with conventional methods.[3] In particular, palladium and copper complexes stood out as competent catalysts in a diversity of transformations for introduction of the CF_3 group, thus enabling the formation

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[1] (a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320. (c) Smart, B. E.; *Chem. Rev*. **1996**, *96*, 1555. (d) Smart, B. E.; *J. Fluorine Chem*. **2001**, *109*, 3.

[2] (a) Prakash, G. K. S.; Yudin, A. K.; *Chem. Rev*. **1997**, *97*, 757. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320. (c) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev*. **2011**, *111*, 4475.

[3] (a) Booth, H. S.; Esley, H. M.; Burchfield, P. E. *J. Am. Chem. Soc*. **1935**, *57*, 2066. (b) Umemoto, T.; Ishihara, S. *Tetrahedron Lett*. **1990**, *31*, 3579. (c) Simons, J. H.; Lewis, C. J. *J. Am. Chem. Soc*. **1938**, *60*, 492. (d) Castafler, J.; Riera, J.; Carilla, J.; Robert, A.; Molins, E.; Miravitlles, C. *J. Org. Chem*. **1991**, *56*, 103.

of sp^3 C-CF$_3$,[4] sp^2 C-CF$_3$[5] and sp C-CF$_3$[6] bonds efficiently. What needs to be further pointed out is that, although many reported protocols rely on the employment of prefunctionalized substrates, elegant works done by Yu,[7] Qing[8] and other groups[9] gradually pave the road for realizing directly C-H trifluoromethylation, making it a much more ideal and straightforward process.

As for the sp^2 C-CF$_3$ bond formation, while much advancement has been attained for the construction of aryl C-CF$_3$ bond, relatively less attention has been paid to formation of the olefinic C-CF$_3$ counterpart. Quite recently, Buchwald[10] reported a general method for

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[4] (a) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem. Int. Ed*. **2007**, *46*, 754. (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (c) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. (d) Mu, X.; Wu, T.; Wang, H.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (e) Umemoto, T.; Adachi, K. *J. Org. Chem*. **1994**, *59*, 5692. (f) Herrmann, A. T.; Smith, L. L.; Zakarian, A. *J. Am. Chem. Soc*. **2012**, *134*, 6976. (*g*) Chu, L.; Qing, F.-L. *Org. Lett*., **2012**, *14*, 2106. (*h*) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc*., **2012**, *134*, 10769. (*i*) Pham, P. V.; Nagib, D. A.; Macmillan, D. W. C. *Angew. Chem. Int. Ed*., **2011**, *50*, 6119.

[5] For selected examples of trifluoromethylation of aryl boronic acids, see: (a) Liu, T.; Sheng, Q. *Org. Lett.* **2011**, *13*, 2342. (b) Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 5060. (c) Xu, J.; Luo, D. F.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Fu, Y.; Liu, L. *Chem. Commun*. **2011**,*47*, 4300. (d) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. *Angew. Chem. Int. Ed*. **2012**, *51*, 540. (e) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem*. **2011**, *76*, 1174. (f) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **2012**, *51*, 536. For selected examples of trifluoromethylation of aryl halides, see: (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (b) Samant, B. S.; Kabalka, G. W. *Chem. Comm*. **2011**, *47*, 7236. (c) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun*. **2009**, 1909. (d) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed*. **2011**, *50*, 3793. (e) Tomashenko, O. A.; Escudero-Adan, E. C.; Belmonte, M. M.; Grushin, V. V. *Angew. Chem., Int. Ed*. **2011**, *50*, 7655. (f) Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. *Angew. Chem., Int. Ed*. **2011**, *50*, 1896. (g) Dubinina, G. G.; Furutachi, H.; Vicic, D. A. *J. Am. Chem. Soc*. **2008**, *130*, 8600. (h) Knauber, T.; Arikan, F.; Roschenthaler, G.-V.; Gooßen, L. J. *Chem. Eur. J*. **2011**, *17*, 2689. (*i*) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc*., **2012**, *134*, 9034.

[6] (a) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc*. **2010**, *132*, 7262. (*b*) Jiang, X.; Chu, L.; Qing, F.-L. *J. Org. Chem*., **2012**, *77*, 1251.

[7] Wang, X.-S.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648.

[8] Chu, L.; Qing, F.-L. *J. Am. Chem. Soc*. **2012**, *134*, 1298.

[9] (a) Shimizu, R.; Egami, H.; Nagi, T.; Chae, J.; Hamashima, Y.; Sodeoka, M. *Tetrahedron Lett*. **2010**, *51*, 5947. (b) Mu, X.; Chen, S.-J.; Zhen, X.-L.; Liu, G.-S.; *Chem. Eur. J*. **2011**, *17*, 6039. (c) Wiehn, M. S.; Vinogradova, E. V.; Togni, A. *J. Fluorine Chem*. **2010**, *131*, 951. (d) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 5464. (e) Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 14682. (f) Hafner, A.; Brase, S. *Angew. Chem. Int. Ed*. **2012**, *51*, 3713.

[10] Parsons, A. T.; Senecal, T.D.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2012**, *51*, 2947.

the formation of this moiety using vinyltrifluoroborates (Scheme 4.1, a) and Hu[11] developed a cascade trifluoromethylation-decarboxylation process for the construction of olefinic C-CF_3 bond via α,β-unsaturated carboxylic acids (Scheme 4.1, b). However, to the best of our knowledge there is still no report on the realization of olefinic C-CF_3 bond formation through the replacement of olefinic C-H moiety with CF_3 group. This transformation, if realized, would bring about more advantages compared to existing methods not only because of the omission of substrate preactivation, but also the byproducts formed otherwise. With our longstanding interest in elaboration of olefin functionality, [12] we would like to report herein the first example of C-H trifluoromethylation of enamides for the direct formation of olefinic C-CF_3 bond (Scheme 4.1, c).

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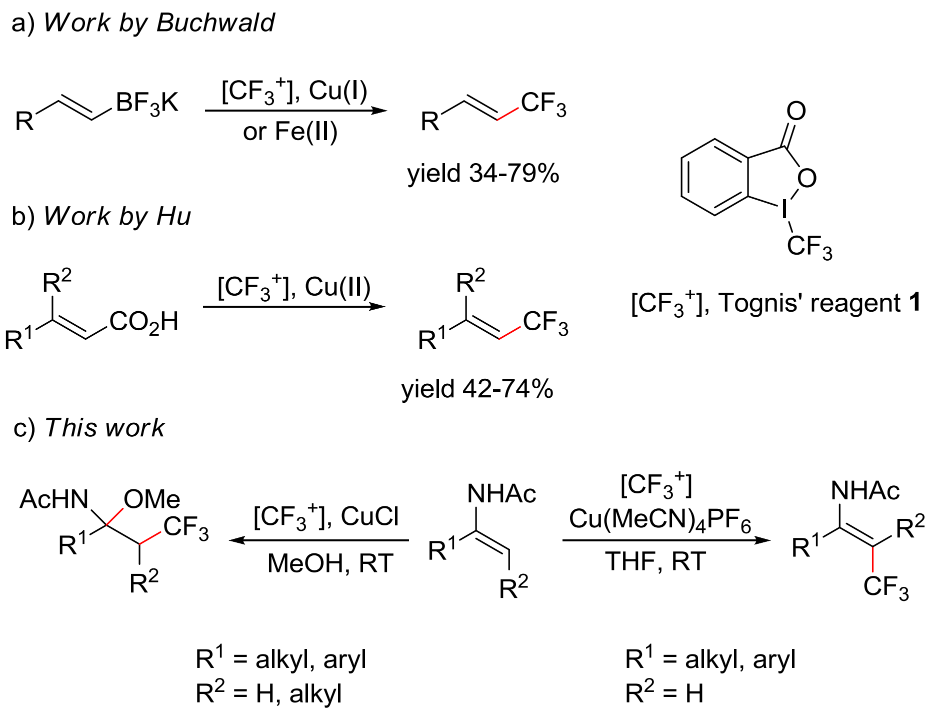
[11] He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 3944.

[12] (a) Zhou, H.; Chung, W. J.; Xu, Y. H.; Loh, T. P. *Chem. Commun*. **2009**, 3472. (b) Zhou, H.; Xu, Y. H.; Chung, W. J.; Loh, T. P. *Angew. Chem. Int. Ed*. **2009**, *48*, 5355 (c) Feng, C.; Loh, T. P. *J. Am. Chem. Soc*. **2010**, *132*, 17710. (d) Feng, C.; Loh, T. P. *Chem. Commun*. **2011**, 10458. (e) Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Chem. Soc*. **2009**, *131*, 1372.



Scheme 4.1 Cu or iron-catalyzed olefinic trifluoromethylation

Recently, groups of Buchwald,[13] Wang[14] and Liu[15] reported, independently, the ene type trifluoromethylation of simple olefins, whereby allylic sp^3 C-CF$_3$ moiety is selectively formed. Shortly after that, Sodeoka reported a variant for realizing allylic trifluoromethylation by utilization of allylsilanes (Scheme 4.2).[16]

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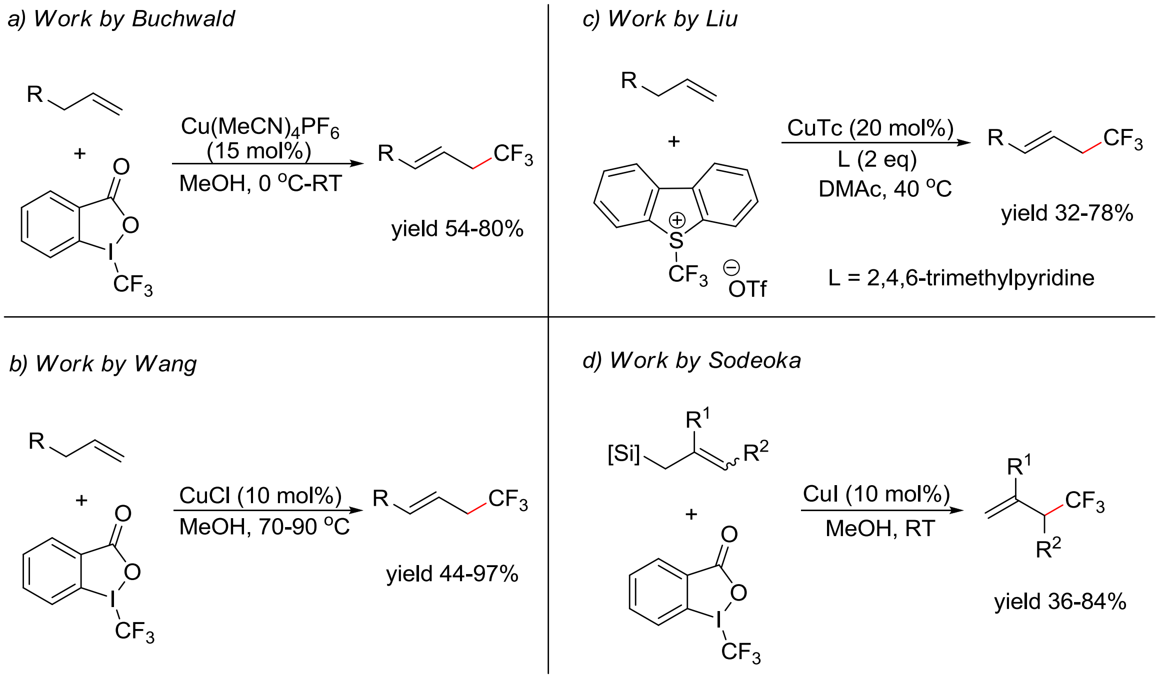
[13] Parsons, A. T.; Buchwald, S. L. *Angew, Chem. Int. Ed*. **2011**, *50*, 9120.

[14] Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410.

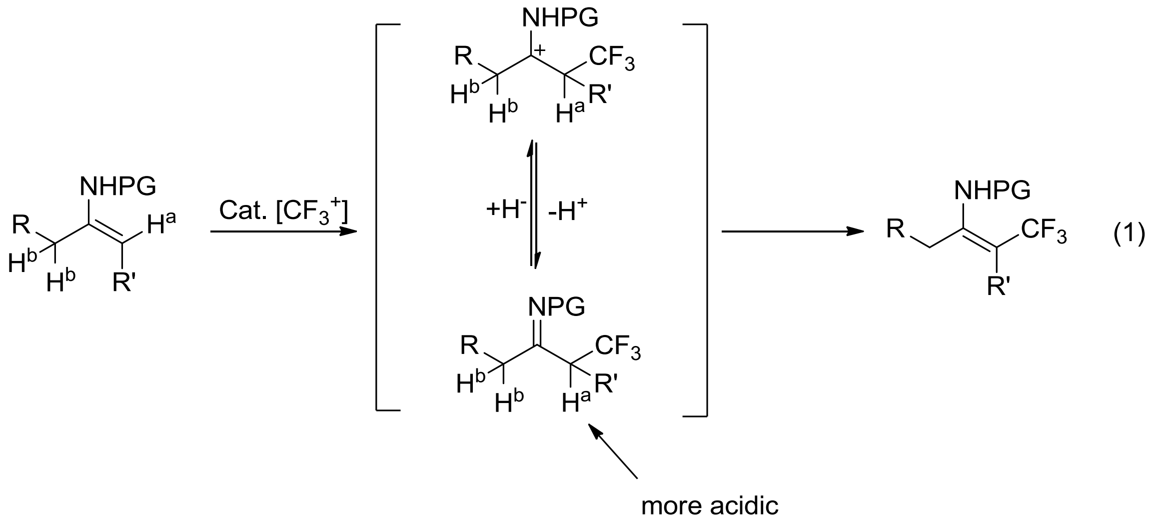
[15] Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300.

[16] Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4577.



Scheme 4.2 Cu-catalyzed allylic trifluoromethylation

We envisaged that olefinic C-H trifluoromethylation may be achieved simply through installation of an amido group onto the olefin moiety. As illustrated in Eq. (1), the amido moiety introduced not only can stabilize the putatively formed α-carbonium, but also induce subsequent proton elimination or migration process. It is reasonable to expect the selective formation of olefinic trifluoromethylation product due to the increased acidity of proton H^a resulting from the CF_3 substituent introduced.

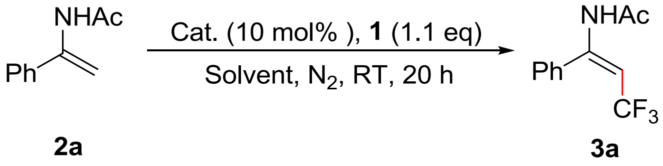


3.2 Results and discussion

With this idea in mind, *N*-(1-phenylvinyl)acetamide (**2a**) was treated with Togni's reagent **1** (1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one) and CuCl in methanol. To our surprise, what we found was the quantitative formation of *N*-(3,3,3-trifluoro-1-methoxy-1-phenylpropyl)acetamide (**4a**), which, we surmise, is due to sequestration of the *in situ* generated imine intermediate by methanol. Thus, a systematic solvent-screening was conducted in the hope of realizing the desired olefinic trifluoromethylation in high efficiency. Pleasingly, when ^{t}BuOH was used in place of MeOH as solvent, the desired reaction indeed occurred, albeit providing the desired product in low yield. While MeCN turned out to be an inappropriate choice, toluene was found to mediate the reaction in very good efficiency. However in this case, the desired product was isolated as a mixture of *E/Z* stereoisomers in the ratio of 1.6 : 1. Chlorinated solvents, which enabled the reaction to proceed with high efficiency, also exhibited low stereoselectivity. Much to our delight, when using THF as solvent the desired olefinic trifluoromethylation product was formed both in high yield and with excellent stereoselectivity. Other ethereal solvents such as 1,4-

dioxane, diethyl ether and DME were also examined and proved to be less effective than THF in terms of reaction yield. Replacement of Cu(I) catalyst by other transition metal complexes met with little success, with only trace amount of the desire product observed in the presence of $Pd(OAc)_2$, $Fe(OAc)_2$, or even $CuCl_2$. As anticipated, no reaction occurred in the absence of CuCl catalyst and Tognis' reagent **1** remained as precipitate in the mixture throughout the reaction, implying the indispensability of Cu(I) catalyst for the activation of Tognis' reagent **1**.

Table 4.1 Reaction Conditions Optimization.[a]

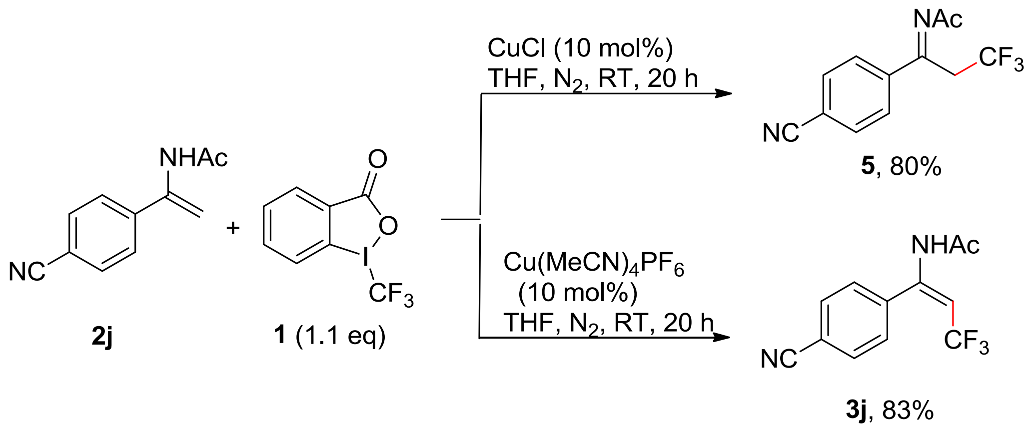


entry	catalyst	solvent	yield (%)[b]
1	CuCl	MeOH	99[c]
2	CuCl	^{t}BuOH	24
3	CuCl	MeCN	53
4	CuCl	Toluene	80[d]
5	CuCl	DCM	88[e]
6	CuCl	DCE	86[e]
7	CuCl	Dioxane	37
8	CuCl	Et_2O	48
9	CuCl	DME	43
10	CuCl	THF	81
11	$Pd(OAc)_2$	THF	trace
12	$Fe(OAc)_2$	THF	trace
13	$CuCl_2$	THF	trace

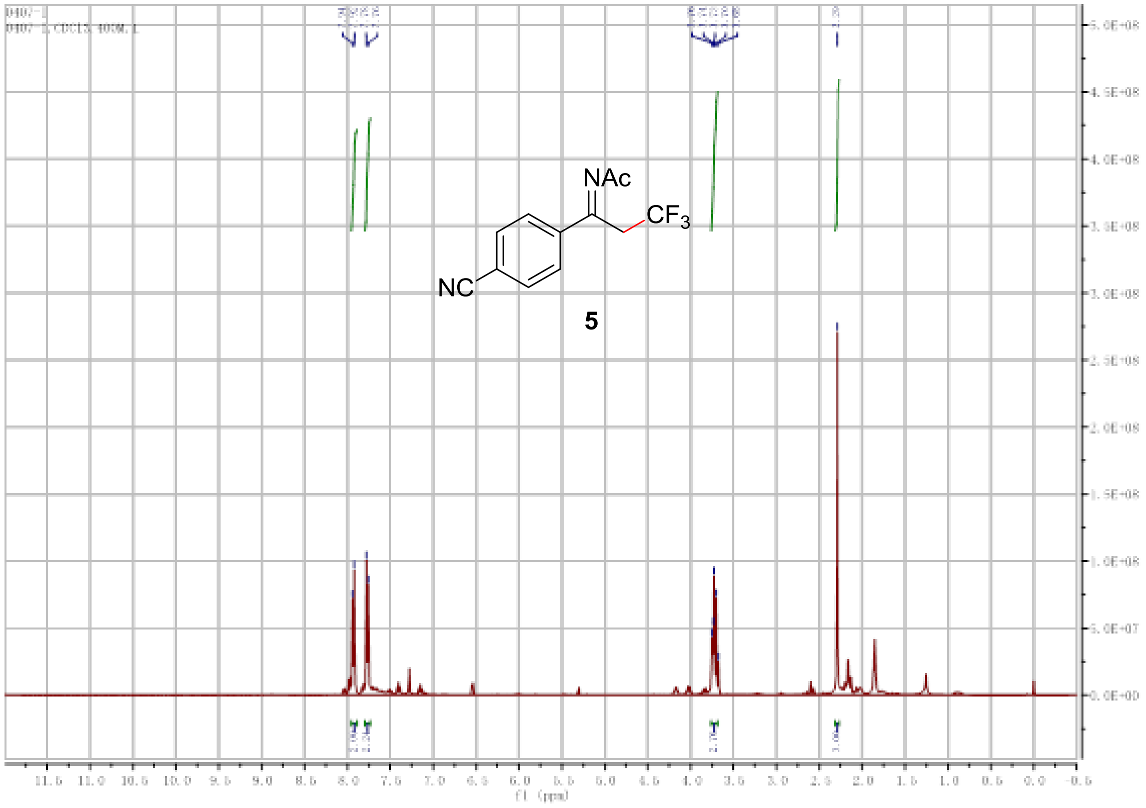
14	-	THF	NR

[a] Unless otherwise noted, the reactions were carried out at room temperature using **2a** (0.1 mmol), **1** (0.11mmol), catalyst (0.01mmol) in solvent (0.5 mL) for 20 h. [b] Isolated yields. [c] α-Trifluoromethyl aminal was formed quantitatively. [d] *E*/*Z* = 1.6:1. [e] *E*/*Z* = 2:1

With the optimized condition in hand, we were keen to explore the substrate scope of this C-H trifluoromethylation reaction. However, what stood out to be unexpected is that when *p*-cyano containing enamide **2j** was subjected to the optimal reaction condition, the formation of α-trifluoromethylated imine **5** was observed instead of the expected product **3j** [Eq. (2)]. This outcome may be rationalized by the decreased nucleophilicity of the imine nitrogen, due to the electron-withdrawing cyano substituent, thus totally impeding the hydrogen transfer process. We surmise that this dilemma may be resolved through the employment of a more Lewis acidic catalyst, which at the same time is capable of activating Tognis' reagent **1**. In line with our hypothesis, $Cu(MeCN)_4PF_6$ was found to be a competent catalyst, affording the olefinic trifluoromethylation product **3j** in 83% yield. The geometry of **3j** was determined through single-crystal X-ray diffraction analysis, revealing that the introduced CF_3 group is located *trans* to the amido functionality.

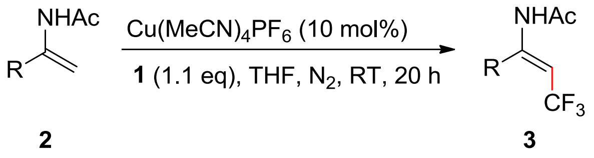


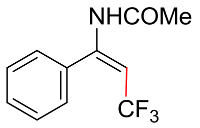
(2)



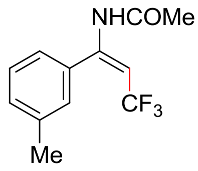
Based on the refined reaction condition, the reaction scope of olefinic trifluoromethylation was systematically investigated, exhibiting a wide spectrum of functionality tolerance. Generally, substrates possessing both electron-releasing and electron-withdrawing substituents worked nicely, affording the respective trifluoromethylation products in good to excellent yield. Functionalities such as acetyl, cyano and sulfonyl, which serve as useful reaction handles for further elaborations, were all well-tolerated under the mild reaction condition (Table 4.2, **3i**, **3j**, **3k**). In addition, the substitution pattern of the aromatic system was found to have little influence on the reaction efficiency, with *ortho*-, *meta*- and *para*-substituted substrates reacting smoothly to provide the products in high yield. It is noteworthy that aryl halides, which are widely employed in transition metal-catalyzed trifluoromethylation with CF_3^-, proved to be inert in this reaction, thus making it possible to further capitalized on these as electrophiles in traditional cross-coupling reactions (Table 4.2, **3l**, **3m**, **3n**). Heterocycle based enamide such as **2p** was also viable substrate albeit giving the desired product in low yield. Notably, this reaction is not only limited to terminal olefin derived enamides, but those derived from indanone were also effective, affording the desired products in excellent yield (Table 4.2, **3p**, **3r**). In addition, it is important to be noted that, in accordance with what we have proposed for the preferential generation of olefinic trifluoromethylation product over the allylic variant due to the differentiation of proton elimination or transfer process upon introduction of the CF_3 group, simple aliphatic enamides were also amenable to this reaction condition and inclined to generate the olefinic trifluoromethylation products in synthetically useful chemical yield (Table 4.2, **3s**).

Table 4.2 Exploration of the substrate scope of copper-catalyzed C-H olefinic trifluoromethylation.[a,b]

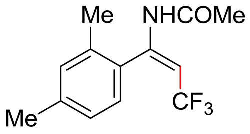




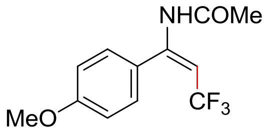
3a, 90%



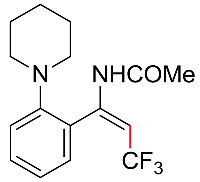
3b, 86%



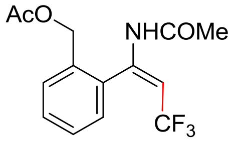
3c, 84%



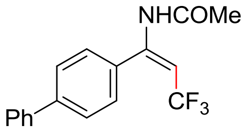
3d, 77%



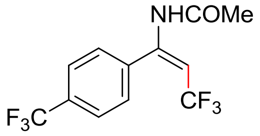
3e, 90%



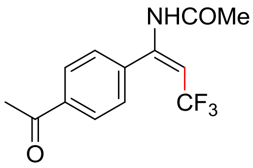
3f, 76%



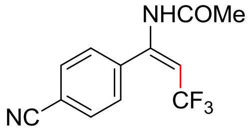
3g, 84%



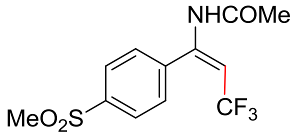
3h, 84%



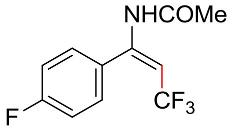
3i, 92%



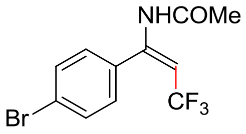
3j, 83%



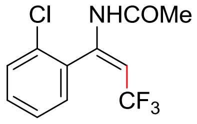
3k, 85%



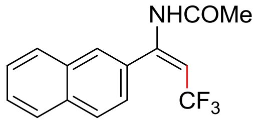
3l, 80%



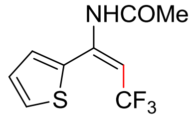
3m, 85%



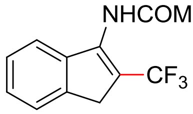
3n, 84%



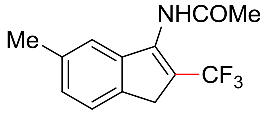
3o, 83%



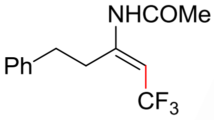
3p, 40% (53%)[c]



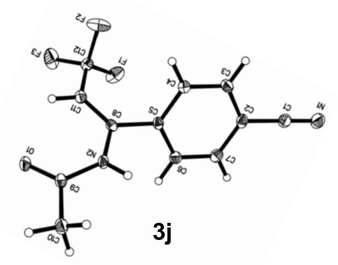
3q, 87%



3r, 86%



3s, 60%

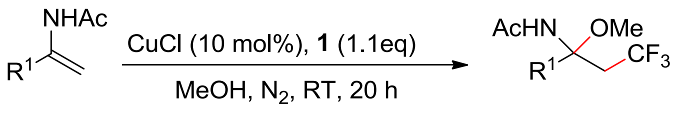


3j

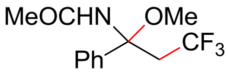
[a] Unless otherwise noted, the reactions were carried out at room temperature using Tongnis' regent **1** (0.11 mmol), **2** (0.1 mmol), Cu(MeCN)$_4$PF$_6$ (0.01 mmol) in THF(0.5 mL) for 20 h. [b] Isolated yields. [c] Cu(MeCN)$_4$PF$_6$ (20 mol%).

Considering that mixed acetal represents a class of important intermediate that can be manipulated as precursor of reactive imine, thereby allowing a diversity of ensuing synthetically usful C-C bond formation reactions, we proceed to briefly examine the reaction generality of the oxytrifluoromethylation with CuCl/MeOH system (Table 4.1, entry 1). As shown in Table 4.3, this reaction displayed good tolerance towards a wide variety of functionalities. Similar to the aforementioned olefinic trifluoromethylation, this reaction also did not exhibit any electronic bias, with substrates carrying both electron-donating and electron-withdrawing substituents affording the desired products in quantitative yield. As expected, heterocyclic and simple aliphatic enamides were transformed into the respective α-trifluoromethyl aminals without any complication. It is noteworthy that for all reactions tabulated, no column chromatographic purification was required wherein simple saturated $NaHCO_3$ washing was adopted to deliver the pure products in quantitative yield.

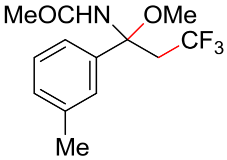
Table 4.3 Exploration of the substrate scope of copper-catalyzed oxytrifluoromethylation.[a, b]



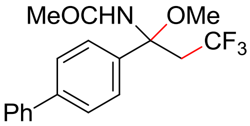
2 **4**



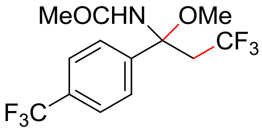
4a, 99%



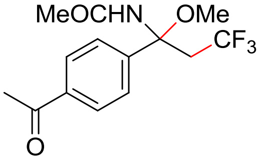
4b, 99%



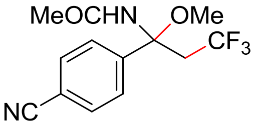
4g, 98%



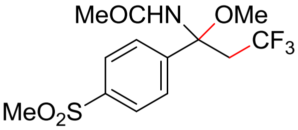
4h, 99%



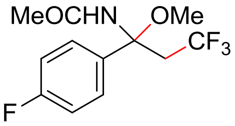
4i, 98%



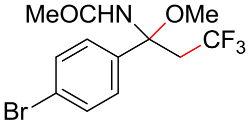
4j, 97%



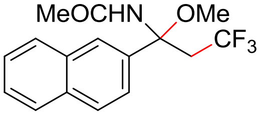
4k, 98%



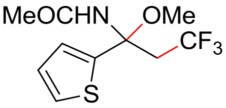
4l, 99%



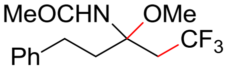
4m, 99%



4o, 98%



4p, 96%

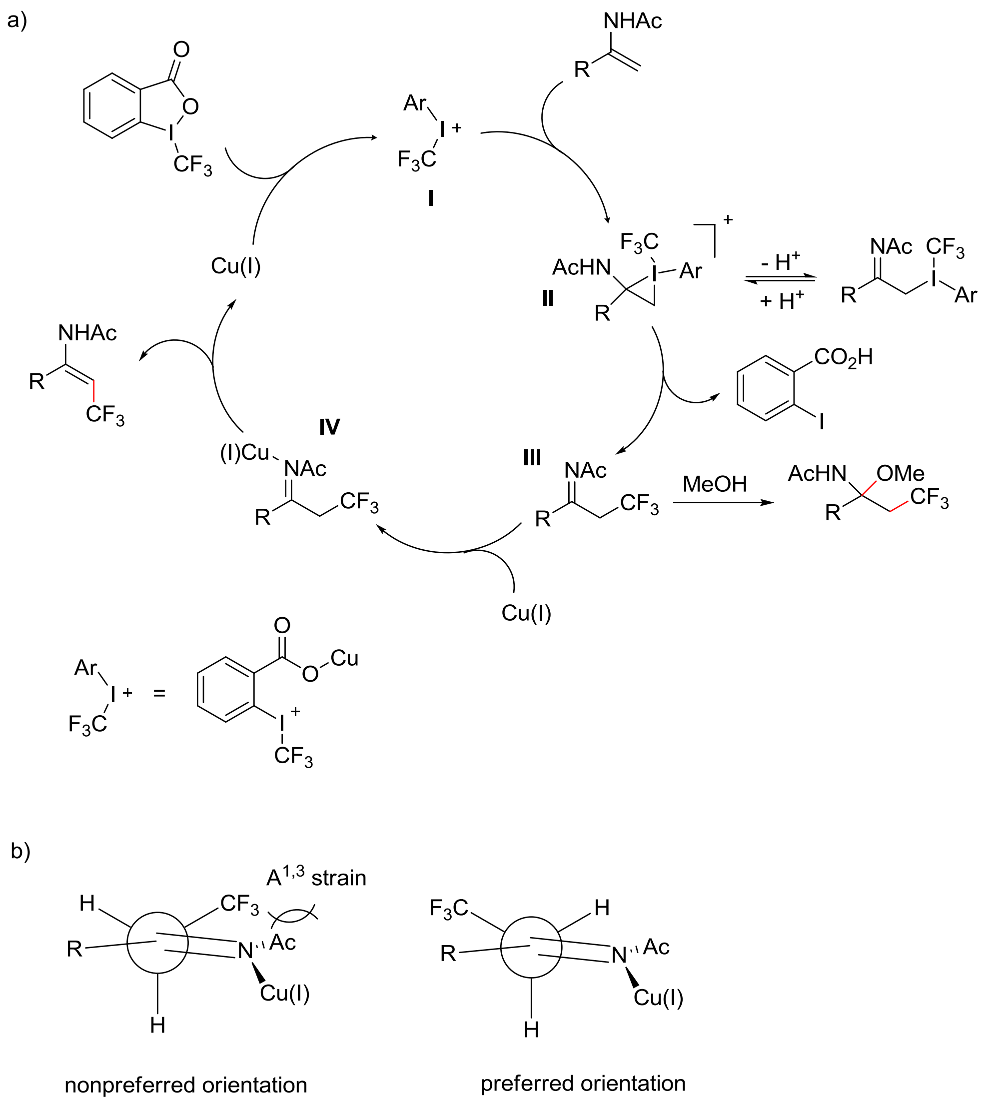


4s, 96%

[a] Unless otherwise noted, the reactions were carried out at room temperature using Tognis' regent **1** (0.11 mmol), **2** (0.1 mmol), CuCl (0.01 mmol) in MeOH (0.5 mL) for 20 h. [b] Isolated yields.

In order to gain insight into the reaction mechanism, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-*di*-*t*-butyl-*p*-cresol (BHT) were added as radical scavengers in the reaction of **2a** and Tognis' regent **1** separately. While TEMPO substantially inhibited the reaction with only trace amount of **3a** formed, BHT, however, did not show any deleterious effect on the reaction. Though, we could not firmly preclude the involvement of radical species in this reaction process at this stage, we are more inclined towards a cationic reaction mechanism.

On the basis of our experimental results and other related precedents, the reaction mechanism proposed is as depicted in Scheme 4.3. The reactive intermediate **I**, arising from the reaction between Tognis' regent **1** and Cu(I), reacts with enamide to produce the iodo(III) cyclopropane **II**, which is expected to be in equilibrium with the corresponding α-iodo(III) imine. Subsequent reductive elimination from **II** generates the α-trifluoromethyl imine intermediate **III**, which can react via two divergent routes depending on the solvent and catalyst used. At this stage, the possibility of generation of intermediate **III** through direct nucleophilic substitution reaction between enamide substrate and intermediate **I** could not be firmly excluded. Using CuCl/methanol system, the imine intermediate is sequestered by the methanol solvent to form the α-trifluoromethyl aldmine products, while with the $Cu(MeCN)_4PF_6$/THF system, intermediated **III** goes on to form complex **IV** with the nitrogen bound to the *Lewis* acidic Cu(I) catalyst, which in turn induces α-proton elimination or transfer to deliver the final olefinic trifluoromethylation product and concomitantly regenerates Cu(I) catalyst. The stereochemical outcome of this olefinic trifluoromethylation may arise from $A^{1,3}$ interaction between CF_3 and acetyl (or copper complex) group, therefore, delivering the *E*-product through the transition state, in which the CF_3 substituent is directed away from the acetyl group.



Scheme 4.3 Proposed Mechanism

4.3 Conclusion

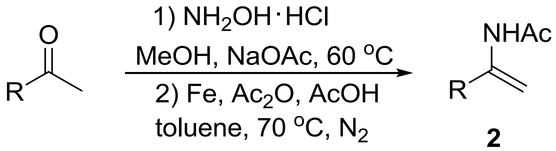
In conclusion, we have reported a novel cationic Cu(I)-catalyzed olefinic trifluoromethylation of enamide, which selectively delivers the *E*-products in high to excellent yield. In addition, the *Lewis* acidity of the copper catalyst was demonstrated to have pivotal effect on the success of this transformation. Using nitrogen containing substituent as activating group for the olefin moiety and Tognis' reagent as the cationic CF_3 source, this reaction represents the first example of transformation of vinyl C-H bond to the vinyl C-CF_3 counterpart. Compared with the documented methods for the construction of olefinic C-CF_3 bond, this reaction prove to be more environment friendly and atom economic because of its obviation of the use of vinyl halids or vinyl metallic species, which, otherwise, are traditionally employed. By using CuCl as catalyst and methanol as solvent, the reaction diverts from olefinic C-H trifluoromethylation to the oxytrifluoromethylation and delivers the α-trifluoromethyl aminals in quantitative yield in most cases.

4.4 Experiment Section

Cu(MeCN)$_4$PF$_6$, CuCl, anhydrous MeOH were purchased from commercial suppliers and used as received unless otherwise noted. All reactions were carried out using standard Schlenk technic. THF was freshly distilled under sodium/benzophenone ketyl. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible using basic solution of potassium permanganate or acidic solution of ceric molybdate as stain, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. HRMS spectra were recorded on a Waters Q–Tof Permier Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe$_4$ (δ 0.0) and relative to the signal of SiMe$_4$ (δ 0.00, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); td (triplet of doublet); m (multiplets); ddt (doublet of doublet of triplet) and etc. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet).

Rreparation of enamides

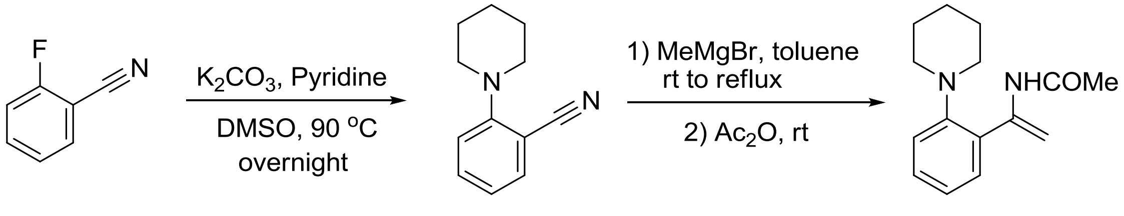
General procedure for 2a-2d, 2g-2r



Synthetic procedure: a) A mixture of ketone (10 mmol), NaOAc (12 mmol) and hydroxylamine hydrochloride (12 mmol) in methanol (5mL) was stirred for 2 h at 60 ℃. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate (2×50 mL) dried over $MgSO_4$. The organic solvent was evaporated to afford the ketoxime pure enough for next step.

b) To an oven-dried 50 mL two-neck RBF assembled with condenser was added ketoxime. The flask was vacuumed and backfilled with N_2 for three times. Anhydrous toluene (20 mL) was added followed by acetic anhydride (30 mmol), acetic acid (30 mmol) and iron powder (20 mmol). The reaction flask was put into a 70 ^{o}C preheated oil bath and allowed to stir for 5 hours under nitrogen atmosphere. After cooling to room temperature, ethyl acetate was added and the mixture was filtered through a short pad of celite. The solution thus obtained was evaporated to product crude enamide, which was directly purified by column chromatography.

Reaction scheme for 2e synthesis

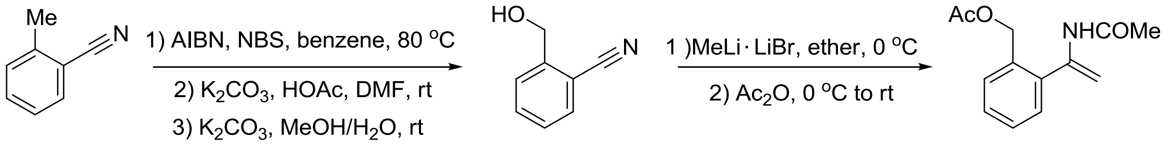


2e

Synthetic procedure: a) An 50 mL RBF was charged with 2-fluorobenzonitrile (10 mmol), K_2CO_3 (20 mmol), pyridine (12 mmol), and DMSO (5 mL) sequentially. The reaction flask was subjected to a 90 ^oC preheated oil bath and stirred overnight, at which time the resulting mixture was cooled down to room temperature, diluted with ethyl acetate, and washed thoroughly with water. Removal of the solvent in *vacuo* and purification of the residue by silica gel column chromatography afforded the desired product 2-(piperidin-1-yl)benzonitrile in 90% yield.

b) To an oven-dried 50 mL two-neck RBF assembled with condenser was added 2-(piperidin-1-yl)benzonitrile and dry toluene (15 mL). MeMgBr (12 mmol, 3M in ether) was added to the solution under N_2 at room temperature. After stirring 10 minutes, the mixture was subjected to a 110 ^oC preheated oil bath and stirred overnight. After cooling to room temperature, Ac_2O (15 mmol) was added into the solution dropwise and the resulting mixture was stirred at room temperature for 2 hours, at which time saturated $NaHCO_3$ solution was added followed by extraction with ethyl acetate (2×50 mL), and drying over $MgSO_4$. The organic solvent was evaporated and the residue was subjected to column chromatography on silica gel to deliver the product **2e** in 56% yield.

Reaction scheme for 2f synthesis



2f

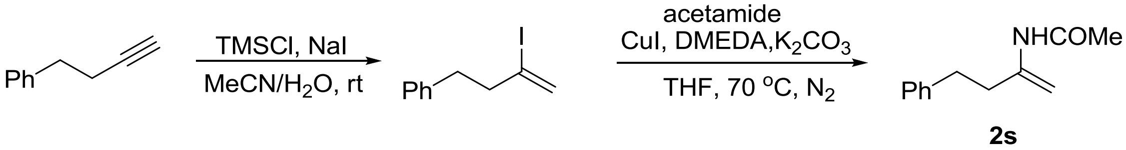
Synthetic procedure: a) The mixture of *o*-tolunitrile (20 mmol), NBS (21 mmol), and AIBN (1 mmol) in benzene (20 ml) was stirred at 80 ℃ for 1 h. After cooling to room temperature, the reaction was quenched with water and the mixture was extracted with ether followed by drying over $MgSO_4$. The organic solvent was evaporated to give the residue which is used directly in next step without purification.

b) To a suspension of AcOH (80 mmol) and K_2CO_3 (80 mmol) in DMF (90 mL) was added the crude 2-(bromomethyl)benzonitrile in DMF (10 mL) at room temperature, and the mixture was stirred at the same temperature for 1 hour. After quenching with water the mixture was extracted with ether followed by drying over $MgSO_4$. The organic solvent was evaporated to give the residue which is used directly in next step without purification.

c) To a suspension of K_2CO_3 (100 mmol) in 30 mL $MeOH/H_2O$ (2:1) was added the above obtained 2-cyanobenzyl acetate. The mixture was stirred at room temperature and the progress of reaction was monitored through TLC. Once the reaction finished, water was added and thus resulting solution was extracted with ethyl acetate. After drying over $MgSO_4$, the organic solvent was evaporated and the residue was subjected to silica gel column chromatography to afford the desired product 2-(hydroxymethyl)benzonitrile in 75% yield.

d) To an oven-dried 50 mL two-neck RBF assembled with condenser was added 2-(hydroxymethyl)benzonitrile (5 mmol) and dry ether (10 mL). MeLi·LiBr (7.5 mmol, 1M in ether) was slowly added into the solution under N_2 at 0 ^oC. After stirring for 2 hours at the same temperature, Ac_2O (15 mmol) was added and the resulting mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ solution was added followed by extraction with ethyl acetate (2 ×50 mL), and drying over $MgSO_4$. The organic solvent was evaporated and the residue was subjected to column chromatography on silica gel to deliver the product **2f** in 23% yield.

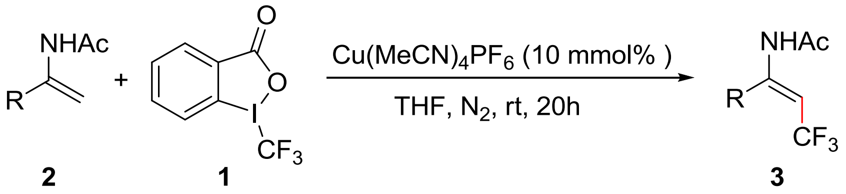
Reaction scheme for 2s synthesis



Synthetic procedure: a) At room temperature TMSCl (10 mmol) was added to a solution of NaI (10 mmol) in MeCN (10 mL) followed by H_2O (5 mmol). After stirring for 10 minutes, but-3-ynylbenzene (6 mmol) was added and the resulting solution was stirred for 1 hour at room temperature. The reaction was quenched with H_2O (20 mL) and extracted with ethyl acetate followed by drying over $MgSO_4$. The organic solvent was evaporated to give the crude (3-iodobut-3-enyl)benzene, which is used directly in next step without further purification.

b) To an oven-dried 50 mL two-neck RBF assembled with condenser was added CuI (1.5 mmol), K_2CO_3 (9 mmol), acetamide (12 mmol). The flask was vacuumed and backfilled with N_2 for three times. Anhydrous THF (5 mL) was added followed by DMEDA (3 mmol) and crude (3-iodobut-3-enyl)benzene. The reaction flask was put into a 70 ^{o}C preheated oil bath and allowed to stir overnight. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate (2 ×50 mL) followed by drying over $MgSO_4$. The organic solvent was evaporated and the residue was subjected to column chromatography on silica gel to deliver the product **2s** in 33% yield.

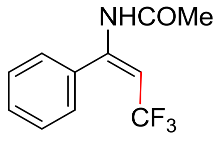
Copper-catalyzed olefinic C-H trifluoromethylation of enamides



Synthetic procedure: An oven-dried 5mL Schlenk tube was charged with Tognis' regent **1** (0.11 mmol), **2** (0.1 mmol), $Cu(MeCN)_4PF_6$ (0.01 mmol) in sequence. The Schlenk tube was vacuumed and backfilled with nitrogen for three times followed by adding anhydrous THF (0.5 mL) through syringe and then closed tightly. After stirring at room temperature for 20 hours, saturated $NaHCO_3$ solution (20 mL) was added and the resulting mixture was extracted with dichloromethane (2x20 mL). Removal of the solvent in vacuo and purification of the residue by silica gel column chromatography afforded the desired product **3**.

Characterization of Products

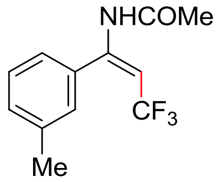
(*E*)-*N*-(3,3,3-trifluoro-1-phenylprop-1-enyl)acetamide:



3a

Yield: 90%; White solid. m.p. = 141-143 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.08 (s, 3H), 6.72 (s, 1H), 7.05 (q, $^3J_{HF}$ = 8.2 Hz, 1H), 7.34-7.38 (m, 2H), 7.40-7.47 (m, 3H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.9, 103.0 (q, *J* = 35.1 Hz), 122.9, 125.6, 128.1 (d, *J* = 1.4 Hz), 128.6, 129.8, 135.0, 143.7 (q, *J* = 5.7 Hz), 169.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.22 (d, $^3J_{HF}$ = 8.2 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{11}H_{11}NOF_3$ [M+H]$^+$ 230.0793, found: 230.0782.

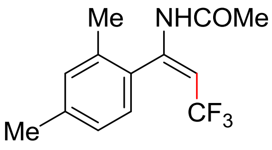
(*E*)-*N*-(3,3,3-trifluoro-1-m-tolylprop-1-enyl)acetamide:



3b

Yield: 86%; White solid. m.p. = 137-139 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.08 (s, 3H), 2.39 (s, 3H), 6.68 (s, 1H), 7.04 (q, $^3J_{HF}$ = 8.3 Hz, 1H), 7.16 (s, 2H), 7.24-7.32 (m, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 21.3, 24.9, 102.7 (q, *J* = 34.8 Hz), 122.9, 125.2 (d, *J* = 1.4 Hz), 125.6, 128.5, 128.6 (d, *J* = 1.3 Hz), 130.5, 134.9, 138.5, 143.9 (q, *J* = 6.0 Hz), 168.9 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.24 (d, $^3J_{HF}$ = 8.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{13}NOF_3$ [M+H]$^+$ 244.0949, found: 244.0959.

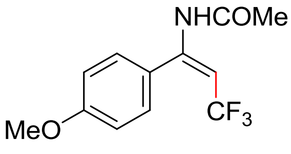
(*E*)-*N*-(1-(2,4-dimethylphenyl)-3,3,3-trifluoroprop-1-enyl)acetamide:



3c

Yield: 84%; White solid. m.p. = 144-146 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.06 (s, 3H), 2.27 (s, 3H), 2.34 (s, 3H), 6.56 (s, 1H), 7.02-7.13 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 18.8, 21.2, 24.8, 103.5 (q, *J* = 34.71 Hz), 122.9, 125.6, 126.5, 128.9 (d, *J* = 1.3 Hz), 131.1, 131.4, 135.6, 139.6, 143.3 (q, *J* = 5.9 Hz), 169.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -41.15 (d, $^3J_{HF}$ = 10.9 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{14}NOF_3Na$ [M+Na]$^+$ 280.0925, found: 280.0924.

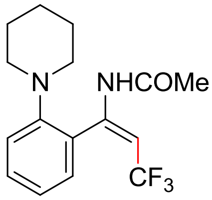
(*E*)-*N*-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-enyl)acetamide:



3d

Yield: 77%; White solid. m.p. = 142-144 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.09 (s, 3H), 3.83 (s, 3H), 6.69 (s, 1H), 6.89-7.00 (m, 3H), 7.27-7.30 (m, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.9, 55.3, 102.9 (q, *J* = 34.9 Hz), 114.0, 123.0, 125.7, 127.2, 129.5 (d, *J* = 1.5 Hz), 143.5 (q, *J* = 6.3 Hz), 160.6, 169.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.15 (d, $^3J_{HF}$ = 8.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{13}NO_2F_3$ [M+H]$^+$ 260.0898, found: 260.0890.

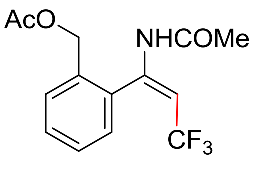
(*E*)-*N*-(3,3,3-trifluoro-1-(2-(piperidin-1-yl)phenyl)prop-1-enyl)acetamide:



3e

Yield: 90%; White solid. m.p. = 131-133 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 1.58-1.60 (m, 2H), 1.64-1.69 (m, 4H), 2.10 (s, 3H), 2.99-3.01 (m, 4H), 7.01-7.14 (m, 3H), 7.35-7.39 (m, 2H), 8.00 (s, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.0, 24.9, 26.8, 52.6, 102.9 (q, *J* = 35.0 Hz), 118.8, 119.2, 122.3, 123.1, 125.8, 127.5, 130.8, 132.1 (q, *J* = 3.1 Hz), 144.7 (q, *J* = 6.4 Hz), 150.2, 169.1 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.12 (d, $^3J_{HF}$ = 9.4 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{16}H_{20}N_2OF_3$ [M+H]$^+$ 313.1528, found: 313.1527.

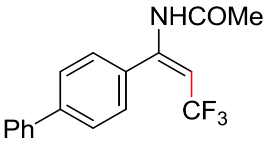
(*E*)-2-(1-acetamido-3,3,3-trifluoroprop-1-enyl)benzyl acetate:



3f

Yield: 76%; White solid. m.p. = 107-109 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.08 (s, 3H), 2.11 (s, 3H), 4.96 (d, *J* = 13.0 Hz, 1H), 5.17 (d, *J* = 13.0 Hz, 1H), 7.19 (q, $^{3}J_{HF}$ = 8.2 Hz, 1H), 7.27-7.29 (m, 1H), 7.34-7.38 (m, 1H)7.41-7.45 (m, 2H), 7.56 (s, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 21.0, 24.8, 63.9, 104.3 (q, *J* = 34.8 Hz), 122.8, 125.5, 128.3 (d, *J* = 4.4 Hz), 129.7 (d, *J* = 1.7 Hz), 130.0, 133.2, 134.1, 142.4 (q, *J* = 5.9 Hz), 169.4, 171.3 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -55.24 (d, $^{3}J_{HF}$ = 8.10 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{14}H_{15}NO_3F_3$ [M+H]$^+$ 302.1004, found: 302.1003.

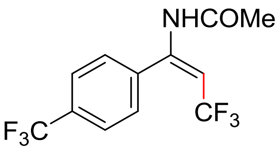
(*E*)-*N*-(1-(biphenyl-4-yl)-3,3,3-trifluoroprop-1-enyl)acetamide:



3g

Yield: 84%; White solid. m.p. = 164-166 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.10 (s, 3H), 6.75 (s, 1H), 7.08 (q, $^{3}J_{HF}$ = 8.3 Hz, 1H), 7.37-7.48 (m, 5H), 7.58-7.65 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.9, 103.1 (q, *J* = 35.0 Hz), 122.9, 125.6, 127.1, 127.3, 127.9, 128.6 (d, *J* = 1.7 Hz), 128.9, 133.8, 139.9, 142.7, 143.5 (q, *J* = 6.0 Hz), 169.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.11 (d, $^{3}J_{HF}$ = 8.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{17}H_{14}NOF_3Na$ [M+Na]$^+$ 328.0925, found: 328.0912.

(*E*)-*N*-(3,3,3-trifluoro-1-(4-(trifluoromethyl)phenyl)prop-1-enyl)acetamide:

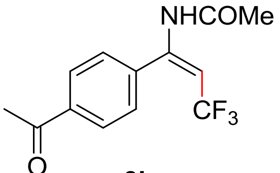


3h

Yield: 84%; White solid. m.p. = 98-100 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.08 (s, 3H), 6.77 (s, 1H), 7.08 (q, $^{3}J_{HF}$ = 8.3 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), ppm; **^{13}C**

NMR (100 MHz, CDCl$_3$): δ 24.8, 103.9 (q, *J* = 35.2 Hz), 122.3, 122.6, 125.0, 125.3, 125.7 (q, *J* = 3.9 Hz), 127.7, 127.9, 128.8 (d, *J* = 1.5 Hz), 132.0 (q, *J* = 32.7 Hz), 138.3, 142.3 (q, *J* = 5.9 Hz), 169.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.34 (d, $^3J_{HF}$ = 8.3 Hz, 3F); -63.93 (s, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{10}NOF_6$ [M+H]$^+$ 298.0667, found: 298.0658.

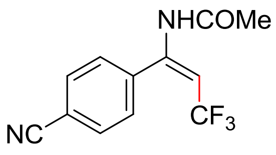
(*E*)-*N*-(1-(4-acetylphenyl)-3,3,3-trifluoroprop-1-enyl)acetamide:



3i

Yield: 92%; White solid. m.p. = 126-128 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.15 (s, 3H), 2.56 (s, 3H), 7.09 (q, $^3J_{HF}$ = 8.3 Hz, 1H), (s, 1H), 7.26 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 2H), ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.8, 26.6, 103.5 (q, *J* = 34.9 Hz), 122.7, 125.4, 128.4, 128.6, 137.5, 139.3, 142.8 (q, *J* = 6.1 Hz), 169.3, 197.7 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.18 (d, $^3J_{HF}$ = 8.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{12}NO_2F_3Na$ [M+Na]$^+$ 294.0718, found: 294.0724.

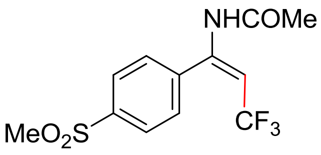
(*E*)-*N*-(1-(4-cyanophenyl)-3,3,3-trifluoroprop-1-enyl)acetamide:



3j

Yield: 83%; White solid. m.p. = 159-161 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.11 (s, 3H), 7.02 (s, 1H), 7.09 (q, $^3J_{HF}$ = 8.3 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.7, 104.0 (q, *J* = 35.1 Hz), 113.4, 118.0, 122.5, 125.2, 129.4 (d, *J* = 1.4 Hz), 132.3, 139.2, 141.9 (q, *J* = 6.2 Hz), 169.2 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.26 (d, $^3J_{HF}$ = 8.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{10}N_2OF_3$ [M+H]$^+$ 255.0745, found: 255.0747.

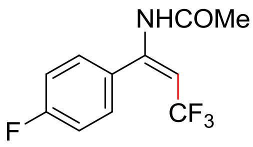
(*E*)-*N*-(3,3,3-trifluoro-1-(4-(methylsulfonyl)phenyl)prop-1-enyl)acetamide:



3k

Yield: 85%; Light yellow solid. m.p. = 163-165 ℃; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.15 (s, 3H), 3.01 (s, 3H), 7.14 (q, $^{3}J_{HF}$ = 8.3 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.62 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 24.7, 44.6, 103.7 (q, *J* = 34.9 Hz), 122.7, 125.4, 127.2, 129.8 (d, *J* = 1.3 Hz), 140.2, 140.6, 142.2 (q, *J* = 5.9 Hz), 169.6 ppm; **^{19}F NMR (282 MHz, $CDCl_3$):** δ -53.92 (d, $^{3}J_{HF}$ = 8.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{13}NO_3F_3S$ $[M+H]^+$ 308.0568, found: 308.0575.

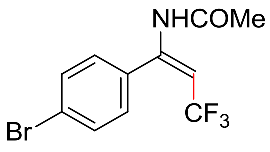
(*E*)-*N*-(3,3,3-trifluoro-1-(4-fluorophenyl)prop-1-enyl)acetamide:



3l

Yield: 80%; White solid. m.p. = 175-177 ℃; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.10 (s, 3H), 6.66 (s, 1H), 7.04 (q, $^{3}J_{HF}$ = 8.3 Hz, 1H), 7.08-7.14 (m, 2H), 7.33-7.36 (m, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 24.9, 103.5 (q, *J* = 34.8 Hz), 115.8 (d, *J* = 21.8 Hz), 122.8, 125.5, 130.3 (dd, J_1 = 8.6 Hz, J_2 = 1.4 Hz), 130.9 (d, *J* = 3.7 Hz), 142.7 (q, *J* = 6.1 Hz), 162.4 (d, *J* = 250.6 Hz), 168.9 ppm; **^{19}F NMR (282 MHz, $CDCl_3$):** δ -54.29 (d, $^{3}J_{HF}$ = 8.3 Hz, 3F), -111.38 (s, 1F) ppm; **HRMS (ESI, m/z):** calcd for $C_{11}H_{10}NOF_4$ $[M+H]^+$ 248.0699, found: 248.0709.

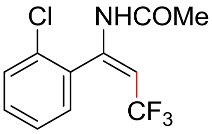
(*E*)-*N*-(1-(4-bromophenyl)-3,3,3-trifluoroprop-1-enyl)acetamide:



3m

Yield: 85%; White solid. m.p. = 143-145 ℃; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.09 (s, 3H), 6.69 (s, 1H), 7.04 (q, $^{3}J_{HF}$ = 8.3 Hz, 1H), 7.22-7.25 (m, 2H), 7.55-7.58 (m, 2H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 24.8, 103.6 (q, *J* = 35.0 Hz), 122.7, 124.2, 125.4, 129.8 (d, *J* = 1.4 Hz), 131.9, 133.7, 142.6 (q, *J* = 6.3 Hz), 168.9 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.24 (d, $^3J_{HF}$ = 8.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{11}H_{10}NOF_3Br$ [M+H]$^+$ 307.9898, found: 307.9897.

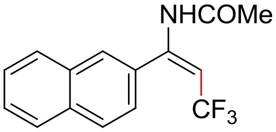
(*E*)-*N*-(1-(2-chlorophenyl)-3,3,3-trifluoroprop-1-enyl)acetamide:



3n

Yield: 84%; White solid. m.p. = 155-157 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.10 (s, 3H), 6.67 (s, 1H), 7.13 (q, $^3J_{HF}$ = 8.2 Hz, 1H), 7.30-7.35 (m, 2H), 7.37-7.41 (m, 1H), 7.46 (d, *J* = 7.9 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.8, 104.5 (q, *J* = 34.9 Hz), 122.6, 125.2, 126.9, 129.9, 130.9 (d, *J* = 1.5 Hz), 131.1, 132.7, 133.3, 140.8 (q, *J* = 6.0 Hz), 169.1 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -56.17 (d, $^3J_{HF}$ = 8.2 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{11}H_{10}NOF_3Cl$ [M+H]$^+$ 264.0403, found: 264.0395.

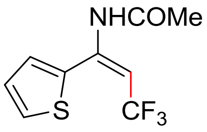
(*E*)-*N*-(3,3,3-trifluoro-1-(naphthalen-2-yl)prop-1-enyl)acetamide:



3o

Yield: 83%; White solid. m.p. = 153-155 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.07 (s, 3H), 6.79 (s, 1H), 7.12 (q, $^3J_{HF}$ = 8.3 Hz, 1H), 7.41 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.53-7.59 (m, 2H), 7.84-7.90 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.9, 103.3 (q, *J* = 34.7 Hz), 122.9, 125.2 (d, *J* = 1.3 Hz), 125.6, 126.9, 127.3, 127.8, 127.9 (d, *J* = 1.5 Hz), 128.3, 128.5, 132.2, 132.7, 133.5, 143.7 (q, *J* = 5.9 Hz), 169.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.16 (d, $^3J_{HF}$ = 8.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{15}H_{13}NOF_3$ [M+H]$^+$ 280.0949, found: 280.0946.

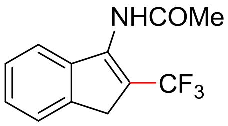
(*E*)-*N*-(3,3,3-trifluoro-1-(thiophen-2-yl)prop-1-enyl)acetamide:



3p

Yield: 40%; Light yellow solid. m.p. = 134-136 °C; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.12 (s, 3H), 6.79 (s, 1H), 7.05-7.07 (m, 2H), 7.25 (d, *J* = 3.5 Hz, 1H), 7.45 (d, *J* = 5.0 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** 24.9, 105.3 (q, *J* = 35.3 Hz), 122.6, 125.3, 127.3, 127.9, 129.8 (d, *J* = 2.1 Hz), 134.4, 136.9 (q, *J* = 6.5 Hz), 168.7 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.69 (d, $^3J_{HF}$ = 8.2 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_9H_9NOF_3S$ [M+H]$^+$ 236.0357, found: 236.0357.

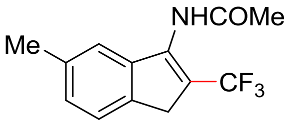
***N*-(2-(trifluoromethyl)-1H-inden-3-yl)acetamide:**



3q

Yield: 87%; White solid. m.p. = 173-175 °C; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.20 (s, 3H), 3.54 (s, 2H), 7.30-7.34 (m, 2H), 7.40-7.45 (m, 2H), 7.50 (s, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 23.4, 35.4, 121.9, 122.8, 124.0, 124.6, 126.7, 127.7, 139.2, 140.3 (q, *J* = 4.4 Hz), 140.9, 168.9 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -59.69 (s, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{11}NOF_3$ [M+H]$^+$ 242.0793, found: 242.0795.

***N*-(5-methyl-2-(trifluoromethyl)-1H-inden-3-yl)acetamide:**

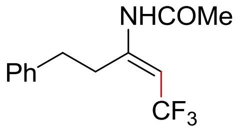


3r

Yield: 86%; White solid. m.p. = 191-193 °C; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.22 (s, 3H), 2.38 (s, 3H), 3.51 (s, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.23 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.40 (s,1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 21.5, 23.5, 35.0, 121.9, 123.2, 123.7, 124.6, 128.7, 136.5, 138.1, 139.4, 140.2 (q, *J* = 4.3 Hz), 168.8 ppm; **^{19}F NMR (282 MHz,**

CDCl$_3$): δ -59.64 (s, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{13}NOF_3$ $[M+H]^+$ 256.0949, found: 256.0950.

(*E*)-*N*-(1,1,1-trifluoro-5-phenylpent-2-en-3-yl)acetamide:

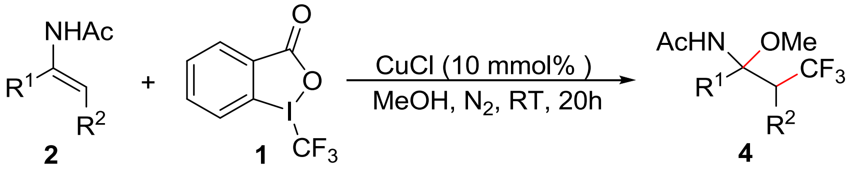


3s

Yield: 60%; White solid. m.p. = 77-79 ℃; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 1.8 (s, 3H), 2.60(t, *J* = 7.4 Hz, 2H), 2.88 (t, *J* = 7.4 Hz, 2H), 6.21 (s, 1H), 6.76 (q, $^3J_{HF}$ = 8.8 Hz, 1H), 7.2-7.29 (m, 3H), 7.32-7.36 (m, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.6, 33.9, 34.9, 102.3 (q, *J* = 35.1 Hz), 123.7, 126.4, 126.8, 128.4, 128.9, 140.1, 144.7 (q, *J* = 5.9 Hz), 168.9 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -54.84 (d, $^3J_{HF}$ = 8.7 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{15}NOF_3$ $[M+H]^+$ 258.1106, found: 258.1107.

Copper-catalyzed oxytrifluoromethylation of enamides

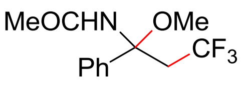
General reaction scheme



Synthetic procedure: An oven-dried 5mL Schlenk tube was charged with Tognis' regent **1** (0.11 mmol), **2** (0.1 mmol), CuCl (0.01 mmol) in sequence. The Schlenk tube was vacuumed and backfilled with nitrogen for three times followed by adding anhydrous MeOH (0.5 mL) through syringe and then closed tightly. After stirring at room temperature for 20 hours, saturated $NaHCO_3$ solution (20 mL) was added and the resulting mixture was extracted with dichloromethane (2x20 mL). Removal of the solvent in vacuo afforded the desired product **4**, which is pure enough for NMR characterization.

Characterization of products

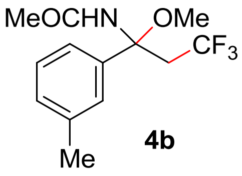
N-(3,3,3-trifluoro-1-methoxy-1-phenylpropyl)acetamide:



4a

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.50 (s, 3H), 3.10 (s, 3H), 3.28-3.37 (m, 1H), 3.42-3.51 (m, 1H), 6.32 (s, 1H), 7.35-7.44 (m, 5H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.0, 40.4 (q, *J* = 26.8 Hz), 49.9, 86.5 (d, *J* = 2.8 Hz), 123.5, 125.9, 126.3, 128.6, 128.8, 138.9, 170.2 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -62.98 (t, $^3J_{HF}$ = 10.2 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{14}NO_2F_3Na$ $[M+Na]^+$ 284.0874, found: 284.0878.

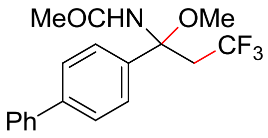
N-(3,3,3-trifluoro-1-methoxy-1-m-tolylpropyl)acetamide:



4b

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (s, 3H), 2.39 (s, 3H), 3.10 (s, 3H), 3.29-3.37 (m, 1H), 3.43-3.56 (m, 1H), 6.15 (s, 1H), 7.17-7.32 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 21.6, 24.2, 40.4 (q, *J* = 26.8 Hz), 49.9, 86.5 (d, *J* = 3.3 Hz), 123.0, 123.5, 126.3, 126.4, 128.5, 129.6, 138.4, 138.9, 170.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.78 (t, $^3J_{HF}$ = 10.5 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{16}NO_2F_3Na$ $[M+Na]^+$ 298.1031, found: 298.1035.

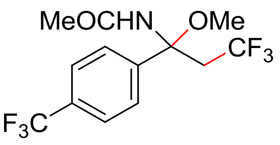
N-(1-(biphenyl-4-yl)-3,3,3-trifluoro-1-methoxypropyl)acetamide:



4g

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (s, 3H), 3.14 (s, 3H), 3.32-3.56 (m, 2H), 6.23 (s, 1H), 7.34-7.38 (m, 1H), 7.43-7.50 (m, 4H), 7.58-7.64 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.1, 40.2 (q, J = 26.7 Hz), 50.0, 86.5, 123.6, 126.3, 126.4, 127.1, 127.3, 127.7, 128.8, 137.9, 140.1, 141.6, 170.1 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.62 (t, $^3J_{HF}$ = 10.5 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{18}H_{18}NO_2F_3Na$ [M+Na]$^+$ 360.1187, found: 360.1185.

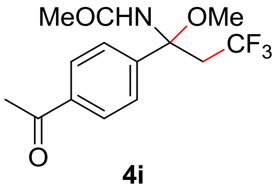
***N*-(3,3,3-trifluoro-1-methoxy-1-(4(trifluoromethyl)phenyl)propyl)acetamide:**



4h

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.06 (s, 3H), 3.14 (s, 3H), 3.32-3.43 (m, 2H), 6.23 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.0, 39.8 (q, J = 26.9 Hz), 50.3, 86.3 (d, J = 2.8 Hz), 122.4, 123.3, 125.1, 125.6 (q, J = 3.6 Hz), 126.1, 126.6, 131.0 (q, J = 32.6 Hz), 143.2, 170.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.61 (t, $^3J_{HF}$ = 10.4 Hz, 3F), -63.76 (s, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{13}NO_2F_6Na$ [M+Na]$^+$ 352.0748, found: 352.0757.

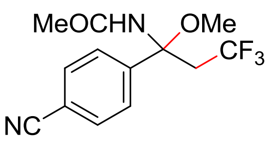
***N*-(1-(4-acetylphenyl)-3,3,3-trifluoro-1-methoxypropyl)acetamide:**



4i

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (s, 3H), 2.61 (s, 3H), 3.15 (s, 3H), 3.38 (q, J = 10.4 Hz, 2H), 6.34 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.0, 26.6, 39.9 (q, J = 27.0 Hz), 50.2, 86.3 (d, J = 2.8 Hz), 123.4, 126.1, 126.4, 128.6, 137.2, 144.2, 170.0, 197.5 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.60 (t, $^3J_{HF}$ = 10.4 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{14}H_{16}NO_3F_3Na$ [M+Na]$^+$ 326.0980, found: 326.0986.

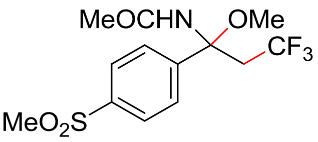
N-(1-(4-cyanophenyl)-3,3,3-trifluoro-1-methoxypropyl)acetamide:



4j

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.08 (s, 3H), 3.18 (s, 3H), 3.23-3.39 (m, 2H), 6.21 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.0, 39.7 (q, *J* = 27.1 Hz), 50.5, 86.1 (d, *J* = 3.1 Hz), 112.7, 118.2, 127.0, 132.4, 144.6, 169.9 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.51 (t, $^3J_{HF}$ = 10.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{13}N_2O_2F_3Na$ [M+Na]$^+$ 309.0827, found: 309.0829.

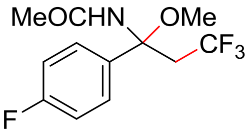
N-(3,3,3-trifluoro-1-methoxy-1-(4(methylsulfonyl)phenyl)propyl)acetamide:



4k

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.09 (s, 3H), 3.06 (s, 3H), 3.17 (s, 3H), 3.27-3.43 (m, 2H), 6.51 (s, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.0, 40.1 (q, *J* = 27.1 Hz), 44.4, 50.4, 86.1 (d, *J* = 2.7 Hz), 123.2, 126.0, 127.4, 127.5, 140.5, 145.7, 170.3 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.45 (t, $^3J_{HF}$ = 10.3 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{13}H_{16}NO_4F_3SNa$ [M+Na]$^+$ 362.0650, found: 362.0655.

N-(3,3,3-trifluoro-1-(4-fluorophenyl)-1-methoxypropyl)acetamide:

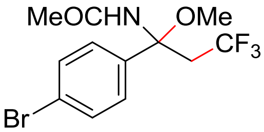


4l

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.07 (s, 3H), 3.11 (s, 3H), 3.31-3.44 (m, 2H), 6.15 (s, 1H), 7.07-7.11 (m, 2H), 7.40-7.44 (m, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.1, 40.1 (q, *J* = 27.0 Hz), 50.0, 86.3 (d, *J* = 2.9 Hz), 115.5, 115.7, 123.5, 126.2, 128.0, 128.0, 135.0, 162.8 (d, *J* = 248.1 Hz), 170.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.75 (t, $^3J_{HF}$ = 10.5 Hz, 3F), 113.89-

113.94 (m, 1F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{13}NO_2F_4Na$ $[M+Na]^+$ 302.0780, found: 302.0779.

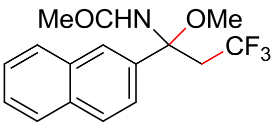
***N*-(1-(4-bromophenyl)-3,3,3-trifluoro-1-methoxypropyl)acetamide:**



4m

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.06 (s, 3H), 3.11 (s, 3H), 3.29-3.43 (m, 2H), 6.17 (s, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.1, 39.8 (q, *J* = 26.9 Hz), 50.1, 86.3 (d, *J* = 2.1 Hz), 123.1, 123.4, 126.2, 127.8, 131.8, 138.3, 170.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.66 (t, $^3J_{HF}$ = 10.5 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{12}H_{13}NO_2F_3NaBr$ $[M+Na]^+$ 361.9979, found: 361.9986.

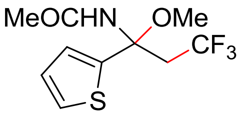
***N*-(3,3,3-trifluoro-1-methoxy-1-(naphthalen-2-yl)propyl)acetamide:**



4o

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.10 (s, 3H), 3.13 (s, 3H), 3.40-3.64 (m, 2H), 6.31 (s, 1H), 7.50-7.54 (m, 3H), 7.84-7.89 (m, 4H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.2, 39.9 (q, *J* = 27.0 Hz), 50.1, 86.7 (d, *J* = 2.7 Hz), 123.2, 125.5, 126.6, 126.9, 127.6, 128.4, 128.8, 132.8, 133.2, 136.4, 170.0 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -61.69 (t, $^3J_{HF}$ = 10.6 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{16}H_{16}NO_2F_3Na$ $[M+Na]^+$ 334.1031, found: 334.1045.

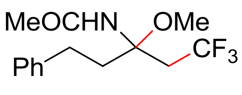
***N*-(3,3,3-trifluoro-1-methoxy-1-(thiophen-2-yl)propyl)acetamide:**



4p

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.06 (s, 3H), 3.15 (s, 3H), 3.39-3.55 (m, 2H), 6.23 (s, 1H), 6.98-7.00 (m, 1H), 7.07 (d, *J* = 3.3 Hz, 1H), 7.35 (d, *J* = 5.1 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.0, 39.7 (q, *J* = 26.9 Hz), 50.1, 85.1 (d, *J* = 3.1 Hz), 123.4, 126.0, 126.1, 126.6, 126.8, 128.9, 143.9, 169.8 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -62.36 (t, $^3J_{HF}$ = 10.4 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{10}H_{12}NO_2F_3NaS$ [M+Na]$^+$ 290.0439, found: 290.0439.

_N_-(1,1,1-trifluoro-3-methoxy-5-phenylpentan-3-yl)acetamide:



4s

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.95 (s, 3H), 2.02-2.11 (m, 1H), 2.28-2.36 (m, 1H), 2.63 (t, *J* = 8.4 Hz, 2H), 2.88-3.00 (m, 1H), 3.12-3.21 (m, 1H), 3.28 (s, 3H), 5.60 (s, 1H), 7.17-7.22 (m, 3H), 7.27-7.31 (m, 3H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 24.0, 28.7, 35.8, 35.9 (q, *J* = 26.7 Hz), 48.8, 85.9 (d, *J* = 2.4 Hz), 123.8, 126.2, 126.5, 128.3, 128.6, 140.8, 169.7 ppm; **^{19}F NMR (282 MHz, CDCl$_3$):** δ -62.38 (t, $^3J_{HF}$ = 11.0 Hz, 3F) ppm; **HRMS (ESI, m/z):** calcd for $C_{14}H_{18}NO_2F_3Na$ [M+Na]$^+$ 312.1187, found: 312.1187.

Palladium-Catalyzed C-H Olefination of Benzylamine Derivatives

5.1 Introduction

The Mizoroki-Heck reaction is one of the most important and widely used synthetic methods for olefination.[1] However, the unavoidable employment of organic halide coupling partner, which would ultimately create undesired halide waste, to some extent, rendered this versatile synthetic transformation not very environment-friendly and atom-economical. Palladium-catalyzed direct olefination of aromatic compounds, also known as the Fujiwara-Moritani reaction, partially solved this dilemma, however, the Friedel-Crafts nature of the reaction made it difficult to control the regioselectivity.[2] Since then much effort has been directed to specifically install olefin groups using directing group assisted C-H bond activation. In this aspect, significant progress has been made in developing a series of directing groups for C-H bond olefination, such as hydroxyl,[3] acetamide,[4]

---

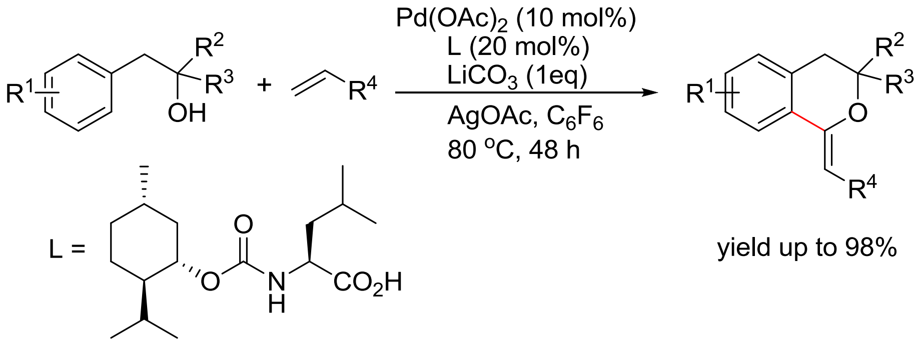
[1] (a) Beletskaya, I.; Cheprakov, P. A. V. *Chem. Rev.* **2000**, *100,* 3009. (b) Dounay, A. B.; Overman, L. E.; *Chem. Rev.* **2003**, *103*, 2945. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. (e) Ruan, J.; Li, X.; Saidi, O.; Xiao, J. *J. Am. Chem.* Soc. **2008**, *130*, 2424. (f) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett*. **2002**, *4*, 2079.

[2] (a) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (b) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, *9*, 633. (c) Moritani, S.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. (d) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. Science **2000**, *287*, 1992. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (f) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221.

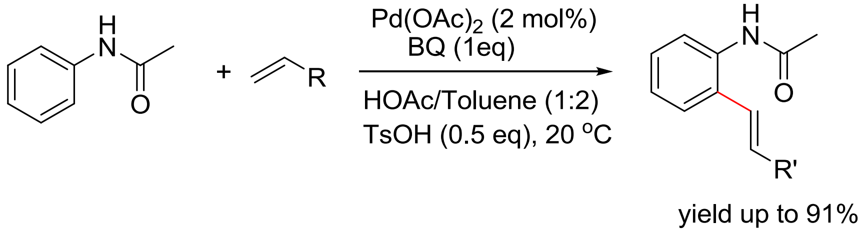
[3] Lu, Y.; Wang, D. H.; Engle, K. M.; Yu, J. Q. *J. Am. Chem.* Soc. **2010**, *132*, 5916.

[4] (a) Horino, H.; Inoue, N.; *J. Org. Chem.* **1981**, *46*, 4416. (b) Boele, M. D. K.; Strijdonck, G. P. F.; Vries, A. H. M.; Kamer, P. C. J.; Vries, J. G.; Leeuwen, P. W. N. M. *J. Am. Chem.* Soc. **2002**, *124*, 1586. (c) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem.* Soc. **2005**, *127*, 4156. (d) Wang, J. R.; Yang, C. T.; Lei, L.; Guo, Q. X. *Tetrahedron Lett.* **2007**, 4*8*, 5449. (e) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972. (f) Lyons, T. W.; M. Sanford, S. *Chem. Rev*. **2010**, *110*, 1147.

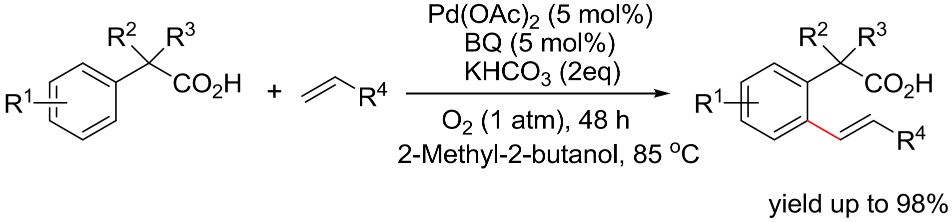
a) Hydroxyl as directing group



b) Actamido as directing group



c) Acid as directing group



Scheme 5.1 Selected example of monodentate directing group assisted C-H olefination

N-oxide,[5] trifamide,[6] urea,[7] pyridyl,[8] oxime,[9] and ketone.[10] Additionally, Yu's group has made breakthrough in developing C-H olefination of phenylacetic acid and 3-

---

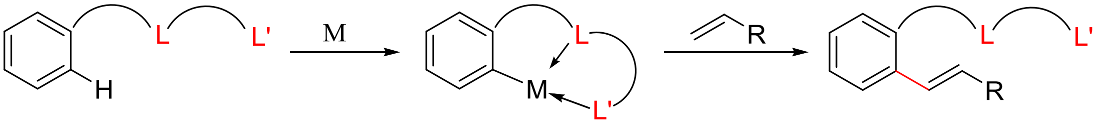
[5] (a) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem.* Soc. **2008**, *130*, 9254. (b) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem.* Soc. **2009**, *131*, 13888.

[6] J. J. Li, T. S. Mei, J. Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47,* 6452.

[7] (a) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagne, M. R.; Jones, G. C. L.; Milburn, K. I. B. *J. Am. Chem.* Soc. **2008**, *130*, 10066. (b) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagne, M. R.; Jones, G. C. L.; Milburn, K. I. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 1830. (c) Nishikata, T.; Lipshutz, B. H. *Org. Lett*. **2010**, *12*, 1972.

phenylpropionic acid substrates, in which the carboxylic acid acts as directing group for introducing olefin substituents at the ortho position (Scheme 5.1).[11]

Although, much advancement has been attained in the arena of C-H olefination in the past decade, in most cases reported to date, a monodentate directing group has been adopted, while to our best knowledge, there is still no reports of such C-H olefination reaction employing bidentate directing group (Scheme 5.2). We do believe that this is also highly desirable for developing new C-H olefination reactions.[12]



Scheme 5.2 C-H olefination employing bidentate directing group

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[8] (a) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094. (b) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309. (c) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem.* Soc. **2007**, *129*, 9858. (d) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854. (e) Rubia, A. G.; Arrayas, R.G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 6511.

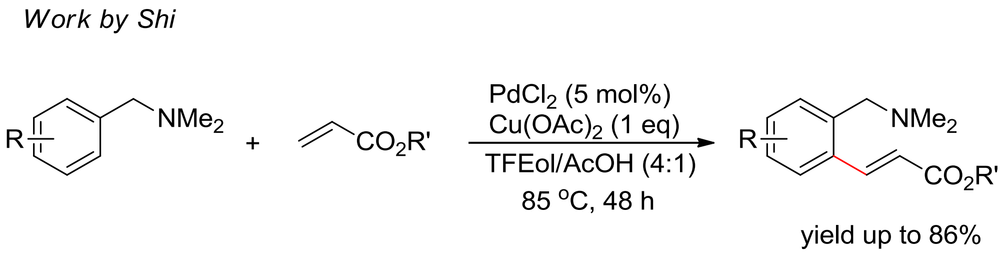
[9] Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540.

[10] Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1604.

[11] Wang, D. H.; Engle, K. M.; Shi, B. F.; Yu, J. Q. Science **2010**, *327*, 315.

[12] For C-H activation employing bidentate systems, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 13154. (b) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett*. **2006**, *8*, 3391. (c) Inoue, S.; Shiota, H.; Fukunoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898. (d) Gou, F. R.; Wang, X. C.; Huo, P. F.; Bi, H. P.; Guan, Z. H.; Liang, Y. M. *Org. Lett.* **2009**, *11*, 5726. (e) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070. (f) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc*. **2012**, *134*, 3. (g) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc*. **2012**, *134*, 7. (h) He, G.; Chen, G. *Angew. Chem. Int. Ed*. **2011**, *50*, 5192. (i) Zhao, Y.; Chen, G. *Org. Lett*. **2011**, *13*, 4850. (j) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett*. **2010**, *12*, 3414. (k) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc*. **2012**, *134*, 7313.

In our effort to functionalize amino acids or derivatives to synthesize complex molecules, and our interest in palladium-catalyzed oxidative coupling reactions,[13] we are interested in the olefination of benzylamine derivatives via C-H activation. While Shi has elegantly demonstrated the viability of carrying out C-H olefination of *N*,*N*-dimethyl benzylamine derivatives (Scheme 5.3).[14] The requirement to use more easily removable protecting group as well as further expanding the scope of the olefin coupling partner encouraged us to recourse new type of C-H olefination approach. Initial studies employing triflamide as directing group encountered problem with only very low yield of the olefination product formed. Therefore, experiments using a series of other protecting groups were investigated. Fortunately the bidentate directing group, 2-pyridinecarbonyl (abbreviate as Pic), was found to be optimal for the desired C-H olefination.



Scheme 5.3 C-H olefination of *N,N*-dimethylbenzylamine derivatives

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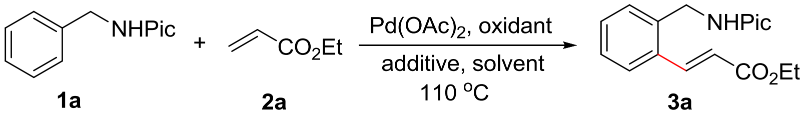
[13] (a) Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Chem. Soc*. **2009**, *131*, 1372. (b) Zhou, H.; Xu, Y. H.; Chung, W. J.; Loh, T. P. *Angew. Chem. Int. Ed*. **2009**, *48*, 5355. (c) Zhou, H.; Chung, W. J.; Xu, Y. H.; Loh, T. P. *Chem. Commun*. **2009**, 3472. (d) Feng, C.; Loh, T. P. *J. Am. Chem. Soc*. **2010**, *132*, 17710. (e) Feng, C.; Loh, T. P. *Chem. Commun*. **2010**, 4779. (f) Feng, C.; Loh, T. P. *Chem. Commun*. **2011**, 10458.

[14] Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc*. **2007**, *129*, 7666.

5.2 Results and discussion

The optimization of the C-H olefination was first examined using picolyl protected benzylamine and ethyl acrylate as coupling partner. Initially, when the model reaction was carried out in DMSO with $Pd(OAc)_2$ as catalyst under oxygen atmosphere, 33% isolated yield of the desired product was obtained.(Table 5.1, entry 1). Additional screening of the oxidants revealed that other oxidants such as Ag_2CO_3, $PhI(OAc)_2$, TEMPO, $Cu(OAc)_2$ which were quite often employed for C-H activation systems, were not suitable for the present olefination (Table 5.1, entries 2-5). Solvent screening shown that DMSO is the optimal choice, whereas no desired product was formed when using other solvents such as 1,4-dioxane, DMF and NMP (Table 5.1, entries 6-8). Halide additives had deleterious effect on this reaction, probably due to the high affinity of halide ion for the palladium center, which diminishes the electrophilicity of the active catalyst (Table 5.1, entries 9). Much to our pleasure, the yield increased substantially when PTSA was used as additive. Further screening of the acid additive proved that CSA was the optimal choice, while significant improvement was achieved by employing BQ/O_2 as oxidant system providing the desired product in 72% yield (Table 5.1, entry13). Trace amount of product was obtained when $Pd(MeCN)_2Cl_2$ was chosen as the catalyst, which was coincident with the aforementioned deleterious role that halide ion exerts on catalyst activity. $Pd(TFA)_2$ shown comparative catalytic effect to $Pd(OAc)_2$. Attempt to decrease the amount of catalyst loading was accompanied by decrease in yield (Table 5.1, entry14).

Table 5.1 Reaction Conditions Optimization.[a]

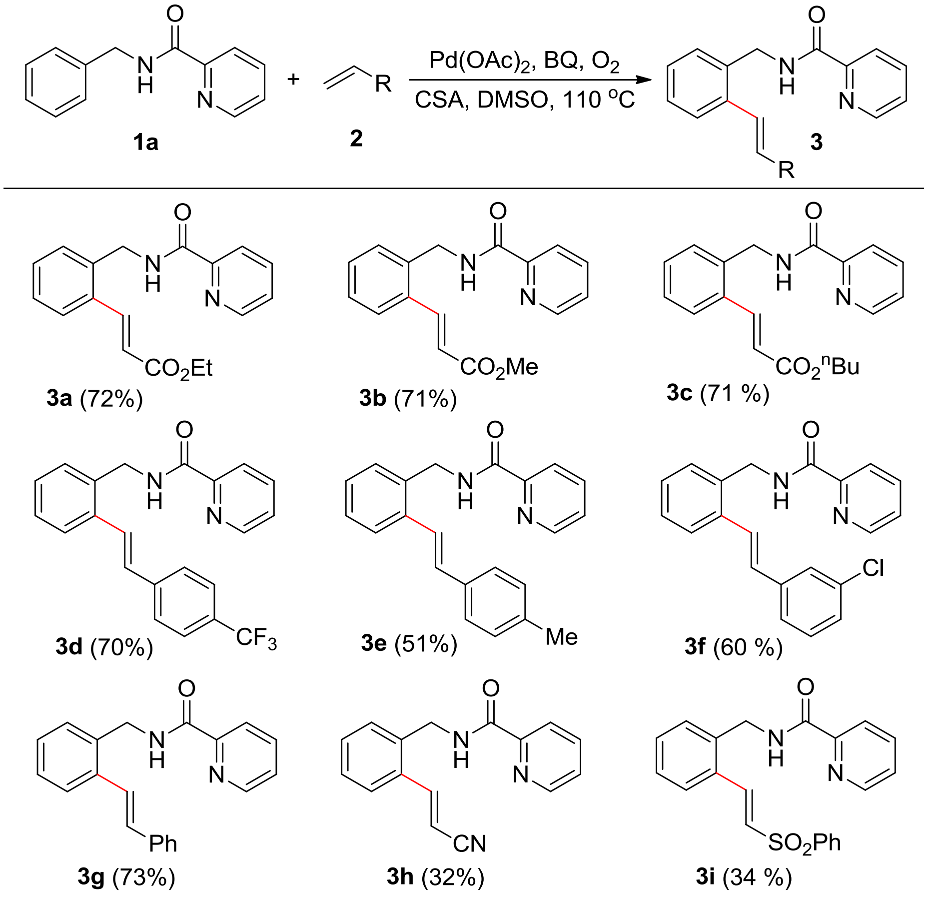


Entry	Oxidant	Additive	Solvent	Yield (%)[b]
1	O_2	-	DMSO	33
2	Ag_2CO_3	-	DMSO	NR
3	$PhI(OAc)_2$	-	DMSO	13
4	TEMPO	-	DMSO	trace
5	$Cu(OAc)_2$	-	DMSO	NR
6	O_2	-	Dioxane	NR
7	O_2	-	DMF	trace
8	O_2	-	NMP	trace
9	O_2	LiCl	DMSO	trace
10	O_2	PTSA	DMSO	45
11	O_2	CSA	DMSO	55
12	O_2	HOAc	DMSO	34
13	BQ/O_2	CSA	DMSO	72
14	BQ/O_2	CSA	DMSO	52[c]

[a] unless otherwise noted the reactions were carried out at 110 °C using **1a** (0.1 mmol), **2a** (0.4 mmol), catalyst (0.02 mmol), oxidant (0.1 mmol) for 24 h. [b] Isolated yields. [c] 10 mol% $Pd(OAc)_2$ was used.

With the optimized reaction conditions in hand, the reaction generality was investigated with different types of olefin. As can be clearly seen in Table 5.2, acrylate derivatives were appropriate substrates for this reaction delivering the desired products in good yields (3a-3c). It is noteworthy that styrene derivatives either with electron-donating or electron-withdrawing substituents could also be smoothly transformed into the desired products in moderate to good yields (3d-3g). This result is in sharp contrast with Shi's protocol where the styrene was proved not to be effective coupling partner. It should also be noted that the chloro-substituted substrate 2f was tolerated under this reaction condition which could allow further elaboration. Furthermore, vinyl cyanide and vinyl phenyl sulfone were not good substrates for this reaction affording the desired products in low yields (3h, 3i).

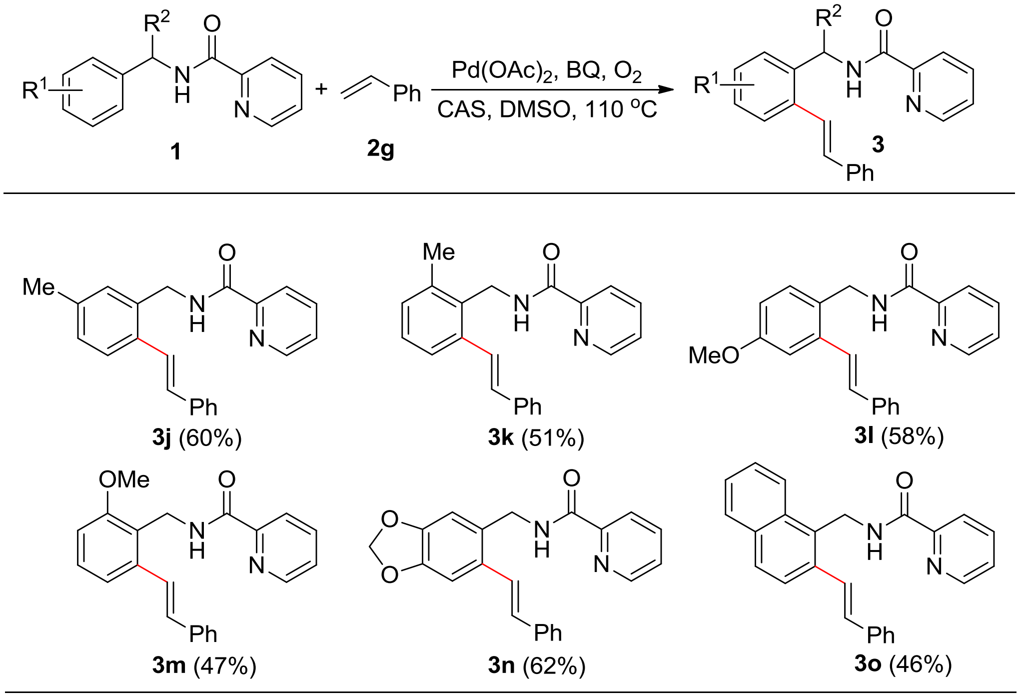
Table 5.2 Direct olefination between 1a and various olefins.[a,b]



[a] Unless otherwise noted, the reactions were carried out at 110 °C using **1a** (0.1 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), CSA (0.04 mmol), BQ (0.1 mmol), DMSO (0.4 mL) for 24 h under oxygen atmosphere. [b] Isolated yields.

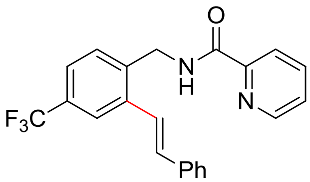
In order to further investigate the scope of the direct olefination a series of benzylamine derivatives with different kinds of substituents were explored, employing styrene as the coupling partner. Under the aforementioned optimized reaction conditions, both electron-withdrawing and electron-donating groups are tolerated, as are halogen-substituted substrates, affording the desired products in moderate yields. Furthermore, when employing the substrates with substituents such as methyl and ethyl groups on the benzylic position as reaction partners, good yields of **3s** and **3t** were obtained, which is in sharp contrast with Liang's protocol, where a methyl group on the benzylic position totally impedes the reaction.[12d] Interestingly, when phenylethylamine derivative, which is one carbon elongated, was subjected to the optimized reaction, the desired product was obtained in good yield, which implied the feasibility of remote C-H activation in this case (**3u**).

Table 5.3 Direct olefination between various benzyl amine derivatives and **2g**.[a,b]

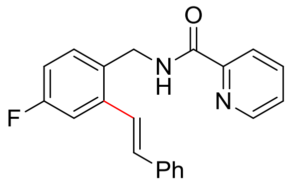


3j (60%) **3k** (51%) **3l** (58%)

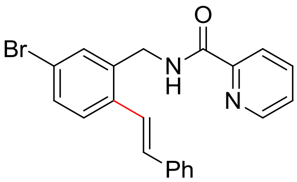
3m (47%) **3n** (62%) **3o** (46%)



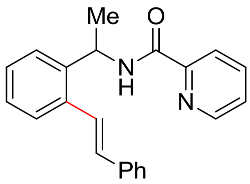
3p (42%)



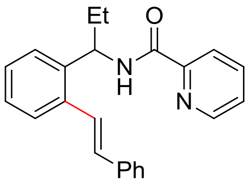
3q (48%)



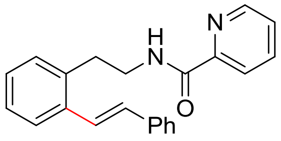
3r (53%)



3s (75%)

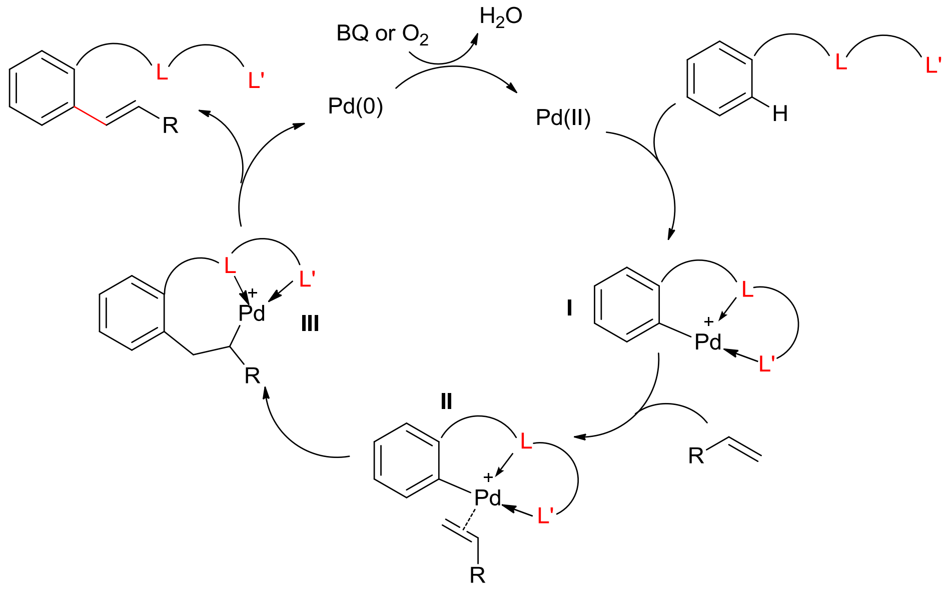


3t (73%)



3u (67%)

A proposed reaction mechanism is illustrated in Scheme 5.2. Initially, the bidentate directing group coordinates with the palladium(II) and at the same time activates the *ortho* C-H bond delivering the intermediate **I**. After subsequent migratory insertion through the π-complex **II**, the intermediate **III** is formed, which after β-hydride elimination produces the final desired product as well as the palladium(0), which is oxidized back to palladium(II) by molecular BQ or oxygen.



Scheme 5.2 Proposed Mechanism

5.3 Conclusion

In conclusion, we have developed an intermolecular palladium(II)-catalyzed direct olefination of benzylamine derivatives employing a bidentate system. The use of DMSO as solvent proves to be key point for the success of this transformation. We, therefore, assumed that DMSO acts as a ligand throughout the reaction on one hand to stabilize the organopalladium species and on the other hand to prevent the formation of palladium black, thus resulting catalyst deactivation. Furthermore, the employment of bidentate directing group allows not only acrylate derivatives but also electron-neutral olefins be smoothly transformed into the desired products, which further broaden the scope of palladium-catalyzed oxidative olefination reactions.

5.4 Experiment Section

$Pd(OAc)_2$ (98% purity) and DMSO were purchased from Aldrich without further purification. The protected benzylamines were synthesized using reported method.[1,] Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with acidic solution of ceric molybdate or iodine. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions. High Resolution Mass (HRMS) spectra were obtained using Waters Q-Tof Permies Mass

Spectrometer. ^{1}H NMR (300MHz), (400 MHz) and ^{13}C (75 MHz), (100 MHz) were registered on Bruker spectrometers with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in units (ppm) by assigning TMS resonance in the ^{1}H spectrum as 0.00 ppm and $CDCl_3$ resonance in the^{13}C spectrum as 77.0 ppm. All coupling constants (*J* values) were reported in Hertz (Hz). Multiplicities were given as: s (singlet); d (doublet); dd (doublets of doublet); t (triplet); q (quartet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH.

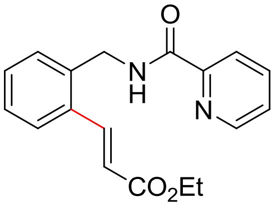
Palladium-Catalyzed C-H Olefination of Benzylamine Derivatives using bidentate directing group

General procedure: An oven-dried 8 mL sample vial was charged with 1a (21.2 mg, 0.1 mmol), 2a (38.4 mg, 0.4 mmol), palladium acetate (4.4 mg, 0.02 mmol), camphorsulphonic acid (9.3 mg, 0.04 mmol), benzoquinone (10.8mg, 0.1 mmol) and DMSO (0.4 mL) sequentially. After purged with oxygen the sample vial was closed tightly and heated at 110 °C with stirring for 24 hours. After reaction, the mixture was diluted with dichloromethane, and filtered through a short pad of celite. Removal of the solvent in vacuo and purification of the residue by silica gel column chromatography afforded the desired product 3a (22.3mg, 72 % yield).

CHAPTER 5

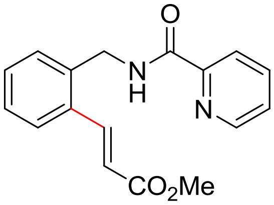
Characterization of Products

(*E*)-ethyl 3-(2-(picolinamidomethyl)phenyl)acrylate (3a).



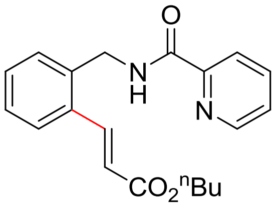
FTIR (NaCl, neat): *v* 1705, 1666, 1633cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 1.32 (t, *J* = 7.04 Hz, 3H), 4.25 (q, *J* = 7.0 Hz, 2H), 4.81 (d, *J* = 5.9 Hz, 2H), 6.38 (d, *J* = 15.8 Hz, 1H), 7.32-7.39 (m, 2H), 7.41-7.44 (m, 2H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.84-7.88 (m, 1H), 8.05 (d, *J* = 15.8 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.32 (s, 1H), 8.53 (d, *J* = 4.4 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 14.3, 41.0, 60.6, 121.0, 122.4, 126.3, 127.0, 128.1, 129.2, 130.2, 133.4, 136.9, 137.4, 141.0, 148.1, 149.6, 164.1, 166.6 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{18}H_{19}N_2O_3$: 311.1398, found [M+H]$^+$: 311.1396.

(*E*)-methyl 3-(2-(picolinamidomethyl)phenyl)acrylate (3b).



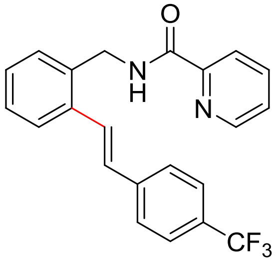
FTIR (NaCl, neat): *v* 1714, 1666, 1633cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 3.79 (s, 3H), 4.81 (d, *J* = 6.0 Hz, 2H), 6.39 (d, *J* = 15.8 Hz, 1H), 7.31-7.39 (m, 2H), 7.41-7.44 (m, 2H), 7.59-7.61 (m, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H), 8.06 (d, *J* = 15.8 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.32 (s, 1H), 8.53 (d, *J* = 4.7 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 40.9, 51.7, 120.5, 122.3, 126.3, 126.9, 128.1, 129.2, 130.3, 133.3, 136.9, 137.3, 141.3, 148.1, 149.6, 164.1, 167.0 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{17}H_{17}N_2O_3$: 297.1241, found [M+H]$^+$: 297.1239.

(*E*)-butyl 3-(2-(picolinamidomethyl)phenyl)acrylate (3c).



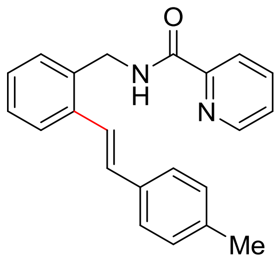
FTIR (NaCl, neat): *v* 1710, 1665, 1630cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.37-1.46 (m, 2H), 1.64-1.71 (m, 2H), 4.20 (t, *J* = 6.7 Hz, 2H), 4.81 (d, *J* = 5.9 Hz, 2H), 6.39 (d, *J* = 15.8 Hz, 1H), 7.31-7.39 (m, 2H), 7.41-7.44 (m, 2H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 8.04 (d, *J* = 15.7 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.30 (s, 1H), 8.53 (d, *J* = 4.7 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 13.7, 19.2, 30.7, 41.0, 64.5, 121.0, 122.4, 126.3, 127.0, 128.1, 129.2, 130.2, 133.5, 136.9, 137.3, 140.9, 148.1, 149.6, 164.1, 166.7 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{20}H_{23}N_2O_3$: 339.1718, found [M+H]$^+$: 339.1709.

(*E*)-*N*-(2-(4-(trifluoromethyl)styryl)benzyl)picolinamide (3d).



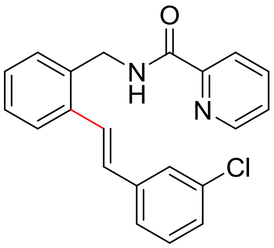
FTIR (NaCl, neat): *v* 1658, 1614cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.84 (d, *J* = 5.9 Hz, 2H), 7.00 (d, *J* = 16.1 Hz, 1H), 7.30-7.44 (m, 4H), 7.56-7.62 (m, 4H), 7.67 (d, *J* = 7.4 Hz, 2H), 7.79-7.83 (m, 1H), 8.20-8.28 (m, 2H), 8.46 (d, *J* = 4.6 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 41.6, 122.3, 125.5, 125.5, 126.1, 126.2, 126.8, 128.0, 128.3, 128.3, 129.5, 129.7, 135.6, 136.0, 137.4, 140.7, 148.0, 149.6, 163.7 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{18}F_3N_2O$: 383.1366, found [M+H]$^+$: 383.1371.

(*E*)-*N*-(2-(4-methylstyryl)benzyl)picolinamide (3e).



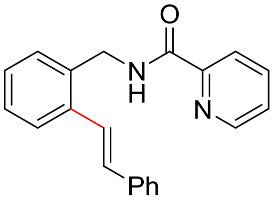
FTIR (NaCl, neat): *ν* 1666, 1633cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 2.34 (s, 3H), 4.82 (d, *J* = 5.72 Hz, 2H), 7.00 (d, *J* = 16.1 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.23-7.34 (m, 7H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.79-7.83 (m, 1H), 8.21-8.26 (m, 2H), 8.46 (d, *J* = 4.2 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 21.2, 41.6, 122.3, 124.2, 125.9, 126.1, 126.6, 127.6, 128.1, 129.3, 129.4, 131.2, 134.5, 135.0, 136.7, 137.3, 137.6, 148.0, 149.7, 163.9 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{21}N_2O$: 329.1655, found [M+H]$^+$: 329.1654.

(*E*)-*N*-(2-(3-chlorostyryl)benzyl)picolinamide (3f).



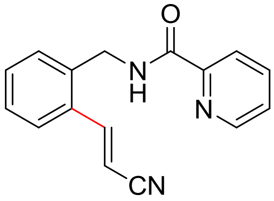
FTIR (NaCl, neat): *ν* 1705, 1666, 1591cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 4.83 (d, *J* = 5.9 Hz, 2H), 6.92 (d, *J* = 16.1 Hz, 1H), 7.19-7.49 (m, 9H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.82 (td, *J$_1$* = 7.7 Hz, *J$_2$* = 1.4 Hz, 1H), 8.23-8.28 (m, 2H), 8.47 (d, *J* = 3.9 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 41.6, 122.4, 124.8, 126.0, 126.2, 126.7, 126.9, 127.5, 128.1, 128.2, 129.5, 129.7, 129.8, 134.5, 135.5, 136.2, 137.3, 139.2, 148.0, 149.7, 163.8 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{21}H_{18}ClN_2O$: 349.1110, found [M+H]$^+$: 349.1108.

(*E*)-*N*-(2-styrylbenzyl)picolinamide (3g).



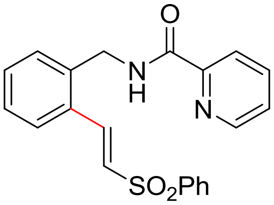
FTIR (NaCl, neat): *ν* 1666, 1620cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 4.83 (d, *J* = 5.8 Hz, 2H), 7.02 (d, *J* = 16.1 Hz, 1H), 7.23-7.39 (m, 7H), 7.45 (d, *J* = 16.1 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.79-7.83 (m, 1H), 8.21-8.27 (m, 2H), 8.47 (d, *J* = 4.5 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 41.6, 122.3, 125.2, 126.0, 126.1, 126.7, 127.7, 127.8, 128.1, 128.6, 129.4, 131.3, 135.2, 136.6, 137.2, 137.3, 148.0, 149.7 163.9 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{21}H_{19}N_2O$: 315.1502, found $[M+H]^+$: 315.1497.

(*E*)-*N*-(2-(2-cyanovinyl)benzyl)picolinamide (3h).



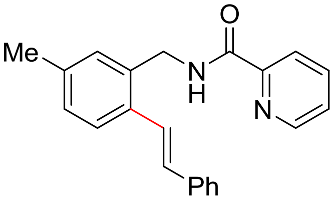
FTIR (NaCl, neat): ν 2218, 1658, 1616cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.75 (d, *J* = 6.0 Hz, 2H), 5.84 (d, *J* = 16.5 Hz, 1H), 7.34-7.38 (m, 1H), 7.40-7.46 (m, 3H), 7.51-7.53 (m, 1H), 7.82-7.89 (m, 2H), 8.23-8.25 (m, 1H), 8.30 (s, 1H), 8.52-8.53(m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 41.0, 98.8, 117.8, 122.5, 126.3, 126.4, 128.4, 129.8, 131.2, 132.7, 136.8, 137.5, 147.5, 148.1, 149.4, 164.1 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{16}H_{14}N_3O$: 264.1134, found $[M+H]^+$: 264.1137.

(*E*)-*N*-(2-(2-(phenylsulfonyl)vinyl)benzyl)picolinamide (3i).



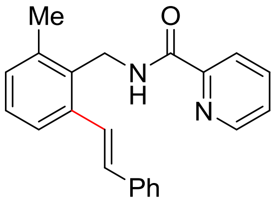
FTIR (NaCl, neat): ν 1666, 1614cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.81 (d, *J* = 6.1 Hz, 2H), 6.83 (d, *J* = 15.2 Hz, 1H), 7.29-7.33 (m, 1H), 7.44-7.51 (m, 5H), 7.55-7.60 (m, 1H), 7.86-7.89 (m, 1H), 7.90-7.94 (m, 2H), 8.05 (d, *J* = 15.2 Hz, 1H), 8.26 (td, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 8.33 (s, 1H), 8.52-8.54 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 41.1, 122.5, 126.4, 127.5, 127.8, 128.3, 129.3, 129.6, 129.8, 131.2, 131.3, 133.4, 137.5, 137.5, 139.1, 140.4, 148.1 149.5, 164.2 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{21}H_{19}N_2O_3S$: 379.1113, found $[M+H]^+$: 379.1116.

(*E*)-*N*-(5-methyl-2-styrylbenzyl)picolinamide (3j).



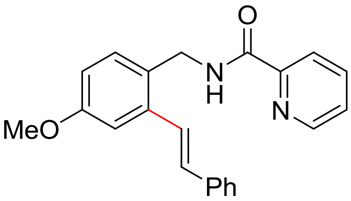
FTIR (NaCl, neat): ν 1660, 1620cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.35 (s, 3H), 4.79 (d, J = 5.8 Hz, 2H), 6.98 (d, J = 16.0 Hz, 1H), 7.13-7.23 (m, 3H), 7.31-7.44 (m, 4H), 7.51 (d, J = 7.9 Hz, 1H), 7.79-7.83 (m, 1H), 8.21-8.25 (m, 2H), 8.46 (d, J = 4.2 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 21.1, 41.6, 122.3, 125.1, 125.9, 126.1, 126.6, 127.5, 128.6, 128.9, 130.3, 133.7, 135.0, 137.3, 137.4, 137.7, 148.0, 149.8, 163.8 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{21}N_2O$: 329.1646, found $[M+H]^+$: 329.1654.

(*E*)-*N*-(2-methyl-6-styrylbenzyl)picolinamide (3k).



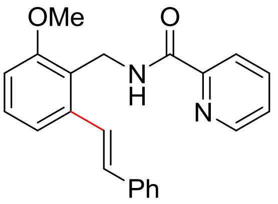
FTIR (NaCl, neat): ν 1666, 1618cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 2.45 (s, 3H), 4.83 (d, J = 5.2 Hz, 2H), 6.99 (d, J = 16.1 Hz, 1H), 7.15-7.16 (m, 1H), 7.20-7.28 (m, 2H), 7.31-7.37 (m, 3H), 7.51-7.55 (m, 4H), 7.78-7.82 (m, 1H), 8.03 (s, 1H), 8.21-8.23 (m, 1H), 8.42-8.43 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 19.9, 37.7, 122.2, 124.3, 126.1, 126.7, 127.7, 128.1, 128.6, 130.0, 131.8, 133.1, 137.2, 137.3, 137.8, 137.9, 148.0, 149.7, 163.9 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{21}N_2O$: 329.1653, found $[M+H]^+$: 329.1654.

(*E*)-*N*-(4-methoxy-2-styrylbenzyl)picolinamide (3l).



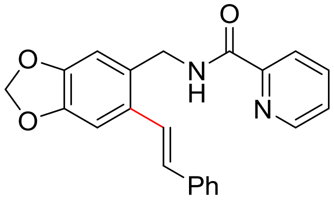
FTIR (NaCl, neat): ν 1666, 1602cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 3.86 (s, 3H), 4.76 (q, J = 5.8 Hz, 2H), 6.83 (dd, J_1 = 8.4 Hz, J_2 = 2.6 Hz, 1H), 7.01 (d, J = 16.1 Hz, 1H), 7.20 (d, J = 2.6 Hz, 1H), 7.26-7.37 (m, 5H), 7.43 (d, J = 16.1 Hz, 1H), 7.52 (d, J = 7.7 Hz, 2H), 7.81 (td, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 8.16-8.22 (m, 2H), 8.46 (d, J = 4.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.1, 55.4, 111.2, 113.3, 122.3, 125.3, 126.1, 126.8, 127.8, 128.7, 131.1, 131.4, 137.2, 137.3, 137.9, 148.0, 149.8, 159.5, 163.8 ppm; HRMS (ESI, m/z): Calcd. for $C_{22}H_{21}N_2O_2$: 345.1612, found $[M+H]^+$: 345.1603.

(E)-*N*-(2-methoxy-6-styrylbenzyl)picolinamide (3m).



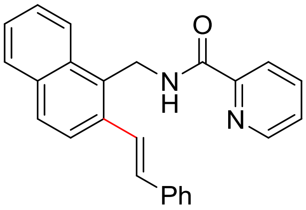
FTIR (NaCl, neat): ν 1666, 1616cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.90 (s, 3H), 4.86 (q, J = 6.0 Hz, 2H), 6.82-6.86 (m, 1H), 7.00 (d, J = 16.1 Hz, 1H), 7.24-7.28 (m, 3H), 7.33-7.37 (m, 3H), 7.58-7.60 (m, 2H), 7.77-7.81 (m, 2H), 8.21-8.23 (m, 1H), 8.33 (s, 1H), 8.47-8.48 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 34.5, 55.7, 109.4, 118.4, 122.3, 124.0, 125.9, 126.0, 126.8, 127.6, 128.6, 128.7, 131.7, 137.1, 137.3, 138.4, 148.0, 150.2, 158.4, 163.7 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{21}N_2O_2$: 345.1598, found $[M+H]^+$: 345.1603.

(*E*)-*N*-((6-styrylbenzo[d][1,3]dioxol-5-yl)methyl)picolinamide (3n).



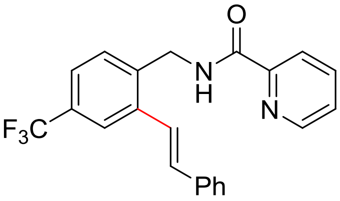
FTIR (NaCl, neat): ν 1664, 1621cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.77 (d, J = 5.8 Hz, 2H), 6.07 (s, 2H), 6.70 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 7.22-7.26 (m, 2H), 7.31-7.40 (m, 3H), 7.47 (d, J = 16.4 Hz, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.79-7.83 (m, 1H), 8.19-8.24 (m, 2H), 8.45-8.46 (m, 1H) ppm; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 41.7, 101.1, 106.8, 119.3, 120.3, 122.3, 123.2, 126.1, 126.7, 127.8, 128.6, 129.2, 134.5, 137.3, 137.6, 145.7, 147.5, 148.0, 149.7, 163.6 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{19}N_2O_3$: 359.1395, found $[M+H]^+$: 359.1396.

(*E*)-*N*-((2-styrylnaphthalen-1-yl)methyl)picolinamide (3o).



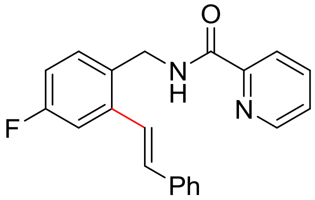
FTIR (NaCl, neat): ν 1664, 1632cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 5.29 (d, *J* = 5.3 Hz, 2H), 7.17 (d, *J* = 16.1 Hz, 1H), 7.26-7.29 (m, 1H), 7.32-7.40 (m, 3H), 7.46-7.49 (m, 1H), 7.54-7.61 (m, 3H), 7.79-7.85 (m, 5H), 8.18-8.20 (m, 2H), 8.25-8.27 (m, 1H), 8.37-8.39 (m, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 36.4, 122.3, 123.9, 125.8, 125.8, 126.1, 126.8, 127.2, 127.9, 128.6, 128.7, 128.8, 129.9, 132.5, 132.6, 133.3, 134.8, 137.2, 137.3, 148.0, 149.6, 163.9 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{25}H_{21}N_2O$: 365.1659, found [M+H]$^+$: 365.1654.

(*E*)-*N*-(2-styryl-4-(trifluoromethyl)benzyl)picolinamide (3p).



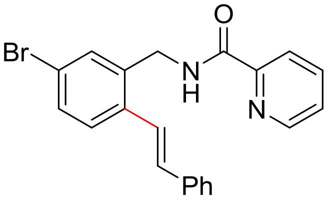
FTIR (NaCl, neat): ν 1666, 1622cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.86 (d, *J* = 6.1 Hz, 2H), 7.07 (d, *J* = 16.1 Hz, 1H), 7.27-7.30 (m, 1H), 7.35-7.39 (m, 2H), 7.40-7.46 (m, 2H), 7.49 (s, 2H), 7.54-7.56 (m, 2H), 7.83 (td, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1H), 7.88 (s, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 8.36 (s, 1H), 8.49 (d, *J* = 4.6 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** δ 41.1, 122.4, 122.9 (d, *J* = 3.7 Hz), 123.9, 124.1 (d, *J* = 3.7 Hz), 126.4, 126.9, 128.2, 128.7, 129.4, 130.2, 133.0, 136.7, 137.3, 137.4, 138.9, 148.1, 149.5, 164.1 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{18}F_3N_2O$: 383.1370, found [M+H]$^+$: 383.1371.

(*E*)-*N*-(4-fluoro-2-styrylbenzyl)picolinamide (3q).



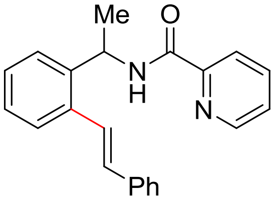
FTIR (NaCl, neat): *ν* 1666, 1608cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 4.79 (d, *J* = 5.9 Hz, 2H), 6.96 (td, J_1 = 8.3 Hz, J_2 = 2.7 Hz, 1H), 7.01 (d, *J* = 16.1 Hz, 1H), 7.25-7.28 (m, 1H), 7.32-7.43 (m, 6H), 7.52-7.54 (m, 2H), 7.82 (td, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H), 8.21-8.24 (m, 2H), 8.48 (d, *J* = 4.7 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 40.9, 112.4 (d, *J* = 22.3 Hz), 114.4 (d, *J* = 21.5 Hz), 122.3, 124.3 (d, *J* = 2.6 Hz), 126.2, 126.9, 128.1, 128.7, 131.1 (d, *J* = 3.5 Hz), 131.3 (d, *J* = 8.5 Hz), 132.3, 136.8, 137.4, 138.7 (d, *J* = 7.9 Hz), 148.1, 149.6, 161.4, 163.9 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{21}H_{18}FN_2O$: 333.1404, found [M+H]$^+$: 333.1403.

(*E*)-*N*-(5-bromo-2-styrylbenzyl)picolinamide (3r).



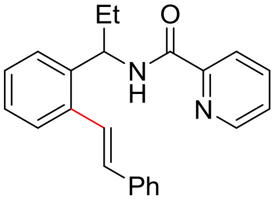
FTIR (NaCl, neat): *ν* 1666, 1615cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** *δ* 4.78 (d, *J* = 6.1 Hz, 2H), 6.99 (d, *J* = 16.1 Hz, 1H), 7.28-7.45 (m, 6H), 7.50-7.53 (m, 4H), 7.82 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 8.20-8.23 (m, 1H), 8.31 (s, 1H), 8.47-8.49 (m, 1H) ppm; **^{13}C NMR (75 MHz, CDCl$_3$):** *δ* 41.0, 121.4, 122.4, 124.1, 126.3, 126.8, 127.5, 128.0, 128.7, 131.1, 131.8, 131.9, 135.5, 136.9, 137.3, 137.3, 148.1, 149.5, 164.0 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{21}H_{18}BrN_2O$: 393.0599, found [M+H]$^+$: 393.0602.

(*E*)-*N*-(1-(2-styrylphenyl)ethyl)picolinamide (3s).



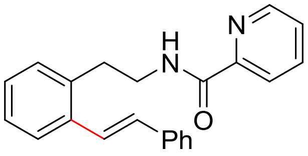
FTIR (NaCl, neat): *ν* 1666, 1623cm^{-1}; **^{1}H NMR (500 MHz, CDCl$_3$):** *δ* 1.63 (d, *J* = 6.9 Hz, 3H), 5.69- 5.74 (m, 1H), 7.23-7.26 (m, 1H), 7.29-7.32 (m, 2H), 7.33-7.39 (m, 3H), 7.45-7.46 (m, 1H), 7.53-7.55 (m, 2H), 7.60-7.63 (m, 2H), 7.78-7.82 (m, 1H), 8.17-8.19 (m, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.49-8.50 (m, 1H) ppm; **^{13}C NMR (125 MHz, CDCl$_3$):** *δ* 21.8, 45.4, 122.2, 125.2, 125.8, 126.1, 126.6, 127.5, 127.6, 127.9, 128.6, 131.4, 136.1, 137.3, 137.4, 140.6, 148.0, 149.8, 163.1 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{21}N_2O$: 329.1652, found [M+H]$^+$: 329.1654.

(*E*)-*N*-(1-(2-styrylphenyl)propyl)picolinamide (3t).



FTIR (NaCl, neat): *ν* 1666, 1623cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 0.99 (t, *J* = 7.4 Hz, 3H), 1.94-2.02 (m, 2H), 5.48-5.54 (m, 1H), 6.96 (d, *J* = 15.9 Hz, 1H), 7.26-7.31 (m, 3H), 7.35-7.42 (m, 4H), 7.57-7.62 (m, 3H), 7.69 (d, *J* = 16.1 Hz, 1H), 7.80 (td, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.39 (d, *J* = 8.5 Hz, 1H), 8.52 (d, *J* = 4.7 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 10.9, 29.3, 51.1, 122.3, 125.6, 126.1, 126.6, 126.7, 127.4, 127.6, 127.8, 128.6, 131.4, 136.5, 137.3, 137.5, 139.8, 148.0, 149.9, 163.5 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{23}H_{23}N_2O$: 343.1805, found [M+H]$^+$: 343.1810.

(*E*)-*N*-(2-styrylphenethyl)picolinamide (3u).



FTIR (NaCl, neat): *ν* 1664, 1630cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** *δ* 3.12 (t, *J* = 7.2 Hz, 2H), 3.70-3.75 (m, 2H), 6.97 (d, *J* = 16.1 Hz, 1H), 7.23-7.30 (m, 4H), 7.32-7.37 (m, 3H), 7.46-7.52 (m, 3H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.76-7.79 (m, 1H), 8.15 (d, *J* = 7.7 Hz, 2H), 8.45 (d, *J* = 4.7 Hz, 1H) ppm; **^{13}C NMR (100 MHz, CDCl$_3$):** *δ* 33.3, 40.6, 122.1, 125.8, 126.0, 126.0, 126.6, 127.0, 127.6, 127.8, 128.6, 130.2, 130.8, 136.6, 136.8, 137.2, 137.4,147.9, 149.8, 164.4 ppm; **HRMS (ESI, m/z):** Calcd. for $C_{22}H_{21}N_2O$: 329.1641, found [M+H]$^+$: 329.1654.

List of Publications

1. 'Palladium-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with arylboronic acids' **Chao Feng**, Teck-Peng Loh, *Chem. Commun*. **2010**, 4779.
2. 'Palladium-catalyzed bisolefination of C-C triple bonds: a facile method for the synthesis of naphthalene derivatives' **Chao Feng**, Teck-Peng Loh, *J. Am. Chem. Soc.* **2010**, *132*, 17710.
3. 'Rhodium-catalyzed direct ortho C-H olefination of phenol derivatives' **Chao Feng**, Teck-Peng, Loh, *Chem. Commun*. **2011**, 10458.
4. 'Rhodium-catalyzed hydroarylation of alkynes' **Chao Feng**, Teck-Peng, Loh, submitted.
5. 'Copper-catalyzed olefinic C-H trifluoromethylation of enamides at room temperature' **Chao Feng**, Teck-Peng, Loh, *Chem. Sci*. **2012**, *3*, 3458.
6. 'Palladium-catalyzed oxidative C-H olefination benzylamine derivatives' **Chao Feng**, Teck-Peng, Loh, manuscript in preparation.