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Normandie Université

THESE

Pour obtenir le diplôme de doctorat

Spécialité Chimie Organique

Préparée au sein de l'INSA de Rouen

Palladium-catalyzed directed introduction of α-CF_3-vinyl and SCF_3 groups by C-H bond functionalization

Présentée et soutenue par

Qun Zhao

Thèse soutenue publiquement le 11 D'ecembre 2017 devant le jury composé de		
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Abbreviations and Acronyms

AcOH	acetic acid
acac	acetylacetonate
CAN	ammonium ceric nitrate
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
PivOH	pivalic acid
p-T_SOH	*p*-toluenesulfonic acid
m-CPBA	3-chloroperoxybenzoic acid
NFSI	*N*-fluorobenzenesulfonimide
Selectfluor	*N*-chloromethyl-*N′*-fluorotriethylenediammonium bis(tetrafluoroborate)
BQ	1,4-benzoquinone
CF_3	trifluoromethyl
SCF_3	trifluoromethylthio
Mes	mesityl
THP	tetrahydropyran
TIPS	triisopropylsilyl
tmhd	2,2,6,6-tetramethyl-3,5-heptanediaonate
t-AmOH	*tert*-amyl alcohol

COD	1,5-cyclooctadiene
COE	cyclooctene
BDMAE	bis(2-dimethylaminoethyl)ether
DABCO	1,4-diazabicyclo[2.2.2]octane
HMPA	hexamethylphosphoric acid triamide
BINAP	1,1'-binaphthyl-2.2'-diphemyl phosphine
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
dppf	1,1’-Ferrocenediyl-bis(diphenylphosphine)
dppb	1,4-bis(diphenylphosphino)butane
dppm	bis(diphenylphosphino)methane
phen	1,10-phenanthroline
dppe	1,2-bis(diphenyphosphanyl)ethane
dppen	(*Z*)-1,2-bis(diphenylphosphino)ethene
$FcPCy_2$	(dicyclohexylphosphinyl)ferrocene
$1\text{-}AdCO_2Cs$	cesium 1-adamantyl carboxylate
p-cymene	4-isopropyltoluene
TMSCl	trimethylsilyl chloride
TMEDA	tetramethylethylenediamine
DCIB	1,2-dichloroisobutane
DG	directing group
TM	transition metal
DCE	1,2-dichloroethane

Abbreviations and Acronyms

DMA	dimethylacetamide
DMI	1,3-dimethyl-2-imidazolidinone
NMP	*N*-methyl-2-pyrrolidone
HFIP	hexafluoro-2-propanol
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
equiv	equivalent
rt	room temperature
GC-MS	gas chromatography-mass spectroscopy
HRMS	high resolution mass spectroscopy
NMR	nuclear magnetic resonance (spectroscopy)

Abstract

Recent years have witnessed a great development of the organofluorine chemistry field. In particular, the introduction of emergent fluorinated moieties onto various scaffolds has attracted the attention of the scientific community because of their special properties. Besides, transition metal-catalyzed directed C-H bond functionalization strategy has brought a revolution in the development of original synthetic methodologies, since it allows straightforward and more atom-economical processes. Thus, the design of new synthetic approaches for the introduction of fluorinated moieties by transition metal-catalyzed C-H bond functionalization pathway is particularly appealing. Therefore, in this Ph.D. thesis, we focused on the development of new methodologies for the direct introduction of fluorinated moieties onto arenes and olefins by transition metal catalyzed directed C(sp^2)-H bond functionalization. In particular, we turned our attention to the 2-bromo-3,3,3-trifluoropropene (BTP), an inexpensive fluorinated reagent coming from industry waste, used as a potential halon replacement for fire suppression and as a fluorinated building block in organic synthesis (Chapter 1). The first part of this Ph.D. thesis was dedicated to the development of new methodologies for the direct introduction of a CF_3-vinyl moiety onto arenes and olefins by a Pd-catalyzed directed C(sp^2)-H bond functionalization with BTP. Then, this approach was extended to the functionalization of α,β-unsaturated esters, although a different reaction pathway is probably involved (Chapter 2). In the second part of this Ph.D. thesis, we developed a new methodology for the direct

introduction of the SCF_3 group onto arenes and olefins by Pd-catalyzed directed C(sp^2)-H bond functionalization using the Munavalli reagent (Chapter 3).

Résumé

Ces dernières années ont été témoin de l'énorme développement de la chimie organique du fluor. Notamment, l'introduction de groupements fluorés émergents sur des « briques » moléculaires variées a attiré l'attention de la communauté scientifique en raison de leurs propriétés particulières. De plus, la stratégie de fonctionnalisation dirigée de la liaison C-H par catalyse par les métaux de transition, a conduit à une révolution dans le développement de méthodologies synthétiques originales. Par conséquent, la conception de nouvelles approches synthétiques pour l'introduction de groupements fluorés par fonctionnalisation de la liaison C-H catalysée par les métaux de transition est particulièrement attirante. Dans cette thèse, nous nous sommes concentrés sur le développement de nouvelles méthodologies d'introduction directe des groupements fluorés sur des arènes et des oléfines par fonctionnalisation directe de liaison C(sp^2)-H catalysée par les métaux de transition. En particulier, nous avons tourné notre attention sur le 2-bromo-3,3,3-trifluoropropène (BTP), un réactif fluoré bon marché et provenant de déchets de l'industrie. Ce dernier est utilisé comme potentiel agent de remplacement de halon pour la suppression des incendies et, utilisé comme « brique » moléculaire en synthèse organique (Chapitre 1). La première partie de cette thèse est dédiée au développement de nouvelles méthodologies pour l'introduction directe du groupement CF_3-vinyl sur des arènes et des oléfines par fonctionnalisation de la liaison C(sp^2)-H catalysée par le palladium. Ensuite, cette approche a été étendue à la fonctionnalisation d'esters α,β-insaturés, bien qu'un mécanisme différent soit probablement impliqué (Chapitre 2). Dans la seconde partie de cette thèse, nous

avons développé une nouvelle méthodologie pour l'introduction directe du groupement SCF_3 sur des arènes et des oléfines par fonctionnalisation de la liaison C(sp^2)-H catalysée par le palladium, utilisant le réactif de Munavalli (Chapitre 3).

Chapter 1
General introduction

1. General introduction

1.1 A brief introduction of fluorine

Fluorine ranks 13th in earth abundance among all the elements. It is the most electronegative element in the periodic table and the carbon-fluorine bond is one of the strongest bonds in organic chemistry.[1] Therefore, the introduction of a fluorine atom or fluorinated moieties can dramatically impact the physical and biological properties of the targeted molecules, such as the acidity or basicity of the neighboring groups, the dipole moment, the lipophilicity, the metabolic stability and the bioavailability of the molecules, for instance.[1-2] Nowadays, more and more molecules containing variously sized and shaped fluorinated substituents can be found in different applications, especially in agrochemicals[3] and pharmaceuticals (Figure 1).[2b, 2c, 4]

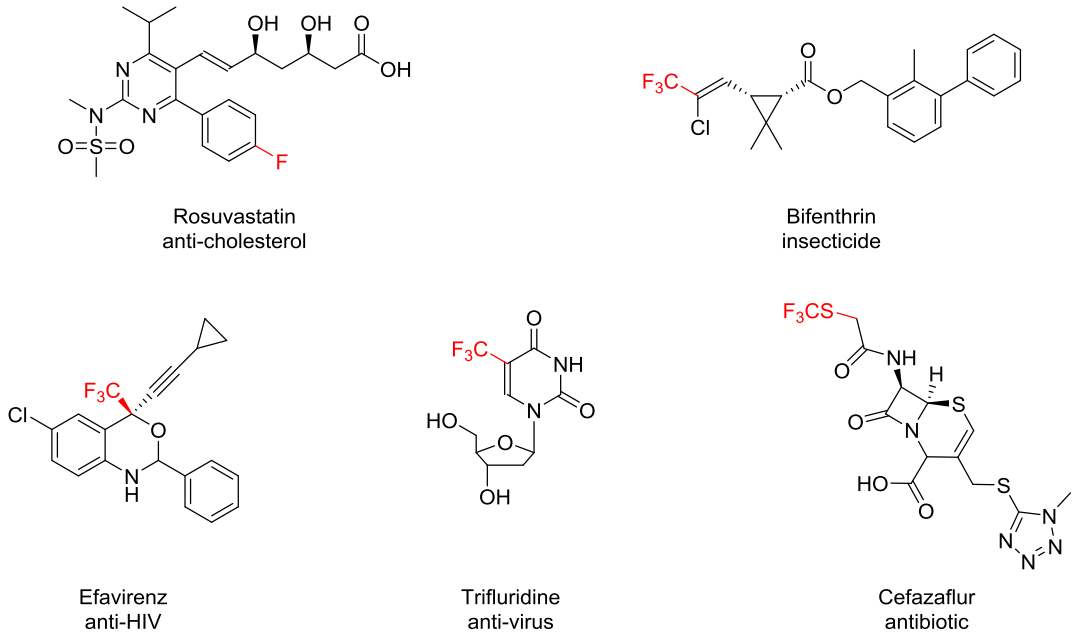
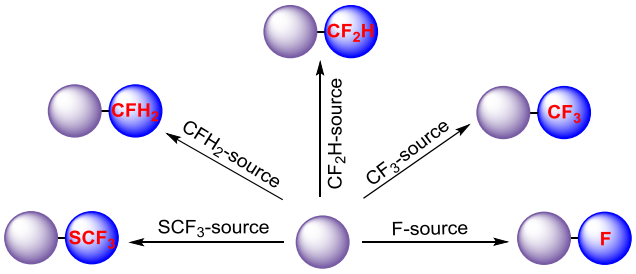


Figure 1: Examples of fluorine-containing agrochemicals and pharmaceuticals.

So far, less than 20 natural molecules containing a fluorine atom are known. This could

be explained by the fact that only few fluoroperoxidase enzymes have been identified,[5] which is in contrast with the thousands of chlorinated and brominated natural molecules obtained from haloperoxidase enzymes. Hence, the development of different methods to introduce a fluorine atom or fluorinated groups has attracted the attention of organic chemists. Nowadays, tremendous methodologies have been developed for the introduction of the fluorine atom or fluorinated moieties into molecules, such as $-CF_3$, $-CF_2H$, $-CH_2F$ or $-SCF_3$ groups (Scheme 1).[6] However, there is still room for further developments and organofluorine chemistry is still an attracting and hot research area.



Scheme 1: The introduction of the fluorine atom or fluorinated moieties into molecules.

1.2 A brief introduction of C-H bond functionalization

Due to their wide applications, the classic transition metal-catalyzed cross-coupling reactions are quite attractive. Indeed, during the past decades, significant achievements allowed the development of useful methodologies for the synthesis of molecules relying on transition metal-catalyzed cross-coupling reactions. As a result, this research area culminated with the Nobel Prize of Heck, Suzuki, and Negishi in 2010 for the palladium-catalyzed cross-coupling reaction.[7] Despite the high interest for this approach, several limitations remain. For example, traditional cross-coupling

reactions required the use of prefunctionalized starting materials (eg. halo or organometallic derivatives), obviously increasing the cost and the number of chemical-steps. Furthermore, the generation of waste may also be considered as another major drawback (Figure 2).

Since C-H bonds are ubiquitous in organic compounds, their directed functionalization would afford a straightforward and more atom-economical synthetic pathway for the construction of complex organic frameworks.

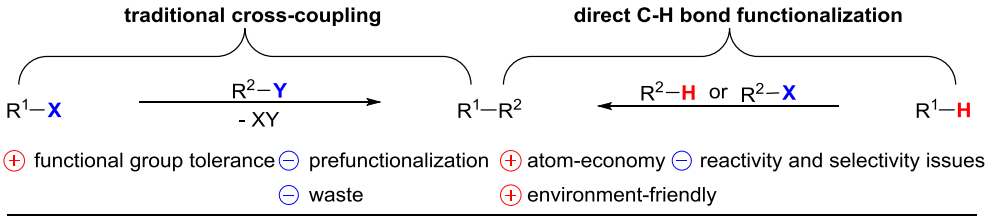
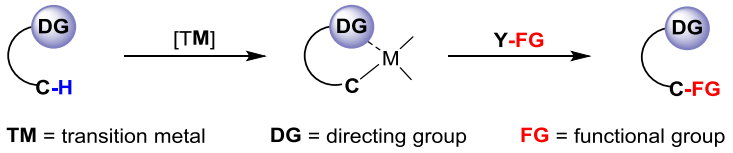


Figure 2: The comparison of the two methodologies.

The transition metal-catalyzed directed C-H bond functionalization strategy sprouted in the 1960s and started to bloom from the 1990's.[8] Nowadays, it has brought a revolution in the development of synthetic methodologies.[9] Thanks to the contributions of the scientific community, the C-H bond functionalization can now be considered as an important tool in organic synthesis. Nevertheless, several challenges still remain. The first problem is related with the reactivity: indeed, the C-H bond is thermodynamically stable (bond energies of C(sp^3)-H and C(sp^2)-H bonds range from 90 to 110 kcal/mol). Additionally, the selectivity of these transformations is also a challenge, since the C-H bonds are ubiquitous in organic molecules and usually quite similar. Therefore, the regio- and stereoselective functionalization of the targeted C-H bond is a great challenge.[10] So far, the tricks to tackle these problems are respectively the use of transition metals (M) and chelating directing groups (DG). By coordination

with a DG, the transition metal will be placed at the close proximity of the C-H bond to functionalize, leading to the formation of a five- or six-membered metallacycle intermediate. Then, reaction with the coupling partner followed by a reductive elimination will provide the expected product (Scheme 2).



Scheme 2: The general process of C-H bond functionalization.

Recently, the transition metal-catalyzed directed C(sp^2)-H bond functionalization of aromatic derivatives has been widely studied. However, in comparison, transition metal-catalyzed C(sp^2)-H bond functionalization of olefin is still underdeveloped.[11] Firstly, the directing groups on the olefin (for example, carbonyl groups) could activate the olefin towards competitive transformations, such as conjugate addition, which are not at play for aromatic system. In addition, the olefin is prone to undergo polymerization.[11] Those above-mentioned reasons make the functionalization of olefinic C(sp^2)-H bond a challenging research field.

1.3 Olefinic C(sp^2)-H bond functionalization

1.3.1 Challenges

When olefins are conjugated to an electron withdrawing directing group, this conjugated system tends to undergo the Michael addition pathway instead of a C-H bond functionalization process. In addition, olefins are prompt to polymerization, even at low temperature. Thus, the versatile olefins are challenging to deal with and require

specific conditions to be functionalized according to a C-H bond activation event.

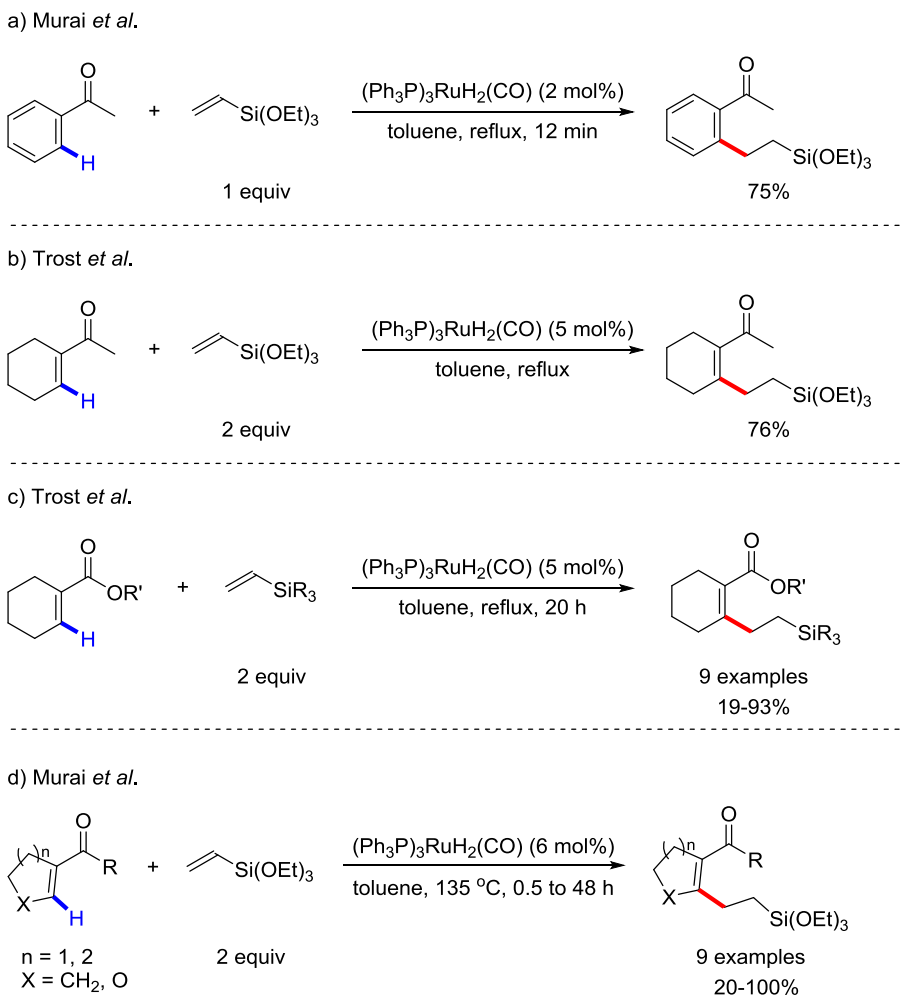
1.3.2 State of the art

In this part, only transition metal-catalyzed olefinic C(sp^2)-H bond functionalization with a directing group assistance events will be reviewed. Protocols beyond an olefinic C(sp^2)-H pathway, such as radical process, will not be included. Until now, there are few reviews concerning olefinic C(sp^2)-H bond functionalizations.[11-12]

1.3.2.1 Ru-catalysis

1.3.2.1.1 Ru-catalyzed alkylation

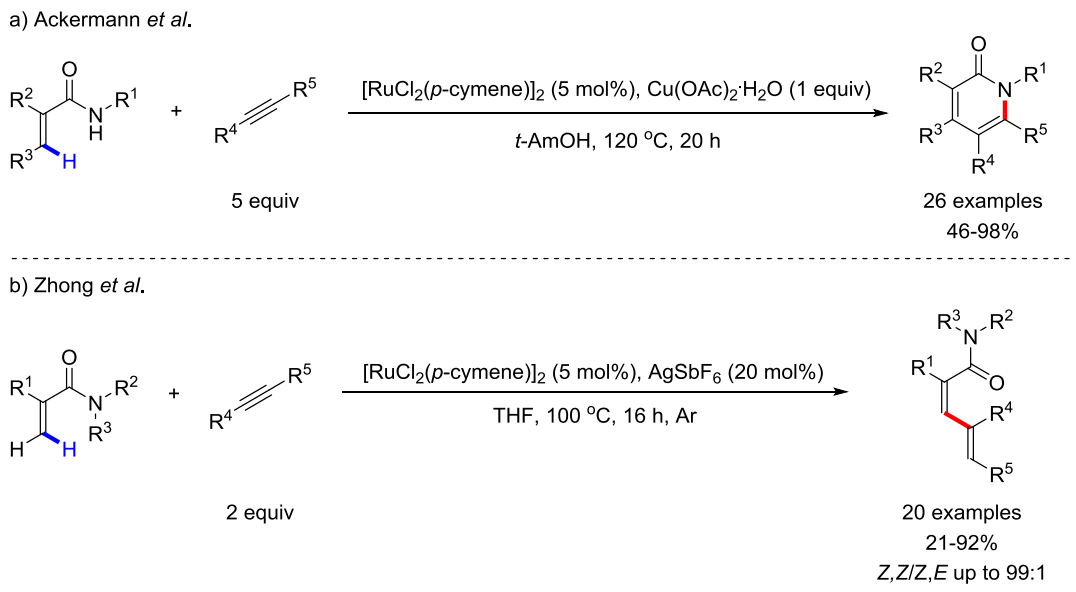
The first pioneer work was reported by Trost and co-workers in 1995.[13] Their initial work focused on the reaction between 1-acetylcyclohexene and triethoxy vinylsilane with the ruthenium complexes $(Ph_3P)_3RuH_2(CO)$, which have been successfully used with aromatic systems by Murai and co-workers (Scheme 3, a).[14] Fortunately, the corresponding product was obtained in 76% isolated yield (Scheme 3, b). With this promising result in hand, they investigated different directing groups and silanes. Several substrates were successfully converted into the corresponding products in low to excellent yields (Scheme 3, c). The same year another pioneer work was reported by Murai and co-workers. They described a similar transformation by using α,β-enones as substrates and several olefins were converted into the corresponding products in low to excellent yields (Scheme 3, d).[15]



Scheme 3: The typical pioneer work from Trost and Murai.

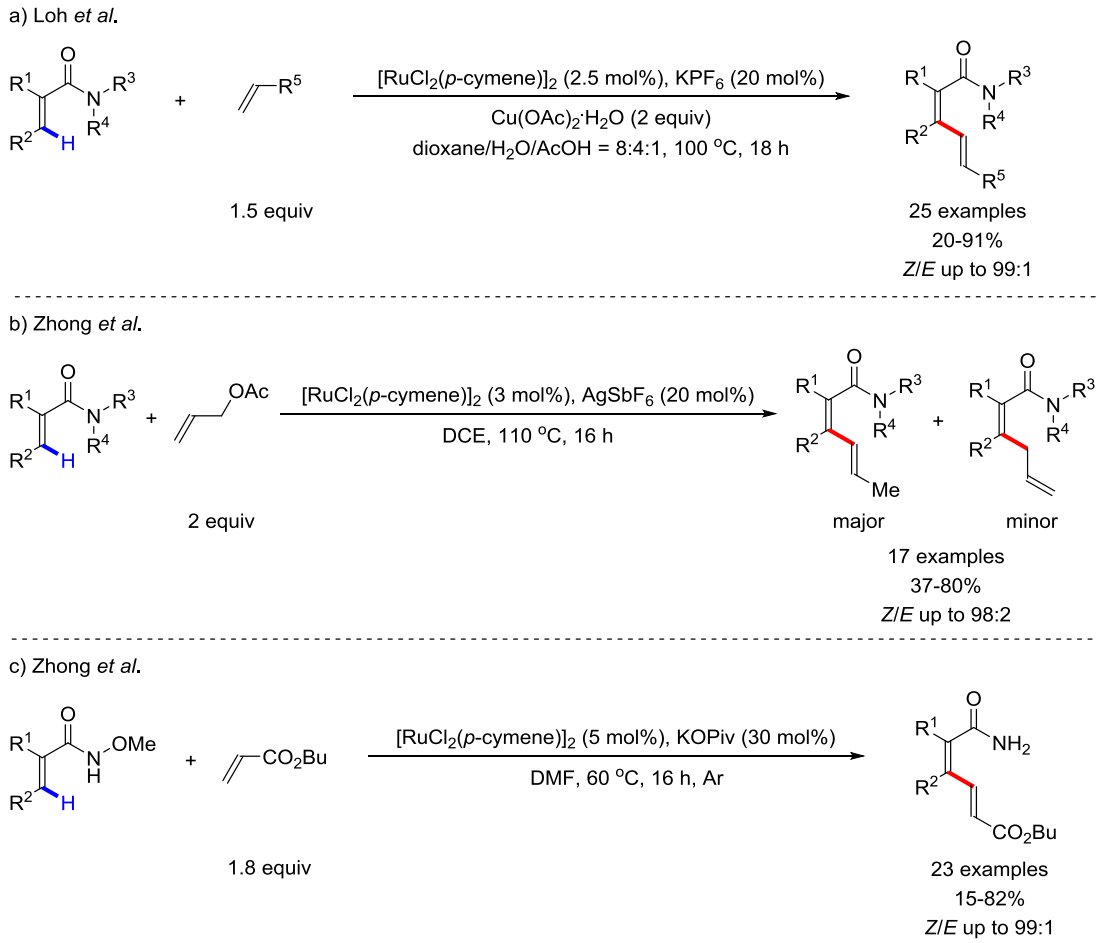
1.3.2.1.2 Ru-catalyzed alkenylation

In 2011, Ackermann and co-workers described the $[RuCl_2(p\text{-cymene})]_2$ catalyzed alkenylation of acrylamides with alkynes and then the resulting products annulated to afford 2-pyridones in good to excellent yields (Scheme 4, a).[16] In 2017, Zhong and co-workers revealed another $[RuCl_2(p\text{-cymene})]_2$ catalyzed alkenylation of alkynes with acrylamides to access substituted (*Z*,*Z*)-1,3-butadienes with a good stereoselectivity. An amide was used as a directing group in both cases (Scheme 4, b).[17]



Scheme 4: $[RuCl_2(p\text{-cymene}]_2$ catalyzed alkenylation of acrylamides with alkynes.

In 2012, Loh and co-workers disclosed the $[RuCl_2(p\text{-cymene}]_2$ catalyzed alkenylation of acrylamides with alkenes to produce (*Z*,*E*)-1,3-butadienes in low to excellent yields with a good stereoselectivity (Scheme 5, a).[18] The catalytic system tolerated different functional groups, such as $-CO_2R$, -COMe, $-SO_2Ph$, -CONHBn, -CN, $-PO(OEt)_2$, as well as Weinreb amide. In 2016, Zhong and co-workers described a regio- and stereoselective method for the allylation of acrylamides with allyl acetate. Note that an oxidant was not required in this reaction. This method afforded an alternative way to access the valuable (*Z*,*E*)-1,3-butadienes (Scheme 5, b).[19] One year later, the same group reported another oxidant-free cross-coupling reaction between acrylamides with various acrylates to prepare (*Z*,*E*)-1,3-butadienes with an excellent stereoselectivity. The -CONH(OMe) moiety was used as an internal oxidizing directing group and it was transformed into the $-CONH_2$ group (Scheme 5, c).[20]

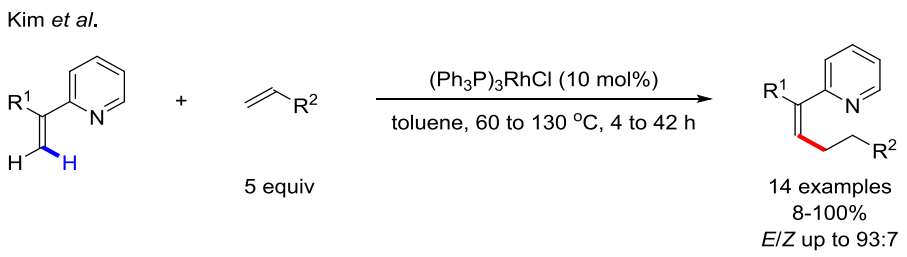


Scheme 5: $[RuCl_2(p\text{-cymene}]_2$ catalyzed alkenylation of acrylamides with alkenes.

1.3.2.2 Rh-catalysis

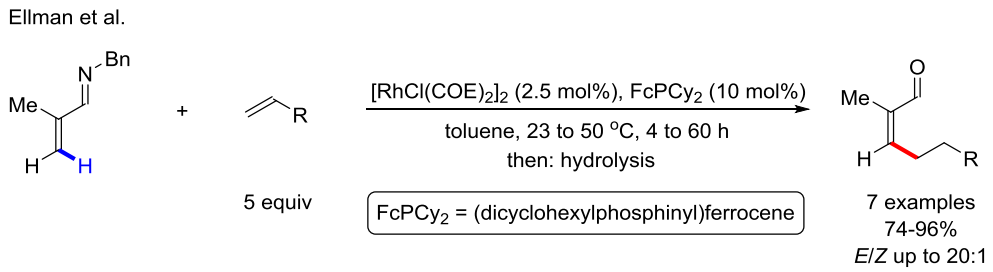
1.3.2.2.1 Rh-catalyzed alkylation

The first Rh-catalyzed olefinic C-H bond functionalization was reported by Kim and co-workers in 1996. They revealed the $(Ph_3P)_3RhCl$ (Wilkinson's catalyst) catalyzed alkylation of 2-vinylpyridines with different olefins in toluene at reflux. A wide range of substrates were successfully converted into the corresponding products with an excellent stereoselectivity (Scheme 6).[21]



Scheme 6: The $(Ph_3P)_3RhCl$ catalyzed alkylation of 2-vinylpyridines.

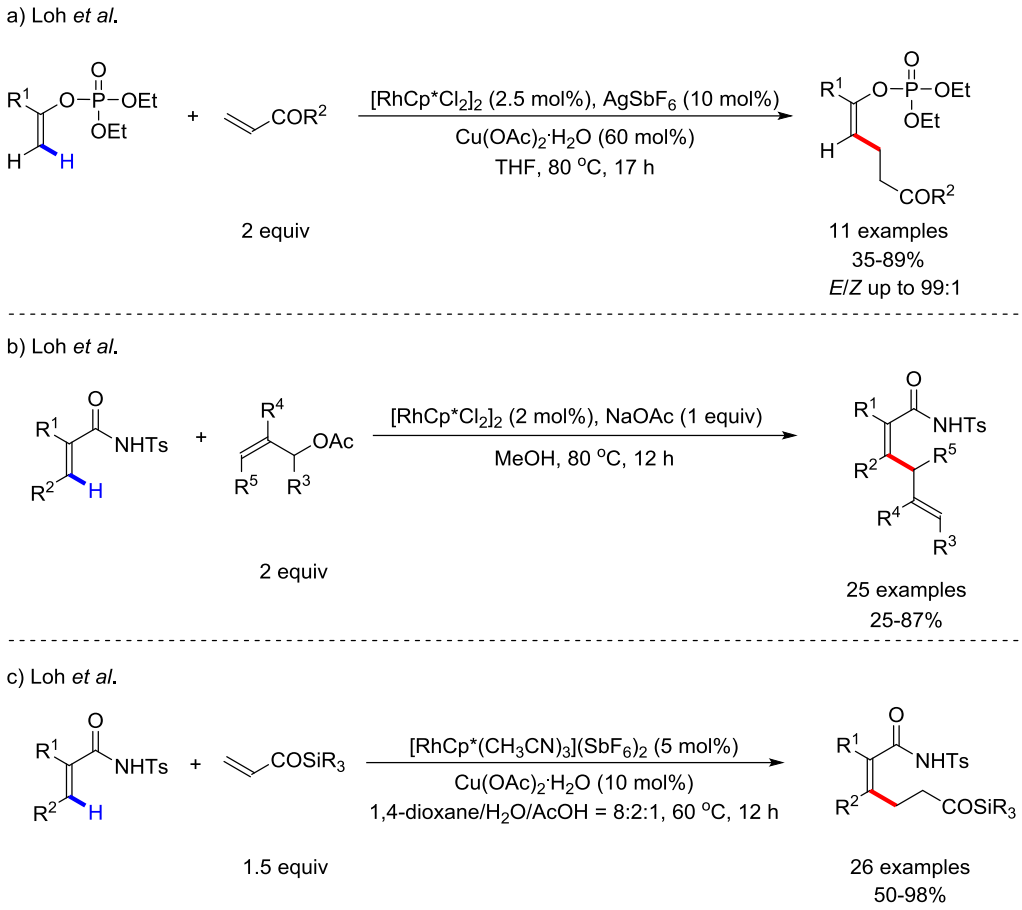
In 2006, Ellman and co-workers depicted the stereoselective alkylation between α,β-unsaturated imines and various olefins with the $[RhCl(COE)_2]_2$ catalyst under mild conditions (Scheme 7).[22] Note that the use of the (dicyclohexylphosphinyl)ferrocene ligand $FcPCy_2$ was crucial to decrease the reaction time, temperature and to selectively form the (*Z*)-isomers.



Scheme 7: The $[RhCl(coe)_2]_2$ catalyzed alkylation of imines.

In 2015 and 2017, Loh and co-workers reported three Rh-catalyzed olefinic C-H bond functionalizations by using a phosphate and an amide as directing groups, respectively. The phosphate directed alkylation with enones delivered the conjugate addition products in moderate to excellent yields (Scheme 8, a).[23] The phosphate directing group was easily removed by reacting with DIBAL-H or TBAF in THF. The -CONHTs directed allylation of acrylamides with allyl acetates paved a new way to access 1,4-diene derivatives (Scheme 8, b).[24] The allyl acetates were easily available electrophiles and a broad range of functional groups were tolerated. Besides, the -CONHTs directed alkylation with acryloylsilanes gave β-alkylated acrylamides in

good to excellent yields. The transformation was efficient (26 examples, 50-98%) and also demonstrated a high functional group tolerance (Scheme 8, c).[25]

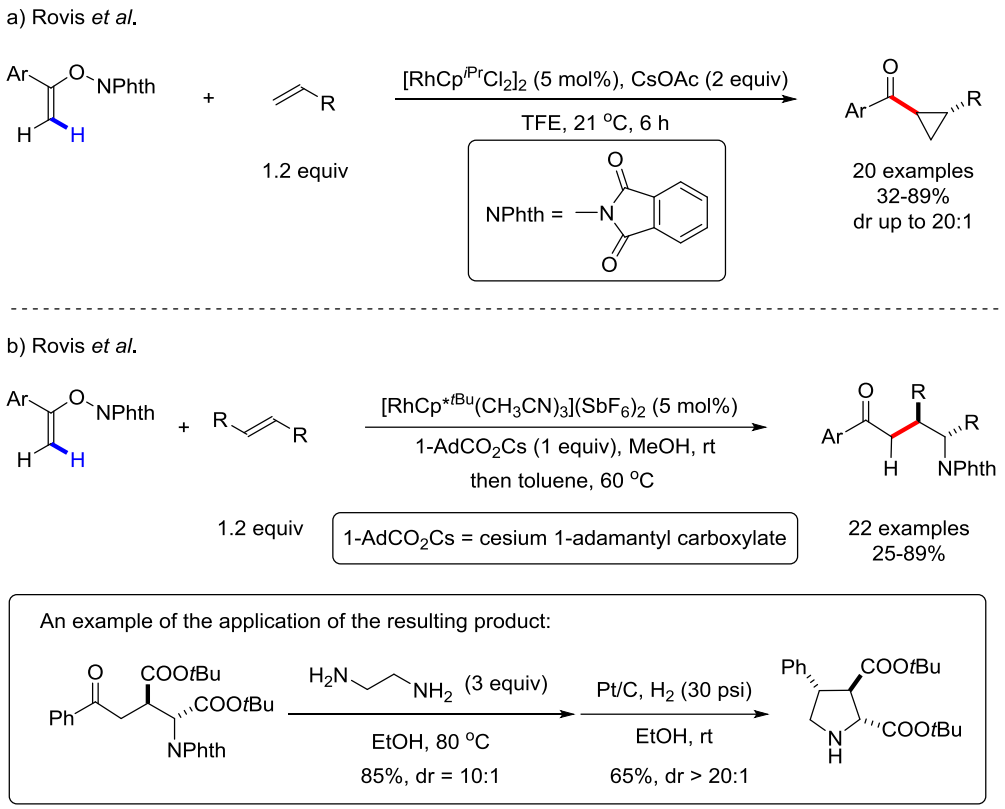


Scheme 8: The phosphate and amide directed olefinic C-H bond alkylations.

In 2014, Rovis and co-workers reported the Rh-catalyzed cyclopropanation between *N*-enoxyphthalimides and alkenes by using the -ONPhth as a directing group. A high diastereoselectivity was achieved in this cyclopropanation reaction (Scheme 9, a).[26] Note that the newly designed isopropylcyclopentadienyl ligand $[RhCp^{iPr}Cl_2]_2$ drastically improved the yield and enabled the high diastereoselectivity.

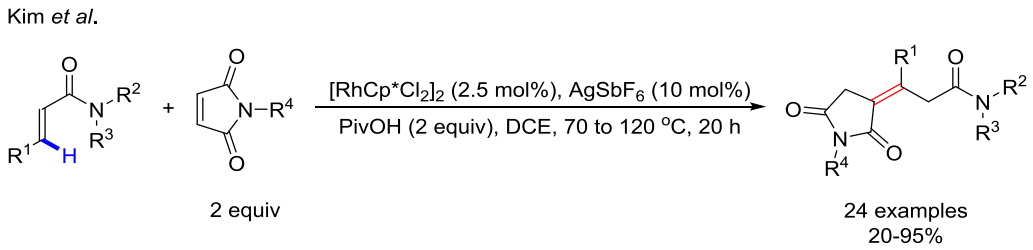
One year later, they used the same directing group to realize the *syn*-carboamination of disubstituted symmetric alkenes with another designed ligand $[RhCp^{*tBu}(CH_3CN)_3](SbF_6)_2$ (Scheme 9, b).[27] The screening of the ligands revealed that bulky ligands altered the chemoselectivity of this transformation. This method provided

a new way leading to the convergent and stereoselective assembly of pyrrolidines with controlled chiral centers. One example for this kind of application was shown in Scheme 9.



Scheme 9: The -ONPhth directed cyclopropanation and *syn*-carboamination.

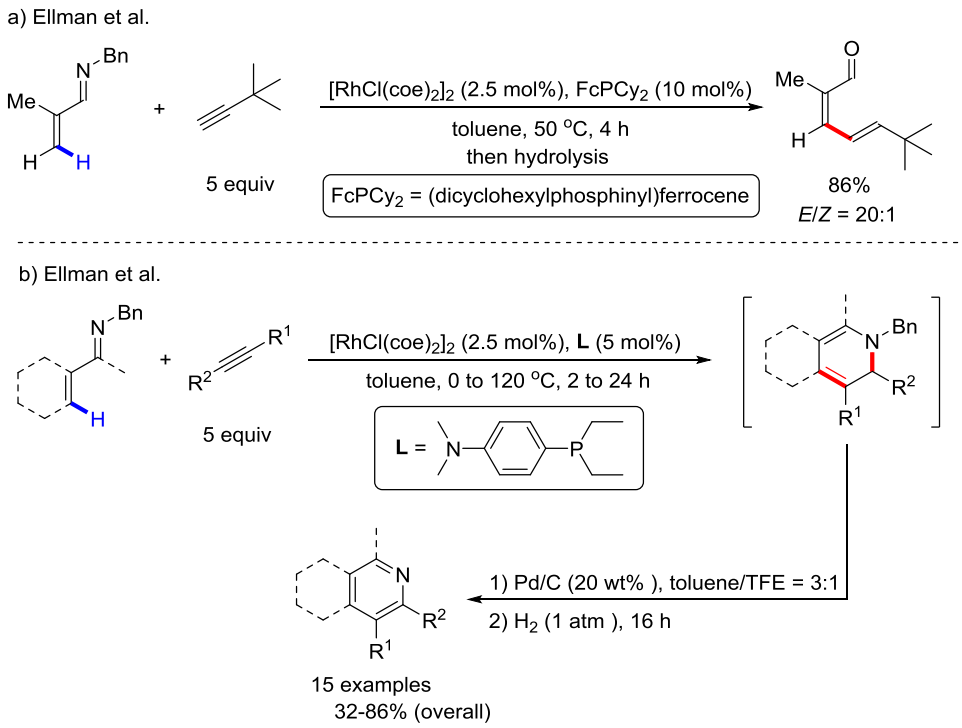
In 2016, Kim and co-workers reported the Rh-catalyzed cross-coupling reaction between acrylamides and maleimides. This reaction displayed a good stereoselectivity as well as a high functional group tolerance and this protocol offered a new way to access highly functionalized succinimides (Scheme 10).[28]



Scheme 10: The Rh-catalyzed cross-coupling reaction between acrylamides and maleimides.

1.3.2.2.2 Rh-catalyzed alkenylation

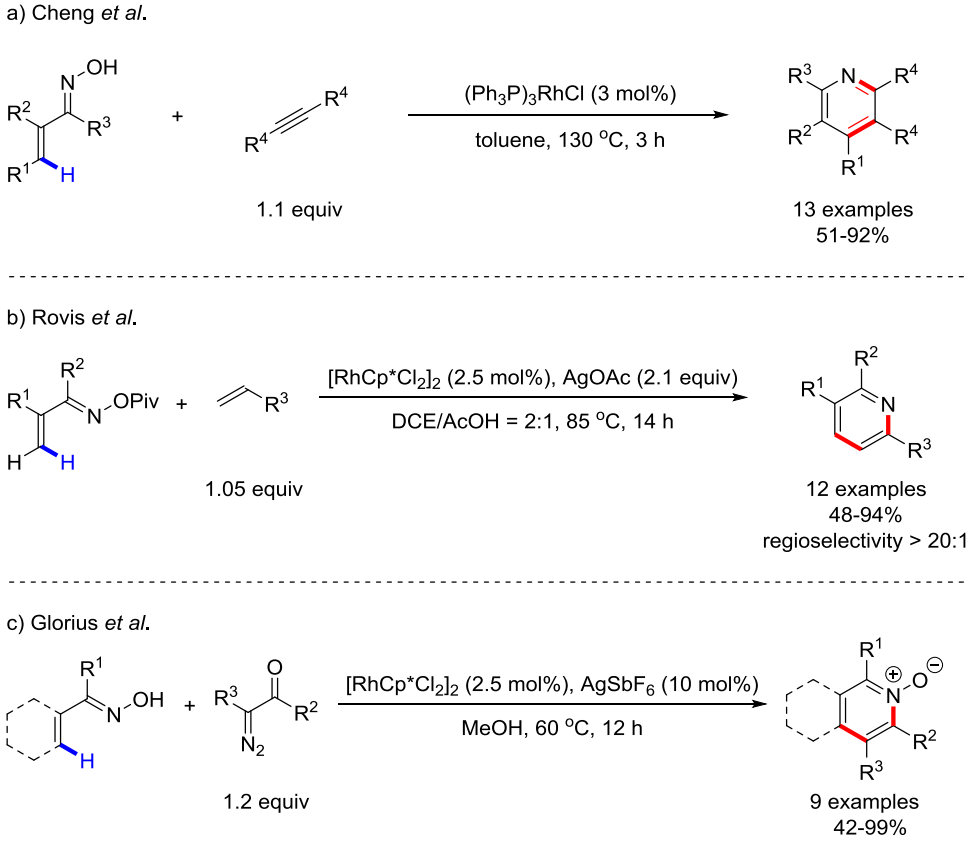
In 2006, during the development of the alkylation reaction,[22] Ellman and co-workers showed that the stereoselective alkenylation of the α,β-unsaturated imines can be also achieved by using an alkyne as the coupling partner (Scheme 11, a), instead of alkenes (Scheme 7). In 2008, they described the one pot synthesis of the polysubstituted pyridines from α,β-unsaturated imines and alkynes. It is worth to mention that the cascade of C-H bond alkenylation, electro cyclization and aromatization reactions was involved. A panel of imines was successfully converted into the corresponding pyridines in good to excellent yields (Scheme 11, b).[29]



Scheme 11: The imine directed alkylation with alkynes.

Several similar processes were reported by Cheng (2008, Scheme 12, a),[30] Rovis (2013, Scheme 12, b)[31] and Glorius (2013, Scheme 12, c)[32] with respect to the synthesis of polysubstituted pyridines and pyridine *N*-oxides. Glorius and co-workers

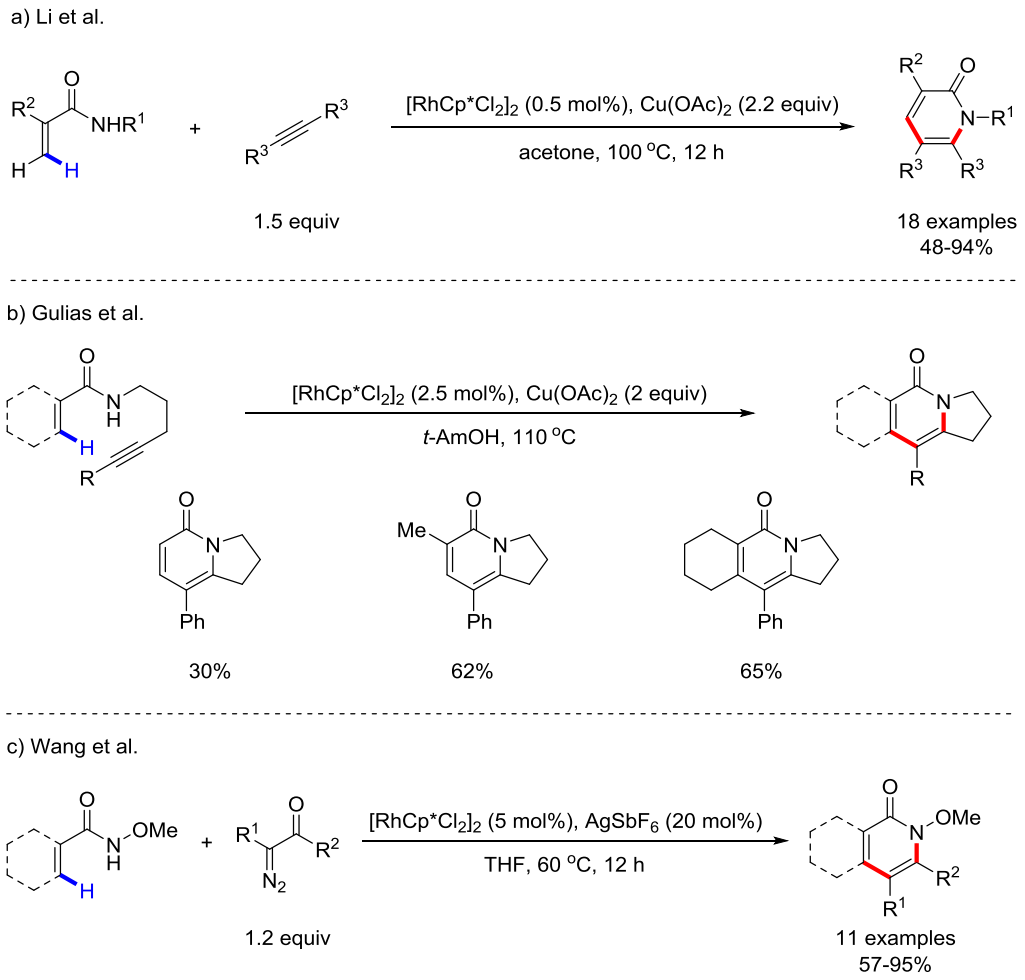
also showed that the replacement of the olefinic substrates by the aromatic ones led to the corresponding isoquinoline *N*-oxides instead of pyridine *N*-oxides.



Scheme 12: The synthesis of polysubstituted pyridines and pyridine *N*-oxides.

In 2010, Li and co-workers revealed the synthesis of polysubstituted 2-pyridones via the oxidative coupling between acrylamides and internal alkynes. $[RhCp^*Cl_2]_2$ was used as the catalyst and $Cu(OAc)_2$ was selected as the oxidant. Note that the 2-pyridones were obtained as the products while the formation of iminoesters was favored when R^1 was a bulky *N*-aryl group. This reaction demonstrated a great functional group tolerance and a series of polysubstituted 2-pyridones was obtained in moderate to good yields (Scheme 13, a).[33] Similar works concerning the synthesis of polysubstituted 2-pyridones were also reported by Gulias (2013) and Wang (2015). Gulias and co-workers described the Rh-catalyzed intramolecular annulations of

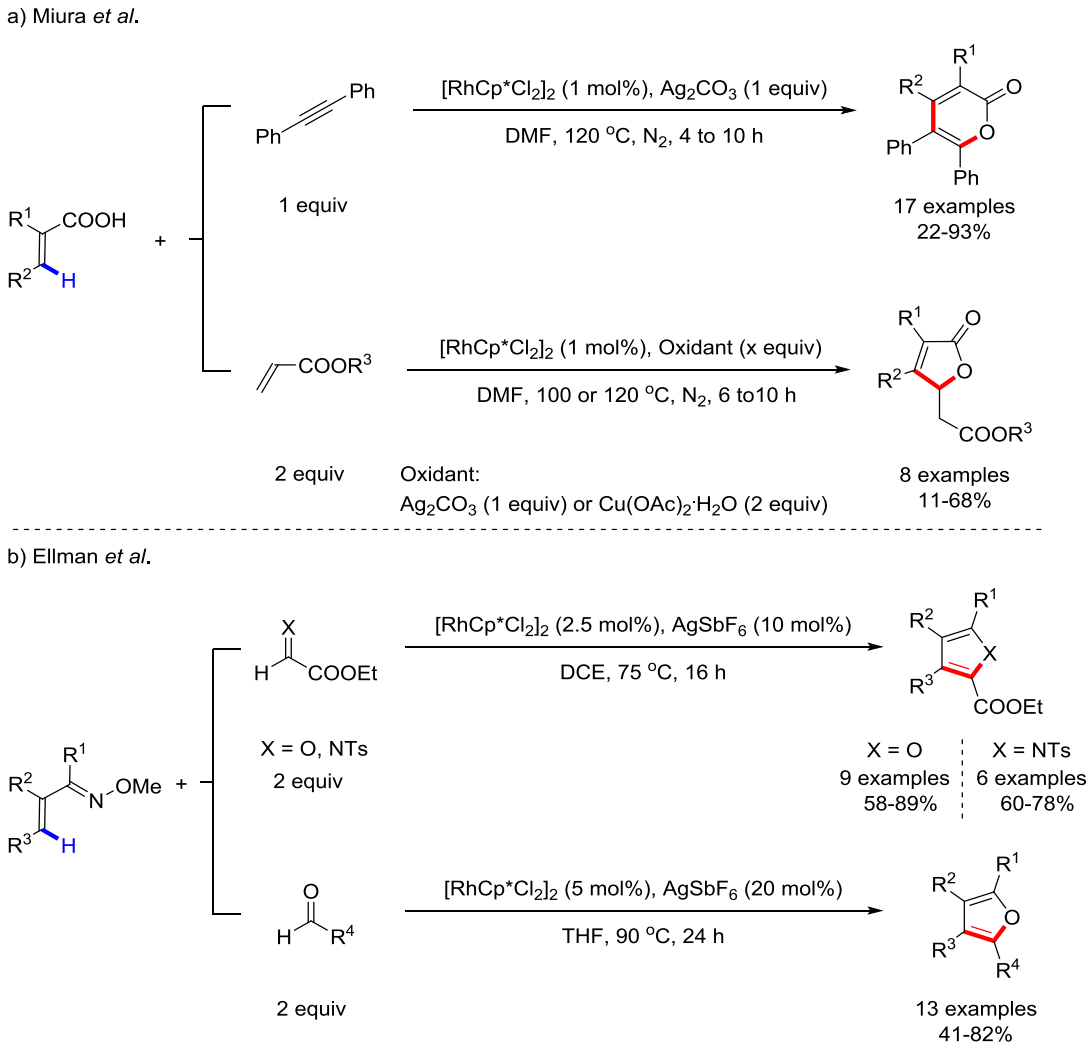
alkyne-tethered benzamides to give tricyclic isoquinoline derivatives. This reaction also worked well with alkyne-tethered acrylamides to produce 2-pyridone derivatives (Scheme 13, b).[34] Wang and co-workers revealed the Rh-catalyzed regioselective synthesis of 2-pyridone derivatives by using readily available starting material: *N*-methoxymethacrylamide and diazo compounds as coupling partners (Scheme 13, c).[35]



Scheme 13: The synthesis of polysubstituted 2-pyridones.

Besides the formation of different *N*-heterocycles, the synthesis of various *O*-heterocycles through the Rh-catalyzed alkenylation process was also developed. In 2009, Miura and co-workers described the oxidative coupling of acrylic acids with alkynes and alkenes leading to α-pyrone and γ-butenolide derivatives via a C-H bond

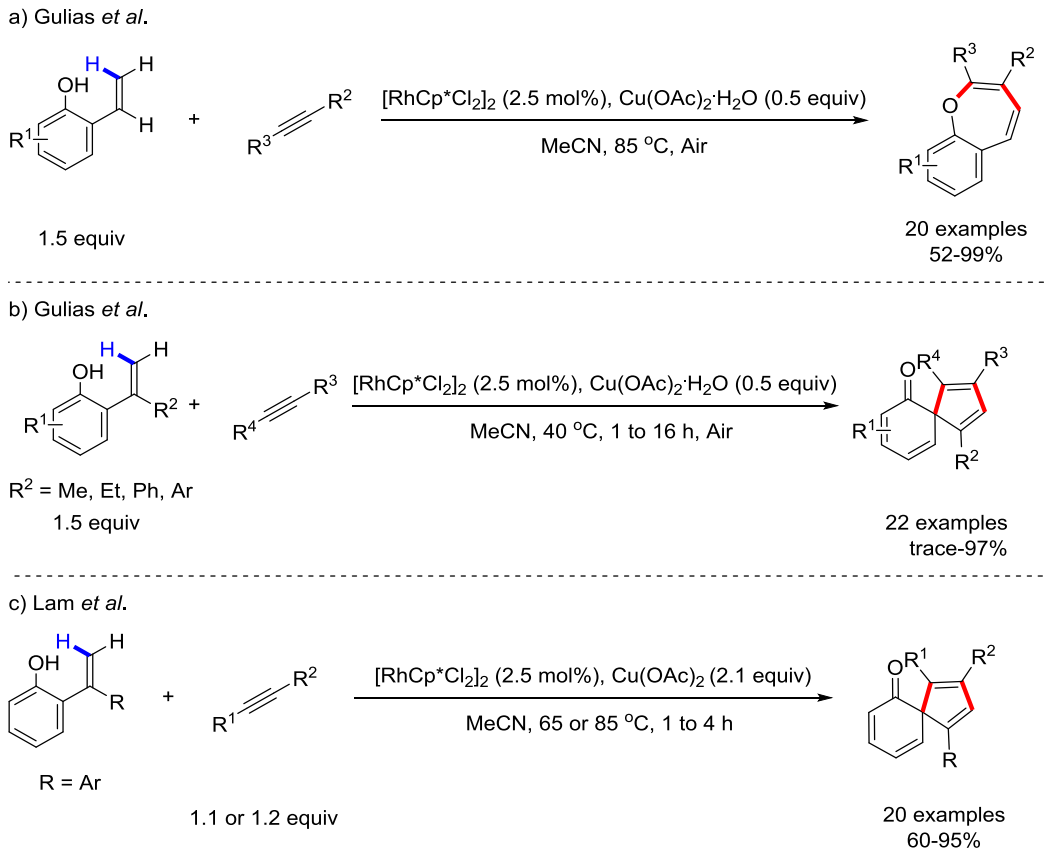
activation pathway. A similar catalytic pathway was involved in both cases (Scheme 14, a).[36] In 2013, Ellman and co-workers developed a straightforward way for the synthesis of multi-functionalized furans by reacting α,β-unsaturated oximes with ethyl glyoxylate and different aldehydes (Scheme 14, b).[37] It is worth to mention that replacing the ethyl glyoxylate by the corresponding *N*-tosyl imine in THF led to the formation of highly functionalized pyrroles.



Scheme 14: The synthesis of different *O*- and *N*-heterocycles.

In 2013, Gulias and co-workers developed the oxidative [5+2] cycloaddition of *o*-vinylphenols and alkynes leading to the benzoxepine products. The $[RhCp^*Cl_2]_2$ catalyzed C-H bond activation pathway was involved (Scheme 15, a).[38] Note that the

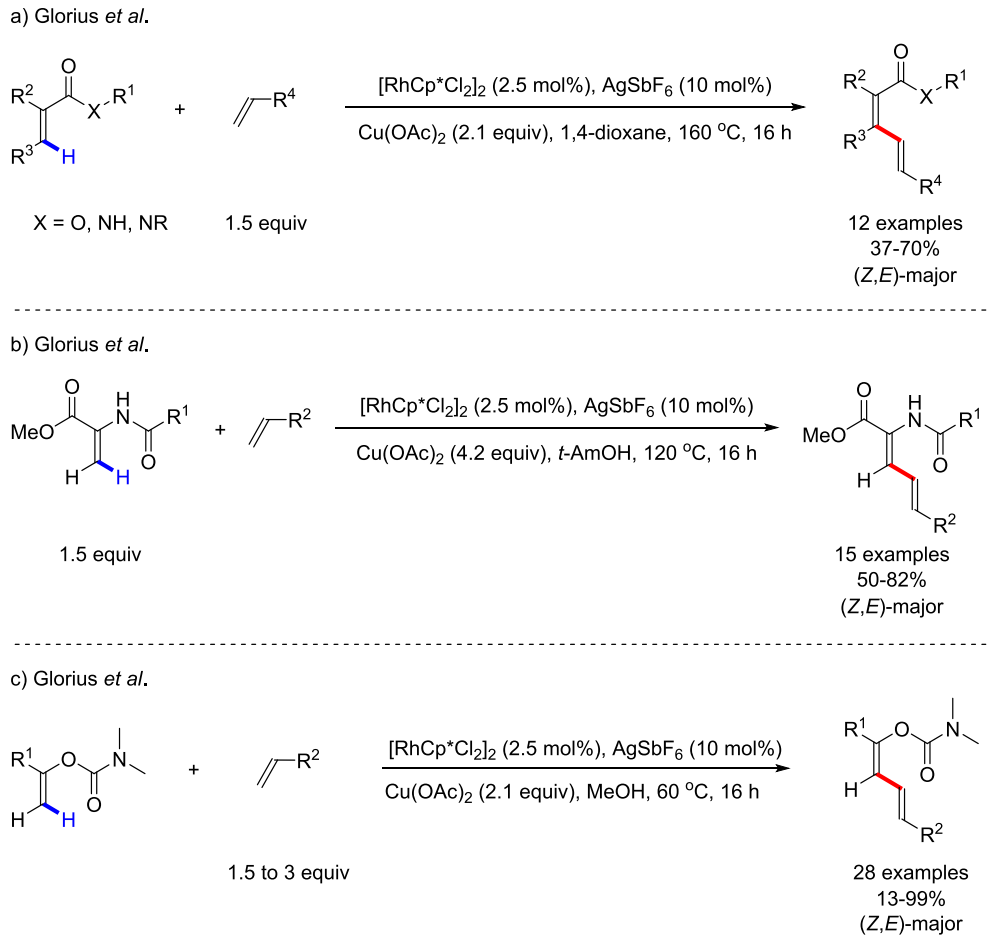
replacement of alkynes by CO allowed the formation of coumarin derivatives. Based on this work, they observed that the spirocyclopentadienes were obtained when *o*-vinylphenols were replaced by α-substituted vinyl phenol derivatives (2014, Scheme 15, b).[39] This reaction proceeded well even at lower temperature (40 °C), compared with their previous work (85 °C). In the same year, Lam and co-workers reported a similar work and a wide range of substrates were smoothly converted into the spirocyclopentadiene products (Scheme 15, c).[40]



Scheme 15: The synthesis of benzoxepines and spirocyclopentadienes.

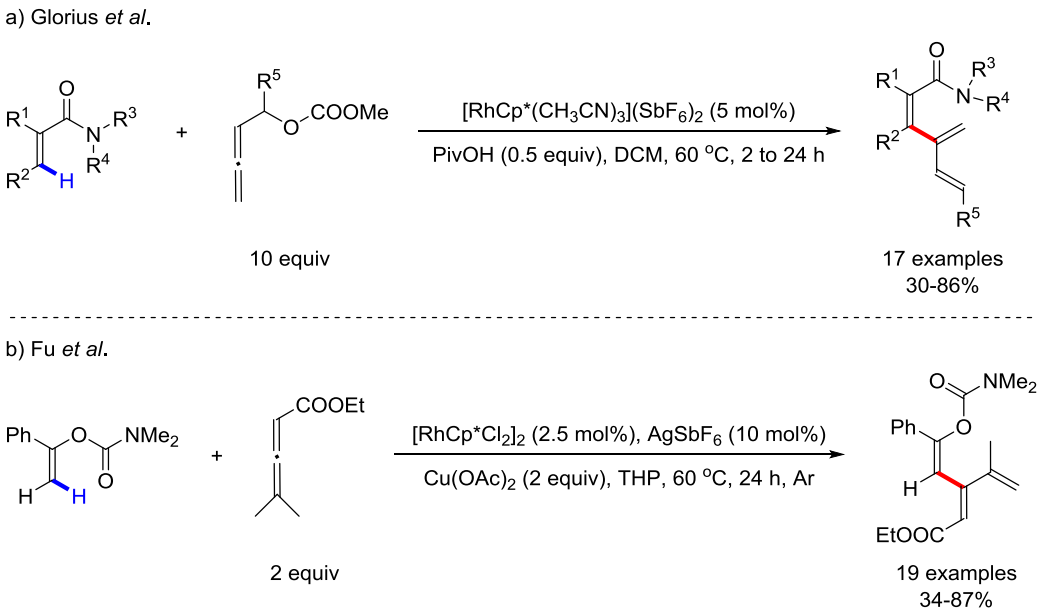
The formation of highly functionalized 1,3-butadienes was also achieved via Rh-catalyzed olefinic C-H bond activation method. In 2011, Glorius and co-workers described the synthesis of 1,3-butadienes via a Rh-catalyzed oxidative C-H bond olefination pathway. The (*Z*, *E*)-1,3-butadienes were obtained as the major products in

moderate to good yields (Scheme 16, a).[41] Besides, they successfully applied this protocol to access α,β,γ,δ-unsaturated α-amino acid derivatives by using a similar Rh-catalysis system in *t*-AmOH, instead of 1,4-dioxane (Scheme 16, b).[41] In 2014, they realized the alkenylation of enol carbamates under the same Rh-catalysis system at a lower temperature (60 °C instead of 120 °C). This reaction allowed the construction of 1,3-butadienes from a wide range of enolates with different coupling partners (Scheme 16, c).[42] The cleavage of the carbamate directing group led to the valuable β,γ-unsaturated ketone skeleton. Similar works were also reported by Loh (2012),[18] Zhang (2014)[43] and Zhong (2017)[44] by using an amide, ester or Weinreb amide as the directing group, respectively.



Scheme 16: The synthesis of (*Z*, *E*)-1,3-butadienes developed by Glorius and co-workers.

In 2013, Glorius and co-workers developed the synthesis of dendralenes via a Rh-catalyzed olefinic C-H activation followed by a coupling reaction with allenyl carbinol carbonates. Various dendralene derivatives were obtained with a great efficiency. In addition, this reaction demonstrated a good functional group and directing group tolerance (Scheme 17, a).[45] Note that this catalytic system was also applicable for the corresponding aromatic C-H bond functionalization. One year later, Fu and co-workers reported the Rh-catalyzed olefinic C-H activation with allenes to access dendralenes (Scheme 17, b).[46] This reaction was also applicable to aromatic C-H bond activation and was compatible with various functional groups. In order to show the synthetic utility of the resulting product, both research groups performed post-functionalization of dendralenes through the Diels-Alder reaction.

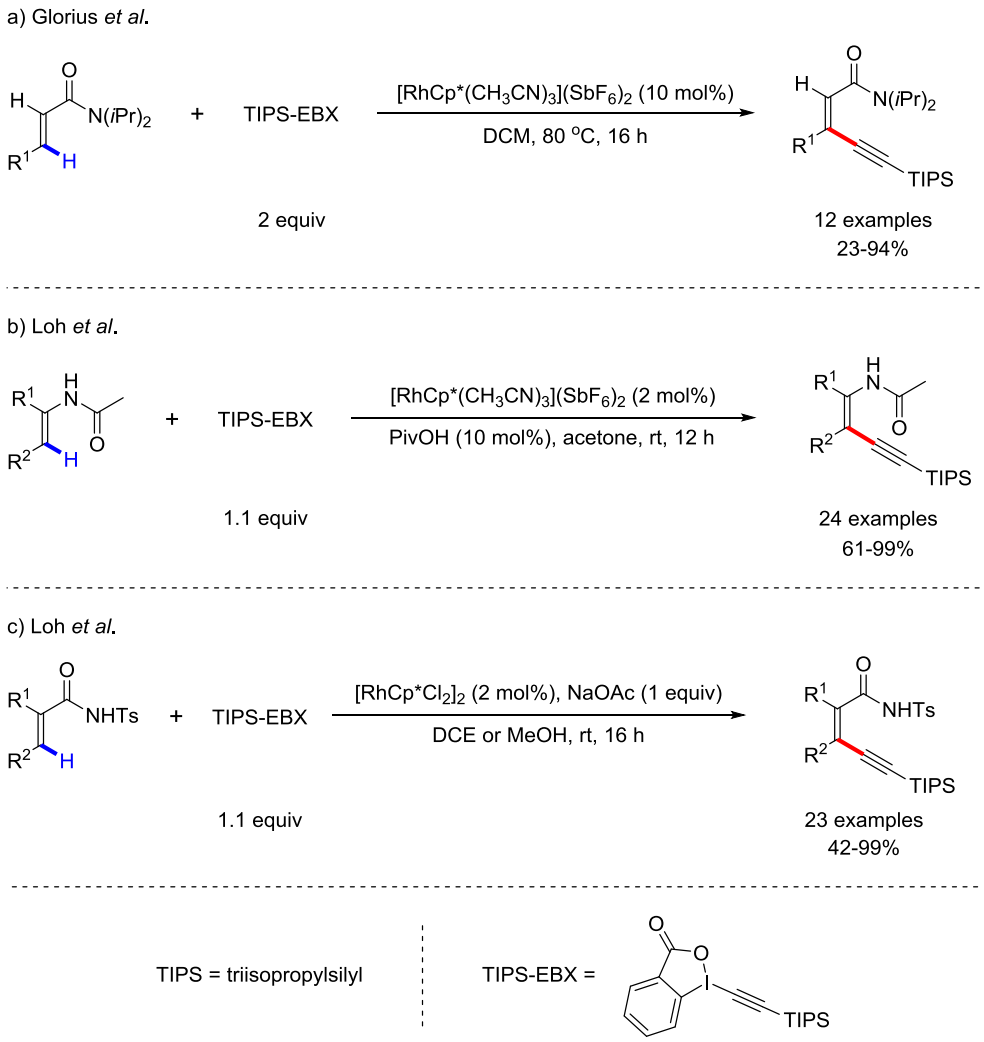


Scheme 17: The synthesis of dendralenes.

1.3.2.2.3 Rh-catalyzed alkynylation

In 2014, Glorius and co-workers depicted the Rh-catalyzed alkynylation of acrylamides

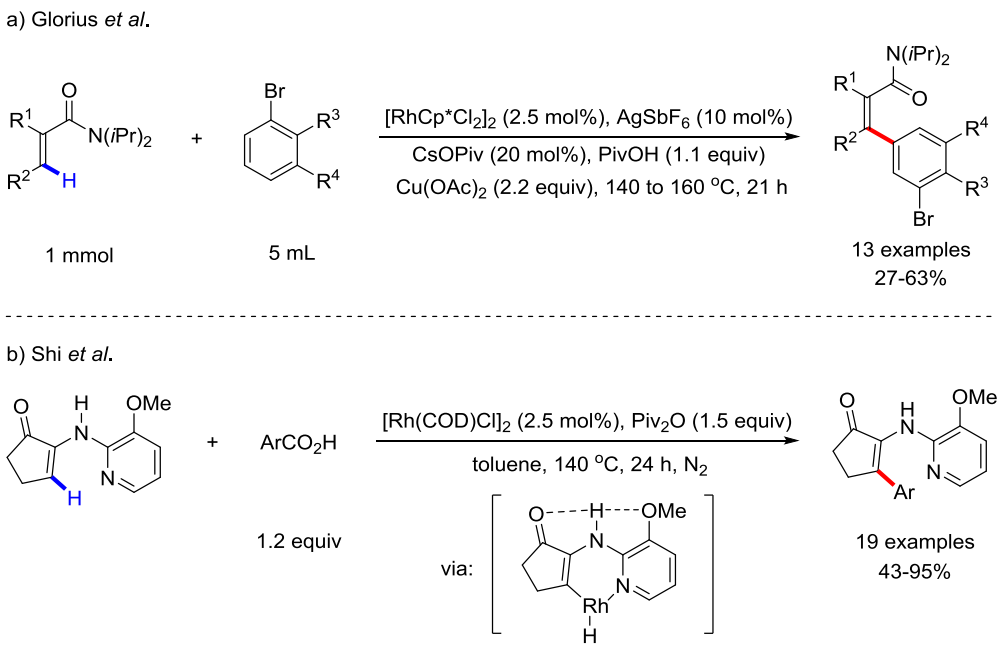
with a commercially available alkyne source: TIPS-EBX. This reaction gave access to highly functionalized 1,3-enyne derivatives in excellent yields (Scheme 18, a).[47] In the same year, Loh and co-workers reported two Rh-catalyzed olefinic C-H bond alkynylation reactions by using an electron-donating (-HNCOMe)[48] and an electron-withdrawing (-CONHTs)[49] directing group, respectively (Scheme 18, b and c). In both cases, the TIPS-EBX was used as the alkyne source and a wide range of substrates were successfully converted into the corresponding polyfunctionalized 1,3-enynes. Note that both reactions performed well at room temperature.



Scheme 18: The Rh-catalyzed olefinic C-H bond alkynylations.

1.3.2.2.4 Rh-catalyzed arylation

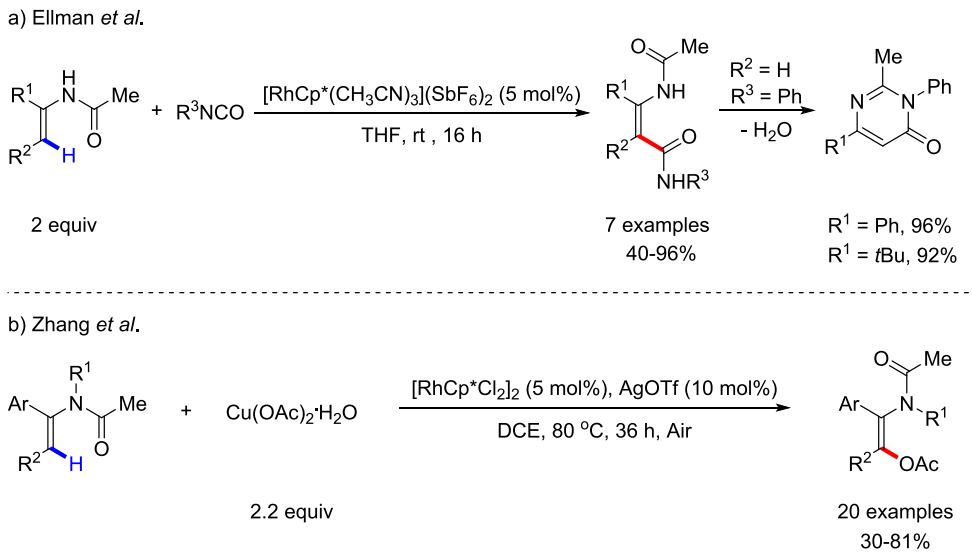
In 2012, Glorius and co-workers depicted the Rh-catalyzed dehydrogenative alkene-arene coupling reaction to selectively access tri- and tetrasubstituted olefins. This reaction demonstrated excellent (*Z*)-selectivity, albeit limited by moderate yields (Scheme 19, a).[50] In 2014, Shi and co-workers developed the Rh-catalyzed olefinic C-H bond arylations of cyclic enamines with various carboxylic acids. A wide range of acids were subjected to this coupling reacion to afford the corresponding products in high yields. Note that the -OMe group plays an important role to place the directing group in the most favorable orientation toward the targeted olefinic C-H bond, since the removal or replacement of this -OMe group led to disappointing yields (Scheme 19, b).[51]



Scheme 19: The Rh-catalyzed olefinic C-H bond arylations.

1.3.2.2.5 Rh-catalyzed amidation and acetoxylation

In 2011, Ellman and co-workers reported the Rh-catalyzed amidation of *N*-acyl enamines with isocyanates. To show the utility of the resulting products, the post-functionalization of two *N*-acyl enamine amides was performed to access pyrimidin-4-one heterocycles (Scheme 20, a).[52] It is worth to mention that this protocol is also applicable to *N*-acyl anilides. In 2014, Zhang and co-workers reported the Rh-catalyzed acetoxylation of enamides with excellent regio- and stereoselectivity to produce the (*Z*)-isomers. This acetoxylation reaction was efficient with a wide range of enamides and demonstrated a great functional group tolerance. Note that $Cu(OAc)_2$ served as the acetate source as well as the oxidant in the transformation (Scheme 20, b).[53]

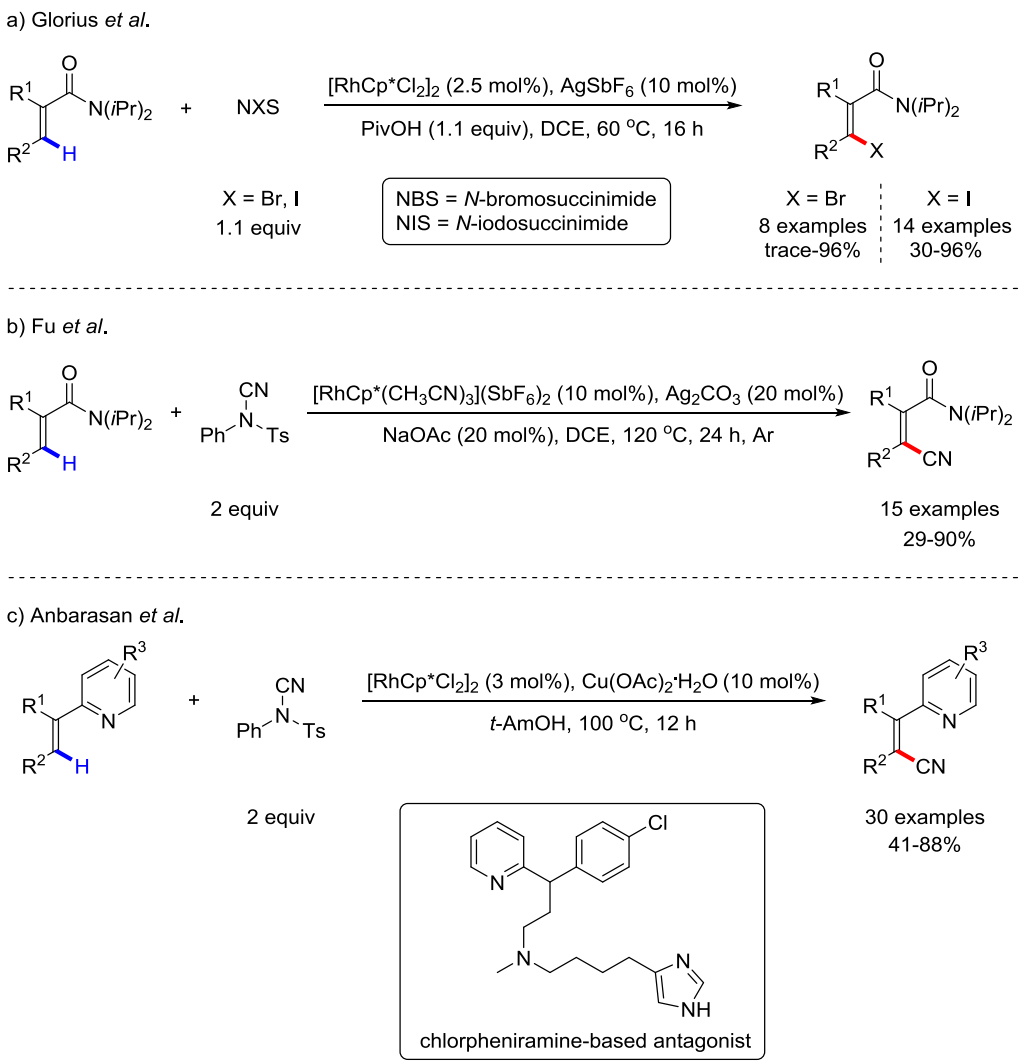


Scheme 20: The Rh-catalyzed olefinic C-H bond amidations and acetoxylations.

1.3.2.2.6 Rh-catalyzed halogenation and cyanation

In 2013, Glorius and co-workers depicted the Rh-catalyzed iodination/bromination of

acrylamides to access (*Z*)-iodo and (*Z*)-bromo acrylic acid derivatives. This reaction exhibited great regio- and stereoselectivities and allowed the presence of a variety of synthetically useful functional groups (Scheme 21, a).[54] Two years later, by using the same amide directing group (-CON*i*Pr_2), Fu and co-workers developed the Rh-catalyzed olefinic C-H bond cyanation reaction for the synthesis of acrylonitriles (Scheme 21, b).[55] Note that this C–H bond cyanation process is also applicable to ketoxime substrates. In the same year, Anbarasan and co-workers reported a similar cyanation protocol by using pyridine as the directing group. Diverse acrylonitriles were obtained in good yields and a chlorpheniramine-based antagonist was synthesized to show the synthetic utility of this protocol (Scheme 21, c).[56] In both cyanation reactions, the environmentally benign reagent: *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) was selected as the -CN source and excellent (*Z*)-selectivity was achieved.



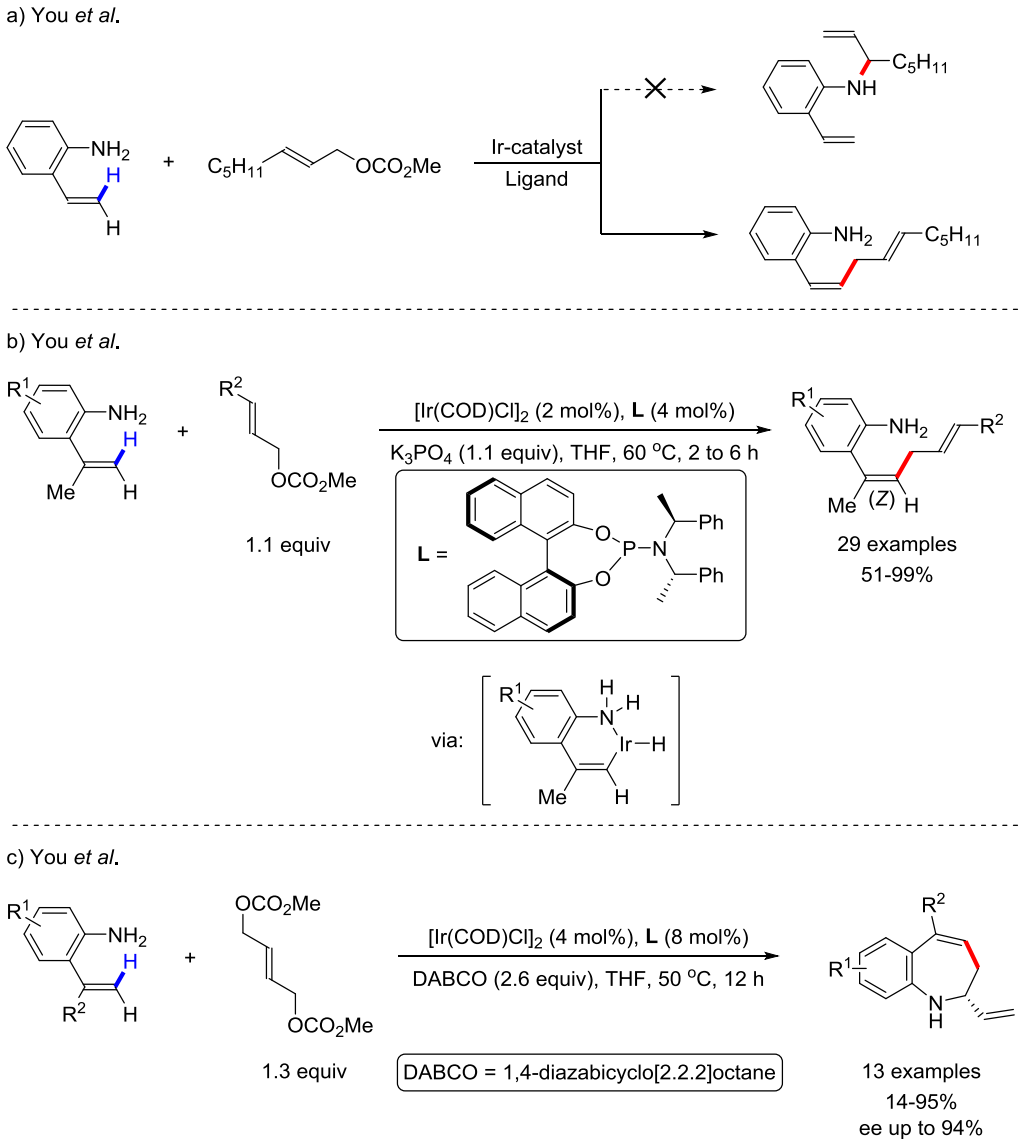
Scheme 21: The Rh-catalyzed olefinic C-H bond halogenations and cyanations.

1.3.2.3 Ir-catalysis

1.3.2.3.1 Ir-catalyzed alkylation

In 2009, You and co-workers described a Ir-catalyzed alkylation of *ortho*-amino styrenes with allylic carbonates, which was discovered from a side reaction. They originally designed an allylic amination reaction between the *ortho*-amino styrene and an allylic carbonate. Surprisingly, a Heck-type product was obtained instead of the desired amination product (Scheme 22, a).[57] Based on this serendipity, they developed

the $[Ir(COD)Cl]_2$ catalyzed coupling reaction to access skipped (*Z*)/(*E*)-1,4-butadienes via an olefinic C-H bond functionalization pathway (Scheme 22, b).[57-58] After modifying the reaction conditions, the tandem allylic vinylation/allylic amination reaction was achieved to afford the 2,3-dihydro-1H-benzo[b]azepine derivatives with high enantioselectivities (Scheme 22, c).[59]

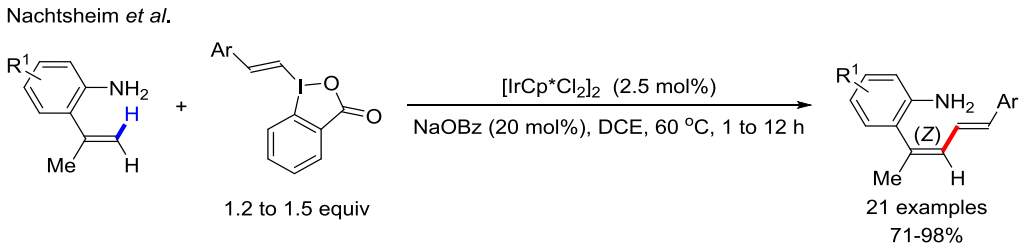


Scheme 22: The Ir-catalyzed olefinic C-H bond alkylation.

1.3.2.3.2 Ir-catalyzed alkenylation

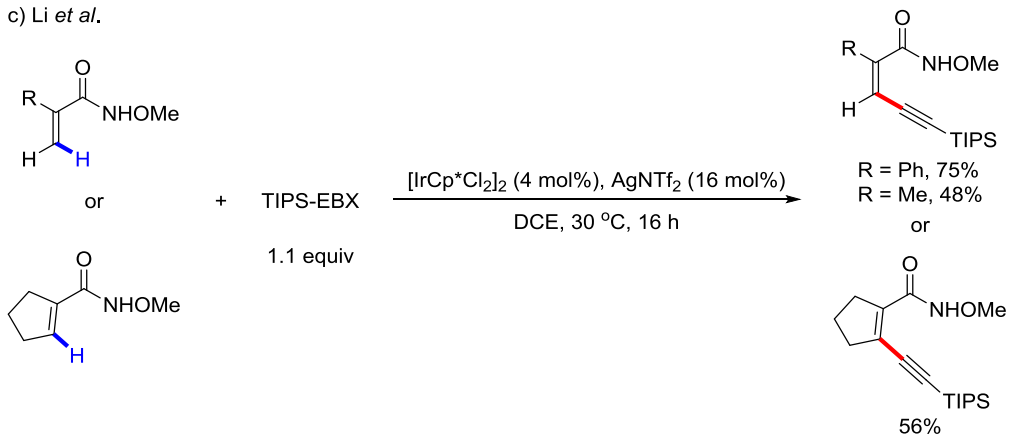
In 2017, Nachtsheim and co-workers developed the Ir-catalyzed alkenylation of *ortho*-

amino styrenes with vinylbenziodoxolones to access 1,3-dienes in excellent yields with high (*Z*,*E*)-stereoselectivity. This reaction demonstrated a great functional group tolerance and a broad substrates scope. Note that the free aromatic amine was used as the directing group, which was synthetically valuable since it can be easily transformed into other functional groups (Scheme 23).[60]



Scheme 23: The Ir-catalyzed olefinic C-H bond alkenylation.

In 2014, Li and co-workers reported the Ir-catalyzed alkynylation of *N*-methoxycarboxamides with TIPS-EBX. The olefinic substrates bearing the same directing group (3 examples) also proceeded well under the same conditions (Scheme 24).[61]

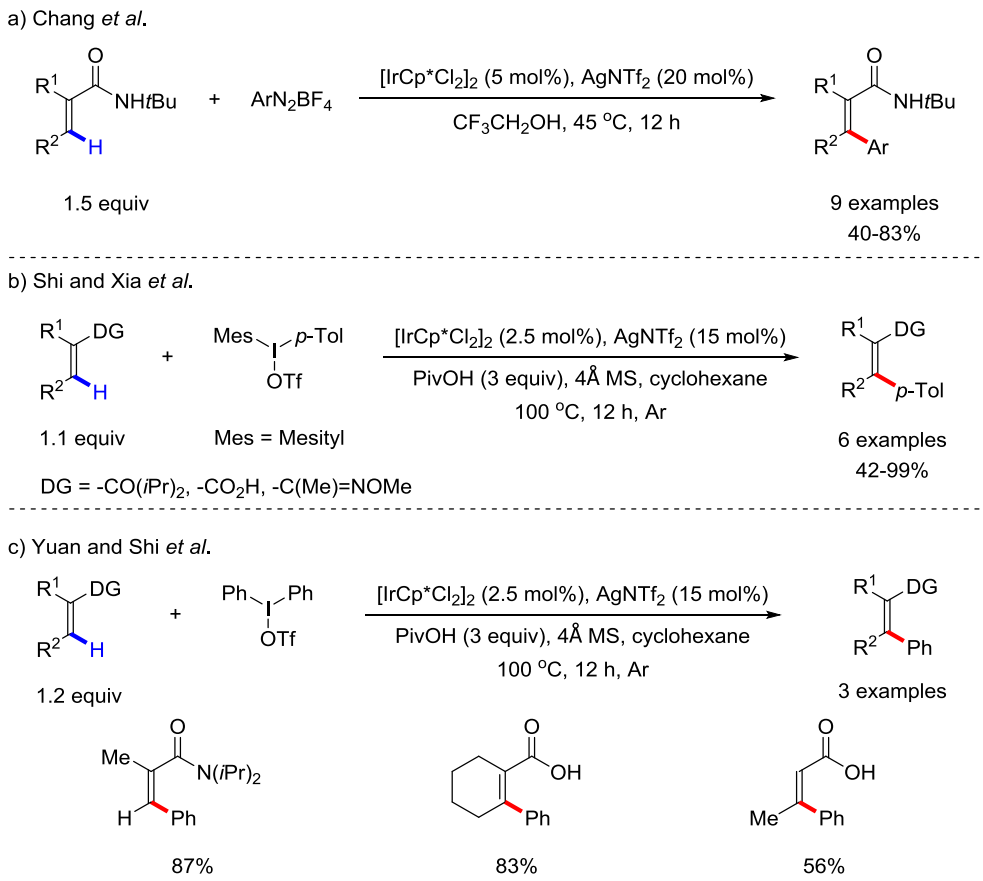


Scheme 24: The Ir-catalyzed olefinic C-H bond alkynylation.

1.3.2.3.3 Ir-catalyzed arylation

In 2015, Chang and co-workers reported the Ir-catalyzed olefinic C(sp^2)-H bond

arylation between acrylamides with aryldiazonium tetrafluoroborates. The (*Z*)-selective arylation of a panel of enamides was achieved in moderate to good yields (Scheme 25, a).[62] In the same year, Shi, Xia and co-workers developed a versatile Ir-catalyzed aliphatic C(sp^3)-H bond arylation system and this C-C coupling reaction was also successfully applied to olefinic C(sp^2)-H bond arylation (Scheme 25, b).[63] One year later, Yuan, Shi and co-workers described similar results (3 examples) under the same catalytic system with diaryliodonium salt Ph_2IOTf (Scheme 25, c).[64]

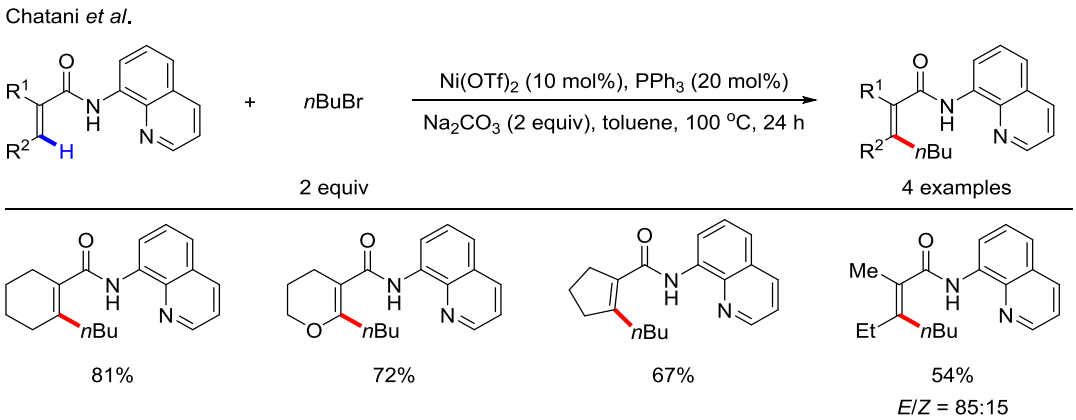


Scheme 25: The Ir-catalyzed olefinic C-H bond arylation.

1.3.2.4 Ni-catalysis

1.3.2.4.1 Ni-catalyzed alkylation

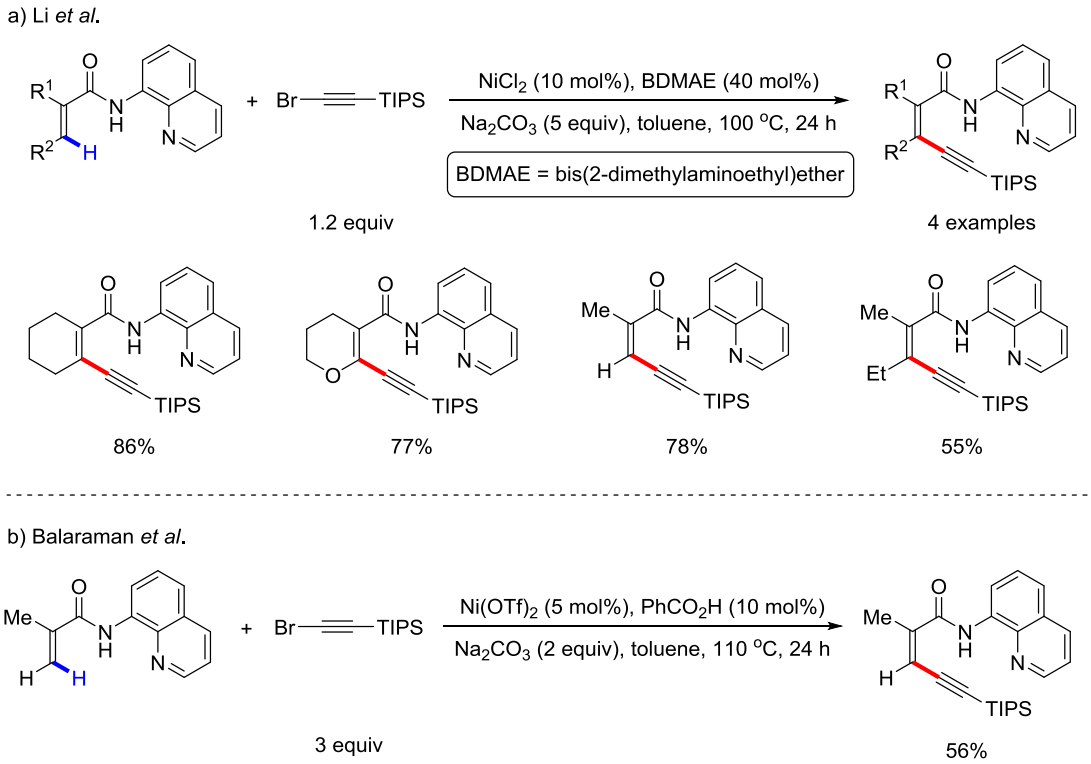
In 2013, Chatani and co-workers reported the Ni-catalyzed C(sp^2)-H bond alkylation with different alkyl halides by using 8-aminoquinoline moiety as the bidentate directing group. The reaction proceeded well with a variety of benzamides as well as few acrylamides (4 examples) in good yields (Scheme 26).[65] The bulky and heavy bidentate directing group was not removable, which was a drawback for this protocol.



Scheme 26: The Ni-catalyzed olefinic C-H bond alkylation.

1.3.2.4.2 Ni-catalyzed alkynylation

In 2015 and 2016, Li (Scheme 27, a)[66] and Balaraman (Scheme 27, b)[67] independently reported two Ni-catalyzed C(sp^2)-H bond alkynylation reactions. Both methods were applicable to a wide range of benzamides while limited to few acrylamides: 4 and 1 examples, respectively. The 8-aminoquinoline motif was used as the directing group in both olefinic C(sp^2)-H bond alkynylation protocols and was cleaved after the catalytic reactions.

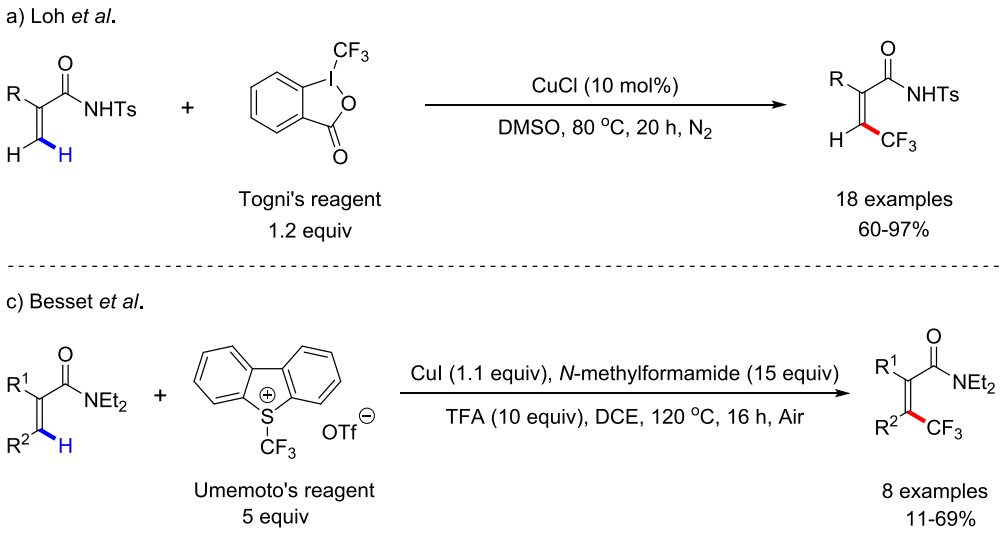


Scheme 27: The Ni-catalyzed olefinic C-H bond alkynylation.

1.3.2.5 Cu-catalysis

1.3.2.5.1 Cu-catalyzed/mediated trifluoromethylation

In 2013, Loh and co-workers reported the Cu-catalyzed olefinic C(sp^2)-H bond trifluoromethylation with Togni's reagent. The -CONHTs moiety acted as the directing group for the regio- and stereoselectivities and a wide range of terminal olefins were converted into the trifluoromethylated products in good to excellent yields (Scheme 28, a).[68] In 2014, Besset and co-workers depicted the Cu-mediated olefinic C(sp^2)-H bond trifluoromethylation with the Umemoto's reagent by using -$CONEt_2$ moiety as the directing group. The protocol was not limited to terminal olefins, albeit a stoichiometric amount of CuI was needed (Scheme 28, b).[69] Some other relevant works were reviewed.[12a]



Scheme 28: The Cu-catalyzed/mediated olefinic C-H bond trifluoromethylation.

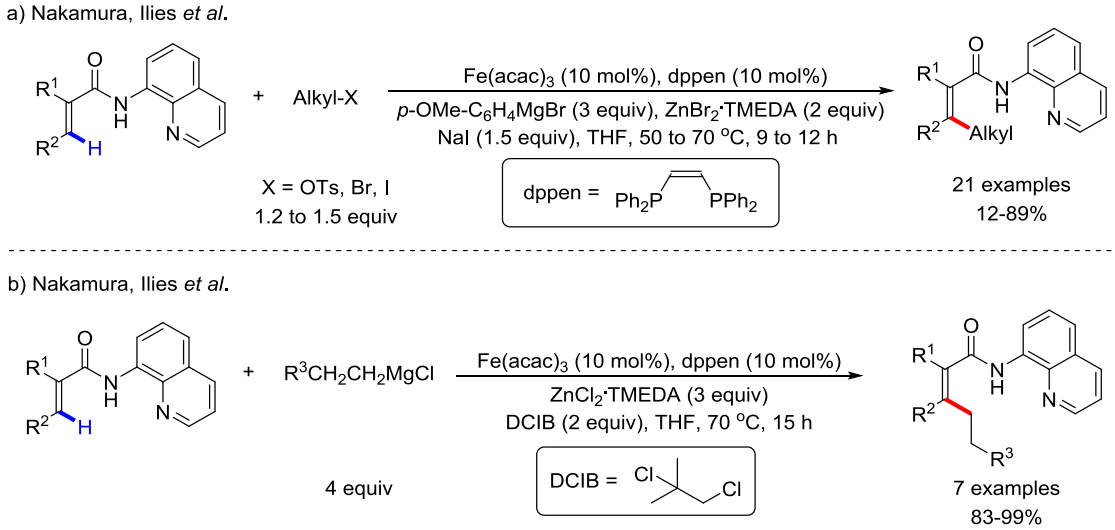
1.3.2.6 Fe-catalysis

The iron-catalyzed C-H bond functionalization has recently attracted more attention because of the low-cost, natural abundance, and low toxicity of iron. Those reviews[70] would help to get a comprehensive picture of the iron-catalyzed C-H bond functionalization.

1.3.2.6.1 Fe-catalyzed alkylation

In 2014, Nakamura, Ilies and co-workers described the Fe-catalyzed coupling reaction between acrylamides and alkyl electrophiles. The reaction proceeded efficiently with high regio- and stereoselectivities and it was also applicable to aromatic carboxamides (Scheme 29, a).[71] One year later, the same research group reported another Fe-catalyzed olefinic C(sp^2)-H bond alkylation reaction. This protocol proceeded smoothly between acrylamides and primary or secondary *in situ* generated alkylzinc halides (Scheme 29, b).[72] The 8-aminoquinoline moiety was used as the bidentate

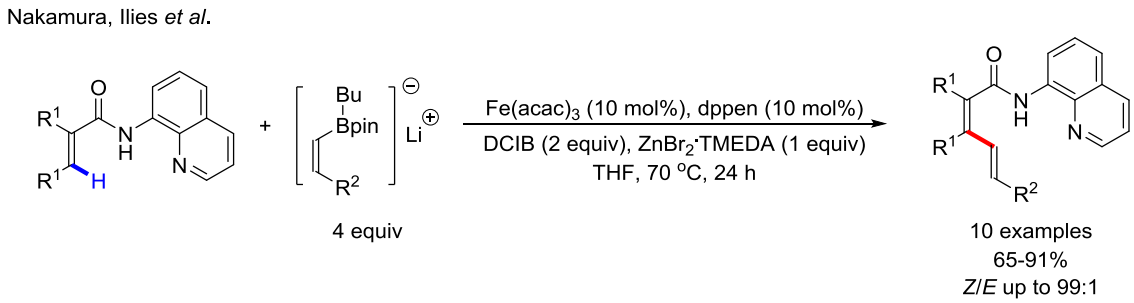
directing group in both cases and it was not removable after the catalytic reactions. Note that other Fe-catalyzed olefinic C(sp^2)-H bond alkylation events were depicted by Cook (2014),[73] Nakamura, Ilies (2014)[74] and Ackermann (2016),[75] while limited to few examples.



Scheme 29: The Fe-catalyzed olefinic C-H bond alkylation.

1.3.2.6.2 Fe-catalyzed alkenylation

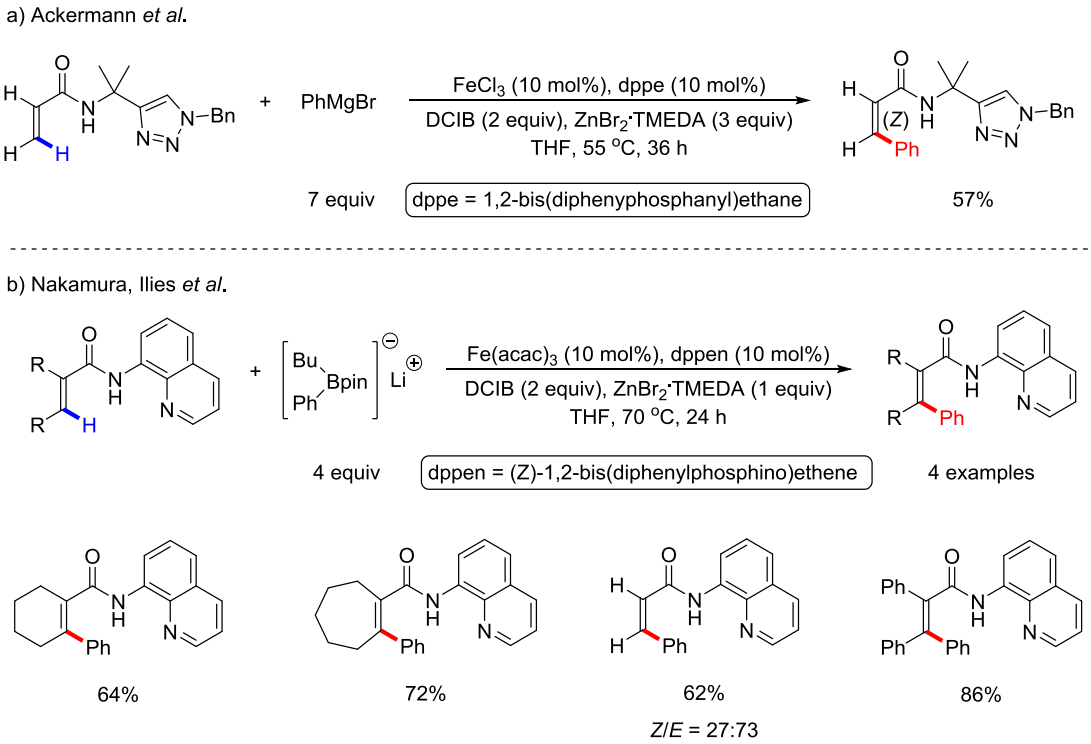
In 2014, Nakamura, Ilies and co-workers depicted the Fe-catalyzed olefinic C(sp^2)-H bond alkenylation reaction between acrylamides and alkenyl boronate compounds. A panel of alkenylated products was stereospecifically obtained in good yields (Scheme 30).[74]



Scheme 30: The Fe-catalyzed olefinic C-H bond alkenylation.

1.3.2.6.3 Fe-catalyzed arylation

In 2014, Ackermann and co-workers developed the powerful Fe-catalyzed aromatic and olefinic C(sp^2)-H as well as aliphatic C(sp^3)-H bond arylations under the similar reaction conditions. One example concerning olefinic C(sp^2)-H bond arylation was shown (Scheme 31, a).[76] In 2014, during the development of the alkenylation reaction, Nakamura, Ilies and co-workers also succeeded in the arylation with 4 examples by using an aryl boronate coupling partner (Scheme 31, b).[74]



Scheme 31: The Fe-catalyzed olefinic C-H bond arylation.

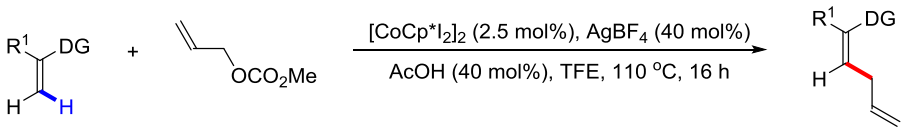
1.3.2.7 Co-catalysis

In 1955, Murahashi reported the ability of cobalt to catalyze C-H bond functionalization.[77] Then, more than 60 years after, the Co-catalyzed C-H bond functionalization has become a powerful tool for sustainable synthesis.[78]

1.3.2.7.1 Co-catalyzed alkylation

In 2015, Glorius and co-workers reported the Co-catalyzed allylation of benzamides and acrylamides via a C-H bond functionalization process. Five acrylamides were successfully converted into skipped dienes with a high (*Z*)-stereoselectivity (Scheme 32).[79] Note that this protocol was applicable with a panel of amide directing groups.

Glorius *et al.*



2 equiv

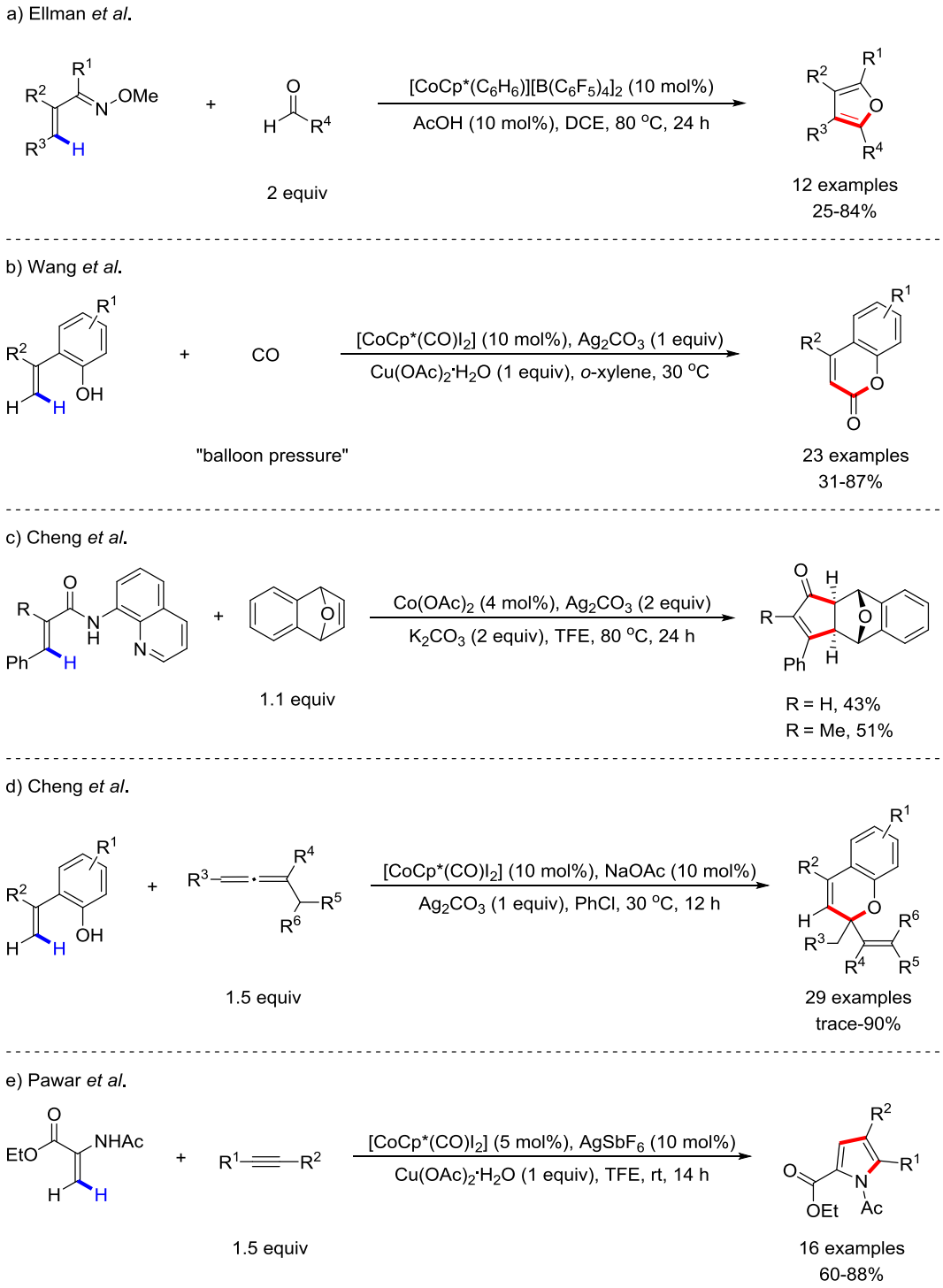
5 examples
22-66%

DG = -CONEt$_2$, -CONH*n*Bu, -CON(*i*Pr)$_2$

Scheme 32: The Co-catalyzed olefinic C-H bond alkylation.

1.3.2.7.2 Co-catalyzed C-H bond functionalization/cyclization cascades

In 2015, Ellman and co-workers developed the Co-catalyzed cyclization of α-methyl oximes with aldehydes to access furans under mild reaction conditions (Scheme 33, a).[80] The C-H bond functionalization was followed by an *in situ* cyclization process. Note that this reaction proceeded well when the original additive AgOAc was replaced by the inexpensive AcOH. The same year, Wang and co-workers described the Co-catalyzed cyclization of 2-alkenylphenols with CO to access coumarins. The reaction demonstrated a great functional groups tolerance as well as a wide substrates scope (Scheme 33, b).[81] Similar C-H bond functionalization/cyclization cascade protocols were reported by Cheng (2016, Scheme 33, c and d)[82] and Pawar (2016, Scheme 33, e).[83]



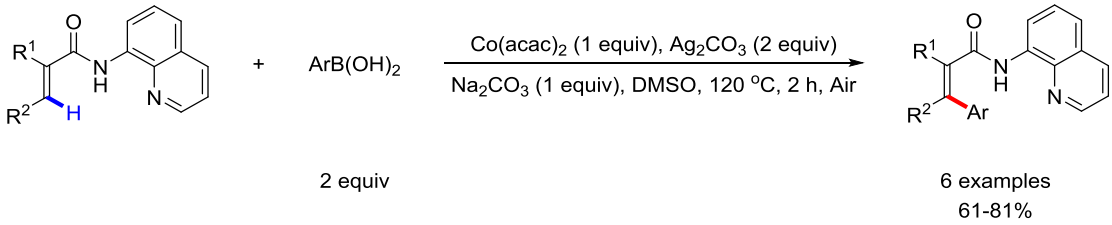
Scheme 33: The Co-catalyzed C-H bond functionalization/cyclization cascades.

1.3.2.7.3 Co-mediated arylation

In 2016, Tan and co-workers developed the Co-mediated arylation of acrylamides with arylboronic acids via a C-H bond functionalization pathway to obtain arylated products

in good yields (Scheme 34).[84] The 8-aminoquinoline moiety was used as the directing group and it was removed in NaOH/EtOH at 130 °C after 48 h. A stoichiometric amount of $Co(acac)_2$ was required for this transformation.

Tan *et al*.

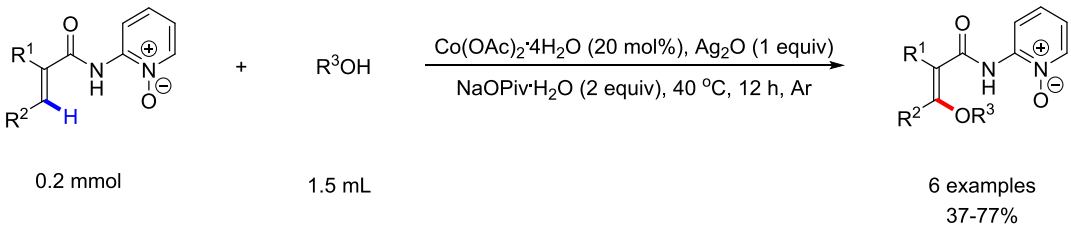


Scheme 34: The Co-mediated olefinic C-H bond arylation.

1.3.2.7.4 Co-catalyzed alkoxylation

In 2016, Song, Niu and co-workers reported the Co-catalyzed olefinic C(sp^2)-H bond alkoxylation of acrylamides with alcohols by using the 2-aminopyridine-*N*-oxide moiety as a bidentate directing group (Scheme 35).[85] Note that this method was applicable to a wide range of benzamides and the directing group was easily removed from the resulting products in NaOH/EtOH at 80 °C after 10 h.

Song, Niu *et al*.



Scheme 35: The Co-catalyzed olefinic C-H bond alkoxylation.

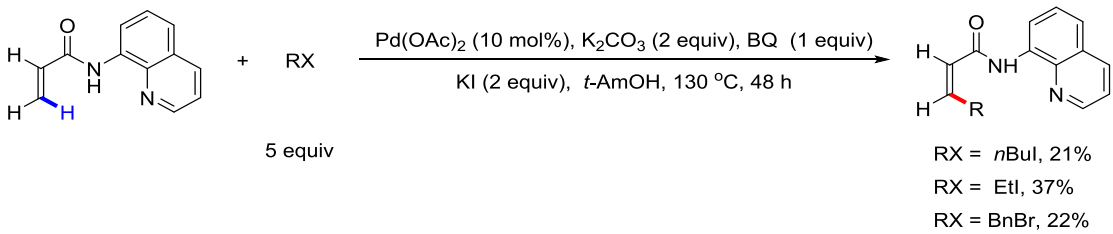
1.3.2.8 Pd-catalysis

1.3.2.8.1 Pd-catalyzed alkylation

In 2016, Jiang, Xue and co-workers reported the Pd-catalyzed olefinic C(sp^2)-H bond

alkylation of an unsubstituted acrylamide with three different alkyl halides. This reaction was less efficient since low conversions and low yields were obtained (Scheme 36).[86] However, this protocol proceeded pretty well with aryl iodides (see: Scheme 41).

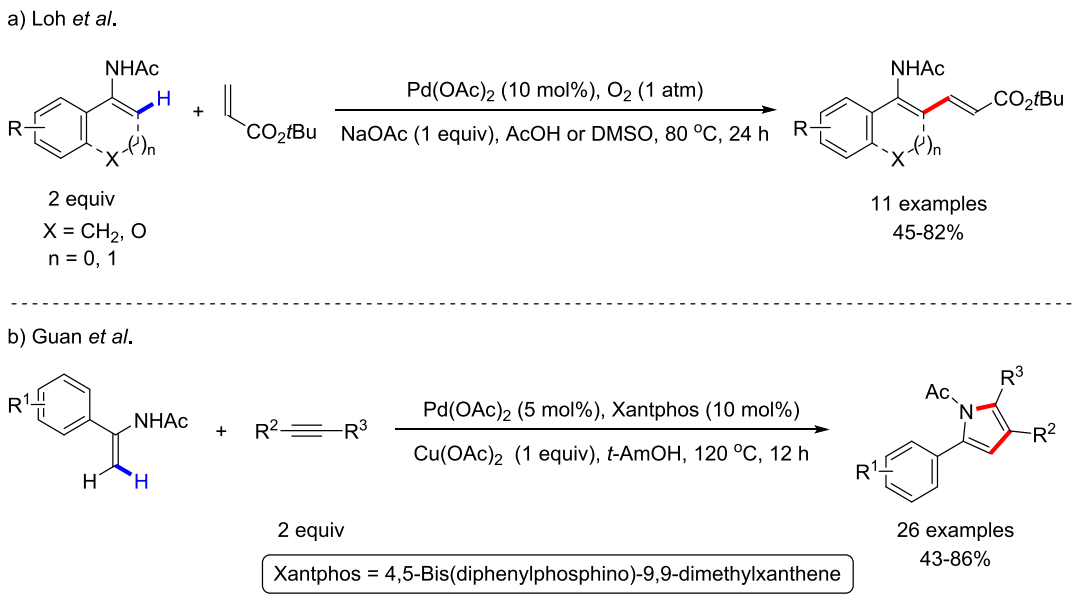
Jiang, Xue *et al*.



Scheme 36: The Pd-catalyzed olefinic C-H bond alkylation.

1.3.2.8.2 Pd-catalyzed alkenylation

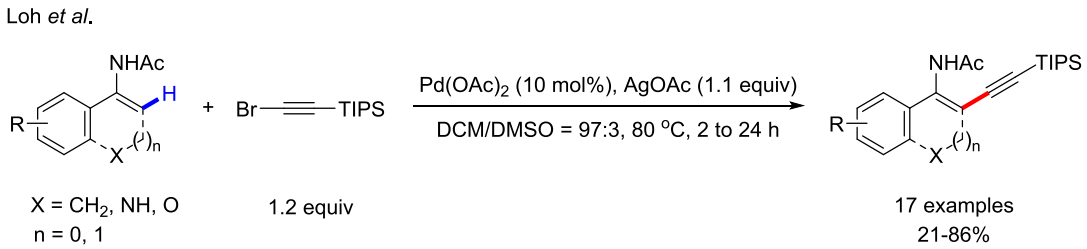
In 2011, Loh and co-workers depicted the Pd-catalyzed coupling reaction between enamides and *tert*-butyl acrylate by using the -NHAc moiety as the directing group. The alkenylated products were obtained in moderate to good yields under mild reaction conditions (Scheme 37, a).[87] In 2014, Guan and co-workers reported the Pd-catalyzed olefinic C(sp^2)-H bond alkenylation of enamides with internal alkynes to access polysubstituted pyrroles. This reaction tolerated a wide range of functional groups and several tri-substituted pyrroles were obtained in high yields (Scheme 37, b).[88]



Scheme 37: The Pd-catalyzed olefinic C-H bond alkenylation.

1.3.2.8.3 Pd-catalyzed alkynylation

In 2011, Loh and co-workers described the Pd-catalyzed olefinic C(sp^2)-H bond alkynylation of enamides with (bromoethynyl)triisopropylsilane under mild reaction conditions. A wide range of conjugated enynes was prepared in moderate to high yields (Scheme 38).[89]

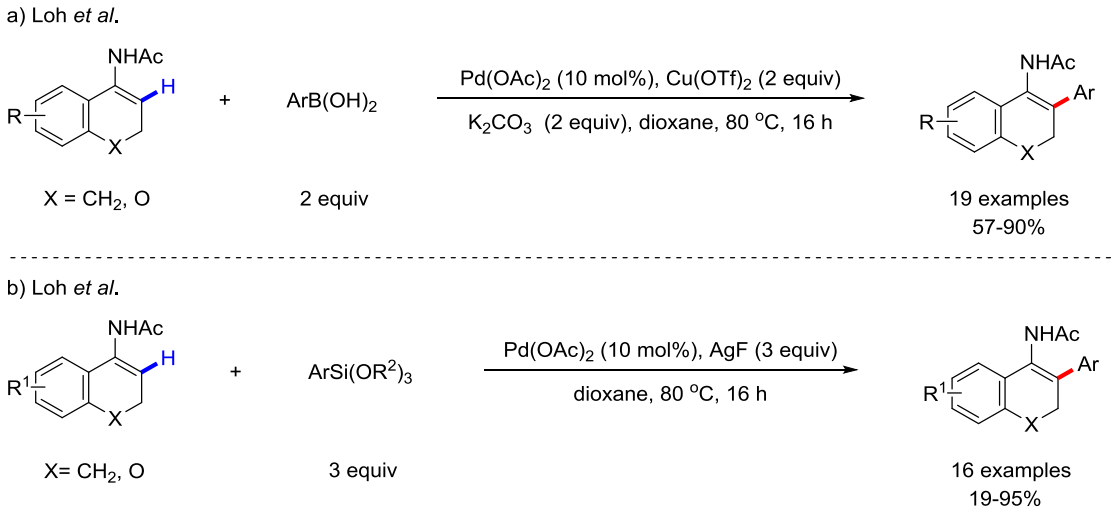


Scheme 38 : The Pd-catalyzed olefinic C-H bond alkynylation.

1.3.2.8.4 Pd-catalyzed arylation

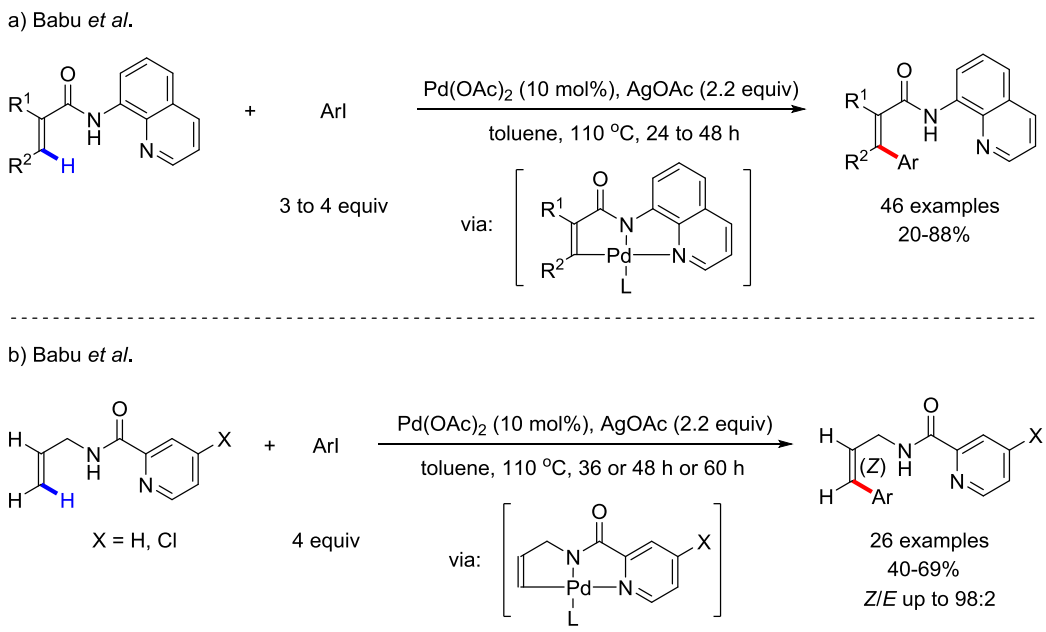
In 2009, Loh and co-workers developed two Pd-catalyzed olefinic C(sp^2)-H bond arylation reactions of cyclic enamides with aryl boronic acids[90] and aryl trialkoxy

silanes,[91] respectively. A variety of cyclic enamide derivatives was obtained in moderate to excellent yields under mild conditions in both methods (Scheme 39, a and b).



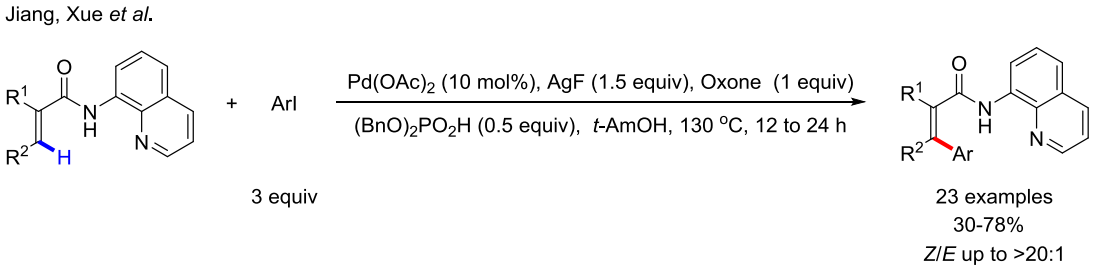
Scheme 39: The Pd-catalyzed olefinic C-H bond arylation developed by Loh.

In 2015 and 2017, Babu and co-workers depicted the Pd-catalyzed olefinic C(sp^2)-H bond arylation reactions of olefins with aryl iodides by using two different bidentate directing groups: 8-aminoquinoline[92] and picolinamide,[93] respectively. A wide range of acrylamides was converted into the (*Z*)-arylated products in moderate to good yields (Scheme 40, a and b). Both reactions demonstrated a good functional group tolerance and a high stereoselectivity.



Scheme 40: The Pd-catalyzed olefinic C-H bond arylation developed by Babu.

In 2016, Jiang, Xue and co-workers reported the Pd-catalyzed olefinic C(sp^2)-H bond arylation between acrylamides and aryl iodides with the assistance of the bidentate directing group: 8-aminoquinoline moiety. Good yields and excellent (*Z*)-stereoselectivity were observed with the unsubstituted acrylamide, while the yields decreased significantly with the α,β-substituted ones (Scheme 41).[86]

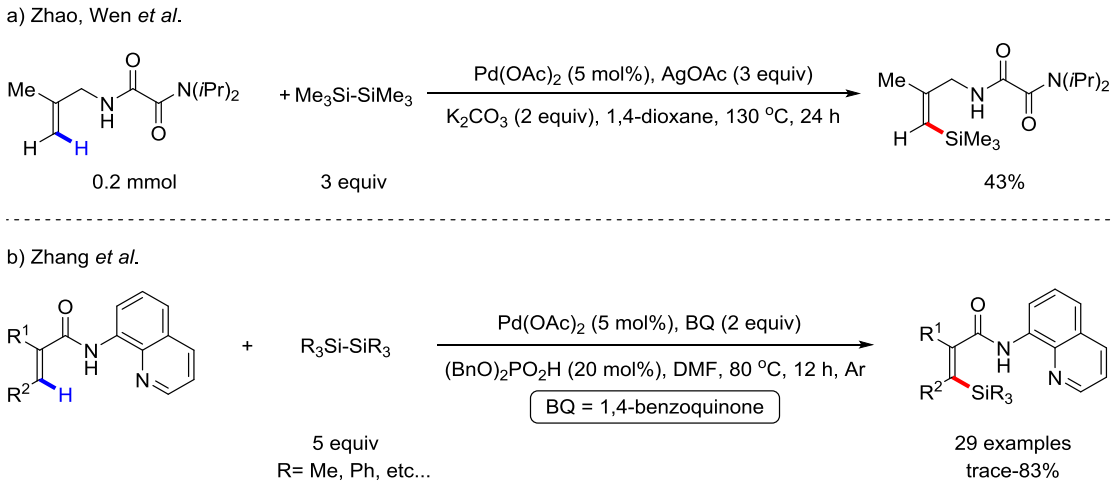


Scheme 41: The Pd-catalyzed olefinic C-H bond arylation developed by Jiang and Xue.

1.3.2.8.5 Pd-catalyzed silylation

In 2015, Zhao, Wen and co-workers reported the Pd-catalyzed olefinic C(sp^2)-H bond silylation of oxalyl amide-protected benzylamines with the commercially available 1,1,1,2,2,2-hexamethyldisilane. One oxalyl amide-protected allylamine derivative was

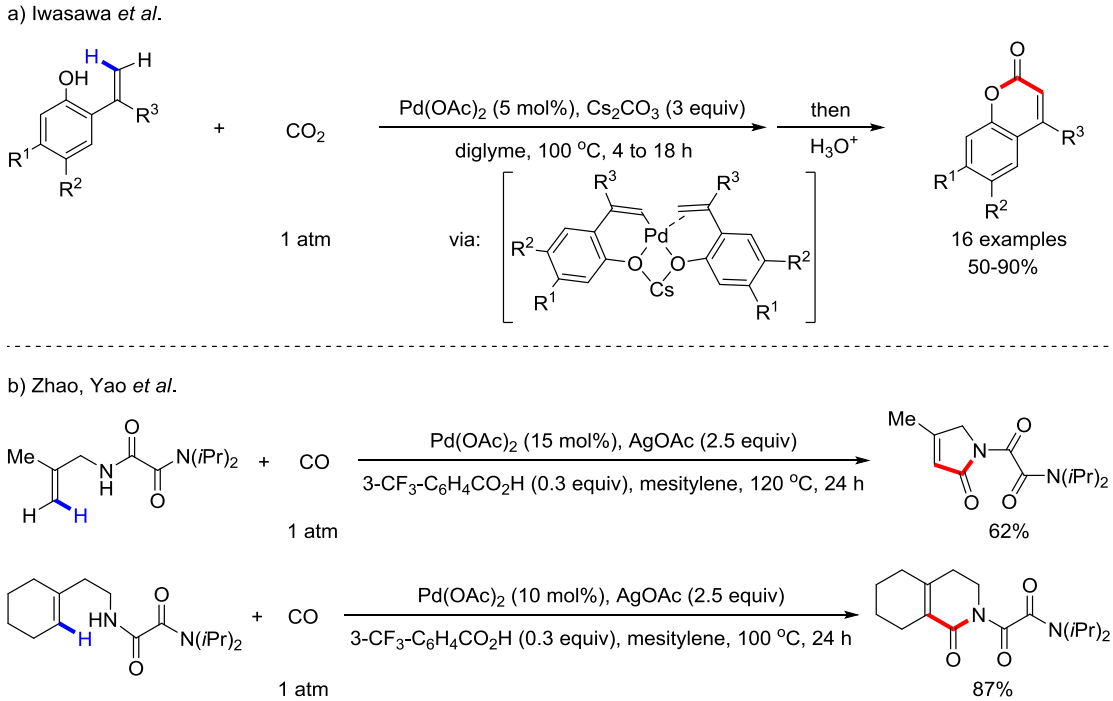
tested under the standard reaction conditions and the (*Z*)-silylated product was obtained in 43% yield (Scheme 42, a).[94] In 2017, Zhang and co-workers developed the Pd-catalyzed direct silylation of acrylamides with disilanes to exclusively access (*Z*)-vinylsilanes. A broad range of acrylamides were converted into the corresponding products in reasonable to good yields with the assistance of a removable bidentate directing group: the 8-aminoquinoline moiety (Scheme 42, b).[95]



Scheme 42: The Pd-catalyzed C-H bond silylation.

1.3.2.8.6 Pd-catalyzed C-H bond functionalization/cyclization cascades

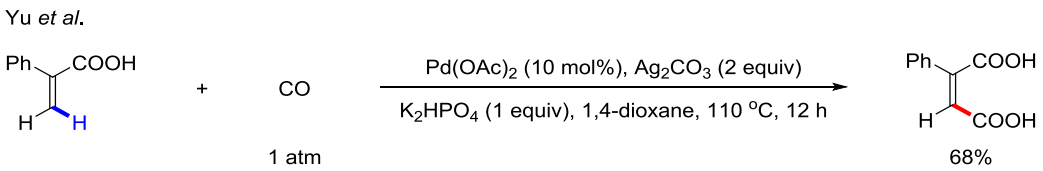
In 2013, Iwasawa and co-workers developed the Pd-catalyzed direct carboxylation of olefinic C(sp^2)-H bond of 2-hydroxystyrenes with CO_2. A series of coumarin derivatives was obtained in good to excellent yields (Scheme 43, a).[96] Mechanistic studies demonstrated that a Pd-catalyzed C-H bond activation step was involved in this process. In 2015, Zhao, Yao and co-workers reported the Pd-catalyzed remote carbonylation of two oxalyl amide protected aliphatic amines by using oxalyl amide as a bidentate directing group (Scheme 43, b).[97] This reaction was applied to a wide range of aliphatic substrates and only two olefinic substrates.



Scheme 43: The Pd-catalyzed C-H bond functionalization/cyclization cascades.

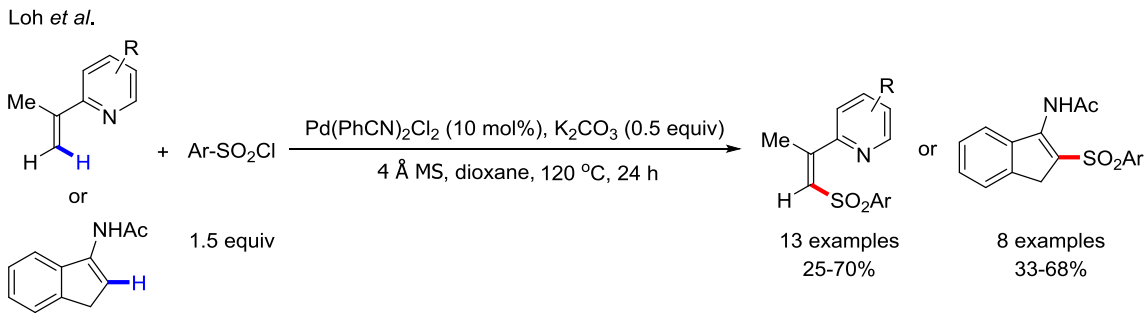
1.3.2.8.7 Miscelaneous

In 2008, Yu and co-workers developed the Pd-catalyzed carboxylation of benzoic acid derivatives to form dicarboxylic acids. As a single example, when 2-phenylacrylic acid was tested under similar reaction conditions as benzoic acids, the (*Z*)-selectively dicarboxylated product was obtained in 68% yield (Scheme 44).[98]



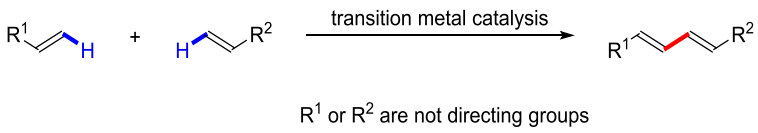
Scheme 44: The Pd-catalyzed C-H bond carboxylation of 2-phenylacrylic acid.

In 2013, Loh and co-workers depicted the Pd-catalyzed olefinic C(sp^2)-H bond sulfonylation of vinyl pyridines and enamides to afford the desired products in good yields (Scheme 45).[99]



Scheme 45: The Pd-catalyzed C-H bond sulfonylation.

In addition, the Pd-catalyzed cross-coupling reactions between olefins and different coupling partners (acrylates, olefins, alkynes, etc…) without the directing group assistance were reported by different research groups (Scheme 46).[100] A nice review is recommended concerning this Heck-type cross-coupling reactions.[101]

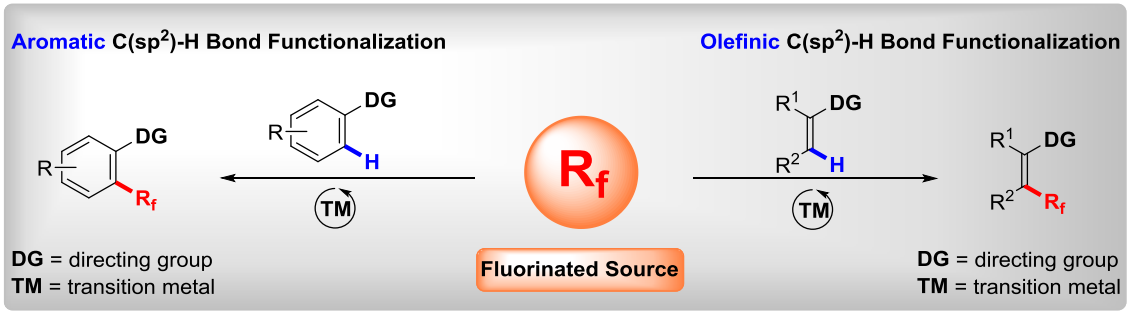


Scheme 46: The Heck-type cross-coupling reaction.

1.4 The objectives of the Ph.D. thesis

As above-mentioned, the transition metal-catalyzed olefinic C(sp^2)-H bond functionalization (alkylation, alkenylation, alkynylation, arylation and so on) strategy has attracted much attention during the past years, since it would afford a straightforward and more atom-economical synthetic pathway for the construction of complex organic frameworks. However, the introduction of fluorinated moieties by transition metal-catalyzed olefinic C(sp^2)-H bond functionalization pathway is less developed.[12a, 68-69] In this thesis, we aim at tackling these challenges. We will focus on the development of new synthetic methodologies for the introduction of fluorinated motifs onto olefins by transition metal-catalyzed directed C-H bond functionalization

with a directing group assistance. Since olefins are more challenging to handle compared with arenes, we will start our investigations from arenes. Then, we will move our attention to the olefins (Scheme 47).



Scheme 47: The objectives of the Ph.D. thesis.

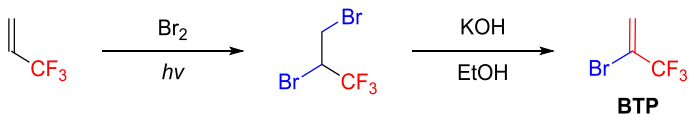
Chapter 2
Introduction of CF_3-vinyl moiety with BTP

2. Introduction of the CF_3-vinyl moiety with BTP

2.1 Introduction of BTP

2.1.1 Source

2-Bromo-3,3,3-trifluoropropene (CH_2=$CBrCF_3$, BTP, CAS Number: 1514-82-5), as a kind of tropospheric degrading halocarbon,[102] is believed to be a potential halon replacement for fire suppression.[103] Nowadays, the preparation of BTP in industry adopts a two-step reactions procedure as follows: a photocatalytic reaction between 3,3,3-trifluoropropene and Br_2, followed by a selective elimination of HBr under basic condition.[104] The resulting solution is distilled and BTP is collected from the 25-35 °C distillation fractions (Scheme 48).



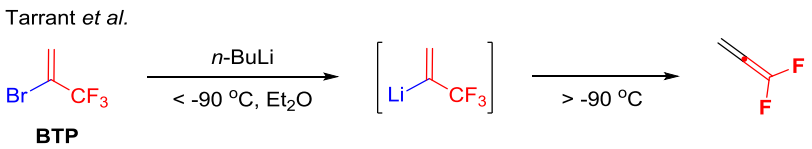
Scheme 48: The preparation of BTP in industry.

2.1.2 Applications in organic synthesis

Except the application as a gas extinguishing agent, BTP has been also used in organic synthesis as a fluorinated building block.[105]

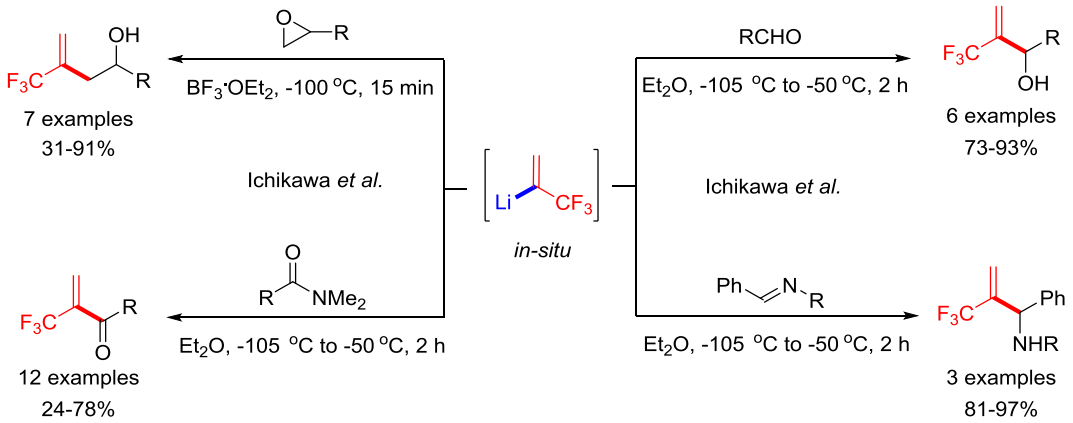
2.1.2.1 BTP as a precursor of α-(trifluoromethyl)ethenyl carbanion synthetic equivalent

In 1968, Tarrant and co-workers reported that α-(trifluoromethyl)ethenyl lithium was prepared *in situ* by reaction of BTP with *n*-butyllithium at a temperature lower than -90 °C. The resulting α-(trifluoromethyl)ethenyl lithium is not stable at a temperature higher than -90 °C and it decomposes, leading to 1,1-difluoroallene according to a defluorination pathway (Scheme 49).[106]



Scheme 49: The preparation of α-(trifluoromethyl)ethenyl lithium.

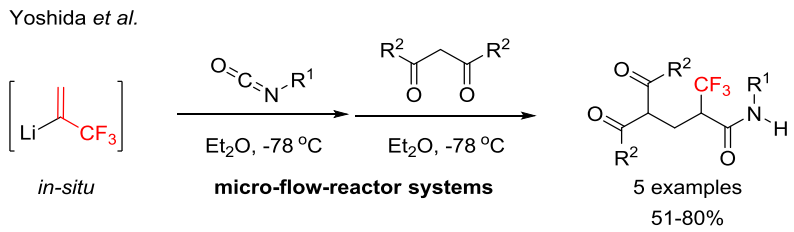
The α-(trifluoromethyl)ethenyl lithium species can be trapped with different electrophiles, such as aldehydes,[107] imines,[107] oxirane derivatives[108] and carboxamides at low temperature[107] (Scheme 50).



Scheme 50: Reaction of α-(trifluoromethyl)ethenyl lithium with electrophiles.

In 2014, Yoshida and co-workers showed that the α-(trifluoromethyl)ethenyl lithium species could be obtained at a slightly higher temperature (-78 °C) by using micro-flow-reactor systems, giving the desired products in good yields without using

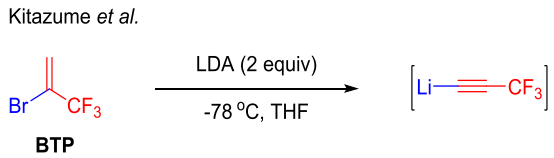
an excess amount of the lithium reagent (Scheme 51).[109]



Scheme 51: The reaction of α-(trifluoromethyl)ethenyl lithium with an isocyanate followed by a Michael addition.

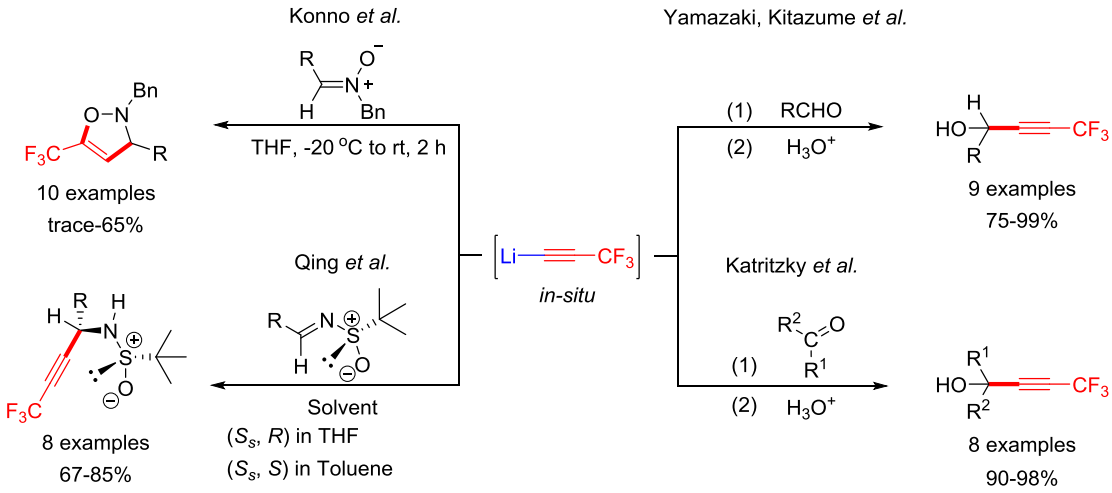
2.1.2.2 BTP as a precursor of 3,3,3-trifluoropropynyl anion synthetic equivalent

In 1995, Kitazume and co-workers reported that the 3,3,3-trifluoropropynyl lithium species was synthesized *in situ* by the treatment of BTP with LDA (2 equivalents) in THF at -78 °C (Scheme 52).[110]



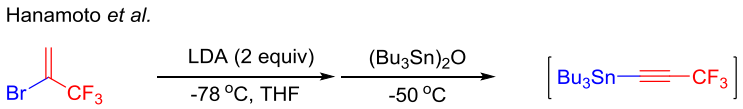
Scheme 52: The preparation of 3,3,3-trifluoropropynyl lithium.

The 3,3,3-trifluoropropynyl lithium species can be efficiently trapped with aldehydes,[110b, 111] ketones,[112] nitrones[113] and sulfinylaldimines (Scheme 53).[114]



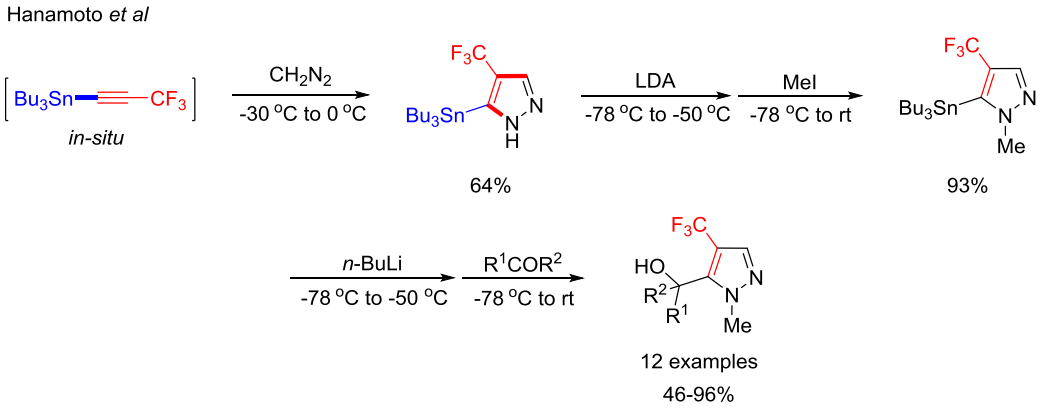
Scheme 53: 3,3,3-Trifluoropropynyl lithium is trapped by electrophiles.

In 2006, Hanamoto and co-workers reported that the 3,3,3-trifluoropropynyl lithium species was transformed into the corresponding 3,3,3-trifluoropropynyl tributyltin by reacting with $(Bu_3Sn)_2O$ (Scheme 54).[115]



Scheme 54: The preparation of 3,3,3-trifluoropropynyl tributyltin.

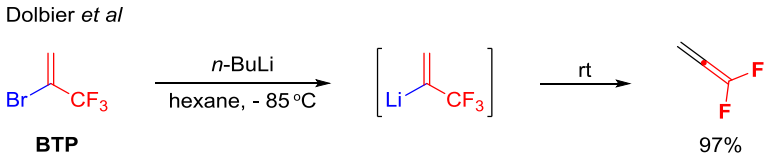
Then, the *in situ* generated 3,3,3-trifluoropropynyl tin was reacted with diazomethane through a [2+3] cycloaddition reaction to furnish the corresponding 5-tributylstannyl-4-trifluoromethyl-1H-pyrazole.This resulting intermediate was easily transformed into the corresponding *N*-methylpyrazole, followed by the nucleophilic addition onto aldehydes or ketones to furnish the (1-methyl-pyrazol-5-yl)methanol derivatives in moderate to high yields (Scheme 55).[115]



Scheme 55: Reaction of 3,3,3-Trifluoropropynyl tributyltin with electrophiles.

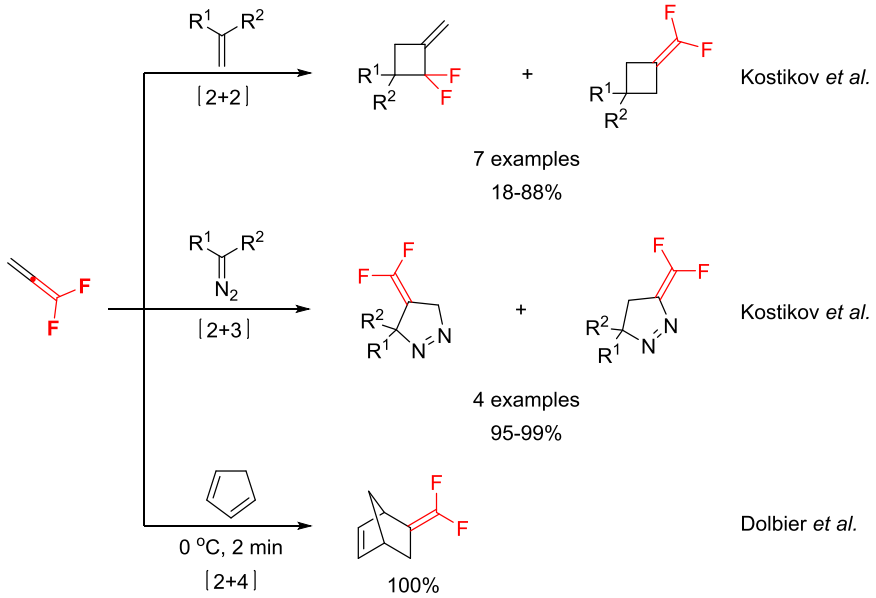
2.1.2.3 BTP as an electron acceptor in 1,3-dipolar cycloadditions

In 1982, Dolbier and co-workers prepared the 1,1-difluoroallene from BTP via a straightforward way. The 1,1-difluoroallene was collected through distillation in excellent 97% yield (Scheme 56).[116]



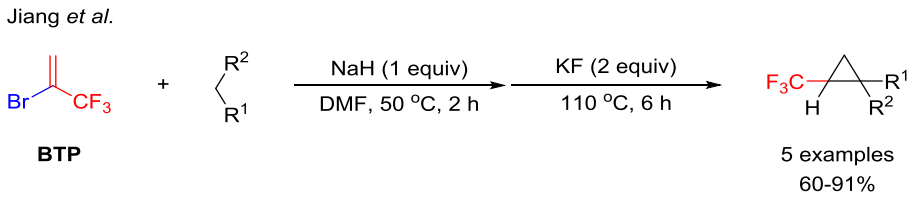
Scheme 56: The preparation of 1,1-difluoroallene.

The 1,1-difluoroallene turned out to be an excellent reactive species in cycloaddition reactions, such as allene-alkene [2+2], allene–diazo [2+3] and allene-alkene [2+4] cycloadditions (Scheme 57).[117]



Scheme 57: [2+2], [2+3], [2+4] Cycloadditions of 1,1-difluoroallene.

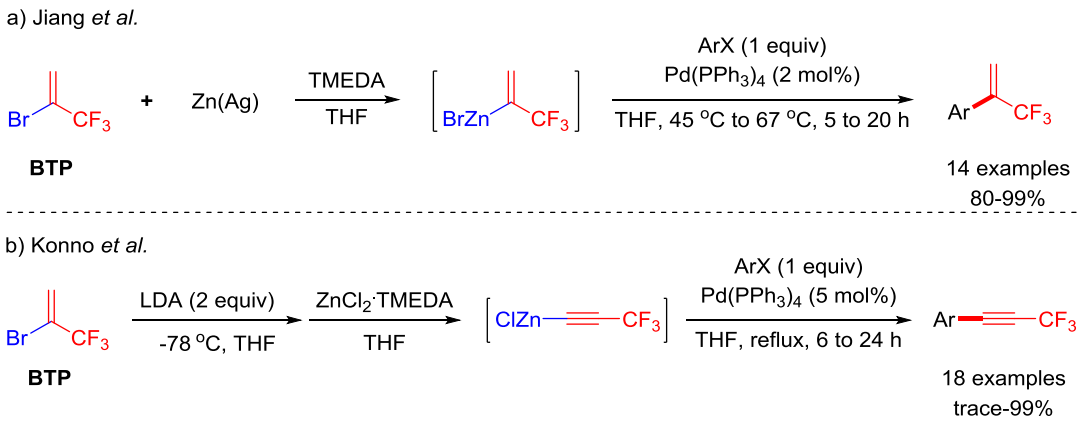
In 2003, Jiang and co-workers revealed the stereoselective synthesis of trifluoromethylated polyfunctionalized cyclopropanes in good to high yields by reacting BTP with active methylenes precusors (Scheme 58).[118]



Scheme 58: [2+1] Cycloaddition with BTP.

2.1.2.4 BTP as a coupling partner in transition metal-catalyzed cross-coupling reactions

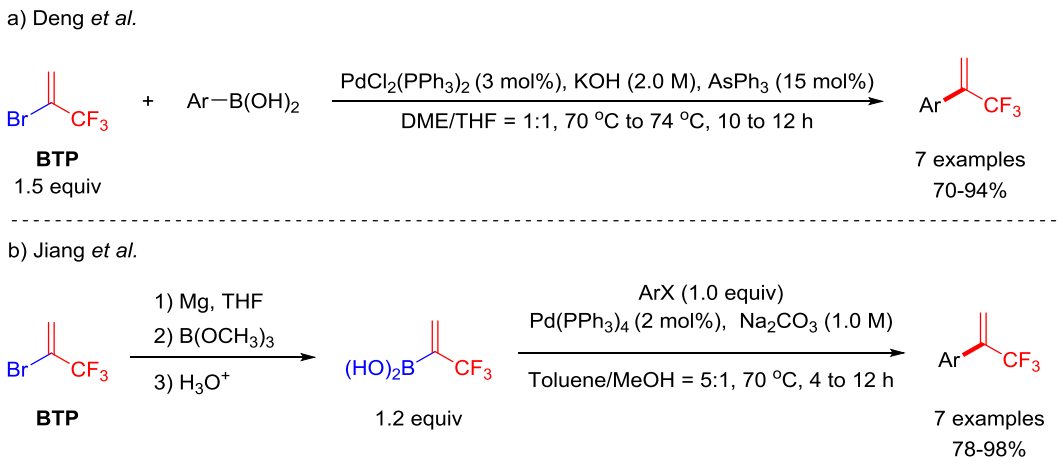
In 1991, Jiang and co-workers reported a Negishi type cross-coupling reaction with BTP. The addition of tetramethylethylene diamine (TMEDA) to a mixture of BTP and Zn (Ag) couple in THF led to the formation of the corresponding zinc reagent. Then, this *in situ* generated zinc species reacted with aryl halides in the presence of a Pd-catalyst to afford a series of α-(trifluoromethyl)styrene derivatives in good to excellent yields (Scheme 59, a).[119] In 2003, Konno and co-workers showed that the 3,3,3-trifluoropropynylzinc species was prepared from BTP as follows: 3,3,3-trifluoropropynyl lithium was *in situ* prepared from BTP and LDA in THF at -78 °C, then, the resulting intermediate was converted into 3,3,3-trifluoropropynylzinc by addition of the $ZnCl_2$·TMEDA complex into the reaction mixture. This Zn-species was then reacted in a Negishi type cross-coupling reaction with aryl iodides to access trifluoromethylated acetylenes in good to high yields (Scheme 59, b).[120] Note that no defluorination reaction was observed in both cases.



Scheme 59: Negishi type cross-coupling reactions of BTP.

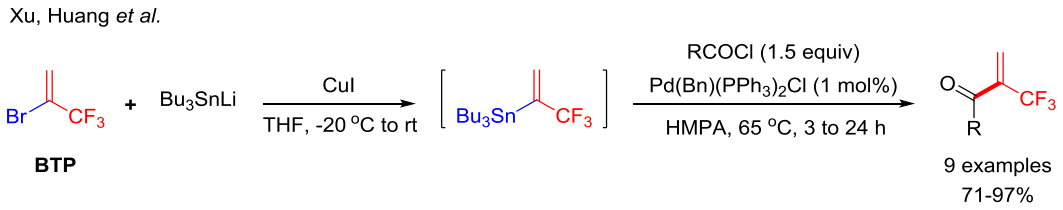
In 1999, Deng and co-workers described a Suzuki type cross-coupling reaction

between arylboronic acids and BTP (Scheme 60, a).[121] In 2001, Jiang and co-workers reported the convenient α-(trifluoromethyl)ethenyl boronic acid preparation from BTP. The Suzuki type cross-coupling reaction of this boronic acid with aryl halides also proceeded very efficiently (Scheme 60, b).[122] A series of α-trifluoromethylated styrene derivatives was obtained in good to excellent yields in both cases.



Scheme 60: Suzuki type cross-coupling reactions of BTP.

In 1994, Xu, Huang and co-workers described a Stille type cross-coupling reaction between α-(trifluoromethyl)ethenyltributyl tin and a panel of acyl chlorides. The active organotin species was prepared *in situ* by Cu-catalyzed reaction between BTP and tributylstannyl lithium in THF. Then, the reaction with acyl chlorides with $Pd(Bn)(PPh_3)_2Cl$ as a catalyst gave access to different α-(trifluoromethyl)ethenyl ketones in good to excellent yields (Scheme 61).[123]

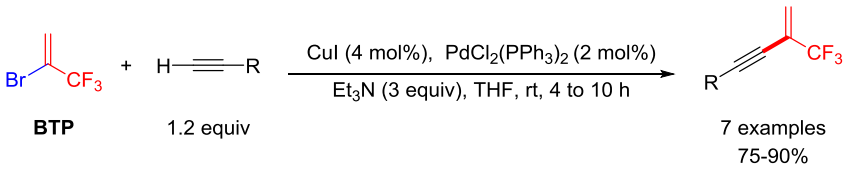


Scheme 61: Stille type cross-coupling reaction of BTP.

In 1993, Hu and co-workers reported the Pd-catalyzed reaction of BTP with terminal

alkynes to produce α-trifluoromethylated enynes in good to high yields (Scheme 62).[124] It offered an attractive and straightforward pathway for the preparation of α-trifluoromethylated enyne derivatives.

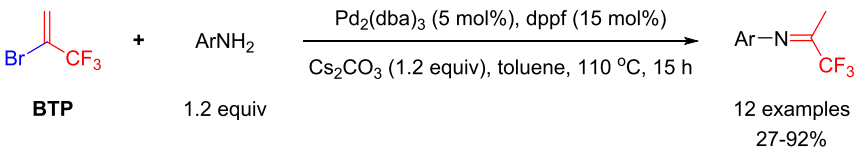
Hu *et al.*



Scheme 62: Sonogashira type cross-coupling reaction of BTP.

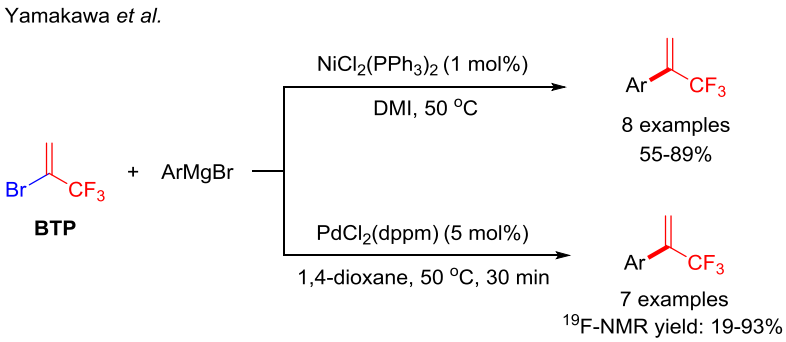
In 2008, Yamakawa and co-workers reported the Pd-catalyzed cross-coupling reaction of anilines and BTP. The yields of the imine products were dependent on the phosphine ligand used. BINAP, dppf and dppb were effective for this reaction, while dppf gave the best yields. The resulting imines can be easily transformed into the corresponding amines by reduction with $LiAlH_4$ or H_2 with Pd/C (Scheme 63).[125]

Yamakawa *et al.*



Scheme 63: Buchwald-Hartwig type cross-coupling reaction of BTP.

In 2009, the same group reported the Pd- and Ni-catalyzed Kumada cross-coupling reactions between BTP and a series of aryl Grignard reagents.[126] A panel of α-trifluoromethylated styrene derivatives was obtained. Note that the dppm was found to be exclusively effective in the Pd-catalyzed reaction (Scheme 64).

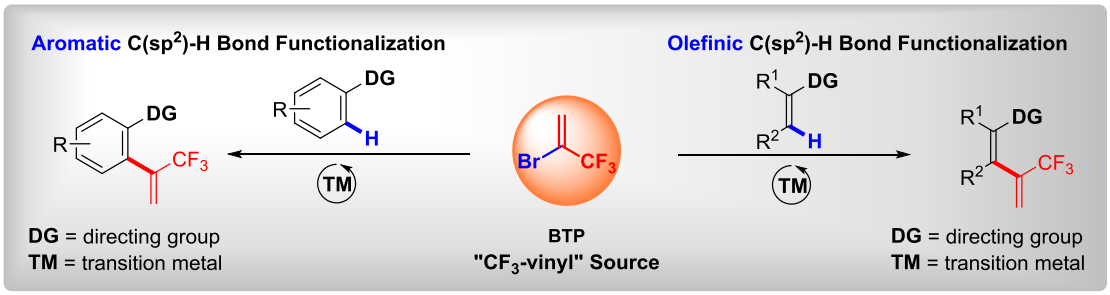


Scheme 64: Kumada cross-coupling reaction of BTP.

In conclusion, BTP is a versatile fluorinated building block, which has been widely used in organic synthesis. However, at the beginning of my Ph.D. thesis (2015), no report regarding the transition metal-catalyzed α-(trifluoromethyl)ethenylation by using BTP as a fluorinated coupling partner in a C-H bond functionalization event was reported. Thus, from a synthetic point of view, the direct introduction of α-(trifluoromethyl)ethenyl group by transition metal-catalyzed C-H bond functionalization with BTP appeared highly desirable.

2.2 Objectives

At the beginning of this project, we envisioned to realize the first α-(trifluoromethyl)ethenylation of arenes and olefins via transition metal-catalyzed C(sp^2)-H bond functionalization (Scheme 65).



Scheme 65: Our objectives.

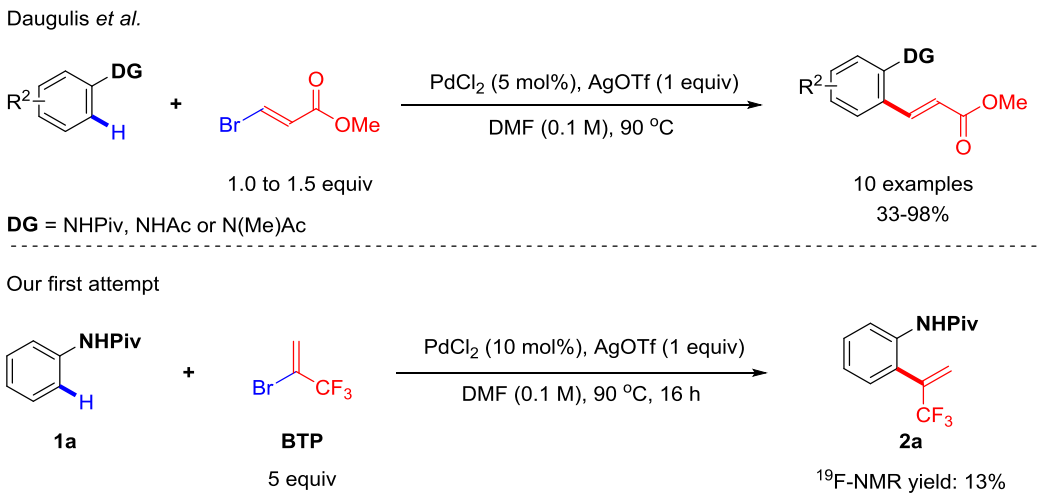
2.3 Transition metal catalyzed aromatic C(sp^2)-H bond functionalization with BTP

Since the C(sp^2)-H bond functionalization of arenes are easier to deal with, compared with the corresponding olefins, we started our investigations of the C(sp^2)-H bond α-(trifluoromethyl)ethenylation by using arenes substrates.

2.3.1 Optimization of the reaction conditions

2.3.1.1 Preliminary results

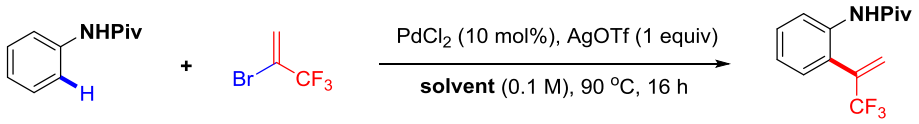
At the outset of this study, we devoted our efforts to hunt the target. Inspired from the study of Daugulis and co-workers dealing with the Pd-catalyzed coupling of β-haloacrylate with anilides (Scheme 66),[127] we decided to test at first the reaction with BTP by using the similar reaction conditions. Gratifyingly, we found the expected product in 13% NMR yield, when the NHPiv moiety was installed as a directing group on the arene (Scheme 66).



Scheme 66: Pd-catalyzed coupling of haloacrylate with anilides and our first attempt.

2.3.1.2 Screening of the solvents

With this promising result in hand, we pursued our investigations by screening the reaction conditions, since parameters such as solvents, additives, catalysts, temperatures and reaction time would be crucial for the transformation. First, we screened a panel of solvents with different polarity (Table 1). Notably, the reaction performed in 1,4-dioxane gave the best result, 38% yield (Table 1, entry 4). A slightly lower yield was obtained in THF (Table 1, entry 5). In DMSO, DCE and NMP, the desired product was detected, albeit low yields (Table 1, entries 2, 6 and 7). No trace of product was observed in MeCN and Toluene (Table 1, entries 3 and 8).



1a **BTP** **2a**

Entry	**solvent**	Yield (%)[b]
1	DMF	13
2	1, 4-dioxane	38
3	THF	18
4	DMSO	2
5	DCE	3
6	NMP	5
7	MeCN	0
8	toluene	0

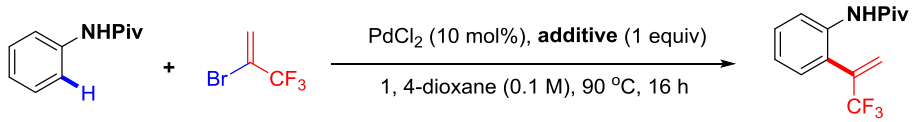
Table 1: Investigation of the solvents.[a]

[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $PdCl_2$ (0.02 mmol, 10 mol%), AgOTf (0.2 mmol, 1 equiv), solvent (2 mL), 90 °C, Ar, 16 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.3.1.3 Screening of the additives

Next, several additives were evaluated. To our great surprise, when other silver salts

were tried (Table 2, entries 2-7), no expected product was found, which indicated that the counter-anion ($^-$OTf) played an important role in this transformation. Then, when AgOTf was replaced by $Cu(OTf)_2$ (Table 2, entry 8), no trace of the desired product was detected. It showed that the counter-cation (Ag^+) was also crucial for this reaction.



1a **BTP** **2a**

Entry	**additive**	Yield (%)[b]
1	AgOTf	38
2	Ag_2O	0
3	Ag_2CO_3	0
4	AgOAc	0
5	$AgSbF_6$	0
6	Ag_3PO_4	0
7	AgF	0
8	$Cu(OTf)_2$	0

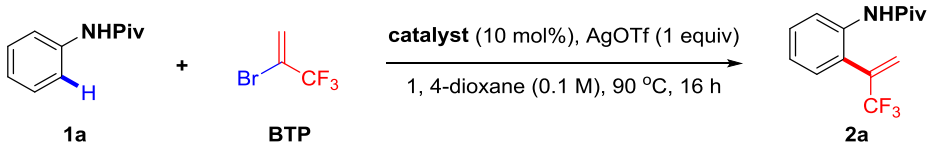
Table 2: Investigation of the additives.[a]

[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $PdCl_2$ (0.02 mmol, 10 mol%), additive (0.2 mmol, 1 equiv), 1,4-dioxane (2 mL), 90 °C, Ar, 16 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.3.1.4 Screening of the catalysts

After assessing the best solvent and additive, we began to screen different palladium-catalysts (Pd(0) and Pd(II)). No trace of the desired product was observed when two typical Pd(0)-catalysts: $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ were tested (Table 3, entries 2 and 3). Then, different Pd(II)-catalysts were evaluated. Only trace of the product was detected when PdI_2 was tested (Table 3, entry 7). A similar yield was obtained in $Pd(CH_3CN)_2(BF_4)_2$ (Table 3, entry 6) and a lower yields were detected with

$Pd(OAc)_2$ and $Pd(TFA)_2$ (Table 3, entries 4 and 5). When $PdCl_2$ was replaced by $PdBr_2$, the yield was slightly increased to 40% (Table 3, entry 8). Furthermore, a decrease of the temperature to 70 °C combined with a slight increase of the AgOTf stoichiometry (1.5 equiv) and the amount of $PdBr_2$ (15 mol%) for 24 hours provided the best NMR yield with an acceptable 74% isolated yield (Table 3, entry 11).



Entry	catalyst	Yield (%)[b]
1	$PdCl_2$	38
2	$Pd(PPh_3)_4$	0
3	$Pd_2(dba)_3$	0
4	$Pd(OAc)_2$	18
5	$Pd(TFA)_2$	19
6	$Pd(CH_3CN)_2(BF_4)_2$	38
7	PdI_2	1
8	$PdBr_2$	40
9[c]	$PdBr_2$	61
10[d]	$PdBr_2$	89
11[e]	$PdBr_2$	99 (74)[f]

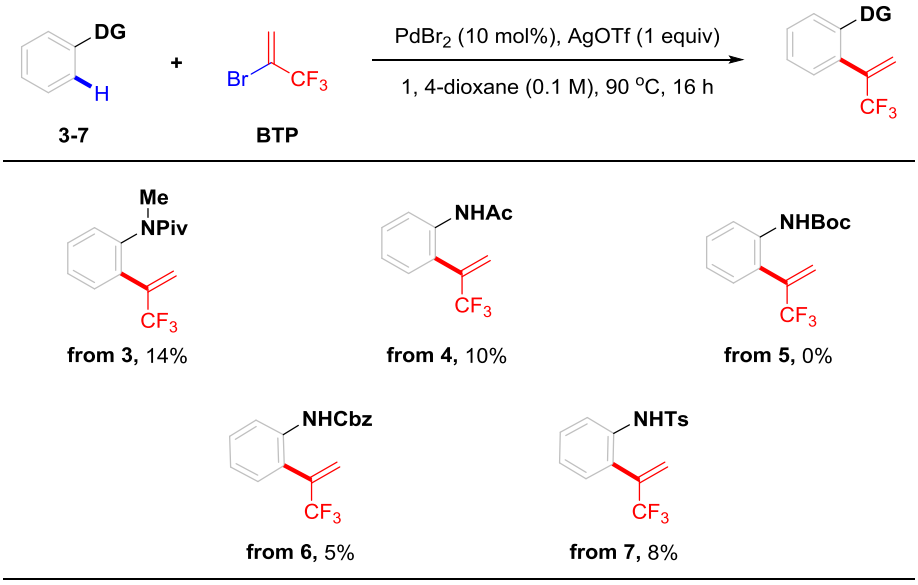
Table 3: Investigation of the catalysts.[a]

[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), catalyst (0.02 mmol, 10 mol%), AgOTf (0.2 mmol, 1 equiv), 1,4-dioxane (2 mL), 90 °C, Ar, 16 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard. [c] 1.5 equiv of AgOTf was used. [d] 1.5 equiv of AgOTf, 70 °C. [e] $PdBr_2$ (15 mol%), 1.5 equiv of AgOTf, 70 °C, 24 h. [f] Isolated yield.

2.3.1.5 Screening of the directing groups

Meanwhile the screening of the palladium-catalysts, other directing groups were also tested. Unfortunately, no expected product or nearly trace of product were obtained with other directing groups (Scheme 67). Interestingly, the replacement of the

acetanilide proton by a methyl group on the nitrogen atom **3** gave only trace of product, which demonstrated the importance of the proton for the success of the transformation.



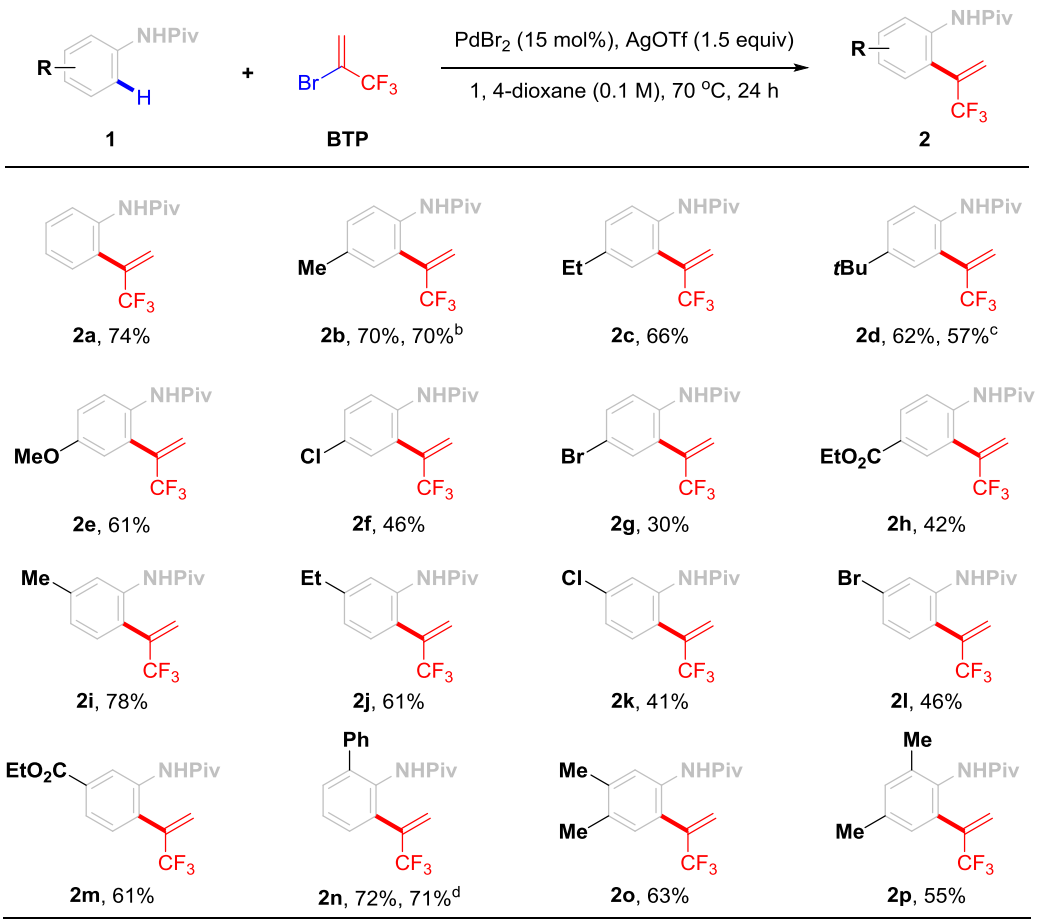
Scheme 67: Investigation of the directing groups.[a]

[a] Reaction conditions: **3-7** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $PdBr_2$ (0.02 mmol, 10 mol%), AgOTf (0.2 mmol, 1 equiv), 1,4-dioxane (2 mL), 90 °C, Ar, 16 h. The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.3.2 Investigation of the substrates scope

With these optimized conditions in hand, the substrates scope and the limitations of the reaction with respect to anilides were then investigated. Substrates with electron-donating groups at the *para*- or *meta*- and even *ortho*-position were readily converted into the corresponding products in good yields (Scheme 68, **2b**-**2e**, **2i**, **2j** and **2n**). Note that the reaction can be performed on a larger scale without loss of efficiency. For example, **2b** and **2d** were obtained in similar yields on a *ca*. 4 mmol scale. Moreover, **2n** was obtained in 71% yield on a gram scale (1.5 g), compared with 72% yield based on a 0.2 mmol scale. Then, substrates containing

electron-withdrawing groups, such as halides and ester were tested. Interestingly, anilides bearing a halogen atom at the *para*- or *meta*-position gave moderate yields (Scheme 68, **2f**-**2g** and **2k**-**2l**). Note that no alteration of the halogen atom, resulting from a Pd-catalyzed dehalogenation process, was observed. An ester moiety was also compatible with this transformation, since **2h** and **2m** were obtained in 42% and 61% yield, which demonstrated the functional-group tolerance of this method. Disubstituted anilides **1o** and **1p** reacted also smoothly to give the corresponding products **2o** and **2p** in moderate to good yields.



Scheme 68: Substrates scope.[a]

[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $PdBr_2$ (0.03 mmol, 15 mol%), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (2 mL), 70 °C, Ar, 24 h. [b] The reaction was carried out on a 4.18 mmol scale. [c] Reaction was carried out on a 4.26 mmol scale. [d] The reaction was carried out on a 3.95 mmol scale.

2.3.3 Proposed mechanism

Based on previous works,[127] a possible mechanism for the directed C-H bond functionalization of anilides with BTP was proposed in Figure 3. The catalytic cycle was initiated by the formation of the palladacycle **A** resulting from the reaction of the anilide **1** with the Pd-catalyst. Then, the palladacycle **A** coordinated to the BTP (intermediate **B**) and performed a carbopalladation on the alkene (BTP). The resulting organopalladium species **C** underwent a β-halide elimination to deliver the product **2** and to regenerate the catalyst.[127-128] Although the exact role of AgOTf has not been elucidated at this stage, we speculated that AgOTf would favor the β-halide elimination process by halide trapping. However, a plausible Pd(II)/Pd(IV) catalytic pathway cannot be ruled out, since no clear evidence of the reaction mechanism was obtained yet.

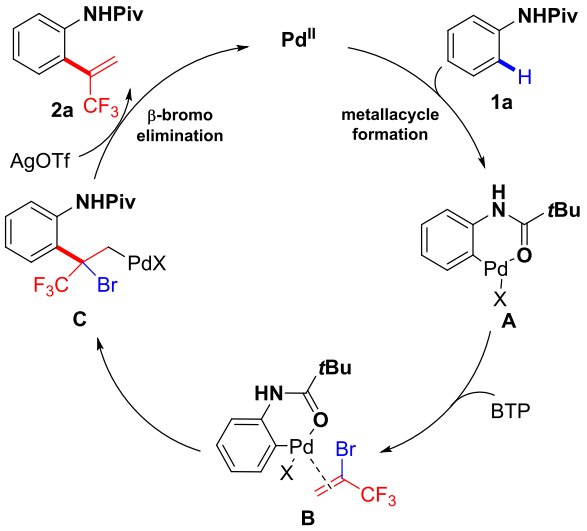


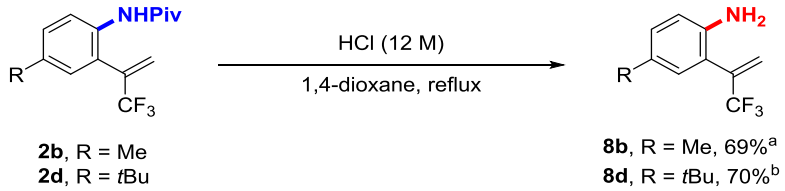
Figure 3: Proposed mechanism.

2.3.4 Post-functionalization reactions of products

Cleavage of the directing group

Finally, we decided to showcase the versatility of the resulting products. The directing

group was removed under acidic conditions, leading to the corresponding α-(trifluoromethyl)ethenyl anilines. Good yields were obtained with **2b** and **2d** on 3 mmol scale and 1 mmol scale, respectively (Scheme 69).

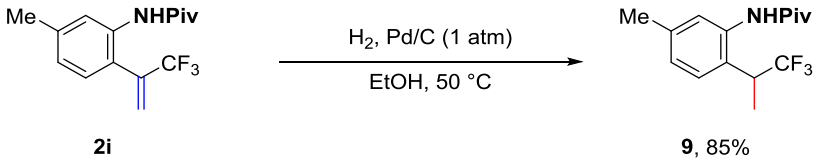


Scheme 69: Cleavage of the directing group.

[a] Reaction was performed on a 3 mmol scale. [b] Reaction was performed on a 1 mmol scale.

Selective reduction of olefinic double bond

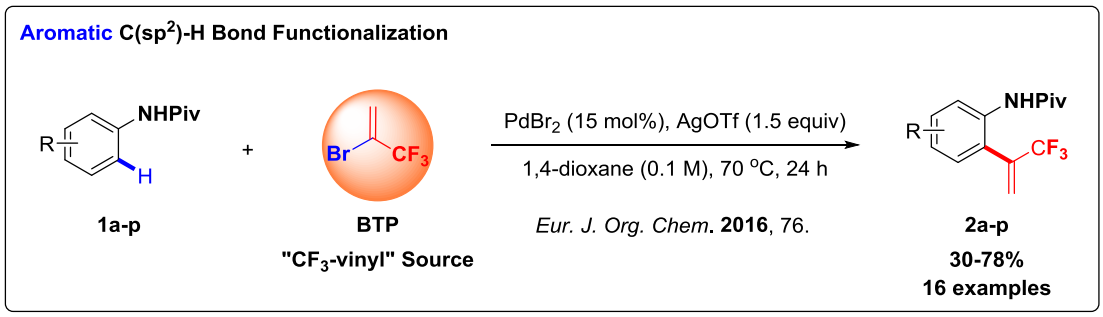
The olefinic double bond was selectively reduced and gave the anilide derivative **9** in a decent 85% yield (Scheme 70).



Scheme 70: Selective reduction of olefinic double bond on a 0.1 mmol scale.

2.3.5 Brief summary

In conclusion, this part was dedicated to the development of a new methodology for the introduction of the α-(trifluoromethyl)ethenyl moiety into arenes through a palladium-catalyzed directed C(sp^2)-H bond functionalization reaction.



Scheme 71: Aromatic C(sp^2)-H bond functionalization.

This method was applied to a broad range of anilide derivatives (16 examples) to give

the corresponding α-(trifluoromethyl)styrene derivatives in moderate to good yields (30-78%, Scheme 71). The products were subsequently modified to demonstrate the versatility of these α-(trifluoromethyl)ethenylated building blocks.

2.4 Transition metal catalyzed olefinic C(sp^2)-H bond functionalization with BTP

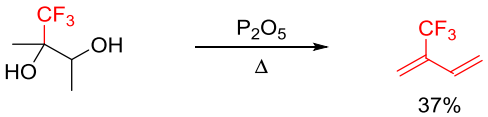
Since we succeeded in the introduction of α-(trifluoromethyl)ethenyl motif onto arenes, we turned our attention to versatile olefins, which are more challenging to deal with. The introduction of the BTP motif onto olefins would offer a straightforward access to the corresponding trifluoromethylated 1,3-butadienes. The 1,3-butadiene backbone is a very important structural motif found in both pharmaceuticals and complex natural products.[129] Thus, the development of efficient synthetic methodologies to access these scaffolds is highly valuable. To our knowledge, the Wittig reaction[130] and the cross-coupling reactions[129c, 131] (eg. Heck cross-coupling reaction) are two popular and general approaches for the synthesis of 1,3-butadienes. In contrast, only few examples involving a transition metal-catalyzed directed C-H bond functionalization are reported.[18, 41-43, 45-46, 51, 87, 132] Since the CF_3-group could be considered as an important motif in industry, trifluoromethylated butadienes appear as attractive building blocks for design of new pharmaceuticals, for instance.

The synthesis of fluorinated 1,3-butadienes and particularly the trifluoromethylated ones is underexplored, in spite of the obvious advantage that this motif represents in the toolbox of fluorinated building blocks. At the outset of the project, only limited

reports can be found to get access to this kind of motif.

In 1959, Tarrant and Taylor reported the dehydration of the α-(trifluoromethyl) -2,3-butanediol to synthesize the corresponding β-(trifluoromethyl)-butadiene in a low yield (Scheme 72).[133] Harsh conditions were employed, since the dehydration step was accomplished by heating the starting material with phosphorus pentoxide.

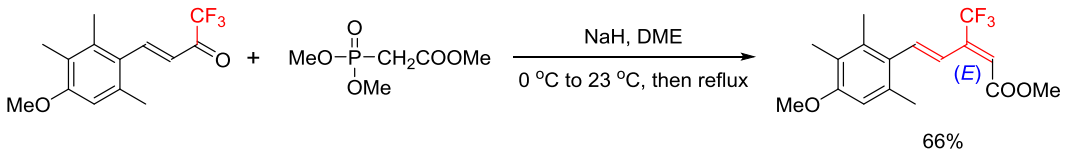
Tarrant and Taylor.



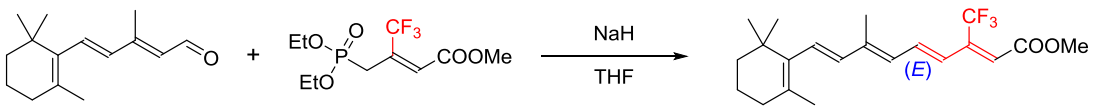
Scheme 72: Dehydration of the α-(trifluoromethyl)-2,3-butanediol.

Pawson (1979)[134] and Gaertner (1981)[135] reported a couple of examples of the synthesis of α-trifluoromethylated 1,3-butadiene derivatives by using Wittig-Horner reaction, respectively. In 1984, Sepiol[136] employed the Wittig reaction with a α,β-unsaturated β-trifluoromethylated ketone with malononitrile to give a mixture of α-trifluoromethylated 1,3-butadiene derivatives in 45% yield (Scheme 73).

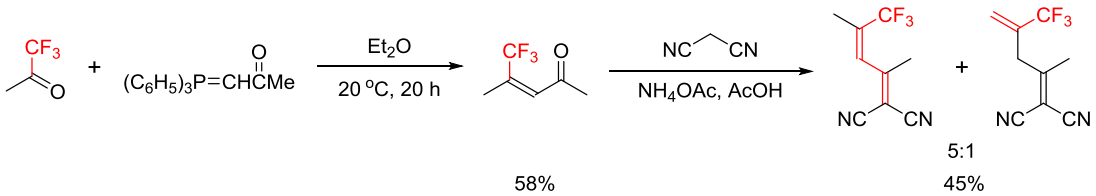
Pawson *et al.*



Gaertner *et al.*

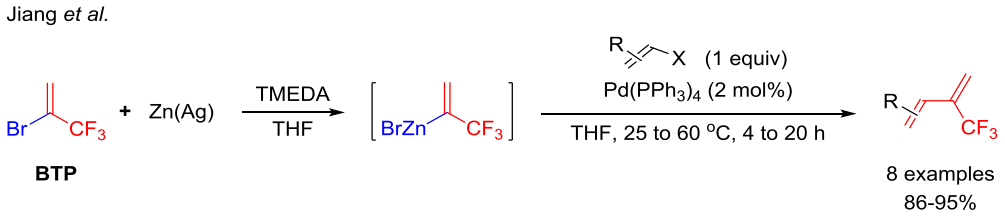


Sepiol *et al.*



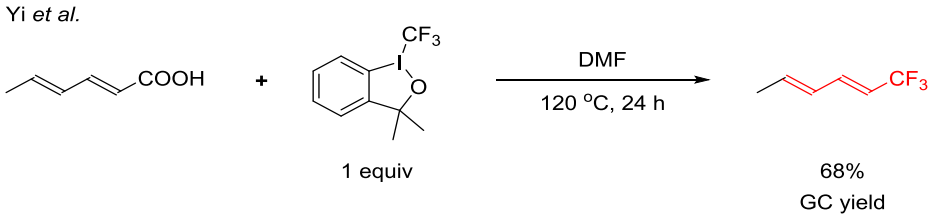
Scheme 73: Wittig-Horner reactions and Wittig reaction.

In 1992, Jiang and Xu reported a stereoselective synthesis of α-trifluoromethylated 1,3-butadiene derivatives via a palladium-catalyzed cross-coupling of trifluoroisopropenyl zinc reagent with vinyl halides in 86-95% yields (Scheme 74).[137]



Scheme 74: Negishi type cross-coupling reaction.

In 2015, Yi and co-workers showed an unique example of decarboxylative trifluoromethylation of an α,β,γ,δ-unsaturated carboxylic acid with the Togni(II) reagent in 68% GC yield (Scheme 75).[138]



Scheme 75: Decarboxylative trifluoromethylation.

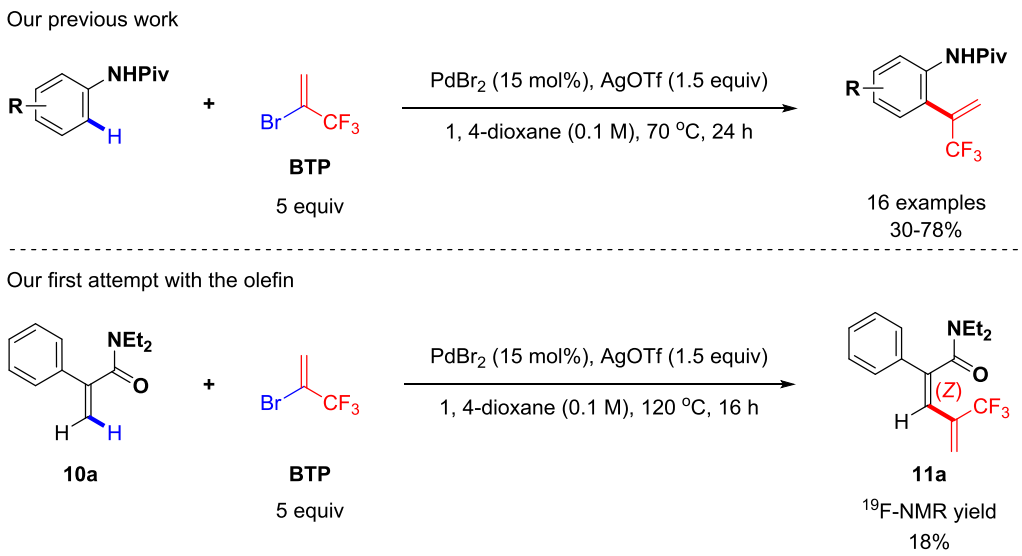
Thus, the development of efficient, stereoselective and practical synthetic methodology to build up functionalized trifluoromethyl 1,3-butadienes would be highly desirable. Especially, the functionalization of olefins leading selectively to the (*Z*) -isomer is a real challenge. To reach that goal, we hypothesized that the presence of a directing group would be beneficial. Indeed, the coordination of the transition metal to the directing group should favor the formation of a metallacycle, which would selectively afford the (*Z*)-olefin after the reaction with BTP.

2.4.1 Optimization of the reaction conditions

2.4.1.1 Preliminary results

At the outset of the project, we selected an electron-withdrawing group (EWG) as the directing group, since it has already successfully been used in directed C-H bond functionalization.[11]

In our preliminary attempt, we used *N,N*-diethyl-2-phenylacrylamide as a model substrate. Our first test was performed by using similar conditions as our previous work. Gratifyingly, using *N,N*-diethyl-2-phenylacrylamide with $PdBr_2$ as a catalyst and AgOTf as an additive in 1,4-dioxane at 120 °C, the expected product **11a** was obtained in 18% ^{19}F NMR yield (Scheme 76). The structure of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HRMS) analysis.

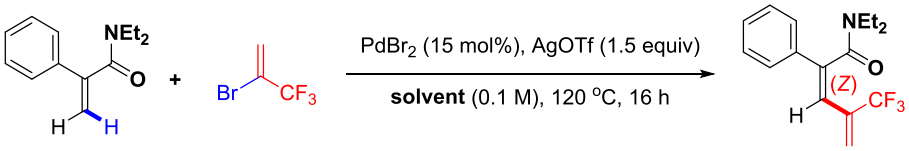


Scheme 76: Preliminary results.

2.4.1.2 Screening of the solvents

With this promising result in hand, a panel of solvents was screened (Table 4, entries

2-8). Low yields were observed using PhCl, THF and toluene (Table 4, entries 2, 5 and 8), while a shutdown of the reaction was observed with DCE (Table 4, entry 6). Notably, the reaction performed in NMP gave the best result, 24% yield (Table 4, entry 7). Since there is no significant difference between DMF (Table 4, entry 4) and NMP (Table 4, entry 7), DMF was chosen as the solvent to continue the optimization due to its lower boiling point.



10a **BTP** **11a**

Entry	solvent	Yield (%)[b]
1	1, 4-dioxane	18
2	PhCl	2
3	DMA	20
4	DMF	20
5	THF	12
6	DCE	0
7	NMP	24
8	toluene	7

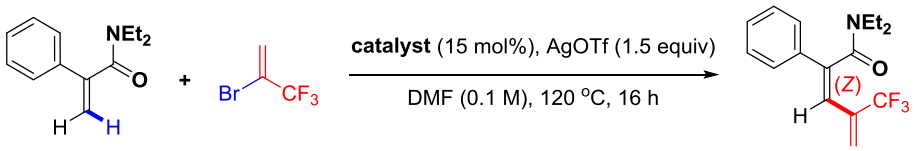
Table 4: Screening of the solvents.[a]

[a] Reaction conditions: **10a** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $PdBr_2$ (0.03 mmol, 15 mol%), AgOTf (0.3 mmol, 1.5 equiv), solvent (2 mL), 120 °C, Ar, 16 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.4.1.3 Screening of the catalysts

Subsequently, we investigated the effect of the catalyst on this transformation (Table **5**, entries 2-7). Different Pd(II)-catalysts were tested and similar yields were obtained with $Pd(OAc)_2$, $Pd(TFA)_2$ and $Pd(CH_3CN)_4(BF_4)_2$ (Table 5, entries 2-4). These data indicated that they displayed a similar reactivity to catalyze this olefination reaction. A survey of Pd-halides did not afford significant improvement of the yield (Table 5, entries

1, 5 and 6). Gratifyingly, $Pd(acac)_2$ afforded the best result and the desired product was obtained in 31% yield (Table 5, entry 7). Note that a control experiment was performed and no product was detected in the absence of the catalyst, demonstrating the importance of the Pd-catalyst in our transformation (Table 5, entry 8).



10a **BTP** **11a**

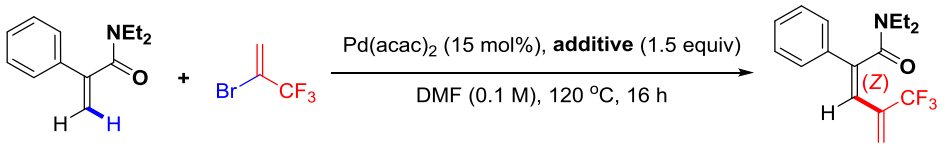
Entry	catalyst	Yield (%)[b]
1	$PdBr_2$	20
2	$Pd(OAc)_2$	23
3	$Pd(TFA)_2$	23
4	$Pd(CH_3CN)_4(BF_4)_2$	24
5	$PdCl_2$	23
6	PdI_2	16
7	$Pd(acac)_2$	31
8	-	0

Table 5: Screening of the catalysts.[a]

[a] Reaction conditions: **10a** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), catalyst (0.03 mmol, 15 mol%), AgOTf (0.3 mmol, 1.5 equiv), DMF (2 mL), 120 °C, Ar, 16 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.4.1.4 Screening of the additives

Next, different additives were tested (Table 6, entries 2-7). The reaction was completely suppressed when AgOTf was replaced by $Cu(OAc)_2$ and $Cu(OTf)_2$ (Table 6, entries 6 and 7), which indicated that silver salt played an important role for this transformation. Moreover, the yields dramatically decreased when AgOAc and Ag_2CO_3 were employed (Table 6, entries 2 and 3). However, similar yields were obtained with $AgBF_4$ and $AgSbF_6$ (Table 6, entries 4 and 5). Since AgOTf is less expensive, this additive was used for further optimization.



10a **BTP** **11a**

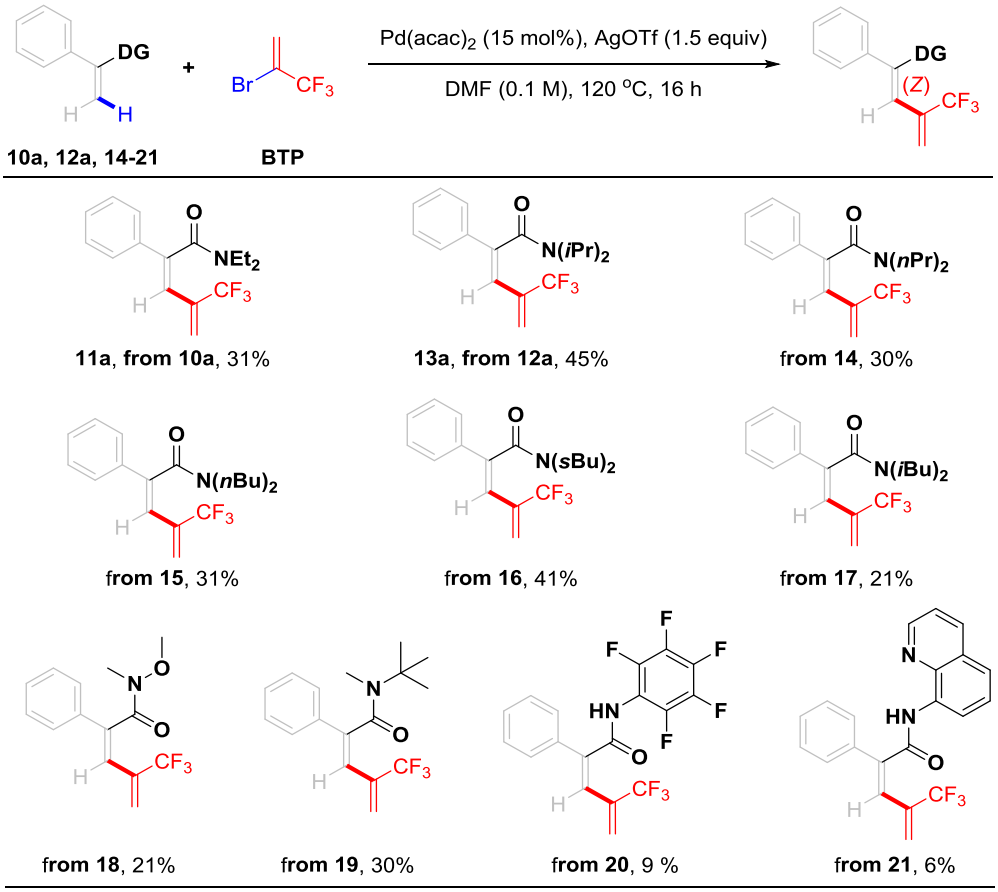
Entry	**additive**	Yield (%)[b]
1	AgOTf	31
2	AgOAc	3
3	Ag_2CO_3	8
4	$AgBF_4$	30
5	$AgSbF_6$	30
6	$Cu(OAc)_2$	0
7	$Cu(OTf)_2$	0

Table 6: Screening of the additives.[a]

[a] Reaction conditions: **10a** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.03 mmol, 15 mol%), additive (0.3 mmol, 1.5 equiv), DMF (2 mL), 120 °C, Ar, 16 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.4.1.5 Screening of directing groups

To study the influence of the directing group, several acrylamides were synthesized and tested using our best conditions. The reaction tolerated a range of amide-based directing groups, including tertiary (Scheme 77, **10a**, **12a**, **14-19**) and secondary amides (Scheme 77, **20**-**21**). Note that the latters gave lower yields, 9% and 6%, respectively. Finally, the $CON(iPr)_2$ directing group proved to be the best one, since it offered the desired compound in a promising 45% yield.



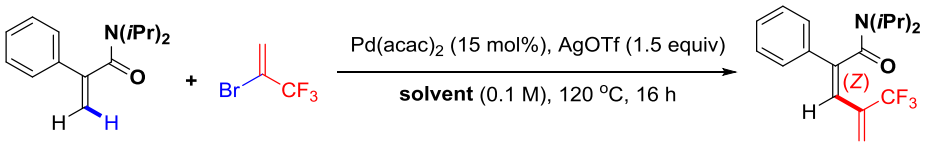
Scheme 77: Investigation of the directing groups.[a]

[a] Reaction conditions: **10a, 12a, 14-21** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.03 mmol, 15 mol%), AgOTf (0.3 mmol, 1.5 equiv), DMF (2 mL), 120 °C, Ar, 16 h. The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.4.1.6 Screening of other parameters

To fine-tune the reaction conditions, we performed an additional solvent screening with the newly developed conditions. With the best Pd-catalyst, additive and directing group, the use of DMA and NMP improved the yield to 52% and 53%, respectively (Table 7, entries 1 and 2). Note that an increase of the AgOTf stoichiometry from 1.5 to 2 equivalents combined with a decrease of the quantity of $Pd(acac)_2$ from 15 mol% to 10 mol% enhanced the reaction yield to 66% (Table 7, entry 4). Pleasingly, using these slightly modified conditions, DMI gave the best result (Table 7, entry 6, 76% yield),

while NMP and DMPU gave lower or similar yields (Table 7, entries 4 and 5). In order to lower the cost of the solvent, some mixture of solvents were tried (DMI/DMF = 1:1 and DMI/DMA = 1:1), however, the yields slightly decreased (Table 7, entries 7 and 8).



12a **BTP** **13a**

Entry	solvent	Yield (%)[b]
1	DMA	52
2	NMP	53
3[c]	NMP	63
4[d]	NMP	66
5[d]	DMPU	75
6[d]	DMI	76
7[d]	DMI/DMF = 1:1	57
8[d]	DMI/DMA = 1:1	69

Table 7: Screening of other parameters.[a]

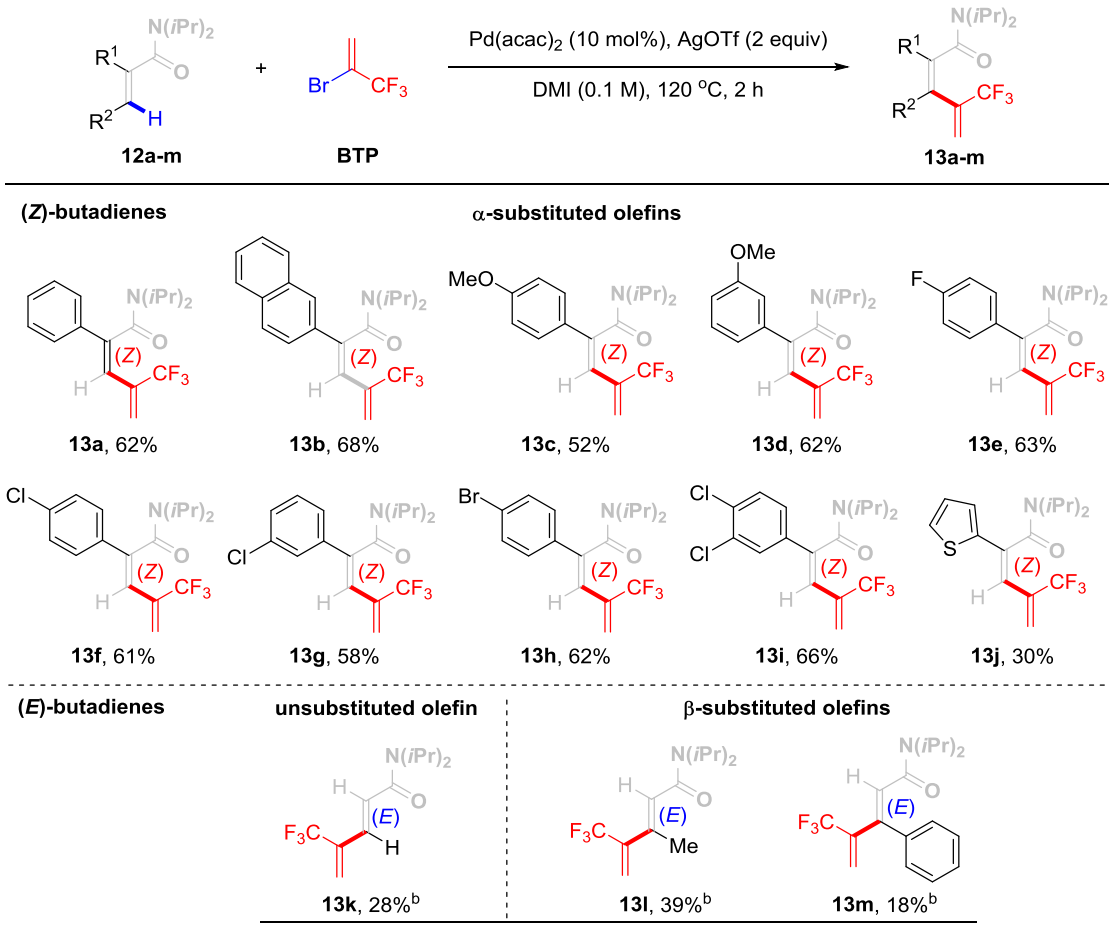
[a] Reaction conditions: **12a** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.03 mmol, 15 mol%), AgOTf (0.3 mmol, 1.5 equiv), solvent (2 mL), 120 °C, Ar, 16 h. [b] the yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard. [c] AgOTf (2 equiv), 2 h. [d] $Pd(acac)_2$ (10 mol%), AgOTf (2 equiv), 2 h.

2.4.2 Investigation of the substrates scope

2.4.2.1 The reaction with BTP

Having the best conditions in hand, we next explored the scope and limitations of this reaction. The results are depicted in Scheme 78. First, we examined the effects of the aryl substitution using a range of *N,N*-diisopropyl-2-aryl-acrylamide derivatives (Scheme 78, **12a-12i**). The effect of the substituents on the aromatic ring was not obvious. Indeed, electron-donating groups as well as electron-withdrawing groups were both well tolerated and gave similar yields. Notably, halide substituents were

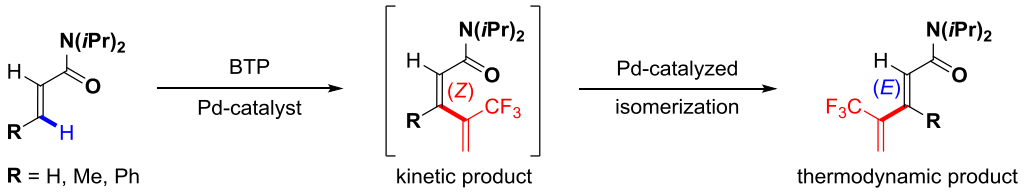
compatible, which is very useful for further transformations. Heteroarene derivative could also be used, since the thiophene derivative (Scheme 78, **12j**) reacted smoothly to afford the desired product (Scheme 78, **13j**), albeit with a lower yield. *N,N*-Diisopropylacrylamide **12k** was found to be an extremely reactive substrate and the reaction was completed within 15 min. However, the isolated yield was quite low since the starting material was prompt to polymerize. In contrast with our previous results, this starting material furnished the 1,3-diene (Scheme 78, **13k**) with the (*E*)-configuration of the olefin. Then, we tested two different β-substituted olefins (Scheme 78, **12l** and **12m**) and the same inversion of configuration was observed.



Scheme 78: Substrates scope.[a]

[a] Reaction conditions: **12a-m** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), DMI (2 mL), 120 °C, Ar, 2 h. [b] On 0.6 mmol scale.

To explain these unexpected results, we hypothesized that the (*E*)-isomer could be thermodynamically more stable than the (*Z*)-isomer and the formation of the (*E*)-isomer can result from an *in situ* isomerization of the (*Z*)-product mediated by the Pd-catalyst as already reported (Scheme 79).[139]



Scheme 79: Isomerization of (*Z*)-product to (*E*)-product.

Note that preliminary DFT calculations were performed and confirmed this hypothesis regarding the relative stability of the products (Figure 4).[140] It is clear that the compound (*Z*)-**13k** is less stable than (*E*)-**13k** (ΔG = -4.8 kcal/mol at 298K), while (*Z*)-**13a** is more stable than (*E*)-**13a** (ΔG = +1.3 kcal/mol at 298K), according to the relative Gibbs energy of the (*Z*)/(*E*)-isomers.

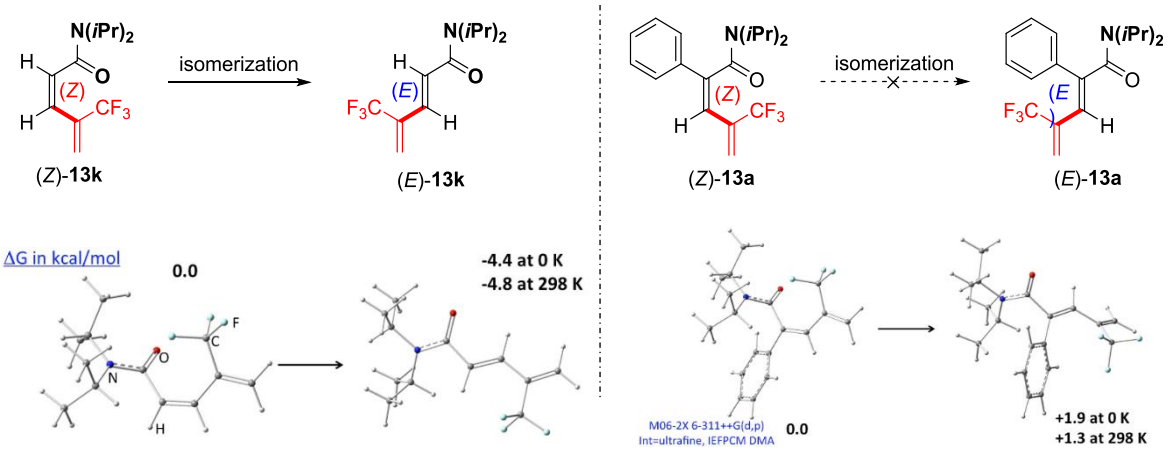
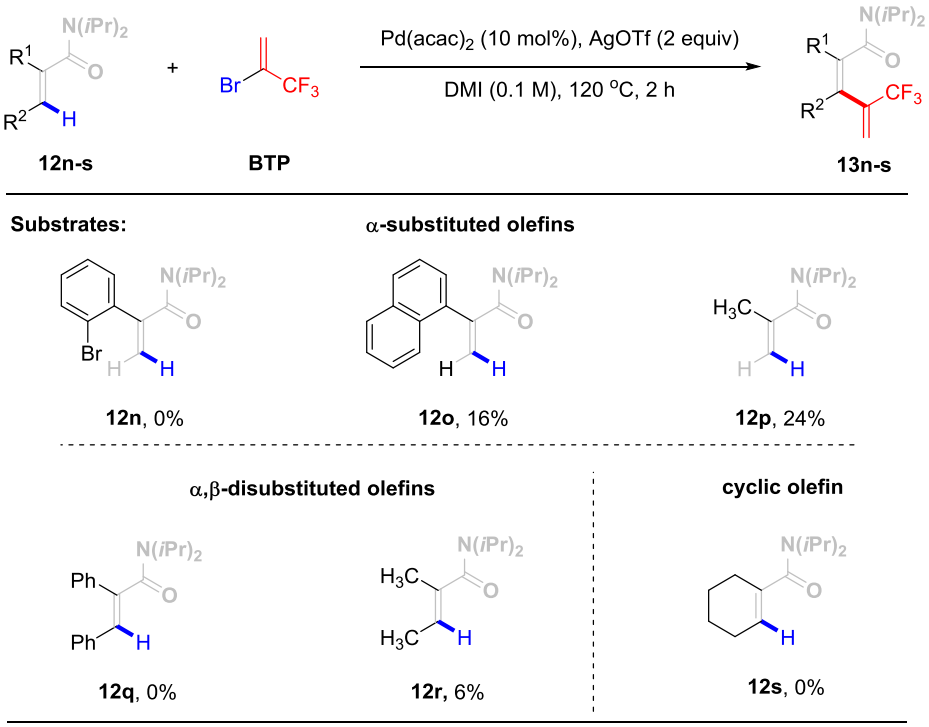


Figure 4: DFT calculations.

2.4.2.2 The limitations with BTP

It is worth to mention that some limitations of this catalytic system were observed

during the investigation of the scope of the reaction (Scheme 80, **12n**-**12s**). The *ortho*-substituted aromatic substrate **12n** was unreactive in this transformation and the naphthyl derivative **12o** furnished the corresponding product in a very low yield. Both of these disappointing results could be attributed to the steric hindrance. α-Alkyl-substituted acrylamide gave the corresponding product in a low yield (Scheme 80, **12p**). It was also disappointing that α,β-disubstituted substrates (Scheme 80, **12q** and **12r**) and the cyclic olefin (Scheme 80, **12s**) did not provide the expected products under our reaction conditions.



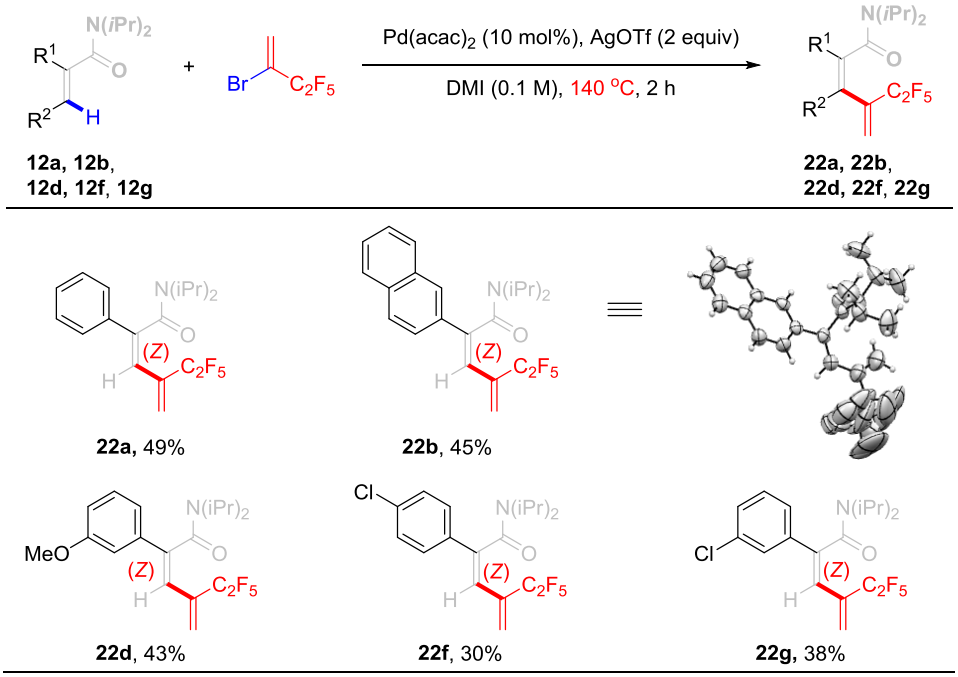
Scheme 80: Ineffective substrates.[a]

[a] Reaction conditions: **12n-s** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), DMF (2 mL), 120 °C, Ar, 2 h. The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.4.2.3 The reaction with the C_2F_5-analogue of BTP

In order to show the power of this transformation, the C_2F_5-analogue of the BTP was

tested in our conditions with some typical substrates (Scheme 81, **12a**, **12b**, **12d**, **12f**, **12g**). By a slight increase of the temperature from 120 °C to 140 °C, these substrates were converted into the corresponding C_2F_5-substituted products in moderate yields (30%-49%). The absolute configuration of **22b** was confirmed by X-ray analysis and it is consistent with the two-dimension NMR analysis (see experimental part).



Scheme 81: Reactions with the C_2F_5-analogue of BTP.[a]

[a] Reaction conditions: **12a, 12b, 12d, 12f, 12g** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), DMI (2 mL), 140 °C, Ar, 2 h.

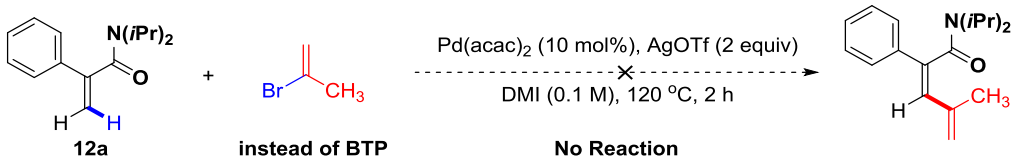
2.4.3 Mechanistic studies

To gain insight into this reaction, we conducted mechanistic studies. Fluorine effect[141] and KIE effect[142] were investigated, respectively.

2.4.3.1 Fluorine Effect

When BTP reagent was replaced by 2-bromopropene as a coupling partner, no trace

of the corresponding product was detected under the standard conditions. This result demonstrated the strong influence of the fluorinated group on the olefin and thus, the importance of the "fluorine effect" for this transformation (Scheme 82).[141]

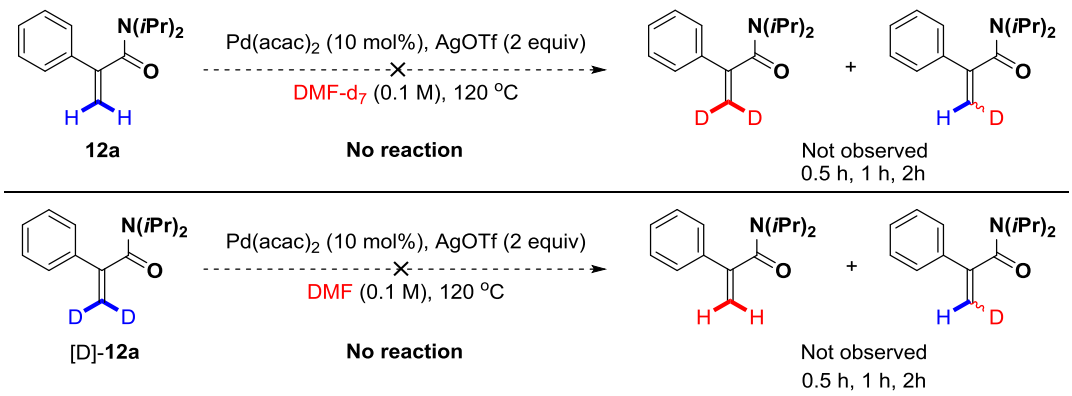


Scheme 82: Fluorine effect study.

2.4.3.2 Kinetic Isotope Effect (KIE)

2.4.3.2.1 Scrambling experiment (without BTP)

In order to confirm the occurrence of H/D exchange, scrambling reactions were carried out (Scheme 83). H/D exchange was not observed when **12a** was reacted in DMF-d_7 under the standard reaction conditions without BTP. A similar result was obtained with [D]-**12a** when it was reacted in DMF. In this case, parallel reactions with [D]-**12a** can be carried out without using deuterated solvent.

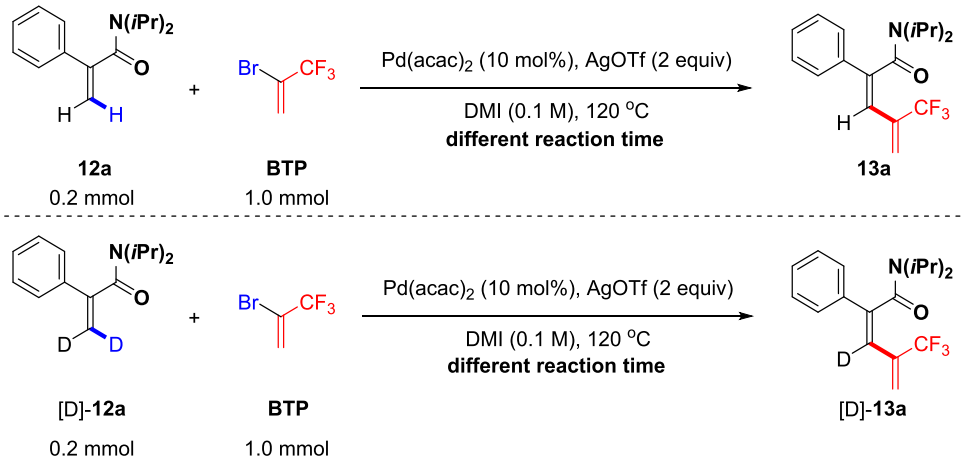


Scheme 83: Scrambling reactions.

2.4.3.2.2 Kinetic Isotope Effect (KIE) measurements

Since no H/D scrambling was observed, parallel reactions with **12a** and [D]-**12a** were

both performed in DMI for different reaction time (10 min, 20 min, 30 min, 40 min and 50 min) without using deuterated solvent (Scheme 84).



Scheme 84: The parallel reactions with **12a** or [D]**-12a** for different reaction time.

The reactions were followed by ^{19}F NMR over reaction time (Figure 5). With these data, the KIE value was determined according to the following equation: KIE = K_H/K_D = 3.1/2.75 = 1.1. This result indicated that the C-H bond activation is not the rate determining step of the transformation.

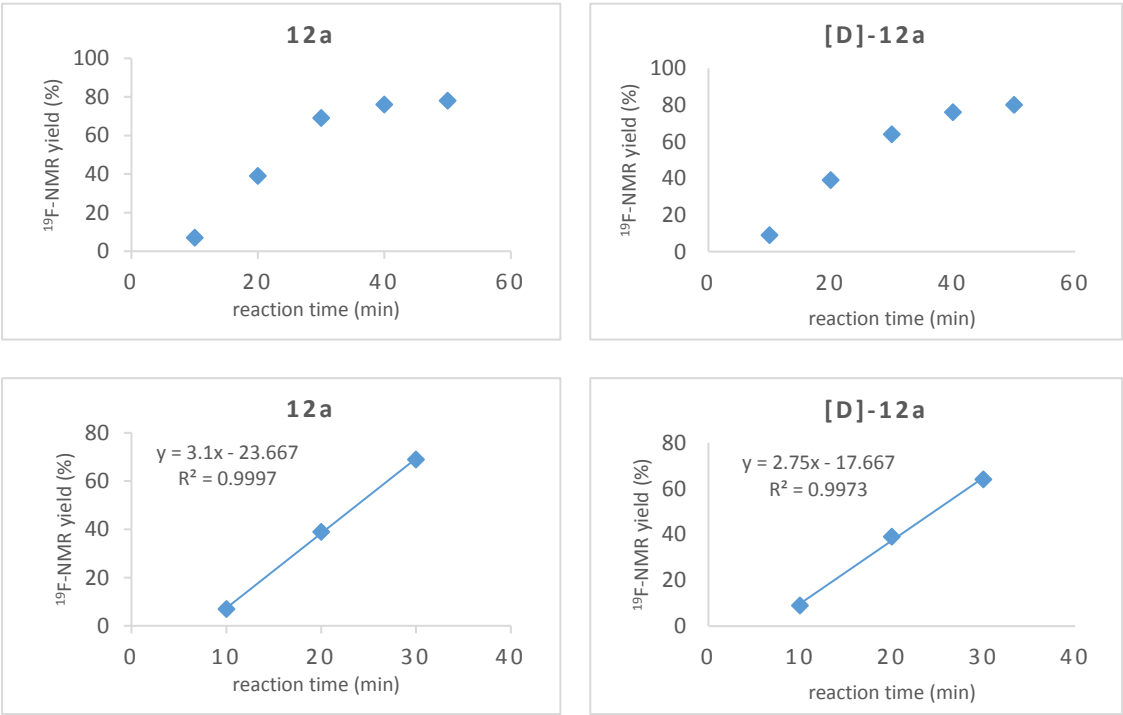


Figure 5: The ^{19}F NMR yield (%) of **13a** and [D]**-13a** over reaction time (min).

2.4.4 Proposed mechanism

Based on the above observations and previous studies reported in the literature,[127, 143] a possible mechanism (Figure 6) was proposed as follows: first, the palladacycle intermediate **A** was formed after the activation of the C(sp^2)-H bond according to a plausible concerted metalation-deprotonation pathway. Then, **A** coordinated to BTP to generate intermediate **B**. Subsequently, **B** underwent a carbopalladation reaction leading to the organopalladium intermediate **C**. Finally, the desired product was released according to a β-bromide elimination step favored by the Ag salt.[127]

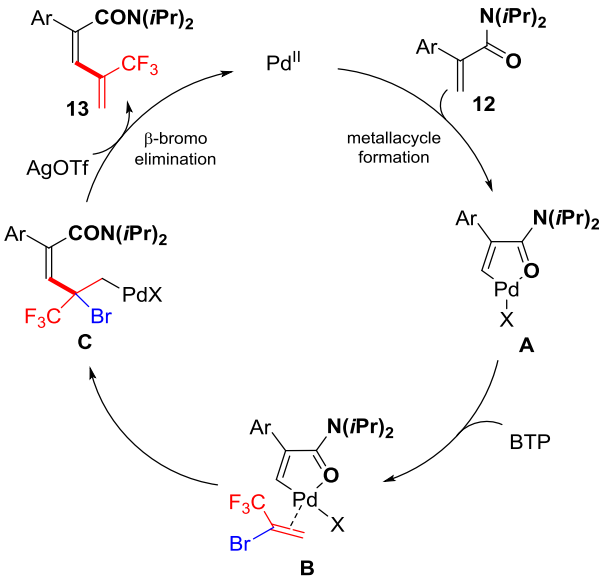


Figure 6: Proposed mechanism.

2.4.5 DFT calculations

This proposed mechanism was supported by DFT calculations at the M06-L/6-311+G(d)-SDD level of theory.[144] According to the DFT calculations, a Pd(II)/Pd(IV) mechanism can be ruled out in favor of a redox-neutral Pd(II)/Pd(II) pathway, since the formation of the Pd(IV)-species **D** needs more energy than that of

the Pd(II)-species **C** (10.4 kcal/mol vs -15.1 kcal/mol) (Figure 7).

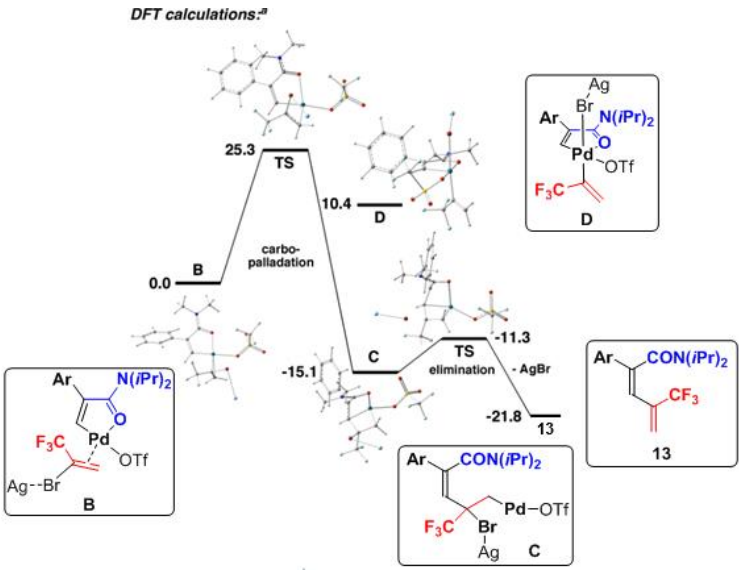
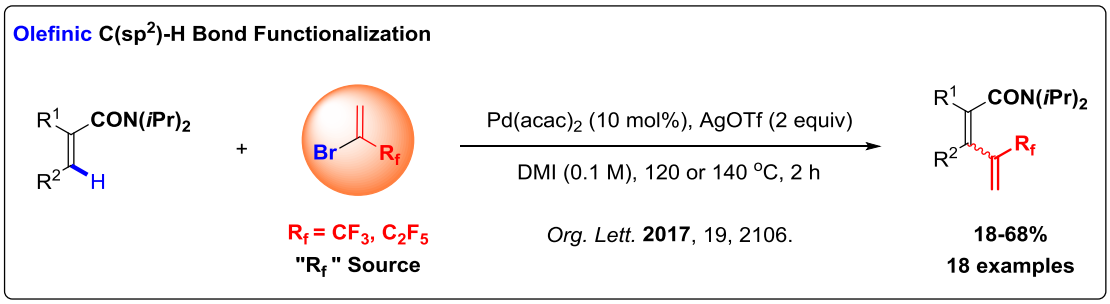


Figure 7: DFT calculations.

2.4.6 Brief summary

In conclusion, this part of work was dedicated to the development of a new methodology for the introduction of the α-(trifluoromethyl)ethenyl moiety into olefins through a transition metal-catalyzed directed C(sp^2)-H bond functionalization reaction.



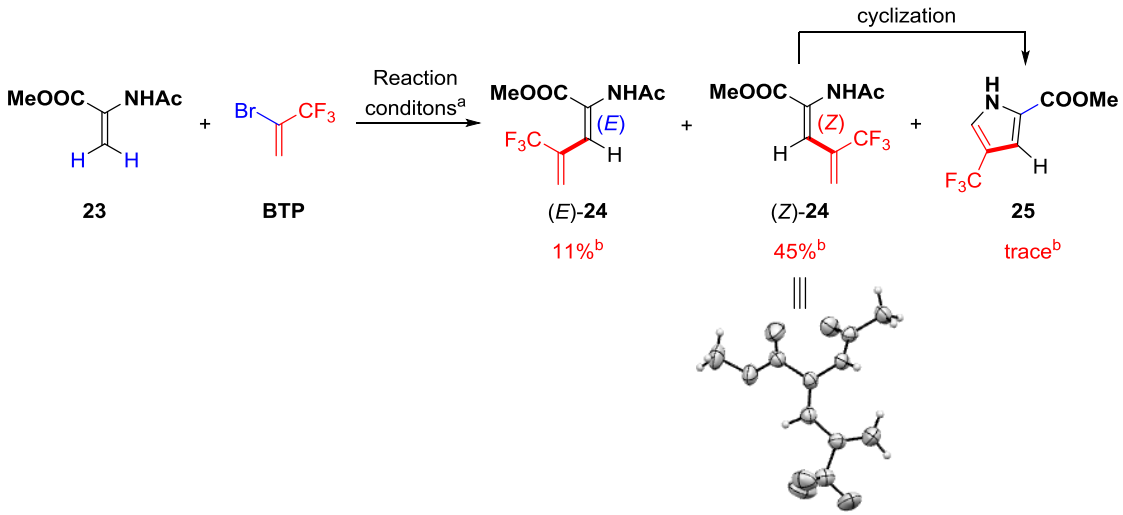
Scheme 85: Olefinic C(sp^2)-H Bond Functionalization.

This method was applied to a broad range of olefins, including α-substituted, β-substituted and α,β-substituted olefins (Scheme **85**, 18 examples, 18-68% yields). This protocol provided a stereoselective and efficient access to the polysubstituted 1,3-butadienes. Note that investigations regarding the reaction mechanism were

carried out, including mechanistic experiments and DFT calculations. Based on those experiments, a neutral Pd(II)/Pd(II) pathway was suggested.

2.5 Functionalization of α,β-unsaturated esters

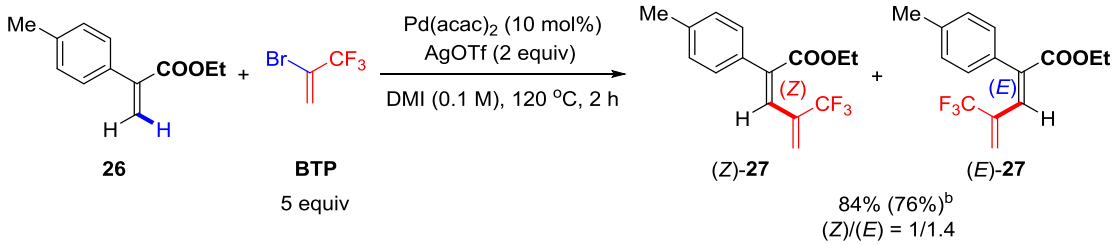
During the process of exploring the scope of the coupling reaction, we tested the amino acid derivative, **23**, under the standard reaction conditions and an interesting result was observed. The corresponding (*E*)-**24** and (*Z*)-**24** products were obtained in 11% and 45% isolated yields, accompanied with trace of the cyclic product **25** (Scheme 86). Since this reaction led to a mixture of the (*E*)- and (*Z*)-products, we speculated that the ester group could compete with the amide directing group to selectively activate the olefinic C-H bond.



Scheme 86: The coupling reaction between the amino acid derivative **23** and BTP.[a]
[a] Reaction conditions: **23** (1.0 mmol, 1 equiv), BTP (5.0 mmol, 5 equiv), $Pd(acac)_2$ (0.1 mmol, 10 mol%), AgOTf (2.0 mmol, 2 equiv), DMI (10 mL), 120 °C, Ar, 2 h. [b] Isolated yield.

In order to confirm our hypothesis, the substrate **26** was synthesized and reacted with BTP under the standard conditions. In the first test, a mixture of (*Z*)- and (*E*)-**27** was obtained in an overall 76% isolated yield, with a (*Z*)/(*E*) ratio of 1/1.4 (Scheme 87).

Our first test with **26**



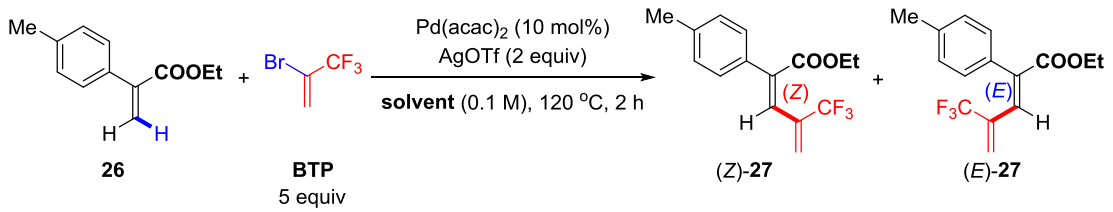
Scheme 87: First test with ester substrate **26**.[a]

[a] Reaction conditions: **26** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), DMI (2 mL), 120 °C, Ar, 2 h. The yield and (*Z*)/(*E*) ratio were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard. [b] Isolated yield in parenthesis.

2.5.1 Optimization of the reaction conditions

2.5.1.1 Screening of the solvents

Firstly, a panel of solvents with different polarity was evaluated. The yield decreased significantly when DMI was replaced by DMF (Table 8, entry 2). Only trace of the product was observed in DCE and 1,4-dioxane (Table 8, entries 3 and 4), while no product was detected in toluene (Table 8, entry 5). Thus, DMI was chose as the solvent to continue the optimization.



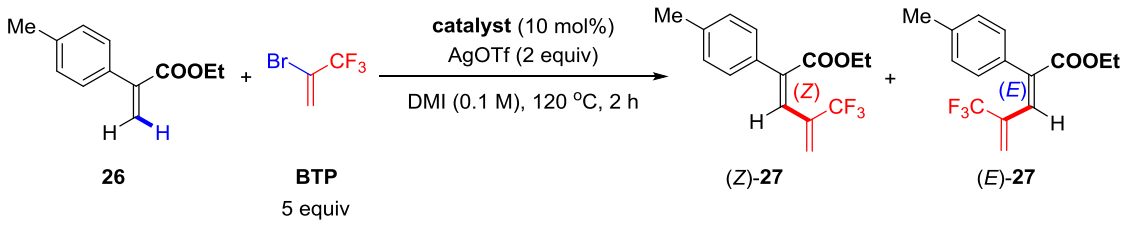
Entry	solvent	Yield (%)[b]
1	DMI	84
2	DMF	28
3	DCE	trace
4	1, 4-dioxane	6
5	toluene	0

Table 8: Screening of the solvents.[a]

[a] Reaction conditions: **26** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), solvent (2 mL), 120 °C, Ar, 2 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.5.1.2 Screening of the catalysts

Next, we screened different Pd-catalysts. $Pd(TFA)_2$, $Pd(CH_3CN)_4(BF_4)_2$ and $PdBr_2$ gave lower yield with similar stereoselectivity compared to $Pd(acac)_2$ (Table 9, entries 2, 3 and 4). Noted that $Pd(PPh_3)_4$ reversed the ratio of (*Z*)/(*E*) from 1/1.4 to 1/0.3, albeit in only 27% NMR yield (Table 9, entry 5). So we continued the screening with $Pd(acac)_2$ as the catalyst.



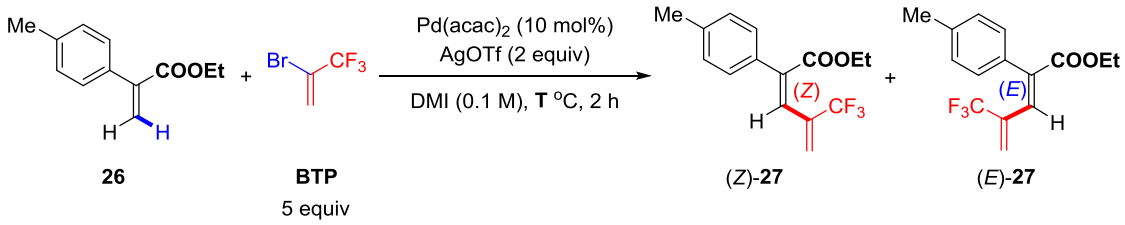
Entry	catalyst	Yield (%)[b]	(*Z*)/(*E*)[b]
1	$Pd(acac)_2$	84	1/1.4
2	$Pd(TFA)_2$	49	1/1.3
3	$Pd(CH_3CN)_4(BF_4)_2$	67	1/1.4
4	$PdBr_2$	80	1/1.4
5	$Pd(PPh_3)_4$	27	1/0.3

Table 9: Screening of the catalysts.[a]

[a] Reaction conditions: **26** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), catalyst (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), DMI (2 mL), 120 °C, Ar, 2 h. [b] The yields and (*Z*)/(*E*) ratio were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

2.5.1.3 Screening of the temperature

Different temperatures were also evaluated. When the reaction was carried out at 90 °C, only trace of the desired product was detected (Table 10, entry 1). When the temperature was increased to 140 °C, the yield decreased significantly with a similar (*Z*)/(*E*) ratio (Table 10, entry 3). Thus, 120 °C was considered as the best temperature for this transformation.



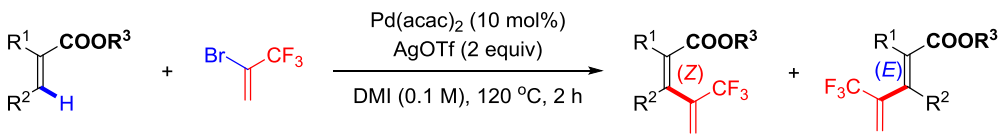
Entry	**T** (°C)	Yield (%)[b]	(*Z*)/(*E*)[b]
1	90	trace	--
2	120	84 (76)[c]	1/1.4
3	140	39	1/1.3

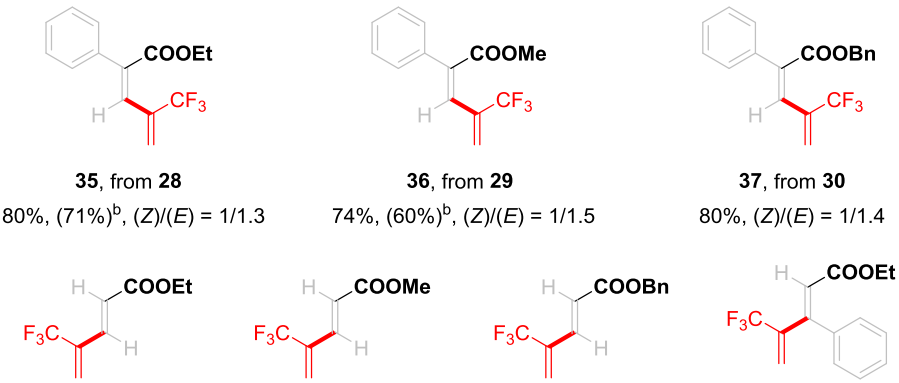
Table 10: Screening of the temperature.[a]

[a] Reaction conditions: **26** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), DMI (2 mL), T °C, Ar, 2 h. [b] The yields and (*Z*)/(*E*) ratio were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard. [c] Isolated yield in parenthesis.

2.5.1.4 Screening of the ester substrates

Next, we investigated different ester derivatives. When α-phenyl substrates with different size of ester moieties were evaluated, similar yields as well as similar selectivity were observed (Scheme 88, **28**, **29** and **30**). Interestingly, the reactions of unsubstituted substrates **31**, **32** and **33** selectively gave the corresponding (*E*)-isomers as the single products. Unfortunately, the β-phenyl substrate **34** was not a suitable substrate since only trace of the desired product was detected.





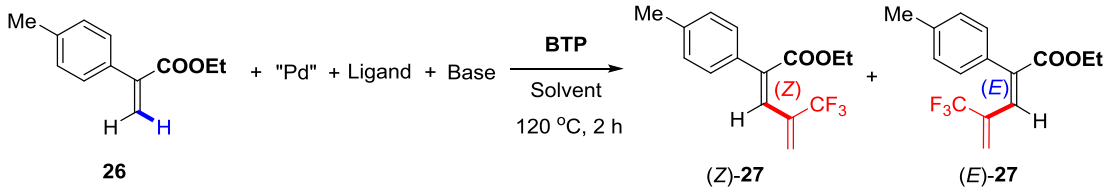
Scheme 88: Screening of the ester substrates.[a]

[a] Reaction conditions: **28-34** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), solvent (2 mL), 120 °C, Ar, 2 h. The yields and (*Z*)/(*E*) ratio were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard. [b] Isolated yield. [c] Isolated yield based on a 0.6 mmol scale.

2.5.1.5 Refining the reaction conditions

We started a new round of conditions screening based on Heck-type reaction conditions. When this reaction was performed by using $Pd(PPh_3)_4$ as the catalyst, K_2CO_3 as the base in 1,4-dioxane at 120 °C for 2 h, 38% of ^{19}F NMR yield combined with 1/2.5 of the (*Z*)/(*E*) ratio were detected (Table 11, entry 2). Next, different Pd-catalysts and solvents were evaluated and no improvement was observed (Table 11, entries 3-6). To our delight, when $Pd(TFA)_2$ was tested, 77% yield and 1/2.2 (*Z*)/(*E*) ratio were obtained (Table 11, entry 7). Then, different bases (Table 11, entries 8-10) and ligands (Table 11, entries 11-12) were screened, but only traces or no product were observed. Until now, the best result (77% and (*Z*)/(*E*) =1:2.2) was obtained by

using $Pd(TFA)_2$ as the catalyst, Ag_2CO_3 as the base in 1,4-dioxane at 120 °C for 2 h (Table 11, entry 7).



Entry	"Pd"	Ligand	Base	Solvent	Yield (%)[b]	(Z)/(E)[b]
1	$Pd(PPh_3)_4$	--	K_2CO_3	DMI	0	--
2	$Pd(PPh_3)_4$	--	Ag_2CO_3	1,4-dioxane	38	1/2.5
3	$PdCl_2(PPh_3)_2$	--	Ag_2CO_3	1,4-dioxane	16	1/3
4	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	1,4-dioxane	30	1/2
5	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	toluene	trace	--
6[c]	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	MeCN	0	--
7	$Pd(TFA)_2$	PPh_3	Ag_2CO_3	1,4-dioxane	77	1/2.2
8	$Pd(TFA)_2$	PPh_3	Cs_2CO_3	1,4-dioxane	0	--
9	$Pd(TFA)_2$	PPh_3	K_3PO_4	1,4-dioxane	0	--
10	$Pd(TFA)_2$	PPh_3	CsOAc	1,4-dioxane	trace	--
11	$Pd(TFA)_2$	(tricyclohexyl)phosphine	Ag_2CO_3	1,4-dioxane	11	--
12	$Pd(TFA)_2$	(trimesityl)phosphine	Ag_2CO_3	1,4-dioxane	trace	--

Table 11: Refining the reaction conditions.[a]

[a] Reaction conditions: **26** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), "Pd" (0.02 mmol, 10 mol%), base (0.4 mmol, 2 equiv), ligand (0.25 mmol, 1.25 equiv), solvent (2 mL), 120 °C, Ar, 2 h. [b] The yields and (*Z*)/(*E*) ratio were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard. [c] The reaction was carried out at 80 °C.

The extension of this methodology to other substrates is currently in progress in our laboratory.

2.5.2 Mechanistic discussion

In theory, the ester directed C-H bond functionalization pathway should lead to the selective formation of the (*Z*)-product. The above-mentioned results indicate that the reaction proceeds rather via the Heck reaction pathway than an ester directed C-H

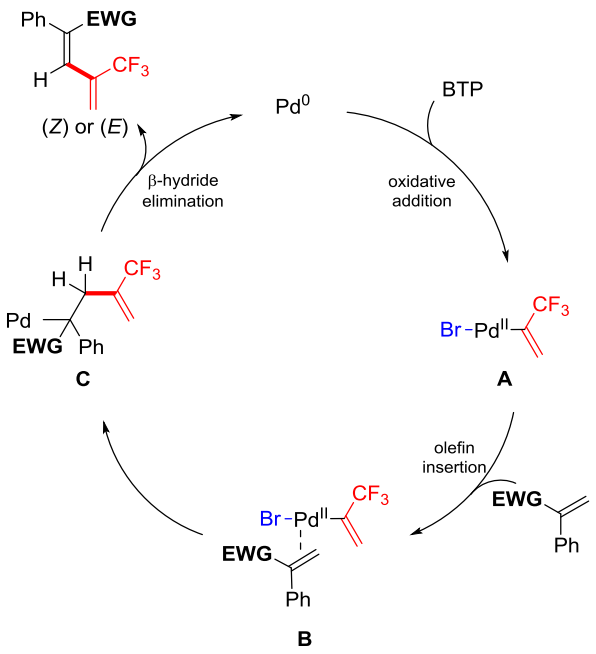
bond functionalization pathway. In order to rule out the C-H bond functionalization pathway and to access only Heck-type reaction product, we considered a substrate without a directing group. Since the cyano-moiety is not a directing group in this case, the cyano-containing substrate **42** was selected and subjected to the standard conditions. According to the ^{19}F NMR and GC-MS analysis, only one isomer was detected in 18% yield. In order to isolate and identify the configuration of the product, we performed this reaction on a 0.8 mmol scale and 6% of the (*Z*)-product **43** was obtained (Scheme 89). The (*Z*)-configuration was confirmed by 2D-NMR analysis (see experimental data). Note that the substrate **42** is prompt to polymerization even at room temperature, which explain the very low yield.

Scheme 89: Heck-type reaction of **42**.[a]

[a] Reaction conditions: **42** (0.2 mmol, 1 equiv), BTP (1.0 mmol, 5 equiv), $Pd(acac)_2$ (0.02 mmol, 10 mol%), AgOTf (0.4 mmol, 2 equiv), DMI (2 mL), 120 °C, Ar, 2 h. The yield was determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard. [b] Isolated yield in parenthesis based on a 0.8 mmol scale.

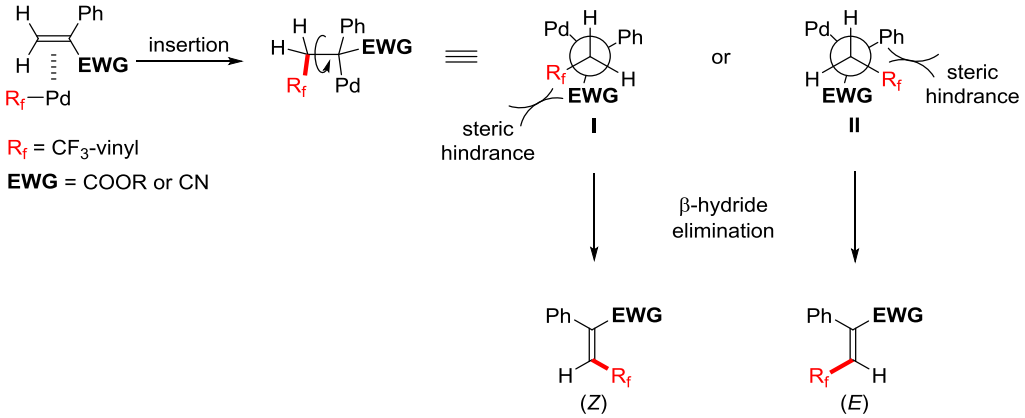
2.5.3 Proposed mechanism

A typical Heck-type reaction mechanism was proposed to explain the outcome of the reaction of **26** and **42**. The oxidative addition of Pd(0) species with BTP followed by the insertion into the olefin by Pd(II)-complex. Then, the β-hydride elimination occurred and afforded the desired product (Scheme 90).



Scheme 90: Proposed mechanism.

Concerning the (*Z*)/(*E*)-stereoselectivity, it depends on the comparison of the steric hindrance in **I** and **II**, as shown with the Newman views (Scheme 91). When EWG is an -COOR moiety, the difference of the steric hindrance in **I** and **II** are not significant, thus a mixture of the (*Z*)-**27** and (*E*)-**27** isomers is obtained. When EWG is the -CN group, the species **I** is highly favored compared with species **II** because of the poor hindrance of CN-group. As a result, (*Z*)-**43** isomer is selectively obtained.

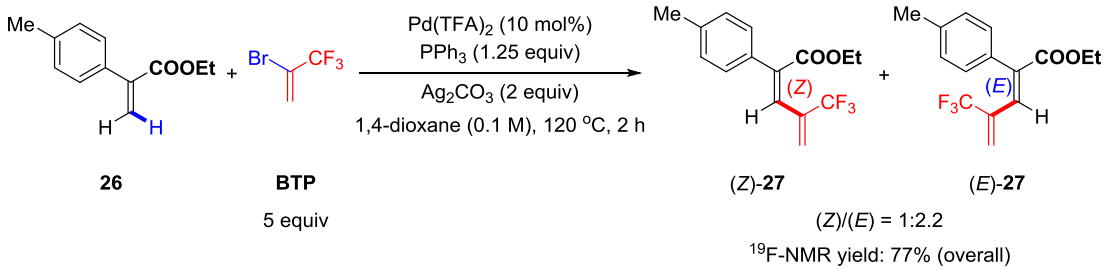


Scheme 91: The explaination for the (*Z*)/(*E*)-stereoselectivity.

Note that the ester directed C-H bond functionalization pathway cannot be ruled out.

2.5.4 Conclusion

With the promising results in hand (Scheme 92), we will continue to improve the stereoselectivity and then, start to evaluate the substrate scope and the limitations of this reaction. This part of work is currently undergoing in our lab.



Scheme 92: The functionalization of α,β-unsaturated ester **26** with BTP.

Chapter 3
Trifluoromethylthiolation with the Munavalli reagent

3. Trifluoromethylthiolation with the Munavalli reagent

3.1 Generality of the SCF_3 moiety

3.1.1 Properties of the SCF_3 group

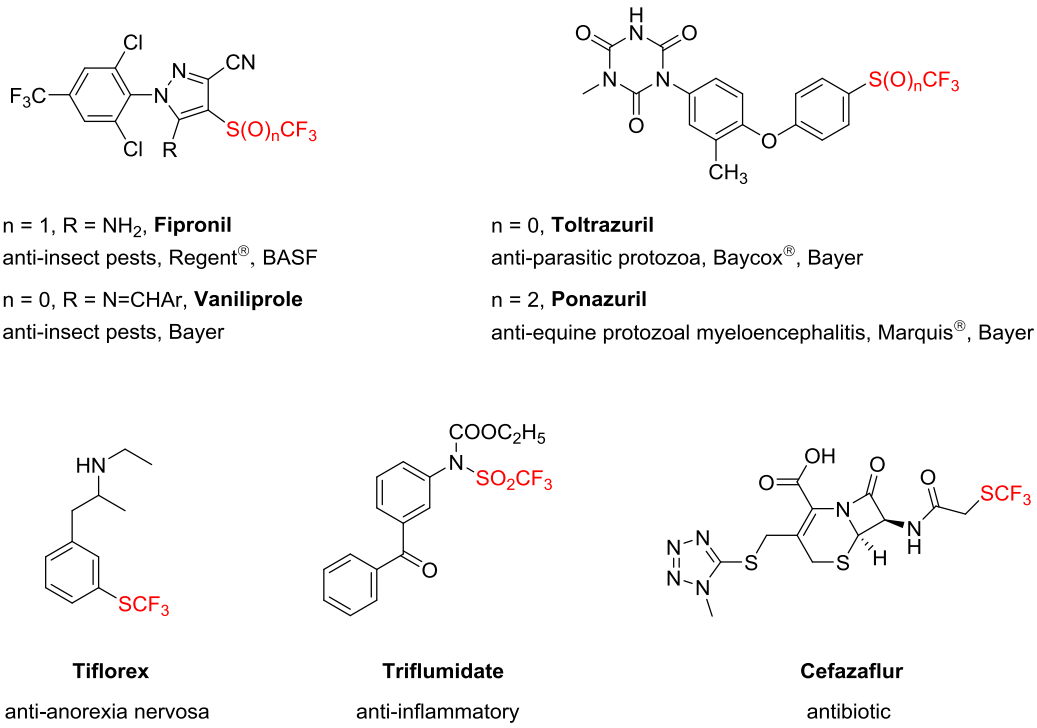
As one member of the perfluoroalkyl groups, the trifluoromethylthio (SCF_3) group exhibits quite special physical and chemical properties, such as a high Hansch lipophilicity parameter and a strong electron-withdrawing character. The incorporation of the SCF_3 group into molecules can substantially alter their physical, chemical and biological properties. The high Hansch lipophilicity parameter[145] (π = 1.44, Table 12) of the SCF_3 group can improve the lipophilicity and the bioavailability of the parent molecules. The strong electron-withdrawing character may increase the acidity and basicity of the neighboring groups and decrease the electron density of the molecule, thus leading to higher metabolic stability against an oxidative process. Besides, the SCF_3 group can be easily transformed into the corresponding $SOCF_3$- and SO_2CF_3-groups, offering alternative ways to modify the parent molecules.

Substituent	π	Substituent	π
-H	0.00	$-CF_3$	0.88
-F	0.14	$-OCF_3$	1.04
-Cl	0.71	**$-SCF_3$**	**1.44**
-Br	0.86	$-SO_2CF_3$	0.55
$-CH_3$	0.56	$-SF_5$	1.23

Table 12: Hansch π values (π **=** log*P*C_6H_5X - log*P*C_6H_5 for substituted benzenes)[145b]

3.1.2 SCF_3-Containing bioactive molecules

Because of the unique properties of the SCF_3 group, the SCF_3-containing compounds and the resulting derivatives have attracted a continuous interest in the pharmaceutical and agrochemical industries. Some examples of bioactive molecules can be found in Scheme 93.[146]



Scheme 93: Selected examples of relevant SCF_3-containing compounds.

For example, Fipronil,[147] a non-competitive GABA antagonist, is highly effective against a variety of insect pests. Vaniliprole,[148] which contains a SCF_3 group on the heterocyclic ring, also demonstrates great pesticidal activity. Toltrazuril,[149] bearing a *para*-SCF_3-phenoxy group, is used as a prophylactic and chemotherapeutic coccidiocide against parasitic protozoa. Ponazuril,[150] a derivative of the toltrazuril precursor, is a drug currently approved for the treatment of equine protozoal myeloencephalitis in horses, caused by sarcocystis neurona. The Tiflorex[151], a

SCF_3-substituted amphetamine derivative, shows efficacy against anorexia nervosa. Triflumidate,[152] containing a SO_2CF_3-group, shows strong *anti*-inflammatory activity against arthritis. It has nearly the same potency as aspirin for the inhibition of carrageenin induced edema. Cefazaflur,[153] containing a SCF_3 group next to the amide group, is a first-generation cephalosporin antibiotic which exhibits good in vitro activity against grampositive cocci and many of the members of the enterobacteriaceae.

3.2 Synthesis of SCF_3-containing alkene derivatives

The past few years have witnessed great advances for the synthesis of trifluoromethylthiolated molecules. However, most of the development has been focused on the construction of aryl-SCF_3, alkyl-SCF_3 and alkynyl-SCF_3 bonds.[146b, 154] The straightforward synthesis of SCF_3-containing alkene derivatives still remains a challenging task.

3.2.1 State of the art

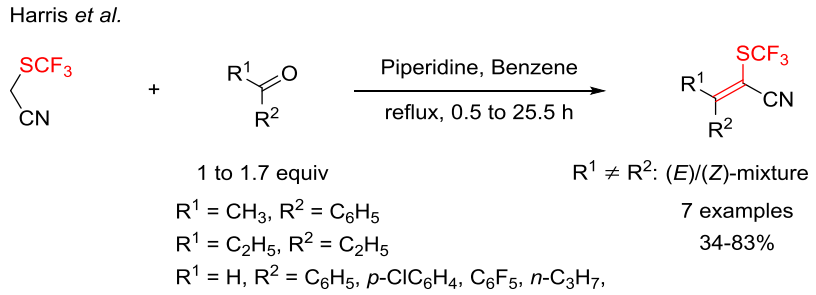
3.2.1.1 Indirect approaches

Before the description of approaches allowing the direct formation of a C(sp^2)-SCF_3 bond on vinyl derivatives, few reports dealing with the synthesis of SCF_3-containing olefins from different starting materials were summarized.

3.2.1.1.1 From aldehydes and ketones

In 1972, Harris and co-workers reported a pioneer work by using the venerable

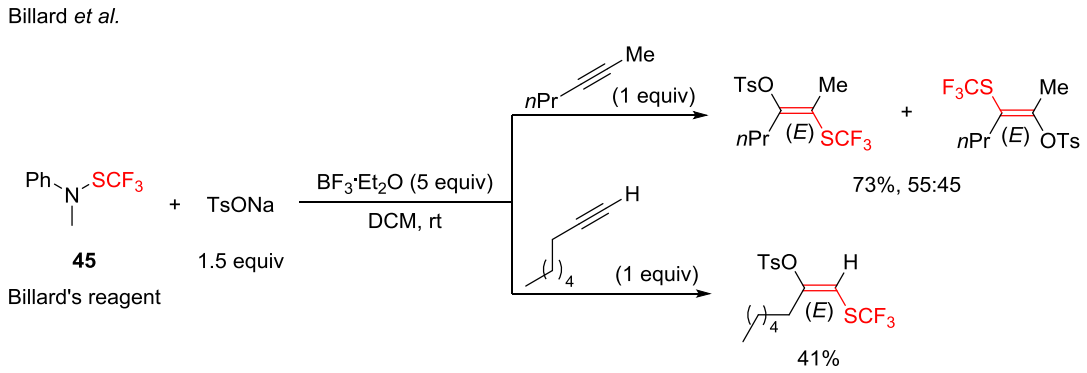
Knoevenagel reaction. The condensation of α-(trifluoromethylthio)acetonitrile with aldehydes or ketones in the presence of the piperidine as a base afforded the corresponding α,β-unsaturated products in moderate to good yields, albeit limited to few examples (Scheme 94).[155]



Scheme 94: The reaction of α-(trifluoromethylthio)acetonitrile with aldehydes and ketones.

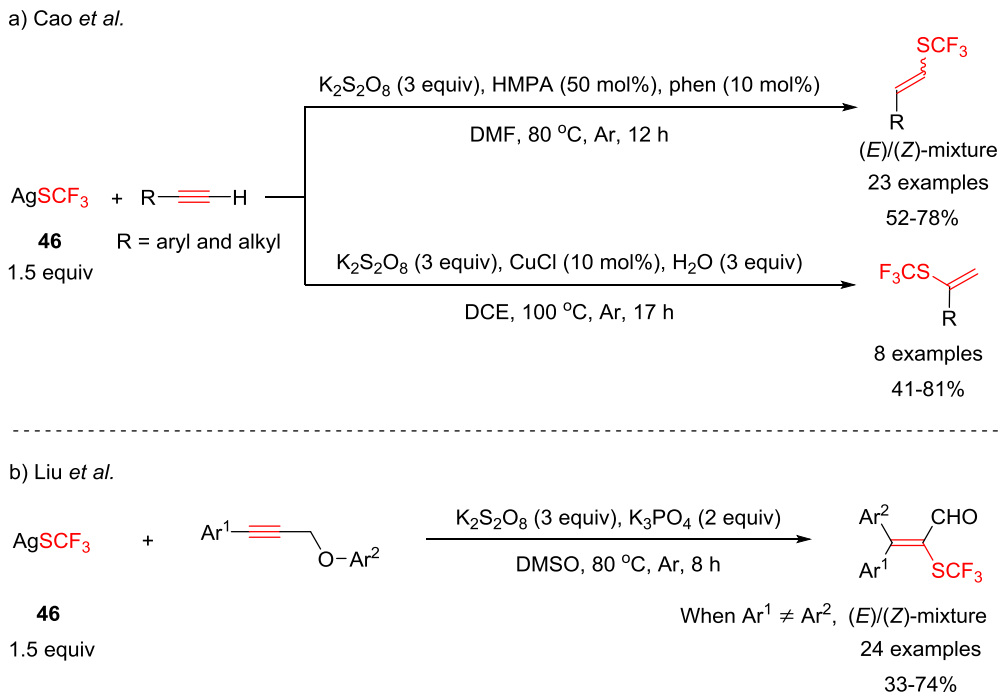
3.2.1.1.2 From alkynes

In 2009, Billard and co-workers described the formation of trifluoromethylthiolated olefins starting from the Billard's reagent[154c, 156] and alkynes, in the presence of TsONa. Satisfactory yields were obtained, albeit limited to only two examples. The regioselectivity of the reaction was not controlled in the case of the internal alkyne since a 55:45 ratio of the two regioisomers was obtained (Scheme 95).[157] As an *anti*-addition was observed with olefinic substrates, the (*E*)-selectivity of the product was reasonably postulated.



Scheme 95: The trifluoromethylthiolation reaction of alkynes.

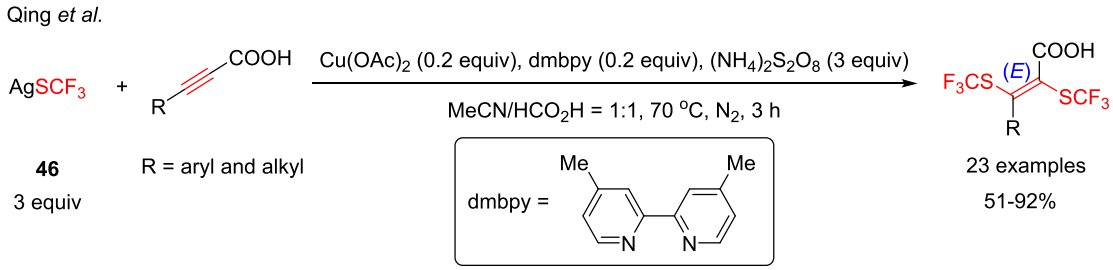
In 2016, Cao and co-workers reported a hydrotrifluoromethylthiolation of terminal alkynes by using $AgSCF_3$ as a nucleophilic SCF_3-source and $K_2S_2O_8$ as an oxidant. It is worth to mention that the Markovnikov and *anti*-Markovnikov hydrotrifluoromethylthiolated products were selectively obtained in moderate to good yields via two different reaction systems and both reactions proceeded via a radical pathway (Scheme 96, a).[158] In 2017, Liu and co-workers described the synthesis of the polysubstituted acrylaldehydes through difunctionalization of aryl propynyl ethers with $AgSCF_3$. A variety of 3,3-diaryl-2-(trifluoromethylthio)acrylaldehydes was synthesized in moderate to good yields under mild reaction conditions (Scheme 96, b).[159]



Scheme 96: Hydrotrifluoromethylthiolation of alkynes.

In 2017, Qing and co-workers disclosed a Cu-catalyzed chemo- and stereoselective oxidative bis-trifluoromethylthiolation of propiolic acid derivatives with $AgSCF_3$. Note that the carboxylic acid group in the substrate played a role to activate the alkyne and to coordinate with the copper salt. The use of formic acid as the co-solvent was crucial

for this reaction since it stabilized the Cu-alkyne complex. The transformation was efficient (23 examples, 51-91%) and demonstrated a high functional group tolerance (-CHO, -COMe, -CO_2Me, -CN, -NO_2, -CF_3, OCF_3, -F, -Cl and -Br) (Scheme 97).[160]

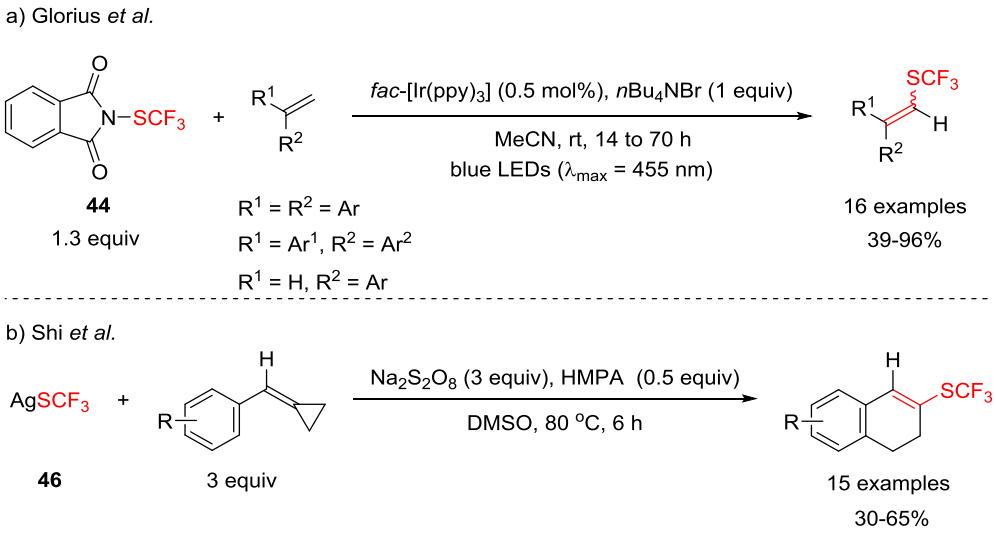


Scheme 97: Bis-trifluoromethylthiolation of propiolic acid derivatives.

3.2.1.2 Direct approaches

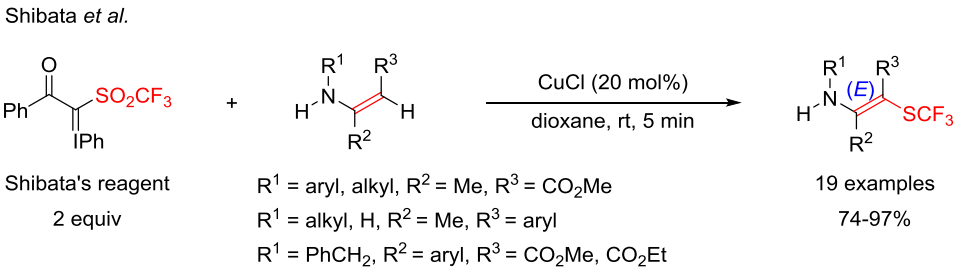
3.2.1.2.1 From olefins, enamines and glycals

In 2016, Glorius and co-workers reported the trifluoromethylthiolation of olefins with the electrophilic Munavalli reagent via a photocatalytic pathway. The control experiments demonstrated that the photocatalyst *fac*-[Ir(ppy)$_3$] (transfering single electron), the inexpensive tetrabutylammonium bromide (nBu$_4$NBr) and the visible light were all crucial for this transformation. A wide range of olefins, which could generate a stable radical intermediate, was successfully transformed into the corresponding (*Z*)/(*E*)-mixture of trifluoromethylthiolated olefins in good to excellent yields at room temperature (Scheme 98, a).[161] The same year, Shi and co-workers disclosed another methodology for the trifluoromethylthiolation of olefins. When using the combination of $AgSCF_3$ and $Na_2S_2O_8$, a wide range of (*E*)-trifluoromethylthiolated olefins was obtained in good yields through a radical pathway (Scheme 98, b).[162]



Scheme 98: Trifluoromethylthiolation of olefins.

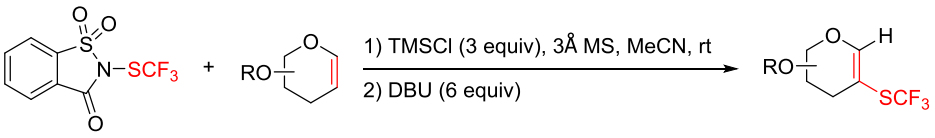
In 2013, Shibata and co-workers reported the trifluoromethylthiolation of enamines with the shelf-stable Shibata's reagent. Using this strategy, a wide range of α-trifluoromethylthiolated enamines has been prepared in good to excellent yields. Note that this transformation was extremely efficient since it proceeds at room temperature in 5 min and showed excellent (*E*)-selectivity (Scheme 99).[163]



Scheme 99: Trifluoromethylthiolation of enamines with the Shibata's reagent.

In 2016, Ye and co-workers developed a mild and efficient approach to the 2-trifluoromethylthiolation of glycals. In this protocol, the *N*-trifluoromethylthiosaccharin (Shen's reagent)[164] was employed as the electrophilic reagent, TMSCl as the activator and DBU as the base. A series of 2-trifluoromethylthioglycals was obtained in good to almost quantitative yields (Scheme 100).[165]

Ye *et al.*



51
Shen's reagent
1.1 equiv

R = OMe, Bn, BMP,

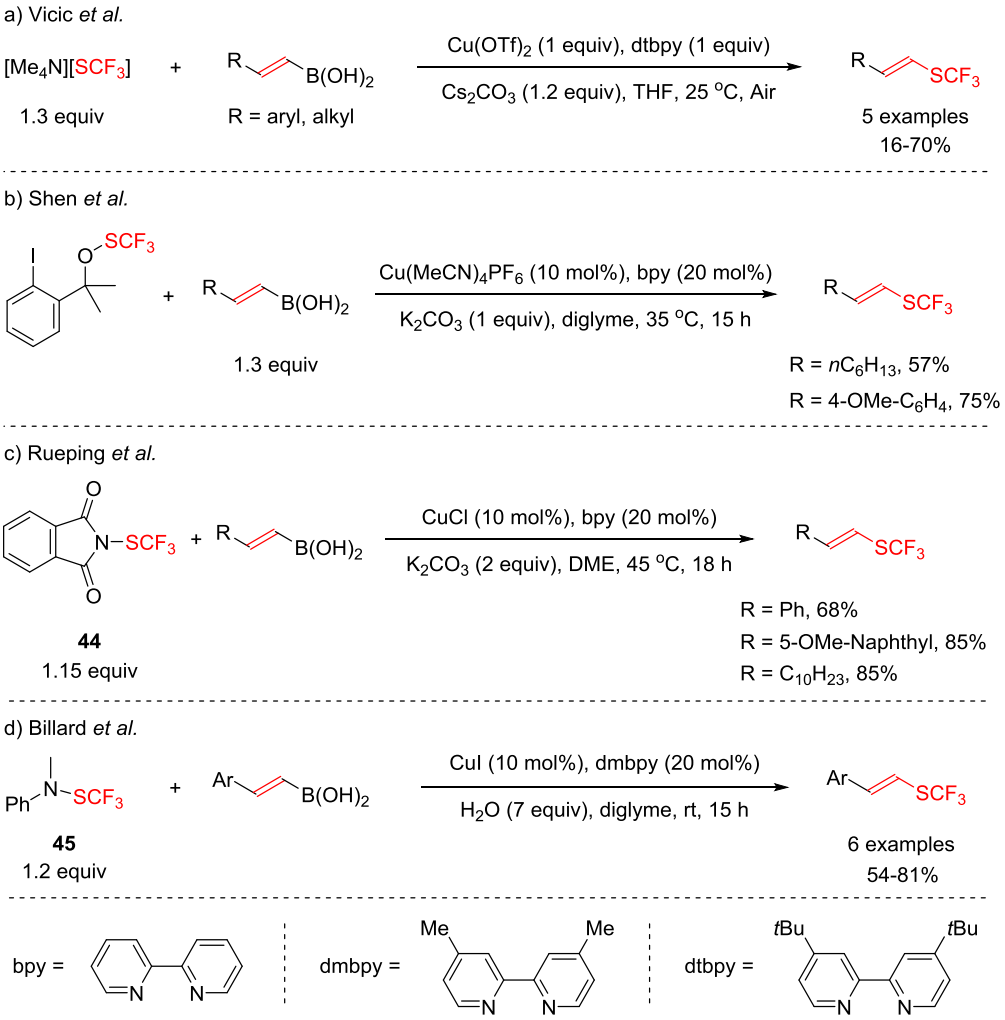
13 examples
64-99%

Scheme 100: Trifluoromethylthiolation of enamines with the Shen's reagent.

3.2.1.2.2 From vinyl boronic acids, vinyl halides, pseudo halides and vinyl carboxylic acids

The first trifluoromethylthiolation of vinyl boronic acids was reported by Vicic[166] and Zhang in 2012. They developed the Cu-mediated trifluoromethylthiolation of aryl and vinyl boronic acids (5 examples, Scheme 101, a) at room temperature. In this transformation, $[Me_4N][SCF_3]$ (Yagupolskii's reagent)[167] was used as the nucleophilic SCF_3-source. In 2013, Shen[168] and co-workers described the Cu-catalyzed trifluoromethylthiolation of boronic acids (2 examples of vinyl boronic acids, Scheme 101, b) under mild conditions. In this case, the electrophilic trifluoromethylthiolated iodine reagent[168b] was used as the SCF_3-source. In 2014, Rueping[169] and co-workers successfully used another electrophilic trifluoromethylthiolation reagent, the *N*-(trifluoromethylthio)phthalimide **44**, in the Cu-catalyzed trifluoromethylthiolation of boronic acids (3 examples of vinyl boronic acids, Scheme 101, c). Similar with the methodology of Shen, this transformation also proceeded well under mild conditions. In 2015, Billard[170] and co-workers disclosed the Cu-catalyzed trifluoromethylthiolation of boronic acids (6 examples of vinyl boronic acids, Scheme 101, d) with the electrophilic Billard's reagent **45** in good yields. It is worth to mention that the presence

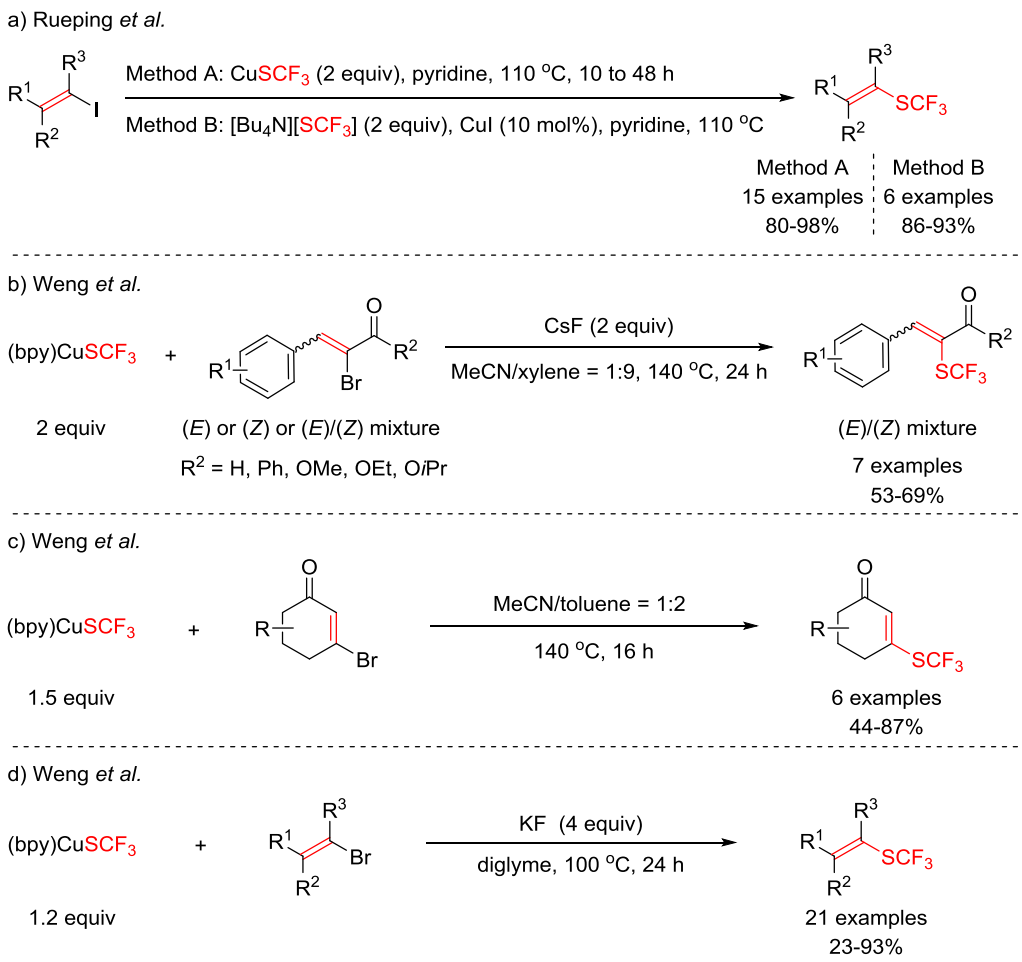
of H_2O favored this cross-coupling reaction. Noteworthy, all these reactions occurred with the retention of the stereochemistry of the starting materials.



Scheme 101: Trifluoromethylthiolation of vinyl boronic acids.

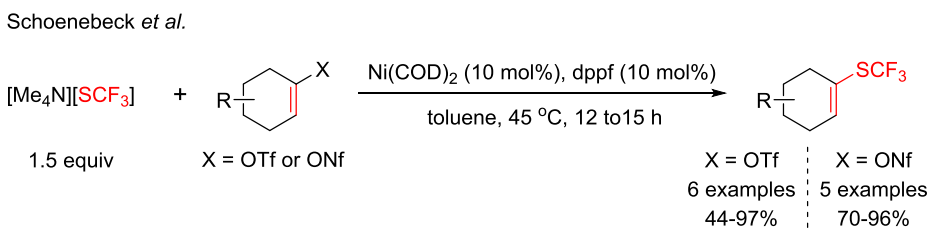
Trifluoromethylthiolated olefin products were also obtained through the trifluoromethylthiolation of the corresponding vinyl halides. In 2013, Rueping[171] and co-workers disclosed the Cu-catalyzed trifluoromethylthiolation of vinyl iodides with $CuSCF_3$ or $[Bu_4N][SCF_3]$. A wide range of vinyl iodides was successfully transformed into the corresponding trifluoromethylthiolated olefins in good to excellent yields (Scheme 102, a). In 2014, Weng and co-workers applied the (bpy)$CuSCF_3$ complex in the Cu-mediated trifluoromethylthiolation of α-halo-α,β-unsaturated carbonyl

derivatives. Different (*E*) or (*Z*) or (*E*)/(*Z*) mixture of the carbonyl derivatives were converted into the corresponding (*E*)/(*Z*)-mixture of triluoromethylthiolated products (Scheme 102, b).[172] As a logical extension of this work, then they turned their attention to other kind of halogenated substrates. Indeed, one year later, they succeeded in the functionalization of the related ketone derivatives by modifying the reaction conditions. A panel of β-bromo-α,β-unsaturated ketones was converted into β-trifluoromethylthio-α,β-unsaturated ketones in a mixture of MeCN/xylene at 140 °C (Scheme 102, c).[173] Note that the presence of a base was not required in this reaction. They also found that the reaction of (bpy)$CuSCF_3$ with a broad range of vinyl bromide derivatives could afford the corresponding vinyl trifluoromethylthioethers by using KF as the base, diglyme as the solvent at 100 °C (Scheme 102, d).[174] A variety of functional groups, including cyano, nitro, trifluoromethyl, alkoxy, amino, halides, and heterocyclic groups were tolerated in the reaction conditions.



Scheme 102: Trifluoromethylthiolation of vinyl halides.

In 2016, Schoenebeck and co-workers reported the Ni-catalyzed C–SCF_3 coupling reaction between $[Me_4N][SCF_3]$ and different vinyl pseudo halides (vinyl triflates and nonaflates). It is worth to mention that this reaction proceeded under mild conditions and was operationally simple (Scheme 103).[175]

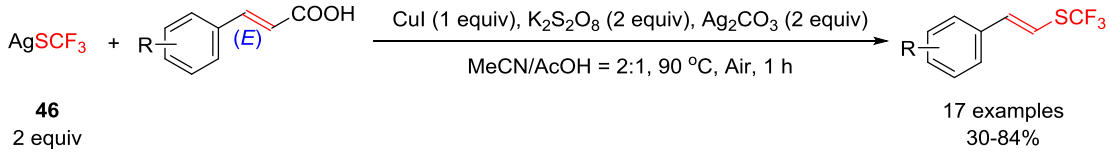


Scheme 103: Trifluoromethylthiolation of vinyl pseudo halides.

In 2016, Qing and co-workers developed the Cu-mediated decarboxylative trifluoromethylthiolation of α,β-unsaturated carboxylic acids with $AgSCF_3$. This reaction

was efficient leading to the corresponding products in moderated to good yields in 1 h (Scheme 104).[176] Note that this reaction proceeded with a total retention of the configuration.

Qing *et al.*

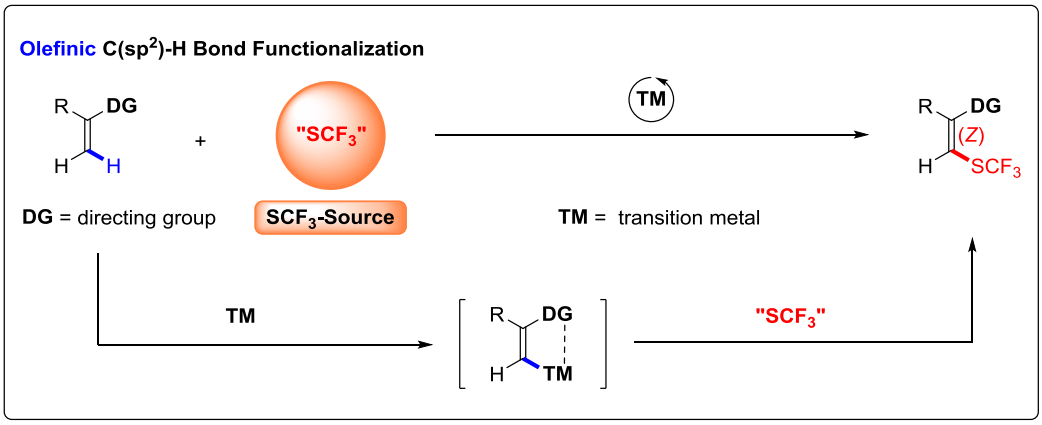


Scheme 104: Trifluoromethylthiolation of vinyl carboxylic acids.

In conclusion, since the pioneer work from Harris in 1972 (Knoevenagel reaction),[155] various strategies were developed to access the trifluoromethylthiolated olefins.[157-158, 160-163, 165-166, 168-176] These strategies include the difunctionalization of internal alkynes,[157, 160] the hydrotrifluoromethylthiolation of terminal alkynes,[158] the trifluoromethylthiolation of olefins, enamines and glycals,[161-163, 165] the Cu-mediated or catalyzed trifluoromethylthiolation of vinyl boronic acids and vinyl halides,[166, 168-174] the Ni-catalyzed trifluoromethylthiolation of vinyl pseudo halides (vinyl triflates and nonaflates)[175] and the Cu-catalyzed trifluoromethylthiolation of α,β unsaturated vinyl carboxylic acids.[176] Among those reported methods, (*E*)-trifluoromethylthiolated olefins or (*E*)/(*Z*)-mixtures were obtained. Note that depending on the mechanism, electrophilic and nucleophilic SCF_3-sources were successfully employed. To our surprise, no method for the selective synthesis of the difficult-to-prepare (*Z*)-trifluoromethylthiolated olefins from non-prefunctionalized alkenes was reported to date. Thus, the development of new methodologies to offer an access to the (*Z*)-trifluoromethylthiolated olefins will be highly valuable and will be discussed in the next section.

3.2.2 Objectives

Based on our previous work,[143-144] we envisioned that the introduction of the SCF_3 moiety onto olefins through a transition metal catalyzed direct C(sp^2)-H bond functionalization pathway could be a promising approach to selectively access the (*Z*)-trifluoromethylthiolated olefins (Scheme 105). Indeed, the use of a suitable directing group will orientate the formation of a metallacycle and, after the functionalization, will promote the selective synthesis of SCF_3-containing olefins with a total control of the stereochemistry towards the (*Z*)-isomer.



Scheme 105: Our objectives: transition metal catalyzed directed olefinic C(sp^2)-H bond functionalization with a SCF_3 group.

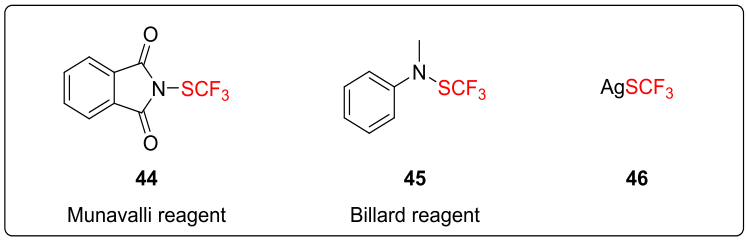
3.2.3 Transition metal catalyzed olefinic C(sp^2)-H bond functionalization with the Munavalli reagent

3.2.3.1 Optimization of the reaction conditions

3.2.3.1.1 Preliminary results

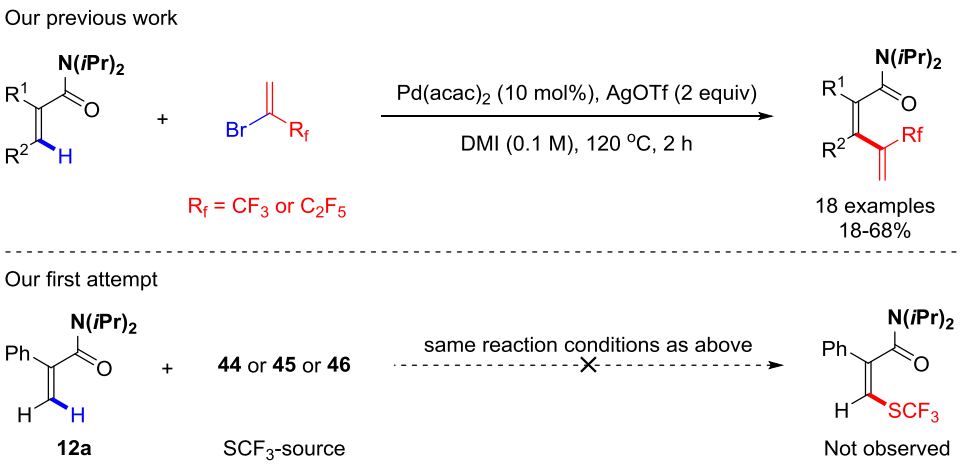
At the beginning of this study, we selected three typical trifluoromethylthiolating

reagents as SCF_3-sources: two electrophilic SCF_3-sources (**44** and **45**) and one nucleophilic SCF_3-source **46** (Scheme 106).



Scheme 106: Three typical trifluoromethylthiolating reagents.

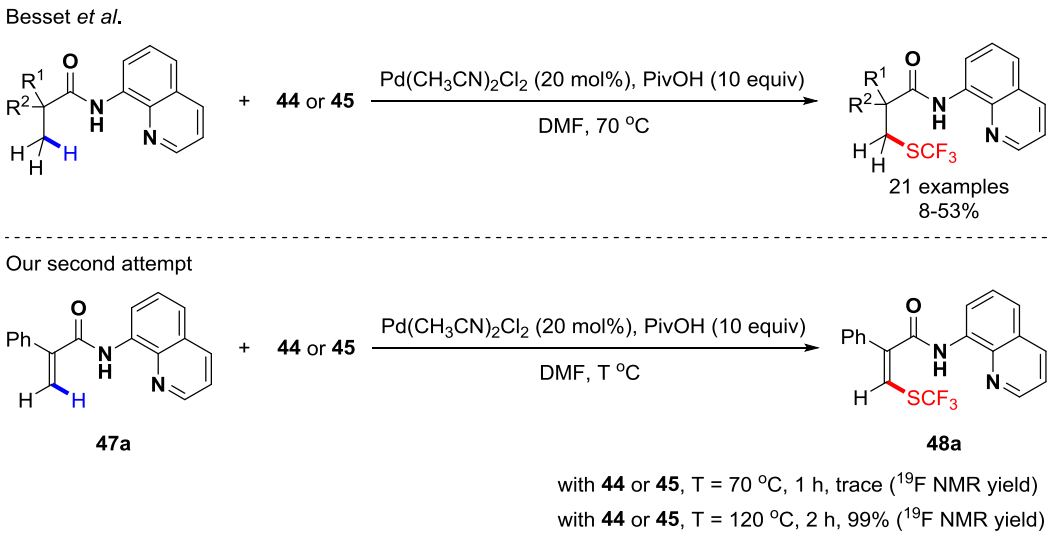
As a logical extension of our previous work with olefins,[144] we started our first test by replacing BTP with the trifluoromethylthiolating reagents **44**, **45** and **46** under similar reaction conditions (Scheme 107). Unfortunately, the desired product was not observed and the starting material remained.



Scheme 107: Pd-catalyzed coupling of acrylamides with BTP and our first attempt.

In 2015, Besset and co-workers developed the first C(sp^3)-SCF_3 bond formation at the β-position of alkyl amides by means of Pd-catalyzed C(sp^3)-H bond functionalization.[177] Inspired by this work, we applied the similar reaction conditions to the corresponding olefinic substrate, namely the 2-phenyl-*N*-(quinolin-8-yl)acrylamide **47a**. Pleasingly, traces of the desired product **48a** were observed at 70 °C for 1 h. In order to get a better yield, we performed this reaction at higher temperature and finally,

99% NMR yield of the product **48a** was obtained at 120 °C for 2 h (Scheme 108). With this promising result in hand, we examined the reaction conditions for this transformation.



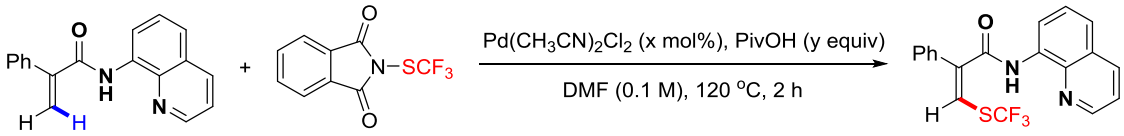
Scheme 108: Pd-catalyzed C(sp^3)-H bond trifluoromethylthiolation and our second attempt.

Since the Munavalli reagent **44** and the Billard's reagent **45** showcased a similar reactivity in the preliminary tests, we randomly chose the Munavalli reagent **44** to further study the reaction.

3.2.3.1.2 Screening of the catalyst loading and additives

From a catalytic point of view, the loadings of $Pd(CH_3CN)_2Cl_2$ (20 mol%) and PivOH (10 equivalents) seemed unsatisfactory. Thus, at the outset of the study, we tested lower quantities of the catalyst and additive (Table 13). Using 15 mol% of the Pd catalyst afforded a similar result (Table 13, entry 1). A satisfying 96% NMR yield was obtained with 10 mol% of $Pd(CH_3CN)_2Cl_2$ (Table 13, entry 2) and the yield decreased significantly when the catalyst loading reached 5 mol% (Table 13, entry 3). Note that no product was detected in the absence of Pd, which demonstrated its crucial role for

this transformation (Table 13, entry 4). Then, different stoichiometric amount of PivOH (5 equiv, 2 equiv, 1 equiv, Table 13, entries 5-7) were tested and no influence on the yield was observed. Interestingly, 99% NMR yield was also obtained when the PivOH was removed from the reaction system (Table 13, entry 8).



47a **Munavalli reagent 44** 1 equiv **48a**

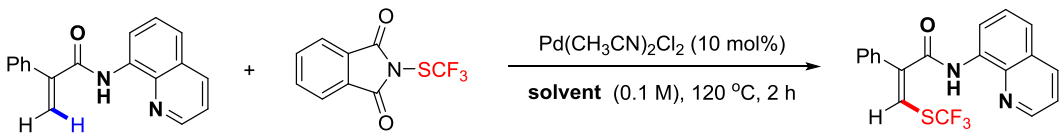
Entry	$Pd(CH_3CN)_2Cl_2$ (x mol%)	^{19}F-NMR yield[b]	Entry	PivOH (y equiv)	^{19}F-NMR yield[b]
1	0.15	99%	5	5.0	99%
2	0.10	96%	6	2.0	99%
3	0.05	46%	7	1.0	99%
4	0	0%	8	0	99%

Table 13: Screening of the loadings of the catalyst and additive.[a]

[a] Reaction conditions: **47a** (0.1 mmol, 1 equiv), Munavalli reagent **44** (0.1 mmol, 1 equiv), DMF (1 mL), 120 °C, Ar, 2 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

3.2.3.1.3 Screening of the solvents

Then, several solvents with different polarity were tested (Table 14). Other solvents such as 1,4-dioxane, DCE, toluene and EtOAc were inefficient since no trace of **48a** was detected (Table 14, entries 2-5). Note that the reaction was not sensitive to water, since a mixture of DMF/H_2O (9:1) allowed the formation of **48a** in 60% NMR yield (Table 14, entry 6). Thus, DMF was the best solvent to continue the optimization.



47a **Munavalli reagent 44** **48a**

1 equiv

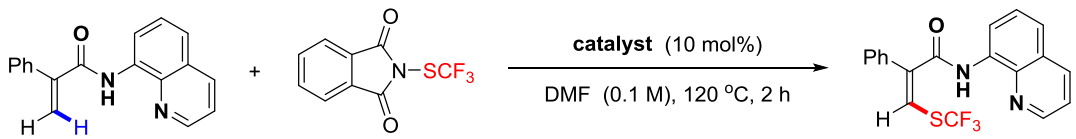
Entry	**solvent**	Yield (%)[b]
1	DMF	99
2	1, 4-Dioxane	0
3	DCE	0
4	toluene	0
5	EtOAc	0
6	DMF/H_2O = 9:1	60

Table 14: Screening of the solvents.[a]

[a] Reaction conditions: **47a** (0.1 mmol, 1 equiv), Munavalli reagent **44** (0.1 mmol, 1 equiv), $Pd(CH_3CN)_2Cl_2$ (0.01 mmol, 10 mol%), solvent (1 mL), 120 °C, Ar, 2 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

3.2.3.1.4 Screening of the catalysts

Next, we began to screen different kind of catalysts (Table 15). Firstly, other Pd(II)-catalysts were tested: $Pd(OAc)_2$, $Pd(TFA)_2$ and $Pd(acac)_2$ gave no trace of product **48a** (Table 15, entries 1-3). $PdCl_2$ allowed the formation of **48a** in 99% NMR yield while $PdBr_2$ gave a slightly lower yield (Table 15, entries 4 and 5). Then, two typical Pd(0)-catalysts were evaluated and no product was detected in both cases (Table 15, entries 6 and 7). So, $PdCl_2$ was selected as the best catalyst.



47a **Munavalli reagent 44** (1 equiv) **48a**

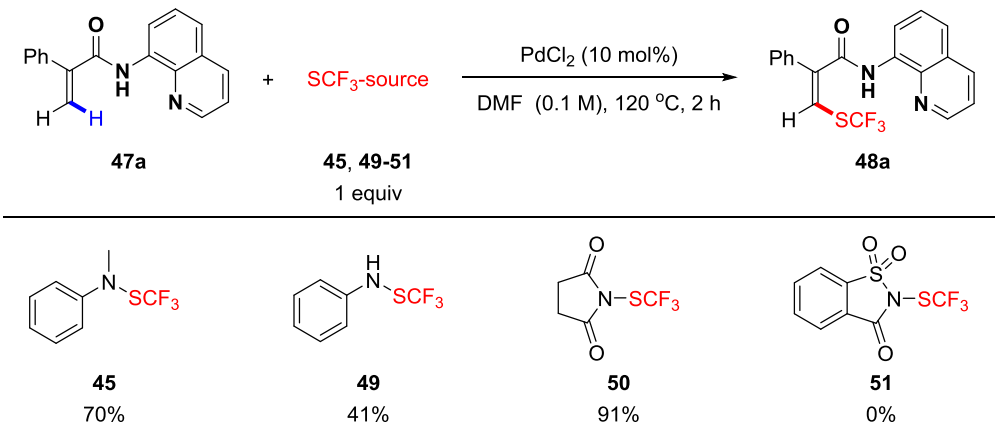
Entry	catalyst	Yield (%)[b]
1	$Pd(OAc)_2$	0
2	$Pd(TFA)_2$	0
3	$Pd(acac)_2$	0
4	$PdCl_2$	99
5	$PdBr_2$	93
6	$Pd(PPh_3)_4$	0
7	$Pd(dba)_2$	0

Table 15: Screening of the catalysts.[a]

[a] Reaction conditions: **47a** (0.1 mmol, 1 equiv), Munavalli reagent **44** (0.1 mmol, 1 equiv), catalyst (0.01 mmol, 10 mol%), DMF (1 mL), 120 °C, Ar, 2 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

3.2.3.1.5 Screening of the SCF_3-sources

Then, we examined the efficiency of other electrophilic trifluoromethylthiolating reagents (Scheme 109). Reagents **45**, **49** and **50** led to the desired product **48a** in 70%, 41% and 91% NMR yields, respectively. All of them were less efficient than the Munavalli reagent (99%). No product was observed with the Shen's reagent **51**. Thus, the Munavalli reagent was the best SCF_3-source.

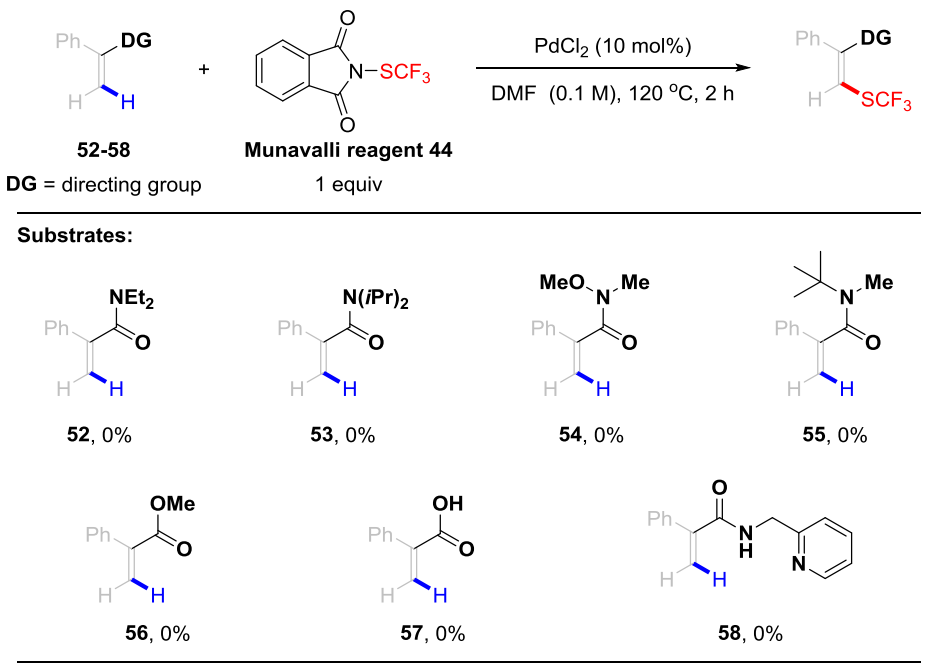


Scheme 109: Screening of the electrophilic trifluoromethylthiolating reagents.[a]

[a] Reaction conditions: **47a** (0.1 mmol, 1 equiv), **45** or **49-51** (0.1 mmol, 1 equiv), $PdCl_2$ (0.01 mmol, 10 mol%), DMF (1 mL), 120 °C, Ar, 2 h. The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

3.2.3.1.6 Screening of the directing groups

With the best conditions in hand, we investigated the influence of the nature of the directing group on the synthesis of the trifluoromethylthiolated product (Scheme 110). No trace of the product was obtained when different monodentate directing groups were tested (Scheme 110, **52-57**). It is worth to mention that the bidentate amide directing group in **58** was also ineffective since no product was formed.

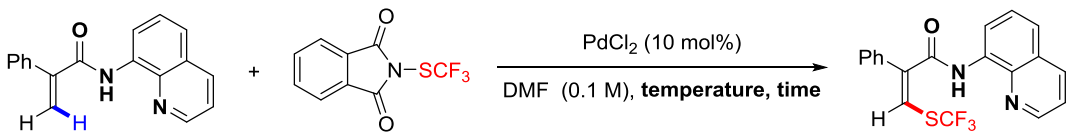


Scheme 110: Screening of the directing groups.[a]

[a] Reaction conditions: **52-58** (0.1 mmol, 1 equiv), Munavalli reagent **44** (0.1 mmol, 1 equiv), $PdCl_2$ (0.01 mmol, 10 mol%), DMF (1 mL), 120 °C, Ar, 2 h. The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

3.2.3.1.7 Screening of the temperature and the reaction time

In our preliminary attempts, we observed that the temperature played an important role on the efficiency of this transformation. In order to find the right balance between the temperature, time and the efficiency, several reactions were performed. A satisfying 99% NMR yield was obtained at 100 °C for 2 h, 80 °C for 14 h and 70 °C for 24 h (Table 16, entries 1-3). In consideration of the efficiency, the conditions 80 °C/14 h was selected as the best conditions. The efficiency decreased a lot when a temperature of 50 °C was applied, giving **48a** in 36% yield after 40 h (Table 16, entry 4). Note that the reaction was shut down at room temperature since no product was detected even after 40 h (Table 16, entry 5). Interestingly, the reaction performed equally well under an air atmosphere (Table 16, entry 6).



47a **Munavalli reagent 44** 1 equiv **48a**

Entry	temperature/time	Yield (%)[b]
1	100 °C/2 h	99
2	80 °C/14 h	99
3	70 °C/24 h	99
4	50 °C/40 h	36
5	rt /40 h	0
6[c]	80 °C/14 h	99

Table 16: Screening of the temperature and the reaction time.[a]

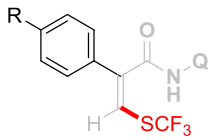
[a] Reaction conditions: **47a** (0.1 mmol, 1 equiv), Munavalli reagent **44** (0.1 mmol, 1 equiv), $PdCl_2$ (0.01 mmol, 10 mol%), DMF (1 mL), 120 °C, Ar, 2 h. [b] The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard. [c] The reaction was performed under air.

3.2.3.2 Investigation of the substrate scope

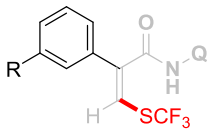
With the optimized reaction conditions in hand, we then evaluated the substrate scope of this reaction (Scheme 111). A variety of α-aryl-substituted acrylamides was functionalized in good to high yields (55-88%). The reaction demonstrated a good tolerance to aromatic rings substituted with electron-donating (OMe, Me, Ph and *t*Bu, Scheme 111, **47b**, **47c**, **47d**, **47e**, **47j**, **47k**, **47n** and **47o**) and electron-withdrawing groups (F, Cl, Br, I and CF_3, Scheme 111, **47f**, **47g**, **47h**, **47i**, **47l**, **47m** and **47p**). The substitution patterns on the aromatic ring did not affect the outcome of the transformation since similar yields were obtained with different α-aryl-substituted acrylamides. The trifluoromethylthiolated products containing a halogen (Scheme 111, **48g**, **48h**, **48i**, **48m**, **48p** and **48v**) on the aromatic ring allowed further functionalization by cross-coupling reactions (see: Scheme 121, **47i**). Note that the stereochemistry of

compound **48e** was unambiguously ascertained by X-ray crystallographic analysis. Due to the wide applications of pyridine derivatives in medicinal and agrochemistry,[178] **47v** was subjected to the standard conditions and the corresponding product **48v** was isolated in a moderate 49% yield. Finally, the trifluoromethylthiolation of the acrylamide bearing an α-methyl moiety was investigated. To our delight, using 30 mol% of $PdCl_2$ and 2 equivalents of Munavalli reagent, the desired product **48w** was obtained in 30% yield without isomerization of the double bond. This protocol was also extended to the more challenging α,β-disubstituted acrylamide **47x**. The expected tetrasubstituted acrylamide **48x** was obtained in 20% yield, showcasing the potential of this approach for the synthesis of polyfunctionalized trifluoromethylthiolated olefins with a complete control of the geometry.

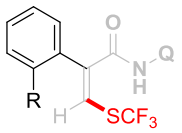
47a-x + **Munavalli reagent 44** (1 equiv) → **48a-x**



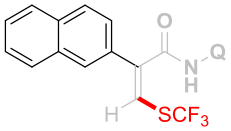
48a, R = H, 78%, 74%,[b] 67%[c]
48b: R = OMe, 70%
48c: R = Me, 75%
48d: R = Ph, 80%
48e: R = *t*Bu, 89%
X-ray (CCDC 1564064)
48f: R = F, 77%
48g: R = Cl, 75%
48h: R = Br, 70%
48i: R = **I**, 73%



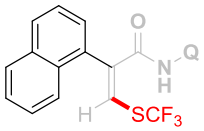
48j: R = OMe, 83%
48k: R = Me, 82%
48l: R = CF_3, 62%
48m: R = Cl, 88%



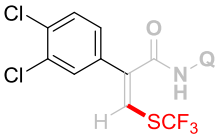
48n: R = OMe, 78%
48o: R = Me, 80%
48p: R = Cl, 82%



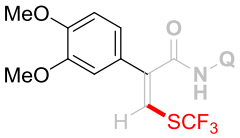
48q, 78%



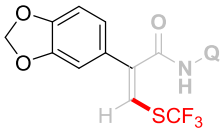
48r, 85%



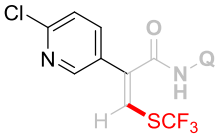
48s, 77%



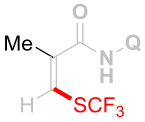
48t, 55%



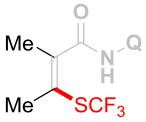
48u, 65%



48v, 49%[d]



48w, 30%[e]



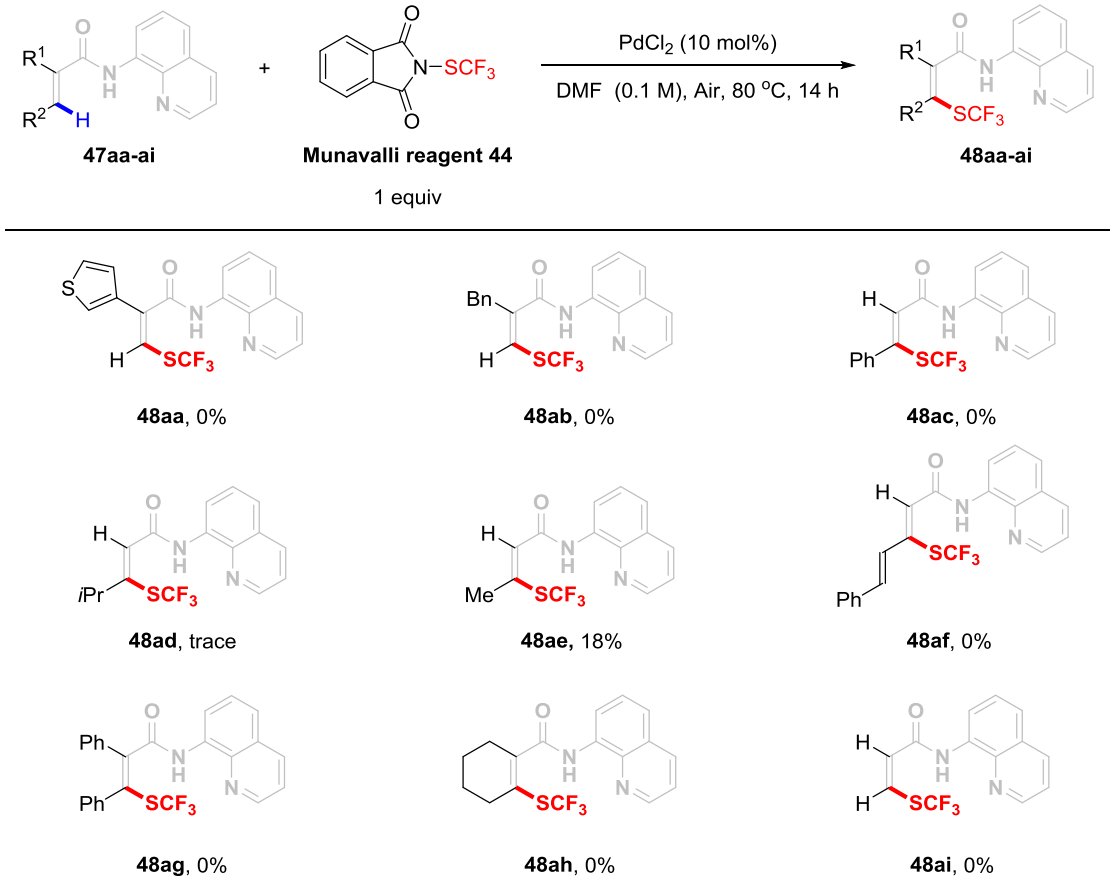
48x, 20%[e]

Scheme 111: Substrate scope.[a]

[a] Reaction conditions: **47a-x** (0.2 mmol, 1 equiv), Munavalli reagent **44** (0.2 mmol, 1 equiv), $PdCl_2$ (0.02 mmol, 10 mol%), DMF (2 mL), 80 °C, Air, 14 h. Q = 8-quinolyl. [b] The reaction was performed under Ar. [c] The reaction was performed on a 2 mmol scale. [d] Munavalli reagent **44** (2 equiv), $PdCl_2$ (0.2 equiv), 36 h. [e] Munavalli reagent **44** (2 equiv), $PdCl_2$ (0.3 equiv), 14 h.

It is worth to mention that some limitations were observed in the scope investigation (Scheme 112). The α-thiophenyl and benzyl substrates were inert in this reaction (Scheme 112, **47aa** and **47ab**). The β-substituted substrates were less efficient since only trace or no product was detected under the standard conditions (Scheme 112, **47ac**, **47ad**, **47ae** and **47af**). The α,β-disubstituted substrate **47ag** was also ineffective

probably due to the steric hindrance. In order to decrease the hindrance, the cyclic olefin **47ah** was tested, unfortunately, no trace of the product **48ah** was detected. Finally, a simple nonsubstituted acrylamide **47ai** was not a suitable substrate.



Scheme 112 : Reaction limitations: ineffective substrates.[a]

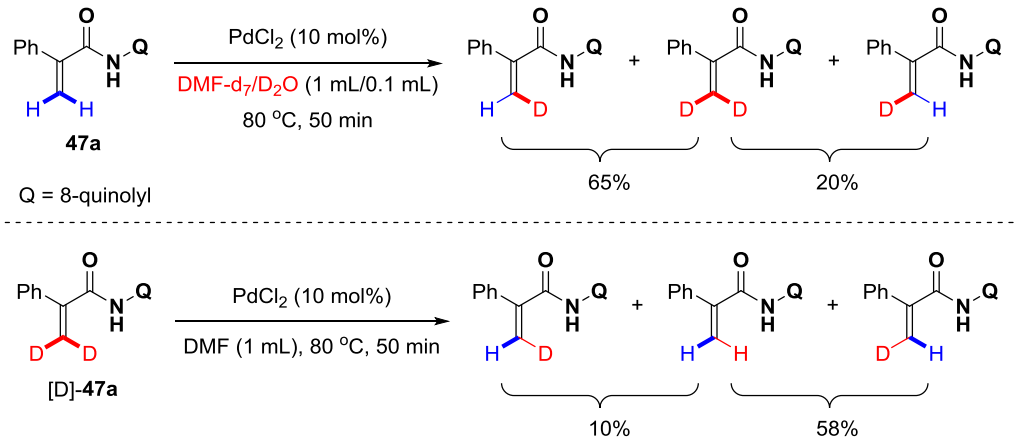
[a] Reaction conditions: **47aa-ai** (0.2 mmol, 1 equiv), Munavalli reagent **44** (0.2 mmol, 1 equiv), $PdCl_2$ (0.02 mmol, 10 mol%), DMF (2 mL), 80 °C, Air, 14 h. The yields were determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCOCF_3$ as the internal standard.

3.2.3.3 Mechanistic studies

To gain insight into this reaction, mechanistic studies were conducted with experiments involving isotopically labeled substrates.

3.2.3.3.1 Scrambling experiment (without the Munavalli reagent)

In order to confirm the occurrence of a H/D exchange, scrambling reactions were carried out (Scheme 113). A H/D exchange was observed when **47a** was reacted in DMF-d_7 under the standard reaction conditions without the Munavalli reagent. A similar result was obtained with [D]-**47a** when it was reacted in DMF. Therefore, the competition experiment starting from a 1:1 mixture of **47a** and [D]-**47a** could not be carried out.

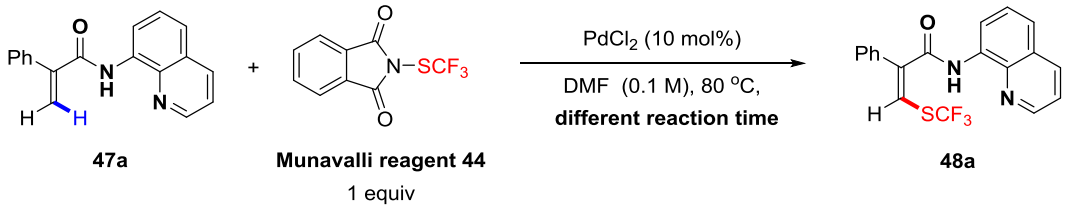


Scheme 113: Scrambling experiments (without the Munavalli reagent **44**).

Those results demonstrated that the C-H bond activation step, ie. the formation of the palladacycle, is reversible (Figure 10).

3.2.3.3.2 Kinetic Isotope Effect (KIE) measurements

In order to find out the linear relationship between the yield and the reaction time, six parallel reactions with **47a** were performed under the standard conditions for different reaction time (15 min, 30 min, 45 min, 60 min, 75 min and 90 min) (Scheme 114).



Scheme 114: Six parallel reactions with **47a** for different reaction time.

The correlation of the ^{19}F NMR yield over the reaction time is shown in Figure 8. It is clear that the linear range started from 15 min to 45 min. Therefore, KIE measurement will be carried out from 15 min to 30 min.

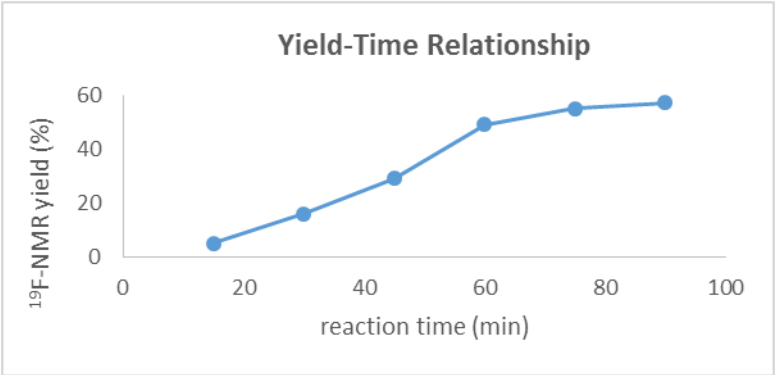
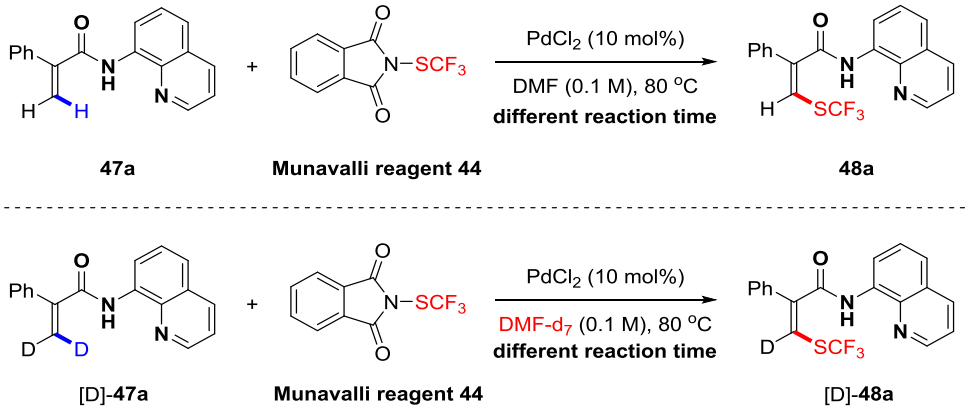


Figure 8: The ^{19}F NMR yield (%) of **48a** over reaction time (min).

Then, with these data in hand, parallel reactions with **47a** and [D]**-47a** were performed in DMF and DMF-d_7, respectively (Scheme 115).



Scheme 115: The parallel reactions with **47a** or [D]**-47a** for different reaction time.

The reactions were followed by ^{19}F NMR over the reaction time (Figure 9). With these data, the KIE value was determined according to the following equation: KIE = K_H/K_D, namely KIE = 0.8/0.34 = 2.4. Such KIE value of 2.4 indicated that the C-H bond

activation is the rate determining step of the transformation.

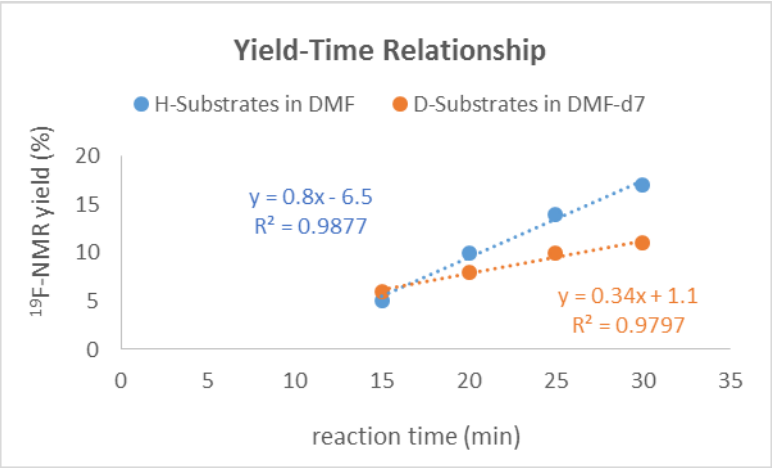


Figure 9: The ^{19}F NMR yield (%) of **48a** and [D]**-48a** over reaction time (min).

3.2.3.4 Proposed mechanism

In light of these results and the literature data,[6b, 154c, 179] a plausible mechanism (Figure 10) was proposed as follows. First, the intermediate **A** was formed by the coordination of the catalyst to the bidentate directing group. Then, the metallacycle **B** was generated after the activation of the C(sp^2)-H bond in a reversible fashion. Subsequently, it underwent an oxidative addition with the electrophilic Munavalli reagent to afford a putative Pd(IV) species **C**. Finally, a reductive elimination regenerated the Pd(II)-catalyst and furnished the product **48a**.

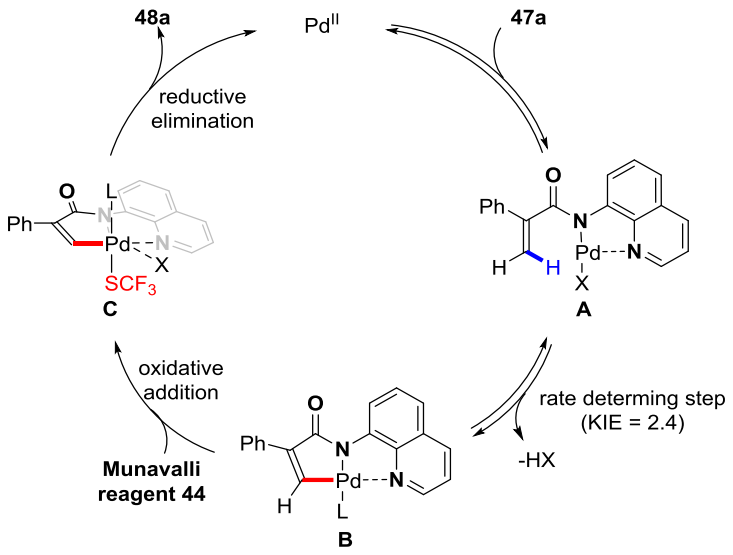


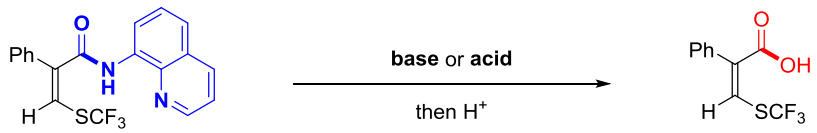
Figure 10: Proposed mechanism.

3.2.3.5 Post-functionalization reactions of products

Finally, in order to showcase the versatility of our resulting products, the post-functionalization of the products was investigated.

3.2.3.5.1 Cleavage of the directing group

Many efforts were made to cleave the 8-aminoquinoline group from compound **48a** to access the product **59**. Firstly, different bases and acids were tested to remove the directing group (Table 17).[177, 180] Unfortunately, no trace of the carboxylated product **59** was detected in these reactions.

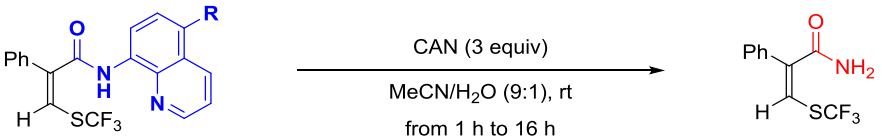


48a **59**

base (3 equiv)		Yield (%)	**acid** (10 equiv)		Yield (%)
NaOH	in EtOH at rt, 50 °C or 90 °C	0	CF_3SO_3H	in Tol/H_2O = 6:1 at 90 °C	0
KOH	in EtOH at rt or 50 °C	0	HCl (aq. 12 M)		0
LiOH	in THF at 70 °C	0			

Table 17: Removal of the directing group with bases and acids.

In 2013, Chen[181] and co-workers reported that the installation of a methoxy group at the 5-position of the 8-aminoquinoline directing group could enable its easy removal with ceric ammonium nitrate (CAN) under mild conditions. Thus, compound **60** was reacted with CAN in a mixture of MeCN/H_2O. However, only trace of the product **61** was obtained (Scheme 116, **60**). Note that in the presence of CAN, compound **48a** also led to trace of the desired product (Scheme 116, **48a**).

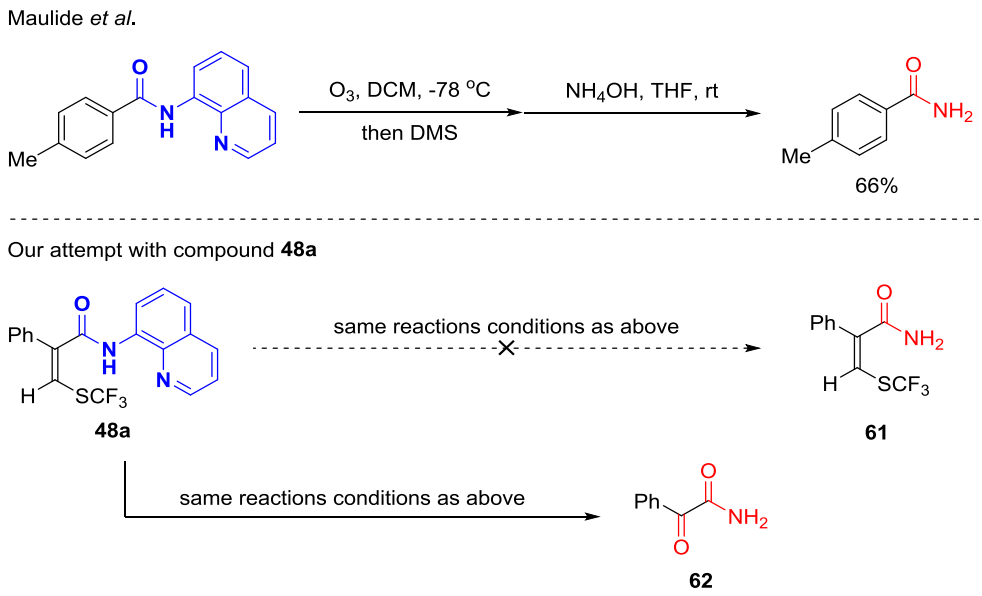


R = OMe, 60
R = H, 48a

61
trace

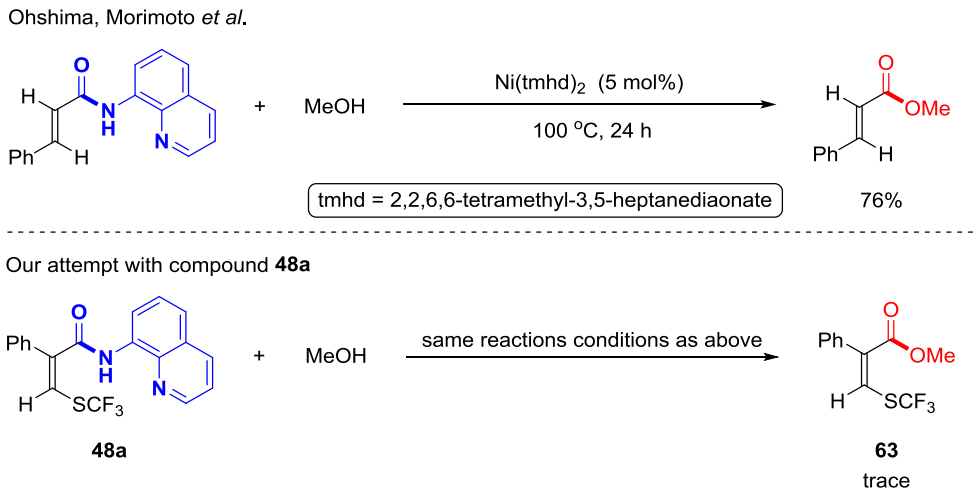
Scheme 116: Removal of the directing group with ceric ammonium nitrate.

In 2016, Maulide[182] and co-workers reported a simple oxidative protocol to cleave the 8-aminoquinoline directing group. We used the same conditions with compound **48a**. Unfortunately, there was no selectivity to cleave the 8-aminoquinoline directing group and the olefinic C-C double bond was also oxidized. Indeed, only **62** was obtained and no **61** was detected after the ozonolysis reaction (Scheme 117).



Scheme 117: Removal of the directing group by ozonolysis.

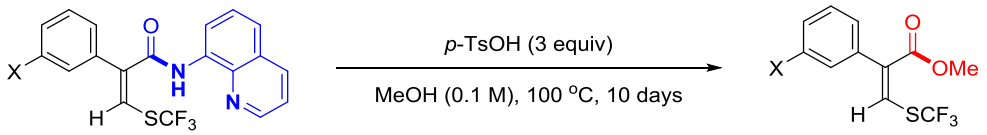
In 2016, Ohshima, Morimoto[183] and co-workers described the Ni-catalyzed alcoholysis of amides derived from 8-aminoquinoline, affording the corresponding esters in good yields with a broad functional group tolerance. The compound **48a** was examined under the standard reaction conditions but only trace of the corresponding ester product **63** was detected after 24 h (Scheme 118). Note that no improvement was observed by extension of the reaction time.



Scheme 118: Removal of the directing group by Ni-catalyzed alcoholysis.

Finally, the removal of the 8-aminoquinoline directing group was realized in the presence of *para*-toluenesulfonic acid (*p*-TsOH) in MeOH, leading to the corresponding

ester in good yield, albeit after a long reaction time (Scheme 119). It is reasonable to think that a better efficiency could be obtained with micro-wave assistance, although we did not try such conditions due to lack of time.



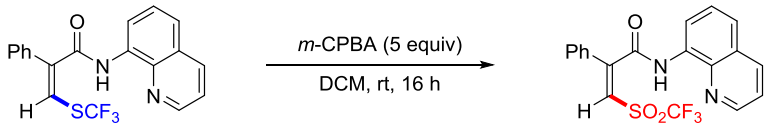
48a, X = H
48j, X = Cl

63a, 66%
based on 0.4 mmol scale: **63j**, 54%

Scheme 119: Removal of the directing group in the presence of *p*-TsOH.

3.2.3.5.2 Oxidation of the SCF_3 group

The synthetic value of our approach was further demonstrated by offering an efficient access to another valuable fluorinated group, the SO_2CF_3 residue. In the presence of *m*-CPBA,[177] the SCF_3 group was selectively oxidized into the corresponding sulfone **64** in 74% yield (Scheme 120).



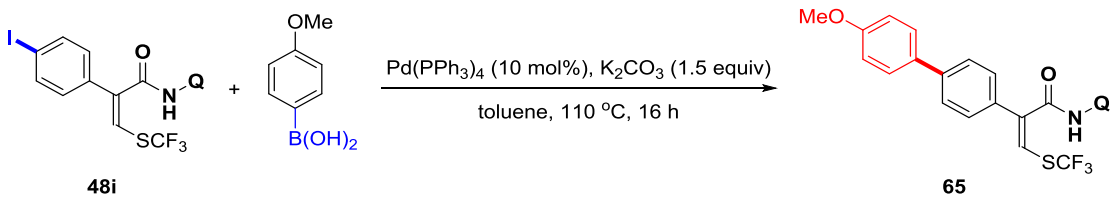
48a

64
74%

Scheme 120: Oxidation of the SCF_3 group with *m*-CPBA.

3.2.3.5.3 Suzuki cross-coupling reaction

The trifluoromethylthiolated products containing a halogen on the aromatic ring allowed further functionalization by cross-coupling reactions. In order to demonstrate this hypothesis, **48g** was subjected to the Suzuki cross-coupling reaction conditions and the coupling product **65** was isolated in a satisfying 79% yield (Scheme 121).



48i
Q = 8-quinolyl

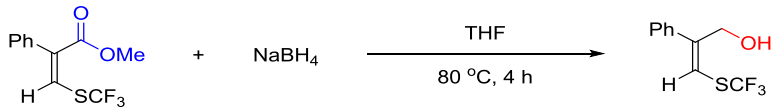
65
79%

Scheme 121: The Suzuki cross-coupling reaction of **48i**.

3.2.3.5.4 Miscelaneous

Other post-functionalization reactions were also investigated. Such as the selective reduction of the ester moiety of **63**, the selective reduction of the olefinic C-C double bond of **48c** and **64**, the trimethylsilylation reaction of **48h**.

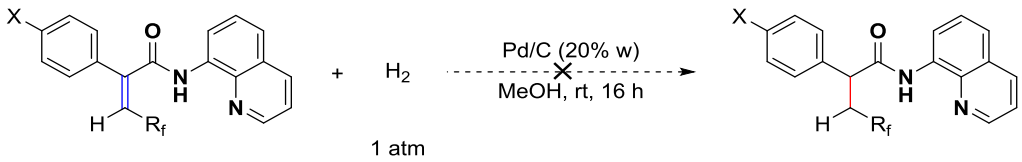
When compound **63** was treated with the reductant $NaBH_4$ in THF at reflux for 4 h, it was easily transformed into the corresponding alcohol derivative **66** (Scheme 122). However, many efforts to trap and to purify the alcohol **66** failed due to its high volatility. Note that the formation of **66** was confirmed by HRMS and ^{19}F NMR analysis.



63 2 equiv **66**

Scheme 122: The selective reduction of the ester moiety of **63**.

The compounds **48c** and **64** were tested under 1 atm of H_2 with Pd/C (20% w) in methanol at room temperature for 16 h (Scheme 123). However, no desired product was detected and the starting materials **48c** and **64** were recovered.

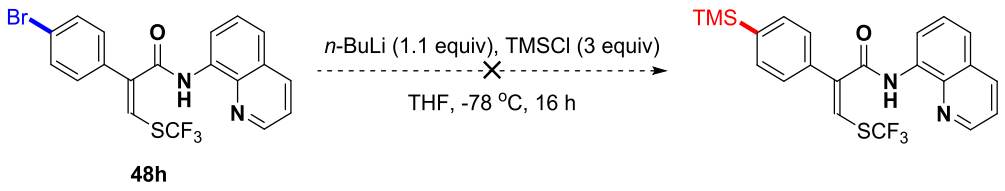


48c: X = Me, R_f = SCF_3
64: X = H, R_f = SO_2CF_3

Scheme 123: the selective reduction of the olefinic C-C double bond.

When compound **48h** was treated with TMSCl (3 equiv) and *n*-BuLi (1.1 equiv) in THF

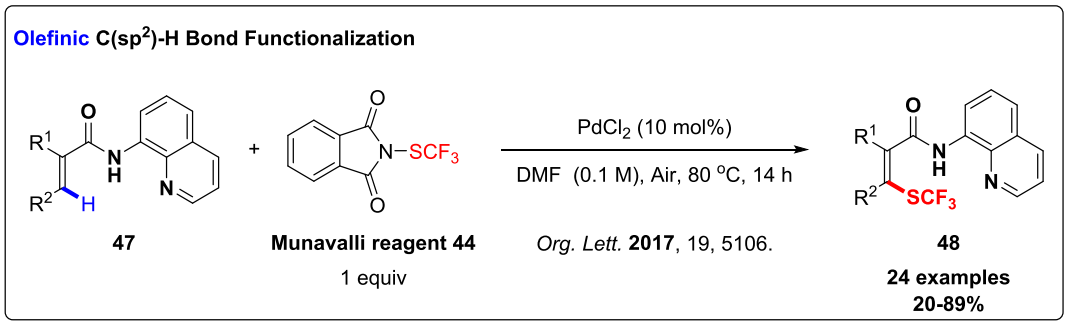
at -78 °C for 16 h (Scheme 124), no expected silylation occurred and the starting material **48h** remained intact.



Scheme 124: The trimethylsilylation of **48h**.

3.2.3.6 Brief summary

In conclusion, this part of work focused on the development of a new methodology for the direct introduction of the SCF_3 moiety onto olefins through a transition metal-catalyzed directed olefinic C(sp^2)-H bond functionalization reaction. A broad range of functionalized acrylamides was efficiently trifluoromethylthiolated with this straightforward protocol (24 examples, 20-89%). A plausible Pd(II)/Pd(IV) reaction mechanism was suggested to explain the outcome of the reaction. This new methodology provided an access to new fluorinated building blocks, inaccessible so far (Scheme 125).



Scheme 125: Olefinic C(sp^2)-H bond trifluoromethylthiolation of acrylamides.

3.3 Synthesis of SCF_3-containing aromatic derivatives

After we succeeded in the direct introduction of the SCF_3 moiety onto olefins, the

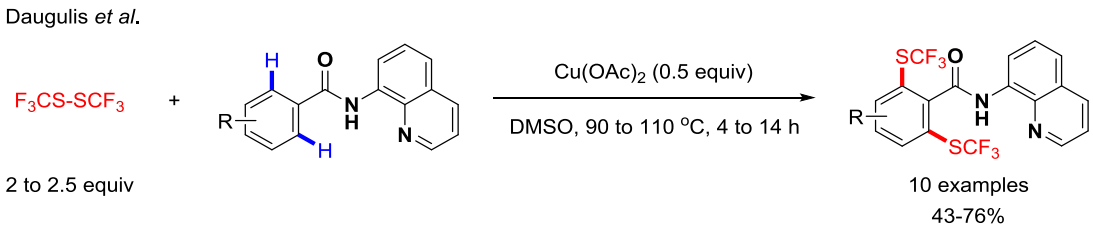
extension of this work for the functionalization of arenes was evaluated. By retrieving the literatures, only few reports concerning the transition metal-catalyzed trifluoromethylthiolation of arenes with a directing group assistance via a C(sp^2)-H bond activation pathway were found before we started this part of work.

3.3.1 State of the art

Note that reports dealing with the trifluoromethylthiolation reactions through an aromatic electrophilic substitution process will not be depicted.[163-164, 184]

3.3.1.1 Cu-mediated aromatic C(sp^2)-H bond trifluoromethylthiolation

In 2012, Daugulis and co-workers reported the Cu(II)-mediated C-H bond bis-trifluoromethylthiolation of arenes. In this method, the toxic and volatile CF_3SSCF_3 reagent was employed as the SCF_3-source and the selective mono-trifluoromethylthiolation of arenes was not achieved (Scheme 126).[185] However, as the pioneer work of the direct trifluoromethylthiolation via an aromatic C(sp^2)-H bond activation pathway, it inspired the following efforts in the field.

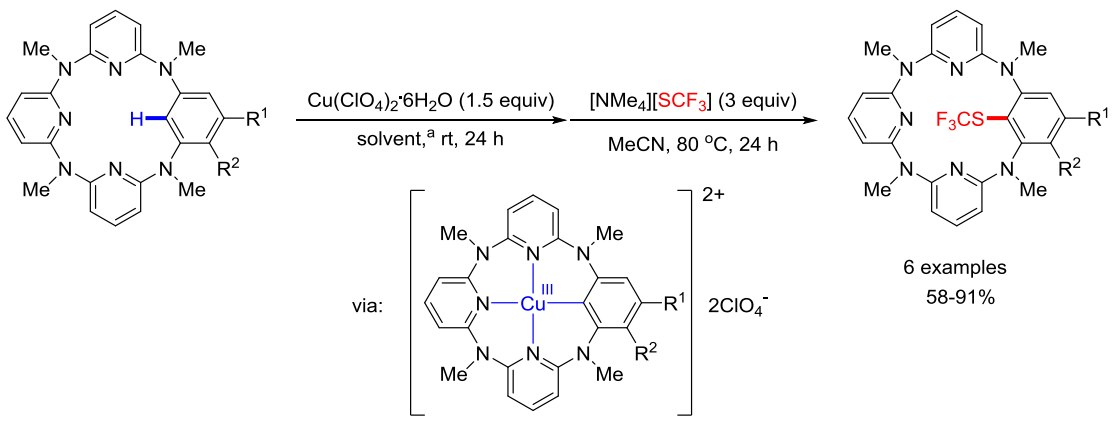


Scheme 126: Cu(II)-mediated aromatic C(sp^2)-H bond bis-trifluoromethylthiolation.

In 2016, Wang and co-workers reported the aromatic C(sp^2)-H bond monotrifluoromethylthiolation reaction of a high valent Cu(III) complex. A panel of

azacalix[1]arene[3]pyridine derivatives were successfully converted into the corresponding trifluoromethylthiolated products by using the nucleophilic $[NMe_4][SCF_3]$ source (Scheme 127).[186]

Wang *et al.*



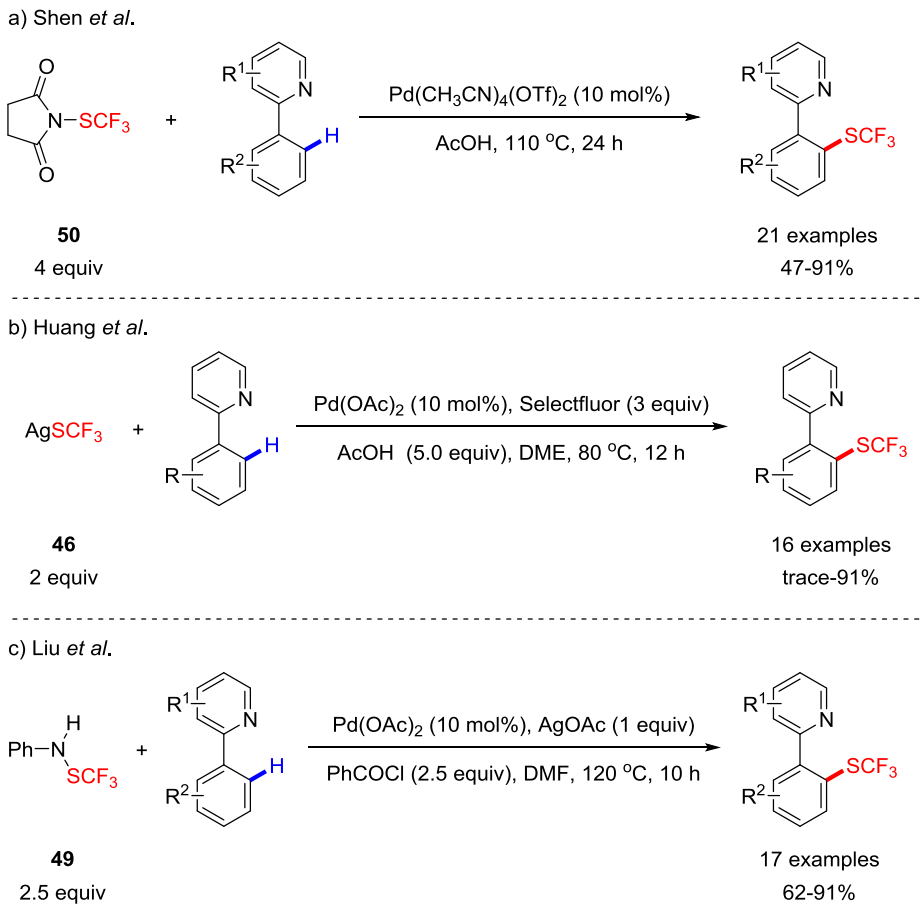
[a] solvent: $CHCl_3$/MeOH/MeCN = 10:10:1 or $CHCl_3$/MeOH = 1:1

Scheme 127: Monotrifluoromethylthiolation of a Cu(III) complex.

3.3.1.2 Pd-catalyzed aromatic C(sp^2)-H bond trifluoromethylthiolation

In 2014, Shen and co-workers reported the Pd(II)-catalyzed directed aromatic C(sp^2)-H bond trifluoromethylthiolation by using the electrophilic SCF_3-reagent **50**. A wide range of trifluoromethylthiolated arenes was obtained in good yields and it demonstrated a good functional group tolerance (Scheme 128, a).[187] In the same year, Huang and co-workers reported the Pd(II)-catalyzed oxidative aromatic C(sp^2)-H bond trifluoromethylthiolation by using $AgSCF_3$ as the nucleophilic SCF_3-source and Selectfluor® as the oxidant. Noted that AcOH was crucial to minimize the oxidative dimerization of the starting materials (Scheme 128, b).[188] In 2015, Liu and co-workers described another Pd(II)-catalyzed directed aromatic C(sp^2)-H bond

trifluoromethylthiolation by using the Billard's reagent **49** as the electrophilic SCF_3-source. PhCOCl was employed to activate the Billard's reagent to release "$^{+}SCF_3$" in this transformation (Scheme 128, c).[189]

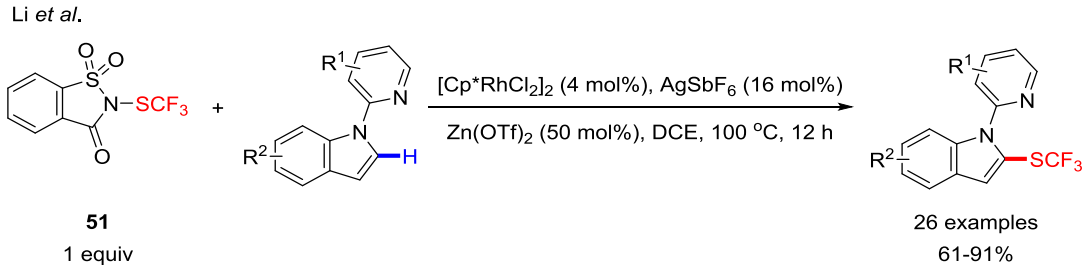


Scheme 128: Pd(II)-catalyzed directed aromatic C(sp^2)-H bond trifluoromethylthiolation.

3.3.1.3 Rh-catalyzed heteroaromatic C(sp^2)-H bond trifluoromethylthiolation

In 2015, Li and co-workers developed the first example of a Rh(III)-catalyzed electrophilic trifluoromethylthiolation of arenes via a C-H bond functionalization pathway. The *N*-trifluoromethylthiosaccharin was selected as the electrophilic SCF_3-source. This reaction occurred selectively at the 2-position of indole and tolerated a broad range of substrates with different functional groups. Noted that, in

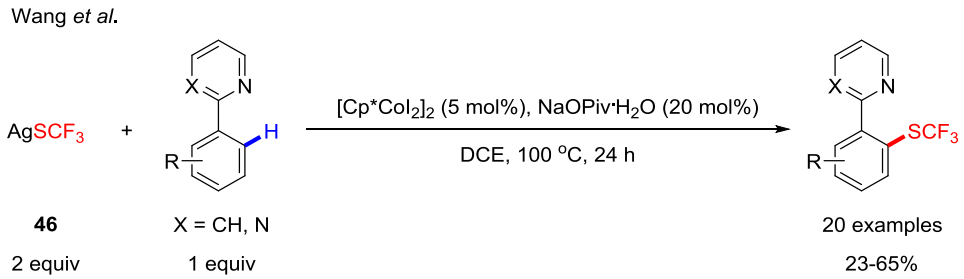
the absence of the $[Cp^*RhCl_2]_2$ and $AgSbF_6$, the reaction of indoles with blocked 3-position could also proceed, albeit in lower yields. This observation indicated that this reaction could also be catalyzed by $Zn(OTf)_2$ as a Lewis acid (Scheme 129).[190]



Scheme 129: Rh-catalyzed directed heteroaromatic C(sp^2)-H bond trifluoromethylthiolation.

3.3.1.4 Co-catalyzed aromatic C(sp^2)-H bond trifluoromethylthiolation

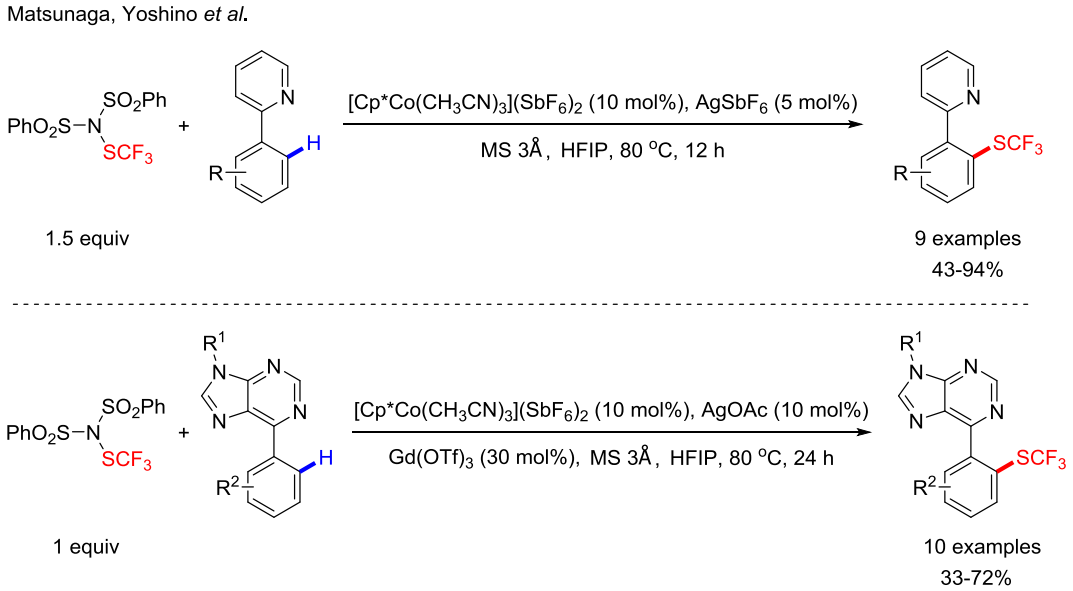
Recent years have witnessed an explosion in the application of the Co-catalysts in the direct C–H bond functionalization.[78d, 191] In 2017, Wang and co-workers described that the $[Cp^*CoI_2]_2$ catalyzed the electrophilic trifluoromethylthiolation of arenes through a C-H bond functionalization pathway. This reaction featured redox-neutrality, showed a broad substrate scope and demonstrated good functional group tolerance (Scheme 130).[192]



Scheme 130: Co(III)-catalyzed directed aromatic C(sp^2)-H bond trifluoromethylthiolation.

In the same year, Matsunaga, Yoshino and co-workers reported another Co(III)-catalyzed C(sp^2)-H bond trifluoromethylthiolation by using $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ as

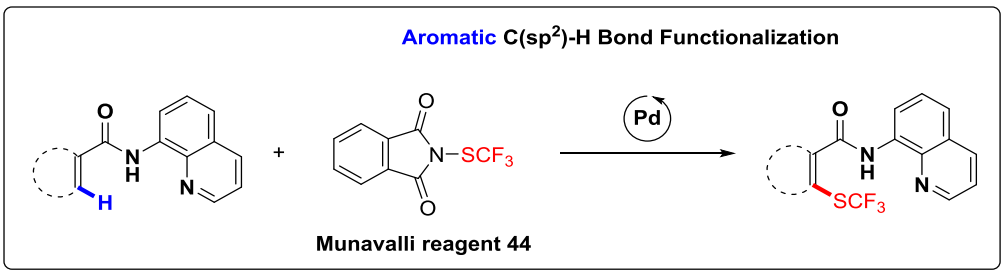
the catalyst and *N*-trifluoromethylthiodibenzenesulfonimide as the electrophilic SCF_3-source. Both of 2-arylpyridines and 6-arylpurines were smoothly transformed into the corresponding monotrifluoromethylthiolated products in moderate to good yields (Scheme 131).[193]



Scheme 131: Co(III)-catalyzed directed aromatic C(sp^2)-H bond trifluoromethylthiolation.

3.3.2 Objectives

Our goal is to develop a general approach for the direct olefinic and aromatic C(sp^2)-H bond trifluoromethylthiolation under a similar reaction system. Therefore, a straightforward way to access the trifluoromethylthiolated olefins and arenes will be possible (Scheme 132).



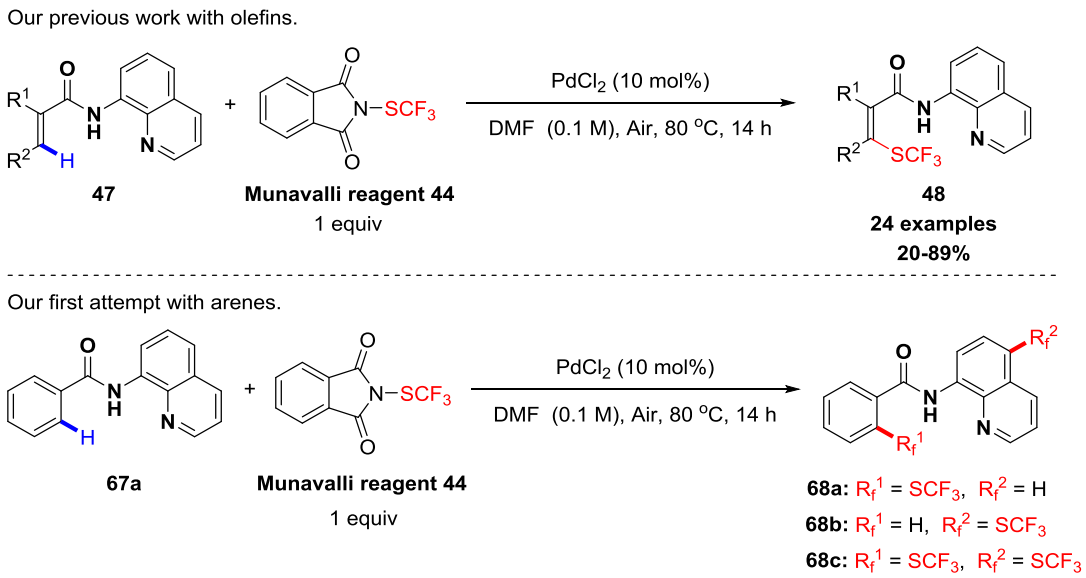
Scheme 132: Our objectives.

3.3.3 Transition metal catalyzed aromatic C(sp^2)-H bond functionalization with the Munavalli reagent

3.3.3.1 Optimization of the reaction conditions

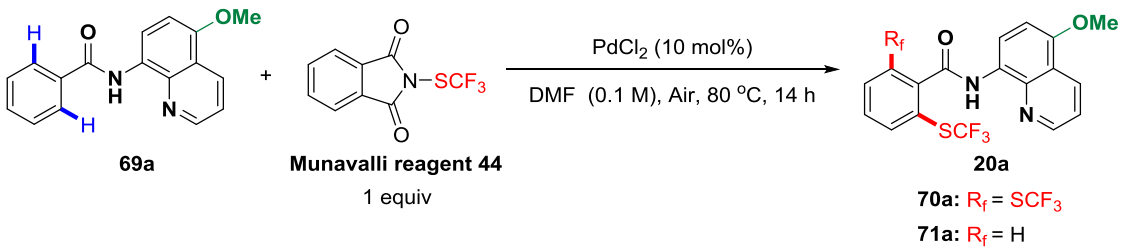
3.3.3.1.1 Preliminary results

Our first attempt with **67a** using our previous developed reaction conditions furnished the expected product **68a** detected by GC-MS analysis, along with two by-products, **68b** and **68c** (Scheme 133).



Scheme 133: Our first attempt with **67a**.

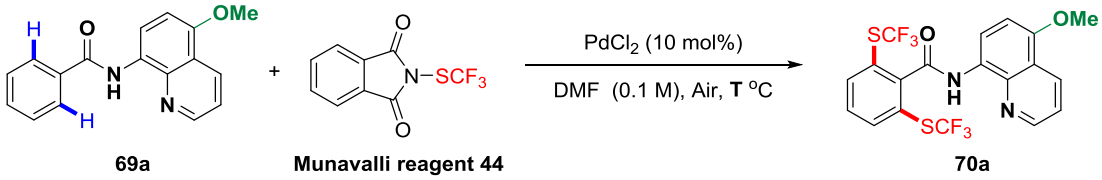
To circumvent the multiple functionalization issue, we selected **69a**, the corresponding acrylamide with the blocked 5-position on the 8-aminoquinoline part, to optimize the reaction under similar conditions. When reacting **69a** with Munavalli reagent **44** under this conditions, a mixture of *di*- and *mono*-trifluoromethylthiolated products **70a** and **71a** was observed (Scheme 134). Moreover, the full conversion of this reaction was not achieved after 14 h.



Scheme 134: Our first attempt with **69a**.

3.3.3.1.2 Screening of the reagent loading, temperature and reaction time

In the light of these preliminary results, we performed the reaction with an excess of the Munavalli reagent at higher temperature (100 and 120 °C) for a longer reaction time in order to reach a full conversion into the di-trifluoromethylthiolated product. To our delight, 56% isolated yield of **70a** was obtained by using 2.2 equivalents of Munavalli reagent at 120 °C after 20 h (Table 18).



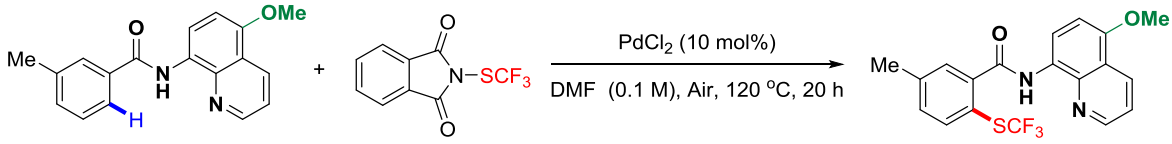
Entry	x	T °C	time (h)	full conversion[b]
1	2.5	80	20	No
2	2.5	100	14	No
3	2.5	100	20	No
4	2.5	120	14	No
5	2.5	120	20	Yes
6	2.2	120	20	Yes (56%)[c]

Table 18: Optimization of the reaction conditions.[a]

[a] Reaction conditions: **69a** (0.1 mmol, 1 equiv), Munavalli reagent **44** (x equiv), $PdCl_2$ (0.01 mmol, 10 mol%), DMF (1 mL), Air. [b] Detected by GC-MS analysis. [c] Isolated yield in parenthesis.

In order to investigate the effect of the substitutions on the aromatic ring on the reaction, the compound **69b** was prepared and examined with different stoichiometry of the Munavalli reagent under the optimized reaction conditions. Interestingly, the di-trifluoromethylthiolated product was not observed even by using 2.2 equivalents of

Munavalli reagent. A full conversion with 54% isolated yield of the desired product **70b** was obtained by using 1.2 equivalent of the Munavalli reagent (**Table 19**).



69b **Munavalli reagent 44** **70b**

x equiv

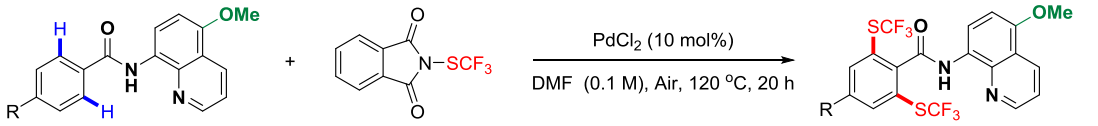
Entry	x equiv	full conversion[a]	di-trifluoromethylthiolated product[b]
1	2.2	Yes	Not observed
2	1.2	Yes (54%)[c]	Not observed

Table 19: Substitution effect of the aryl moiety on the reaction outcome.[a]

[a] Reaction conditions: **69b** (0.1 mmol, 1 equiv), Munavalli reagent **44** (x equiv), $PdCl_2$ (0.01 mmol, 10 mol%), DMF (1 mL), Air, 120 °C, 20 h. [b] Detected by GC-MS analysis. [c] Isolated yield in parenthesis.

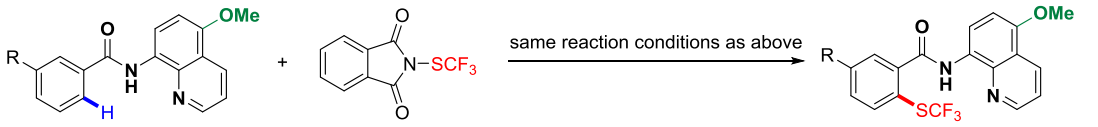
3.3.3.2 Conclusion

With the promising results in hand (Scheme 135), we will start to evaluate the substrate scope and the limitations of this reaction. This part of work is currently undergoing in our laboratary.



Munavalli reagent 44 **70a**, R = H, 56%

2.2 equiv



Munavalli reagent 44 **70b**, R = Me, 54%

1.2 equiv

Scheme 135: The synthesis of SCF_3-containing aromatic derivatives

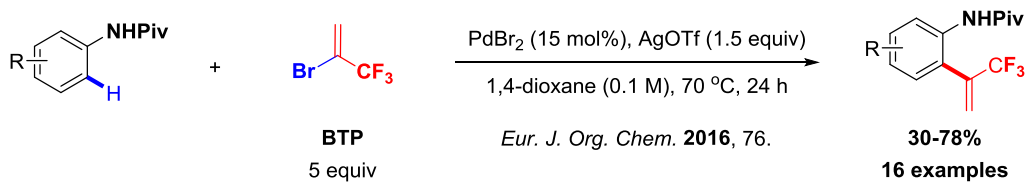
General conclusion and perspectives

4. General conclusion and perspectives

4.1 General conclusion

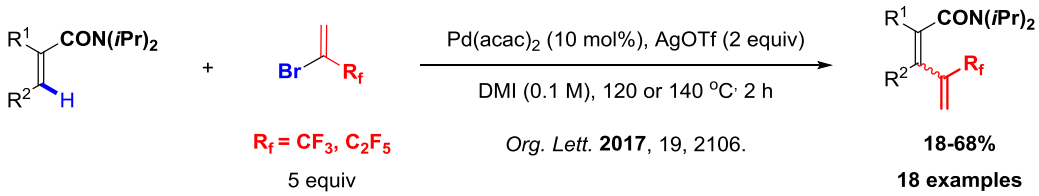
In this Ph.D. thesis, we have focused on the development of new methodologies for the direct introduction of fluorinated moieties (CF_3-vinyl and SCF_3) onto arenes and olefins by transition metal catalyzed directed C(sp^2)-H bond functionalization.

First, we developed a new methodology for the synthesis of α-(trifluoromethyl)styrenes by means of a Pd-catalyzed directed C-H bond functionalization. This transformation was applied to a broad range of anilide derivatives and the corresponding products were obtained in moderate to good yields (Scheme 136).



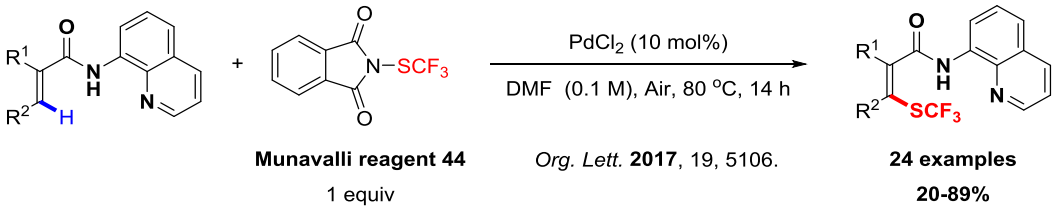
Scheme 136: Pd-catalyzed directed aromatic C(sp^2)-H bond functionalization with BTP.

Taking benefit from this first experience in transition metal-catalyzed aromatic C(sp^2)-H bond activation, we then moved our attention to the more challenging olefins. We developed the Pd-catalyzed synthesis of 3-trifluoromethyl-substituted 1,3-butadienes by means of directed C−H bond functionalization. This method was applied to a panel of olefins, including α-substituted, β-substituted and α,β-substituted ones (18 examples, 18-68% yields). This protocol provided a stereoselective and efficient access to the polysubstituted 1,3-butadienes with a total control of the selectivity to the (*Z*)-isomers in case of the α-substituted olefins (Scheme 137).



Scheme 137: Pd-catalyzed directed olefinic C(sp^2)-H bond functionalization.

Then, the approach was extended to the functionalization of α,β-unsaturated esters and cyanides. Note that in that case a different reaction pathway is most likely involved. After, we turned our attention to the SCF_3-containing reagents instead of the BTP. We developed a new methodology for the introduction of the SCF_3 group onto olefins via the Pd-catalyzed C(sp^2)-H bond functionalization pathway. The Pd-catalyzed trifluoromethylthiolation of a wide range of acrylamides was successfully achieved and this transformation showed excellent (*Z*)-stereoselectivity (Scheme 138).



Scheme 138: Pd-catalyzed olefinic C(sp^2)-H bond trifluoromethylthiolation of acrylamides.

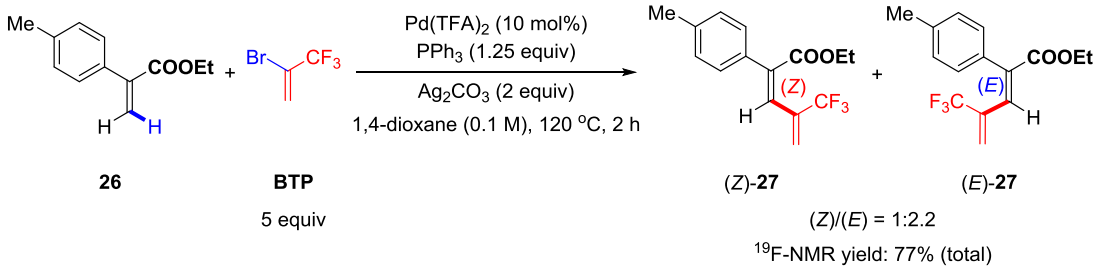
4.2 Perspectives

4.2.1 The functionalization of α,β-unsaturated esters with BTP

During the development of Pd-catalyzed C(sp^2)-H bond functionalization with the BTP, a Heck-type cross-coupling reaction between α,β-unsaturated esters and the BTP was observed. Preliminary tests on the α,β-unsaturated ester **26** showed that by using $Pd(TFA)_2$ as a catalyst, PPh_3 as a ligand and Ag_2CO_3 as a base, a (*Z*)/(*E*)-mixture of

the coupling product **27** was obtained (Scheme 139).

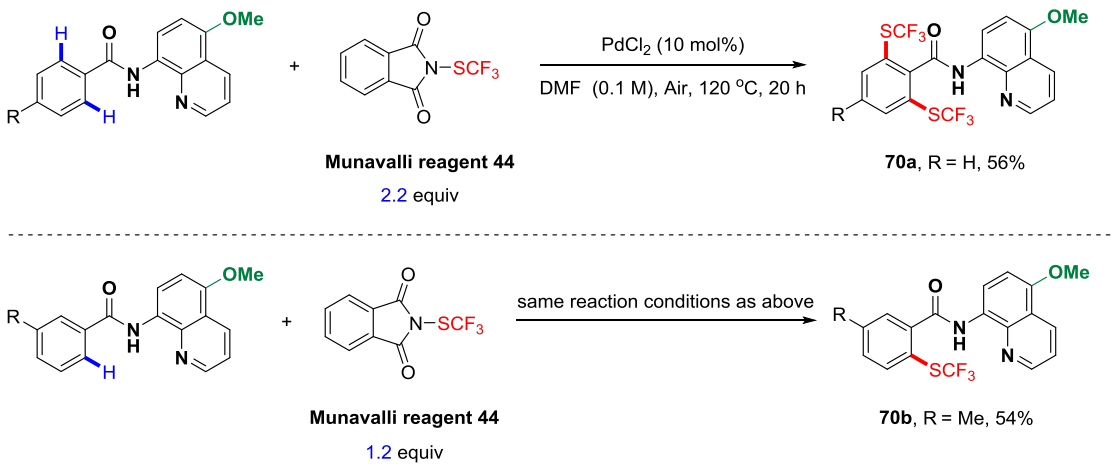
With the promising results in hand, we will continue to improve the stereoselectivity and then, start to investigate the substrate scope and the limitations of this reaction.



Scheme 139: The functionalization of α,β-unsaturated ester **26** with BTP.

4.2.2 Synthesis of SCF_3-containing aromatic derivatives

After we succeeded in the direct trifluoromethylthiolation of olefins via a transition metal-catalyzed C(sp^2)-H bond functionalization pathway (Scheme 138), we extended this protocol to arenes. Fortunately, we found that the direct trifluoromethylthiolation of arenes was also achieved by slightly modifying the directing group and the reaction conditions (Scheme 140). With the promising results in hand, we will start to evaluate the substrate scope and the limitations of this reaction.



Scheme 140: The synthesis of SCF_3-containing aromatic derivatives.

Experimental Section

Experimental Section

General information

All reactions were carried out using oven dried glassware and magnetic stirring under an atmosphere of argon unless otherwise stated. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. NMR spectra were recorded on a Bruker DXP 300, ^{1}H NMR spectra at 300.1 MHz, ^{13}C NMR spectra at 75.5 MHz, ^{19}F NMR spectra at 282.4 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) relative to residual solvent peak for $CDCl_3$ (δ_H = 7.26 ppm; δ_C = 77.0 ppm; or relative to external $CFCl_3$: δ = 0.0 ppm). The following abbreviations have been used: δ (chemical shift), *J* (coupling constant), br (broad), s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet). High-Resolution Mass Spectra (HRMS) were recorded on Waters LCT Premier. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer Paragon 100 (ATR) ; the wave numbers (v) of recorded IR-signals are quoted in cm^{-1}. Melting points were recorded on Kofler bench and are uncorrected. Analytical thin layer chromatography was performed on precoated 200 µm layer thickness silica gel 60 Alugram® Xtra SIL G/UV_{254}. Visualization was accomplished with short wave UV light (λ = 254 nm), phosphomolybdic acid or $KMnO_4$ staining solution followed by heating. Flash chromatography was performed on Merck silica gel (40-63 mesh) either by standard technique or by Biotage Isolera One Flash Purification System (gradient of solvents; PE = petroleum ether, DCM = dichloromethane, EA = ethyl acetate). Reverse phase chromatography was performed

on a puriFlash®215 using a puriFlash® C18HP 15µm 55G Flash column.

Materials

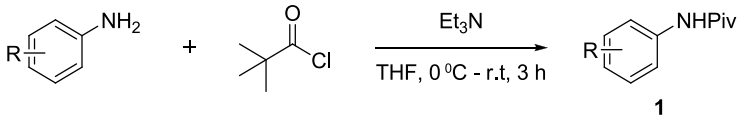
1,4-dioxane (in sealed bottle without molecular sieves) and dry DMF (*N*,*N*-dimethylformamide, in sealed bottle with molecular sieves) were purchased from Acros Organics. Dry DMI (1,3-Dimethyl-2-imidazolidinone, in sealed bottle with molecular sieves) was purchased from Sigma-Aldrich Ltd. 2-bromo-3,3,3-trifluoropropene (BTP) and 2-bromo-3,3,4,4,4-pentafluorobutene were purchased from Fluorochem Ltd and were used without further purification. AgOTf and $Pd(acac)_2$ were purchased from Sigma-Aldrich Ltd and were stored in a glove box. $PdBr_2$ and $PdCl_2$ were purchased from Sigma-Aldrich Ltd and were used as received.

1 Introduction of CF_3-vinyl moiety with BTP

1.1 Transition metal catalyzed aromatic C(sp2)-H bond functionalization with BTP

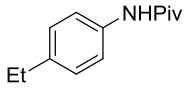
1.1.1 General procedure for the synthesis of pivalamides 1

Pivaloyl chloride was slowly added at 0 °C to a solution of the aniline derivative (1.2 g, 10 mmol, 1 equiv) and Et_3N (1.5 mL, 11 mmol, 1.1 equiv) in dry THF (30 mL). The reaction mixture was then allowed to warm to room temperature and stirred for an additional 3 hours. The formed triethylammonium chloride was removed by filtration and the solvents were removed under vacuum. The residue was purified by chromatography on silica gel.



All the spectra data of pivalamides (**1a**, **1b**, **1f),**[194] **1d**,[195] (**1e, 1h**),[196] **1g,**[197] **1i**,[198] (**1k**, **1l**,

1m, **1p**),[199] **1n**,[200] **1o**[201] were in agreement with the literature.



1c

***N*-(4-Ethylphenyl)pivalamide (1c)**: Purification by silica gel column chromatography (height 100 mm, width 80 mm, eluent: PE/EA, from 80/20 to 66/34). Yield: 86% (0.89 g, based on a 5.0 mmol scale). R_f (PE/Et_2O, 66/34): 0.75.

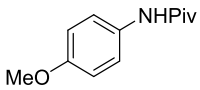
White solid; **m.p.**: 117-118 °C.

IR: 3325, 2955, 1651, 1599, 1514, 1407, 833, 712.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.28 (brs, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 2.61 (q, *J* = 7.5 Hz, 2H), 1.31 (s, 9H), 1.21 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.4, 140.2, 135.6, 128.2, 120.1, 39.5, 28.3, 27.6, 15.7.

HRMS (ESI^+): calcd for $C_{13}H_{20}NO$ *m/z* 206.1545 $[M+H]^+$, found 206.1544 (0.5 ppm).



1e

***N*-(4-Methoxyphenyl)pivalamide (1e)**:

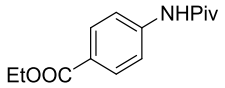
White solid; **m.p.**: 121-122 °C.

IR: 3302, 2967, 1645, 1512, 1232, 1171, 1035, 827.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H), 7.50-7.30 (brs, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 3H), 1.28 (s, 9H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.4, 156.2, 131.1, 121.9, 113.9, 55.3, 39.3, 27.5.

HRMS (ESI$^+$): calcd for $C_{12}H_{18}NO_2$ *m/z* 208.1338 $[M+H]^+$, found 208.1334 (-1.9 ppm).



1h

Ethyl 4-pivalamidobenzoate (1h):

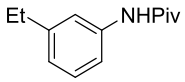
White solid; **m.p.**: 90-91 °C.

IR: 3293, 2969, 1710, 1594, 1514, 1520, 1405, 1275, 1249, 1102, 769, 697.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.52 (brs, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 9H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.8, 166.1, 142.1, 130.7, 125.8, 118.9, 60.8, 39.8, 27.5, 14.3.

HRMS (ESI$^+$): calcd for $C_{14}H_{20}NO_3$ *m/z* 250.1443 $[M+H]^+$, found 250.1449 (-2.2 ppm).



1j

***N*-(3-Ethylphenyl)pivalamide (1j)**: Purification by silica gel column chromatography (height 100 mm, width 80 mm, eluent: PE/EA, from 80/20 to 66/34). Yield: 89% (1.21 g, based on a 6.6 mmol scale). R_f (PE/EA, 66/34): 0.78.

White solid; **m.p.**: 121-122 °C.

IR: 3310, 2968, 1652, 1590, 1539, 1428, 794, 697.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.38-7.28 (m, 2H), 7.24-7.17 (m, 1H), 6.95 (d, *J* = 6.6 Hz, 1H), 2.64 (q, *J* = 7.5 Hz, 2H), 1.33 (s, 9H), 1.24 (t, *J* = 7.5 Hz, 3H).

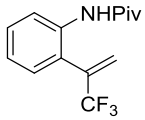
^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 145.3, 138.0, 128.8, 123.7, 119.5, 117.2, 39.6,

28.9, 27.6, 15.5.

HRMS (ESI$^+$): calcd for $C_{13}H_{20}NO$ *m/z* 206.1545 $[M+H]^+$, found 206.1541 (-1.9 ppm).

1.1.2 Typical procedure for Pd-catalyzed synthesis of α-trifluoromethylstyrenes

A dried tube was loaded with $PdBr_2$ (8.0 mg, 0.03 mmol, 0.15 equiv), AgOTf (77.1 mg, 0.3 mmol, 1.5 equiv) and amide **1** (0.2 mmol, 1 equiv) under Ar. Then 1,4-dioxane (2 mL) and 2-bromo-3,3,3-trifluoropropene (0.1 mL, 1 mmol, 5 equiv) were added. The tube was sealed with a rubber septum and the suspension was stirred at 70 °C for 24 h. The reaction mixture was diluted with diethyl ether (10 mL) and filtered through a plug of Celite®. The solvents were removed under vacuum and the crude was purified by a flash chromatography with a Biotage Isolera One Flash Purification System.



2a

***N*-(2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)pivalamide (2a)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 90/10 to 80/20). Yield: 74% (40 mg). R_f (PE/Et_2O, 75/25): 0.39.

Beige solid; **m.p.**: 66-67 °C.

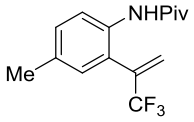
IR: 3328, 2963, 1694, 1651, 1510, 1174, 1163, 1119, 770, 749.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.1 Hz, 1H), 7.48 (brs, 1H), 7.43-7.37 (m, 1H), 7.21-7.11 (m, 2H), 6.27 (s, 1H), 5.69 (s, 1H), 1.26 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 136.7 (q, *J* = 31.5 Hz), 136.0, 130.1, 130.0, 125.0 (q, *J* = 5.4 Hz), 124.2, 124.0, 122.7 (q, *J* = 274.0 Hz), 122.3, 40.0, 27.5.

HRMS (ESI$^+$): calcd for $C_{14}H_{17}F_3NO$ *m/z* 272.1262 $[M+H]^+$, found 272.1258 (-1.5 ppm).



2b

***N*-(4-Methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2b)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 90/10 to 80/20). Yield: 70% (40 mg); 70% (850 mg, based on a 4.18 mmol scale). R_f (PE/Et_2O, 75/25): 0.42.

Beige solid; **m.p.**: 46-47 °C.

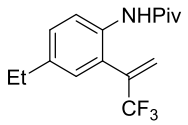
IR: 3325, 2962, 1652, 1505, 1154, 1124, 1119, 1071, 819, 806, 749.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.38 (brs, 1H), 7.20 (dd, *J* = 8.1 Hz, *J* = 1.2 Hz, 1H), 7.00 (brs, 1H), 6.23 (d, *J* = 1.2 Hz, 1H), 5.65 (d, *J* = 1.2 Hz, 1H), 2.32 (s, 3H), 1.25 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 136.3 (q, *J* = 31.6 Hz), 133.9, 133.3, 130.6, 130.5, 124.7 (q, *J* = 5.1 Hz), 124.6, 122.7 (q, *J* = 274.1 Hz), 122.5, 39.7, 27.5, 20.7.

HRMS (ESI$^+$): calcd for $C_{15}H_{19}F_3NO$ *m/z* 286.1419 $[M+H]^+$, found 286.1421 (0.7 ppm).



2c

***N*-(4-Ethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2c)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 85/15 to 75/25). Yield: 66% (39 mg). R_f (PE/Et_2O, 75/25): 0.37. White solid; **m.p.**: 49-50 °C.

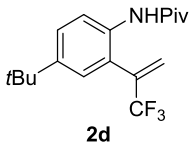
IR: 3272, 2982, 1646, 1514, 1166, 1153, 1126, 1069, 960, 825, 648.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.40 (brs, 1H), 7.23 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 6.24 (d, *J* = 1.2 Hz, 1H), 5.67 (d, *J* = 1.2 Hz, 1H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.25 (s, 9H), 1.22 (t, *J* = 7.5 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.4, 140.2, 136.4 (q, *J* = 31.6 Hz), 133.5, 129.4, 129.3, 124.7 (q, *J* = 5.1 Hz), 124.6, 122.7 (q, *J* = 274.1 Hz), 122.6, 39.7, 28.1, 27.5, 15.5.

HRMS (ESI$^+$): calcd for $C_{16}H_{20}F_3NONa$ *m/z* 322.1395 $[M+Na]^+$, found 322.1389 (-1.9 ppm).



2d

***N*-(4-(*tert*-Butyl)-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2d)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 90/10 to 80/20). Yield: 62% (41 mg); 57% (800

mg, based on a 4.26 mmol scale). R_f (PE/Et_2O, 75/25): 0.40.

Beige solid; **m.p.**: 76-77 °C.

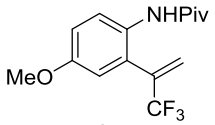
IR: 3278, 2967, 1645, 1514, 1395, 1368, 1344, 1267, 1176, 1128, 1071, 956, 820, 639.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.42 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 7.41 (brs, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 6.25 (d, *J* = 1.2 Hz, 1H), 5.68 (d, *J* = 1.2 Hz, 1H), 1.30 (s, 9H), 1.25 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.4, 147.1, 136.6 (q, *J* = 31.5 Hz), 133.3, 127.0, 126.9, 124.7 (q, *J* = 5.1 Hz), 124.1, 122.8 (q, *J* = 274.3 Hz), 122.1, 39.8, 34.3, 31.2, 27.5.

HRMS (ESI$^+$): calcd for $C_{18}H_{25}F_3NO$ *m/z* 328.1888 $[M+H]^+$, found 328.1873 (-4.6 ppm).



2e

***N*-(4-Methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2e)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 92/8 to 85/15). Yield: 61% (37 mg). R_f (PE/Et_2O, 75/25): 0.17.

Beige solid; **m.p.**: 60-61 °C.

IR: 3309, 2840, 1646, 1614, 1501, 1220, 1174, 1118, 1066, 1041, 803.

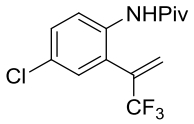
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.93 (d, *J* = 9.0 Hz, 1H), 7.26 (brs, 1H), 6.94 (dd, *J* = 9.0 Hz, *J* = 3.0 Hz, 1H), 6.75 (d, *J* = 3.0 Hz, 1H), 6.21 (d, *J* = 1.2 Hz, 1H), 5.67 (d, *J* =

1.2 Hz, 1H), 3.79 (s, 3H), 1.25 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.5 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.6, 156.2, 136.0 (q, *J* = 31.7 Hz), 128.9, 127.0, 125.0, 124.7 (q, *J* = 5.2 Hz), 122.7 (q, *J* = 274.0 Hz), 115.7, 115.0, 55.5, 39.6, 27.5.

HRMS (ESI$^+$): calcd for $C_{15}H_{19}F_3NO_2$ *m/z* 302.1368 $[M+H]^+$, found 302.1370 (0.7 ppm).



2f

***N*-(4-Chloro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2f)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 90/10 to 80/20). Yield: 46% (28 mg). R_f (PE/Et_2O, 75/25): 0.44. White solid; **m.p.**: 67-68 °C.

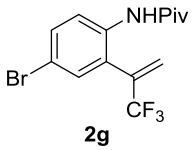
IR: 3321, 2963, 1651, 1497, 1169, 1165, 1123, 897, 818, 802, 641.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.43 (brs, 1H), 7.37 (dd, *J* = 9.0 Hz, *J* = 1.8 Hz, 1H), 7.19 (d, *J* = 1.8 Hz, 1H), 6.30 (s, 1H), 5.71 (s, 1H), 1.25 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.5 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 135.2 (q, *J* = 32.0 Hz), 134.7, 130.1, 129.9, 129.1, 125.7 (q, *J* = 5.1 Hz), 125.6, 123.4, 122.4 (q, *J* = 274.1 Hz), 39.9, 27.4.

HRMS (ESI$^+$): calcd for $C_{14}H_{15}{}^{35}ClF_3NONa$ *m/z* 328.0692 $[M+Na]^+$, found 328.0683 (-2.7 ppm).



2g

***N*-(4-Bromo-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2g)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 95/5 to 85/15). Yield: 30% (21 mg). R_f (PE/Et_2O, 75/25): 0.44.

Yellow solid; **m.p.**: 78-79 °C.

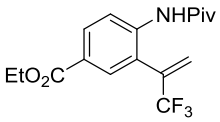
IR: 3305, 2962, 1717, 1652, 1494, 1256, 1164, 1121, 1067, 883, 816, 799, 638.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.43 (brs, 1H), 7.33 (s, 1H), 6.30 (s, 1H), 5.71 (s, 1H), 1.25 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.5 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 135.2, 135.1 (q, *J* = 32.0 Hz), 133.0, 132.7, 125.9 (q, *J* = 5.1 Hz), 125.8, 123.6, 122.4 (q, *J* = 274.1 Hz), 116.6, 39.9, 27.4.

HRMS (ESI$^+$): calcd for $C_{14}H_{15}{}^{79}BrF_3NONa$ *m/z* 372.0187 $[M+Na]^+$, found 372.0179 (-2.2 ppm).



2h

Ethyl 4-pivalamido-3-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (2h): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 95/5 to 85/15). Yield: 42% (29 mg). R_f (PE/Et_2O, 75/25): 0.25.

Beige solid; **m.p.**: 45-46 °C.

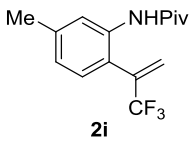
IR: 3447, 2975, 1717, 1585, 1512, 1480, 1285, 1264, 1170, 1123, 1107, 1069, 1022, 768, 637.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.47 (d, *J* = 8.7 Hz, 1H), 8.07 (dd, *J* = 8.7 Hz, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.65 (brs, 1H), 6.36 (d, *J* = 1.2 Hz, 1H), 5.74 (d, *J* = 1.2 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.27 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 165.6, 140.1, 135.6 (q, *J* = 32.1 Hz), 131.7, 131.6, 126.0 (q, *J* = 5.1 Hz), 125.5, 123.0, 122.4 (q, *J* = 274.3 Hz), 120.4, 61.1, 40.2, 27.4, 14.3.

HRMS (ESI^+): calcd for $C_{17}H_{20}F_3NO_3Na$ *m/z* 366.1293 $[M+Na]^+$, found 366.1290 (-0.8 ppm).



2i

***N*-(5-Methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2i)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 80/20 to 70/30). Yield: 78% (44 mg). R_f (PE/Et_2O, 75/25): 0.50. Beige solid; **m.p.**: 93-94 °C.

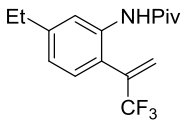
IR: 3305, 2968, 1646, 1514, 1480, 1344, 1186, 1159, 1125, 816, 612.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.45 (brs, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.24 (d, *J* = 1.2 Hz, 1H), 5.65 (d, *J* = 1.2 Hz, 1H), 2.37 (s, 3H), 1.26 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 140.3, 136.2 (q, *J* = 31.6 Hz), 135.7, 129.9, 124.9 (q, *J* = 5.1 Hz), 124.8, 122.73 (q, *J* = 274.1 Hz), 122.66, 121.4, 39.9, 27.5, 21.5.

HRMS (ESI$^+$): calcd for $C_{15}H_{19}F_3NO$ *m/z* 286.1419 $[M+H]^+$, found 286.1412 (-2.4 ppm).



2j

***N*-(5-Ethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2j)**: Purification by silica gel column chromatography (Biotage system 25g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 80/20 to 70/30). Yield: 61% (37 mg). R_f (PE/Et_2O, 75/25): 0.43. White solid; **m.p.**: 79-80 °C.

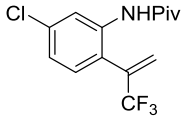
IR: 3326, 2968, 1652, 1494, 1346, 1189, 1167, 1116, 1075, 965, 831, 627.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.12 (d, *J* = 1.5 Hz, 1H), 7.47 (brs, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.97 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 6.25 (d, *J* = 1.2 Hz, 1H), 5.66 (d, *J* = 1.2 Hz, 1H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.26 (s, 9H), 1.25 (t, *J* = 7.5 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 146.6, 136.2 (q, *J* = 31.5 Hz), 135.8, 129.9, 129.8, 124.9 (q, *J* = 5.1 Hz), 123.6, 122.7 (q, *J* = 274.1 Hz), 121.5, 39.9, 28.9, 27.5, 15.3.

HRMS (ESI$^+$): calcd for $C_{16}H_{20}F_3NONa$ *m/z* 322.1395 $[M+Na]^+$, found 322.1397 (0.6 ppm).



2k

***N*-(5-Chloro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2k)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 90/10 to 80/20). Yield: 41% (25 mg). R_f (PE/Et_2O, 75/25): 0.37.

White solid; **m.p.**: 187-188 °C.

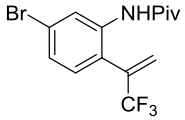
IR: 3315, 2969, 1659, 1496, 1342, 1220, 1166, 1149, 1126, 1087, 966, 795, 781, 726, 664.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.29-7.18 (m, 2H), 7.04 (brs, 1H), 6.04 (s, 1H), 5.69 (s, 1H), 1.28 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -66.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 177.0, 135.6 (q, *J* = 31.6 Hz), 134.9, 133.5, 133.2, 130.5, 129.1, 128.2, 124.0 (q, *J* = 5.1 Hz), 122.8 (q, *J* = 273.5 Hz), 39.2, 27.4.

HRMS (ESI$^+$): calcd for $C_{14}H_{15}{}^{35}ClF_3NONa$ *m/z* 328.0692 $[M+Na]^+$, found 328.0699 (2.1 ppm).



2l

***N*-(5-Bromo-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2l)**: Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 95/5 to 85/15). Yield: 46% (32 mg). R_f (PE/Et_2O, 75/25): 0.56.

White solid; **m.p.**: 114-115 °C.

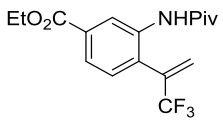
IR: 3319, 2969, 1652, 1479, 1342, 1187, 1163, 1127, 1084, 817, 609.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.55 (d, *J* = 1.8 Hz, 1H), 7.47 (brs, 1H), 7.27 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.30 (d, *J* = 1.2 Hz, 1H), 5.70 (d, *J* = 1.2 Hz, 1H), 1.25 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 137.2, 135.5 (q, *J* = 31.9 Hz), 131.1, 127.0, 125.7 (q, *J* = 5.2 Hz), 124.7, 124.1, 122.5, 122.4 (q, *J* = 274.1 Hz), 40.0, 27.4.

HRMS (ESI^+): calcd for $C_{14}H_{15}{}^{79}BrF_3NONa$ *m/z* 372.0187 $[M+Na]^+$, found 372.0196 (2.4 ppm).



2m

Ethyl 3-pivalamido-4-(3,3,3-trifluoroprop-1-en-2-yl)benzoate (2m): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 95/5 to 85/15). Yield: 61% (42 mg). R_f (PE/Et_2O, 75/25): 0.19.

Beige solid; **m.p.**: 60-61 °C.

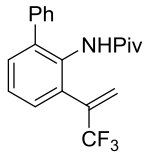
IR: 3272, 2969, 1717, 1653, 1485, 1287, 1256, 1227, 1191, 1171, 1111, 1064, 1024, 903, 774, 742, 628.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 8.76 (d, *J* = 1.5 Hz, 1H), 7.76 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 1H), 7.43 (brs, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.23 (d, *J* = 1.2 Hz, 1H), 5.64 (d, *J* = 1.2 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.4 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.6, 165.8, 136.2, 135.6 (q, *J* = 32.0 Hz), 132.3, 130.2, 128.6, 125.3 (q, *J* = 5.1 Hz), 125.2, 123.3, 122.4 (q, *J* = 274.4 Hz), 61.3, 39.9, 27.4, 14.3.

HRMS (ESI^+): calcd for $C_{17}H_{20}F_3NO_3Na$ *m/z* 366.1293 $[M+Na]^+$, found 366.1302 (2.5 ppm).



2n

***N*-(3-(3,3,3-Trifluoroprop-1-en-2-yl)-[1,1'-biphenyl]-2-yl)pivalamide (2n)**:

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 90/10 to 75/25). Yield: 72% (50 mg); 71% (970 mg, based on a 3.95 mmol scale). R_f (PE/Et_2O, 75/25): 0.17.

Yellow solid; **m.p.**: 160-161 °C.

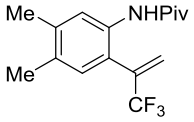
IR: 3314, 2974, 1651, 1497, 1455, 1219, 1167, 1122, 964, 757, 738, 699.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.32-7.18 (m, 8H), 6.82 (brs, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 5.75 (d, *J* = 1.2 Hz, 1H), 1.02 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -66.9 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 177.2, 141.6, 139.0, 136.1 (q, *J* = 31.3 Hz), 133.7, 133.0, 131.1, 130.0, 128.8, 128.1, 127.5, 127.4, 123.7 (q, *J* = 5.1 Hz), 123.1 (q, *J* = 273.6 Hz), 38.8, 27.2.

HRMS (ESI^+): calcd for $C_{20}H_{20}F_3NONa$ *m/z* 370.1395 $[M+Na]^+$, found 370.1389 (1.6 ppm).



2o

***N*-(4,5-Dimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2o)**:

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 90/10 to 80/20). Yield: 63% (38 mg). R_f (PE/Et_2O, 75/25): 0.37.

Yellow solid; **m.p.**: 82-83 °C.

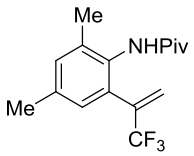
IR: 3272, 2963, 1651, 1495, 1455, 1175, 1119, 1103, 949, 876, 675, 640.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.36 (brs, 1H), 6.96 (s, 1H), 6.21 (d, *J* = 0.9 Hz, 1H), 5.63 (d, *J* = 0.9 Hz, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 1.25 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.5, 138.7, 136.2 (q, *J* = 31.5 Hz), 133.5, 132.7, 130.8, 124.6 (q, *J* = 5.1 Hz), 123.7, 122.8 (q, *J* = 274.1 Hz), 122.2, 39.7, 27.5, 19.8, 19.1.

HRMS (ESI$^+$): calcd for $C_{16}H_{21}F_3NO$ *m/z* 300.1575 $[M+H]^+$, found 300.1563 (-4.0 ppm).



2p

***N*-(4,6-Dimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pivalamide (2p)**:

Purification by reverse phase chromatography (performed on a puriFlash® C18HP 15μm 55G Flash column, eluent: H_2O/CH_3CN). Yield: 30% (18 mg). R_f (PE/Et_2O, 75/25): 0.23.

White solid; **m.p.**: 152-153 °C.

IR: 3332, 2961, 1651, 1506, 1355, 1237, 1162, 1152, 1116, 966, 861, 667.

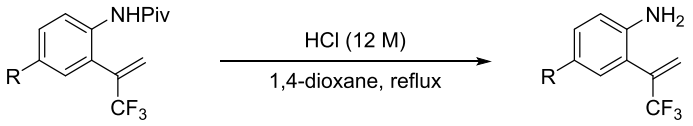
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.91 (brs, 2H), 6.01 (s, 1H), 5.57 (s, 1H), 2.31 (s, 3H), 2.19 (s, 3H), 1.26 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.4 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): 177.0, 136.9, 136.8, 136.4 (q, *J* = 31.2 Hz), 132.2, 132.1, 131.2, 128.6, 123.1 (q, *J* = 5.3 Hz), 123.0 (q, *J* = 273.5 Hz), 39.1, 27.6, 20.9, 18.2.

HRMS (ESI$^+$): calcd for $C_{16}H_{21}F_3NO$ *m/z* 300.1575 $[M+H]^+$, found 300.1570 (-1.7 ppm).

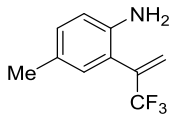
1.1.3 The procedure for the removal of the directing group



R = Me, **2b**
*t*Bu, **2d**

R = Me, **8b**
*t*Bu, **8d**

Compound **2b** or **2d** (1 mmol) was dissolved in 1,4-dioxane (5 mL) and HCl (12 M, 5 mL) and the reaction mixture was heated at reflux overnight. After cooling down to room temperature, Na_2CO_3 (sat.aq) was added until pH = 9-10. The mixture was extracted with ethyl acetate (3 × 30 mL), washed with brine (20 mL), dried over anhydrous $MgSO_4$ and then the solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography.



8b

4-Methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (8b): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 95/5 to 85/15). Yield: 69% (412 mg, based on a 3 mmol scale). R_f (PE/Et_2O, 75/25): 0.40.

Yellow liquid.

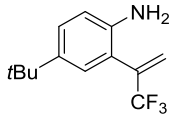
IR: 3385, 2924, 1624, 1506, 1344, 1156, 1117, 958, 814.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 6.94 (d, *J* = 8.1 Hz, 1H), 6.93 (s, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 6.12 (s, 1H), 5.61 (s, 1H), 3.55 (brs, 2H), 2.21 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.2 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 142.0, 136.4 (q, *J* = 31.0 Hz), 130.5, 130.4, 127.2, 123.8 (q, *J* = 5.3 Hz), 123.1 (q, *J* = 274.0 Hz), 118.9, 115.9, 20.0.

HRMS (ESI$^+$): calcd for $C_{10}H_{11}F_3N$ *m/z* 202.0844 $[M+H]^+$, found 202.0840 (-2.0 ppm).



8d

4-(*tert*-Butyl)-2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (8d): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 95/5 to 85/15). Yield: 70% (171 mg). R_f (PE/Et_2O, 75/25): 0.36.

Yellow liquid.

IR: 3347, 2964, 1623, 1505, 1345, 1162, 1124, 969, 826.

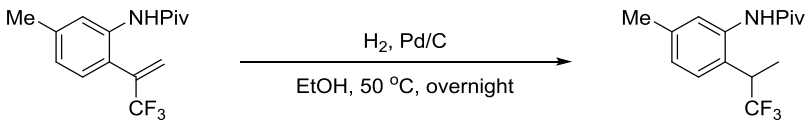
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.4 Hz, 1H), 7.09 (s, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.20 (s, 1H), 5.69 (s, 1H), 3.67 (brs, 2H), 1.29 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -67.3 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 141.8, 141.1, 136.7 (q, *J* = 31.0 Hz), 126.98, 126.94, 124.0 (q, *J* = 5.2 Hz), 123.1 (q, *J* = 274.4 Hz), 118.7, 115.7, 33.9, 31.4.

HRMS (ESI^+): calcd for $C_{13}H_{17}F_3N$ *m/z* 244.1313 $[M+H]^+$, found 244.1314 (0.4 ppm).

1.1.4 Selective reduction of olefinic double bond



2i **9**

***N*-(5-Methyl-2-(1,1,1-trifluoropropan-2-yl)phenyl)pivalamide (9)**: Compound **2i** (28 mg, 0.1 mmol) and 10% Pd/C (100 mg) was added into EtOH (2 mL). The suspension was stirred at 50 °C under H_2 (1 atm) overnight. After cooling down to room temperature, the reaction mixture was diluted with diethyl ether (10 mL) and filtered through a plug of Celite®. The solvents were removed under vacuum and the crude was purified by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, 80/20 to 75/25). Yield: 85% (24 mg). R_f (PE/Et_2O, 75/25): 0.22.

White solid; **m.p.**: 110-111 °C.

IR: 3282, 2925, 1647, 1496, 1163, 1129, 1106, 1042, 986, 812.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.1 Hz, 1H), 7.28 (s, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 3.61-3.50 (m, 1H), 2.34 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.34 (s, 9H); note

that one proton (NH) is missing.

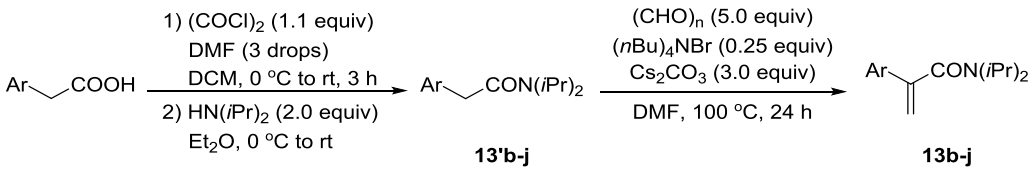
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -71.8 (d, *J* = 9.0 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): 177.3, 138.7, 135.5, 127.9, 127.7, 127.6, 127.5 (q, *J* = 280.1 Hz), 127.4, 39.4, 37.7 (q, *J* = 27.1 Hz), 27.6, 20.9, 13.7 (q, *J* = 3.0 Hz).

HRMS (ESI^+) calcd for $C_{15}H_{21}F_3NO$ *m/z* 288.1575 $[M+H]^+$, found 288.1573 (-0.7 ppm).

1.2 Transition metal catalyzed olefinic C(sp^2)-H bond functionalization with BTP

1.2.1 General procedure for the synthesis of *N*,*N*-diisopropylacrylamide 13b-j



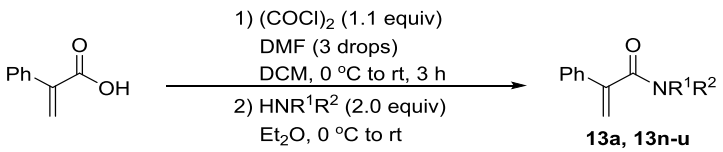
Synthetic procedure: Oxalyl chloride (11 mmol, 1.1 equiv) was slowly added at 0 °C to a solution of the acid (10 mmol, 1 equiv) and DMF (3 drops) in dry DCM (15 mL). After stirring at room temperature for 3 h, the solvent was removed under vacuum and the residue was dissolved in dry Et_2O. Diisopropylamine (20 mmol, 2 equiv) was added and the reaction was followed by TLC until it completed. Water (100 mL) was added and the resulting mixture was extracted with Et_2O (3 × 150 mL). Removal of the solvent under vacuum and purification of the residue by silica gel column chromatography afforded the desired intermediate **13'**.

Amide 1**3'** (8 mmol), $(CHO)_n$ (40 mmol, 5 equiv), $(nBu)_4NBr$ (2 mmol, 0.25 equiv) and Cs_2CO_3 (24 mmol, 3 equiv) was dissolved in DMF (100 mL) and stirred at 100 °C for

24 h. Water (100 mL) was added and the resulting mixture was extracted with Et_2O (3 × 150 mL). Removal of the solvent under vacuum and purification of the residue by Biotage and recrystallization if necessary afforded the desired product **13**.

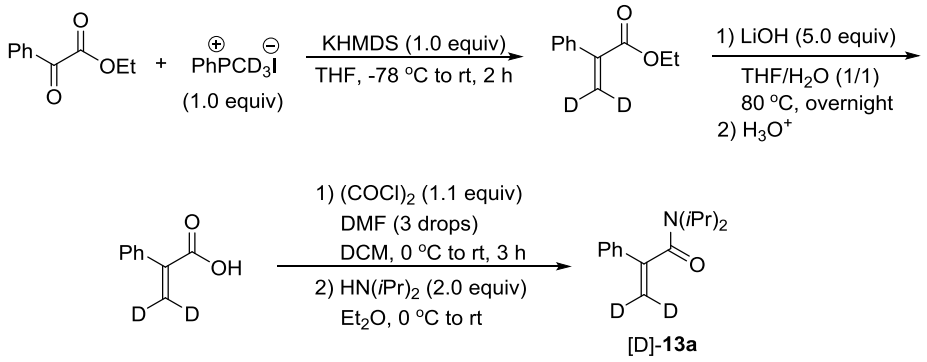
13k, 13l, 13m were synthesized following the known literature procedure.[202]

1.2.2 General procedure for the synthesis of acrylamide 13a, 13n-u



Synthetic procedure: Oxalyl chloride (11 mmol, 1.1 equiv) was slowly added at 0 °C to a solution of the acid (10 mmol, 1 equiv) and DMF (3 drops) in dry DCM (15 mL). After stirring at room temperature for 3 h, the solvent was removed under vacuum and the residue was dissolved in dry Et_2O. Amine HNR^1R^2 (20 mmol, 2 equiv) was added and the reaction was followed by TLC until it completed. Water (100 mL) was added and the resulting mixture was extracted with Et_2O (3 × 150 mL). Removal of the solvent under vacuum and purification of the residue by Biotage and recrystallization if necessary afforded the desired product **13**.

1.2.3 Synthesis of the deuterated acrylamide [D]-13a



Synthetic procedure: Methyl-d_3-triphenylphosphonium iodide was synthesized following the known literature procedure.[203]

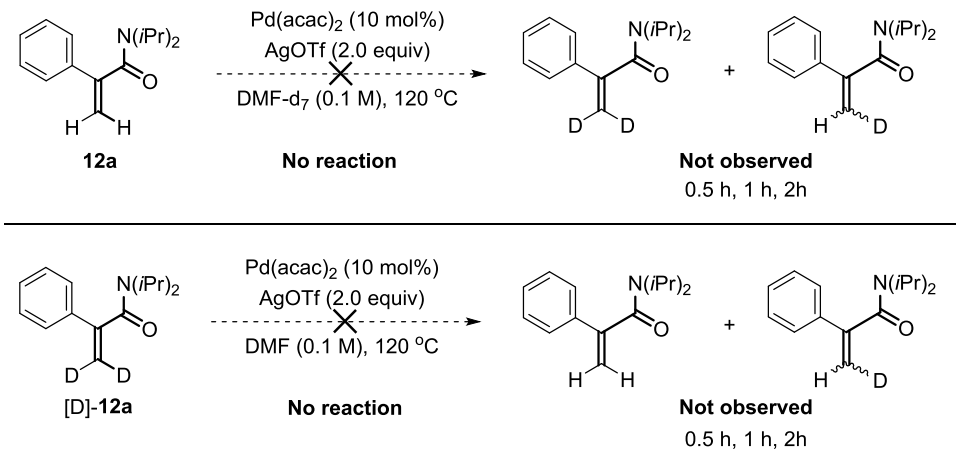
Methyl-d_3-triphenylphosphonium iodide (13 mmol, 1 equiv) was dried under vacuum for at least 1h before starting the reaction (quite important step). The freshly dried Methyl-d_3-triphenylphosphonium iodide (13 mmol, 1 equiv) was dissolved in dry THF (100 mL) and stirred at -78 °C for 15 min. KHMDS (13 mmol, 1 equiv) was added dropwise (a golden yellow precipitate was observed quickly) and then the mixture was stirred for another 2 h at room temperature. The ester (2.5 g, 14.3 mmol, 1.1 equiv) was added dropwise at -78 °C and then the mixture was stirred for another 1 h. Then allowed to stir at room temperature and the reaction was followed by TLC until completion. Water (50 mL) was added and the resulting mixture was extracted with Et_2O (3 × 100 mL). Removal of the solvent under vacuum and purification of the residue by silica gel column chromatography afforded the desired intermediate (1.6 g, 9.3 mmol).

Then, the ester (1.6 g, 9.3 mmol, 1 equiv) and LiOH (46.5 mmol, 5 equiv) was dissolved in THF/H_2O (20 mL/20 mL) and stirred at 80 °C overnight. The reaction was quenched

with 1.0 M HCl and extracted by Et_2O (3 × 50 mL). Removal of the solvent under vacuum and purification of the residue by silica gel column chromatography afforded the desired acid. The acid was converted into [D]-**13a** according to the standard procedure used for the synthesis of **13**.

1.2.4 Mechanistic Studies

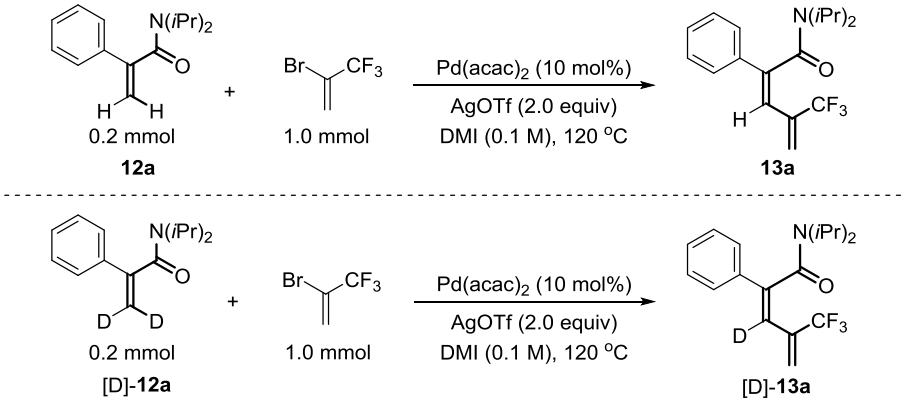
1.2.4.1 Scrambling experiment (without BTP)



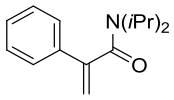
A dried tube was loaded with $Pd(acac)_2$ (6.0 mg, 0.02 mmol, 0.1 equiv), AgOTf (102.8 mg, 0.4 mmol, 2 equiv) and amide **12a** or [D]-**12a** (0.2 mmol, 1 equiv) under Ar. Then, DMF-d_7 or DMF (2 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at 120 °C. Three reactions were carried out and stirred at 120 °C for different reaction time (0.5 h, 1 h, 2 h). The reaction mixture was then diluted with diethyl ether (10 mL) and filtered through a plug of Celite®. The solution was washed with brine (3 × 5 mL) and dried with $MgSO_4$. The solvents were removed under vacuum and the crude was directly analyzed by ^{1}H-NMR spectroscopy. No deuteration was observed.

1.2.4.2 Kinetic Isotope Effect (KIE) measurements

Parallel reactions:



Ten parallel reactions (five were charged with **12a**, while another five were charged with [D]-**12a**) were performed for different reaction time (10 min, 20 min, 30 min, 40 min and 50 min). Each dried tubes was charged with $Pd(acac)_2$ (6.0 mg, 0.02 mmol, 0.1 equiv), AgOTf (102.8 mg, 0.4 mmol, 2 equiv) and amide **12a** or [D]-**12a** (0.2 mmol, 1 equiv) under argon. Then, DMI (2 mL) and 2-bromo-3,3,3-trifluoropropene (0.1 mL, 1 mmol, 5 equiv) were added. The tube was sealed with a rubber septum and the suspension was stirred at 120 °C at different reaction time. The yield of each reaction was determined by ^{19}F NMR analysis of the reaction mixture.



12a

***N*,*N*-Diisopropyl-2-phenylacrylamide (12a)**:

White solid; **m.p.**: 81-82 °C.

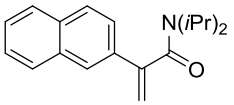
IR: 2968, 2929, 1626, 1443, 1349, 1135, 902, 787, 698.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.51-7.42 (m, 2H), 7.42-7.30 (m, 3H), 5.63 (s, 1H),

5.27 (s, 1H), 4.11-3.90 (m, 1H), 3.54-3.34 (m, 1H), 1.56 (d, *J* = 6.6 Hz, 6H), 1.02 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.1, 146.7, 135.9, 128.7, 128.4, 125.6, 111.5, 50.7, 45.6, 20.44, 20.37.

HRMS (ESI$^+$): calcd for $C_{15}H_{22}NO$ *m/z* 232.1701 $[M+H]^+$, found 232.1696 (-2.2 ppm).



12b

***N*,*N*-Diisopropyl-2-(naphthalen-2-yl)acrylamide (12b)**:

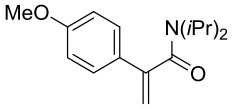
White solid; **m.p.**: 88-89 °C.

IR: 2966, 2931, 1620, 1443, 1370, 1331, 1210, 1136, 1039, 905, 825.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.85-7.75 (m, 3H), 7.69-7.59 (m, 1H), 7.51-7.42 (m, 2H), 5.77 (s, 1H), 5.36 (s, 1H), 4.16-3.92 (m, 1H), 3.60-3.29 (m, 1H), 1.62 (d, *J* = 6.6 Hz, 6H), 0.99 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.9, 146.5, 133.1, 133.0, 132.9, 128.3, 128.2, 127.4, 126.2, 126.2, 125.0, 122.9, 111.6, 50.5, 45.4, 20.3, 20.2.

HRMS (ESI$^+$): calcd for $C_{19}H_{24}NO$ *m/z* 282.1858 $[M+H]^+$, found 282.1869 (3.9 ppm).



12c

***N*,*N*-Diisopropyl-2-(4-methoxyphenyl)acrylamide (12c)**:

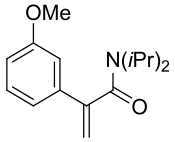
White solid; **m.p.**: 90-91 °C.

IR: 2966, 2931, 1626, 1602, 1510, 1442, 1246, 1182, 1032, 902, 847.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.49 (s, 1H), 5.12 (s, 1H), 4.06-3.91 (m, 1H), 3.80 (s, 3H), 3.49-3.34 (m, 1H), 1.53 (d, *J* = 6.6 Hz, 6H), 1.01 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): 170.3, 159.7, 146.1, 128.4, 126.9, 114.0, 109.3, 55.2, 50.6, 45.5, 20.4, 20.4.

HRMS (ESI^+): calcd for $C_{16}H_{24}NO_2$ *m/z* 262.1807 $[M+H]^+$, found 262.1809 (0.8 ppm).



12d

***N*,*N*-Diisopropyl-2-(3-methoxyphenyl)acrylamide (12d)**:

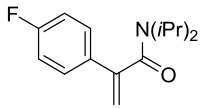
Yellow oil.

IR: 2966, 2935, 1629, 1441, 1344, 1271, 1209, 1038, 906, 784.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.22 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.96 (s, 1H), 6.87-6.79 (m, 1H), 5.58 (s, 1H), 5.23 (s, 1H), 4.05-3.89 (m, 1H), 3.77 (s, 3H), 3.49-3.31 (m, 1H), 1.51 (d, *J* = 6.6 Hz, 6H), 0.99 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.9, 159.7, 146.6, 137.2, 129.6, 118.1, 114.1, 111.7, 110.9, 55.1, 50.6, 45.4, 20.30, 20.28.

HRMS (ESI^+): calcd for $C_{16}H_{23}NO_2Na$ *m/z* 284.1262 $[M+Na]^+$, found 284.1626 (0.0 ppm).



12e

2-(4-Fluorophenyl)-*N*,*N*-diisopropylacrylamide (12e):

White solid; **m.p.**: 92-93 °C.

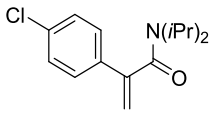
IR: 2967, 1628, 1510, 1372, 1351, 1221, 1174, 903, 854, 592.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.52-7.32 (m, 2H), 7.11-6.92 (m, 2H), 5.53 (s, 1H), 5.21 (s, 1H), 4.07-3.82 (m, 1H), 3.53-3.31 (m, 1H), 1.51 (d, *J* = 6.6 Hz, 6H), 1.00 (d, *J* = 6.6 Hz, 6H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -113.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.7, 162.8 (d, *J* = 248.2 Hz), 145.6, 132.0 (d, *J* = 3.4 Hz), 127.3 (d, *J* = 8.2 Hz), 115.9 (d, *J* = 21.7 Hz), 111.2 (d, *J* = 1.8 Hz), 50.6, 45.5, 20.3, 20.3.

HRMS (ESI^+): calcd for $C_{15}H_{20}FNONa$ *m/z* 272.1427 $[M+Na]^+$, found 272.1426 (-0.4 ppm).



12f

2-(4-Chlorophenyl)-*N*,*N*-diisopropylacrylamide (12f):

White solid; **m.p.**: 95-96 °C.

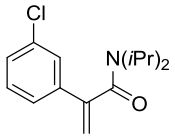
IR: 2973, 2933, 1627, 1616, 1371, 1344, 1134, 903, 855, 826.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 5.52 (s, 1H), 5.18 (s, 1H), 3.95-3.78 (m, 1H), 3.44-3.27 (m, 1H), 1.45 (d, *J* = 6.6 Hz, 6H),

0.93 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.4, 145.4, 134.3, 134.2, 128.8, 126.8, 111.9, 50.6, 45.5, 20.3, 20.3.

HRMS (ESI^+): calcd for $C_{15}H_{20}ClNONa$ *m/z* 288.1131 $[M+Na]^+$, found 288.1129 (-0.7 ppm).



12g

2-(3-Chlorophenyl)-*N*,*N*-diisopropylacrylamide (12g):

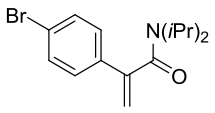
White solid; **m.p.**: 42-43 °C.

IR: 2968, 2934, 1626, 1442, 1371, 1344, 1133, 1038, 905, 795.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.29-7.14 (m, 3H), 5.55 (s, 1H), 5.22 (s, 1H), 4.00-3.75 (m, 1H), 3.45-3.23 (m, 1H), 1.45 (d, *J* = 6.6 Hz, 6H), 0.94 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.2, 145.4, 137.6, 134.6, 129.9, 128.3, 125.5, 123.8, 112.6, 50.6, 45.5, 20.3, 20.3.

HRMS (ESI^+): calcd for $C_{15}H_{21}ClNO$ *m/z* 266.1312 $[M+H]^+$, found 266.1315 (1.1 ppm).



12h

2-(4-Bromophenyl)-*N*,*N*-diisopropylacrylamide (12h):

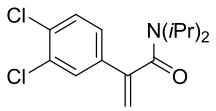
White solid; **m.p.**: 110-111 °C.

IR: 2972, 2932, 1626, 1445, 1371, 1343, 1133, 1007, 901, 854.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 5.53 (s, 1H), 5.19 (s, 1H), 3.96-3.77 (m, 1H), 3.43-3.26 (m, 1H), 1.44 (d, *J* = 6.6 Hz, 6H), 0.93 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.3, 145.5, 134.7, 131.7, 127.1, 122.4, 112.0, 50.6, 45.5, 20.3, 20.3.

HRMS (ESI^+): calcd for $C_{15}H_{20}BrNONa$ *m/z* 332.0626 $[M+Na]^+$, found 332.0625 (-0.3 ppm).



12i

2-(3,4-Dichlorophenyl)-*N*,*N*-diisopropylacrylamide (12i):

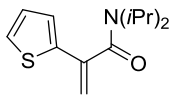
White solid; **m.p.**: 92-93 °C.

IR: 2966, 2934, 1622, 1443, 1370, 1344, 1136, 1029, 889, 839.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 5.62 (s, 1H), 5.30 (s, 1H), 4.01-3.83 (m, 1H), 3.53-3.34 (m, 1H), 1.52 (d, *J* = 6.6 Hz, 6H), 1.03 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.9, 144.5, 135.9, 132.9, 132.4, 130.6, 127.5, 125.0, 113.1, 50.8, 45.7, 20.44, 20.36.

HRMS (ESI^+): calcd for $C_{15}H_{20}Cl_2NO$ *m/z* 300.0922 $[M+H]^+$, found 300.0908 (-4.7 ppm).



12j

***N*,*N*-Diisopropyl-2-(thiophen-2-yl)acrylamide (12j)**:

White solid; **m.p.**: 90-91 °C.

IR: 3073, 2968, 1622, 1587, 1444, 1349, 1333, 1040, 888, 729.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.21 (d, *J* = 4.8 Hz, 1H), 7.05-6.89 (m, 2H), 5.48 (s, 1H), 5.08 (s, 1H), 4.29-3.92 (m, 1H), 3.58-3.33 (m, 1H), 1.53 (d, *J* = 6.6 Hz, 6H), 1.08 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.7, 140.7, 140.3, 127.5, 125.7, 125.5, 109.9, 50.8, 45.6, 20.5, 20.4.

HRMS (ESI^+): calcd for $C_{13}H_{20}NOS$ *m/z* 238.1266 $[M+H]^+$, found 238.1272 (2.5 ppm).

12k

***N*,*N*-Diisopropylacrylamide (12k)**:

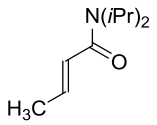
Yellow oil.

IR: 2968, 2935, 1642, 1607, 1142, 1371, 1316, 1211, 1132, 953, 793.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 6.50 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.16 (dd, *J* = 17.1 Hz, 1.8 Hz, 1H), 5.54 (dd, *J* = 10.5 Hz, 1.8 Hz, 1H), 4.00 (m, 1H), 3.73 (m, 1H), 1.34 (m, 6H), 1.22 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.1, 130.7, 125.6, 48.1, 45.6, 21.3, 20.5.

HRMS (ESI^+): calcd for $C_9H_{18}NO$ *m/z* 156.1388 $[M+H]^+$, found 156.1391 (1.9 ppm).



12l

(*E*)-*N*,*N*-diisopropylbut-2-enamide (12l):

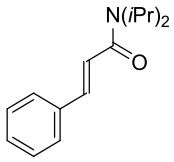
Yellow oil.

IR: 2966, 2935, 1659, 1610, 1435, 1332, 1209, 1113, 1046, 964.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 6.86-6.61 (m, 1H), 6.17 (d, *J* = 15.5 Hz, 1H), 3.99 (m, 1H), 3.70 (m, 1H), 1.81 (m, 3H), 1.31 (m, 6H), 1.21 (brs, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.3, 138.2, 123.9, 47.2, 44.7, 20.4, 19.9, 17.2.

HRMS (ESI^+): calcd for $C_{10}H_{20}NO$ *m/z* 170.1545 $[M+H]^+$, found 170.1542 (-1.8 ppm).



12m

***N*,*N*-Diisopropylcinnamamide (12m)**:

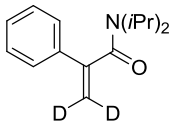
Yellow oil.

IR: 2968, 2936, 1616, 1447, 1328, 1154, 1115, 1023, 940, 760.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.59 (d, *J* = 15.6 Hz, 1H), 7.50 (d, *J* = 6.9 Hz, 2H), 7.42-7.28 (m, 3H), 6.84 (d, *J* = 15.6 Hz, 1H), 4.11 (m, 1H), 3.85 (m, 1H), 1.39 (m, 6H), 1.31 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.0, 140.7, 135.6, 129.1, 128.6, 127.4, 120.5, 47.9, 45.7, 21.5, 20.6.

HRMS (ESI^+): calcd for $C_{15}H_{22}NO$ *m/z* 232.1701 $[M+H]^+$, found 232.1705 (1.7 ppm).



[D]-**12a**

***N*,*N*-Diisopropyl-2-phenylacrylamide-d$_2$ (**[D]-**12a)**:

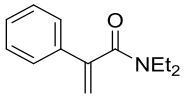
White solid; **m.p.**: 72-73 °C.

IR: 2996, 2931, 1623, 1442, 1346, 1255, 1211, 1136, 789, 733.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.40-7.26 (m, 3H), 5.60 (s, 0.08H), 5.24 (s, 0.08H), 4.10-3.88 (m, 1H), 3.51-3.33 (m, 1H), 1.54 (d, *J* = 6.6 Hz, 6H), 1.00 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.0, 146.5, 135.8, 128.6, 128.3, 125.5, 110.9, 50.5, 45.5, 20.35, 20.28.

HRMS (ESI$^+$): calcd for $C_{15}H_{20}D_2NO$ *m/z* 234.1827 $[M+H]^+$, found 234.1823 (-1.7 ppm).



10a

***N*,*N*-Diethyl-2-phenylacrylamide (10a)**:

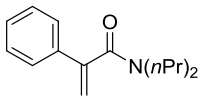
Yellow oil.

IR: 2935, 2974, 1627, 1432, 1380, 1174, 1144, 1082, 907, 780.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.31-7.17 (m, 3H), 5.61 (s, 1H), 5.24 (s, 1H), 3.42 (q, *J* = 7.2 Hz, 2H), 3.14 (q, *J* = 7.2 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.8, 145.1, 135.3, 128.4, 128.1, 125.2, 112.6, 42.4, 38.4, 13.6, 12.4.

HRMS (ESI$^+$): calcd for $C_{13}H_{18}NO$ *m/z* 204.1388 $[M+H]^+$, found 204.1380 (-3.9 ppm).



14

2-Phenyl-*N*,*N*-di(*n*-propyl)acrylamide (14):

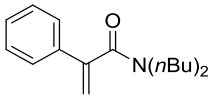
Yellow oil.

IR: 2964, 2933, 1631, 1464, 1427, 1227, 1145, 1096, 902, 703.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.39-7.29 (m, 3H), 5.68 (s, 1H), 5.31 (s, 1H), 3.40 (t, *J* = 7.8 Hz, 2H), 3.10 (t, *J* = 7.8 Hz, 2H), 1.73-1.59 (m, 2H), 1.51-1.35 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.72 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.6, 145.8, 136.0, 128.7, 128.5, 125.7, 113.4, 50.2, 46.0, 21.9, 20.6, 11.5, 11.1.

HRMS (ESI^+): calcd for $C_{15}H_{22}NO$ *m/z* 232.1701 $[M+H]^+$, found 232.1699 (-0.9 ppm).



15

***N*,*N*-Di(*n*-butyl)-2-phenylacrylamide (15)**:

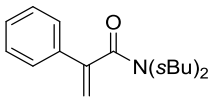
Yellow oil.

IR: 2958, 2932, 1633, 1466, 1426, 1211, 1144, 1098, 904, 703.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.8 Hz, 2H), 7.39-7.29 (m, 3H), 5.67 (s, 1H), 5.31 (s, 1H), 3.43 (t, *J* = 7.8 Hz, 2H), 3.11 (t, *J* = 7.8 Hz, 2H), 1.67-1.53 (m, 2H), 1.46-1.28 (m, 4H), 1.19-1.05 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.5, 145.8, 136.0, 128.7, 128.4, 125.7, 113.4, 48.3, 44.2, 30.7, 29.5, 20.3, 19.9, 13.9, 13.7.

HRMS (ESI^+): calcd for $C_{17}H_{26}NO$ *m/z* 260.2014 $[M+H]^+$, found 260.2004 (-1.5 ppm).



16

***N*,*N*-Di-(sec-butyl)-2-phenylacrylamide (16)**:

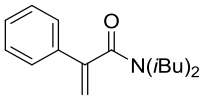
Yellow oil.

IR: 2968, 2936, 1630, 1437, 1354, 1241, 1150, 1058, 989, 698.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.39-7.28 (m, 3H), 5.59 (s, 1H), 5.26 (s, 1H), 3.76-3.58 (m, 1H), 3.10-2.86 (m, 1H), 2.38-2.10 (m, 1H), 1.96-1.75 (m, 1H), 1.49 (d, *J* = 6.9 Hz, 3H), 1.43-1.25 (m, 2H), 0.99-0.87 (m, 6H), 0.69 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.5, 147.1, 136.3, 128.64, 128.62, 125.8, 112.3, 56.7, 52.2, 27.7, 27.4, 18.5, 17.8, 12.2, 11.5.

HRMS (ESI^+): calcd for $C_{17}H_{26}NO$ *m/z* 260.2014 $[M+H]^+$, found 206.2006 (-3.1 ppm).



17

***N*,*N*-Diisobutyl-2-phenylacrylamide (17)**:

Yellow oil.

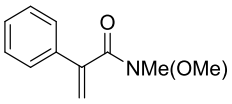
IR: 2959, 2871, 1634, 1466, 1433, 1232, 1147, 1097, 907, 704.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.37-7.25 (m, 3H), 5.66 (s, 1H), 5.31 (s, 1H), 3.31 (d, *J* = 7.5 Hz, 2H), 2.97 (d, *J* = 7.5 Hz, 2H), 2.17-2.00 (m, 1H), 1.92-1.75 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.72 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.1, 146.0, 136.1, 128.5, 128.2, 125.7, 114.4, 55.4,

50.8, 26.6, 25.9, 20.1, 19.7.

HRMS (ESI$^+$): calcd for $C_{17}H_{26}NO$ *m/z* 260.2014 $[M+H]^+$, found 260.2001 (-5.0 ppm).



18

***N*-Methoxy-*N*-methyl-2-phenylacrylamide (18)**:

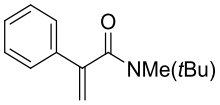
Yellow oil.

IR: 2937, 1652, 1422, 1379, 1178, 996, 911, 783, 699.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.51-7.29 (m, 5H), 5.70 (s, 1H), 5.50 (s, 1H), 3.48 (brs, 3H), 3.25 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 144.5, 135.8, 128.3, 128.1, 125.5, 115.2, 60.7.

HRMS (ESI$^+$): calcd for $C_{11}H_{14}NO_2$ *m/z* 192.1025 $[M+H]^+$, found 192.1026 (0.5 ppm).



19

***N*-(tert-Butyl)-*N*-methyl-2-phenylacrylamide (19)**:

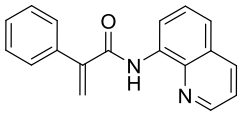
Yellow oil.

IR: 2963, 1636, 1474, 1449, 1391, 1365, 1208, 699.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.39-7.28 (m, 3H), 5.62 (s, 1H), 5.30 (s, 1H), 2.81 (s, 3H), 1.50 (s, 9H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.7, 147.7, 136.1, 128.7, 128.3, 125.7, 112.9, 56.6, 34.0, 28.0.

HRMS (ESI$^+$): calcd for $C_{14}H_{20}NO$ *m/z* 218.1545 $[M+H]^+$, found 218.1539 (-2.8 ppm).



21

2-Phenyl-*N*-(quinolin-8-yl)acrylamide (21):

White solid; **m.p.**: 86-87 °C.

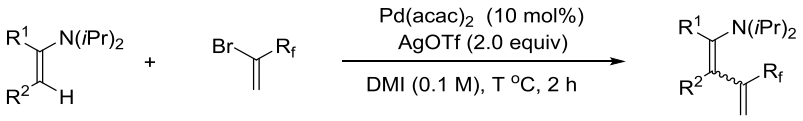
IR: 3365, 3050, 1674, 1532, 1488, 1424, 1166, 929, 825, 685.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.26 (brs, 1H), 8.90 (d, *J* = 7.2 Hz, 1H), 8.64 (d, *J* = 3.9 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.65-7.33 (m, 8H), 6.33 (s, 1H), 5.84 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.8, 148.2, 145.8, 138.7, 136.7, 136.2, 134.4, 128.7, 128.6, 128.3, 127.9, 127.3, 122.2, 121.8, 121.5, 116.6.

HRMS (ESI$^+$): calcd for $C_{18}H_{15}N_2O$ *m/z* 275.1184 $[M+H]^+$, found 275.1180 (-1.5 ppm).

1.2.5 General procedure for the Pd-catalyzed synthesis of 3-trifluoromethyl substituted 1,3-butadienes

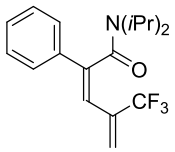


12 (5.0 equiv) **13**

R_f = CF_3: **BTP**
R_f = C_2F_5: **Analogue of BTP**

A dried tube was loaded with $Pd(acac)_2$ (6.0 mg, 0.02 mmol, 0.1 equiv), AgOTf (102.8 mg, 0.4 mmol, 2 equiv) and amide **12** (0.2 mmol, 1 equiv) under Ar. Then DMI (2 mL) and **BTP** or 2-bromo-3,3,4,4,4-pentafluorobutene (1 mmol, 5 equiv) were added. The tube was sealed with a rubber septum and the suspension was stirred at 120 °C or 140 °C (**BTP**: 120 °C; 2-bromo-3,3,4,4,4-pentafluorobutene: 140 °C) for 2 h. The reaction mixture was diluted with diethyl ether (10 mL) and filtered through a plug of

Celite®. The solution was washed with brine (3 × 5 mL) and dried with $MgSO_4$. The solvents were removed under vacuum and the crude was purified by a flash chromatography with a Biotage Isolera One Flash Purification System.



13a

(*Z*)-*N*,*N*-Diisopropyl-2-phenyl-4-(trifluoromethyl)penta-2,4-dienamide (13a): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 85/15). Yield: 62% (40 mg); 60% (39 mg, reaction performed in the air); 55% (715 mg, based on a 4 mmol scale). R_f (PE/Et_2O, 67/33): 0.52.

White solid; **m.p.**: 46-47 °C.

IR: 3060, 2976, 1615, 1334, 1172, 1119, 762, 695.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.54-7.46 (m, 2H), 7.42-7.29 (m, 3H), 6.37 (s, 1H), 6.19 (s, 1H), 5.88 (s, 1H), 4.04-3.88 (m, 1H), 3.48-3.35 (m, 1H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H).

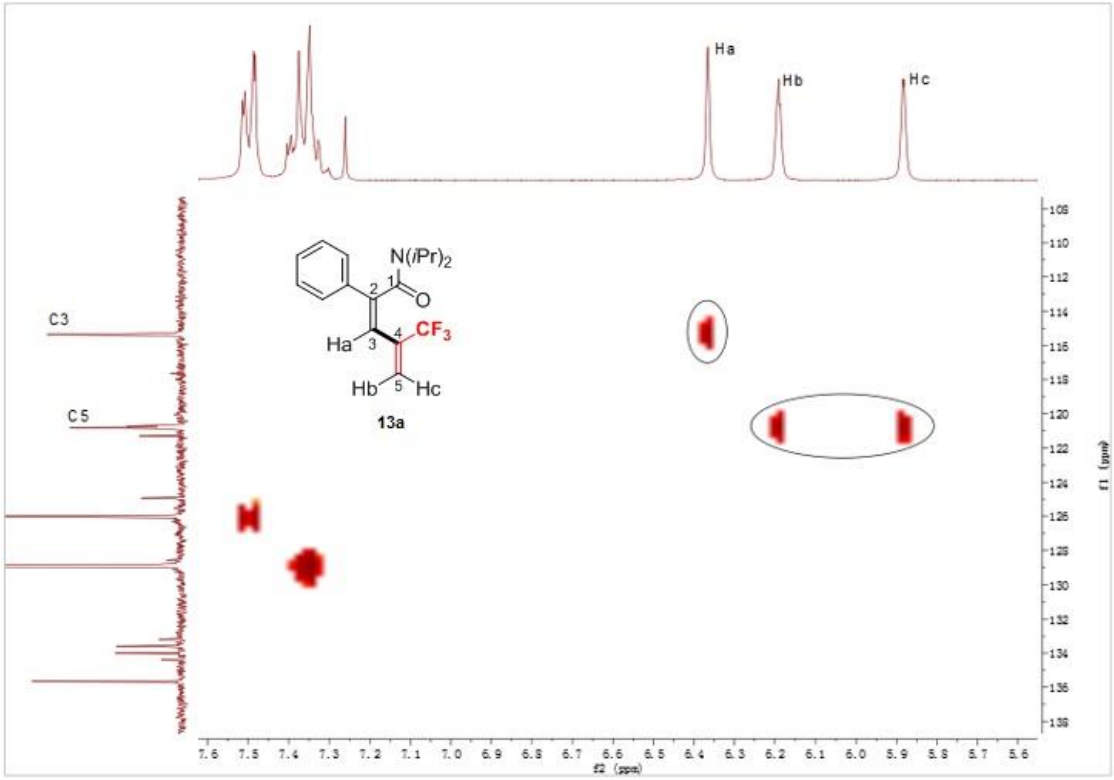
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.6, 143.0, 135.7, 133.8 (q, *J* = 31.5 Hz), 128.94, 128.86, 126.0, 123.1 (q, *J* = 274.4 Hz), 120.8 (q, *J* = 5.2 Hz), 115.4 (q, *J* = 1.8 Hz), 51.0, 45.6, 20.8, 20.5, 20.3, 20.1.

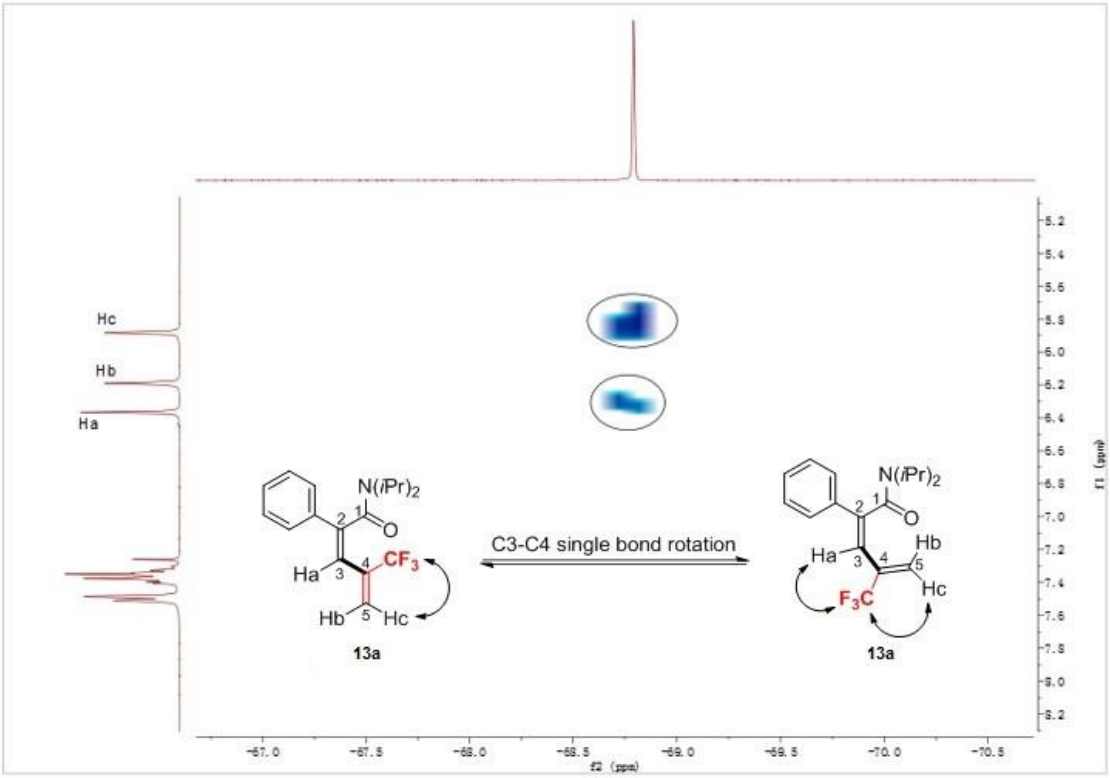
HRMS (ESI$^+$): calcd for $C_{18}H_{22}F_3NONa$ *m/z* 348.1551 $[M+Na]^+$, found 348.1554 (0.9 ppm).

The structure of **13a** was confirmed by 2D NMR experiments.

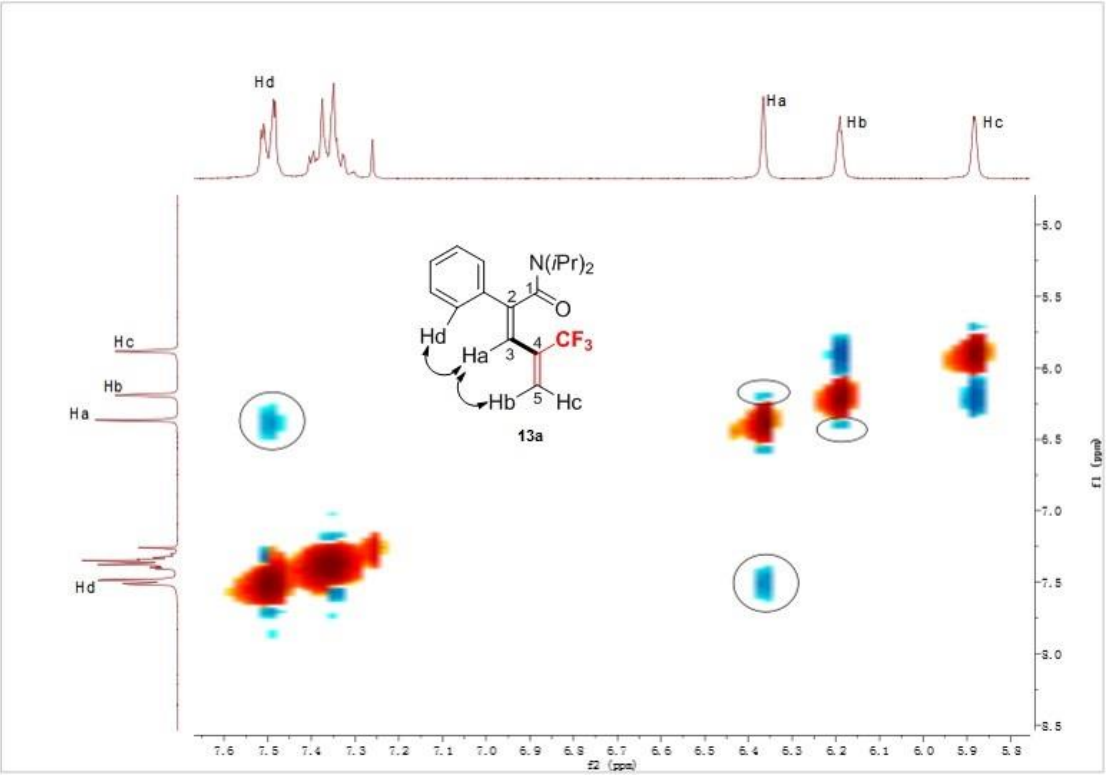
The HMQC 2D NMR of **13a**:

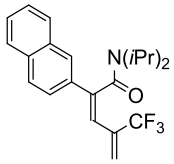


The HOESY 2D NMR of **13a**:



The NOESY 2D NMR of **13a**:





13b

(*Z*)-*N*,*N*-Diisopropyl-2-(naphthalen-2-yl)-4-(trifluoromethyl)penta-2,4-dienamide (13b): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 97/3 to 85/15). Yield: 68% (51 mg). R_f (PE/Et_2O, 67/33): 0.60.

White solid; **m.p.**: 62-63 °C.

IR: 2970, 2930, 1615, 1444, 1332, 1173, 1117, 820, 754.

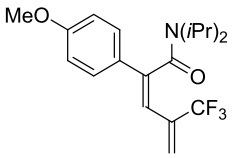
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.88-7.77 (m, 3H), 7.71-7.61 (m, 1H), 7.57-7.43 (m, 2H), 6.52 (s, 1H), 6.26 (s, 1H), 5.93 (s, 1H), 4.10-3.92 (m, 1H), 3.56-3.36

(m, 1H), 1.64 (d, *J* = 6.6 Hz, 3H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.7, 143.0, 133.9 (q, *J* = 29.7 Hz), 133.4, 133.3, 132.9, 128.7, 128.5, 127.6, 126.8, 126.6, 126.1, 123.2 (q, *J* = 274.4 Hz), 123.1, 120.9 (q, *J* = 5.2 Hz), 115.6 (q, *J* = 1.8 Hz), 51.2, 45.7, 20.8, 20.6, 20.4, 20.2.

HRMS (ESI^+): calcd for $C_{22}H_{25}F_3NO$ *m/z* 376.1888 $[M+H]^+$, found 376.1891 (0.8 ppm).



13c

(*Z*)-*N*,*N*-Diisopropyl-2-(4-methoxyphenyl)-4-(trifluoromethyl)penta-2,4-dienamide (13c): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 80/20). Yield: 52% (37 mg). R_f (PE/Et_2O, 67/33): 0.51.

White solid; **m.p.**: 40-41 °C.

IR: 2963, 2930, 1612, 1513, 1339, 1172, 1113, 1031, 826.

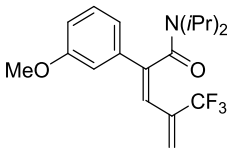
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.26 (s, 1H), 6.14 (s, 1H), 5.84 (s, 1H), 3.99-3.89 (m, 1H), 3.82 (s, 3H), 3.49-3.34 (m, 1H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.9, 160.2, 142.4, 133.9 (q, *J* = 29.6 Hz), 128.1,

127.4, 123.2 (q, *J* = 274.4 Hz), 120.0 (q, *J* = 5.3 Hz), 114.2, 113.3 (q, *J* = 1.8 Hz), 55.3, 51.0, 45.6, 20.8, 20.6, 20.3, 20.2.

HRMS (ESI$^+$): calcd for $C_{19}H_{24}F_3NO_2Na$ *m/z* 378.1657 [M+Na]$^+$, found 378.1657 (0.0 ppm).



13d

(*Z*)-*N*,*N*-Diisopropyl-2-(3-methoxyphenyl)-4-(trifluoromethyl)penta-2,4-dienamide (13d): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 80/20). Yield: 62% (44 mg). R_f (PE/Et_2O, 67/33): 0.52.

White solid; **m.p.**: 44-45 °C.

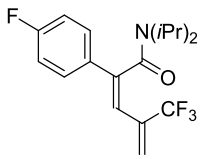
IR: 2969, 2937, 1616, 1337, 1169, 1117, 1042, 837, 779.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.22 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.97 (s, 1H), 6.94-6.79 (m, 1H), 6.31 (s, 1H), 6.13 (s, 1H), 5.83 (s, 1H), 4.00-3.83 (m, 1H), 3.76 (s, 3H), 3.44-3.28 (m, 1H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.5, 159.9, 142.9, 137.1, 133.8 (q, *J* = 29.8 Hz), 129.9, 123.1 (q, *J* = 274.3 Hz), 120.8 (q, *J* = 5.2 Hz), 118.5, 115.6 (q, *J* = 1.8 Hz), 114.7, 111.4, 55.2, 51.0, 45.6, 20.8, 20.5, 20.3, 20.1.

HRMS (ESI$^+$): calcd for $C_{19}H_{24}F_3NO_2Na$ *m/z* 378.1657 [M+Na]$^+$, found 378.1655 (-0.5 ppm).



13e

(*Z*)-2-(4-Fluorophenyl)-*N*,*N*-diisopropyl-4-(trifluoromethyl)penta-2,4-dienamide (13e): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 97/3 to 82/18). Yield: 63% (43 mg). R_f (PE/Et_2O, 67/33): 0.58.

White solid; **m.p.**: 46-47 °C.

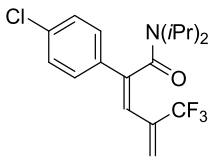
IR: 2980, 2937, 1614, 1651, 1509, 1336, 1121, 837, 817.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.55-7.42 (m, 2H), 7.15-6.99 (m, 2H), 6.29 (s, 1H), 6.16 (s, 1H), 5.88 (s, 1H), 4.00-3.84 (m, 1H), 3.49-3.33 (m, 1H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.8 (s, 3F), -112.6 to -112.7 (m, 1F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.4, 163.1 (d, *J* = 249.4 Hz), 141.9, 133.7 (q, *J* = 29.9 Hz), 131.8 (d, *J* = 3.4 Hz), 127.9 (d, *J* = 8.2 Hz), 123.0 (q, *J* = 274.3 Hz), 120.8 (q, *J* = 5.2 Hz), 115.9 (d, *J* = 21.8 Hz), 115.3 (q, *J* = 1.8 Hz), 51.1, 45.6, 20.8, 20.5, 20.2, 20.1.

HRMS (ESI^+): calcd for $C_{18}H_{21}F_4NONa$ *m/z* 366.1457 $[M+Na]^+$, found 366.1462 (1.4 ppm).



13f

(*Z*)-2-(4-Chlorophenyl)-*N*,*N*-diisopropyl-4-(trifluoromethyl)penta-2,4-dienamide (13f): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 85/15). Yield: 61% (44 mg). R_f (PE/Et_2O, 67/33): 0.53.

White solid; **m.p.**: 40-41 °C.

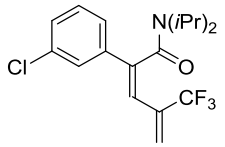
IR: 2988, 2937, 1614, 1336, 1180, 1122, 853, 824.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.33 (s, 1H), 6.18 (s, 1H), 5.90 (s, 1H), 3.98-3.82 (m, 1H), 3.49-3.31 (m, 1H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.2, 141.9, 134.9, 134.2, 133.6 (q, *J* = 29.9 Hz), 129.5, 127.3, 123.0 (q, *J* = 274.0 Hz), 120.8 (q, *J* = 5.1 Hz), 115.8 (q, *J* = 1.8 Hz), 51.1, 45.7, 20.8, 20.6, 20.2, 20.1.

HRMS (ESI^+): calcd for $C_{18}H_{21}ClF_3NONa$ *m/z* 382.1161 $[M+Na]^+$, found 382.1154 (-1.8 ppm).



13g

(*Z*)-2-(3-Chlorophenyl)-*N*,*N*-diisopropyl-4-(trifluoromethyl)penta-2,4-dienamide (13g): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 80/20). Yield: 58% (42 mg). R_f (PE/Et_2O, 67/33): 0.51.

White solid; **m.p.**: 42-43 °C.

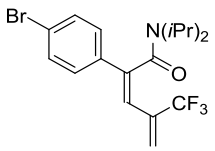
IR: 2969, 2937, 1612, 1338, 1175, 1118, 957, 789, 701.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.41-7.28 (m, 3H), 6.35 (s, 1H), 6.19 (s, 1H), 5.91 (s, 1H), 4.00-3.82 (m, 1H), 3.50-3.33 (m, 1H), 1.55 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.9, 141.7, 137.5, 134.9, 133.6 (q, *J* = 30.0 Hz), 130.1, 129.0, 126.0, 124.2, 123.0 (q, *J* = 274.4 Hz), 121.4 (q, *J* = 5.2 Hz), 116.5 (q, *J* = 1.8 Hz), 51.1, 45.7, 20.8, 20.6, 20.2, 20.1.

HRMS (ESI^+): calcd for $C_{18}H_{22}ClF_3NO$ *m/z* 360.1342 $[M+H]^+$, found 360.1328 (-3.9 ppm).



13h

(*Z*)-2-(4-Bromophenyl)-*N*,*N*-diisopropyl-4-(trifluoromethyl)penta-2,4-dienamide (13h): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 85/15). Yield: 62% (50 mg). R_f (PE/Et_2O, 67/33): 0.55.

White solid; **m.p.**: 44-45 °C.

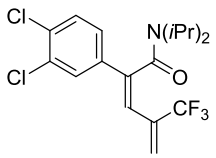
IR: 2976, 2937, 1614, 1167, 1120, 1006, 823, 853.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.34 (s, 1H), 6.18 (s, 1H), 5.90 (s, 1H), 3.99-3.82 (m, 1H), 3.51-3.28 (m, 1H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.1, 141.9, 134.6, 133.6 (q, *J* = 29.9 Hz), 132.1, 127.6, 123.2, 123.0 (q, *J* = 274.3 Hz), 121.2 (q, *J* = 5.3 Hz), 115.8 (q, *J* = 1.8 Hz), 51.1, 45.7, 20.8, 20.6, 20.2, 20.1.

HRMS (ESI^+): calcd for $C_{18}H_{21}BrF_3NONa$ *m/z* 426.0656 $[M+Na]^+$, found 426.0648 (-1.9 ppm).



13i

(*Z*)-2-(3,4-Dichlorophenyl)-*N*,*N*-diisopropyl-4-(trifluoromethyl)penta-2,4-dienamide (13i): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 97/3 to 82/18). Yield: 66% (52 mg). R_f (PE/Et_2O, 67/33): 0.49.

White solid; **m.p.**: 54-55 °C.

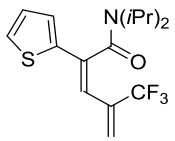
IR: 2983, 2937, 1611, 1454, 1372, 1336, 1175, 1119, 956, 831.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.34 (s, 1H), 6.19 (s, 1H), 5.92 (s, 1H), 3.97-3.79 (m, 1H), 3.52-3.32 (m, 1H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.6, 140.8, 135.7, 133.5 (q, *J* = 30.2 Hz), 133.2, 133.1, 130.8, 127.8, 125.3, 122.9 (q, *J* = 274.4 Hz), 121.7 (q, *J* = 5.2 Hz), 116.8 (q, *J* = 1.8 Hz), 51.2, 45.8, 20.8, 20.7, 20.2, 20.1.

HRMS (ESI^+): calcd for $C_{18}H_{21}Cl_2F_3NO$ *m/z* 394.0952 $[M+H]^+$, found 394.0945 (-1.8 ppm).



13j

(*E*)-*N*,*N*-Diisopropyl-2-(thiophen-2-yl)-4-(trifluoromethyl)penta-2,4-dienamide (13j): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 97/3 to 85/15). Yield: 30% (20 mg). R_f (PE/Et_2O, 67/33): 0.50.

White solid; **m.p.**: 46-47 °C.

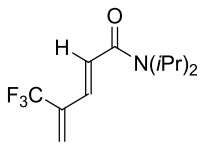
IR: 2976, 2930, 1614, 1447, 1371, 1327, 1172, 1119, 947, 709.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.27 (d, *J* = 5.7 Hz, 1H), 7.05 (d, *J* = 3.6 Hz, 1H), 7.03-6.96 (m, 1H), 6.25 (s, 1H), 6.12 (s, 1H), 5.86 (s, 1H), 4.09-3.92 (m, 1H), 3.53-3.37 (m, 1H), 1.57 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.5, 140.5, 137.2, 133.6 (q, *J* = 30.0 Hz), 127.8, 126.9, 126.3, 122.9 (q, *J* = 274.4 Hz), 120.5 (q, *J* = 5.2 Hz), 113.5 (q, *J* = 1.8 Hz), 51.2, 45.7, 20.9, 20.8, 20.2, 20.2.

HRMS (ESI$^+$): calcd for $C_{16}H_{21}F_3NOS$ *m/z* 332.1296 $[M+H]^+$, found 332.1285 (-3.3 ppm).



13k

(*E*)-*N*,*N*-Diisopropyl-4-(trifluoromethyl)penta-2,4-dienamide (13k): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 88/12). Yield: 28% (42 mg, based on a 0.6 mmol scale). R_f (PE/Et_2O, 67/33): 0.45.

Yellow oil.

IR: 2970, 2937, 1651, 1621, 1440, 1327, 1164, 1116, 1044, 964.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.13 (d, *J* = 15.9 Hz, 1H), 6.57 (d, *J* = 15.9 Hz, 1H), 5.94 (s, 1H), 5.76 (s, 1H), 4.06-3.81 (m, 2H), 1.41-1.19 (m, 12H).

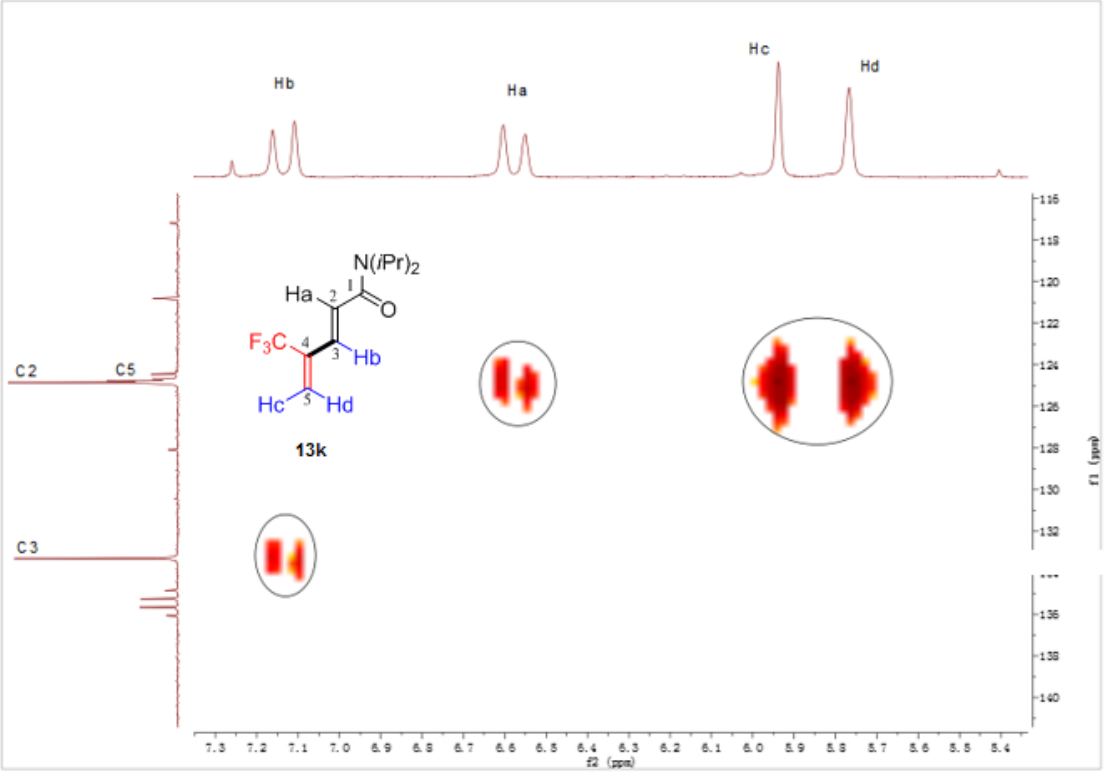
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -66.3 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.1, 135.5 (q, *J* = 30.4 Hz), 133.3, 124.9, 124.8 (q, *J* = 5.5 Hz), 122.6 (q, *J* = 274.3 Hz), 47.6, 45.9, 21.7, 21.7, 20.4, 20.4.

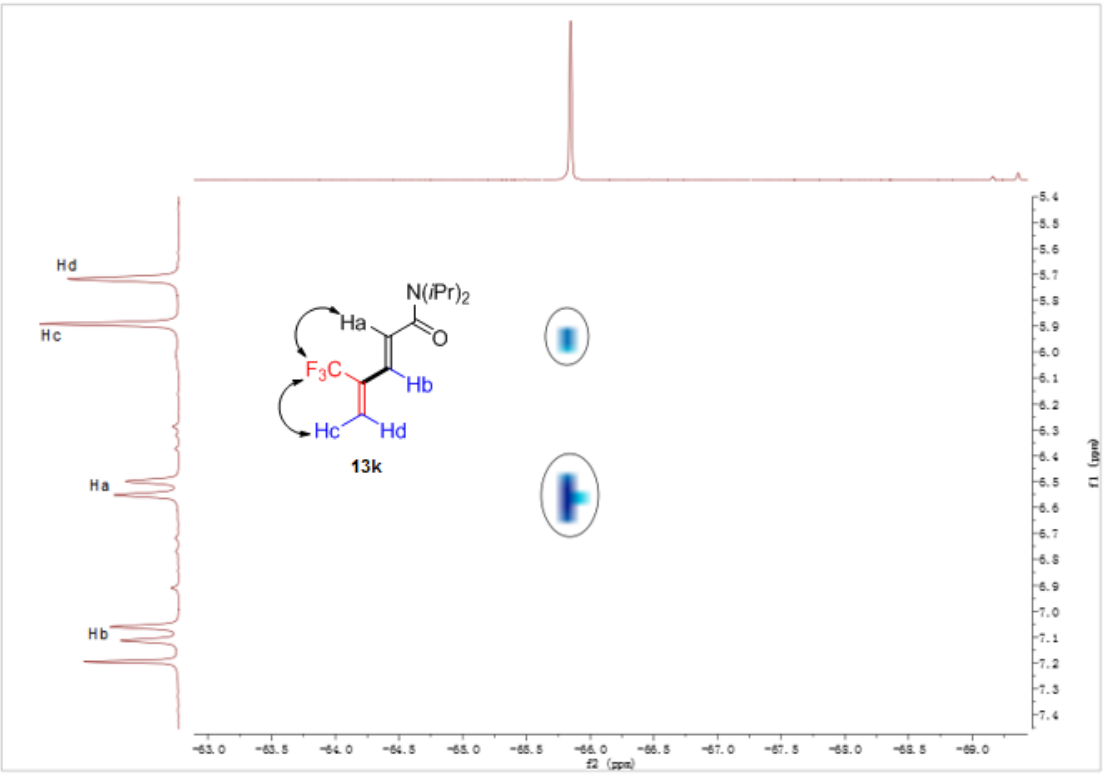
HRMS (ESI^+): calcd for $C_{12}H_{19}F_3NO$ *m/z* 250.1419 $[M+H]^+$, found 250.1415 (-1.6 ppm).

The structure of **13k** was confirmed by 2D NMR experiments.

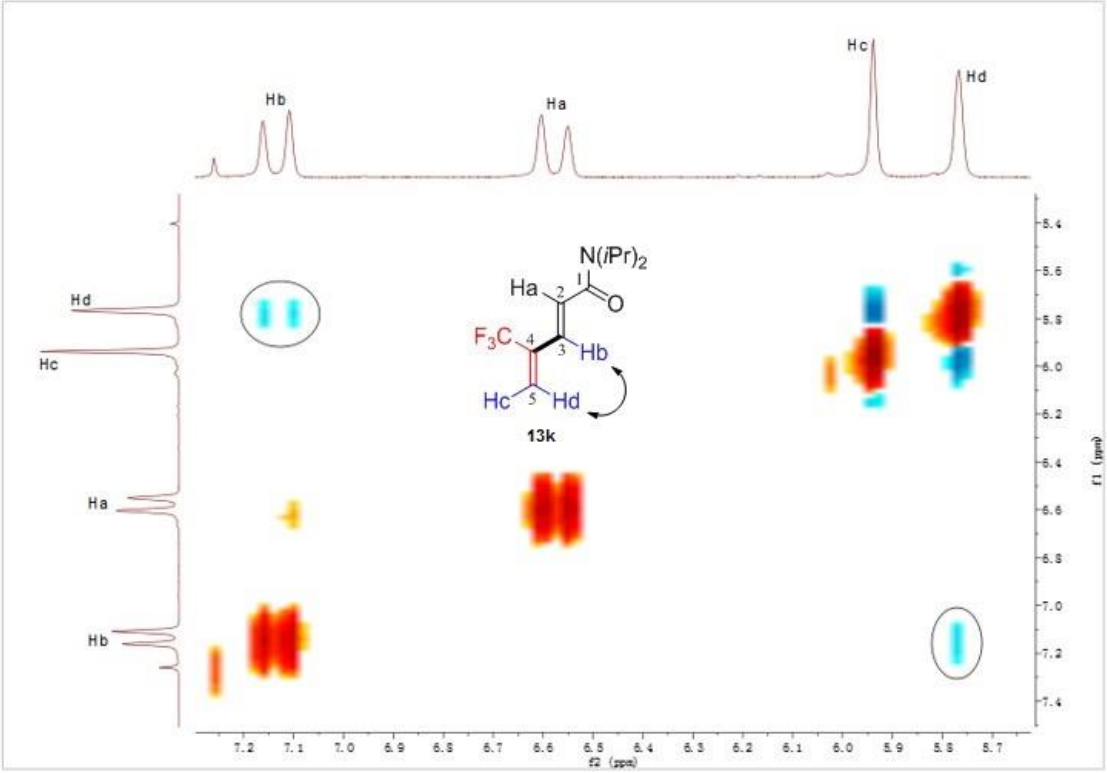
The HMQC 2D NMR of **13k**:

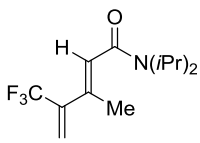


The HOESY 2D NMR of **13k**:



The NOESY 2D NMR of **13k**:





13l

(*E*)-*N*,*N*-Diisopropyl-3-methyl-4-(trifluoromethyl)penta-2,4-dienamide (13l):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 97/3 to 89/11). Yield: 39% (61 mg, based on a 0.6 mmol scale). R_f (PE/Et_2O, 67/33): 0.49.

Yellow oil.

IR: 2972, 2935, 1629, 1439, 1336, 1304, 1158, 1120, 1094, 942.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 6.15 (s, 1H), 5.81 (s, 1H), 5.62 (s, 1H), 4.02-3.82 (m, 1H), 3.63-3.39 (m, 1H), 1.92 (s, 3H), 1.38 (m, 6H), 1.12 (m, 6H).

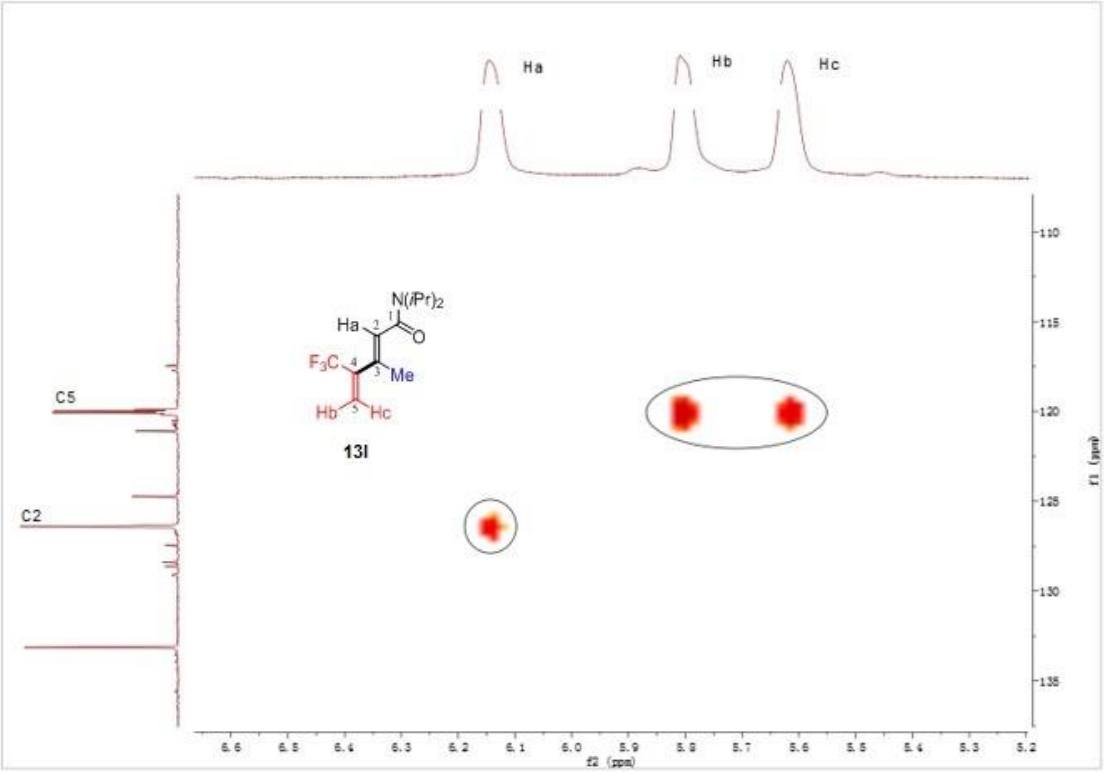
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -64.0 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.9, 139.0 (q, *J* = 28.9 Hz), 133.1, 126.4, 122.9 (q, *J* = 274.8 Hz), 120.0 (q, *J* = 6.0 Hz), 49.7, 45.5, 20.8, 20.8, 20.3, 20.3, 16.5.

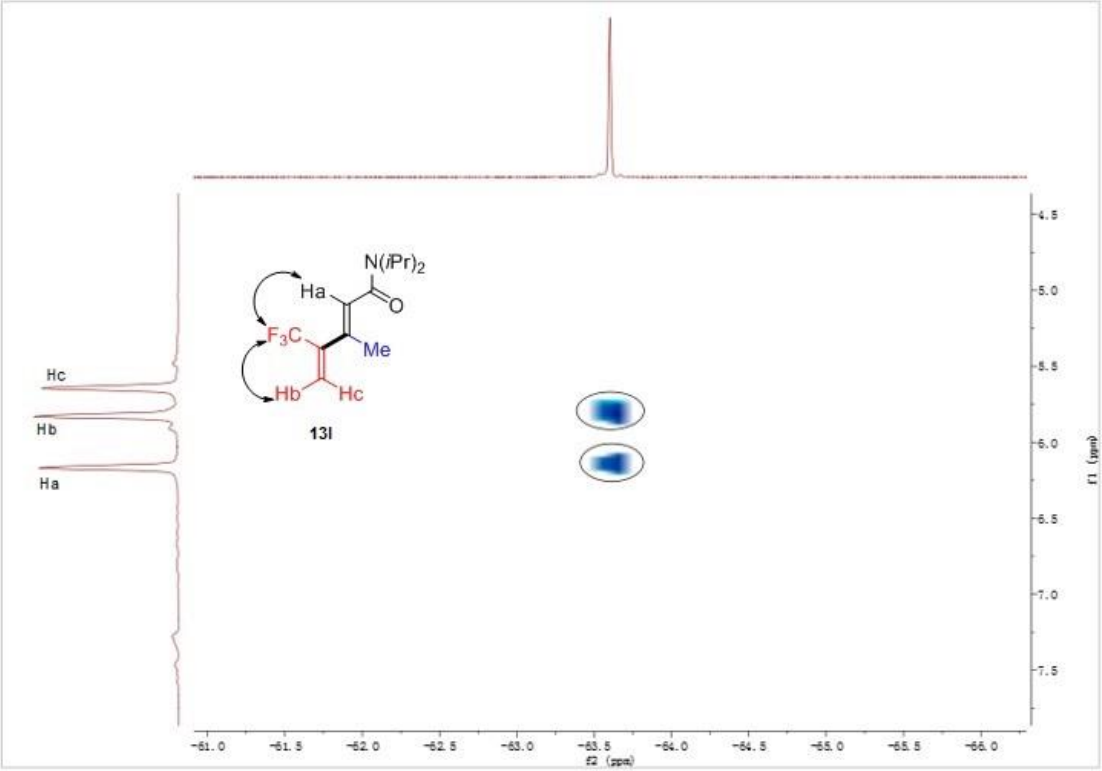
HRMS (ESI^+): calcd for $C_{13}H_{21}F_3NO$ *m/z* 264.1575 $[M+H]^+$, found 264.1577 (0.8 ppm).

The structure of **13l** was confirmed by 2D NMR experiments.

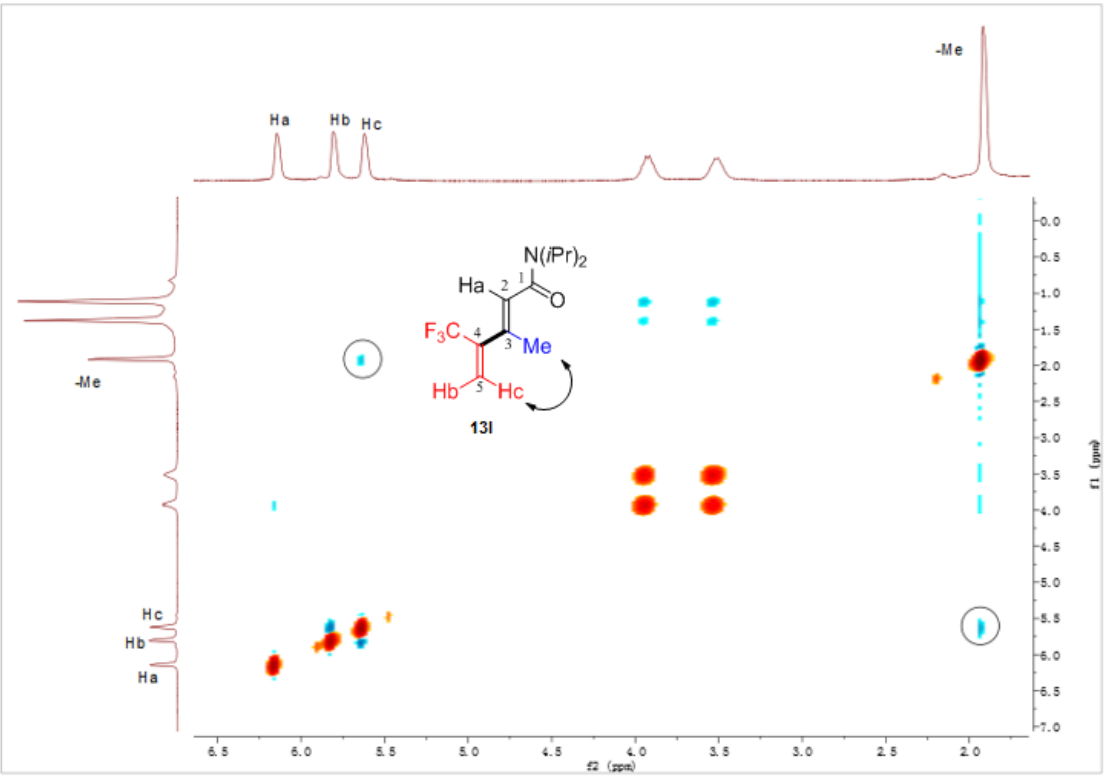
The HMQC 2D NMR of **13l**:

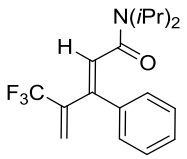


The HOESY 2D NMR of **13l**:



The NOESY 2D NMR of **13l**:





13m

(*E*)-*N*,*N*-Diisopropyl-3-phenyl-4-(trifluoromethyl)penta-2,4-dienamide (13m):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 88/12). Yield: 18% (35 mg, based on a 0.6 mmol scale). R_f (PE/Et_2O, 67/33): 0.53.

Yellow solid; **m.p.**: 38-39 °C.

IR: 2966, 2934, 1644, 1596, 1437, 1335, 1128, 1045, 976, 762.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.56-7.42 (m, 2H), 7.35-7.20 (m, 3H), 6.78 (s, 1H), 5.91 (s, 1H), 5.70 (s, 1H), 3.93-3.78 (m, 1H), 3.76-3.23 (m, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.46 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.45 (d, *J* = 6.6 Hz, 3H).

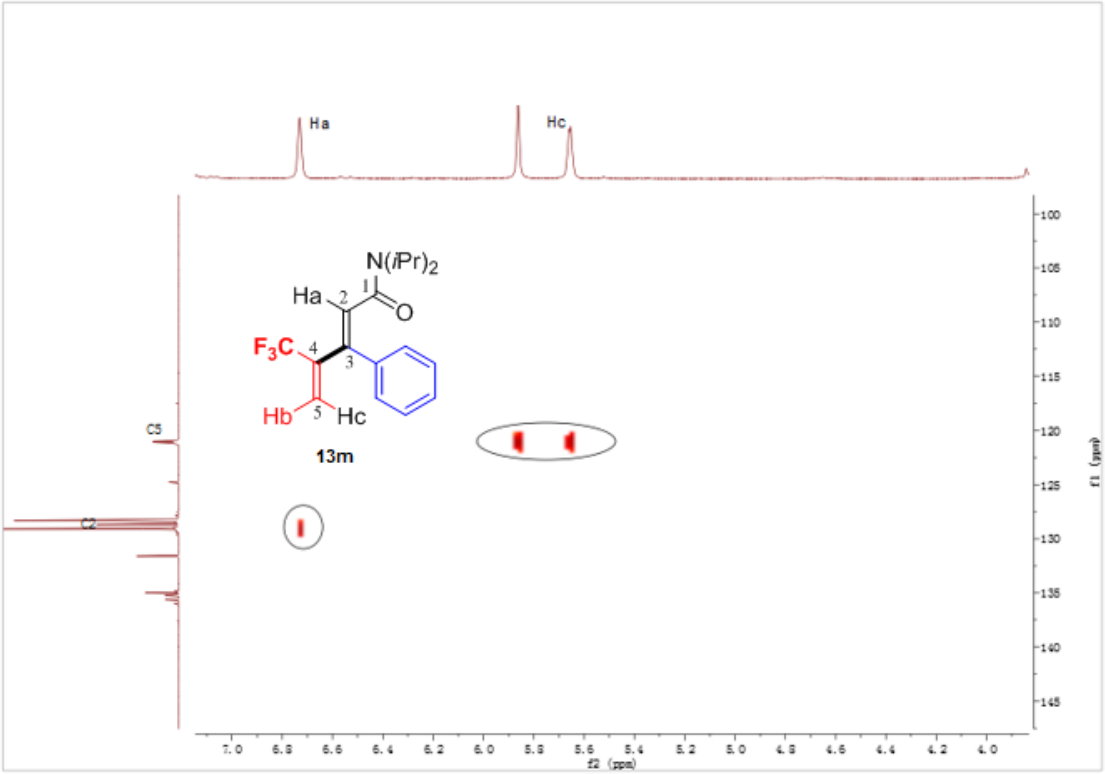
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -63.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.0, 135.4 (q, *J* = 29.4 Hz), 135.0, 131.6, 129.1, 129.1, 128.7, 128.3, 123.0 (q, *J* = 275.2 Hz), 121.0 (q, *J* = 5.8 Hz), 50.9, 45.9, 20.9, 20.1, 20.0, 19.6.

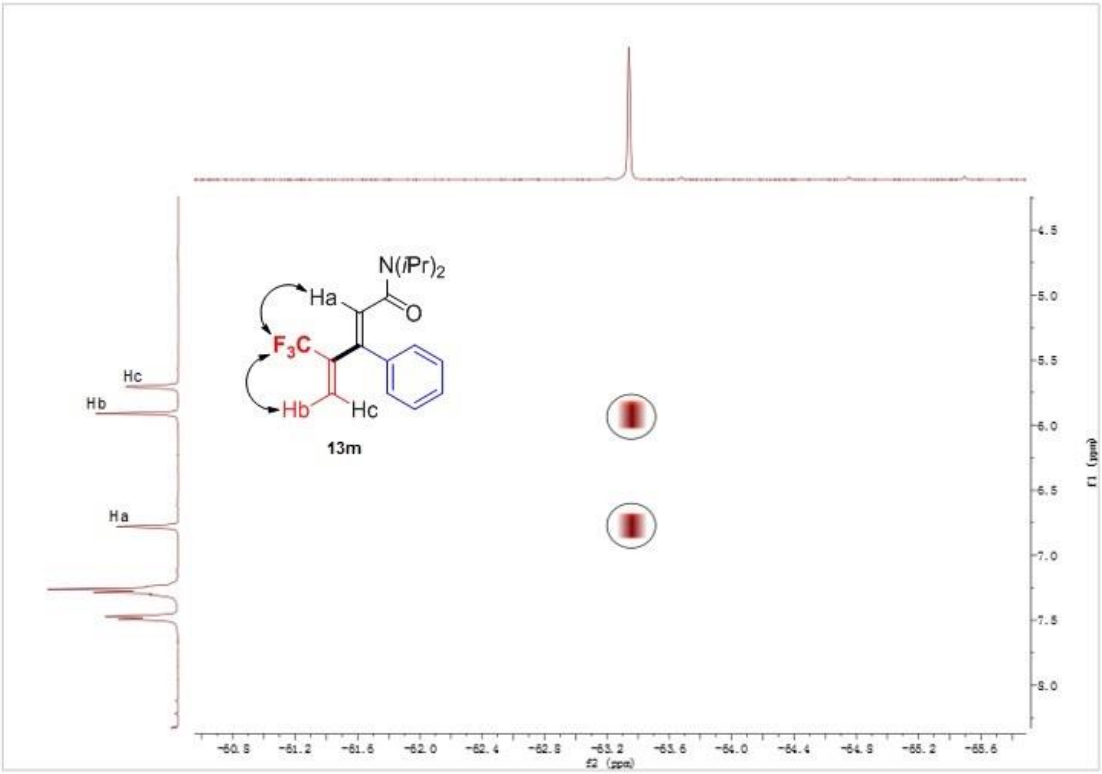
HRMS (ESI^+): calcd for $C_{18}H_{23}F_3NO$ *m/z* 326.1732 $[M+H]^+$, found 326.1731 (-0.3 ppm).

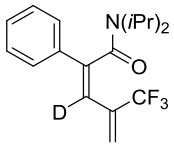
The structure of **13m** was confirmed by 2D NMR experiments.

The HMQC 2D NMR of **13m**:



The HOESY 2D NMR of **13m**:





[D]-**13a**

(*Z*)-*N*,*N*-diisopropyl-2-phenyl-4-(trifluoromethyl)penta-2,4-dienamide ([D]-13a): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 85/15). Yield: 62% (40 mg). R_f (PE/Et_2O, 67/33): 0.52.

White solid; **m.p.**: 50-51 °C.

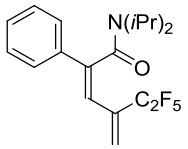
IR: 2973, 2937, 1618, 1442, 1333, 1170, 1120, 1033, 953, 692.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.50 (d, *J* = 6.6 Hz, 2H), 7.43-7.28 (m, 3H), 6.37 (s, 0.08H), 6.20 (s, 1H), 5.88 (s, 1H), 4.04-3.84 (m, 1H), 3.49-3.32 (m, 1H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.49 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.6, 143.0, 135.7, 133.8 (q, *J* = 31.5 Hz), 128.95, 128.87, 126.0, 123.1 (q, *J* = 274.4 Hz), 120.8 (q, *J* = 5.2 Hz), 115.4, 51.0, 45.6, 20.8, 20.5, 20.3, 20.2.

HRMS (ESI^+): calcd for $C_{18}H_{22}DF_3NO$ *m/z* 327.1795 $[M+H]^+$, found 327.1794 (-0.3 ppm).



22a

(*Z*)-5,5,6,6,6-Pentafluoro-*N*,*N*-diisopropyl-4-methylene-2-phenylhex-2-enamide (22a): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 89/11). Yield: 49% (37 mg). R_f (PE/Et_2O, 67/33): 0.70.

Yellow solid; **m.p.**: 60-61 °C.

IR: 2931, 2854, 1622, 1438, 1328, 1166, 1123, 895, 763, 691.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.52-7.44 (m, 2H), 7.42-7.29 (m, 3H), 6.40 (s, 1H), 6.32 (s, 1H), 5.89 (s, 1H), 3.99-3.80 (m, 1H), 3.48-3.32 (m, 1H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H).

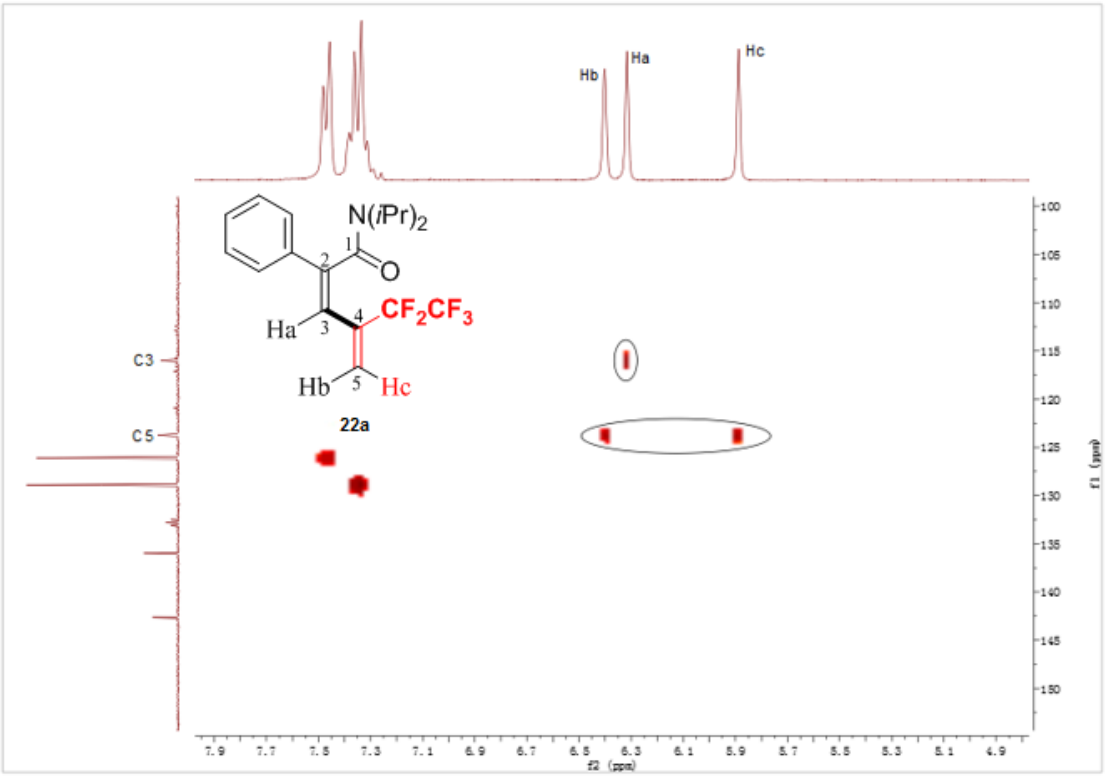
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -84.4 (s, 3F), -117.0 (d, *J* = 28.5 Hz, 2F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.6, 142.8, 136.0, 132.9 (t, *J* = 21.7 Hz), 128.9, 128.8, 126.0, 123.6 (t, *J* = 7.8 Hz), 119.0 (qt, *J* = 286.6 Hz, *J* = 38.8 Hz), 116.0, 112.6 (tq, *J* = 254.7 Hz, *J* = 37.9 Hz), 50.9, 45.6, 20.7, 20.3, 20.3, 20.0.

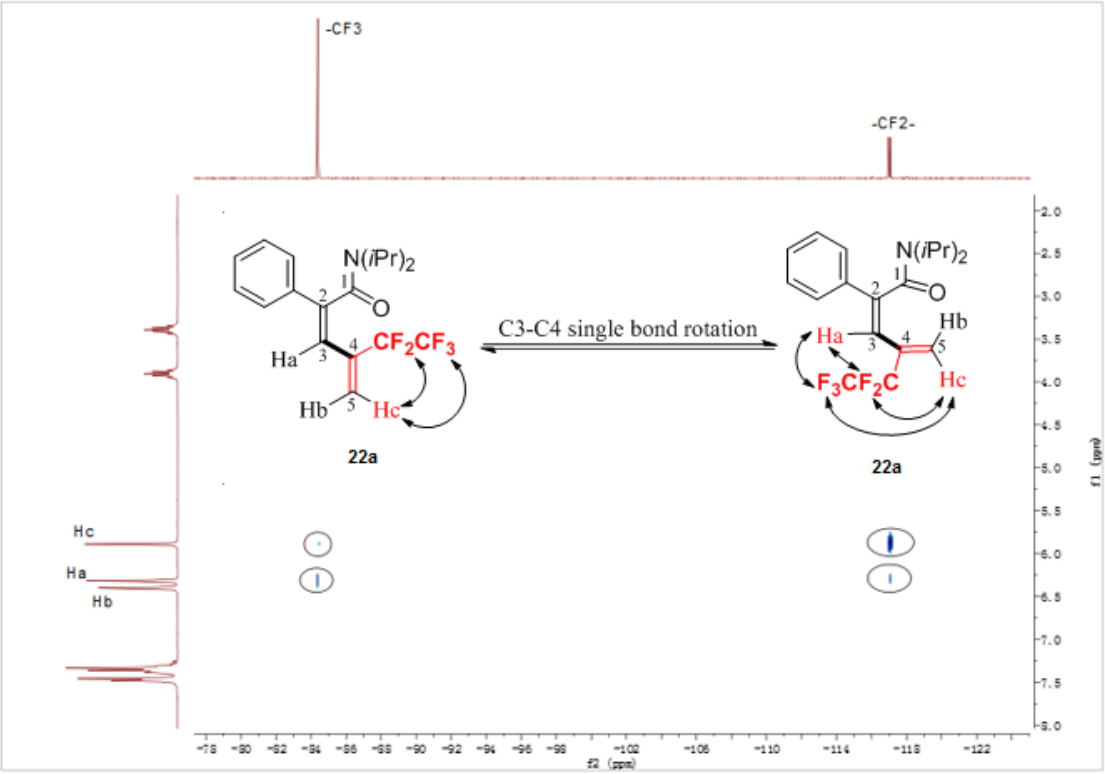
HRMS (ESI^+): calcd for $C_{19}H_{23}F_5NO$ *m/z* 376.1700 $[M+H]^+$, found 376.1717 (4.5 ppm).

The structure of **22a** was confirmed by 2D NMR experiments.

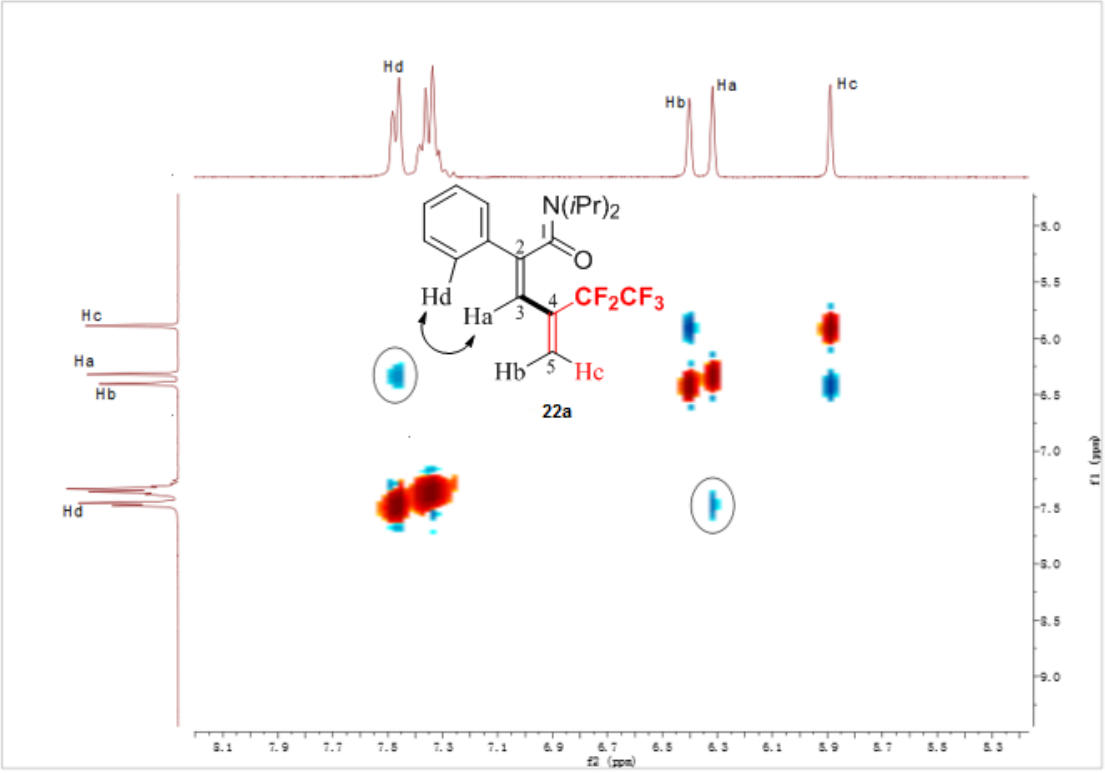
The HMQC 2D NMR of **22a**:

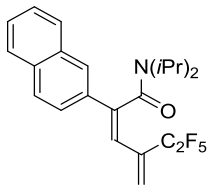


The HOESY 2D NMR of **22a**:



The NOESY 2D NMR of **22a**:





22b

(*Z*)-5,5,6,6,6-Pentafluoro-*N*,*N*-diisopropyl-4-methylene-2-(naphthalen-2-yl)hex-2-enamide (22b): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 88/12). Yield: 45% (38 mg). R_f (PE/Et_2O, 67/33): 0.75.

Yellow solid; **m.p.**: 76-77 °C.

IR: 2981, 1614, 1446, 1207, 1117, 1020, 823, 756.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7. 90 (s, 1H), 7.88-7.79 (m, 3H), 7.67-7.59 (m, 1H), 7.54-7.46 (m, 2H), 6.47 (s, 2H), 5.94 (s, 1H), 4.12-3.84 (m, 1H), 3.56-3.32 (m, 1H),

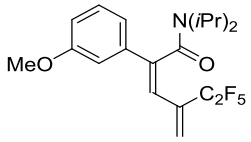
1.63 (d, *J* = 6.6 Hz, 3H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -84.3 (s, 3F), -116.9 (d, *J* = 23.4 Hz, 2F).

Selected **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 167.7, 142.6, 133.4, 133.3, 133.2, 132.9 (t, *J* = 21.7 Hz), 128.7, 128.5, 127.6, 126.7, 126.6, 126.1, 123.8 (t, *J* = 7.7 Hz), 123.1, 116.3, 51.0, 45.7, 20.9, 20.5, 20.4, 20.2 (-CF_2- and -CF_3 are not visible).

HRMS (ESI$^+$): calcd for $C_{23}H_{25}F_5NO$ *m/z* 426.1856 $[M+H]^+$, found 426.1868 (2.8 ppm).

The structure of **22b** has been confirmed by X-ray analysis.



22d

(*Z*)-5,5,6,6,6-Pentafluoro-N,N-diisopropyl-2-(3-methoxyphenyl)-4-methylenehex-2-enamide (22d): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 88/12). Yield: 43% (35 mg). R_f (PE/Et_2O, 67/33): 0.60.

Yellow solid; **m.p.**: 62-63 °C.

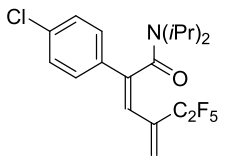
IR: 2965, 1615, 1595, 1456, 1199, 1180, 1119, 1024, 952, 790.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.22 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.95 (s, 1H), 6.83 (m, 1H), 6.34 (s, 1H), 6.26 (s, 1H), 5.84 (s, 1H), 3.91-3.80 (m, 1H), 3.76 (s, 3H), 3.41-3.29 (m, 1H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -84.4 (s, 3F), -117.0 (d, *J* = 29.9 Hz, 2F).

Selected **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 167.5, 159.8, 142.5, 137.4, 132.8 (t, *J* = 21.9 Hz), 129.9, 123.8 (t, *J* = 7.8 Hz), 118.5, 116.2, 114.6, 111.5, 55.2, 50.9, 45.6, 20.8, 20.4, 20.3, 20.0 (-CF_2- and -CF_3 are not visible).

HRMS (ESI$^+$): calcd for $C_{20}H_{25}F_5NO_2$ *m/z* 406.1805 [M+H]$^+$, found 406.1809 (0.5 ppm).



22f

(*Z*)-2-(4-Chlorophenyl)-5,5,6,6,6-pentafluoro-*N*,*N*-diisopropyl-4-methylenehex-2-enamide (22f): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 88/12). Yield: 30% (25 mg). R_f (PE/Et_2O, 67/33): 0.65.

Yellow solid; **m.p.**: 62-63 °C.

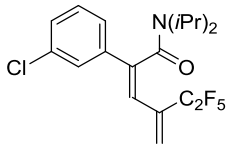
IR: 2984, 1613, 1325, 1209, 1147, 1121, 1021, 954, 817.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.38 (s, 1H), 6.28 (s, 1H), 5.90 (s, 1H), 3.97-3.78 (m, 1H), 3.48-3.31 (m, 1H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -84.4 (s, 3F), -117.0 (d, *J* = 28.8 Hz, 2F).

Selected **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 167.2, 141.4, 134.9, 134.5, 132.6 (t, *J* = 21.9 Hz), 129.1, 127.3, 124.1 (t, *J* = 7.8 Hz), 116.4, 51.0, 45.7, 20.8, 20.5, 20.3, 20.1. (-CF_2- and -CF_3 are not visible).

HRMS (ESI$^+$): calcd for $C_{19}H_{22}ClF_5NO$ *m/z* 410.1310 [M+H]$^+$, found 410.1315 (0.5 ppm).



22g

(*Z*)-2-(3-Chlorophenyl)-5,5,6,6,6-pentafluoro-*N*,*N*-diisopropyl-4-methylenehex-2-enamide (22g): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 88/12). Yield: 38% (31 mg). R_f (PE/Et_2O, 67/33): 0.62.

Yellow solid; **m.p.**: 64-65 °C.

IR: 2967, 1616, 1371, 1322, 1203, 1123, 1023, 952, 789, 695.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.38-7.27 (m, 3H), 6.40 (s, 1H), 6.30 (s, 1H), 5.92 (s, 1H), 3.96-3.78 (m, 1H), 3.49-3.32 (m, 1H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H).

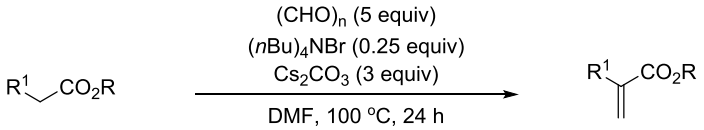
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -84.4 (s, 3F), -116.9 (d, *J* = 29.9 Hz, 2F).

Selected **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 167.0, 141.3, 137.8, 134.9, 132.6 (t, *J* = 21.9 Hz), 130.1, 128.9, 126.0, 124.4 (t, *J* = 7.8 Hz), 124.3, 117.1, 51.0, 45.7, 20.8, 20.4, 20.2, 20.0. (-CF_2- and -CF_3 are not visible).

HRMS (ESI$^+$): calcd for $C_{19}H_{22}ClF_5NO$ *m/z* 410.1310 $[M+H]^+$, found 410.1313 (0.7 ppm).

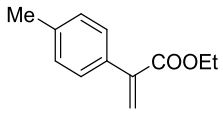
1.3 Functionalization of α,β-unsaturated esters

1.3.1 General procedure for the synthesis of α,β-unsaturated esters 26, 28-30



26, 28-30

Synthetic procedure: The ester starting materials (8 mmol), $(CHO)_n$ (40 mmol, 5 equiv), $(n\text{Bu})_4\text{NBr}$ (2 mmol, 0.25 equiv) and Cs_2CO_3 (24 mmol, 3 equiv) was dissolved in DMF (100 mL) and stirred at 100 °C for 24 h. Water (100 mL) was added and the resulting mixture was extracted with Et_2O (3 × 150 mL). Removal of the solvent under vacuum and purification of the residue by Biotage and recrystallization if necessary afforded the desired product **26**, **28-30**.



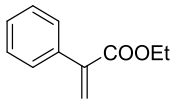
26

Ethyl 2-(*p*-tolyl)acrylate (26):

Colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.39 (d, *J* = 0.9 Hz, 1H), 5.92 (d, *J* = 0.9 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.4, 141.1, 137.5, 133.6, 128.4, 127.8, 125.1, 60.6, 20.7, 13.8.

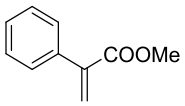


28

Ethyl 2-phenylacrylate (28):

Colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.49-7.27 (m, 5H), 6.26 (d, *J* = 0.9 Hz, 1H), 5.80 (d, *J* = 0.9 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).



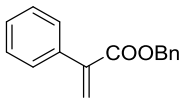
29

Methyl 2-phenylacrylate (29):

Colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.45-7.05 (m, 5H), 6.21 (s, 1H), 5.72 (s, 1H), 3.64 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.9, 141.1, 136.5, 128.0, 127.9, 127.8, 126.5, 51.8.



30

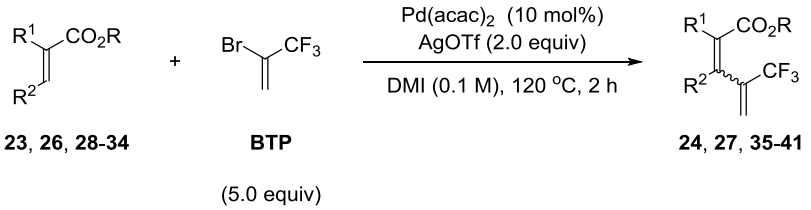
Benzyl 2-phenylacrylate (30):

Colorless oil.

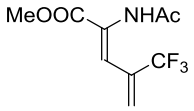
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.75-7.37 (m, 10H), 6.56 (s, 1H), 6.05 (s, 1H), 5.43 (s, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.1, 140.9, 136.3, 135.7, 128.3, 128.1, 127.9, 127.84, 127.82, 126.7, 66.4 (Note that one carbon is missing).

1.3.2 General procedure for the Pd-catalyzed functionalization of the amino acid derivative 23 and the α,β-unsaturated esters 26, 28-34 with BTP



A dried tube was loaded with $Pd(acac)_2$ (6.0 mg, 0.02 mmol, 0.1 equiv), AgOTf (102.8 mg, 0.4 mmol, 2 equiv) and substrate (0.2 mmol, 1 equiv) under Ar. Then DMI (2 mL) and BTP (1 mmol, 5 equiv) were added. The tube was sealed with a rubber septum and the suspension was stirred at 120 °C for 2 h. The reaction mixture was diluted with diethyl ether (10 mL) and filtered through a plug of Celite®. The solution was washed with brine (3 × 5 mL) and dried with $MgSO_4$. The solvents were removed under vacuum and the crude was purified by a flash chromatography with a Biotage Isolera One Flash Purification System.



(*Z*)-24

(*Z*)-Methyl-2-acetamido-4-(trifluoromethyl)penta-2,4-dienoate ((*Z*)-24):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 88/12). Yield: 45% (106 mg, based on a 1.0 mmol scale). R_f (PE/Et_2O, 33/67): 0.20.

Yellow solid; **m.p.**: 60-61 °C.

IR: 3244, 2955, 1733, 1664, 1509, 1253, 1176, 1104, 1128, 966, 759.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7. 67 (brs, 1H), 6.72 (s, 1H), 6.06 (s, 1H), 5.78 (s, 1H), 3.78 (s, 3H), 2.05 (s, 3H).

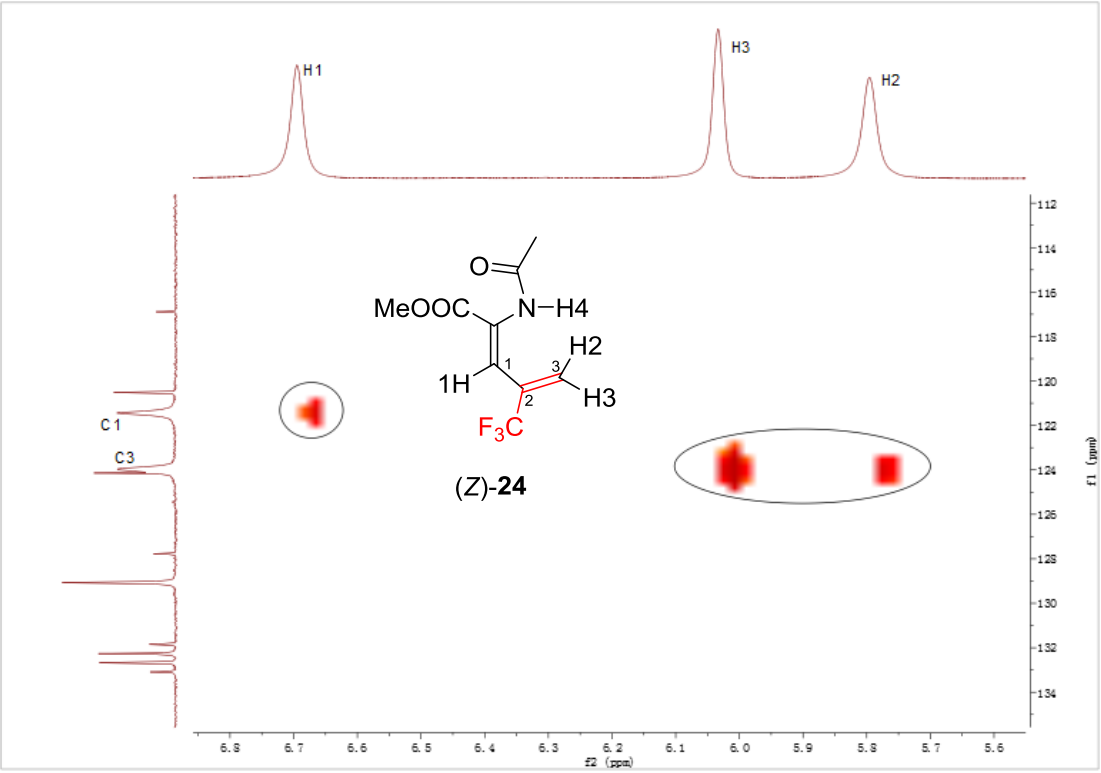
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.4 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.0, 164.7, 132.4 (q, *J* = 31.2 Hz), 129.0, 123.9, 122.3 (q, *J* = 274.0 Hz), 121.3, 52.7, 22.8.

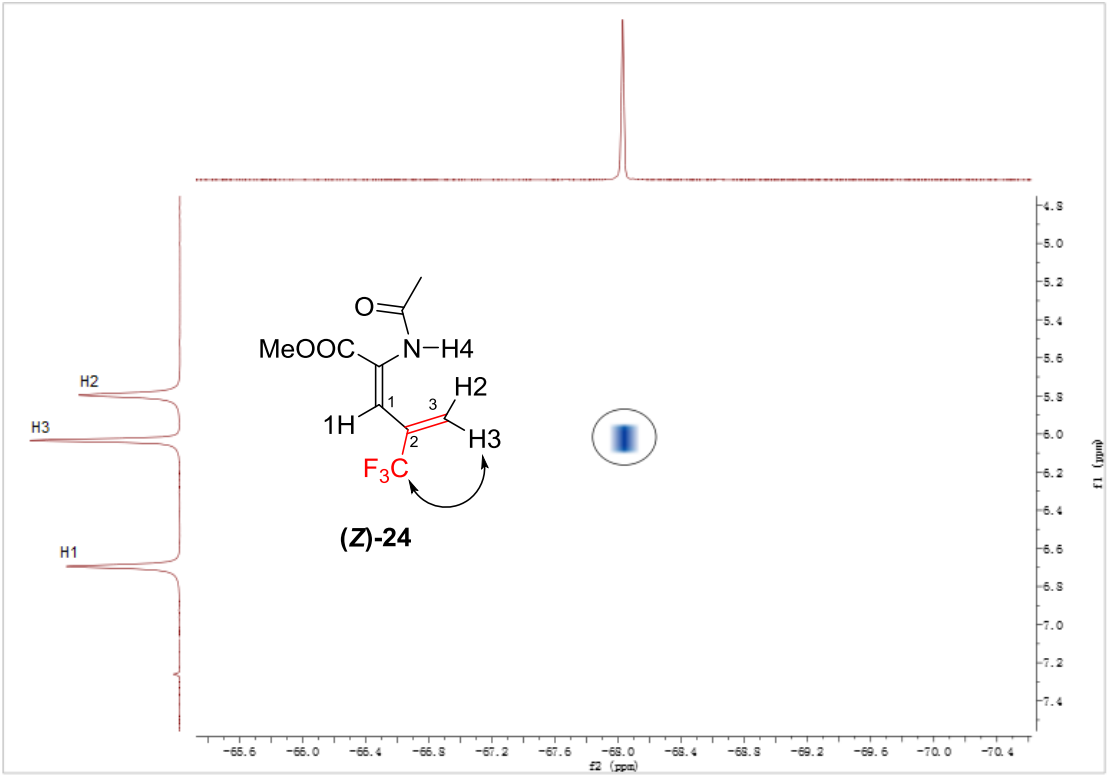
HRMS (ESI$^+$): calcd for $C_9H_{11}F_3NO_3$ *m/z* 238.0691 $[M+H]^+$, found 238.0688 (-1.3 ppm).

The structure of **(*Z*)-24** has been confirmed by X-ray analysis.

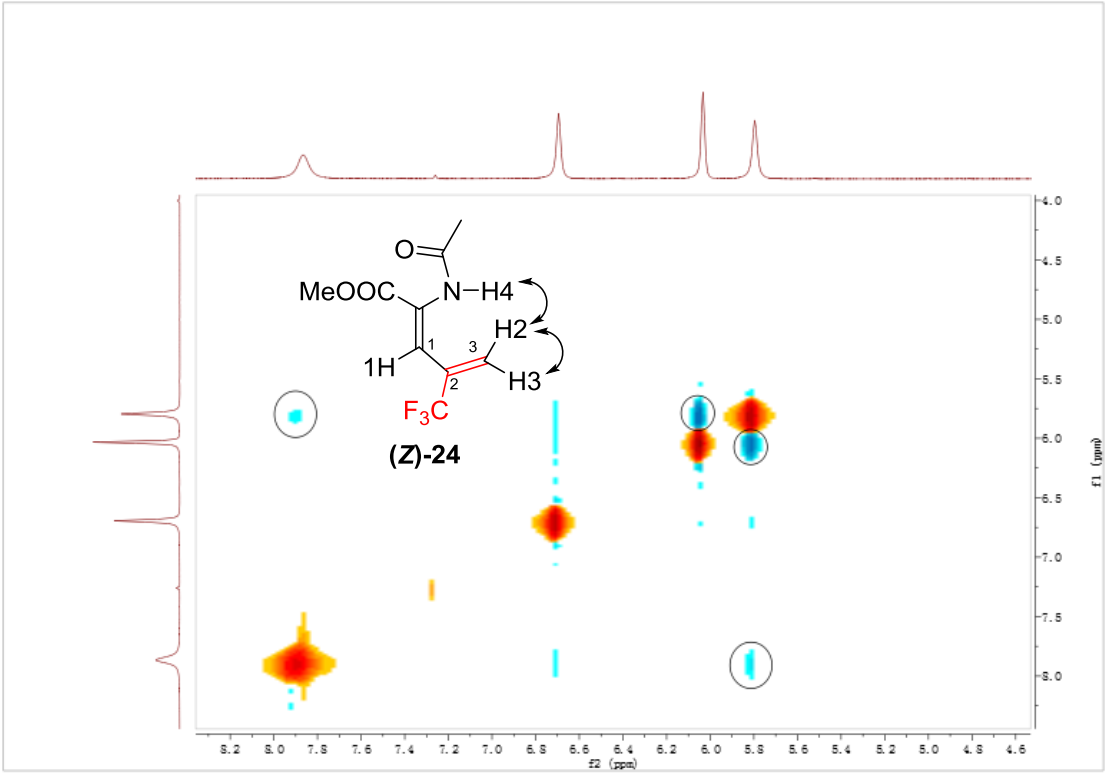
The HMQC 2D NMR of (*Z*)-**24**:

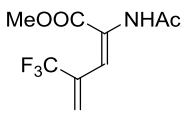


The HOESY 2D NMR of (*Z*)-**24**:



The NOESY 2D NMR of (*Z*)-**24**:





(*E*)-**24**

(*E*)-Methyl-2-acetamido-4-(trifluoromethyl)penta-2,4-dienoate ((*E*)-24):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 88/12). Yield: 11% (26 mg, based on a 1.0 mmol scale). R_f (PE/Et_2O, 33/67): 0.25.

Yellow solid; **m.p.**: 50-51 °C.

IR: 3288, 2955, 1741, 1671, 1376, 1281, 1167, 1124, 951, 877.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7. 91 (brs, 1H), 7.15 (s, 1H), 5.79 (s, 1H), 5.46 (s, 1H), 3.75 (s, 3H), 2.10 (s, 3H).

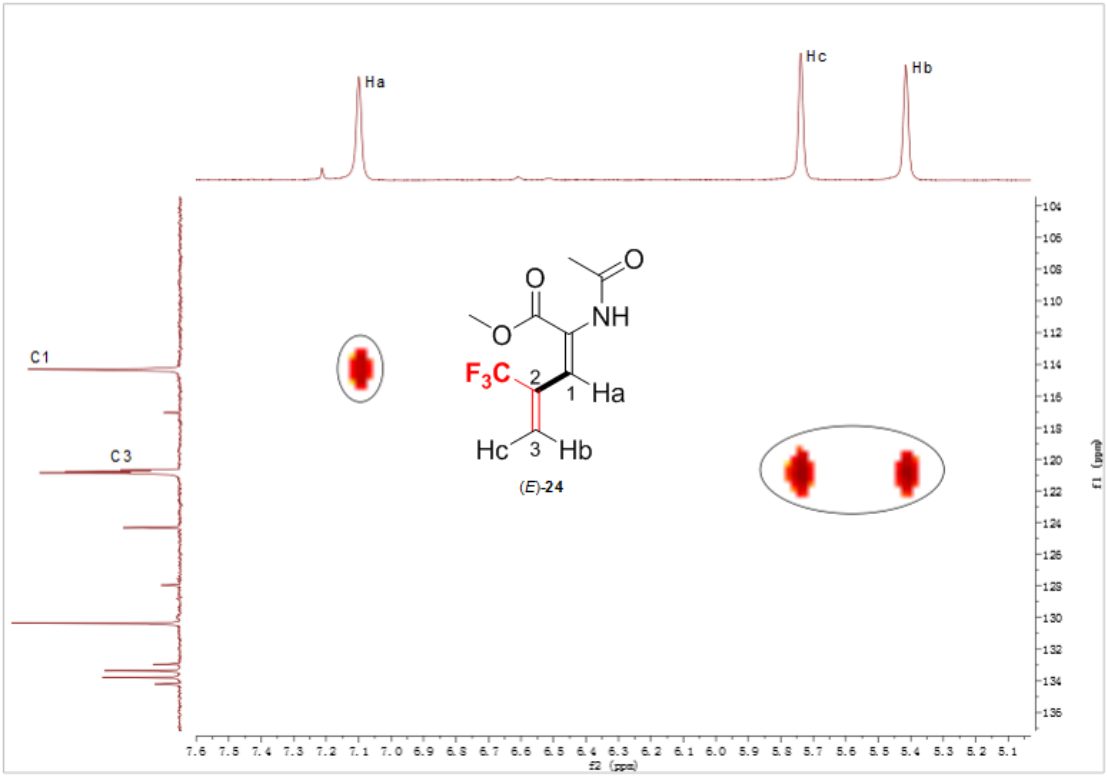
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.2 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.0, 164.3, 133.3 (q, *J* = 31.6 Hz), 130.3, 122.5 (q, *J* = 273.9 Hz), 120.8 (q, *J* = 5.0 Hz), 114.3, 52.6, 24.1.

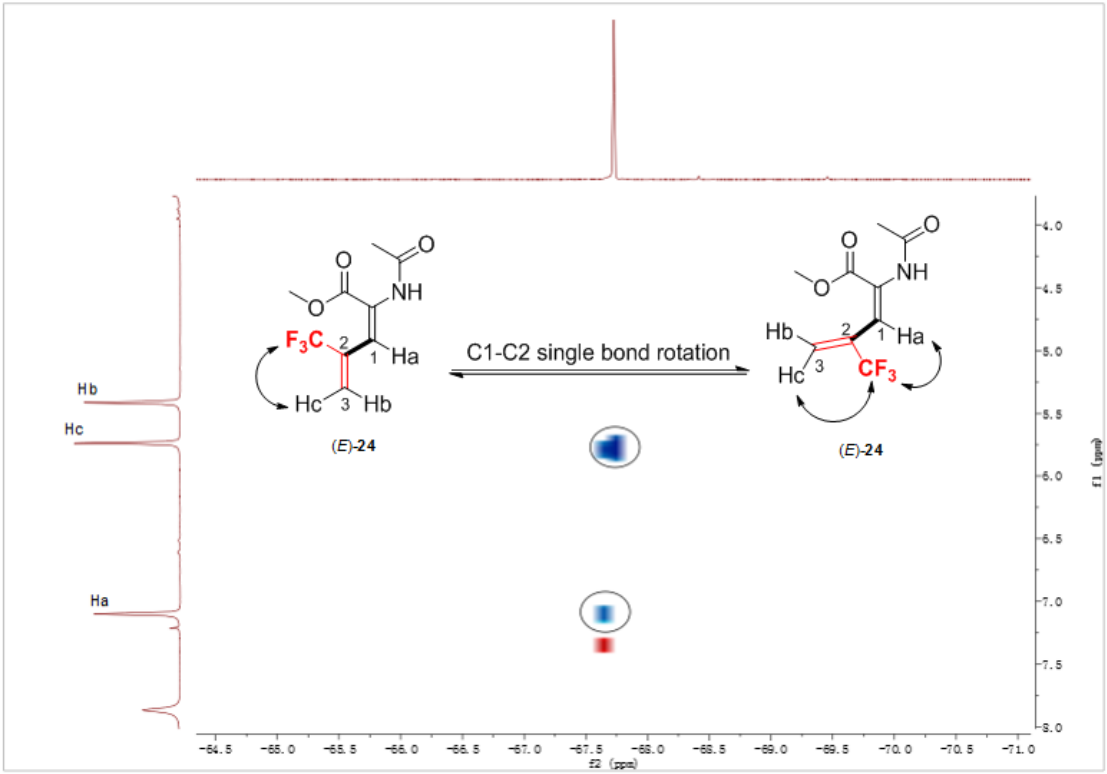
HRMS (ESI^+): calcd for $C_9H_{11}F_3NO_3$ *m/z* 238.0691 $[M+H]^+$, found 238.0684 (-2.9 ppm).

The structure of (*E*)-**24** was confirmed by NMR experiment.

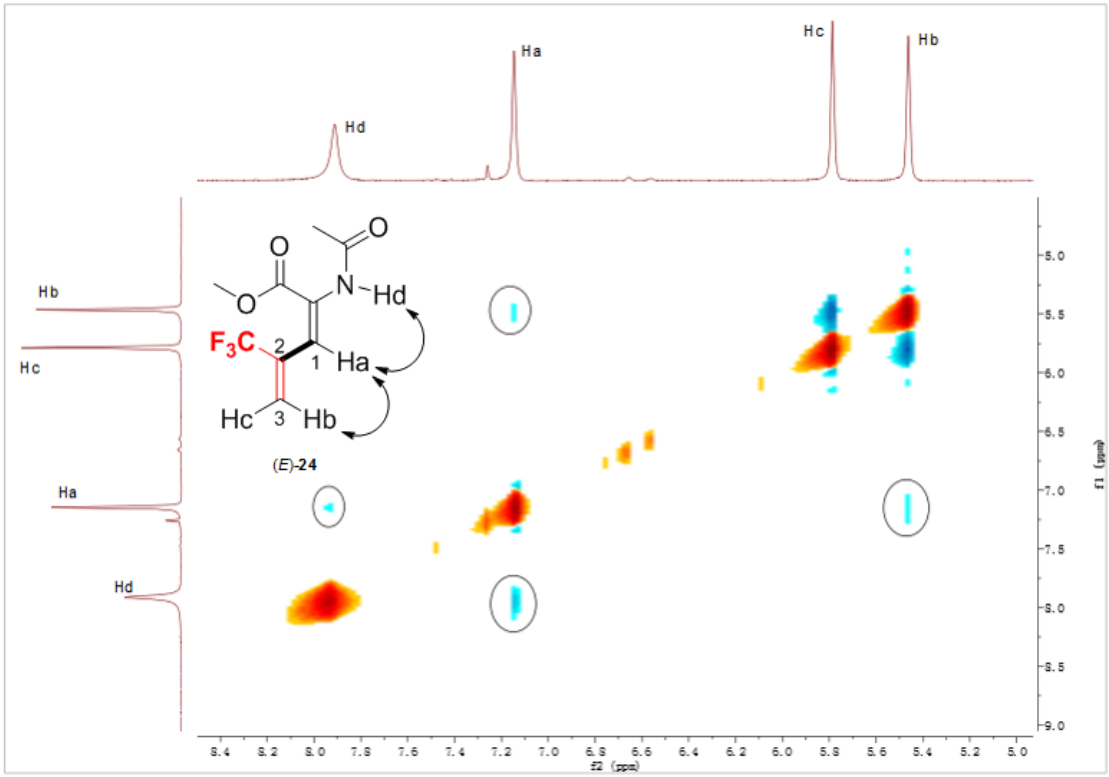
The HMQC 2D NMR of (*E*)-**24**

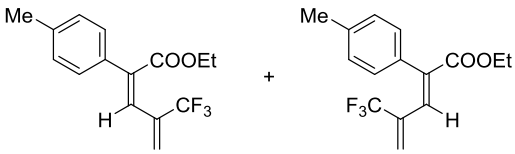


The HOESY 2D NMR of (*E*)-**24**:



The NOESY 2D NMR of (*E*)-**24**:





(*Z*)-**27** (*E*)-**27**

Ethyl-2-(*p*-tolyl)-4-(trifluoromethyl)penta-2,4-dienoate (27): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 99/1 to 93/7). Yield: 76% (43 mg). R_f (PE/Et_2O, 75/25): 0.75.

Colorless oil. Mixture of (*Z*)/(*E*) = 1:1.26

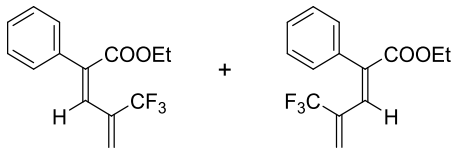
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.1 Hz, 2.32H), 7.27 (s, 1.26H), 7.21 (d, *J* = 8.1 Hz, 4.52H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.45 (s, 1H), 5.87 (s, 1H), 5.74 (s, 2.26H), 5.12 (s, 1.26H), 4.38-4.23 (m, 4.52H), 2.39 (s, 6.78H), 1.38-1.26 (m, 6.78H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.6 (s, 3F), -68.9 (s, 3.78F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.3, 166.6, 140.5, 139.3, 138.6, 138.0, 135.0 (q, *J* =

31.0 Hz), 133.5 (q, *J* = 30.5 Hz), 132.4, 131.5, 129.9 (q, *J* = 1.7 Hz), 129.5, 129.3, 128.9, 126.3, 124.3 (q, *J* = 5.3 Hz), 122.7 (q, *J* = 274.0 Hz), 122.6 (q, *J* = 274.1 Hz), 120.2 (q, *J* = 5.1 Hz), 120.0 (q, *J* = 1.7 Hz), 61.52, 61.49, 21.24, 21.18, 14.1, 13.8.

HRMS (EI^+): calcd for $C_{15}H_{15}F_3O_2$ *m/z* 284.1024 $[M]^+$, found 284.1022 (-0.7 ppm).



(*Z*)-**35** (*E*)-**35**

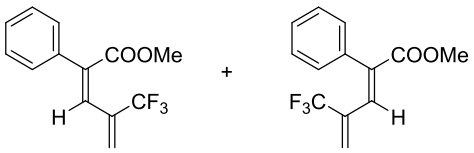
Ethyl-2-phenyl-4-(trifluoromethyl)penta-2,4-dienoate (35): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 99/1 to 93/7). Yield: 71% (38 mg). R_f (PE/Et_2O, 75/25): 0.70.

Colorless oil. Mixture of (*Z*)/(*E*) = 1:1.09

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.48-7.34 (m, 8.36H), 7.29 (s, 1.09H), 7.24-7.17 (m, 2.09H), 6.47 (s, 1H), 5.87 (s, 1H), 5.75 (s, 1H), 5.72 (s, 1.09H), 5.06 (s, 1.09H), 4.37-4.20 (m, 4.18H), 1.36-1.24 (m, 6.27H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.6 (s, 3F), -68.9 (s, 3.27F).

HRMS (EI^+): calcd for $C_{14}H_{13}F_3O_2$ *m/z* 270.0868 $[M]^+$, found 270.0868 (0.0 ppm).



(*Z*)-**36** (*E*)-**36**

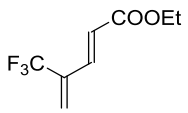
Methy-2-phenyl-4-(trifluoromethyl)penta-2,4-dienoate (36): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent:

PE/Et_2O, from 100/0 to 70/30). Yield: 82% (63 mg). R_f (PE/Et_2O, 50/50): 0.60.

Colorless oil. Mixture of (*Z*)/(*E*) = 1:1.15

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.46-7.34 (m, 8.6H), 7.31 (s, 1.15H), 7.24-7.17 (m, 2.15H), 6.48 (s, 1H), 5.88 (s, 1H), 5.72 (s, 2.15H), 5.06 (s, 1.15H), 3.83 (s, 3H), 3.79 (s, 3.45H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.6 (s, 3F), -69.0 (s, 3.45F).



38

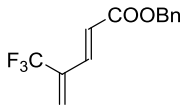
(*E*)-Ethyl-4-(trifluoromethyl)penta-2,4-dienoate (38): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 99/1 to 93/7). Yield: 30% (35 mg, based on a 0.6 mmol scale). R_f (PE/Et_2O, 75/25): 0.35.

Colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.26 (d, *J* = 16.2 Hz, 1H), 6.22 (d, *J* = 16.2 Hz, 1H), 6.07 (s, 1H), 5.90 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.33 (q, *J* = 7.2 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -66.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.0, 136.7, 135.1 (q, *J* = 31.0 Hz), 126.2 (q, *J* = 5.4 Hz), 123.0, 122.3 (q, *J* = 274.2 Hz), 60.9, 14.2.



40

(*E*)-Benzyl-4-(trifluoromethyl)penta-2,4-dienoate (40): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 99/1 to 93/7). Yield: 25% (38 mg, based on a 0.6 mmol scale). R_f (PE/Et_2O, 75/25): 0.42.

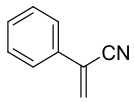
Colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.34-7.23 (m, 5H), 7.23 (d, *J* = 16.5 Hz, 1H), 6.16 (dd, *J* = 16.2 Hz, *J* = 1.2 Hz, 1H), 5.95 (s, 1H), 5.77 (s, 1H), 5.13 (s, 2H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -66.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.8, 137.3, 135.6, 134.9 (q, *J* = 31.1 Hz), 128.6, 128.4, 128.3, 126.7 (q, *J* = 5.4 Hz), 122.5 (q, *J* = 1.1 Hz), 122.2 (q, *J* = 274.3 Hz), 66.7.

HRMS (EI^+): calcd for $C_{13}H_{11}F_3O_2$ *m/z* 256.0711 $[M]^+$, found 256.0701 (-3.9 ppm).



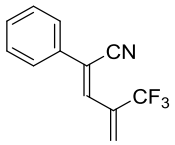
42

2-Phenylacrylonitrile (42):

Colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.57-7.36 (m, 2H), 7.25-7.12 (m, 3H), 6.16 (s, 1H), 5.92 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 132.0, 129.6, 128.7, 127.8, 125.4, 122.5, 117.4.



43

(*Z*)-2-Phenyl-4-(trifluoromethyl)penta-2,4-dienenitrile (43): A dried tube was loaded with $Pd(acac)_2$ (24.0 mg, 0.08 mmol, 0.1 equiv), AgOTf (411.2 mg, 1.6 mmol, 2 equiv) and amide **1** (0.8 mmol, 1 equiv) under Ar. Then DMI (8 mL) and BTP (4.0 mmol, 5.0 equiv) were added. The tube was sealed with a rubber septum and the suspension was stirred at 120 °C for 2 h. The reaction mixture was diluted with diethyl ether (40 mL) and filtered through a plug of Celite®. The solution was washed with brine (3 × 15 mL) and dried with $MgSO_4$. The solvents were removed under vacuum and the crude was purified by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 98/2 to 82/8). Yield: 6% (11 mg, based on a 0.8 mmol scale).

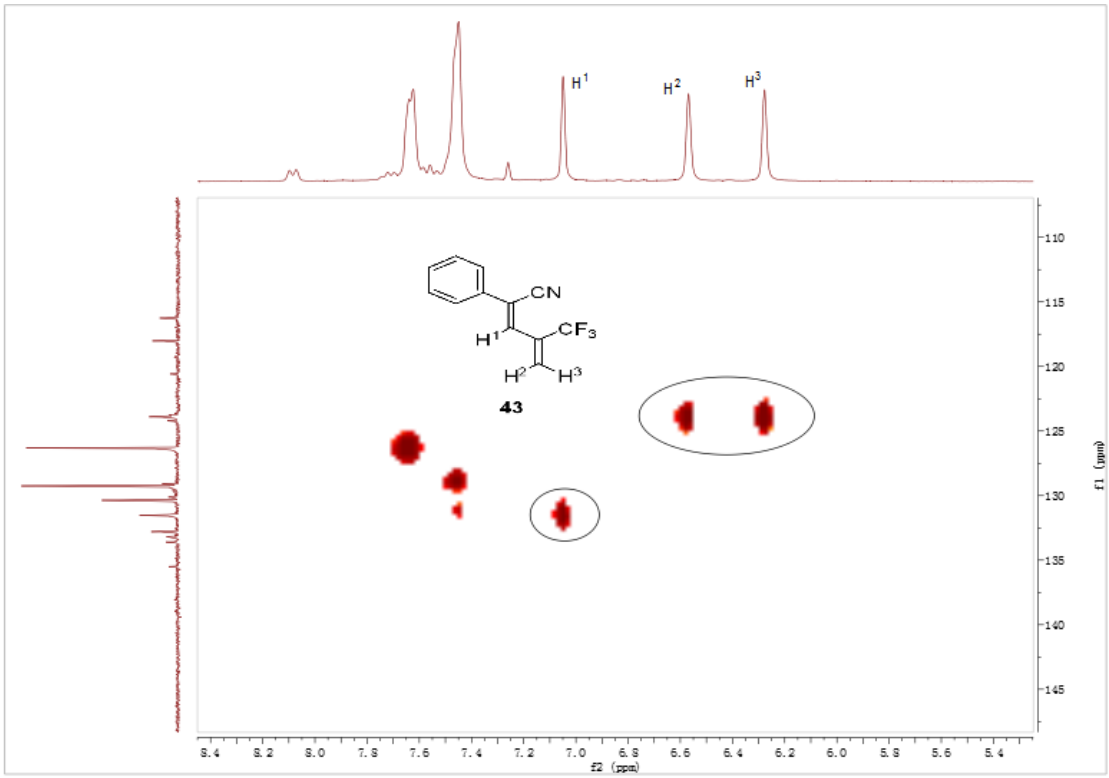
Colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.69-7.59 (m, 2H), 7.54-7.38 (m, 3H), 7.05 (s, 1H), 6.57 (s, 1H), 6.28 (s, 1H).

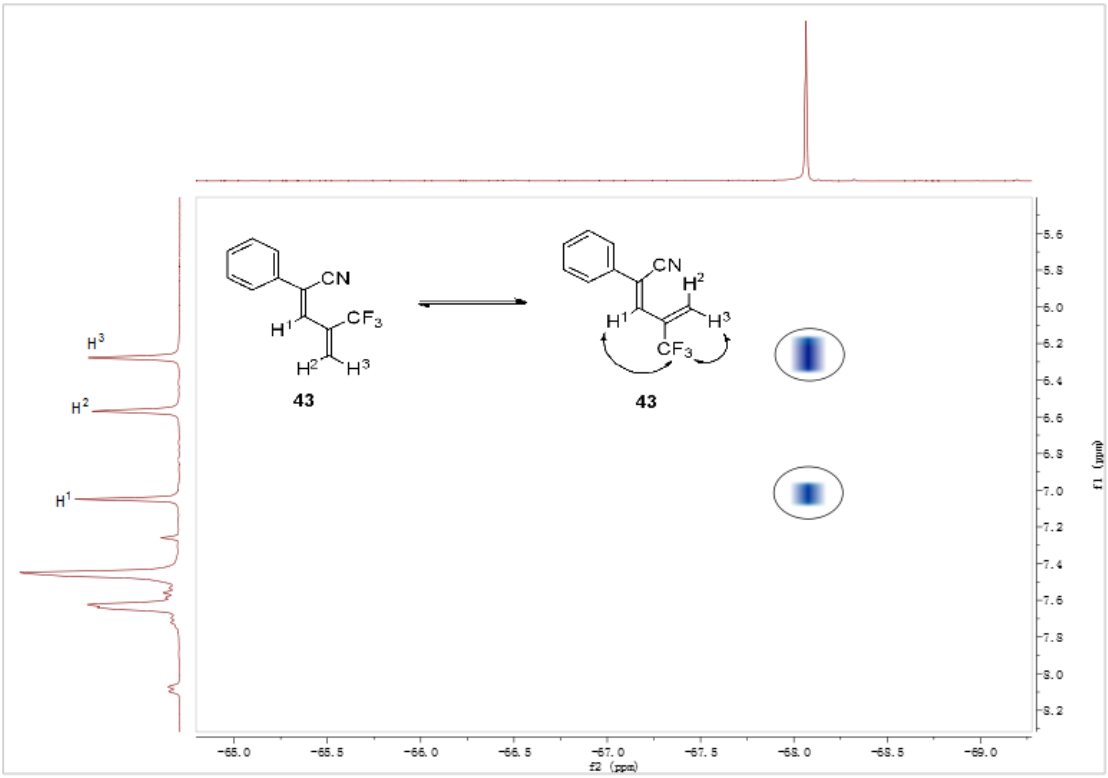
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -68.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 135.5, 133.4 (q, *J* = 32.1 Hz), 132.8, 131.5 (q, *J* = 1.8 Hz), 130.4, 129.2, 126.3, 123.9 (q, *J* = 5.2 Hz), 122.4 (q, *J* = 274.3 Hz), 118.0.

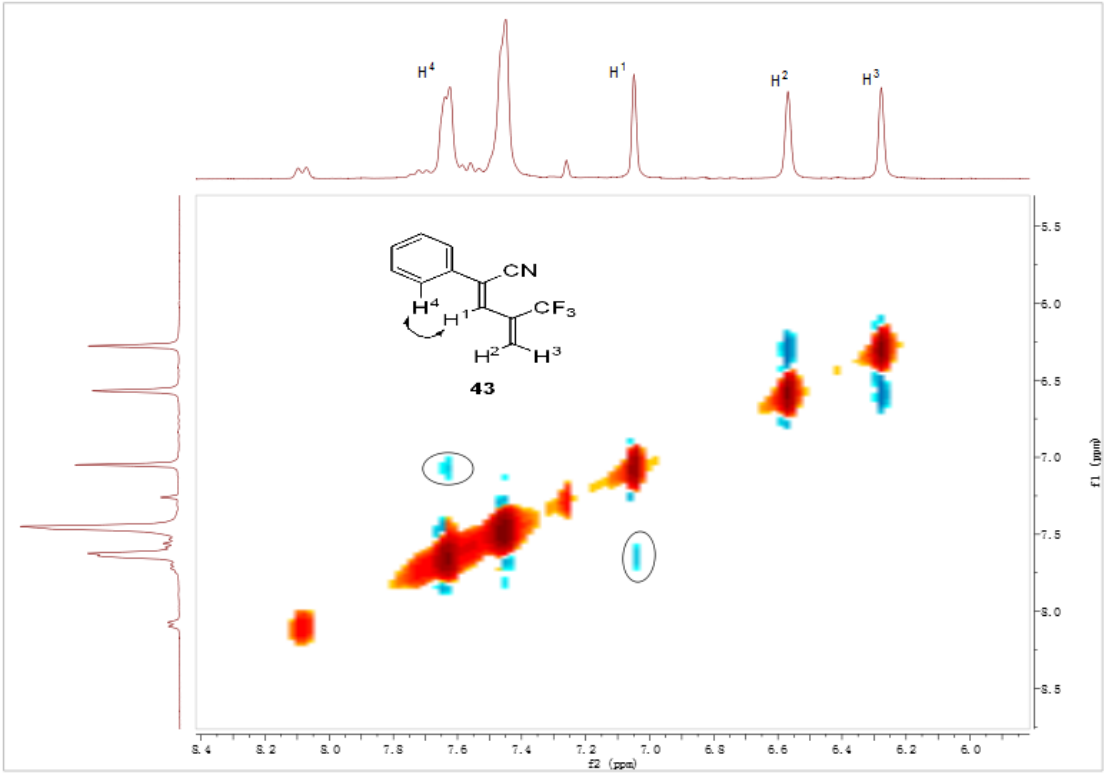
The HMQC 2D NMR of **43**:



The HOESY 2D NMR of **43**:



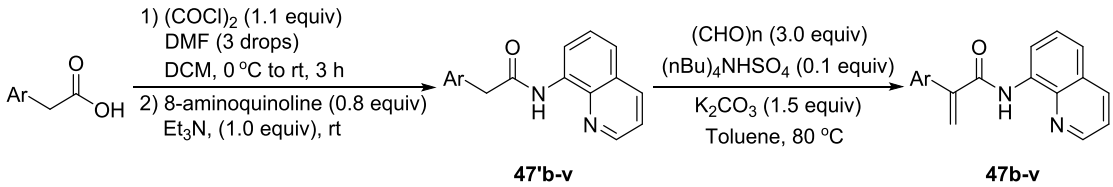
The NOESY 2D NMR of **43**:



2 Trifluoromethylthiolation with the Munavalli reagent

2.1 Transition metal catalyzed olefinic C(sp^2)-H bond functionalization with the Munavalli reagent

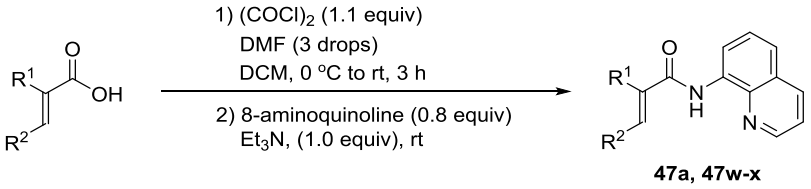
2.1.1 General procedure for the synthesis of 2-arene-*N*-(quinolin-8-yl)acrylamide 47b-v.



Oxalyl chloride (11 mmol, 1.1 equiv) was slowly added at 0 °C to a solution of the acid (10 mmol, 1 equiv) and DMF (3 drops) in dry DCM (15 mL). After stirring at room temperature for 3 h, the solvent was removed under vacuum and the residue was dissolved in dry DCM. 8-Aminoquinoline (8 mmol, 0.8 equiv) was added and the reaction was followed by TLC until it was completed. Water (100 mL) was added and the resulting mixture was extracted with DCM (3 × 150 mL). Removal of the solvent under vacuum and purification of the residue by Biotage afforded the desired intermediate **47'**.

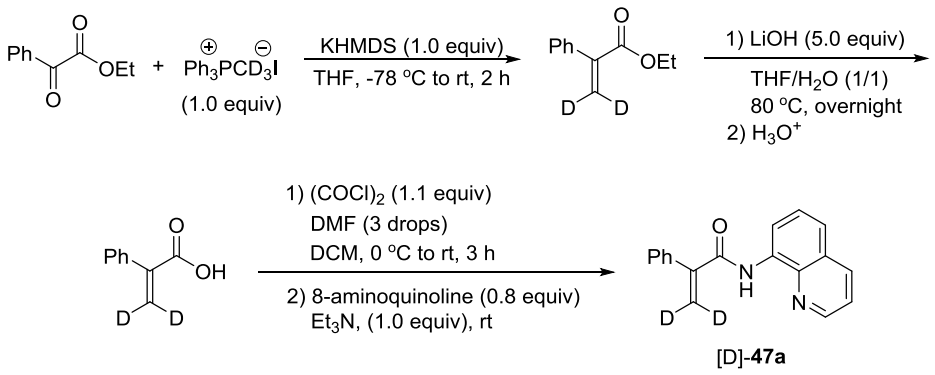
47' (5 mmol), $(CHO)_n$ (15 mmol, 3 equiv), $(n\text{Bu})_4NHSO_4$ (0.5 mmol, 0.1 equiv) and K_2CO_3 (7.5 mmol, 1.5 equiv) was added in toluene (80 mL) and stirred at 80 °C. The reaction was followed by TLC until completed. Water (100 mL) was added and the resulting mixture was extracted with Et_2O (3 × 150 mL). Removal of the solvent under vacuum and purification of the residue by Biotage afforded the desired product **47**.

2.1.2 General procedure for the synthesis of acrylamide 47a, 47w-x.



Oxalyl chloride (11 mmol, 1.1 equiv) was slowly added at 0 °C to a solution of the acid (10 mmol, 1 equiv) and DMF (3 drops) in dry DCM (15 mL). After stirring at room temperature for 3 h, the solvent was removed under vacuum and the residue was dissolved in dry DCM. 8-Aminoquinoline (8 mmol, 0.8 equiv) was added and the reaction was followed by TLC until completed. Water (100 mL) was added and the resulting mixture was extracted with Et_2O (3 × 150 mL). Removal of the solvent under vacuum and purification of the residue by Biotage afforded the desired product **47**.

2.1.3 Synthesis of the deuterated acrylamide [D]-47a.



Methyl-d_3-triphenylphosphonium iodide was synthesized following the known literature procedure.[203]

Methyl-d_3-triphenylphosphonium iodide (13 mmol, 1 equiv) was dried under vacuum for at least 1h before starting the reaction (quite important step). The freshly dried

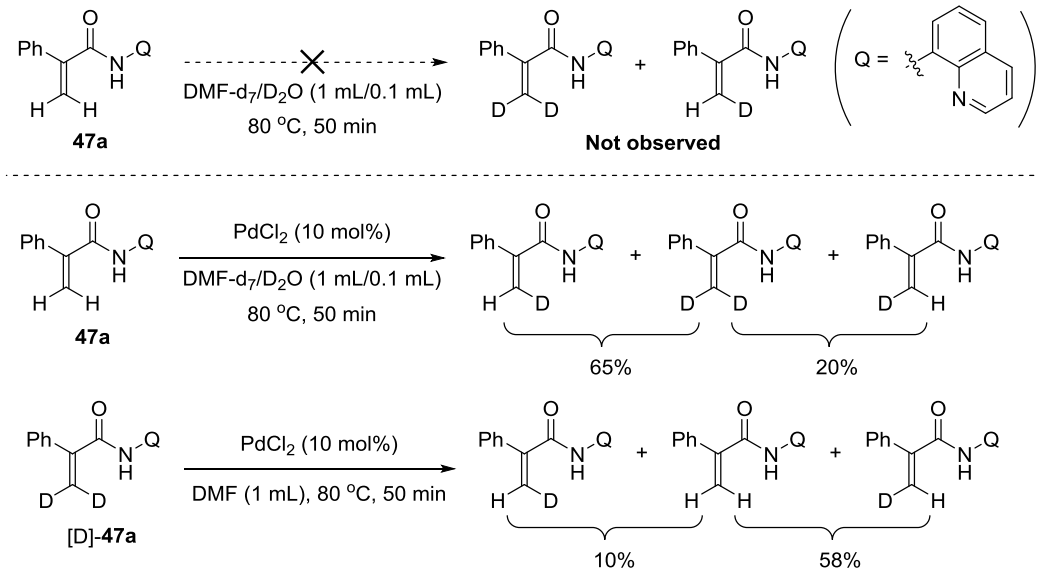
Methyl-d_3-triphenylphosphonium iodide (13 mmol, 1 equiv) was dissolved in dry THF (100 mL) and stirred at -78 °C for 15 min. KHMDS (13 mmol, 1 equiv) was added dropwise (a golden yellow precipitate was observed quickly) and then the mixture was stirred for another 2 h at room temperature. The ester (2.5 g, 14.3 mmol, 1.1 equiv) was added dropwise at -78 °C and then the mixture was stirred for another 1 h. The reaction was followed by TLC until completion. Water (50 mL) was added and the resulting mixture was extracted with Et_2O (3 × 100 mL). Removal of the solvent under vacuum and purification of the residue by silica gel column chromatography afforded the desired intermediate (1.6 g, 9.3 mmol).

The ester (1.6 g, 9.3 mmol, 1 equiv) and LiOH (46.5 mmol, 5 equiv) dissolved in THF/H_2O (20 mL/20 mL) and stirred at 80 °C overnight. The reaction was quenched with 1.0 M HCl and extracted by Et_2O (3 × 50 mL). Removal of the solvent under vacuum and purification of the residue by silica gel column chromatography afforded the desired acid.

The acidwas converted into [D]-**47a** according to the standard procedure used for the synthesis of **47**.

2.1.4 Mechanistic Studies

2.1.4.1 Scrambling experiment (without Phth-SCF$_3$).

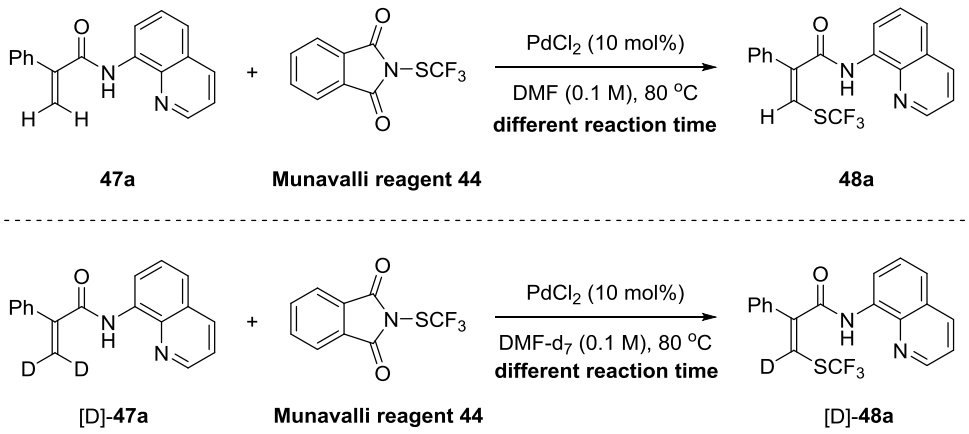


A dried tube was loaded amide **47a** (0.1 mmol). Then, DMF-d$_7$/D$_2$O (1 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at 80 °C for 50 min. The reaction mixture was directly analyzed by ^{1}H-NMR spectroscopy. Deuteration was not observed. This result shows that the olefinic C-H bond is not reactive without PdCl$_2$.

A dried tube was loaded with PdCl$_2$ (1.8 mg, 0.01 mmol, 0.1 equiv), amide **47a** or **[D]-47a** (0.1 mmol, 1 equiv). Then, DMF-d$_7$/D$_2$O or DMF (1 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at 80 °C for 50 min. The reaction mixture was directly analyzed by ^{1}H-NMR spectroscopy. Deuteration was observed. Those results demonstrate that the C-H bond activation step is reversible.

2.1.4.2 Kinetic Isotope Effect (KIE) measurements.

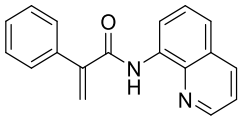
Parallel reactions:



Six reactions were performed for different reaction time (15 min, 30 min, 45 min, 60 min, 75 min, 90 min). Each dried tube was charged with $PdCl_2$ (1.8 mg, 0.01 mmol, 0.1 equiv), Munavalli reagent **44** (24.7 mg, 0.1 mmol, 1 equiv) and amide **47a** (27.4 mg, 0.1 mmol, 1 equiv). Then, DMF (1 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at 80 °C for different reaction time. The yield of each reaction was determined by ^{19}F NMR analysis of the reaction mixture.

Due to the H/D exchange observed in the scrambling experiments, the competition experiment starting from a 1:1 mixture **47a**:[D]-4**7a** couldn't be carried out. Thus, parallel experiments were undertaken in separate vials as following:

Parallel reactions (four reactions were charged with **47a**, while another four were charged with [D]-**47a**) were performed for different reaction time (15 min, 20 min, 25 min, 30 min). Each dried tube was charged with $PdCl_2$ (1.8 mg, 0.01 mmol, 0.1 equiv), Munavalli reagent **44** (24.7 mg, 0.1 mmol, 1 equiv) and amide **47a** or [D]-4**7a** (0.1 mmol, 1 equiv). Then, DMF or DMF-d_7 (1 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at 80 °C for different reaction time. The yield of each reaction was determined by ^{19}F NMR analysis of the reaction mixture.



47a

2-Phenyl-*N*-(quinolin-8-yl)acrylamide (47a): R_f (PE/Et_2O, 50/50): 0.68.

White solid; **m.p.**: 78-79 °C.

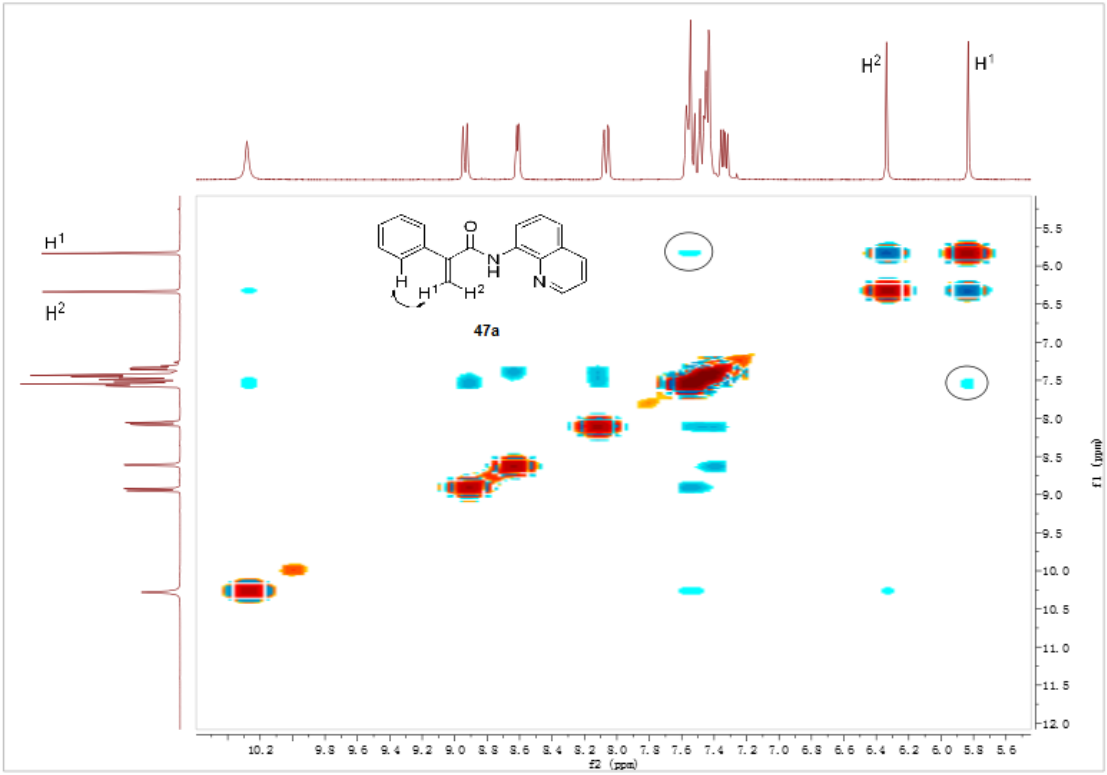
IR: 3333, 3047, 1668, 1520, 1484, 1324, 830, 797, 777, 759, 561.

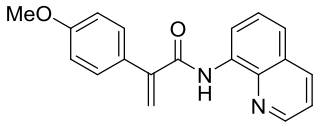
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.28 (brs, 1H), 8.94 (dd, *J* = 7.5 Hz, 0.9 Hz, 1H), 8.61 (dd, *J* = 4.4 Hz, 1.5 Hz, 1H), 8.07 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 7.62-7.40 (m, 7H), 7.37-7.30 (m, 1H), 6.34 (s, 1H), 5.83 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.6, 148.0, 145.7, 138.4, 136.5, 136.0, 134.2, 128.5, 128.4, 128.1, 127.6, 127.1, 122.0, 121.7, 121.4, 116.4.

HRMS (ESI$^+$): calcd for $C_{18}H_{15}N_2O$ *m/z* 275.1184 $[M+H]^+$, found 275.1180 (-1.5 ppm).

The NOESY 2D NMR of **47a**:





47b

***N*-(Quinolin-8-yl)-2-(*p*-methoxyphenyl)acrylamide (47b)**: R_f (PE/Et_2O, 50/50): 0.53.

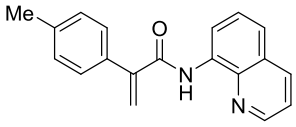
White solid; **m.p.**: 78-79 °C.

IR: 3370, 3007, 1679, 1525, 1512, 1486, 1254, 1182, 823, 789, 667.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.29 (brs, 1H), 8.94 (dd, *J* = 7.8 Hz, 0.9 Hz, 1H), 8.62 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.04 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.58-7.42 (m, 4H), 7.36-7.28 (m, 1H), 7.01-6.90 (m, 2H), 6.22 (s, 1H), 5.76 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.9, 159.7, 148.0, 145.1, 138.3, 135.9, 134.2, 129.2, 128.7, 127.6, 126.9, 121.6, 121.3, 120.2, 116.3, 113.8, 55.0.

HRMS (ESI^+): calcd for $C_{19}H_{17}N_2O_2$ *m/z* 305.1290 $[M+H]^+$, found 305.1288 (-0.7 ppm).



47c

***N*-(Quinolin-8-yl)-2-(*p*-tolyl)acrylamide (47c)**: R_f (PE/Et_2O, 50/50): 0.69.

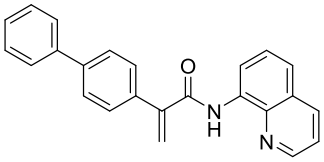
White solid; **m.p.**: 111-112 °C.

IR: 3358, 1662, 1515, 1485, 1325, 914, 836, 822, 801, 759.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.14 (brs, 1H), 8.79 (dd, *J* = 7.2 Hz, 1.5 Hz, 1 H), 8.51 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 7.96 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 7.45-7.29 (m, 4H), 7.27-7.20 (m, 1H), 7.17-7.05 (m, 2H), 6.14 (s, 1H), 5.67 (s, 1H), 2.29 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.0, 148.1, 145.7, 138.6, 138.4, 136.1, 134.4, 133.7, 129.3, 128.1, 127.8, 127.2, 121.7, 121.4, 121.3, 116.5, 21.2.

HRMS (ESI$^+$): calcd for $C_{19}H_{17}N_2O$ *m/z* 289.1341 $[M+H]^+$, found 289.1330 (-3.8 ppm).



47d

2-([1,1'-Biphenyl]-4-yl)-*N*-(quinolin-8-yl)acrylamide (47d): R_f (PE/Et_2O, 50/50): 0.58.

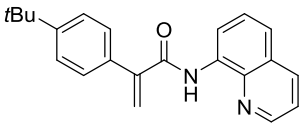
White solid; **m.p.**: 75-76 °C.

IR: 3338, 3034, 1672, 1519, 1483, 1326, 825, 790, 770, 753.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.44 (brs, 1H), 9.09 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 8.64 (dd, *J* = 5.4 Hz, 1.5 Hz, 1H), 8.04 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.78-7.37 (m, 11H), 7.35-7.27 (m, 1H), 6.39 (s, 1H), 5.93 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.5, 147.9, 145.1, 140.9, 139.9, 138.2, 135.8, 135.1, 134.1, 128.5, 128.3, 127.4, 127.2, 126.9, 126.6, 121.6, 121.3, 121.2, 116.2 (one carbon is missing).

HRMS (ESI$^+$): calcd for $C_{24}H_{19}N_2O$ *m/z* 351.1497 $[M+H]^+$, found 351.1488 (-3.8 ppm).



47e

2-(4-(*tert*-Butyl)phenyl)-*N*-(quinolin-8-yl)acrylamide (47e): R_f (PE/Et_2O, 50/50): 0.70.

White solid; **m.p.**: 88-89 °C.

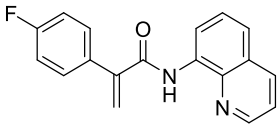
IR: 3339, 2956, 1666, 1519, 1485, 938, 841, 827, 793, 758.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.33 (brs, 1H), 8.97 (dd, *J* = 9.0 Hz, 1.2 Hz, 1H), 8.61

(dd, *J* = 4.2 Hz, 1.8 Hz, 1H), 8.07 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.62-7.45 (m, 6H), 7.41-7.31 (m, 1H), 6.33 (s, 1H), 5.86 (s, 1H), 1.42 (s, 9H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.8, 151.4, 147.9, 145.5, 138.4, 135.9, 134.3, 133.6, 127.9, 127.6, 127.1, 125.4, 121.6, 121.3, 121.1, 116.3, 34.4, 31.1.

HRMS (ESI^+): calcd for $C_{22}H_{23}N_2O$ *m/z* 331.1810 $[M+H]^+$, found 331.1809 (-0.3 ppm).



47f

2-(4-Fluorophenyl)-*N*-(quinolin-8-yl)acrylamide (47f): R_f (PE/Et_2O, 50/50): 0.66.

White solid; **m.p.**: 110-111 °C.

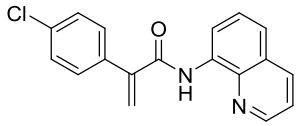
IR: 3364, 3098, 1670, 1531, 1508, 1220, 835, 822, 789, 666.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.25 (brs, 1H), 8.88 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.67 (dd, *J* = 4.4 Hz, 1.5 Hz, 1H), 8.13 (dd, *J* = 8.3 Hz, 1.2 Hz, 1H), 7.65-7.46 (m, 4H), 7.45-7.37 (m, 1H), 7.20-7.05 (m, 2H), 6.29 (s, 1H), 5.81 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -113.5 ~ -113.6 (m).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.6, 162.9 (d, *J* = 248.2 Hz), 148.3, 144.8, 138.6, 136.2, 134.3, 132.7 (d, *J* = 3.5 Hz), 130.1 (d, *J* = 8.2 Hz), 127.8, 127.3, 122.0, 121.8 (d, *J* = 26.4 Hz), 116.6, 115.7, 115.4.

HRMS (ESI^+): calcd for $C_{18}H_{14}FN_2O$ *m/z* 293.1090 $[M+H]^+$, found 293.1088 (-0.7 ppm).



47g

2-(4-Chlorophenyl)-*N*-(quinolin-8-yl)acrylamide (47g): R_f (PE/Et_2O, 50/50): 0.67.

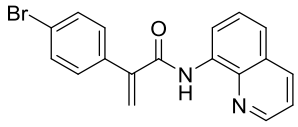
White solid; **m.p.**: 140-141 °C.

IR: 3356, 3092, 1673, 1527, 1487, 1390, 821, 788, 751.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.25 (brs, 1H), 8.87 (dd, *J* = 6.0 Hz, 1.5 Hz, 1H), 8.68 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.13 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.79-7.30 (m, 7H), 6.29 (s, 1H), 5.84 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.5, 148.4, 144.9, 138.6, 136.3, 135.2, 134.7, 134.3, 129.7, 128.9, 127.9, 127.4, 122.3, 122.1, 121.7, 116.7.

HRMS (ESI$^+$): calcd for $C_{18}H_{14}ClN_2O$ *m/z* 309.0795 $[M+H]^+$, found 309.0796 (0.3 ppm).



47h

2-(4-Bromophenyl)-*N*-(quinolin-8-yl)acrylamide (47h): R_f (PE/Et_2O, 50/50): 0.63.

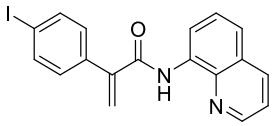
White solid; **m.p.**: 152-153 °C.

IR: 3357, 3092, 1675, 1525, 1486, 1390, 821, 787, 746.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.25 (brs, 1H), 8.87 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.68 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.11 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.62-7.47 (m, 4H), 7.46-7.36 (m, 3H), 6.29 (s, 1H), 5.84 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.3, 148.3, 144.8, 138.5, 136.2, 135.5, 134.2, 131.7, 129.8, 127.8, 127.2, 122.8, 122.1, 122.0, 121.6, 116.6.

HRMS (ESI$^+$): calcd for $C_{18}H_{14}BrN_2O$ *m/z* 353.0290 [M+H]$^+$, found 353.0290 (0 ppm).



47i

2-(4-Iodophenyl)-*N*-(quinolin-8-yl)acrylamide (47i): R_f (PE/Et_2O, 50/50): 0.63.

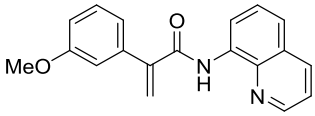
White solid; **m.p.**: 126-127 °C.

IR: 3357, 1671, 1526, 1485, 1387, 821, 756, 736.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.25 (brs, 1H), 8.87 (dd, *J* = 7.1 Hz, 1.8 Hz, 1H), 8.70 (dd, *J* = 4.2 Hz, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.7 Hz, 1.5 Hz, 1H), 7.84-7.70 (m, 2H), 7.60-7.49 (m, 2H), 7.45-7.39 (m, 1H), 7.35-7.27 (m, 2H), 6.28 (s, 1H), 5.85 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.3, 148.3, 145.0, 138.6, 137.7, 136.23, 136.22, 134.3, 130.0, 127.8, 127.3, 122.2, 122.0, 121.6, 116.7, 94.5.

HRMS (ESI$^+$): calcd for $C_{18}H_{14}IN_2O$ *m/z* 401.0151 [M+H]$^+$, found 401.0150 (-0.2 ppm).



47j

2-(3-Methoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (47j): R_f (PE/Et_2O, 50/50): 0.53.

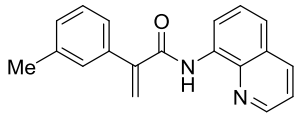
White solid; **m.p.**: 76-66 °C.

IR: 3325, 1657, 1515, 1484, 1227, 960, 792, 780, 690.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.32 (brs, 1H), 8.93 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 8.62 (dd, *J* = 3.3 Hz, 1.5 Hz, 1H), 8.05 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.60-7.28 (m, 4H), 7.22-7.07 (m, 2H), 7.01-6.91 (m, 1H), 6.38 (s, 1H), 5.84 (s, 1H), 3.82 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.1, 159.5, 148.0, 145.4, 138.4, 137.8, 135.9, 134.2, 129.5, 127.6, 127.0, 122.5, 121.7, 121.3, 120.6, 116.4, 114.3, 113.4, 55.0.

HRMS (ESI$^+$): calcd for $C_{19}H_{17}N_2O_2$ *m/z* 305.1290 [M+H]$^+$, found 305.1279 (-3.6 ppm).



47k

***N*-(Quinolin-8-yl)-2-(*m*-tolyl)acrylamide (47k)**: R_f (PE/Et_2O, 50/50): 0.64.

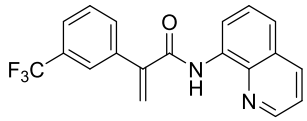
Yellow liquid.

IR: 3332, 1675, 1520, 1483, 1326, 825, 789, 728, 713.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.33 (brs, 1H), 8.95 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 8.66 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.12 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.62-7.49 (m, 2H), 7.44-7.32 (m, 4H), 7.30-7.29 (m, 1H), 6.36 (s, 1H), 5.85 (s, 1H), 2.44 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.6, 148.1, 145.8, 138.6, 138.2, 136.6, 136.0, 134.4, 129.2, 128.9, 128.5, 127.7, 127.2, 125.3, 122.1, 121.7, 121.4, 116.5, 21.3.

HRMS (ESI$^+$): calcd for $C_{19}H_{17}N_2O$ *m/z* 289.1341 [M+H]$^+$, found 289.1333 (-2.8 ppm).



47l

***N*-(Quinolin-8-yl)-2-(3-trifluoromethylphenyl)acrylamide (47l)**: R_f (PE/Et_2O, 50/50): 0.62.

White solid; **m.p.**: 58-59 °C.

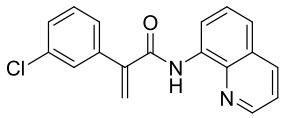
IR: 3358, 3047, 1670, 1529, 1488, 1334, 1296, 1164, 1120, 827, 759, 692.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.30 (brs, 1H), 8.87 (dd, *J* = 7.2 Hz, 1.8 Hz, 1H), 8.65 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.10 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.87 (s, 1H), 7.78-7.65 (m, 2H), 7.59-7.47 (m, 3H), 7.41-7.34 (m, 1H), 6.39 (s, 1H), 5.90 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -63.1 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.8, 148.2, 144.6, 138.5, 137.4, 136.1, 134.0, 131.7 (q, *J* = 1.1 Hz), 130.9 (q, *J* = 32.4 Hz), 129.1, 127.7, 127.1, 125.2 (q, *J* = 3.8 Hz), 124.9 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.7 Hz), 123.2, 122.1, 121.6, 116.6.

HRMS (ESI$^+$): calcd for $C_{19}H_{14}F_3N_2O$ *m/z* 343.1058 $[M+H]^+$, found 343.1057 (-0.2 ppm).



47m

2-(3-Chlorophenyl)-*N*-(quinolin-8-yl)acrylamide (47m): R_f (PE/Et_2O, 50/50): 0.63.

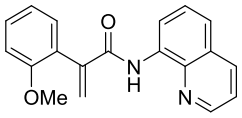
White solid; **m.p.**: 48-49 °C.

IR: 3345, 3047, 1672, 1531, 1486, 825, 786, 752, 666.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.28 (brs, 1H), 8.86 (dd, *J* = 6.9 Hz, 1.8 Hz, 1H), 8.69 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H), 8.14 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.62-7.49 (m, 3H), 7.48-7.32 (m, 4H), 6.34 (s, 1H), 5.86 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.1, 148.3, 144.7, 138.6, 138.5, 136.2, 134.5, 134.2, 129.9, 128.7, 128.4, 127.9, 127.3, 126.5, 122.9, 122.0, 121.6, 116.7.

HRMS (ESI$^+$): calcd for $C_{18}H_{14}ClN_2O$ *m/z* 309.0795 $[M+H]^+$, found 309.0791 (-1.3 ppm).



47n

2-(2-Methoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (47n): R_f (PE/Et_2O, 50/50): 0.50.

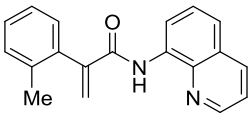
White solid; **m.p.**: 94-95 °C.

IR: 3333, 1679, 1526, 1485, 1234, 827, 794, 761, 683.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.22 (brs, 1H), 8.95 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.56 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.01 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.56-7.36 (m, 4H), 7.32-7.26 (m, 1H), 7.13-6.92 (m, 2H), 6.53 (s, 1H), 5.74 (s, 1H), 3.69 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.0, 156.6, 147.7, 143.3, 138.2, 135.7, 134.4, 130.8, 130.0, 127.4, 126.9, 126.1, 123.9, 121.11, 121.08, 120.7, 116.1, 110.8, 55.2.

HRMS (ESI$^+$): calcd for $C_{19}H_{17}N_2O_2$ *m/z* 305.1290 $[M+H]^+$, found 305.1277 (-4.3 ppm).



47o

***N*-(Quinolin-8-yl)-2-(o-tolyl)acrylamide (47o)**: R_f (PE/Et_2O, 50/50): 0.66.

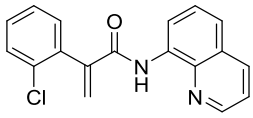
White solid; **m.p.**: 115-116 °C.

IR: 3312, 2925, 1673, 1527, 1484, 1326, 949, 829, 768, 692.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.11 (brs, 1H), 8.94 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 8.54 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.07 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.64-7.26 (m, 7H), 6.73 (s, 1H), 5.72 (s, 1H), 2.38 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.3, 148.0, 144.9, 138.6, 136.62, 136.58, 135.8, 134.3, 130.3, 130.0, 128.6, 127.6, 127.1, 126.2, 125.1, 121.6, 121.3, 116.3, 19.8.

HRMS (ESI$^+$): calcd for $C_{19}H_{17}N_2O$ *m/z* 289.1341 $[M+H]^+$, found 289.1330 (-3.8 ppm).



47p

2-(2-Chlorophenyl)-*N*-(quinolin-8-yl)acrylamide (47p): R_f (PE/Et_2O, 50/50): 0.50.

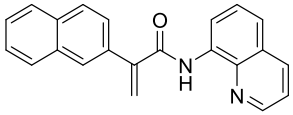
White solid; **m.p.**: 130-131 °C.

IR: 3308, 1678, 1532, 1465, 1387, 1074, 827, 792, 766, 715.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.13 (brs, 1H), 8.90 (dd, *J* = 7.5 Hz, 0.9 Hz, 1H), 8.51 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 7.98 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.55-7.32 (m, 6H), 7.30-7.23 (m, 1H), 6.63 (s, 1H), 5.75 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.7, 147.9, 143.6, 138.2, 135.9, 135.8, 134.0, 133.4, 131.3, 129.8, 129.5, 127.4, 127.0, 126.9, 125.4, 121.5, 121.2, 116.0.

HRMS (ESI^+): calcd for $C_{18}H_{14}ClN_2O$ *m/z* 309.0795 $[M+H]^+$, found 309.0780 (-4.9 ppm).



47q

2-(Naphth-2-yl)-*N*-(quinolin-8-yl)acrylamide (47q): R_f (PE/Et_2O, 50/50): 0.51.

White solid; **m.p.**: 130-131 °C.

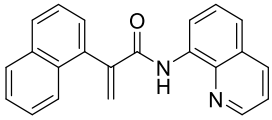
IR: 3332, 1661, 1518, 1481, 948, 828, 794, 765, 756.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.22 (brs, 1H), 8.81 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.35 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H), 7.96-7.85 (m, 2H), 7.78-7.66 (m, 3H), 7.55-7.28 (m, 5H), 7.19-7.10 (m, 1H), 6.24 (s, 1H), 5.80 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.8, 148.1, 145.7, 138.5, 136.0, 134.3, 133.9, 133.2, 133.1, 128.3, 128.2, 127.7, 127.6, 127.2, 126.4, 126.3, 125.7, 122.3, 121.8, 121.4,

116.6 (one carbon is missing).

HRMS (ESI$^+$): calcd for $C_{22}H_{17}N_2O$ *m/z* 325.1341 [M+H]$^+$, found 325.1340 (-0.3 ppm).



47r

2-(Naphth-1-yl)-*N*-(quinolin-8-yl)acrylamide (47r): R_f (PE/Et_2O, 50/50): 0.50.

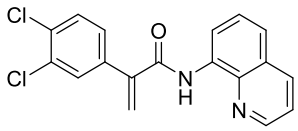
White solid; **m.p.**: 88-89 °C.

IR: 3319, 3053, 1675, 1522, 1480, 1423, 1384, 1325, 777, 766.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.10 (brs, 1H), 8.94 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 8.36-7.68 (m, 5H), 7.68-7.20 (m, 6H), 7.14-7.02 (m, 1H), 6.95 (s, 1H), 5.87 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.4, 147.6, 143.7, 138.2, 135.5, 134.5, 134.0, 133.5, 131.7, 128.9, 128.1, 127.5, 127.3, 126.8, 126.5, 126.4, 126.0, 125.3, 125.2, 121.5, 121.0, 116.0.

HRMS (ESI$^+$): calcd for $C_{22}H_{17}N_2O$ *m/z* 325.1341 [M+H]$^+$, found 325.1340 (-0.3 ppm).



47s

2-(3,4-Dichlorophenyl)-*N*-(quinolin-8-yl)acrylamide (47s): R_f (PE/Et_2O, 50/50): 0.50.

White solid; **m.p.**: 140-141 °C.

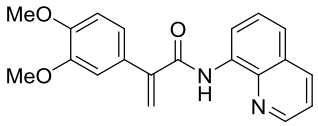
IR: 3353, 1670, 1543, 948, 821, 788, 748, 676, 646.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.28 (brs, 1H), 8.84 (dd, *J* = 6.6 Hz, 2.4 Hz, 1H), 8.73 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.16 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H),

7.61-7.36 (m, 5H), 6.31 (s, 1H), 5.89 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.9, 148.4, 143.9, 138.6, 136.6, 136.3, 134.1, 132.8, 130.5, 130.1, 127.9, 127.6, 127.3, 122.8, 122.1, 121.7, 116.7 (one carbon is missing).

HRMS (ESI$^+$): calcd for $C_{18}H_{13}Cl_2N_2O$ *m/z* 343.0405 [M+H]$^+$, found 343.0396 (-2.6 ppm).



47t

2-(3,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (47t): R_f (PE/Et_2O, 50/50): 0.26.

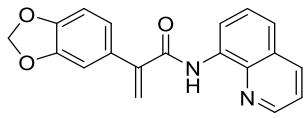
White solid; **m.p.**: 118-119 °C.

IR: 3368, 2930, 1672, 1514, 1257, 1230, 1148, 1020, 786, 763, 666.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.35 (brs, 1H), 8.94 (dd, *J* = 7.2 Hz, 1.5 Hz, 1H), 8.70 (dd, *J* = 6.6 Hz, 1.5 Hz, 1H), 8.15 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.66-7.50 (m, 2H), 7.48-7.38 (m, 1H), 7.20-7.10 (m, 2H), 7.01-6.93 (m, 1H), 6.33 (s, 1H), 5.81 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.7, 149.4, 148.9, 148.2, 145.3, 138.7, 136.1, 134.4, 129.4, 127.8, 127.3, 121.8, 121.7, 121.5, 121.1, 116.6, 111.3, 111.2, 55.9, 55.8.

HRMS (ESI$^+$): calcd for $C_{20}H_{19}N_2O_3$ *m/z* 335.1396 [M+H]$^+$, found 335.1385 (-3.3 ppm).



47u

2-(Benzo[d][1,3]dioxol-5-yl)-*N*-(quinolin-8-yl)acrylamide (47u): R_f (PE/Et_2O, 50/50): 0.40.

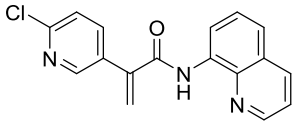
White solid; **m.p.**: 110-111 °C.

IR: 3360, 2910, 1672, 1532, 1488, 1447, 1236, 1040, 815, 791.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.27 (brs, 1H), 8.88 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 8.66 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.09 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.60-7.44 (m, 2H), 7.42-7.31 (m, 1H), 7.11-6.95 (m, 2H), 6.90-6.78 (m, 1H), 6.20 (s, 1H), 5.98 (s, 2H), 5.74 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.8, 148.2, 147.9, 147.8, 145.3, 138.5, 136.1, 134.3, 130.5, 127.7, 127.2, 122.1, 121.8, 121.4, 120.9, 116.5, 108.5, 108.3, 101.2.

HRMS (ESI^+): calcd for $C_{19}H_{15}N_2O_3$ *m/z* 319.1083 $[M+H]^+$, found 319.1068 (-4.7 ppm).



47v

2-(6-Chloropyridin-3-yl)-*N*-(quinolin-8-yl)acrylamide (47v): R_f (PE/Et_2O, 50/50): 0.32.

White solid; **m.p.**: 155-156 °C.

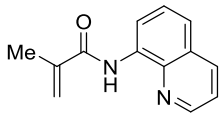
IR: 3343, 3094, 3059, 1663, 1532, 1462, 1120, 821, 788, 754.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.29 (brs, 1H), 8.78 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 8.70 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.55 (dd, *J* = 2.4 Hz, 0.6 Hz, 1H), 8.11 (dd, *J* = 8.4 Hz, 1.5

Hz, 1H), 7.84 (dd, *J* = 8.2 Hz, 2.7 Hz, 1H), 7.57-7.47 (m, 2H), 7.43-7.37 (m, 1H), 7.36-7.31 (m, 1H), 6.30 (s, 1H), 5.92 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.5, 151.3, 148.7, 148.3, 141.7, 138.4, 138.3, 136.2, 133.9, 131.4, 127.7, 127.1, 123.7, 122.8, 122.1, 121.6, 116.6.

HRMS (ESI$^+$): calcd for $C_{17}H_{13}ClN_3O$ *m/z* 310.0747 $[M+H]^+$, found 310.0747 (0.0 ppm).



47w

***N*-(Quinolin-8-yl)methacrylamide (47w)**: R_f (PE/Et_2O, 50/50): 0.60.

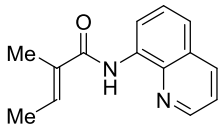
White solid; **m.p.**: 70-71 °C.

IR: 3358, 2925, 1673, 1523, 1485, 1325, 825, 790, 754.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.36 (brs, 1H), 8.96-8.68 (m, 2H), 8.26-8.06 (m, 1H), 7.63-7.47 (m, 3H), 6.04 (s, 1H), 5.55 (s, 1H), 2.19 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.4, 148.2, 140.7, 138.6, 136.3, 134.4, 127.9, 127.4, 121.6, 121.5, 120.6, 116.4, 18.7.

HRMS (ESI$^+$): calcd for $C_{13}H_{13}N_2O$ *m/z* 213.1028 $[M+H]^+$, found 213.1026 (-0.9 ppm).



47x

(*E*)-2-Methyl-*N*-(quinolin-8-yl)but-2-enamide (47x): R_f (PE/Et_2O, 50/50): 0.58.

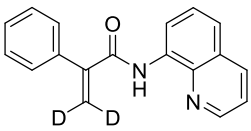
White solid; **m.p.**: 54-55 °C.

IR: 3358, 1669, 1634, 1524, 1484, 1323, 823, 788, 763.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.21 (brs, 1H), 8.80 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 8.71 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.01 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.51-7.26 (m, 3H), 6.79-6.62 (m, 1H), 2.02 (s, 3H), 1.81 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.0, 147.8, 138.3, 135.9, 134.4, 132.5, 131.6, 127.6, 127.0, 121.2, 121.0, 115.9, 14.0, 12.1.

HRMS (ESI^+): calcd for $C_{14}H_{15}N_2O$ *m/z* 227.1184 $[M+H]^+$, found 227.1182 (-0.9 ppm).



[D]-**47a**

2-Phenyl-N-(quinolin-8-yl)acrylamide-3,3-d$_2$ ([D]-47a): R_f (PE/Et_2O, 50/50): 0.65.

White solid; **m.p.**: 81-82 °C.

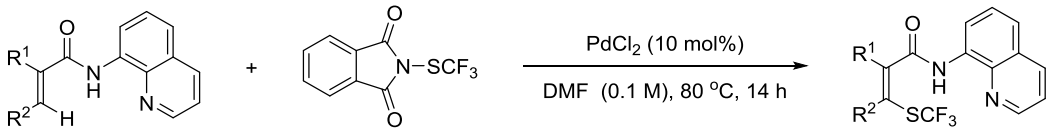
IR: 3366, 3049, 1671, 1528, 1487, 826, 754, 689.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.28 (brs, 1H), 8.93 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.61 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.07 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.60-7.41 (m, 7H), 7.36-7.30 (m, 1H), 6.32 (s, 0.08H), 5.82 (s, 0.08H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.6, 148.0, 145.5, 138.4, 136.5, 136.0, 134.2, 128.5, 128.4, 128.1, 127.6, 127.1, 122.1, 121.7, 121.4, 116.4.

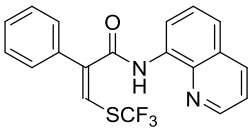
HRMS (ESI^+): calcd for $C_{18}H_{13}D_2N_2O$ *m/z* 277.1310 $[M+H]^+$, found 277.1307 (-1.1 ppm).

2.1.5 General Procedure for Pd-Catalyzed Diastereoselective Trifluoromethylthiolation of Functionalized Acrylamides



47 **Munavalli reagent 44** 1 equiv **48**

A dried tube was loaded with $PdCl_2$ (3.5 mg, 0.02 mmol, 0.1 equiv), Munavalli reagent **44** (49.4 mg, 0.2 mmol, 1 equiv) and amide **47** (0.2 mmol, 1 equiv). Then DMF (2 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at 80 °C for 14 h. After cooling, the reaction mixture was directly purified by a flash chromatography with a Biotage Isolera One Flash Purification System to give the desired product.



48a

(*Z*)-2-phenyl-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48a): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 78% (58 mg); 74% (55 mg, reaction performed in argon); 67% (500 mg, based on a 2 mmol scale). R_f (PE/Et_2O, 50/50): 0.66.

White solid; **m.p.**: 140-141 °C.

IR: 3322, 3066, 1650, 1531, 1487, 1158, 1128, 1091, 825, 792, 748, 688.

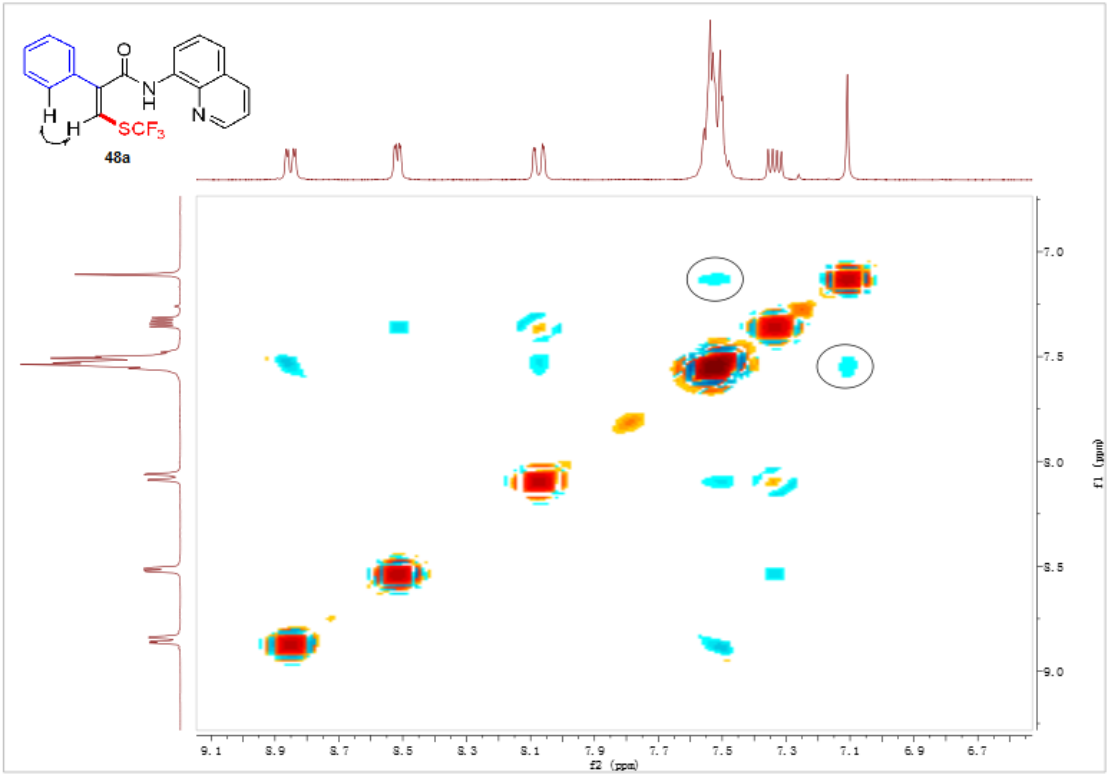
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.34 (brs, 1H), 8.85 (dd, *J* = 6.6 Hz, 2.1 Hz, 1H), 8.51 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.07 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.63-7.44 (m, 7H), 7.38-7.29 (m, 1H), 7.11 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

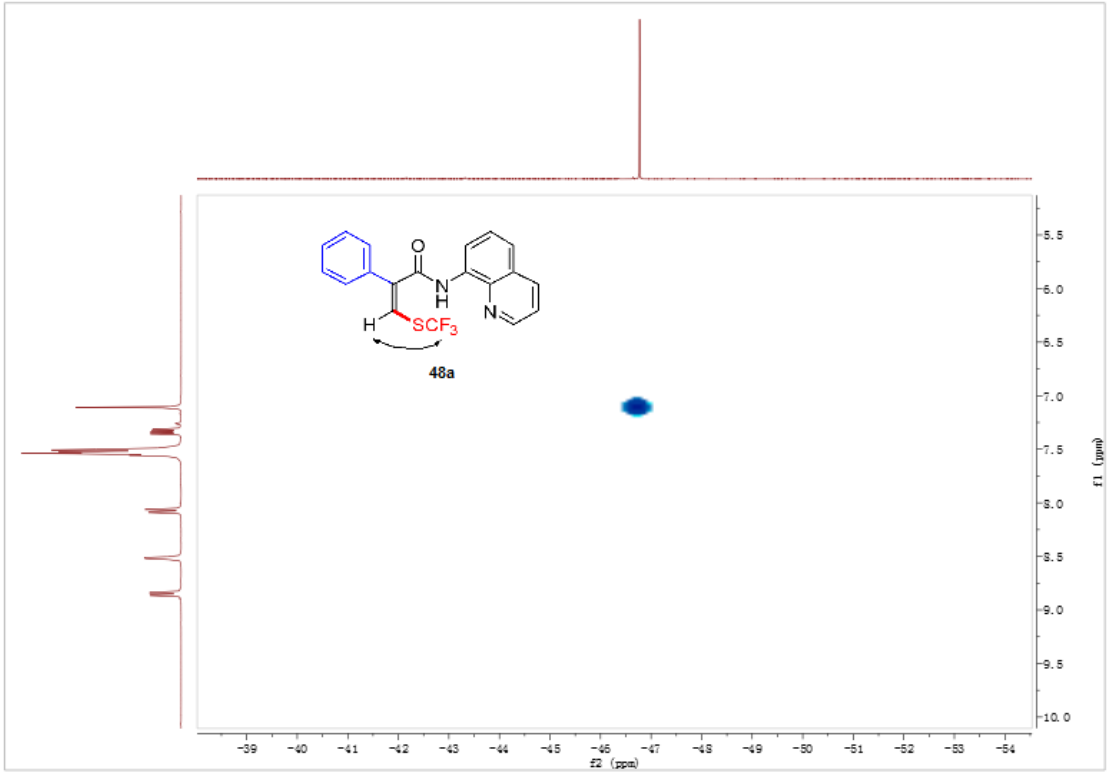
^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.3, 148.2, 138.6, 136.0, 135.6, 133.7, 133.2 (q, *J* = 0.9 Hz), 131.4 (q, *J* = 4.2 Hz), 129.6 (q, *J* = 311.2 Hz), 129.20, 129.17, 129.0, 127.7, 127.1, 122.2, 121.5, 116.4.

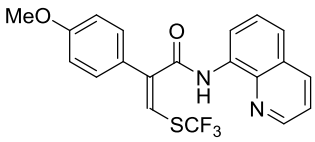
HRMS (ESI$^+$): calcd for $C_{19}H_{14}F_3N_2OS$ *m/z* 375.0779 $[M+H]^+$, found 375.0794 (4.0 ppm).

The NOESY 2D NMR of **48a**:



The HOESY 2D NMR of **48a**:





48b

(*Z*)-2-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48b): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 70% (57 mg). R_f (PE/Et_2O, 50/50): 0.50.

White solid; **m.p.**: 160-161 °C.

IR: 3325, 2845, 1645, 1612, 1532, 1511, 1248, 1125, 1099, 824, 791.

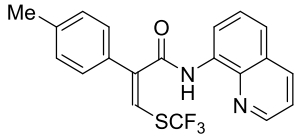
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.34 (brs, 1H), 8.84 (dd, *J* = 6.6 Hz, 2.1 Hz, 1H), 8.56 (dd, *J* = 3.9 Hz, 1.5 Hz, 1H), 8.10 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.58-7.32 (m, 5H), 7.11-

7.00 (m, 3H), 3.91 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.7, 160.2, 148.3, 138.7, 136.1, 133.8, 132.9 (q, *J* = 0.9 Hz), 130.6 (q, *J* = 4.2 Hz), 130.5, 129.5 (q, *J* = 311.1 Hz), 127.9, 127.8, 127.2, 122.2, 121.5, 116.5, 114.6, 55.4.

HRMS (ESI^+): calcd for $C_{20}H_{16}F_3N_2O_2S$ *m/z* 405.0886 $[M+H]^+$, found 405.0894 (2.2 ppm).



48c

(*Z*)-*N*-(Quinolin-8-yl)-2-(*p*-tolyl)-3-(trifluoromethylthio)acrylamide (48c): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 75% (58 mg). R_f (PE/Et_2O, 50/50): 0.66.

White solid; **m.p.**: 156-157 °C.

IR: 3323, 1651, 1532, 1488, 1150, 1128, 1096, 825, 802, 790.

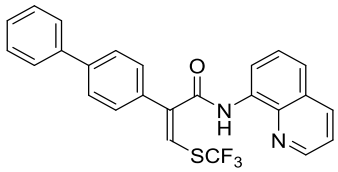
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.25 (brs, 1H), 8.75 (dd, *J* = 6.9 Hz, 1.5 Hz, 1H), 8.46 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 7.99 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.48-7.37 (m, 2H), 7.34-7.21 (m, 5H), 6.96 (s, 1H), 2.38 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.6, 148.3, 139.0, 138.7, 136.1, 133.9, 133.2 (q, *J* = 1.0 Hz), 132.7, 131.0 (q, *J* = 4.2 Hz), 129.7 (q, *J* = 311.2 Hz), 129.9, 129.0, 127.8,

127.2, 122.2, 121.5, 116.5, 21.3.

HRMS (ESI$^+$): calcd for $C_{20}H_{16}F_3N_2OS$ *m/z* 389.0935 $[M+H]^+$, found 389.0937 (0.5 ppm).



48d

(*Z*)-2-([1,1'-Biphenyl]-4-yl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48d): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 80% (72 mg). R_f (PE/Et_2O, 50/50): 0.55.

White solid; **m.p.**: 175-176 °C.

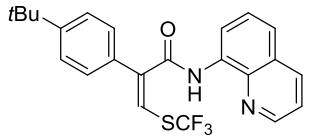
IR: 3327, 1651, 1531, 1487, 1106, 824, 791, 775, 753.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.42 (brs, 1H), 8.88 (dd, *J* = 7.2 Hz, 1.5 Hz, 1H), 8.53 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.10 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.84-7.40 (m, 11H), 7.38-7.31 (m, 1H), 7.16 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.3, 148.3, 141.8, 140.2, 138.6, 136.1, 134.5, 133.8, 132.9 (q, *J* = 0.9 Hz), 131.5 (q, *J* = 4.2 Hz), 129.65 (q, *J* = 311.3 Hz), 129.61, 128.9, 127.83, 127.79, 127.76, 127.2, 127.1, 122.3, 121.5, 116.5.

HRMS (ESI$^+$): calcd for $C_{25}H_{18}F_3N_2OS$ *m/z* 451.1092 $[M+H]^+$, found 451.1081 (-2.4 ppm).



48e

(*Z*)-2-(4-(*tert*-Butyl)phenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48e): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 89% (77 mg). R_f (PE/Et_2O, 50/50): 0.68.

White solid; **m.p.**: 148-149 °C.

IR: 3293, 2962, 1652, 1532, 1485, 1149, 1107, 818, 792, 758.

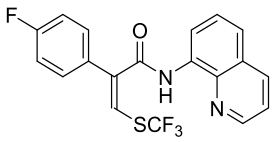
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.35 (brs, 1H), 8.84 (dd, *J* = 6.9 Hz, 1.8 Hz, 1H), 8.48 (dd, *J* = 4.2 Hz, 1.8 Hz, 1H), 8.09 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.62-7.41 (m, 6H), 7.39-7.32 (m, 1H), 7.10 (s, 1H), 1.44 (s, 9H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.6, 152.2, 148.1, 138.6, 136.1, 133.9, 133.1 (q, *J* = 0.9 Hz), 132.7, 130.8 (q, *J* = 4.2 Hz), 129.7 (q, *J* = 311.1 Hz), 129.0, 127.8, 127.2, 126.1, 122.2, 121.5, 116.3, 34.8, 31.3.

HRMS (ESI^+): calcd for $C_{23}H_{22}F_3N_2OS$ *m/z* 431.1405 $[M+H]^+$, found 431.1397 (-1.9 ppm).

The structure of **48e** has been confirmed by X-ray analysis.



48f

(*Z*)-2-(4-fluorophenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48f): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 77% (60 mg). R_f (PE/Et_2O, 50/50): 0.63.

White solid; **m.p.**: 192-193 °C.

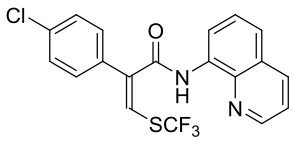
IR: 3332, 3066, 1652, 1532, 1509, 1128, 1092, 824, 792, 698.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.28 (brs, 1H), 8.85 (dd, *J* = 5.4 Hz, 1.8 Hz, 1H), 8.58 (dd, *J* = 3.9 Hz, 1.5 Hz, 1H), 8.13 (dd, *J* = 9.6 Hz, 1.5 Hz, 1H), 7.64-7.46 (m, 4H), 7.45-7.36 (m, 1H), 7.32-7.21 (m, 2H), 7.09 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s, 3F), - 112.9 ~ -112.6 (m, 1F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.2, 163.1 (q, *J* = 249.2 Hz), 148.4, 138.6, 136.2, 133.7, 132.1 (q, *J* = 3.6 Hz), 131.9 (q, *J* = 3.6 Hz), 131.6 (d, *J* = 3.5 Hz), 131.2 (q, *J* = 8.4 Hz), 129.6 (q, *J* = 311.4 Hz), 127.8, 127.2, 122.4, 121.6, 116.5, 116.2.

HRMS (ESI^+): calcd for $C_{19}H_{13}F_4N_2OS$ *m/z* 393.0685 $[M+H]^+$, found 393.0685 (0.0 ppm).



48g

(*Z*)-2-(4-Chlorophenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48g): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 75% (61 mg). R_f (PE/Et_2O, 50/50): 0.65.

White solid; **m.p.**: 194-195 °C.

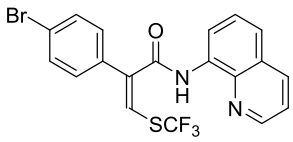
IR: 3325, 1654, 1532, 1488, 1129, 1094, 825, 808.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.26 (brs, 1H), 8.81 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 8.58 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.11 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.61-7.41 (m, 6H), 7.41-7.34 (m, 1H), 7.08 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.0, 148.5, 138.6, 136.2, 135.3, 134.1, 133.7, 132.3 (q, *J* = 4.2 Hz), 132.0 (q, *J* = 1.0 Hz), 130.6, 129.53 (q, *J* = 311.4 Hz), 129.49, 127.8, 127.2, 122.5, 121.7, 116.6.

HRMS (ESI^+): calcd for $C_{19}H_{13}ClF_3N_2OS$ *m/z* 409.0389 $[M+H]^+$, found 409.0391 (0.5 ppm).



48h

(*Z*)-2-(4-Bromophenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48h): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 70% (63 mg). R_f (PE/Et_2O, 50/50): 0.60.

White solid; **m.p.**: 180-181 °C.

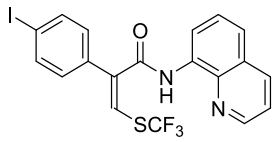
IR: 3325, 3053, 1655, 1531, 1486, 1130, 1093, 826, 807.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.26 (brs, 1H), 8.81 (dd, *J* = 5.4 Hz, 2.7 Hz, 1H), 8.58 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.11 (dd, *J* = 9.3 Hz, 1.5 Hz, 1H), 7.76-7.30 (m, 7H), 7.08 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.9, 148.5, 138.6, 136.2, 134.6, 133.6, 132.5, 132.3 (q, *J* = 4.2 Hz), 132.0 (q, *J* = 0.9 Hz), 130.9, 129.5 (q, *J* = 311.4 Hz), 127.8, 127.2, 123.4, 122.5, 121.7, 116.5.

HRMS (ESI$^+$): calcd for $C_{19}H_{13}BrF_3N_2OS$ *m/z* 452.9884 $[M+H]^+$, found 452.9876 (-1.8 ppm).



48i

(*Z*)-2-(4-Iodophenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48i): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 73% (73 mg). R_f (PE/Et_2O, 50/50): 0.58.

White solid; **m.p.**: 184-185 °C.

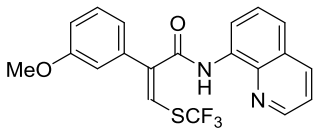
IR: 3325, 3040, 1652, 1531, 1483, 1162, 1103, 827, 805, 791.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.20 (brs, 1H), 8.74 (dd, *J* = 5.7 Hz, 3.0 Hz, 1H), 8.53 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H), 8.05 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.90-7.72 (m, 2H), 7.51-7.41 (m, 2H), 7.38-7.29 (m, 1H), 7.23-7.15 (m, 2H), 7.01 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.9, 148.5, 138.6, 138.4, 136.2, 135.2, 133.6, 132.2 (q, *J* = 4.2 Hz), 132.1 (q, *J* = 0.9 Hz), 131.0, 129.5 (q, *J* = 311.4 Hz), 127.8, 127.2, 122.5, 121.7, 116.6, 95.1.

HRMS (ESI^+): calcd for $C_{19}H_{13}F_3IN_2OS$ *m/z* 500.9745 $[M+H]^+$, found 500.9744 (-0.2 ppm).



48j

(*Z*)-2-(3-Methoxyphenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48j):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 83% (67 mg). R_f (PE/Et_2O, 50/50): 0.50.

White solid; **m.p.**: 140-141 °C.

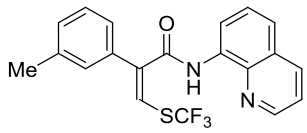
IR: 3300, 3040, 1654, 1531, 1159, 1113, 825, 791, 759.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.43 (brs, 1H), 8.84 (dd, *J* = 6.6 Hz, 2.1 Hz, 1H), 8.57 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.09 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.59-7.40 (m, 3H), 7.39-7.32 (m, 1H), 7.18-6.96 (m, 4H), 3.88 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.2, 160.1, 148.3, 138.7, 136.9, 136.1, 133.8, 132.9 (q, *J* = 0.9 Hz), 131.7 (q, *J* = 4.2 Hz), 130.4, 129.6 (q, *J* = 310.8 Hz), 127.8, 127.2, 122.3, 121.6, 121.5, 116.5, 115.1, 114.2, 55.3.

HRMS (ESI$^+$): calcd for $C_{20}H_{16}F_3N_2O_2S$ *m/z* 405.0885 $[M+H]^+$, found 405.0876 (-2.2 ppm).



48k

(*Z*)-*N*-(Quinolin-8-yl)-2-(*m*-tolyl)-3-(trifluoromethylthio)acrylamide (48k):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 82% (63 mg). R_f (PE/Et_2O, 50/50): 0.60.

White solid; **m.p.**: 145-146 °C.

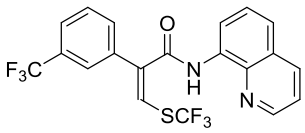
IR: 3332, 3315, 1648, 1532, 1488, 1129, 1099, 854, 824, 787.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.30 (brs, 1H), 8.73 (dd, *J* = 6.6 Hz, 2.1 Hz, 1H), 8.45 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.00 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.51-7.27 (m, 7H), 6.99 (s, 1H), 2.37 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.4, 148.3, 139.1, 138.7, 136.1, 135.6, 133.8, 133.2 (q, *J* = 0.9 Hz), 131.3 (q, *J* = 4.2 Hz), 129.8, 129.73, 129.68 (q, *J* = 311.2 Hz), 129.1, 127.8, 127.2, 126.3, 122.2, 121.6, 116.5, 21.4.

HRMS (ESI^+): calcd for $C_{20}H_{16}F_3N_2OS$ *m/z* 389.0935 $[M+H]^+$, found 389.0951 (4.1 ppm).



48l

(*Z*)-*N*-(Quinolin-8-yl)-2-(3-trifluoromethylphenyl)-3-(trifluoromethylthio)acryl-amide (48l): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 62% (55 mg). R_f (PE/Et_2O, 50/50): 0.58.

White solid; **m.p.**: 166-167 °C.

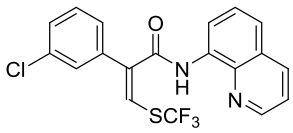
IR: 3325, 1646, 1533, 1153, 1112, 1093, 1077, 825, 801, 789.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.30 (brs, 1H), 8.80 (dd, *J* = 7.2 Hz, 1.8 Hz, 1H), 8.53 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.10 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.88-7.76 (m, 2H), 7.74-7.64 (m, 2H), 7.57-7.47 (m, 2H), 7.40-7.32 (m, 1H), 7.17 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s, 3F), -63.2 (s, 3F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.5, 148.3, 138.6, 136.5, 136.1, 133.5, 133.4 (q, *J* = 4.2 Hz), 132.8 (q, *J* = 1.0 Hz), 131.9, 131.6, 131.5, 130.0, 129.5 (q, *J* = 311.5 Hz), 127.8, 127.1, 126.0-125.7 (m, 1C), 123.8 (q, *J* = 272.8 Hz), 122.5, 121.7, 116.5.

HRMS (ESI$^+$): calcd for $C_{20}H_{13}F_6N_2OS$ *m/z* 443.0653 $[M+H]^+$, found 443.0655 (0.5 ppm).



48m

(*Z*)-2-(3-Chlorophenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48m):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 88% (72 mg). R_f (PE/Et_2O, 50/50): 0.60.

White solid; **m.p.**: 172-173 °C.

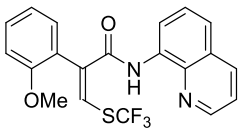
IR: 3331, 3060, 1644, 1531, 1488, 1152, 1131, 1099, 902, 823, 780.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.33 (brs, 1H), 8.80 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 8.59 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.11 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.62-7.31 (m, 7H), 7.12 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.7, 148.5, 138.7, 137.4, 136.1, 135.2, 133.6, 132.7 (q, *J* = 4.2 Hz), 131.8 (q, *J* = 1.0 Hz), 129.5 (q, *J* = 309.1 Hz), 130.5, 129.3, 129.2, 127.8, 127.5, 127.2, 122.4, 121.7, 116.5.

HRMS (ESI$^+$): calcd for $C_{19}H_{13}ClF_3N_2OS$ *m/z* 409.0389 $[M+H]^+$, found 409.0396 (0.7 ppm).



48n

(*Z*)-2-(2-Methoxyphenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide

(48n): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 78% (63 mg). R_f (PE/Et_2O, 50/50): 0.45.

White solid; **m.p.**: 112-113 °C.

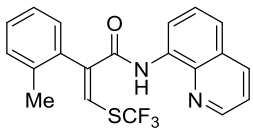
IR: 3319, 2839, 1653, 1526, 1486, 1255, 1108, 825, 790, 752.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.18 (brs, 1H), 8.82 (dd, *J* = 7.2 Hz, 1.5 Hz, 1H), 8.53 (dd, *J* = 4.1 Hz, 1.5 Hz, 1H), 8.09 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.58-7.45 (m, 3H), 7.40-7.31 (m, 2H), 7.16-7.06 (m, 2H), 7.05 (s, 1H), 3.77 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.5, 157.2, 148.1, 138.6, 136.1, 134.1, 131.8, 131.4 (q, *J* = 4.2 Hz), 130.9, 130.5 (q, *J* = 0.9 Hz), 129.7 (q, *J* = 311.1 Hz), 127.8, 127.3, 124.4, 121.9, 121.5, 121.3, 116.5, 111.3, 55.5.

HRMS (ESI$^+$): calcd for $C_{20}H_{16}F_3N_2O_2S$ *m/z* 405.0885 $[M+H]^+$, found 405.0869 (-3.9 ppm).



48o

(*Z*)-*N*-(Quinolin-8-yl)-2-(*o*-tolyl)-3-(trifluoromethylthio)acrylamide (48o):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 80% (62 mg). R_f (PE/Et_2O, 50/50): 0.63.

White solid; **m.p.**: 95-96 °C.

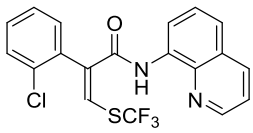
IR: 3301, 3040, 1653, 1526, 1485, 1148, 1124, 1111, 822, 788, 751.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.03 (brs, 1H), 8.82 (dd, *J* = 6.9 Hz, 1.5 Hz, 1H), 8.47 (dd, *J* = 4.2 Hz, 0.9 Hz, 1H), 8.08 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.58-7.29 (m, 7H), 7.03 (s, 1H), 2.33 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.4, 148.3, 138.6, 137.6, 136.0, 134.7, 133.8, 132.4 (q, *J* = 0.9 Hz), 131.3 (q, *J* = 4.2 Hz), 130.9, 130.6, 129.5 (q, *J* = 311.1 Hz), 129.4, 127.7, 127.2, 126.7, 122.2, 121.5, 116.4, 19.9.

HRMS (ESI$^+$): calcd for $C_{20}H_{16}F_3N_2OS$ *m/z* 389.0935 $[M+H]^+$, found 389.0931 (-1.0 ppm).



48p

(*Z*)-2-(2-Chlorophenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48p): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 82% (67 mg). R_f (PE/Et_2O, 50/50): 0.46.

White solid; **m.p.**: 135-136 °C.

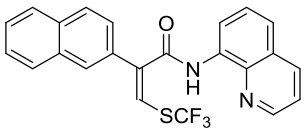
IR: 3306, 3047, 1662, 1526, 1150, 1118, 824, 789, 758, 690.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.02 (brs, 1H), 8.81 (dd, *J* = 6.9 Hz, 1.5 Hz, 1H), 8.46 (dd, *J* = 4.1 Hz, 1.5 Hz, 1H), 8.06 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.63-7.43 (m, 6H), 7.37-7.29 (m, 1H), 7.11 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.6, 148.2, 138.5, 136.0, 134.6, 134.0, 133.7, 133.1 (q, *J* = 4.2 Hz), 132.0, 129.5 (q, *J* = 311.2 Hz), 130.7, 130.4 (q, *J* = 0.9 Hz), 130.3, 127.7, 127.6, 127.1, 122.2, 121.5, 116.3.

HRMS (ESI^+): calcd for $C_{18}H_{13}ClF_3N_2OS$ *m/z* 409.0389 $[M+H]^+$, found 409.0392 (0.7 ppm).



48q

(*Z*)-2-(Naphthalen-2-yl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48q): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 78% (66 mg). R_f (PE/Et_2O, 50/50): 0.45.

White solid; **m.p.**: 166-167 °C.

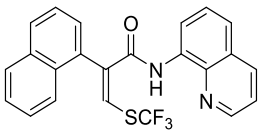
IR: 3324, 3057, 1651, 1533, 1157, 1129, 1101, 824, 791, 753.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.34 (brs, 1H), 8.75 (dd, *J* = 7.2 Hz, 1.5 Hz, 1H), 8.21 (dd, *J* = 4.4 Hz, 1.5 Hz, 1H), 7.98-7.77 (m, 5H), 7.53-7.35 (m, 5H), 7.19-7.13 (m, 1H), 7.10 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.3, 148.3, 138.6, 136.0, 133.8, 133.4, 133.2, 133.0, 131.9 (q, *J* = 4.2 Hz), 129.7 (q, *J* = 311.3 Hz), 129.1, 128.6, 128.2, 127.8, 127.7, 127.1, 126.90, 126.85, 126.4, 122.3, 121.5, 116.6 (one carbon is missing).

HRMS (ESI^+): calcd for $C_{23}H_{16}F_3N_2OS$ *m/z* 425.0935 $[M+H]^+$, found 425.0927 (0.7 ppm).



48r

(*Z*)-2-(Naphth-1-yl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48r): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 85% (72 mg). R_f (PE/Et_2O, 50/50): 0.44.

White solid; **m.p.**: 146-147 °C.

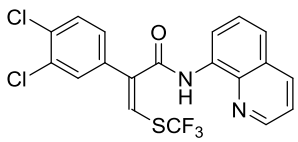
IR: 3325, 3053, 1641, 1528, 1490, 1150, 1113, 1103, 849, 799.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 9.89 (brs, 1H), 8.69 (dd, *J* = 7.5 Hz, 0.6 Hz, 1H), 8.02 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 7.94 (dd, *J* = 5.4 Hz, 1.5 Hz, 1H), 7.89-7.78 (m, 3H), 7.57-7.47 (m, 2H), 7.45-7.28 (m, 4H), 7.11 (s, 1H), 7.09-7.03 (m, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.6 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.7, 147.9, 138.3, 135.8, 133.9, 133.6, 132.6 (q, *J* = 4.2 Hz), 132.5, 132.3, 131.2 (q, J = 0.9 Hz), 129.8, 129.7 (q, J = 311.4 Hz), 128.5, 127.6, 127.1, 127.0, 126.5, 125.5, 125.2, 122.1, 121.3, 116.2 (one carbon is missing).

HRMS (ESI^+): calcd for $C_{23}H_{16}F_3N_2OS$ *m/z* 425.0924 $[M+H]^+$, found 425.0927 (0.7 ppm).



48s

(*Z*)-2-(3,4-Dichlorophenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48s): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 77% (68 mg). R_f (PE/Et_2O, 50/50): 0.45.

White solid; **m.p.**: 180-181 °C.

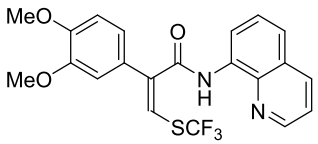
IR: 3334, 1645, 1532, 1154, 1130, 1107, 825, 813, 791, 765.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.30 (brs, 1H), 8.83-8.74 (m, 1H), 8.63 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.13 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 7.69-7.49 (m, 4H), 7.45-7.32 (m, 2H), 7.12 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.4, 148.6, 138.7, 136.2, 135.5, 133.6, 133.57, 133.53, 133.3 (q, *J* = 4.2 Hz), 131.2, 131.1, 130.8 (q, *J* = 1.0 Hz), 129.4 (q, *J* = 311.6 Hz), 128.6, 127.8, 127.2, 122.6, 121.8, 116.6.

HRMS (ESI^+): calcd for $C_{19}H_{12}Cl_2F_3N_2OS$ *m/z* 442.9999 $[M+H]^+$, found 443.0005 (1.4 ppm).



48t

(*Z*)-2-(3,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48t): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 100/0 to 70/30). Yield: 55% (48 mg). R_f (PE/Et_2O, 50/50): 0.22.

White solid; **m.p.**: 165-166 °C.

IR: 3325, 3007, 1640, 1530, 1514, 1138, 1122, 1091, 805, 789.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.43 (brs, 1H), 8.84 (dd, *J* = 6.6 Hz, 2.4 Hz, 1H), 8.58 (dd, *J* = 4.2 Hz, 1.8 Hz, 1H), 8.10 (dd, *J* = 8.3 Hz, 1.8 Hz, 1H), 7.60-7.47(m, 2H), 7.42-7.32 (m, 1H), 7.10-7.00 (m, 4H), 3.98 (s, 3H), 3.93 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.9 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.5, 149.6, 149.2, 148.3, 138.7, 136.2, 133.8, 132.7 (q, *J* = 1.0 Hz), 131.0 (q, *J* = 4.2 Hz), 129.7 (q, *J* = 311.2 Hz), 128.1, 127.8, 127.2, 122.3, 122.0, 121.6, 116.6, 111.7, 111.6, 56.0, 55.9.

HRMS (ESI$^+$): calcd for $C_{21}H_{18}F_3N_2O_3S$ *m/z* 435.0990 $[M+H]^+$, found 435.0989 (-0.2 ppm).

48u

(*Z*)-2-(Benzo[d][1,3]dioxol-5-yl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48u): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 100/0 to 70/30). Yield: 65% (54 mg). R_f (PE/Et_2O, 50/50): 0.35.

White solid; **m.p.**: 177-178 °C.

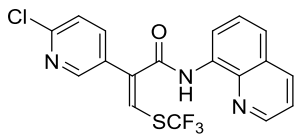
IR: 3332, 3047, 1647, 1532, 1488, 1250, 1126, 1094, 807, 788.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.37 (brs, 1H), 8.82 (dd, *J* = 6.5 Hz, 2.4 Hz, 1H), 8.60 (dd, *J* = 4.2 Hz, 1.8 Hz, 1H), 8.10 (dd, *J* = 8.3 Hz, 1.8 Hz, 1H), 7.60-7.48 (m, 2H), 7.41-7.34 (m, 1H), 7.04 (s, 1H), 7.00-6.93 (m, 3H), 6.08 (s, 2H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.5, 148.4, 148.30, 148.28, 138.7, 136.1, 133.8, 132.7 (q, *J* = 1.0 Hz), 131.1 (q, *J* = 4.2 Hz), 129.7 (q, *J* = 311.2 Hz), 129.2, 127.8, 127.2, 123.1, 122.3, 121.6, 116.5, 109.6, 108.9, 101.5.

HRMS (ESI^+): calcd for $C_{20}H_{14}F_3N_2O_3S$ *m/z* 419.0666 $[M+H]^+$, found 419.0678 (2.9 ppm).



48v

(*Z*)-2-(6-Chloropyridin-3-yl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48v): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 49% (40 mg). R_f (PE/Et_2O, 50/50): 0.28.

White solid; **m.p.**: 144-145 °C.

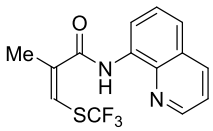
IR: 3325, 3053, 1657, 1531, 1329, 1128, 1106, 894, 824, 792.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.16 (brs, 1H), 8.85-8.72 (m, 1H), 8.65-8.51 (m, 2H), 8.13 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 7.83 (dd, *J* = 8.3 Hz, 2.4 Hz, 1H), 7.63-7.47 (m, 3H), 7.44-7.37 (m, 1H), 7.15 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.7 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.3, 152.3, 149.8, 148.6, 139.3, 138.5, 136.3, 134.3 (q, *J* = 4.2 Hz), 133.3, 130.6, 129.3 (q, *J* = 311.7 Hz), 128.4 (q, *J* = 1.0 Hz), 127.8, 127.2, 124.6, 122.7, 121.8, 116.6.

HRMS (ESI$^+$): calcd for $C_{18}H_{12}ClF_3N_3OS$ *m/z* 410.0342 $[M+H]^+$, found 410.0338 (-1.0 ppm).



48w

(*Z*)-2-Methyl-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)acrylamide (48w):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 100/0 to 70/30). Yield: 30% (19 mg). R_f (PE/Et_2O, 50/50): 0.55.

White solid; **m.p.**: 150-151 °C.

IR: 3318, 1643, 1538, 1489, 1129, 1100, 1023, 822, 808, 783.

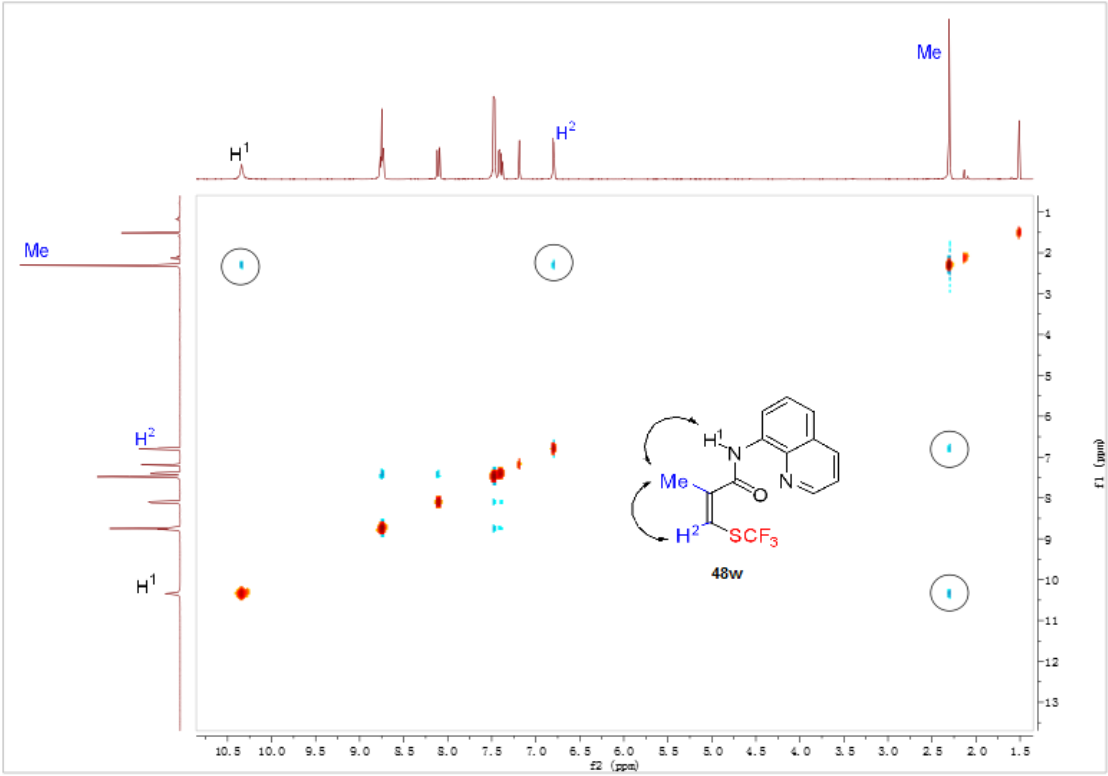
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.41 (brs, 1H), 8.87-8.77 (m, 2H), 8.17 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 7.59-7.52 (m, 2H), 7.51-7.44 (m, 1H), 6.87 (d, *J* = 0.9 Hz, 1H), 2.38 (d, *J* = 0.9 Hz, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -47.0 (s).

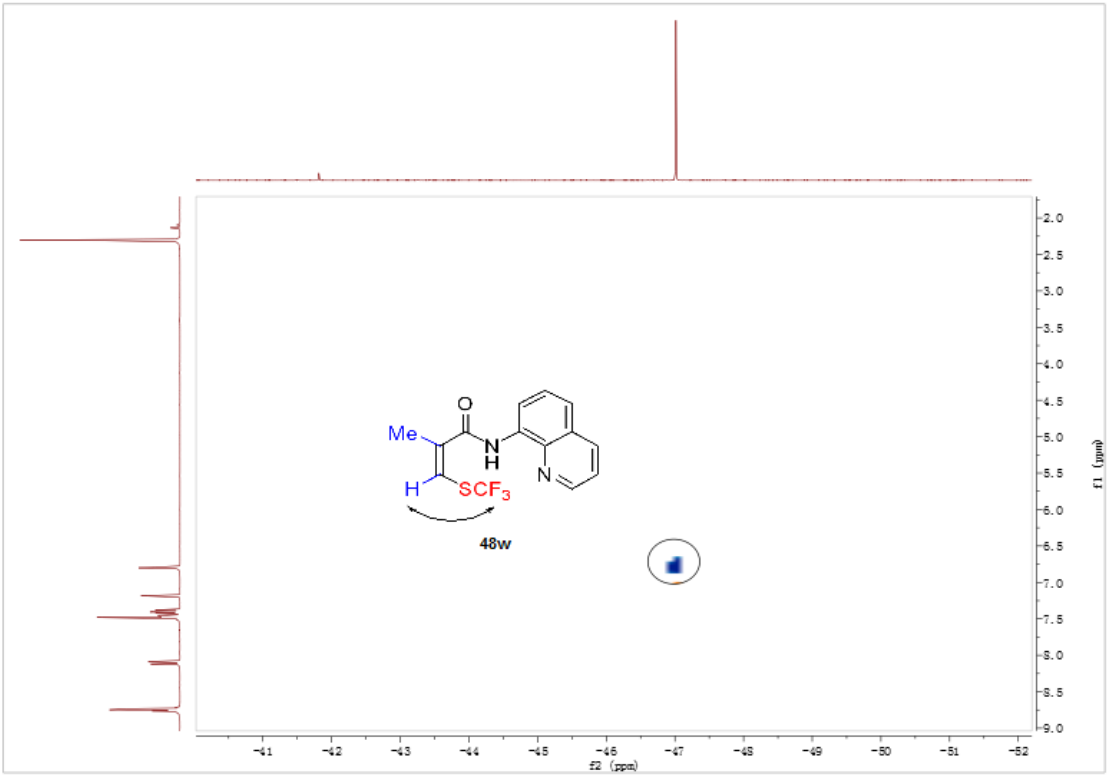
^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.1, 148.4, 138.6, 136.4, 133.7, 129.8 (q, *J* = 310.8 Hz), 129.0 (q, *J* = 4.2 Hz), 127.9, 127.3, 125.8 (q, *J* = 1.0 Hz), 122.2, 121.8, 116.6, 18.5.

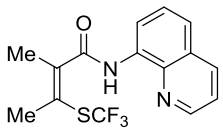
HRMS (ESI^+): calcd for $C_{14}H_{12}F_3N_2OS$ *m/z* 313.0622 $[M+H]^+$, found 313.0620 (-0.6 ppm).

The NOESY 2D NMR of **48w**:



The HOESY 2D NMR of **48w**:





48x

(*Z*)-2-Methyl-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)but-2-enamide (48x):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 100/0 to 70/30). Yield: 20% (13 mg). R_f (PE/Et_2O, 50/50): 0.53.

White solid; **m.p.**: 70-71 °C.

IR: 3318, 2917, 1644, 1526, 1487, 1083, 822, 784, 757.

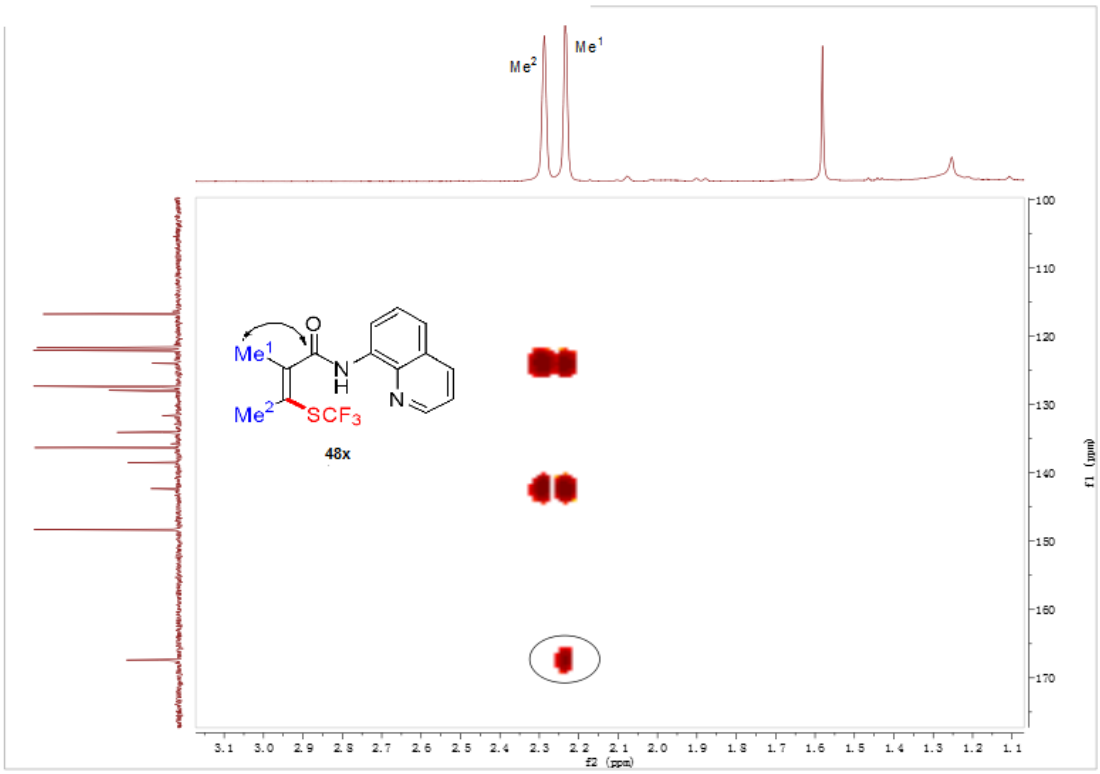
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.00 (brs, 1H), 8.86-8.76 (m, 2H), 8.18 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 7.62-7.52 (m, 2H), 7.50-7.43 (m, 1H), 2.29 (s, 3H), 2.23 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -39.9 (s).

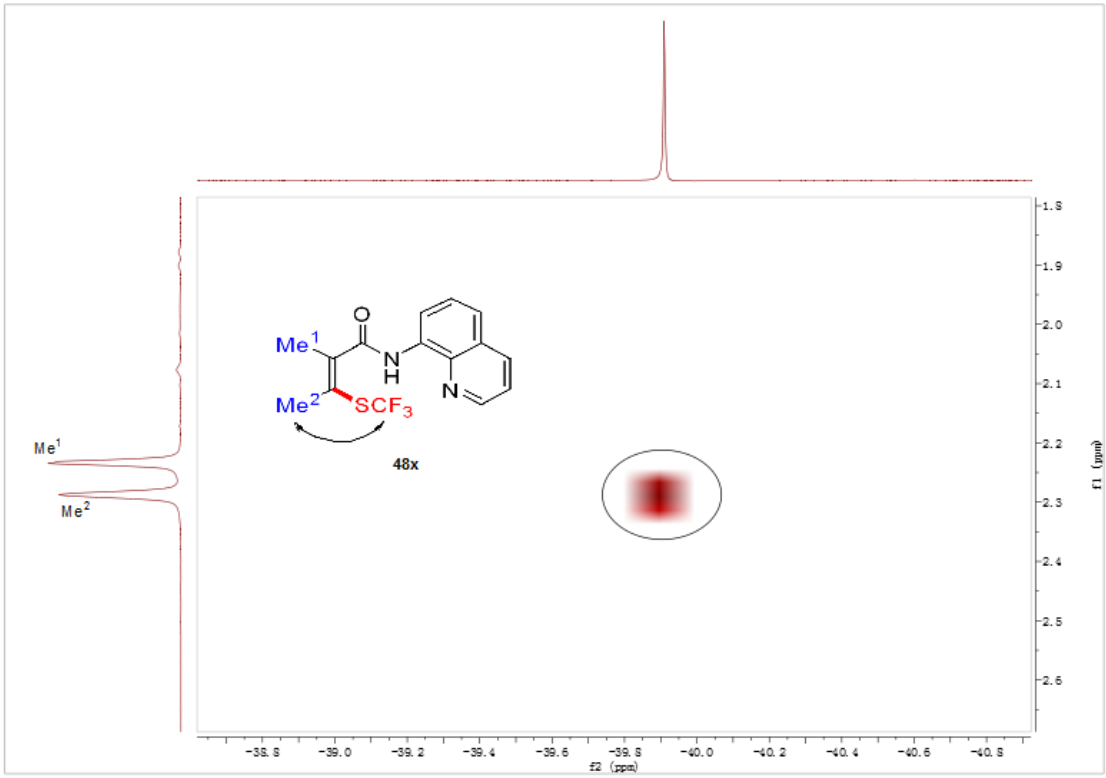
^{13}C NMR (75.5 MHz, $CDCl_3$): δ 167.4, 148.3, 142.3 (q, *J* = 1.0 Hz), 138.5, 136.3, 134.1, 129.6 (q, *J* = 310.4 Hz), 127.9, 127.3, 124.0, 122.1, 121.7, 116.8, 21.2, 18.0.

HRMS (ESI$^+$): calcd for $C_{15}H_{14}F_3N_2OS$ *m/z* 327.0779 $[M+H]^+$, found 327.0768 (-3.4 ppm).

The HMBC 2D NMR of **48x**:

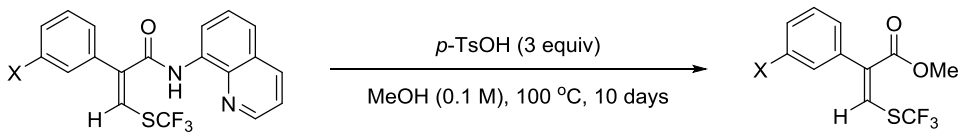


The HOESY 2D NMR of **48x**:



2.1.6 Post-Functionalization of the Resulting Product

2.1.6.1 Cleavage of the directing group



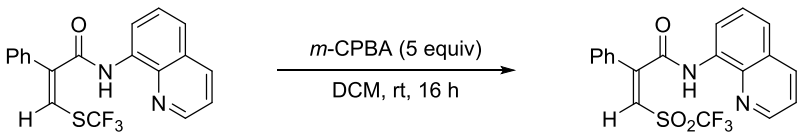
48a, X = H
48j, X = Cl

63a, 66%
63j, 54%

A dried tube was loaded with **48a** (37.4 mg, 0.1 mmol, 1 equiv) and *p*-toluenesulfonic acid (258 mg, 0.15 mmol, 1.5 equiv). Then dry MeOH (2 mL) was injected. The tube was sealed with a rubber septum and stirred at room temperature. Another batch of *p*-toluenesulfonic acid (258 mg, 0.15 mmol, 1.5 equiv) was added after 7 days. The reaction was followed by GC-MS until full conversion (10 days). Then, the solvent was removed under reduced pressure. The residue was purified by a flash chromatography with a Biotage Isolera One Flash Purification System.

Note that the **63j** was prepared based on a 0.4 mmole scale from **48j**.

2.1.6.2 Oxidation



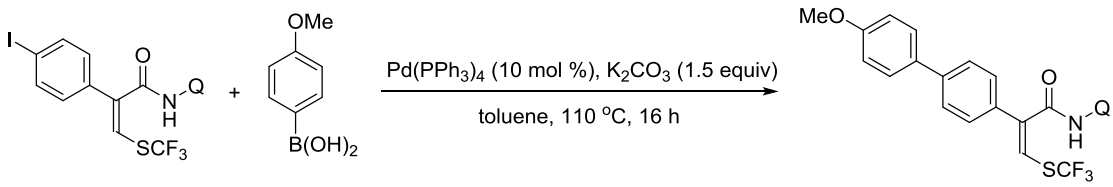
48a

64
74%

A dried tube was loaded with **48a** (37.4 mg, 0.1 mmol, 1 equiv) and *m*-CPBA (287 mg, 0.5 mmol, 5 equiv, assay ca. 30%). Then dry DCM (2 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at room temperature

overnight. Then, the reaction mixture was diluted with DCM (10 mL), washed with a saturated Na_2SO_3 aqueous solution (10 mL), a saturated $NaHCO_3$ aqueous solution (10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by a flash chromatography with a Biotage Isolera One Flash Purification System.

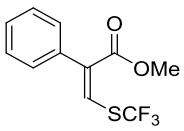
2.1.6.3 Suzuki cross-coupling reaction



48i
Q = 8-quinolyl

65
79%

A dried tube was loaded with **48i** (50.0 mg, 0.1 mmol, 1 equiv), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 10 mol %), (4-methoxyphenyl)boronic acid (16.7 mg, 0.11 mmol, 1.1 equiv) and K_2CO_3 (20.7 mg, 0.15 mmol, 1.5 equiv). Fresh distilled toluene (2 mL) was injected and then the solution was degassed under reduced pressure for three times. The tube was sealed with a rubber septum and stirred at 110 °C for 16 h. Then, the solvent was removed under reduced pressure. The residue was purified by a flash chromatography with a Biotage Isolera One Flash Purification System.



63a

Methyl-(Z)-2-phenyl-3-(trifluoromethylthio)acrylate (63a): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 66% (17 mg). R_f (PE/Et_2O, 50/50): 0.45.

Colorless oil.

IR: 2959, 1694, 1346, 1231, 1109, 1013, 748, 696, 646.

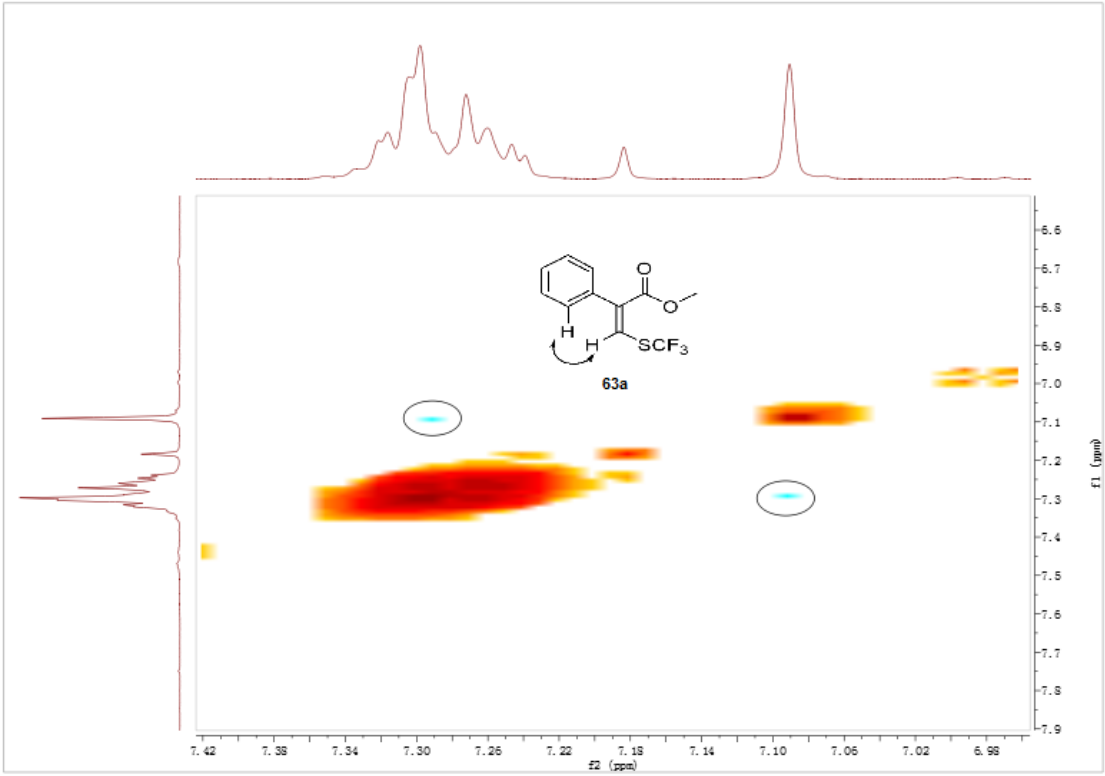
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.37-7.21 (m, 5H), 3.76(s).

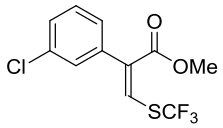
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -45.8 (s).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 135.8, 134.4 (q, *J* = 4.1 Hz), 134.3, 130.6, 129.3 (q, *J* = 310.4 Hz), 128.7, 128.4, 128.3, 52.7.

HRMS (ESI$^+$): calcd for $C_{11}H_{10}F_3O_2S$ *m/z* 263.0354 $[M+H]^+$, found 263.0355 (0.4 ppm).

The NOESY 2D NMR of **63a**:





63j

Methyl-(*Z*)-2-(3-chlorophenyl)-3-(trifluoromethylthio)acrylate (63j): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm,

eluent: PE/Et_2O, from 100/0 to 70/30). Yield: 54% (64 mg, based on a 0.4 mmol scale).

R_f (PE/Et_2O, 75/25): 0.75.

Colorless oil.

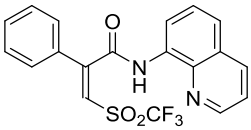
IR: 3056, 2956, 1695, 1252, 1109, 1021, 792, 716, 691.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.37-7.27 (m, 3H), 7.25-7.16 (m, 2H), 3.84 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -45.8 (s).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 137.4, 135.5 (q, *J* = 4.2 Hz), 134.2, 129.5, 129.20 (q, *J* = 1.1 Hz), 129.18 (q, *J* = 310.7 Hz), 128.8, 128.4, 126.9, 52.7.

HRMS (EI^+): calcd for $C_{11}H_8ClF_3O_2S$ *m/z* 295.9886 $[M]^+$, found 295.9883 (-0.3 ppm).



64

(*Z*)-2-Phenyl-*N*-(quinolin-8-yl)-3-(trifluoromethylsulfonyl)acrylamide (64):

Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: EA). Yield: 74% (30 mg). R_f (EA): 0.39.

Yellow solid; **m.p.**: 95-96 °C.

IR: 1736, 1650, 1531, 1488, 1410, 1182, 1170, 1158, 1059, 817, 746.

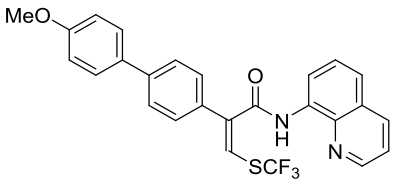
^{1}H NMR (300.1 MHz, $CDCl_3$): δ 14.90 (brs, 1H), 9.16 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.22 (dd, *J* = 6.0 Hz, 1.0 Hz, 1H), 7.78 (dd, *J* = 8.6 Hz, 1.5 Hz, 1H), 7.68-7.51 (m, 7H), 7.25-7.19 (m, 1H), 6.76 (s, 1H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -71.1 (s).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 151.0, 137.5, 137.4 (q, *J* = 2.4 Hz), 133.1, 132.6,

132.1, 130.9, 129.4, 129.3, 129.1, 128.8, 125.4 (q, *J* = 338.2 Hz), 123.8, 123.2, 120.8, 120.3.

HRMS (ESI$^+$): calcd for $C_{19}H_{14}F_3N_2O_3S$ *m/z* 407.0677 [M+H]$^+$, found 407.0674 (-0.7 ppm).



65

(*Z*)-2-(4'-Methoxy-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)-3-(trifluoromethylthio)-acrylamide (65): Purification by silica gel column chromatography (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 85/15 to 65/35). Yield: 79% (38 mg). R_f (PE/DCM, 50/50): 0.45.

White solid; **m.p.**: 175-176 °C.

IR: 3327, 2927, 1645, 1531, 1487, 1148, 1126, 1101, 811, 791, 685.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.40 (brs, 1H), 8.86 (dd, *J* = 6.9 Hz, 2.1 Hz, 1H), 8.53 (dd, *J* = 4.2 Hz, 1.8 Hz, 1H), 8.07 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 7.77-7.50 (m, 8H), 7.38-7.32 (m, 1H), 7.13 (s, 1H), 7.08-7.02 (m, 2H), 3.89 (s, 3H).

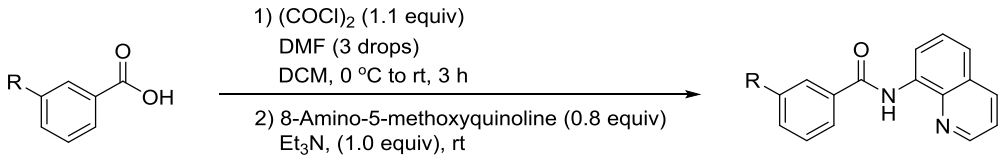
^{19}F NMR (282.4 MHz, $CDCl_3$): δ -46.8 (s).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.5, 159.5, 148.4, 141.5, 138.7, 136.1, 133.9, 133.8, 133.0 (q, *J* = 0.8 Hz), 132.7, 131.4 (q, *J* = 4.5 Hz), 129.7 (q, *J* = 311.2 Hz), 129.6, 128.1, 127.8, 127.4, 127.2, 122.3, 121.6, 116.5, 114.4, 55.4.

HRMS (ESI$^+$): calcd for $C_{26}H_{20}F_3N_2O_2S$ *m/z* 481.1198 [M+H]$^+$, found 481.1208 (2.1 ppm).

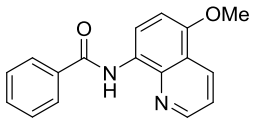
2.2 Transition metal catalyzed aromatic C (sp^2) -H bond functionalization with the Munavalli reagent

2.2.1 The procedure for the synthesis of 69a and 69b.



69a, R = H
69b, R = Me

Oxalyl chloride (1.1 mmol, 1.1 equiv) was slowly added at 0 °C to a solution of the acid (1 mmol, 1 equiv) and DMF (1 drops) in dry DCM (5 mL). After stirring at room temperature for 3 h, the solvent was removed under vacuum and the residue was dissolved in dry DCM. 8-Amino-5-methoxyquinoline (0.8 mmol, 0.8 equiv) was added and the reaction was followed by TLC until completed. Water (100 mL) was added and the resulting mixture was extracted with Et_2O (3 × 150 mL). Removal of the solvent under vacuum and purification of the residue by Biotage afforded the desired product **69a** and **69b**.



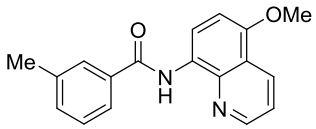
69a

***N*-(5-Methoxyquinolin-8-yl)benzamide (69a)**:

White solid;

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.49 (brs, 1H), 8.92-8.79 (m, 2H), 8.61 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 8.11-8.04 (m, 2H), 7.61-7.41 (m, 4H), 6.89 (d, *J* = 8.7 Hz, 1H), 4.00 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.1, 150.4, 148.7, 139.4, 135.3, 131. 6, 131.3, 128.7, 127.9, 127.1, 120.7, 120.5, 116.7, 104.3, 55.7.



69b

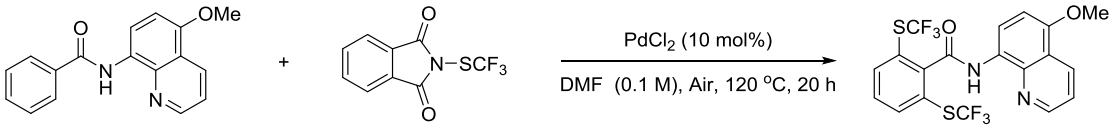
***N*-(5-Methoxyquinolin-8-yl)-3-methylbenzamide (69b)**:

Yellow solid;

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.43 (brs, 1H), 8.88-8.75 (m, 2H), 8.53 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.87-7.78 (m, 2H), 7.47-7.28 (m, 3H), 6.89 (d, *J* = 8.7 Hz, 1H), 3.95 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ165.1, 150.2, 148.5, 139.2, 138.4, 135.2, 132.2, 131.1, 128.4, 127.9, 127.8, 124.0, 120.6, 120.3, 116.5, 104.1, 55.6, 21.4.

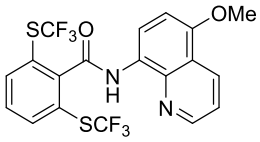
2.2.1 The procedure for the synthesis of 70a and 70b.



69a **Munavalli reagent 44** 2.2 equiv **70a**

A dried tube was loaded with $PdCl_2$ (3.5 mg, 0.02 mmol, 0.1 equiv), Munavalli reagent **44** (108.7 mg, 0.44 mmol, 2.2 equiv) and amide **69a** (55.6 mg, 0.2 mmol, 1 equiv). Then DMF (2 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at 120 °C for 20 h. After cooling, the reaction mixture was directly purified by a flash chromatography with a Biotage Isolera One Flash

Purification System to give the desired product **70a** (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/Et_2O, from 99/1 to 70/30). Yield: 56% (54 mg). R_f (PE/Et_2O, 50/50): 0.32.



70a

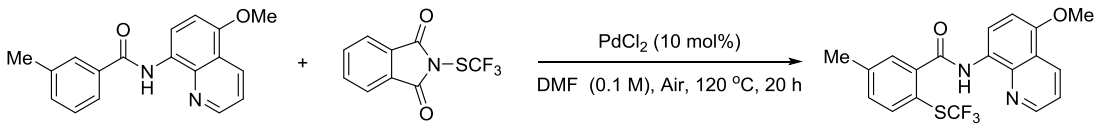
***N*-(5-Methoxyquinolin-8-yl)-2,6-bis((trifluoromethyl)thio)benzamide (70a)**:

White solid;

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 9.89 (brs, 1H), 8.87 (d, *J* = 8.4 Hz, 1H), 8.73 (dd, *J* = 4.2 Hz, 1.5 Hz, 1H), 8.59 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 7.97-7.93 (m, 2H), 7.64-7.54 (m, 1H), 7.46-7.39 (m, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 4.02 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -42.1 (s).

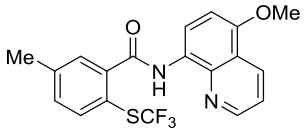
^{13}C NMR (75.5 MHz, $CDCl_3$): δ 162.9, 151.1, 149.8, 148.8, 139.8, 139.2, 131.2, 130.5, 128.9 (q, *J* = 309.6 Hz), 127.2, 123.8 (q, *J* = 2.0 Hz), 120.9, 120.5, 117.3, 104.1, 55.8.



69b **Munavalli reagent 44** 1.2 equiv **70b**

A dried tube was loaded with $PdCl_2$ (3.5 mg, 0.02 mmol, 0.1 equiv), Munavalli reagent **44** (59.3 mg, 0.24 mmol, 1.2 equiv) and amide **69b** (58.4 mg, 0.2 mmol, 1 equiv). Then DMF (2 mL) was injected. The tube was sealed with a rubber septum and the suspension was stirred at 120 °C for 20 h. After cooling, the reaction mixture was

directly purified by a flash chromatography with a Biotage Isolera One Flash Purification System to give the desired product **70b** (Biotage system 25 g, height 80 mm, width 30 mm, eluent: PE/DCM, from 99/1 to 70/30). Yield: 54% (42 mg). R_f (PE/DCM, 50/50): 0.35.



70b

***N*-(5-Methoxyquinolin-8-yl)-5-methyl-2-(trifluoromethylthio)benzamide (70b)**

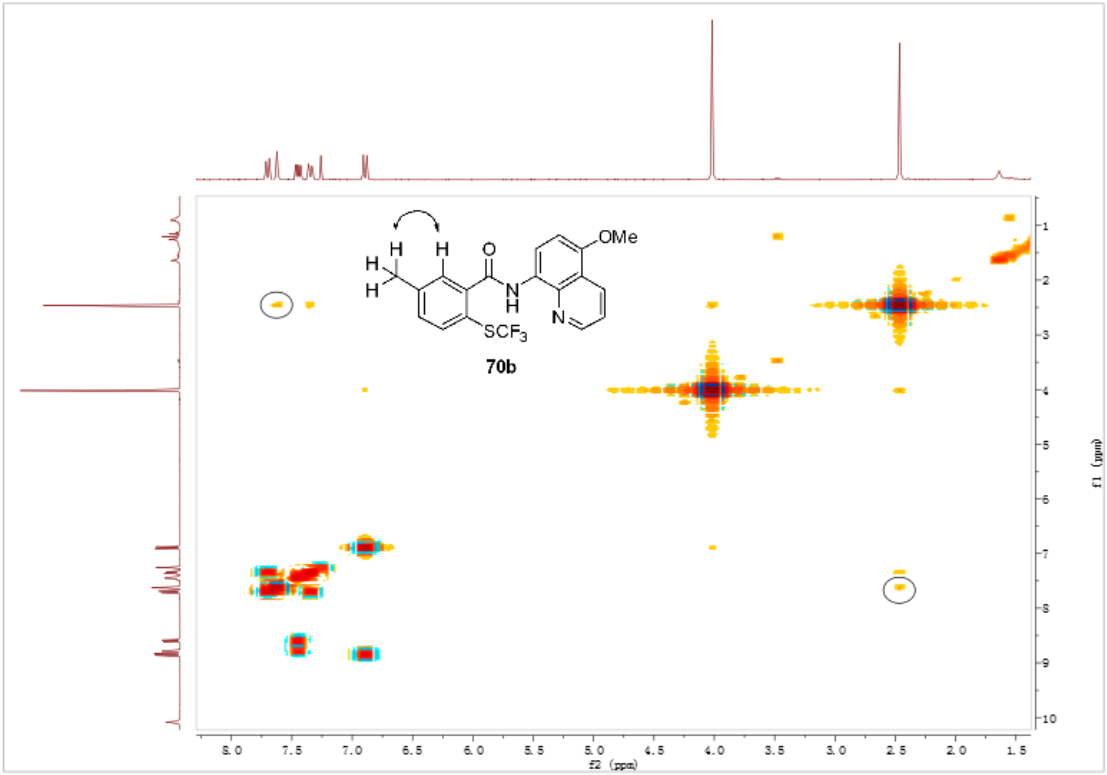
White solid;

^{1}H NMR (300.1 MHz, $CDCl_3$): δ 10.09 (brs, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 8.79 (dd, *J* = 4.2 Hz, 1.2 Hz, 1H), 8.60 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.62 (s, 1H), 7.49-7.40 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.02 (s, 3H), 2.47 (s, 3H).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ -42.4 (s).

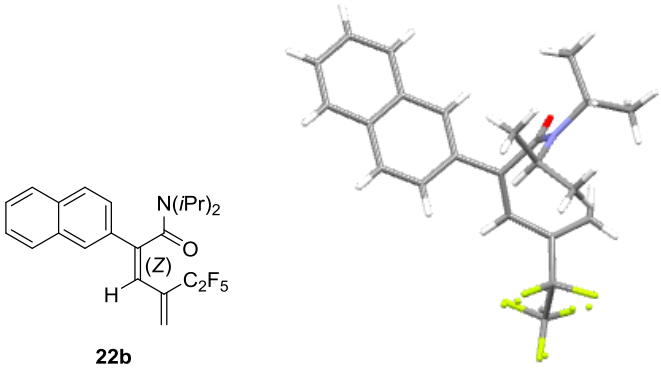
^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.4, 150.8, 148.8, 142.1, 141.3, 139.3, 136.6, 135.6, 131.6, 129.5 (q, *J* = 309.2 Hz), 131.3, 129.3, 127.7, 120.8, 120.5, 119.8 (q, *J* = 2.0 Hz), 117.1, 104.2, 55.8, 21.3.

The COSY 2D NMR of **70b**:



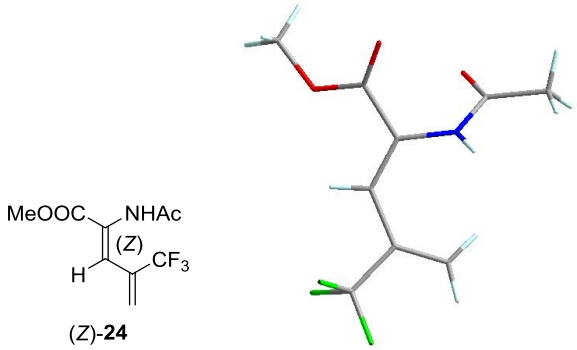
3 X-ray analysis

X-Ray diffraction analysis for compound (**22g**): $C_{23}H_{24}F_5NO$, M = 425.43, Monoclinic, $P2_1/c$, a = 14.853(3) Å, b = 7.5783(13) Å, c = 19.985(3) Å, V = 2201.7(6) Å^3, Z, Z' = 4, 1, d_{calc} = 1.283. The data have been deposit to the Cambridge Crystallographic Data Centre (Nr CCDC 1510671).



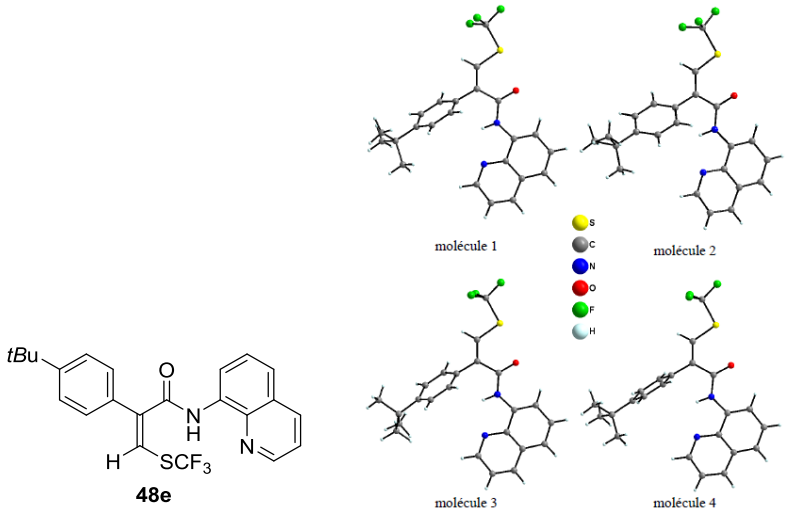
X-ray diffraction analysis of compound (**22b**).

X-Ray diffraction analysis for compound ((*Z*)-**24**): $C_9H_{10}F_3NO_3$, M = 237.18, Monoclinic, $P2_1/c$, a = 4.8239(6) Å, b = 19.410(2) Å, c = 11.5351(14) Å, V = 1080.1(2) Å^3, Z, Z' = 4, 1, d_{calc} = 1.459. The data have been deposit to the Cambridge Crystallographic Data Centre (Nr CCDC 1490131).



X-ray diffraction analysis of compound (*Z*)-**24**.

X-Ray diffraction analysis for compound (**48e**): $C_{23}H_{21}F_3N_2O_1S_1$, M = 430.5, Monoclinic, $P2_1/n$, a = 17.843(2) Å, b = 22.613(2) Å, c = 23.019(2) Å, V = 8993(1) Å^3, Z = 16, d_{calc} = 1.272. The data have been deposit to the Cambridge Crystallographic Data Centre (Nr CCDC 1564064).



X-ray diffraction analysis of compound **48e**.

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Annex

Curriculum Vitae

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Education

10/2014-present: Ph.D. student in Organic Chemistry, UMR 6014-COBRA, France.

09/2011-07/2014: Research Master, Medicinal Chemistry, Fudan University, China.

09/2005-07/2009: Bachelor, Pharmaceutical Engineering, Wuhan University of Technology, China.

Professional Experiences

10/2014-Present: "*Transition Metal-Catalyzed Directed Introduction of Fluorinated Moieties by C-H Bond Functionalization*". Ph.D. studies in the group of Prof. Xavier Pannecoucke, UMR 6014-CNRS, INSA de Rouen, Mont Saint Aignan, France.

09/2011-07/2014: "*Asymmetric Synthesis of* Δ^3*-2-Hydroxybakuchiol, Bakuchiol and ent-Bakuchiol*". Master studies in the group of Prof. Xinsheng Lei, Fudan Universtiy, Shanghai, China.

04/2011-07/2011: Research assistant, Hangzhou Adamerck Pharmlabs Inc., China.

03/2010-12/2010: Research assistant, Zhejiang Dragon Chemical Group Company, China.

09/2005-07/2009: "*Synthesis of an Anti-Epileptic Agent's Derivatives*". Bachelor studies in the group of Prof. Hanbin Teng, Wuhan University of Technology, Wuhan, China.

Poster and Oral Communications

06/2017: **Journées Nord-Ouest Européennes des Jeunes Chercheurs (JNOEJC)**, Caen, France (oral communication).

06/2017: **Journées des écoles doctorales**, Rouen, France (oral communication).

07/2016: **15th Belgian Organic Synthesis Symposium,** Antwerpen, Belgium (Poster).

05/2015: **Journées Nord-Ouest Européennes des Jeunes Chercheurs (JNOEJC)**, Rouen, France (Poster).

10/2013: **1st Sino-Swiss Stepping Symposium on Natural Products and Drug Discovery**, Shanghai, China.

09/2013: **24th International Society of Heterocyclic Chemistry Congress**, Shanghai, China.

11/2011, 11/2012, 11/2013: Yangtze River Delta Symposium on Medicinal Chemistry, Nanjing (2011), China; Hangzhou (2012), China (Poster and oral communication); Shanghai (2013), China.

Publications

From my Ph.D. thesis:

(1) **Zhao, Q.**; Poisson, T.; Pannecoucke, X.; Bouillon, J.-P.; Besset, T. "*Pd-Catalyzed Diastereoselective Trifluoromethylthiolation of Functionalized Acrylamides*".

Org. Lett. **2017**, *19*, 5106.

(2) **Zhao, Q.**; Tognetti, V.; Joubert, L.; Besset, T.; Pannecoucke, X.; Bouillon, J.-P.; Poisson, T. "*Palladium-Catalyzed Synthesis of 3-Trifluoromethyl-Substituted 1,3-Butadienes by Means of Directed C–H Bond Functionalization*".

Org. Lett. **2017**, *19*, 2106.

(3) **Zhao, Q.**; Poisson, T.; Pannecoucke, X.; Besset, T. "*The Transient Directing Group Strategy: A New Trend in Transition-Metal-Catalyzed C–H Bond Functionalization*".

Synthesis **2017**, DOI: 10.1055/s-0036-1590878.

(4) **Zhao, Q.** *2-Bromo-3,3,3-trifluoropropene* in *Encyclopedia of Reagents for Organic Synthesis.* John Wiley & Sons Ltd., **2017**, DOI: 10.1002/047084289X.rn00216.pub2.

(5) **Zhao, Q.**; Besset, T.; Poisson, T.; Bouillon, J.-P.; Pannecoucke, X. "*Palladium-Catalysed Synthesis of α-(Trifluoromethyl)styrenes by Means of Directed C–H Bond Functionalization* ".

Eur. J. Org. Chem. **2016**, 76.

From my master thesis:

(1) **Zhao, Q.**; Xu, Q.; Shan, G.; Dong, C.; Zhang, H.; Lei, X. "*Synthesis of* Δ^3*-2-Hydroxybakuchiol Analogues and Their Growth Inhibitory Activity against Rat UMR106 Cells*".

Molecules **2014**, *19*, 2213.

(2) Xu, Q.-Q.; **Zhao, Q.**; Shan, G.-S.; Yang, X.-C.; Shi, Q.-Y.; Lei, X. "*A facile asymmetric synthesis of* Δ^3*-2-Hydroxybakuchiol, Bakuchiol and ent-Bakuchiol*".

Tetrahedron **2013**, *69*, 10739.

(3) Zhang, Q.; Deng, C.; Fang, L.; Xu, W.; **Zhao, Q.**; Zhang, J.; Wang, Y.; Lei, X. "*Synthesis and evaluation of the analogues of penicillide against cholesterol ester transfer protein*".

Chin. J. Chem. **2013**, *31*, 355.

(4) Lei, X.; Lin, G.; Xu, Q.-Q.; **Zhao, Q.** "*Asymmetric synthesis method for* Δ^3*-2-hydroxybakuchiol and analog compounds*."

Chinese patent **2015**. *CN 104341276 A*.

(5) Lei, X.; Lin, G.; **Zhao, Q.**; Xu, Q.-Q.; Shan, G. "*Natural product fructus psoraleae phenol and asymmetric synthesis method of enantiomer thereof*."

Chinese patent **2015**. *CN 104418707A*.

Research interests

Organic fluorine chemistry

Transition metal catalysis, Asymmetric catalysis

C-H bond activation, C-N bond activation, C-O bond activation

Recent years have witnessed a great development of the organofluorine chemistry field. In particular, the introduction of emergent fluorinated moieties onto various scaffolds has attracted attention of the scientific community because of their special properties. Besides, transition metal-catalyzed directed C-H bond functionalization strategy has brought a revolution in the development of original synthetic methodologies, since it allows straightforward and more atom-economical processes. Thus, the design of new synthetic approaches for the introduction of fluorinated moieties by transition metal-catalyzed C-H bond functionalization pathway is particularly appealing. Therefore, in this Ph.D. thesis, we focused on the development of new methodologies for the direct introduction of fluorinated moieties onto arenes and olefins by transition metal catalyzed directed C(sp^2)-H bond functionalization. In particular, we turned our attention to the 2-bromo-3,3,3-trifluoropropene (BTP), an inexpensive fluorinated reagent coming from industry waste, used as a potential halon replacement for fire suppression and as a fluorinated building block in organic synthesis (Chapter 1). The first part of this Ph.D. thesis was dedicated to the development of new methodologies for the direct introduction of a CF_3-vinyl moiety onto arenes and olefins by a Pd-catalyzed directed C(sp^2)-H bond functionalization with BTP. Then, this approach was extended to the functionalization of α,β-unsaturated esters, although a different reaction pathway is probably involved (Chapter 2). In the second part of this Ph.D. thesis, we developed a new methodology for the direct introduction of the SCF_3 group onto arenes and olefins by Pd-catalyzed directed C(sp^2)-H bond functionalization using the Munavalli reagent (Chapter 3).

Ces dernières années ont été témoin de l'énorme développement de la chimie organique du fluor. Notamment, l'introduction de groupements fluorés émergents sur des « briques » moléculaires variées a attiré l'attention de la communauté scientifique en raison de leurs propriétés particulières. De plus, la stratégie de fonctionnalisation dirigée de la liaison C-H par catalyse par les métaux de transition, a conduit à une révolution dans le développement de méthodologies synthétiques originales. Par conséquent, la conception de nouvelles approches synthétiques pour l'introduction de groupements fluorés par fonctionnalisation de la liaison C-H catalysée par les métaux de transition est particulièrement attirante. Dans cette thèse, nous nous sommes concentrés sur le développement de nouvelles méthodologies d'introduction directe des groupements fluorés sur des arènes et des oléfines par fonctionnalisation directe de liaison C(sp^2)-H catalysée par les métaux de transition. En particulier, nous avons tourné notre attention sur le 2-bromo-3,3,3-trifluoropropène (BTP), un réactif fluoré bon marché et provenant de déchets de l'industrie. Ce dernier est utilisé comme potentiel agent de remplacement de halon pour la suppression des incendies et, utilisé comme « brique » moléculaire en synthèse organique (Chapitre 1). La première partie de cette thèse est dédiée au développement de nouvelles méthodologies pour l'introduction directe du groupement CF_3-vinyl sur des arènes et des oléfines par fonctionnalisation de la liaison C(sp^2)-H catalysée par le palladium. Ensuite, cette approche a été étendue à la fonctionnalisation d'esters α,β-insaturés, bien qu'un mécanisme différent soit probablement impliqué (Chapitre 2). Dans la seconde partie de cette thèse, nous avons développé une nouvelle méthodologie pour l'introduction directe du groupement SCF_3 sur des arènes et des oléfines par fonctionnalisation de la liaison C(sp^2)-H catalysée par le palladium, utilisant le réactif de Munavalli (Chapitre 3).