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PALLADIUM(II)-CATALYZED ALKENYL C-H BOND FUNCTIONALIZATION

XU YUNHE

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XU YUNHE

School of Physical and Mathematical sciences

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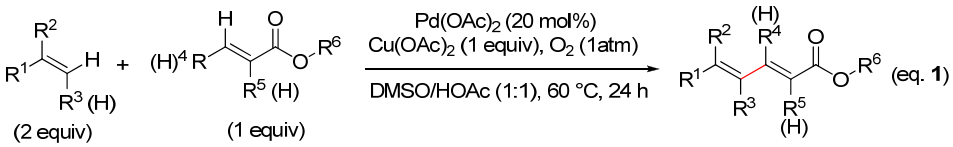
TABLE OF CONTENTS

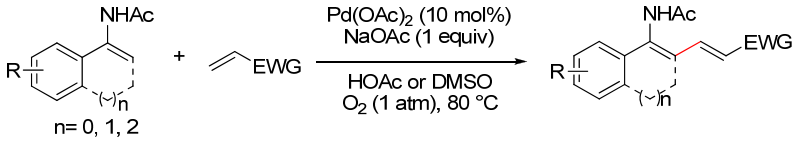
SUMMARY

Palladium-catalyzed coupling reactions have been developed as important tools for constructing new carbon-carbon and carbon-heteroatom bonds in modern organic synthesis. Among the various palladium catalyzed coupling reactions developed, one of the most challenging problems associated with these methods is the need to use halogenated substrates and/or organometallics which are not environmentally friendly. To improve the efficiency of coupling reactions and avoide the use of environmentally unfriendly compounds, research into direct oxidative cross-coupling has attracted much attention over the years. Palladium-catalyzed direct cross-coupling reactions between arenes and olefins, alkanes and olefins, and alkynes and olefins have been reported in the past decades. However, the direct cross-coupling reaction of olefins with alkenes is not well studied. Herein, we carried out a series of studies for the direct oxidative cross-coupling between olefins.



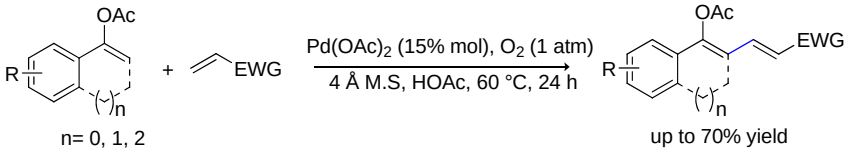
Firstly, we have developed an efficient methodology for the oxidative cross-coupling reaction of olefins with acrylates catalyzed by palladium under mild conditions to form the corresponding dienoates. In our method, both aromatic and aliphatic alkenes could afford the desired dienoate compounds in moderate to good yields. Besides terminal olefins, internal alkenes could also afford the corresponding products. This protocol offers several advantages including commercially available starting materials, operational simplicity, mild reaction conditions, high atom-economy, and moderate to high yields, which makes it

potentially a useful and attractive strategy for the synthesis of dienoate compounds.



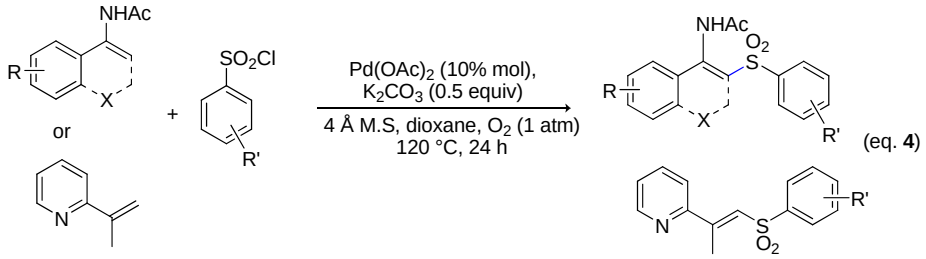
(eq. **2**)

Next, we have developed the first successful olefination reaction of enamides at the *β*-position with electron-poor alkenes catalyzed by $Pd(OAc)_2$ and 1 atm oxygen as the sole oxidant (eq. **2**). The corresponding products were obtained in moderate to high yields with excellent regioselectivity. The mechanism of this coupling reaction was also well studied by ^1H NMR spectroscopic analysis, which showed that a vinylpalladium intermediate was involved in the coupling process. This novel method produces highly functionalized, versatile compounds which can be converted to a wide variety of building blocks and complex molecules.



(eq. **3**)

We have also developed an efficient cross-coupling of vinyl acetates with acrylates via $Pd(OAc)_2$ catalyzed C-H activation of vinyl acetates to afford products in moderate to high yields with high regioselectivity (eq. **3**). Moreover, this cross coupling reaction is a very novel method since no metal oxidant and/or additive is used. This elegant protocol allows for the formation of highly functionalized, versatile compounds which can be further manipulated to form a wide variety of synthetic intermediates and complex products.



(eq. **4**)

Finally, we focus on developing new methods for constructing carbon-heteroatom bond via direct cross-coupling. A sulfonylation reaction between olefins and sulfonyl chlorides, which was catalyzed by palladium, was developed (eq **4**). The corresponding sulfones which are also potential useful intermediates for further transformation were obtained in moderate to good yields.

In summary, we have developed a general method for intermolecular alkenylation of olefins via palladium-catalyzed C-H bonds functionlization. In subsequent work, efforts will be directed towards the improvement of the efficiency and scope of the reactions. Time will also be devoted to a more in-depth mechanistic study and application of our protocol to the total synthesis of some natural products.

ABBREVIATION

Ac	Acetyl
atm	Atmospheric pressure
n-Bu	*n*-Butyl
t-Bu	*tert*-Butyl
br	Broad singlet
°C	Degree centigrade
cm^{-1}	Inverse centimeter
δ	Chemical shift
d	Doublet
dd	Doublet of doublet
dt	Doublet of triplets
DMF	Dimethylformamide
EI	Electron impact ionization
equiv	Equivalent
Et	Ethyl
EA	Ethyl Acetate
g	Gram
h	Hour
H	Hydrogen
Hex	Hexane
HOAc	Acetic acid
HRMS	High resolution mass spectroscopy
Hz	Hertz
FTIR	Fourier transformation infrared spectrum
i-Pr	Iso-Propyl
m	Multiplet
Me	Methyl
min	Minute
mL	Millilitres
mol	Moles

mmol	Millimoles
mol%	Molar percent
MS	Mass spectrum
MS4Å	Molecule sieve 4Å
NMR	Nuclear magnetic resonance
OTf	Trifluoromethane sulfonate
Ph	Phenyl
ppm	Part per million
Py	Pyridine
q	Quartet
r.t	Room temperature
R_f	Retention factor
s	Singlet
t	Triplet
tert	Tertiary
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

CHAPTER 1

Pd(II)-Catalyzed Direct C-H Bond Activation/Functionalization

Pd(II)-Catalyzed Direct C–H Bond Activation/Functionalization

1.1 OVERVIEW OF THE BACKGROUD

Transition metal catalyzed coupling reactions have been developed as an important tool for constructing new carbon-carbon and carbon-heteroatom bonds in modern organic synthesis.[1] Among them, palladium catalysts and reagents are particularly useful and versatile as a result of the following important features: first and foremost, they offer abundant possibilities of forming new carbon-carbon bonds, an ability unmatched by any other transition metals; secondly, palladium catalysts and reagents are usually easy to handle in reactions and are not sensitive to oxygen or moisture; thirdly the wide tolerance towards various functional groups during palladium-catalyzed reactions is also noteworthy.[2] Due to these merits, palladium catalysts and reagents have been widely used in the synthesis of many pharmaceuticals, dyes, organic conductors and semi-conductors, polymers and natural products.[3] Among the many reactions, the palladium-catalyzed coupling reactions have been the most popular. The following table summarizes the most well-known palladium-catalyzed coupling reaction.[4]

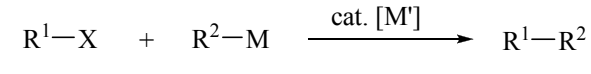
---

[1] (a) *Handbook of organopalladium chemistry for organic synthesis*; Negish, E.; Ed.; Wiley and Sons: New York, 2002. (b) Tsuji, J. *Palladium Reagents and Catalysts*: *Innovations in Organic Synthsis*; Wiley and Sons: New York, 1995. (c) Tsuji, J. *Palladium in Organic Synthesis*; Springer: Berlin, 2005.

[2] *Palladium Reagents and catalysis*: *New Perspectives for the 21st Century*; Tsuji, J. Ed.; Wiley and Sons: New York, **2003**.

[3] (a)Bünsow, J.; Kelby, T. S.; Huck, W. T. S. *Acc. Chem. Res*. **2010**, *43*, 466-474.(b) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science*. **2009**, *325*, 1661-1664. (d) Rubin, A. E.; Tummala, S.; Both, D. A.; Wang, C.; Delaney, E. J. *Chem*. *Rev*. **2006**, *106*, 2794-2810.

[4] (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am*. *Chem*. *Soc*. **1972**, *94*, 4374-4376. (b) Heck, R. F.; Nolley, J. P. *J. Org*. *Chem*. **1972**, *37*, 2320-2322. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467-4470. (d) King, A. O.; Okukado, N.; Negishi, E.-i. *J. Chem*. *Soc*.; *Chem*. *Commun*. **1977**, 683-684. (e) Milstein, D.; Stille, J. K. *J. Am*. *Chem*. *Soc*. **1978**, *100*, 3636-3638. (f) Miyaura, N.; Suzuki, A. *Chem*. *Commun*. **1979**, 866-867. (g) Hiyama, T. *J. Org*. *Chem*. **1988**, *53*, 918-920. (h) Wolfe, J. P.; Buchwald, S. L.



X = *I, Br, Cl, OTf*.....

Name	cat.M'	M
Heck	Pd	H
Kumada -Tamao -Corriu	Pd Ni	Mg
Sonogashira	Pd	Cu, H
Suzuki -Miyaura	Pd Ni	B
Stille -Migita -Kosugi	Pd	Sn
Hiyama -Hatanaka	Pd	Si
Negishi -Nozaki -Oshima	Pd Ni	Zn, Al

Among the various palladium catalyzed coupling reactions developed, one of the most challenging problems associated with these methods is the need to use halogenated substrates and/or organometallics which are not very environmentally friendly. Therefore, over the past few decades many research groups have focused on exploring Pd-catalyzed coupling reactions *via* direct C–H bond activation and functionalization to generate new carbon-carbon or carbon-heteroatom bonds.[5]

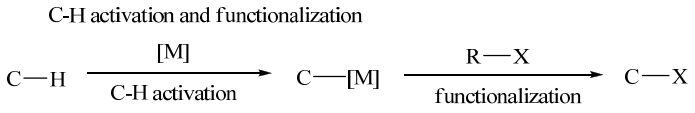
As we know, there is an abundance of carbon-hydrogen (C–H) bonds in organic molecules. If their use as functional group equivalents could be achieved, it would shorten synthetic schemes and facilitate chemists by

Org. *Synth*. **2004**, *10*, 423-423. (i) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett*. **1998**, *39*, 3189-3192.

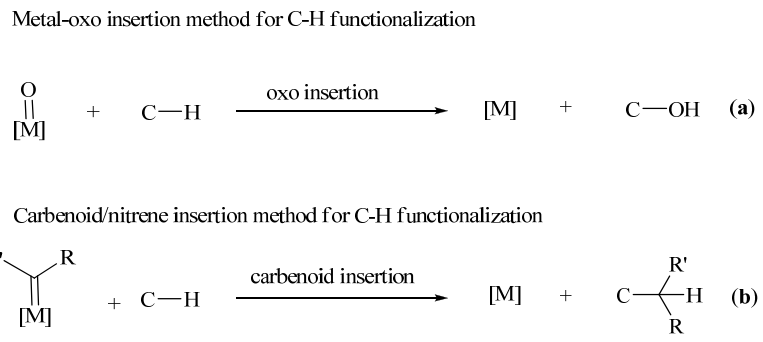
[5] For reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem*. *Rev*. **2010**, *110*, 1147-1169. (b) Chen, X.; Engle, K. M.; Wang, D-H.; Yu, J-Q. *Angew*. *Chem*. *Int*. *Ed*. **2009**, *48*, 5094-5115. (c) Daugulis, O.; Do, H-Q.; Shabashov, D. *Acc*. *Chem*. *Res*. **2009**, *42*, 1074-1086. (d) Hartwig, J. F. *Nature* **2008**, *455*, 314-322. (e) Bergman, R. G. *Nature* **2007**, *466*, 391-393. (f) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem*. *Rev*. **2007**, *107*, 5318-5365. (g) Godula, K.; Sames, D. *Science* **2006**, *312*, 67-72. (h) Yu, J. Q.; Giri, R.; Chen, X. *Org*. *Biomol*. *Chem*. **2006**, *4*, 4041-4047. (i) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507-514. (j) Ritleng, V.; Sirlin, C.; Pfreffer,M. *Chem*. *Rev*. **2002**, *102*, 1731-1770. (k) Crabtree, R. H. *J*. *Chem*. *Soc*.; *Dalton Trans*. **2001**, 2437-2450. (l) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc*. *Chem*. *Res*. **2001**, *34*, 633-639. (m) Dyker, G. *Angew*. *Chem*. *Int*. *Ed*. **1999**, *38*, 1698-1712. (n) Shilov, A. E.; Shul'pin, G. B. *Chem*. *Rev*. **1997**, *97*, 2879-2932. (o) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc*. *Chem*. *Res*. **1995**, *28*, 154-162. (p) Crabtree, R. H. *Chem*. *Rev*. **1985**, *85*, 245-269.

allowing efficient disconnections in retrosynthesis, and would reduce the byproducts generated during the synthesis. Up to this day, direct utilization of unactivated C–H bonds in the total synthesis of natural products remains limited.[6]

In literature, the terms "C–H activation" and "C–H functionalization" are usually used interchangeably.[7] Herein, the term "C–H activation" specifically refers to the direct transformation of C–H bonds into C–M bonds; while the term "C–H functionalization" indicates the overall transformation of C–H bond into C–X bonds *via* a C–M intermediate or involving other metal bonds (Scheme **1**).[8]



Scheme **1**



Scheme **2**

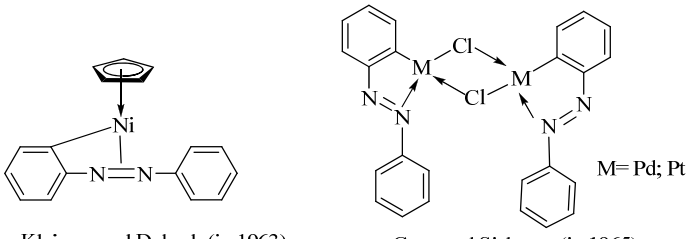
[6] (a) Stang, E. M.; White, M. C. *Nat. Chem*. **2009**, *1*, 547-551. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev*. **2005**, *105*, 2873-2920. (c) Zeni, G.; Larock, R. C. *Chem. Rev*. **2004**, *104*, 2285-2310. (d) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc*. **2002**, *124*, 7904-7905. (e) Daves, G. D., Jr. *Acc. Chem. Res*. **1990**, *23*, 201-206. (f) Trost, B. M.; Godleski, S. A.; Genêt, J. P. *J. Am. Chem. Soc*. **1978**, *100*, 3930-3931.

[7] (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417-424. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439-2463.

[8] Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507-514.

In fact, studies on C–H activation catalyzed by transition metals, including metal-oxo insertion into C–H bonds [9] (Scheme **2a**) and metal carbenoid/nitrenoid insertion into C–H bonds [10] (Scheme **2b**) have attracted much attention in the past few decades. Herein, we would however like to focus on the discussion of another important method for C–H functionalization, namely, the direct insertion of metal into C–H bonds.

Early in the 1960s, several pioneering works reported the demonstration of such metal catalyzed C–H activation and subsequent functionalization reactions.[11] In 1963, Kleiman and Dubeck found that Cp_2Ni could activate the C–H bond of azobenzene, in which the nitrogen-nitrogen double bond was observed to coordinate with the nickel metal through π-electron interaction (Scheme 3).[12] In 1965, Cope and Siekman discovered that $PdCl_2$ and K_2PtCl_4 could also react with azobenzene and activate the *ortho* C–H bond of the phenyl ring.[13] The proposed structure is similar to the product of the reaction between dicyclopentadienylnickel and azobenzene.



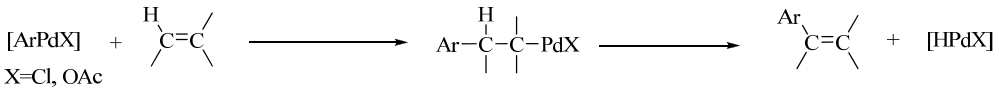
Kleiman and Dubeck (in 1963) Cope and Siekman (in 1965)

Scheme **3**

In the late 1960s, Heck reported that olefins could be arylated by reacting

[9] Goldman, A. S.; Goldberg, K. I. In *Activation and Functionalization of C-H Bonds*, Goldberg, K. I.; Goldman, A. S.; Eds.; ACS Symposium Series 885; American Chemical Society: Washington, DC, 2004, 1-45.
[10] Colby, D. A.; Bergman, R, G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624-655.
[11] (a) Ryabov, A. D. *Synthesis* **1985**, 233-252. (b) Newkome, G. R.; Puckett, W. E.; Gupta, V. K.; Kiefer, G. E. *Chem. Rev.* **1986**, *86*, 451-489. (c) Chatt, J.; Davidson, J. M. *J. Chem. Soc.* **1965**, 843-855.
[12] Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544-1545.
[13] Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272-3273.

with stoichiometric amounts of Ar-Pd-Cl or Ar-Pd-OAc, generated *in situ* by reacting ArHgCl with $PdCl_2$ or ArHgOAc with $Pd(OAc)_2$ respectively.[14] A mechanism was proposed which involved a *syn* migratory insertion of the olefin into the arylpalladium species, followed by a *syn* β-hydride elimination of a hydridopalladium [HPdX] (X= Cl, OAc) (Scheme **4**). Subsequently, a reaction using organo-palladium salts, formed by the direct reaction of aryl iodides with finely divided palladium, to react with alkenes was developed by Heck, and discovered independently by Mizoroki at the same time.[15] This discovery opened the way to a new reaction later called the Mizoroki-Heck reaction.



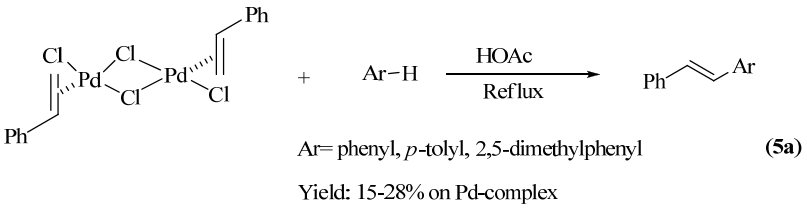
Scheme **4**. Mechanism for Heck Coupling

In 1967, Fujiwara and Moritani described a styrene-palladium chloride complex that reacted with excess arenes to give stilbenes, which is the first example of a palladium mediated olefination reaction (Scheme **5a**).[16] The use of catalytic loading of palladium in this reaction was subsequently developed by using catalytic amounts of $Pd(OAc)_2$, together with an oxidant such as Ag(I), Cu(II), O_2, *t*-BuO_2H, or $PhCO_3Bu$-*t*.[17]

[14] (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526. (b) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707-6714. (c) Heck, R. F. *J. Am. Chem. Soc.* **1971**, *93*, 6896-6901.
[15] (a) Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, *37*, 2320-2322. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581-581. (c) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505-1508.
[16] Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119-1122.
[17] (a) Fujiwara, Y.; Moritani, I.; Danno, S.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166-7169. (b) Fujiwara, Y.; Danno, S.; Moritani, I.; Teranishi, S. *J. Org. Chem.* **1976**, *41*, 1681-1683. (c) Fujiwara, Y.; Maruyama O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851-855. (d) Fuchita, Y.; Hiraki, K.; Kamogawa, Y.; Suenaga, M.; Toggoh, K.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1081-1085. (d) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699-2702. (e) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097-2100.

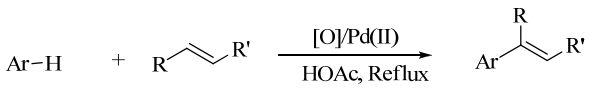
On the basis of these initial studies, a broad range of new reaction conditions were developed to directly transform C–H bonds into C–C or C–heteroatom bonds *via* C–H activation. These reactions can be divided into two wide categories, non-directing group assisted reactions and with directing group assisted reactions.

Reaction without directing group assistance refers to those where the C–H bond is cleaved through direct metal insertion without the presence of heteroatoms for metal chelation or to act as directing groups. The challenges of discriminating between various types of chemically similar C–H bonds within the hydrocarbon skeleton remain to be addressed.



Ar= phenyl, *p*-tolyl, 2,5-dimethylphenyl **(5a)**

Yield: 15-28% on Pd-complex



(5b)

ArH: benzenoid and *non*-benzenoid

R= H, CH_3, Ph; R'= Ph, COMe, CO_2Et, CHO, CN, CO_2H

Yield: 10-90% on olefin

Scheme **5**

As for directing group assisted C–H activation reactions, heteroatoms such as nitrogen or oxygen are usually present in the substrates, which allow for coordination with the metal and its localization at specific positions in the substrate molecule. In other words, the heteroatoms serve as directing groups of the metal and help to selectively activate C–H bonds. In the following sections, we will focus on the discussion of these two types of direct C–H bond functionalizations.

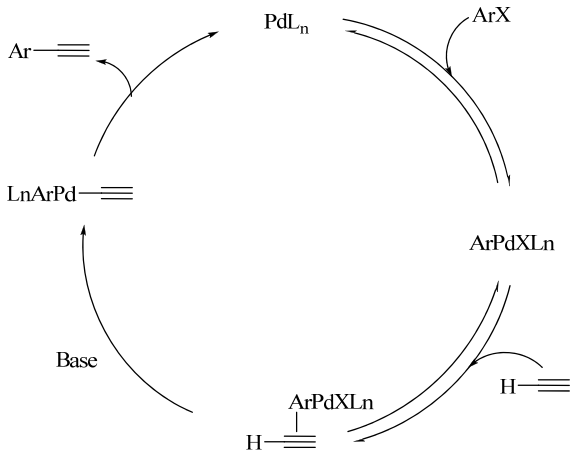
1.2 DIRECT TRANSFORMATION OF *SP* C–H BONDS

Acidity of the terminal acetylene proton (pK_a = 25) permits easy deprotonation of the terminal C–H to form a *sp*-hybridized carbon that is readily available for reactions. This characteristic has led to various methods being developed for the generation of metal acetylides which could be applied in coupling reactions. In the presence of copper salts, usefulness of the metalation of terminal acetylenes has been recognized for some time. In 1869, Glaser discovered the first oxidative homocoupling reaction of terminal acetylenes by using CuCl, base and dioxygen.[18] In 1959, Eglinton and Galbraith found that copper(II) acetate in methanol-pyridine was an effective reagent for the oxidative coupling of acetylenes.[19] In this reaction, excess of the copper(II) acetate was used because the reaction proceeded slowly with catalytic quantities of copper(II) salt. It was not until 1962 that Hay used 5 mol% CuCl as the catalyst and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine as the ligand to develop an efficient catalytic system for the homocoupling of terminal alkynes.[20] The palladium-catalyzed cross-coupling of terminal alkynes with an aryl or a vinyl halide is an efficient method in organic synthesis to provide *sp*-sp^2 carbon-carbon bonds.[21] In the presence of cuprous iodide, this reaction which is now known as the Sonogashira reaction, was first discovered in 1975 by Sonogashira.[22] The use of a copper(I) cocatalyst allowed the coupling to proceed rapidly at room temperature. However, its addition to the reaction also

[18] Glaser,C. *Ber*. *Dtsch*. *Chem*. *Ges*. **1869**, *2*, 422-424.
[19] Eglinton, G.; Galbraith, A. R. *J*. *Chem*. *Soc*. **1959**, 889-896.
[20] Hay, A. S. *J*. *Org*. *Chem*. **1962**, *27*, 3320-3321.
[21] (a) Negishi, E.; Anastasia, L. *Chem*. *Rev*. **2003**, *103*, 1979-2018. (b) Sonogashira, K. *J*. *Organomet*. *Chem*. **2002**, *653*, 46-49. (c) Tykwinski, R. R. *Angew*. *Chem*. *Int*. *Ed*. **2003**, *42*, 1566-1568.
[22] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *50*, 4467-4470.

came with drawbacks. The acetylene self-coupling product is usually formed as a side-product.[21a]

To overcome this problem, the utilization of a copper-free system has been developed, further broadening the reaction scope. The reaction under such conditions is termed copper-free Sonogashira reaction[23] or Heck alkynylation,[24] depending on the exact conditions, substrates and author. Two mechanistic pathways without involving copper seem feasible (Scheme **6**), but are often decribed in opposition. They both involve an initial oxidative addition of an aryl or alkenyl halide with Pd(0), followed by an alkyne coordination. While one of them completes the cycle by subsequent deprotonation and reductive elimination (Scheme **6a**), the other involves consecutive carbopalladation and hydride elimination (Scheme **6b**). [24a, 25, 26]



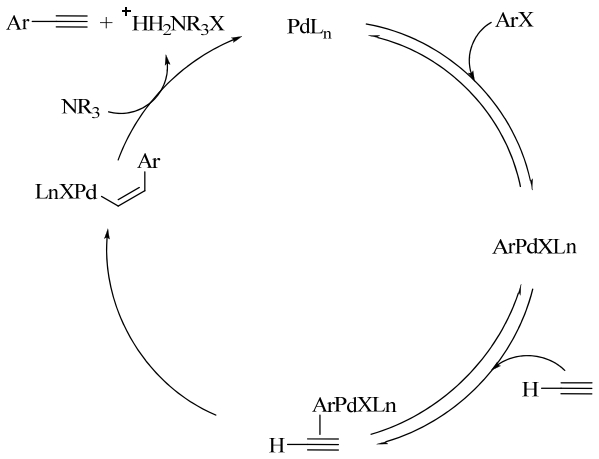
[23] (a) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679-3681. (b) Leadbeater, N. E.; Tominack, B. J.; *Tetrahedron Lett.* **2003**, *44*, 8653-8656. (c) Kim, J.-H.; Lee, D.-H.; Jun, B.-H.; Lee, Y.-S. *Tetrahedron Lett.* **2007**, *48*, 7079-7084. (d) Soheili, A.; Albaneze-Walker, J.; Murry, A.; Dormer, P. G.; Hughes, D, L. *Org. Lett.* **2003**, *5*, 4191-4194. (e) Cheng, J.; Sun, Y.; Wang, F.; Guo, M.; Xu, J.-H.; Pan, Y.; Zhang, Z. *J. Org. Chem.* **2004**, *69*, 5428-5432. (f) Tong, L. H.; Pascu, S. I.; Jarrosson, T.; Sanders, J. K. M. *Chem. Commun.* **2006**, 1085-1087. (g) Ljungdahl, T.; Pettersson, K.; Albinsson, B.; Mårtensson, J. *J. Org. Chem.* **2006**, *71*, 1677-1687. (h) Ljungdahl, T.; Bennur, T.; Dallas, A.; Emtenäs, H.; Mårtensson, *J. Organomet. Chem.* **2008**, *27*, 2490-2498.

[24] (a) Dieck, H. A.; Hech, F. R. *J. Organomet. Chem.* **1975**, *93*, 259-263. (b) Hierso, J.-C.; Boudon, J.; Picquet, M.; Meunier, P. *Eur. J. Org. Chem.* **2007**, 583-587. (c) Boukouvalas, J.; Côté, S.; Ndzi, B. *Tetrahedron Lett.* **2007**, *48*, 105-107.

[25] Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A. *J. Organomet. Chem.* **2004**, *689*, 4642-4646.

[26] Negishi, E. I.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365-394.

Scheme **6a**



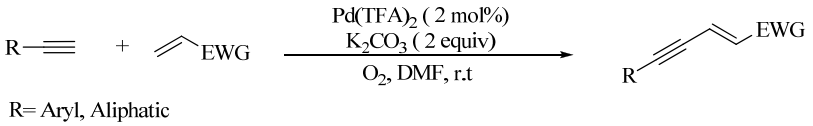
Scheme **6b**

An easy and convenient catalytic system for the cross-coupling reaction of arylboronic reagents with terminal alkynes was reported by using cyclopalladated ferrocenylimine (**I**)/silver oxide as the catalyst at room temperature.[27] Electron-poor alkynes that do not react using the traditional Sonogashira protocol worked well under these conditions. After which, copper-catalyzed cross-coupling reactions of arylboronic acids with terminal alkynes, especially electron-poor analogues were developed. This method represents a practical alternative to the Sonogashira reaction.[28] Compared with other transition-metal catalyst systems, this protocol avoids the use of air-sensitive and/or expensive catalysts.

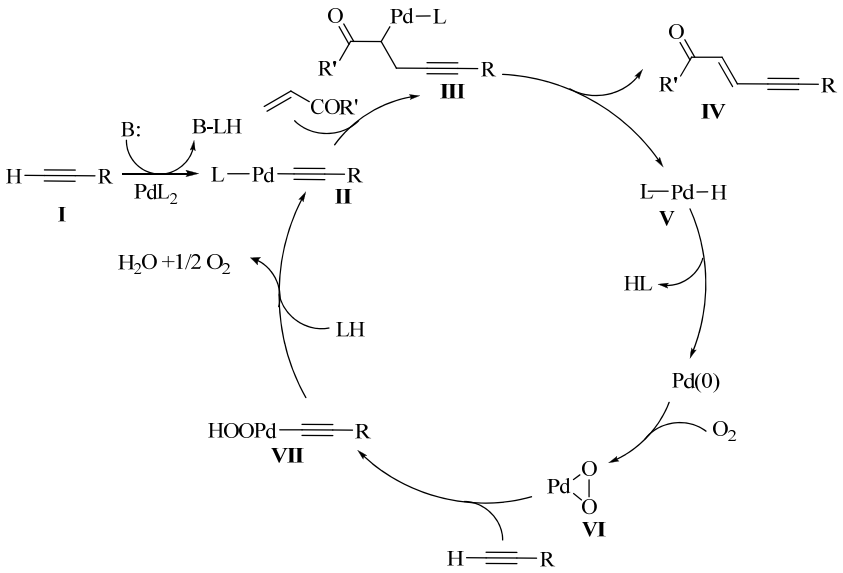
Very recently, an oxidative Pd(II)-catalyzed Heck-type coupling of terminal alkynes with electron-poor olefins was developed by Jung and co-workers (Scheme **7**), which is the first example of oxidative cross-coupling resulting in *sp*-*sp*^{2} carbon-carbon bond formation.[29] The proposed mechanism is depicted in

[27] Yang, F.; Wu, Y. *Eur. J. Org. Chem*. **2007**, 3476-3479.
[28] (a) Pan, C.; Luo, F.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron Lett*. **2009**, *50*, 5044-5046. (b) Wu, M.; Mao,J.; Guo, J.; Ji, S. *Eur. J. Org. Chem*. **2008**, 4050-4054.
[29] Hadi, V.; Yoo, K. S.; Jeong, M.; Jung, K. W. *Tetrahedron Lett*. **2009**, *50*, 2370-2373.

Scheme **8**. The reaction is initiated by the formation of an alkynyl palladium complex **II** via base assisted deprotonation. Consequent steps involve a migratory insertion to form the alkenyl double bond, followed by a *β*-hydride elimination to produce cross-coupling product **IV**. The Pd(0) species generated during reduction can be reoxidized by oxygen.



Scheme **7**



Scheme **8**. Mechanism for the Oxidative Pd(II)-Catalyzed Heck-Type Coupling of Terminal Alkynes with Electron-Poor Olefins

1.3 DIRECT TRANSFORMATION OF sp^2 C–H BONDS

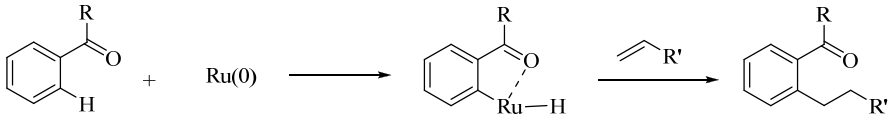
Direct and catalytic transformation of arenes to various useful products *via* C–H activation is of considerable interest to the chemical industry, and was

previously a challenge to chemists for a long time.[30] The development of catalytic systems for the catalytic functionalization of saturated as well as aromatic and olefinic hydrocarbons remains as an extremely important field of contemporary chemistry.[31] The success of such processes would provide potentially economical and clean methods for making many chemicals directly from hydrocarbons. One of the main reasons behind this challenging process is the strength of C–H bonds in arenes (*e.g.* benzene, 110 kcal/mol).

Over the past 30 years, great efforts have been made to achieve selective C–H bond activation by transition metal complexes.[30] The study of aryl C–H bond activation using transition metal compounds began in the 1960s and saw the successful development of acid-catalyzed and acid-promoted Friedel-Crafts arene alkylation and acylation chemistry in the early part of the 20th century. In 1967, Fujiwara disclosed that Pd(II) complexes could mediate the coupling of arenes with olefins in refluxing HOAc.[32] This reaction is one of the earliest examples of aromatic C–H bond activation by transition metal compounds, which involves an electrophilic substitution of aromatic C–H bonds by Pd(II) species.[33] However, compared with the large number of examples of stoichiometric aryl C–H bond activation by transition metal compounds, only relatively few catalytic systems of such type that are synthetically practical have

[30] (a) Shilov, E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879-2932. (b) Kakiuchi, F.; Murai, S. Activation of C-H Bonds: *Catalytic Reactions. In Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: New York, **1999**; 47-79. (c) Jones, W. D. Activation of C-H Bonds: *Stoichiometric Reactions. In Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: New York, **1999**; 9-46. (d) Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698-1712. (e) Fujiwara, Y.; Takaki, K.; Taniguchi, Y. *Synlett* **1996**, 591-599. (f) Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 840-841 and references therein. (g) Reis, P. M.; Silva, J. A. L.; da Silva, J. J. R. F.; Pombeiro, A. J. L. *Chem. Commun.* **2000**, 1845-1846.
[31] Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281.
[32] Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119-1122.
[33] Fujiwara, Y.; Moritani, I.; Danno, S.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166-7169.

been reported thus far. *Ortho*-chelation assisted aromatic C–H bond activation is a promising example of such (Scheme **9**), involving an oxidative addition of a low-valent transition metal compound followed by addition to C–C multiple bonds.[30b,34] However, synthetically useful catalytic C–H activation of arenes catalyzed by transition metals remains uncommon. In most cases, the direct use of aromatic compounds in synthesis relies on the presence of a more reactive group than a C–H bond. For example, it is very common to employ activation of the C–X



Scheme **9**

(X = Cl, Br, or I) bond of aryl or alkenyl halides to transfer aryl or alkenyl groups.[35] This chemistry can be very successful and catalytically efficient, if not for the fact that manufacture of aryl halides or vinyl halides is not an environmentally friendly process. Moreover, reactions that activate C–X bonds of aryl or alkenyl halides typically produce halide salts as byproducts. Thus, it is hoped that the development of practical catalytic procedures to directly activate C–H bonds of arenes or olefins would allow for arylation or olefination to proceed by such direct C–H bond activation in the future.[36]

1.3.1 Pd-CATALYZED DIRECT COUPLING BETWEEN ARENES VIA C–H BONDS ACTIVATION

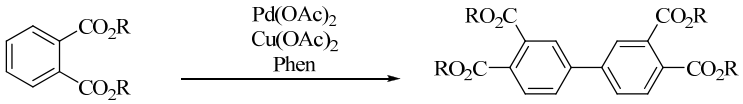
[34] (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529-531. (b) Christian, P. L.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616-6623. (c) Matsumoto, T.; Taube, D. J.; Periana, R. A.; Taube, H.; Yoshida, H. *J. Am. Chem. Soc.* **2000**, *122*, 7414-7415.
[35] (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.
[36] Jia, C.-G.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633-639.

Since biphenyl compounds are key building blocks in the synthesis of various pharmaceutical and agrochemical compounds, several synthetic methodologies to form such compounds have been developed.[37] Oxidative coupling between two arenes or heteroarenes to form a biaryl or biheteroaryl is however a more economical and efficient route. The first reported homocoupling of arenes to form biaryl was achieved in the presence of $PdCl_2$ and sodium acetate in HOAc.[38] It was also noted that no reaction occurred in the absence of sodium acetate due to breakdown of the organopalladium intermediate initiated by this salt.

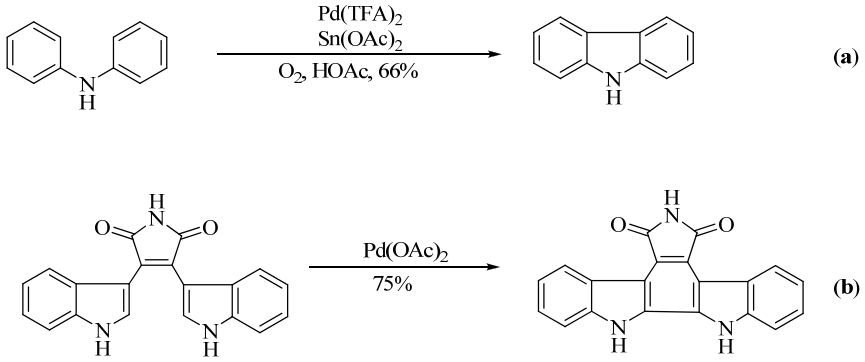
The scope of homocoupling has been studied.[39] A commercial production of biphenyltetracarboxylate was carried out by coupling of dimethyl phthalate using $Pd(OAc)_2$ and $Cu(OAc)_2$, and the addition of phenanthroline was important for the formation of the regioselective 3,4,3′,4′-isomer (Scheme **10**).[40] In addition to benzene derivatives, the intramolecular coupling of heteroaromatic compounds was also developed. Åkermark and co-workers found that carbazole could be synthesized using $Pd(TFA)_2$ and $Sn(OAc)_2$ under oxygen in HOAc (Scheme **11a**).[41] Intramolecular coupling of indole rings allowed for preparation of staurosporine aglycone and a similar protocol was

[37] (a) Li, X. L.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J. M.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500-5511. (b) Gao, J.; Reibenspies, J. H.; Martell, A. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 6008-6012. (c) Sakakura, T.; Sodeyama, T.; Tokunaga, Y.; Tanaka, M. *Chem. Lett.* **1987**, 2211-2214. (d) Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2005**, *127*, 6632-6640.
[38] van Helden, R.; Verberg, G. *Recl. Trav. Chim. Pays-Bas.* **1965**, *84*, 1263-1265.
[39] (a) Itatani, H.; Yoshimoto, H. *Chem. Ind.* **1966**, 457-459. (b) Itatani, H.; Yoshimoto, H. *J. Org. Chem.* **1973**, *38*, 76-79. (c) Clark, R. R. S.; Norman, R. O. C.; Thomas, C. B.; Wilson, J. S. *J. Chem. Soc. Perkin I.* **1974**, 1289-1294.
[40] (a) Shiotani, A.; Itatani, H.; Inagaki, T. *J. Mol. Catal.* **1986**, *34*, 57-66. (b) Shiotani, A.; Yoshikiyo, M.; Itatani, H. *J. Mol. Catal.* **1983**, *18*, 23-31.
[41] (a) Hagelin, H.; Oslob, J. D.; Åkermark, B. *Chem. Eur. J.* **1999**, *5*, 2413-2416. (b) Knölker, H. J.; Knöll, J. *Chem. Commun.* **2003**, 1170-1171.

used in the synthesis of carbazomadurin A (Scheme **11b**).[41,42] The reaction of thiophene, furan and pyrrole were also investigated.[43]



Scheme **10**



Scheme **11**

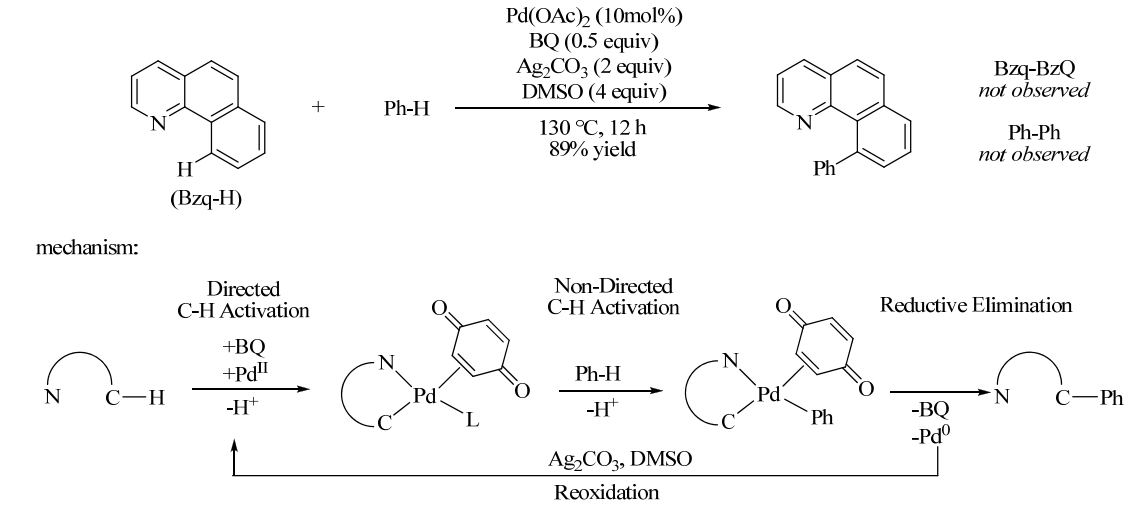
Following on the heels of studies on palladium(II)-catalyzed arene-arene homocoupling, great effort was also devoted to the development of oxidative cross-coupling between different arenes. Such reactions are particularly limited due to difficulty in controlling both the chemo- and regioselectivity of the product. An example of the preparation of unsymmetrical biaryls as the major or sole products *via* aromatic C–H activation has been achieved by using the catalytic system of $Pd(OAc)_2/TFA/K_2S_2O_8$.[44] Although this method is not practical currently due to its low yields and turnover number, it provides some valuable insight into the synthesis of unsymmetrical biaryls from simple arenes *via* aromatic C–H activations. A drastically improved protocol was subsequently developed by Buchwald and co-workers, which allowed coupling

[42] Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron Lett*. **1993**, *34*, 8361-8364.
[43] (a) Itahara, T. *Heterocycle*. **1980**, *14*, 100-102. (b) Boger, D. L.; Patel, M. *J. Org. Chem*. **1988**, *53*, 1405-1460.
[44] Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973-5975.

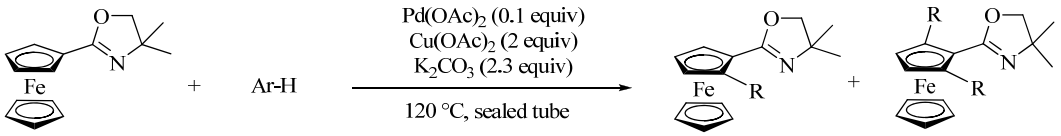
of anilides and arenes catalyzed by palladium in the presence of atmospheric oxygen as the only oxidant.[45]

The use of a directing group has also been successfully employed to achieve the direct coupling between arenes.[46] In 2007, Sanford described a new Pd-catalyzed cross-coupling of arenes and benzo[*h*]quinoline with high chemo- and regioselectivity (Scheme **12**).[46a, 47] The mechanism study indicated that this transformation proceeded *via* two discrete C–H activation steps. It was also found that the selectivities were predominantly controlled by proximity to a ligand (first C–H activation) or by the steric environment around the arene C–H bond (second C–H activation) (Scheme **12**). At the same time, the coupling of simple arenes and ferrocenyl oxazoline, where the oxazoline was employed as a directing group, was developed *via* double sp^2 C–H activations catalyzed by palladium (Scheme **13**).[46b] Excellent diastereoselectivities could be achieved when chiral ferrocenyl oxazolines were used in this coupling reaction. This protocol provides a facile method to synthesize planar chiral aryl-substituted ferrocenyl oxazolines.

[45] Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org*. *Lett*. **2008**, *10*, 2207-2210.
[46] (a) Hull, K. L.; Sanford, M. S. *J*. *Am*. *Chem*. *Soc*. **2007**, *129*, 11904-11905. (b) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869-4871. (c) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew*. *Chem*. *Int*. *Ed*. **2008**, *47*, 1115-1118.
[47] Hull, K. L.; Sanford, M. S. *J*. *Am*. *Chem*. *Soc*. **2009**, *131*, 9651-9653.



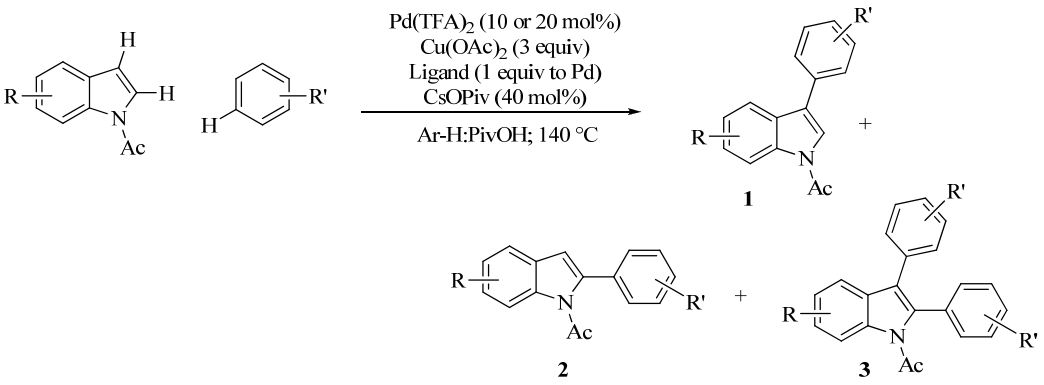
Scheme **12**



Scheme **13**

Recently, Keith Fagnou presented a Pd-catalyzed oxidative cross-coupling protocol between *N*-protected indoles and arenes that demonstrated a high degree of regiocontrol.[48] This result afforded a new opportunity for control of reactivity and selectivity in Pd-catalyzed oxidative cross-coupling reactions, and avoided the use of stoichiometric amount of activating groups (Scheme **14**). It also highlights the potential of such an approach in the synthesis of biaryl molecules.

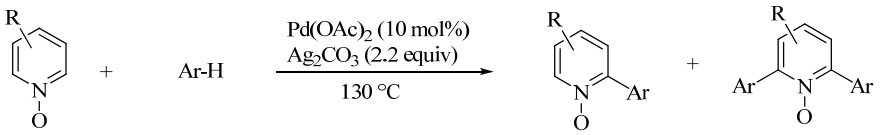
[48] (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172-1175. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072-12073.



Scheme **14**

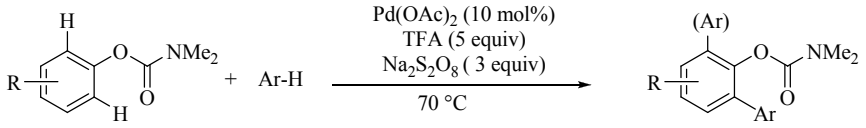
Palladium-catalyzed direct arylation of pyridine *N*-oxides with excess of unactivated arenes was also reported with Ag_2CO_3 as oxidant, and the corresponding cross-coupling products were obtained in good yields and with excellent regioselectivities (Scheme **15**).[49] This example provides another notable method to control site-selectivity by the employment of different directing groups within the same molecular skeleton.

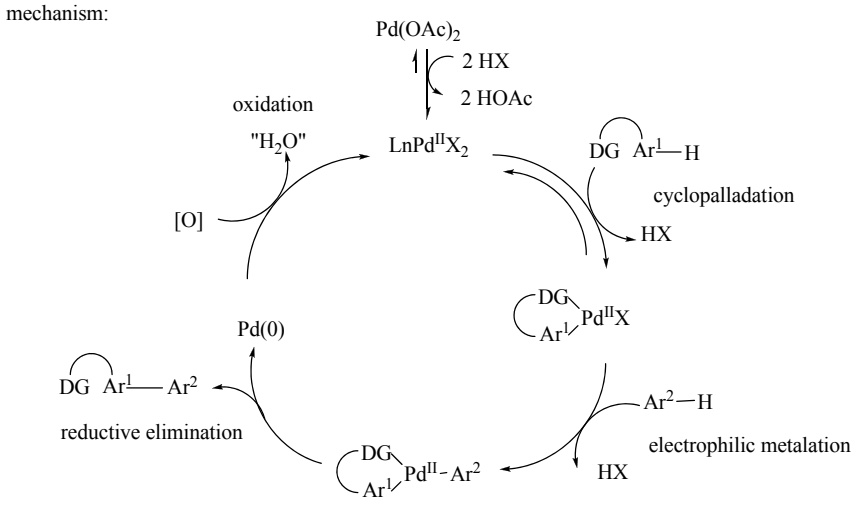
Very recently, directing group assisted aryl C–H bond activation and arylation of *o*-phenylcarbamates with simple arenes was achieved with palladium catalysis under very mild conditions.[50] The mechanism study by X-ray crystallography proved that the coupling reaction involved two C–H bond activations that proceeded *via* cyclopalladation and electrophilic metalation, within a Pd(0)/Pd(II) catalytic cycle (Scheme **16**).



Scheme **15**

[49] Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254-9256.
[50] (a) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837-5844. (b) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331-336.





Scheme **16**

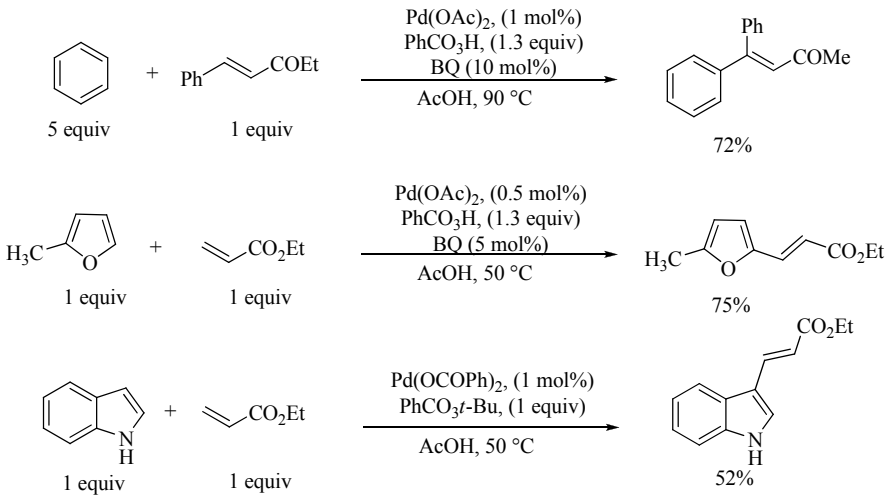
1.3.2 Pd-CATALYZED DIRECT COUPLING BETWEEN ARENES AND OLEFINS VIA C–H BONDS ACTIVATION

Over the past decades, various direct coupling reactions between arenes and olefins catalyzed by palladium have been developed. As mentioned previously, the first example of olefination reaction between a styrene-palladium(II) chloride complex and benzene derivatives was reported by Fujiwara and Moritani in 1967, in which it was found that the use of acetic acid as solvent was crucial to afford the desired products and palladium(II) acetate was the most efficient catalyst.[16] However, the need for a stoichiometric amount of expensive palladium(II) acetate limited the usefulness of the olefin arylation. Following this, the development of efficient catalytic systems by adding various oxidants to recycle the catalyst in reactions has been widely studied.[17] Aside from arene substrates, aromatic heterocycles such as furan and thiophene have

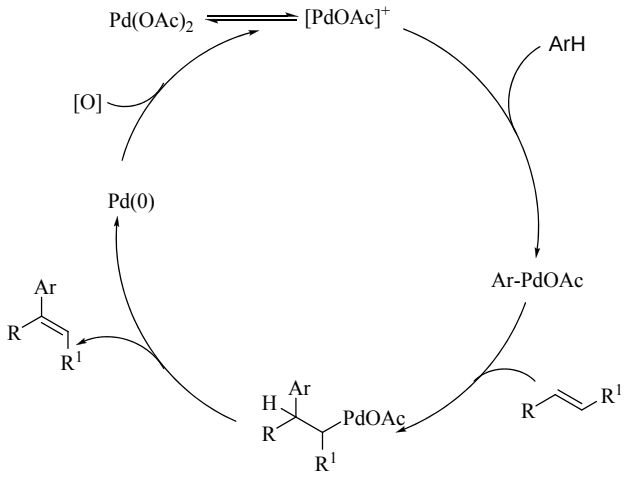
been employed to react with electron deficient alkenes to yield mono- and dialkylated derivatives at the 2- and 5-positions in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$.[51] Relatively high turnovers (over 20) were obtained in this reaction. A breakthrough was made in improving the efficiency of the reoxidation system when *tert*-butyl perbenzoate was used as oxidant to regenerate Pd(II) *in situ* from Pd(0).[52] Up to 34 and 67 turnovers were obtained for benzene and furan respectively when olefins and excess benzene or furan were heated at 100 °C in acetic acid solution. Equimolar amounts of benzoic acid and *tert*-butyl alcohol were obtained from the perester, which showed that the perester acted as a hydrogen acceptor in this reaction and excluded possibility of the participation of radical species.

A highly efficient catalytic system for the coupling of benzene, furan and indole with activated olefins has been developed in the presence of palladium(II) acetate and benzoquinone (BQ) with *tert*-butyl hydroperoxide as the oxidant (Scheme **17**).[53] Up to 280 turnovers could be achieved when benzene and ethyl (*E*)-cinnamate were used in this oxidative coupling to give ethyl 3-phenyl-cinnamate with high regioselectivity. It was proposed that a σ-aryl-Pd intermediate was formed *via* electrophilic attack of the aromatic C–H bond by a cationic $[PdOAc]^+$ species, followed by addition to the olefin and *β*-hydride elimination.

[51] Maruyama, O.; Yoshidomi, M.; Fujiwara, Y.; Taniguchi, H. *Chem*. *Lett*. **1979**, *8*, 1229-1230.
[52] Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699-2702.
[53] Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org*. *Lett*. **1999**, *1*, 2097-2010.



Scheme **17**



Mechanism for Pd-catalyzed coupling of arenes with olefins

Scheme **18**

Formation of the σ-bonded aryl-Pd complex was believed to be the rate-determining step during the coupling (Scheme **18**). The first asymmetric example of the "Fujiwara-Moritani" reaction has been reported recently in the arylation of substituted cyclic olefins using $Pd(OAc)_2$ with a chiral sulfonylamino-oxazoline ligand and *tert*-butyl perbenzoate as oxidant. [54] Optically active phenylsubstituted cyclohexenes were obtained by reacting benzene with various cyclohexenes. *Syn β-H*-elimination from the opposite side

[54] Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett.* **1999**, *28*, 55-56.

to the entering phenyl group resulted in modest enantioselectivity Despite the effort that has been made to improve the turnover number, it still remains a challenge for possible industrial application. Moreover, the use of peroxide oxidants is problematic from the industrial point of view. Therefore, the development of a more efficient system for direct olefination is still desirable.

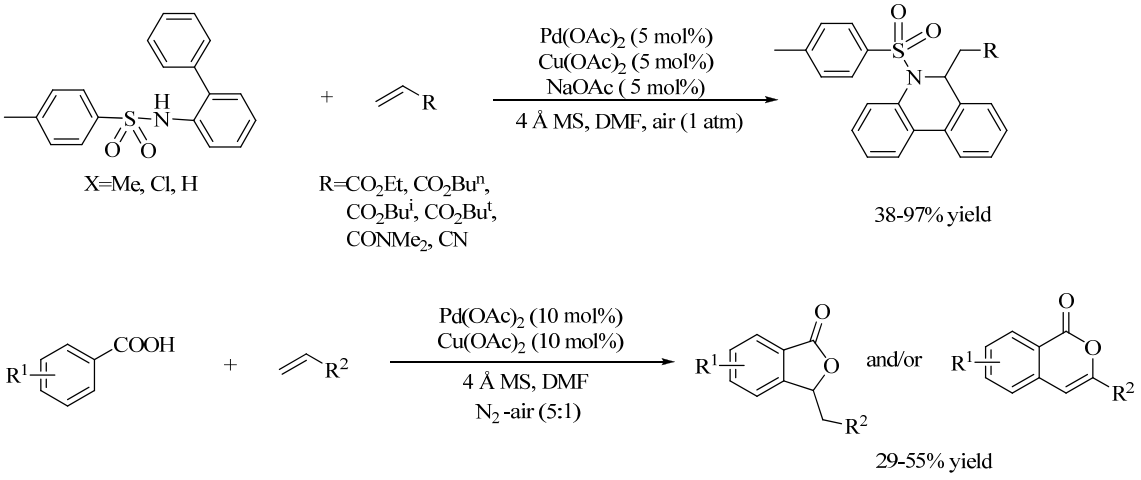
Quite recently,[55] Ishii and co-workers documented a highly efficient coupling reaction of furan, benzene and derivatives with acrylates, using a $Pd(OAc)_2$/HPMoV/NaOAc catalytic system under 1 atm O_2 atmosphere in acetic acid solution at 80 °C. The use of molybdovanadophosphoric acid (HPMoV) was important for high conversion and yield. When mono-substituted benzene derivatives were tested in this reaction, the corresponding coupling products were obtained as mixture of regioisomers. In fact, excellent control of the regioselectivity in transition-metal catalyzed coupling reactions still remains a huge challenge up to this day.

In 1998, Miura and co-workers described the reaction of *N*-(2′-phenylphenyl)benzenesulfonamides with electron-poor alkenes, such as acrylates *via* cleavage of the *ortho* aromatic C–H bond using a palladium catalyst.[56] The proposed coupling process involved initial orthopalladation by the reaction of *N*-(2'-phenylphenyl)benzenesulfonamides with the palladium species. The subsequent coupling reaction with acrylate followed by intramolecular nucleophilic cyclization afforded the dihydrophenanthridines. Furthermore, it was found that structurally related compounds such as benzoic and naphthoic acids were able to react with acrylate ester and styrene (Scheme

[55] (a) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476-1477. (b) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221-1226. (c) Yamada, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 5471-5474.
[56] Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211-5215.

19).

An example of triflamide-directed C–H activation and alkenylation catalyzed by palladium was reported by Yu's group. A wide range of substrates were tolerated in this coupling and monoalkenylated products were obtained in 50–65% yield along with dialkenylated products in 10–20% yield.[57] Notably, when vinyl ketones were applied in this reaction, a tandem C–H alkenylation and aza-Michael addition occurred to give tetrahydroisoquinolines in good yield and high diastereoselectivity (Scheme **20**).

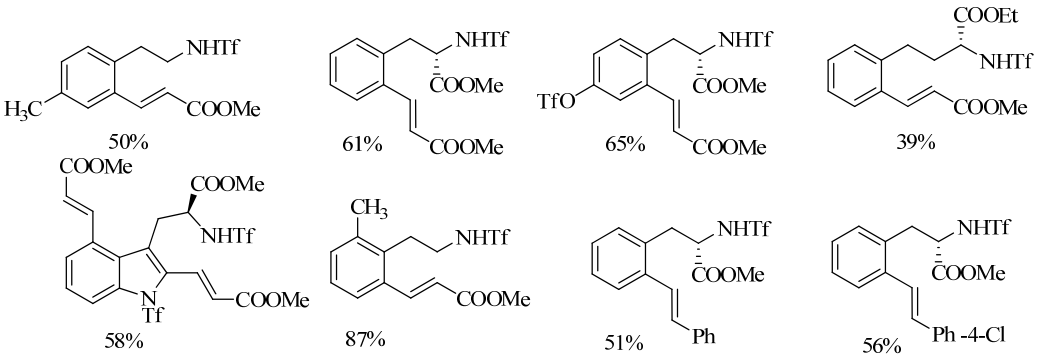


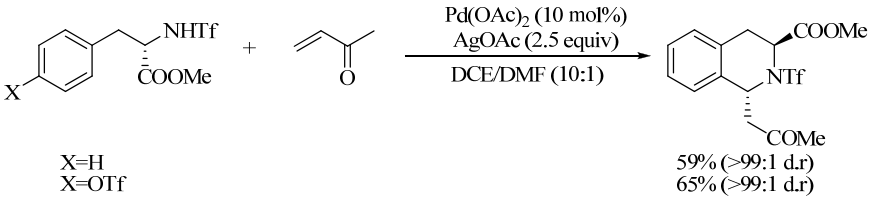
Scheme **19**

The nucleus of aniline derivatives is particularly reactive toward electron-deficient olefins. Its coupling with *n*-butyl acrylate, in the presence of $Pd(OAc)_2$ and in AcOH at room temperature with BQ serving as oxidant and ligand, resulted in alkenylation at only the *ortho*-position due to the strong *ortho*-directing effect of the amide group. Here, the double bond of acrylate was retained in the coupling product (Scheme **21**).[58]

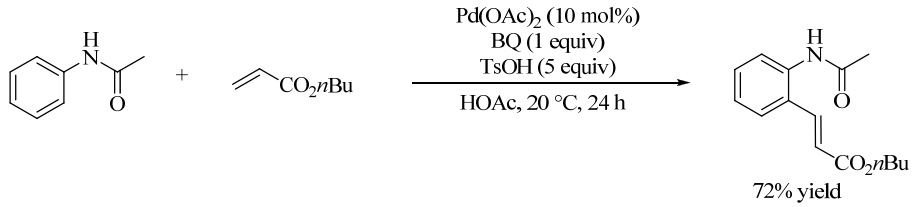
[57] Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452-6455.
[58] Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586-1587.

Triflamide-directed C-H activation and alkenylation reaction catalyzed by $Pd(OAc)_2$





Scheme **20**

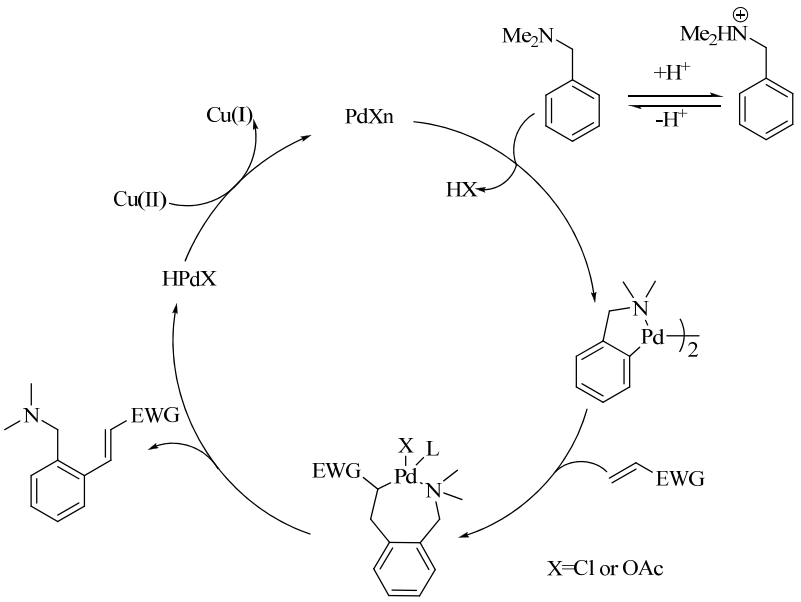


Scheme **21**

Compared with other directing groups, the difficulty of controlling the coordinating ability of the *N*,*N*-dimethylamino group with transition metal catalyst limited its utility as a directing group for catalytic C–H functionalization.[59] By tuning the acidity of the reaction conditions, an efficient *ortho*-olefination of *N*,*N*-dimethylbenzylamines catalyzed by palladium was developed by Shi's group. To elucidate the mechanism of this transformation, a palladacycle intermediate compound was prepared, which could undergo *ortho*-olefination stoichiometrically with *n*-butyl acrylate, and could also be used as a catalyst to efficiently catalyze the *ortho*-olefination under the typical reported conditions. In light of this, the palladacycle compound was proposed as the key

[59] Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666-7673.

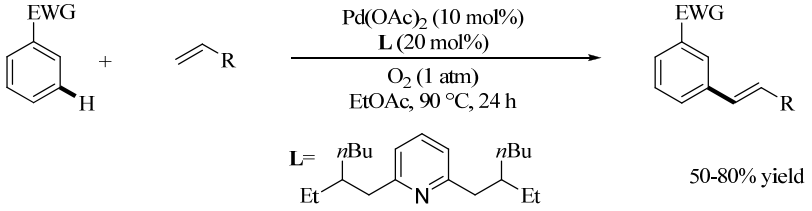
intermediate during the catalytic cycle. Furthermore, the result of a kinetic isotopic effect experiment indicated that cleavage of the C–H bond at the *ortho* position of the directing group was the rate-determining step. Based on the obtained results, a mechanism of this oxidative coupling is depicted below (Scheme **22**). Under proper acidic conditions, free tertiary amines could bind to the Pd(II) cation, which would electrophilically attack the benzene ring regioselectively to form the five-membered palladacycle intermediate. After an insertion of the double bond of the acrylate into the C–Pd bond of the palladacycle compound, followed by *β*-hydride elimination, the desired olefinated products were obtained in good yields and excellent regioselectivities.



Scheme **22**

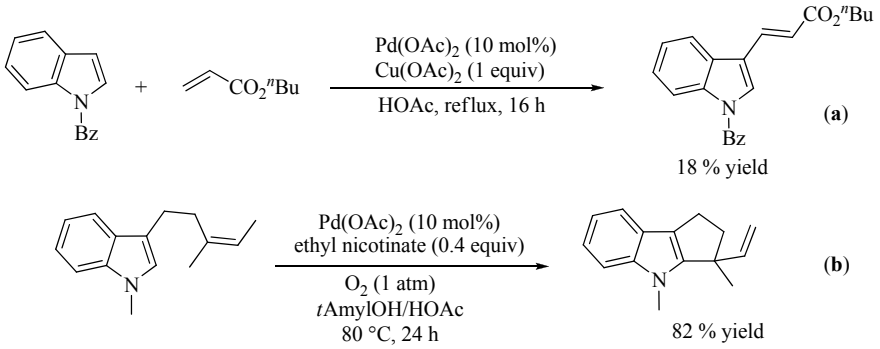
Among the reported palladium-catalyzed olefination reaction of arenes, studies were almost only limited to electron-rich arene substrates, while the reactivity of electron-poor arenes remained a big challenge. It was not until recently that Yu and co-workers reported a palladium-catalyzed olefination of

arenes with strong electron-withdrawing groups using 2,6-dialkylpyridines as ligands (Scheme **23**).[60] *Meta*-C–H olefination compounds were obtained as the major products in this reaction, this method provides a new efficient synthetic route for the preparation of 1,2,4-trisubstituted arenes, which are useful skeletons in medicinal chemistry.



Scheme **23**

As early as 1983, catalytic olefination of indoles had been reported by Itahara and co-workers, using $Pd(OAc)_2$ and Ag(I) and Cu(II) salts as oxidants. However, low yields of the desired products restricted its practical application (Scheme **24a**).[61] Recently, several studies have advanced this chemistry. Ferreira and Stoltz[62] demonstrated the first example of oxidative indole annulations carried out using a Pd-pyridine catalytic system with molecular oxygen as the sole stoichiometric oxidant (Scheme **24b**). The reaction proceeded with good yield under the mild conditions.

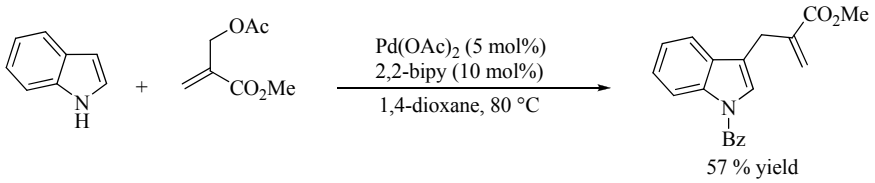


Scheme **24**

[60] Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072-5074.
[61] Itahara, T.; Ikeda, M.; Sakakibara, T. *J. Chem. Soc. Perkin Trans. 1.* **1983**, 1361-1363.
[62] Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578-9579.

Another notable cross coupling reaction of indoles was developed using catalytic palladium(II) acetate and 2,2-bipyridine as ligand, in which use of the oxidant was cleverly avoided by using allylic acetates as the coupling partners (Scheme **25**).[63] The authors proposed that direct C–H activation took place in the first step followed by an intermolecular carbopalladation with the allylic acetates. *β*-OAc elimination would form the product and regenerate the active catalyst, $Pd(OAc)_2$.

In 2005, Gaunt and coworkers disclosed a selective intermolecular alkenylation of indoles catalyzed by palladium (Scheme **26a**).[64] The nature of the solvent is crucial in



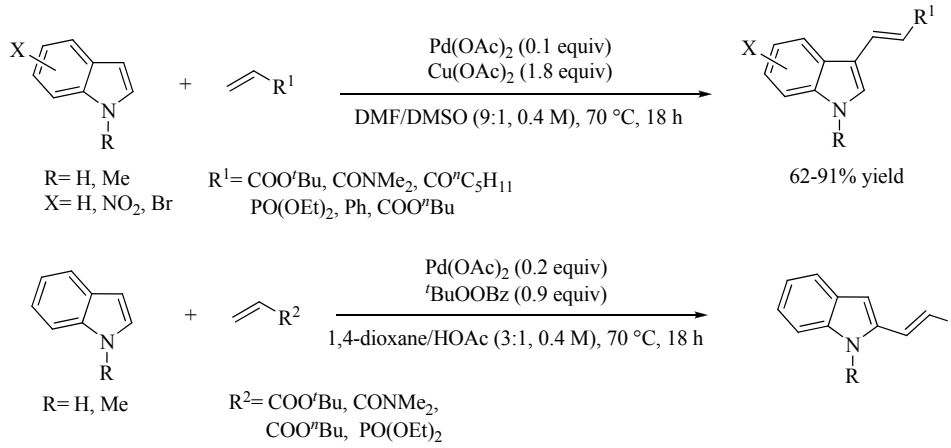
Scheme **25**

determining the regioselectivity of the products. Following which, another mild aerobic palladium(II) catalyst system was developed by the same group for regioselective C–H bond alkenylation and annulations of pyrroles (Scheme **26b**).[65] This work is remarkable in using different *N*-protecting group to adjust the stereoelectronic properties to control the regioselective activation and functionalization of pyrroles under mild conditions. An elegant synthetic application *via* intramolecular olefination of a 3, 5-disubstituted pyrrole has been successfully developed to prepare the natural product rhazinicine (Scheme

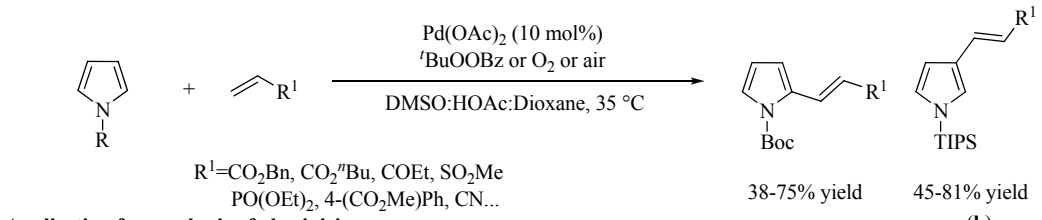
[63] Ma, S.; Yu, S. *Tetrahedron Lett*. **2004**, *45*, 8419-8422.
[64] Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125-3129.
[65] Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528-2529.

26c).[66]

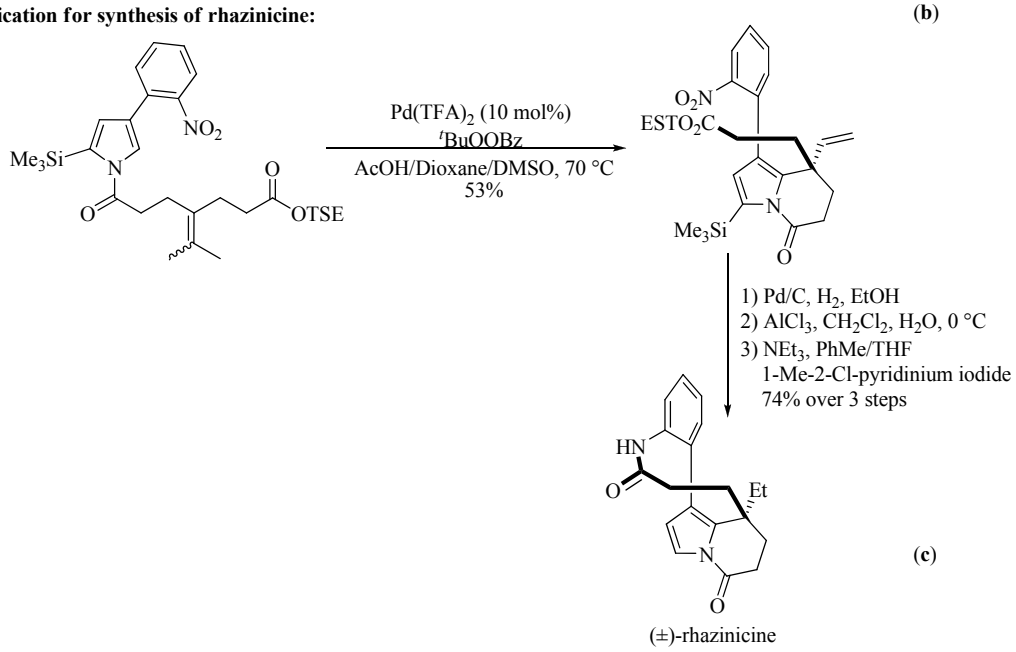
Regioselective functionalization of indoles:



Regioselective functionalization of pyrroles:



Application for synthesis of rhazinicine:

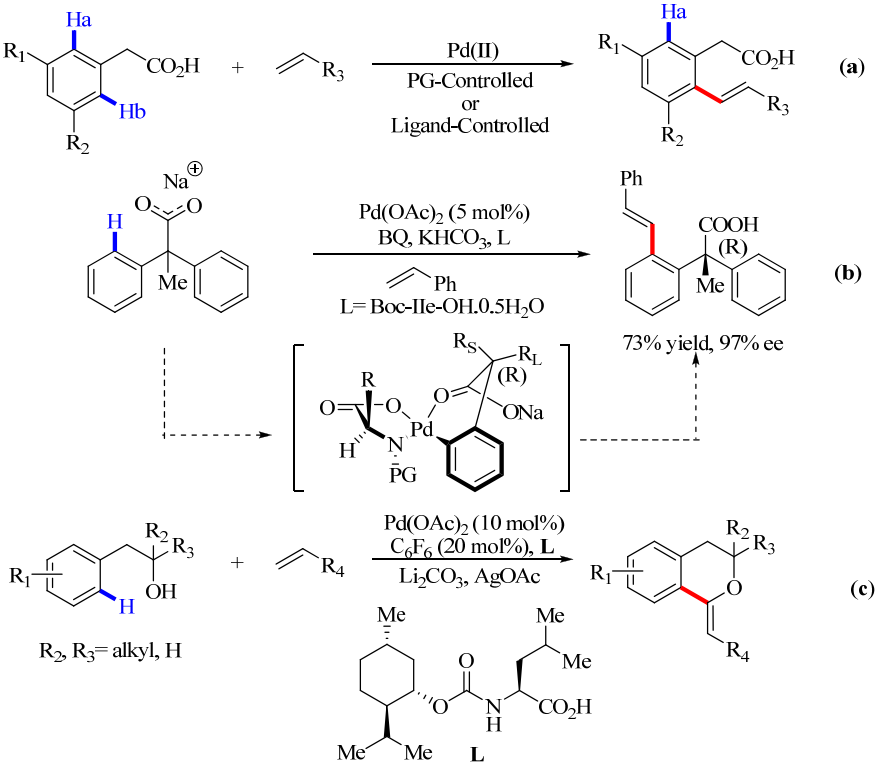


Scheme **26**

[66] Gaunt, M. J.; Beck, E. M.; Hartley, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 3004-3007.

A very recent report by Chang and co-workers demonstrated another selective alkenylation reaction using pyridine *N*-oxide and its derivatives as reactants.[67] Yu and co-workers also studied a similar regioselective olefination reaction using phenylacetic acid, 3-phenylpropionic acid and their derivatives with acrylates (Scheme **27a**).[68] Under mild conditions, catalytic $Pd(OAc)_2$ was used as catalyst, and the corresponding products were obtained in high yields and with excellent regioselectivities at *ortho*-position. It was noted that the positional selectivity of C–H activation of arenes with multiple substituents could be controlled *via* two methods: substrate control, such as appending a protecting group to alter the steric environment, and catalyst control, using ligands to change the steric and electronic properties around the metal center. In this study, some *N*-protected amino acids were screened as ligands to affect steric control of the palladium center. It was also found that amino acids such as Formyl-Ile-OH could definitely serve as efficient ligands to increase the catalytic ability and regioselectivity of palladium. On the basis of the above results, a asymmetric protocol was developed for the Pd(II)-catalyzed olefination reaction of *α*,*α*-diphenylacetic acid using Boc-L-isoleucine as a chiral ligand (Scheme **27b**).[68b] Recently, the same group broadened the directed C–H olefination scope by using the hydroxyl group as a directing group, which could alleviate the limitation of current directing groups used in the area of C–H activation that require installation and detachment to afford the product of interest (Scheme **27c**).[69]

[67] Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254-9256.
[68] (a) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315-319. (b) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J-.Q. *J. Am. Chem. Soc.* **2010**, *132*, 460-461.
[69] Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J-.Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916-5921.



Scheme **27**

1.3.3 Pd-CATALYZED OXIDATIVE COUPLING REACTIONS OF ALKENES

Although simple olefins are an important carbon source in the synthesis of fine chemicals, they are rarely used directly as coupling reactants. In 1979, a pioneering work involving intramolecular addition of silyl enol ethers to olefins was reported by Saegusa and co-workers, in which 0.5 equivalent of palladium was used and cyclic α, β-unsaturated ketones were obtained in high yields.[70] Several recent works have advanced this chemistry. Cyclopentenones were formed from α-alkoxydienones using 20 mol% $Pd(OAc)_2$ in DMSO under oxygen atmosphere at 80 °C. More direct approaches to form C–C bonds *via* intramolecular addition from alkenyl-substituted β-dicarbonyls catalyzed by

[70] Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494-496.

palladium were observed in high yields.[71] The need for pre-functionalized starting materials or the difficulty in achieving intermolecular reactions limited wide-spread application of the method. There are however a few examples of intermolecular self-coupling between olefins that have been applied to synthesize natural products. A terpene derivative was applied to the Pd-catalyzed oxidative coupling reaction in the presence of BQ as oxidant, forming the homocoupling product in low yield.[72] Oxidative self-coupling of vinyl acetate catalyzed by $Pd(OAc)_2$ to form 1,4-diacetoxy-1,3-butadiene has also been reported.[73] It was not until 2004 however that Ishii and co-workers demonstrated the first direct oxidative cross-coupling between vinyl acetates and acrylates, which is also the first example of the direct formation of diene products with olefins catalyzed by palladium.[74] The mechanism proposed invokes a σ-vinylpalladium intermediate formed by vinyl acetate reacting with $Pd(OAc)_2$, followed by an insertion of the acrylate into the Pd-vinyl bond leading to a σ-alkyl palladium complex. After *β*-hydride elimination, the coupled diene product was formed. However, only limited substrates were tested in this reaction, and the use of a complex acid, $H_4PMo_{11}VO_{40}$ as additive was necessary.

In a rare study of the catalytic oxidative cross-coupling reaction between olefins, our group recently investigated the direct cross-coupling between common olefins and alkenes with electron-withdrawing groups using catalytic

[71] Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927-4930.
[72] (a) Da Silva.; M. J.; Gusevskaya, E. V. *J. Mol. Catal. A: Chem.* **2001**, *176*, 23-27. (b) Da Silva.; Gonçalves, J. A.; Alves, B. R.; Howarth, O. W.; Gusevskaya, E. V. *J. Organomet. Chem.* **2004**, *689*, 302-308.
[73] Kohll, C. F.; Van Helden, R. *Recl. Trav. Chim. Pays-Bas.* **1967**, *86*, 1930 [CAN 66:104490].
[74] Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623-4625.

$Pd(OAc)_2$ in the presence of $Cu(OAc)_2$ and oxygen as oxidant.[75] In this protocol, both aromatic and aliphatic alkenes could afford the desired dienoate compounds in moderate to good yields.

Besides terminal olefins, internal alkenes could also afford the corresponding products. This protocol offers several advantages including commercial availability of starting materials, operational simplicity, mild reaction conditions, good atom-economy, and moderate to high yields, making it a potentially useful and attractive strategy for the synthesis of dienoate compounds.

1.4 DIRECT CROSS-COUPLING BETWEEN SP^3 C–H BONDS

Unactivated sp^3 C–H bonds are ubiquitous in organic compounds, so it would be highly atom-economical and synthetically efficient if it is possible to directly use C–H bonds as functional groups.[76] In recent decades, together with the development of homogeneous catalysis, significant advances in direct coupling *via* sp^3 C–H bond activation have been made. Early work involving regioselective C(sp^3)–H activation could be achieved intramolecularly by heteroatom-assisted coordination in stoichiometric organometallic reactions.[77] Sames and co-workers reported a selective activation of the C(sp^3)–H bond of a *tert*-butyl group in the synthesis of the teleocidin B-4 core (Scheme **28**).[78] With coordinated assistance from an imine and a methoxy group, a palladacycle was generated *via* direct activation of the C(sp^3)–H bond.

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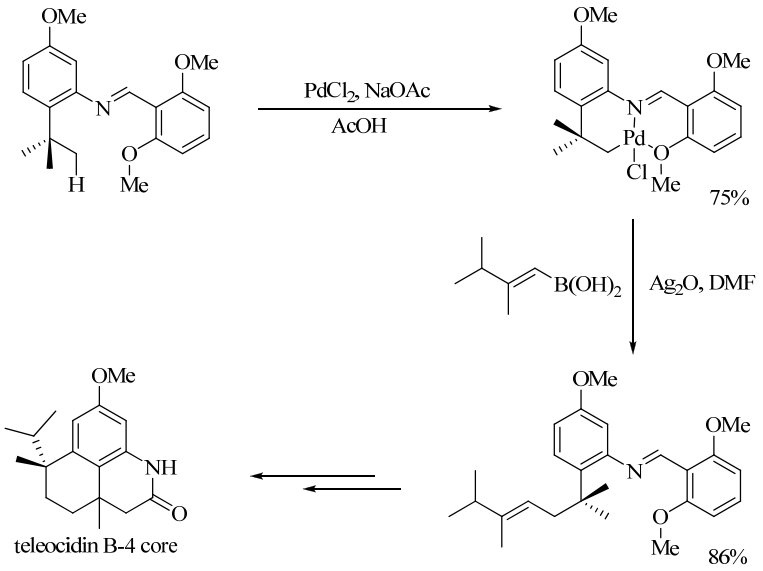
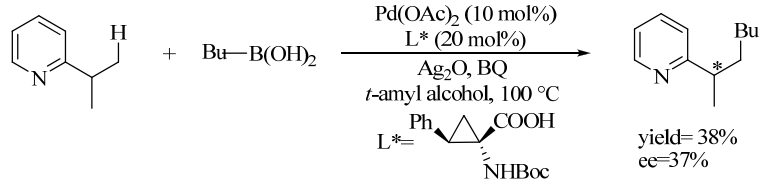
[75] Xu Y.-H, Lu, J. Loh. T-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372-1373.
[76] *Handbook of C-H Transformations* Dyker, G.; Ed.; Wiley-VCH: Weinheim, 2005.
[77] (a) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403-424. (b) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2423-2428. (c) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041-4047. (d) Ackermann, L. *Top. Organomet. Chem.* **2008**, *24*, 35-60. (e) Kalyani, D.; Sanford, M. S. *Top. Organomet. Chem.* **2007**, *24*, 85-116.
[78] Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856-11857.



Scheme **28**

A catalytic protocol was developed by Yu and co-workers, in which the pyridine group directed an alkylation reaction *via* Pd-catalyzed C(sp^3)–H bond activation.[79] Other directing groups such as carboxylic acid,[80] and *O*-methyl hydroxamic acid[81] were employed to facilitate the C(sp^3)–H bonds activation, and subsequent arylation or alkylation was achieved by using organoboronic or organohalide reagents.[82] The first enantioselective C(sp^3)–H bond activation/C–C coupling example using pyridine as a directing group was developed by Yu and co-workers (Scheme **29**).[80b] The chiral cyclopropanecarboxylate ligand combined with $Pd(OAc)_2$ to give a modest yield and enantioselectivity of the C–C coupling product with *n*-butylboronic acid.

[79] Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634-12635.
[80] (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510-3511. (b) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882-4886.
[81] Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190-9191.
[82] (a) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657-3659. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382-3388.



Scheme **29**

Over the same period, directing group assisted Pd-catalyzed acetoxylation,[83] halogenation[84] and amination[85] reactions *via* C(sp^3)–H bond activation have been reported by various groups. As described above, Pd-catalyzed direct C–H bond olefination of arenes, olefins and alkynes *via* either electrophilic palladation or the C–H activation pathway has been widely studied in recent decades. However, the Pd-catalyzed olefination of unactivated sp^3 C–H bonds remained undisclosed until Yu and co-workers reported the first example of such chemistry (Scheme **30**).[86] The reason why this protocol remained undisclosed for a long time was believed to be the difficulty in sp^3 C–H cleavage and the few examples of carbopalladation intermediate from sp^3 C–H activation across a double bond.[87] It was found that *N*-arylamide containing strong electron-withdrawing groups as the directing group could facilitate this reaction well in the presence of a mixture of $Cu(OAc)_2$ and AgOAc (1:1) as

[83] (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542-9543. (b) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149-8150. (c) Kalberer, E. W. Whitfield, S. R.; Sanford, M. S. *J. Mol. Catal. A*: *Chem.* **2006**, *251*, 108-113. (d) Wang, D.; Hao, X.; Wu, D.; Yu J.-Q. *Org. Lett.* **2006**, *8*, 3387-3390. (e) Reddy, B. V.S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391-3394. (f) Giri, R.; Liang, J.; Lei, J.; Li, J.; Wang, D.; Chen, X.; Naggar, I.C.; Guo, C.; Foxman, B. M. Yu, J.-Q. *Angew. Che*m. *Int. Ed.* **2005**, *44*, 7420-7424.

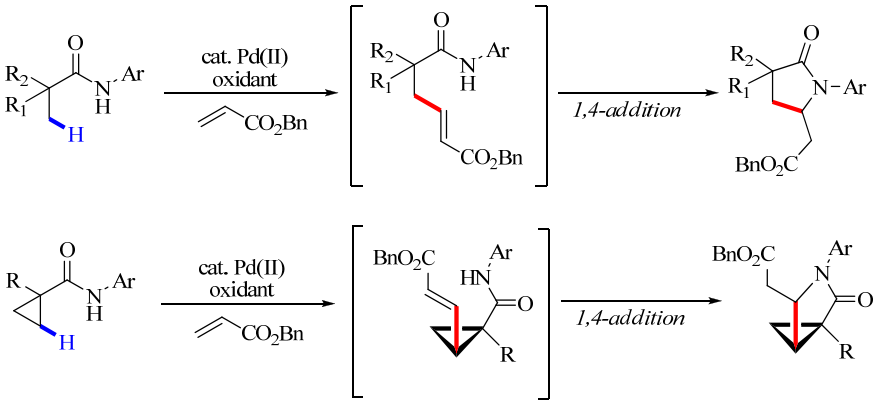
[84] (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112-2115. (b) Giri, R.; Chen, X.; Hao, X.; Li, J.; Liang, J.; Fan, Z.; Yu, J.-Q. *Tetrahedron Asymmetry* **2005**, *16*, 3502-3505. (c) Giri, R.; Wasa, M.; Breazzano, S. P.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 5685-5688.

[85] Thu, H.; Yu, W.; Che, C. *J. A*m. *Chem. Soc.* **2006**, *128*, 9048-9049.

[86] Wasa, M.; Engle, K. M.; Yu, J-.Q. *J. Am. Chem. Soc.* **2010***, 132,* 3680-3681.

[87] (a) For carbopalladation of alkylpalladium complexes across olefins, see: Balavoine, G.; Clinet, J. C. *J. Organomet. Chem.* **1990**, *390*, C84-C88. (b) For olefination of alkylpalladium complexes with vinylboronic acids, see: Dangel, B. D.; Godula, K.; Youn, S. W.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856-11857.

oxidant with lithium chloride (2 equivalent) as an additive in DMF solution at 120 °C under N_2 atmosphere. After *β*-C-H olefination, the corresponding lactam products were obtained from 1,4-conjugate addition of the amide.



Scheme **30**

1.5 CHALLENGES OF C–H ACTIVATION

In the past few decades, transition-metal, especially palladium-catalyzed coupling reactions *via* C–H bond activation, for the construction of C–C and C–heteroatom bonds, have shown powerful feasibility. However, the reactivity, selectivity and cost-effectiveness still remained as challenges. In many C–H activation protocols, harsh conditions such as high temperature and pressure are required to force the reaction to proceed as designed. In the case of the substrate with several similar C–H bonds, usually directing groups are installed to assist the metal catalyst to achieve the selectivity. However, the additional installation and detachment steps restricted the methodology in practical application. Moreover, many reported reactions required excessive substrates loading or high catalysts loading, to bring about the desired transformation, which make the operational cost high and the method less efficient and attractive. To overcome the above problems, other less expensive transition metals such as Cu, Fe and Ni can be developed as catalysts in these transformations. In addition,

the development of new efficient and versatile reaction conditions is required in future research.

CHAPTER 2

Direct Cross-Coupling Reaction of Simple Alkenes with Electron-Poor Olefins Catalyzed by Palladium

Chapter 2. Direct Cross-Coupling Reaction of Simple Alkenes with Electron-Poor Olefins Catalyzed by Palladium

2.1 INTRODUCTION

Cross-coupling reactions catalyzed by palladium have been shown to be one of the most powerful methods for the construction of C–C bonds.[88] As such, they have been applied extensively in the synthesis of a wide variety of natural products and pharmaceuticals.[89] One of the most challenging problems associated with this method is the need for use of halogenated substrates and/or organometallics.[90] Therefore, many research groups have focused on exploring Pd-catalyzed coupling reaction through direct C–H bond activation and/or functionalization.[91] Of the many methods developed, direct coupling between

[88] (a) Tsuji, J. *Palladium Reagents and Catalysts*: *Innovations in Organic Synthesis*; Wiley and Sons: New York, 1995. (b) Tsuji, J. *Palladium Reagents and Catalysts*: *New Perspectives for the 21th Century*; Wiley and Sons: New York, 2003. (c) Egle, M. B.; Gianluigi, B.; Michela, M.; Silvia, S. *Chem. Rev*. **2007**, *107*, 5318-5365. (d) Zeni, G.; Larock, R, C. *Chem. Rev*. **2006**, *106*, 4644-4680. (e) Tietze, L. F.; Ila, H.; Bell, H, P. *Chem. Rev*. **2004**, *104*, 3453-3516. (f) Dounay, A. B.; Overman, L. E. *Chem. Rev*. **2003**, *103*, 2945-2964. (g) Negishi, E.; Anastasia, L. *Chem. Rev*. **2003**, *103*, 1979-2018. (h) Trost, B. M. *Acc*. *Chem*. *Res*. **1980**, *13*, 385-393.

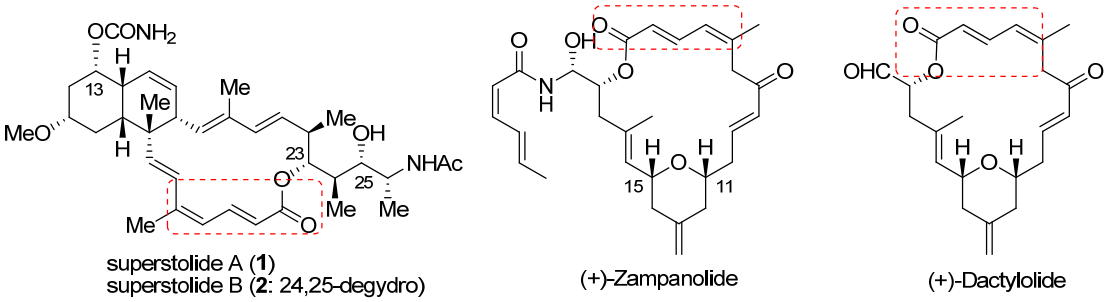
[89] (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174-238. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed*. **2005**, *44*, 4442-4489. (c) Ge, H. B.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc*. **2008**, *130*, 3708-3709.

[90] (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37***,** 2320-2322. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467-4470. (d) King, A. O.; Okukado, N.; Negishi, E.-i. *J*. *Chem*. *Soc*.; *Chem. Commun.* **1977**, 683-684. (e) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636-3638. (f) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866-867. (g) Hiyama, T. *J. Org. Chem*. **1988**, *53*, 918-920. (h) Wolfe, J. P.; Buchwald, S. L. *Org. Synth.* **2004**, *10*, 423-423. (i) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189-3192.

[91] For recent references: (a) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133-173. (b) Lee, J. M.; Ahn, D-S.; Jung, D. Y.; Lee, J.; Do,Y.; Kim, S. K.; Chang, S. *J. Am. Chem. Soc.* **2006**, *128*, 12954-12962. (c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc*. **2008**, *130*, 9254-9256. (d) Iwai, Y.; Gligorich, K. M.; Sigman, M. S. *Angew. Chem. Int. Ed*. **2008**, *47*, 3219-3222. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633-639. (f) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879-2932. (g) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc*. **2008**, *130*, 11270-11271. (h) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190-7191. (i) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066-6067. (j) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570-14571. (k) Cárdenas, D. J.; Martin-Matute. B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033-5040. (l) Chu, J-H.; Chen, C-C.; Wu, M-J. *Organometallics* **2008**, *27*, 5173-5176.

non-prefunctionalized reactants offers the most promising protocol to construct new carbon-carbon and carbon-heteroatom bonds due to its high atom economy and environmental benefits.[92] Here, we focus on the study of direct olefination reaction catalyzed by palladium.

As we noticed, dienolate fragments exist in many natural product molecules (Scheme **1**).[93] Traditionally, the synthetic methods for the preparation of these fragments involve Wittig reactions (eq 1 and 2) and classic palladium-catalyzed coupling reactions (eq 3 and 4). However, the use of Wittig reagents is wasteful in terms of atom economy. In addition, while few steps are required to prefunctionalize vinyl substrates and organic halide compounds used in coupling reactions, the halide byproducts generated after the reaction are not environmentally friendly.

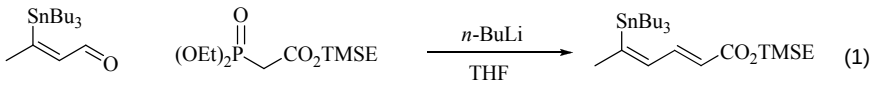


Scheme **1**

[92] (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245-269. (b) Shilov, A. E. Shulpin, G. B. *Chem. Rev.* **1997**, *97*, 2879-2932. (c) Stahl, S. S.; Labinger, J. A. Bercaw, J. E. *Angew. Chem. Int. Ed.* **1998**, *37*, 2180-2192. (d) Bergman, R. G. *Nature* **2007**, *446*, 391-393.

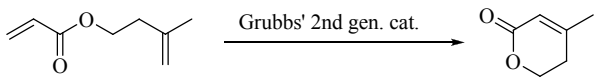
[93] (a) Smith, III, A. B.; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102-11113. (b) Smith, III, A. B.; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635-637. (c) Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053-3056. (d) Louis, I.; Hungerford, N. L.; Humphries, E. J.; Mcleod, M. D. *Org. Lett.* **2006**, *8*, 1117-1120. (e) Ding, F.; Jennings, M. P. *J. Org. Chem.* **2008**, *73*, 5965-5976. (f) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 2722-2723. (g) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 9657-9667. (h) Fürstner, A.; Flügge, S.; Larionov, O.; Takahashi, Y.; Kubota, T.; Kobayashi, J. *Chem. Eur. J.* **2009**, *15*, 4011-4029. (i) Guinchard, X.; Bugaut, X.; Cook, C.; Roulland, E. *Chem. Eur. J.* **2009**, *15*, 5793-5798.

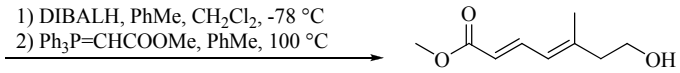
To develop a new efficient method as a tool for constructing the dienolate structure, a review of previous research involving palladium catalyzed direct cross coupling is first necessary to briefly introduce the work done thus far.



(1)

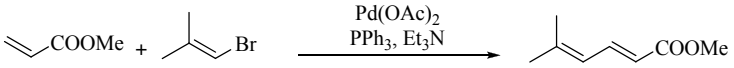
Roush, W. R. *et al*. *J*. *Org*. *Chem*. **2008**, *73*, 9657 – 9667





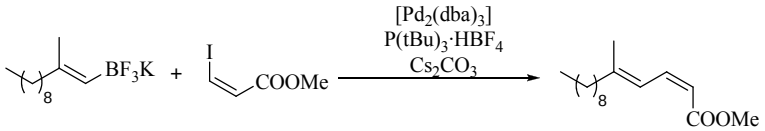
(2)

Mcleod, M. D. *et al*. *Org*. *Lett*. **2005**, *8*, 1117 – 1120



(3)

Fürstner, A. *et al*. *Che*m. *Eur*. *J*. **2009**, *15*, 4011 – 4029



(4)

Roulland, E. *et al*. *Chem*. *Eur*. *J*. **2009**, *15*, 5793 – 5798

The coupling of arenes and olefins with the cleavage of aromatic C–H bonds in the presence of stoichiometric amounts of Pd compounds is the earliest example of such a reaction developed by Fujiwara and co-workers in 1967.[94] Subsequently, cases using catalytic amount of Pd together with oxidation systems such as $Cu(OAc)_2/O_2$,[95] $AgOAc/O_2$,[96] BQ[97] or *tert*-butyl perbenzoate were developed.[98] The σ-aryl-Pd(II) complexes generated *via* electrophilic metalation of aromatic C–H bonds were elucidated to be the intermediates during the coupling process.[95,99] Other coupling reactions between heteroarenes

[94] Moritani, I.; Fujiwara, Y. *Tetrahedron Lett*. **1967**, *8*, 1119-1122.
[95] Fujiwara, Y.; Moritani, I.; Danno, S. *J*. *Am*. *Chem*. *Soc*. **1969**, *91*, 7166-7169.
[96] Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett*. **1968**, *9*, 3863-3865.
[97] Jia, C.; Lu, W.; Kitamura, S.; Fujiwara, Y. *Org*. *Lett*. **1999**, *1*, 2097-2100.
[98] Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699-2702.
[99] Fuchita, Y.; Hiraki, K.; Kamogawa, Y. *Bull*. *Chem*. *Soc*. *Jpn*. **1989**, *62*, 3863-3865.

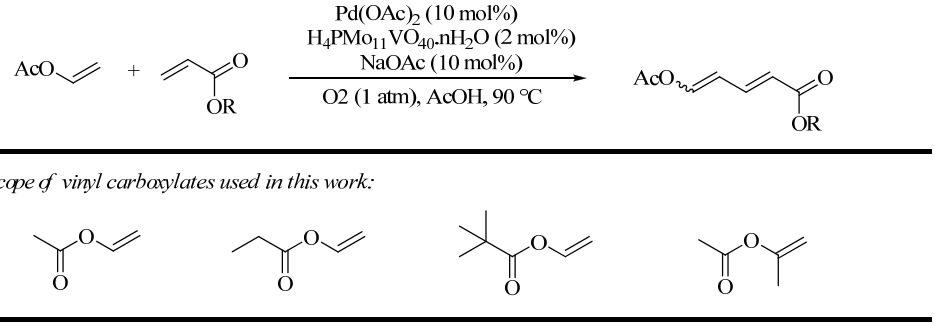
and olefins were also reported using stoichiometric or catalytic loading of Pd.[100] However, regioselective control in the coupling products corresponding to polysubstituted arenes has remained a challenge for a long time.[101]

In bid to overcome this shortcoming, an early attempt using benzoic acid to achieve *ortho* selectivity, stands as an encouraging step forward.[102] In response to this regioselectivity problem, aniline derivatives were used by de Vries and co-workers as substrates to couple with olefins.[103] High *ortho* selectivity was found in the corresponding coupling products, although limited substrates were tested in this reaction. By adjusting the acidity of the reaction conditions, a very efficient *ortho* olefination of *N*,*N*-dimethylbenzylamines catalyzed by palladium was developed by Shi and co-workers.[104] It was found that both the acidity and quantity of the Brönsted acid used was crucial to controlling the efficiency of this *ortho* olefination. Recently, Chang and co-workers described a useful olefination of pyridine *N*-oxides, forming solely *ortho* selective products.[105]

However, the direct cross-coupling reaction using simple alkenes to form dienes has not been well studied. This is due to the difficulty in activating the alkenyl C–H bond, although self-coupling byproducts in the palladium

[100] (a) Asano, R.; Moritani, I.; Fujiwara, Y.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 663-664. (b) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851-855. (c) Maruyama, O.; Yoshidomi, M.; Fujiwara, Y. Taniguchi, H. *Chem. Lett*, **1979**, *8*, 1229-1230.
[101] Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315-319.
[102] Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211-5215.
[103] Boele, M. D.; van Strijdonck, G. P. F.; de Vries, A. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwan, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586-1587.
[104] Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666-7673.
[105] Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254-9256.

catalyzed oxidation of monoterpenes and vinyl acetate have been reported.[106] In 2004, Ishii and co-workers elegantly demonstrated the Pd(II)-catalyzed oxidative cross-coupling reaction of acrylates with vinyl carboxylates in the presence of vanadomolybdophospholic acids under O_2.[107] (Scheme 2) However, as far as we know, the direct cross coupling reaction between simple alkenes and acrylates has not been reported. On the basis of the above research background, we decided to study the direct cross-coupling reaction between simple olefins and acrylates using palladium catalyst.



Scheme **2.** Pd-Catalyzed Coupling Reaction of Vinyl Acetate with Acrylate

2.2 EXPERIMENTS AND RESULTS

Initially, *α*-methylstyrene and *tert*-butyl acrylate were selected as reactants for the model study. The reaction was carried out in the presence of palladium catalyst under various conditions. In light of previous results of the Fujiwara-Moritani reaction,[106] we used excess amount of *α*-methylstyrene (5 equiv) to react with *tert*-butyl acrylate (1 equiv) in the presence of 20 mol% $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ (2 equiv) as oxidant in acetic acid solution. It was found that 16% yield of (*E*)-*tert*-butyl 3-acetoxyacrylate was obtained and palladium black was observed on the wall of the round bottom flask. Only trace amounts

[106] (a) Da Silva, M. J.; Gusevskaya, E. V. *J. Mol. Catal. A*: *Chem.* **2001**, *176*, 23-27. (b) Kohll, C. F.; Van Helden, R. *Recl. Trav. Chim. Pays-Bas*. **1967**, *86*, 1930, [CAN 66:104490].
[107] Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett*. **2004**, *6*, 4623-4625.

of the desired product was obtained when the reaction mixture was stirred at room temperature for 48 hours. To our delight, when the mixture was heated at 80 °C for 24 hours, the desired product was obtained in 61% yield. It was noticed that a significant amount of palladium black was still generated at the end of the reaction. The use of decreased amounts of α-methylstyrene (2 equiv) and $Cu(OAc)_2$ (1 equiv) did not affect the yield significantly (59% yield). The temperature could also be lowered to 60 °C, affording the product in 60% yield. As the choice of solvent is usually crucial for the coupling,[107] various solvents were tested using 20 mol% loading of $Pd(OAc)_2$ and one equivalent of $Cu(OAc)_2$ in acetic acid solution at 60 °C. The results are summarized in Table 1. Some solvents which are often used in Fujiwara-Moritani reactions were tested under our conditions. Unfortunately, DMF, ^{t}BuOH, Dioxane, THF, and CH_3CN failed to give the desired product. Only DMSO afforded traces of product. However, it was found that a mixture of DMSO and HOAc (volume ration = 1:1) as solvent gave a better result, affording the product in 71% yield. It was also noted that comparatively less palladium black was observed at the end of the reaction with DMSO as solvent. Hence, we believe that DMSO could stabilize the palladium catalyst during the coupling process.[108] However, when acetic acid was replaced with propionic acid, only 43% yield of the product was obtained.

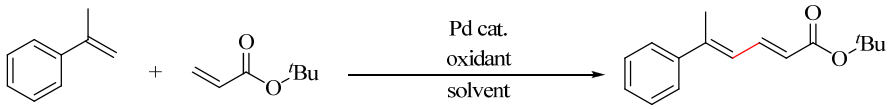
When the loading of $Pd(OAc)_2$ was increased to 30 mol%, the yield of product increased slightly to 78% (Table **2**, entry 1), while only 33% yield was obtained with 10 mol% loading of the catalyst (Table **2**, entry 2). Other catalysts such as $Pd(TFA)_2$ (Table **2**, entry 7) and $PdCl_2$ (Table **2**, entry 8)

[108] Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400-3420.

afforded the product in only 16% and 21% yields respectively. Similar results were also obtained by using $Pd(PhCN)_2Cl_2$ (Table **2**, entry 4) or $Pd(CH_3CN)_2Cl_2$ (Table **2**, entry 5) as catalyst. However, $Pd(PPh_3)_2Cl_2$ failed to give any product (Table **2**, entry 3). Thus we proposed that stronger electron-donating ligands may block the catalytic cycle by coordinating to the Pd(II) center, thereby decreasing its electrophilicity. At room temperature, the reaction proceeded very slowly, resulting in only 22% yield of the desired product obtained even after prolonged stirring. Benzoquinone (BQ) and other copper(II) salts, such as $CuCl_2$ and $Cu(OTf)_2$, were also tested as oxidants in the reaction, but all were less efficient than $Cu(OAc)_2$.

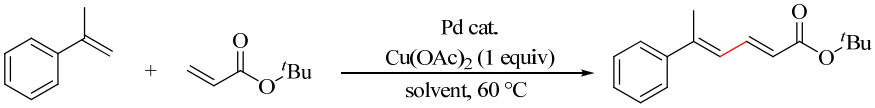
With the optimized conditions at hand, 20 mol% $Pd(OAc)_2$, $Cu(OAc)_2$ (1 equiv) in mixed solvent of DMSO and HOAc (v/v=1:1), we then examined the scope of this protocol. The results are summarized in Table 3. Substrates with various substitution patterns all gave the expected products in moderate to good yields.

Table **1**. Direct oxidative cross-coupling of *α*-methylstyrene with *tert*-butyl acrylate in various solvents.



entry	catalyst (mol%)	oxidant (equiv)	solvent	temperature (°C)	yield (%)
1	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	DMF	60	—
2	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	^{t}BuOH	60	—
3	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	DMSO	60	trace
4	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	Dioxane	60	—
5	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	THF	60	—
5	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	^{t}BuOH/DMSO (1:1)	60	—
6	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	CH_3CN	60	—
7	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	DMSO/HOAc (1:1)	60	71
8	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (1)	DMSO/CH_3CH_2COOH (1:1)	60	43

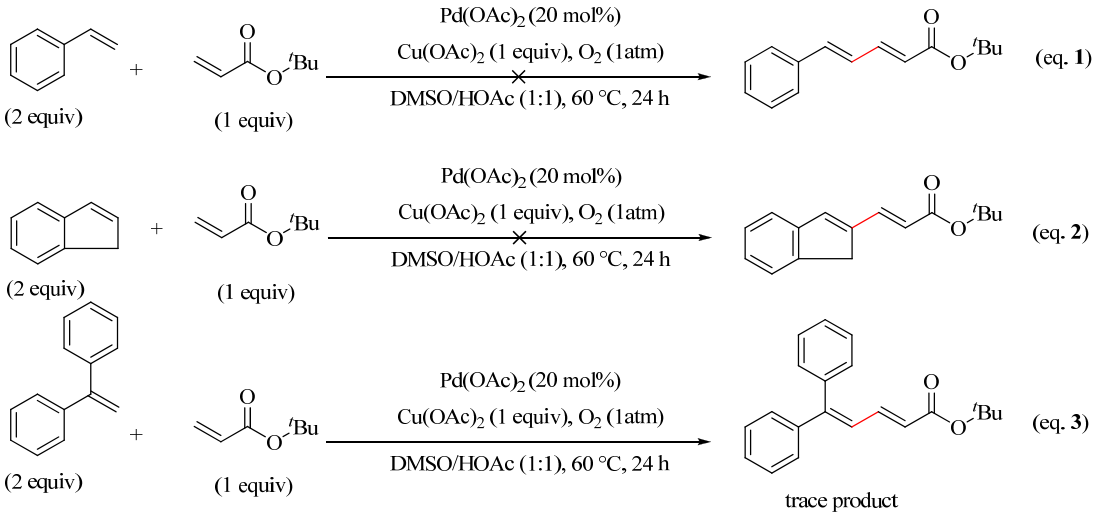
Table **2**. Direct oxidative cross-coupling of *α*-methylstyrene with *tert*-butyl acrylate using different palladium catalysts.



entry	catalyst (mol%)	time (h)	oxidant	yield (%)
1	$Pd(OAc)_2$ (30)	24	$Cu(OAc)_2$	78
2	$Pd(OAc)_2$ (10)	24	$Cu(OAc)_2$	33
3	$Pd(PPh_3)_2Cl_2$ (20)	24	$Cu(OAc)_2$	0
4	$Pd(PhCN)_2Cl_2$ (20)	24	$Cu(OAc)_2$	31
5	$Pd(CH_3CN)_2Cl_2$ (20)	24	$Cu(OAc)_2$	25
6	$Pd(PPh)_4$ (20)	24	$Cu(OAc)_2$	0
7	$Pd(TFA)_2$ (20)	24	$Cu(OAc)_2$	16
8	$PdCl_2$ (20)	24	$Cu(OAc)_2$	21

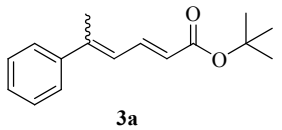
Substitutions at the *para*-, *meta*-, or *ortho*-positions of *α*-methylstyrene were tolerated (Table 3, **3b**, **3c**, **3d**), though substituent at the *ortho*-position (Table 3, **3d**) decreased the yield slightly. Both electron-poor (Table 3, **3e**) and electron-rich substrates could be efficiently alkenylated (Table 3, **3f**, **3g**, **3h**), although for the former, the yield was lower. Internal alkenes were also successfully employed for the cross-coupling reaction (**3i**), and 5-methoxy-3-methyl-1*H*-indene afforded **3j** in 87% yield. It appeared that the steric property of the substituents on the double bonds had a rather significant influence on the reaction yields (Table 3, **3k**, **3l**, **3m**). *α*-Ethyl styrene reacted with *tert*-butyl acrylate to furnish **3k** in moderate yield. However, the reaction of *α*-methylstyrene with methyl *trans*-2-pentenoate or methyl methacrylate only afforded the corresponding products in 33% and 34% yields respectively. In addition, the direct cross-coupling reaction of aliphatic olefins with *tert*-butyl acrylate was screened. When ethyl 4-methyl-4-pentenoate and 2-methylhexene were allowed to react with *tert*-butyl acrylate under the same catalytic conditions, dienoates **3n** and **3o** were obtained in 41% and 36% yields respectively.

When styrene or 1*H*-indene was used to couple with *tert*-butyl acrylate under the standard conditions, an intractable mixture resulted without any trace of the desired cross-coupling product (eq 1, 2). As such, the substituents at the *α*-position of double bond are crucial for generating the coupling products. We also observed that only trace desired coupling product was formed (determined from crude ^{1}H NMR spectrum) when 1,1-diphenylethylene was applied in this reaction. The reason for the lower reactivity of 1,1-diphenylethylene may be due to steric hindrance.



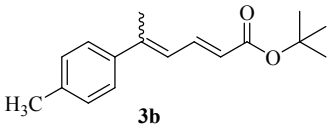
Different electron deficient coupling partners were also screened for the coupling reaction with *α*-methylstyrene under the optimized reaction conditions (Table 4). Methyl acrylate afforded the corresponding product in 62% yield; ethyl acrylate only gave the desired product in 25% yield, while *N*-phenylacrylamide furnished the product in 48% yield. As for acrylonitrile, styrene or methyl vinyl ketone, no desired product was obtained.

Table **3**. $Pd(OAc)_2$ catalyzed direct cross-coupling of alkenes with tert-butyl acrylate.*



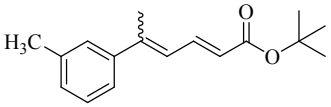
3a

71% yield
(E:Z = 87:13)



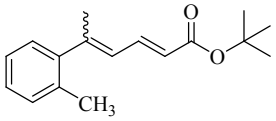
3b

74% yield
(E:Z = 88:12)



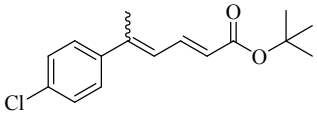
3c

68% yield
(E:Z = 90:10)



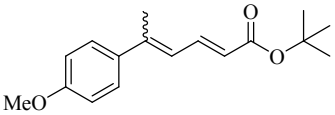
3d

52% yield
(E:Z = 62:38)



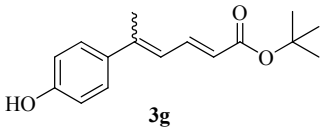
3e

51% yield
(E:Z = 90:10)



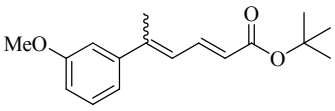
3f

78% yield
(E:Z = 91:9)



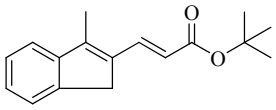
3g

83% yield
(E:Z = 90:10)



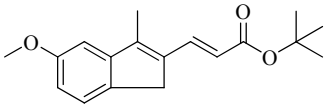
3h

67% yield
(E:Z = 89:11)



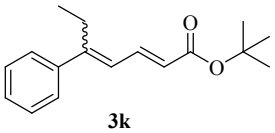
3i

83% yield
(E:Z > 99:1)



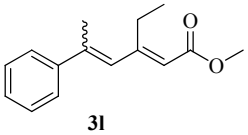
3j

87% yield
(E:Z > 99:1)



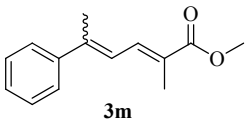
3k

65% yield
(E:Z = 84:16)



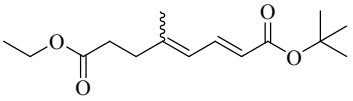
3l

33% yield
(E:Z = 84:16)



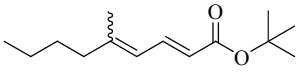
3m

34% yield
(E:Z = 83:17)



3n

41% yield
(E:Z = 68:32)

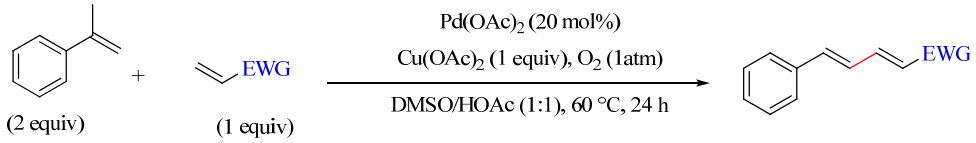


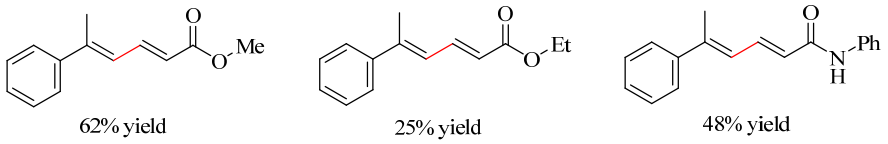
3o

36% yield
(E:Z = 60:40)

* All the reactions were carried out under following conditions: olefin (0.4 mmol, 2 equiv), acrylate (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (20 mol%) and $Cu(OAc)_2$ (1equiv) in HOAc/DMSO (v/v=1/1) at 60 °C under 1 atm O_2 for 24 hours. Yields are isolated yield.

Table **4**. $Pd(OAc)_2$ catalyzed direct cross-coupling of α-methylstyrene with different coupling partners.*





* All the reactions were carried out under following conditions: olefin (0.4 mmol, 2 equiv), acrylate (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (20 mol%) and $Cu(OAc)_2$ (1equiv) in HOAc/DMSO (v/v=1/1) at 60 °C under 1 atm O_2 for 24 hours. Yields are isolated yield.

2.3 MECHANISM STUDY

In the cross-coupling reaction of α-methylstyrene with *tert*-butyl acrylate, other than the desired product, a homo-coupling product of α-methylstyrene was found in 8% yield, 1-phenylvinyl acetate (3% yield), acetophenone (3% yield) and (*E*)-*tert*-butyl 3-acetoxyacrylate (4% yield) were also obtained as byproducts. The oxidative dimerization of α-methylstyrene catalyzed by palladium has been reported previously,[106a] and the possible mechanism proposed is depicted in Scheme **3**. A σ-vinylpalladium species **1** was suggested to account for the oxidative dimerization. It is probable that **1** would couple with another molecule of α-methylstyrene *via* three possible pathways, to form (2*E*,4*E*)-hexa-2,4-diene-2,5-diyldibenzene.

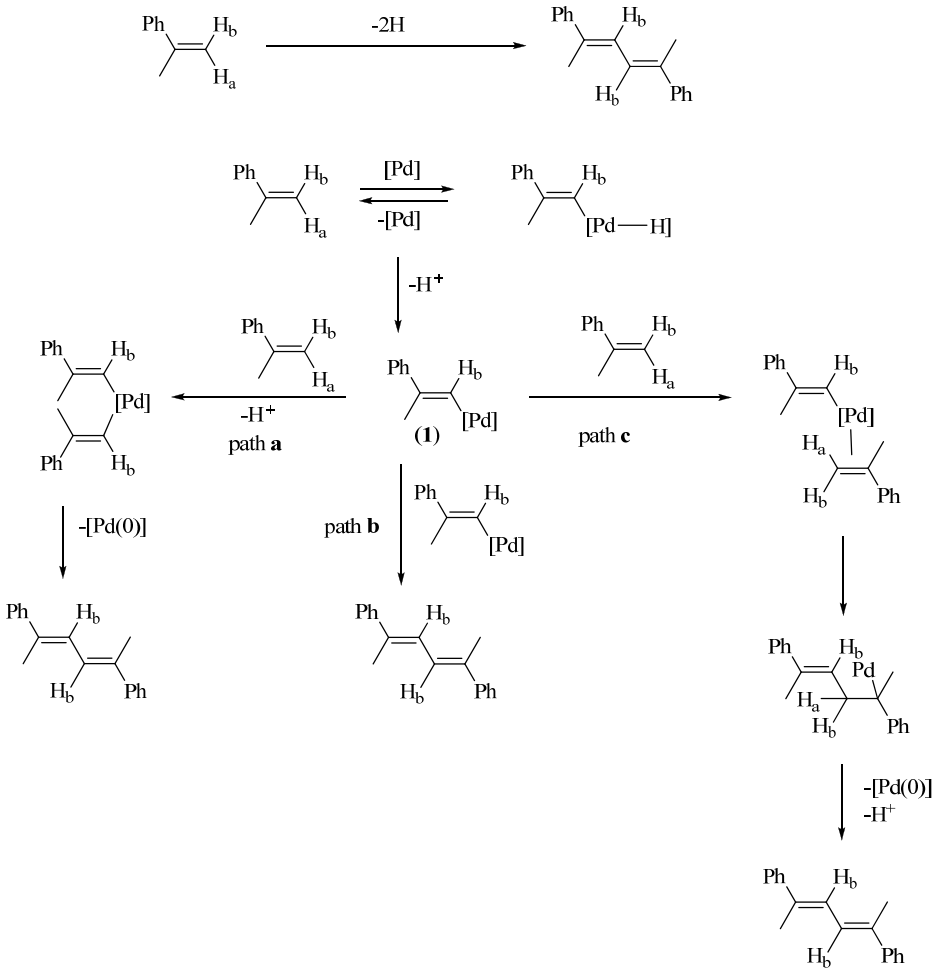
The 2-phenylallyl acetate generated from the α-methylstyrene could be generated *via* two possible pathways according to reported literature,[109] that are shown in Scheme **4**. In path **d**, a π-allylpalladium intermediate could firstly be formed by eliminating one molecule of acetic acid. The attack of an acetic anion will generate a vinylpalladium complex which is not stable, and will easily decompose to form 2-phenylallyl acetate under acidic conditions. Another possibility shown is path **e,** where the $Pd(OAc)_2$ coordinates first with the double bond of α-methylstyrene. An alternative *anti*-Markovnikov adduct is then generated *via* a migratory insertion, followed by a *syn* β-hydride elimination to give 2-phenylallyl acetate. In theory, it is however difficult for hindered alkenes to undergo such kind of *anti*-Markovnikov addition.[110]

One possible pathway to form the coupling product is shown in Scheme **3**. A π-allylpalladium intermediate is first formed by the reaction of α-methylstyrene with $Pd(OAc)_2$, with the elimination of one molecule of HOAc. With *tert*-butyl acrylate acting as a nucleophile, an unstable vinylpalladium species is formed *in situ*, and is reduced to compound **3** under acidic conditions. The desired product **4** is formed from compound **3** *via* an isomerization under acidic conditions by heating.

To elucidate the mechanism, α-methylstyrene-methyl-d_3 (94% atom D) was prepared and used to react with *tert*-butyl acrylate under our catalytic conditions. Interestingly, the product was obtained as a mixture of geometrical isomers (*E*/*Z*=89/11) with retention of the amount of deuterated methyl group in the product (94% atom D). On the basis of these results, we can now rule out the

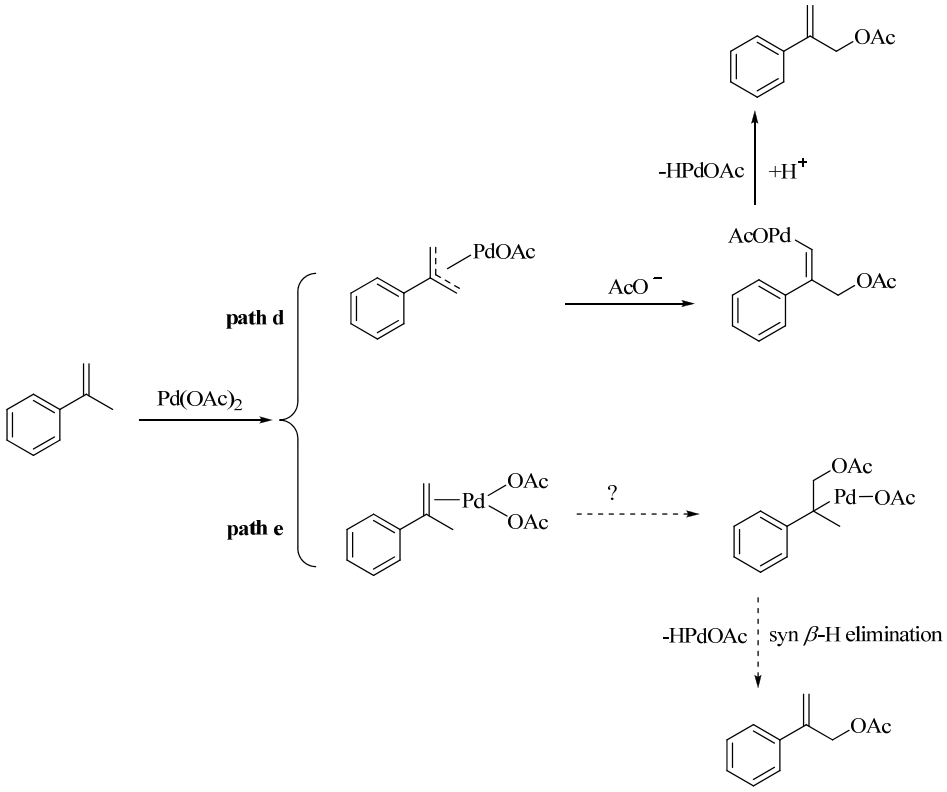
[109] Norman R. O.C.; Thomas, C. B.; Watson, G. *J. Chem. Soc., Perkin Trans. 2*. **1980**. 1099-1104.
[110] Brown, R. G.; Chaudhari, R. V.; Davidson, J. M. *J. Chem. Soc., Dalton Trans*. **1977**, 183-193.

possibility depicted in Scheme **5** as the coupling process. As for the acetophenone obtained, it was believed to be the Wacker oxidation byproduct in the presence of $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ as oxidant.[111] The other byproduct, (*E*)-*tert*-butyl 3-acetoxyacrylate is generated *via* the coordination of $Pd(OAc)_2$ with *tert*-butyl acrylate first rather than with *α*-methylstyrene during the coupling process. We found that *tert*-butyl acrylate can easily reduce $Pd(OAc)_2$ into palladium black under our catalytic conditions, so two equivalents of *α*-methylstyrene were applied in our reaction to suppress this side-reaction.

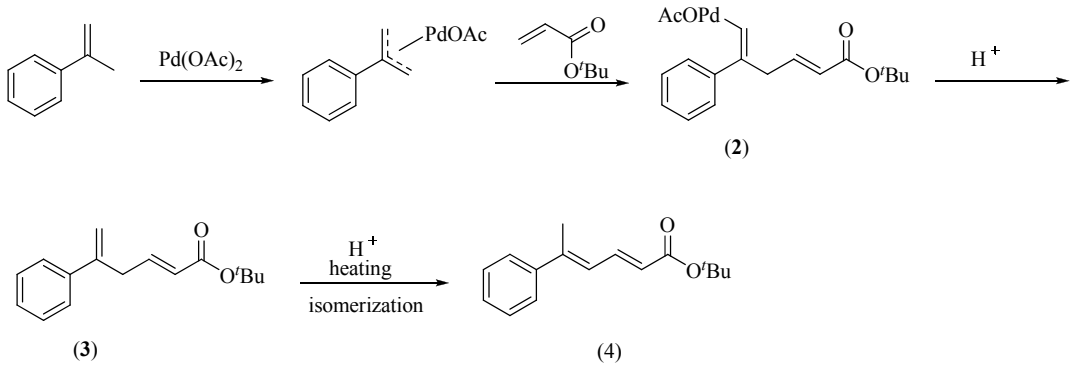


Scheme **3**. Possible Mechanism for Dimerization of Olefins

[111] Wang, A.; Jiang, H. *J. Org. Chem*. **2010**, *75*, 2321-2326.



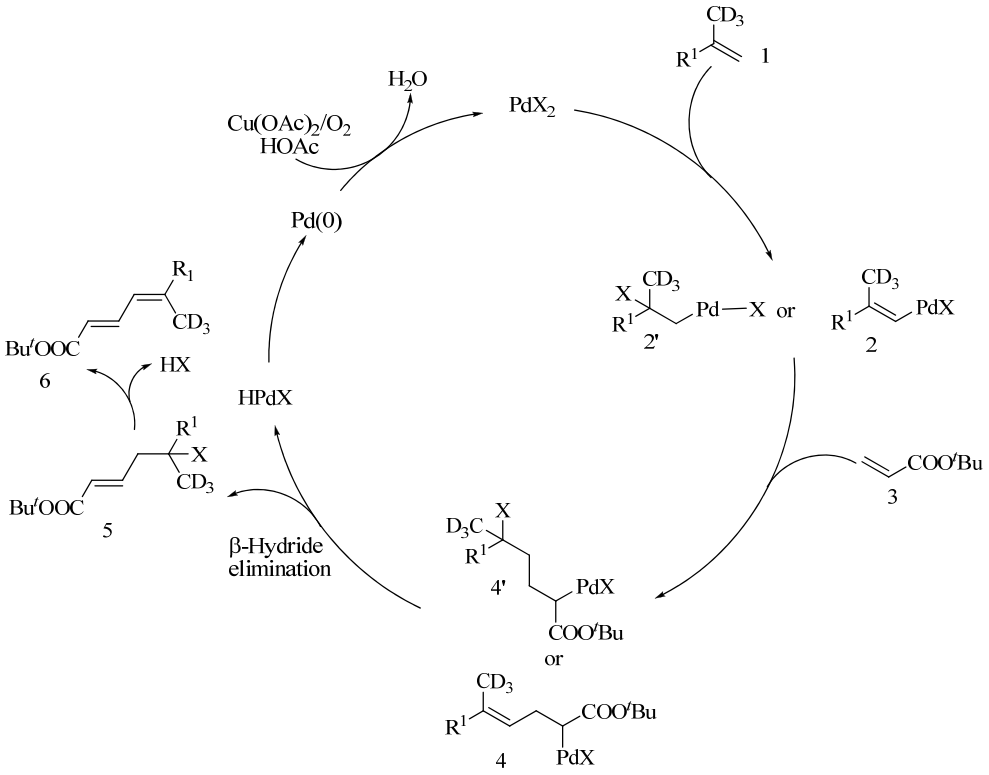
Scheme **4**



Scheme **5**

Based on the above information, we proposed two possible mechanisms as shown in Scheme **6**. At this moment, we are unable to distinguish between direct C–H activation of the vinyl proton to form intermediate **2** or the formation of intermediate **2′** by direct addition of the palladium catalyst. Following migratory insertion into *tert*-butyl acrylate, a new σ-alkylpalladium

intermediate **4** or **4′** is generated. After *β*-hydride elimination the desired coupling product **6** or intermediate product **5** (which undergoes further elimination of one molecule of HOAc) is obtained. The reduced palladium catalyst is reoxidized by $Cu(OAc)_2$ and molecular oxygen to Pd(II) for participation in subsequent catalytic cycles.



Scheme **6.** Proposed Possible Mechanism for Coupling of Olefins with Acrylate

In summary, we have developed an efficient method for the Pd(II)-catalyzed direct cross-coupling reaction of simple olefins with acrylates under mild reaction conditions. This method potentially broadens the scope of coupling reactions which provides a direct entry to dienoates which are important building blocks in many natural products.

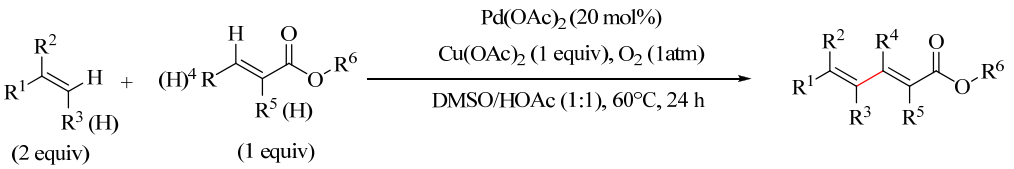
2.4 EXPERIMENTAL SECTION

All commercially obtained reagents for the cross-coupling reaction were used as received: anhydrous DMSO and acetic acid were obtained from Sigma-Aldrich and used as received. The olefin starting materials were prepared according to the reported references (**1b**-**1h** and **1k**;[112] **1i** and **1j**;[113] **1l**[114]), except **1a**, **1n** and **1p** which were purchased from Sigma-Aldrich. All cross-coupling reactions were run under 1atm O_2 and no precautions taken to exclude moisture. Thin-layer chromatography (TLC) was conducted with Merck 60 F254 precoated silica gel plate (0.2 mm thickness) and visualized with UV and potassium permanganate staining, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. ^{1}H NMR spectra were performed on a Bruker Advance 300, 400 and 500 NMR spectrometer and are reported in ppm downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (J = 7.264, singlet). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Advance 300 (75 MHz), Bruker Advance 400 (100 MHz) or Bruker Advance 500 (125 MHz) JEOL ECA-400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). Regioselectivity of the cross-coupling was determined by NMR analysis of the crude product. IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in

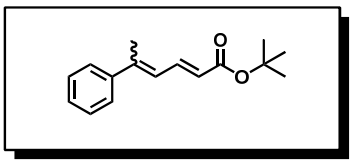
[112] Andrade, R M; Munoz, A. H; Tamariz, J. *Synth. Commun*. **1992**, *22*, 1603-1609.
[113] Adamczyk, M; Watt, D S.; Netzel, D A. *J. Org. Chem*. **1984**, *49*, 4226-4237.
[114] Waser, J.; Gaspar, B,; Nambu, H.; Carreira, E M. *J. Am. Chem. Soc*. **2006**, *128*, 11693-11712.

frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-Tof Permies Mass Spectrometer.

Representative experimental procedure for the direct cross-coupling reaction.

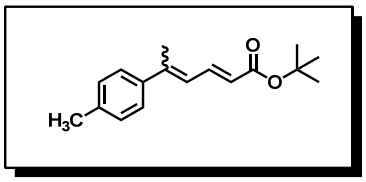


A 5 mL dry round bottom flask was charged sequentially with a stirring bar, $Pd(OAc)_2$ (20 mol%, 0.04 mmol), $Cu(OAc)_2$ (1 equiv, 0.2 mmol), mixed solvents DMSO/HOAc (v/v 1/1) (0.4 ml). The *α*-methylstyrene (2 equiv, 0.4 mmol) and *tert*-butyl acrylate (1 equiv, 0.2 mmol) were added into the solution in sequence. The reaction mixture was stirred at 60 ºC under 1 atm of oxygen (balloon pressure) for 24 h. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with distilled water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated to give the crude product which was directly applied to a flash column chromatography (EtOAc/Hexanes mixtures) to afford the pure product.

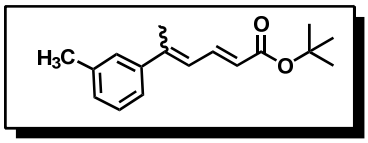


(*2E*)-*tert*-butyl 5-phenylhexa-2,4-dienoate (3a) (*E:Z* = 87:13)**;** This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.70 (dd, *J* = 11.8, 15.1 Hz, 1H), 7.47 (d, *J* = 7.1 Hz, 2H), 7.29-7.38 (m, 3H), 6.54 (d, *J* =

11.8 Hz, 1H), 5.90(d, *J* = 15.1 Hz, 2H), 2.28 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 144.6, 142.0, 139.6, 128.4, 128.1, 125.8, 124.7, 123.2, 80.1, 28.1, 16.4. FTIR (NaCl, cm^{-1}): 2953, 2924, 2852, 2240, 1714, 1620, 1456, 1456, 1375, 1313, 1247, 1136, 977, 848, 759, 696. HRMS (ESI) *m/z* calculated for $C_{16}H_{20}O_2Na$ $[M+Na]^+$: 267.1361, found 267.1350. R_f = 0.35; EA/Hexane (1:9).

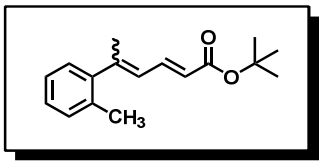


(*2E*)-*tert*-butyl 5-*p*-tolylhexa-2,4-dienoate (3b) (*E:Z* = 88:12); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 74%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.73 (dd, *J* = 15.2, 11.7 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.54 (d, *J* = 11.2 Hz, 1H), 5.90 (d, *J* = 15.2 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 144.6, 139.9, 139.1, 138.2, 129.1, 125.8, 123.9, 122.8, 80.1, 28.2, 21.1, 16.4. FTIR (NaCl, cm^{-1}): 2976, 2927, 1699, 1620, 1512, 1456, 1367, 1311, 1290, 1249.87, 1138, 979, 813. HRMS (ESI) *m/z* calculated for $C_{17}H_{22}O_2Na$ $[M+Na]^+$: 281.1517, found 281.1517. R_f= 0.35; EA/Hexane (1:9).

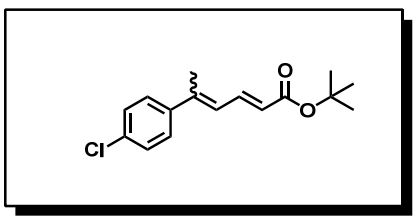


(*2E*)-*tert*-butyl 5-*m*-tolylhexa-2,4-dienoate (3c) (*E:Z* = 90:10); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.74 (dd, *J* =

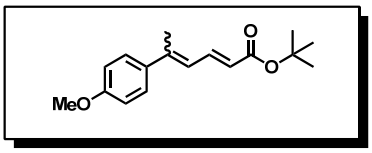
15.2, 11.8 Hz, 1H), 7.14-7.38 (m, 3H), 6.54 (d, *J* = 11.8 Hz, 1H), 5.91 (d, *J* = 15.2 Hz, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 144.9, 142.1, 139.7, 137.9, 128.9, 128.3, 124.6, 123.1, 80.1, 28.2, 21.5, 16.5. FTIR (NaCl, cm^{-1}): 2976, 1699, 1620, 1454, 1367, 1315, 1255, 1136, 979, 783, 732. HRMS (ESI) *m/z* calculated for $C_{17}H_{22}O_2Na$ $[M+Na]^+$: 281.1517, found 281.1516. R_f = 0.35; EA/Hexane (1:9).



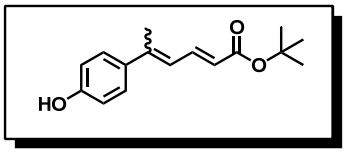
(*2E*)-*tert*-butyl 5-*o*-tolylhexa-2,4-dienoate (3d) (*E:Z* = 62:38); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.67 (dd, *J* = 15.2, 11.8 Hz, 1H), 7.14-7.18 (m, 4H), 6.06 (d, *J* = 11.8 Hz, 1H), 5.81 (d, *J* = 15.2 Hz, 1H), 2.27 (s, 3H), 2.18 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 147.4, 141.1, 139.3, 134.4, 130.3, 127.5, 127.3, 127.0, 125.7, 122.9, 80.2, 28.2, 19.8, 19.1. FTIR (NaCl, cm^{-1}): 2976, 2929, 1705, 1631, 1456, 1367, 1313, 1278, 1244, 1166, 1136, 981, 761, 729. HRMS (ESI) *m/z* calculated for $C_{17}H_{22}O_2Na$ $[M+Na]^+$: 281.15171, found 281.1518. R_f = 0.35; EA/Hexane (1:9).



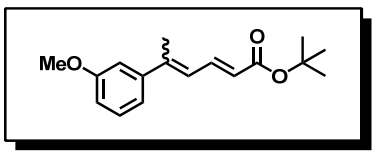
(*2E*)-*tert*-butyl 5-(4-chlorophenyl)hexa-2,4-dienoate (3e) (*E:Z* = 90:10); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 51%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.66 (dd, *J* = 11.6, 15.1 Hz 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 11.6 Hz, 1H), 5.93 (d, *J* = 15.1 Hz, 1H), 2.25 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 143.2, 140.5, 139.3, 134.0, 128.6, 127.2, 125.0, 123.8, 80.3, 28.9, 16.4. FTIR (NaCl, cm^{-1}): 2978, 2931, 1702, 1620, 1489, 1367, 1315, 1290, 1247, 1138, 1093, 1010, 977, 823, 734. HRMS (ESI) *m/z* calculated for $C_{16}H_{20}ClO_2$ $[M+H]^+$: 279.1152, found 279.1147. R_f = 0.33; EA/Hexane (1:9).



(*2E*)-*tert*-butyl 5-(4-methoxyphenyl)hexa-2,4-dienoate (3f) (*E:Z* = 91:9); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.72 (dd, *J* = 15.2, 11.8 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 11.8 Hz, 2H), 5.90 (d, *J* = 15.2 Hz, 1H), 3.84 (s, 3H), 2.28 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 159.7, 144.1, 140.0, 134.4, 127.1, 123.1, 122.3, 113.8, 80.0, 55.3, 28.2, 16.3. FTIR (NaCl, cm^{-1}): 2922, 1708, 1618, 1600, 1512, 1458, 1367, 1315, 1253, 1138, 1033, 983, 821. HRMS (ESI) *m/z* calculated for $C_{17}H_{23}O_3Na$ $[M+H]^+$: 275.1647, found 275.1647. R_f = 0.30; EA/Hexane (1:9).

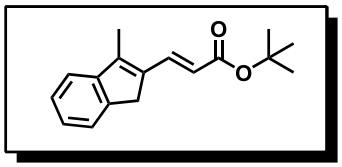


(*2E*)-*tert*-butyl 5-(4-hydroxyphenyl)hexa-2,4-dienoate (3g) (*E:Z* = 90:10); This compound was prepared by the General Procedure described above and was obtained as a white solide. Yield = 83%, mp =133-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.72 (dd, *J* = 11.7, 15.2 Hz 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.10 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.47 (d, *J* = 11.7 Hz, 1H), 5.86 (d, *J* = 15.2 Hz 1H), 2.20 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 156.6, 144.9, 140.7, 133.9, 127.3, 122.7, 121.7, 115.4, 80.7, 28.2, 16.3. FTIR (NaCl, cm^{-1}): 2953, 1714, 1608, 1516, 1435, 1371, 1265, 1178, 1041, 908, 837. HRMS (ESI) *m/z* calculated for $C_{16}H_{20}O_3Na$ $[M+Na]^+$: 283.1310, found 283.1313. R_f = 0.30; EA/Hexane (1:5).

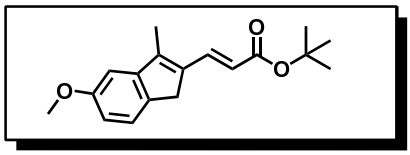


(*2E*)-*tert*-butyl 5-(3-methoxyphenyl)hexa-2,4-dienoate (3h) (*E:Z* = 89:11); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.69 (dd, *J* = 15.2, 11.5 Hz, 1H), 7.25 (t, *J* = 8.2 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 11.5, 1H), 5.77 (d, *J* = 15.2, 1H), 3.82 (s, 3H), 2.26 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 159.6, 144.5, 143.6, 139.6, 129.4, 124.9, 123.4, 118.5, 113.4, 111.9, 80.2, 55.2, 28.2, 16.6. FTIR (NaCl, cm^{-1}): 2976, 1697, 1620, 1573, 1485, 1454, 1429, 1367, 1315, 1292, 1255, 1163, 1134, 1047, 977, 910, 852, 779, 732.

HRMS (ESI) *m/z* calculated for $C_{17}H_{22}O_3Na$ $[M+Na]^+$: 297.1467, found 297.1466. R_f = 0.30; EA/Hexane (1:9).

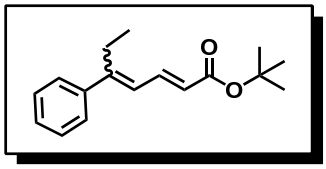


(*E*)-*tert*-butyl 3-(3-methyl-1*H*-inden-2-yl)acrylate (3i) (*E:Z* > 99:1); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 15.8 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.24-7.33 (dd, *J* = 7.9, 7.2 Hz, 2H), 5.97 (d, *J* = 15.8 Hz, 1H), 3.52 (s, 2H), 2.27 (s, *3*H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 146.1, 144.9, 142.8, 136.9, 136.7, 126.7, 126.6, 123.6, 119.9, 118.8, 80.2, 37.1, 28.2, 10.8. FTIR (NaCl, cm^{-1}): 2976, 1693, 1614, 1475, 1454, 1390, 1367, 1309, 1282, 1147, 975, 910, 850, 804, 732. HRMS (ESI) *m/z* calculated for $C_{17}H_{20}O_2Na$ $[M+Na]^+$: 279.1361, found 279.1363. R_f = 0.40; EA/Hexane (1:9).

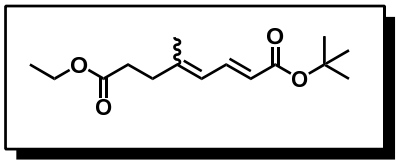


(*E*)-*tert*-butyl 3-(5-methoxy-3-methyl-1*H*-inden-2-yl)acrylate (3j) (*E:Z* > 99:1); This compound was prepared by the General Procedure described above and was obtained as a white solide. Yield = 87%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 15.8 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.98(d, *J* = 15.8 Hz, 1H), 3.87 (s, 3H), 3.47 (s, 2H), 2.26 (s, 3H), 1.56 (9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 159.1,

147.5, 144.7, 138.3, 136.7, 134.9, 124.1, 118.8, 112.8, 105.4, 80.2, 55.5, 36.4, 28.2, 10.8. FTIR (NaCl, cm^{-1}): 2922, 1705, 1614, 1456, 1377, 1280, 1147, 966, 719. HRMS (ESI) *m/z* calculated for $C_{18}H_{23}O_3$ $[M+H]^+$: 287.1647, found 287.1646. R_f = 0.33; EA/Hexane (1:9).

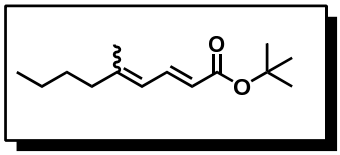


(*2E*)-*tert*-butyl 5-phenylhepta-2, 4-dienoate (3k) (*E:Z* = 84:16); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 65%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.67 (dd, *J* = 15.2, 11.8 Hz, 1H), 7.14-7.38 (m, 3H), 6.54 (d, *J* = 11.8 Hz, 1H), 5.91 (d, *J* = 15.2 Hz, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 144.9, 142.1, 139.7, 137.9, 128.9, 128.3, 124.6, 123.1, 80.1, 28.2, 21.5, 16.5. FTIR (NaCl, cm^{-1}): 2974, 2933, 1703, 1620, 1456, 1367, 1257, 1168, 1136, 979, 765. HRMS (ESI) *m/z* calculated for $C_{17}H_{22}O_2Na$ $[M+Na]^+$: 281.1517, found 281.1512. R_f = 0.36; EA/Hexane (1:9).

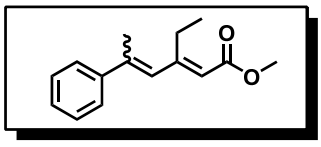


(*2E*)-1-*tert*-butyl 8-ethyl 5-methylocta-2,4-dienedioate (3l) (*E:Z* = 68:32); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.50 (dd, *J* = 15.1, 11.7 Hz, 1H), 5.96 (d, *J* = 11.7 Hz, 1H), 5.71 (d, *J* = 15.1 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 8.2 Hz, 0.5H), 2.45 (s, 3H), 2.40 (t, *J* = 8.2 Hz, 0.5H), 1.88 (s, 3H), 1.48 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 168.8, 146.4, 125.0, 123.6, 121.6, 80.0, 60.4, 34.9, 32.5, 27.8, 17.1, 14.2. FTIR (NaCl, cm^{-1}): 2978, 2933, 1735, 1705, 1637, 1456, 1367, 1280, 1149, 981, 854, 732. HRMS (ESI) *m/z* calculated for $C_{15}H_{25}O_4$ $[M+H]^+$: 269.1753, found 267.1739. R_f = 0.28; EA/Hexane (1:9).

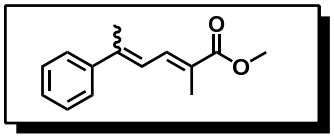


(*2E*)-*tert*-butyl 5-methylnona-2,4-dienoate (3m) (*E:Z* = 60:40); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 36%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.52 (dd, *J* = 15.1, 11.7 Hz, 1H), 5.94 (d, *J* = 11.9 Hz, 1H), 5.68 (d, *J* = 15.1 Hz, 1H), 2.24 (t, *J* = 7.2 Hz, 2H), 2.06-2.14 (m, 4H), 1.49 (s, 9H), 0.90 (t, *J* = 4.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 149.4, 140.0, 123.0, 120.6, 79.8, 39.9, 29.8, 28.2, 24.3, 22.3, 17.1, 13.9. FTIR (NaCl, cm^{-1}): 2958, 2931, 1707, 1335, 1456, 1367, 1278, 1138, 979, 732. HRMS (ESI) *m/z* calculated for $C_{14}H_{25}O_2$ $[M+H]^+$: 225.1855, found 225.1846. R_f = 0.30; EA/Hexane (1:9).



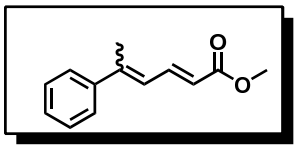
(*2E*)-methyl 3-ethyl-5-phenylhexa-2,4-dienoate (3n) (*E:Z* = 84:16); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 2H), 7.35 (dd, *J* = 7.3 Hz, 2H), 5.71 (t, *J* = 7.2 Hz, 1H), 6.25 (s, 1H), 5.76 (s, 1H), 3.73 (s, 3H), 2.76 (q, *J* =7.4 Hz, 2H), 2.22 (s, 3H), 1.10 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 160.2, 143.1, 140.0, 128.8,

128.3, 127.6, 126.0, 116.9, 51.0, 26.1, 17.8, 12.9. FTIR (NaCl, cm^{-1}): 2947, 1714, 1625, 1433, 1379, 1276, 1209, 1149, 1029, 889, 758. HRMS (ESI) *m/z* calculated for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1385, found 231.1377. R_f = 0.37; EA/Hexane (1:9).



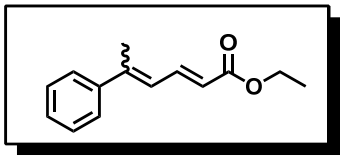
(*2E*)-methyl 2-methyl-5-phenylhexa-2,4-dienoate (3o) (*E:Z* = 83:17); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 34%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 11.6 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.29 (m, 3H), 6.69 (d, *J* = 11.6 Hz, 1H), 3.79 (s, 3H), 2.30 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 143.5, 139.0, 137.2, 128.2, 126.8, 125.7, 125.0, 124.0, 51.9, 30.9, 15.8. FTIR (NaCl, cm^{-1}): 2949, 1737.86, 1708, 1616, 1435, 1278, 1234, 1112, 750, 696. HRMS (ESI) *m/z* calculated for $C_{14}H_{17}O_2$ $[M+H]^+$: 217.1229, found 217.1226.

R_f = 0.37; EA/Hexane (1:9).

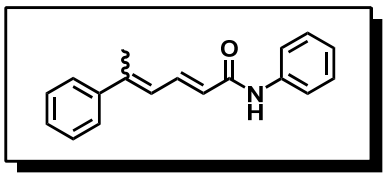


(*2E*)-methyl 5-phenylhexa-2,4-dienoate (*E:Z* = 85:15); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 11.7, 15.1 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.29-7.38 (m, 3H), 6.56 (d, *J* = 11.7 Hz, 1H), 5.96 (d, *J* = 15.1 Hz, 1H), 3.77 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 167.9, 145.6, 142.0, 141.0, 128.5, 128.4, 126.0, 124.7, 120.8, 51.6, 16.7. FTIR (NaCl, cm^{-1}): 3018, 2951, 1708, 1618, 1435, 1313, 1215, 1145, 977, 756, 667. HRMS (ESI) *m/z* calculated for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1072, found 203.1077. R_f = 0.35; EA/Hexane (1:9).



(*2E*)-ethyl 5-phenylhexa-2,4-dienoate (*E:Z* = 83:17); This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 25%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (q, *J* = 11.6, 15.1 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.29-7.38 (m, 3H), 6.56 (d, *J* = 11.6 Hz, 1H), 5.96 (d, *J* = 15.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 145.3, 142.0, 140.6, 128.4, 128.3, 125.9, 124.7, 121.3, 60.3, 16.6, 14.3. FTIR (NaCl, cm^{-1}): 3018, 2981, 1701, 1620, 1444, 1367, 1309, 1244, 1143, 1031, 977, 756. HRMS (ESI) *m/z* calculated for $C_{14}H_{16}O_2Na$ $[M+Na]^+$: 239.1048, found 239.1048. R_f =0.35; EA/Hexane (1:9).



(*2E*)-N, 5-diphenylhexa-2,4-dienamide (*E:Z* = 86:14); This compound was prepared by the General Procedure described above and was obtained as a white solide. Yield = 48%, mp =126-130 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.77 (q, *J* = 14.7, 11.7 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.24-7.43 (m, 8H), 6.48 (d, *J* = 11.7, 1H), 6.16 (d, *J* = 14.7 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 165.0, 144.9, 142.0, 138.5, 138.3, 129.0, 128.4, 128.1, 128.0, 125.9, 124.7, 124.3, 120.1, 16.4. FTIR (NaCl, cm^{-1}): 3018, 1668, 1612, 1598, 1521, 1438, 1332, 1215, 1143, 769, 669. HRMS (ESI) *m/z* calculated for $C_{18}H_{17}NONa$ $[M+Na]^+$: 239.1048, found 239.1048. R_f = 0.32; EA/Hexane (1:4).

(1) Preparation of the starting material.

Acetophenone-*methyl-d*$_3$: A similar procedure as reported in the literature was applied,[115] a mixture of acetophenone (1.44 g, 12 mmol), NaOH (0.04 g, 1 mmol) and D_2O (99% D) (8.0 ml, 400 mmol) was stirred at room temperature for 16 h under N_2. The reaction mixture was diluted with dry diethyl ether (10 ml). The organic layer was dried with $MgSO_4$, filtered and concentrated. The crude product of acetophenone-*methyl-d*$_3$ (94% atom D) was obtained and directly used in next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.99 (dd, *J* = 7.2, 1.3Hz, 2H), 7.56-7.61 (td, *J* = 7.6, 1.8Hz, 1H), 7.40-7.50 (dd, *J* = 7.7, 7.1Hz, 2H), 2.58-2.61 (m, *J* = 2.25 Hz, 0.18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 137.1, 133.1, 128.5, 128.3, 26.3, 26.1, 25.6, 25.6. FTIR (NaCl, cm^{-1}): 1670, 16471, 1448, 1267. HRMS (ESI) *m/z* calculated for $C_8H_6D_3O$ $[M+H]^+$: 124.0842, found 124.0843.

***α*-Methylstyrene-*methyl-d*$_3$:[112]** In a dry round bottom flask, to a dissolved methyltriphenylphosphonium bromide(3.64 g, 10.2 mmol) in dry THF solution (10 ml) was added dropwise *n*-butyllithium (9.76 mmol, 6.1 ml) in THF solution under N_2 protection at -40 ºC. After addition, the mixture was allowed to stir for 30 minutes at the same temperature, before acetophenone-*methyl-d*$_3$ (0.63 g, 5.1 mmol) in 1 ml THF was added dropwise by syringe. The

[115] Horino, Y.; Kimura, M.; Tanaka, S.; Okajima, T.; Tamaru, Y. *Chem. Eur. J.* **2003**, *9*, 2419-2438.

temperature was warmed to room temperature, then the mixture was stirred for 12 hours. The resulting solution was quenched with saturated NH_4Cl (5 ml) at 0 ºC and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*, the crude product was applied to flash column chromatography eluted with hexane to give the titled product (0.41 g, 69% yield, 94% atom D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.2, 1.1Hz, 2H), 7.32-7.36 (td, *J* = 5.3, 0.9, 2H), 7.27-7.29 (dd, *J* = 5.3, 7.2Hz, 1H), 5.38 (d, *J* = 1.2Hz, 1H), 5.10 (s, 1H), 2.14 (b, 0.20H). ^{13}C NMR (400 MHz, CDCl3) δ 143.2, 141.2, 128.2, 127.4, 125.4, 112.4, 21.4, 21.2, 21.2, 21.0, 20.8. FTIR (NaCl, cm^{-1}): 3084, 3055, 3026, 2924, 2229, 2206, 2065, 1624, 1492, 1444, 1303, 1217, 1045, 896, 862, 773, 758, 702. HRMS (ESI) *m/z* calculated for $C_9H_8D_3$ $[M+H]^+$: 122.1049, found 122.1048.

(2) Direct cross-coupling reaction.

(2*E*)-*tert*-butyl 5-phenylhexa-2,4-dienoate-d_3: The above product (60 mg, 0.50 mmol, 2equiv) was dissolved in HOAc/DMSO (v/v 1:1; 0.50 ml) and charged in a dry 5 ml round bottom flask. To the solution, was added $Cu(OAc)_2$ (46 mg, 0.25 mmol, 1 equiv) and $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.2 equiv) followed by addition of *tert*-butyl acrylate (32 mg, 0.25 mmol, 1equiv). The reaction flask was fitted with an oxygen ballon, heated to 60 °C, and stirred for 24 hours. The reaction was cooled to room temperature, diluted with ethyl acetate (5 ml) and washed with water (5 ml x2) and brine (5 ml). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*, and subjected to column chromatograph. Elution with Hexane/EtOAc (25:1), afforded *tert*-butyl 5-phenylhexa-2,4-dienoate-*methyl*-d_3

(42 mg, 68% yield, E/Z ratio = 91:9, 94% atom D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.70 (dd, *J* = 11.7, 15.1Hz, 1H), 7.47 (d, *J* = 8.0Hz, 2H), 7.36 (t, *J* = 7.1 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 11.7 Hz,1H), 5.91 (d, *J* = 15.1Hz,1H), 2.30 (b, 0.19H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 144.6, 142.0, 139.7, 128.4, 128.2, 125.9, 124.7, 123.2, 80.2, 28.2, 15.9, 15.7, 15.5. FTIR (NaCl, cm^{-1}): 3005, 2978, 2931, 2250, 1703, 1693, 1618, 1492, 1446, 1390, 1315, 1296, 1247, 1132, 981, 910, 852, 756, 732, 694. HRMS (ESI) *m/z* calculated for $C_9H_8D_3$ $[M+H]^+$: 122.1049, found 122.1048.

CHAPTER 3

Palladium Catalyzed Olefination Reaction of Enamides at the β-Position of the Double Bond and Its Mechanism Study

Chapter 3. Palladium Catalyzed Olefination Reaction of Enamides at the *β*-Position of the Double Bond and Its Mechanism Study

3.1 INTRODUCTION

One of the most important palladium-catalyzed reactions is the arylation or vinylation of olefins with aryl or vinyl halides or pseudohalides, termed the Heck reaction, which has become one of the most powerful tools for constructing new carbon-carbon bonds in synthetic chemistry.[116] In most reported Heck reactions involving olefins with electron-withdrawing groups, such as $-CO_2R$ and CN, the arylation and olefination is largely selective towards the less-substituted *β*-position of the olefin double bond. However, under normal conditions, the arylation or olefination products resulting from olefins with electron-rich substituents usually give rise to a mixture of both the *α*- and *β*-substituted regioisomeric olefins.[117] The regioselectivity of the Heck reaction has remained a hot research topic for many years.

Earlier studies by Hallberg and co-workers had found that the regiocontrol of enol ethers could be influenced by the electronic properties of the aromatic rings and the choice of halide additives and ligands.[118] Important progress was

[116] (a) *The Mizoroki-Heck Reaction*. Oestveich, M. Ed. Wiley and Sons: Chichester, **2009**. (b) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449-7476. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066.

[117] For a few papers on the topic of insertion and regioselectivity, see: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417-1419. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2-7. (c) Ludwig, M.; Stromberg, S.; Svensson, M.; Åkermark, B. *Organometallics*. **1999**, *18*, 970-975. (d) Larhed, M.; Hallberg, A. *In Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; Ed.; John Wwiley & Sons: New York, **2002**.

[118] (a) Davis, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433-1445. (b) Larhed, M.; Andersson, C. M.; Hallberg, A. *Tetrahedron*. **1994**, *50*, 285-304. (c) Andersson, C. M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757-5761.

made by Cabri and co-workers,[117b,119] who found that the regioselectivity of the arylation of electron-rich olefins could be controlled by the choice of ligands and the leaving groups of the aryl substrates. Subsequently, works detailing regioselective arylation or olefination of electron-rich olefins, such as acyclic enol ethers,[120] silanes,[121] and enol amides[122] have been well-developed.

Enamides are another class of electron-rich olefins, and are an important functional group found in many natural products and some designed medicinal agents.[123] The arylation and olefination of enamides have attracted much attention due to the synthetical importance of the products. Earlier in 1990, Hallberg and co-workers reported a palladium-catalyzed tandem α-arylation/isomerization reaction of cyclic enamides,[124] which offers an alternative route to α-substituted nitrogen heterocycles by using aryl iodides and cyclic enamides under catalytic conditions. The mechanistic study showed that a *syn* 1,2-addition to the double bond of the enamide occurred, resulting in an unstable σ-adduct which decomposed by *syn* elimination of palladium and hydride. A non-conjugated olefin was formed which underwent further re-

[119] (a) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1993**, *58*, 7421-7426. (b) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1992**, *57*, 3558-3563. (c) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S. *J. Org. Chem.* **1992**, *57*, 1481-1486. (d) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Tetrahedron Lett.* **1991**, *32*, 1753-1756. (e) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3654-3655.

[120] (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082-1146. (b) Andersson, C-M.; Hallberg, A.; Jr, G. D. D. *J. Org. Chem.* **1987**, *52*, 3529-3536.(c) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1979**, *44*, 21-23.

[121] (a) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286-5290. (b) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1773-1776. (c) Alvisi, D.; Blart, E.; Bonini, B. F.; Mazzanti, G.; Ricci, A.; Zani, P. *J. Org. Chem.* **1996**, *61*, 7139-7146.

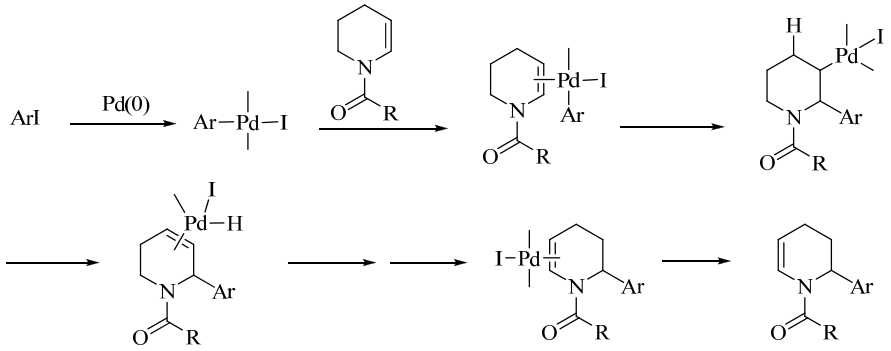
[122] Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234-245.

[123] *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, **1977**; Vol. 3.

[124] (a) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464-2470. For some other examples on related enamides application, see: (b) Lander, P.; Hegedus, L.S. *J. Am. Chem. Soc.* **1994**, *116*, 8126-8132. (c) Rappoport, Z. The Chemistry of Enamines in The Chemistry of Functional Groups; John Wiley and Sons: New York, 1994. (d) Ko, C.; Hsung, R. P.; Al-Rashid, Z. F.; Feltenberger, J. B.; Lu, T.; Yang, J-H.; Wei, Y.; Zificsak, C. A. *Org. Lett.* **2007**, *9*, 4459-4462, and references therein. (e) Feltenberger, J .B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3666-3669.

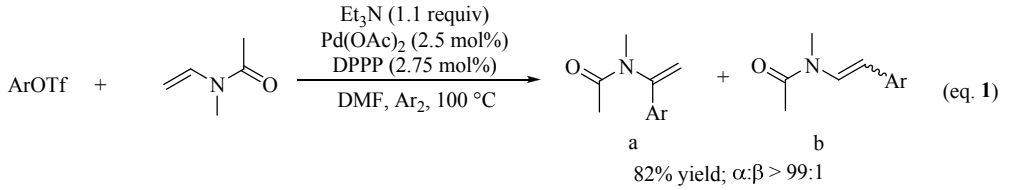
addition and re-elimination of palladium hydride, allowing the double bond to migrate and conjugate with the π-electrons of nitrogen, reforming an enamide (Scheme 1).

A significant advancement was made by Cabri and co-workers soon after.[119a,119b] By using trifluoromethanesulfonate as the leaving group on the aryl moiety for arylation



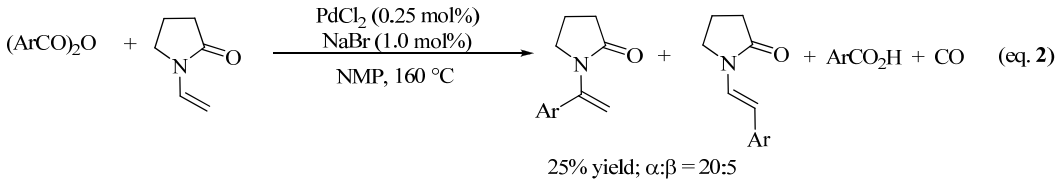
Scheme **1**

of *N*-methyl-*N*-vinylacetamide and vinyl pyrrolidinone, and using DPPP as the palladium ligand, almost complete *α*-regioselectivity was observed in this reaction (eq. **1**). In contrast, only a 40/60 *α*/*β* ratio of regioselectivity was obtained when tri-*o*-tolylphosphine was used as the palladium ligand in a previously reported work.[125]

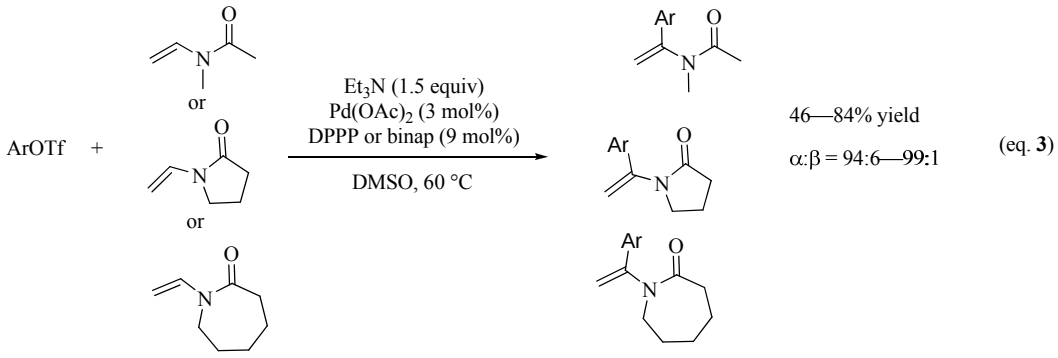


When aromatic carboxylic anhydrides were used as the arylating source, *N*-vinyl-2-pyrrolidinone was arylated to give a mixture of isomeric *N*-styrylpyrrolidinones (*α*:*β*=4:1) in 25% yield of the isolated product (eq. 2).[126]

[125] Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949-2952.
[126] Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem. Int. Ed.* **199**8, *37*, 662-664.

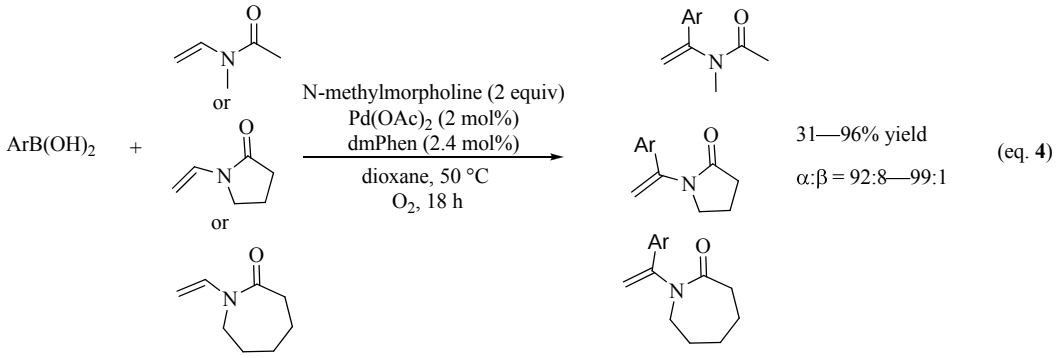


In another example, electron-rich enamides reacted with triflates, catalyzed by $Pd(OAc)_2$ in the presence of bidentate phosphine ligands and triethylamine as base in DMSO. The arylated enamides were obtained in moderate to high yields and good regioselectivities (eq. **3**).[127]

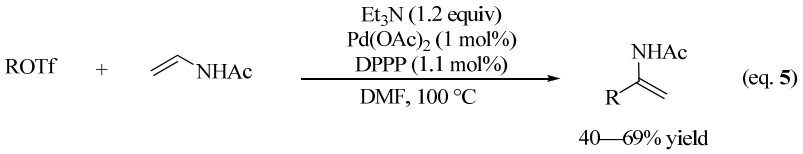


Recently, Larhed and co-workers reported the successful regioselective coupling of enamides with arylboronic acids in dioxane catalyzed by $Pd(OAc)_2$ in the presence of a phenanthroline derivative as ligand under an atmosphere of oxygen (eq. **4**).[128] The conditions described by Cabri *et al.*[119a] were extended to *N*-vinylacetamide without alkyl protection on nitrogen atom. Moderate to good yields of products and >19:1 ratio of regioisomers were obtained in this catalytic system (eq. **5**).[129] However, limited substrates were tested in this work.

[127] Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639-6645.
[128] Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212-5218.
[129] Harrison, P.; Meek, G. *Tetrahedron Lett*. **2004**, *45*, 9277-9280.

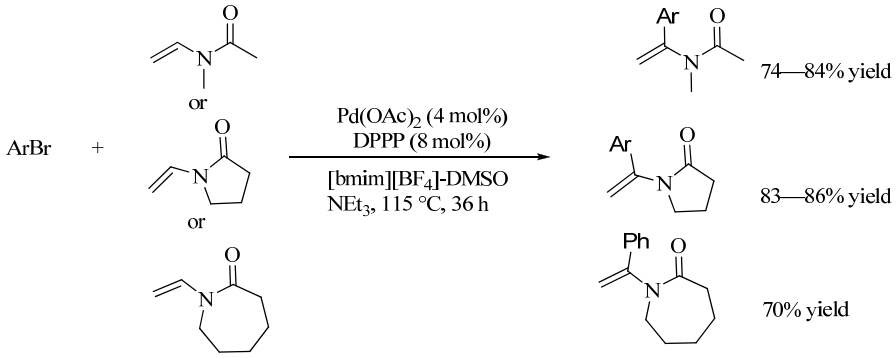


A detailed work regarding the Pd(0)-catalyzed coupling of *N*-vinylacetamide or *N*-acyl-*N*-vinylamines with aryl triflates was reported by Skrydstrup and co-workers.[130] The products were obtained with good to excellent yields and excellent α-regio-selectivities. Products lacking an *N*-alkyl substituent would provide compounds with potential synthetic versatility and value.



Very recently, Xiao and co-workers demonstrated the arylation of enamides under Pd-DPPP catalysis with various aryl bromides and iodides, using the ionic liquid [bmim][BF_4] as solvent(eq. **6**).[131] All the reactions furnished only the branched olefins in high isolated yields. The ionic liquid was believed to play a pivotal role in furnishing the branched products by facilitating the dissociation of the halide anion from palladium.

[130] Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997-6003.
[131] (a) Mo, J.; Xiao, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 4152-4157. (b) Mo, J.; Liu, S.; Xiao, J. *Tetrahedron*. **2005**, *61*, 9902-9907. (c) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751-760.



(eq. **6**)

On the basis of the above studies, we found that direct coupling between enamides and non-prefuctionalized starting materials, especially for *β*-position functionalization of enamides, has been rarely studied. As depicted in Chapter 2, we have developed a direct cross-coupling between olefins catalyzed by palladium, in which the diene-containing products were formed in moderate to good yields.[132] Herein, we present development of the olefination reaction of enamides at the *β*-position.

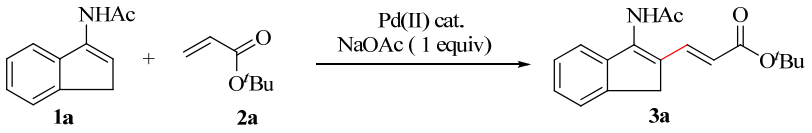
3.2 EXPERIMENTS AND RESULTS

Our initial efforts were focused on the optimization of the reaction conditions and the development of an efficient catalytic system. To this end, the reaction of *N*-(3*H*-inden-1-*yl*) enamide (**1a**) and *tert*-butyl acrylate (**2a**) was carried out under various reaction conditions using different palladium catalysts and oxidants. The results are shown in Table **1**. When the reaction was carried out under our previously reported conditions with 20 mol% $Pd(OAc)_2$ as catalyst, and $Cu(OAc)_2$ (1 equiv) and one atmosphere of oxygen as oxidant in the solvent mixture of DMSO/HOAc (v/v=1:1), the desired product was obtained in 50% isolated yield after heating for 24 hours at 60 °C (Table **1**, entry 1). We found that the low yield was partially attributed to the decomposition of the starting material during the coupling process. The ratio of decomposed starting material

[132] Xu Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372-1373.

with desired product was observed to be 1.5:1. When the reaction was carried out without $Cu(OAc)_2$, the ratio decreased to 1:1. Other organic oxidants were then tested in this reaction. We found that benzoquinone (BQ) and *tert*-butyl hydroperoxide were less efficient in furnishing the desired product, while only trace amount of product was obtained with nearly quantitative decomposition of enamide when using H_2O_2 as oxidant. The reaction did not proceed in DMSO and the starting material was recovered after 24 hours (Table **1**, entry 2). It was found that by only using acetic acid as solvent, with 10 mol% of palladium(II) acetate as catalyst, oxygen as the sole oxidant and with one equivalent of sodium acetate as additive under 80 °C, the desired product could be obtained in 80% yield (Table **1**, entry 3). However, decreasing the catalyst loading to 5 mol% would lower the yield significantly (Table **1**, entry 4), while there was no significant effect on the yield by increasing the amount of NaOAc (Table **1**, entry 5). Other palladium catalysts were also investigated in this reaction and $Pd(TFA)_2$, $PdCl_2$, $Pd(CH_3)_2Cl_2$ and $Pd(PhCN)_2Cl_2$ were all found to give the product in moderate yields (Table **1**, entries 6, 8, 9 and 10); no desired product was obtained when $Pd(PPh_3)Cl_2$ was used as catalyst (entry 7). We also observed that only 37% yield was achieved when the ratio of **1a** and **2a** was changed to 1:4. The control experiment was also carried out, and no desired product was obtained in the absence of palladium catalyst.

Table **1.** Direct Cross-coupling Reaction of *α*-Methylstyrene with *tert*-Butyl Acrylate[a].



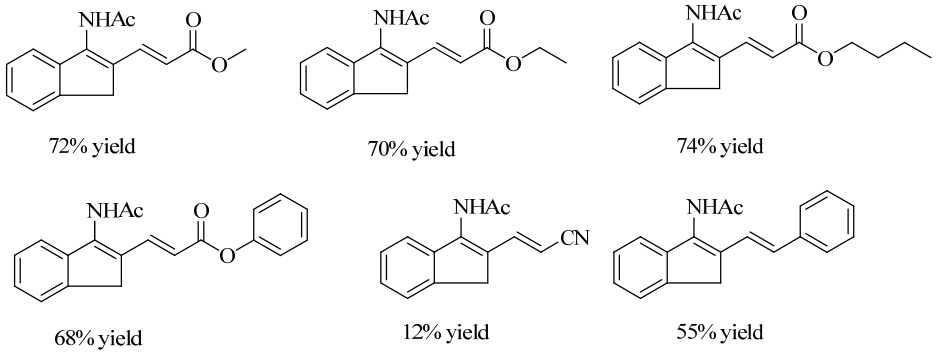
1a **2a** **3a**

entry	oxidant	Pd (II)(mol %)	solvent	yield[b] (%)
1[c]	$Cu(OAc)_2$ + O_2	$Pd(OAc)_2$ (10)	DMSO+ HOAc (1:1)	50
2[a]	O_2	$Pd(OAc)_2$ (10)	DMSO	-
3	O_2	$Pd(OAc)_2$ (10)	HOAc	80
4	O_2	$Pd(OAc)_2$ (5)	HOAc	55
5[e]	O_2	$Pd(OAc)_2$ (10)	HOAc	81
6	O_2	$Pd(TFA)_2$ (10)	HOAc	58
7[i]	O_2	$Pd(PPh_3)Cl_2$ (10)	HOAc	-
8	O_2	$PdCl_2$ (10)	HOAc	35
9	O_2	$Pd(PhCN)_2Cl_2$ (10)	HOAc	73
10	O_2	$Pd(CH_3)_2Cl_2$ (10)	HOAc	51
11[g]	O_2	$Pd(OAc)_2$ (10)	HOAc	37

[a] Reaction conditions unless otherwise specified: 1a (2 equiv), 2a (1 equiv, 0.5M) and Pd(II) (0.1 equiv), oxygen (1 atm) at 80 °C in acetic acid; [b] Isolated yields. [c] without NaOAc as additive [d] No reactin. [e] 4 equivlent of NaOAc was used. [f] The starting material decomposed. [g] 1a:2a=1:4. HOAc: acetic acid; TFA: trifluoroacetate

In addition to *tert*-butyl acrylate, different electron deficient coupling partners were tested in this cross-coupling reaction under the optimized conditions (Table **2**). Methyl acrylate, ethyl acrylate, *n*-butyl acrylate and phenyl acrylate all furnished the desired product in high yields. As for acrylonitrile, only 12% yield was obtained, while styrene afforded the corresponding cross-coupling product in 55% yield. Therefore *tert*-butyl acrylate was established as the best coupling partner in our system.

Table **2.** Direct Cross-coupling Reaction of *α*-Methylstyrene with various coupling partners.*

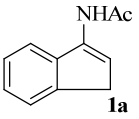
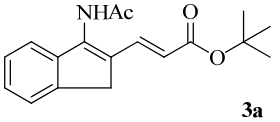
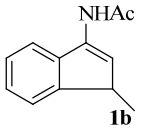
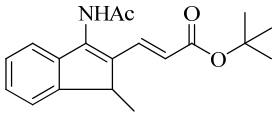
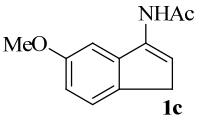
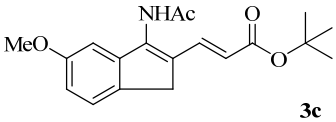
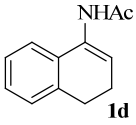
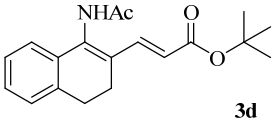
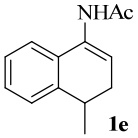
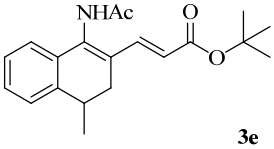
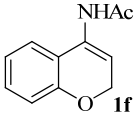
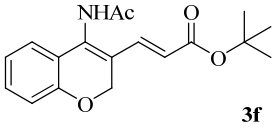
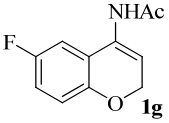
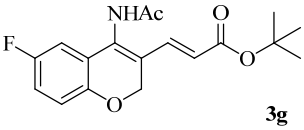
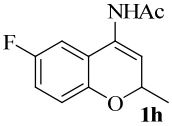
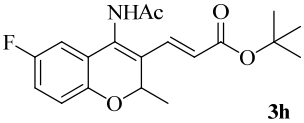
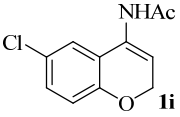
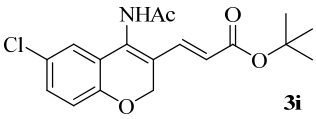
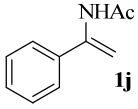
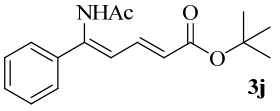
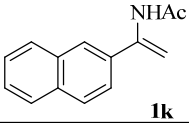
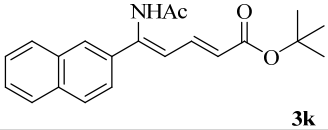


*Reaction conditions unless otherwise specified: *α*-Methylstyrene (0.4 mmol, 2 equiv), compound **2** (0.2 mmol, 1 equiv) and $Pd(OAc)_2$ (0.02 mmol,.0.1 equiv), oxygen (1 atm) at 80 °C in acetic acid (0.5 mL).

Following which, a variety of enamides derivatives were screened with *tert*-butyl acrylate using 10 mol% $Pd(OAc)_2$. The results are shown in Table **3**. It can be seen that both cyclic enamides (Table **3**, entries 1–9) and acyclic enamides (Table **3**, entries 10 and 11) generate the products in moderate to high yields. The effect of the substituents on the benzene ring is not obvious; electron-donating groups are well-tolerated (Table **3**, entry 3), while moderately electron-withdrawing groups decrease the product yield slightly (Table **3**, entries 7–9). The presence of a methyl group on the alicyclic ring diminishes the yield in acetic acid (Table **3**, entries 2 and 5). Notably, halide substituents were tolerated, which is useful for further transformations (Table **3**, entries 7-9). The choice of solvent was found to be crucial for the success of this coupling reaction. For indanone- and tetralone-derived enamides, the desired products can be obtained in good yields with acetic acid as solvent (Table **3**, entries 1–5). On the other hand, 4-chromanone-derived enamide **1f** completely decomposed in acetic acid, while a high yield of 76% was achieved in DMSO. Substrates **1g** and **1h** can furnish the desired product in moderate yields in both acetic acid

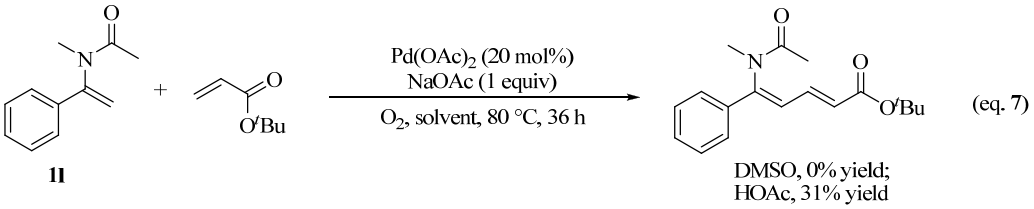
and DMSO. Acyclic substrates are only compatible with DMSO, providing the corresponding products in moderate yields (Table **3**, entries 10 and 11).

Table **3**. Direct Cross-coupling Reaction of α-Methylstyrene with various coupling partners.*

entry	staring material	product	solvent	yield(%)[a]
1	 **1a**	 **3a**	HOAc	80
2	 **1b**	 **3b**	HOAc	67
3	 **1c**	 **3c**	HOAc	79
4	 **1d**	 **3d**	HOAc	74
5	 **1e**	 **3e**	HOAc	57 (82)[c]
6	 **1f**	 **3f**	DMSO	76
7	 **1g**	 **3g**	HOAC DMSO	55 70*
8	 **1h**	 **3h**	HOAc DMSO	57 45[b]*
9	 **1i**	 **3i**	DMSO	65*
10	 **1j**	 **3j**	DMSO	67*
11	 **1k**	 **3k**	DMSO	64*

[a] Isolated yields of the mixture of isomers. [b] 48 h. [c] 15 mol% $Pd(OAc)_2$ was used as catalyst. * 1.5 equivlent of enamide was used in the reaction.

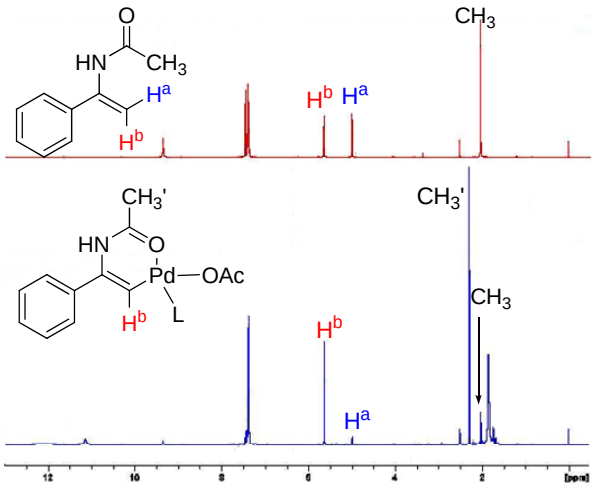
We also found that the *N*-methyl protected enamide **1l** was less reactive under this protocol even though 20 mol% of $Pd(OAc)_2$ was used as catalyst and the reaction was stirred for 36 h in HOAc at 80 °C (eq. **7**). Only 31% yield was obtained for the desired product and **1l** was recovered in 55% yield (on the basis of the amount of **1l** used). However, the *N*-acetyl protected enamide **1m** could not generate any desired product when the reaction mixture was stirred in DMSO or HOAc for 36 h. We believe that $Pd(OAc)_2$ may be poisoned by the nitrogen atom in **1l** due to its strong coordinating ability, Brönsted base **1l** being protonated under acidic condition thus limited its ability to bind metal ions to some extent could afford the corresponding product in low yield. However, the instability of **1m** may be the crucial reason for its poor reactivity in this reaction.



3.3 MECHANISM STUDY

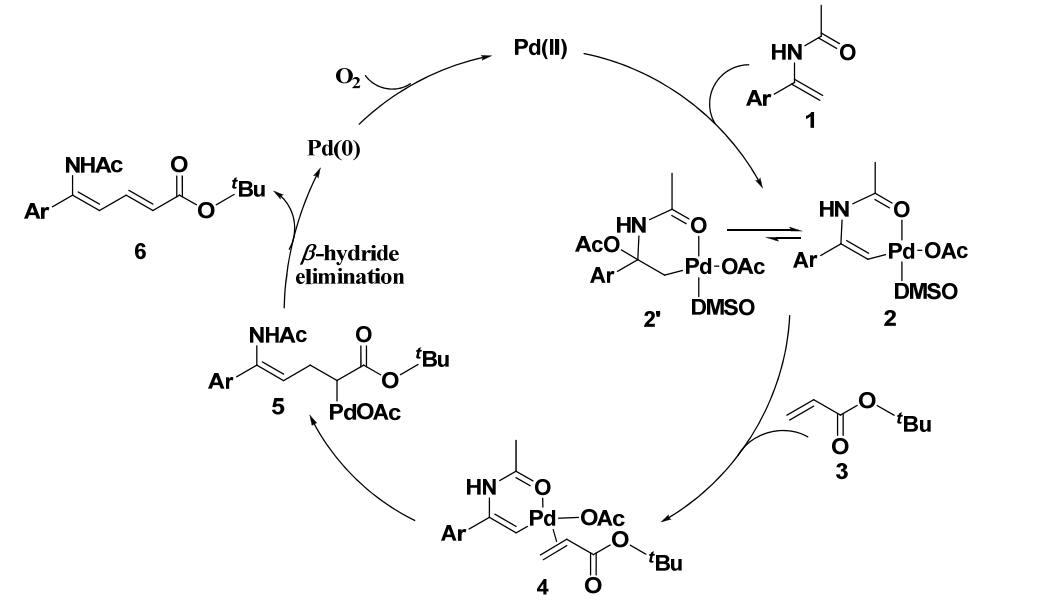
In this work, we also attempted to delineate the mechanism of this coupling reaction. We mixed *N*-(1-phenylvinyl)acetamide (0.1 mmol) and palladium(II) acetate (0.11 mmol) together in a NMR tube at room temperature (25 °C) in DMSO-d_6 (0.5 ml). The solution was shaken for 15 minutes at 25 °C and monitored using ^{1}H NMR spectroscopy. It was found that the signal of the terminal alkenyl proton $\mathbf{H^a}$, which was distinguished from $\mathbf{H^b}$ by 2-D NOESY

spectroscopic analysis showing correlation between $\mathbf{H^b}$ and the aryl protons, disappeared from the spectrum almost completely (Scheme **1**). A slight downfield shift of the peak of the acetal methyl group was observed when *N*-(1-phenylvinyl)acetamide was mixed with $Pd(OAc)_2$ in DMSO-d_6, which indicated the possibility of coordination between the carbonyl group and the Pd atom. Based on the above observation, a six-membered cyclic vinylpalladium intermediate was proposed.



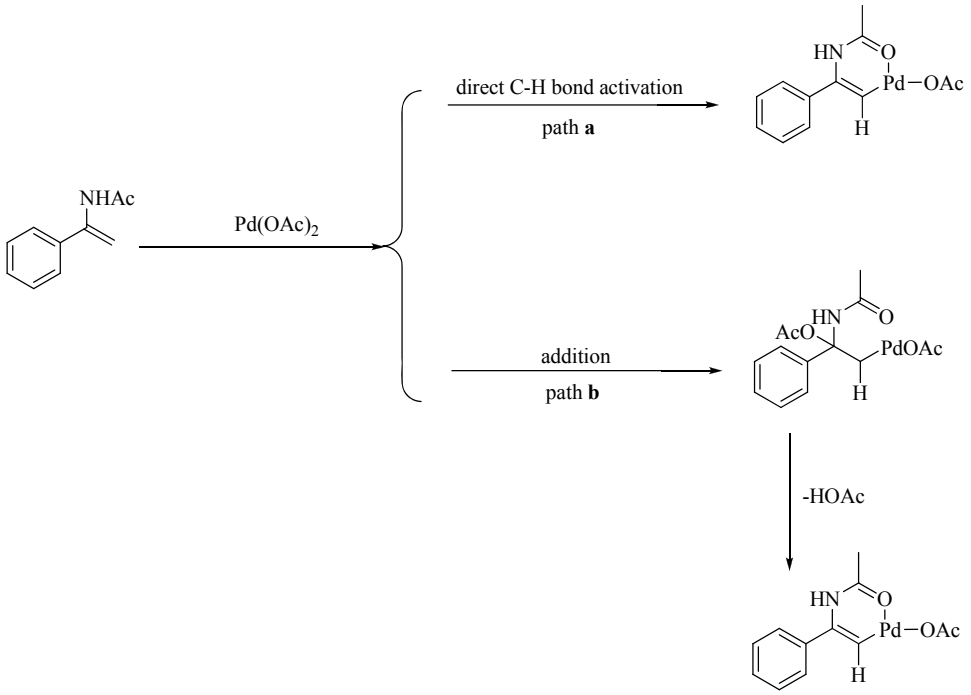
To prove that six-membered cyclic vinylpalladium compound was the key intermediate during the coupling process, *tert*-butyl acrylate was introduced into the DMSO-d_6 solution with the vinylpalladium intermediate, and the mixture was heated at 80 °C for another 24 hours. The desired product **3j** was observed and isolated in 43% yield. Therefore, a plausible mechanism is proposed in Scheme **2**. The sp^2 C–H bond of enamide **1** is firstly activated by the Pd(II) complex to form the six-membered palladacycle intermediate **2** (Another possibility involving an intermediate 2′ cannot be ruled out during this reaction). Next, coordination of the acrylate to Pd, followed by a migratory insertion, gave intermediate **5**. The target molecule **6** is finally obtained after *β*-

hydride elimination. The Pd(0) that was generated is then reoxidised back to Pd(II) by the oxidant.



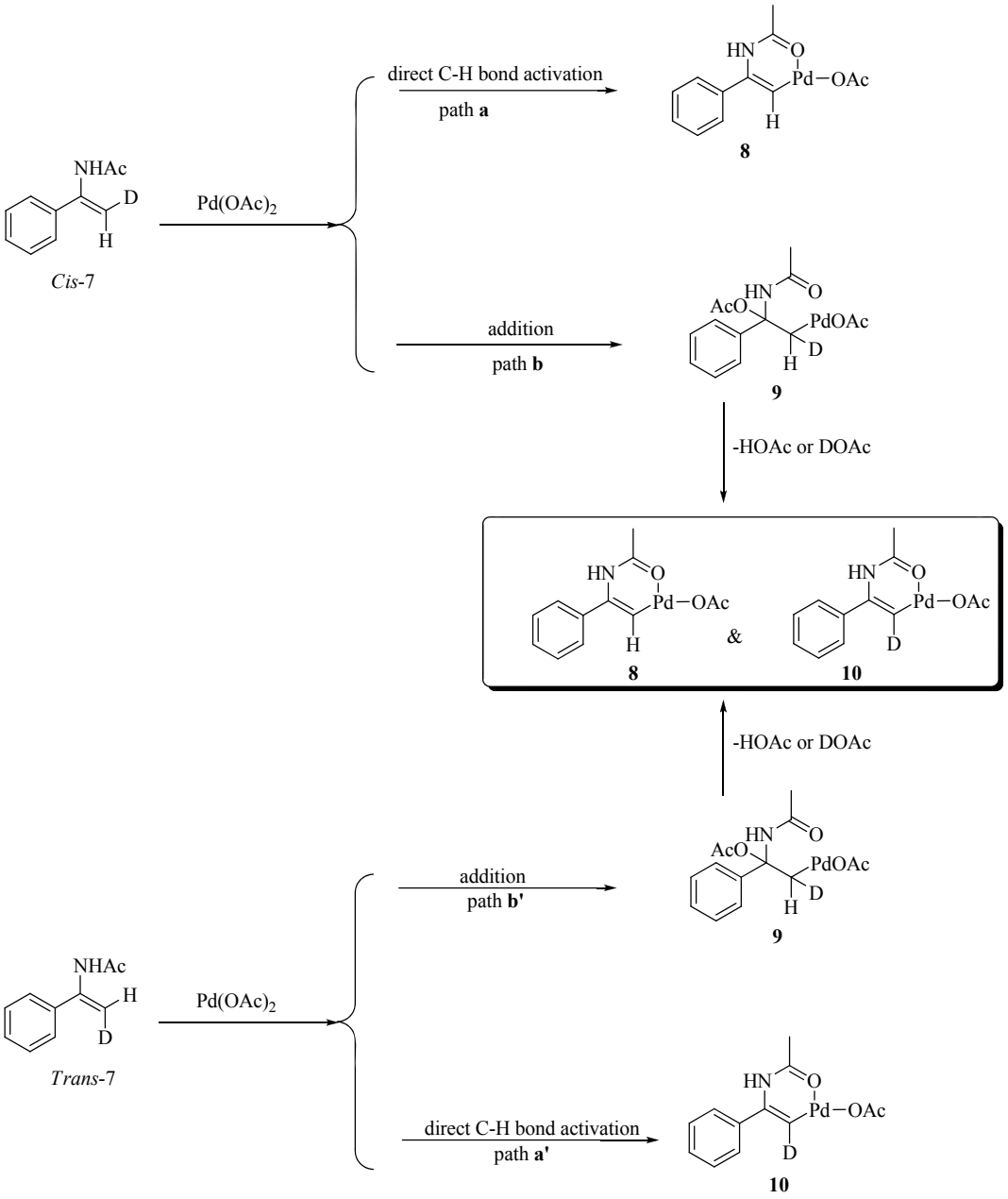
Scheme **2** Proposed Possible Mechanism for the Coupling Reaction Between Enamide and Acrylate

Though the vinylpalladium intermediate has been established by this NMR study, the process of forming this compound still remains unclear. Two possible pathways could be involved to generate the vinylpalladium intermediate: path **a,** direct C–H bond activation with elimination of one molecule of HOAc; path **b,** addition of $Pd(OAc)_2$ to the olefin double bond to form a σ-alkylpalladium compound, which is unstable, following an elimination of one molecule of HOAc. (Scheme **3**)



Scheme **3**

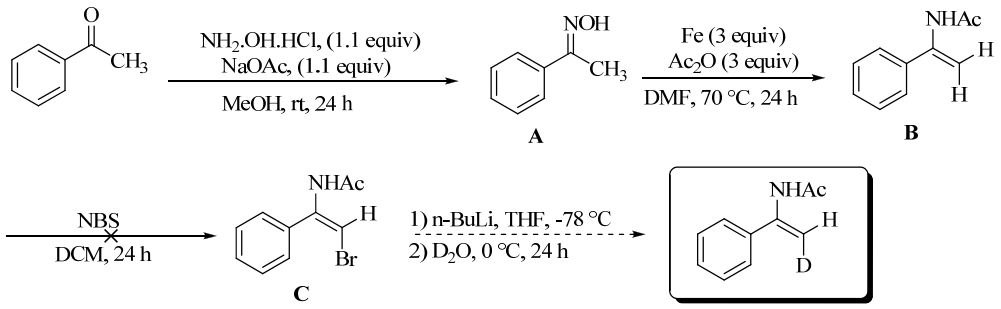
To elucidate this process in detail, we proposed that a deuterated *N*-(1-phenylvinyl)acetamide **7** (Cis or Trans) could be prepared and used to react with $Pd(OAc)_2$. If the reaction proceeds by path **a** or path a′to give the vinylpalladium compound, only one olefinic proton H or D will be left in the vinylpalladium product **8** or **10**. However, if the vinylpalladium intermediate was generated *via* path **b** or path b′, both starting materials of *Cis*-**7** and *Trans*-**7** would afford the same σ-alkylpalladium intermediate **9**, which would lead to a mixture of vinylpalladium compounds **8** and **10** upon elimination of one molecule of HOAc or DOAc. (Scheme **4**)



Scheme **4**

With this idea in mind, we designed synthetic route to prepare the deuterated enamide. As shown in scheme **3**, oxime **A** was synthesized by reacting acetophenone and hydroxylamine hydrochloride in dry methanol under room temperature with sodium acetate as base. For the conversion of the oxime into the enamide, 3 equivalents of iron powder and acetic anhydride were added in DMF, and the mixture was heated at 70 °C for 24 hours under nitrogen

atmosphere. The enamide **B** was obtained in 56% yield, which was then reacted with *N*-bromosuccinimide (NBS) in dichloromethane at room temperature. Unfortunately, the reaction was messy and no desired brominated enamide **C** was observed, possibly due to its instability (Scheme **5**).



Scheme 5

In summary, we have developed the first successful olefination reaction of enamides with electron-poor alkenes catalyzed by $Pd(OAc)_2$ and 1 atm oxygen as sole oxidant. The corresponding products were ontained in moderate to high yields and with excellent regioselectivities. The mechanism of this coupling reaction was also well-studied by ^1H NMR spectroscopic analysis. This novel method produces highly functionalized, versatile compounds which can be converted to a wide variety of building blocks and complex molecules.

3.4 EXPERIMENTAL SECTION

All commercially obtained reagents for the cross-coupling reaction were used as received: anhydrous DMSO and acetic acid were obtained from Sigma-Aldrich and used as received. DMSO-d_6 and $CDCl_3$ were obtained from Cambridge Isotope Laboratories, Inc. and used as received. The starting materials of enamides were prepared according to the reported references.[133] All

[133] (a) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084-6085. (b) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1679-1681.

cross-coupling reactions were run under 1 atm O_2. Thin-layer chromatography (TLC) was conducted with Merck 60 F254 precoated silica *gel* plate (0.2 mm thickness) and visualized with UV and potassium permanganate staining, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. ^{1}H NMR spectra were performed on a Bruker Advance 300, 400 and 500 NMR spectrometer and are reported in ppm downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (*J* = 7.26, singlet), dimethyl sulfoxide-*d* (*J* = 2.50, singlet) or acetone-*d* (*J* = 2.05, singlet). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Advance 300 (75 MHz), Bruker Advance 400 (100 MHz) or Bruker Advance 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm, DMSO-d_6 at 39.52 ppm and acetone-d_6 at 205.87, 30.60). Regioselectivity of the cross-coupling was determined by NMR analysis of the crude product. IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-Tof Permies Mass Spectrometer.

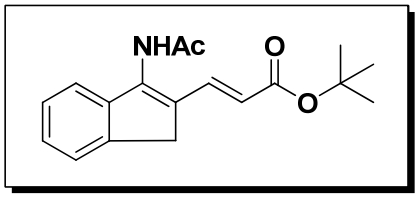
Representative experimental procedure for the direct cross-coupling reaction:

A 5 mL dry round bottom flask was charged sequentially with a stirring bar, $Pd(OAc)_2$ (10 mol%, 0.02 mmol), NaOAc (1 equiv, 0.2 mmol), and HOAc (0.5

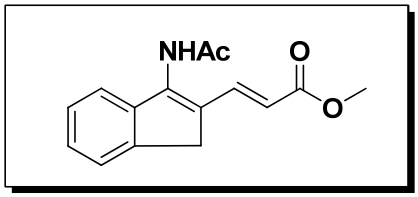
(c) Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505-507.

ml) as solvent. The flask was then vacuumed and refilled with oxygen. The starting material enamide **1** (2 equiv, 0.4 mmol) and *tert*-butyl acrylate (1 equiv, 0.2 mmol) were added into the solution in sequence. The reaction mixture was stirred at 80 ºC under 1 atm of oxygen (balloon pressure) for 24 h. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with distilled water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated to give the crude product which was purified on silica gel (EtOAc/Hexanes mixtures) to give the pure product.

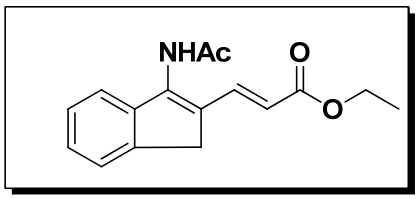
Characterization Data:



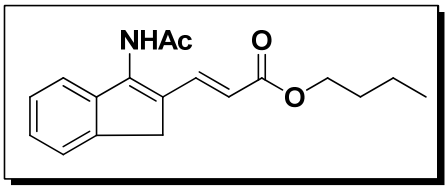
3a (*E*)-*tert*-butyl 3-(3-acetamido-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solide. Yield= 80%. m.p = 201-202 °C. R_f = 0.35 (EA/Hexane = 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.61 (d, J = 15.6 Hz, 1H), 7.25-7.43 (m, 4H), 5.96 (d, J = 15.6 Hz, 1H), 3.60 (s, 2H), 2.14 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 166.4, 142.3, 141.7, 141.5, 137.0, 130.3, 127.3, 126.6, 124.3, 121.8, 118.8, 80.1, 35.4, 28.3, 23.4. FTIR (NaCl, cm^{-1}): 3412, 2725, 1697, 1656, 1606, 1571, 1290, 1155. HRMS (ESI) *m/z* calculated for $C_{18}H_{21}NO_3Na$ $[M+Na]^+$: 322.1419, found 322.1424.



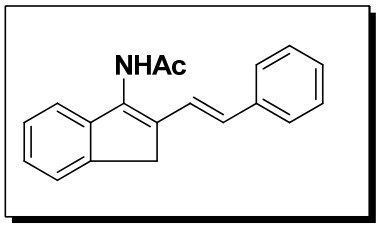
(*E*)-methyl 3-(3-acetamido-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solide. Yield= 72%. m.p = 226-228 °C. R_f = 0.33 (EA/Hexane = 2:3). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.10 (s, 1H), 7.69 (d, *J* = 16.0 Hz, 1H), 7.26-7.43 (m 4H), 6.04 (d, *J* = 16.0 Hz, 1H), 3.68 (s, 3H), 3.61 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.1, 166.8, 141.8, 141.6, 140.9, 137.3, 129.4, 126.9, 126.1, 123.8, 121.4, 116.1, 51.2, 34.9, 22.9. FTIR (NaCl, cm^{-1}): 3259, 1712, 1666, 1606, 1533, 1300, 1269, 1163, 1153. HRMS (ESI) *m/z* calculated for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$: 280.0950, found 280.0941.



(*E*)-ethyl 3-(3-acetamido-1H-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solide. Yield = 70%. m.p = 190-192 °C. R_f = 0.34 (EA/Hexane = 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) 10.07 (s, 1H), 7.66 (d, *J* = 15.6 Hz, 1H), 7.27-7.42 (m, 4H), 6.03 (d, *J* = 15.6 Hz, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.81 (s, 2H), 2.13 (s, 3H), 1.21 (t, *J* =6.8 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.3, 167.0, 142.3, 142.0, 141.4, 137.7, 130.3, 127.5, 126.7, 124.4, 121.8, 117.2, 60.3, 35.5, 23.4, 14.7. FTIR (NaCl, cm^{-1}): 1712, 1697, 1604, 1568, 1519, 1435, 1373, 1294, 1271. HRMS (ESI) m/z calculated for $C_{16}H_{17}NO_3Na$ $[M+Na]^+$: 294.1106, found 294.1105.

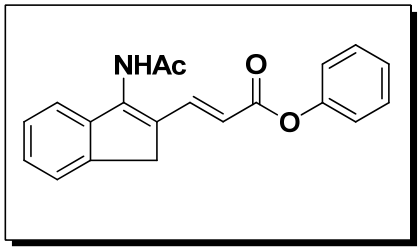


(*E*)-butyl 3-(3-acetamido-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solide. Yield= 74%. m.p = 178-180 °C. R_f = 0.34 (EA/Hexane = 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) 10.06 (s, 1H), 7.69 (d, *J* = 15.6 Hz, 1H), 7.26-7.44 (m, 4H), 6.04 (d, *J* = 15.6, 1H), 4.11 (t, *J* = 6.6 Hz, 2H), 3.62 (s, 2H), 2.14 (s, 3H), 1.56-1.62 (m, 2H), 1.31-1.40 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 167.0, 142.4, 142.1, 141.5, 137.8, 130.1, 127.5, 126.7, 124.3, 121.9, 117.0, 63.9, 35.5, 30.8, 23.5, 19.1, 14.1. FTIR (NaCl, cm^{-1}): 1712, 1606, 1525, 1284, 1215, 1166. HRMS (ESI) m/z calculated for $C_{18}H_{21}NO_3Na$ $[M+Na]^+$: 322.1419, found 322.1406.

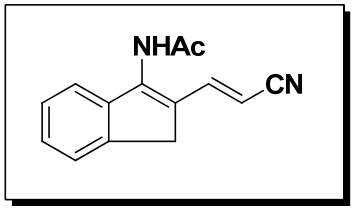


(*E*)-*N*-(2-styryl-1H-inden-3-yl)acetamide. This compound was prepared by the General Procedure described above and was obtained as a yellow oil. Yield = 55%. m.p = 227-229 °C. R_f = 0.37 (EA/Hexane = 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.38-7.43 (m, 3H), 7.18-7.36 (m, 5H), 6.81 (d, *J* = 16.0 Hz, 1H), 3.68 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 142.6, 141.4, 137.8, 136.4, 133.6, 129.2, 128.9, 127.9, 126.7, 126.5, 125.8, 124.0, 122.7, 120.8, 35.6, 23.5. FTIR (NaCl, cm^{-1}):

3256, 1645, 1507, 1374. HRMS (ESI) *m/z* calculated for $C_{19}H_{17}NONa$ $[M+Na]^+$: 298.1208, found 298.1206.

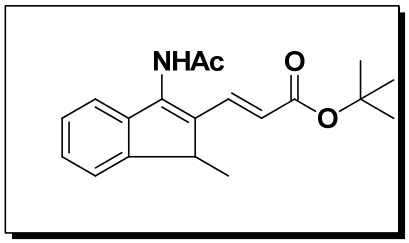


(*E*)-phenyl 3-(3-acetamido-1*H*-inden-2-yl)acrylate. This compound was prepared by the General Procedure described above and was obtained as a colorless oil. Yield = 68%. m.p = 214-215 °C. R_f = 0.32 (EA/Hexane = 3:2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.90 (d, *J* = 12.4 Hz, 1H), 7.42-7.46 (m, 4H), 7.25-7.28 (m, 3H), 7.16 (d, *J* = 6.2 Hz, 2H), 6.27 (d, *J* = 12.4 Hz, 1H), 3.71 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 165.7, 151.1, 143.1, 142.7, 141.3, 139.8, 130.0, 127.8, 126.7, 126.2, 124.4, 122.3, 122.2, 115.8, 35.5, 23.5. FTIR (NaCl, cm^{-1}): 3249, 1733, 1670, 1615, 1530, 1527, 1423, 1286, 1138. HRMS (ESI) *m/z* calculated for $C_{20}H_{17}NO_3Na$ $[M+Na]^+$: 342.1106, found 342.1109.

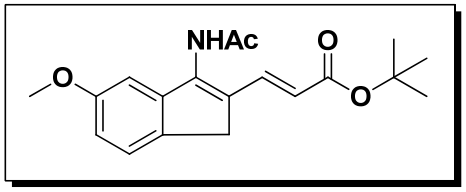


(*E*)-*N*-(2-(2-cyanovinyl)-1*H*-inden-3-yl)acetamide. This compound was prepared by the General Procedure described above and was obtained as a colorless oil. Yield = 12%. R_f = 0.40 (EA/Hexane = 2:3). ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.23 (s, 1H), 7.64 (d, *J* = 16.2 Hz, 1H), 7.44-7.52 (m, 2H), 7.26-

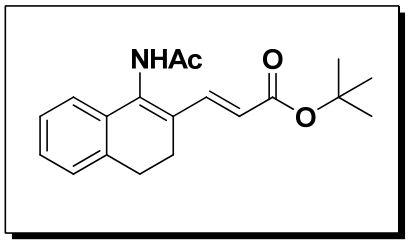
7.33 (m, 2H), 5.66 (d, *J* = 16.2 Hz, 1H), 3.63 (s, 2H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 173.5, 148.6, 147.3, 146.5, 146.2, 132.7, 131.6, 129.1, 126.4, 124.1, 96.8, 39.8, 27.8, 4.3. FTIR (NaCl, cm^{-1}): 3416, 2400, 2208, 1660. HRMS (ESI) *m/z* calculated for $C_{14}H_{12}N_2ONa$ $[M+Na]^+$: 247.0847, found 247.0853.



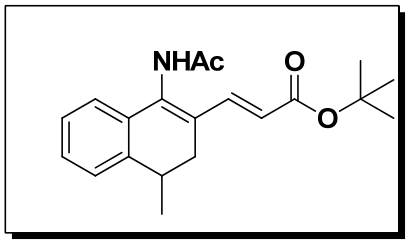
(*E*)-*tert*-butyl 3-(3-acetamido-1-methyl-1*H*-inden-2-yl)acrylate (3b) This compound was prepared by the General Procedure described above and was obtained as a colorless oil. Yield = 67%. R_f = 0.33 (EA/Hexane = 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.56 (d, *J* = 15.9 Hz, 1H), 7.45 (d, *J* =7.2 Hz, 1H), 7.32 (d, *J* = 6.8 Hz, 1H), 7.24-7.29 (m, 2H), 5.86 (d, *J* = 15.9 Hz, 1H), 3.69, (q, *J* =7.2 Hz, 1H), 2.14 (s, 3H), 1.46 (s, 9H), 1.25 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 166.4, 149.3, 141.2, 139.8, 136.0, 135.1, 127.6, 126.8, 123.4, 122.0, 119.3, 80.1, 28.3, 23.4, 18.6. FTIR (NaCl, cm^{-1}): 3402, 1695, 1653, 1603, 1570, 1292, 1152. HRMS (ESI) *m/z* calculated for $C_{19}H_{23}NO_3Na$ $[M+Na]^+$: 336.1576, found 336.1568.



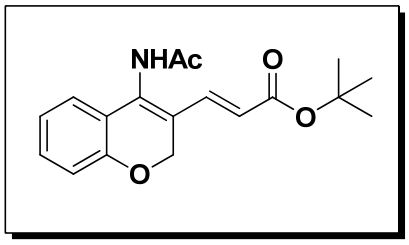
(*E*)-*tert*-butyl 3-(3-acetamido-5-methoxy-1*H*-inden-2-yl)acrylate. (**3c**) This compound was prepared by the general procedure described above and was obtained as a white solide. Yield = 79%. m.p = 200-201 °C. R_f = 0.30 (EA/Hexane = 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.56 (d, J = 15.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.82-6.91 (m, 2H), 5.92 (d, J = 15.6 Hz, 1H), 3.73 (s, 3H), 3.51 (s, 2H), 2.13 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 166.4, 158.8, 142.9, 141.4, 137.2, 134.4, 131.6, 124.9, 118.7, 113.8, 106.7, 80.1, 55.7, 34.7, 28.3, 23.5. FTIR (NaCl, cm^{-1}): 2968, 1660, 1608, 1300, 1143. HRMS (ESI) m/z calculated for $C_{19}H_{23}NO_4Na$ $[M+Na]^+$: 352.1525, found 352.1516.



(*E*)-*tert*-butyl 3-(1-acetamido-3,4-dihydronaphthalen-2-yl)acrylate. (**3d**) This compound was prepared by the general procedure described above and was obtained as a white solide. Yield = 74%. m.p = 169-171 °C. R_f = 0.34 (EA/Hexane = 1:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.58 (d, J =15.5 Hz, 1H), 7.19-7.21 (m, 4H), 5.98 (d, J = 15.5 Hz, 1H), 2.76 (t, J = 7.8 Hz, 2H), 2.48 (t, J = 7.8 Hz, 2H), 2.09 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.4, 166.4, 140.7, 137.4, 136.6, 132.7, 128.9, 128.8, 127.8, 126.8, 124.7, 119.7, 80.1, 28.3, 27.1, 23.1, 23.0. FTIR (NaCl, cm^{-1}): 1666, 1612, 1504, 1369, 1311, 1151. HRMS (ESI) m/z calculated for $C_{19}H_{23}O_3NNa$ $[M+Na]^+$: 336.1576, found 336.1578.

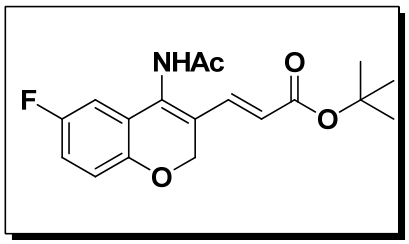


(*E*)-*tert*-butyl 3-(1-acetamido-4-methyl-3,4-dihydronaphthalen-2-yl)acrylate. (**3e**) This compound was prepared by the General Procedure described above and was obtained as a white solide. Yield = 57%. m.p = 180-183 °C. R_f = 0.35 (EA/Hexane = 1:1).^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51(s, 1H), 7.58 (d, *J* = 15.6 Hz, 1H), 7.21-7.25 (m, 4H), 5.98 (d, *J* = 15.6 Hz, 1H), 2.93 (m, 1H), 2.59 (dd, *J* = 16.0, 6.0Hz, 1H), 2.33 (dd, *J* = 16.0, 6.4Hz, 1H), 2.08 (s, 3H), 1.44 (s, 9H), 1.15 (d, *J* =6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 166.5, 142.4, 141.0, 135.9, 131.9, 129.2, 127.3, 126.7, 126.5, 124.6, 119.7, 80.2, 31.3, 30.5, 28.2, 23.0, 20.2. FTIR (NaCl, cm^{-1}): 3422, 1704, 1654, 1617, 1312, 1274, 1155. HRMS (ESI) *m/z* calculated for $C_{20}H_{25}NO_3Na$ $[M+Na]^+$: 350.1732, found 350.1726.

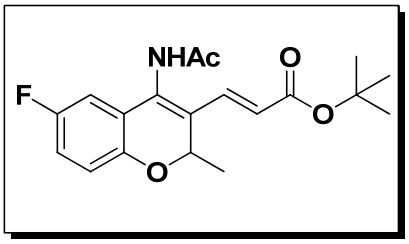


(*E*)-*tert*-butyl 3-(4-acetamido-2*H*-chromen-3-yl)acrylate. (**3f**) This compound was prepared by the General Procedure described above and was obtained as a yellow oil. Yield = 76%. R_f = 0.32 (EA/Hexane = 3:2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.37 (d, *J* = 16.0 Hz, 2H), 7.16-7.23 (m, 2H), 6.85-6.95 (m, 2H), 5.91 (d, *J* = 16.0 Hz, 1H), 4.96 (s, 2H), 2.09 (s, 3H),

1.44 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.5, 166.1, 155.6, 136.7, 133.6, 131.2, 125.3, 122.1, 121.9, 121.5, 119.9, 116.3, 80.4, 65.1, 28.2, 23.1. FTIR (NaCl, cm^{-1}): 1699, 1598, 1514, 1485.19, 1367, 1321, 1273, 1151. HRMS (ESI) m/z calculated for $C_{18}H_{21}O_4NNa$ $[M+Na]^+$: 338.1368, found 338.1370.

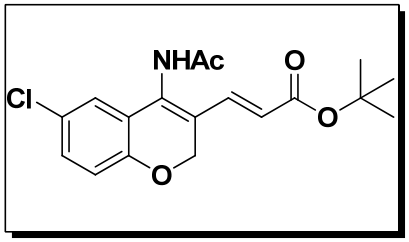


(*E*)-*tert*-butyl 3-(4-acetamido-6-fluoro-2*H*-chromen-3-yl)acrylate. (**3g**) This compound was prepared by the General Procedure described above and was obtained as a yellow solide. Yield = 55%. m.p = 162-164 °C. R_f = 0.34 (EA/Hexane = 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 7.37 (d, *J* = 16.0 Hz, 1H), 6.90-7.10 (m, 3H), 5.99 (d, *J* =16.0 Hz, 1H), 4.99 (s, 1H), 2.13 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 166.0, 157.3 (*J* = 235.0 Hz), 151.7, 136.4, 132.8, 123.3, 122.9 (*J* = 8.0 Hz), 120.8, 117.7 (*J* = 9.0 Hz), 117.4 (*J* = 24.0 Hz), 111.5 (*J* = 25.0 Hz), 80.5, 65.3, 28.2, 23.2. FTIR (NaCl, cm^{-1}): 3415, 1700, 1662, 1625, 1301, 1151. HRMS (ESI) *m/z* calculated for $C_{18}H_{20}NO_4FNa$ $[M+Na]^+$: 356.1274, found 356.1275.

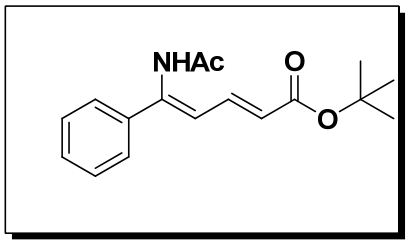


(*E*)-*tert*-butyl 3-(4-acetamido-6-fluoro-2-methyl-2*H*-chromen-3-yl)acrylate. (3h) This compound was prepared by the General Procedure described above and was obtained as a yellow solide. Yield = 57%. m.p = 153-156 °C. R_f = 0.34

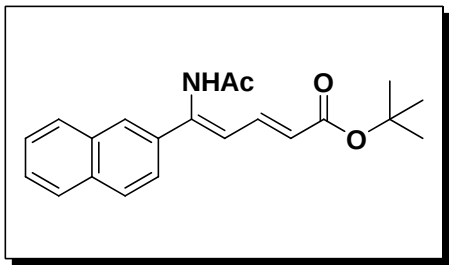
(EA/Hexane = 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.38 (d, J = 16.0 Hz, 1H), 7.07-7.12 (m, 1H), 6.99-7.03 (m, 1H), 6.89-6.93 (m, 1H), 6.02 (d, J =16.0 Hz, 1H), 5.46 (q, J = 6.4 Hz, 1H), 2.12 (s, 3H), 1.44 (s, 9H), 1.23 (d, J =6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 166.0, 157.2 (J =235.0 Hz), 149.2, 136.6, 131.9, 127.7, 122.1 (J = 8.0 Hz), 120.2, 118.6 (J = 8.0 Hz), 117.7 (J = 24.0), 111.3 (J = 24.0 Hz), 80.5, 70.9, 28.2, 23.2, 19.0. FTIR (NaCl, cm^{-1}): 1705, 1664, 1300, 1287, 1161. HRMS (ESI) *m/z* calculated for $C_{19}H_{22}NO_4FNa$ $[M+Na]^+$: 370.1431, found 370.1429.



(*E*)-*tert*-butyl 3-(4-acetamido-6-chloro-2*H*-chromen-3-yl)acrylate. (**3i**) This compound was prepared by the General Procedure described above and was obtained as a white solide. Yield = 65%. m.p = 174-177 °C. R_f = 0.32 (EA/Hexane = 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 7.37 (d, J = 16.0 Hz, 1H), 7.26 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 5.99 (d, J = 16.0 Hz, 1H), 5.03 (s, 2H), 2.14 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 165.9, 154.2, 136.3, 132.2, 130.5, 125.8, 124.5, 123.2, 123.1, 120.9, 118.2, 80.6, 65.4, 28.2, 23.2. FTIR (NaCl, cm^{-1}): 3271, 1701, 1665, 1617, 1302, 1152. HRMS (ESI) *m/z* calculated for $C_{18}H_{20}NO_4ClNa$ $[M+Na]^+$: 372.0979, found 372.0972.



(2*E*, 4*Z*)-*tert*-butyl 5-acetamido-5-phenylpenta-2,4-dienoate. (**3j**) (E:Z = 60:40) This compound was prepared by the General Procedure described above and was obtained as a white solide. Yield = 67%. R_f = 0.36 (EA/Hexane = 3:2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 0.85H), 9.70 (s, 0.72H), 7.45-7.48 (m, 4.3H), 7.20-7.41 (m, 6.5H), 6.94-7.03 (dd, *J* = 15.0, 15.0 Hz, 0.67H), 6.55 (d, *J* = 11.6 Hz, 1H), 5.99 (d, *J* = 15.5 Hz, 1H), 5.73 (d, *J* = 15.0 Hz, 0.68H), 2.06 (s, 3H), 2.00 (s, 2.1H), 1.43 (s, 9H), 1.34 (s, 1.3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.9, 169.1, 166.3, 166.2, 145.4, 142.7, 141.8, 140.0, 137.4, 135.5, 129.8, 129.5, 129.3, 128.8, 128.8, 126.6, 122.9, 119.4, 112.3, 80.1, 79.5, 28.2, 28.1, 24.5, 23.3. FTIR (NaCl, cm^{-1}): 3222, 1691, 1668, 1621, 1301, 1284, 1158. HRMS (ESI) *m/z* calculated for $C_{17}H_{21}NO_3Na$ $[M+Na]^+$: 310.1419, found 310.1415.



(2*E*, 4*E*)-*tert*-butyl 5-acetamido-5-(naphthalene-2-yl)penta-2,4-dienoate. (**3k**) (E:Z = 60:40) This compound was prepared by the General Procedure described above and was obtained as a white solide. Yield = 64%. R_f = 0.35 (EA/Hexane = 3:2). ^{1}H NMR (400 MHz, DMF-d_7) δ 9.11 (s, 1H), 8.99 (s,

0.66H), 8.06 (s, 1H), 7.85 (m, 6H), 7.67 (d, J = 8.4 Hz, 1H), 7.45 (m, 6H), 7.18 (dd, J = 15.0, 15.0 Hz, 0.66H), 6.66 (d, J = 11.4 Hz, 1H), 6.01 (d, J = 15.0 Hz, 1H), 5.80 (d, J = 15.0 Hz, 0.66H), 2.21 (s, 3H), 2.11 (s, 2H), 1.50 (s, 9H), 1.33 (s, 6H). ^{13}C NMR (100 MHz, DMF-d_7) δ 169.0, 168.3, 166.0, 165.8, 144.5, 142.1, 141.5, 139.1, 135.0, 133.6, 133.4, 133.3, 133.1, 132.9, 128.9, 128.4, 128.2, 128.0, 127.8, 127.6, 127.5, 126.9, 126.8, 126.6, 126.5, 126.4, 125.7, 124.1, 122.9, 119.8, 119.6, 112.4, 79.4, 78.8, 26.6, 22.4. FTIR (NaCl, cm^{-1}): 3276, 1695, 1682, 1615, 1520, 1506, 1138. HRMS (ESI) *m/z* calculated for $C_{21}H_{23}NO_3Na$ $[M+Na]^+$: 360.1576, found 360.1579.

Mechanistic investigation:

Procedure:

N-(1-phenylvinyl)acetamide (0.1 mmol, 16.1 mg) in 0.5 ml DMSO-d_6 solution in NMR tube was analyzed at 25 °C using a Bruker Advance 500 NMR. The ^{1}H NMR spectrum is shown as Figure **1**-(**a**). The two terminal alkenyl protons were assigned at 4.99 and 5.64 ppm respectively. Palladium(II) acetate (0.11 mmol, 1.1 equiv, 24.7 mg) was added into the solution and the NMR tube was shaken for 15 minutes at 25 °C. The mixture was then analyzed again using the same Bruker Advance 500 NMR. It was found one of the alkenyl proton signal disappeared from the spectrum almost completely (spectrum b). It was noted that there was a slight downfield shift of the acetyl methyl group from 2.02 to 2.29 ppm (see Figure **2**). Following which *tert*-butyl acrylate (0.10 mmol, 1.0 equiv, 12.8 mg) was introduced into the mixture, and the ^{1}H NMR spectrum is as shown in Figure **1**-(**c**). We found the mixture exhibited no change even after 24 hours at 25 °C, which was confirmed by ^{1}H NMR. The mixture was then heated at 80 °C for another 12 hours and checked again with

^{1}H NMR. The desired product **3j** (*tert*-butyl 5-acetamido-5-phenylpenta-2, 4-dienoate) was obtained in 43% yield and was accompanied by palladium black from the reduction of $Pd(OAc)_2$.

On the basis of the above results, a six-membered cyclic vinylpalladium intermediate was proposed. 2-D NOESY spectroscopic analysis showed a correlation between proton $\mathbf{H^b}$ and aryl protons. This indicates the *syn*-position of the palladium substituent with the acetamide group in the intermediate. Therefore, a plausible mechanism is proposed as shown in Scheme **2**.

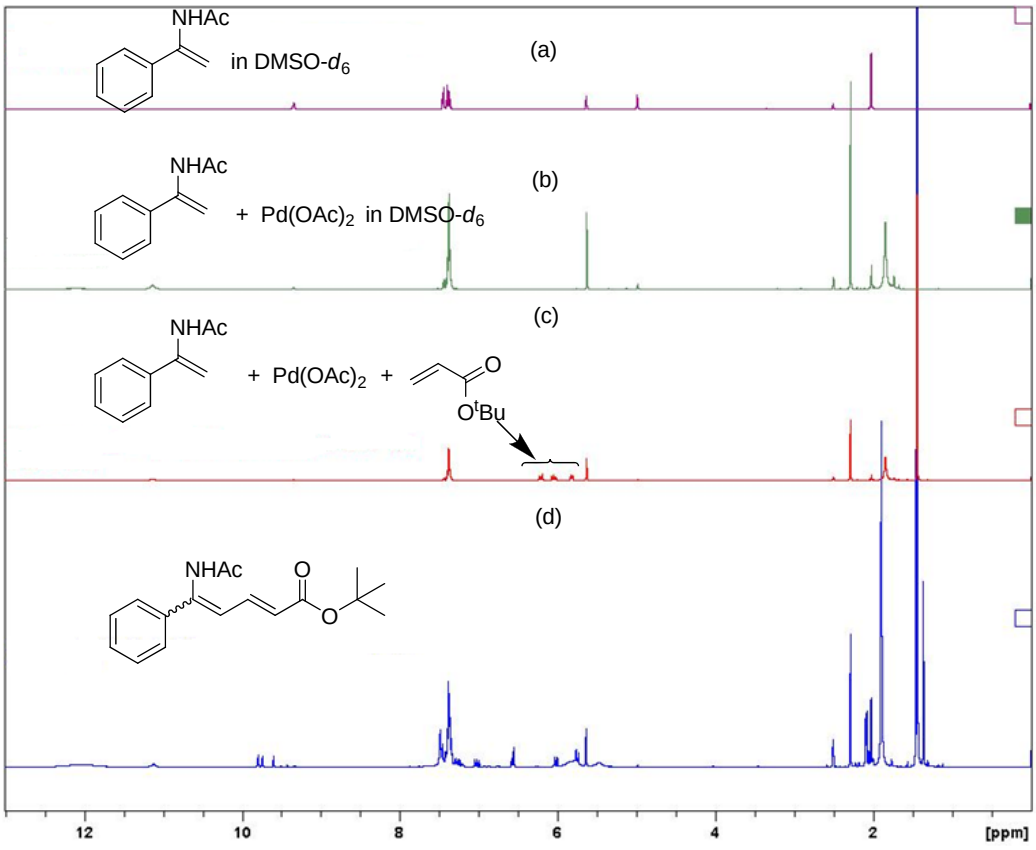


Figure 1. ^{1}H NMR spectroscope study of the coupling mechanism

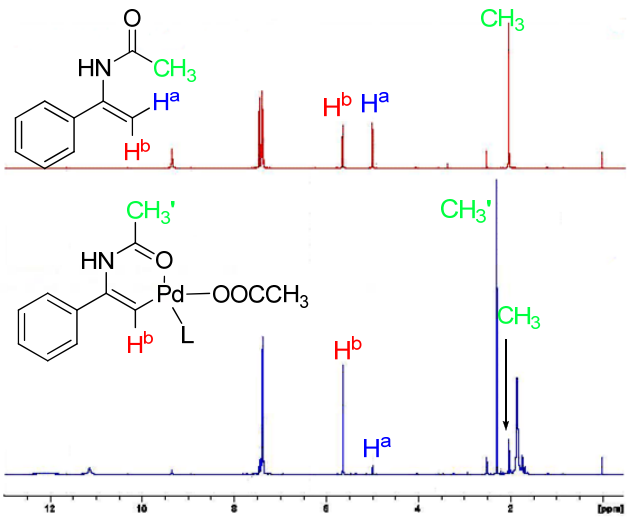


Figure 2. ^{1}H NMR spectrums of *N*-(1-phenylvinyl)acetamide

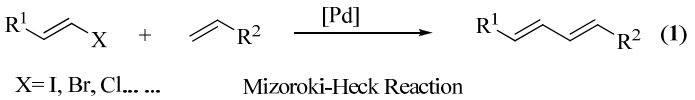
CHAPTER 4

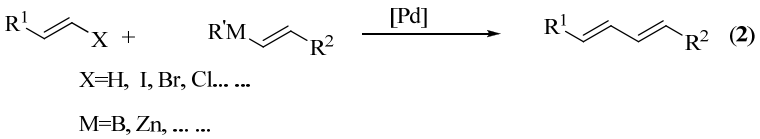
Direct Cross-Coupling Reaction of Vinyl Acetates with Acrylates Free of Organohalogen and Organometallic Components: Molecular Oxygen as the Sole Oxidant

Chapter 4. Direct Cross-Coupling Reaction of Vinyl Acetates with Acrylates Free of Organohalogen and Organometallic Components: Molecular Oxygen as the Sole Oxidant

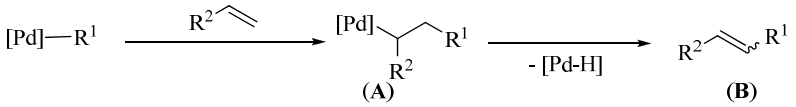
4.1 INTRODUCTION

Pd-catalyzed coupling of alkenes with vinyl halides (Mizoroki-Heck reaction, eq **1**) [134] or vinyl organometallic species (Suzuki-Miyaura [135] and Stille [136] reactions) are widely used for the construction of diene products in organic synthesis.





Significant effort has been devoted to development of the catalytic system and investigation of the mechanism. As shown in Scheme **1**, the general mechanism involves the formation of a σ-bond Pd intermediate, followed by olefin insertion to generate σ-alkyl Pd intermediate **A,** then hydride elimination or olefin dissociation to give product **B**.



Scheme **1**

However, the generation of halide salts as byproduct in the coupling reaction is not environmental friendly while the use of organometallic compounds is not

[134] For reviews of the Heck reaction, see: (a) Heck, R. F. *Org*. *React*. **1982**, *27*, 345-390. (b) Gürtler, C.; Buchwald, S. L. *Chem*. *Eur*. *J*. **1999**, *5*, 3107-3112. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem*. *Rev*. **2000**, *100*, 3009-3066.

[135] For reviews of the Suzuki-Miyaura reaction, see: (a) Miyaura, N. *J*. *Organomet*. *Chem*. **2002**, *653*, 54-57. (b) Suzuki, A. *J*. *Organomet*. *Chem*. **1999**, *576*, 147-168. (c) Miyaura, N.; Suzuki, A. *Chem*. *Rev*. **1995**, *95*, 2457-2483.

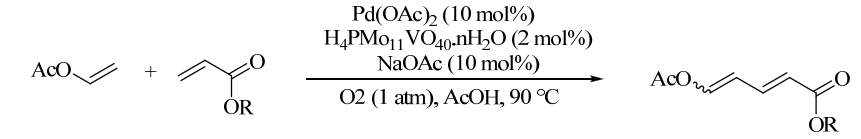
[136] For reviews of the Stille reaction, see: (a) Stille, J. K. *Angew*. *Chem*. *Int*. *Ed*. **1986**, *25*, 508-524. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org*. *React*. **1997**, *50*, 1-652.

atom economical. Direct oxidative cross-coupling between olefins would be an efficient method to overcome these limitations. However, direct cross-coupling through C–H bond activation of two different olefins is quite difficult to carry out due to the difficulty in activating the alkenyl C–H bond. Examples of homodimerization of functional olefins such as acrylates and acrylonitrile leading to dicarboxylates and dinitriles catalyzed by various transition metal compounds such as Co,[137] Ru,[138] Rh,[139] Ni[140] and Pd[141] have been reported. However, it is difficult to achieve the oxidative homocoupling reaction of simple olefins, with only few works reported having poor results. [142] Furthermore, examples of oxidative cross-coupling reactions between different olefins are even rarer. In chapter **2**, we have successfully developed an oxidative cross-coupling reaction between simple olefins and acrylates catalyzed by palladium under mild conditions.[143] To our knowledge, there has been little study on the catalytic oxidative cross-coupling reaction between functional olefins.

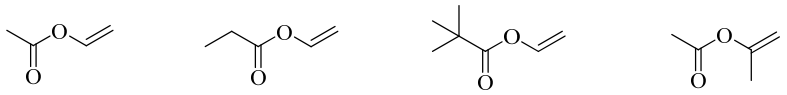
In 2004, Ishii and co-workers elegantly reported an oxidative cross-coupling of acrylates with vinyl carboxylates catalyzed by a $Pd(OAc)_2$/HPMoV/O_2

[137] (a) Kanai, H.; Okada, M. *Chem*. *Lett*. **1975**, *4*, 167-168. (b) Kanai, H.; Ishii, K. *Bull*. *Chem*. *Soc*. *Jpn*. **1981**, *54*, 1015-1018.
[138] (a) Mckinney, R. J.; Conton, M. C. *Organometallics* **1986**, *5*, 1080-1085. (b) Mckinney, R. J. *Organometallics* **1986**, *5*, 1752. (c) Bennet, M. A. *Organometallics* **1995**, *14*, 2565-2569.
[139] (a) Alderson, T.; Jenner, E. T.; Lindsey, R. V. J. *J*. *Am*. *Chem*. *Soc*. **1965**, *87*, 5638-5645. (b) Brookhart, M.; Sabo-Etienne, S. *J*. *Am*. *Chem*. *Soc*. **1991**, *113*, 2777-2779. (c) Hauptiman, E.; Sabo-Etienne, S.; White, P. S.; Brookhart, M.; Garner, J. M.; Fagan, P. J.; Calabrese, J. C. *J*. *Am*. *Chem*. *Soc*. **1994**, *116*, 8038-8060.
[140] Wilke, G. *Angew*. *Chem*. *Int*. *Ed*. **1988**, *27*, 185-206.
[141] (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett*. **1979**, *20*, 3437-3440. (b) Nugent, W. A. Hobbs, F. W. J. *J*. *Org*. *Chem*. **1983**, *48*, 5364-5366. (c) Tkatchenko, I.; Neibecker, D.; Grenouillet, P. *Organometallics* **1984**, *3*, 1130-1132.
[142] (a) Da Silva, M. J.; Gusevskaya, E. V. *J*. *Mol*. *Catal*. *A*: *Chem*. **2001**, *176*, 23-27. (b) Da Silva, M. J.; Gonçalves, J. A.; Alves, B. R.; Howarth, O. W.; Gusevskaya, E. V. *J*. *Organomet*. *Chem*. **2004**, *689*, 302-308.
[143] Xu, Y.-H.; Lu, J.; Loh, T.-P. *J*. *Am*. *Chem*. *Soc*. **2009**, *131*, 1372-1373.

system (Scheme **2**).[144] The corresponding diene products were obtained in moderate to good yields, but limited vinyl carboxylates were tested in this work. In the previous chapter, we developed an efficient oxidative cross-coupling of enamides with electron-poor alkenes catalyzed by palladium. Both cyclic and acyclic enamides worked well and afforded the cross-coupling products in moderate to good yields under our catalytic conditions.



Scope of vinyl carboxylates used in this work:



Scheme **2**

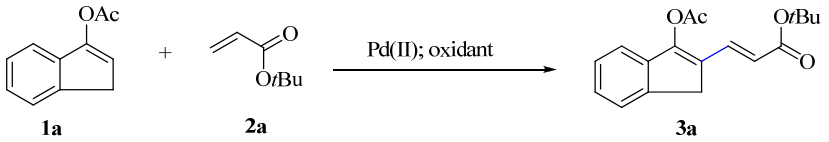
Alkenyl acetates are functional olefins, which could be easily produced through ester exchange, and are good candidates for the study of direct cross-coupling between alkenes. As described above, examples reporting use of the acetoxy group as a functional group to activate the alkenyl C–H bond are rare compared with other functional groups. In this chapter, we present the development of an oxidative direct cross-coupling reaction between alkenyl esters and electron-poor olefins using $Pd(OAc)_2$ as the catalyst under very mild conditions.

4.2 EXPERIMENTS AND RESULTS

Our initial efforts were focused on optimizing the reaction conditions. Therefore, 3*H*-inden-1-yl acetate (**1a)** and *tert*-butyl acrylate (**2a)** were choosen

[144] Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett*. **2004**, *6*, 4623-4625.

as reactants for the model studies. The reactions were carried out using different palladium catalysts and oxidants and the results are summarized in Table **1**.



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

Table 1. Optimization of Reaction Conditions Using 3*H*-inden-1-*yl* acetate **1a** and *tert*-Butyl acrylate **2a**

entry	catalyst	oxidant	solvent	additive	yield (%) [a]
1	$Pd(PhCN)_2Cl_2$ [b]	$Cu(OAc)_2$ [c]	DMSO/HOAc [d]	—	17
2	$Pd(PhCN)_2Cl_2$ [b]	$Cu(OAc)_2$ [c]	HOAc	—	0
3	$Pd(PhCN)_2Cl_2$ [b]	$Cu(OAc)_2$ [c]	DMSO	—	0
4	$Pd(OAc)_2$	$Cu(OAc)_2$ [c]	DMSO/HOAc [d]	—	23
5	$Pd(PhCN)_2Cl_2$ [f]	O_2	HOAc	NaOAc [g]	0
6	$Pd(TFA)_2$ [f]	O_2	HOAc	NaOAc [h]	25
7	$Pd(OAc)_2$ [f]	O_2	HOAc	NaOAc [g]	66
8	$Pd(OAc)_2$ [i]	O_2	HOAc	NaOAc [g]	60
9	$Pd(OAc)_2$ [f]	O_2	HOAc	NaOAc [j]	35
10	$Pd(OAc)_2$ [f]	O_2	HOAc	—	53
11	$Pd(OAc)_2$ [i]	O_2	HOAc	—	70

[a] Isolated yield. [b] 20 mol% loading of $Pd(PhCN)_2Cl_2$. [c] 2 equivalent of $Cu(OAc)_2$. [d] Ratio is 1:1(v/v). [e] 30 mol% loading of $Pd(OAc)_2$. [f] 10 mol% loading of $Pd(TFA)_2$. [g] 1 equivalent of NaOAc. [h] 0.1 equivalent of NaOAc. [i] 15 mol% loading of $Pd(OAc)_2$. [j] 2 equivalent of NaOAc.

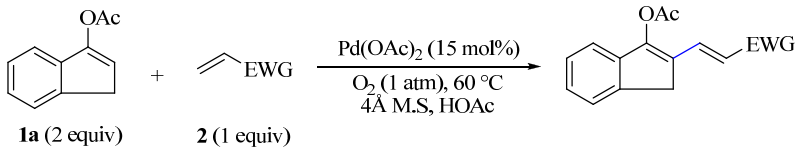
Initially, we tested previously established conditions for the coupling of olefins with acrylates for vinyl acetates. However, we observed that the use of these conditions only afforded the desired product in low yield (entry 4).

Therefore, various catalysts such as $Pd(PhCN)_2Cl_2$ and $Pd(TFA)_2$ were screened, and $Pd(OAc)_2$ emerged as the best catalyst. In addition, we also found that the use of the oxidant, $Cu(OAc)_2$, would increase the rate of decomposition of the vinyl acetates, resulting in low yield. Further investigation of the additive was carried out in hopes that stabilization of the catalyst would improve the yield, subsequent experiments showed that a reduction in the amount of NaOAc resulted in increased reaction yields (entries 7–11). Various solvents such as DMSO, HOAc/DMSO (1:1) were also investigated and HOAc afforded the product in highest yield with 15 mol% of catalyst loading. In summary, our optimized reaction conditions are as follows: 15 mol% $Pd(OAc)_2$ with O_2 at 1 atm in HOAc, in the presence of 4Å moleculer sieves at 60 °C for 24 h. Under these conditions, 70% of **3a** was isolated with excellent regioselectivity.

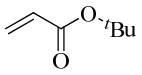
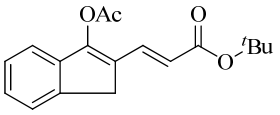
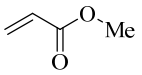
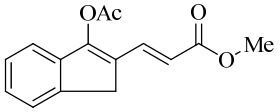
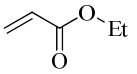
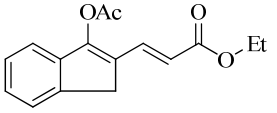
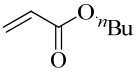
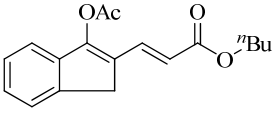
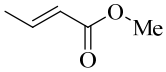
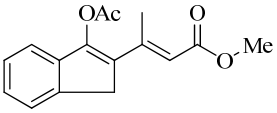
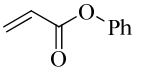
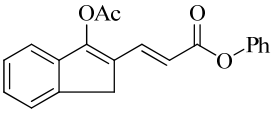
Before screening different vinyl acetates, various electron-deficient coupling partners were tested in this cross-coupling reaction under our optimized reaction conditions (Table **2**). *n*-Butyl acrylate gave the desired product in 52% yield (Table **2**, entry 4), phenyl acrylate afforded the desired product in 63% yield (Table **2**, entry 6), while methyl acrylate and ethyl acrylate furnished the desired product in 43% and 31% yields respectively (Table **2**, entries 2 and 3). Unfortunately, (*E*)-methyl but-2-enoate gave the product in only 9% yield (Table **2**, entry 5), which may be due to the steric hindrance of its methyl group. No desired product was obtained for the couplings with styrene, acrylonitrile *N*-phenylacrylamide and acrylamide with 3*H*-inden-1-*yl* acetate. Therefore, *tert*-butyl acrylate was established as the best coupling partner in this reaction (Table **2**, entry 1).

Next, we extended our optimized reaction conditions to other vinyl acetates. The results are shown in Table **3**. Methyl and methoxy substituted vinyl acetates (entries 2-4) gave unexpectedly lower yields as compared to the original substrate (Table **3,** entry 1) and the reasons are still unclear to us. The vinyl acetate with a six-membered ring **1e** resulted in only 32% yield, which was due to decompostion of the starting material (Table **3,** entry 5). The reaction using 1-phenyl vinyl acetate **1f** resulted in 51% yield of the product (Table **3,** entry 6). The influence of an electron-donating methyl-substituent on the *para*- and *meta*- position on the phenyl ring typically furnished the product in higher yield (Table **3,** entries 7 and 8). 72% and 60% yields were obtained respectively for the coupling of 1-(naphthalen-2-yl)vinyl acetate and acyclic isopropenyl acetate to produce **3i** and **3j** (Table **3,** entries 9 and 10).

Table 2. Cross-coupling reaction of 3*H*-inden-1-yl acetate (**1a**) with different coupling partners.[a]

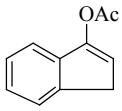
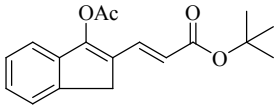
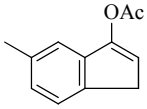
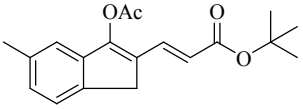
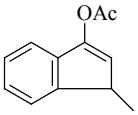
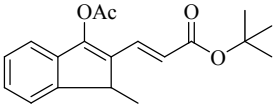
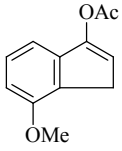
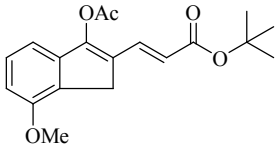
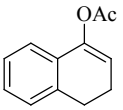
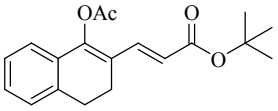
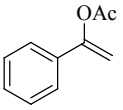
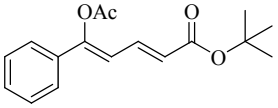
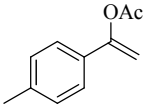
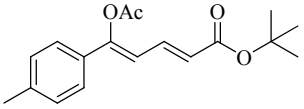
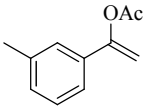
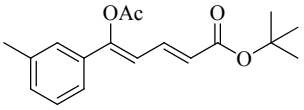
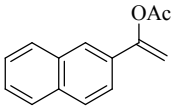
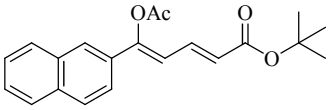
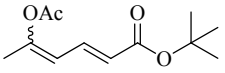


1a (2 equiv) **2** (1 equiv)

entry	starting material		product	yield (%)[b] (*E*/*Z*)[c]
1		**2a**		70 (> 99:1)
2		**2b**		43 (> 99:1)
3		**2c**		31 (> 99:1)
4		**2d**		52 (> 99:1)
5		**2e**		9 (> 99:1)
6		**2f**		63 (> 99:1)

[a] The cross-coupling reactions were carried out under following conditions: 3*H*-inden-1-yl acetate (**1a**) (0.4 mmol, 2 equiv), compound **2** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (0.03 mmol, 15 mol%) and 50 mg 4 Å molecular sieves powder (M.S) in 0.8 mL anhydride acetatic acid (HOAc) at 60 °C under O_2 atmosphere (1 atm). [b] Isolated yield. [c] Determined from crude ^{1}H NMR spectrum.

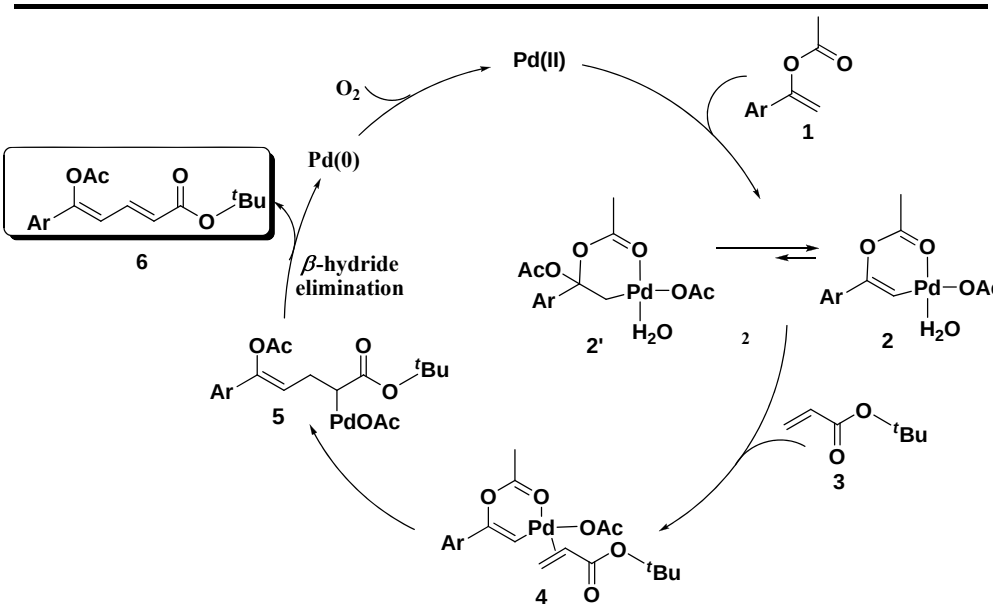
Table 3. Palladium-catalyzed cross-coupling reaction of vinyl acetates with *tert*-butyl acrylate.

entry	vinyl acetate		product		yield (%)[b] (*E*:*Z*)[c]
1		**1a**		**3a**	70 (> 99:1)
2		**1b**		**3b**	55 (> 99:1)
3		**1c**		**3c**	62 (> 99:1)
4		**1d**		**3d**	67 (> 99:1)
5		**1e**		**3e**	32 (> 99:1)
6		**1f**		**3f**	51 (> 99:1)
7		**1g**		**3g**	63 (> 99:1)
8		**1h**		**3h**	61 (> 99:1)
9		**1i**		**3i**	72 (> 99:1)
10		**1j**		**3j**	60 (59:41)

[a] The cross-coupling reactions were carried out under following conditions: 3*H*-inden-1-yl acetate (**1a**) (0.4 mmol, 2 equiv), compound **2** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (0.03 mmol, 15 mol%) and 50 mg 4 Å molecular sieves powder (M.S) in 0.8 mL anhydride acetatic acid (HOAc) at 60 °C under O_2 atmosphere (1 atm). [b] Isolated yield. [c] Determined from crude ^1H NMR spectrum.

A plausible mechanism is as proposed in Scheme **3**. The sp^2 C–H bond of vinyl acetate **1** is activated by the Pd(II) complex to form intermediate **2**. Intermediate **D** is then formed by coordination of *tert*-butyl acrylate **C** to **B**.

Subsequently, the Pd complex adds to the α-position of the ester group and a C–C bond is then formed between the sp^2 carbon and the terminal carbon of the acrylate to produce intermediate **E**. The target molecule **F** is finally obtained upon β-hydride elimination. Pd(II) is regenerated *via* oxidation of Pd(0) by molecular oxygen to participate in subsequent catalytic cycles.



Scheme **3**. Proposed mechanism for the palladium-catalyzed cross-coupling reaction of vinyl acetates with *tert*-butyl acrylate

In summary, we have developed an efficient cross-coupling of vinyl acetates with acrylates *via* $Pd(OAc)_2$ catalyzed C–H activation of vinyl acetates to afford products in moderate to high yields with high regioselectivity. Moreover, this cross coupling reaction is a very novel method since no metal oxidant and/or additive is used. This novel method produces highly functionalized, versatile compounds which can be further manipulated to form a wide variety of building blocks and complex molecules.

4.3 EXPERIMENTAL SECTION

4.3.1 GENERAL METHOD FOR THE CROSS-COUPLING REACTION OF VINYL ACETATES WITH ACRYLATES

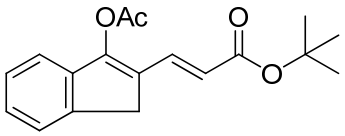
All commercially obtained reagents for the cross-coupling reaction were used as received: acetic acid were obtained from Sigma-Aldrich and used as received. The starting materials of vinyl acetates were prepared according to the reported references.[145] All cross-coupling reactions were run under 1 atm O_2 and no precautions were taken to exclude moisture. Thin-layer chromatography (TLC) was conducted with Merck 60 F254 precoated silica gel plate (0.2 mm thickness) and visualized with UV and potassium permanganate staining, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. ^{1}H NMR spectra were performed on a Bruker Advance 300, 400 and 500 NMR spectrometer and are reported in ppm downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (*J* =7.26, singlet). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Advance 300 (75 MHz), Bruker Advance 400 (100 MHz) or Bruker Advance 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). Regioselectivity of the cross-coupling was determined by NMR analysis of the crude product. IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-Tof Permies Mass Spectrometer.

[145] (a) House, H. O.; Trost, B. M.; *J. Org. Chem*. **1965**, *30*, 2502-2512. (b) Eames, J.; Coumbarides, G. S.; Weerasooriya, N. J. *Label Compd. Radiopharm*. **2001**, *44*, 871-879. (c) Eames, J.; Coumbarides, M. J. Suggate.; Weerasooriya, N. *Eur. J. Org. Chem*. **2003**, 634-641.

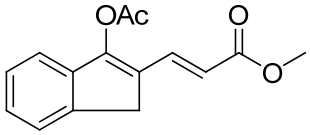
4.3.2 REPRESENTATIVE EXPERIMENTAL PROCEDURE FOR DIRECT CROSS-COUPLING BETWEEN VINYL ACETATES AND ACRYLATES

A 10 ml dried round bottom flask was charged sequentially with a stirring bar, $Pd(OAc)_2$ (15 mol%, 0.03 mmol), and HOAc (0.8 ml). The starting material, vinyl acetate **1** (2 equiv, 0.4 mmol), acrylate (1 equiv, 0.2 mmol) and 4Å molecular sieve powder (100 mg) were added into the solution in sequence. The reaction mixture was stirred at 60 ºC under 1 atm of oxygen (balloon pressure) for 24 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with distilled water and brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated to give the crude product which was purified on silica gel (EtOAc/Hexanes mixtures).

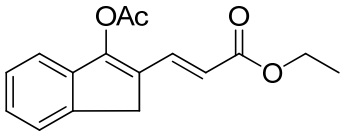
4.3.3 CHARACTERIZATION DATAS FOR THE DIENOATES



(*E*)-*tert*-butyl 3-(3-acetoxy-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solid. Yield = 70%. mp = 98-100 °C; R_f = 0.37 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 15.7 Hz, 1H), 7.42-7.44 (m, 1H), 7.28-7.31 (m, 2H), 7.17-7.20 (m, 1H), 6.02 (d, *J* = 15.7 Hz, 1H), 3.57 (s, 2H), 2.42 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 166.4, 151.5, 140.9, 138.5, 133.6, 127.4, 127.4, 126.8, 124.4, 120.3, 119.4, 80.5, 34.0, 28.2, 20.6; FTIR (NaCl, cm^{-1}): 3022, 2980, 2932, 1779, 1703, 1622, 1457, 1368, 1283, 1148, 1084, 979, 851, 755. HRMS (ESI) m/z calculated for $C_{18}H_{20}O_4Na$ $[M+Na]^+$: 323.1259, Found 323.1258.

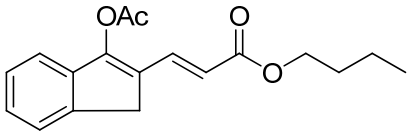


(*E*)-methyl 3-(3-acetoxy-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solid. Yield = 43%. mp = 115-118 °C; R_f = 0.35 (EA:Hexane = 1:4).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 15.8 Hz, 1H), 7.38-7.39 (m, 1H), 7.22-7.29 (m, 2H), 7.14-7.19 (m, 1H), 5.97 (d, *J* = 15.8 Hz, 1H), 3.75 (s, 3H), 3.54 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.4, 152.0, 141.0, 138.4, 134.8, 127.6, 127.2, 126.9, 124.4, 119.5, 117.9, 51.7, 34.0, 20.6; FTIR (NaCl, cm^{-1}): 3020, 2952, 1777, 1716, 1625, 1437, 1367, 1281, 1193, 1085, 755. HRMS (ESI) m/z calculated for $C_{15}H_{14}O_4Na$ $[M+Na]^+$: 281.0790, Found 281.0790.

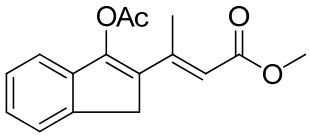


(*E*)-ethyl 3-(3-acetoxy-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solid. Yield = 31%. mp = 92-94 °C; R_f = 0.35 (EA:Hexane = 1:4). 1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* =15.8 Hz, 1H, 7.37-7.39 (m, 1H), 7.25-7.29 (m, 2H) 7.14-7.18 (m, 1H), 5.97 (d, *J* = 15.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 2.40 (s, 3H), 1.29 (t, 3H, *J* =7.1 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 167.9, 167.0, 151.9, 141.0, 138.4, 134.6, 127.6, 127.3, 126.8, 124.4, 119.5, 118.4, 60.5, 34.0, 20.6, 14.3; FTIR (NaCl, cm^{-1}): 3077, 2981, 2937, 2898, 1775, 1704, 1622,

1462, 1367, 1283, 1165, 1084, 884, 857, 758. HRMS (ESI) m/z calculated for $C_{16}H_{16}O_4Na$ $[M+Na]^+$: 295.0946, Found 295.0942.

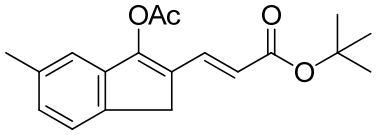


(*E*)-butyl 3-(3-acetoxy-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solid. Yield = 52%. mp = 79-81 °C; R_f = 0.33 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 15.8 Hz, 1H) 7.42-7.43 (m, 1H), 7.28-7.31 (m, 2H), 7.20-7.21 (m, 1H), 6.06 (d, *J* = 15.8 Hz, 1H), 4.20 (t, *J* = 6.6 Hz, 2H), 3.58 (s, 2H), 2.43 (s, 3H), 1.61-1.73 (m, 2H) 1.42 (m, 2H, *J* = 7.3 Hz), 0.97 (t, 2H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.1, 151.9, 141.0, 138.4, 134.6, 127.6, 127.3, 126.8, 124.4, 119.5, 118.4, 64.4, 34.0, 30.7, 20.6, 19.2, 13.7; FTIR (NaCl, cm^{-1}): 3021, 2962, 1776, 1700, 1624, 1366, 1281, 1168, 755. HRMS (ESI) m/z calculated for $C_{18}H_{20}O_4Na$ $[M+Na]^+$: 323.1259, Found 323.1258.

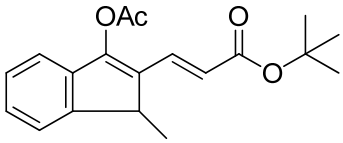


(*E*)-methyl 3-(3-acetoxy-1*H*-inden-2-yl)but-2-enoate. This compound was prepared by the general procedure described above and was obtained as a white solid. Yield = 9%. mp = 110-111 °C; R_f = 0.32 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.42 (m, 1H), 7.27-7.30 (m, 2H), 7.13-7.15 (m, 1H), 6.08 (d, *J* = 1.1 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 2H), 2.52 (d, *J* = 1.1 Hz, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 167.3, 149.4, 148.8, 139.9,

139.3, 130.5, 127.2, 126.7, 124.0, 118.9, 116.7, 51.1, 36.5, 20.8, 16.4; FTIR (NaCl, cm^{-1}): 3020, 2950, 1763, 1709, 1602, 1436, 1369, 1195, 1148, 1076, 756. HRMS (ESI) m/z calculated for $C_{16}H_{16}O_4Na$ $[M+Na]^+$: 295.0946, Found 295.0943.

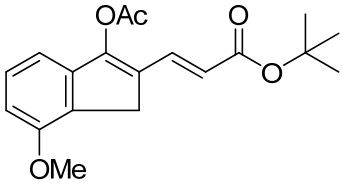


(*E*)-*tert*-butyl 3-(3-acetoxy-5-methyl-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solid. Yield = 55%. mp = 135-137 °C; R_f = 0.35 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 15.8 Hz, 1H, 7.25 (t, *J* = 7.7 Hz,1H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.95 (s, 1H), 5.95 (d, *J* = 15.8 Hz, 1H), 3.47 (s, 2H), 2.38 (s, 3H), 2.34 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 164.5, 151.5, 138.6, 138.1, 136.6, 133.7, 128.4, 127.6, 124.1, 120.1, 119.8, 80.5, 33.6, 28.2, 21.4, 20.6; FTIR (NaCl, cm^{-1}): 3019, 2981, 2930, 1765, 1694, 1616, 1456, 1367, 1295, 1149, 1081, 978, 855, 754.66. HRMS (ESI) m/z calculated for $C_{19}H_{22}O_4Na$ $[M+Na]^+$: 337.1416, Found 337.1418.

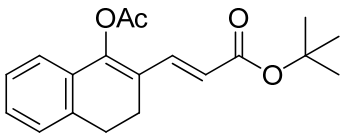


(*E*)-*tert*-butyl 3-(3-acetoxy-1-methyl-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a colorless oil. Yield = 62%. R_f = 0.35 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 16.0 Hz, 1H), 7.41-7.43 (m, 1H), 7.28-7.31 (m, 2H), 7.16-7.19 (m, 1H), 5.97 (d, *J* = 16.0 Hz, 1H), 3.53 (q, *J* = 7.4 Hz, 1H), 2.41 (s, 3H),

1.53 (s, 9H), 1.42 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 162.3, 150.9, 148.1, 136.8, 132.8, 132.1, 127.6, 126.9, 123.2, 120.8, 119.5, 80.5, 40.2, 28.2, 20.6, 17.7; FTIR (NaCl, cm^{-1}): 3019, 2981, 2933, 1774, 1703, 1621, 1368, 1299, 1150, 756. HRMS (ESI) m/z calculated for $C_{19}H_{23}O_4$ $[M+H]^+$: 315.1596, Found 315.1599.

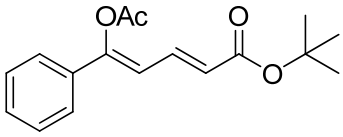


(2*E*)-*tert*-butyl 3-(3-acetoxy-7-methoxy-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a yellow oil. Yield = 67%. Rf = 0.30 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 15.8 Hz, 1H, 7.25-7.30 (m, 1H), 6.81-6.84 (m, 2H), 7.13-7.18 (m, 1H), 6.03 (d, J = 15.8 Hz, 1H), 3.89 (s, 3H), 3.51 (s, 2H), 2.40 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 166.4, 155.3, 151.1, 140.1, 133.6, 128.6, 128.0, 127.6, 120.4, 112.3, 109.7, 80.5, 55.3, 31.4, 28.1, 20.5; FTIR (NaCl, cm^{-1}): 3019, 1770, 1698, 1622, 1483, 1369, 1150, 1070, 767. HRMS (ESI) m/z calculated for $C_{19}H_{22}O_5Na$ $[M+Na]^+$: 353.1365, Found 353.1363.

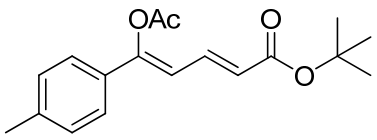


(*E*)-*tert*-butyl 3-(1-acetoxy-3,4-dihydronaphthalen-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a yellow solid. Yield = 32%. Mp = 97-98 °C; R_f = 0.33 (EA:Hexane

= 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 15.8 Hz, 1H), 7.13-7.22 (m, 4H), 5.57 (d, *J* = 15.8 Hz, 1H), 2.92 (t, *J* = 8.0 Hz, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 166.4, 147.1, 137.2, 137.0, 130.1, 129.0, 127.6, 126.6, 122.3, 122.2, 120.5, 80.4, 28.1, 27.1, 22.7, 20.5; FTIR (NaCl, cm^{-1}): 3021, 2980, 2937, 2898, 1764, 1700, 1615, 1368, 1319, 1248, 1152, 1071, 1027, 979, 862, 758. HRMS (ESI) m/z calculated for $C_{19}H_{22}O_4Na$ $[M+Na]^+$: 337.1416, Found 317.1414.

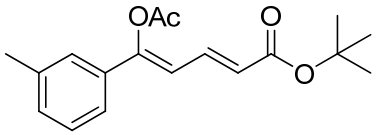


(2*E*, 4*Z*)-*tert*-butyl 5-acetoxy-5-phenylpenta-2,4-dienoate. This compound was prepared by the general procedure described above and was obtained as a yellow oil. Yield = 51%. R_f = 0.41 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.45 (m, 2H), 7.22-7.40 (m, 4H), 6.49 (d, *J* = 11.5 Hz, 1H), 5.95 (d, *J* = 15.4 Hz, 1H), 2.33 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.1, 151.7, 136.0, 133.7, 129.7, 128.8, 125.0, 124.6, 114.6, 80.5, 28.1, 20.6; FTIR (NaCl, cm^{-1}): 3020, 2981, 2933, 1762, 1704, 1630, 1479, 1369, 1333, 1247, 1139, 1037, 908, 755. HRMS (ESI) m/z calculated for $C_{17}H_{20}O_4Na$ $[M+Na]^+$: 311.1259, Found 311.1255.

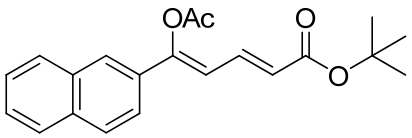


(2*E*, 4*Z*)-*tert*-butyl 5-acetoxy-5-*p*-tolylpenta-2,4-dienoate. This compound was prepared by the general procedure described above and was obtained as a yellow oil. Yield = 60%. R_f = 0.40 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.19-7.43 (m, 3H), 7.16-7.19 (m, 2H), 6.49 (d, *J* = 11.5 Hz, 1H), 5.95 (d, *J* = 15.3 Hz, 1H), 2.36 (s, 6H), 1.451 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.2, 151.9, 140.0, 136.2, 130.9, 129.5, 124.9, 124.1, 113.8, 80.4, 28.1, 21.3, 20.6; FTIR (NaCl, cm^{-1}): 3019, 2981, 2932, 1763, 1707, 1629, 1608, 1369, 1331, 1247, 1182, 1139, 757. HRMS (ESI) m/z calculated for $C_{18}H_{22}O_4Na$ $[M+Na]^+$: 325.1416, Found 325.1411.

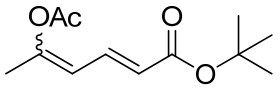


(2*E*, 4*Z*)-*tert*-butyl 5-acetoxy-5-m-tolylpenta-2,4-dienoate. This compound was prepared by the general procedure described above and was obtained as a yellow oil. Yield = 60%. R_f = 0.40 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.43 (m, 5H), 6.52 (d, *J* = 11.5 Hz, 1H), 5.97 (d, *J* = 15.3 Hz, 1H), 2.37 (s, 6H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 166.1, 151.9, 138.4, 136.1, 133.7, 130.6, 128.7, 125.6, 124.4, 122.2, 114.5, 80.5, 28.1, 21.4, 20.6; FTIR (NaCl, cm^{-1}): 3019, 2981, 2930, 1763, 1702, 1629, 1369, 1330, 1253, 1139, 1040, 757. HRMS (ESI) m/z calculated for $C_{18}H_{23}O_4$ $[M+H]^+$: 303.1596, Found 303.1589.



(2*E*, 4*Z*)-*tert*-butyl 5-acetoxy-5-(naphthalen-2-yl)penta-2,4-dienoate. This compound was prepared by the general procedure described above and was obtained as a white solid. Yield = 72%. Mp = 91-94 °C; R_f = 0.36 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.81-7.85 (m, 3H), 7.59-

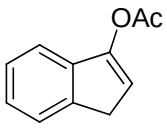
7.62 (m, 1H), 7.41-7.51 (m, 3H), 6.68 (d, *J* = 11.5 Hz, 1H), 6.05 (d, *J* = 15.3 Hz, 1H), 244 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.1, 151.7, 136.1, 133.7, 133.0, 131.0, 128.6, 128.6, 127.7, 127.1, 126.7, 124.8, 124.7, 122.2, 115.1, 80.5, 28.1, 20.7; FTIR (NaCl, cm^{-1}): 3019, 2981, 2932, 1767, 1703, 1622, 1369, 1324, 1254, 1138, 1032, 982, 756. HRMS (ESI) m/z calculated for $C_{21}H_{22}O_4Na$ $[M+Na]^+$: 361.1416, Found 361.1411.



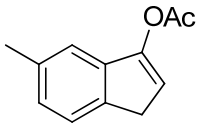
***tert*-butyl 5-acetoxyhexa-2,4-dienoate (E/Z isomers)**. This compound was prepared by the general procedure described above and was obtained as colourless oil. Yield = 60% (E:Z = 59:41). R_f = 0.38 (EA:Hexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.35 (m, 1.7H), 5.92 (d, *J* = 12.0 Hz, 1H), 5.73-5.82 (m, 2.4H), 2.21 (s, 3H), 2.15 (s, 2.1H), 2.09 (s, 2.1H), 2.04 (s, 3H), 1.48 (s, 6.3H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 168.4, 166.3, 166.1, 154.4, 152.7, 137.5, 135.9, 123.4, 122.3, 116.7, 115.4, 80.3, 28.1, 21.0, 20.8, 20.2; FTIR (NaCl, cm^{-1}): 3280, 3018, 2981, 1700, 1613, 1506, 1479, 1369, 1152, 1090, 908, 759. HRMS (ESI) m/z calculated for $C_{12}H_{18}O_4Na$ $[M+Na]^+$: 249.1103, Found 249.1100.

Representative experimental procedure for preparation of vinyl acetates

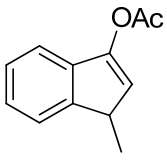
10 mmol carbonyl compound and 20 mg *p*-TsOH. H_2O as catalyst were added into isopropenyl acetate (5 mL), and the mixture was refluxed for 16 hours under N_2 atmosphere. Excess isopropenyl acetate was removed under reduced pressure after reaction, and the desired product was isolated by flash chromatography on silica gel (EA/Hexane).



3*H*-inden-1-yl acetate. This compound was prepared by the general procedure described above and was obtained as a pale yellow oil. Yield = 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.48 (d, *J* = 7.1 Hz, 1H), 7.25-7.35 (m, 3H), 6.36 (t, *J* =2.3 Hz), 3.44 (d, *J* =2.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 149.1, 141.7, 139.0, 126.2, 125.6, 124.1, 118.0, 115.5, 35.0, 21.1; FTIR (NaCl, cm^{-1}): 3022, 2894, 1768, 1603, 1578, 1362, 1166, 1111, 769. HRMS (ESI) m/z calculated for $C_{11}H_{11}O_2$ $[M+H]^+$: 175.0759, Found 175.0764.

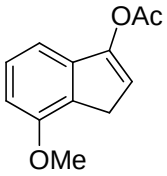


6-methyl-3*H*-inden-1-yl acetate. This compound was prepared by the general procedure described above and was obtained as a white solid. Yield = 78%. Mp = 35-37 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.32 (t, *J* = 2.3 Hz), 3.39 (d, *J* = 2.1 Hz, 2H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 162.3, 149.0, 139.1, 138.9, 126.5, 123.8, 118.6, 115.8, 34.5, 21.4, 21.3; FTIR (NaCl, cm^{-1}): 3021, 2921, 1767, 1575, 1477, 1370, 1163, 1009, 913, 806, 754. HRMS (ESI) m/z calculated for $C_{12}H_{13}O_2$ $[M+H]^+$: 189.0916, Found 189.0913.

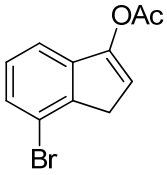


3-methyl-3*H*-inden-1-yl acetate. This compound was prepared by the general procedure described above and was obtained as a pale yellow oil. Yield = 70%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.43 (m, 1H), 7.27-7.31 (m, 3H), 6.31 (d, *J* = 2.1 Hz, 1H), 3.57 (qd, *J* = 2.1, 7.5 Hz, 1H), 2.34 (s, 3H), 1.37 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 147.9, 147.2, 138.2, 126.4, 125.9, 122.8, 122.1, 118.1, 41.3, 21.2, 16.3; FTIR (NaCl, cm^{-1}): 3022, 2967, 1767, 1615, 1575, 1461, 1362, 1166, 1074, 886, 761. HRMS (ESI) m/z calculated for $C_{12}H_{13}O_2$ $[M+H]^+$: 189.0916, Found 189.0913.

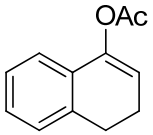


4-methoxy-3*H*-inden-1-yl acetate. This compound was prepared by the general procedure described above and was obtained as a white soild. Yield = 60%. mp 57-59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.33 (m, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.33 (t, *J* = 2.2 Hz, 1H), 3.90 (s, 3H), 3.38 (d, *J* = 2.2 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 155.3, 148.8, 140.8, 128.7, 128.1, 115.6, 111.2, 108.1, 55.2, 32.3, 21.1; FTIR (NaCl, cm^{-1}): 3019, 2939, 2838 1764, 1612, 1580, 1480, 1363, 1266, 1166, 1055, 916, 765. HRMS (ESI) m/z calculated for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0865, Found 205.0864.



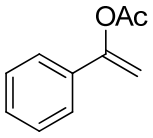
4-bromo-3*H*-inden-1-yl acetate. This compound was prepared by the general procedure described above and was obtained as a yellow oil. Yield = 57%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 1H), 7.18-7.38 (m, 2H), 6.41 (t, *J* = 2.2 Hz,

1H), 3.39 (d, *J* = 2.2 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 148.6, 141.7, 140.6, 128.8, 128.2, 119.2, 117.2, 116.3, 36.4, 21.1; FTIR (NaCl, cm^{-1}): 3069, 3020, 2889, 1768, 1563, 1357, 1163, 1008, 892, 775. HRMS (ESI) m/z calculated for $C_{11}H_{10}O_2Br$ $[M+H]^+$: 252.9864, Found 252.9862.

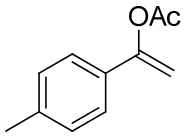


3,4-dihydronaphthalen-1-yl acetate. This compound was prepared by the general procedure described above and was obtained as a pink solid. Yield = 95%. mp = 44-45 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.22 (m, 4H), 5.74 (t, *J* = 4.6 Hz, 1H), 2.89 (t, *J* = 8.0 Hz, 2H), 2.44-2.53 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 145.6, 136.4, 130.4, 127.9, 127.6, 126.4, 120.7, 115.5, 27.4, 22.0, 20.8; IR (neat, cm^{-1}): 2930, 1740, 1660, 1370, 1210, 1130, 1080, 1040, 770, 740.

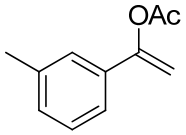
HRMS (ESI) (m/z) calculated for $C_{12}H_{12}O_2$ $[M+H]^+$:189.0837, Found 189.0835.



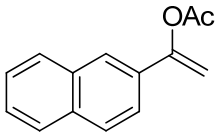
1-phenylvinyl acetate. This compound was prepared by the general procedure described above and was obtained as a pale yellow oil. Yield = 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.50 (m, 2H), 7.33-7.40 (m, 3H), 5.50 (d, *J* = 2.2 Hz, 1H), 5.05 (d, *J* = 2.2 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 152.9, 134.2, 128.9, 128.5, 124.8, 102.1, 21.0; IR (film, cm^{-1}): 1685, 1598. HRMS m/z calculated for $C_{10}H_{10}O_2$ $[M+H]^+$: 163.1852, Found 163.1854.



1-*p*-tolylvinyl acetate. This compound was prepared by the general procedure described above and was obtained as a pale yellow oil. Yield = 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.46 (d, *J* = 2.1 Hz, 1H), 5.01 (d, *J* = 2.1 Hz, 1H), 2.38 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 153.0, 138.9, 131.4, 129.2, 124.8, 101.2, 21.2, 20.9; FTIR (NaCl, cm^{-1}): 3020, 2924, 1761, 1645, 1513, 1370, 1183, 1090, 960, 769. HRMS (ESI) m/z calculated for $C_{11}H_{13}O_3$ $[M+H]^+$: 177.0916, Found 177.0913.



1-*m*-tolylvinyl acetate. This compound was prepared by the general procedure described above and was obtained as a pale yellow oil. Yield = 65%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.29 (m, 3H), 7.14-7.16 (m, 1H), 5.46 (d, *J* = 2.1 Hz, 1H), 5.01 (d, *J* = 2.1 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 153.1, 138.1, 134.2, 129.7, 128.4, 125.5, 122.0, 101.9, 21.4, 21.0; FTIR (NaCl, cm^{-1}): 3021, 2922, 1764, 1644, 1489, 1369, 1279, 1019, 960, 757. HRMS (ESI) m/z calculated for $C_{11}H_{13}O_2$ $[M+H]^+$: 177.0916, Found 177.0910.



1-(naphthalen-2-yl)vinyl acetate. This compound was prepared by the general procedure described above and was obtained as a white soild. Yield = 72%. Mp = 88-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.89 (m, 4H), 7.60-7.64 (m, 1H), 7.48-7.52 (m, 2H), 5.64 (d, *J* = 2.3 Hz, 1H), 5.15 (d, *J* = 2.3 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 152.9, 133.4, 133.0, 131.5, 128.4, 128.4, 127.6, 126.6, 126.5, 124.0, 122.6, 102.7, 21.0; IR (film, cm^{-1}): 1751; HRMS m/z calculated for $C_{14}H_{13}O_2$ $[M+H]^+$: 213.2887 Found 213.2882.

CHAPTER 5

Palladium-Catalyzed New C-S Bond Formation Using Olefins and Arylsulfonyl Chlorides

Chapter 5. Palladium-Catalyzed New C-S Bond Formation Using Olefins and Arylsulfonyl Chlorides

5.1 INTRODUCTION

Organosulfones are widely used as synthetic building blocks in organic chemistry,[146] making the development of simple and efficient synthetic methods necessary. Great efforts have been made towards this target over the years. Traditionally, aromatic sulfones are prepared by oxidation of the corresponding sulfides and sulfoxides [147] or by a displacement reaction of sodium arenesulfinate with an alkyl halide.[148] A Friedel-Crafts method employing sulfonyl chlorides and aromatic hydrocarbons with aluminium chloride as catalyst, to prepare aryl sulfones was developed with good yields,[149] while Gilman and co-workers have reported the synthesis of aryl sulfones by the reaction of Grignard reagents with aryl-*p*-toluene sulfinates.[150] Aromatic sulfones can also be synthesized in good yields by heating and stirring together a mixture of an aromatic sulfonic acid and an aromatic hydrocarbon in the presence of strong acids.[151] Some metal halides,[146a] Brönsted acids,[152] bismuth triflate,[153] Fe(III)-exchanged montmorillonite clay,[154] and indium triflate[155] have been successfully used for the catalytic sulfonylation of arenes. Lithium

[146] (a) Jensen, F. R.; Goldman G. In *Friedel-Crafts and Related Reactions*; Olah, G.; Ed.; Wiley-Interscience: New York, 1964; Vol. III, pp 1319-1367. (b) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993.
[147] For a review of the older methods of preparing sulfones, see Suter, C. M. *The Organic Chemistry of Sulfur*; John Wiley and Sons, Inc., New York, 1944, p 658.
[148] Block, E. In *The Chemistry of Functional Groups*; Patai, S.; Ed.; Wiley: New York, 1980; Suppl. E, Part 1, Chapter 13.
[149] (a) Beckurts, H.; Otto, R. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 472-473. (b) Beckurts, H.; Otto, R. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 2066-2070.
[150] Gilman, H.; Benber, N. J.; Myers, C. H. *J. Am. Chem. Soc.* **1925**, *47*, 2047-2052.
[151] Graybill, B. M. *J. Org. Chem.* **1967**, *32*, 2931-2933.
[152] Smith, K.; Ewart, G. M.; Randles, K. R. *J. Chem. Soc., Perkin Trans 1.* **1997**, *9*, 1085-1086.
[153] Repichet, S.; Leroux, C.; Dubac, J. *J. Org. Chem.* **1999**, *64*, 6479-6482.
[154] Choudary, B. M.; Chowdary, N. S.; Kantam, M. L.; Kannan, R. *Tetrahedron Lett.* **1999**, *40*, 2859.
[155] Frost, C. G.; Hartley, J. P. Whittle, A. J. *Synlett* **2001**, *6*, 830-832.

perchlorate[156] and sodium perchlorate[157] were also reported as efficient catalysts for sulfonylation of arenes under neutral conditions. However, the limited availability of sulphides for the oxidative process, the formation of mixtures of isomeric products and reaction inefficiency with arenes bearing strong electron-withdrawing groups for the electrophilic approach, and the lack of functionality tolerance for organometallic regents, all restricted the wide-spread applications of the above methods. Recently, an efficient copper-catalyzed one-step transformation of aryl iodides and sulfinic acid salts into methyl and diaryl sulfones was developed.[158] Subsequently, Ma and co-workers reported a more effective Cu(I) catalytic system, which permitted aryl iodides and aryl bromides to couple with sulfinic acid at relatively low temperatures.[159] In 2007, an efficient and general method for the synthesis of methyl-aryl, aryl-aryl, and heteroaryl sulfones catalyzed by copper was developed, which could be extended to the preparation of vinyl sulfones.[160] An example of palladium-catalyzed synthesis of diaryl sulfones from aryl iodides and sodium *p*-toluenesulfinate was developed using $Pd_2(dba)_3$ as catalyst, nBu$_4$NCl as additive in the presence of Xantphos (9,9-dimethyl-4,6-bis-(diphenyl-phosphino)xanthenes) as ligand at 80 °C.[161] Subsequently, Bandgar and co-workers reported a palladium-catalyzed catalytic Suzuki-Miyaura cross-coupling of boronic acids and sulfonyl chlorides at 25 °C to prepare diaryl sulfones.[162]

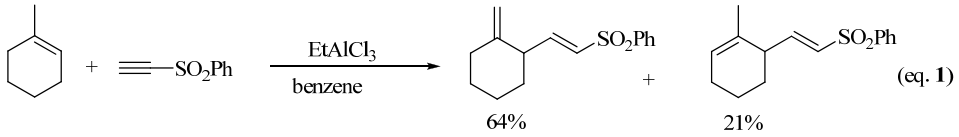
[156] Bandgar, B. P.; Kamble, V. T.; Sadavarte, V. S.; Uppalla, L. S. *Synlett* **2002**, *5*, 735-738.
[157] Bandgar, B. P.; Kamble, V. T.; Fulse, D. B.; Deshmukh, M. V. *New. J. Chem*. **2002**, *26*, 1105-1107.
[158] Baskin, J. M.; Wang, Z. *Org. Lett*. **2002**, *4*, 4423-4425.
[159] Zhu, W.; Ma, D. *J. Org. Chem*. **2005**, *70*, 2696-2700.
[160] Kar, A.; Sayyed, I. S.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Org. Lett*. **2007**, *9*, 3405-3408.
[161] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Org. Lett*. **2002**, *4*, 4719-4721.
[162] Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Org. Lett*. **2004**, *6*, 2105-2108.

As analogues of aryl sulfones, vinyl sulfones are important intermediates in many organic reactions.[163] As such, synthetic studies of vinyl sulfones have attracted much attention. An early example was reported using toluene-*p*-sulphonyl radical to react with 1,1-diphenylethylene under light to prepare (2-tosylethene-1,1-diyl)dibenzene in moderate yield.[164] In 1971, Truce and Wolf reported that sulfonyl iodides could be directly added to the triple bond of alkynes, and the corresponding inter- and intra- *β*-substituted vinyl sulfones were obtained in moderate to good yields.[165] Other methods involving the addition of sulfonyl radicals to olefinic compounds for the preparation of sulfones, along with electrophilic addition reactions, have also been developed. Usually, sulfonyl radicals are generated from sulfonyl halides by exposure to light,[165] by action of peroxide,[166] or by reduction with metallic reagents at high temperatures.[167] These conditions restrict practical application of the above methods in view of safety considerations.

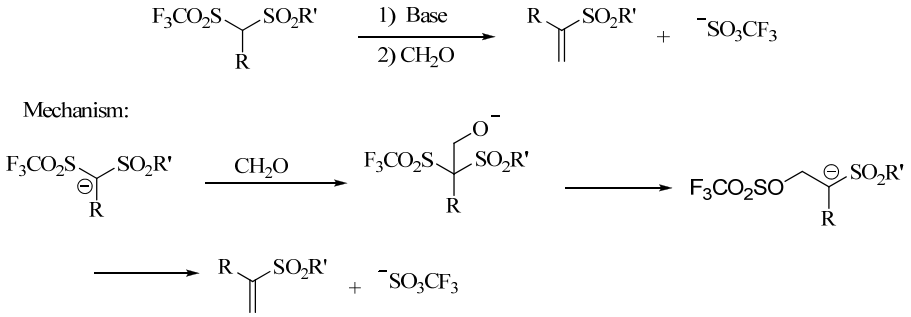
A Lewis acid catalyzed ene-reaction of olefins with ethynyl *p*-tolyl sulfone afforded the corresponding vinyl sulfones in moderate to high yields (eq. **1**).[168] Subsequently, a very mild and convenient unexpected synthesis of methylene sulfones using the mesyltriflone reagent was reported.[169] The mechanism involves trifyl transfer from carbon to oxygen, followed by elimination of the

[163] (a) Takaki, K.; Nakagawa, K.; Negoro, K. *J. Org. Chem.* **1980**, *45*, 4789-4791. (b) Cory, R. M.; Renneboog, R. M. *J. Org. Chem.* **1984**, *49*, 3898-3904. (c) Back, T. G.; Parvez, M.; Zhai, H. *J. Org. Chem.* **2003**, *68*, 9389-9393. (d) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1982**, *104*, 3733-3735. (d) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624-1625. (e)Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601-9613.
[164] da Silva Corrêa, C. M. M.; Waters, W. A. *J. Chem. Soc.* (*C*) **1968**, 1874-1879.
[165] Truce, W. E.; Wolf, G. C. *J. Org. Chem.* **1971**, *36*, 1727-1732.
[166] Kharasch, M. S.; Mosher, R. A. *J. Org. Chem.* **1952**, *17*, 453-456.
[167] (a) Liu, L. K.; Chi, Y.; Jen, K.-Y. *J. Org. Chem.* **1980**, *45*, 406-410. (b) Kamigata, N.; Sawada, H.; Kobayashi, M. *J. Org. Chem.* **1983**, *48*, 3793-3796. (c) Kamigata, N.; Ozaki, J.; Kobayashi, M. *J. Org. Chem.* **1985**, *50*, 5045-5050.
[168] Suider, B. B.; Kirk, T. C.; Roush, D. M. Conzalez, D. *J. Org. Chem.* **1980**, *45*, 5015-5017.
[169] Hendrickson, J. B.; Palumbo, P. S. *Tetrahedron Lett.* **1985**, *26*, 2849-2852.

triflate anion as depicted in Scheme **1**. Use of the remarkably reactive phenyl 2-(trimethylsilyl)-ethynyl sulfone as an acceptor for Michael addition reaction generates the corresponding vinyl sulfones, which can in turn be attacked by various enolizable compounds.[170]



Trans-*β*-substituted vinyl sulfones can be formed by using *α*-lithiated sulfones and cupric acetate.[171] The strategy of hydrozirconation of alkynes, followed by sulfonylation, is a direct route to form (*E*)-disubstituted vinyl sulfones (eq. **2**).[172] Subsequent work involved the treatment of 1-alkynyl sulfones with $Cp_2Zr(H)Cl$ to afford Z-*β*-zirconated vinyl sulfones predominantly. The Z-*β*-zirconated vinyl sulfone products could be easily

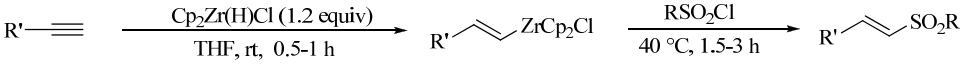


Scheme **1**

further functionalized at the *β*-position with the retention of configuration (eq. **3**).[173]

[170] Ohnuma, T.; Hata, N.; Fujiwara, H.; Ban, Y. *J. Org. Chem*. **1982**, *47*, 4713-4717.
[171] Baudin, J-B.; Julia, M.; Rolando, C.; Verpeaux, J-N. *Tetrahedron Lett*. **1984**, *25*, 3203-3204.
[172] Duan, D.-H.; Huang, X. *Synlett* **1999**, *3*, 317-318.
[173] Huang, X.; Duan, D.; Zheng, W. *J. Org. Chem*. **2003**, *68*, 1958-1963.

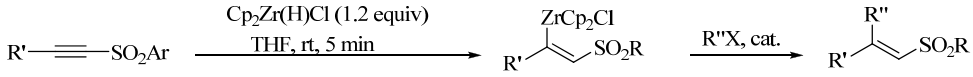
An example of *anti*-hydrotelluration of 1-alkynyl sulfones was also developed by Huang and co-workers.[174] A plausible mechanism for the formation of *E*-2-aryltelluro-1-alkenyl sulfones was proposed to be the regiospecific addition of a sulfonyl radical to the alkyne. The possible 2-sulfonylvinyl radical intermediate **A** would undergo a fast reaction with diaryl ditelluride to produce the highly stereoselective product, while a similar reaction for intermediate **B** is difficult due to steric hindrance of SO_2Ar^1 (Scheme **2**).



R'=Ph, *n*-Bu, CH_3OCH_2, $TMSCH_2$, $HOCH_2$, $BrCH_2$;

R=Ph, *p*-Tol, CH_3

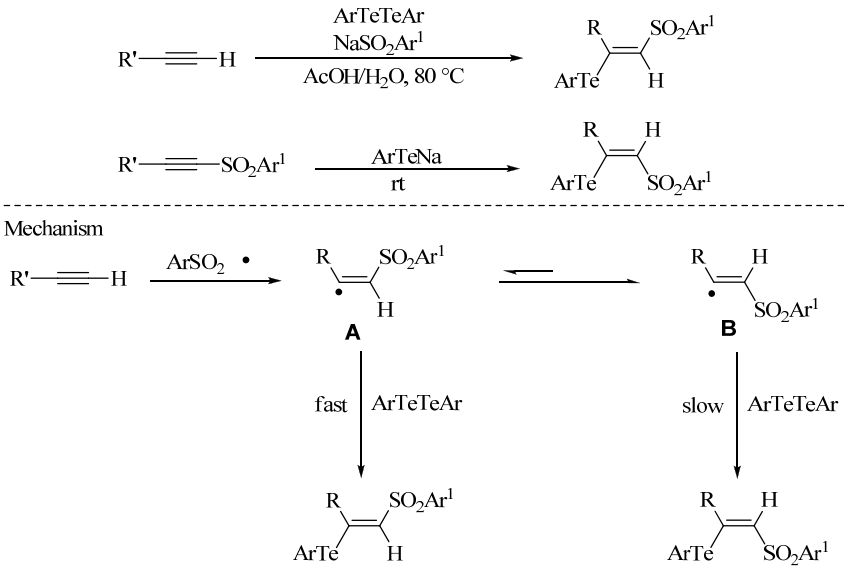
(eq. **2**)



(eq. **3**)

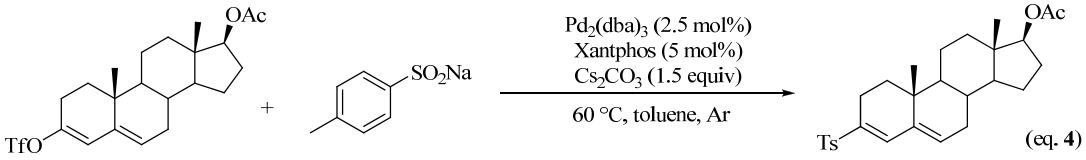
Aside from previous examples of the sulfonylation of olefins by the utilization of sulfonyl radicals,[165-167] oxidative sulfonylation of electron-rich olefins with sodium arylsulfinates and manganese(III) or cerium(IV) compounds has also been developed by Narasaka and co-workers.[175] The sulfonyl radical was generated under very mild conditions.

[174] Huang, X.; Liang, C.-G.; Xu, Q.; He, Q.-W. *J. Org. Chem.* **2001**, *66*, 74-80.
[175] (a) Narasaka, K.; Mochizuki, T.; Hayakawa, S. *Chem. Lett.* **1994**, *23*, 1705-1708. (b) Mochizuki, T.; Hayakawa, S.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2317-2325.



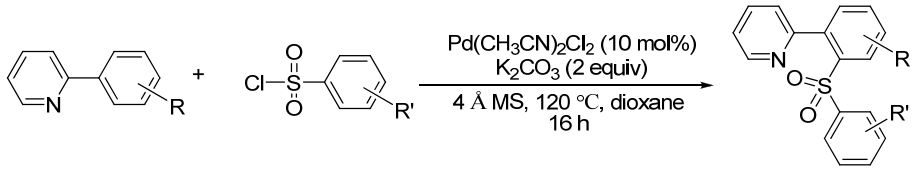
Scheme **2**

However, all the above procedures have their drawbacks. The need for special starting materials,[169] or the use of stoichiometric amount of inorganic or organometallic reagents[168,172-175] limited their practical application. Recently, palladium-catalyzed sulfonylation of vinyl triflates was reported, which provided an attractive alternative to existing methods (eq. **4**).[176] While the use of the triflate group is necessary, this is wasteful in terms of atom economy. More recently, Dong and co-workers presented a cross-coupling between arylsulfonyl chlorides and 2-phenylpyridine derivatives, which was catalyzed by palladium (eq **5**).[177]



(eq. **4**)

[176] Cacci, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608-5614.
[177] Zhao, X.; Dimitrijević, E.; and Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466-3467.



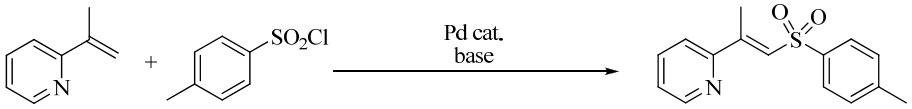
(eq **5**)

Herein, we report a direct sulfonylation of olefins catalyzed by palladium using *α*-methyl-vinyl pyridine and enamides with sulfonyl chlorides. With our method, a large variety of arylsulfonyl chlorides including an aliphatic sulfonyl chloride could couple with *α*-methyl-vinyl pyridine or enamides, and the corresponding products were obtained in moderate to good yields.

5.2 EXPERIMENTS AND RESULTS

Initially, *α*-methyl-vinyl pyridine was selected as the substrate to investigate the best conditions. We first examined different palladium catalysts in dioxane with 0.5 equivalent of K_2CO_3. The best result (71% yield of product) was obtained with 10 mol% $Pd(PhCN)_2Cl_2$; both $Pd(CH_3CN)_2Cl_2$ and $Pd(OAc)_2$ also could afford the desired product in moderate yields, but low yield was obtained when $Pd(TFA)_2$ or $Pd(acac)_2$ was used as catalyst. It was noted that increasing or decreasing the amount of K_2CO_3 would lower the product's yield. The use of other inorganic bases, such as Na_2CO_3 or K_3PO_4, in this reaction could provide the product in moderate yield, while low yields were obtained when organic bases like triethylamine or pyridine were used. Furthermore, it was found that the choice of solvent is important for this reaction. No desired product was formed in DMF or THF. In the control experiment with absence of the palladium catalyst, only the starting materials were recovered, without detection of any other compounds.

Table **1**. Sulfonylation of *α*-methyl-vinyl pyridine with *p*-toluene sulfonyl chloride under different conditions.*

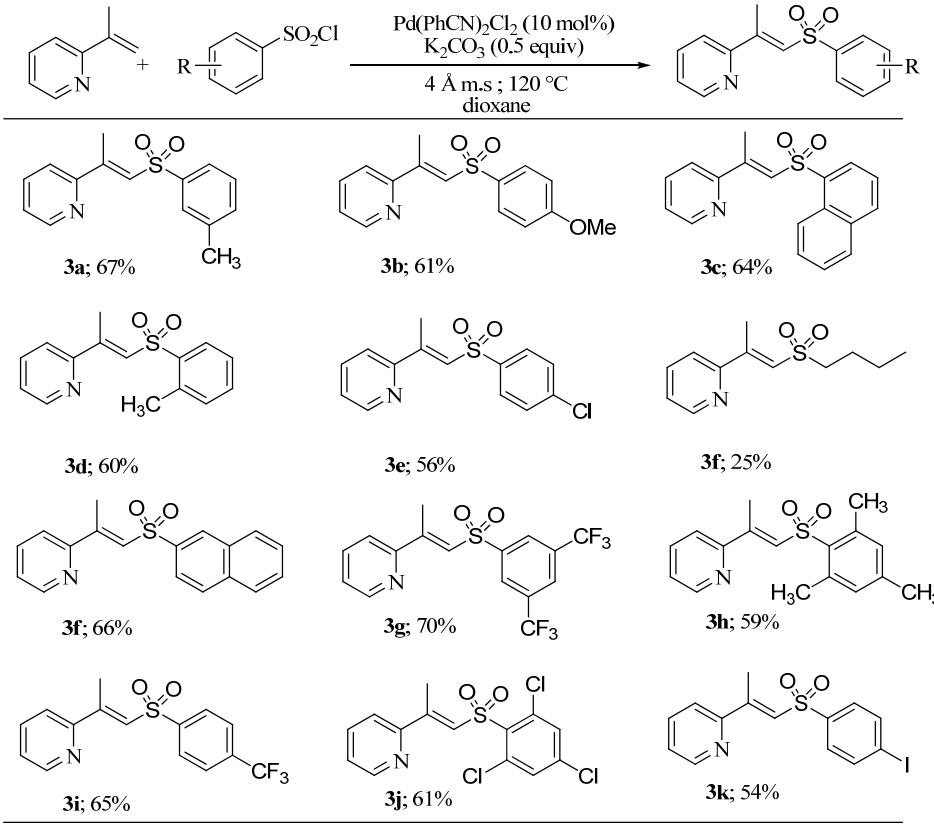


entry	cat/ mol%	base/equiv	solvent	time/h	yield (%)[a]
1	$Pd(CH_3CN)_2Cl_2$/ 10	K_2CO_3/ 0.5	dioxane	24	59
2	$Pd(OAc)_2$/ 10	K_2CO_3/ 0.5	dioxane	24	65
3	$Pd(TFA)_2$/ 10	K_2CO_3/ 0.5	dioxane	24	26
4	$Pd(acac)_2$/ 10	K_2CO_3/ 0.5	dioxane	24	13
5	$PdCl_2$/ 10	K_2CO_3/ 0.5	dioxane	24	60
6	$Pd(PhCN)_2Cl_2$/ 10	K_2CO_3/ 0.5	dioxane	24	71
7	$Pd(PhCN)_2Cl_2$/ 10	K_2CO_3/ 0.2	dioxane	24	51
8	$Pd(PhCN)_2Cl_2$/ 10	K_2CO_3/ 2	dioxane	24	40
9	$Pd(PhCN)_2Cl_2$/ 10	Na_2CO_3/ 0.5	dioxane	24	61
10	$Pd(PhCN)_2Cl_2$/ 10	K_3PO_4/ 0.5	dioxane	24	52
11	$Pd(PhCN)_2Cl_2$/ 10	Et_3N/ 0.5	dioxane	24	34
12	$Pd(PhCN)_2Cl_2$/ 10	Pyridine/ 0.5	dioxane	24	25
13	—	K_2CO_3/ 0.5	dioxane	24	—
14[b]	$Pd(PhCN)_2Cl_2$/ 10	K_2CO_3/ 0.5	dioxane	48	32
15	$Pd(PhCN)_2Cl_2$/ 10	K_2CO_3/ 0.5	DMF	24	—
16	$Pd(PhCN)_2Cl_2$/ 10	K_2CO_3/ 0.5	THF	24	—

*The reactions were carried out under following conditions: the mixture of *α*-methyl-vinyl pyridine (0.2 mmol, 1 equiv), p-toluene sulfonyl chloride (0.3 mmol, 1.5 equiv), K_2CO_3 and palladium catalyst in solvent was heated at 120 °C under O_2 (1 atm). [a] Isolated yield. [b] At 80 °C.

Next, the scope of sulfonyl chlorides was examined using 10 mol% $Pd(PhCN)_2Cl_2$, 0.5 equivalent of K_2CO_3 in dioxane with 4Å m.s and with heating at 120 °C. The results are as follows in Table 2. We found that in addition to arylsulfonyl chlorides bearing electron-donating groups, substrates containing even strong electron-withdrawing groups all afforded the corresponding products in good yields. Notably, 25% yield of the coupling product could be obtained when 1-butanesulfonyl chloride was reacted with *α*-methyl-vinyl pyridine. The tolerance of halide substituents on the phenyl ring permits possible further transformations.

Table **2**. Sulfonylation of α-methyl-vinyl pyridine with various sulfonyl chlorides.*

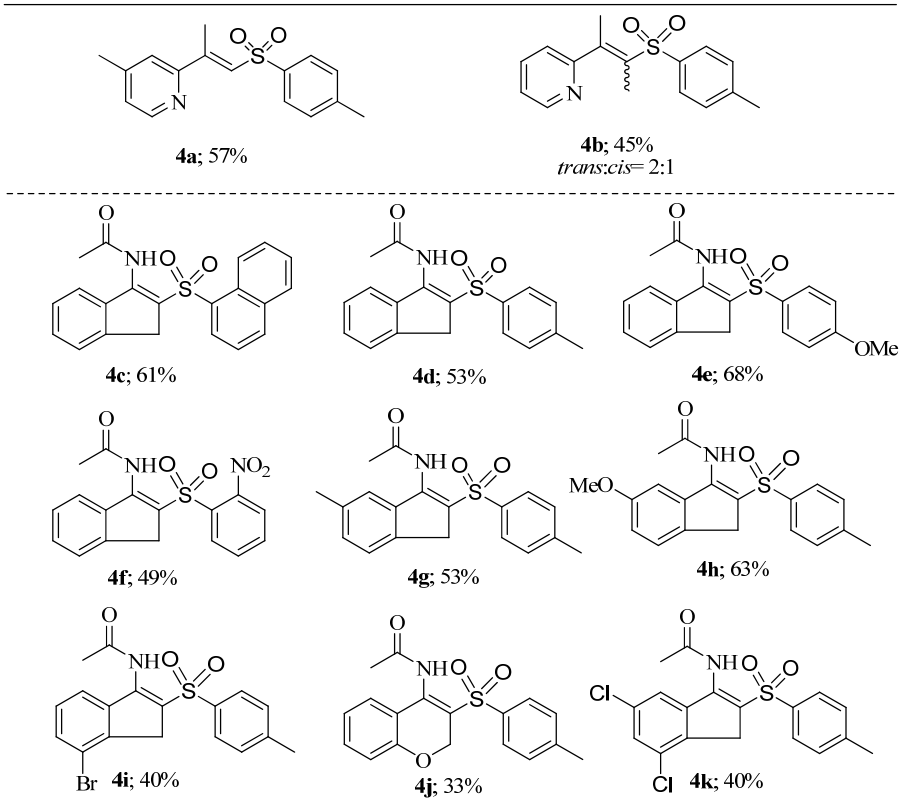


* Reaction conditions: α-methyl-vinyl pyridine **(**0.2 mmol) and sulfonyl chloride (0.3 mmol), $Pd(PhCN)_2Cl_2$ (10 mmol%), K_2CO_3 (0.1 mmol) and 50 mg 4Å molecular sieves in dioxane (1 ml) were heated for 24 h at 120 °C.

A wide range of functionalized olefins were also found to be compatible with this protocol (Table **3**). The substituents on the pyridine ring affected the yields dramatically; an electron-donating group such as the methyl group increased the yield slightly, while low yield was obtained with the bromo-substituted vinylpyridine derivative. We also observed that a pyridine with an internal olefin could be applied for this C–H sulfonylation reaction giving the product with 2:1 regioselectivity. On the basis of this result, we tested enamide compounds in this reaction using slightly modified conditions. It was observed that arylsulfonyl chlorides with electron-donating groups could afford the

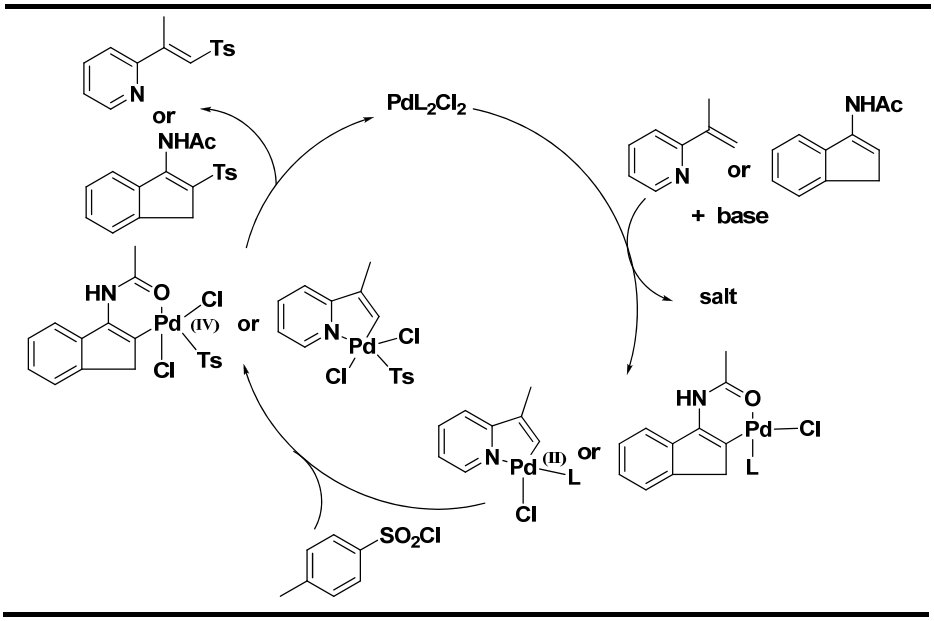
products in moderately high yields, while substrates with strong electron-withdrawing groups gave the product in moderate yield. The indanone-derived enamides were screened under the optimized conditions; substrates with electron-donating groups easily gave the products in good yields (Table **3**, **4g, 4h**), while only comparatively low yields were obtained for substrates with halide substituents (Table **3**. **4i**, **4k**). It was noted that the chromenone-derived enamide could also afford the desired product albeit in a rather low yield of 33% (Table **3**, **4j**).

Table **3**. Palladium-catalyzed sulfonylation of vinylpyridine derivatives and enamides.*



*Reaction conditions for vinylpyridine derivatives: vinyl pyridine **(**0.2 mmol) and sulfonyl chloride (0.3 mmol), $Pd(PhCN)_2Cl_2$ (10 mmol%), K_2CO_3 (0.1 mmol) and 50 mg 4Å molecular sieves in dioxane (1 ml) were heated for 24 h at 120 °C under O_2 (1 atm).
Reaction conditons for enamides: enamide **(**0.2 mmol) and sulfonyl chloride (0.3 mmol), $Pd(CH_3CN)_2Cl_2$ (10 mmol%), K_2CO_3 (0.1 mmol) and 50 mg 4Å molecular sieves in dioxane (1 ml) were heated for 24 h at 120 °C under O_2 (1 atm).

The proposed mechanism is shown in Scheme **3**. The vinylpalladium intermediate is generated by heteroatom-assisted chelation. Following an insertion into the SO_2-Cl bond, and a reductive elimination, the vinyl sulfone is obtained. The Pd(II) generated in situ is involved into next catalytic cycle.



Scheme **3** Proposed mechanism for sulfonylation of olefins

5.3 EXPERIMENTAL SECTION

All commercially obtained reagents for the cross-coupling reaction were used as received: anhydrous dioxane was obtained from Sigma-Aldrich and used as received. The starting materials of enamides and vinyl pyridines were prepared according to the reported references.[178] All cross-coupling reactions were run under 1 atm O_2 and no precautions taken to exclude moisture. Thin-layer chromatography (TLC) was conducted with Merck 60 F254 precoated silica gel plate (0.2 mm thickness) and visualized with UV and potassium permanganate staining, followed by heating on a hot plate. Flash chromatography was

[178] (a) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Che*m. *Soc*. **2006**, *128*, 11693-11712. (b) Nuñez, A.; Abarca, B.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem*. **2009**, *74*, 4166-4176.

performed using Merck silica gel 60 with distilled solvents. ^{1}H NMR spectra were performed on a Bruker Advance 300, 400 and 500 NMR spectrometer and are reported in ppm downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (*J* =7.26, singlet). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Advance 300 (75 MHz), Bruker Advance 400 (100 MHz) or Bruker Advance 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). Regioselectivity of the cross-coupling was determined by NMR analysis of the crude product. IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-Tof Permies Mass Spectrometer.

General procedures for direct cross-coupling reaction of *α*-methyl-vinyl pyridine with sulfonyl chlorides, method A:

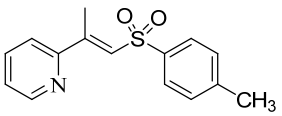
A 10 ml dried round bottom flask was charged sequentially with a stirring bar, $Pd(PhCN)_2Cl_2$ (0.02 mmol, 10 mol%), K_2CO_3 (0.5 equiv), *p*-toluene sulfonyl chloride (1.5 equiv) and 4 Å molecular sieve (30 mg). Dry dioxane (1 mL) and *α*-methyl-vinyl pyridine (0.2 mmol, 1 equiv) were added the mixture in sequence, and the resultant mixture was stirred at 120 ºC under 1 atm of oxygen (balloon pressure) for 24 hours. After cooling down, the mixture was diluted with ethyl acetate. After removing the organic solvent under reduced pressure,

the crude product was purified by silica gel flash column chromatography(EtOAc/Hexanes mixtures).

General procedures for direct cross-coupling reaction of enamides with sulfonyl chlorides, method B:

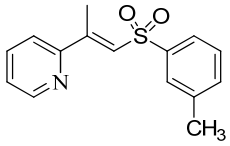
A 10 ml dried round bottom flask was charged sequentially with a stirring bar, enamide starting material (0.2 mmol, 1 equiv), $Pd(CH_3CN)_2Cl_2$ (0.02 mmol, 10 mol%), K_2CO_3 (0.5 equiv), *p*-toluene sulfonyl chloride (1.5 equiv) and 4 Å molecular sieve (30 mg). Dry dioxane (1 mL) was introduced into the mixture, and the resultant mixture was stirred at 120 ºC under 1 atm of oxygen (balloon pressure) for 24 hours. After cooling down, the mixture was diluted with ethyl acetate. After removing the organic solvent under reduced pressure, the crude product was purified by silica gel flash column chromatography (EtOAc/Hexanes mixtures).

Characterization Data for the vinyl sulfones :

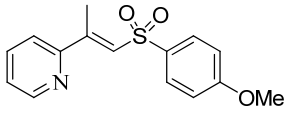


(*E*)-2-(1-tosylprop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 71%. mp = 98-99 °C; R_f = 0.35 (EA:Hexane = 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.23 Hz, 1H), 7.87 (d, *J* = 8.25 Hz, 2H), 7.68-7.74 (td, *J* = 7.77, 1.70, 1H), 7.50 (d, *J* = 7.95 Hz, 1H), 7.34 (d, *J* = 8.25 Hz, 2H), 7.25-7.29 (m, 2H), 2.59 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 149.6, 149.3, 144.2, 139.0, 136.8, 129.9, 129.8, 127.4, 124.1, 121.0, 21.5, 15.0; IR (film, cm^{-1}): 3020, 1597,

1581, 1568, 1465, 1431, 1311, 1301, 1215, 1145, 1085; HRMS m/z calculated for $C_{14}H_{13}O_2$ $[M+H]^+$: 213.2887 Found 213.2882.

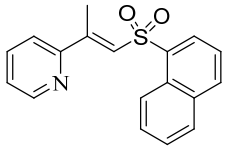


(*E*)-2-(1-(m-tolylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 67%. mp = 65-66 °C; R_f = 0.35 (EA:Hexane = 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57-8.60 (m, 2H), 7.77-7.80 (m, 2H), 7.69-7.74 (td, *J* = 7.76, 1.7 Hz, 1H), 7.50-7.53 (m, 1H), 7.41-7.43 (m, 2H), 7.25-7.30 (m, 2H), 2.60 (d, *J* = 1.23 Hz, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 149.9, 149.4, 141.7, 139.5, 136.9, 134.1, 129.8, 129.1, 127.7, 124.5, 124.2, 121.1, 21.3, 15.1; IR (film, cm^{-1}): 3020, 1610, 1581, 1566, 1465, 1431, 1313, 1300, 1215, 1139, 1083; HRMS m/z calculated for $C_{15}H_{16}NO_2S$ $[M+H]^+$: 274.0902 Found 274.0901.

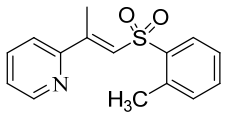


(*E*)-2-(1-(4-methoxyphenylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 61%. mp = 50-51 °C; R_f = 0.36 (EA:Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.52 Hz, 1H), 7.89 (d, *J* = 9.00 Hz, 2H), 7.70 (t, *J* = 7.84 Hz, 1H), 7.48 (d, *J* = 7.84 Hz, 1H), 7.23-7.26 (m, 2H), 6.98 (d, *J* = 9.00 Hz, 2H), 3.85 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 155.8, 149.3, 149.1, 136.9, 133.5, 130.2, 129.6, 124.2, 121.1, 55.7, 14.9; IR (film, cm^{-}

[1]): 3020, 1595, 1579, 1568, 1496, 1431, 1315, 1296, 1261, 1141, 1026; HRMS m/z calculated for $C_{15}H_{16}NO_3S$ $[M+H]^+$: 290.0851 Found 290.0849.

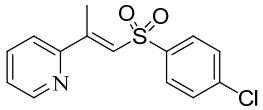


(*E*)-2-(1-(naphthalen-1-ylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 64%. mp = 102-104 °C; R_f = 0.33 (EA:Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.60 Hz, 1H), 8.53 (d, *J* = 4.60 Hz, 1H), 8.43 (d, *J* = 7.36 Hz, 1H), 8.09 (d, *J* = 8.24 Hz, 1H), 7.93 (d, *J* = 8.12 Hz, 1H), 7.55-7.69 (m, 4H), 7.45-7.47 (m, 2H), 7.21-7.26 (m, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 150.2, 149.4, 136.9, 136.8, 134.9, 134.2, 130.2, 129.2, 129.1, 128.7, 128.4, 126.9, 124.5, 124.3, 124.2, 121.0, 15.2; IR (film, cm^{-1}): 3018, 1618, 1581, 1564, 1508, 1465, 1431, 1305, 1215, 1155, 1124; HRMS m/z calculated for $C_{18}H_{16}NO_2S$ $[M+H]^+$: 310.0902 Found 310.0900.

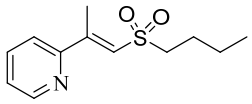


(*E*)-2-(1-(o-tolylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 60%. mp = 63-65 °C; R_f = 0.37 (EA:Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.16 Hz, 1H), 8.12 (d, *J* = 7.84 Hz, 1H), 7.71 (t, *J* = 7.74 Hz, 2H), 7.45-7.51 (dd, *J* = 8.00, 7.44 Hz, 2H), 7.36 (t, *J* = 7.60 Hz, 1H), 7.25-7.31 (m, 3H), 2.65 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 150.2, 149.4, 139.8, 137.9, 137.0, 133.3, 132.5, 129.5, 128.7, 126.3, 124.3, 121.0, 20.4,

15.1; IR (film, cm^{-1}): 3020, 1639, 1465, 1431, 1305, 1215, 1149, 1058; HRMS m/z calculated for $C_{15}H_{16}NO_2S$ $[M+H]^+$: 274.0902 Found 274.0901.

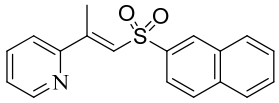


(*E*)-2-(1-(4-chlorophenylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 56%. mp = 65-67 °C; R_f = 0.30 (EA:Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.48 Hz, 1H), 7.91 (d, *J* = 8.52 Hz, 2H), 7.71 (td, *J* = 7.76, 1.40 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 3H), 7.26-7.29 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 150.6, 149.4, 140.4, 140.0, 137.0, 129.5, 129.2, 128.9, 124.5, 121.1, 15.1; IR (film, cm^{-1}): 3020, 1612, 1581, 1568, 1465, 1431, 1394, 1315, 1215, 1147, 1085, 1014; HRMS m/z calculated for $C_{14}H_{13}NO_2SCl$ $[M+H]^+$: 294.0356 Found 294.0350.

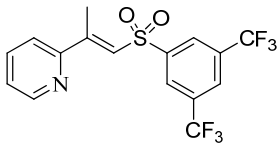


(*E*)-2-(1-(butylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a yellow oil. Yield = 25%. R_f = 0.4 (EA:Hexane = 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63-8.65 (m, 1H), 7.76 (td, *J* = 7.85, 1.80 Hz, 1H), 7.53-7.56 (m, 1H), 7.30-7.34 (m, 1H), 7.18-7.20 (m, 1H), 3.08-3.13 (m, 2H), 2.62 (d, *J* = 1.29 Hz, 3H), 1.81-1.91 (m, 2H), 1.42-1.55 (m, 2H), 0.96 (t, *J* = 7.19 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.4, 149.4, 137.0, 127.2, 124.4, 121.1, 55.7, 24.2, 21.7, 15.2, 13.5;

IR (film, cm^{-1}): 2962, 1618, 1581, 1568, 1465, 1431, 1298, 1128; HRMS m/z calculated for $C_{12}H_{18}NO_2S$ $[M+H]^+$: 240.1058 Found 240.1053.

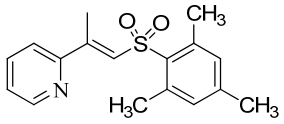


(*E*)-2-(1-(naphthalen-2-ylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 66%. mp = 75-77 °C; R_f = 0.33 (EA:Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55-8.56 (m, 2H), 7.88-7.98 (m, 4H), 7.58-7.71 (m, 3H), 7.49 (d, *J* = 7.92 Hz, 1H), 7.37 (s, 1H), 7.23-7.26 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 150.2, 149.4, 138.7, 136.9, 135.1, 132.2, 129.6, 129.6, 129.4, 129.1, 128.8, 127.9, 127.6, 124.3, 122.4, 121.1, 15.1; IR (film, cm^{-1}): 3018, 1618, 1581, 1568, 1465, 1431, 1309, 1215, 1145, 1126, 1070; HRMS m/z calculated for $C_{18}H_{16}NO_2S$ $[M+H]^+$: 310.0902 Found 310.0896.

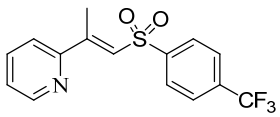


(*E*)-2-(1-(3,5-bis(trifluoromethyl)phenylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 70%. mp = 98-100 °C; R_f = 0.31 (EA:Hexane = 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60-8.62 (m, 1H), 8.43 (s, 2H), 8.11 (s, 1H), 7.76 (td, *J* = 7.80, 1.80 Hz, 1H), 7.55-7.58 (m, 1H), 7.30-7.37 (m, 2H), 2.66 (d, *J* = 1.23 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 152.5, 149.5, 144.6, 137.1, 133. 4, 132.9, 127.8 (m), 127.6, 126.9 (m), 124.5 (d, *J* = 52.03 Hz), 120.9 (d, *J* = 60.46 Hz), 15.21; IR (film, cm^{-1}): 3018, 1612, 1581, 1568, 1433, 1359, 1330,

1313, 1280, 1215, 1186, 1149, 1107; HRMS m/z calculated for $C_{16}H_{12}NO_2SF_6$ $[M+H]^+$: 396.0493 Found 396.0493.

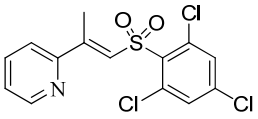


(*E*)-2-(1-(mesitylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 59%. mp = 120-122 °C; R_f = 0.35 (EA:Hexane = 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57-8.59 (m, 1H), 7.69-7.74 (td, *J* = 7.80, 1.93 Hz, 1H), 7.50 (d, *J* = 7.95 Hz, 1H), 7.32-7.34 (m, 1H), 7.24-7.29 (m, 1H), 6.94 (s, 2H), 2.69, (s, 3H), 2.49 (d, *J* = 1.23 Hz, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 149.4, 147.9, 142.9, 139.4, 136.9, 135.5, 132.1, 131.9, 124.1, 120.9, 22.6, 21.0, 14.9; IR (film, cm^{-1}): 3018, 1602, 1581, 1566, 1465, 1431, 1301, 1215, 1134, 1053; HRMS m/z calculated for $C_{17}H_{20}NO_2S$ $[M+H]^+$: 302.1215 Found 302.1218.

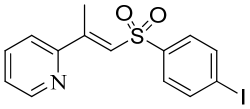


(*E*)-2-(1-(4-(trifluoromethyl)phenylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 65%. mp = 67-69 °C; R_f = 0.32 (EA:Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55-8.59 (m, 1H), 8.12 (d, *J* = 8.16 Hz, 2H), 7.81 (d, *J* = 8.16 Hz, 2H), 7.73 (t, *J* = 8.60 Hz, 1H), 7.52 (d, *J* = 7.92 Hz, 1H), 7.25-7.32 (m, 2H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 151.5, 149.5, 145.4, 137.0, 134.9 (q, *J* = 33.07 Hz), 128.6, 128.0, 126.4 (q, *J* = 3.39 Hz),

124.5 (d, *J* = 9.07 Hz), 121.5 (d, *J* = 59.06 Hz), 15.1; IR (film, cm^{-1}): 3024, 1606, 1581, 1566, 1465, 1433, 1404, 1321, 1215, 1172, 1149, 1085, 1062, 1016; HRMS m/z calculated for $C_{15}H_{13}NO_2SF_3$ $[M+H]^+$: 328.0619 Found 328.0618.

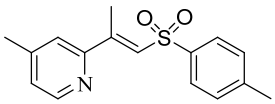


(*E*)-2-(1-(2,4,6-trichlorophenylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 61%. mp = 122-124 °C; R_f = 0.28 (EA:Hexane = 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61-8.63 (m, 1H), 7.72-7.78 (td, *J* = 7.77, 1.80 Hz, 1H), 7.53-7.56 (m, 1H), 7.50-7.52 (m, 1H), 7.47 (s, 2H), 7.29-7.33 (m, 1H), 2.51 (d, *J* = 1.20 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 151.7, 149.6, 138.9, 137.0, 136.5, 135.2, 131.3, 130.1, 124.6, 121.2, 15.4; IR (film, cm^{-1}): 3020, 1581, 1562, 1537, 1431, 1363, 1328, 1215, 1159, 1136; HRMS m/z calculated for $C_{14}H_{11}NO_2SCl_3$ $[M+H]^+$: 361.9576 Found 361.9579.

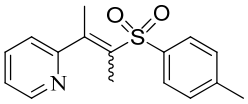


(*E*)-2-(1-(4-iodophenylsulfonyl)prop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 59%. mp = 97-99 °C; R_f = 0.30 (EA:Hexane = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56-8.61 (m, 1H), 7.90 (d, *J* = 8.40 Hz, 2H), 7.68-7.74 (m, 3H), 7.51 (d, *J* = 7.92 Hz, 1H), 7.25-7.30 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 152.9, 133.4, 133.0, 131.5, 128.4, 128.4, 127.6, 126.6, 126.5, 124.0, 122.6, 102.7, 21.0; IR (film, cm^{-1}): 3018, 1612, 1581, 1568, 1467, 1431, 1384,

1315, 1215, 1147, 1082, 1055, 1006; HRMS m/z calculated for $C_{14}H_{13}NO_2SI$ $[M+H]^+$: 385.9712 Found 385.9716.

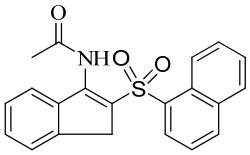


(*E*)-4-methyl-2-(1-tosylprop-1-en-2-yl)pyridine. This compound was prepared by the general procedure **A** and was obtained as a white solid. Yield = 57%. mp = 61-63 °C; R_f = 0.35 (EA:Hexane = 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.89 Hz, 1H), 7.84 (d, *J* = 8.22 Hz, 2H), 7.33 (s, 1H), 7.30 (s, 2H), 7.21 (m, 1H), 7.07 (d, *J* = 4.77 Hz, 1H), 2.57 (s, 3H), 2.41 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 150.0, 149.1, 148.1, 144.2, 139.1, 129.8, 127.4, 125.1, 122.1, 21.5, 21.1, 15.1; IR (film, cm^{-1}): 3020, 1597, 1444, 1379, 1311, 1301, 1215, 1145, 1085; HRMS m/z calculated for $C_{16}H_{18}NO_2S$ $[M+H]^+$: 288.1058 Found 288.1056.

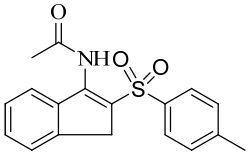


2-(3-tosylbut-2-en-2-yl)pyridine. The mixture was prepared by the general procedure **A.** The *trans*-isomer was obtained as a white solid (*trans*-isomer) and a yellow oil (*cis*-isomer). Yield (mixture)= 45%. mp = 80-81 °C (*trans*-isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.36 Hz, 1H), 7.83 (d, *J* = 8.00 Hz, 2H), 7.70 (t, *J* = 7.52 Hz, 1H), 7.34 (d, *J* = 8.00 Hz, 2H), 7.15-7.23 (m, 2H), 2.52 (s, 3H), 2.44 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 149.6, 147.5, 144.1, 138.1, 136.6, 135.6, 129.8, 127.4, 122.6, 122.5, 21.6, 20.9, 17.3; *cis*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.32 Hz, 1H), 7.64-7.70 (m, 3H), 7.32 (d, *J* = 7.84 Hz, 1H), 7.19-7.26 (m, 3H), 2.39 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 148.7, 146.6, 143.7,

137.3, 135.7, 134.2, 129.5, 128.0, 123.5, 122.2, 23.5, 21.5, 15.3; IR (film, cm^{-1}): 3018, 1587, 1467, 1429, 1301, 1288, 1215, 1161, 1132, 1080; HRMS m/z calculated for $C_{16}H_{18}NO_2S$ $[M+H]^+$: 288.1058 Found 288.1057.

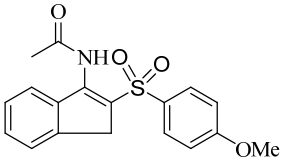


N-(2-(naphthalen-1-ylsulfonyl)-1*H*-inden-3-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 61%. mp = 188-189 °C; R_f = 0.31 (EA:Hexane = 2:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.61-8.35 (dd, *J* = 7.40, 1.08 Hz, 1H), 8.07 (d, *J* = 8.24 Hz, 1H), 7.90 (d, *J* = 7.84 Hz, 1H), 7.81-7.83 (m, 1H), 7.52-7.63 (m, 3H), 7.25-7.30 (s, 3H), 3.48 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 147.4, 142.3, 137.5, 135.7, 135.3, 134.2, 129.2, 128.9, 128.6, 128.6, 127.1, 126.9, 126.4, 124.4, 123.9, 123.5, 121.3, 36.5, 24.4; IR (film, cm^{-1}): 3018, 1710, 1612, 1595, 1566, 1506, 1371, 1357, 1296, 1215, 1153, 1124, 1109; HRMS m/z calculated for $C_{21}H_{17}NO_3SNa$ $[M+Na]^+$: 386.0827 Found 386.0828.

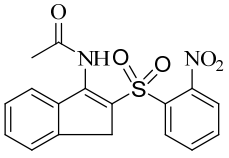


N-(2-tosyl-1*H*-inden-3-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 53%. mp = 173-174 °C; R_f = 0.33 (EA:Hexane = 2:3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.83-7.86 (m, 1H), 7.80-7.82 (m, 1H), 7.77-7.79 (m, 1H), 7.30-7.35 (m, 5H), 3.57 (s, 2H), 2.41 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

168.3, 146.8, 144.7, 142.4, 138.2, 137.5, 130.0, 128.8, 126.9, 126.5, 123.9, 121.4, 36.2, 24.4, 21.5; IR (film, cm^{-1}): 3018, 1708, 1612, 1597, 1568, 1371, 1359, 1298, 1215, 1145, 1076; HRMS m/z calculated for $C_{18}H_{17}NO_3SNa$ $[M+Na]^+$: 350.0827 Found 350.0826.

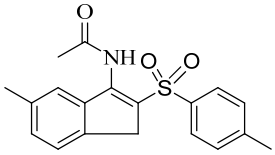


N-(2-(4-methoxyphenylsulfonyl)-1*H*-inden-3-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 68%. mp = 165-167 °C; R_f = 0.35 (EA:Hexane = 2:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.79-7.81 (m, 3H), 7.31-7.33 (m, 3H), 6.94-6.96 (m, 2H), 3.81 (s, 3H), 3.53 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 163.7, 146.2, 142.3, 137.5, 132.6, 129.2, 128.8, 126.9, 126.4, 123.9, 122.0, 114.7, 55.7, 36.2, 24.4; IR (film, cm^{-1}): 3018, 1708, 1612, 1595, 1568, 1496, 1371, 1359, 1294, 1261, 1215, 1143, 1118; HRMS m/z calculated for $C_{18}H_{17}NO_4SNa$ $[M+Na]^+$: 366.0776 Found 366.0779.

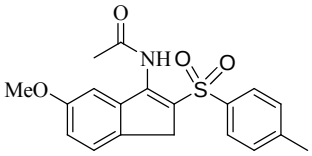


N-(2-(2-nitrophenylsulfonyl)-1*H*-inden-3-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 49%. mp = 166-167 °C; R_f = 0.30 (EA:Hexane = 2:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.20-8.24 (m, 1H), 7.89-7.93 (m, 1H), 7.73-7.79 (m, 3H), 7.32-7.36 (m, 3H), 3.62 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

169.1, 152.9, 133.4, 133.0, 131.5, 128.4, 128.4, 127.6, 126.6, 126.5, 124.0, 122.6, 102.7, 21.0; IR (film, cm^{-1}): 2945, 2833, 1654, 1448, 1417, 1217, 1112, 1029; HRMS m/z calculated for $C_{17}H_{14}N_2O_5SNa$ $[M+Na]^+$: 381.0521 Found 381.0519.

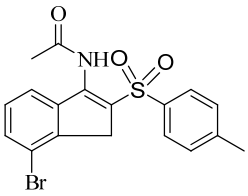


N-(5-methyl-2-tosyl-1*H*-inden-3-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 53%. mp = 187-189 °C; R_f = 0.30 (EA:Hexane = 2:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.74 (d, *J* = 8.08 Hz, 2H), 7.61 (s, 1H), 7.28 (d, *J* = 8.08 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 1H), 7.12 (d, *J* = 7.72 Hz, 1H), 3.49 (s, 2H), 2.38 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 146.8, 144.6, 139.6, 138.2, 137.6, 136.7, 130.0, 129.9, 126.9, 126.6, 123.6, 121.7, 35.8, 24.4, 21.5, 21.5; IR (film, cm^{-1}): 2252, 1707, 1595, 1571, 1350, 1298, 1215, 1141; HRMS m/z calculated for $C_{19}H_{19}NO_3SNa$ $[M+Na]^+$: 364.0983 Found 364.0983.

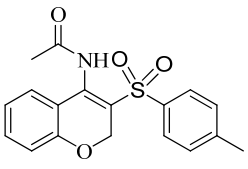


N-(5-methoxy-2-tosyl-1*H*-inden-3-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 63%. mp = 157-159 °C; R_f = 0.30 (EA:Hexane = 2:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.74 (d, *J* = 8.08 Hz, 2H), 7.38-7.39 (m, 1H), 7.28 (d, *J* = 8.08 Hz, 1H), 7.20 (d, *J* = 8.32 Hz, 1H), 6.87-6.90 (m, 1H), 3.78 (s, 3H), 3.47

(s, 2H), 2.38 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 158.8, 146.7, 144.7, 138.6, 138.1, 134.8, 130.1, 126.9, 124.4, 122.4, 116.8, 110.5, 55.6, 35.5, 24.5, 21.6; IR (film, cm^{-1}): 3018, 2945, 2835, 1708, 1595, 1571, 1474, 1350, 1288, 1215, 1026; HRMS m/z calculated for $C_{19}H_{19}NO_4SNa$ $[M+Na]^+$: 380.0932 Found 380.0939.

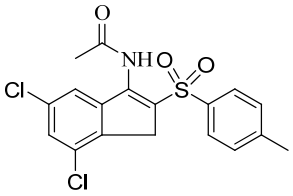


N-(7-bromo-2-tosyl-1*H*-inden-3-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 40%. mp = 204-206 °C; R_f = 0.30 (EA:Hexane = 2:3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.82 (d, *J* = 8.08 Hz, 2H), 7.81 (s, 1H), 7.50 (d, *J* = 7.88 Hz, 1H), 7.36 (d, *J* = 8.08 Hz, 2H), 7.23-7.28 (m, 1H), 3.55 (s, 2H), 2.45 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 146.0, 145.0, 142.3, 138.9, 137.7, 131.8, 130.2, 128.7, 127.0, 125.6, 122.3, 118.6, 37.7, 24.3, 21.6; IR (film, cm^{-1}): 3018, 2399, 1712, 1606, 1589, 1475, 1371, 1357, 1215, 1141; HRMS m/z calculated for $C_{18}H_{16}NO_3SBrNa$ $[M+Na]^+$: 427.9932 Found 427.9931.



N-(3-tosyl-2*H*-chromen-4-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 33%. mp = 172-174 °C; R_f = 0.31 (EA:Hexane = 3:2).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.77 (d, *J* = 8.08 Hz, 2H), 7.30-7.35 (m, 2H), 7.26 (d, *J* = 8.08 Hz, 2H),

6.93-6.99 (m, 1H), 6.87 (d, *J* = 7.43 Hz, 1H), 4.84 (s, 2H), 2.43 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 156.0, 145.3, 139.9, 137.6, 132.8, 130.2, 127.3, 126.9, 121.7, 118.7, 117.1, 63.7, 24.1, 21.6; IR (film, cm^{-1}): 3018, 1670, 1618, 1477, 1369, 1301, 1215, 1138, 1016; HRMS m/z calculated for $C_{18}H_{17}NO_4SNa$ $[M+Na]^+$: 366.0776 Found 366.0780.



N-(5,7-dichloro-2-tosyl-1*H*-inden-3-yl)acetamide. This compound was prepared by the general procedure **B** and was obtained as a white solid. Yield = 51%. mp = 214-215 °C; R_f = 0.28 (EA:Hexane = 2:3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.77-7.80 (m, 3H), 7.34-7.36 (m, 3H), 3.53 (s, 2H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 152.9, 133.4, 133.0, 131.5, 128.4, 128.4, 127.6, 126.6, 126.5, 124.0, 122.6, 102.7, 21.0; IR (film, cm^{-1}): 3016, 2945, 2833, 1681, 1591, 1560, 1338, 1215, 1141, 1026; HRMS m/z calculated for $C_{18}H_{15}NO_3SCl_2Na$ $[M+Na]^+$: 418.0047 Found 418.0049.