CARBON–CARBON BOND FORMATION REACTIONS

PART I : CLASSICAL ALDOL REACTION

PART II : CONTEMPORARY C–H BOND ACTIVATION/FUNCTIONALIZATION

CHOK YEW KEONG

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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(On the Spine)

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CHOK YEW KEONG

School of Physical and Mathematical sciences

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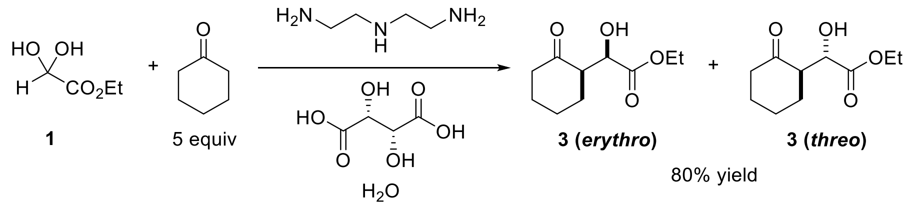
SUMMARY

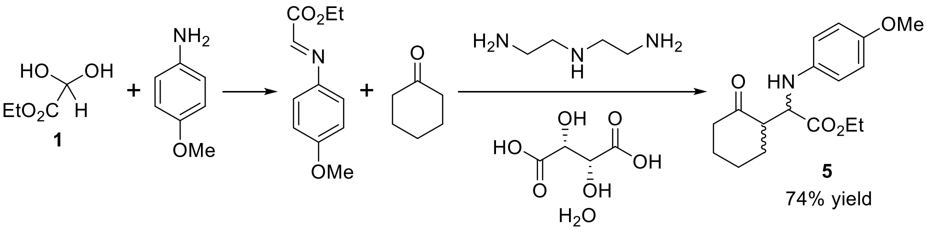
Since the serendipitous synthesis of urea by Frederich Wöhler in 1828, which marked the birth of organic synthesis, this craft had been perfected by synthetic chemistry to such an extent where not only can such biomacromolecules as proteins and genes be manipulated and assembled *in vitro* at will, but also natural products of seemingly boundless complexity and intrigue can be synthesized in the laboratory following logical approaches from readily available starting materials.

Nevertheless, regardless of how elaborated contemporary organic synthesis may look, deep down at its core, it is still business as usual, where the forging of carbon–carbon bonds take centre stage. Assembly of the carbon skeletal framework of even a seemingly simple organic compound represents a critical component of its synthesis, and is not simply a task of piecing together the correct number of carbon atoms.

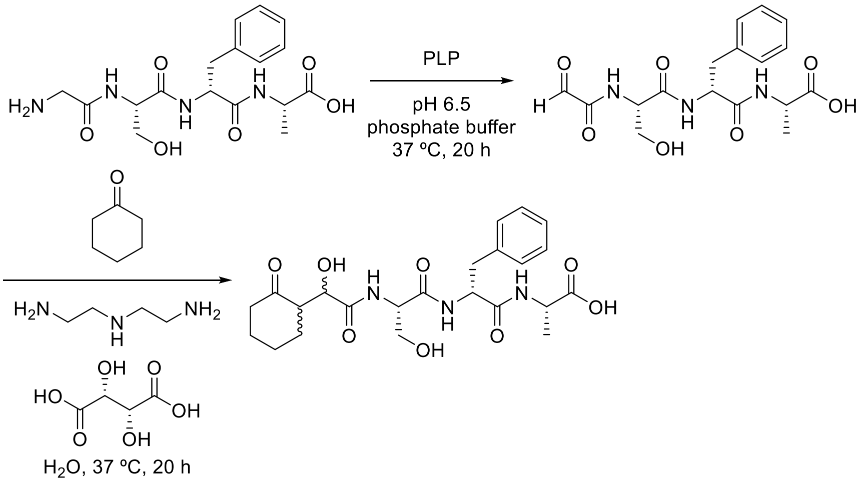
Organic chemists are blessed to have experienced a supernova of novel and robust organic reactions and reagents, which opens up an innumerable number of carbon–carbon bond-forming reactions. Examples include the variety of organometallic reagents, aldol reaction, Wittig reaction, Diels-Alder reaction, the huge class of palladium-catalyzed carbon–carbon bond-forming reactions, olefin metathesis, and the list goes on. Herein, we will explore the chemistry of two carbon–carbon bond forming reactions, one classical – the aldol reaction involving the use of organocatalysts, and the second a contemporary rendition of palladium-catalyzed reactions involving C–H bond activation and functionalization.



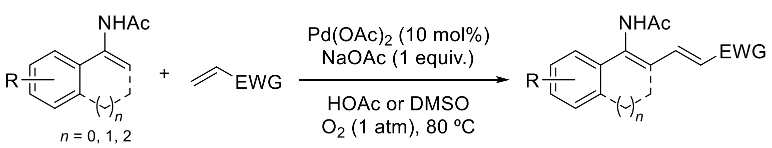
We managed to develop a simple organocatalytic system, consisting of diethylenetriamine and tartaric acid (40 mol%), to effect the ketone aldol addition to aldehyde in water. The system is amenable to catalysing the one-pot Mannich reaction of aromatic amines in water as well :



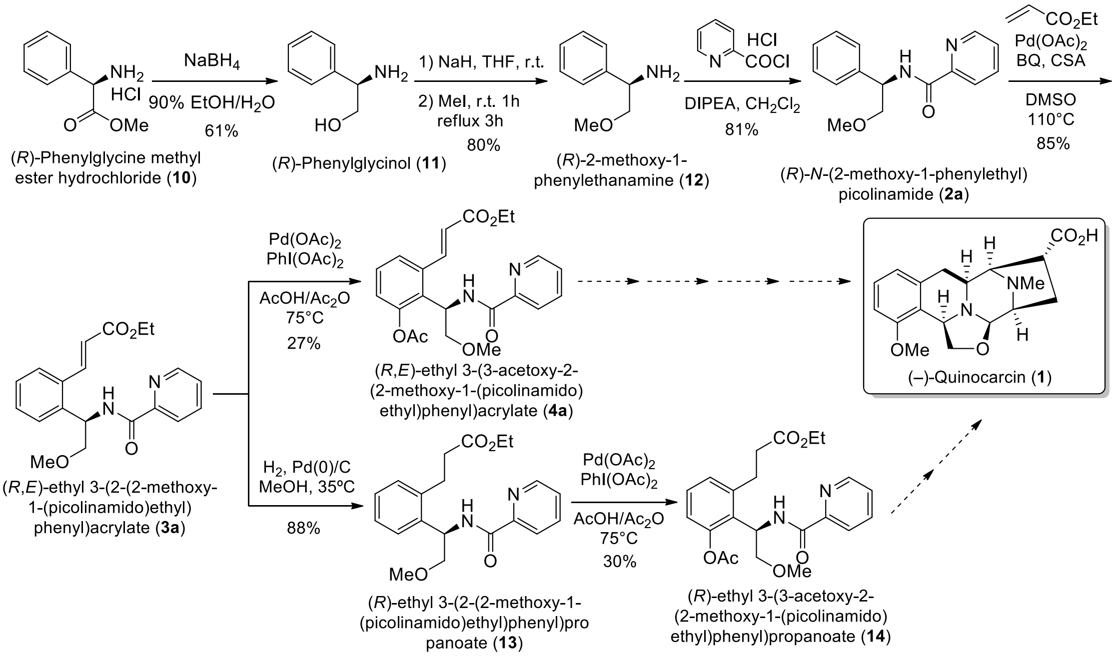
and subsequently successfully applied to effect the ketone aldol reaction of *N*-terminally modified tetrapeptides :



This serves as a plausible model for subsequent application to *N*-terminally modified proteins, to effect conjugation.



Next, we also successful developed the first olefination of enamides at the β-position with electron-deficient alkenes catalyzed by $Pd(OAc)_2$ and 1 atm oxygen as the sole oxidant. The reaction proceeded smoothly to provide products in moderate to high yields and with excellent β-regioselectivities. An in-depth study of the mechanism was also undertaken by means of ^{1}H NMR spectroscopic analysis. This novel method generates highly functionalized, versatile compounds which holds potential for organic synthesis.



Our synthetic study of (–)-quinocarcin commenced with the synthesis of (*R*)-phenylglycinol (**11**) which is then *O*-methyl protected and finally amidated to furnish picolinamide **2a**, the substrate for our next stage of exploration – ligand-directed aryl C–H activation. The synthesis of **2a** in good yields and reproducibility enable us to easily advance to the C–H functionalization stage. Building upon our group's previous unpublished work, acrylation was tested and optimized to give satisfactory results.

Subsequent acetoxylation, however, does not proceed as smoothly as we had expected, suffering from severe undesired competing side reactions. Suspecting that the carbon–carbon double bond interferes with the reaction, we attempted reduction of the double bond prior to acetoxylation. Indeed, very slightly higher yield was achieved, but more importantly, much cleaner product was obtained, which tallies with our hypothesis that the double bond affect the reaction in an undesirable manner. Therefore, moving forward, new solutions to circumvent this problem have to be thought out.

ABBREVIATION

Ac	acetyl
aq	aqueous
atm	atmospheric pressure
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BQ	benzoquinone
br s	broad singlet
°C	degree centigrade
c	concentration (10 mg/mL)
calcd	calculated
cm^{-1}	wavenumber
d	doublet
dd	doublets of doublet
ddd	doublets of doublets of doublet
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublets of triplet
EA	ethyl acetate
ee	enantiomeric excess
EI	electron impact ionization
equiv.	Mole equivalent
Et	ethyl
FTIR	Fourier transformation infrared spectrum
g	Ggram
h	hour
H	hydrogen
Hex	hexane
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i-Pr	isopropyl
LC-MS	liquid chromatography-mass spectrometry
M	molar
m	multiplet

m/*z*	mass to charge ratio
M^+	parent ion peak (mass spectrum)
Me	methyl
MHz	megahertz
min	minute
mL	millilitres
mmol	millimoles
mol	moles
mol%	molar percent
MS	mass spectrum
MS4Å	molecule sieve 4Å
n-Bu	*n*-Butyl
NMR	nuclear magnetic resonance
OTf	trifluoromethane sulfonate
p	para
Ph	phenyl
ppm	part per million
q	quartet
r.t	room temperature
R_f	retention factor
s	singlet
t	triplet
t-Bu	*tert*-Butyl
tert	tertiary
tt	triplets of triplet
TfOH	triflic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
δ	chemical shift

CHAPTER 1

Formation of Carbon–Carbon Bond

CHAPTER 1 FORMATION OF CARBON–CARBON BOND

1.1 ORGANIC SYNTHESIS

In the words of two-times Nobel Laureate, Linus Pauling, "*chemistry is the science substance – their structure, their properties, and the reactions that change them into other substances*."[1] Hence, it came as no surprise that chemistry, being the science of substance, is also known as the "central science" since it serves to connect such other natural sciences as physics and biology,[2] by providing man with an arsenal of ways to fabricate molecules from other less, or sometimes more complex, molecules. Chemical synthesis, "the construction of complex chemical compounds from simpler ones"[3], is of upmost importance to the welfare of human beings, for it makes available to us many of the substances vital to everyday life.

Organic chemistry, one of the major branches of chemistry, is concerned with "the study of the structure, properties, composition, reactions, and preparation of carbon-containing compounds, which include not only hydrocarbons but also compounds with any number of other elements, such as hydrogen (most compounds contain at least one carbon–hydrogen bond), nitrogen, oxygen, halogens, phosphorus, silicon, and sulphur".[4] The history of organic chemistry can be traced back to antiquity when medicine men extracted chemicals from natural resources to treat their tribe. Science, let alone chemistry, is still unheard of then and these medicine men simply kept

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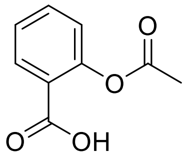
[1] Pauling. L. *General Chemistry*; Dover Publications Inc.: New York. 1970; pp 1.

[2] (a) Brown, T. L.; Lemay, H. E.; Bursten, B. E.; Murphy, C. J.; Woodward, P. M. *Chemistry: The Central Science*, 12th ed.; Pearson Prentice Hall: USA, 2012; pp 5–6. (b) Reinhardt, C. *Chemical Sciences in the 20th Century: Bridging Boundaries*; Wiley-VCH: Germany, 2001; pp 1–2.

[3] Encyclopedia Britannica, chemical synthesis. http://global.britannica.com/EBchecked/topic/108907/chemical-synthesis (accessed Jan 17, 2015).

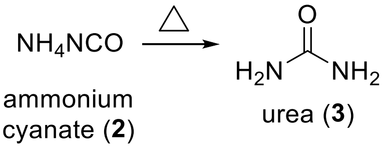
[4] American Chemical Society, Careers, College to Career, Areas of Chemistry, Organic Chemistry. http://www.acs.org/content/acs/en/careers/college-to-career/areas-of-chemistry/organic-chemistry.html (accessed Jan 17, 2015).

records of the beneficial properties of things like willow bark which was used as an analgesic (Now we know that willow bark contains acetylsalicylic acid (**1**), the active ingredient in aspirin, and chewing on the bark leaches the aspirin).


acetylsalicylic acid (**1**)

It was not until the early 1800's that organic chemistry was made a branch of modern chemistry by Jon Jacob Berzelius. Chemical compounds were classified by Berzelius into two main groups: those with origin from living or once-living matter were termed organic, while those that originate from "mineral" or non-living matter were termed inorganic. Similar to most chemists of that era, he believed that organic compounds could only come from living organisms mediated by some vital force, known as Vitalism.[5]

In 1828, Frederich Wöhler, ironically a student of Berzelius, serendipitously demonstrated for the very first time, that an organic compound can be synthesised from an inorganic source, which eventually led to the rejection of Vitalism as a scientific theory. While heating to dry a sample of ammonium cyanate (**2**), an inorganic salt he was preparing, Wöhler accidentally obtained the organic compound, urea (**3**), instead (Scheme **1**)!



Scheme **1**. Wöhler's synthesis of urea from ammonium cyanate

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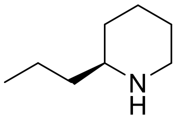
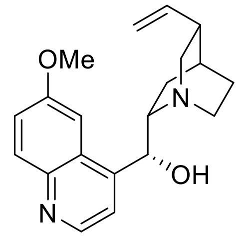
[5] Bechtel, W.; Richardson, R. C. Vitalism. In *Routledge Encyclopedia of Philosophy*; Craig, E., Ed.; London: Routledge, 1998.

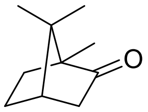
This transformation also signified the birth of organic synthesis, a sub-discipline of chemical synthesis, which is primarily involved in the construction of substances, both man-made and naturally occurring, where carbon is the main constituent element. The development of practical experimental techniques and the isolation of such natural products as coniine (**4**), quinine (**5**), camphor (**6**), morphine (**7**), tropinone (**8**) and strychnine (**9**) during the transition from the 18th to 19th century, paved the path and set the stage for the rise of organic synthesis.[6]



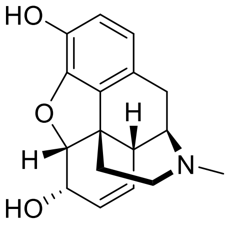
coniine (**4**)



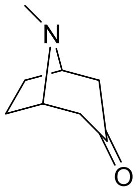
quinine (**5**)



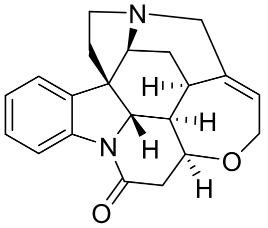
camphor (**6**)



morphine (**7**)



tropinone (**8**)



strychnine (**9**)

In fact, at that time, Sir Robert Robinson whom determined the structure of strychnine (**9**) commented that it is the most complex organic substance known for its molecular size.[7] Hence, the total synthesis of which by Robert Burns Woodward[8] in 1954 was and is still considered a major feat in organic synthesis.

---

[6] Nicolaou, K. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 131–146.

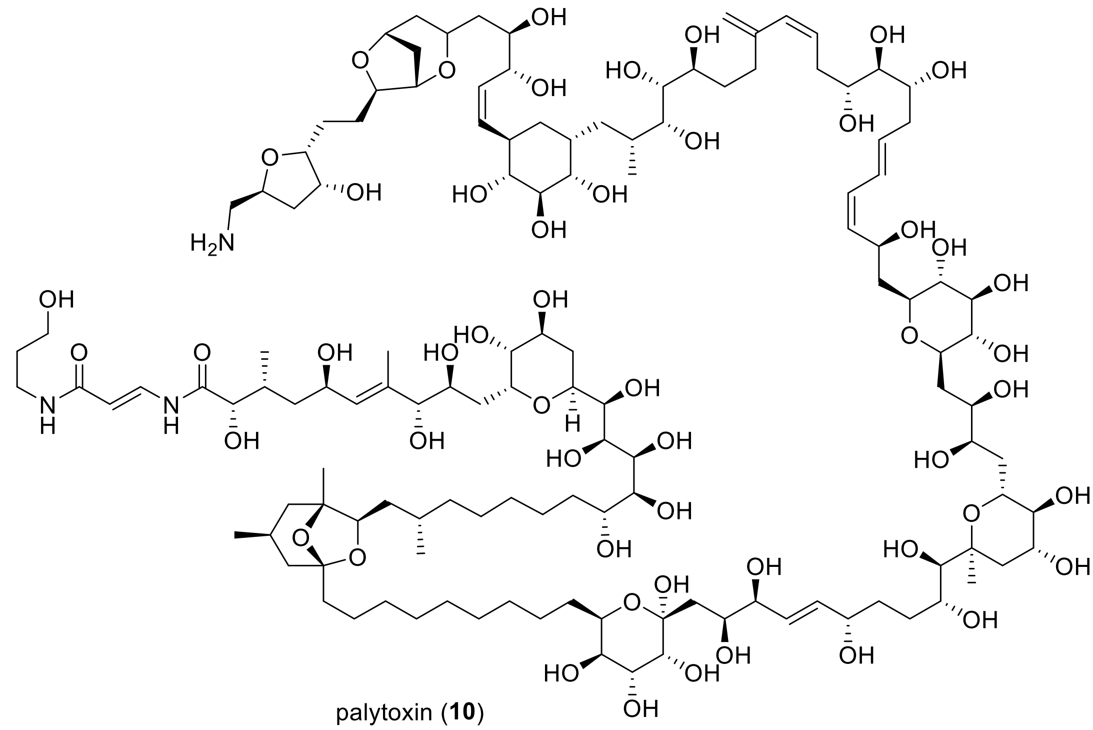
[7] Robinson, R. *Prog. Org. Chem.* **1952**, *1*, 2.

[8] Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247–288.

1.2 THE CARBON-CARBON BOND

With its humble beginning in the 1800s, organic synthesis can still be considered a juvenile science. However, since the synthesis of urea by Wöhler, the craft of organic synthesis had been perfected by synthetic chemists to such a stage where not only can proteins and genes be assembled *in vitro* at will, but also natural products of seemingly boundless complexity and intrigue can be synthesized in the laboratory following logical approaches from readily available starting materials.

The total synthesis of palytoxin (**10**), one of the most gigantic natural products isolated from marine organisms and also among the most poisonous substances known which is a non-peptide, by Yoshito Kishi's group[9] some twenty years ago, is one testimony to the prowess of contemporary organic synthesis.



palytoxin (**10**)

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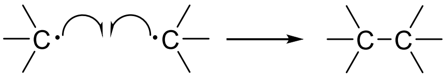
[9] Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.-i.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7530. Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11205.

With such impressive arsenals at the disposal of contemporary organic synthetic chemists, to execute the concise and efficient stereocontrolled synthesis of complex molecules, it is also possible to synthesize almost any arbitrary organic architecture thought-up to be tested for an assortment of real-life applications, ranging from biomedical trackers and pharmaceutical leads to valuable materials for use in the cosmetics and information technological industries.

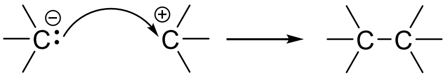
However, except for the formation of some simple organic molecules containing up to six or seven carbon atoms, where functional group interconversions involving commercially available starting material suffices; by and large, assembly of the carbon skeleton of even a seemingly simple organic compound represents a crucial component of its synthesis, and is not simply a task of piecing together the correct number of carbon atoms! In other words, the crux of a synthesis lies in our ability to suitably connect all the structural fragments together *via* formation of carbon–carbon bonds. This process is in fact guided by the position of functional groups in the target molecule.

A carbon–carbon bond can be viewed simply as the sharing of one pair of electrons between two carbon atoms. There are two ways in which this bond may be envisaged to form:

1. Each carbon atom contributes one electron to the bond.



2. One of the carbon atom provides both electrons to the bond.



The first process is a radical reaction, while the second process is the more usual reaction between a nucleophile and an electrophile taken to the extreme. The position of functional groups in the molecule of interest will determine which carbon atom is likely to assume the role of a radical, nucleophile or electrophile, and hence suggest plausible fragments to be constructed and pieced together to form the carbon skeleton.

This idea forms the basis of the principles of retrosynthetic analysis, first published by Elias James Corey in 1961,[10] in which he laid out a systematic and rational approach to designing a synthesis for organic molecules, for which he received the Nobel Prize for Chemistry in 1990.[11]

The foundation of organic synthesis is set in the myriad of chemical transformations and synthetic approaches. Despite the rarity of such tools in the 1900s, it is lucky that chemistry has seen a supernova of novel and robust organic reactions and reagents, which opens up an innumerable number of carbon–carbon bond-forming reactions. Examples include the variety of organometallic reagents such as Grignard reagents and Gilman reagents, the aldol reaction between carbonyl compounds involving enolates, the Wittig reaction between carbonyl compounds and phosphorus ylides to forge carbon–carbon double bonds, the Diels-Alder reaction involving the combination of dienes with dienophiles to construct cyclohexene ring systems propagated by steroid synthesis, the huge class of palladium-catalyzed carbon–carbon bond-forming reactions such as Heck, Suzuki and Stille coupling, and olefin metathesis, not forgetting the array of formidable radical-based processes.

In the following chapters, we will explore the chemistry of two carbon–carbon bond forming reactions, one classical – the aldol reaction involving the use of organocatalysts, and the second a contemporary rendition of palladium-catalyzed reactions involving C–H bond activation and functionalization.

---

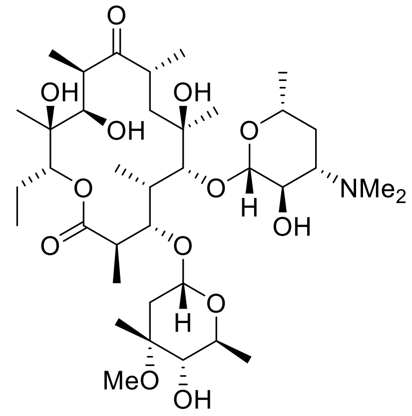
[10] Corey, E. J.; Ohno, M.; Vatakenchery, P. A.; Mitra, R. B. *J. Am. Chem. Soc*. **1961**, *83*, 1251.

[11] The Nobel Prize in Chemistry 1990. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1990/ (accessed 17 Jan 2015).

1.3 ALDOL REACTION MEDIATED BY ORGANOCATALYSTS

The aldol reaction is among the pioneer organic reactions first described by Kane in 1838.[12] However, it remained essentially underdeveloped for use in organic synthesis, not until challenges accompanying the construction of macrolides, which are characterized by the presence of a large (usually 14-, 15- or 16-membered) macrocyclic lactone ring, provided the impetus for the realization of the full potential of the aldol reaction, borrowing from Nature's armoury for the biosynthesis of such polyketides. This possibly inspired, in part, Woodward's lament on the "hopelessly complex" architecture of erythromycin-A (**11**):[13]

> "Erythromycin, with all of our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers."



Erythromycin-A (**11**)

1.3.1 ALDOL REACTION

In the classical aldol reaction, an enolizable carbonyl compound (either an aldehyde or a ketone) reacts with another carbonyl compound, in which the enolizable

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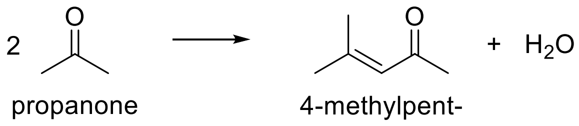
[12] (a) Kane, R. *Ann. Phys. Chem., Ser. 2* **1838**, *44*, 475. (b) Kane, R. *J. Prakt. Chem.* **1838**, *15*, 129.

[13] Woodward, R. B. Synthesis. In *Perspectives in Organic Chemistry*; Todd, A. Ed.; Wiley-Interscience, New York, 1956; pp 160.

carbonyl compound, functioning as the nucleophile, must possess at least one acidic α-hydrogen. In the original meaning of the term "aldol reaction", the substrates are constraint to aldehydes and ketones only, which may or may not be identical. The same term, in contemporary context, can be applied to *any* enolizable compounds, including carboxylic acid derivatives such as carboxylic esters and amides, which reacts with electrophilic aldehydes or ketones.

The first-formed products are β-hydroxycarbonyl compounds, which may undergo further elimination under the reaction conditions to furnish α,β-unsaturated carbonyl compounds in what is termed as "aldol condensation". The "classical" aldol reaction is reversible and takes place under thermodynamic control,[14] catalyzed by either acids or bases. On the other hand, the "modern" aldol reactions is based on the irreversible pre-formation of enolates which are then added to the carbonyl substrates. Regardless, the aldol reaction has proven to be one of the most dependable methods for formation of carbon–carbon bond, yielding either 1,3-dioxyenated carbon chains, or alkenes *via* an addition-elimination sequence.

Kane was the first to observe the formation of 4-methylpent-3-en-2-one (**12**) in the acid-catalyzed self-condensation of propanone (Scheme **2**).[12(b)]



Scheme **2**. Acid-catalyzed self-condensation of propanone

Wurtz was the first to realize that the product resulting from the acid-catalyzed self-reaction of ethanal contains both an aldehyde and an alcohol functionality (Scheme

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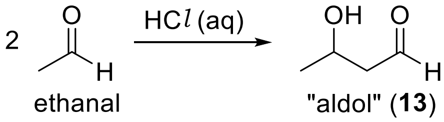
[14] Nielsen, A. T.; Houlihan, W. J. *Organic Reactions* **1968**, Vol. 16.

3),[15] hence termed “aldol” (**13**), which afterwards was used synonymously to identify with the reaction itself.



Scheme **3**. “Aldol” resulting from the self-reaction of ethanal

The first example of aldol condensation under basic conditions was demonstrated by by Schmidt[16] and by Claisen and Claparède[17], where a non-enolizable aromatic aldehyde is reacted with either an aliphatic aldehyde or ketone, and subsequently named “Claisen–Schmidt condensation”.

1.3.2 Organocatalyzed Aldol Addition

Despite the aldol reactions of carbonyl compounds in the presence of amines having been known for more than one hundred years, however, the synthetic potential of the reaction, particularly with respect to stereocontrol and catalytic implementation has only been developed steadily over the last two decades. For overviews of the development in organocatalyzed aldol ractions, see references.[18]

The real-life working model of such amine-catalyzed aldol reaction can be found in the mode of action of class I aldolases, which is fundamental to metabolism of sugar, involving the direct intermolecular aldol reaction between two carbonyl compounds. The carbon–carbon bond formation or cleavage is initiated when the substrate binds to the enzymes reversibly and covalently, *via* the amino group from a lysine residue involving an enamine-imine equilibrium as shown in Scheme **4**. However, only very

---

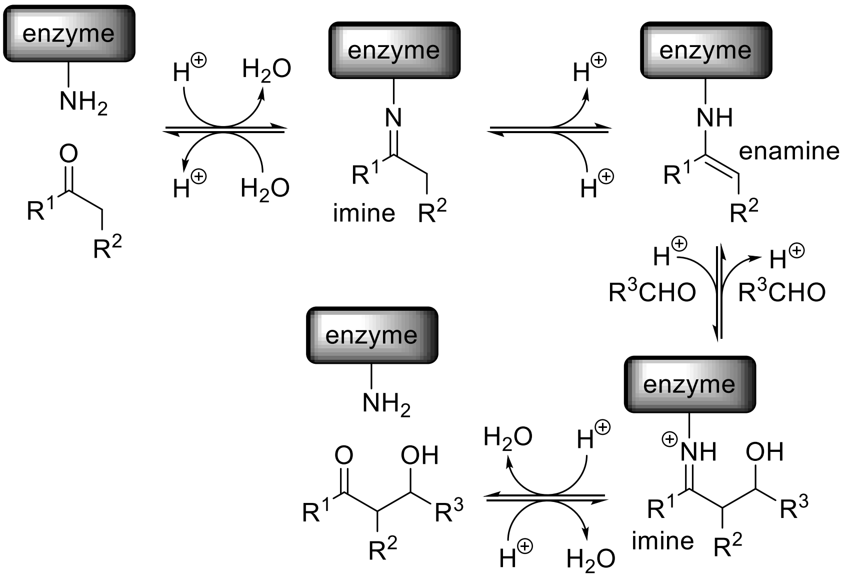
[15] Wurtz, W. *Ber. Dtsch. Chem. Ges.* **1872**, *5*, 326.

[16] Schmidt, J. G. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2342; Schmidt, J. G. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1459.

[17] Claisen, L.; Claparède, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 349.

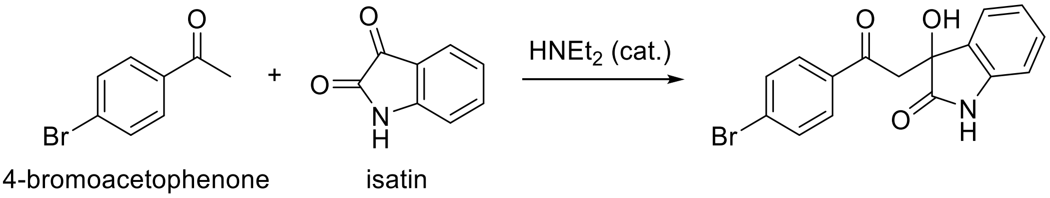
[18] (a) List, B. *Tetrahedron* **2002**, *58*, 5572. (b) List, B. Amine-catalyzed Aldol Reactions. In *Modern Aldol Additions, Vol. 1*; Mahrwald, R. Ed.; Wiley-VCH: Weinheim; pp 161. (c) Gaunt, M. J.; Johansson, C. C. C.; McNally, M.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8.

few instances of the actual synthetic application of such intermolecular aldol reaction have been reported before the end of the twentieth century.

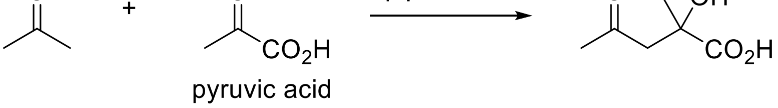


Scheme **4**. Mode of action of class I aldolases

The reactions were usually carried out using primary or secondary amines as catalysts, in the presence of a carboxylic acid. One early examples of a secondary amine-catalysed aldol processes is the Knoevenagel type condensation between acetophenone and isatin:[19]



Another example involves the aldol reaction between pyruvic acid and propanone (which also serves as the solvent) in the presence of piperidine:[20]



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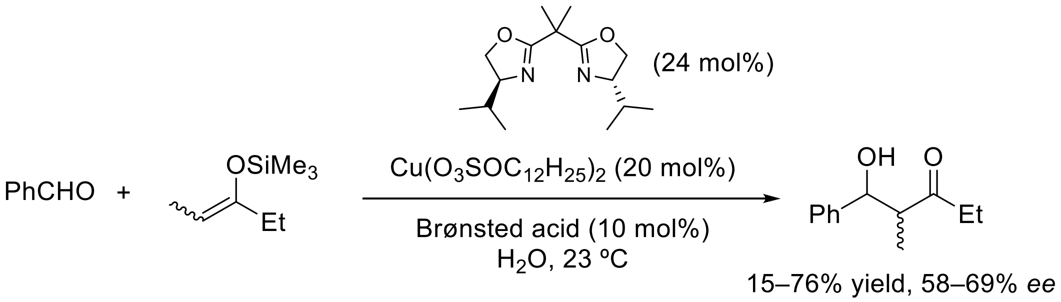
[19] Lindwall, H. G.; Maclennan, J. S. *J. Am. Chem. Soc.* **1932**, *54*, 4739.
[20] Buchta, E.; Satzinger, G. *Chem. Ber.* **1959**, *92*, 449.

In view of the harsh conditions frequently employed in these reactions, subsequent dehydrations of the initially formed β-hydroxycarbonyl compounds are common to afford the corresponding α,β-unsaturated ketones.

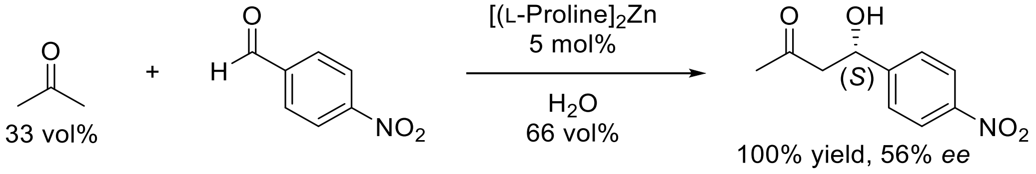
1.3.3 ORGANOCATALYZED ALDOL ADDITION IN THE PRESENCE OF WATER

In Nature, enzymes and antibodies are well adapted for catalyzing the asymmetric aldol reaction using water as a medium,[21] where the substrates are often isolated and reacted in a specialized hydrophobic environment. There are numerous reports of the asymmetric aldol reaction in the presence of water, for example, Kobayashi *et. al.* reported the Mukaiyama aldol reaction catalysed by a combined chiral Lewis acid/surfactant catalyst in the presence of water (Scheme **5**).[22]



Scheme **5**. Asymmetric aldol reactions in water

Darbre and Machuqueiro also reported moderate enantioselectivity in the Zn/proline- promoted aldol reaction between propanone and acetophenone in aqueous media (Scheme **6**).[23] A mixed solvent consisting of 1:2 propanone:water was used, where the propanone functions both as a nucleophile and as a co-solvent.



Scheme **6**. Zn-Proline catalyzed direct aldol reaction in aqueous media

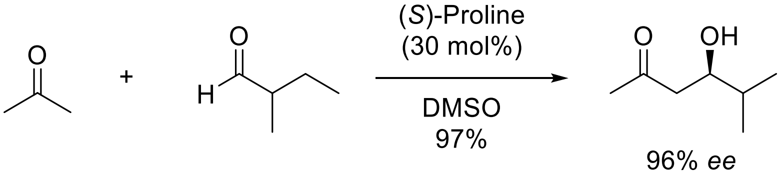
---

[21] Machajewski, T. D.; Wong, C.-H. *Angew. Chem.* **2000**, *112*, 1406; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

[22] Kobayashi, S.; Mori, Y.; Nagayama, S.; Manabe, K. *Green Chem.* **1999**, *1*, 175.

[23] Darbre, T.; Machuqueiro, M. *Chem. Commun.* **2003**, 1090.

In 2000, List, Lerner, and Barbas reported the ground-breaking finding of asymmetric aldol reaction mediated by proline in polar organic solvent.[24] Although at first, proline does not appear to facilitate the reaction between aldehydes, nonetheless, if a large excess of a ketone nucleophile is used instead, the intermolecular reaction with an aldehyde electrophile proved successful (Scheme **7**).



Scheme **7**. Highly enantioselective proline-catalyzed intermolecular aldol reaction

Subsequently, Barbas and co-workers also reported the first use of water in an organocatalyzed aldol reaction, where it was found that 4-nitrobenzene and propanone react successfully in the presence of a small amount (< 4 vol%) of water.[25] Increasing the amount of water is found to be detrimetral to the enantioselectivity. Since then, numerous similar asymmetric aldol reactions have appeared in the literature, including those taking place under aqueous conditions, [26], [27] where the reactivity and stereoselectivity appeared to improve in the presence of water.[26]

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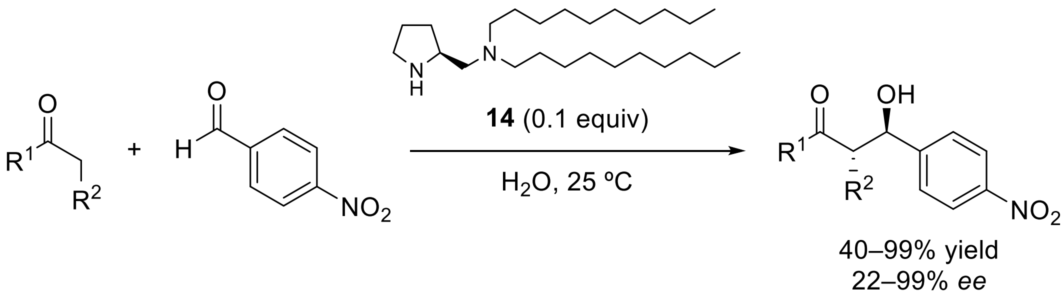
[24] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[25] Sakthivel, K.; Notz, W.; Bui T.; Barbas III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.

[26] (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem.* **2004**, *116*, 2017; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983. (b) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891. (c) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285. (d) Casas, J.; Sunden, H.; Cordova, A. *Tetrahedron Lett.* **2004**, *45*, 6117. (e) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347. (f) Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3363. (g) Amedjkouh, M. *Tetrahedron: Asymmetry* **2005**, *16*, 1411. (h) Cordova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586. (i) Wu, Y.-S.; Chen, Y.; Deng, D.-S.; Cai, J. *Synlett* **2005**, 1627. (j) Dziedzic, P.; Zou, W.; Hafren, J.; Cordova, A. *Org. Biomol. Chem.* **2006**, *4*, 38. (k) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317.

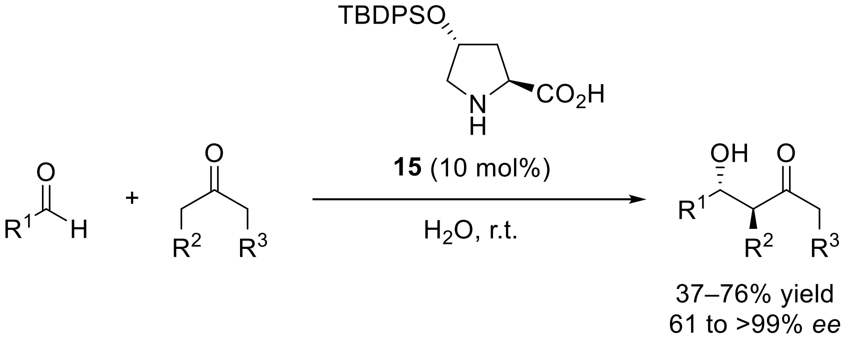
[27] (a) Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970. (b) Cordova, A.; Notz, W.; Barbas III, C. F. *Chem. Commun.* **2002**, 3024. (c) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220. (d) Peng, Y.-Y.; Ding, Q.-P.; Li, Z.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3871. (e) Wu, Y.-S.; Shao, W.-Y.; Zheng, C.-Q.; Huang, Z.-L.; Cai, J.; Deng, Q.-Y. *Helv. Chim. Acta* **2004**, *87*, 1377. (f) Dickerson, T. J.; Lovell, T.; Meijler, M. M.; Noodleman, L.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 6603. (g) Chimni, S. S.; Mahajan, D.; Babu, V. V. S. *Tetrahedron Lett.* **2005**, *46*, 5617. (h) Rogers, C. J.; Dickerson, T. J.; Brogan, A.

The next breakthrough came in towards the end of 2005, when Barbas and co-workers[28] and Hayashi and co-workers[29] independently reported the organocatalyzed asymmetric aldol reaction in the presence of water without using any organic solvent. Barbas and co-workers found that the hydrophobic diamine organocatalyst **14** acts as an effective bifunctional catalyst in the aldol reaction between 4-nitrobenzaldehyde and ketones in water as solvent (Scheme **8**).



Scheme **8**. Diamine-catalyzed aldol reactions of various ketones and 4-nitrobenzaldehyde in water

Simultaneously, Hayashi and co-workers reported use of the *O*-silyl-protected hydroxyproline **15** as organocatalyst in the aldol reaction of ketones with both aliphatic and aromatic aldehydes in water, with up to 99% *ee* (Scheme **9**).



Scheme **9**. Catalytic asymmetric aldol reaction in water catalyzed by siloxyproline

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P.; Janda, K. D. *J. Org. Chem.* **2005**, *70*, 3705. (i) Chimni, S. S.; Mahajan, D. *Tetrahedron* **2005**, *61*, 5019. (j) Rogers, C. J.; Dickerson, T. J.; Janda, K. D. *Tetrahedron* **2006**, *62*, 352.

[28] Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 734.

[29] Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem.* **2006**, *118*, 972; *Angew. Chem. Int. Ed.* **2006**, *45*, 958.

In addition to the work mentioned above, a great number of studies in aqueous media or in brine solution have been reported in the last decade.[30,31] However, the role played by the water in enhancing the reactivity and selectivity observed in many organocatalytic processes is not entirely known. Nonetheless, such exceptional physical properties as high polarity, high dielectric, high surface tension, inherent capacity to induce hydrophobic effect and to participate in hydrogen bonding, are often correlated to the observed enhancements.[32]

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[30] For reviews on aqueous organocatalytic reactions, see: (a) Mlynarski, J.; Paradowska, J. *Chem. Soc. Rev.* **2008**, *37*, 1502. (b) Gruttadauria, M.; Giacalone F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33. (c) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687. (d) Mase, N.; Barbas III, C. F. *Org. Biomol. Chem.* **2010**, *8*, 4043. (e) Bhowmick, S.; Bhowmick, K. C. *Tetrahedron: Asymmetry* **2011**, *22*, 1945. For reviews on aqueous asymmetric aldol reaction, see: (f) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131. (g) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600. (h) Chen, X.-H.; Yu, J.; Gong, L.-Z. *Chem. Commun.* **2010**, 6437. (i) Bhanushali, M.; Zhao, C.-G. *Synthesis* **2011**, 1815.

[31] (a) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417. (b) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801. (c) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317. (d) Raj, M.; Maya, V.; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097. (e) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493. (f) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (g) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247. (h) Russo, A.; Botta, G.; Lattanzi, A. *Tetrahedron* **2007**, *63*, 11886. (i) Huang, W.-P.; Chen, J.-R.; Li, X.-Y.; Cao, Y.-J.; Xiao, W.-J. *Can. J. Chem.* **2007**, *85*, 208. (j) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812. (k) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21. (l) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 545. (m) Teo, Y.-C.; Lau, J.-J.; Wu, M.-C. *Tetrahedron: Asymmetry* **2008**, *19*, 186. (n) Hayashi, Y.; Samanta, S.; Gotoh, H.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6634. (o) Tian, H.; Gao, J.-I.; Xu, H.; Zheng, L.-Y.; Huang, W.-B.; Liu, Q.-W. and Zhang, S.-Q. *Tetrahedron: Asymmetry* **2011**, *22*, 1074. (p) Guillena, G.; Nájera, C.; Viózquez, S. F. *Synlett* **2008**, 3031. (q) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas III, C. F. *Org. Lett.* **2008**, *10*, 1621. (r) Zhu, M.-K.; Xu, X.-Y.; Gong, L.-Z. *Adv. Synth. Catal.* **2008**, *350*, 1390. (s) Peng, F.-Z.; Shao, Z.-H.; Pu, X.-W.; Zhang, H.-B. *Adv. Synth. Catal.* **2008**, *350*, 2199. (t) Vishnumaya, M. R.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289. (u) An, Y.-J.; Zhang, Y.-X.; Wu, Y.; Liu, Z.-M.; Pi, C.; Tao, J.-C. *Tetrahedron: Asymmetry* **2010**, *21*, 688. (v) Jiang, Z.; Yang, H.; Han, X.; Luo, J.; Wong, M. W.; Lu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1368. (w) Huang, W.; Tian, H.; Xu, H.; Zheng, L.; Liu, Q.; Zhang, S. *Catal. Lett.* **2011**, *141*, 872. (x) Miura, T.; Ina, M.; Imai, K.; Nakashima, K.; Masuda, A.; Tada, N.; Imai, N.; Itoh, A. *Synlett* **2011**, 410. (y) Bisai, V.; Singh, V. K. *Synlett* **2011**, 481. (z) An, Y.-J.; Wang, C.-C.; Liu, Z.-P.; Tao, J.-C. *Helv. Chim. Acta* **2012**, *95*, 43.

[32] Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.

1.4 PD(II)-CATALYZED DIRECT C–H BOND ACTIVATION/FUNCTIONALIZATION

Transition metal-catalyzed couplings have evolved to become an important arsenal of synthetic organic chemist to effect the construction of new carbon–carbon and carbon–heteroatom bonds in contemporary organic synthesis.[33] Palladium catalysts and reagents stood out among these in view of the following three characteristics: [34]

i. They present an unprecedented ability, not even coming close by other transition metals, for forging new carbon–carbon bonds.
ii. Palladium catalysts and reagents are generally neither air- nor moisture sensitive and hence readily manipulated and stored.
iii. They exhibit extensive tolerance towards a variety of functional groups during palladium-catalyzed reactions.

It does not come as surprise that palladium catalysts and reagents have been extensively employed in the industrial manufacture of numerous pharmaceuticals, colourings, organic as well as semi- conductors, and polymers *etc*,[35] of which, the palladium-catalyzed couplings are the most prevalent. In fact, the 2010 Nobel Prize in Chemistry was jointly awarded to Richard Fred Heck, Ei-ichi Negishi and Akira Suzuki for their work pertaining to palladium-catalyzed cross couplings in organic

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[33] (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.

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

[35] (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. (c) Rubin, A. E.; Tummala, S.; Both, D. A.; Wang, C.; Delaney, E. J. *Chem. Rev*. **2006**, *106*, 2794–2810.

synthesis, establishing beyond doubt the importance of these reactions.[36] Table **1** provides a summary of some of the more well-known palladium-catalyzed coupling reactions.[37]

Table **1**. Summary of well-known palladium-catalyzed coupling reactions

$$R^1{-}X \; + \; R^2{-}M \xrightarrow{\text{cat. [M']}} R^1{-}R^2$$

X = I, Br, C*l*, OTf......

Name	**Catalytic metal, 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
Hiyma-Hatanaka	Pd	Si
Negishi-Nozaki-Oshima	Pd Ni	Zn, Al

One of the main problems plaguing the use of the variety of palladium-catalyzed coupling reactions is the necessity to handle non-environmentally friendly halogenated substrates and/or organometallic reagents. Hence, exploration of palladium-catalyzed coupling reactions *via* direct C–H bond activation and functionalization to forge new

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[36] The Nobel Prize in Chemistry 2010. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/ (accessed 17 Jan 2015).

[37] (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.

carbon–carbon or carbon–heteroatom bonds has emerged and gained prominence in the past few decades.[38]

C–H bonds are ubiquitous in the hydrocarbon framework of organic molecules. If we can tap upon C–H bonds as functional group equivalents, retrosynthetic disconnection can be envisaged more efficiently, thereby allowing for significantly shorter synthetic routes and less by-products generated during synthesis. Unfortunately, there remains limited use of unactivated C–H bonds in the total synthesis of natural products to this date.[39]

The two terms "C–H activation" and "C–H functionalization" are frequently used interchangeably in the literature.[40] Herein, the term "C–H activation" refers solely to the direct transformation of C–H bonds into C–[M] bonds, while the term "C–H functionalization" is used to refer to the overall transformation of C–H bond into C–X bonds *via* a C–[M] intermediate or involving other metal bonds (Scheme **10**).[41]

$$\mathrm{C{-}H} \xrightarrow[\text{C–H activation}]{[\mathrm{M}]} \mathrm{C{-}[M]} \xrightarrow[\text{functionalization}]{\mathrm{R{-}X}} \mathrm{C{-}X}$$

Scheme **10**. C–H activation *versus* C–H functionalization

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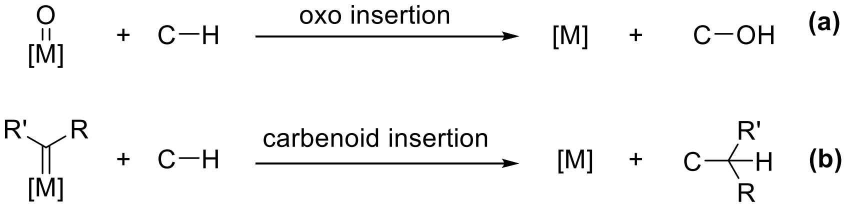
[38] For reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (b) Chen, X.; Engle, K. M.; Wang, D-H.; Yu, J-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115. (c) Daugulis, O.; Do, H-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (d) Hartwig, J. F. *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.

[39] (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.

[40] (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.

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

In the past decades, research mostly focuses on metal-oxo insertion into C–H bonds[42] (Scheme **11(a)**) and metal carbenoid/nitrenoid insertion into C–H bonds[43] (Scheme **11(b)**) as the modes of transition metal-catalyzed C–H activation. However, we would like to focus on the lesser explored, though equally if not more important, direct insertion of metal into C–H bonds.



Scheme **11**. **(a)** Metal-oxo insertion method for C–H functionalization**. (b)** Carbenoid/nitrene insertion method for C–H functionalization

Pioneering work in this area was reported back in the early 1960s.[44] In 1963, Kleiman and Dubeck observed that the C–H bond of azobenzene could be activated with Cp_2Ni, wherein the inserted nickel was coordinated to the nitrogen–nitrogen double bond *via* π-interaction (Scheme **12**).[45] Later, Cope and Siekman reported in 1965 that $PdCl_2$ and K_2PtCl_4 could also activate the *ortho* C–H bond of the phenyl ring in azobenzene.[46] The structures proposed for the products obtained using Ni and Pd bear great similarity.

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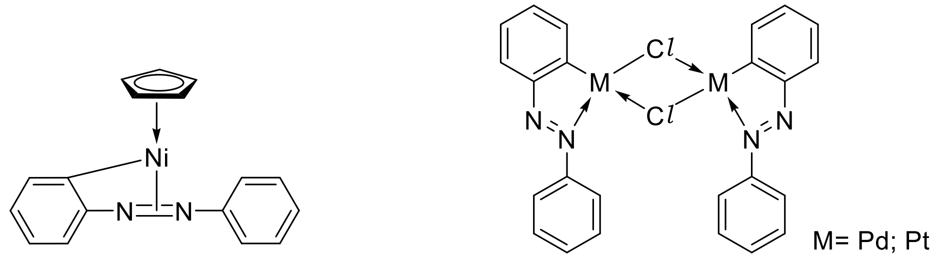
[42] Goldman, A. S.; Goldberg, K. I. In *Activation and Functionalization of C–H Bonds*, Goldberg, K. I.; Goldman, A. S.; Eds.; ACS Symposium Series 885; American Chemical Society: Washington, DC, 2004, 1–45.

[43] Colby, D. A.; Bergman, R, G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655.

[44] (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.

[45] Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544–1545.

[46] Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272–3273.

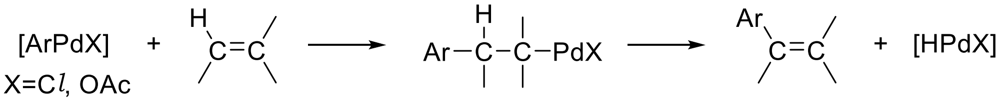


Kleiman and Dubeck (1963)

Cope and Siekman (1965)

Scheme **12**

Later into the 1960s, Heck demonstrated that the arylation of alkenes could be achieved using stoichiometric amounts of Ar–Pd–C*l* or Ar–Pd–OAc, generated *in situ* from ArHgC*l* and $\mathrm{PdC}l_2$, or ArHgOAc and $\mathrm{Pd(OAc)_2}$, respectively.[47] The reaction was proposed to proceed *via syn* migratory insertion of the alkene into the arylpalladium reagent, followed by *syn β*-hydride elimination of a hydridopalladium species, [HPdX] (X= C*l*, OAc) (Scheme **13**). Subsequently, Heck developed this idea into a general reaction between alkenes and organopalladium salts, formed by the insertion of finely divided palladium into aryl iodide, also simultaneously discovered by Mizoroki independently.[48] This new reaction came to be known as the Mizoroki-Heck reaction.



Scheme **13**. Mechanism for Heck coupling

Fujiwara and Moritani revealed a styrene-palladium chloride complex in 1967, which can further react with excess arenes to give stilbenes. This represents the first instance of a palladium-mediated olefination reaction (Scheme **14(a)**).[49] A catalytic version of the reaction was subsequently developed by employing a stoichiometric oxidant such as Ag(I), Cu(II), O_2, $t\text{-BuO}_2\text{H}$, or $\text{PhCO}_3t\text{-Bu}$, together with a catalytic

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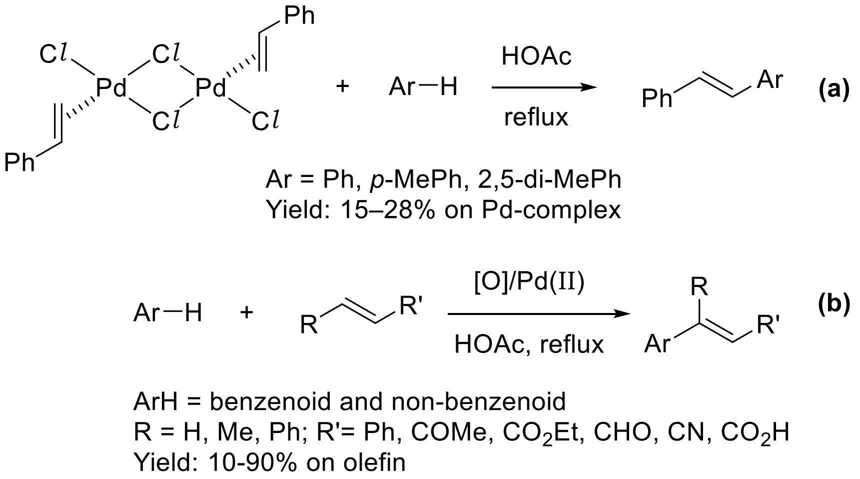
[47] (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526. (b) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707–6714. (c) Heck, R. F. *J. Am. Chem. Soc.* **1971**, *93*, 6896–6901.

[48] (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.

[49] Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119–1122.

amount of $Pd(OAc)_2$ (Scheme **14(b)**).[50]



Ar = Ph, *p*-MePh, 2,5-di-MePh
Yield: 15–28% on Pd-complex

ArH = benzenoid and non-benzenoid
R = H, Me, Ph; R'= Ph, COMe, CO_2Et, CHO, CN, CO_2H
Yield: 10-90% on olefin

Scheme **14**

Building upon these earlier ground works, a wide array of new methodologies utilizing C–H activation to transform C–H bonds directly into C–C or C–heteroatom bonds were developed. These new reactions can be classified into two broad categories, depending on whether the reaction is assisted by a directing group on the substrates.

In cases where insertion of the metal into the C–H proceeds without assistance from heteroatoms, which can potentially chelates to the metal or act as directing groups, discrimination among chemically similar C–H bonds within the same hydrocarbon framework remains a challenge to be surmounted.

On the other hand, the presence of such heteroatoms as oxygen or nitrogen already present on the substrates can potentially coordinate to the metal and localize insertion of the metal into specific positions. In other words, the heteroatoms function as

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[50] (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.

directing groups to direct the metal and activate selective C–H bonds. In the following sections, we will focus on discussion of the latter.

1.4.1 DIRECT TRANSFORMATION OF SP^2 C–H BONDS

The ability to transform arenes directly into commercially useful products *via* catalytic C–H activation had confronted synthetic chemists for many years, and is of significant interest to the chemical industry.[51] Development of the catalytic functionalization of hydrocarbons skeletons, both saturated and unsaturated, continues to be an imperative area of focus in contemporary organic chemistry,[52] potentially providing cost-effective and green methods to directly manufacture daily chemicals from petroleum. The main hurdle to the development of such processes lies in the strength of the C–H bonds in arenes, having a bond dissociation energy of 473 kJ/mol in the case of benzene for instance.

Enormous efforts were devoted to the realization of selective C–H bond activation by transition metal complexes for the past thirty years.[51] Beginning in the 1960s, efforts in developing aryl C–H bond activation culminated in the early 1900s, at the successful development of acid-catalyzed and -promoted Friedel-Crafts alkylation and acylation. The coupling of alkenes with arenes mediated by Pd(II) complexes unveiled by Fujiwara in 1967,[49] is among the earliest reports of aromatic C–H bond activation by transition metal complexes, involving formally electrophilic substitution of the C–

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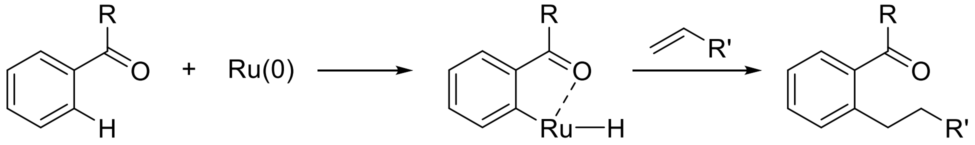
[51] (a) Shilov, E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879–2932. (b) Kakiuchi, F.; Murai, S. Activation of C–H Bonds: *Catalytic Reactions. In Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: New York, **1999**; 47–79. (c) Jones, W. D. Activation of C–H Bonds: *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.

[52] Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281.

H bond by a Pd(II) species.[53]

However, there are comparatively much fewer reported cases of synthetically useful catalytic C–H bond activation by transition metal compounds, in relation to the vast number of stoichiometric systems in literature. One promising example is the *ortho*-chelation assisted aromatic C–H bond activation such as the one shown in *Scheme **15***, which invokes oxidative addition of a low-valent ruthenium complex followed by addition across carbon–carbon double bonds.[51b,54]



Scheme **15**. *ortho*-Chelation assisted aromatic C–H bond activation

The use of aromatic compounds directly in a synthesis still depends heavily on the presence of a bond more reactive than the C–H bond for most cases, for instance, the use of aryl or alkenyl halides,[55] which can be very efficacious, if not for the very fact that manufacture of aryl and vinyl halides, as well as disposable of the halide salt by-products from the reaction, are not environmentally friendly. Therefore, the future goal is still to search for realistic catalytic protocols that would enable direct C–H bond activation in arenes and alkenes.[56]

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[53] Fujiwara, Y.; Moritani, I.; Danno, S.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.

[54] (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.

[55] (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.

[56] Jia, C.-G.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639.

1.4.2 PD-CATALYZED DIRECT COUPLING BETWEEN ARENES AND ALKENES VIA C–H BONDS ACTIVATION

A variety of direct coupling between arenes and alkenes, catalysed by palladium, have been developed over the past few decades, for example, the first olefination reaction between a styrene-palladium(II) chloride complex and benzene derivatives reported in 1967 by Fujiwara and Moritani was described earlier.[49] The use of acetic acid as solvent was critical for the reaction to proceed and palladium(II) acetate was established to be the most efficient catalyst. Nevertheless, the practicality of the reaction was limited by the requirement of stoichiometric amount of costly palladium(II) acetate, which prompted the widespread search for an efficient catalytic systems by recycling the palladium catalyst through use of a cheaper stoichiometric oxidant.[50]

Finally, when *tert*-butyl perbenzoate was employed as the stoichiometric oxidant for the *in situ* regeneration of Pd(II) from Pd(0), a step forward in the efficiency of the reoxidation was made, where up to 34 turnovers were observed for benzene when heated to 100 ºC in acetic acid.[57]. The possibility of radical participation from the perester in the reaction was ruled out by observation of equimolar amounts of benzoic acid and *tert*-butyl alcohol by-products.

The use of benzoquinone (BQ) with *tert*-butyl hydroperoxide as the stoichiometric oxidant provided a highly efficient $Pd(OAc)_2$-catalyzed system for the coupling of benzene, furan and indole with activated alkenes (Scheme **16**).[58] The reaction was proposed to proceed *via* electrophilic attack of a cationic $[PdOAc]^+$ species at the aromatic C–H bond, leading to formation of a σ-aryl–Pd intermediate, followed by addition across the alkene and finally β-hydride elimination. The rate-determing step

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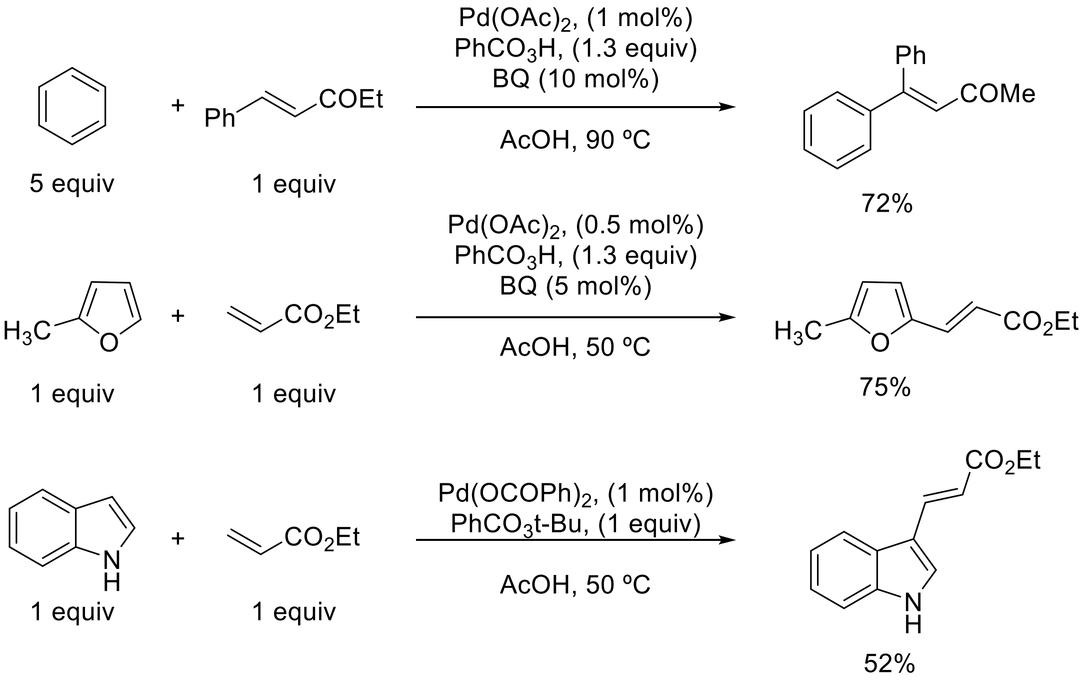
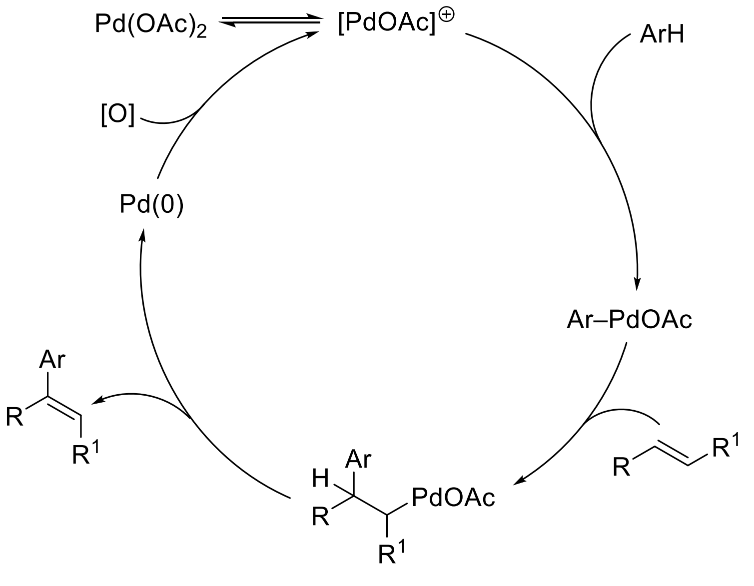
[57] Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699-2702.
[58] Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097-2010.

in the catalytic cycle was thought to be formation of the σ-bonded aryl–Pd complex (Scheme **17**).



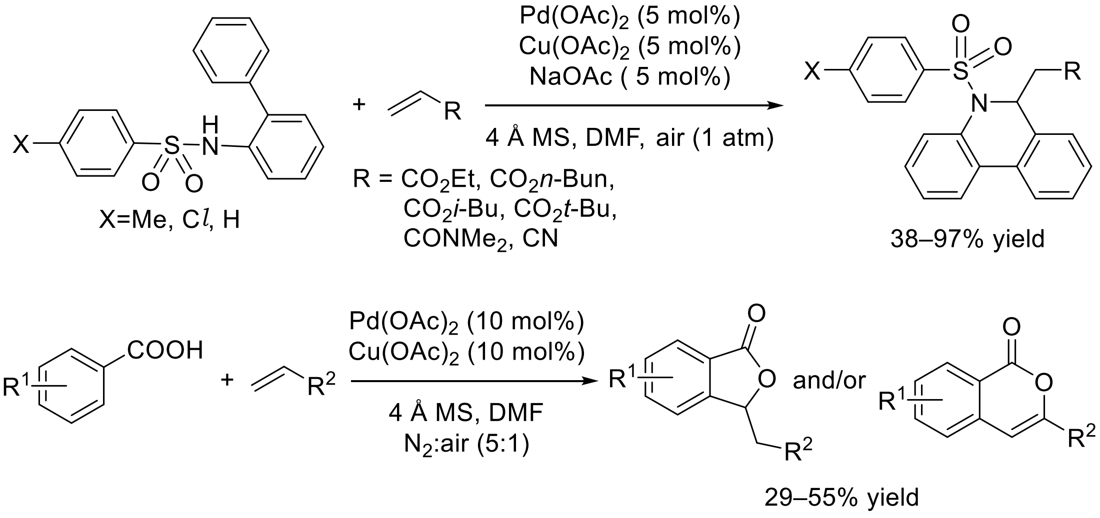
Scheme **16**



Scheme **17**. Mechanism for Pd-catalyzed coupling of arenes with olefins

However, from an industrial viewpoint, the use of peroxide oxidants poses potential hazards, and thus, the development of more efficient systems for direct olefination is still desirable.

Miura and co-workers revealed the palladium-catalyzed reaction of electron-poor alkenes, such as acrylates with *N*-(2′-phenylphenyl)benzenesulfonamides *via* cleavage of the *ortho* aryl C–H bond in 1998.[59] The proposed coupling invoked initial *ortho*-palladation of the *N*-(2'-phenylphenyl)benzenesulfonamides by the palladium species. Subsequent coupling with acrylate followed by intramolecular nucleophilic cyclization provided the dihydrophenanthridines. In addition, such structurally related compounds as benzoic and naphthoic acids were found to react with acrylate ester and styrene (Scheme **18**).



Scheme **18**

Yu’s group described a triflamide-directed palladium-catlyzed C–H activation and alkenylation, which exhibited tolerance towards a wide range of substrates and monoalkenylated products were obtained in 50–65% yield together with 10–20% yield of the dialkenylated products.[60] Notably, tetrahydroisoquinolines were isolated in good yield and high diastereoselectivity when vinyl ketones were subjected to the reaction, involving a tandem C–H alkenylation and aza-Michael addition (Scheme **19**).

The aromatic nucleus of aniline derivatives is exceptionally reactive towards electron-deficient alkenes, and its coupling with *n*-butyl acrylate, catalysed by $Pd(OAc)_2$ in AcOH at room temperature, with BQ functioning as oxidant and ligand,

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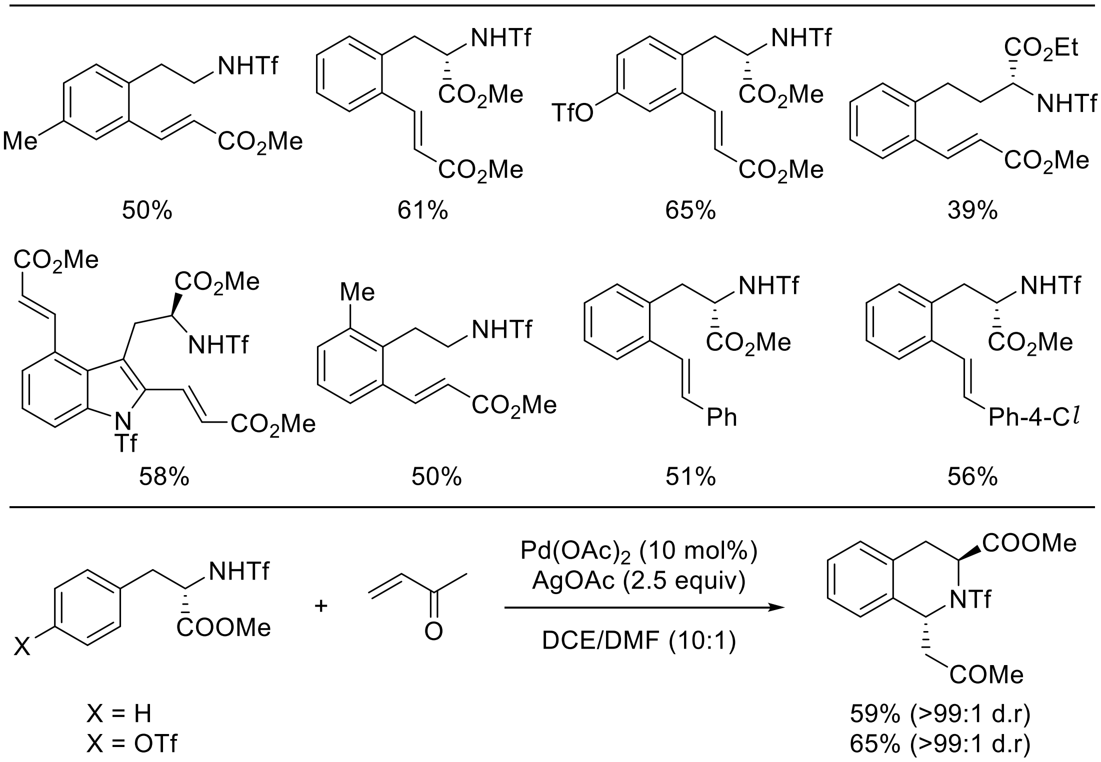
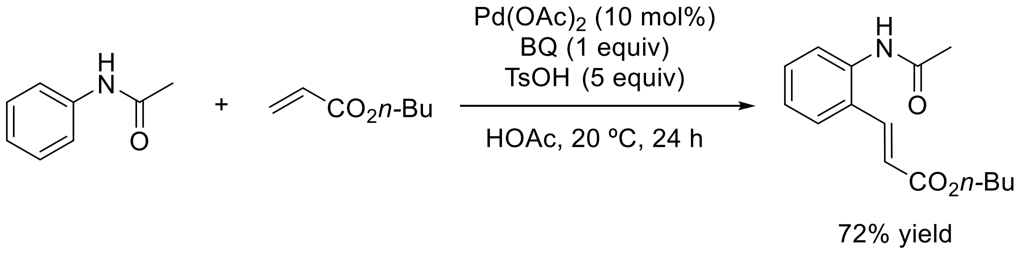
[59] Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63,* 5211–5215.

[60] Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452–6455.

gave rise to alkenylation solely at the *ortho*-position due to the powerful *ortho*-directing effect of the amide group. It is noteworthy that the double bond of the acrylate was retained in the product (Scheme **20**).[61]



Scheme **19**. Triflamide-directed C–H activation and alkenylation reaction catalyzed by $Pd(OAc)_2$



Scheme **20**

Earlier studies of palladium-catalyzed olefination of arenes were almost always limited to electron-rich arene substrates, and the reaction of electron-poor arenes continued to pose a challenge until recently. Employing 2,6-dialkylpyridines as ligands, Yu and co-workers were able to execute palladium-catalyzed olefination of

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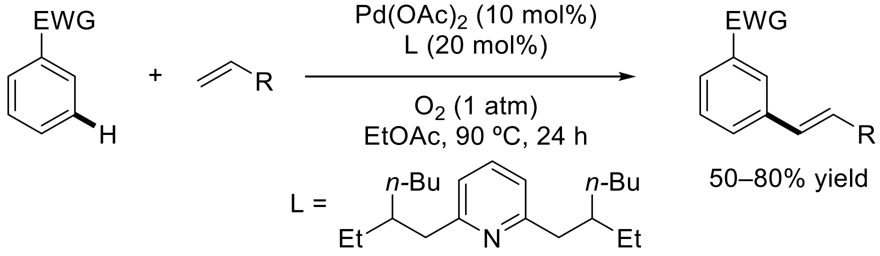
[61] Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586-1587.

arenes containing strongly electron-withdrawing groups (Scheme **21**).[62] The major products obtained in the reaction are the *meta*-C–H olefination compounds, hence providing a novel efficient access to 1,2,4-trisubstituted arenes, which are valuable scaffolds in medicinal chemistry.



Scheme **21**

1.4.3 CHALLENGES IN C–H ACTIVATION

Transition-metal, particularly palladium, -catalyzed coupling reactions *via* C–H bond activation, had proved itself in the past decades, to be a formidable method for the assembly of C–C and C–heteroatom bonds. Nonetheless, these methods are still plagued by several challenges, including reactivity, selectivity and cost-effectiveness. It is not uncommon to employ harsh reaction conditions to coerce many C–H activation reactions to proceed.

Directing groups may be installed in substrates possessing more than one chemically similar C–H bonds, to obtain desirable selectivity. However, practicality of the methodology is limited by the need for additional installation and detachment steps. In addition, excess substrates or high catalyst loadings are mandatory for most of these reactions, rendering the methods operationally unattractive.

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[62] Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074.

To overcome the above problems, development of less expensive transition metals such as Cu and Fe as catalysts, as well the quest for new efficient reaction conditions is the challenge for research in the future.

CARBON–CARBON BOND FORMATION REACTIONS

PART I : CLASSICAL ALDOL REACTION

CHAPTER 2

Model Studies Towards the Aminocatalyzed Ketone Aldol Reaction of N-Terminally Modified Proteins

CHAPTER 2 MODEL STUDIES TOWARDS THE AMINOCATALYZED KETONE ALDOL REACTION OF *N*-TERMINALLY MODIFIED PROTEINS

2.1 INTRODUCTION

Proteins frequently serve as the driving force in natural biological systems, or are at the least, implicated in most biological functions. Hence, if there are ways to follow and track the movement of proteins in these biological systems, it would provide an invaluable tool for man to peep into the biological clockwork of Nature. It is through such in-depth comprehension of biological and mechanistic pathways, that the discovery and design of novel drug candidates is made possible, with the help of computational biology. Site-specific functionalisation of a protein would thus be a useful way of tagging proteins for mechanistic study of biological functions.

Francis and co-workers had developed a method to install a carbonyl group at the *N*-terminus of proteins *via* oxidation using the naturally occurring aromatic aldehyde, pyridoxal 5′-phosphate (PLP), which is the active form of vitamin B_6 functioning as a coenzyme in numerous enzymatic reactions.[1,2] With an understanding of the mode of action of the coenzyme in biological systems, the oxidation is thought to proceed *via* a transamination reaction, wherein pyridoxal 5′-phosphate first condenses with the *N*-terminal amino group to furnish an iminium cation, which subsequently tautomerizes and affords the corresponding α-keto aldehyde upon hydrolysis (Scheme **22**).

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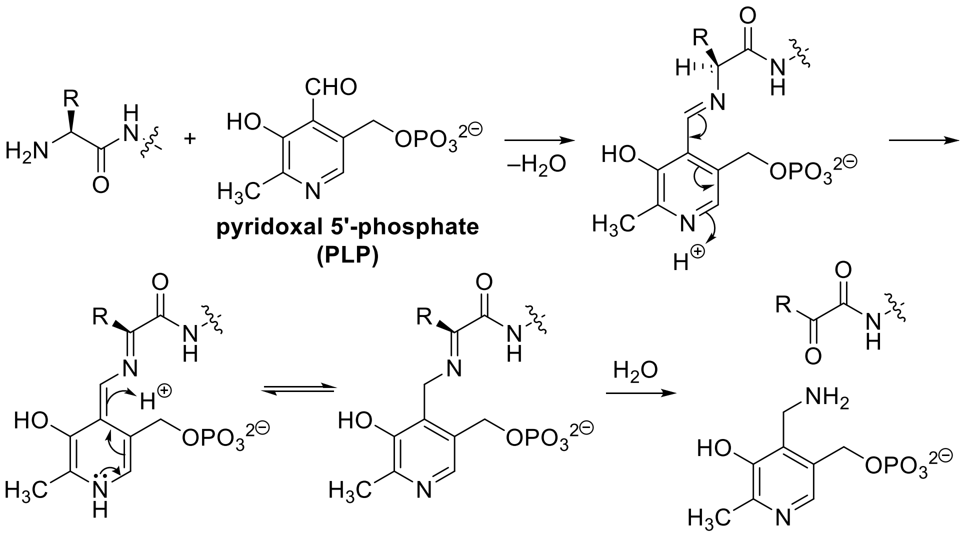
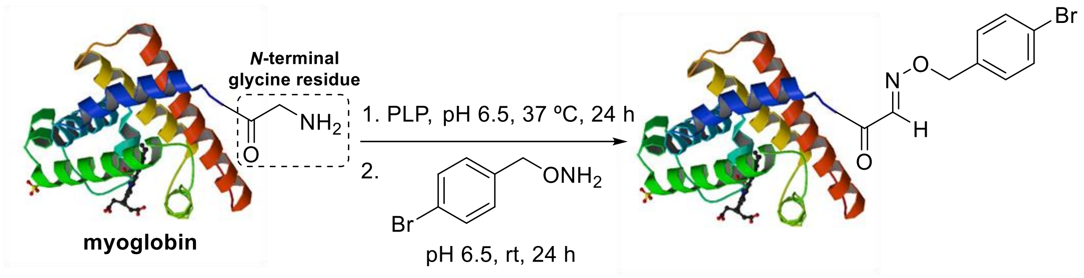
[1] Gilmore, G. M.; Scheck, R. A.; Esser-Khan, A. P.; Joshi, N. S.; Francis, M. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 5307–5311.

[2] Scheck, R.A.; Dedeo, M. T.; Lavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc.* **2008**, *130*, 11762–11770.



Scheme **22**. Transamination reaction of *N*-terminus with pyridoxal 5′-phosphate

Regardless of the primary structure of the protein, the oxidation turns out to be highly *N*-terminus specific, not affecting lysine residues for instance, and is able to convert the *N*-termini of most proteins into carbonyl functionalities, under mild aqueous conditions. Francis *et al.* further modified the protein by subjecting the resulting carbonyl group to reaction with *O*-(4-bromobenzyl)hydroxylamine to furnish an oxime, as exemplified by myoglobin in Scheme **23**.



Scheme **23**. *N*-Terminal transamination of myoglobin followed by oxime formation

Tachibana and co-workers also utilized the same reaction to generate an aldehyde functionality from the *N*-terminal glycine residue of myoglobin. The resulting aldehyde is then trapped with tryptamine analogues by means of the Pictet-Spengler reaction, which is essentially a Mannich-type ring formation involving indole (Scheme **24**).[3]

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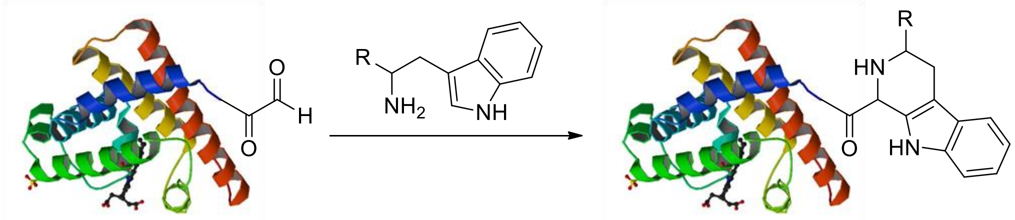
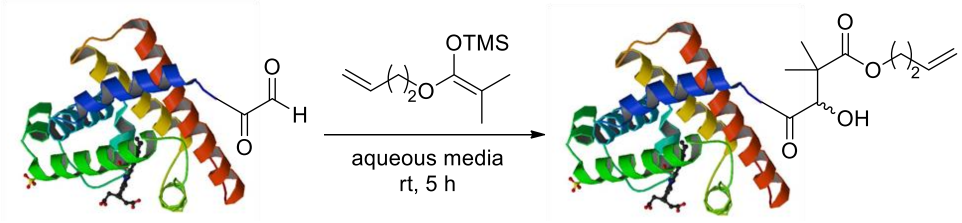
[3] Sasaki, T.; Kodama, K.; Suzuki, H.; Fukuzawa, S.; Tachibana, K. *Bioorganic & Medicinal Chemistry*. **2008**, *18*, 4550–4553.



Scheme **24**. Pictet-Spengler reaction of *N*-terminally modified myoglobin with tryptamine analogues

Loh *et al.* subsequently ascertained that proteins with the *N*-terminal glycine converted to an aldehyde functionality *via* oxidation with PLP were capable of undergoing the Mukaiyama Aldol reaction with silyl enol ethers,[4] again under mild aqueous conditions as demonstrated by myoglobin in Scheme **25**, thus allowing the protein to be tracked in biological systems.



Scheme **25**. Mukaiyama aldol reaction of *N*-terminally modified myoglobin

Having established the reactivity of the aldehyde functionality generated by oxidation of *N*-terminal glycine towards various reagents under mild aqueous conditions, we are interested in determining if an organocatalyzed ketone aldol reaction on *N*-terminally modified proteins would be probable.

Aldol reactions are among the most efficient carbon–carbon bond-formation procedures in organic synthesis.[5] The aldol reaction is highly versatile and amendable to various reaction conditions, being catalyzed by both Brønsted as well as Lewis acids and bases. Such flexibility is inherent to the combination of nucleophilic addition, which is acid-catalyzed, and enol generation, which is both acid- and base-

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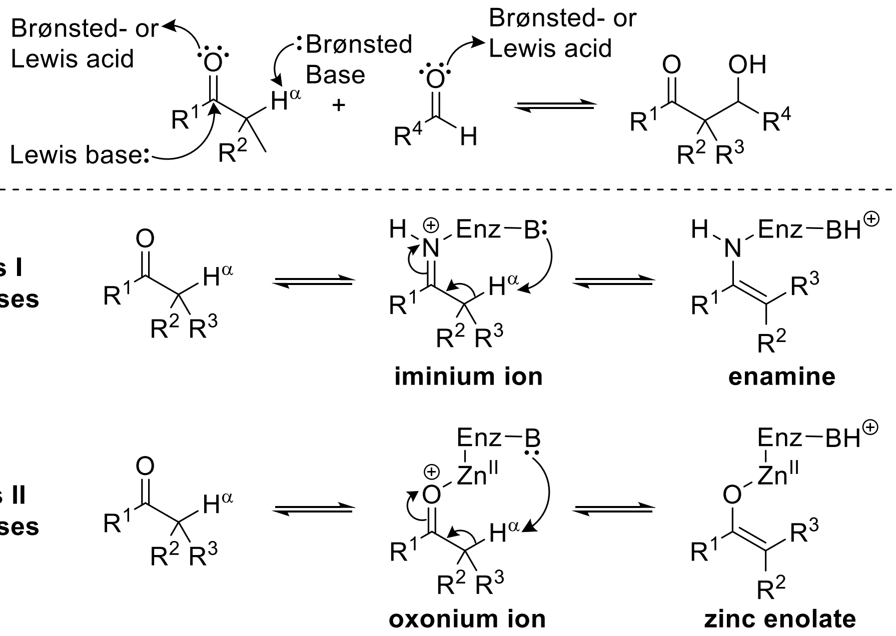
[4] Alam, J.; Keller, T. H.; Loh, T. P. *J. Am. Chem. Soc*, **2010**, *132*, 9546–9548.

[5] *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1 and 2.

catalyzed, in the overall scheme of work (Scheme **26**).[6] Indeed, this is precisely also the strategy Nature employs to realize the direct asymmetric aldol reactions involving unmodified carbonyl compounds in the class of aldolase enzymes.



Scheme **26** Aldol activation and mode of enolization of aldolases

The enzyme aldolases are categorized based on their mode of enolization:

- Class I aldolases employ a primary amino group to effect Lewis base catalysis
- Class II aldolases utilize a Zn^{2+}-containing cofactor as the Lewis acid catalyst.

These enzymes must first transform the carbonyl donor (usually a ketone) into the corresponding cationic iminium or oxonium ion, hence significantly lowering the pK_a of the α-hydrogen, and activating the α-hydrogen under an esssentially neutral, aqueous environment. This then set the stage for a relatively weak Brønsted base co-catalyst to deprotonate the cation, generating the corresponding enamine or zinc enolate as the active nucleophile (Scheme **26**).

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[6] Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H. Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 133.

Despite the fact that aldol reactions are frequently catalyzed by acids and bases in the laboratory, the search for a direct catalytic asymmetric aldol reaction, analogous to the workings of aldolases, was not successful for a long time. However, since the discovery of the first intermolecular direct asymmetric aldol reaction by List and co-workers,[7] using the amino acid proline as catalyst, an avalanche of other successful organocatalysts were subsequently reported in the literature.[8] In order to probe the transition states of the key carbon–carbon bond formation step in the catalytic cycle, Houk and co-workers performed DFT calculations (Scheme **27**), which was further validated by mechanistic studies.[9]

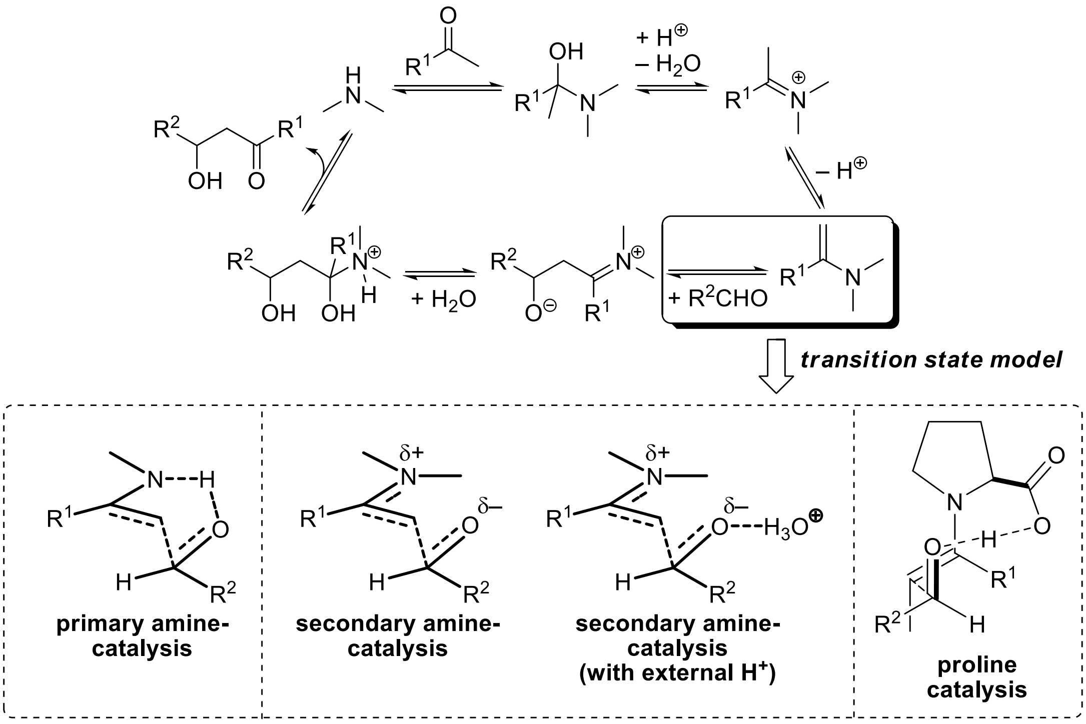
The Houk-List transition state model was developed from these studies (Scheme **27**), where a cyclic half-chair conformation was proposed for the transition state of the primary amine-catalyzed aldol reaction, stabilized by N–H–O hydrogen-bonding. In contrast, the secondary amine-catalyzed aldol reaction was found to proceed *via* an oxetane intermediate, where the zwitterionic transition state embodies formally a [$2_\pi+2_\pi$]-cycloaddition. The corresponding iminium ion is found to ensue from the reaction without any barrier in the presence of an external proton source.

---

[7] (*a*) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396. (*b*) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387. (*c*) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573–575. (*d*) List, B. *Synlett* **2001**, 1675–1686. (*e*) List, B. *Tetrahedron* **2002**, *58*, 5573–5590.

[8] For reviews on organocatalysts, see: (*a*) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. (*b*) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331. (*c*) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (*d*) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660. (*e*) Bertelsen, S.; Jørgensen *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.

[9] (*a*) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 9922–9923. (*b*) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283. (*c*) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16–17. (*d*) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479. (*e*) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839–5842. (*f*) Clemente, F. R.; Houk, K. N. *Angew. Chem.* **2004**, *116*, 5890–5892; *Angew. Chem. Int. Ed.* **2004**, *43*, 5766–5768. For a review, see: (*g*) List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730–1734.



Scheme **27** The enamine catalytic cycle and transition state models

Of particular interest, in the case of proline catalysis developed by List *et al.*, the amino acid is deemed to work as a bifunctional catalyst, serving simultaneously as a Lewis basic secondary aminocatalyst, as well as a Brønsted acid, where the charge of the incipient oxyanion is neutralized by the carboxyl group (Scheme **27**, bottom right).

2.2 METHODOLOGY

From the above discussion, we set out to mimick a Class I aldolase-type catalytic direct asymmetric aldol reaction on the aldehyde functionality of *N*-terminally modified myoglobin, *via* aminocatalysis. We speculate that the aldol reaction may not require an external organocatalyst due to the presence of such Lewis basic residues as lysine in myoglobin. In addition, we are particularly interested in the enantio- as well as diastereo-selectivity outcome of the aldol addition in view of the chiral environment inherent to the protein structure.

We also aimed to perform the direct aldol reactions in water without any organic solvent as the protein could be denatured in the presence of organic solvents. On top of that, from a green chemistry perspective, the use of water offers an added advantage as an environmentally friendly solvent. To this end, model studies were first embarked upon to ascertain the feasibility of the envisaged aminocatalyzed direct aldol in water.

The simplest model substrate for the *N*-terminally modified myoglobin ought to be *N*-alkyl-2-oxoacetamides (Figure **1**). However, preliminary work has shown that this class of substrates is very reactive, readily undergoing polymerization even at low temperatures, rendering their use as model substrate impractical.

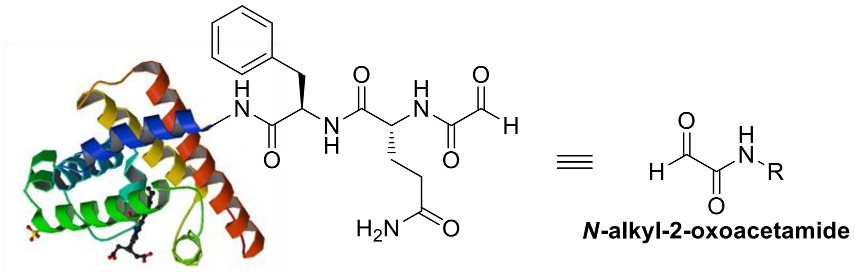
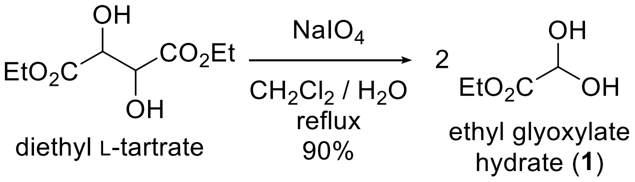


Figure **1**. *N*-Alkyl-2-oxoacetamides as model substrate

We next turned our attention to the ester congener, the alkyl glyoxylates, which can be made easily *via* the periodate oxidative cleavage of dialkyl tartrates. In view of the fact that we will be screening the aldol reaction under aqueous conditions, we choose to work with the more stable ethyl glyoxylate hydrate (**1**)[10] instead of the parent aldehyde which like the amide is also prone to polymerization (Scheme **28**).



Scheme **28**. Preparation of model substrate, ethyl glyoxylate hydrate

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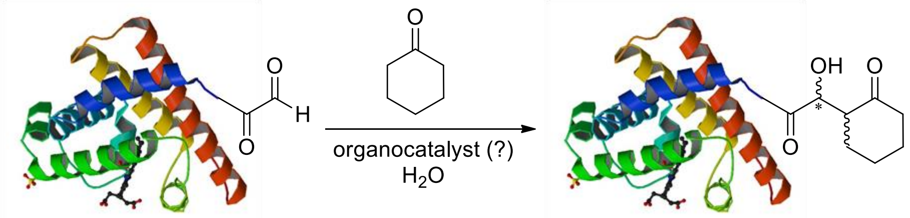
[10] Bailey, P. D.; Smith, P.D.; Pederson, F.; Clegg, W.; Rosair, G. M.; Teat, S. J. *Tetrahedron. Lett.* **2002**, *43*, 1067–1070.

The three-component, one-pot Mannich reactions will also be attempted on the model substrate with different amines, as a logical extension of the aldol reaction, in hope of broadening the scope of the *N*-terminal modification of the protein eventually.

Lastly, a variety of tetrapeptides bearing a *N*-terminal glycine will be synthesized by means of Fmoc Solid Phase Peptide Synthesis (SPPS), [11] followed by transformation of the peptide's *N*-terminal glycine to an aldehyde functionality by means of oxidation with pyridoxal 5′-phosphate (PLP). The amine-catalyzed aldol reaction will then be trialed on the modified tetrapeptides prior to working with myoglobin to ascertain if the desired aldol reaction would proceed on a short chain peptide. This would serve as an indication of the likely success of the reaction on myoglobin (Scheme **29**).



Scheme **29**. Aldol reaction on *N*-terminally modified myoglobin

2.3 EXPERIMENTS AND RESULTS

Screening of Aminocatalysts on Reaction of Ethyl Glyoxylate Hydrate with Acetophenone

Acetophenone was originally chosen as the ketone source to react with ethyl glyoxylate hydrate (**1**). However, it was found to give low yields of the aldol product **2** after several attempts (Table **2**), even under neat condition (Entries 1, 8, 9, 11, 13). Reaction in water with almost all the amino acids trialed proved unsuccessful, except under neat condition, where 4% yield was obtained (Entry 8). The highest yield

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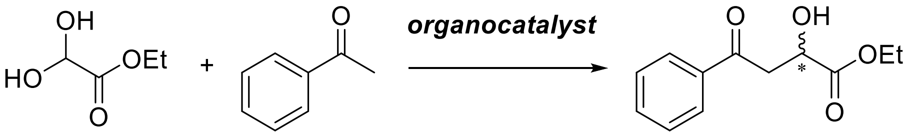
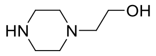
[11] *Fmoc Solid Phase Peptide Synthesis, A Practical Approach*; Chan, W. C.; White, P. D., Eds.; Oxford University Press: New York, USA, 2000.

achieved was 30% when 20 mol% of diethylenetriamine was used as catalyst under neat condition, without water (Entry 9). The low yield could be due to electronic effects from the aromatic ring, rendering the carbonyl carbon less electrophilic, hence the low reactivity observed.

Table **2**. Screening of aminocatalysts for the reaction between ethyl glyoxylate hydrate with acetophenone



1 acetophenone **2**

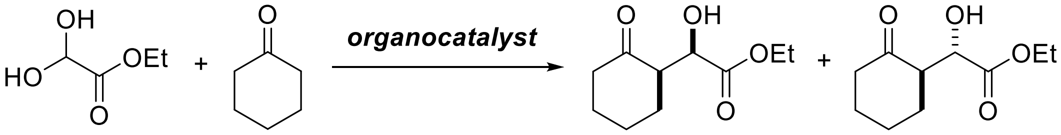
Entry	Organocatalyst	Cat. (mol%)	Ketone (equiv.)	Solvent	Solvent Volume	Additive	Yield of 2 (%)*
1	–	–	5	neat	–	–	0
2	L-Leucine methyl ester HCl	10	1	H_2O	2 mL	–	0
3	L-Tryptophan	10	1	H_2O	2 mL	–	0
4	L-Tyrosine methyl ester HCl	10	1	H_2O	2 mL	–	0
5	D-Threonine	10	1	pH 6.8 P_i buffer	2 mL	–	0
6	L-Lysine HCl	10	1	pH 6.8 P_i buffer	2 mL	–	0
7	D-Threonine	10	5	H_2O	0.9 mL	–	0
8	L-Lysine HCl	10	5	neat	–	–	4
9	$NH(CH_2CH_2NH_2)_2$	20	2	neat	–	–	30
10	$NH(CH_2CH_2NH_2)_2$	20	5	H_2O	0.25 mL	L-(+)-tartaric acid (60 mol%)	7
11		20	2	neat	–	–	8
12	EDDA	20	5	pH 10 NH_3 buffer	0.5 + 0.5 mL $MgSO_4$	–	0
13	EDDA	20	5	neat	–	–	2

* Isolated yield upon column chromatography

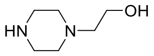
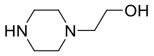
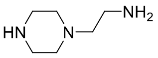
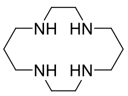
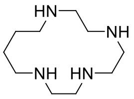
In view that the model reaction is to be carried out in water, we turned our attention next to the slightly water-soluble cyclohexanone as the ketone source instead. One possible complication from using cyclohexanone is that there will be two diastereomeric products possible, namely, the *erthyro* and *threo* isomer.

Screening of Aminocatalysts with Cyclohexanone

Table **3**. Screening of aminocatalysts for the reaction between ethyl glyoxylate hydrate with cyclohexanone



1 **3** (*erythro*) **3** (*threo*)

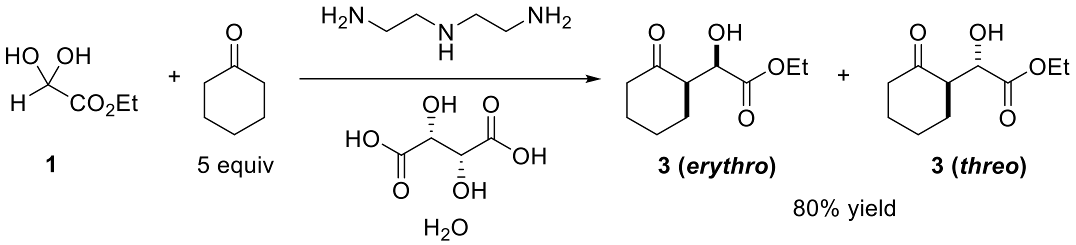
Entry	Organocatalyst	Cat. (mol%)	Ketone (equiv.)	Solvent	Solvent Volume	Additive	Yield of 3 (%)*
1	$NH(CH_2CH_2NH_2)_2$	20	2	$MgSO_4$	1 mL	–	33
2	$NH(CH_2CH_2NH_2)_2$	20	5	$MgSO_4$	0.25 mL	–	40
3	$NH(CH_2CH_2NH_2)_2$	20	2	neat	–	–	46
4	$NH(CH_2CH_2NH_2)_2$	20	5	neat	–	–	57
5	$NH(CH_2CH_2NH_2)_2$	10	5	neat	–	–	66
6	$NH(CH_2CH_2NH_2)_2$	20	5	H_2O	0.25 mL	L-(+)-tartaric acid (20 mol%)	64
7	$NH(CH_2CH_2NH_2)_2$	20	5	H_2O	0.25 mL	L-(+)-tartaric acid (40 mol%)	80
8	$NH(CH_2CH_2NH_2)_2$	20	5	H_2O	0.25 mL	L-(+)-tartaric acid (1 equiv.)	76
9	$NH(CH_2CH_2NH_2)_2$	20	5	H_2O	1.00 mL	L-(+)-tartaric acid (1 equiv.)	78
10	$NH(CH_2CH_2NH_2)_2$	20	5	H_2O	0.30 mL	–	42
11		20	5	neat	–	–	61
12		10	5	neat	–	–	63
13	EDDA	20	5	H_2O	0.5 mL	8 drops of pH 10 BH_3 buffer	49
14	L-Lysine HCl	20	5	H_2O	0.25 mL	–	46
15	L-Threonine	20	5	H_2O	0.25 mL	–	86
16	D-Threonine	20	5	H_2O	0.25 mL	–	83
17	D-Threonine	20	5	H_2O	1.00 mL	–	79
18	L-Tryptophan	20	5	H_2O	0.25 mL	–	61
19	L-Proline	20	5	H_2O	0.25 mL	–	45
20		20	5	H_2O	0.25 mL	–	59
21		20	5	H_2O	0.25 mL	–	21
22		20	5	H_2O	0.25 mL	–	55

* The yield of **3** is the combined yield of both the *erythro* and *threo* diastereomers after separation and isolation by column chromatography. The two diastereomers cannot be separated cleanly on column.

Cyclohexanone proved to be a more superior ketone source for the aldol reaction in water, compared to acetophenone (Table **3**). The amino acids screened (Entries 14–19) were found to give satisfactory results at 20 mol% loading, with the highest yield of **3** from threonine (entries 15 and 16). Increasing the volume of the water solvent four-fold from 0.25 mL to 1.00 mL was found to decrease the yield only slightly (Entry 17). Diethylenetriamine at 20 mol% loading was also found to be a satisfactory organocatalysts for our model system in water (Entries 6–10). Interestingly, the yield of the product was increased significantly when L-(+)-tartaric acid was added into the system (Entries 6–9), presumably serving the same function as the carboxyl group in amino acid catalysts, neutralizing the charge of the incipient oxyanion in the transition state (Scheme **27**). Nevertheless, adding more L-(+)-tartaric acid in fact led to slightly lower yield (Entries 7 and 8), with the highest yield obtained using 40 mol% of the additive (Entry 7).

Model Studies on Ethyl Glyoxylate Hydrate with Different Aminocatalysts

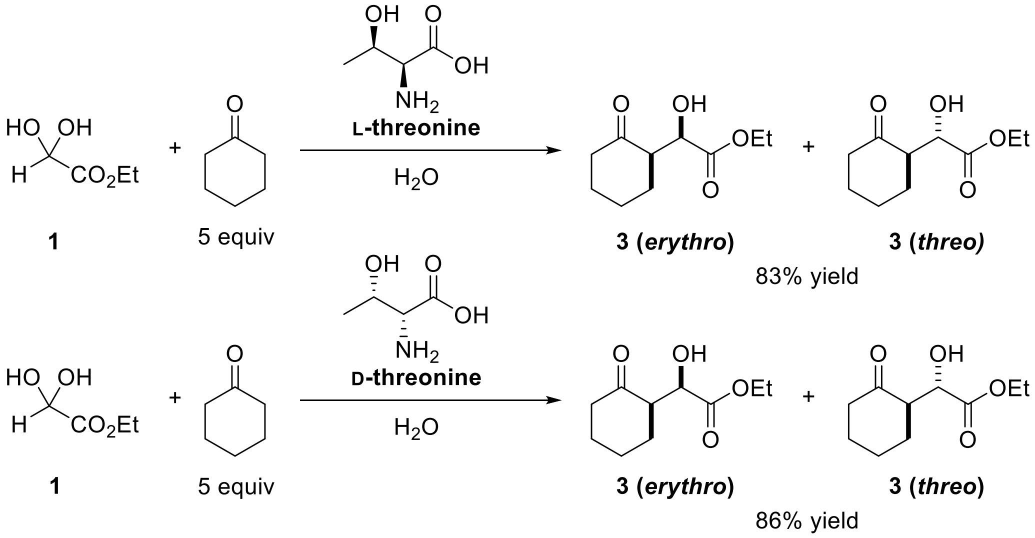
Ethyl glyoxylate hydrate was reacted with cyclohexanone (5 equiv.) using diethylenetriamine (20 mol%) as the organocatalyst and L-(+)-tartaric acid as a co-catalyst (40 mol%) (Scheme **30**). Although diethylenetriamine is achiral, we are interested in determining if addition of the enantiopure L-(+)-tartaric acid co-catalyst induces enantioselectivity in the product.



Scheme **30**. Direct aldol between ethyl glyoxylate hydrate and cyclohexanone, catalyzed by diethylenetriamine with L-(+)-tartaric acid

Following column chromatographic separation, the aldol product **3** was obtained as a mixture of the *erthyro* and *threo* diastereomers, in a combined yield of 80%. Upon benzoyl protection of the hydroxyl group in **3**, which introduces a chromophoric benzene ring, followed by analysis using chiral High Performance Liquid Chromatography (HPLC), negligible (if any) enantiomeric excess was observed for each individual diastereomers in this reaction.

Next, the aldol product obtained using the two enantiomeric amino acids, L- and D-threonine as organocatalysts, were analysed in hope of observing enantioselectivity in the reaction, and also to probe the effect of chirality of the aminocatalyst (Scheme **31**). The combined yields for the two reactions are 83% and 86% for the reaction using L- and D-threonine, respectively. Counter to our anticipation of considerably higher enantioselectivities, the enantiomeric excess was 5.8% for the *erythro* diastereomer and 9.2% for the *threo* diastereomer in the case of L- threonine, and the enantiomeric excess was 13.3% for the *erythro* diastereomer and 10.8% for the *threo* diastereomer in the case of D-threonine.



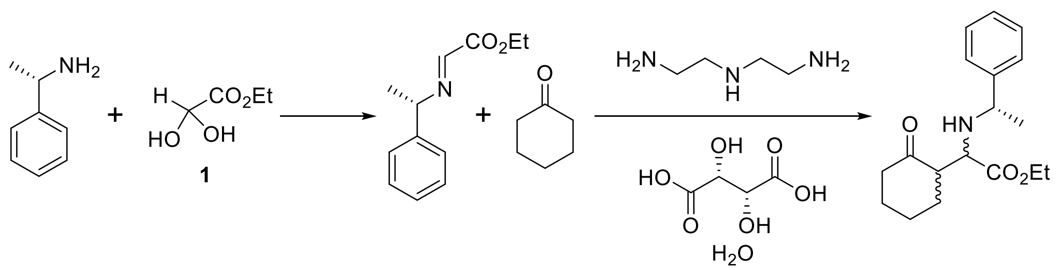
Scheme **31**. Direct aldol between ethyl glyoxylate hydrate and cyclohexanone, catalyzed by L- and D-threonine

Whilst indeed slightly higher enantiomeric excess is observed compared to using diethylenetriamine and L-(+)-tartaric acid, the enantioselectivity is however insignificant. Furthermore, in the two reactions using the pair of enantiomeric L- and D-threonine as organocatalysts, the (*S*)-configuration is favoured at the hydroxyl bearing chiral center in both cases. Hence, we conclude that probably the reaction did not proceed through a cyclic half-chair transition state (Scheme **27**) but possibly *via* an open-chain transition state instead. The (*S*)-configuration is plausibly the more stable configuration for the aldol product **3** inherently, since the aldol reaction should be thermodynamically controlled in this case.

<u>Model Studies on Mannich Reaction</u>

Prior to carrying out a Mannich reaction on the modified *N*-terminus of myoglobin, the aldehyde functionality must first be converted into an imine by condensation with a suitable primary amine, before the ketone-derived enamine can add to give the Mannich product. This also applies to our model studies with ethyl glyoxylate hydrate, where the Mannich reactions were carried out in a one-pot procedure.

We first attempted the one-pot Mannich reaction using an aliphatic primary amine, (*S*)-1-phenylethanamine, as shown in Scheme **32**.



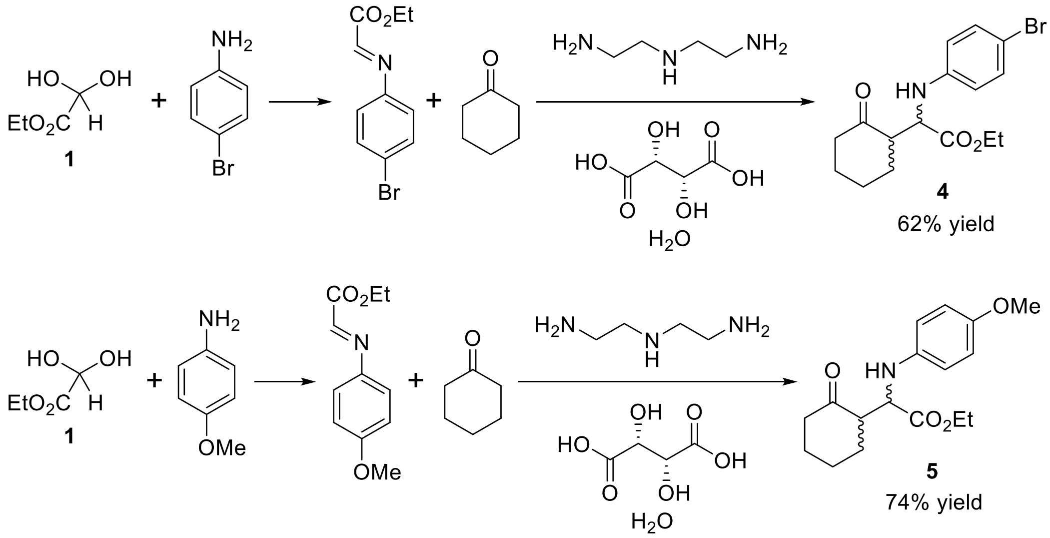
Scheme **32**. Mannich reaction between (*S*)-1-phenylethanamine, ethyl glyoxylate hydrate and cyclohexanone, catalyzed by diethylenetriamine with L-(+)-tartaric acid

Unfortunately, while thin layer chromatography (TLC) indicated that the imine was formed before the addition of cyclohexanone and aminocatalyst, instead the aldol product **3** was obtained in 53% yield rather than the desired Mannich adduct. This can be rationalized based on the fact that stoichiometric amount of (*S*)-1-phenylethanamine is used, which could potentially catalyze the aldol reaction as well. Analysis of the aldol product **3** using chiral HPLC revealed an.

Although the enantioselectivity of this reaction is again not significant, however, chiral HPLC indicated that the (*R*)-configuration is the preferred configuration at the hydroxyl bearing chiral center instead. This is contrary to the aldol reactions carried out previously utilizing L- and D-threonine as organocatalysts. The reason for the reversal in stereochemical is not known at this point in time.

In view of the failure of the aliphatic primary amine to afford the Mannich product, we directed our attention to two aromatic amines instead, namely, 4-bromoaniline and 4-methoxyaniline (Scheme **33**). The products for both reactions cannot be totally and cleanly separate by column chromatography. The yield of the products **4** and **5** after column chromatography was found to be 62% and 74% respectively. In order to isolate sufficient pure product for chiral HPLC analysis, preparatory TLC was performed on a fraction of the product isolated from column chromatography.

Unfortunately, **4** failed to separate on chiral HPLC and thus the enantiomeric excess of the reaction cannot be determined. On the other hand, the chromatogram for amine **5** was well-resolved and the enantiomeric excess was determined to be 8.0% for the *threo* diastereomer and 4.0% for the *erthryo* diastereomer. Once again, like the aldol reaction, the enantioselectivity of the Mannich reaction turns out to be insignificant.

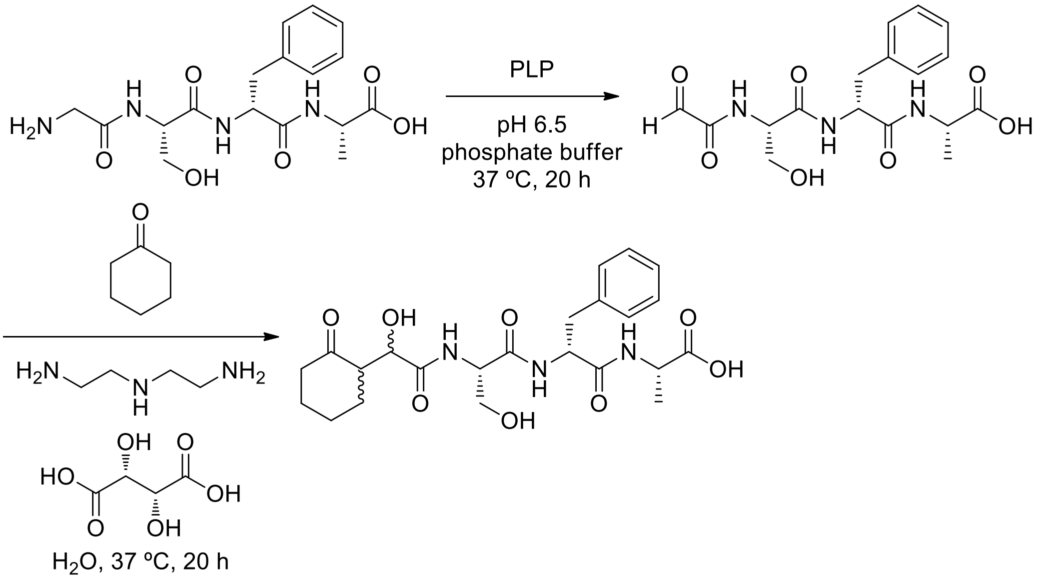


Scheme **33**. Mannich reaction between 4-bromoaniline and 4-methoxyaniline with ethyl glyoxylate hydrate and cyclohexanone, catalyzed by diethylenetriamine with L-(+)-tartaric acid

Model Studies on Tetrapeptides

Fmoc Solid Phase Peptide Synthesis (SPPS) was carried out to synthesize a variety of tetrapeptides required to do the organocatalysed aldol reaction. Each of the tetrapeptide was reacted with pyridoxal 5′-phosphate in a pH 6.5 phosphate buffer solution for 20 hours at 37 ºC.[1,2] The aldehyde obtained was immediately reacted with cyclohexanone, catalyzed by diethylenetriamine with L-(+)-tartaric acid. The two reactions, done in a one-pot manner are as shown in Scheme **34** for the tetrapetide, Gly-Ser-Phe-Ala.

We commenced analysis and tracking of the reaction mixture using reverse-phase LC-MS. Although LC-MS analysis indicated that approximately 85% of the peptide was converted to the corresponding aldehyde by 20 hours, there was not desired aldol addition product detected on LC-MS. This could be due to the rather low solubility of cyclohexanone in water and the larger volume of buffer required as solvent for the reaction with the tetrapeptide, rendering the reaction infeasible. We decided to substitute with hydroxyacetone, which is freely soluble in water, as the source of ketone instead.



Scheme **34** Direct cyclohexanone aldol on *N*-terminally modified tetrapeptide, gly-ser-phe-ala, catalyzed by diethylenetriamine with L-(+)-tartaric acid

As expected, when hydroxyacetone is used, the desired product can be observed in LC-MS. Unfortunately, attempts to isolate the product using semi-preparative HPLC failed. We decided to use LC-MS to determine the percentage conversion for a series of five tetrapeptides synthesized using Fmoc SPPS. The results are tabulated below:

Table **4**. Aldol addition of hydroxyacetone to N-terminally modified tetrapeptides

Peptide	**Ketone**	**% Conversion (based on LC-MS)**
GDAF (gly-asp-ala-phe)	Hydroxyacetone	36%
GDVF (gly-asp-val-phe)		25%
GAVF (gly-ala-val-phe)		36%
GHVF (gly-his-val-phe)		80%
GYVF (gly-tyr-val-phe)		27%

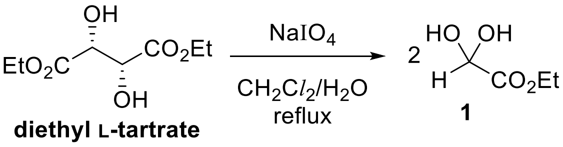
In bid to try to isolate the aldol adducts, we also attempted to perform the transamination and aldol reaction on the Wang resin beads, followed by cleavage. However, cleavage of the modified tetrapeptides from the beads using the standard trifluoroacetic acid cocktail proved too strong and unidentified signals where observed in the LC-MS.

Despite achieving partial success in applying the aminocatalyzed ketone aldol reaction with the tetrapeptides, albeit having problem isolating the modified peptides, more importantly, due to the unavailability of LC-ESI-MS, work on myoglobin was not attempted.

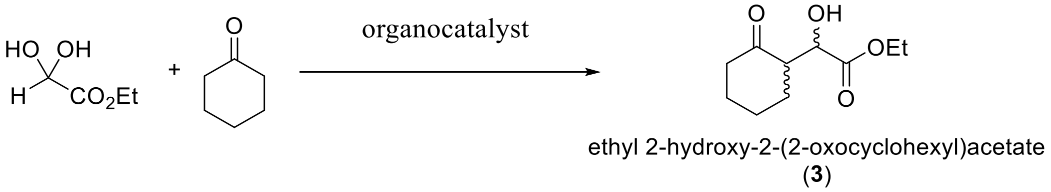
2.4 EXPERIMENTAL SECTION

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. DMSO-d_6 and $CDCl_3$ were obtained from Cambridge Isotope Laboratories, Inc. and used as received. 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, br = 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). 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.

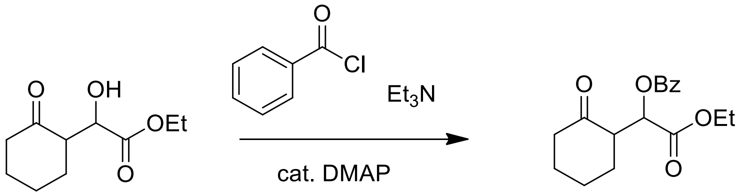
Characterization Data:



Ethyl Glyoxylate Hydrate (1).[10] To a solution of diethyl L-tartrate (5 g, 24.2mmol, 1 equiv.) in CH_2Cl_2 (50 mL), $NaIO_4$ (10.4 g, 46.5 mmol, 2 equiv.) was added at room temperature. Water (10 mL) was then added to the reaction mixture. The mixture was then heated to reflux with rapid stirring for 2 hours. The reaction mixture was then cooled to 0°C and $MgSO_4$ (20 g) was added portion wise with stirring. The mixture was stirred for 15 minutes, after which the solids were removed by vacuum filtration. The solids were washed twice with CH_2Cl_2 (50 mL). The solvent was removed *via vacuo* to give ethyl glyoxylate hydrate, a white opaque oil (3.58 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.31 (t, J = 7.1 Hz, 3H), 4.24 (m, 2H), 4.60–5.40 (br m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.76, 62.32, 88.32, 168.87 ppm.

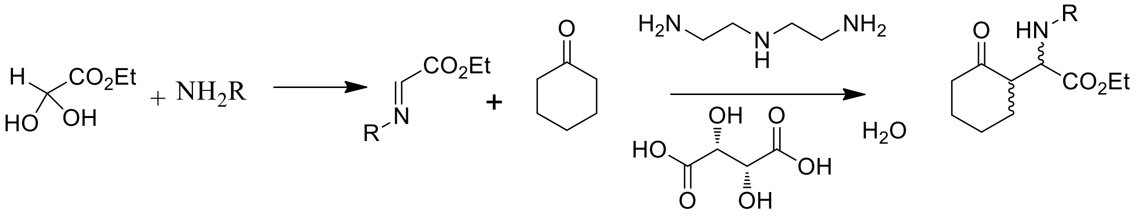


Ethyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (3). Ethyl glyoxylate hydrate (0.20 g, 1.66 mmol, 1 equiv.) was weighed into a round bottomed flask and water (0.25 mL) was added. Cyclohexanone (0.86 ml, 8.33mmol, 5 equiv.) was added and the mixture was stirred. The organocatalyst (0.33 mmol, 20 mol%) was added to the reaction mixture and the mixture was stirred overnight. The reaction mixture was then columned directly (hexane-ethyl acetate, gradient, 0 to 20%) to give a viscous pale yellow oil. R_f = 0.42 (hexane-ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) *anti* δ 1.22 (t, *J* = 7.32 Hz, 3H), 1.54–1.72 (m, 2H), 1.81–1.93 (m, 2H), 1.99–2.09 (m, 2H), 2.20–2.28 (m, 1H), 2.33–2.38 (m, 1H), 2.90 (ddd, *J* = 12.8, 5.49, 3.66 Hz, 1H), 3.15 (d, *J* = 6.10 Hz, 1H), 3.96 (m, 1H), 4.18 (dq, *J* = 1.83, 7.32 Hz, 2H) ppm ; *syn* δ 1.25 (t, *J* = 7.32 Hz, 3H), 1.57–1.69 (m, 2H), 1.82–1.91 (m, 3H), 2.00–2.05 (m, 1H), 2.24–2.33 (m, 1H), 2.40–2.45 (m, 1H), 2.74–2.79 (m, 1H), 2.98 (br s, 1H), 4.21 (q, *J* = 7.32 Hz, 2H), 4.63 (d, *J* = 1.83 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) *anti* δ 14.2, 24.9, 27.0, 30.2, 42.1, 53.8, 61.7, 71.2, 173.5, 211.3 ppm ; *syn* δ 14.3, 24.7, 27.0, 27.2, 42.0, 53.9, 61.8, 69.3, 173.7, 210.5 ppm.

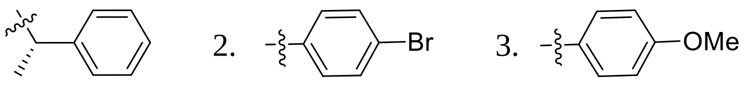


2-Ethoxy-2-oxo-1-(2-oxocyclohexyl)ethyl benzoate. To a solution of ethyl 2-hydroxy-2-(2-oxocyclohexyl)acetate (1 equiv.) in CH_2Cl_2 (4 mL), Et_3N (1.5 equiv.) in CH_2Cl_2 (3 mL) was added as well as DMAP (catalytic amount). The reaction mixture was then stirred at 0 ºC. Benzoyl chloride (1.5 equiv.) in CH_2Cl_2 (3 mL) was then added to the cooled mixture and the mixture was stirred overnight at room temperature. Water (20 mL) was added to the reaction mixture and the mixture was stirred. Aqueous hydrochloric acid (1M, 20 mL) was added to the reaction mixture and the mixture was stirred. The mixture was then extracted with ether (3×30 mL) and the organic phase was washed with concentrated aqueous sodium bicarbonate (1×50 mL) and brine (1×50 mL). Anhydrous magnesium sulphate was then added to the organic phase to remove water. The solvents were then removed under vacuum and the product obtained was columned (hexane-ethyl acetate, gradient, 0 to 10%). R_f = 0.61 (hexane-ethyl acetate, 1:1). HPLC analysis Chiralpak AD-H + AS-H (hexane / ^{i}PrOH = 90 / 10, 0.9 mL/min, 280nm) 23.1 min (2*S*,1'*R*), 24.8 min (*syn*), 26.6 min (2*R*,1'*S*), 32.3 min (*syn*). ^{1}H NMR (400 MHz, $CDCl_3$) distinguishable *anti* δ 1.23 (t, *J* = 7.25 Hz, 3H), 3.23 (dt, *J* = 11.8, 5.44 Hz, 1H), 4.20 (q, *J* = 7.25 Hz, 2H), 5.48 (d, *J* = 4.98 Hz, 1H) ppm; distinguishable *syn* δ 1.25 (t, *J* = 7.25 Hz, 3H), 3.01 (ddd, *J* = 3.17, 5.44, 12.23 Hz, 1H), 4.21 (q, *J* = 7.25 Hz, 2H), 5.88 (d, *J* = 3.17 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) *anti* δ 14.0, 24.5, 26.8, 29.4, 41.7, 51.6, 61.4, 70.9, 128.3, 129.3, 129.8, 133.3, 165.9, 169.1, 207.6 ppm ; *syn* δ 14.0, 24.5, 26.7, 27.7, 41.6, 51.4, 61.5, 70.1, 128.3, 129.5, 129.7, 133.2, 165.5, 169.6, 207.3 ppm.

Mannich Reaction

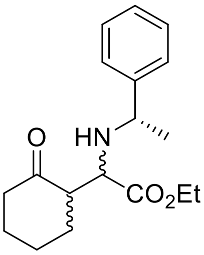


R: 1. 2. 3.



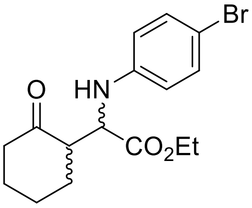
NH_2R (1.83 mmol, 1.1 equiv.) was added to ethyl glyoxylate hydrate (0.20 g, 1.66 mmol, 1 equiv.) at room temperature and the reaction was stirred for half an hour. The reaction mixture was then cooled to 0°C and cyclohexanone (0.86 mL, 8.30 mmol, 5 equiv.) was added and mixture was stirred. Water (0.25 mL) was added to the reaction as well as L-(+)-tartaric acid (0.100 g, 0.66 mmol, 40 mol%). Diethylenetriamine (0.036 mL, 0.33 mmol, 20 mol%) was then added and the reaction was stirred overnight at room temperature. The reaction mixture was columned directly (hexane-ethyl acetate).

R = 1,



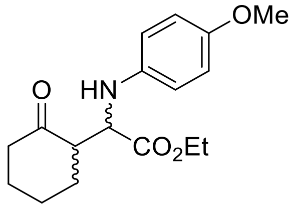
Ethyl 2-(2-oxocyclohexyl)-2-(((S)-1-phenylethyl)amino)acetate. Product not obtained.

R = 2,



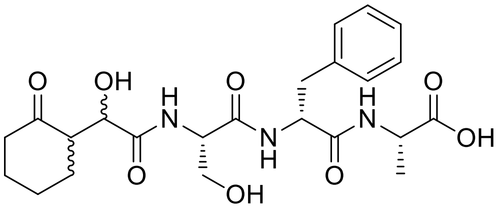
Ethyl 2-((4-bromophenyl)amino)-2-(2-oxocyclohexyl)acetate (4). HPLC analysis Chiralpak AS-H (hexane/ ^{i}PrOH = 90/ 10, 1.0 mL/min, 280nm) Failed to separate. ^{1}H NMR (400 MHz, $CDCl_3$) *anti* δ 1.16 (t, *J* = 7.25 Hz, 3H), 1.53–2.38 (m, 8H), 3.12 (m, 1H), 3.73 (br s, 1H), 4.10 (q, *J* = 7.25 Hz, 2H), 4.56 (d, *J* = 9.97 Hz), 6.48 (m, 2H), 7.18 (m, 2H) ppm ; *syn* δ 1.22 (t, *J* = 7.25 Hz, 3H), 1.62–2.54 (m, 8H), 2.83 (m, 1H), 4.16 (q, *J* = 7.25 Hz, 2H), 4.23 (br s, 1H), 4.36 (d, *J* = 6.80 Hz, 1H), 6.61 (m, 2H), 7.23 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) *anti* δ 14.1, 24.6, 26.9, 30.6, 41.9, 53.4, 57.4, 61.4, 109.7, 115.3, 131.9, 147.2, 172.4, 211.2 ppm ; *syn* δ 14.1, 24.8, 26.9, 29.9, 41.8, 53.3, 56.5, 61.3, 110.0, 115.6, 131.9, 146.1, 172.8, 210.0 ppm.

R = 3,



Ethyl 2-((4-methoxyphenyl)amino)-2-(2-oxocyclohexyl)acetate (5). HPLC analysis Chiralpak AS-H (hexane/ ^{i}PrOH = 90/ 10, 1.0 mL/min, 280nm) 12.2 min (2*R*,1′*S*), 15.2 min (*syn*), 16.7 min (2*S*,1′*R*), 19.1 min (*syn*). ^{1}H NMR (400 MHz, CDCl$_3$) *anti* δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.61–2.46 (m, 8H), 3.08–3.13 (m, 1H), 3.73 (s, 3H), 3.99 (br s, 1H), 4.15 (m, 2H), 4.24 (m, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H) ; *syn* δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.58–2.51 (m, 8H), 2.83 (dt, *J* = 12.4, 5.2 Hz, 1H), 3.77 (s, 3H), 3.92 (br s, 1H), 4.21–4.14 (m, 2H), 4.25 (br s, 1H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 9.2 Hz, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) *anti* δ 14.1, 24.5, 26.8, 30.5, 41.8, 53.6, 55.7, 59.1, 61.2, 114.7, 115.6, 142.1, 152.7, 173.0, 210.9 ppm ; *syn* δ 14.2, 24.8, 26.9, 29.6, 41.9, 53.4, 55.7, 58.1, 61.1, 114.8, 116.1, 141.1, 153.1, 173.5, 210.1 ppm.

Representative experimental procedure for the aldol reaction with tetrapeptides:



(2*S*)-2-((2*R*)-2-((2*S*)-3-Hydroxy-2-(2-hydroxy-2-(2-oxocyclohexyl)acetamido)-propanamido)-3-phenylpropanamido)propanoic acid. To a solution of the tetrapeptide in phosphate buffer (2 mL, 0.0123 mmol, 1 equiv.), phosphate buffer (4.14 mL, 25 mM, pH 6.5) was added. The reaction mixture was placed in a 37 ºC water bath and stirred. Pyridoxal 5′-phosphate in phosphate buffer (6.14 mL, 0.123 mmol, 10 equiv.) was then added to the reaction mixture and the mixture was stirred for 20 hours at 37 ºC. Cyclohexanone (1 mL, 9.65 mmol, 750 equiv.) was then added to the reaction mixture. L-(+)-Tartaric acid (0.1106 g, 0.737 mmol, 60 equiv.) was then added to the mixture. Diethylenetriamine (0.0398 mL, 0.368 mmol, 30 equiv.) was added to the reaction mixture and the mixture was stirred for 23 hours at 37 ºC. The mixture was then extracted with chloroform (3×50 mL) and brine (1×50 mL). Anhydrous sodium sulphate was added to remove water. The solvents were then evaporated under vacuum and the product was columned. Product was not isolable.

CARBON–CARBON BOND FORMATION REACTIONS

PART II : CONTEMPORARY C–H BOND ACTIVATION/FUNCTIONALIZATION

CHAPTER 3

Palladium-Catalyzed Olefination of Enamides at the β-Position of the Double Bond and its Mechanistic Study

CHAPTER 3 PALLADIUM-CATALYZED OLEFINATION OF ENAMIDES AT THE β-POSITION OF THE DOUBLE BOND AND ITS MECHANISTIC STUDY

3.1 INTRODUCTION

Heck reaction, the arylation or vinylation of alkenes with aryl or vinyl halides or pseudohalides, is among the most valuable palladium-catalyzed reactions and has developed into one of the most effective tools for forging new carbon-carbon bonds in organic synthesis.[1] By and large, Heck arylation and olefination of alkenes possessing electron-withdrawing groups (*e.g.* –CO_2R and CN) is largely selective towards the less-substituted β-position of the alkene double bond. On the other hand, similar Heck arylation or olefination of alkenes bearing electron-rich substituents usually provide a mixture of both α- and β-substituted regioisomeric alkenes.[2] Hence, control over regioselectivity of the Heck reaction has remained a widely researched area for many years.

Hallberg and co-workers observed that the electronic properties of the aromatic rings and choice of halide additives and ligands can exert control over the regioselectivity of enol ethers.[3] Significant progress was made by Cabri and co-workers,[2b,4] when they revealed that the choice of ligands and leaving groups of the

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[1] (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.

[2] 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**.

[3] (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.

[4] (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.;

aryl substrates wield control over the regioselectivity of arylation involving electron-rich alkenes. The regioselective arylation or olefination of electron-rich alkenes, such as acyclic enol ethers,[5] enol amides[6] and silanes[7] subsequently became well-established.

Enamide represents an important functional group that is commonly found in natural products as well as some designer pharmaceuticals, which also functions as a class of electron-rich alkenes.[8] Due to the synthetic importance associated with the arylation and olefination products of enamides, the reaction had gained much prominence. Earlier in 1990s, Hallberg and co-workers reported an alternative route to α-substituted nitrogen heterocycles, involving a palladium-catalyzed tandem α-arylation/ isomerization reaction of cyclic enamides with aryl iodides.[9] Mechanistic study revealed that a *syn* 1,2-addition to the enamide double bond first takes place, furnishing an unstable σ-adduct which subsequently decomposes to give a non-conjugated alkene by *syn* elimination of a hydridopalladium species. The alkene undergoes further addition and elimination of hydridopalladium, leading to migration of the double bond and conjugation with the π-electrons of nitrogen, regenerating an enamide (Scheme **35**).

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.

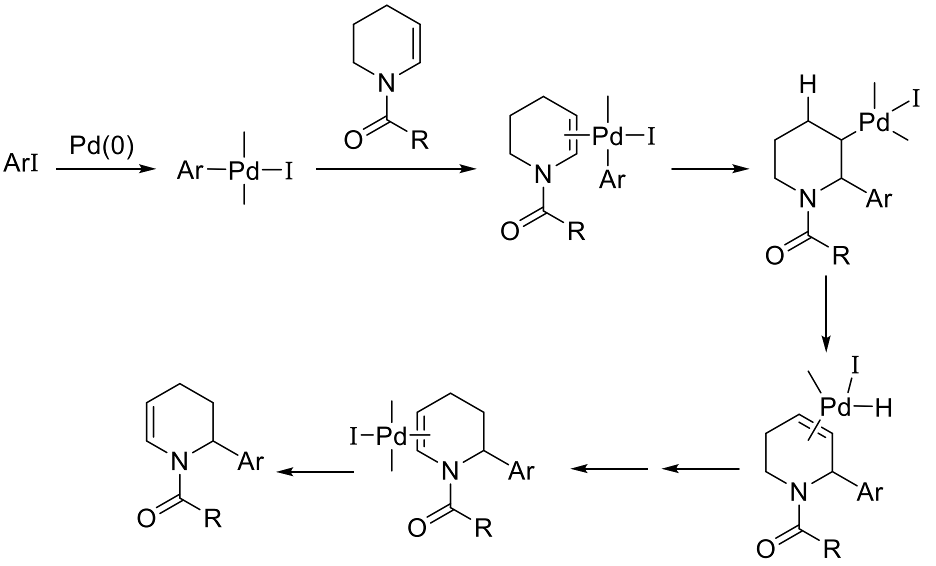
[5] (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146. (b) Andersson, C-M.; Hallberg, A.; Jr, G. D. D. *J. Org. Chem.* **1987**, *52*, 3529–3536.(c) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1979**, *44*, 21–23.

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

[7] (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.

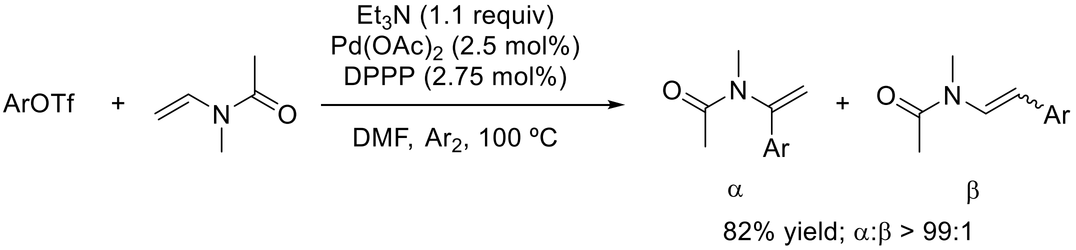
[8] *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, **1977**; Vol. 3.

[9] (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.



Scheme **35**

Soon after, Cabri and co-workers reported a significant development.[4a,4b] Essentially complete α-regioselectivity was observed in the arylation of vinyl pyrrolidinone and *N*-methyl-*N*-vinylacetamide, using trifluoromethanesulfonate as the leaving group on the aryl moiety, and DPPP as the ligand (Scheme **36**). In sharp contrast, when tri-*o*-tolylphosphine was used as the ligand in a previous piece of work, only a regioselectivity of α:β = 40:60 was achieved.[10]



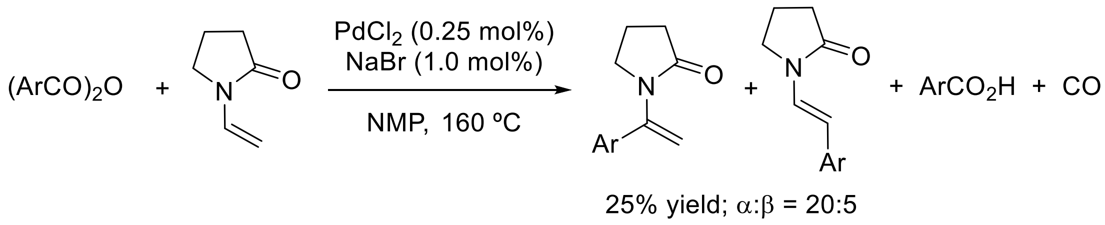
Scheme **36**

Use of aromatic carboxylic anhydrides as the arylating source for *N*-vinyl-2-pyrrolidinone provided a mixture of isomeric *N*-styrylpyrrolidinones (α:β = 4:1) in 25% yield (Scheme **37**).[11]

---

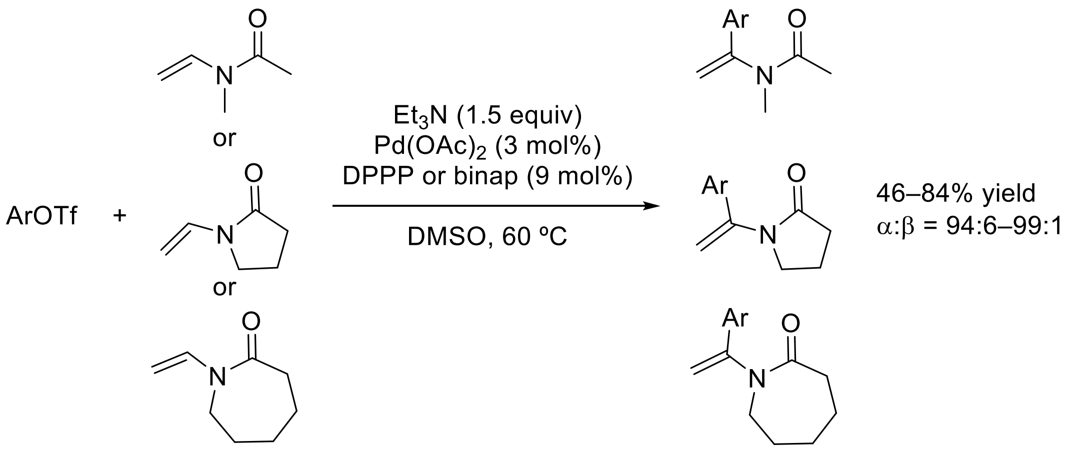
[10] Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949–2952.

[11] Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem. Int. Ed.* **1998**, *37*, 662–664.



Scheme **37**

In yet another example, arylated enamides were obtained in moderate to high yields and good regioselectivities in the reaction between electron-rich enamides with aryl triflates, catalyzed by Pd(OAc)$_2$ in the presence of bidentate phosphine ligands and triethylamine as base, in DMSO solvent (Scheme **38**).[12]



Scheme **38**

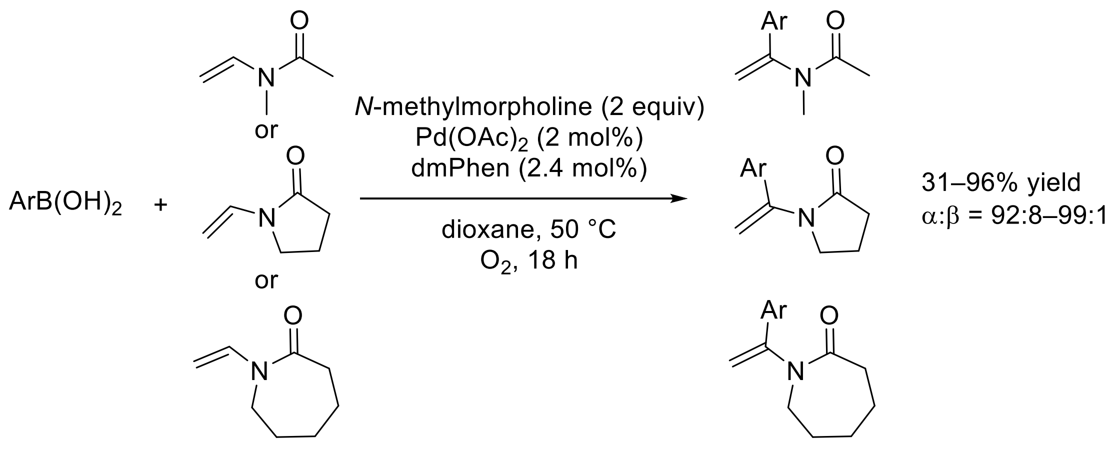
Larhed and co-workers reported the regioselective coupling of enamides with arylboronic acids in dioxane, catalyzed by Pd(OAc)$_2$ in the presence of a phenanthroline derivative ligand, under an atmosphere of oxygen (Scheme **39**).[13] Extension of the catalytic coupling conditions described by Cabri *et al.*[4a] to unprotected *N*-vinylacetamide afforded the products in moderate to good yields and >19:1 regioselectivity (Scheme **40**).[14] However, the substrate scope explored was limited.

---

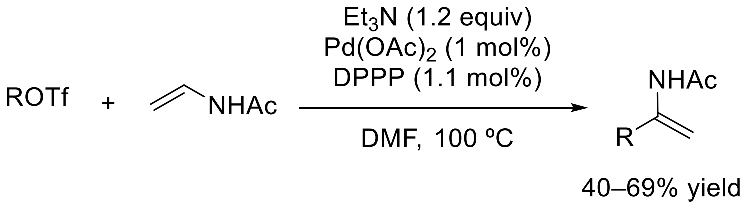
[12] Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639–6645.

[13] Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212–5218.

[14] Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277–9280.



Scheme **39**



Scheme **40**

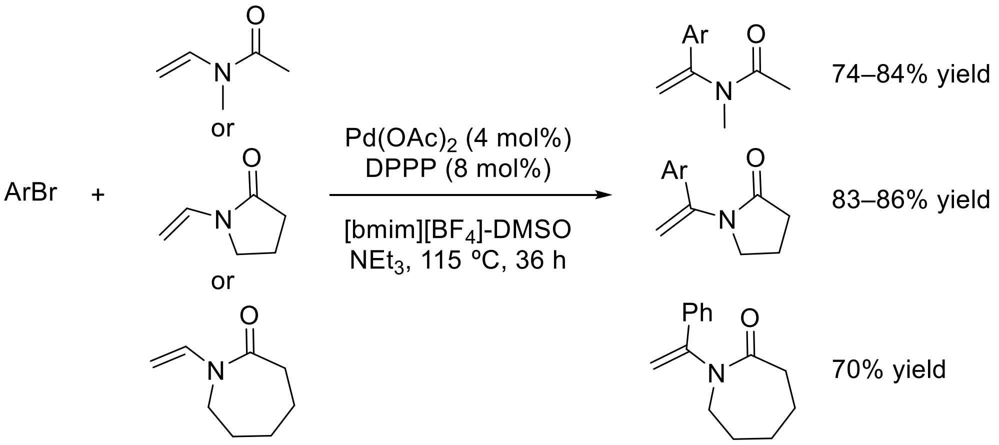
Skrydstrup and co-workers subsequently reported a detailed study on the Pd(0)-catalyzed coupling of *N*-vinylacetamide or *N*-acyl-*N*-vinylamines with aryl triflates,[15] which furnished the desired products in good to excellent yields and excellent α-regioselectivities. More importantly, the products which lack an *N*-alkyl substituent possess potential synthetic versatility and value.

Recently, use of the ionic liquid [bmim][BF_4] as solvent in the arylation of enamides under Pd-DPPP catalysis with a variety of aryl bromides and iodides was unveiled by Xiao and co-workers (Scheme **41**),[16] which provided solely the branched alkenes in high isolated yields. The branched products were believed to result from the dissociation of the halide ion from palladium, facilitated by the ionic liquid.

---

[15] Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997–6003.

[16] (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.



Scheme **41**

On the basis of the above literature review, we realized that direct coupling between enamides and non-prefuctionalized substrates, particularly β-functionalization of enamides, is rarely studied. Our group had developed a direct cross-coupling between alkenes catalyzed by palladium, in which the diene-containing products were obtained in moderate to good yields.[17] Herein, we present development of the olefination reaction of enamides at the β-position.

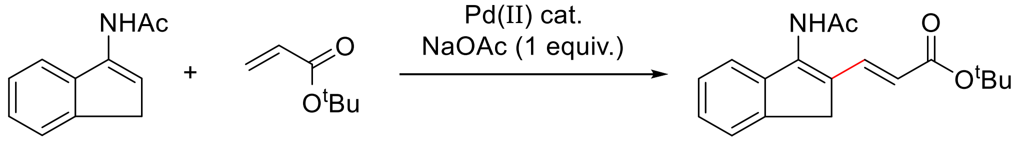
3.2 EXPERIMENTS AND RESULTS

Initial efforts were directed towards the development of an efficient catalytic system and subsequent optimization of the reaction conditions. This involves screening the reaction of *N*-(3*H*-inden-1-*yl*) enamide (**1a**) and *tert*-butyl acrylate (**2a**) under a variety of reaction conditions, as well as employing different palladium catalysts and oxidants. The results are shown in Table **5**. Using the conditions previously developed by our group, consisting of 20 mol% $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ (1 equiv) and one atmosphere of oxygen as oxidant in a solvent mixture of DMSO/HOAc (v/v=1:1), the reaction furnished the desired product in 50% isolated yield upon heating for 24 hours at 60 ºC (Table **5**, entry 1).

---

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

Table **5**. 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[d]	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[f]	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

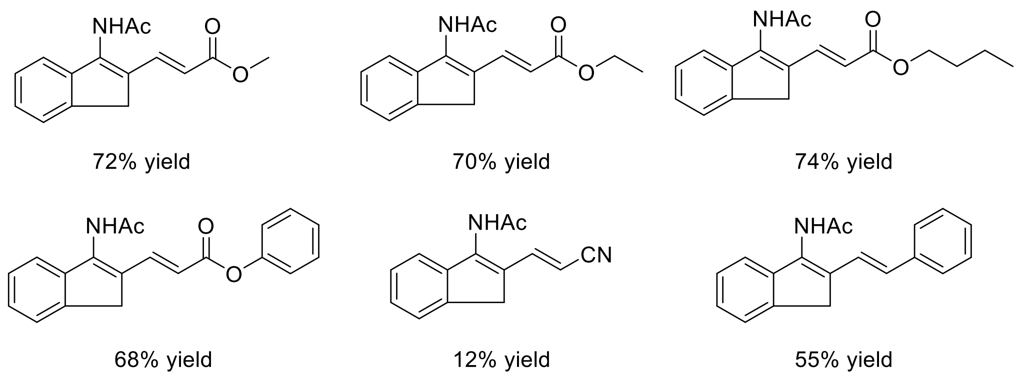
Decomposing of the starting material during the coupling is partly responsible for the low yield observed, where a 3:2 ratio was observed for the ratio of decomposed starting material to desired product, while in the absence of $Cu(OAc)_2$, the ratio decreased to 1:1. Screening of the organic stoichiometric oxidants revealed that benzoquinone (BQ) and *tert*-butyl hydroperoxide were less efficient, while only trace amount of product was observed with H_2O_2 amid essentially quantitative decomposition of the enamide.

DMSO is not a good solvent for the reaction and the starting material was recovered after 24 hours (Table **5**, entry 2). It was found that 80% yield was achieved using acetic acid as solvent, with 10 mol% of palladium(II) acetate as catalyst, oxygen as the sole oxidant and one equivalent of sodium acetate as additive, at 80 °C (Table **5**, entry 3). However, the yield was lowered significantly upon decreasing the catalyst loading to 5 mol% (Table **5**, entry 4), while increasing the amount of NaOAc had no significant effect (Table **5**, 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 **5**, entries 6, 8, 9 and 10), while use of $Pd(PPh_3)Cl_2$ gave no desired product (entry 7). It was also observed that only 37% yield was achieved when the ratio of **1a**:**2a** was changed to 1:4. The control experiment carried out in the absence of palladium catalyst returned no desired product.

Besides *tert*-butyl acrylate, a variety of different electron-deficient coupling partners were subjected to this cross-coupling reaction under the optimized conditions (Table **6**). High yields of the desired product was observed with methyl acrylate, ethyl acrylate, *n*-butyl acrylate and phenyl acrylate. Low yield of only 12% was obtained with acrylonitrile, while styrene furnished the corresponding cross-coupling product in 55% yield. Thus, *tert*-butyl acrylate emerged as the best coupling partner in our system.

Table **6**. Direct cross-coupling reaction of α-methylstyrene with various coupling partners.*



72% yield

70% yield

74% yield

68% yield

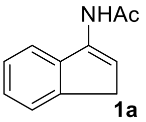
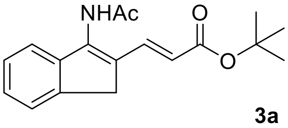
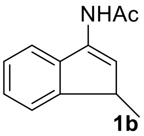
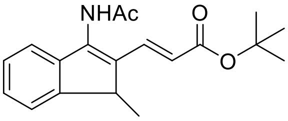
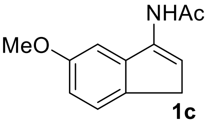
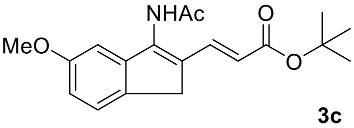
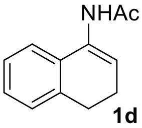
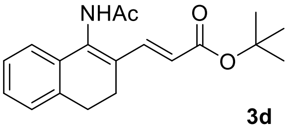
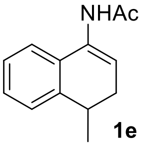
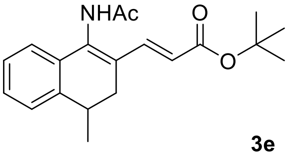
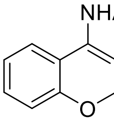
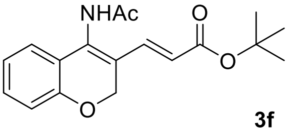
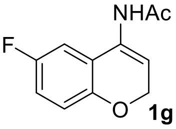
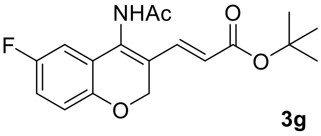
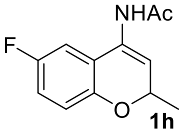
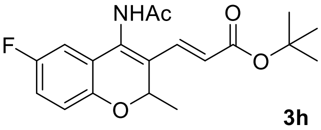
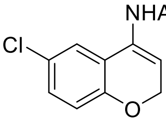
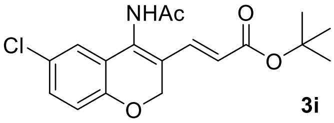
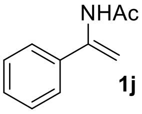
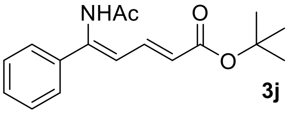
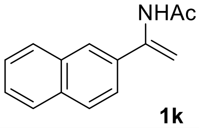
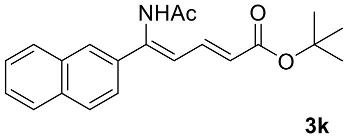
12% yield

55% yield

* 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).

Next, various enamides derivatives were screened with *tert*-butyl acrylate using 10 mol% Pd(OAc)$_2$. From the results in Table **7**, high yields are achieved with both cyclic

Table **7**. Direct cross-coupling reaction of *tert*-butyl acrylate with various coupling partners.*

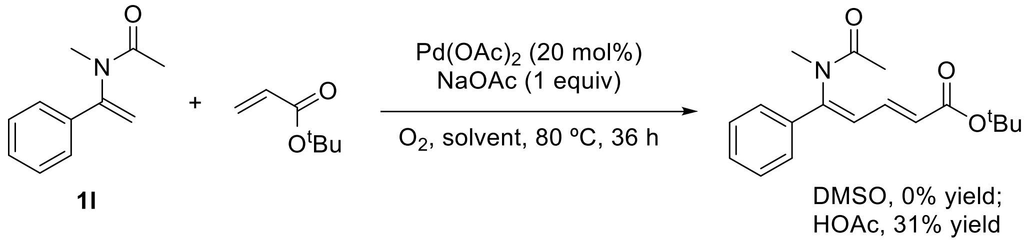
entry	starting material	product	solvent	yield(%)^a
1	 **1a**	 **3a**	HOAc	80
2	 **1b**	 **3b**	HOAc	67
3	 **1c**	 **3c**	HOAc	79
4	 **1d**	 **3d**	HOAc	74
5	 **1e**	 **3e**	HOAc	57 (82)^c
6	 **1f**	 **3f**	DMSO	76
7	 **1g**	 **3g**	HOAC DMSO	55 70*
8	 **1h**	 **3h**	HOAc DMSO	57 45^{b*}
9	 **1i**	 **3i**	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.

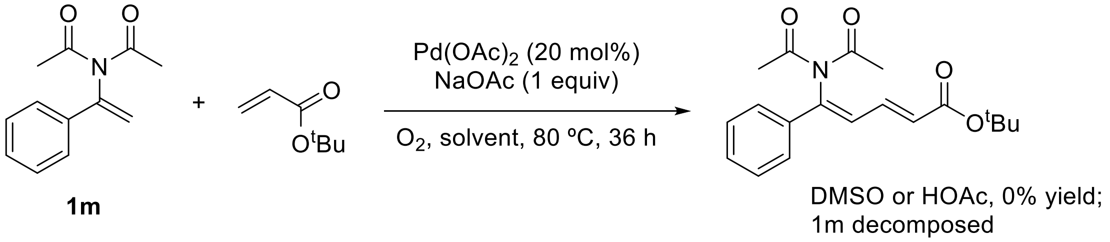
enamide (Table **7**, entries 1–9) as well as acyclic enamides (Table **7**, entries 10 and 11). There are no obvious trends in the effect of ring substituents: the reaction tolerates electron-donating groups well (Table **7**, entry 3), while the yield dropped slightly with moderately electron-withdrawing groups (Table **7**, entries 7–9). The yield in acetic acid was also lowered in the presence of a methyl group on the alicyclic ring (Table **7**, entries 2 and 5). It is noteworthy that halide substituents are tolerated, which can serve as handles for further transformations (Table **7**, entries 7–9).

The success of this coupling reaction was found to be highly dependent upon the choice of solvent. Acetic acid serves as a good solvent in the case of indanone- and tetralone-derived enamides, affording good yields of the products (Table **7**, entries 1–5). On the other hand, the use of DMSO is crucial for obtaining high yield with 4-chromanone-derived enamide **1f**, which otherwise decomposed completely in acetic acid. Both acetic acid and DMSO can furnish the desired product in moderate yields for substrates **1g** and **1h**. DMSO is the solvent of choice for acyclic substrates, providing the corresponding products in moderate yields (Table **7**, entries 10 and 11).

N-methyl protected enamide **1l** was also observed to be less reactive under the reaction condition 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 (*Scheme **42***). The desired product was obtained in only 31% yield with 55% of **1l** recovered (on the basis of the amount of **1l** used). However, no product was obtained with the *N*-acetyl protected enamide **1m** despite stirring in DMSO or HOAc for 36 h (*Scheme **43***). The nitrogen atom in **1l** may poison the $Pd(OAc)_2$ catalyst due to its powerful coordinating ability. Protonation of the basic **1l** under acidic condition could have lowered its ability to bind to the palladium somewhat, hence affording the corresponding product in low yield. On the other hand, the poor reactivity of **1m** in this reaction may be ascribed to its instability.



Scheme **42**



Scheme **43**

3.3 MECHANISTIC STUDY

In attempt to delineate the mechanism of this coupling reaction, *N*-(1-phenylvinyl)acetamide (0.1 mmol) and palladium(II) acetate (0.11 mmol) were added to DMSO-d_6 (0.5 ml) in a NMR tube at room temperature (25 °C) and the solution agitated for 15 minutes at 25 °C followed by monitoring using ^{1}H NMR spectroscopy. The signal from the terminal alkenyl proton $\mathbf{H^a}$ was observed to disappear nearly completely from the spectrum. The signal for $\mathbf{H^a}$ was distinguished from that of $\mathbf{H^b}$ *via* 2-D NOESY experiment where correlation is seen between $\mathbf{H^b}$ and the aryl protons but not $\mathbf{H^a}$ (Figure **2**). The 3H singlet from the acetyl group also exhibited a slight downfield shift, which suggested possible coordination between the carbonyl group and the Pd atom. Both observations seems to point to formation of a six-membered cyclic vinylpalladium intermediate.

In bid to establish the intermediacy of the six-membered cyclic vinylpalladium species in the coupling process, *tert*-butyl acrylate was introduced into the DMSO-d_6

solution containing the vinylpalladium intermediate, and the mixture heated at 80 °C

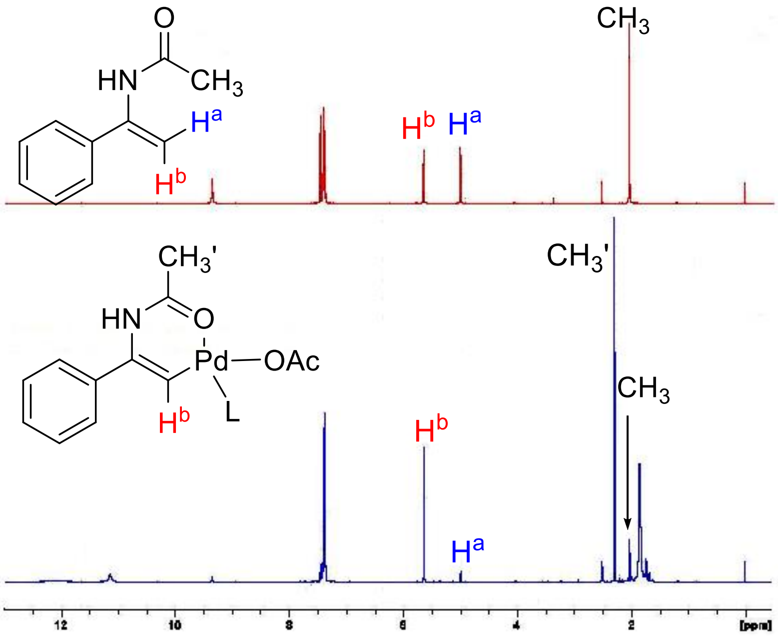
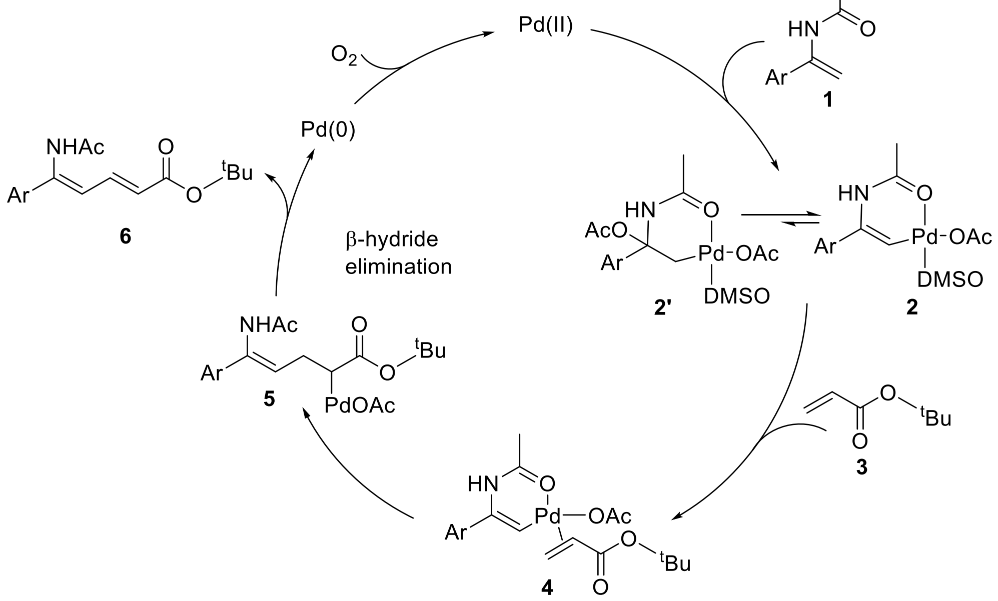


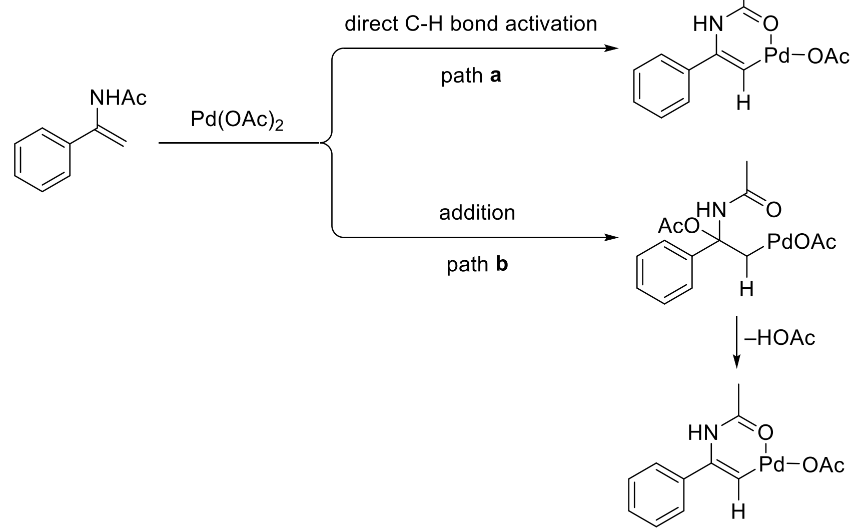
Figure **2.** ^{1}H NMR spectrum of enamide before and after complexation with Pd

for another 24 hours. Not surprisingly, the desired product **3j** was indeed observed and isolated in 43% yield. With this understanding a plausible mechanism is proposed in Scheme **44**, which involves first, activation of the *sp*^{2} C–H bond of enamide **1** by the Pd(II) complex to form the six-membered palladacycle intermediate **2** (intermediate **2´** is another possible intermediate which cannot be ruled out during this reaction). Next, coordination of the acrylate to Pd, followed by migratory insertion, provides intermediate **5**. Finally, β-hydride elimination releases the product **6** together with a Pd(0) species which is subsequently reoxidized back to Pd(II) by the oxidant.

Although the NMR study helped to establish the intermediacy of the vinylpalladium species, what remains unclear is the process by which it is formed. The vinylpalladium intermediate could be generated *via* two pathways: path **a**, involving direct C–H bond activation with elimination of one molecule of HOAc, and path **b**, involving addition of $Pd(OAc)_2$ across the alkene double bond to form an unstable σ-alkylpalladium complex, followed by elimination of one molecule of HOAc. (Scheme **3**)

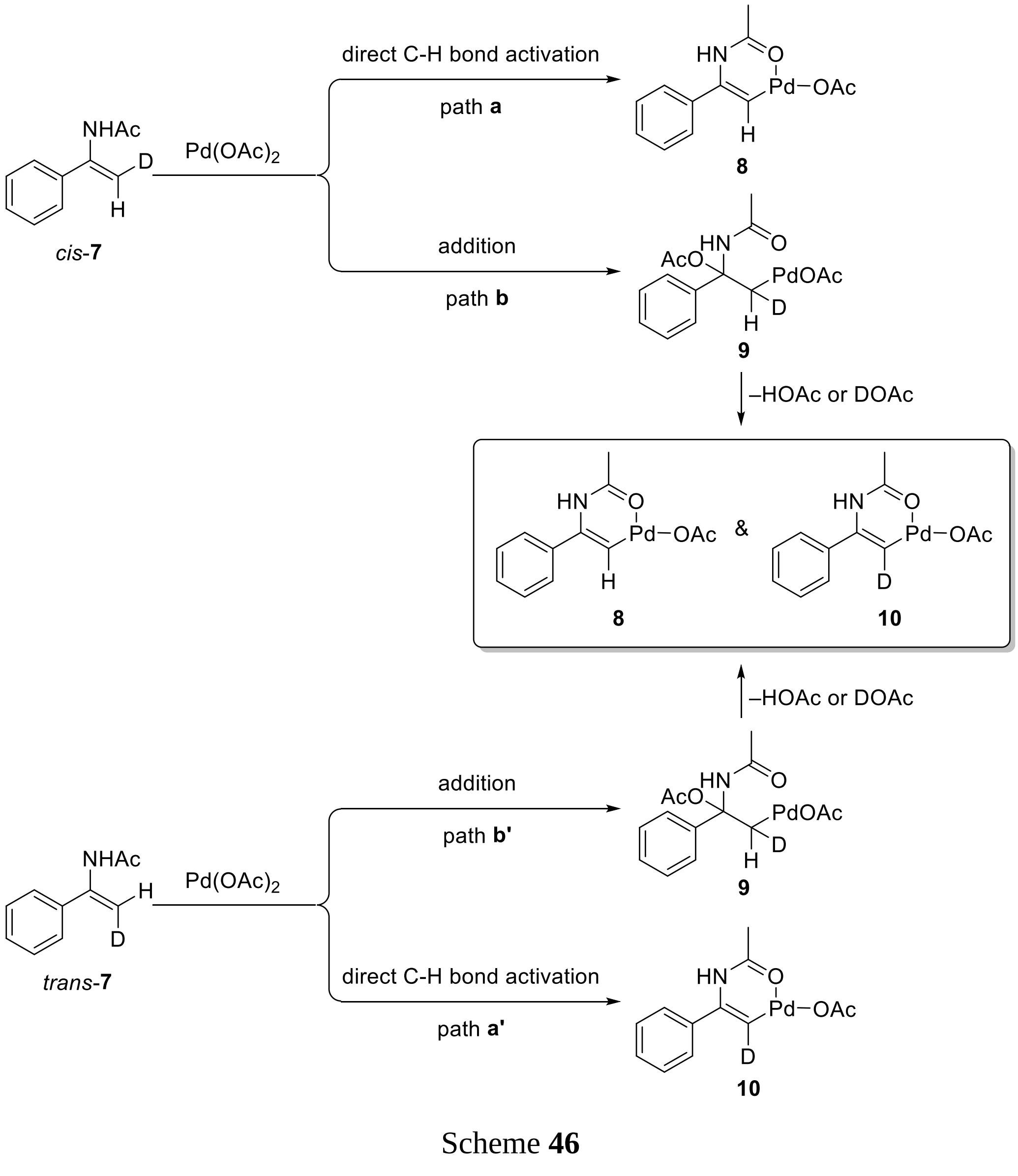


Scheme **44**. Proposed Possible Mechanism for the Coupling Reaction Between Enamide and Acrylate



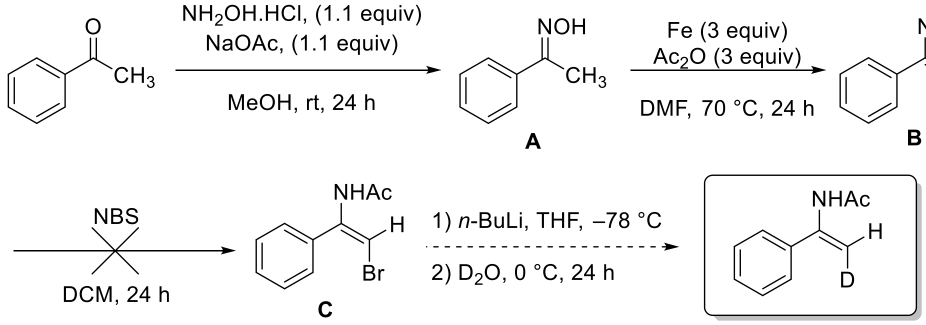
Scheme **45**

One way to determine the actual pathway is to synthesize deuterated *N*-(1-phenylvinyl)acetamide **7** (either *cis* or *trans*) and react with $Pd(OAc)_2$. Only one alkenic proton, either H or D, will remain in the vinylpalladium species **8** or **10**, in the event that the reaction proceeds *via* either path **a** or path **a′**. On the other hand, if the reaction proceeds *via* path **b** or path **b′**, both *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 **46**)



Scheme **46**

A synthetic route was designed to prepare either deuterated *cis*- or *trans*-**7** to test out this idea. The synthesis commenced with the condensation of acetophenone with hydroxylamine hydrochloride in dry methanol under room temperature to furnish oxime **A**. Conversion of **A** into enamide **B** entails heating the oxime with 3 equivalents of iron powder and acetic anhydride in DMF at 70 °C for 24 hours under nitrogen atmosphere, providing enamide **B** in 56% yield. **B** was then treated with *N*-bromosuccinimide (NBS) in dichloromethane at room temperature. Unfortunately, the reaction turned out messy and the desired brominated enamide **C** was not observed, probably due to its inherent instability (Scheme **47**).



Scheme **47**

In summary, we have successfully developed the first olefination reaction of enamides with electron-deficient alkenes, catalyzed by $Pd(OAc)_2$ and 1 atm oxygen as sole oxidant. The reaction proceeded smoothly to provide products in moderate to high yields and with excellent β-regioselectivities. An in-depth study of the mechanism was also undertaken by means of ^1H NMR spectroscopic analysis. This novel method generates highly functionalized, versatile compounds which holds potential for organic synthesis.

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.[18] All 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. ^1H 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, br = 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 ml) as solvent. The flask was then vacuumed and refilled with oxygen. The starting material

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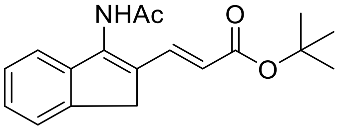
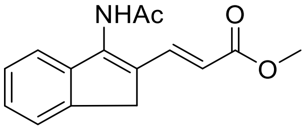
[18] (a) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084-6085. (b) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1679-1681. (c) Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505-507.

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.

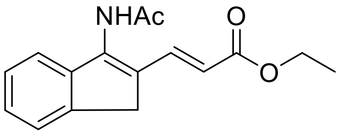
Characterization Data:



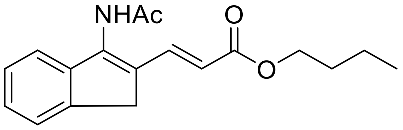
3a (*E*)-*tert*-butyl 3-(3-acetamido-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solide. Yield= 80%. m.p = 201-202 °C. R_f = 0.35 (EA/Hexane = 2:3). ^1H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.61 (d, *J* = 15.6 Hz, 1H), 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* calcd for $C_{18}H_{21}NO_3Na$ $[M+Na]^+$: 322.1419, found 322.1424.



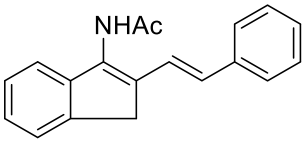
(*E*)-methyl 3-(3-acetamido-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solide. Yield= 72%. m.p = 226-228 °C. R_f = 0.33 (EA/Hexane = 2:3). ^1H NMR (500 MHz, DMSO-d_6) δ 10.10 (s, 1H), 7.69 (d, *J* = 16.0 Hz, 1H), 7.26-7.43 (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* calcd for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$: 280.0950, found 280.0941.



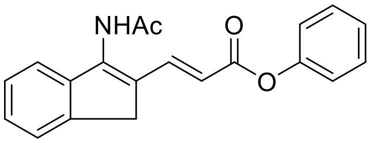
(*E*)-ethyl 3-(3-acetamido-1H-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solide. Yield = 70%. m.p = 190-192 °C. R_f = 0.34 (EA/Hexane = 2:3). ^1H NMR (400 MHz, DMSO-d_6) 10.07 (s, 1H), 7.66 (d, *J* = 15.6 Hz, 1H), 7.27-7.42 (m, 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 calcd for $C_{16}H_{17}NO_3Na$ $[M+Na]^+$: 294.1106, found 294.1105.



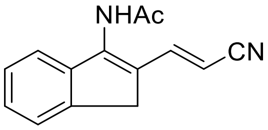
(*E*)-butyl 3-(3-acetamido-1*H*-inden-2-yl)acrylate. This compound was prepared by the general procedure described above and was obtained as a white solide. Yield= 74%. m.p = 178-180 °C. R_f = 0.34 (EA/Hexane = 2:3). ^1H NMR (400 MHz, DMSO-d_6) 10.06 (s, 1H), 7.69 (d, *J* = 15.6 Hz, 1H), 7.26-7.44 (m, 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 calcd for $C_{18}H_{21}NO_3Na$ $[M+Na]^+$: 322.1419, found 322.1406.



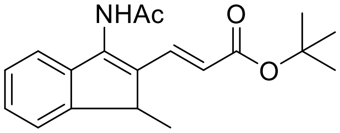
(*E*)-*N*-(2-styryl-1H-inden-3-yl)acetamide. This compound was prepared by the General Procedure described above and was obtained as a yellow oil. Yield = 55%. m.p = 227-229 °C. R_f = 0.37 (EA/Hexane = 2:3). ^1H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.38-7.43 (m, 3H), 7.18-7.36 (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* calcd for $C_{19}H_{17}NONa$ $[M+Na]^+$: 298.1208, found 298.1206.



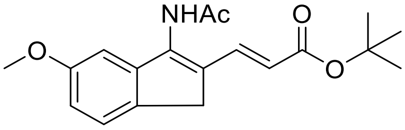
(*E*)-phenyl 3-(3-acetamido-1*H*-inden-2-yl)acrylate. This compound was prepared by the General Procedure described above and was obtained as a colorless oil. Yield = 68%. m.p = 214-215 °C. R_f = 0.32 (EA/Hexane = 3:2). ^1H NMR (500 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.90 (d, *J* = 12.4 Hz, 1H), 7.42-7.46 (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* calcd for $C_{20}H_{17}NO_3Na$ $[M+Na]^+$: 342.1106, found 342.1109.



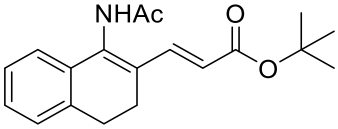
(*E*)-*N*-(2-(2-cyanovinyl)-1*H*-inden-3-yl)acetamide. This compound was prepared by the General Procedure described above and was obtained as a colorless oil. Yield = 12%. R_f = 0.40 (EA/Hexane = 2:3). ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.23 (s, 1H), 7.64 (d, *J* = 16.2 Hz, 1H), 7.44-7.52 (m, 2H), 7.26-7.33 (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* calcd for $C_{14}H_{12}N_2ONa$ $[M+Na]^+$: 247.0847, found 247.0853.



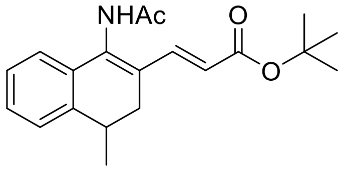
(*E*)-*tert*-butyl 3-(3-acetamido-1-methyl-1*H*-inden-2-yl)acrylate (**3b**) This compound was prepared by the General Procedure described above and was obtained as a colorless oil. Yield = 67%. R_f = 0.33 (EA/Hexane = 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.56 (d, *J* = 15.9 Hz, 1H), 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* calcd for $C_{19}H_{23}NO_3Na$ $[M+Na]^+$: 336.1576, found 336.1568.



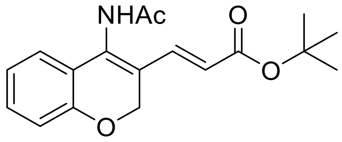
(*E*)-*tert*-butyl 3-(3-acetamido-5-methoxy-1*H*-inden-2-yl)acrylate. (**3c**) This compound was prepared by the general procedure described above and was obtained as a white solide. Yield = 79%. m.p = 200-201 °C. R_f = 0.30 (EA/Hexane = 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.56 (d, *J* = 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 calcd for $C_{19}H_{23}NO_4Na$ $[M+Na]^+$: 352.1525, found 352.1516.



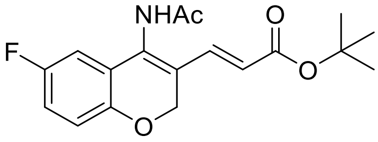
(*E*)-*tert*-butyl 3-(1-acetamido-3,4-dihydronaphthalen-2-yl)acrylate. (**3d**) This compound was prepared by the general procedure described above and was obtained as a white solide. Yield = 74%. m.p = 169-171 °C. R_f = 0.34 (EA/Hexane = 1:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.58 (d, *J* =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 calcd for $C_{19}H_{23}O_3NNa$ $[M+Na]^+$: 336.1576, found 336.1578.



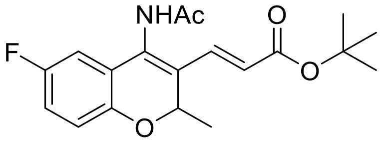
(*E*)-*tert*-butyl 3-(1-acetamido-4-methyl-3,4-dihydronaphthalen-2-yl)acrylate. (**3e**) This compound was prepared by the General Procedure described above and was obtained as a white solide. Yield = 57%. m.p = 180-183 °C. R_f = 0.35 (EA/Hexane = 1:1).^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51(s, 1H), 7.58 (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* calcd for $C_{20}H_{25}NO_3Na$ $[M+Na]^+$: 350.1732, found 350.1726.



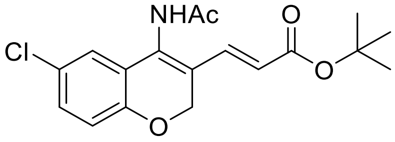
(*E*)-*tert*-butyl 3-(4-acetamido-2*H*-chromen-3-yl)acrylate. (**3f**) This compound was prepared by the General Procedure described above and was obtained as a yellow oil. Yield = 76%. R_f = 0.32 (EA/Hexane = 3:2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.37 (d, J = 16.0 Hz, 2H), 7.16-7.23 (m, 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 calcd for $C_{18}H_{21}O_4NNa$ $[M+Na]^+$: 338.1368, found 338.1370.



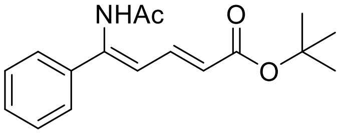
(*E*)-*tert*-butyl 3-(4-acetamido-6-fluoro-2*H*-chromen-3-yl)acrylate. (**3g**) This compound was prepared by the General Procedure described above and was obtained as a yellow solide. Yield = 55%. m.p = 162-164 °C. R_f = 0.34 (EA/Hexane = 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 7.37 (d, *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* calcd for $C_{18}H_{20}NO_4FNa$ [M+Na]$^+$: 356.1274, found 356.1275.



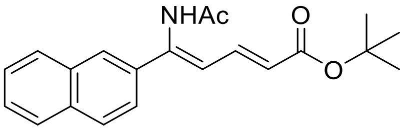
(*E*)-*tert*-butyl 3-(4-acetamido-6-fluoro-2-methyl-2*H*-chromen-3-yl)acrylate. (3h) This compound was prepared by the General Procedure described above and was obtained as a yellow solide. Yield = 57%. m.p = 153-156 °C. R_f = 0.34 (EA/Hexane = 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.38 (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* calcd 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* calcd 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* calcd 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). ^1H 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* calcd 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 ^1H NMR spectrum is shown as Figure **3**-(**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 **3**-(**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 **44**.

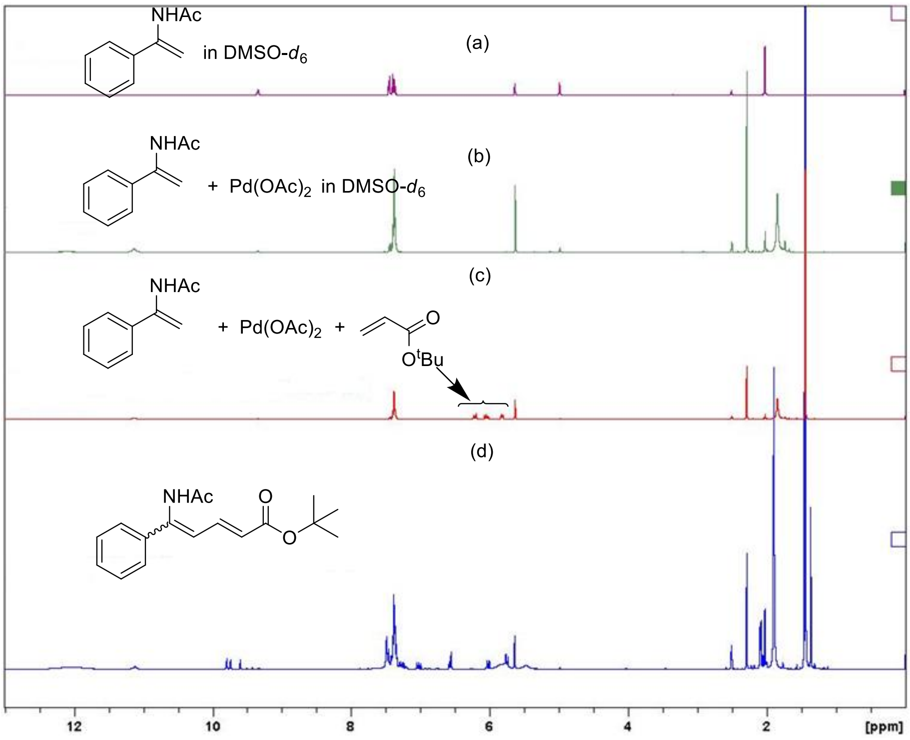


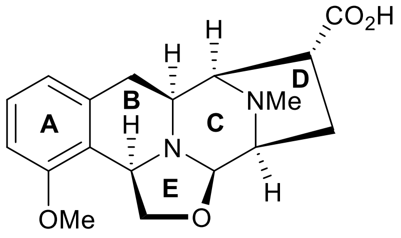
Figure **3**. ^{1}H NMR spectroscope study of the coupling mechanism

CHAPTER 4

Application of C–H Bond Functionalization to the Synthetic Study Towards Quinocarcin

CHAPTER 4 APPLICATION OF C–H BOND FUNCTIONALIZATION TO THE SYNTHETIC STUDY TOWARDS QUINOCARCIN

4.1 INTRODUCTION



(–)-Quinocarcin (**1**)

Figure **4**. Structure of (–)-Quinocarcin (**1**)

(—)-Quinocarcin (**1**, Figure **4**) was first isolated from bacteria *Streptomyces melanovinaceus* in 1983,[1] and had since been shown to possess antimicrobial activity towards Gram negative organisms as well as antitumor activity by inhibition of DNA or RNS synthesis.[2]

Two possible modes had been suggested for its antitumor activity: 1) opening of the oxazolidine ring of quinocarcin to form an iminium ion which alkylates the 2-amino group of guanine in a minor grove of DNA,[3] 2) auto-disproportionation of the oxazolidine ring under aerobic conditions which results in the oxidative cleavage of DNA by a superoxide radical anion.[4] The formation of superoxide was first reported by Tomita's group[2a] in 1984 for Path 2, after which Williams' group came up with the

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[1] (a) Tomita, F.; Takahashi, K.; Shimizu, K. *J. Antibiot.*, **1983**, *36*, 463. (b) Takahashi, K.; Tomita, F. *J. Antibiot.*, **1983**, *36*, 468.

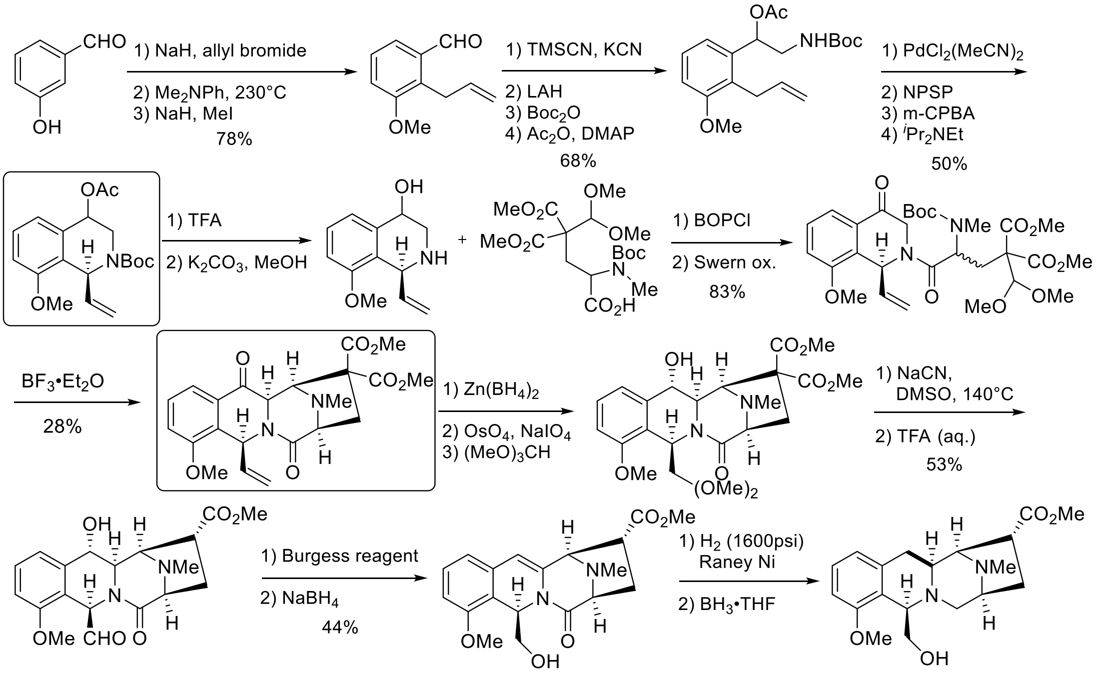
[2] (a) Tomita, F.; Takahashi, K.; Tamaoki, T., *J. Antibiot.*, **1984**, *37*, 1268. (b) Chiang, C-D.; Kanazawa, F.; Matsushima, Y.; Nakano, H.; Nakagawa, K.; Takahashi, H.; Terada, M.; Morinaga, S.; Tsuchiya, R.; Sasaki, Y.; Saijo, N. *J. Pharmacobio-Dyn.* **1987**, *10*, 431. (c) Jett, J. R.; Saijo, N.; Hong, W-S.; Sasaki, Y.; Takahashi, H.; Nakano, H.; Nakagawa, K.; Sakurai, M.; Suemasu, K.; Terada, M., *Investigational New Drugs*, **1987**, *5*, 155. (d) Fujimoto, K.; Oka, T.; Morimoto, M., *Cancer Res.*, **1987**, *47*, 1516. (e) Kanamaru, R.; Konishi, Y.; Ishioka, C; Kakuta, H.; Sato, T.; Ishikawa, A.; Asamura, M.; Wakuri, A., *Cancer Chemother. Pharmacol*, **1988**, *22*, 197. (f) Inaba, S.; Shimoyama, M., *Cancer Res.*, **1988**, *48*, 6029.

[3] Hill, G.C.; Wunz, T. P.; Remers, W. A., *J.Comput.-Aided Mol. Des.* **1988**, *2*, 91.

[4] (a) Williams, R. M.; Glinka, T.; Gallegos, R.; Ehrlich, P. P.; Flanangan, M. E.; Coffman, H.; Park, G., *Tetrahedron* **1991**, *47*, 2629. (b) Williams, R. M.; Glinka, T.; Flanangan, M. E.; Gallegos, R.; Coffman, H.; Pei, D., *J. Am. Chem. Soc.* **1992**, *114*, 733.

mechanistic rationale in 1991.[4] However, it is still not clear which mode of action is responsible for its antitumor activity till this day, although it is clear that the oxazolidine ring in quinocarcin or equivalent is crucial for exhibiting the antitumor activity.

In view of its unique molecular architecture and significant antitumour activity, quinocarcin had attracted much attention for its total synthesis and that of its biologically active structural congeners. In 1985, Danishefsky *et al.*[5] reported the total synthesis of racemic quinocarcinol (Scheme **48**). The key steps involved construction of the B ring *via* an organoselenium-induced cyclization, followed by simultaneous formation of the C and D rings *via* a Lewis acid-promoted double cyclization through an incipient oxonium intermediate.



Scheme **48**. Danishefsky's Total Synthesis Racemic Quinocarcinol

It was not until 1988 that Fukuyama *et al.*[6] reported the first total synthesis of *racemic* quinocarcin (Scheme **49**), wherein the key step entails construction of the B

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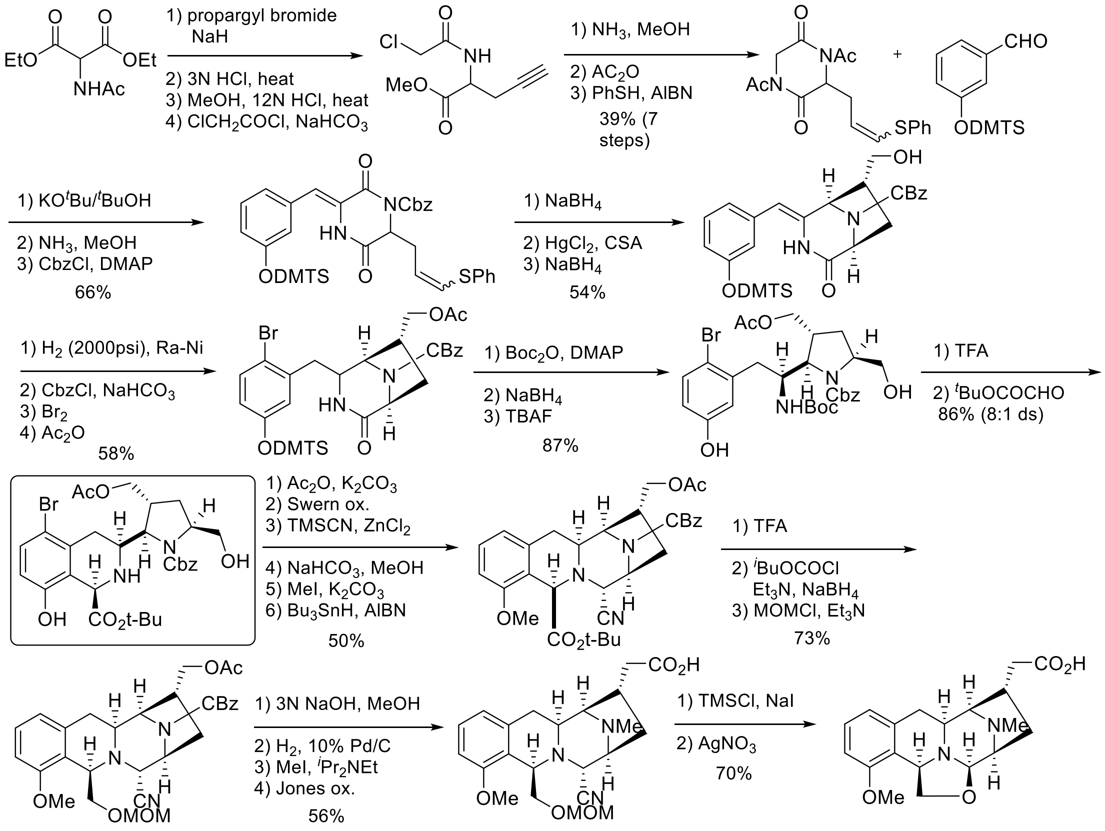
[5] Danishefsky, S. J.; Harison, P. j.; Webb II, R. R.; O'Neill, B. T., *J. Am. Chem. Soc*, **1985**, *107,* 1421.

[6] Fukuyama, T.; Nunes, J. J., *J. Am. Chem. Soc.* **1988**, *110,* 5196.

ring *via* a Pictet-Spengler reaction, a standard protocol for accessing the tetrahydroisoquinoline skeleton,[7] with the D ring already put in place through an earlier substrate.



Scheme **49**. Fukuyama's total synthesis of racemic quinocarcin

Subsequently, Garner *et al.*[8] successfully accomplished the first asymmetric total synthesis of (–)-quinocarcin in 1992 (Scheme **50**) and Williams *et al.*[9] completed the total synthesis of racemic quinocarcinamide. Garner's synthesis featured the use of chiral auxiliaries, first for controlling the stereochemistry of the E ring *via* direct azidation and later, that of the D ring *via* asymmetric 1,3-dipolar cycloaddition.

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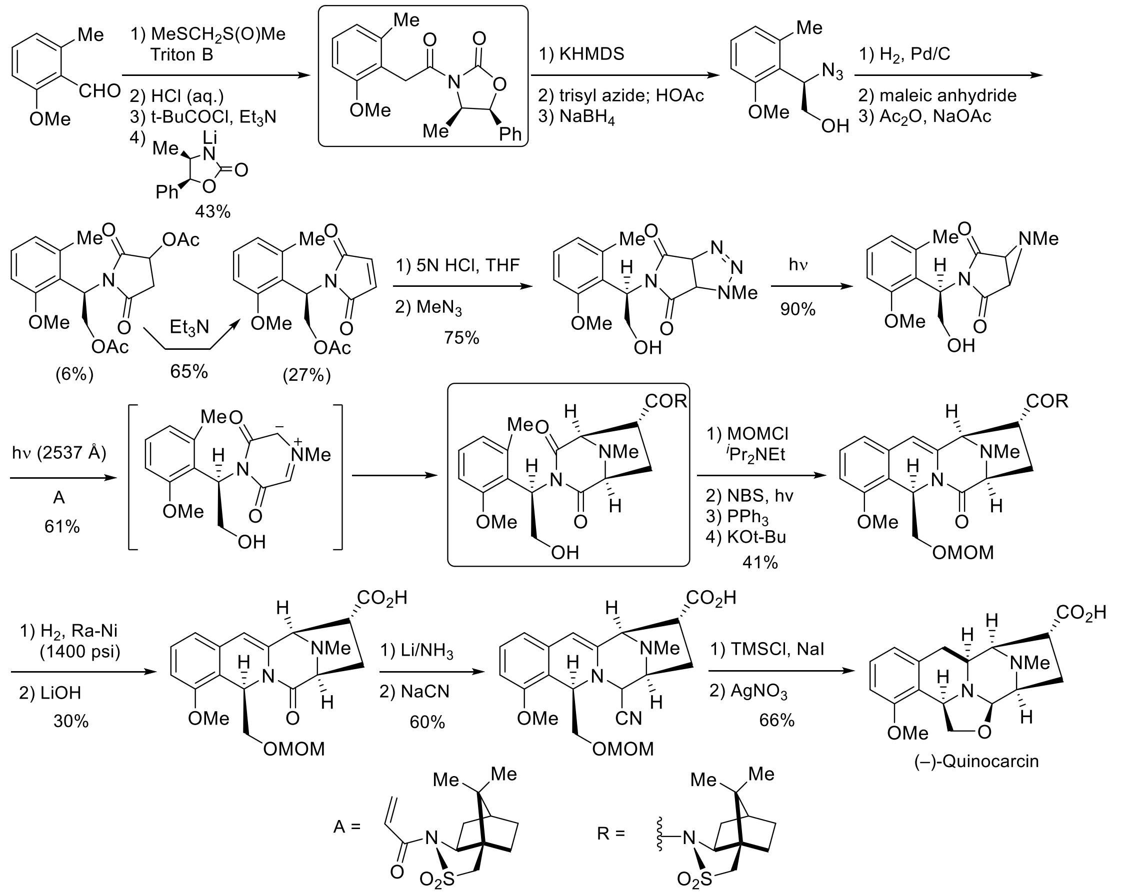
[7] Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.

[8] (a) Gamer, P.; Ho, W. B.; Shin, H., *J. Am. Chem. Soc.* **1992,** *114*, 2767. (b) Gamer, P.; Ho, W. B.; Shin, H., *J. Am. Chem. Soc.* **1993**, *115*, 10742.

[9] Flanagan, M. E.; Williams, R. M., *J. Org. Chem.* **1995**, *60*, 6791.

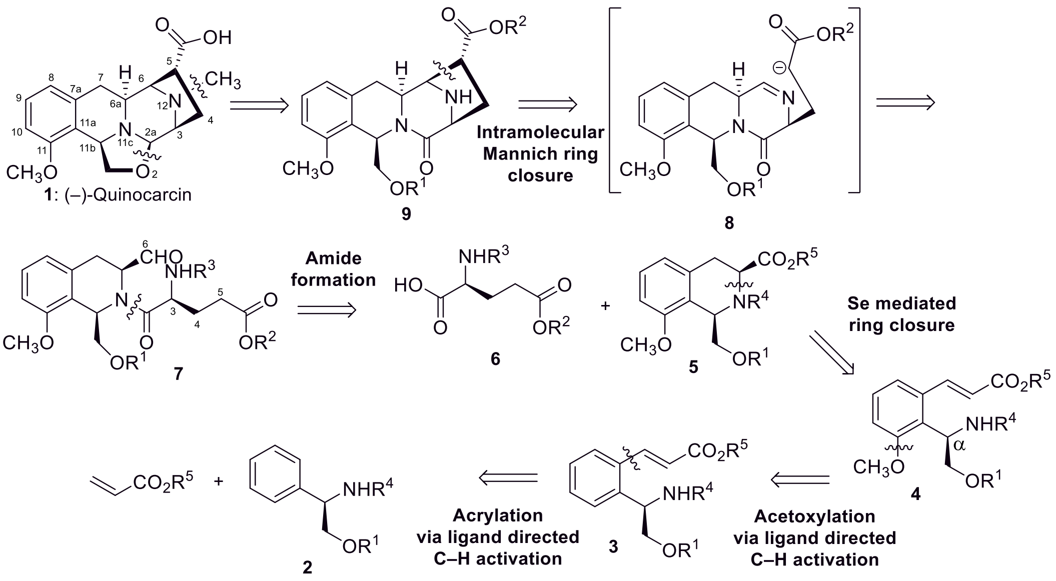


Scheme **50**. Garner’s asymmetric total synthesis of (–)-quinocarcin

4.2 RETROSYNTHETIC ANALYSIS

The retrosynthesis analysis (Scheme **51**) is guided by the arching idea to construct the backbone of quinocarcin starting from commercially and readily available amino acid derivatives, which will then enable us to easily dictate the two chiral centres involving the nitrogen by judicious choice of either the L- or D-amino acid. In addition, we would like to explore the application of C–H functionalization in natural product synthesis.

(–)-Quinocarcin can be obtained from piperazinone **9** through successive reductive E ring closure and *N*-methylation, following construction of the D ring *via* an intramolecular Mannich ring closure involving the imine intermediate **8**, generated *in*



Scheme **51**. Retrosynthetic analysis of (–)-quinocarcin

situ from *N*-deprotection of aminoaldehyde **7**. The amide **7** which possesses the carbon framework of quinocarcin can be promptly accessed *via* amide coupling of protected glutamic acid **6** with the advanced tetrahydroisoquinoline intermediate **5** upon reduction of the ester functionality. It is noteworthy that the configuration at C-3 (see Scheme **51**, **7**) can be controlled simply through judicious choice of commercially available protected D- or L-glutamic acid **6**. However, the construction of compound **5** is more complex and has thus been the main focus in our initial exploration.

Formation of the B ring (compound **5**) is borrowed from the method used in Danishefsky's synthesis,[5] involving intramolecular cyclization with *N*-phenylselenophthalimide (Nicolaou reagent[10]) followed by oxidative elimination of the formed selenide. Presence of the ester group attached to the alkene may present a problem, potentially eroding the reactivity as well as regiochemistry of the cyclization, and deliberations need to be made to circumvent the problem should it arises or another other means of cyclization has to be chosen.

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[10] Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

To gain access to the key structure **5**, it is crucial that **4** should be readily synthesized in few steps and with reasonable yields. We envisaged that the easiest route would be to construct the C^7–C^{7a} bond on **3** and C^{11}–O bond on **4** *via* metal-catalyzed C–H functionalizations under mild reaction conditions, directed by means of coordination to the nitrogen atoms of the amide linkage and the picolinamide of R^4.

As can be seen, C–H functionalization of aryl C–H bonds plays a very important role in the earlier part of this retrosynthetic route. The first C–H activation consists of a ligand-directed aryl C–H activation with subsequent C–C bond formation with an acrylate. The same applies to the second C–H activation except that formation of a C–O bond is envisaged. Palladium was chosen for our synthetic study to forge the desired C–C and C–O bonds in view of the great potential it has demonstrated. In addition, our group previously had some experience in C–H functionalization involving palladium.[11]

4.3 EXPERIMENTS AND RESULTS

Preparation of starting material

The synthesis commences with the preparation of picolinamide **2a**, as shown in Scheme **52** below, wherein the methyl ester **10** is first reduced into (*R*)-phenylglycinol (**11**) using the procedure obtained from Chang and Coates[12] who modified the procedure from Meyers.[13] Subsequent *O*-methyl protection and amidation are general procedures. The yields ranges from moderate to good for each of the steps and are readily reproducible. The simplicity in accessing starting material **2a** is an attractive

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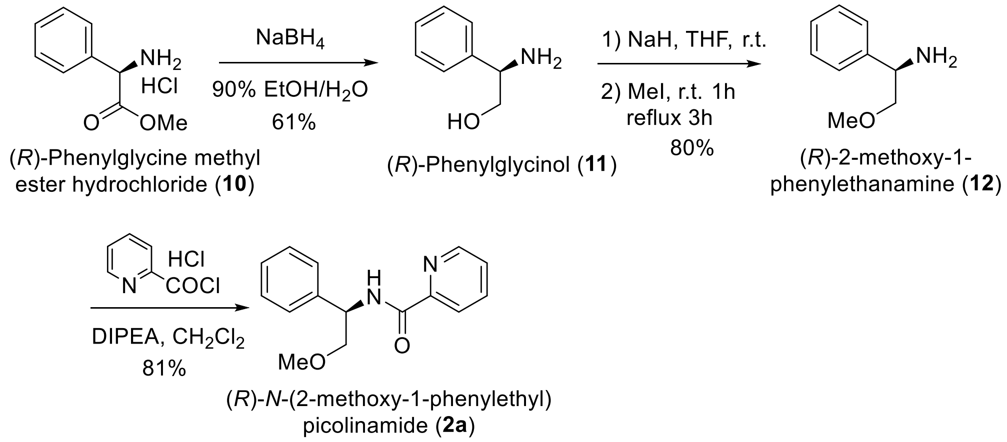
[11] (a) Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 1372. (b) Zhou, H. Chung, W. J.; Xu, Y. H.; Loh, T. P. *Chem. Commun.* **2009**, 3472. (c) Zhou, H.; Xu, Y. H.; Chang, W. J.; Loh, T. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 5355. (d) Xu, Y. H.; Wang, W. J.; Wen, Z. K.; Hartley, J. J.; Loh, T. P. *Tetrahedron Lett.* **2010**, *51*, 3504.

[12] Chang, Z. Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3472.

[13] Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.

point in our synthetic route. In addition, both (*S*)- and (*R*)-phenylglycinol are readily available commercially, and hence amenable to the synthesis of various isomers of the natural product.



Scheme **52**. Preparation of picolinamide **2a**

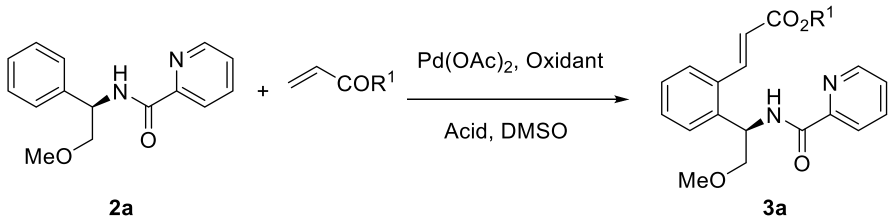
Acrylation

With picolinamide **2a** in hand, the next step would be to attempt the ligand-directed Pd-mediated aryl C–H bond activation, to install the acryl group. The base conditions for acrylation is obtained from unpublished work done by our group, and optimised for our substrates through screening with various alkyl acrylate, acid additive and stoichiometric oxidant (Table **8**), as well as varying the amounts of the essential components (Table **9**).

From Table **8**, it can be seen that entry 4 afforded the highest yield, though the other conditions such as those in entries 1, 2 and 8 also provided comparable yields. Comparing across the different alkyl acrylate substrates (Table **8**, entries 1–4), it can be seen that the reaction is generally applicable except for the case of *tert*-butyl acrylate where no product was obtained despite repeating the reaction one more time (Entry 3). This might be attributed to steric hindrance conferred by the bulky *tert*-butyl group which prevents the acrylate from binding to the palladium, or possibly instability of the acrylate itself under the reaction condition. Nonetheless, ethyl acrylate still offers the best yield, and hence will be chosen for subsequent screenings and other reactions.

Also, there is observable correlation between the strength of the acid (pK_a) and the reaction yields (Table **8**, entries 4, 6, 8, 9 and 10). Yet, a sufficiently strong acid must be present as use of acetic acid and tartartic acid gave no desired products (Table **8**, entries 9 and 10).

Table **8**. Screening of acrylation using palladium



Entry	R^1 (4 eq.)	Catalyst (20 mol%)	Oxidant (0.5 eq.)	Acid (40 mol%)	Solvent	Temp. (°C)	Time (hrs)	Yield[a] (%)
1	Me	$Pd(OAc)_2$	BQ	CSA	DMSO	110	24	56
2	*n*-Bu	$Pd(OAc)_2$	BQ	CSA	DMSO	110	24	65
3	*t*-Bu	$Pd(OAc)_2$	BQ	CSA	DMSO	110	24	0
4	**Et**	**$Pd(OAc)_2$**	**BQ**	**CSA**	**DMSO**	**110**	**24**	**68**
5	Et	$Pd(OAc)_2$	2,5-diMe-BQ	CSA	DMSO	110	24	60[b]
5	Et	$Pd(OAc)_2$	DDQ	CSA	DMSO	110	24	5
6	Et	$Pd(OAc)_2$	BQ	TfOH	DMSO	110	24	46
7	Et	$Pd(OAc)_2$	2,5-diMe-BQ	TfOH	DMSO	110	24	35
8	Et	$Pd(OAc)_2$	BQ	*p*-TSA	DMSO	110	24	62
9	Et	$Pd(OAc)_2$	BQ	AcOH	DMSO	110	24	0
10	Et	$Pd(OAc)_2$	BQ	Tartaric Acid	DMSO	110	24	0
11[c]	Et	$Pd(OAc)_2$	$PhI(OAc)_2$[d]	CSA	DMSO	110	24	3
12	Et	$Pd(OAc)_2$	$Cu(OAc)_2$[d]	CSA	DMSO	110	24	0

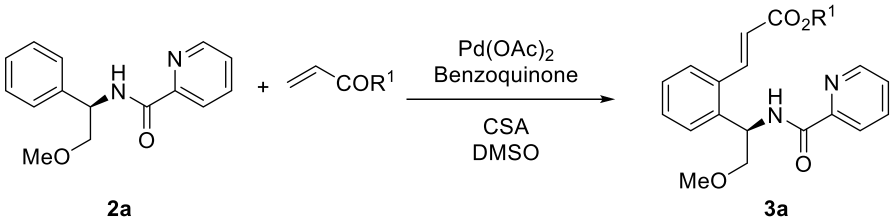
[a] Isolated yield after column chromatography. [b] Product is contaminated with side product which cannot be separated via flash chromatography. Estimated yield is

approximately 60%. [c] Formation of ethyl cinnamate is observed. [d] 1.0 equivalent of oxidant used instead.

A variety of stoichiometric oxidants were also investigated (Table **8**, entries 4–6, 11 and 12), but only benzoquinone and 2,5-dimethylbenzoquinone appears to work well. Although 2,5-dimethylbenzoquinone offer yields comparable to benzoquinone, it generated a by-product which makes purification of the desired product by column chromatography difficult. Hence benzoquinone is chosen as the final oxidant to use.

We then proceed to vary the amounts of catalyst, acid and oxidant used. It is then realized that the yield increased significantly from 68% to 85% when the amount of benzoquinone is increased to 1 equivalent (Table **9**, Entries 1 and 2). Thus, the conditions in Table **9**, entry 2 are used as the optimal conditions and applied to the scaled-up reaction. Purification of the scaled-up reaction proved more tedious than that of small-scale screening and it is helpful if the starting material is very pure.

Table **9**. Screening of acrylation using palladium (cont'd)



Entry	R^1 (4 eq.)	$Pd(OAc)_2$	BQ	CSA	Solvent	Temp. (°C)	Time (hrs)	Yield[a] (%)
1	Et	20 mol%	0.5 eq.	40 mol%	DMSO	110	24	68
2	**Et**	**20 mol%**	**1.0 eq.**	**40 mol%**	**DMSO**	**110**	**24**	**85**
3	Et	30 mol%	0.5 eq.	40 mol%	DMSO	110	24	63
4	Et	20 mol%	0.5 eq.	1 eq.	DMSO	110	24	55

[a] Isolated yield after column chromatography.

The mode of action is believed to operate *via* a Pd(II)/Pd(0) catalytic pathway, as black deposits of Pd(0) can be seen at the end of the reaction (Figure 5). The proposed mechanism consists of directed aryl C–H activation with binding of the substrate ligand to the Pd(II) to generate palladacycle **A**. Subsequent ligand association of the acrylate and migratory insertion occurs to yield the new palladacycle **B**. Finally, β-hydride elimination and ensuing ligand dissociation provides the desired product **C** and Pd(0) which is oxidised back to active Pd(II) by the benzoquinone.

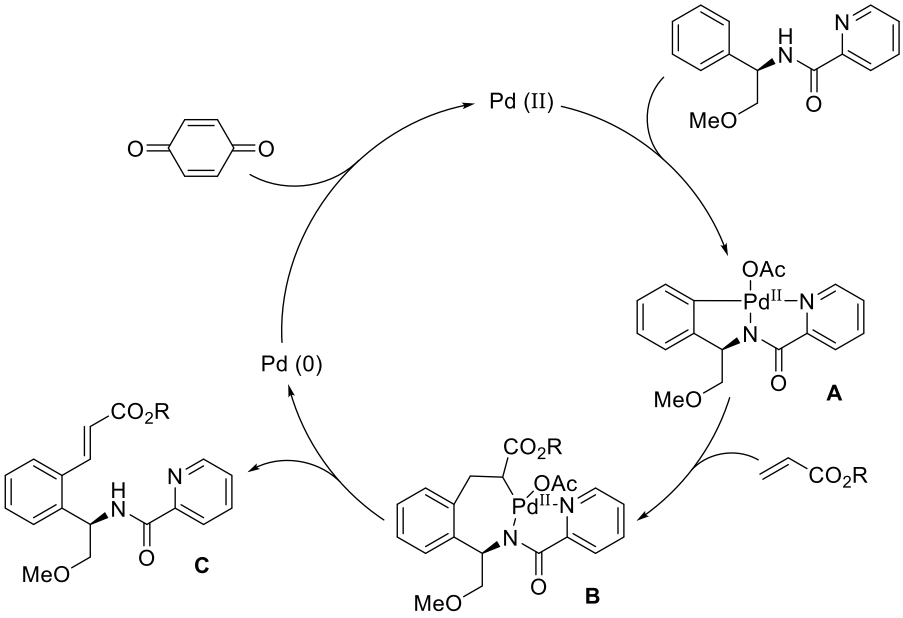


Figure 5. Proposed mechanism of the Pd(II)-catalysed acrylation

Acetoxylation

Liang reported a method for acetoxylation *via* aryl C–H activation on a similar substrate to ours.[14] However, the reaction fails to proceed under the reported conditions for substrates (similar to ours) with a substituent on the α-carbon (see Scheme **51**, **3**). Liang attributed the non-reaction to steric factors, thought this should not be the sole reason as the reaction can proceed when the solvent is changed from toluene to acetonitrile, albeit in low yields. The reaction conditions were first tested

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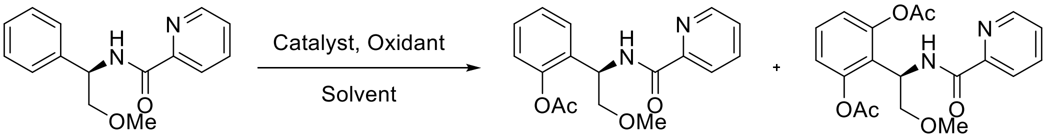
[14] Gou, F. R.; Wang, X. C.; Huo, P. F.; Bi, H. P.; Guan, Z. H.; Liang, Y. M. *Org. Lett.* **2009**, *11*, 5726.

out on (*R*)-*N*-(2-methoxy-1-phenylethyl)picolinamide (**2a**), prior to application to the acrylated product **3a**.

Table **10**. Screening of acetoxylation on unacrylated substrate **2a**



2a Monoacetoxylated pdt (**m**) Diacetoxylated pdt (**d**)

Entry	Catalyst (mol%)	Oxidant (eq.)	Additives (eq.)	Solvent	Temp (°C)	Time (hrs)	Yield[a] (%)
1	Pd(OAc)$_2$/10	PhI(OAc)$_2$/2	AcOH/Ac$_2$O (1:1)/1	PhMe	150	16	0
2	Cu(OAc)$_2$/10	PhI(OAc)$_2$/2	–	AcOH/Ac$_2$O (1:1)	130	24	SM decom-posed
3	Pd(OAc)$_2$/10	PhI(OAc)$_2$/2	AcOH/Ac$_2$O (1:1)/1	DMF	120	24	13 (m) 18 (d)
4	Cu(OAc)$_2$ /10	PhI(OAc)$_2$/2	AcOH/Ac$_2$O (1:1)/1	DMF	120	24	0
5	Pd(OAc)$_2$/10	PhI(OAc)$_2$/2	AcOH/Ac$_2$O (1:1)/1	DMSO	120	24	20[b]
6	Pd(OAc)$_2$/10	PhI(OAc)$_2$/2	AcOH/Ac$_2$O (1:1)/1	CHCl$_3$	80	24	8 (m) 14 (d)
7	Pd(OAc)$_2$/10	PhI(OAc)$_2$/2	AcOH/Ac$_2$O (1:1)/1	CH$_3$CN	120	24	13 (m) 18 (d)
8	**Pd(OAc)$_2$/10**	**PhI(OAc)$_2$/2**	**AcOH/Ac$_2$O (1:1)/3**	**CH$_3$CN**	**100**	**24**	**20 (m) 37 (d)**
9	**Pd(OAc)$_2$/10**	**PhI(OAc)$_2$/2**	**AcOH/Ac$_2$O (1:1)/9**	**CH$_3$CN**	**100**	**24**	**28 (m) 29 (d)**
10	Pd(OAc)$_2$/10	PhI(OAc)$_2$/1.1	Cu(OAc)$_2$/0.1	AcOH/Ac$_2$O (1:1)	80	24	12 (m) 19 (d)
11	Pd(OAc)$_2$/10	PhI(OAc)$_2$/1.1	Cu(OAc)$_2$/0.1; AcOH/Ac$_2$O (1:1)/3	CH$_3$CN	80	24	12 (m) 13 (d)

[a] Isolated yield after column chromatography. [b] Isolated an *ortho*-iodinated product instead of the acetoxylated product in 20% yield.

Expectedly, application of Liang's conditions to our unacrylated picolinamide **2a**, gave no desired product with 41% recovery of starting material (Table **10**, entry 1). However, when the solvent was changed to acetonitrile, the reaction did proceed although the yield is low and both mono- and di-acetoxylation products were obtained (Table **10**, entry 7). Various conditions were then screened in bid to increases yield of the desired product and it was found that the conditions in entries 8 and 9 (Table **10**) gave a decent yield of 57% overall. The ratio of mono- and di-acetoxylated products is not important here since acrylation would be done beforehand, meaning there will only be one position for reaction. The optimal conditions were then applied to the acetoxylation of the acrylated product **3a**.

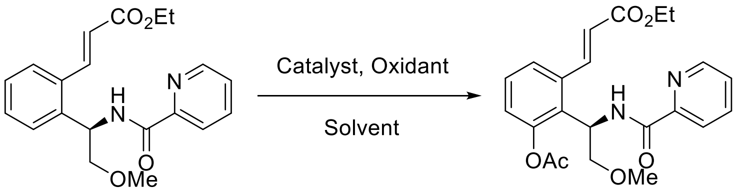
The acrylated product **3a** surprisingly gave intractable mixture when subjected to the optimal conditions obtained for the acetoxylation of the unacrylated picolinamide **2a** (Table **11**, entries 1–3). Even upon decreasing the reaction temperature from 100 ºC to 80 ºC to 60 ºC, the reaction still turned out messy and the desired product was not obtained, as indicated by the LC-MS. We then decided to focus on the screening and optimisation of conditions for the acrylated product **3a** instead.

As seen from Table **11**, C–O bond formation on the acrylated substrate does not take place as smoothly as we hoped. One possible explanation is that conjugation with the carbon–carbon double bond lowers the reactivity (electron density) of the aromatic ring, rendering C–H activation more difficult. In addition, the stoichiometric oxidant must be able to oxidize Pd(II) to Pd(IV) in order to facilitate reductive elimination to form the C–O bond required.

From Table **11** it can be seen that increasing the amount of Pd(II) does liitle to increase the yield. In actual fact, when too much Pd(II) is used, the reaction becomes more messy and the yield suffered (Table **11**, entries 8/12 and 9/13). Probably the additional Pd(II) interacted with the carbon–carbon double bond, leading to more side reactions. Hence, the amount of Pd(II) should be kept low.

Increasing the amount of oxidant did improve the yield slightly, although the increase is insignificant (Table **11**, entries 8–10). Again, there is a limit to how much we can increase the amount of oxidant as seen from the same yield obtained when the amount of oxidant is increased from 8 to 12 equivalents (Table 11, entries 9–10).

Table **11**. Screening of acetoxylation on acrylated substrate **3a**



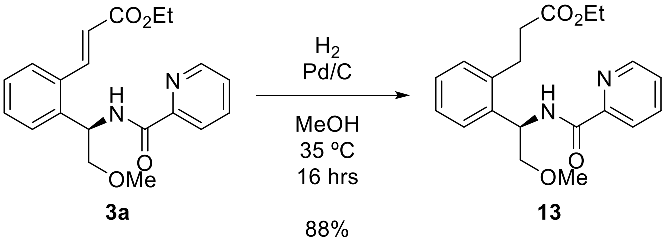
3a **4a**

Entry	Catalyst (mol%)	Oxidant (equiv.)	Additives	Solvent	Temp (°C)	Time (hrs)	Yield[a] (%)
1	$Pd(OAc)_2$/10	$PhI(OAc)_2$/2	$AcOH/Ac_2O$ (1:1)/4	CH_3CN	100	24	Messy[b]
2	$Pd(OAc)_2$/10	$PhI(OAc)_2$/2	$AcOH/Ac_2O$ (1:1)/4	CH_3CN	80	24	Messy[b]
3	$Pd(OAc)_2$/10	$PhI(OAc)_2$/2	$AcOH/Ac_2O$ (1:1)/4	CH_3CN	60	64	Messy[b]
4	$Pd(OAc)_2$/10	$PhI(OAc)_2$/4	$AcOH/Ac_2O$ (1:1)/4	CH_3CN	75	24	20
5	$Pd(OAc)_2$/10	$Cu(OAc)_2$/2 ; AgF/2	$AcOH/Ac_2O$ (1:1)/4	$AcOH/Ac_2O$ (1:1)	75	24	0
6	$Pd(OAc)_2$/10	$Cu(OAc)_2$/2 ; AgF/2	$AcOH/Ac_2O$ (1:1)/4	DMF	120	24	Reactant decomposed
7	$Pd(OAc)_2$/5	$PhI(OAc)_2$/8	–	$AcOH/Ac_2O$ (1:1)	75	24	22
8	$Pd(OAc)_2$/10	$PhI(OAc)_2$/4	–	$AcOH/Ac_2O$ (1:1)	75	24	22
9	$Pd(OAc)_2$/10	$PhI(OAc)_2$/8	–	$AcOH/Ac_2O$ (1:1)	75	24	27
10	$Pd(OAc)_2$/10	$PhI(OAc)_2$/12	–	$AcOH/Ac_2O$ (1:1)	75	48	27
11	$Pd(OAc)_2$/20	$PhI(OAc)_2$/2	–	$AcOH/Ac_2O$ (1:1)	75	24	Messy
12	$Pd(OAc)_2$/20	$PhI(OAc)_2$/4	–	$AcOH/Ac_2O$ (1:1)	75	24	18
13	$Pd(OAc)_2$/20	$PhI(OAc)_2$/8	–	$AcOH/Ac_2O$ (1:1)	75	24	24
14	$Pd(OAc)_2$/10	$PhI(OAc)_2$/2	NaOAc/1	CH_3CN	75	68	0
15	$Pd(OAc)_2$/10	$PhI(OAc)_2$/2	$Cu(OAc)_2$/0.1	CH_3CN	75	68	0
16	$Pd(OAc)_2$/10	$PhI(OAc)_2$/2	–	DMSO/ AcOH (1:1)	80	24	0
17	$Pd(OAc)_2$/10	O_2	–	$AcOH/Ac_2O$ (1:1)	75	24	0
18	$Cu(OAc)_2$/10	O_2	–	$AcOH/Ac_2O$ (1:1)	75	24	0
19	$Pd(OAc)_2$/10	$K_2S_2O_8$/4	–	$AcOH/Ac_2O$ (1:1)	75	24	0

20	$Pd(OAc)_2$/10	BQ/2	–	$AcOH/Ac_2O$ (1:1)	75	24	0
21	$Pd(OAc)_2$/10	SPB/4	Ac_2O/27	CH_3CN	75	24	0
22	$Cu(OAc)_2$/1	–	–	$AcOH/Ac_2O$ (1:1)	130	24	Reactant decom-posed

[a] Isolated yield after column chromatography. [b] Fractions obtained upon column chromatography seems to suggest presence of desired product from ^{1}H NMR, but LC-MS of the fraction indicated very little of the desired product instead.

In contrast to acrylation where the starting material can be recovered cleanly and fully accounted for, acetoxylation does not work as well. Possibly the presence of the carbon–carbon double bond induces various side reactions under catalysis by Pd(II). Hence, we decided to first reduce the double bond before acetoxylation. Attempts to reduce the double bond using $NaBH_4$ and TMSCl-NaI-H_2O[15] proved futile. Finally hydrogenation was found to proceed smoothly and cleanly, providing the double bond-reduced picolinamide **13** in 88% yield (Scheme **53**).



Scheme **53**. Reduction of double bond in α,β-unsaturated ester **3a**

The reduced substrate **13** was subjected to the optimized acetoxylation conditions stated in Table 11, entry 9 and furnished acetate **14** in 30% yield (Scheme **54**). Although not significantly higher than 27% for acetoxylation of **3a**, it is noteworthy that the acetoxylated product **14** was isolated very cleanly after column chromatography, presumably due to lesser side-reactions. The less than significant increase also suggested that presence of the double bond may not be the main reason responsible for the low yield observed.

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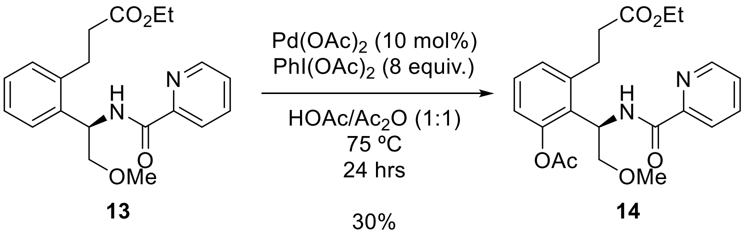
[15] Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1063.



Scheme **54**. Acetoxylation of double bond-reduced picolinamide **13**

Although we did not managed to optimize the acetoxylation key step, we have nonetheless clarified that our substrate is amendable to the procedure and identified interference from the carbon–carbon double bond as one possible reason for the low yields. Also, since the acetoxylated product **14** can be obtained in a cleaner state than **4a**, other possible alternatives could include: 1) first reacting the acrylate and the amide nitrogen to form ring **B** to prevent interference from the double bond during acetoxylation; 2) reducing the double bond *via* hydrogenation prior to acetoxylation and forming ring **B** using other methodologies. Both ways may have their merits and different considerations and it is only through actualizing the two paths that we are able to determine which is better.

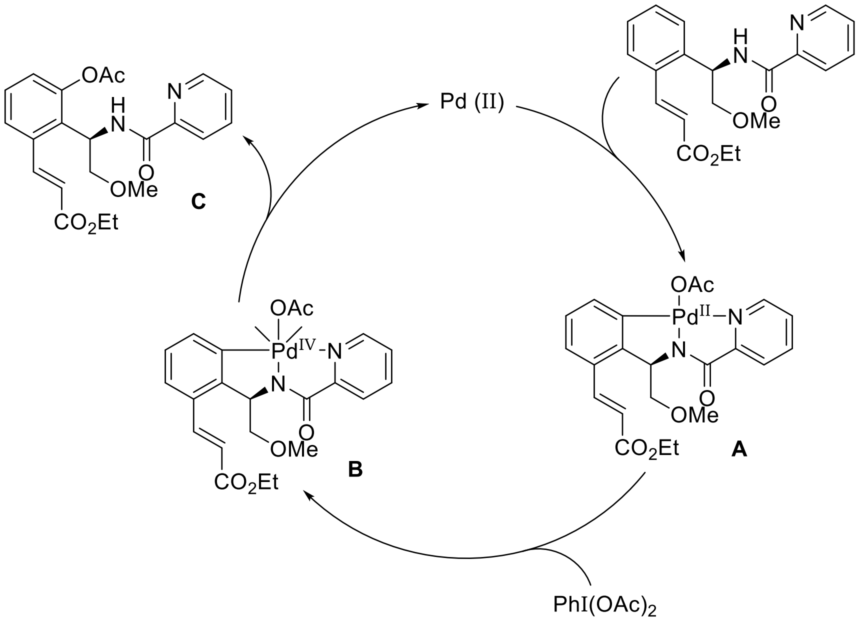
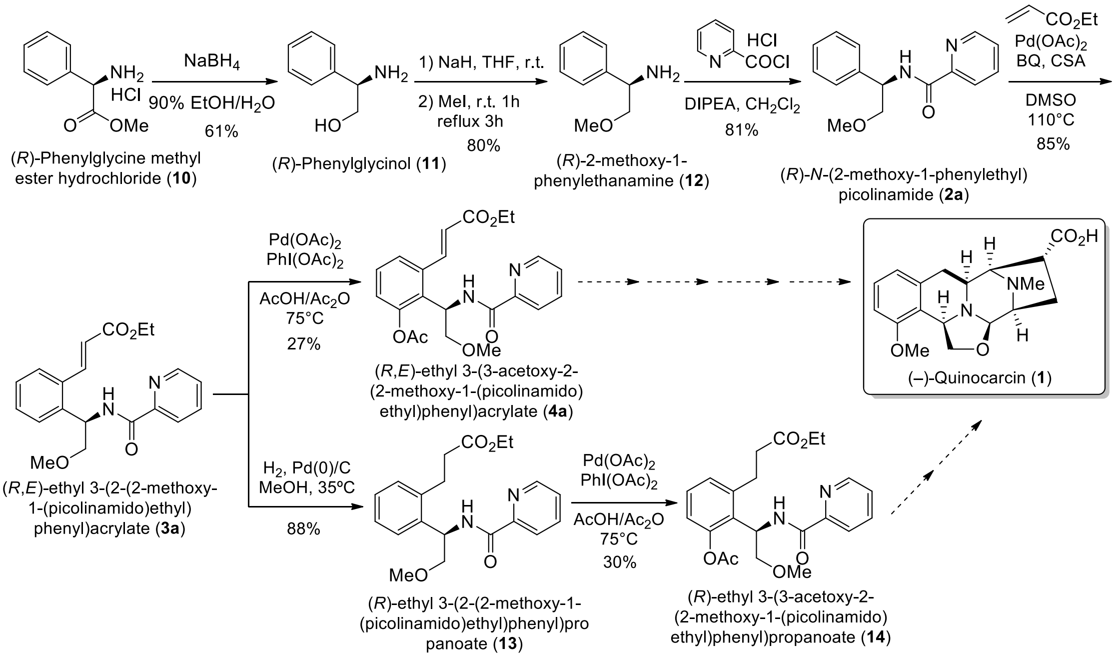


Figure **6**. Proposed mechanism of the Pd(II)-catalysed acetoxylation

The mode of action for acetoxylation is believed to proceed *via* a Pd(II)/Pd(IV) catalytic pathway (Figure **6**). The proposed mechanism commence with directed C–H activation with binding of the substrate ligand to the Pd(II) to give palladacycle **A**. Subsequently, oxidation of Pd(II) to Pd(IV) by the oxidant $PhI(OAc)_2$ affords the new palladacycle **B**. And finally, reductive elimination provides the acetoxylated product **C** and regenerates the active Pd(II) catalyst which is ready for the next C–H activation.

4.4 CONCLUSION



Since the isolation of quinocarcin in 1983, numerous total synthesis of quinocarcin and related congeners have surfaced over the years, such as those of Danishefsky and Fukuyama. However, it was not until nine years later in 1992 that the first asymmetric total synthesis of (–)-quinocarcin was surmounted by Garner. Over this period of time, there were also many other asymmetric synthetic studies reported. Compared to these syntheses, our synthetic route if feasible, necessitates fewer steps and offers ease of stereocontrol simply through judicious choice of substrates derived from natural sources.

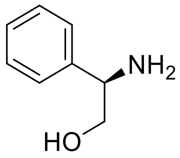
Our synthetic study commenced with the synthesis of (*R*)-phenylglycinol (**11**) which is then *O*-methyl protected and finally amidated to furnish picolinamide **2a**, the substrate for our next stage of exploration – ligand-directed aryl C–H activation. The synthesis of **2a** in good yields and reproducibility enable us to easily advance to the C–H functionalization stage. Building upon our group's previous unpublished work, acrylation was tested and optimized to give satisfactory results.

Subsequent acetoxylation, however, does not proceed as smoothly as we had expected, suffering from severe undesired competing side reactions. Suspecting that the carbon–carbon double bond interferes with the reaction, we attempted reduction of the double bond prior to acetoxylation. Indeed, very slightly higher yield was achieved, but more importantly, much cleaner product was obtained, which tallies with our hypothesis that the double bond affect the reaction in an undesirable manner. Therefore, moving forward, new solutions to circumvent this problem have to be thought out.

4.5 EXPERIMENTAL SECTION

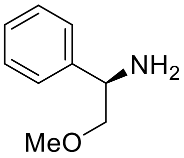
All commercially obtained reagents for the synthesis were used as received. Hydrogenation was conducted under 1 atm H_2 and precautions were taken to exclude O_2. Thin-layer chromatography (TLC) was conducted with Merck 60 F254 precoated silica gel plate (0.2 mm thickness) and visualized with UV and 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 Jeol ECA400 NMR spectrometer and are reported in ppm downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.24, singlet). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Jeol ECA400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). IR spectra were recorded as thin films on NaCl plates for liquid samples and KBr pressed pellets for solid samples 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.

Characterization data:



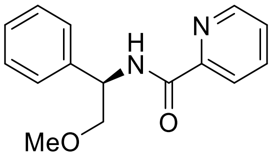
(*R*)-2-amino-2-phenylethanol. A solution of phenylglycine methyl ester hydrochloride (13.11 g, 0.065 mol, 1 eq.) in 50% aqueous ethanol (80 mL) was added dropwise to a stirred solution of $NaBH_4$ (11.73 g, 0.31 mol, 4.77 eq.) in 50% aqueous ethanol (180 mL) cooled at 0 ºC. The resultant suspension was stirred at r.t. for 9 hours, refluxed for 5.5 hours, and stirred at r.t. for a further 8 hours wherein two clear layers had formed. The top layer was decanted and evaporated to give an aqueous solution, while the viscous bottom layer was extracted with ethanol (3 × 25 mL), and the ethanol extracts were combined and evaporated to give wet oil. The aqueous solution from the top layer was combined with the wet oil and extracted with ethyl acetate (5 × 18 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to give a white solid. Recrystallization from ethyl acetate-hexane afforded (*R*)-2-amino-2-phenylethanol as white crystals (5.45 g, 61%).

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.00 (s, 3H), 3.55 (dd, *J* = 10.6, 8.4 Hz, 1H), 3.73 (dd, *J* = 10.9, 4.1 Hz, 1H), 4.05 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 57.5, 68.1, 126.7, 127.7, 128.8, 142.8 ppm; $[\alpha]_D^{23}$ = –55.7° (*c* 0.107, CH$_2$Cl$_2$); IR(KBr) *ν* cm^{-1}: 557, 704, 770, 1045, 1065, 1209, 1358, 1383, 1450, 1497, 1599, 2893, 3264, 3327; HRMS (TOF MS ES+): calcd for C$_8$H$_{12}$NO [M+H]$^+$ 138.0919, found 138.0917.



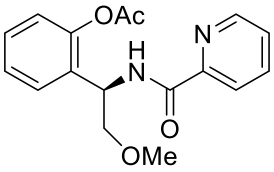
(*R*)-2-methoxy-1-phenylethanamine. (*R*)-(–)-2-Amino-2-phenylethanol (2.00g, 14.58 mmol, 1 eq.) in THF (20mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 1.22 g, 30.62 mmol, 2.1 eq.) in THF (10mL), and the suspension was stirred for 2 hours at room temperature. Iodomethane (0.95 mL, 15.31 mmol, 1.05 eq.) was added and the solution was first stirred for 1 hour, and then heated to reflux for another 3 hours. The reaction mixture was cooled, diluted with cold brine, extracted with diethyl ether, dried (Na$_2$SO$_4$) and evaporated. The crude mixture was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH) to give (*R*)-2-Methoxy-1-phenylethanamine as colourless oil (1.76 g, 80%).

R$_f$ = 0.11 (EA:Hexane = 4:1); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.81 (s, 2H), 3.33-3.37 (m, 1H), 3.37 (s, 3H), 3.49 (dd, *J* = 3.9, 9.4 Hz, 1H), 4.18 (dd, *J* = 3.9, 8.9 Hz, 1H), 7.23–7.38 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 55.5, 59.0, 79.1, 126.9, 127.5, 128.5, 142.6 ppm; $[\alpha]_D^{21}$= –57.2° (*c* 0.756, CH$_2$Cl$_2$); IR(KBr) *ν* cm^{-1}: 615, 702, 760, 860, 968, 1028, 1115, 1194, 1354, 1381, 1452, 1493, 1603, 2887, 2924, 2980, 3026, 3061, 3310, 3377; HRMS (TOF MS ES+): calcd for $C_9H_{14}NO$ $[M+H]^+$ 152.1075, found 152.1078.



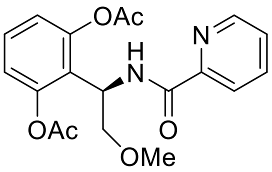
(*R*)-*N*-(2-methoxy-1-phenylethyl)picolinamide. (*R*)-2-Methoxy-1-phenylethanamine (1.00 g, 6.61 mmol, 1 eq.) was weighed into a 50 mL rbf. Dichloromethane (15 mL) was added and the mixture stirred and cooled to 0 ºC. Picolinoyl chloride hydrochloride (1.24 g, 6.94 mmol, 1.05 eq.) was added and the mixture stirred. *N*-ethyldiisopropylamine (2.42 mL, 13.9 mmol, 2.1 eq.) was added dropwise at 0 ºC. Mixture was allowed to stir overnight at r.t. After which, mixture was diluted with 20 mL dichloromethane, extracted with water (3 × 20 mL) and brine (1 × 10 mL). Organic layer was dried over Na_2SO_4, evaporated *in vacuo* and purified by flash column chromatography (CH_2Cl_2/MeOH) to give (*R*)-*N*-(2-methoxy-1-phenylethyl)picolinamide as white yellow solids (1.37g, 81%).

R_f = 0.55 (EA:Hexane = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (s, 3H), 3.74–3.82 (m, 2H), 5.37 (ddd, *J* = 5.3, 5.3, 8.4 Hz, 1H), 7.23–7.44 (m, 6H), 7.83 (td, *J* = 7.8, 1.8 Hz, 1H), 8.17 (d, *J* = 7.3 Hz, 1H), 8.57–8.59 (m, 1H), 8.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.0, 59.3, 75.5, 122.5, 126.4, 127.1, 127.7, 128.8, 137.5, 140.0, 148.3, 150.0, 164.1 ppm; $[\alpha]_D^{22}$ = +39.4° (*c* 0.105, CH_2Cl_2); IR(KBr) *v* cm^{-1}: 550, 588, 636, 704, 750, 818, 876, 908, 976, 1042, 1086, 1130, 1204, 1252, 1285, 1393, 1429, 1464, 1520, 1566, 1589, 1655, 2810, 2891, 2926, 3352, 3368; HRMS (TOF MS ES+): calcd for $C_{15}H_{16}N_2O_2Na$ $[M+Na]^+$ 279.1109, found 279.1109.



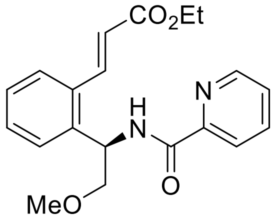
(*R*)-2-(2-methoxy-1-(picolinamido)ethyl)phenyl acetate. (*R*)-N-(2-methoxy-1-phenylethyl)picolinamide (70.9 mg, 0.2 mmol, 1 eq.), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol, 10 mol%), PhI(OAc)$_2$ (128.8 mg, 0.4 mmol, 2.0 eq.) were weighed into a 10 mL rbf in sequence. 2.0 mL of acetonitrile with AcOH/AcO$_2$ (1:1, 3 eq.) was added and the mixture stirred at 100ºC for 24 hours before purification *via* flash column chromatography (EA/Hexane) to give (*R*)-2-(2-methoxy-1-(picolinamido)ethyl)phenyl acetate yellow oil (12.6 mg, 20%).

R$_f$ = 0.45 (EA:Hexane = 4:1); ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.34 (s, 3H), 3.38 (s, 3H), 3.72 (d, *J* = 5.5 Hz, 2H), 5.54–5.59 (m, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.23–7.32 (m, 2H), 7.41–7.44 (m, 1H), 7.50 (dd, *J* = 7.7, 1.4 Hz, 1H) 7.83 (td, *J* =7.7, 1.8 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.56–8.58 (m, 1H), 8.71 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 21.3, 48.1, 59.3, 74.4, 122.5, 123.1, 126.4, 128.5, 128.8, 131.6, 137.5, 148.3, 148.7, 149.9, 163.9, 169.8 ppm



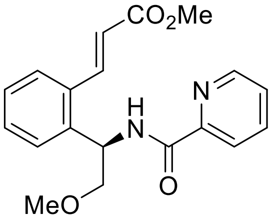
(*R*)-2-(2-methoxy-1-(picolinamido)ethyl)-1,3-phenylene diacetate. (*R*)-N-(2-methoxy-1-phenylethyl)picolinamide (70.9 mg, 0.2 mmol, 1 eq.), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol, 10 mol%), PhI(OAc)$_2$ (128.8 mg, 0.4 mmol, 2.0 eq.) were weighed into a 10 mL rbf in sequence. 2.0 mL of acetonitrile with AcOH/AcO$_2$ (1:1, 3 eq.) was added and the mixture stirred at 100ºC for 24 hours before purification *via* flash column chromatography (EA/Hexane) to give (*R*)-2-(2-methoxy-1-(picolinamido)ethyl)-1,3-phenylene diacetate acetate as yellow oil (14.9 mg, 37%).

R$_f$ = 0.39 (EA:Hexane = 4:1); ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.08 (s, 3H), 3.32 (s, 3H), 3.65 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.72 (dd, *J* = 10.0, 6.3 Hz, 1H), 5.78 (m, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 7.27–7.33 (m, 1H), 7.40–7.44 (m, 1H), 7.83–7.85 (m, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 8.55–8.56 (m, 1H), 9.17 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 21.4, 45.5, 59.0, 74.3, 121.1, 122.6, 123.7, 126.5, 128.5, 137.6, 148.2, 149.8, 149.9, 163.8, 169.1 ppm



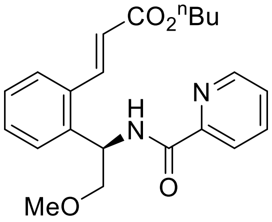
(*R*,*E*)-ethyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate. (*R*)-*N*-(2-methoxy-1-phenylethyl)picolinamide (100.0 mg, 0.390 mmol, 1 eq.), (*R*)-(–)-camphor-10-sulfonic acid (39.0 mg, 0.156 mmol, 40 mol%), Pd(OAc)$_2$ (18.0 mg, 0.078 mmol, 20 mol%), benzoquinone (27.0 mg, 0.195 mmol, 1.0 eq.) were weighed into a 10 mL rbf in sequence. DMSO (2.0 mL) was added and the mixture stirred. Ethyl acrylate (0.17 mL, 1.56 mmol, 4 eq.) was added and the mixture heated at 110 ºC for 24 hours. For very small-scale production in screening, mixture was purified *via* flash column chromatography (EA/Hexane) directly to give (*R*,*E*)-ethyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate as pale orange solids (117.0 mg, 85%). For larger scale, mixture was diluted with water, then extracted with EA, followed by brine, dried over Na$_2$SO$_4$, and evaporated before the purification using flash column chromatography (EA/Hexane).

R$_f$ = 0.55 (EA:Hexane = 4:1); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.35 (t, *J* = 7.3 Hz, 3H), 3.39 (s, 3H), 3.66–3.74 (m, 2H), 4.27 (q, *J* =7.2 Hz, 2H), 5.69 (dd, *J* = 6.1 Hz, 1H), 6.36 (d, *J* = 15.6 Hz, 1H), 7.26–7.55 (m, 5H), 7.83 (td, *J* = 7.8, 1.8 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.22 (d, *J* = 16.0 Hz, 1H), 8.60–8.61 (m, 1H), 8.76 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 49.7, 59.2, 60.7, 74.9, 121.5, 122.5, 126.5, 126.8, 127.4, 128.0, 130.1, 133.3, 137.5, 138.9, 141.6, 148.3, 149.8, 164.0, 166.7 ppm; $[\alpha]_D^{23}$ = +194.9° (*c* 1.750, CH_2Cl_2); IR(KBr) *v* cm^{-1}: 559, 619, 689, 752, 766, 820, 860, 974, 1030, 1117, 1179, 1319, 1369, 1466, 1541, 1632, 1653, 1705, 2812, 2928, 2974, 3065, 3306;HRMS (TOF MS ES+): calcd for $C_{20}H_{23}N_2O_4$ $[M+H]^+$ 355.1658, found 355.1656.



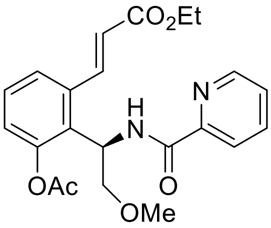
(*R*,*E*)-methyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate. (*R*)-*N*-(2-methoxy-1-phenylethyl)picolinamide (100.0 g, 0.390 mmol, 1 eq.), (*R*)-(–)-camphor-10-sulfonic acid (39 mg, 0.156 mmol, 40 mol%), $Pd(OAc)_2$ (18 mg, 0.078 mmol, 20 mol%), benzoquinone (27 mg, 0.195 mmol, 0.5 eq.) were weighed into a 10 mL rbf in sequence. DMSO (2.0 mL) was added and the mixture stirred. Methyl acrylate (0.14 mL, 1.56 mmol, 4 eq.) was added and the mixture heated at 110 ºC for 24 hours. For very small-scale production in screening, mixture was purified *via* flash column chromatography (EA/Hexane) directly to give (*R*,*E*)-methyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate as white solids (74.3 mg, 56%).

R_f = 0.55 (EA:Hexane = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (s, 3H), 3.66–3.74 (m, 2H), 3.81 (s, 3H), 5.69 (dd, *J* = 5.9 Hz, 1H), 6.38 (d, *J* = 15.6 Hz, 1H), 7.27–7.55 (m, 5H), 7.82 (td, *J* = 7.9, 1.1 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.26 (d, *J* = 15.6 Hz, 1H), 8.59–8.60 (m, 1H), 8.79 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.6, 51.9, 59.2, 74.9, 121.0, 122.4, 126.4, 126.9, 127.3, 128.0, 130.2, 133.2, 137.5, 139.0, 141.9, 148.3, 149.8, 164.0, 167.1 ppm; $[\alpha]_D^{21}$ = +195.6° (*c* 1.450, CH_2Cl_2); IR(KBr) *ν* cm^{-1}: 559, 621, 685, 754, 764, 820, 860, 972, 1115, 1175, 1315, 1371, 1391, 1466, 1535, 1568, 1593, 1647, 1711, 2814, 2882, 2928, 3061, 3312; HRMS (TOF MS ES+): calcd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$ 341.1501, found 341.1499.



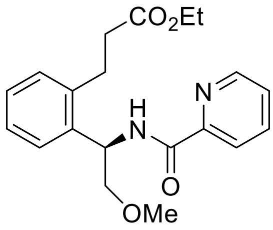
(*R*,*E*)-butyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate. (*R*)-N-(2-methoxy-1-phenylethyl)picolinamide (100.0 g, 0.390 mmol, 1 eq.), (*R*)-(–)-camphor-10-sulfonic acid (39.0 mg, 0.156 mmol, 40 mol%), $Pd(OAc)_2$ (18.0 mg, 0.078 mmol, 20 mol%), benzoquinone (27.0 mg, 0.195 mmol, 0.5 eq.) were weighed into a 10 mL rbf in sequence. DMSO (2.0 mL) was added and the mixture stirred. *n*-Butyl acrylate (0.22 mL, 1.56 mmol, 4 eq.) was added and the mixture heated at 110 ºC for 24 hours. For very small-scale production in screening, mixture was purified *via* flash column chromatography (EA/Hexane) directly to give (*R*,*E*)-butyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate as yellow oil (97.0 mg, 65%).

R_f = 0.65 (EA:Hexane = 4:1); ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.45 (qt, *J* = 7.6, 7.4 Hz, 2H), 1.70 (tt, *J* = 7.5, 7.1 Hz, 2H), 3.39 (s, 3H), 3.66–3.79 (m, 2H), 4.22 (t, *J* = 6.6 Hz, 2H), 5.70 (dd, *J* = 6.1 Hz, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 7.28–7.56 (m, 5H), 7.81 (td, *J* = 7.8, 1.8 Hz, 1H), 8.17 (t, *J* = 8.2 Hz, 1H), 8.24 (d, *J* =16.0 Hz, 1H), 8.57 (td, *J* = 0.9, 5.5 Hz, 1H), 8.79 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 19.3, 30.8, 52.9, 59.2, 64.6, 74.8, 121.4, 122.4, 126.4, 126.8, 127.7, 128.6, 130.1, 133.2, 137.4, 138.8, 139.9, 141.5, 148.2, 164.0, 166.7 ppm; $[\alpha]_D^{22}$ = +127.0° (c 2.290, CH_2Cl_2); IR(film) ν cm^{-1}: 621, 700, 752, 820, 864, 976,992, 1026, 1119, 1177, 1275, 1314, 1383, 1433, 1464, 1518, 1570, 1591, 1634, 1670, 1709, 2830, 2932, 3059, 3389, 3470; HRMS (TOF MS ES+): calcd for $C_{22}H_{27}N_2O_4$ $[M+H]^+$ 383.1971, found 383.1968.



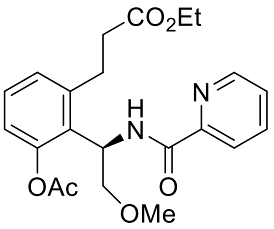
(*R*,*E*)-ethyl 3-(3-acetoxy-2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate. (*R*,*E*)-ethyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate (70.9 mg, 0.2 mmol, 1 eq.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), $PhI(OAc)_2$ (515.4 mg, 1.6 mmol, 8.0 eq.) were weighed into a 10 mL rbf in sequence. 2.0 mL of $AcOH/AcO_2$ (1:1) was added and the mixture stirred at 75°C for 24 hours before purification *via* flash column chromatography (EA/Hexane) to give (*R*,*E*)-ethyl 3-(3-acetoxy-2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate as yellow film (22.3 mg, 27%).

R_f = 0.47 (EA:Hexane = 4:1). ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, J = 6.9 Hz, 3H), 2.45 (s, 3H), 3.36 (s, 3H), 3.68 (dd, J = 10.1, 5.0 Hz, 1H), 3.78 (dd, J = 10.1, 6.4 Hz, 1H), 4.27 (t, J = 6.9 Hz, 2H), 5.77–5.82 (m, 1H), 6.27 (d, J = 15.5 Hz, 1H), 7.14 (dd, J = 7.8, 1.4 Hz, 1H), 7.28–7.35 (m, 2H), 7.40–7.43 (m, 1H), 8.24 (td, J = 7.8, 1.4 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8.24 (d, J = 15.5 Hz, 1H), 8.56 (d, J = 4.6 Hz, 1H), 9.10 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 21.6, 48.0, 59.2, 60.9, 74.2, 122.5, 123.2, 125.1, 125.8, 126.4, 128.6, 129.8, 136.6, 137.6, 142.3, 148.2, 149.7, 149.8, 163.9, 166.4, 169.1 ppm; HRMS (TOF MS ES+): calcd for $C_{22}H_{25}N_2O_6$ $[M+H]^+$ 413.1713, found 413.1702.



(*R*)-ethyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)propanoate. (*R*,*E*)-ethyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)acrylate (0.500 g, 1.41 mmol, 1 eq.) and Pd(0)/C (0.050 g, 10 wt.%) were weighed in sequence into a 25 mL RBF. Methanol (5 mL) was then added. The flask was purged with nitrogen and sealed tightly. Hydrogen gas was then introduced into the mixture directly using a hydrogen balloon and long needle. The reaction mixture was stirred overnight at 35°C before filtering through celite. The organic extract was evaporated *in vacuo* and purified *via* flash column chromatography (EA/Hexane) to give (*R*)-ethyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)propanoate as pale yellow oil (0.44 g, 88%).

R_f = 0.52 (EA:Hexane = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 3H), 2.63–2.71 (m, 1H), 2.84–2.92 (m, 1H), 3.12–3.16 (m, 2H), 3.41 (s, 3H), 3.72 (dd, *J* = 5.9, 1.8 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 5.57 (dd, *J* = 13.6, 5.9 Hz, 1H), 7.20–7.26 (m, 1H), 7.40–7.44 (m, 2H), 7.82 (td, *J* = 7.7, 1.8 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.58–8.59 (m, 1H), 8.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 27.8, 35.5, 49.0, 59.0, 60.4, 74.9, 122.2, 126.2, 126.5,126.8, 127.7, 129.5, 137.3, 137.7, 138.2, 148.1,149.7, 163.8, 173.0 ppm; $[\alpha]_D^{21}$ = +64.7° (*c* 0.266, CH_2Cl_2); IR(film) *v* cm^{-1}: 621, 702, 752, 820, 997, 1042, 1119, 1159, 1192, 1250, 1290, 1373, 1433,1464, 1518, 1570, 1591, 1674, 1730, 2828, 2895, 2932, 2980, 3059, 3387; HRMS (TOF MS ES+): calcd for $C_{20}H_{25}N_2O_4$ $[M+H]^+$ 357.1814, found 357.1826.



(*R*)-ethyl 3-(3-acetoxy-2-(2-methoxy-1-(picolinamido)ethyl)phenyl)propanoate. (*R*)-ethyl 3-(2-(2-methoxy-1-(picolinamido)ethyl)phenyl)propanoate (71.3 mg, 0.2 mmol, 1 eq.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), $PhI(OAc)_2$ (515.4 mg, 1.6 mmol, 8.0 eq.) were weighed into a 10 mL rbf in sequence. 2.0 mL of $AcOH/AcO_2$ (1:1) was added and the mixture stirred at 75°C for 24 hours before purification *via* flash column chromatography (EA/Hexane) to give (*R*)-ethyl 3-(3-acetoxy-2-(2-methoxy-1-(picolinamido)ethyl)phenyl)propanoate as yellow film (24.9 mg, 30%).

R_f = 0.45 (EA:Hexane = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 3H), 2.46 (s, 1H), 2.78 (td, *J* = 15.9, 8.0 Hz, 1H), 2.93 (td, *J* = 15.8, 8.0 Hz, 1H), 3.20 (t, *J* = 7.9 Hz, 2H), 3.36 (s, 3H), 3.65 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.82 (dd, *J* = 10.0, 5.4 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 5.77 (dd, *J* = 14.1, 7.2 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1Hz), 7.10 (d, *J* = 7.7 Hz, 1H), 7.20–7.26 (m, 1H), 7.40–7.43 (m, 1H), 7.83 (td, *J* = 7.7, 1.8 Hz, 1H), 8.16 (d, *J* = 7.3 Hz, 1H), 8.55–8.56 (m, 1H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 21.7, 28.8, 35.5, 47.7, 59.1, 60.7, 74.5, 122.5, 126.4, 127.6, 128.4, 128.9, 137.5, 140.9, 148.2, 149.9, 150.0, 163.8, 169.0, 173.0 ppm; $[\alpha]_D^{22}$ = +28.0° (*c* 0.370, CH_2Cl_2); IR(KBr) *v* cm^{-1}: 592, 621, 700, 752, 820, 872, 1042, 1117, 1180, 1292, 1371, 1435, 1464, 1514, 1570, 1591, 1678, 1732, 1771, 2932, 3399; HRMS (TOF MS ES+): calcd for $C_{22}H_{27}N_2O_6$ $[M+H]^+$ 415.1869, found 415.1871.