UNIVERSITY OF JYVÄSKYLÄ
DEPARTMENT OF CHEMISTRY

RESEARCH REPORT NO. 175

MIKKO V. LESKINEN

REMOTE β'-FUNCTIONALIZATION OF β-KETO ESTERS

Academic Dissertation for
the Degree of Doctor of Philosophy

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BY

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ABSTRACT

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The research described in this thesis focuses on the remote catalytic oxidative functionalization of sp^3 C−H bonds.

The goal of the work was to develop a new method for the cross-dehydrogenative coupling of β-keto esters and indoles. The basic aims of the study were successfully realized, and a new oxidative remote sp^3 β'-C−H functionalization platform was created. The reactions were found to work under benign conditions at room temperature. Cross-dehydrogenative coupling reactions between β-keto esters and electron-rich arenes, such as indoles, proceed with high regiochemical fidelity with a range of β-keto esters and indoles. The mechanism of the reaction between a prototypical β-keto ester, ethyl 2-oxocyclopentanonecarboxylate and *N*-methylindole, has been studied experimentally by monitoring the temporal course of the reaction by ^{1}H NMR, kinetic isotope effect studies, and control experiments. The experimental results indicate that the reaction proceeds via two catalytic cycles. Cycle A, the dehydrogenation cycle, produces an enone intermediate. The dehydrogenation is assisted by *N*-methylindole, which acts as a ligand for Pd(II). The coupling is completed in cycle B, the C–C bond formation cycle, which is catalyzed by Pd(II) and also by trifluoroacetic acid.

Keywords: Remote functionalization, Dehydrogenative cross-coupling, Oxidative coupling, C−H functionalization, Palladium, β-keto esters, Indole

Author's address

Mikko V. Leskinen
Department of Chemistry
P.O. Box 35
40014 University of Jyväskylä
Finland
mikko.v.leskinen@jyu.fi, mikko.v.leskinen@gmail.com

Supervisors

Professor Petri Pihko
Department of Chemistry
University of Jyväskylä

Reviewers

Professor Olivier Baudoin
Institut de Chimie et Biochimie Moléculaires et Supramoléculaires
Université Claude Bernard Lyon 1
Lyon, France

Professor Olafs Daugulis
Department of Chemistry
University of Houston
Houston, USA

Opponents

Professor Thorsten Bach
Technische Universität München
Lehrstuhl für Organische Chemie I
Lichtenbergstraße 4
85747 Garching
Germany

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Jyväskylässä 10.2.2014
Mikko Leskinen

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which in the text are referred to by their Roman numerals.

I Mikko V. Leskinen, Kai-Tai Yip, Arto Valkonen, and Petri M. Pihko, Palladium-Catalyzed Dehydrogenative β'-Functionalization of β-Keto Esters with Indoles at Room Temperature, *J. Am. Chem. Soc.* **2012**, *134*, 5750−5753.
https://doi.org/10.1021/ja300684r

II Kai-Tai Yip, Roshan Y. Nimje, Mikko V. Leskinen, and Petri M. Pihko, Palladium-Catalyzed Dehydrogenative β'-Arylation of β -Keto Esters under Aerobic Conditions: Interplay of Metal and Brønsted Acids, *Chem. Eur. J.* **2012**, *18*, 12590 – 12594.
https://doi.org/10.1002/chem.201201988

III Roshan Y. Nimje, Mikko V. Leskinen, and Petri M. Pihko, A Three-Component Palladium-Catalyzed Oxidative C−C Coupling Reaction: A Domino Process in Two Dimensions, *Angew. Chem. Int. Ed.* **2013**, *52*, 4818 –4822.
https://doi.org/10.1002/ange.201300833

IV Mikko V. Leskinen, Ádám Madarász, Kai-Tai Yip, Aini Vuorinen, Imre Pápai, Antti J. Neuvonen and Petri M. Pihko, Cross-Dehydrogenative Couplings between Indoles and β-Keto Esters: Ligand-Related Kinetic Isotope Effects and Dehydrogenation via a Proton-Assisted Electron Transfer to Pd(II), *Submitted.*
https://doi.org/10.1021/ja501681y

Author's contribution

In paper I, the author conceived and initiated the study and performed the screening of the conditions, explored the substrate scope, and wrote the paper together with the co-authors.

In paper II, the author conceived the studies together with the co-authors and contributed to the control experiments necessary for the mechanistic study. The paper was written together with the co-authors.

In paper III, the author conceived and initiated the study, carried out the kinetic experiments and wrote the paper together with the co-authors.

In paper IV, the author conceived and initiated the study, carried out the kinetic experiments, expanded the substrate scope of the reaction, co-supervised one of the co-authors (A.V.), and wrote the paper together with the co-authors.

ABBREVIATIONS

Ac	Acetyl
AQ	8-Aminoquinoline
BG	Bulky group
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
B-Pin	Boronic acid pinacol ester
BQ	Benzoquinone
Bz	Benzoyl
Cat.	Catalyst
cod	(1*Z*,5*Z*)-cycloocta-1,5-diene
coe	Cyclooctene
de	Diastereometric excess
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density functional theory
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereometric ratio
ee	Enantiometric excess
esp	$\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid
EWG	Electrons withdrawing group
IBX	2-Iodoxybenzoic acid
KIE	Kinetic isotope effect
Lauroyl peroxide	Dodecanoic peroxyanhydride
mep	*N*,*N*′-dimethyl- *N*,*N*′-bis(2-pyridylmethyl-ethane
Me_4phen	3,4,7,8-Tetramethyl-1,10,-phenanthroline
nbe	Norbornen
NMP	1-Methyl-2-pyrrolidone
NPhth	Phtalimidyl
Ns	4-Nitrobenzenesulfonyl
Ms	Methanesulfonyl
Oxone	Potassium peroxymonosulfate, $K_2S_2O_8$
PDP	2-({(*S*)-2-[(*S*)-1-(pyridine-2-ylmethyl)pyrrolidin-2-yl]pyrrolidin-1-}methyl)pyridine
PG	Removable protecting group
Ph-BOX	(−)-2,2′ -Isopropylidenebis[(4S)-4-phenyl-2-oxazoline]
Piv	Pivalic
PivOH	Pivalic acid
RedG	Nonhaem iron-dependent dioxygenase
Selectfluor	1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate
Me_3tacn	1,4,7-trimethyl-1,4,7-triazacyclononane
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TcBoc	2,2,2-Trichloro-*tert*-butyloxycarbonyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Tf	Trifluoromethanesulfonyl

TFA	Trifluoroactetic acid
THF	Tetrahydrofuran
tetramethylTHF	2,2,5,5-Tetramethyltetrahydrofuran
tpa	Triphenylacetate
Ts	*p*-Toluenesulfonyl

CONTENTS

1 REVIEW OF LITERATURE

1.1 Introduction

1.1.1 Selective catalytic oxidative remote functionalization of aliphatic sp^3 C−H bonds

The catalytic functionalization of C−H bonds[1-20]profoundly changed how we think about using them in synthetic chemistry and has the potential to revolutionize the synthesis of complex molecules.[21-30] In particular, the functionalization of C−H bonds has plenty of unreleased potential in the late-state functionalization[31-33] of complex molecules as well as for the streamlining of large-scale manufacturing in pharmaceutical, fine-chemical and agricultural industries.[34-36] At the C−H functionalization, the direct oxidations of the C−H bonds allows for the use of simple (i.e., less functionalized) reagents and often reduces the number of steps it takes for the target molecule to produce better atomy-, redox- and step-economies. With late-state functionalization, it is possible to add functionalities to drug candidates and create new analogues without a need for going back to the beginning of the sequence with pre-functionalized starting materials. The benefit of this kind of strategy includes fewer laborious operations that lead to lower costs and improvements of waste and environmental profiles.

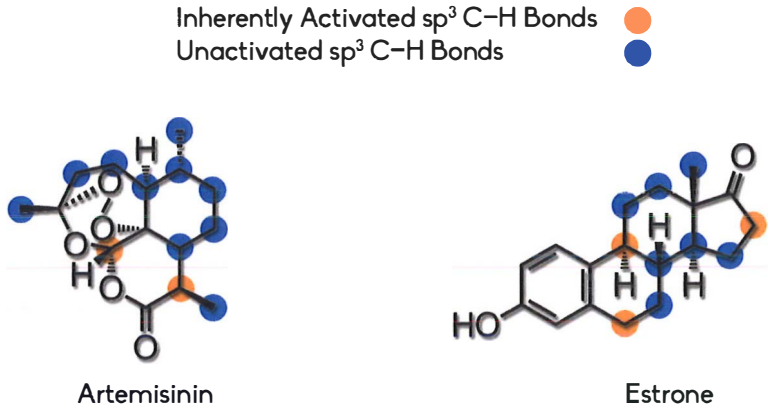
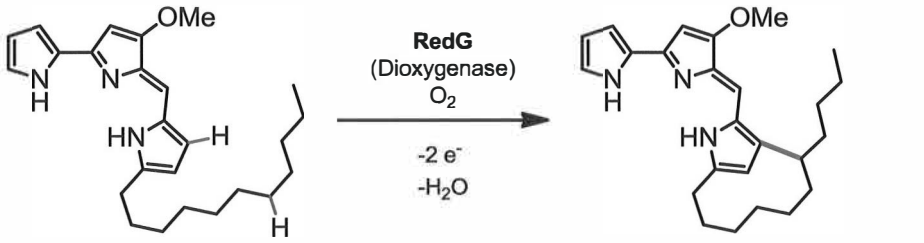


Figure 1. Activated vs. unactivated positions

The thermodynamics of making a new bond (e.g. C–C bond) with a loss of hydrogen is typically unfavorable and thus requires an external driving force, namely, an appropriate sacrificial oxidant. Other challenges include overcoming the low reactivity of C–H bonds, achieving a site selective functionalization of one C–H bond in the presence of all others, and outcompeting dimerization. A classic problem in the field is how to selectively functionalize an sp^3 C–H bond, which is not adjacent to a heteroatom or π system (i.e., α-position). By contrast, there are a lot of tools that can be used for the functionalization of sp^2 and for the α-positions of functional groups. However, the sp^3 C–H bond functionalization of these remote positions is still elusive (Figure 1).[37]

The stoiciometric amounts of expensive metal-salts are commonly used in the functionalization of C–H as an oxidizer. For catalytic purposes, the replacement of metal-salts by using inexpensive and environmentally friendly oxidants such as air and oxygen will dramatically improve the practicality of using C–H coupling reactions. As a result, this offers attractive academic and industrial prospects in the synthetic chemistry.[38-47]



Undecylprodiginine
1

Butyl-*meta*-cycloheptylprodiginine
2

Scheme 1. Proposed biosynthesis scheme for butyl-*meta*-cycloheptylprodiginine by dehydrogenative macrocyclization between sp^3 and sp^2 C−H bonds.

In nature, region- and stereoselective C−H bond functionalizations under ambient reaction conditions come from fundamental transformations catalyzed by enzymes.[48,49] For example, cytochrome P450 mono-oxygenases catalyse (among other oxidative reactions) the O_2-mediated alkyl C−H bond hydroxylation of complex molecules, which is critical for the drug metabolizing and biosynthesis of secondary metabolites.[50-52] In Nature, new C−C bonds are also formed through the oxidative coupling of remote sp^3 C−H bonds (See Scheme 1).[53,54] Reactions such as these can inspire chemists to go beyond biosynthetic pathways by creating new kinds of reactions. Besides the reactions that mimic natural, biosynthetic pathways, chemists can also design new kinds of reactions through metal catalysis, via pathways that are not accessible in Nature

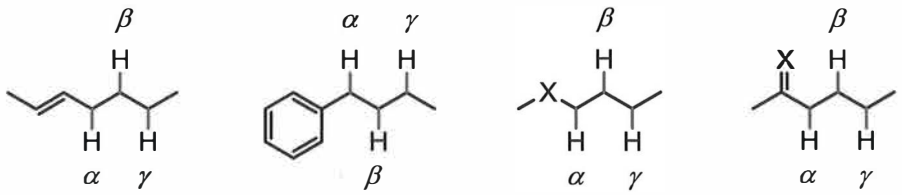
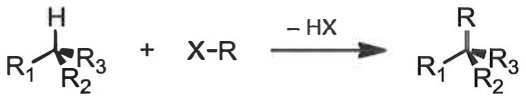


Figure 3. Definition of positions in this review.

The aim of this review is to bring attention to the current state of the field of remote selective catalytic oxidative functionalization of sp^3 C−H bonds. Remote

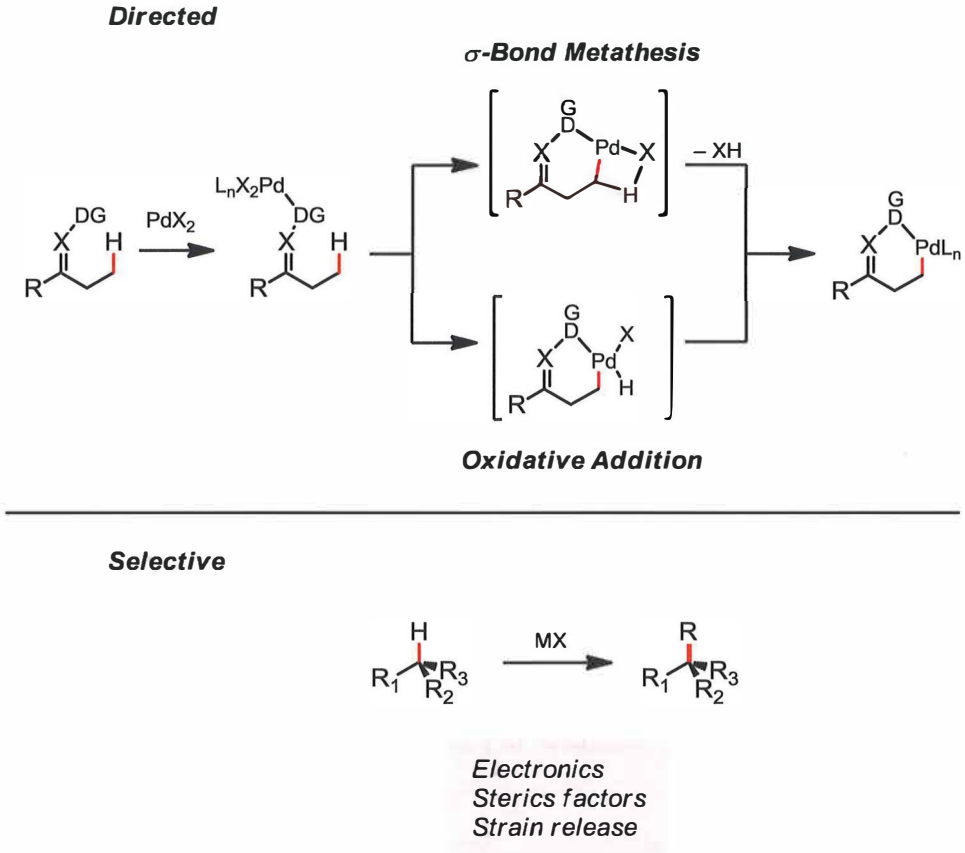
position is defined as all other positions compared to the α-position of the functional group or to the *sp*/*sp2* carbon (Figure 3). It should be noted that halogenated reagents do not need an external oxidant for C−H bond functionalization reactions, hence they are not covered in this review (Scheme 2).



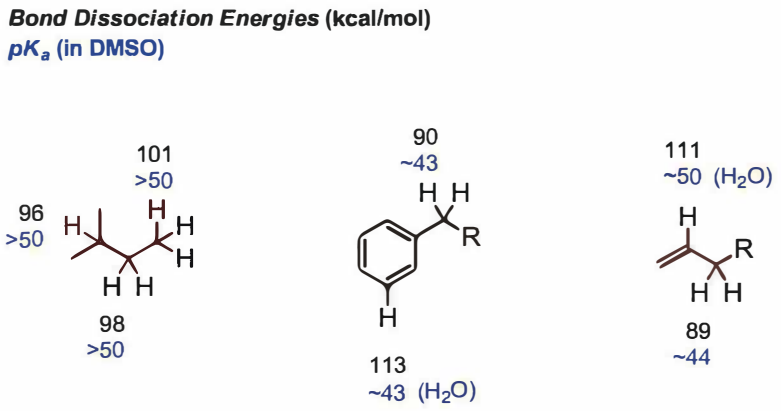
Scheme 2. Halogenated reagents can be used for direct C−H bond functionalization reactions without the need of an external oxidant.

There are two activation modes available for remote sp^3 C−H bond functionalizations; directed and selective (Scheme 3). Directed intramolecular sp^3 C−H activation is facilitated by heteroatom-assisted coordination of the transition metal. The selectivity is controlled by the electronics, sterics and strain release.[55] It must be noted that for sp^3 C−H bonds, pK_a and bond dissociation energies do not vary in aliphatic systems to the extent that they do in aromatic, bencylic or allylic systems. As a result, this makes it harder to distinguish between C−H bonds in an aliphatic system (Scheme 4).[56,57] The activation modes are covered in more detail in later chapters.

It should be noted that oxidative addition through Pd(IV) is unprecedented and extremely unlikely (Scheme 3).



Scheme 3. Indicates activation modes for remote sp^3 C–H bond functionalization.



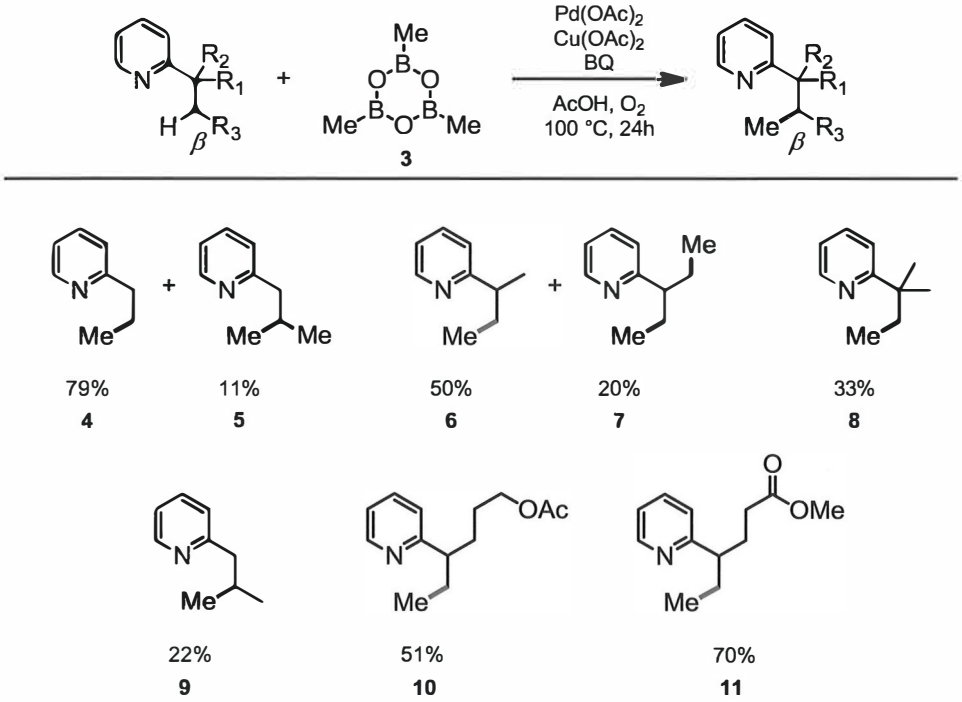
Scheme 4. Selected bond dissociation energies and the pK_a for C–H bonds.

1.2 Oxidative C-C bond formation reactions

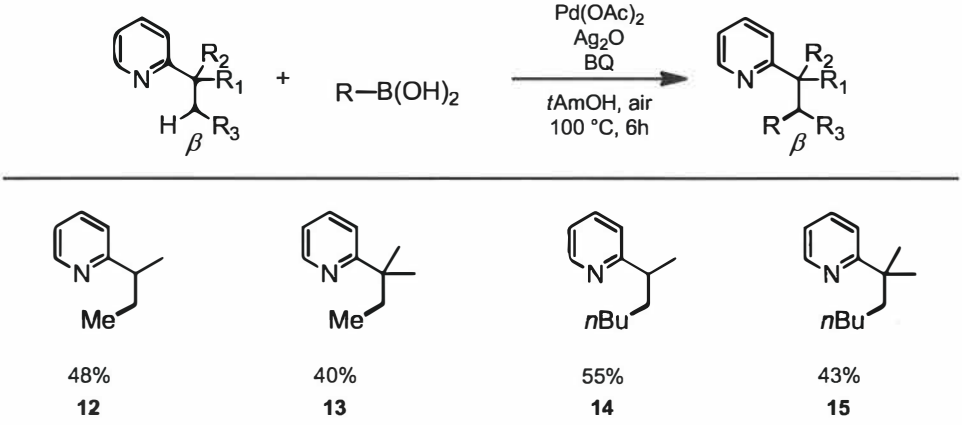
1.2.1 *β*-C-C Bond formation reactions

In 2006, Chen, Goodhue and Yu reported the seminal example of palladium(II)-catalyzed alkylations of remote *β*-sp^3 C−H bonds with either methylboroxine (Scheme 5) or boronic acids (Scheme 6) using pyridine as a directing group.[58] Using an organometallic reagent in C−H activation is challenging because Pd(II)-catalyzed homocoupling might be faster than C−H activation.[59]

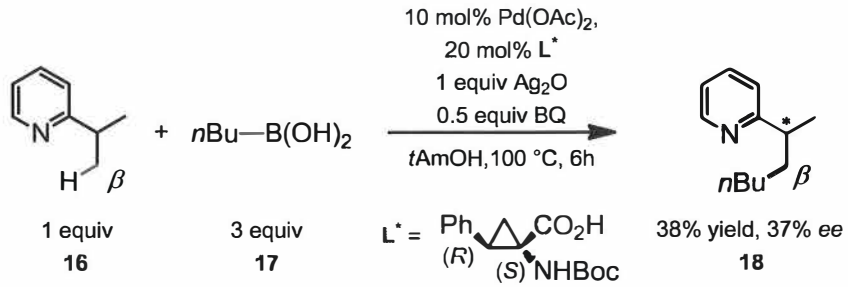
In the alkylation reaction of sp^3 C−H bonds with methylboroxine, the researchers used $Cu(OAc)_2$ as a co-oxidant together with benzoquinone (BQ). Benzoquinone is also important for the reductive elimination step.[60] However, in the alkylation of *β*-sp^3 C−H bonds with boronic acid Ag_2O and had to be used as a co-oxidant because $Cu(OAc)_2$ severely suppressed the coupling reaction. Ag_2O plays a dual role as a co-oxidant and also promotes transmetallation[61]. It is noteworthy that Ag_2O was able to replace $Cu(OAc)_2$ as an oxidant in the coupling reaction with methylboroxines (Scheme 5). A major limitation for using Ag(I) salts as the stoichiometric oxidant is that its use is not practical on a larger scale.



Scheme 5. Pyridine-directed alkylation of β-sp3 C–H bonds with methylboroxine (**3**).[58]



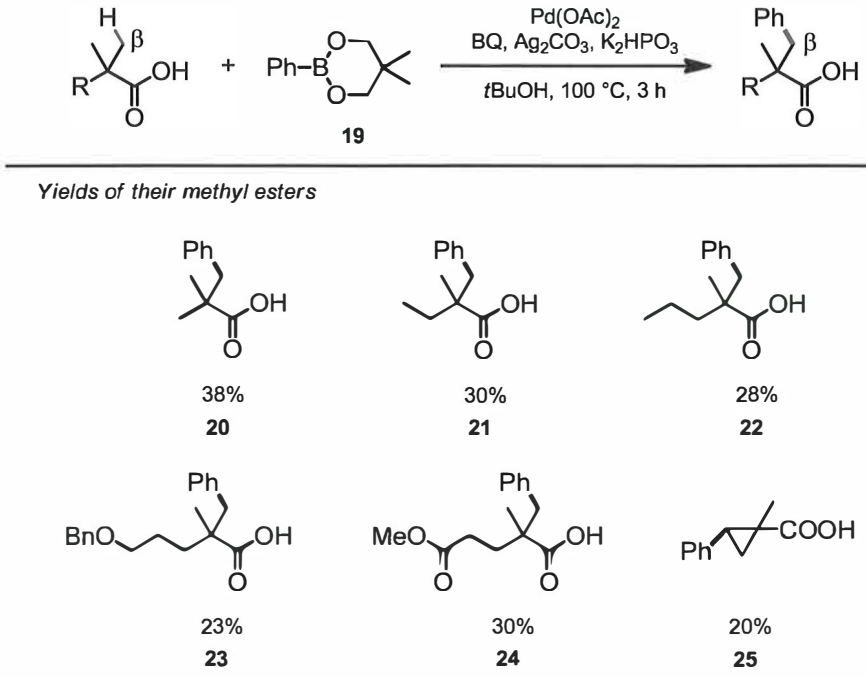
Scheme 6. Pyridine-directed alkylation of sp^3 C–H bonds with alkylboronic acid.[58]



Scheme 7. Enantioselective alkylation of *sp3* C–H bonds with alkylboronic acid.[62]

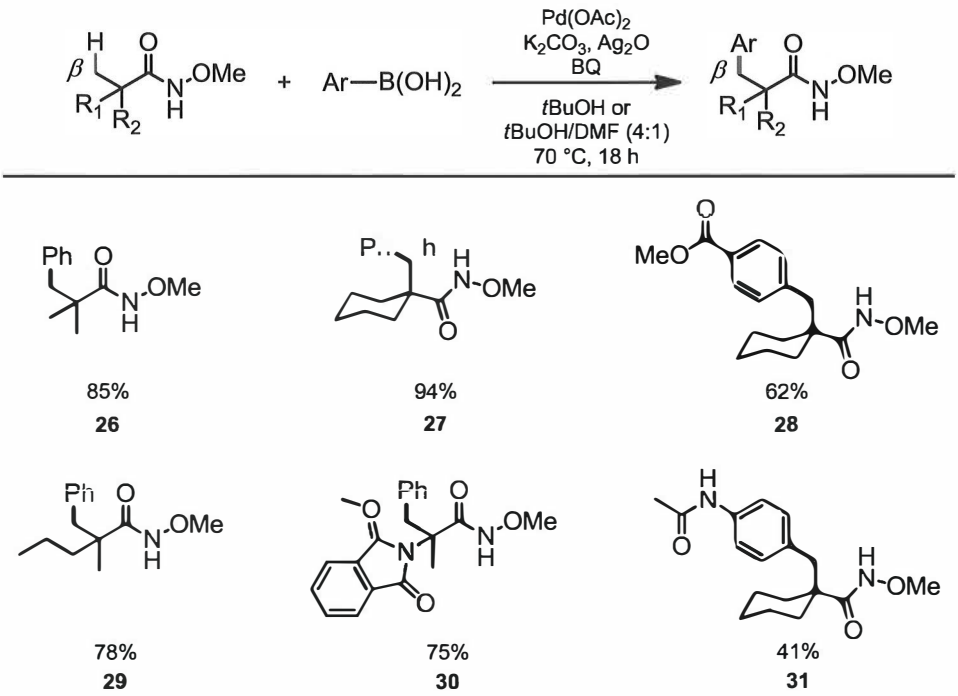
Later, in 2008, Yu and coworkers reported the first example of a catalytic asymmetric sp^3 C–H coupling reaction. They presented only one example of the C–C coupling of a butylboronic acid (**17**) with a primary C–H bond, which afforded only a modest yield and enantioselectivity (Scheme 7).[62]

Yu and coworkers have also investigated the use of a more practical directing group (carboxylic acid) for an oxidative β-sp^3 functionalization reaction.[63] The actual directing-group in this transformation is the in-situ formed carboxylate where K_2HPO_4 is used as a base in the reaction. The yields and scope of the oxidative β-sp^3-arylation reaction were modest (Scheme 8).



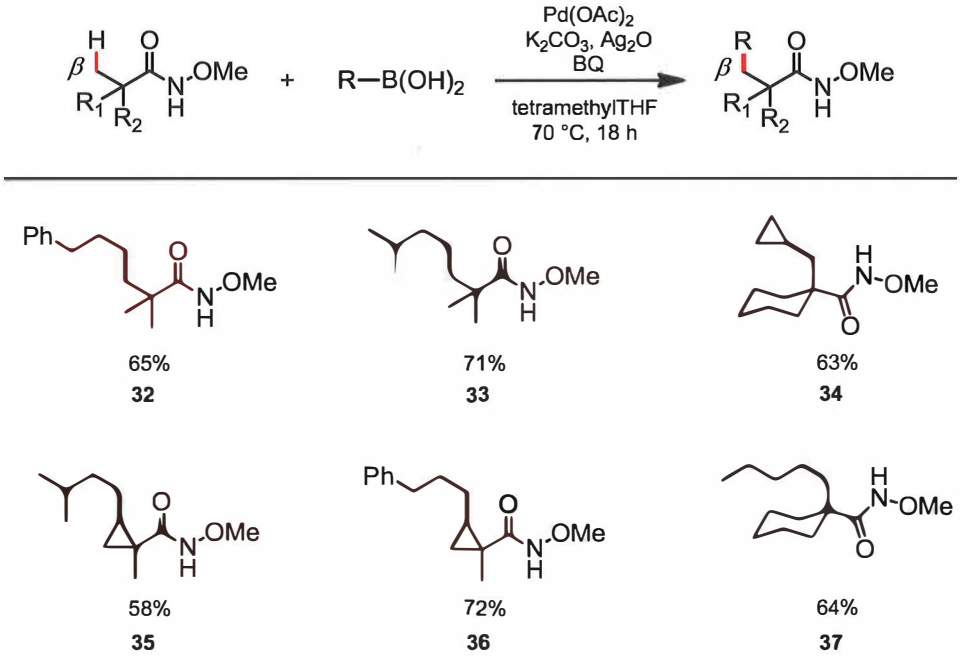
Scheme 8. Carboxylic acid-Directed arylation of β-sp^3 bonds with phenylboronate (**19**).[63]

In 2008, Yu and coworkers reported that *O*-methyl hydroxamic acids, readily available from carboxylic acids, were also viable directing groups in β-C−H activation via Pd-catalysis.[64] Thus, β-arylation of the methyl group proceeded smoothly by stirring the substrate with 0.5 equiv of benzoquinone, 2 equiv of Ag_2O, 2 equiv. of K_2CO_3, 1.6 equiv. of arylboronic acid, and 10 mol % of Pd(OAc)2 in *tert*-BuOH at 70 °C for 18 hours (Scheme 9).



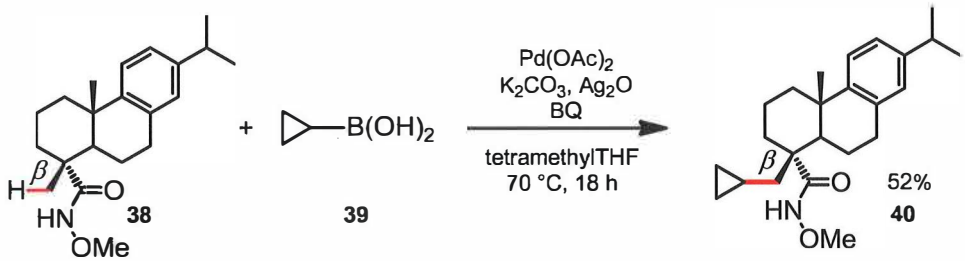
Scheme 9. β-Arylation of O-methyl hydroxyamic acids.[64]

However, the coupling of substrates with a alkylboronic acids under conditions identical to those used with arylboronic acids, (Scheme 9), did not produce any desired product. This is presumably due to β-hydride elimination. Yu speculated that the undesired β-hydride elimination could be suppressed by using a sterically hindered ligand along with a meticulous choice of a good solvent.[65,66] Following this hypothesis, they found that the presence of sterically hindered ligand prevented the reaction, but the use of 2,2,5,5-tetramethyltetrahydrofuran as a solvent allowed for the coupling of a β-sp^3 C−H bond with alkylboronic acids (Scheme 10).



Scheme 10. β-Alkylation of *O*-methyl hydroxyamic acids.[64]

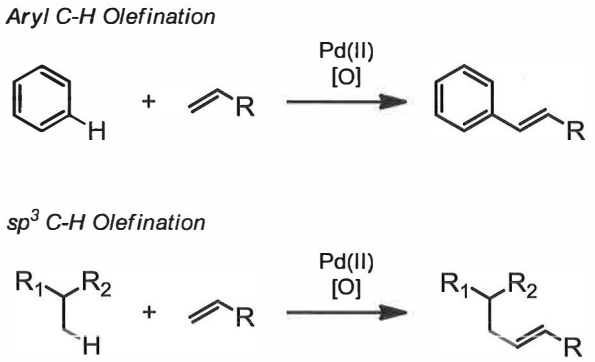
Yu and coworkers also demonstrated the potential for their protocol by alkylating substrate **38**, derived from dehydroabietic acid, with alkylboronic acid **39** Scheme 11). Dehydroabietic acid is identified as a natural product and as an efficient BK channel opener.[67]



Scheme 11. β-Alkylation of dehydroabietic acid derivative **38**.[64]

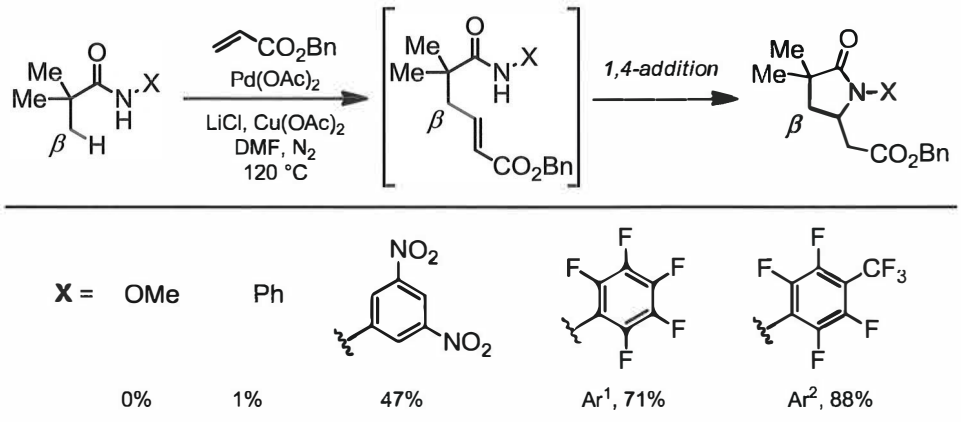
While aryl C−H olefination has been extensively explored in recent years, the olefination of an unactive sp^3 alkyl C−H bond has been a more elusive task (Scheme 12). The first aryl C−H olefination was published by Fujiwara and

Moritani as early as 1967,[68,69] whereas the first olefination of an unactive sp^3 C–H bond was not published until the Yu's group reported success in this area in 2010.[70]



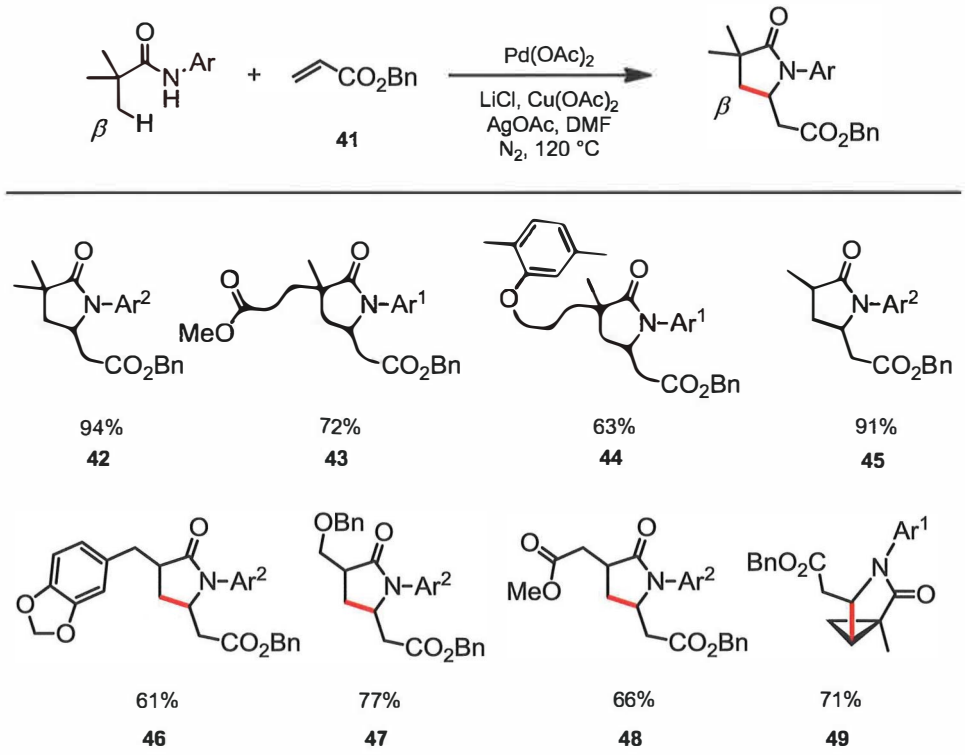
Scheme 12. Aryl and sp^3 C–H olefination.

As established in previous reports, the *N*-arylamide (CONHAr) directing group was highly efficient in a Pd(II)-catalyzed sp^3 C–H activation. This was especially true for electron-withdrawing substituents in an *N*-aryl group (CF_3, F, and NO_2) that enhanced the reactivity of the coupling reactions.[71] By optimizing the directing group, they were able to identify two optimal aryl groups in the olefination of a β-sp^3 C–H bond (Ar^1 and Ar^2 in Scheme 13).



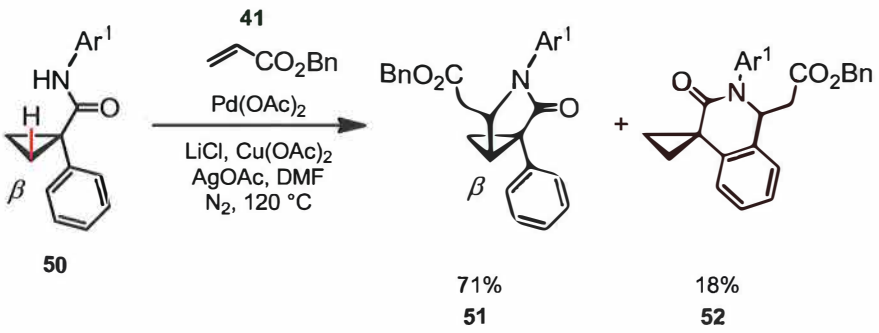
Scheme 13. Directing group optimization.[70]

The choice of solvents was also crucial for their reactivity. Polar and strongly coordinating amide solvents, such as NMP, DMA, and DMF, produced superior results. With the optimized conditions at hand, they β-olefinated a wide variety of amides with their corresponding products (Scheme 14).

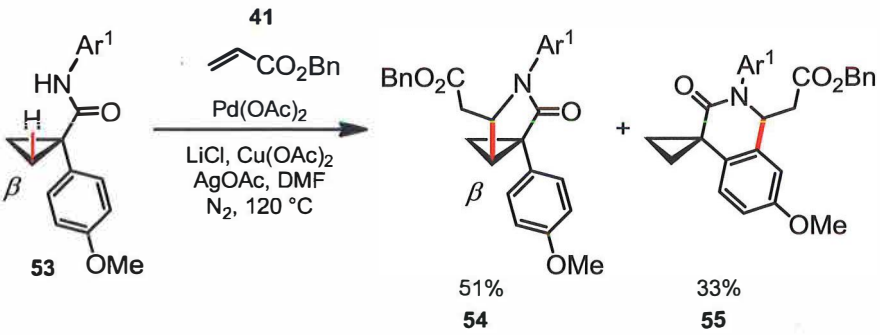


Scheme 14. Amide-directed olefination of sp^3 β-C–H bond.[70]

Remarkably, their olefination protocol was also found to be effective for the β-olefination of cyclopropane substrates (**49**, **50** and **51**). With substrates **50** and **53** serving as a side reaction, the *ortho*-olefination of the aryl groups also took place (Scheme 15 and Scheme 16).

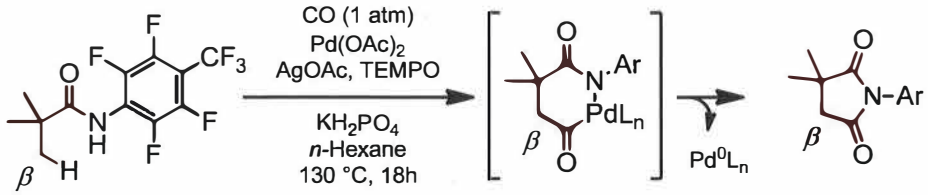


Scheme 15. Amide-directed olefination of cyclopropane **50** sp^3 β-C−H bond.[70]



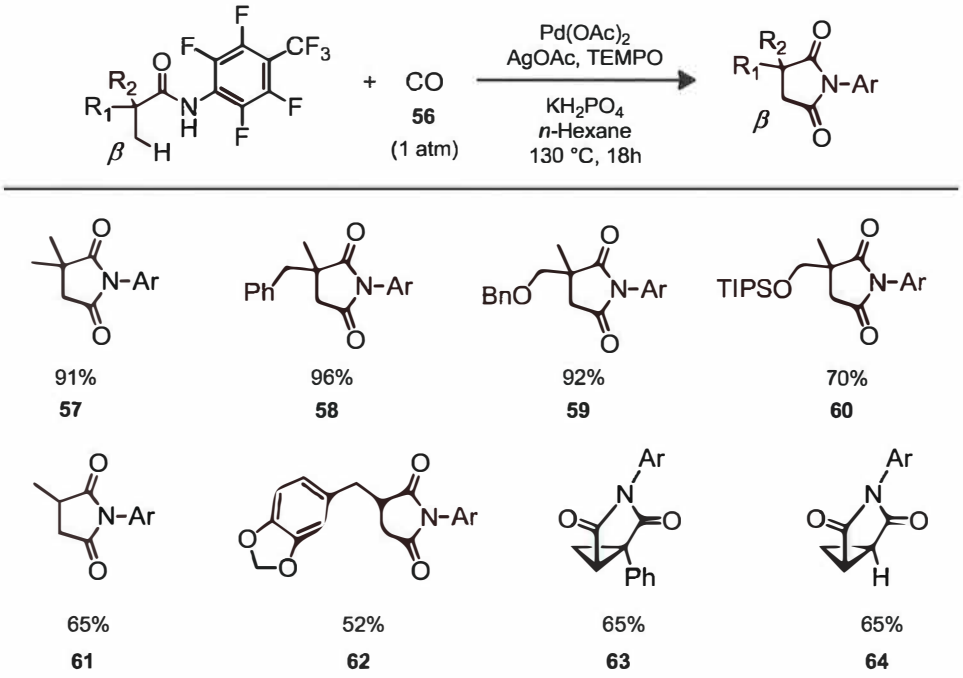
Scheme 16. Amide-directed olefination of cyclopropane **53** sp^3 β-C−H bond[70].

Despite recent landmark developments of the Pd(II)-catalyzed carbonylation of aryl sp^2 C−H bonds[72-77], achieving Pd(II)-catalyzed sp^3 C−H carbonylation has been a more challenging task. By following Fujiwara's[78-80] early footsteps for the carbonylation of a small alkane sp^3 C−H bond, Yoo, Wasa and Yu established the amide-directed carbonylation of a sp^3 β-C−H bond.[81]



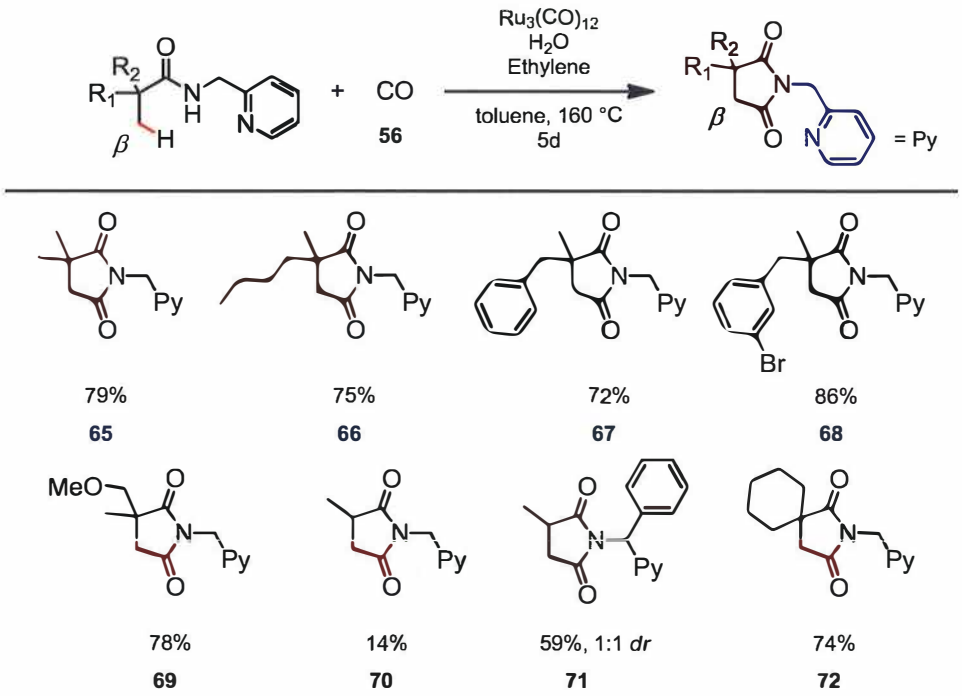
Scheme 17. Amide-directed carbonylation of sp^3 β-C−H bond[81].

They demonstrated the power of their β-carbonylation method with a wide range of different substrates (Scheme 18). Substrates bearing a quaternary α-center provided products with good to excellent yields. It is also intriguing that substrates bearing hydrogen at the α-carbon gave the succinimide products in good yields.



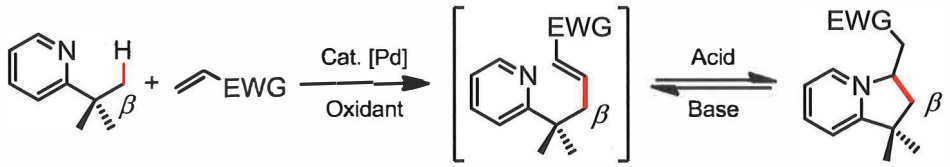
Scheme 18. Amide-directed carbonylation of an sp^3 β-C−H bond[81].

Applications of catalytic sp^3 C−H bond functionalization reactions with low-valent late transition metals are rare. However, Chatani and coworkers have recently demonstrated the use of a low-valent late transition metal catalyst, $Ru(CO)_{12}$, as a catalyst for the regioselective carbonylation of unactivated β sp^3 C−H bonds of aliphatic amides (Scheme 19).[82,83] Interestingly, they use ethylene as an oxidizer in the reaction. Furthermore, they clearly demonstrate a role of the pyridine directing group in the reaction. Hence, a product was not formed in the reaction if the pyridine directing group was replaced by a non-chelating phenyl group.



Scheme 19. Amide-pyridine-directed carbonylation of a sp^3 β-C−H bond.[82,83]

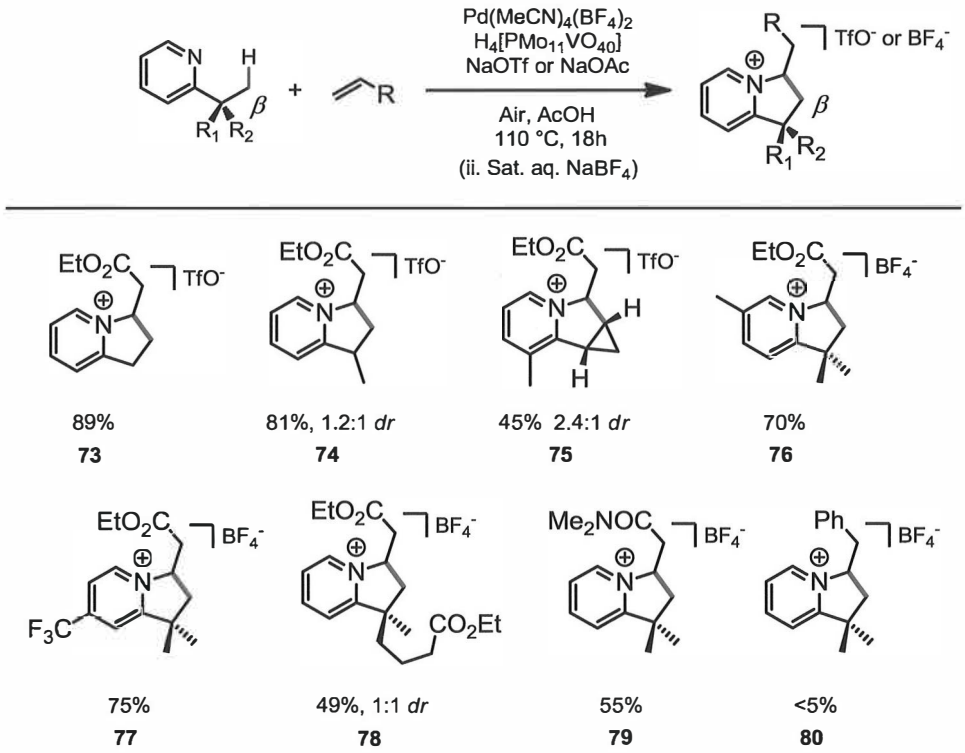
Sanford and coworkers published in 2011 a new method for the Pd/polyoxometalate-catalyzed aerobic olefination of unactivated β-sp^3 bonds.[84] Their strategy involved a sequence of a β-olefination of sp^3 C−H bond followed by a reversible intramolecular Michael addition, which protects the monoalkylated product from over functionalization (Scheme 20).



Scheme 20. β-Olefination followed by a reversible Michael addition.[84]

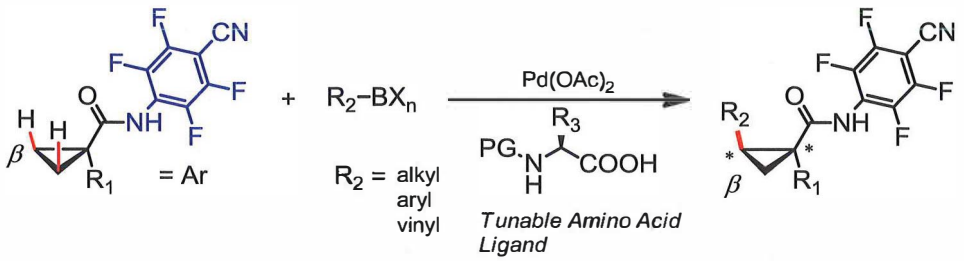
The reaction is executed under similar conditions reported by Obora and Ishii for the Pd/polyoxometalate cocatalyzed aerobic olefination of benzene. [85] Molybdovanadophosporic acid ($H_4[PMo_{11}VO_{40}]$) is serving as reoxidant of the

reduced Pd^0 to Pd^{II} during the reaction course.[84,85] A variety of pyridines could be used as substrates in this β-olefination and cyclization sequence with moderate yields (Scheme 21).[84]



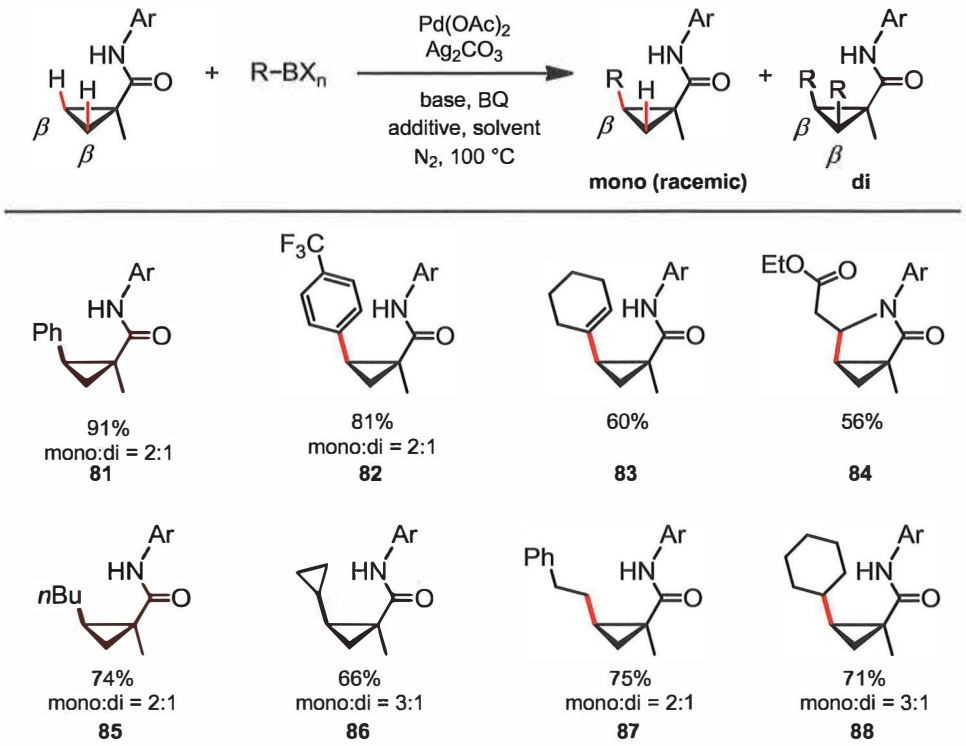
Scheme 21. β-Olefination and cyclization between various pyridines and alkenes.[84]

In 2011, Yu and coworkers made a breakthrough in the enantioselective C−H activation. After laborious screening, they demonstrated the first examples of an enantioselective β-C−H activation of cyclopropanes through a systematic tuning of the mono-*N*-protected amino acid ligand and the reaction conditions (Scheme 22).[86]



Scheme 22. Asymmetric cyclopropane C–H activation.[86]

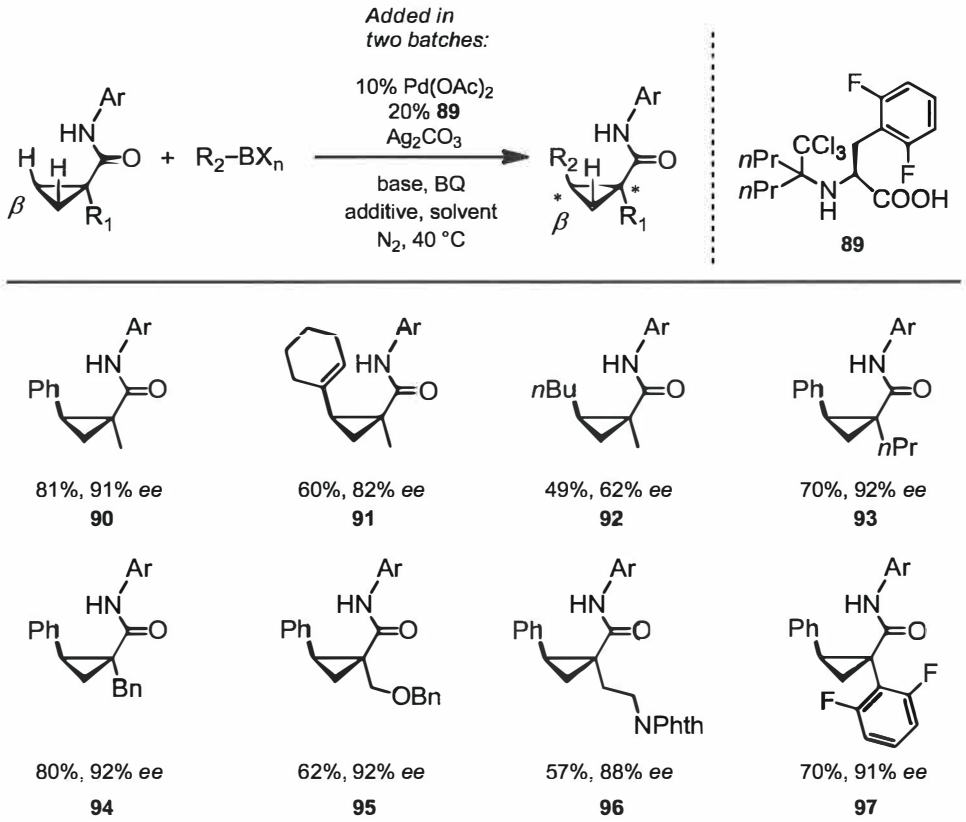
To establish the optimal reaction conditions, they first screened the reaction conditions for the racemic reaction for the β-coupling of cyclopropanes and organoboron reagents (Scheme 23). Building on their earlier success of utilizing acidic *N*-arylamides (Scheme 22, Ar) as weakly coordinating directing groups for a diverse range of alkyl and aryl C–H functionalization reactions,[70,71,81,87-89] they chose amide **81** as a test substrate for a coupling reaction with phenylboronic acid pinacol ester. Extensive screening revealed the need to use four different reaction conditions and two different organoboron reagents (B-Pin and BF_3K) in order to obtain optimal yields.



Scheme 23. Racemic cross-coupling of cyclopropyl C–H bonds with organoboron reagents.[86]

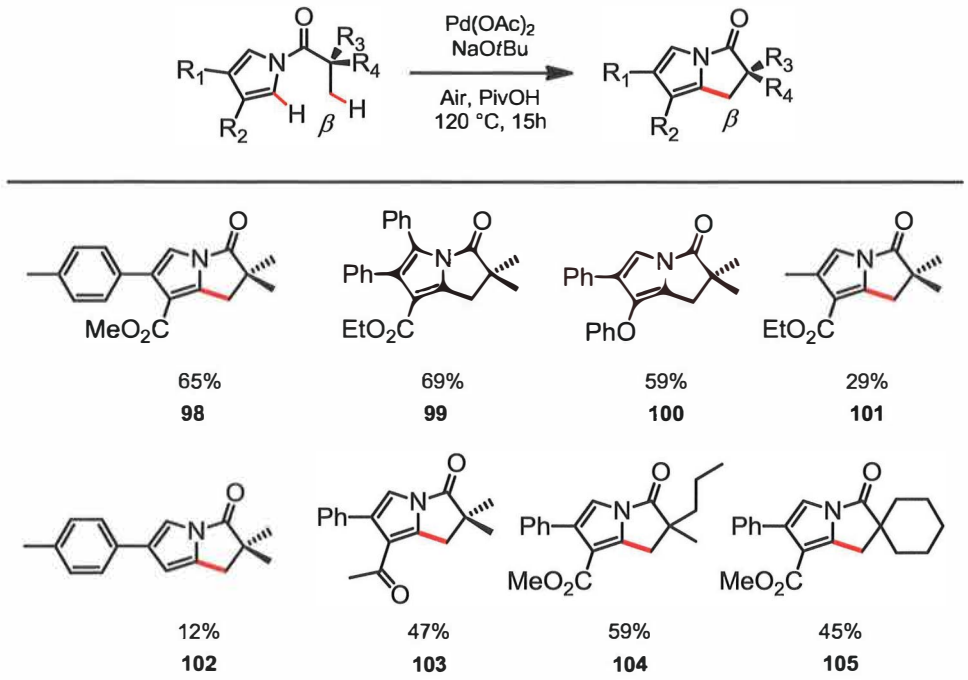
Subsequently, they started to screen optimal ligands for an effective enantioselective coupling reaction. Initially, they focused on screening mono-*N*-protected L-leucine derivatives and found that carbamate groups gave superior *ee* and mono selectivity compared with an amide group (Scheme 22, PG). Among the various carbamate protecting groups that were tested, 2,2,2-trichloro-*tert*-butyloxycarbonyl (TcBoc) gave the best *ee* (78%) and yield (47%). They subsequently investigated the effect of the amino acid backbone and found that having an aryl group on the amino acid side chain was crucial for obtaining a high *ee* (Scheme 22, R_3). After a slight modification of the carbamate protecting group, they finally discovered that amino acid ligand **89** afforded the best *ee*. This ligand afforded moderate yields and a good *ee* (Scheme 24). It is also noteworthy that the reagents were added into two batches, using a 5 mol%

catalyst and a 10 mol% ligand **89** for each batch to afford the optimal yield and *ee*. The addition of the reactants in a single batch resulted in inferior and inconsistent results.



Scheme 24. Enantioselective cross-coupling of cyclopropyl C–H bonds with organoboron reagents.[86]

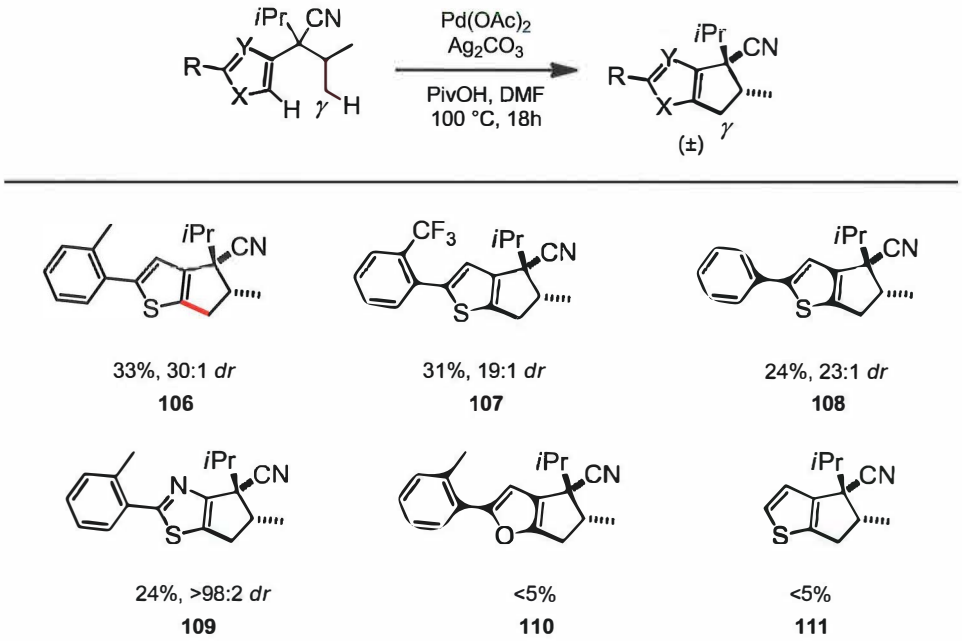
Liègault and Fagnou reported the first example of an intramolecular dehydrogenative coupling between sp^2 and β-sp^3 C–H bonds.[90] They demonstrate the dehydrogenative intramolecular β-coupling reaction by using $Pd(OAc)_2$ as a catalyst and air as the terminal oxidant, which showed moderate scope and efficiency (Scheme 25).



Scheme 25. Intramolecular dehydrogenative β-coupling reaction.[90]

1.2.2 γ-C-C Bond formation reactions

Recently in 2013, Pierre and Baudoin disclosed a method for an intramolecular γ-coupling reaction between sp^2 and γ-sp^3 C−H bonds. This paper showed that the synthesis of fused thiophene-cyclopentanes by Pd^{II}-catalyzed dehydrogenative sp^2 and γ-sp^3 C−H coupling is feasible, with modest yields (Scheme 26). Therefore, they also gave a statement that the reaction, "is currently much less efficient than a two-step sequence composed of electrophilic halogenations and Pd(0)-catalyzed sp^3 C−H arylation, and thus, it cannot be considered as synthetically competitive alternative yet".[91]

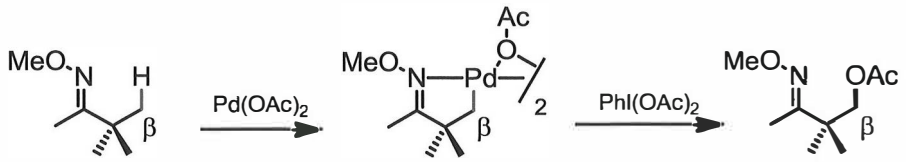


Scheme 26. Intramolecular dehydrogenative γ-coupling reaction.[91]

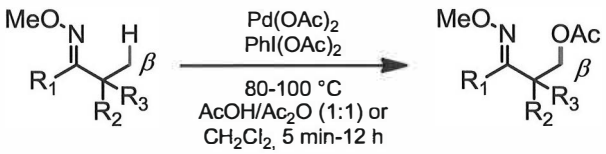
1.3 Oxidative hydroxylations and alkoxylations

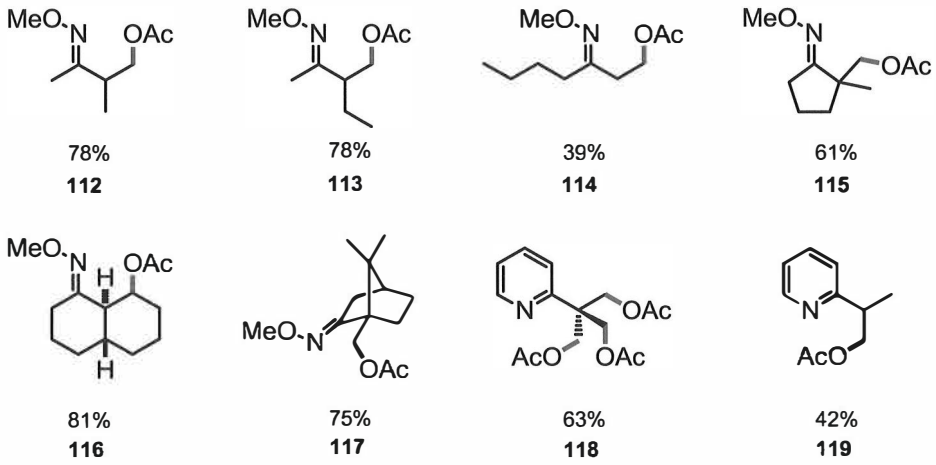
1.3.1 β-Hydroxylations and β-alkoxylations

Sanford and coworkers reported the first acetoxylation of benzylic C−H bonds,[92] and they also extended this methodology to primary unactivated β-sp^3 C−H bonds with *O*-methyl oxime or pyridine as a directing group (Scheme 28).[93] The reactivity and selectivity observed in these reactions arise from the chelating groups, which are both directing and activating the β-sp^3 C−H bond (Scheme 27).



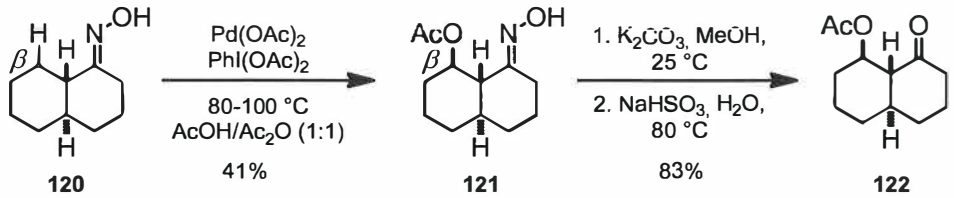
Scheme 27. Chelate-directed β-oxidation of an *O*-methyl oxime.[93]





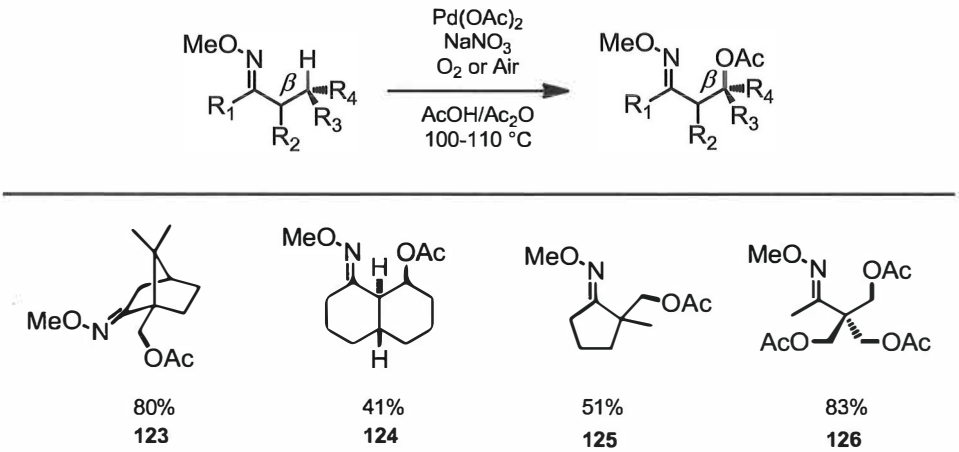
Scheme 28. Oxime-directed β-acetoxylation of an sp^3 C–H bond.[93]

Removal of the oxime ether directing group from the β-functionalized products, as seen in Scheme 28, is challenging. Therefore, Sanford and coworkers developed a more practical method for the β-acetoxylation of an sp^3 C–H bond. They used simple unprotected oximes, which are surrogate to the ketone, as a removable directing group (Scheme 29). While the regeneration of a ketone from the corresponding oxime is plausible, in this case, the feasibility of the oxime hydrolysis was demonstrated in only 5 examples and the yields over two steps were only modest (18-64%).[94]



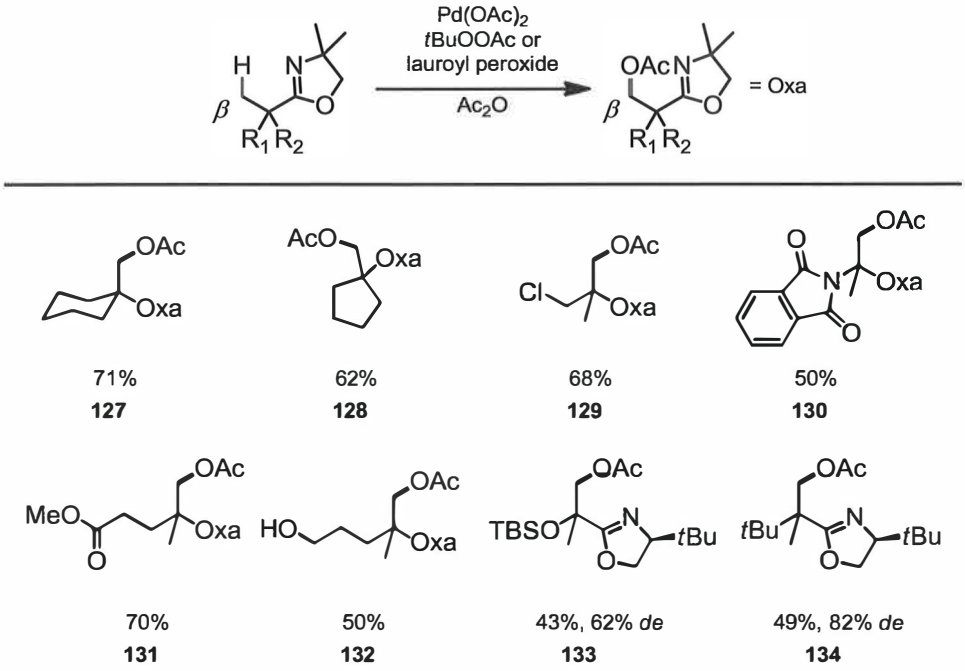
Scheme 29. Hydroxyl oxime-directed acetoxylation of an sp^3 C–H bond.[94]

The development of a metal catalyst for the oxidation of sp^3 C–H bonds into C–O bonds using oxygen as an oxidant is still a major challenge. Notably, the oxidants used in these reactions are typically reagents such as $PhI(OAc)_2$, peroxides, IOAc, or $K_2S_2O_8$, which have significant disadvantages including high cost, poor atom economy and the formation of waste byproducts. Therefore, more sophisticated methods for the acetoxylation of sp^3 C–H bonds is needed. To address these problems, Sanford and coworkers reported, in 2012, a method for the aerobic Pd-catalyzed oxidation of unactivated sp^3 C–H bonds.[95] Their paper demonstrates the use of a combination of $Pd(OAc)_2$ and $NaNO_3$ or $NaNO_2$, as the co-catalyst, to catalyze the aerobic β-acetoxylation of an sp^3 C–H bond (Scheme 30). They also demonstrated that an oxygen atom in the product originates from acetic acid and not from O_2 by carrying out a reaction in the atmosphere of $^{18}O_2$.



Scheme 30. β-Acetoxylation of sp^3 C–H bond using air or O_2 as an oxidant.[95]

In 2005, Yu and coworkers reported the β-acetoxylation of sp^3 C−H bonds using oxazoline as a directing group (Scheme 31).[96] The use of acetic anhydride in this reaction is crucial for catalytic turnover. If acetic anhydride is not used in the reaction, then the yields do not exceed the molar amount of the catalyst. Also, based on a previous characterization of isolated Pd(IV) species formed by the oxidative addition of benzoyl peroxide or an aryl transfer from diphenyliodonium triflate to a 2,2′-bipyridine-coordinated Pd(II) and Pt(II) centers, the researchers concluded that Pd(IV) intermediates might be in involved in the catalytic cycle.[97-99]



Scheme 31. Oxazoline-directed β-acetoxylation of an sp^3 C−H bond.[96]

In 2012, Houk, Yu and coworkers published a study on the origin of the diastereoselectivity at Pd(II)-catalyzed sp^3 C−H bond iodination and acetoxylation reactions. They based their conclusions on the characterization of

a trinuclear chiral C−H insertion intermediate by X-ray and DFT calculations. The solid-state structure revealed that the new (*S*) chiral center which is generated after the C−H cleavage is determinate by *t*-Bu groups on the oxazoline and carboxyclic moieties of the substrates which are remaining in anti-position to each other (Figure 2). The DFT calculations revealed that *t*-Bu substituent in oxazolene ligand is essential to achieve high reactivity. Repleacing the *t*-Bu substituent with the smaller *i*-Pr group leads to a stable resting [bis(oxazoline)]Pd(OAc)$_2$ complex before the C−H activation and increases the overall activation barrier an therefore lowering the reactivity.[100]

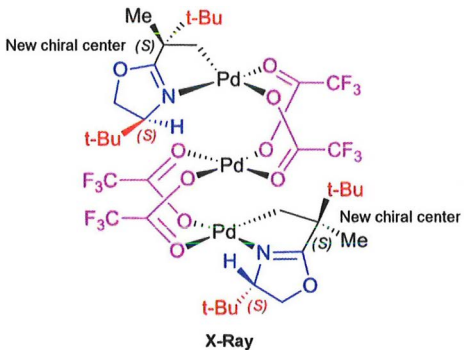
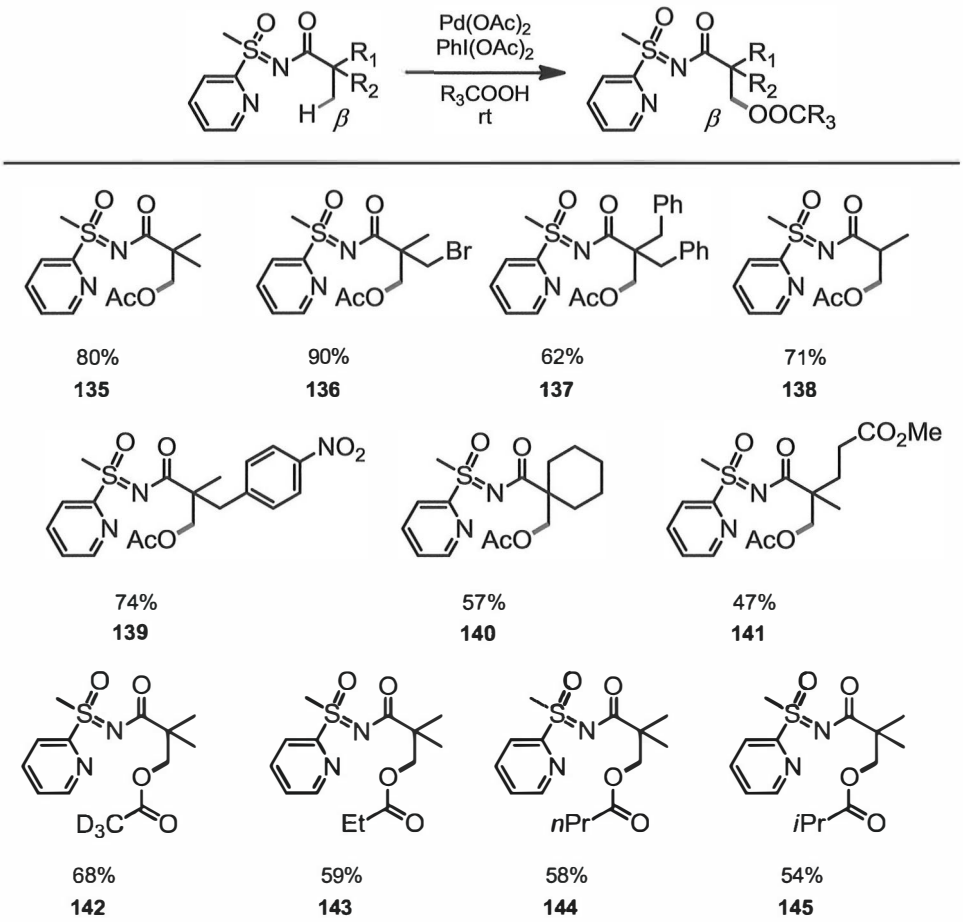
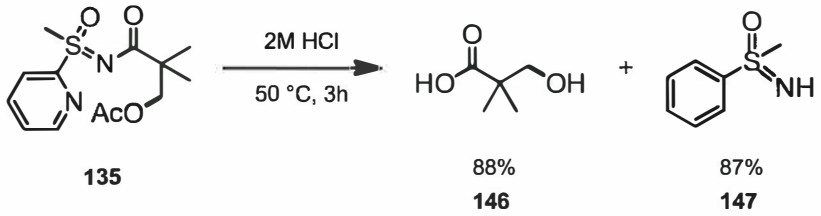


Figure 2. X-ray structure of the trinuclear chiral C−H insertion intermediate.[101]

More recently, in 2012, Sahoo and coworkers used a new removable pyridylsulfoximine-directing group *β*-acetoxylation of *sp*^{3} C−H bonds.[102] They were able to demonstrate the efficiency of their new ligand with several examples (Scheme 32). Also, the removal and recovery of the directing group could be achieved (Scheme 33).



Scheme 32. Pyridyl-sulfoximine-directed β-acetoxylation of a sp^3 C–H bond.[102]



Scheme 33. Recovery of a pyridyl-sulfoximine-directing group.[102]

Synthesis of 1,2-diols directly from monoalcohols via the catalytic oxidation of a sp^3 C–H bond is a more challenging problem than the β-oxidation of monoalcohols to 1,3-diols. Compared to the β-position that gives 1,3-diols, the β-position of an alcohol is relatively electron-deficient due to the inductive ef-

fect of oxygen and is, thus, less reactive toward electrophilic C–H activation. Dong and coworkers developed a β-acetoxylation of *sp3* C–H bonds of alcohols by using an exo-directing group (Figure 3).[103] In an *exo*-palladacycle, formed through the coordination of oxime nitrogen to Pd(II), the π-bond of the directing group is outside of the metallocycle, whereas in an *endo*-palladacycle, the π-bond of the directing group is inside of the metallocycle (Figure 3).

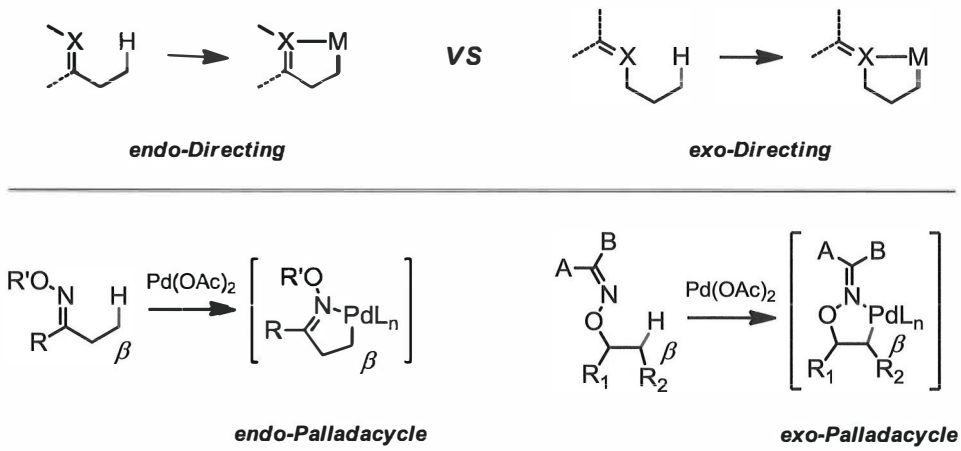
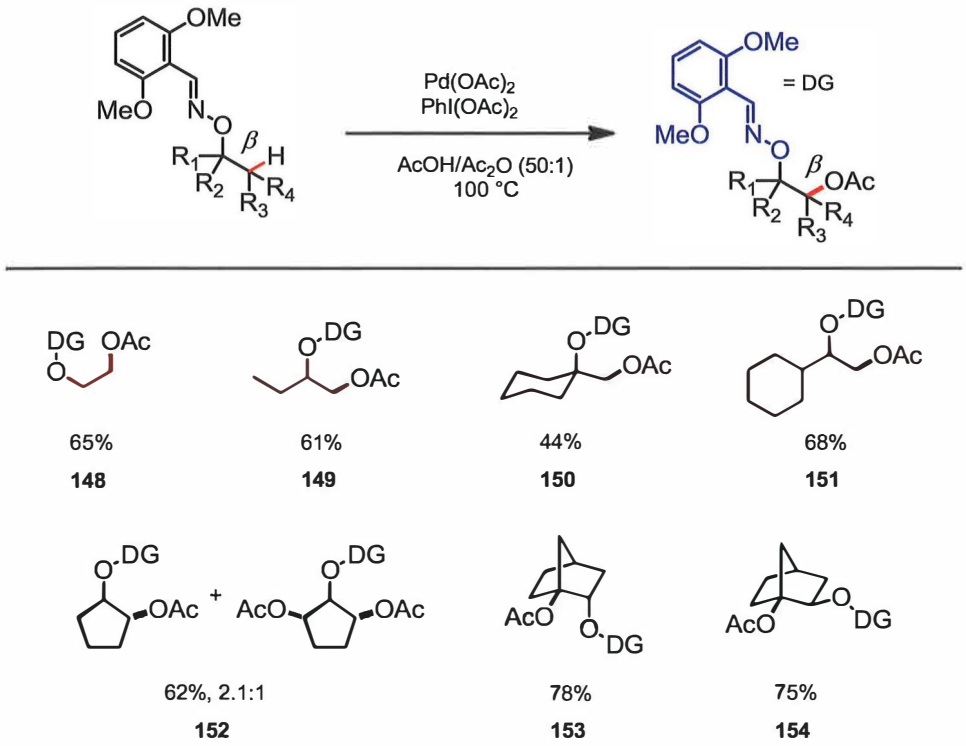


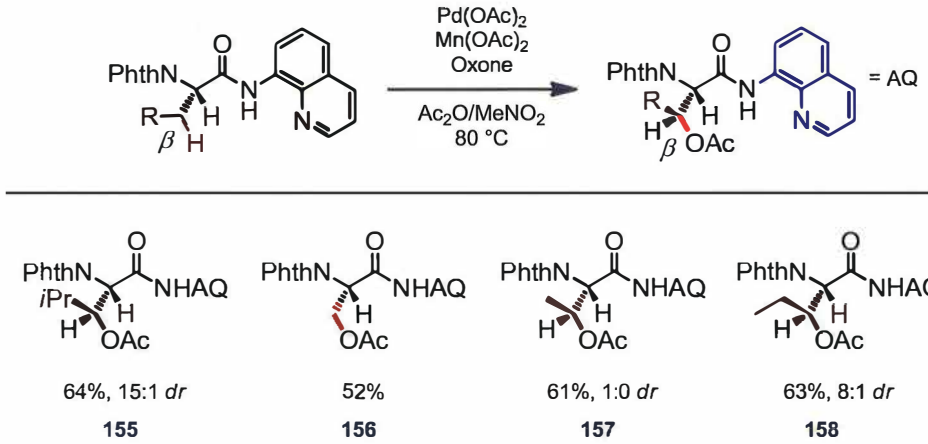
Figure 3. *endo*-Metalation *vs exo*-metalation.[103]

The yields of the reaction are good with numerous substrates. However, the substrate scope seems to be quite limited: there are no examples of any other functional groups than the directing group in the substrates (Scheme 34).



Scheme 34. β-Acetoxylation of sp^3 C–H bond via *exo*-directing group[103]

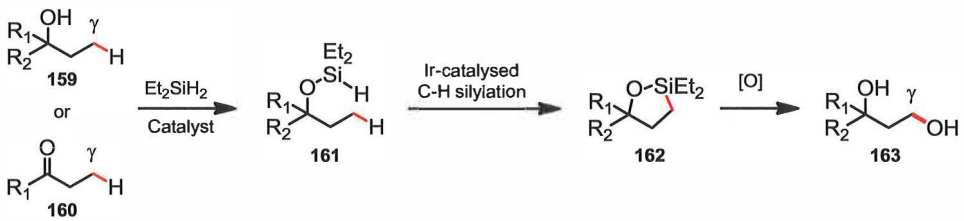
Corey and coworkers have contributed to the development of methods for the β-acetoxylation of *sp3* C–H bonds[104]. They reported, in 2006, a diastereoselective β-acetoxylation of α-amino acid derivatives using 8-aminoquinone as a directing group (Scheme 35).



Scheme 35. β-Acetoxylation of α-amino acid derivatives.[104]

1.3.2 γ-Hydroxylations and γ-alkoxylations

The strategy used by Simmons and Hartwig for the γ-functionalization of unactivated aliphatic C−H bonds directed by a hydroxyl group is outlined below (Scheme 36):[105]

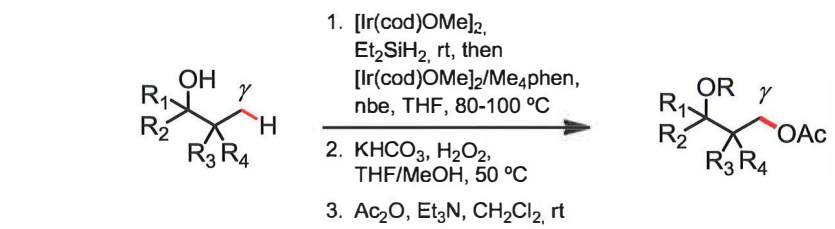


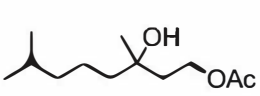
Scheme 36. Strategy for the hydroxyl-directed γ- functionalization of C−H bonds.[105]

In this strategy, dihydrosilane attaches to the oxygen atom of an alcohol **159** or ketone **160** by forming a (hydrido)silyl ether **161** to direct the γ-C−H bond functionalization. The (hydrido)silyl ether **161** is formed through a dehydrogenative coupling with alcohol or by hydrosilylation of the ketone. The Si-H unit of silyl ether undergoes an Ir-catalyzed dehydrogenative functionalization of a primary C−H bond without the isolation of an intermediate **161.** This is followed by a

Fleming-Tamao oxidation[106-112] of the oxasilolane **162** which yields the 1,3-diol **163** (Scheme 36).

Selected products for the γ-functionalization of alcohols and ketones are presented in Scheme 37 and Scheme 38, respectively. Both tertiary and secondary alcohols undergo a primary aliphatic C−H bond functionalization with comparable efficiency. Reactions of phenol **168** also occurred under this condition in a good yield. The reaction was insensitive to the stereochemistry of cyclic *trans*- and *cis*-2-methylcyclohexanol (**165**). However, the reaction with an acyclic ketone, which possesses a diastereotopic methyl group, provided **174** as a major product with good diastereoselectivity (82:18 *dr*).





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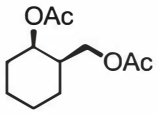

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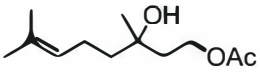

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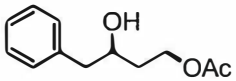

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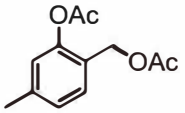

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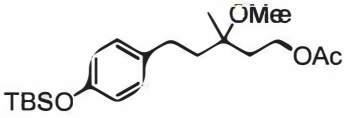

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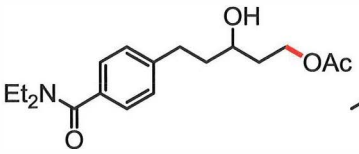

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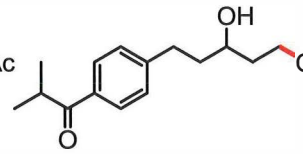

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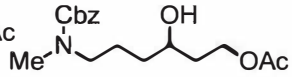

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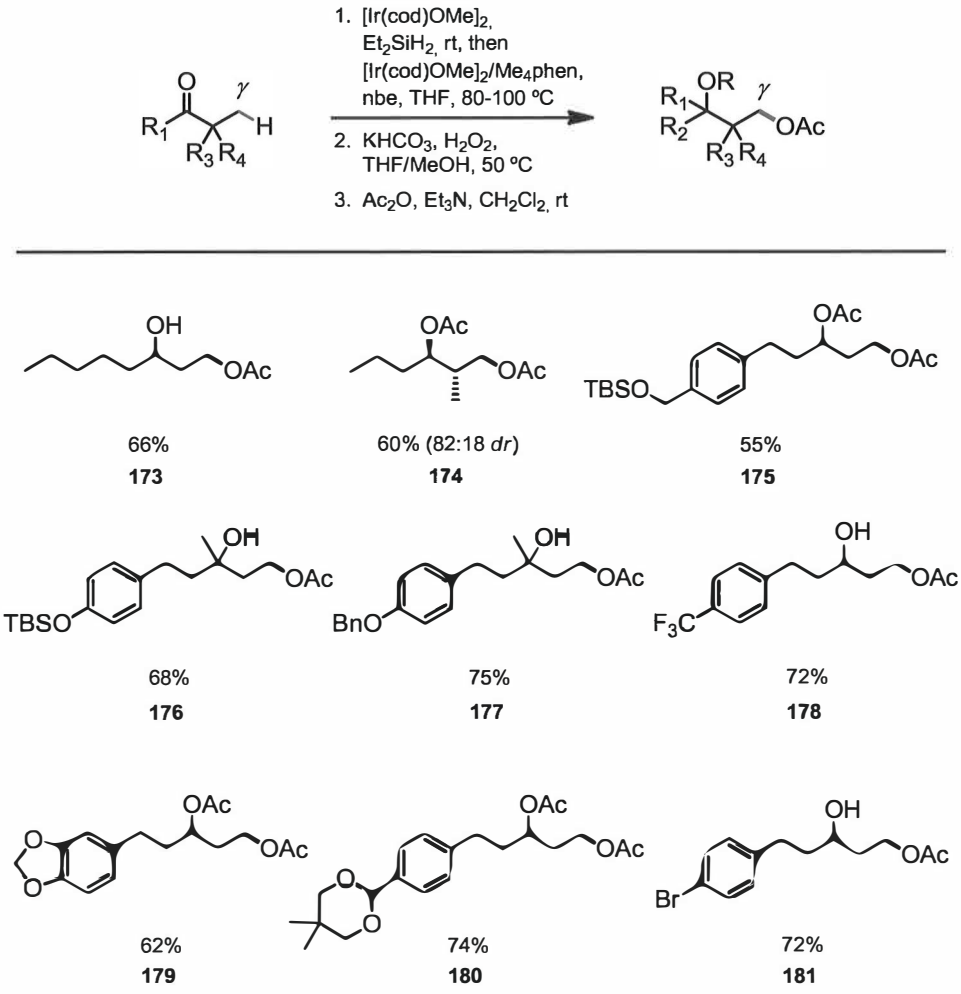
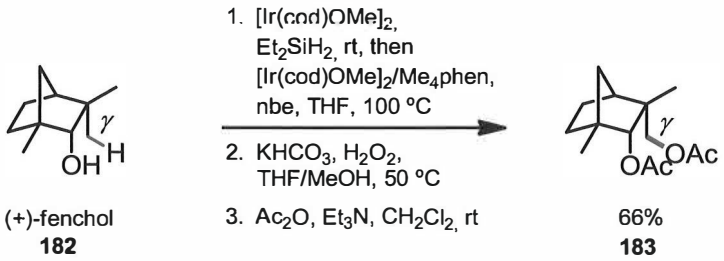
Scheme 37. Hydroxyl-directed γ-oxygenation of alcohols.[105]



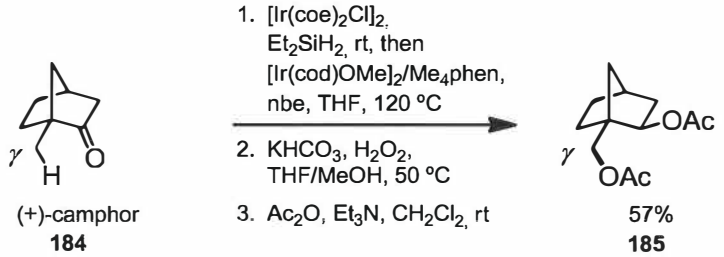
Scheme 38. Hydroxyl-directed γ-oxygenation of ketones.[105]

Because the Ir-catalyzed γ-functionalization tolerates this kind of auxiliary functionality and is highly selective for primary C–H bonds, Simmons and Hartwig were also able to demonstrate the robustness of their reaction with natural product substrates. As an example, (+)-fenchol was oxidized smoothly at the methyl group, affording the oxidized product **183** (Scheme 39).



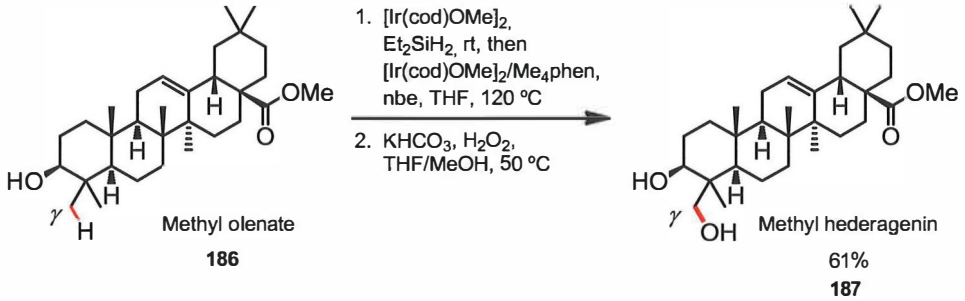
Scheme 39. Directed aliphatic C–H functionalization of (+)-fenchol.[105]

Furthermore, direct γ-functionalization of (+)-camphor via *exo*-selective hydrosilylation followed by C–H functionalization resulted in **185** with a 57% yield (Scheme 40).



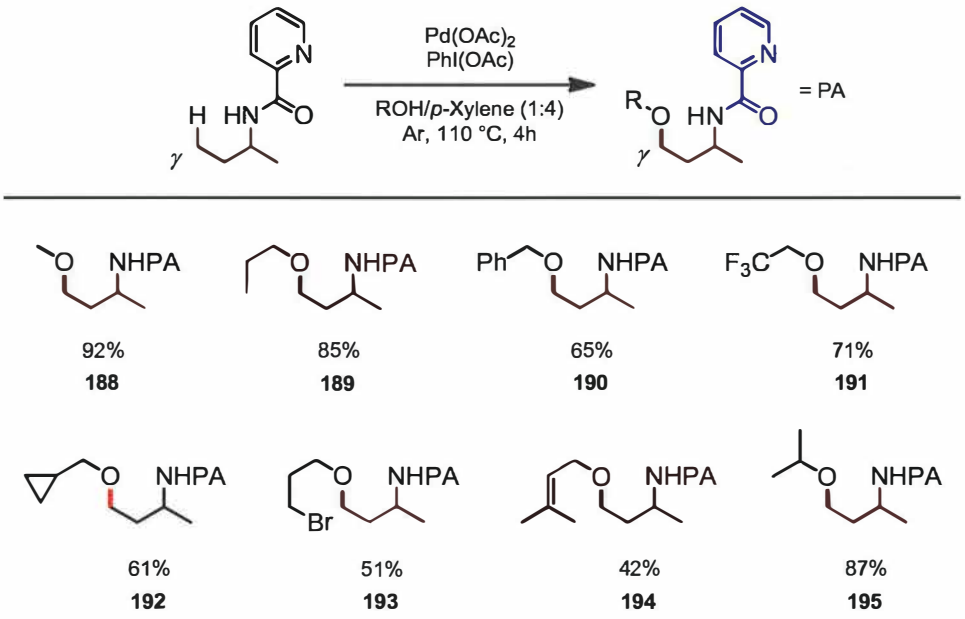
Scheme 40. Direct γ-functionalization of (+)-camphor.[105]

Finally, they conducted the selective C–H functionalization on a pair of triterpenoid saponin aglycons. Triterpenoid saponin aglycons exhibit a range of biological activities *e.g.* anti-inflammatory, anti-fungal and anti-tumor properties. They also possess strong haemolytic activities, and consequently, are interesting synthetic targets.[113] The selective C–H functionalization of methyl olenate resulted in methyl hederagenin (**187**) in one step (Scheme 41).

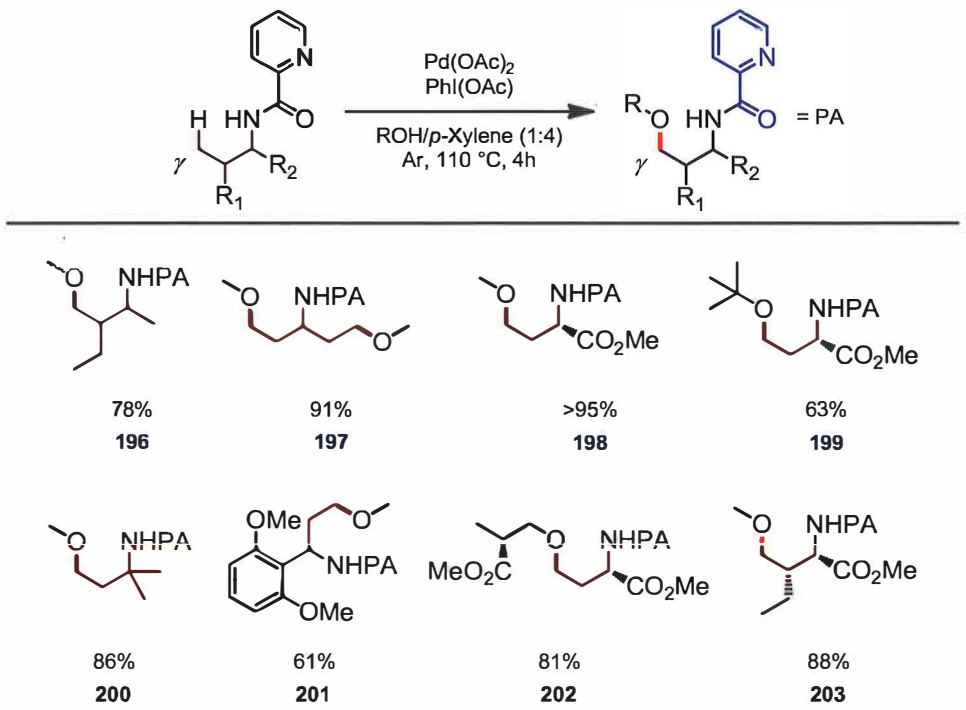


Scheme 41. Hydroxyl-directed γ-functionalization of methyl olenate.[105]

Despite the significant advances in Pd-catalyzed sp^3 C−H acetoxylation reactions by the Sanford and Yu laboratories, the corresponding alkoxylation reactions are rare. As an example of such a reaction, Chen and coworkers reported a highly efficient method for the synthesis of alkyl ether via a Pd-catalyzed, picolinamide directed γ-alkoxylation of sp^3 and sp^2 C−H bonds for remote alcohols.[114] In summary, they have developed a highly efficient method for the synthesis of alkyl ethers via Pd-catalyzed γ-alkoxylation of a wide range of amides (Scheme 42 and Scheme 43).

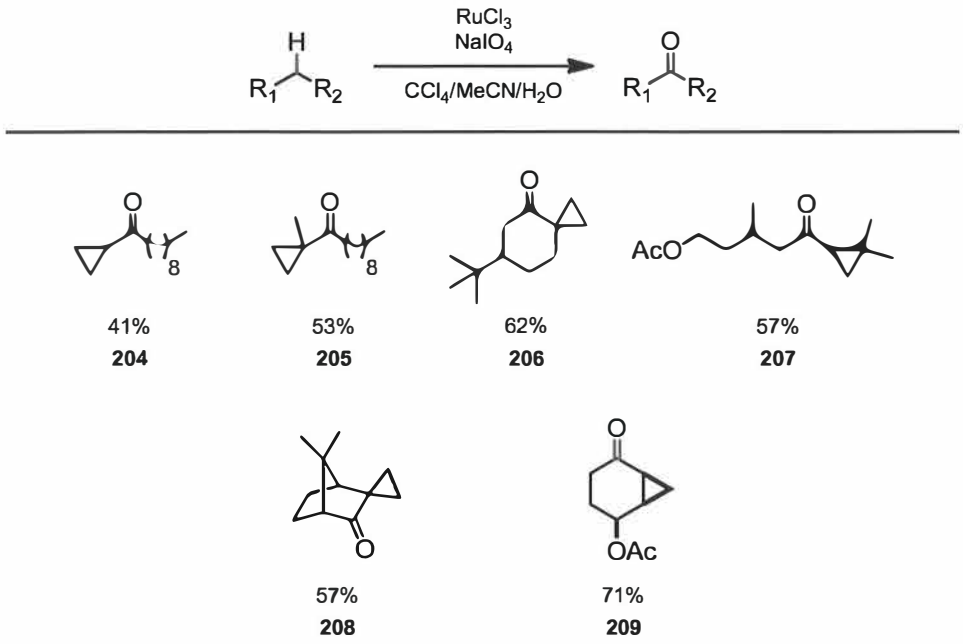


Scheme 42. Picolinamide-directed γ-alkoxylation of sp^3 C−H bond with alcohols.[114]



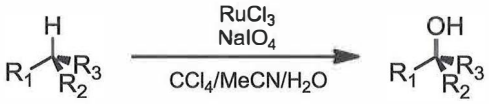
Scheme 43. Substrate scope of picolinamides and alcohols at γ-oxidation reaction.[114]

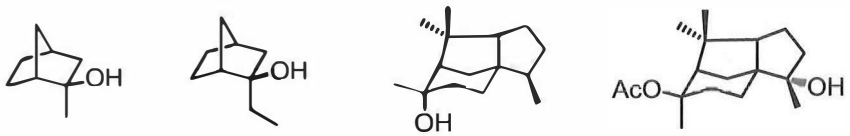
Altough ruthenium tetraoxide was first prepared by Claus[115] in 1860, its use as an unselective oxidant for organic compounds did not begin until 1953 by Djerassi and Engle.[116] However, in 1985, Hasegawa, Niwa and Yamada published their groundbreaking report on the selective oxidation of sp^3 C−H bonds with $RuCl_3$ for ketone functionalities.[117] They present the ruthenium-catalyzed direct oxidation of a sp^3 C−H bond adjacent to a cyclopropane ring that results in the corresponding ketones (Scheme 44).



Scheme 44. Ruthenium-catalyzed oxidation of sp^3 C–H bond.[117]

A seminal report of the selective hydroxylation of alkenes tertiary sp^3 C–H bonds with $RuCl_3$ was disclosed in 1989 by Tenaglia, Terranova and Waegel.[118] They showed that the combination of $RuCl_3$, which forms a catalytically active species (RuO_4) under the reaction conditions, and $NaIO_4$ as a oxidizer in a ternary solvent mixture is capable of hydroxylating the natural product cedrane and a small number of related substrates (Scheme 45).

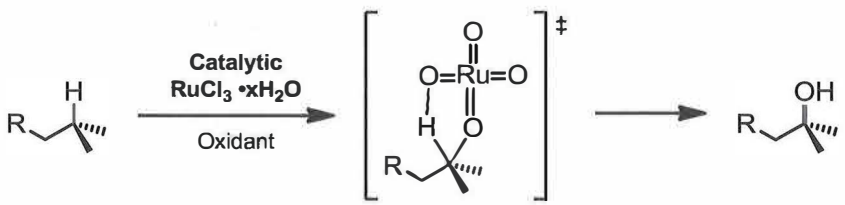




90%	57%	69%	53%
210	**211**	**212**	**213**

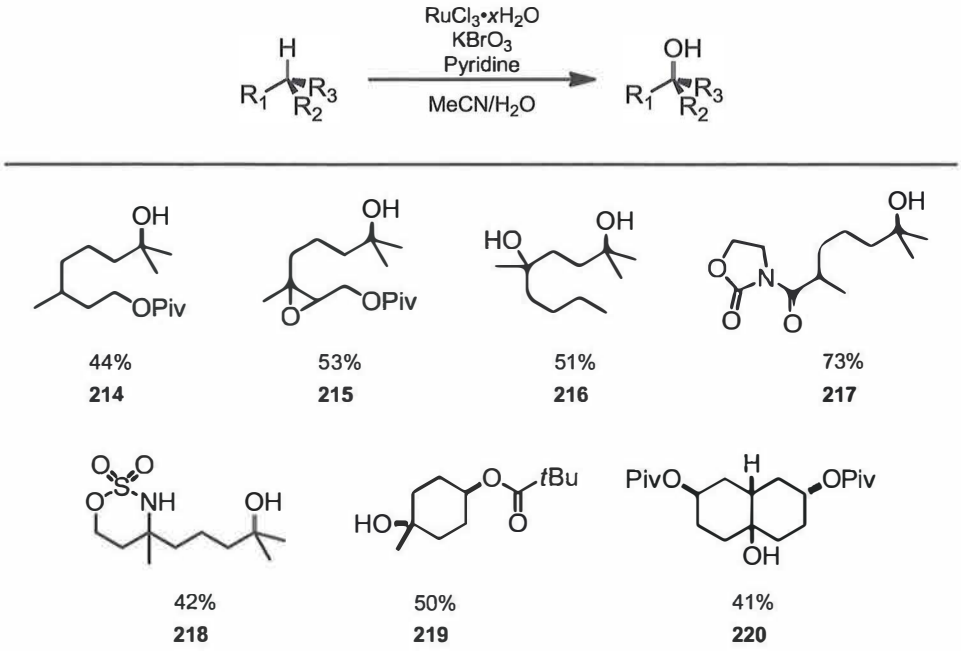
Scheme 45. Ruthenium-catalyzed hydroxylation of tertiary C–H bonds.[118]

The catalytically active species, RuO_4, is formed in-situ in reaction conditions by the oxidation of a lower-valent ruthenium precursor, $RuCl_3$. Subsequently, formed catalytic quantities of RuO_4 are involved in concerted asynchronous [3 + 2] cycloaddition of the substrates where a C–H bond is transformed to an alcohol (Scheme 46).[119-126]



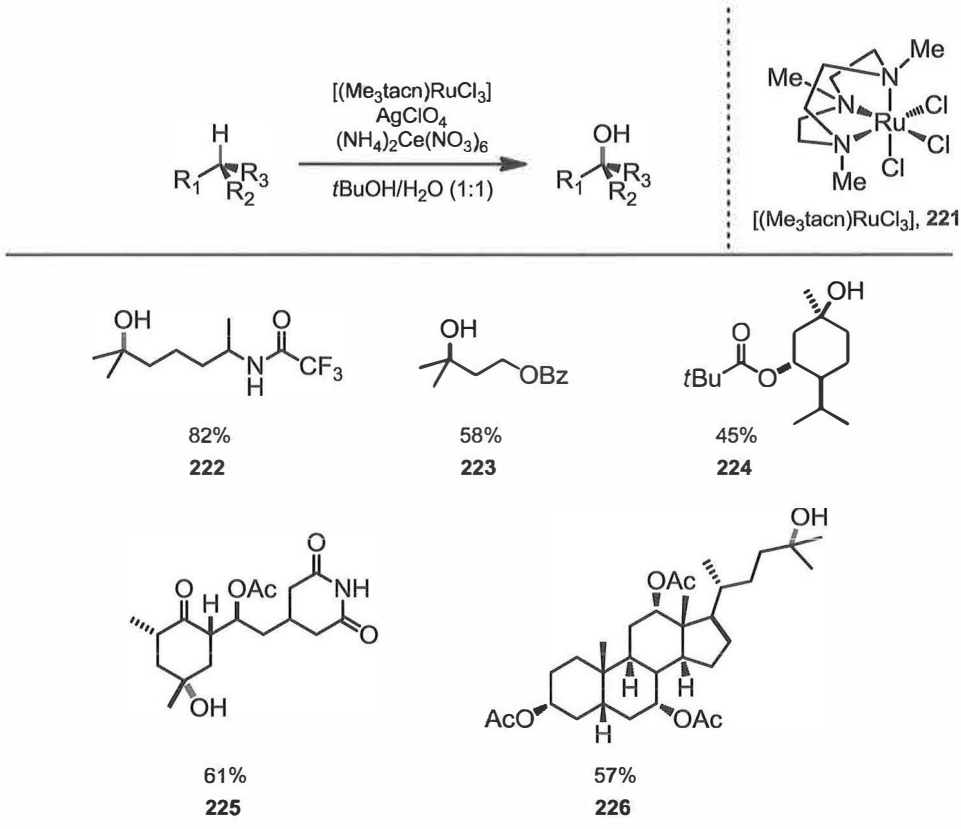
Scheme 46. Proposed transition state for the Ruthenium-catalyzed hydroxylation of tertiary C–H bonds.

In 2010, MacNeill and Du Bois presented an efficient protocol for the selective hydroxylation of unactivated tertiary C–H bonds.[127] The combination of catalytic $RuCl_3$ and pyridine with $KBrO_3$ as the oxidant was shown to promote the hydroxylation of substrates possessing different polar functional groups. This protocol produces the tertiary alcohol products in moderate yields (Scheme 47).



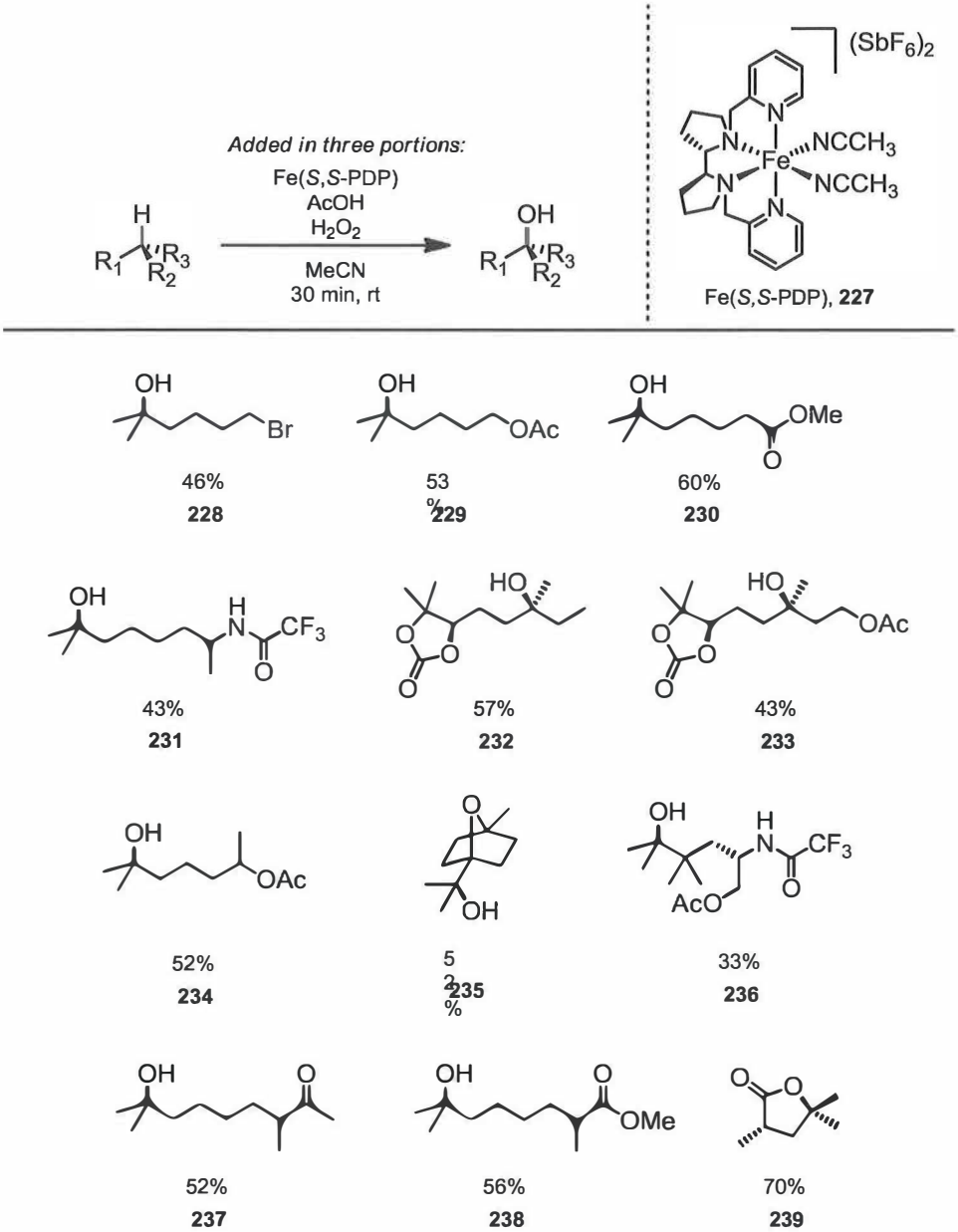
Scheme 47. Ruthenium-catalyzed oxidation of tertiary C–H bonds.[127]

Needless to say, proper ligands are needed in order to efficiently advance and tune these catalysts or steer the catalyst to react enantioselectively. Studies by Che and coworkers[128,129] inspired McNeill and Du Bois to examine (1,4,7-trimethyl-1,4,7-triazacyclononane) ruthenium(III) trichloride, [(Me_3tacn)$RuCl_3$] **221**, as an oxidation precatalyst. They found that a [(Me_3tacn)$RuCl_3$]-precatalyst combined with $AgClO_4$ and $(NH_4)_2Ce(NO_3)_6$ efficiently hydroxylated tertiary C–H bonds in a number of structurally diverse substrates (Scheme 48). They also proposed a mechanism, based on chemoselectivity trends and kinetic isotope effect data, that involves a stepwise radical-rebound C–H abstraction pathway.[130]



Scheme 48. Ru-catalyzed oxidation of tertiary C–H bonds.[130]

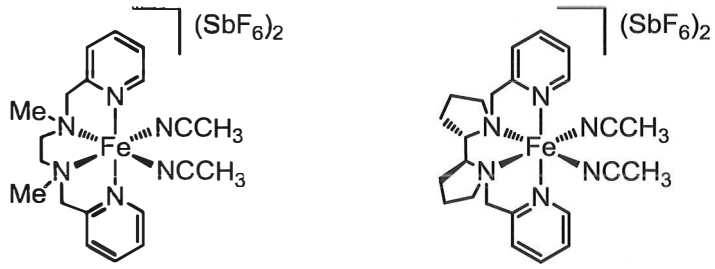
In 2007, based on the work of Lawrence Que's group[131-135] and others[136-140] on non-heme iron catalysts, Chen and White presented a pioneering publication for the selective hydroxylation of tertiary sp^3 C–H bonds.[141] They reported that an iron-based small molecule catalyst, Fe(*S,S*-PDP) **227**, used hydrogen peroxide to hydroxylate a broad range of the substrates bearing tertiary sp^3 C–H bonds (Scheme 49). It is noteworthy that the hydroxylation reaction occurred with the complete retention of stereochemistry (**232** and **233**).



Scheme 49. Fe(*S,S*-PDP)-catalyzed hydroxylation of tertiary sp^3 C–H bonds.[141]

Earlier, in 2001, White, Doyle and Jacobsen have used a similar bulky iron-catalyst, [Fe(II)(mep)(MeCN)$_2$][142,143] **240**, for preparative epoxidations of olefins.[144] Increasing the flexibility of the ligand results in a weaker binding of the

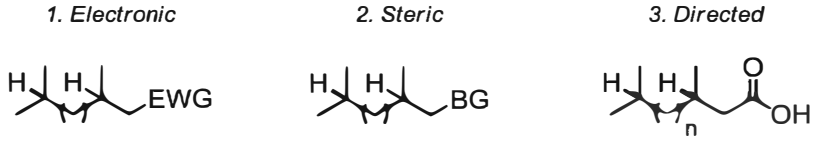
ligand, which increases the decomposition of the catalyst. Unselective oxidations with nonheme iron-catalysts are often attributed to catalyst decomposition.[145] Hence, to improve the site selectivity of the Fe catalyst, Chen and White added more rigidity to the ligand (**241** in Scheme 50).



Scheme 50. Fe(*S,S*-PDP)-Catalyst has more rigid ligand compared to [Fe(II)(mep)(MeCN)$_2$].

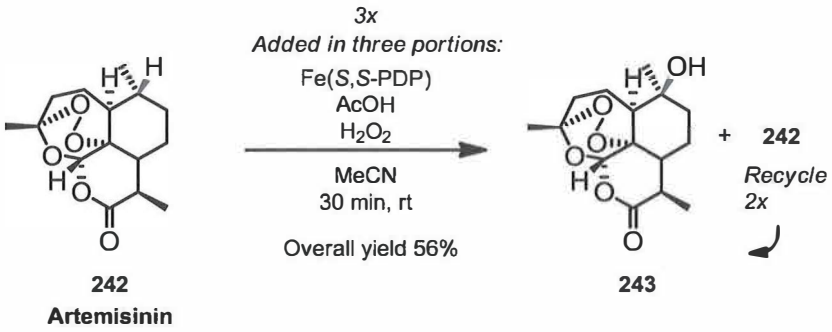
They also propose a model for the site-selectivity of C−H hydroxylation. There are three modes of selectivity:[141]

1. Due to an electrophilic nature of the oxidant generated with Fe(*S,S*-PDP) and H_2O_2, hydroxylation preferentially occurs at the most electron-rich tertiary C−H bond.
2. Hydroxylation occurs at the least sterically hindered and most electron-rich tertiary C−H bond.
3. Hydroxylation is also directed by a free carboxylic acid.



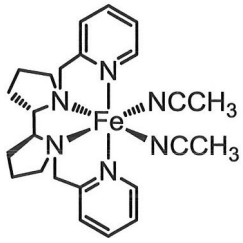
Chen and White demonstrate the value of their protocol through the late-stage hydroxylation of the antimalarial drug artemisin (**242**). On the basis of the selectivity rules outlined above, they were able to identify the most reactive tertiary

C−H bond, which reacted as predicted in the hydroxylation reaction. By recycling the unreacted starting material two times, they were able to isolate the selectively hydroxylated, diastereomerically pure **243** in a 56% overall yield (Scheme 51). Similar yields were also possible to achieve by slowly adding catalyst Fe(*S,S*-PDP) and hydrogen peroxide simultaneously over 45 or 60 min via a syringe pump.[146] Chen and White have also used the same catalyst, Fe(*S,S*-PDP), in unselective methylene oxidations.[147]

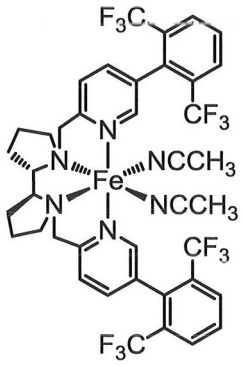


Scheme 51. Selective hydroxylation of antimalarial drug artemisinin.[141]

In 2013, Gormisky and White introduced a new modification of Fe(*S,S*)-PDP), which shows that a catalyst control of site-selectivity in aliphatic C−H oxidation is possible, without the need of a specific match between one catalyst and one substrate (**245** in Scheme 52). The improved site selectivity achieved with this catalyst is based on the steric blocking of larger C−H sites through non-binding bulky *ortho*-CF_3-aryl rings. However, the examples that were presented are still unselective. The authors also disclosed a quantitative mathematical model that relates each the site selectivities of each catalyst with the properties of the substrate.[148]



Fe(*S*,*S*-PDP), **244**



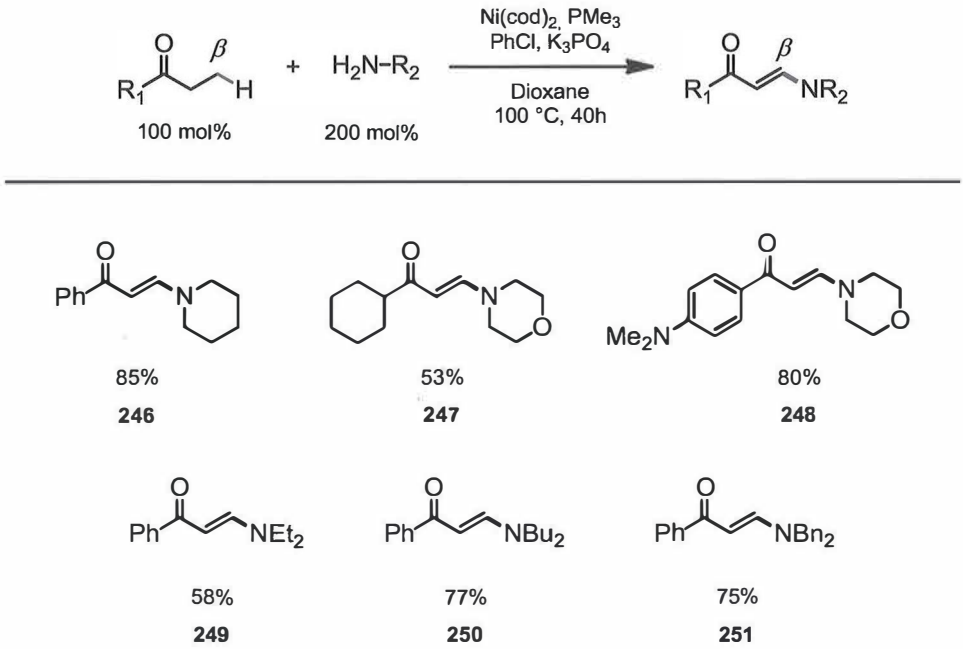
Fe(*S*,*S*-CF_3-PDP), **245**

Scheme 52. Fe(*S*,*S*-PDP) and its derivative Fe(*S*,*S*-CF_3-PDP).[148]

1.4 Aminations

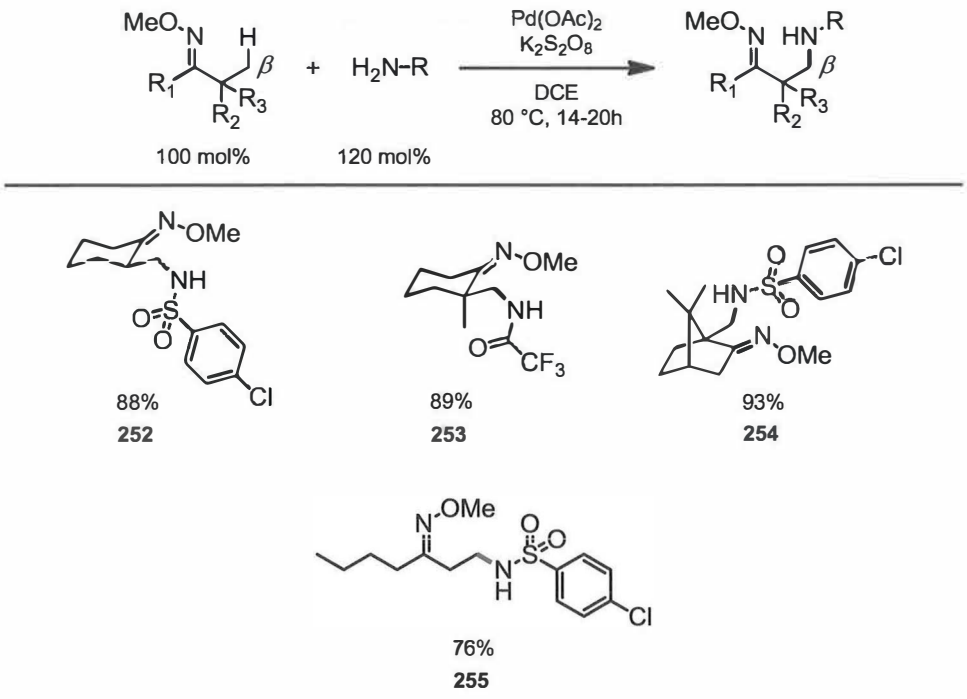
1.4.1 β- and δ-Aminations

In 2009, Kuwano and coworkers presented the first example of an intramolecular nickel-catalyzed one-step coupling between a β-sp^3 C−H bond and an amine, which is followed by a β-hydride elimination to form β-amino substituted unsaturated ketones (enaminones).[149] They used $Ni(cod)_2$ as a catalyst, PMe_3 as a ligand, PhCl as an oxidizer and K_3PO_4 as a base in dioxane at elevated temperatures (Scheme 53).



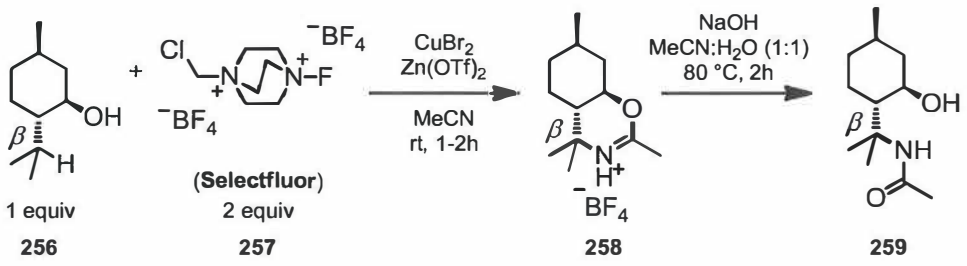
Scheme 53. Nickel-catalyzed sequential β-amination and β-hydride elimination.[149]

Che and coworkers disclosed an intramolecular protocol for the β-amidation of sp^3 C−H bonds.[150] This protocol enables oxime-directed amidation of some alkene substrates by using $Pd(OAc)_2$ as a catalyst and oxone as an oxidizer in dichloroethane at 80 °C (Scheme 54). Their method is also applicable to the β-amidation of sp^2 C−H bonds.

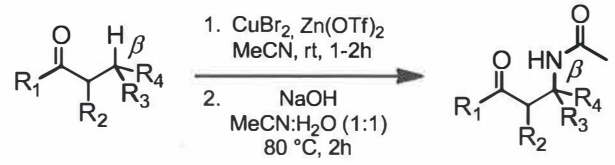


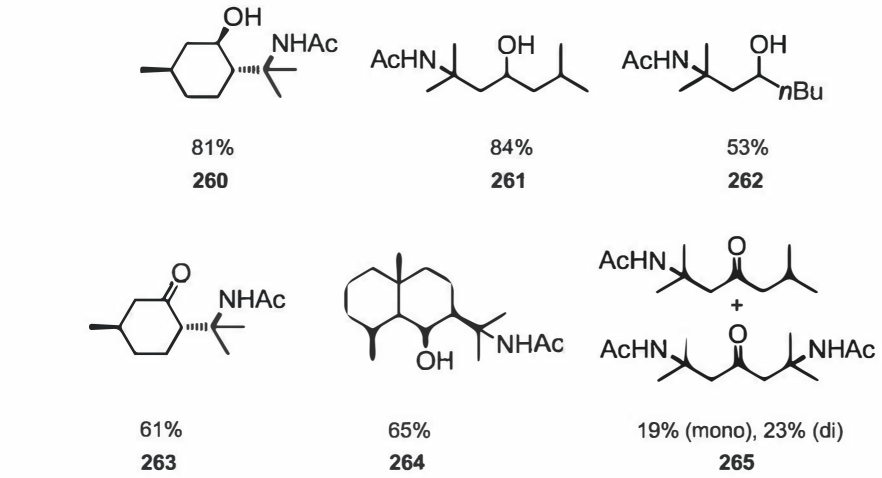
Scheme 54. Oxime-directed β-coupling between amines and sp^3 C–H bonds.[150]

By treading on Barton's[151], Breslow's[152], and Corey's[153] footsteps on the functionalization of C–H bonds in the terpenoid skeleton, Baran and coworkers have made important contributions to the β-amidation of sp^3 C–H bonds in terpenes. Improving the methodology reported by Banks and coworkers,[154] Baran and coworkers were able to conduct a Ritter-type amination of β-sp^3 C–H bonds (Scheme 56).[155] The methodology is based on two steps: First, the β-aminated cyclic imidate **258** is formed by using Selectfluor as the oxidizer and acetonitrile as the amine source. The imidate **258** is then hydrolyzed in a second step for a β-aminated product **259** in one-pot (Scheme 55). The method is also capable for the nonselective mono-amination of hydrocarbon substrates.



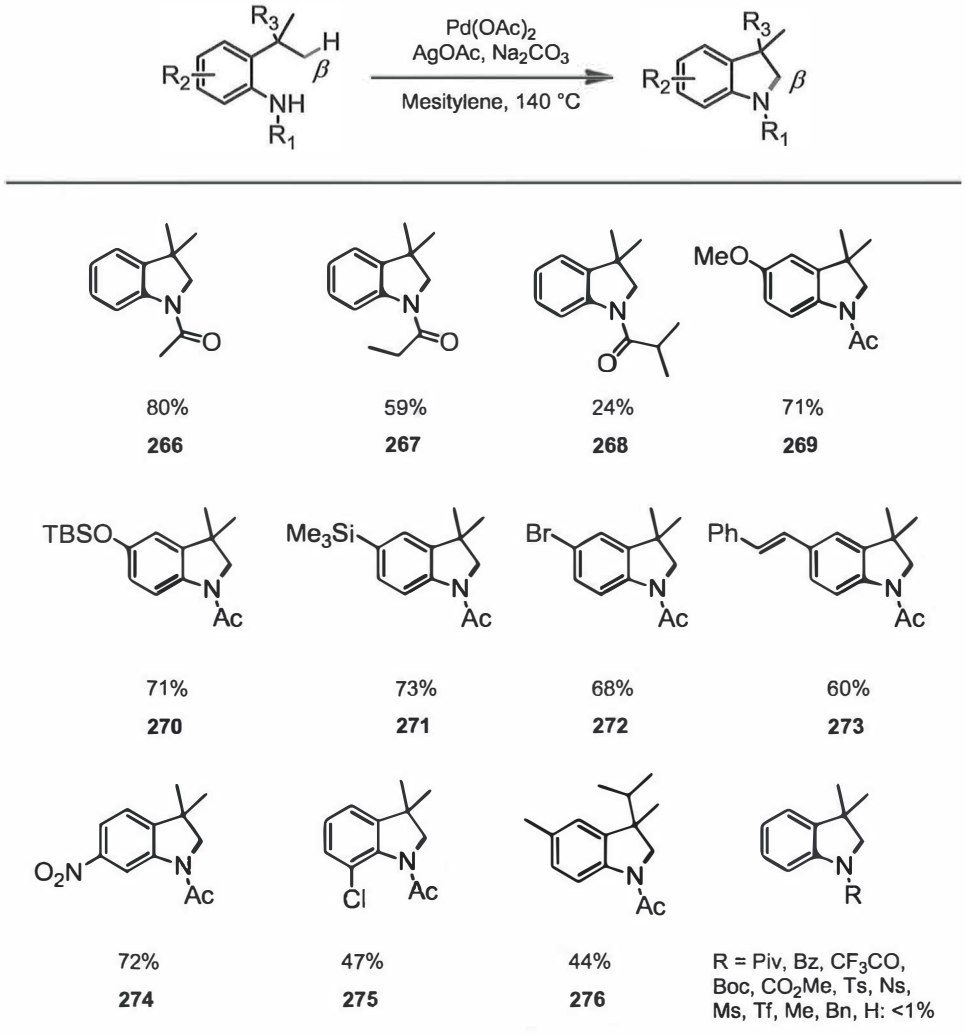
Scheme 55. β-Amination of an sp^3 C–H bond followed by hydrolysis.[155]





Scheme 56. Scope of β-amination of sp^3 C–H bonds for alcohols and ketones.[155]

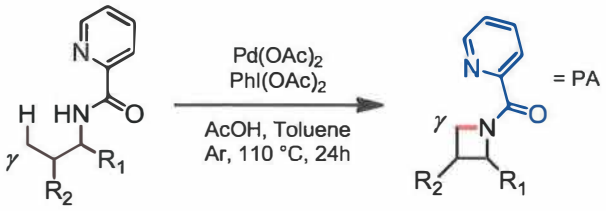
In 2009, Glorius and coworkers reported the intramolecular β-amidation of anilines.[156] They synthesized indolines through a Pd-catalyzed oxidative cyclization of amide substrates by using AgOAc as an oxidizer and K_2CO_3 as a base at high temperature (Scheme 57). A wide range of substrates could be used, but only trace amounts of the product was detected when anything else than the *N*-acetyl group, such as -pivaloyl, -benzoyl, -trifluoroacetyl, or *N*-tosyl group, was used.

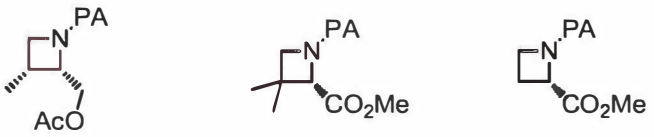


Scheme 57. Intramolecular β-Amination of sp^3 C−H bonds.[156]

Chen and coworkers recently (2012) disclosed an efficient method for synthesizing azetidines, pyrrolidines, and indolines via a Pd-catalyzed intramolecular amination of sp^3 C−H bonds at the γ and δ positions of picolinamide (Scheme 58 and Scheme 59).[157] In a palladium-catalyzed intramolecular amination of γ-$sp3$ C−H bonds, it was found that the use of a typical $PhI(OAc)_2$ oxidizer, in normal conditions, is effective. $Pd(OAc)_2$ and $PhI(OAc)_2$ are commonly used in sp^3 C-H

hydroxylation and alkoxylation rections. Hence, it is not surprising that the primary by-products of the coupling reactions are γ- and δ-acetoxypicolinamides.





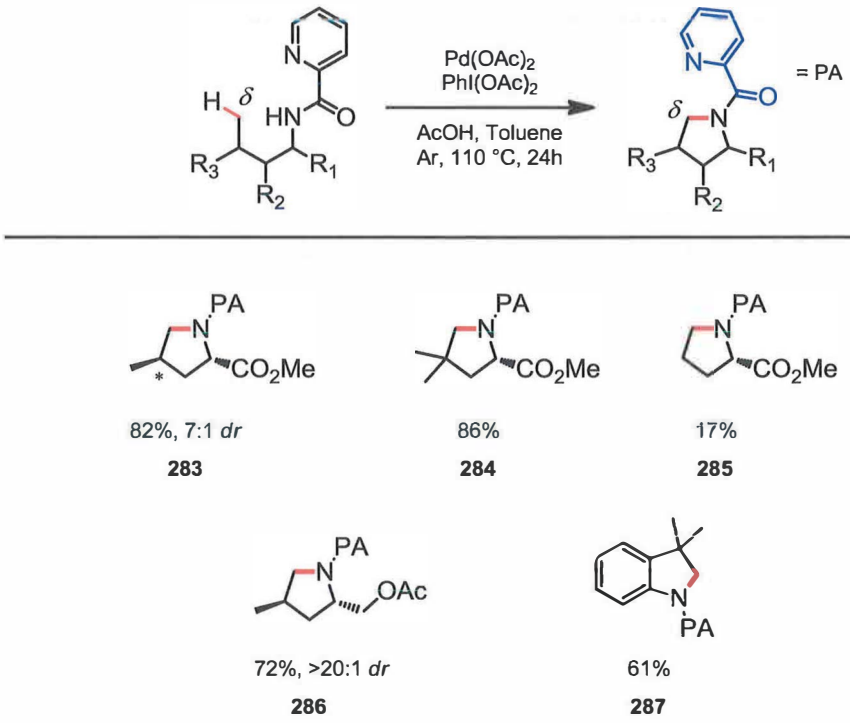
82%, >20:1 *dr* | 91% | 25%

277 | **278** | **279**

70% | 79% | 68%

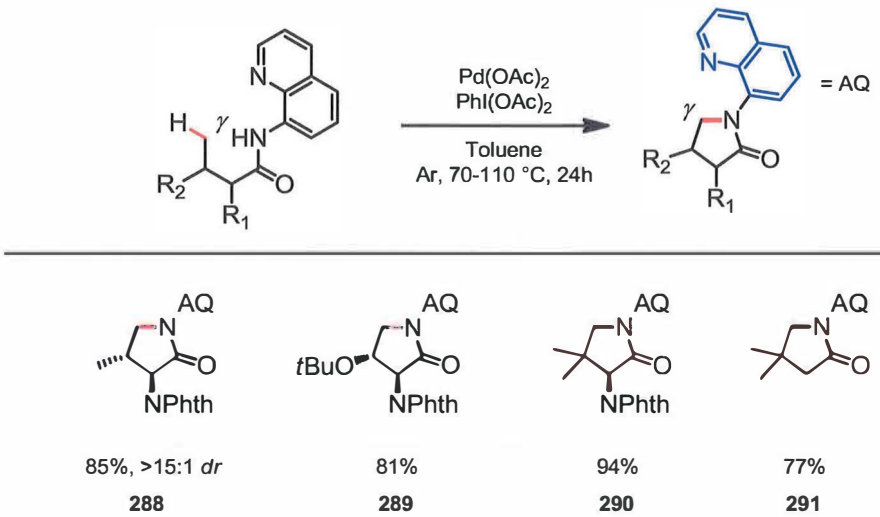
280 | **281** | **282**

Scheme 58. Synthesis of azetidines via an intramolecular amination of γ-sp^3 C–H bonds.[157]

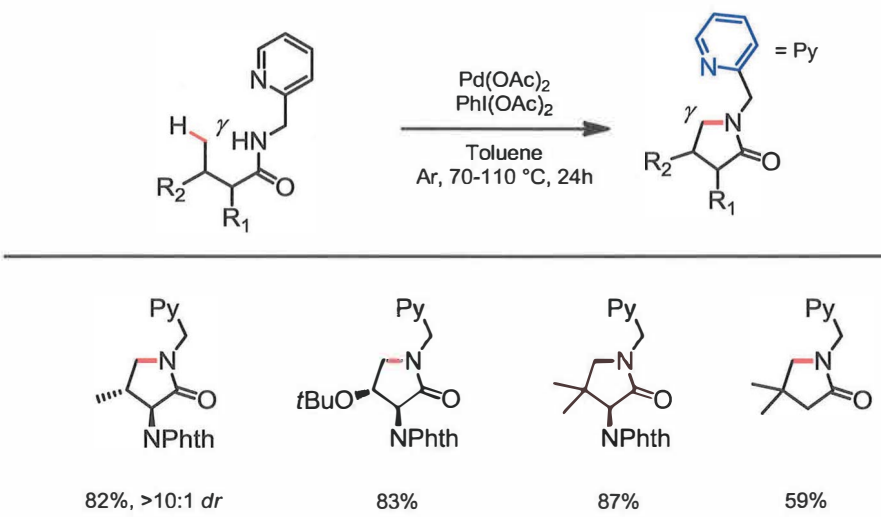


Scheme 59. The synthesis of pyrrolidines via an intramolecular amination of δ-sp^3 C–H bonds.[157]

In 2013, Chen and coworkers introduced a synthesis of pyrrolidones by the palladium-catalyzed intramolecular amination of δ-sp^3 C–H bonds, using 8-aminoquinoline (AQ) or pyridine as the directing group (Scheme 60 and Scheme 61).[158] In this method, they used the same conditions as in their earlier pyrrolidine synthesis,[157] where $Pd(OAc)_2$ served as a catalyst and $PhI(OAc)_2$ as an oxidizer in toluene at elevated temperatures. They also used two different directing groups with the same substrates that had similar results (Scheme 60 and Scheme 61).



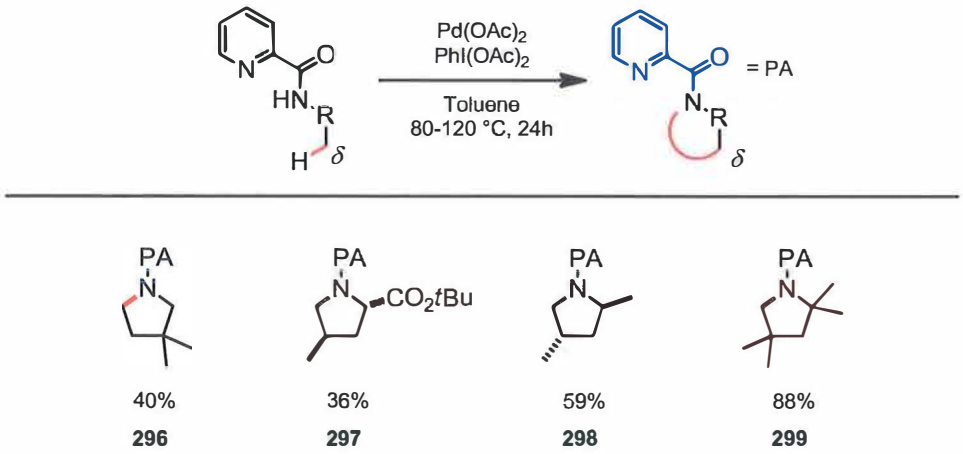
Scheme 60. Intramolecular aminoquinoline-directed γ-amination.[158]



Scheme 61. Intramolecular pyridine-directed γ-amination.[158]

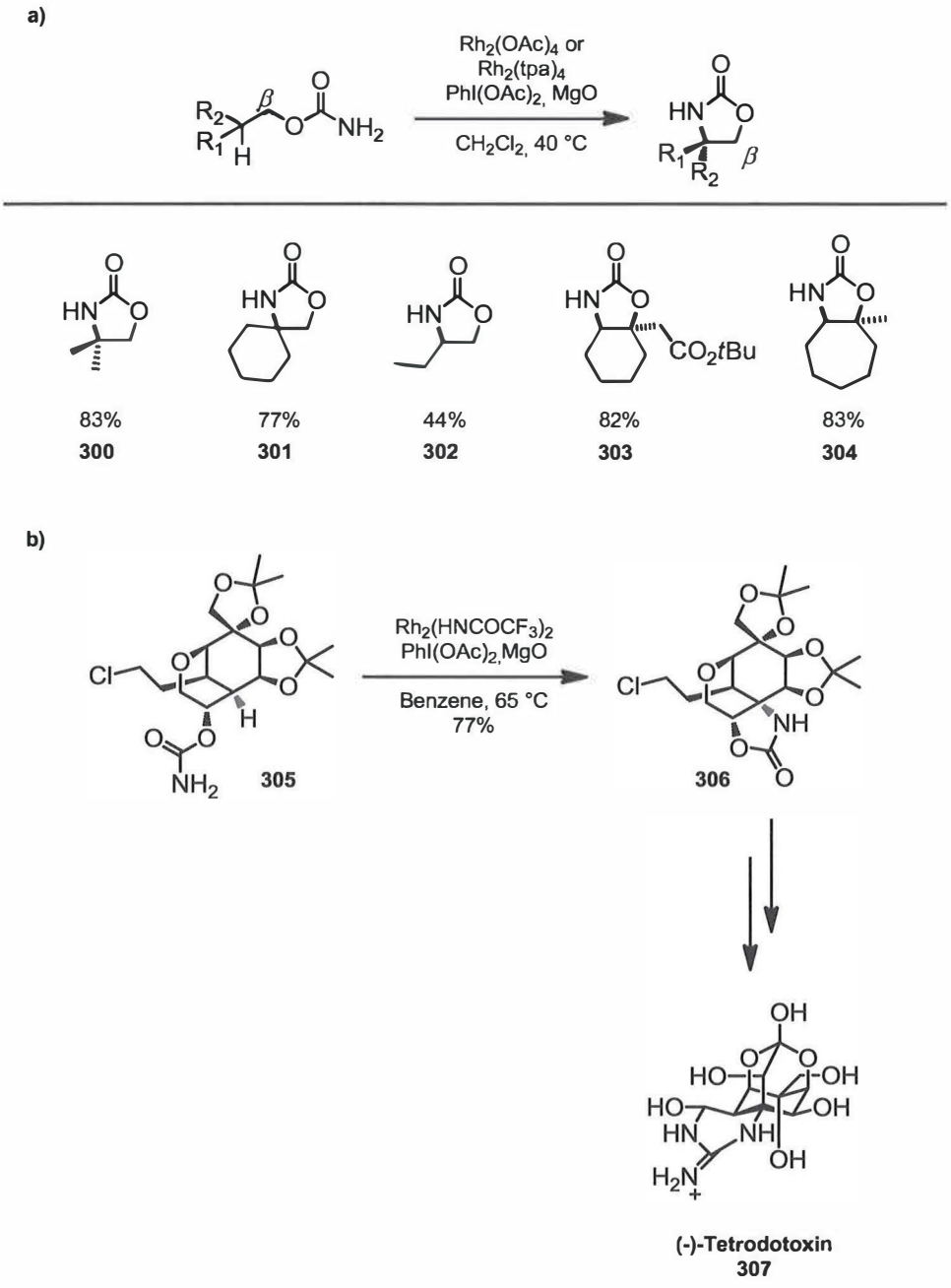
Nadres and Daugulis have published a method for the formation of five-membered heterocycles via a palladium-catalyzed picolinic acid-directed δ-sp^3 C−H/C-N coupling. [159] They used commonly employed conditions, i.e. $Pd(OAc)_2$, as a catalyst and $PhI(OAc)_2$ as an oxidizer in toluene at 80-120 °C, to

synthesize a range of the pyrrolidines (Scheme 62). The cyclization method was also found to be effective for sp^2 as well as for benzylic sp^3 C–H bonds.



Scheme 62. Intramolecular cyclization of alkyl picolinamides.[159]

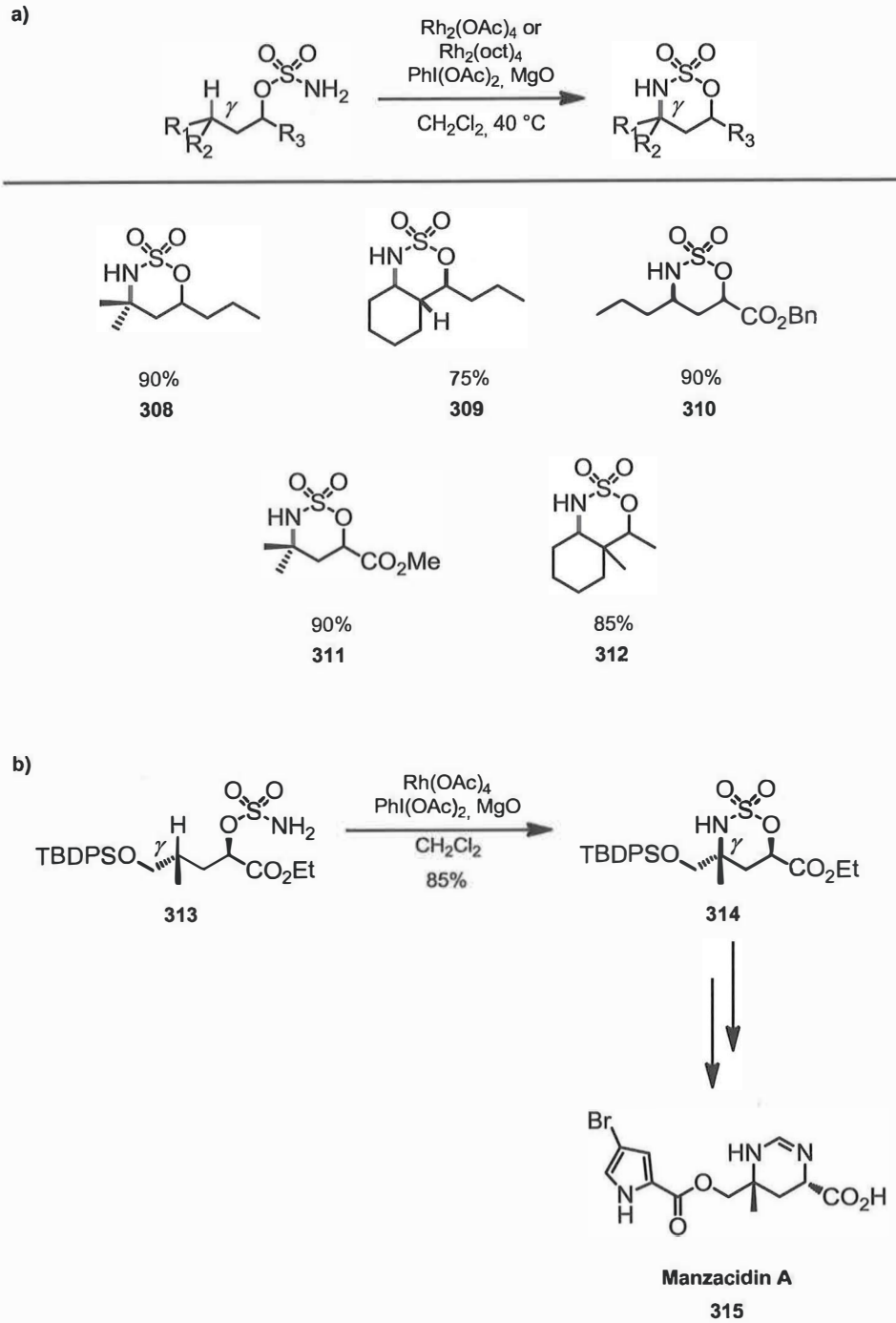
In 2001, based on Breslow's pioneering study's[160-162] Espino and Du Bois disclosed a rhodium-catalyzed intramolecular oxidative cyclization reaction of carbamates to oxazolidinones.[163] Several carbamates were used to illustrate the potential value of their β-C–H bonds amination reaction (a, Scheme 63). Later in 2003, Hinman and Du Bois employed the same protocol in a stereoselective total synthesis of (-)-Tetrodotoxin (b, Scheme 63).[164]



Scheme 63. Intramolecular rhodium-catalyzed oxidative cyclization of carbamates to oxalzolidinones.[163,164]

Also in 2001, Du Bois and co-workers introduced a similar method for the oxidative cyclization of sulfamate esters.[165] A combination of sulfamate with

$PhI(OAc)_2$ and a commercial dirhodium catalyst, $Rh_4(OAc)_4$ or $Rh_2(oct)_4$, resulted in a γ-aminated product with good yields (a, Scheme 64). Wehn and Du Bois also applied the same methodology to the intramolecular γ-amination of *sp3* C−H bonds in the enantioselective synthesis of the alkaloid manzacidin A (b, Scheme 64).[166]



Scheme 64. Intramolecular rhodium-catalyzed γ-amination of sp^3 C–H bonds.[165,166]

In order to improve the scope and efficiency of the amination of *sp3* C−H bonds, efforts have also focused on the design of new catalysts. Du Bois and coworkers have developed a more robust and efficient rhodium(II)-catalyst, $Rh_2(esp)_2$, which shows a superior catalytic activity for intramolecular C−H oxidation with sulfamate, sulfamide and urea substrates (Figure 4).[167] It is noteworthy that $Rh_2(esp)_2$ is also commercially available.[168]

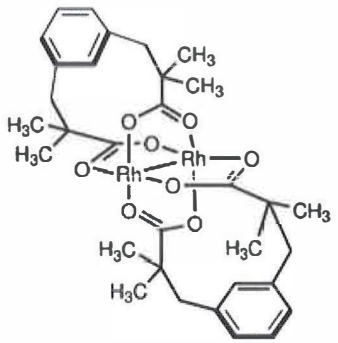
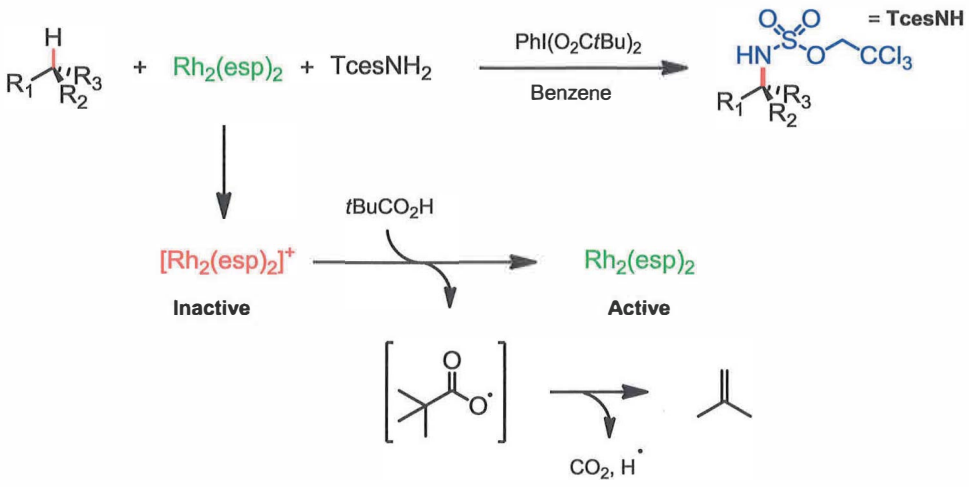


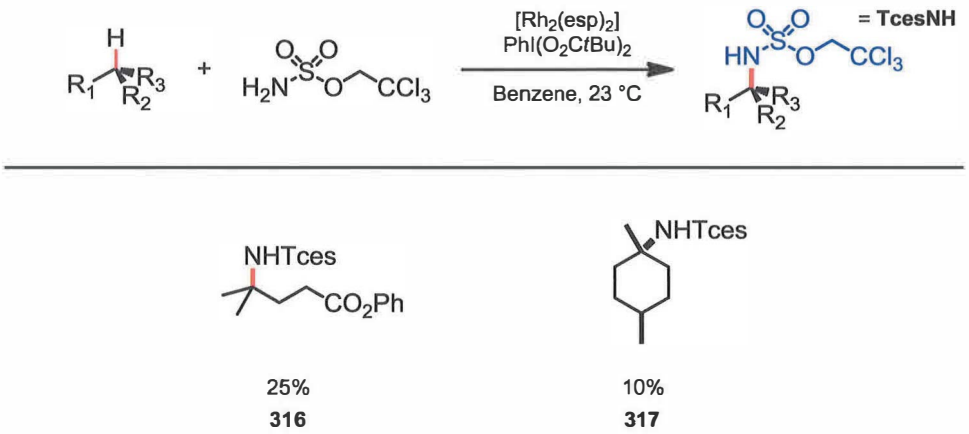
Figure 4. $Rh_2(esp)_2$, Bis[rhodium(α, α, α′, α′-tetramethyl-1,3-benzenedipropionic acid)].[167,168]

Zalatan and Du Bois have also suggested that high performance displayed by $Rh_2(esp)_2$ for catalytic C−H amination is due to the kinetic stability of the catalyst dimer when it comes to oxidative decomposition. Furthermore, remarkably, the carboxylic acid generated as a byproduct under these conditions serves a critical role as a reducting agent to return a mixed-valent Rh^{2+}/Rh^{3+} dimer to a catalytically active neutral form (Scheme 65).[169-171]Zare group, the researchers have also confirmed and identified these reactive transiently dirhodium intermediates by using a high-resolution desorption electrospray ionization mass spectrometry.[172]



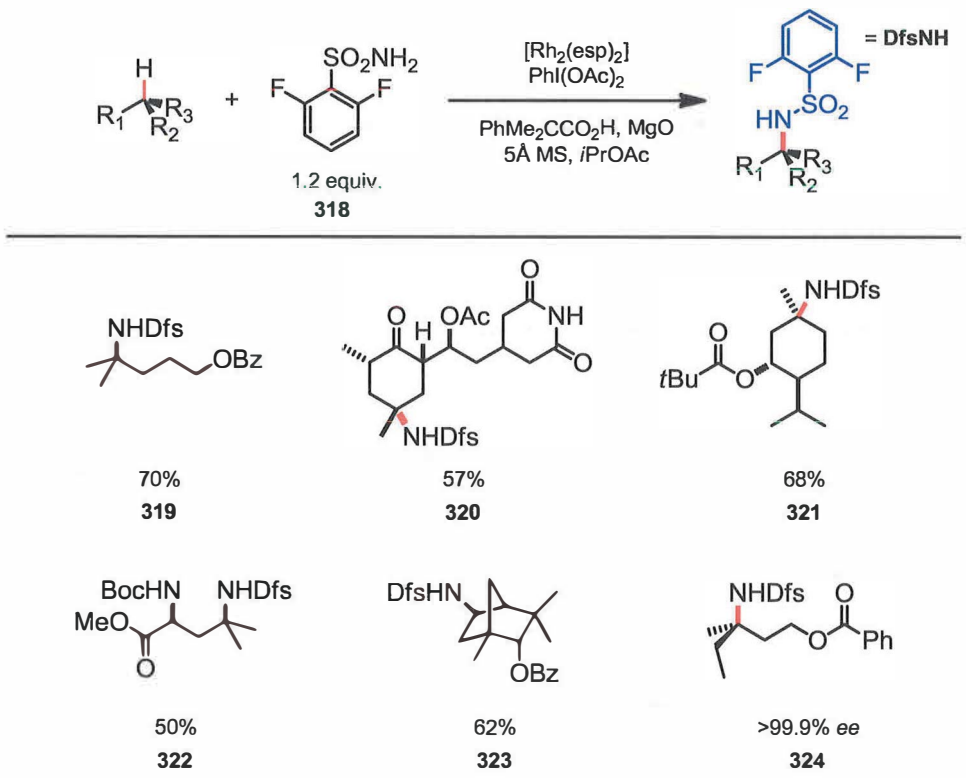
Scheme 65. Reduction of inactive $[Rh_2(esp)_2]^+$ by a carboxylic acid.[167-169]

By using this new efficient catalyst, $Rh_2(esp)_2$, Fiori and Du Bois reported success in the intermolecular amination of benzylic and tertiary C–H bonds.[173] The reaction was conducted with several substrates by using trichloroethylsulfamate as a nitrene precursor in good yields. However, if the reaction was conducted with substrates bearing remote sp^3 C–H bonds the yields were found to be modest (Scheme 66).



Scheme 66. Rhodium-catalyzed intermolecular amination of tertiary C–H bonds.[173]

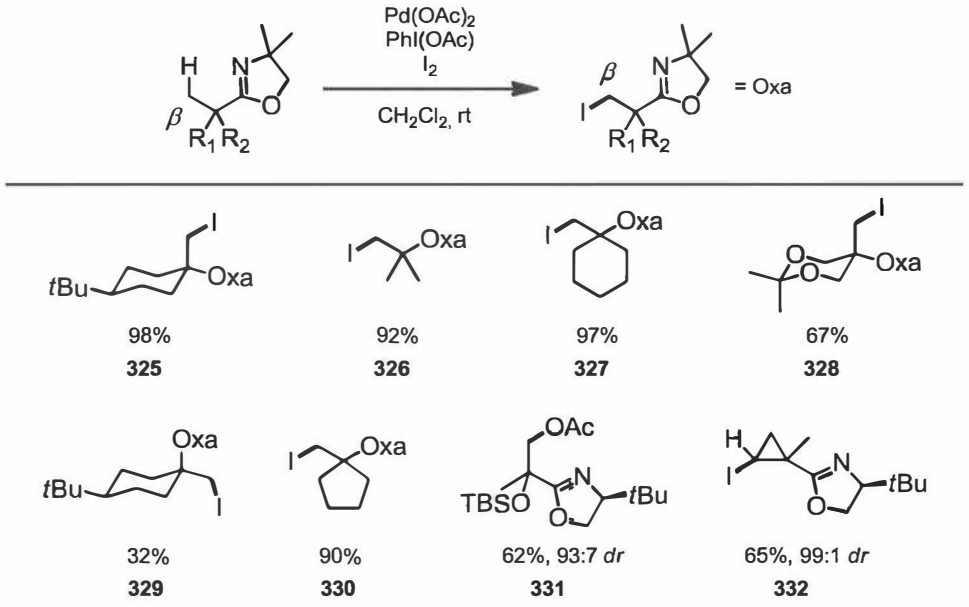
In 2013, Roizen, Zalatan and Du Bois reported a more general method for the selective intramolecular amination of tertiary C–H centers (Scheme 67).[174] The influence of different nitrogen sources compared to the efficiency of the reaction was dramatic. While most of the sulfonamides produced low yields in the reaction, the sulfamate prepared from 2,6-difluorophenol, $DfsNH_2$ **318,** provided a much better yield. A carboxylic acid additive, $PhMe_2CCO_2H$, served as an effective reducing agent for the mixed-valent Rh^{2+}/Rh^{3+} dimer to neutral species and improved catalyst turnover numbers (Scheme 65). It was also observed that the enantiospecific insertion into an optically active tertiary substrate is possible without the loss of enantiopurity (**324**).



Scheme 67. Rhodium-catalyzed intermolecular amination of tertiary C–H bonds.[174]

1.5 Oxidative halogenations

Yu and co-workers used an oxazoline-directing group tactic in order to achieve the iodination of a β-sp^3 C−H bond (Scheme 68).[175] Oxazoline, a chelating chiral auxiliary, was also effective for the asymmetric β-iodination of (**331** and **332**).

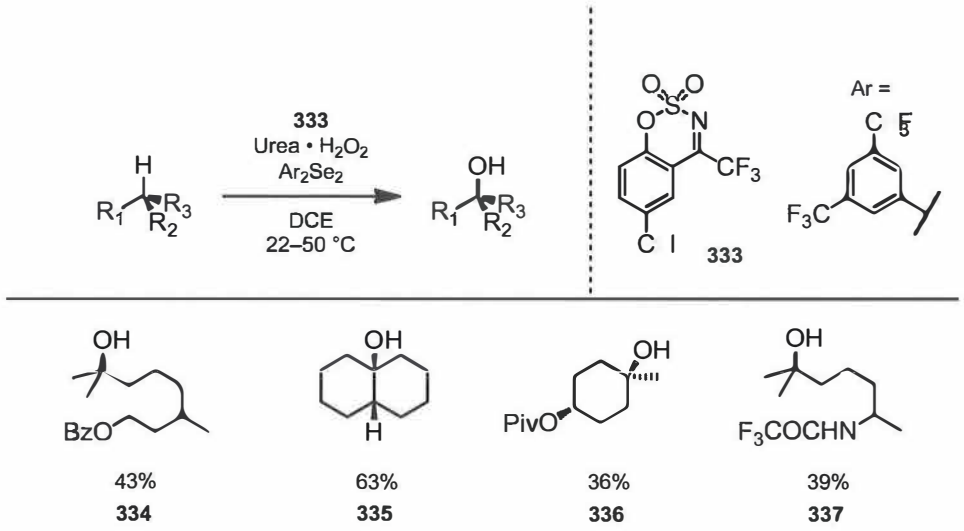


Scheme 68. Oxazoline-directed β-iodination of sp^3 C−H bond.[175]

1.6 Organocatalytic approach

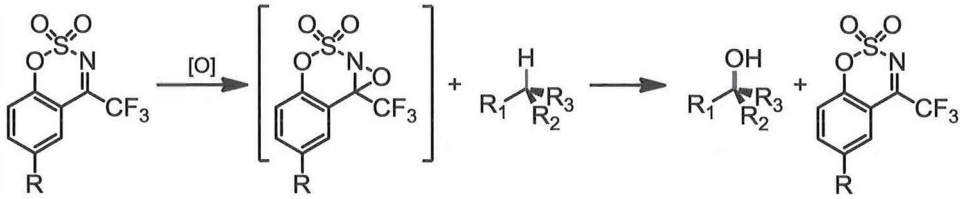
In 2005, Brodsky and Du Bois presented the first organocatalytic oxaziridine-based hydroxylation of tertiary sp^3 C−H bonds.[176] They found that bis(3, 5-bis (trifluoromethyl) phenyl) diselenide, (Ar_2Se_2), reacted with urea-hydrogen peroxide to give perselenic acid, which acts as an oxidizer. They were able to hydroxylate tertiary sp^3 C−H bonds for a modest number of substrates with

moderate yields (Scheme 69). The disadvantage of the method was the use of a toxic and expensive diselenide.



Scheme 69. Organocatalytic benzoaxathiazine-catalyzed sp^3 C–H bond hydroxylation.[176]

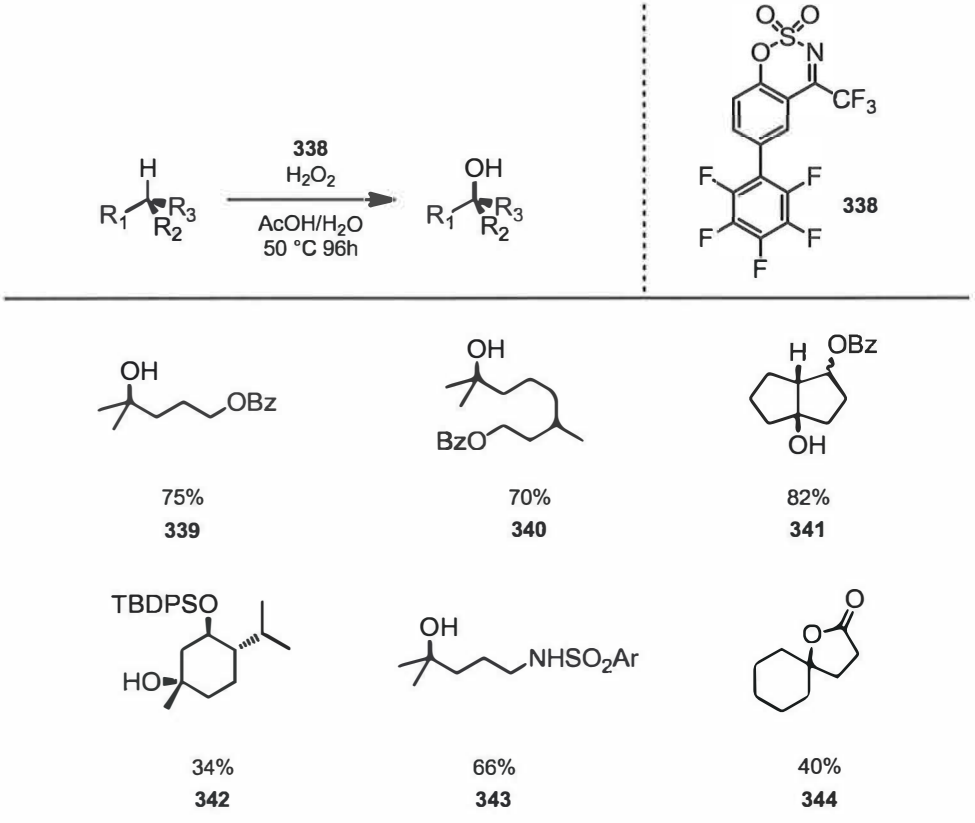
The oxaziridine intermediate is generated *in-situ* by using a terminal oxidant. Subsequently, the formed oxaziridine intermediate hydroxylates the C–H bond (Scheme 70). An oxaziridine-mediated *O*-atom transfer to the C–H bond likely occurs through a concerted, asynchronous process.[177-179]



Scheme 70. Benzoaxathiazine-catalyzed sp^3 C–H bond hydroxylation.[176]

In 2009, Du Bois and co-workers published an improved organocatalytic protocol for the benzoxathiazine-catalyzed sp^3 C–H bond hydroxylation process.[180]

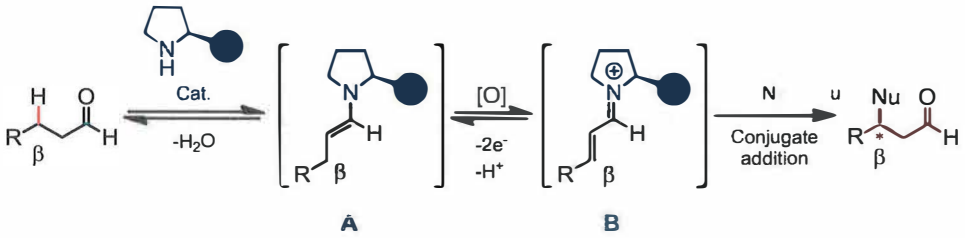
They were able to improve the catalytic activity by systematically exploring the influence of an electronic substitution on catalysts aromatic ring. Moreover, they suggest that aquous H_2O_2 conditions promotes the kinetically slow C–H hydroxylation events throught the hydrophobic aggregation of catalyst and substrate. With the more active catalyst **338** in their hands, they were able to use only H_2O_2 as a terminal oxidant. Additionally, they employed their protocol to a number of architecturally diverse substrates that resulted in good yields (Scheme 71).



Scheme 71. Benzoaxathiazine-catalyzed sp^3 C–H bond hydroxylation by using aqueous hydroperoxide as an oxidizer.[180]

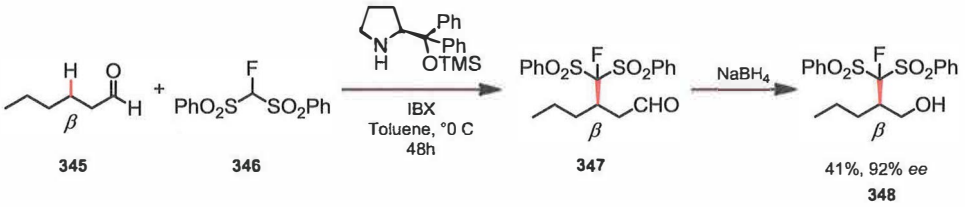
In 2011, Wang and co-workers proposed a new organocatalytic strategy for the enantioselective β-functionalization of aldehydes (Scheme 72).[181] Their oxidative

enamine catalysis strategy is based on the oxidation of enamine **A** to the unsaturated iminium ion **B**. Subsequently, the resulting iminium ion **B** species undergoes an enantioselective conjugation addition to a new chiral product.



Scheme 72. Strategy for organocatalytic access to the β-functionalization of aldehydes.[181]

They demonstrate the efficiency of their protocol with several examples where the β-position of an aldehyde is also a benzylic position. However, there is only one example with an aliphatic aldehyde **345** (Scheme 73).



Scheme 73. Organocatalytic enantioselective cascade oxidation-Michael reaction.[181]

1.7 Conclusion

The reactions discussed above enable the direct, selective and efficient activation of remote sp^3 C–H bonds to form C–C, C–O, C–N and C–I bonds and can be used to generate molecular complexity in the three dimensions. However, although there are plenty of examples of efficient oxidative functionalization of

remote sp^3 C−H bonds, selective dehydrogenative cross-couplings reactions are still rare and their mechanistic investigations are yet elusive.

The utilization of the remote functionalization of the sp^3 C−H bonds beholds great potential to construct the molecular diversity by efficient and "economical" manners. To be sure, in the future the increasing demand of more economical, novel and resourceful reactions to achieve the remote functionalization of sp^3 C−H bonds will keep the field vibrant.

2 RESULTS AND DISCUSSION

2.1 Aims and background of the work

The design of a new drug, which is at the heart of commercialization of biological targets, starts with chemical synthesis. The complexity of the active pharmaceutical ingredients (API) has grown during the years, mostly due to an increased amount of disease pathways (i.e. biological targets) and new regulatory requirements (Figure 5).[182] Today, the number of chemical entities needed from concept to product is enormous and is growing, and the preclinical and clinical studies also need increasing quantities of candidates for testing.

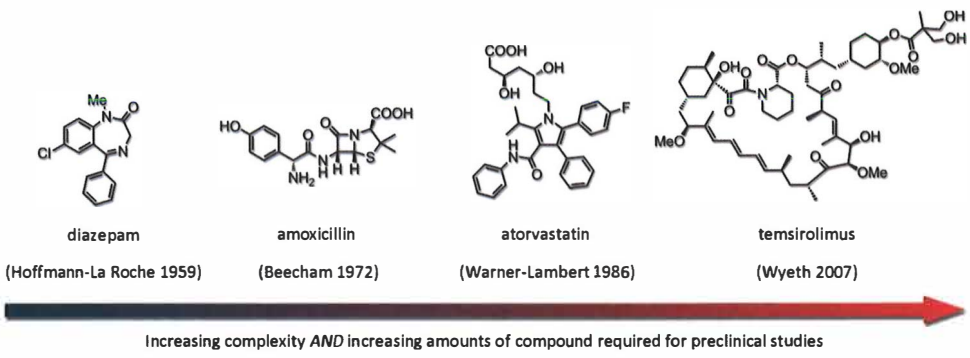
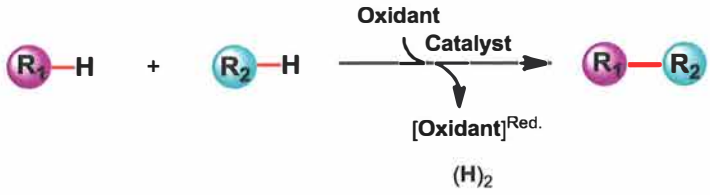


Figure 5. The evolving chemical structural landscape of the pharmaceutical industry.

The development of new complex pharmaceuticals is critically dependent on our ability to synthesize an active molecular species in an efficient manner. The

competitive environment of the pharmaceutical industry continues to undergo dramatic changes. What the pharmaceutical and fine chemicals industry needs in order to survive in this environment is both new products — i.e. new molecules, and fast, robust, innovative technologies to access the ever more difficult target molecules. This can be achieved by developing more efficient, novel synthetic methodologies, which will help us to synthesize new molecules faster and more cost efficiently by using sustainable chemistry. One of the most promising technologies that will answer these requirements are catalytic dehydrogenative cross-coupling reactions (CDC) where two C−H bonds are oxidized by using an external sacrificial oxidant to form a new C−C bond (Scheme 74).[183-185]

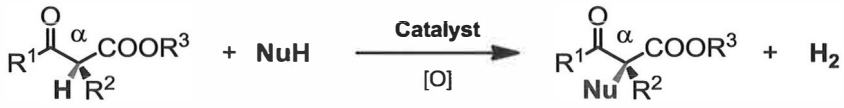


Scheme 74. Catalytic dehydrogenative cross-coupling reaction.

As a part of the Pharma programme of Tekes,[186] a consortium project titled "Enabling Synthesis Technologies − Key Technologies for Enhancing the Competitiveness of Pharmaceutical and Fine Chemical Industry in Finland and Removing the Bottlenecks in Synthesis" was launched in 2008. The industrial consortium behind this project identified the following reaction types as particularly acute problems within the pharmaceutical industry:

1) **Redox reactions**: Organo- and organometallic catalysis for C=O or C=N reduction/alcohol oxidation.
2) **Coupling chemistry**: Catalytic C−C, C−N bond formation reactions, especially asymmetric coupling reactions.
3) **Quaternaries**: Synthesis of quaternary stereocenters, especially all-carbon quaternary centers.

The asymmetric synthesis of molecules bearing quaternary carbon stereocenters represents a remarkably challenging and dynamic area in organic synthesis. The construction of molecules containing these centers with the right catalytic enantioselective manners is particularly demanding and important.[187-192] In order to respond to the problems given above, the project initiated an investigation of the oxidative formation of quaternary centers. The initial idea of this study was to develop an enantioselective oxidative α-functionalization method for β-keto esters to form quaternary stereocenters (Scheme 75).



Scheme 75. Initial idea for oxidative α-functionalization of β-keto esters.

2.2 Dehydrogenative α-coupling reactions with β-keto esters

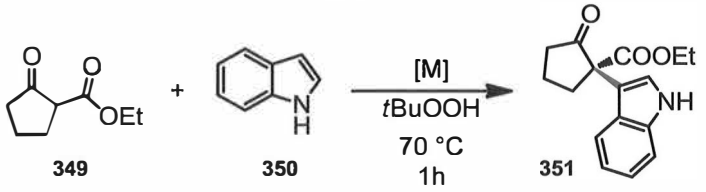
2.2.1 Development of racemic α-functionalization of β-keto esters

Indole is the third most popular ring system found in bioactive molecules[193] and consists of a common core of over 3000 natural products[194]. Because of the central place of heterocycles, especially indole, in medicinal chemistry, the original aim of this study developed an oxidative coupling reaction between indoles and β-keto esters.

This study was initiated by examining the optimal metal-catalyst for the reaction of cyclic β-keto esters **349** and 1-methylindole (**350**) with *t*-BuOOH (in 2,2,4-trimethylpentane, 5.5 M) as an oxidant without any additional solvent. The α-coupled product (**351**) was then obtained in moderate yields with copper-salts

as a catalyst (Table 1, entries 1-12) and similar results were obtained with $Mn(OAc)_2$ and $FeCl_2$. However, the use of $Pd(OAc)_2$ and $(Ph_3P)_3RuCl$ did not provide for a α-coupling product. The most active copper-catalyst $Cu(OAc)_2 \cdot H_2O$ was chosen to use for further achiral screenings.

Table 1. Screen of transition metal catalyst in the oxidative α-functionalization of β-keto esters[a]



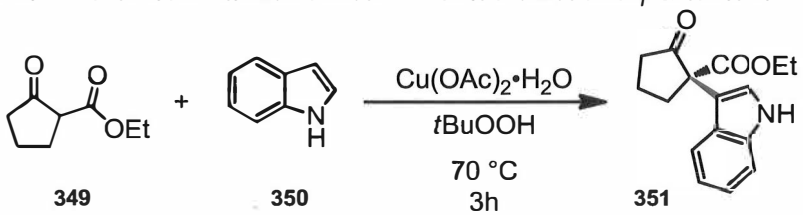
349 **350** **351**

Entry	[M] (10 mol%)	Yield[b]
1	$Cu(OAc)_2$	59%
2	$Cu(OAc)_2 \cdot H_2O$	60%
3	CuBr	47%
4	$CuBr_2$	42%
5	CuCl	52%
6	$CuCl_2$	49%
10	Cu(II) 2-Ethylhexanoate	55%
11	$Cu(BF_4)_2 \cdot xH_2O$	nd
12	CuI	25%
13	$Pd(OAc)_2$	nd
14	$Mn(OAc)_2$	61%
15	$FeCl_3$	25%
16	$(Ph_3P)_3RuCl$	nd
17	$InCl_3$	12%
18	-	nd

a) To the mixture of indole **350** (24 mg, 0.2 mmol, 100 mol%), β-ketoester **349** (62 mg, 0.4 mmol, 200 mol%). Additionally, a transition metal catalyst (10 mol%) was added to *t*BuOOH in 2,2,4-trimethylpentane (45 µl, 0.25 mmol, 125 mol%, 5.5 M) and the reaction mixture was stirred 1h at 70 °C under Ar. b) GC yield. Tetradecane was used as an internal standard.

Subsequently, the effect of an additional solvent was investigated. A survey of different solvents revealed that none of the co-solvents were beneficial for the reaction yields (Table 2).

Table 2. Screen of the solvents in an oxidative α-functionalization of β-keto esters[a]



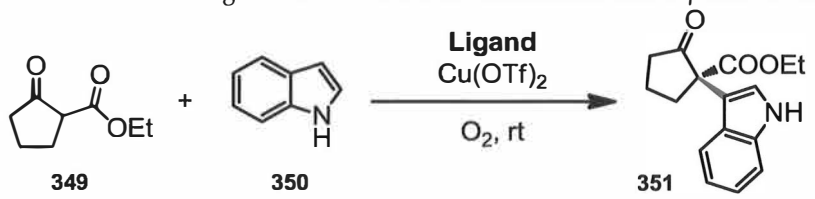
349 350 351

Entry	Solvent	Yield[b]
1	DCE	37%
2	$CHCl_3$	28%
3	Toluene	43%
4	ACN	35%
5	THF	nd
6	Hexane	39%
7	DMF	nd
8	MeOH	12%
9	H_2O	28%

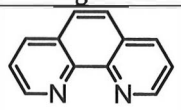
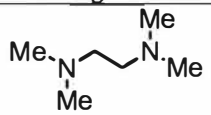
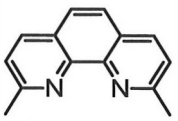
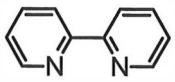
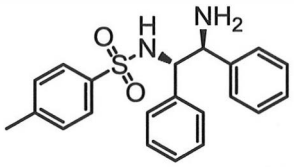
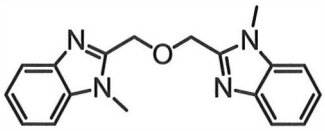
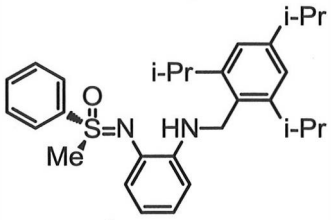
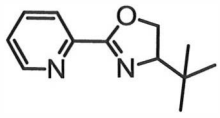
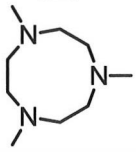
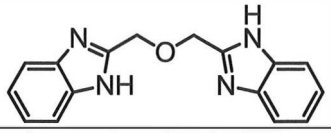
a) To the solution of indole **350** (24 mg, 0,2 mmol, 100 mol%), β-ketoester **349** (62 mg, 0,4 mmol, 200 mol%) and $Cu(OAc)_2 \cdot H_2O$ (4 mg, 0,02 mmol, 10 mol%) in solvent (0.5 ml) was added *t*BuOOH in 2,2,4-trimethylpentane (45 µl, 0,25 mmol, 125 mol%, 5,5 M), and the reaction mixture was stirred 3h at 70 °C under Ar. b) GC yield. Tetradecane was used as an internal standard.

The effect of ligand was also studied. Cu(II) was by far the best cation and triflate was the counteranion of choice in the ligand screens. This is due to the weakly nucleophilic character and weak coordination ability of the triflate ion.[195] The reaction was conducted in CH_2Cl_2 under an O_2 atmosphere. All of the tested ligands gave low (<5%) yields (Table 3). The screen of the achiral ligands revealed that ligands could not improve the yields in the racemic reaction.

Table 3. Screen of the ligands in an oxidative α-functionalization of β-keto esters.[a]



349 **350** **351**

Entry	Ligand	Entry	Ligand
1		7	
2		8	
3		9	
4		10	
5		11	
6			

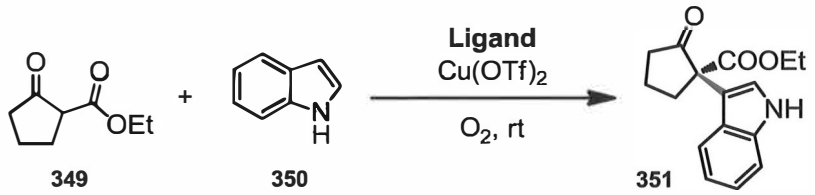
a) To the solution of $Cu(OTf)_2$ (12 mg, 0.03 mmol, 50 mol%) and Ligand (51 mol%) in CH_2Cl_2 (0.5ml) was added indole **350** (8 mg, 0,07 mmol, 100 mol%) and β-ketoester **349** (11 mg, 0,07 mmol, 100 mol%), and the reaction mixture was stirred at rt under O_2 (balloon).

2.2.2 Enantioselective α-functionalization of β-keto esters

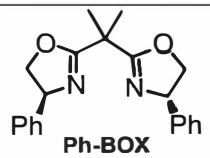
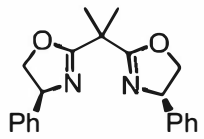
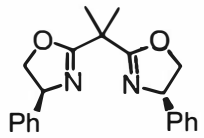
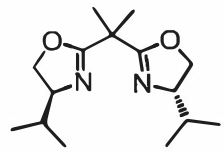
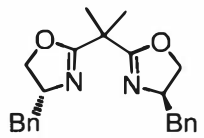
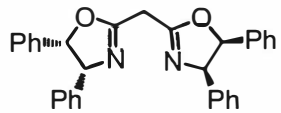
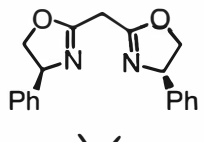
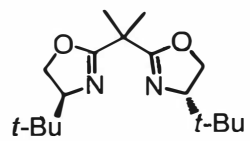
As mentioned in the introduction, the ultimate goal of the project was to develop an enantioselective dehydrogenative α-coupling reaction in order to form chiral quaternary centers. To achieve this goal, several chiral ligands were examined.

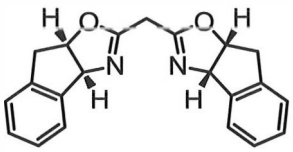
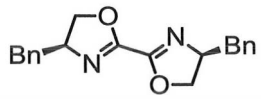
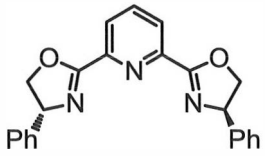
It was found that additional bases could also increase the conversion of the α-coupling product. The most effective bases were triethylamine and *i*Pr$_2$NEt. A stoichiometric amount of base inhibited the reaction, and ca. 20 mol% of the base was optimal. For enantioselectivity screens, several chiral ligands were employed (Table 4). The bis(oxazoline) ligands gave the best selectivities in the enantioselective reaction (Table 4), affording the product at up to 63% *ee*. However, the yield and enantioselectivities were only modest with all of the ligands. Some of the more hindered bis(oxazoline) ligands were ineffective for the reaction due to either the stability or the inhibition of the catalyst. Furthermore, the yields were generally lower than the amount of the catalyst, indicating that the catalytic cycle was not working.

Table 4. Screen of the ligand in the enantioselective oxidative α-functionalization of β-keto esters.[a]



349 350 351

Entry	Ligand	mol%	Base (mol%)	Reaction time	Yield	ee[d]
1	 Ph-BOX	120	-	18h	37%	50%
2		50	15[b]	47h	36%	44%
3		30	10[c]	42h	30%	44%
4		50	-	24h	20%	63%
5		50	16[b]	18h	7%	40%
6		50	20[c]	20h	28%	44%
7		50	-	20h	10%	32%
8[e]					<5%	-

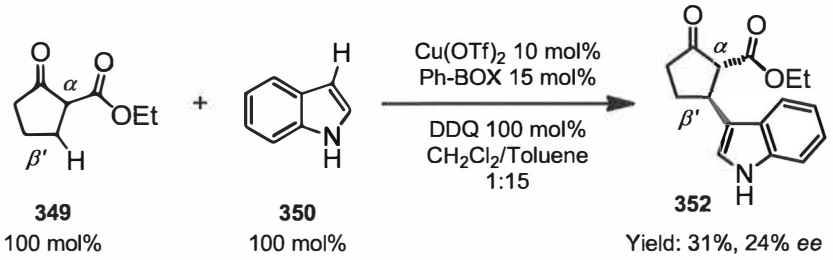
9[e]		<5%	-
10[e]		<5%	-
11[e]		<5%	-

a) Conditions: To a solution of $Cu(OTf)_2$ and ligand in CH_2Cl_2 (0.5ml) was added indole **350** (24 mg, 0,2 mmol, 100 mol%) and β-ketoester **349** (62 mg, 0,4 mmol, 200 mol%), and the reaction mixture was stirred at rt under an O_2 (balloon). b) iPr$_2$NEt c) Et_3N d) Determined by HPLC (Chiralcel IA column). e) Several conditions were screened.

2.3 Dehydrogenative cross-coupling at remote β-position

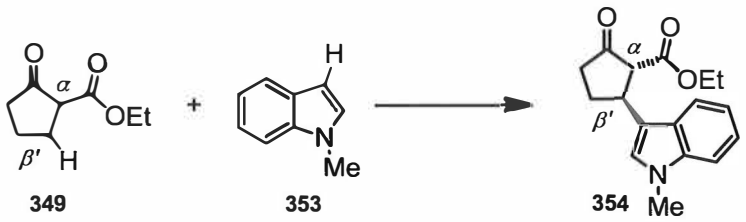
2.3.1 Dehydrogenative β'-functionalization of β-keto esters with indoles

When different oxidizers were tested for the enantioselective α-coupling reaction between β-keto ester **349** and indole (**350**), it was found that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in the formation of a new product (Scheme 76). After characterization, the newly formed product was identified as the unexpected β-coupling product **352**.



Scheme 76. First example of an intermolecular dehydrogenative cross-coupling reaction at β'-Position between the sp^3 and sp^2 C–H bonds.[196]

After this new and exciting discovery of a dehydrogenative cross-coupling reaction that took place at the β-position, further efforts concentrated on developing this reaction. It should be noted that, if the ligand is omitted from the reaction with $Cu(OTf)_2$, no product is formed. The screen of the various ligands revealed the superiority of the Ph-BOX ligand. All other ligands showed lower yields and achiral ligands. In order to overcome the problem with low yields, several copper sources were screened. However, none of them improved the yields. Attention was then switched to other metal salts. To our delight, the use of $Pd(OAc)_2$ gave a significantly improved yield. Instead of indole (**350**), 1-methylindole (**353**) was selected as a model compound for further screening as it was easier to add to the reaction media via a syringe.

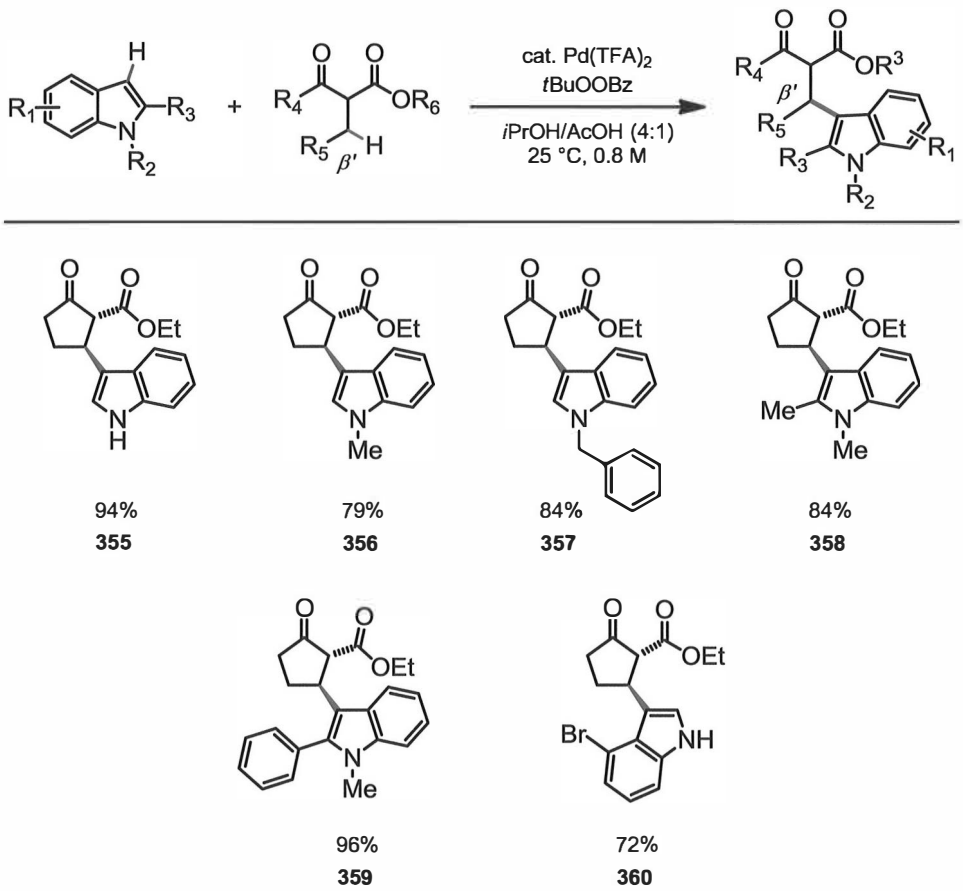


Further screens indicated that $Pd(TFA)_2$ was a more active catalyst than $Pd(OAc)_2$.[1] 1,4-Dioxane and 2-propanol mixed with AcOH gave similar results in the reaction. However, 2-propanol was determined to be the solvent of choice to use due to its lower price, better environmental profile and suitability for in-

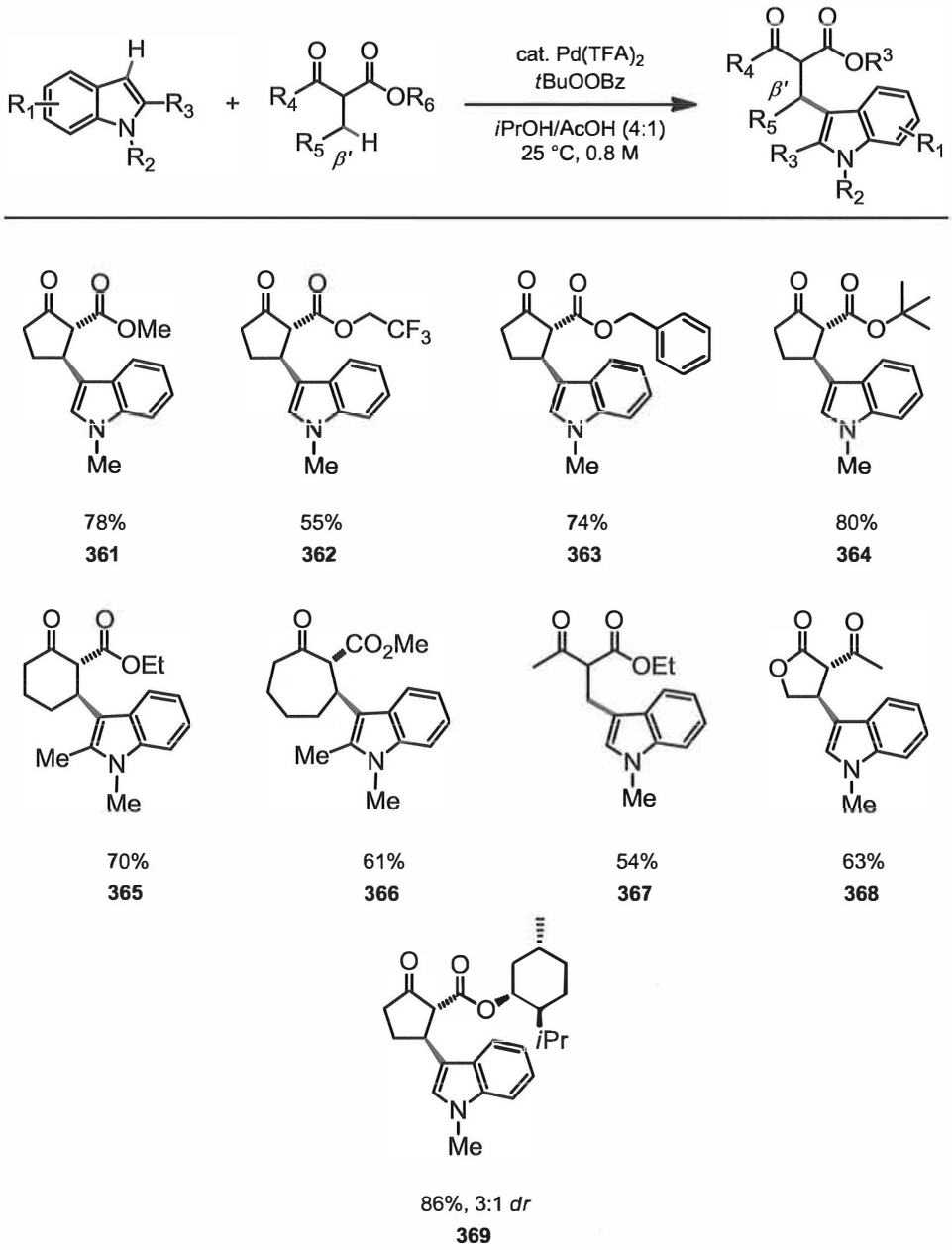
dustrial scale reactions.[197,198] Additionally, with the 2 propanol/AcOH solvent system, the undesired side reaction, a homocoupling of indole **353**,[199] could be minimized.[200] While a wide variety of oxidants gave reasonable conversions at room temperature, *tert*-butyl perbenzoate (*t*BuOOBz) afforded superior results. It should be noted that in addition to the peroxide oxidant, oxygen was also a synthetically useful oxidant. Furthermore, the reaction is really robust and can be conducted with an open vessel without the need of dry solvents. More importantly, the regioselectivity was excellent for both coupling partners and no indole regioisomers could be detected in any of the reactions with the Pd(II) catalyst. These results are presented in full in paper I.

The substrate scope of the dehydrogenative β-coupling reaction was found to be wide. Both unsubstituted **355** as well as *N*-substituted indoles (**356** and **358**) provided good product yields.[I] *N*-Benzyl protected indole **357** also supplied a good product yield.[IV] The reaction is highly tolerant of the substituent with different electronic properties in the indole nucleus, which allowed for further opportunities to conduct synthetic transformations. Furthermore, bulky indoles **360** and **359** bearing an aromatic group for position 3 provided high yields.[IV] The substrate scope with β-keto esters was also wide. The substrates bearing 6- and **7**-membered ring (**365** and **366**), and ester groups (**361-364**) were reacting smoothly in the reaction with good yields.[I,IV] Acyclic β-keto esters and lactones were also seen to be compatible substrates (**367** and **368**).[I]

The diastereoselective synthesis of the β-coupling products were also possible. The use of an enantiopure menthyl-derived ester enabled β-functionalization in a diastereoselective fashion (**369**, *dr* = 3:1 for two trans isomers). The regiochemical identity of both isomers was confirmed by 2D NMR experiments.[I] Later, it was found that higher diastereomeric ratios were achieved by using enantiopure 2-phenyl-menthyl-derived esters as a starting material (*dr* >20:1).[IV]



Scheme 77. Scope of dehydrogenative coupling with different indoles.[I,IV]

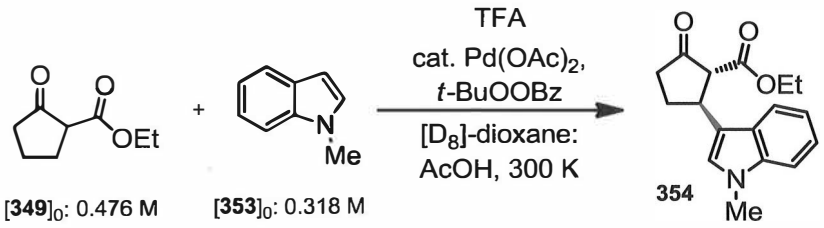


Scheme 78. Scope of dehydrogenative coupling with different β-keto esters.[I,IV]

A more practical and economic option was achieved when a combined reaction of $Pd(OAc)_2$ and trifluoroacetic acid was used instead of $Pd(TFA)_2$ under nor-

mal conditions. This provided comparable reaction rates and yields compared to $Pd(TFA)_2$.[IV]

Table 5. Effect of added trifluoroacetic acid to the coupling reaction catalyzed by $Pd(OAc)_2$.[a,IV]

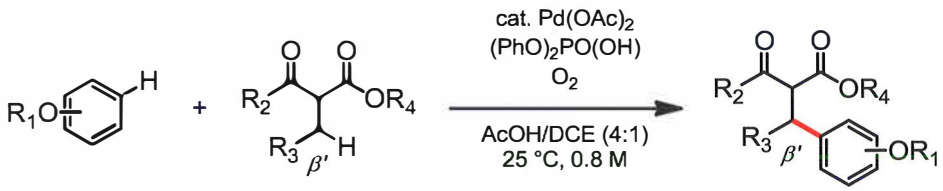


Entry	TFA	Rate 354 (mM min^{-1})[b]
1[c]	0 mol%	1.7
2	0 mol%	0.1
3	10 mol%	1.7
4	20 mol%	2.3
5	30 mol%	2.6
6	40mol%	2.6

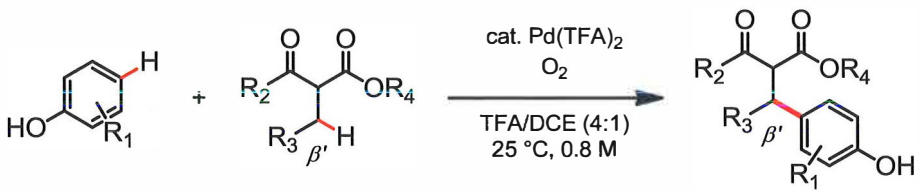
a) The rates were obtained by monitoring the temporal progress of the coupling by ^1H NMR spectroscopy. Reaction conditions: TFA, $[\mathbf{349}]_0$= 0.476 M, $[\mathbf{353}]_0$= 0.318 M, $[t\text{BuOOBz}]_0$= 0.413 M, 10 mol% $Pd(OAc)_2$, 4:1 $[D_8]$-Dioxane/AcOH, 300 K. b) Max rate. c) Used $Pd(TFA)_2$ instead of $Pd(OAc)_2$.

2.3.2 Dehydrogenative β′-arylation of β-keto esters

The expansion to these substrates was carried out by Drs. Kai-Tai Yip and Roshan Nimje at this laboratory. After realizing that indoles could react with β-keto esters it was also postulated that electron-rich aromatics could also react with β-keto esters. After screening the reaction conditions, it was found that by carefully choosing to use a Pd catalyst and a Brønsted acid co-catalyst, electron-rich arenes (Scheme 79) and a variety of phenols (Scheme 80) could undergo a highly regioselective dehydrogenative coupling at room temperature with β-keto esters in the β′-position. The acidic co-catalyst prevented problems associated with the overoxidation or degradation of the product. These result are presented more detailed in paper II.

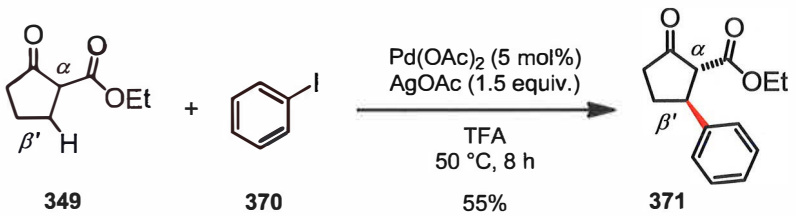


Scheme 79. A dehydrogenative coupling of electron-rich arenes and β-keto esters.[II]



Scheme 80. Dehydrogenative coupling between phenols and β-keto esters.[II]

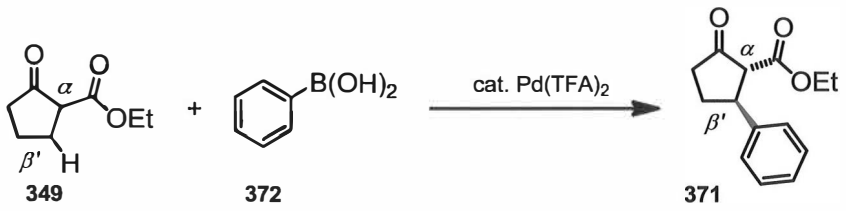
Interestingly enough, the β′-arylation of β-keto esters also proceeded with iodobenzene by using AgOAc as the iodide scavenger in TFA to directly provide for the β′-arylation product **371** (Scheme 81).[II] This direct arylation reaction was discovered at an early stage of the studies in 2012, but we were not able to realize this reaction with good yields and a wider substrate scope. However, in 2013, Huang and Dong published a similar catalytic direct β-arylation reaction of simple ketones with aryl iodides. They cited our single example and expanded the concept through a careful optimization of the reaction conditions and ligands.[201]



Scheme 81. Direct arylation of the β′-position of β-keto esters.[II]

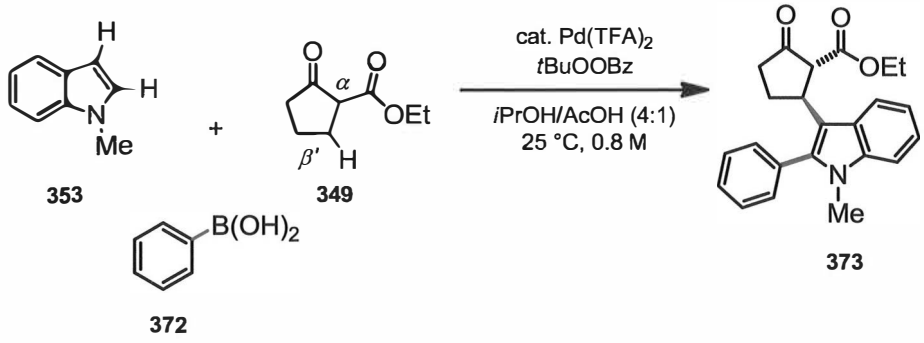
2.3.3 A three-component palladium-catalyzed oxidative C–C coupling reaction

In 2012, I also found that aryl boronic acids could couple at the β'-position of β-keto esters with modest yields (Scheme 82).



Scheme 82.The direct arylation of β'-position of β-keto esters with a phenylboronic acid.

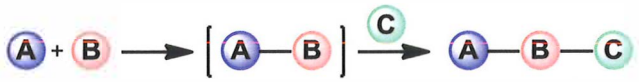
Subsequently, during the competition reaction between indole **353** and phenylboronic acid (**372**) with β-keto ester **349** it was serendipitously discovered that all three components of the reaction could react together (Scheme 83).[III] After this invention, it was easy to rationalize the novelty and the potential of this reaction. Laborious screening revealed that the original reaction conditions were most optimal for the three component reactions. The scope of the reaction, as probed by Dr. Roshan Nimje, turned out to be very wide. Even very hindered atropisomers could be synthesized.[III]



Scheme 83. A novel palladium-catalyzed oxidative three component reaction.[III]

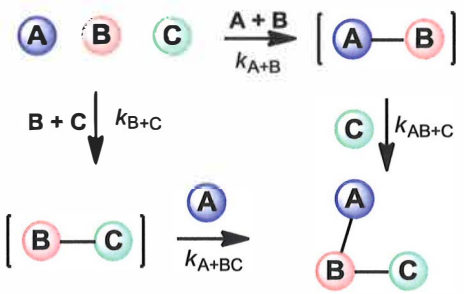
The most interesting aspect of the newly developed reaction was its mechanism. Theoretically, each of the components could react in a homo- or heterocoupling with another component. Typically, multicomponent reactions are considered to proceed in a linear domino mode: in the first stage, components (**A**) and (**B**) give rise to a reactive intermediate (**AB**) which then reacts with a third component (**C**), and so on, until the sequence is terminated. In these classical multicomponent reactions, the reactivity order is controlled largely by the functional groups present.

Linear 3CR ABC Reaction:



By contrast, in an oxidative coupling, the three components (**A**), (**B**), and (**C**) could react with each other in any order. Such three-component domino reactions (3CR) could proceed through an alternative two dimensional split domino process. In such a process, there are two kinetic alternatives that result in the final (**ABC**) product, via the (**AB**) or (**BC**) intermediates. If the steps are irreversible, the efficiency of the process could be compromised if one of the pathways leads to a dead end. Alternatively, unwanted homocoupling or heterocoupling reactions between the components could also jeopardize the projected 3CR process.

Two-Dimensional 3CR ABC Reaction



If the individual steps are irreversible, $k_{A+B} > k_{B+C}$, *and* k_{AB+C} is too small, then **A–B** represents a *dead end*.

Even if the reaction *could* proceed via **B–C**, this will not happen if $k_{A+B} > k_{B+C}$.

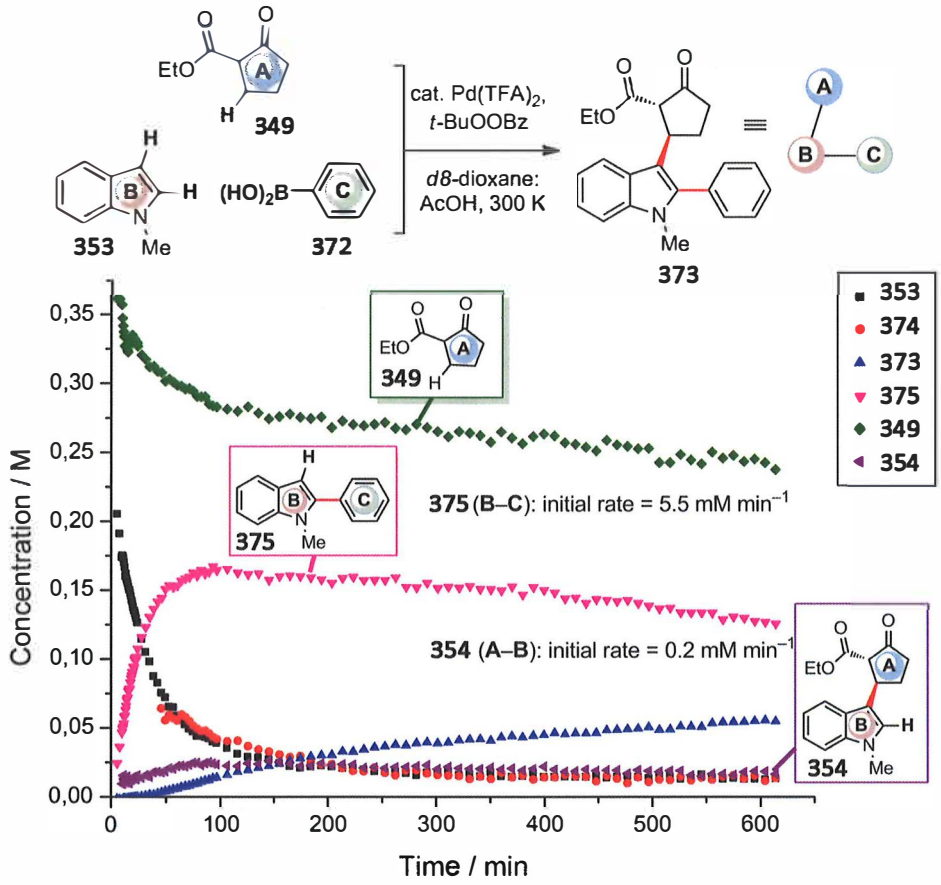
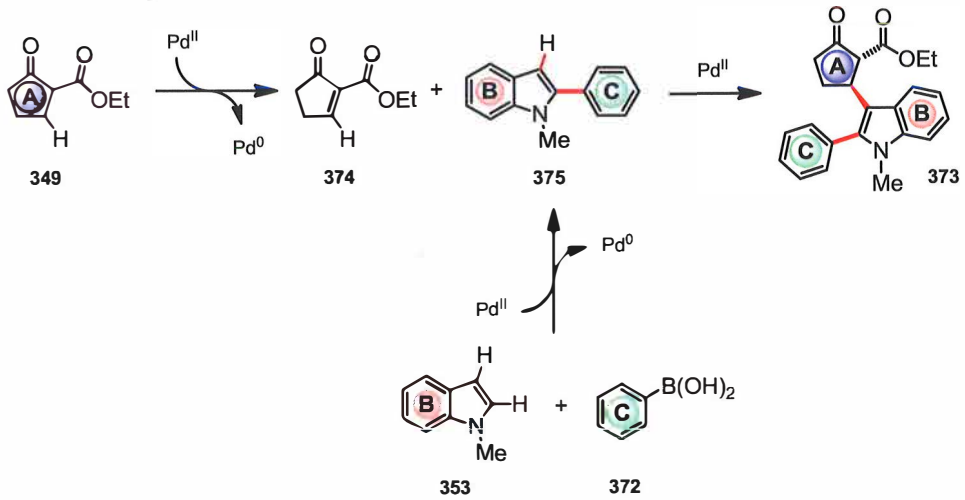


Figure 6. Monitoring of the temporal progress of the 3CR by ^{1}H NMR spectroscopy.[III]

In order to probe whether the 3CR reaction could proceed through either **(A+B)** or **(B+C)** pathways, or whether one of the pathways was dominating, the temporal progress of the reaction was followed by ^{1}H NMR (Figure 6) and each of the binary coupling reactions was also monitored separately in control experiments. The experiments revealed that in the major pathway, indole **353** and boronic acid **372** were coupled first, forming species **BC** (**375**). Subsequently, BC (**375**) reacted with enone **374,** generated from *β*-ketoester **349**, to give the product **376** (**ABC**). These results are presented in full in paper III.



Scheme 84. The dominating reaction pathway of a palladium-catalyzed oxidative three component reaction.[111]

2.4 The reaction mechanism of the β′-functionalization of β-keto esters with indoles

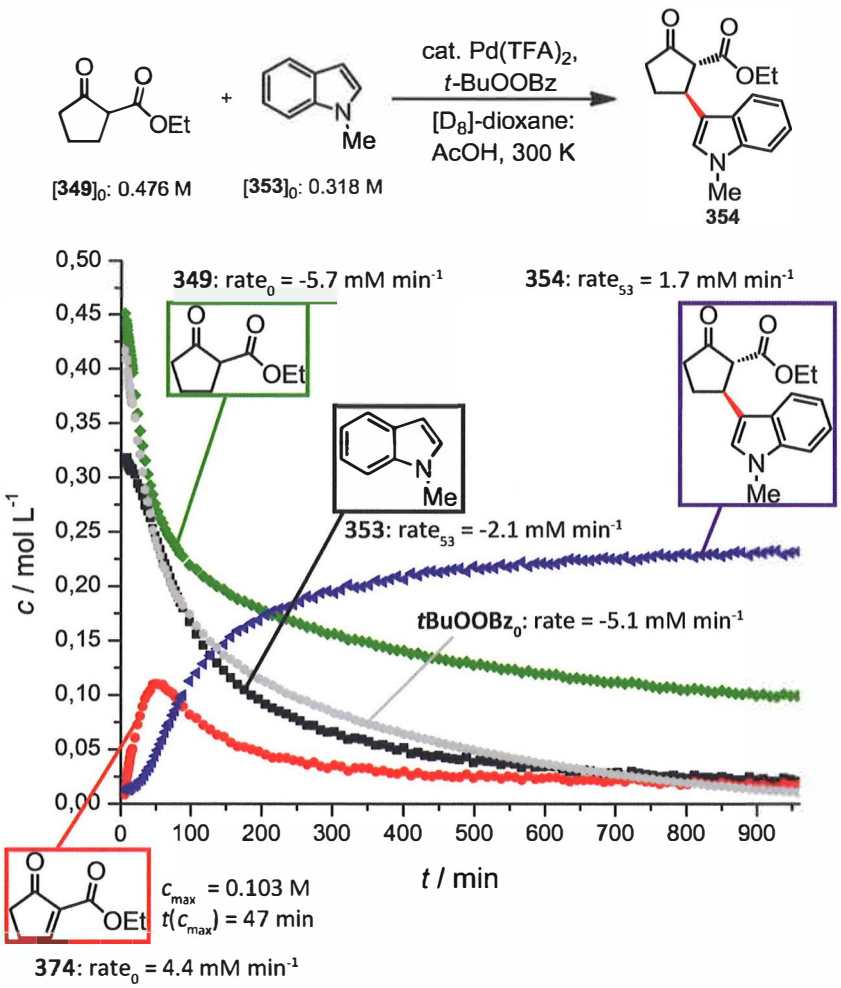
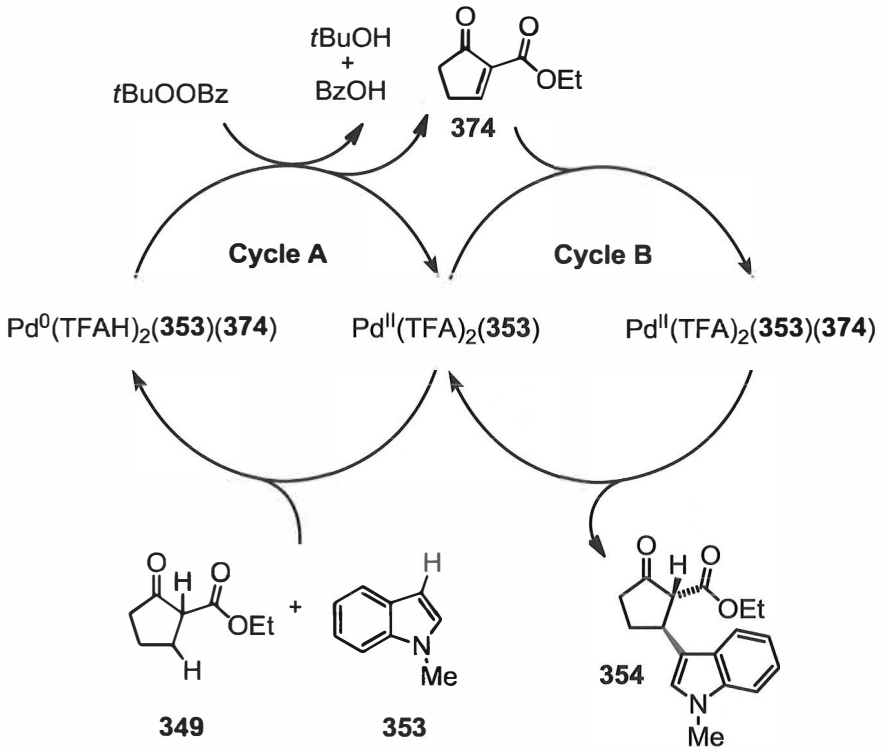


Figure 7. Monitoring of the temporal progress of the coupling by ^{1}H NMR spectroscopy.[IV]

The reaction mechanism was investigated comprehensively by online ^{1}H NMR methods, which allowed the simultaneous monitoring of several species and also enabled the study of kinetic isotope effects via deuterium labeling of the substrates (Figure 7). In summary, kinetic experiments revealed that the reaction likely proceeded in two stages, via an enone intermediate **374**. A proposed

mechanism thus involves two catalytic cycles, the dehydrogenation step (Cycle A) and the C-C coupling step (Cycle B) (Scheme 85).[IV]



Scheme 85. Schematic catalytic cycles for the dehydrogenation and the C-C bond formation steps.[IV]

Key evidence for the roles of each component in the cycle is summarized below.

Cycle A:

- The reaction proceeds smoothly with stoichiometric amount of $Pd(TFA)_2$ without a oxidizer under the Ar → The reaction is Pd(II) catalyzed (Paper I).
- Deuterium labeling of an indole at the C2 position accelerates the formation of enone **374** compared to a non-deuterated indole → Indole is π-coordinated to Pd center (Paper IV, Figure 2).

- Control experiments with 1,3-dimethylindole accelerates formation of enone **374** compared to the reaction without indole **353** –→ Indole is π coordinated to Pd center (Paper IV)
- Intramolecular competition experiment[202] with mono-β′-D-labeled β-keto ester: no kinetic isotope effect (KIE) observed. → Rupture of β′-H bond is not turnover-determining in cycle A (Paper IV, Scheme 6 and Scheme 87).

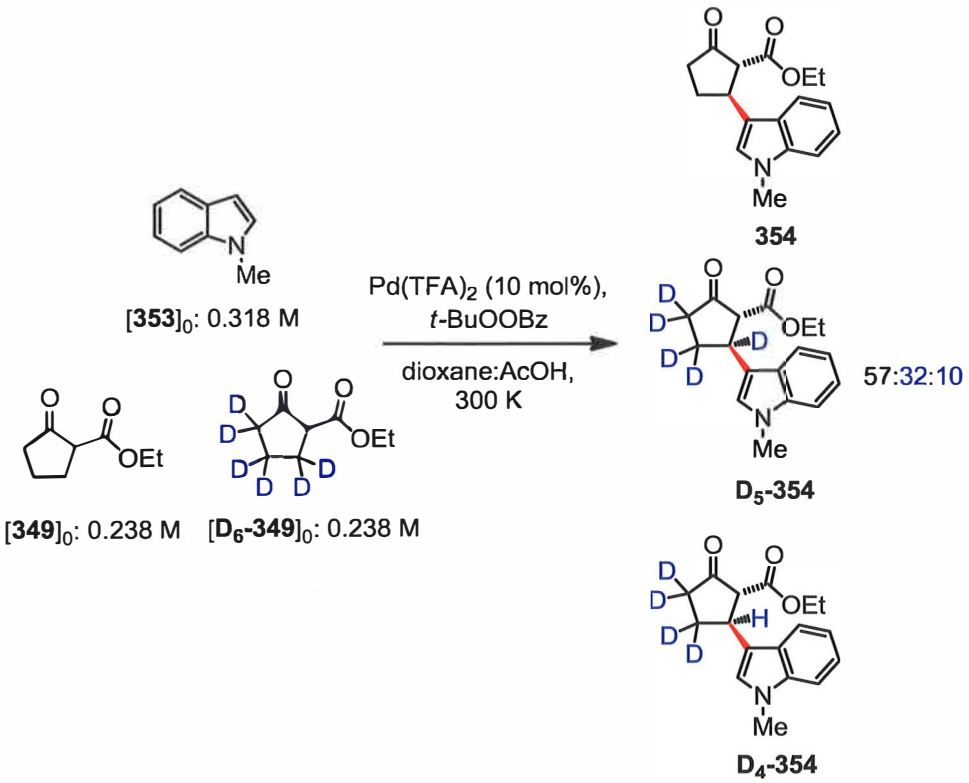
Cycle B:

Cycle B: control experiments with enone under either $Pd(TFA)_2$ or TFA catalysis indicated that only $Pd(TFA)_2$ catalysis afforded rates comparable to the standard reaction conditions → Cycle B is likely Pd(II) catalyzed (Paper IV, Scheme 3).

Although TFA alone was an inefficient catalyst, when $Pd(OAc)_2$ was used as a catalyst with added TFA the formation rate of the enone **374** (Cycle A) as well as the formation rate of the product **354** (Cycle B) was comparable to the reaction rates with $Pd(TFA)_2$ (Paper IV, Table 1). These results indicate that TFA plays a crucial role at the dehydrogenation step (Cycle A) as well as at the C−C bond formation step (Cycle B).

A KIE experiment was also conducted with a deuterium-labelled β-keto ester **D_6-349** (Paper IV, Figure 3). In this case, unfortunately, the formation of the corresponding enone could not be reliably monitored. Although the rate of consumption of **D_6-349** appears to display an inverse KIE, possible initial H/D exchange and/or differences in the rates of the formation of Pd^{II}(**D_6-349**)(**2a**)L_n or Pd^{II}(**D_6-349**)$_2L_n$ complexes could also account for this observation (Cycle A). Indeed, the overall rate of the reaction did not exhibit any KIE (**354:** k_H/k_D = 0.98), and the initial rate of the consumption of the oxidant indicated a small normal KIE (k_H/k_D = 1.07). Since the consumption of the oxidant is likely correlated with the concentration of the enone, thus the rate of formation of enone

D_5-374 is likely lower with deuterated β-keto ester **D_6-349**. This might be due the formation of more stable complex Pd^{II}(**D_6-349**)(**353**)L_n or/and Pd^{II}(**D_6-349**)$_2L_n$ compared to the corresponding non-deuterated complexes. As a result of the higher stability of the *O*-bounded **D_6-349** enolate-Pd(II) complex, the formation of *C*-bound enolate-Pd(II) complex would be slower compared to non-deuterated β-keto ester (Cycle A). If this is true, the formation rate of the product **D_5-354** from the deuterated-enone **D_5-374** would be faster than the formation rate of the product **354** from the enone **374** (Cycle B), indeed the concentration of deuterated enone **D_5-374** is likely lower than concentration of non-deuterated enone **374** (***t*BuOOBz**: k_H/k_D = 1.07) whereas the overall rate exhibits small KIE (**354:** k_H/k_D = 0.98). Furthermore, in the competition reaction between **349** and **D_6-349**, the non-deuterated **349** reacts faster than the deuterated **D_6-349** (Article IV, Scheme 5). This result also suggests that formation rate of enone **D_5-374** derived from **D_6-349** is slower than formation of enone **374**. However, to substantiate this hypothesis the monitoring of the concentrations of deuterated enone **D_5-374** would be essential.

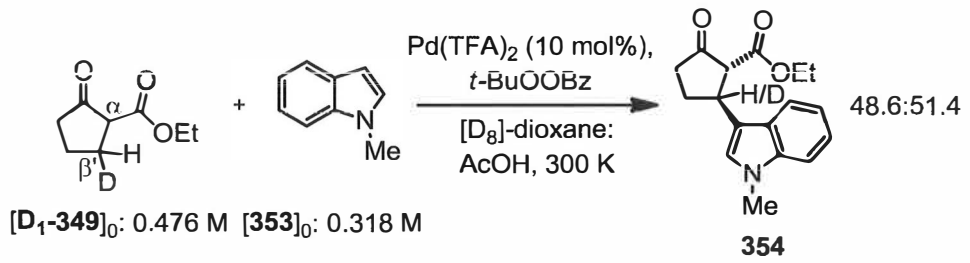


Scheme 86. Intermolecular competition between **D_6-349** and **349** in the coupling process.[IV]

Interestingly, the competition reaction between **349** and **D_6-349** produced three products, instead of two. The products were: non-deuterated **354**, **D_5-354** bearing five deuteriums, and **D_4-354** bearing four deuteriums, with the product distribution 57:32:10, respectively (Paper IV, Scheme 5 and Scheme 86 above). This result may indicate that the dehydrogenation step is reversible to some extent, leading to H/D exchange and the formation of **D_4-354**.

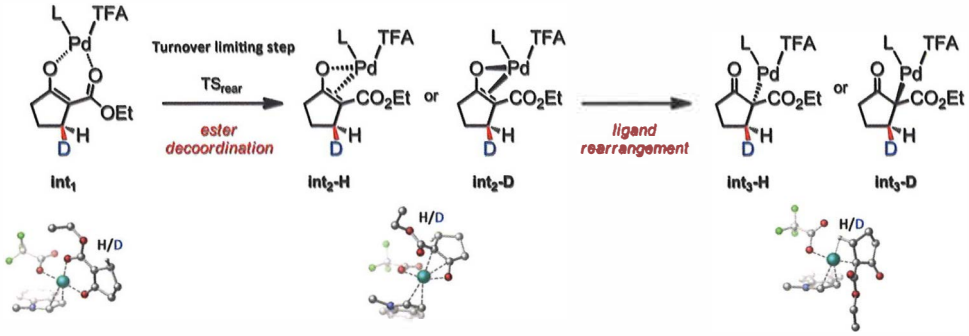
To obtain further insight into the reaction mechanism, the KIEs were also assayed via additional competition studies. The competition reaction between substrates **353** and **D-353,** gives a product distribution k_H/k_D 1:1.22 (Paper IV, Scheme 4). If indole **353** is not dissociated from Pd after the first stage of the reaction (formation of enone **374**, Cycle A), then the observed KIE could be ex-

plained by the more rapid rate of enone formation with **D-353**. However, the fact that a significant concentration of free enone **374** can be observed during the reaction suggests that the catalytic cycle for the final product formation (Cycle B) is separate from the first dehydrogenation cycle that produces enone **374** (Cycle A). Therefore the observed KIE could be related to the C–C bond formation step (Cycle B).



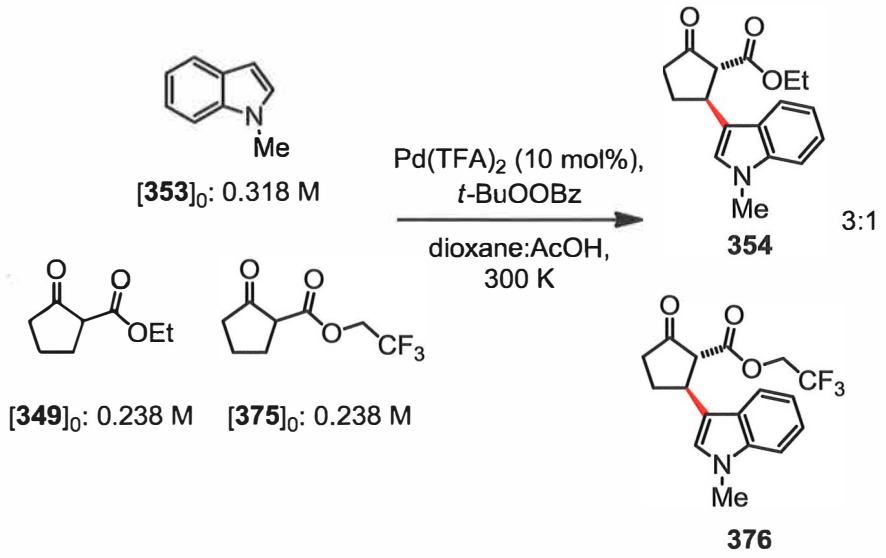
Scheme 87. Intramolecular competition studies with β'-monodeuterated **D$_1$-349**.[IV]

An intramolecular competition experiment, the mono-β'-deuterated **D$_1$-354** was gave rise to product **354** that exhibited a 48.6:51.4 H/D ratio (Scheme 87). The absence of a KIE in this experiment suggests that the β'-H bond cleavage is not turnover-limiting for the dehydrogenation cycle The fact that no 1° KIE is observed even under these conditions can be rationalized by the fact that the different hydrogen isotopes are *not* in an equal environment after the turnover-limiting step (i.e. **TS$_{rearr}$**). The choice between β'-H vs. β'-D abstraction has already been made in the turnover-determining ligand rearrangement step which leads to the formation of *C*-bound enolate **int$_3$** (Scheme 88). The effect of deuterium substitution in the β' position of the ligand on the ligand rearrangement step is expected to be small, resulting in a negligible 1° KIE.[IV]



Scheme 88. Explanation of the product distribution from intramolecular competition study.[IV]

The effect of the electron-withdrawing alkyl ester was studied using β-keto ester **375** bearing a CF_3CH_2O ester group. Under the standard conditions, the reaction between **375** and **353** was significantly slower than the standard reaction between **349** and **353**. (0.52 mM min^{-1} with **375** vs. 1.7 mM min^{-1} with **349**). This rate difference was also confirmed by an intermolecular competition between **349** and **375** (P_{354}/P_{376} = 3) (Paper IV, Figure 2 and Scheme 89). These results indicate that the electron density of the β-keto ester contributes to the reaction rate.



Scheme 89. Intermolecular competition between **375** and **349** in the coupling process.[IV]

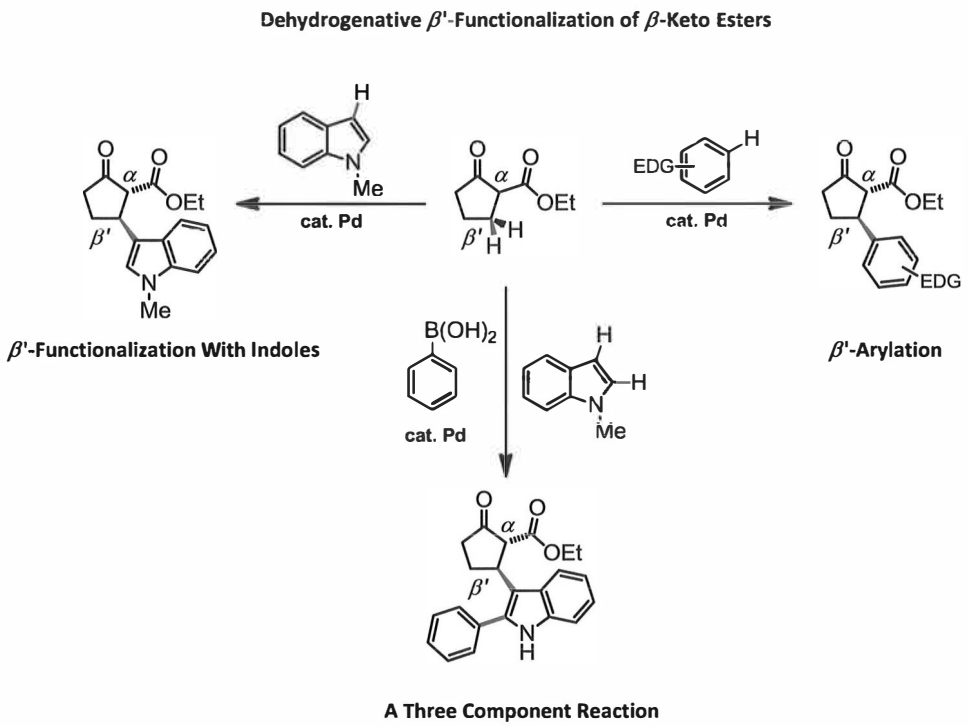
The use of C3 deuterated 1-methylindole in KIE experiments would have given more detailed mechanistic information on C−C bond formation step (Cycle B). Unfortunately, under the reaction conditions, the exchange rate of deuterium to hydrogen at position 3 was much faster than the formation rate of the product **354** (rate of D/H exchange: 5.53 mM min^{-1} vs. rate of formation of **354**: 1.7 mM min^{-1}) (see paper IV, SI).

A more thorough picture of the mechanism is emerging from the computational studies carried out by Imre Pápai and Ádám Madarász. In brief, the computations reinforce the view that indole is an active ligand in the dehydrogenation step and the dehydrogenation step likely proceed via a proton-assisted electron transfer (PCET) process involving proton migration to TFA in concert with an electron transfer to the Pd(II) center.[203,204]

The mechanism for the second step, the formation of the C−C bond, is still elusive. The experimental evidence provides two possibilities for the formation of a C−C bond from enone. Starting from enone **374**, the C−C bond formation proceeds via both acid catalysis as well as via a Pd(II) catalysis. However, the Pd(II)-catalyzed reaction is significantly faster. While several different scenarios for the Pd(II)-catalyzed mechanism could be proposed (see paper IV), at present, an unequivocal mechanism cannot be proposed for the role of Pd(II) in the C−C bond formation stage.

3 SUMMARY AND CONCLUSIONS

The basic aims of the study were successfully realized, and a new oxidative remote sp^3 β'-C−H functionalization platform was created. The platform enables the Pd(II)-catalyzed cross-dehydrogenative coupling between β-ketoester and β-ketolactones and electro-rich aromatics, such as indoles, in a highly chemo- and regioselective manners under mild conditions with a range of β-keto esters and indoles. (Scheme 90). Mechanistic investigations, using online NMR monitoring, revealed that the reaction proceeds in two stages, via an enone intermediate. Surprisingly, the formation of enone was assisted by the second substrate, indole, and the role of indole was confirmed by kinetic isotope effect studies. Furthermore, the proposed mechanism is also supported by DFT calculations. The results of this thesis contribute to the general knowledge of dehydrogenative cross-coupling reactions and especially a palladium-catalyzed dehydrogenative cross-coupling between remote sp^3 β-C−H and sp^2 C−H bonds were achieved by using an external oxidant.



Scheme 90. Novel oxidative sp^3 β'-C−H functionalization reactions.

It should be noted that technology invented in this project was also successfully applied to synthesize real discovery intermediates during my three month researcher visit (23.4.2012-26.7.2012) to the Orion Corporation's Medicinal Chemistry department.

While the α-position of carbonyl compounds can readily be functionalized through palladium-catalyzed chemistry and the technology is widely applied in the industry,[205-208] the corresponding β-C−H functionalization chemistry is still elusive. This is particularly true when it comes to dehydrogenative β-C−H functionalization coupling reactions. The methodology developed in this thesis, will therefore, provide new possibilities for synthesizing new kinds of chemical entities, which have earlier been demanding and burdensome to synthesize. Furthermore, this mechanistic based series of studies highlights that it is possible to

employ indoles as alternative ligands in the dehydrogenation of carbonyl compounds instead of using DMSO as the ligand. Understanding the mechanistic aspects of the dehydrogenative β-coupling reaction might also help to invent new types of dehydrogenative β-coupling reactions.

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ORIGINAL PAPERS

I

THE PALLADIUM-CATALYZED DEHYDROGENATIVE β'-FUNCTIONALIZATION OF β-KETO ESTERS WITH INDOLES AT ROOM TEMPERATURE

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Mikko V. Leskinen, Kai-Tai Yip, Arto Valkonen, and Petri M. Pihko

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II

PALLADIUM-CATALYZED DEHYDROGENATIVE β'-ARYLATION OF β-KETO ESTERS UNDER AEROBIC CONDITIONS: INTERPLAY OF METAL AND BRØNSTED ACIDS

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Kai-Tai Yip, Roshan Y. Nimje, Mikko V. Leskinen, and Petri M. Pihko

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III

A THREE-COMPONENT PALLADIUM-CATALYZED OXIDATIVE C-C COUPLING REACTION: A DOMINO PROCESS IN TWO DIMENSIONS

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Roshan Y. Nimje, Mikko V. Leskinen, and Petri M. Pihko

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IV

CROSS-DEHYDROGENATIVE COUPLINGS BETWEEN INDOLES AND β-KETO ESTERS: SCOPE, MECHANISM, AND EVIDENCE FOR LIGAND-RELATED KINETIC ISOTOPE EFFECTS AND DEHYDROGENATION VIA A PROTON-ASSISTED ELECTRON TRANSFER TO PD(II)

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