Development of Cu-Catalyzed Decarboxylative Heteroarylation and Rh-Catalyzed Carbene Olefination

by

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Abstract

Transition metal-catalyzed cross-coupling reactions are widely used transformations to generate useful chemicals. The development of new variants for transition metal-catalyzed cross-coupling reactions provides more efficient methods for the construction of functionalized molecules. This thesis describes the study of two novel transition metal-catalyzed cross-coupling processes.

Chapter 1 describes the decarboxylative cross-coupling of malonic acid derivatives and heteroarylboronic esters. The use of oxidative Cu catalysis enables the synthesis of monoheteroaryl acetate derivatives containing electrophilic functional groups under mild conditions. This heteroarylation transformation provides a new route for late-stage functionalization for the preparation of drugs. The reaction development and the scope of both malonic acid derivatives and heteroarylboronic esters are detailed.

The discovery of a *Z*-favored Rh-catalyzed olefination between diazo esters and iodonium electrophiles is discussed in Chapter 2. This reaction exhibits complementary stereoselectivity to the established *E*-alkene synthesis via Pd-catalyzed carbene cross-coupling. The preliminary optimization results of the Rh-catalyzed olefination are summarized.

Preface

The substrate scope studies involving heterocyclic aryl boronic esters for the decarboxylative cross-coupling of malonic acid derivatives described in Chapter 1 have been published as a part of the paper "Ambient Decarboxylative Arylation of Malonate Half-Esters via Oxidative Catalysis" Patrick J. Moon, Shengkang Yin, and Rylan J. Lundgren, *J. Am. Chem. Soc.* **2016**, *138*, 13826−13829. Scope studies of heteroarylation and a small amount of substrates synthesis for the arylation are my work in this paper.

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List of Abbreviations and Symbols Used

ºC	degrees Celsius
Ar	generic aryl moiety
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthy
Bn	benzyl
BPin	pinacol boronic ester
Bneop	neopentyl boronic ester
Bu	butyl
COD	1,5-cyclooctadiene
COE	cis-cyclooctene
CFL	compact fluorescent light
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
Cy	cyclohexyl
δ	chemical shift
dba	dibenzylideneacetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DCM	dichloromethane
dioxane	1,4-dioxane
dippf	1,1'-bis(di-*i*-propylphosphino)ferrocene
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ratio
EBX	ethynylbenziodoxolone
ee	enantiomeric excess
eq	equivalents
Et	ethyl
ESI	electrospray ionization (mass spectrometry)

GC	gas chromatography
Hex	hexane
HRMS	high resolusion mass-spectrometry
hν	light
i-Pr	iso-propyl
L	generic ligand
LC-MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
M	mol/L
[M]	generic metal complex
MAHT	malonic acid half thioester
Me	methyl
MeCN	acetonitrile
MTBE	methyl tert-butyl ether
NBD	norbornadiene
n.d.	not determined
NEt_3	triethylamine
NMR	nuclear magnetic ressonance
OAc	acetate
OBoc	tert-butyl carbonate
OTf	triflate
OPiv	pivalate
Ph	phenyl
PTFE	polytetrafluoroethylene
R	generic group
RT	room temperature
SET	single-electron-transfer
TBAF	tetra-n-butylammonium fluoride
TBAI	tetra-n-butylammonium iodide
t-Bu	tert-butyl

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
Ts	4-toluenesulfonyl
UV	ultraviolet
X	generic anion or anionic ligand

Chapter 1 Cu-Catalyzed Decarboxylative Cross-Coupling of Malonic Acid Derivatives and Heteroarylboronic Esters

1.1 Introduction

Synthetic organic chemistry is a powerful tool for chemists to create complex chemicals which contribute to different areas of our daily lives from medicine to agriculture. To meet with the increasing need for preparing complex molecules, chemists are seeking more environmentally friendly and efficient chemical reactions. Transition metal-catalyzed cross-coupling reactions are one of such example of a highly effective and sustainable alternative to traditional methods. The development of Pd-catalyzed cross-coupling reactions enables the selective formation of carbon–carbon bonds under relatively gentle conditions.[1] Due to their tolerance of a wide range of functional groups, palladium catalyzed cross-coupling reactions have achieved great success in the synthesis of pharmaceuticals, biologically active natural products and functional materials.[2-4] Organohalides (or pseudohalide) and organoboron compounds or organometallic reagents are commonly used coupling partners in metal-catalyzed cross-coupling reactions. It is highly desirable to expand the scope of metal-catalyzed cross-coupling reactions to other coupling partners. The development of Cu-catalyzed decarboxylative cross-coupling reactions of malonic acid derivatives and heteroarylboronic esters is discussed in this chapter.

Carboxylic acids and esters are low cost and readily available building blocks for organic synthesis. Esters have been used as temporary activating groups in classical enolate chemistry for a long time. For example, in the alkylation of 1,3-dicarbonyl compounds, the ester group stabilizes the nucleophilic enolate intermediate, thus promoting the alkylation reaction with alkyl electrophiles. To deprotonate α-C–H bonds in simple carbonyl compounds (pK_a 20–25), strong

base like LDA are required to generate to the enolate. While the α-proton in a 1,3-dicarbonyl compounds is acidic enough (pK_a 10–15) to be removed by more mild bases such as alkoxide or carbonate. After the alkylation step, the ester group can be removed as CO_2 by decarboxylation (Figure 1-1).[5] With the help of an ester activating group, the regioselectively problem for alkylation of unsymmetrical ketones can be avoided.

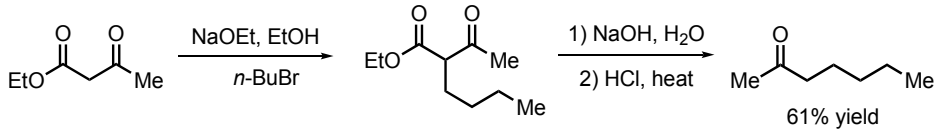


Figure 1-1 Esters as temporary activating group in classical enolate chemistry

Carboxylic acids and carboxylates are used as carbon nucleophile precursors in nature. In the biosynthesis of polyketides and fatty acids, decarboxylative Claisen condensation with malonic acid half thioesters (MAHTs) is the key reaction for carbon chain extension (Figure 1-2).[6, 7] The starter acyl moiety is bound to a cysteine thiol of the enzyme, keto synthase (KS). The malonate unit is attached to a thiol terminus of acyl carrier protein (ACP). Catalyzed by keto synthase, malonic acid half thioester undergoes decarboxylation to generate thioester enolate. The ACP bound thioester enolate attacks the keto synthase bound acyl group to give a tetrahedral intermediate, which then releases the β-ketoacyl product.[8, 9] The resulting β-ketoacyl compound can then undergo various steps. It can be reduced by a keto reductase (KR), dehydrated by a dehydratase (DH) and finally reduced again by an enoyl reductase (ER). The saturated acyl intermediate can be transferred from ACP to the KS and reenter the carbon chain extension cycle. The desired polyketide or fatty acid products are formed after several cycles.

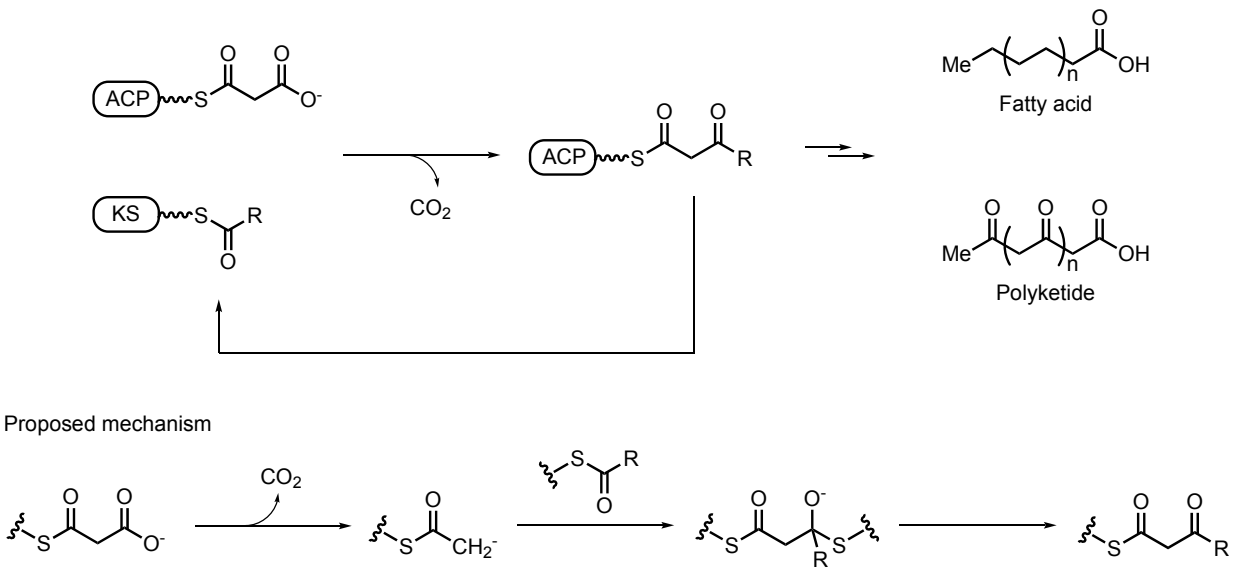


Figure 1-2 Decarboxylative Claisen condensation in biosynthesis of polyketide and fatty acid

ACP: acyl carrier protein; KS: ketosynthase

The biomimetic Claisen condensation reaction under enzyme-free conditions has been known since 1975.[10] In Scott's model reaction for the biosynthesis of polyketides (Figure 1-3 a), intramolecular acetyl transfer occurred when catechol acetate malonate was treated with two equivalents of fresh isopropyl magnesium bromide. Kobuke first reported an intramolecular Claisen condensation reaction mediated by magnesium acetate and imidazole under relatively mild condition (Figure 1-3 b).[11] These early examples show that it is possible to develop new carbon–carbon bond forming reactions by trapping the enolate from malonic acid derivatives without enzymes.

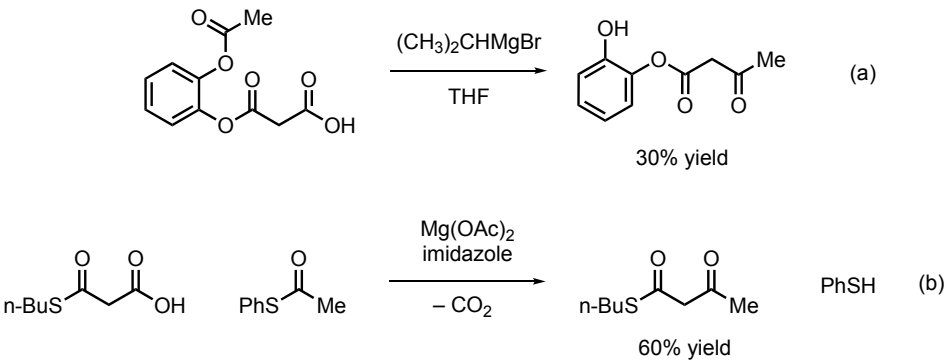


Figure 1-3 Early examples of biomimetic decarboxylative Claisen condensation

The aldol reaction is one of the most important carbon–carbon bond forming reactions in synthetic chemistry. Inspired by the mild and selective activation of malonic acid in nature, Shair and co-workers reported the first biomimetic decarboxylative aldol reaction in 2003.[12] In the presence of Cu(II) catalyst, malonic acid half thioesters react with aldehydes under exceptionally mild conditions, typically in an open vial with wet THF at room temperature (Figure 1-4). Contrary to other catalytic aldol reactions that require pre-enolized nucleophiles,[13] aliphatic enolizable aldehydes were demonstrated to be good substrates in this reaction. The driving force of this reaction is the thermodynamic instability of MAHTs, while the kinetic persistence of MAHTs allows the reaction to be performed under mild conditions.

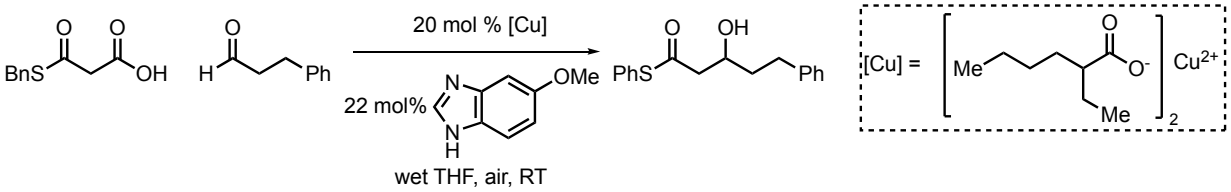


Figure 1-4 Decarboxylative aldol reaction of benzyl MAHTs

Following this initial report, an enantioselective version of the decarboxylative aldol reaction was developed by the same group.[14] In this Cu(II) bis(oxazoline) catalyst system, methyl

malonic acid half thioester undergoes decarboxylative aldol reaction affording *syn S*-phenyl thiopropionates with high enantioselectivity and good diastereomeric ratios (Figure 1-5). Since there is no strong Lewis acids or strongly basic intermediates generated during the reaction, it is compatible with unprotected protic functionality such as hydroxyl groups, phenols, enolizable aldehydes, enolizable methyl ketones, carboxylic acids as well as Lewis acid-sensitive acetals and ketals. In contrast to the mechanism of enzyme-catalyzed decarboxylative Claisen condensations of MAHTs,[8, 15] mechanistic studies show Cu(II)-catalyzed aldol reaction of MAHTs involving decarboxylation after addition to aldehydes.[14]

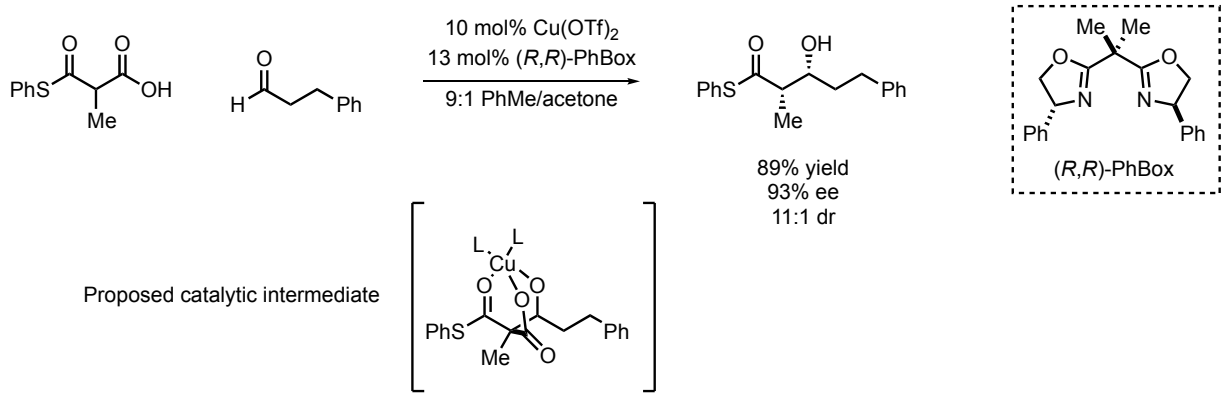


Figure 1-5 Cu-catalyzed enantioselective decarboxylative aldol reaction of MAHTs

Organocatalysts can also be used in decarboxylative aldol reactions. A Cinchona-derived sulfonamide has been successfully used in the asymmetric aldol reaction of methyl-substituted and unsubstituted MAHTs.[16] Fagnou reported that triethylamine can also catalyze decarboxylative aldol reactions with electron-deficient ketones and aldehydes.[17] In both organocatalyst systems, a postnucleophilic addition/predecarboxylation intermediate similar to the proposed intermediate in the Cu-catalyzed pathway was observed.

The scope of decarboxylative aldol reaction can also be expended to unnatural fluorinated malonic acid precursors. Fluorinated malonic acid half thioesters can be exploited as a source of

fluorinated building blocks for incorparation fluorine into a polyketide backbone with engineered polyketide synthase.[18] Stereoselective decarboxylative aldol reactions of fluorinated malonic acid half thioesters were also developed using a urea-based organocatalyst (Figure 1-6). With a chiral Cinchona alkaloid urea catalyst, the reaction proceeds under mild conditions. This method provides a versatile platform for accessing fluorinated analogues of medicinally relevant acetate-derived compounds.[19]

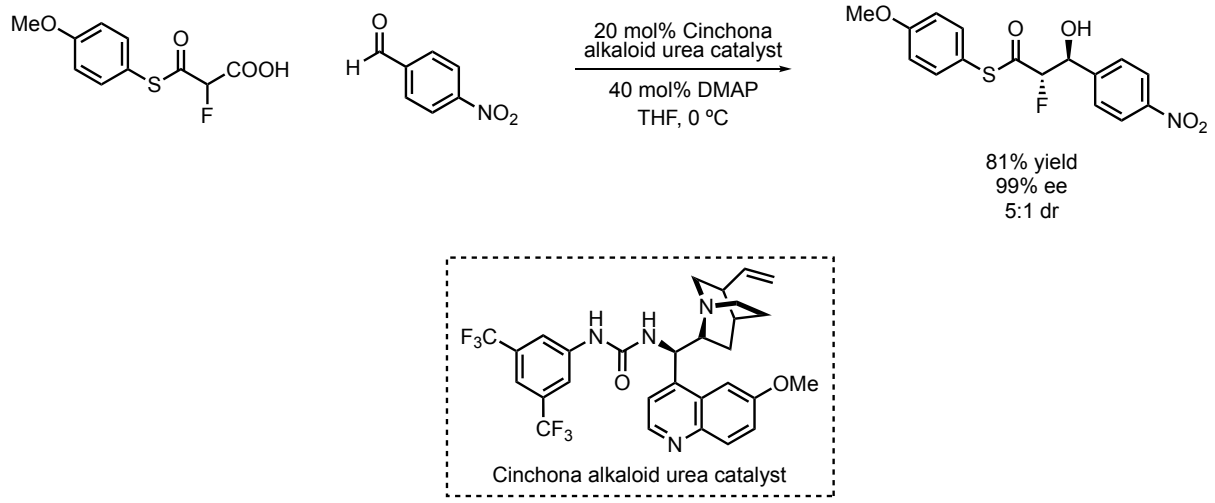


Figure 1-6 Enantioselective decarboxylative aldol reaction of fluorinated MAHTs

The enolate formed from decarboxylative reactions of malonate derivatives and β-keto esters can also be trapped with allyl electrophiles in the presence of a transition metal catalyst. In 1980, the decarboxylative allylation of β-keto allyl esters was reported by the Tsuji[20] and Saegusa groups[21] almost simultaneously (Figure 1-7). Intermolecular coupling of β-keto acids with allyl acetates have been achieved to avoid the use of preformed allyl β-keto esters.[22] Depending on the nature of the α-substitution of the β-ketoesters, the decarboxylative allylation occurs with different mechanisms. Allyl β-ketoesters that contain an α-hydrogen undergo allylation before decarboxylation while fully substituted allyl β-ketoesters undergo the reactions through a

decarboxylation-allylation mechanism.[23] Typical side reactions in these processes are elimination and diallylation. Instead of using selectively preformed enolates, metal enolates can be readily accessed under neutral conditions with loss of CO_2. Reactive intermediates can be generated by site-specific decarboxylation and coupled immediately. The highly enantioselective palladium-catalyzed decarboxylative allylic alkylation of lactams has been developed by the Stoltz group (Figure 1-8).[24] These mild decarboxylative allylation reactions have found utility in the biologically active natural products synthesis.

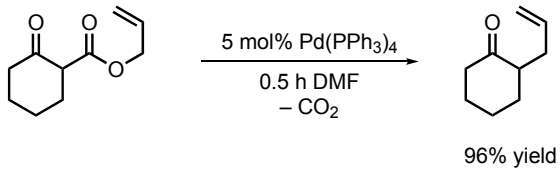


Figure 1-7 Pd-catalyzed decarboxylative allylation

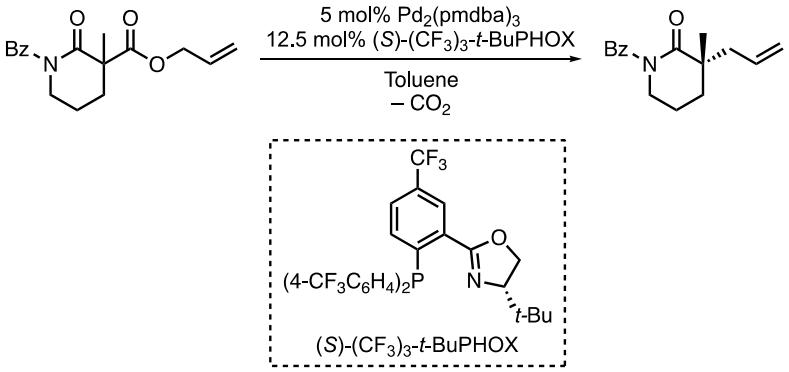


Figure 1-8 Enantioselective Pd-catalyzed decarboxylative allylation of lactams

Unlike the well-developed decarboxylative coupling reactions with acyl and allylic electrophiles, there are limited reports of decarboxylative arylation of malonate derivatives. Pre-deprotonation of the acid and high temperatures (≥ 120 ºC) are necessary for Pd-catalyzed decarboxylative coupling of malonic acid derivatives with aryl halides, presumably for the

generation Pd enolate via thermal decarboxylation (Figure 1-9).[25, 26] With the combination of CuBr and $MgCl_2$, decarboxylative coupling of malonate potassium salts and iodopyridines can be achieved at 100 ºC (Figure 1-10).[27] Formal decarboxylative arylation products can be also formed under two-step Pd-catalyzed arylation/thermal dealkoxycarbonylation or Cu-catalyzed arylation/thermal deacylation conditions.[28 29]

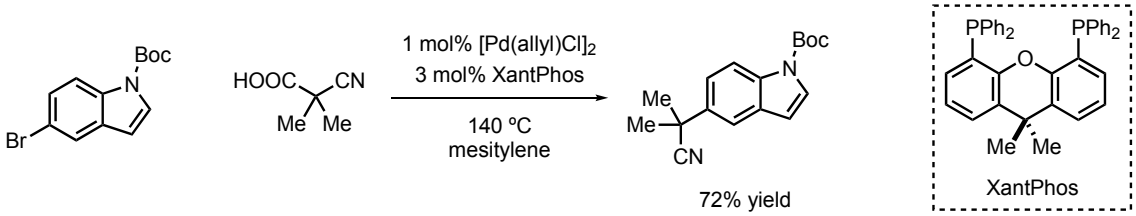


Figure 1-9 Pd-catalyzed decarboxylative arylation of malonate derivatives

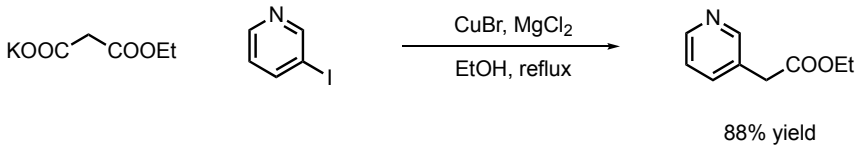


Figure 1-10 CuBr-mediated decarboxylative pyridine acetate synthesis

Instead of generating nucleophilic enolate equivalents, carboxylic acids and their derivatives can also be used as radical precursors for arylation reactions.[30, 31] By merging nickel catalysis with visible-light photoredox catalysis, decarboxylative sp^3-sp^2 coupling between carboxylic acids and aryl halides has been achieved (Figure 1-11).[32, 33] In the proposed mechanism, a carboxyl radical is generated by single-electron-transfer (SET) with the photoredox catalyst. This carboxyl radical could deliver an α-amino radical upon loss of CO_2. The α-amino radical can be intercepted by the nickel catalyst to complete the cross-coupling reaction with the aryl halide

partner. With catalytic activation by photoredox catalyst, simple and readily available carboxylic acids can serve as a useful sp^3 coupling partner in this reaction.

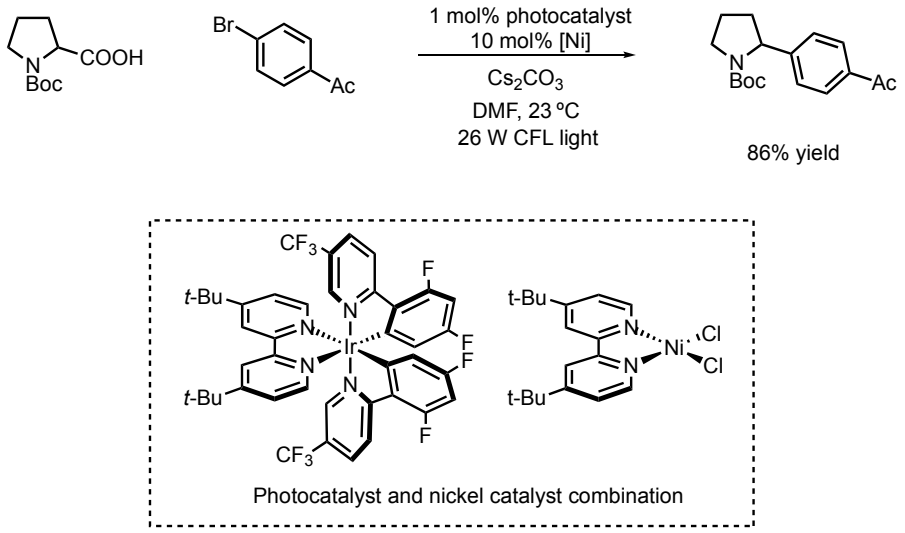


Figure 1-11 Radical arylative decarboxylation via photoredox catalysis

Redox-active esters have been demonstrated as another class of successful substrates for decarboxylative radical arylations (Figure 1-12).[34-37] Baran and co-workers proposed that the redox active ester could be reduced by a Ni(I) intermediate to give the radical anion via single-electron-transfer step. This radical anion would undergo decarboxylation by extrusion of CO_2 and generate desired alkyl radical and the phthalimide anion. The alkyl radical can undergo further reaction in the nickel catalytic cycle and finally affords the cross-coupling product. Redox active ester groups need to be installed before the reaction and become byproducts after the reaction.

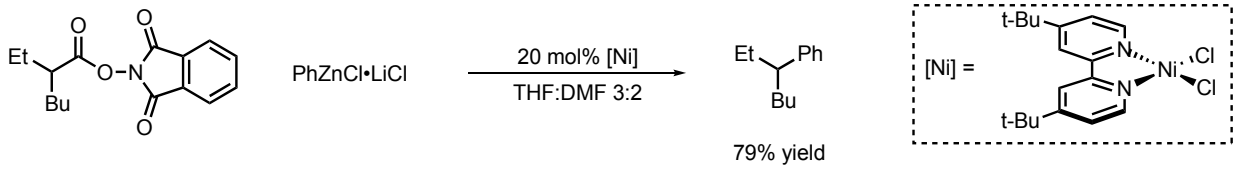


Figure 1-12 Radical arylative decarboxylation via redox-active esters

In 1998, the Chan, Evans and Lam groups independently discovered the copper mediated oxidative cross-coupling of aryl boron and heteroatom nucleophiles (Figure 1-13).[38-40] In contrast to the classic copper-mediated Ullmann–Goldberg reaction which generates aryl amines and ethers with aryl halides typically under elevated temperatures (more than 110 ºC) and with strong bases,[41, 42] the Chan-Lam reaction usually proceeds under very mild condition using weak bases, low cost copper/ligand systems, at room temperature in air. The Chan-Lam reaction also has advantages over the Buchwald-Hartwig coupling reaction, the Pd-catalyzed cross-coupling reaction between heteroatom nucleophiles and aryl halides, because the Buchwald-Hartwig coupling reaction often requires high temperature, strong base and expensive Pd/phosphine ligand catalyst.[43-45] Since the reaction occurs between two nucleophilic coupling partners, Chan-Lam coupling can tolerate electrophilic functional groups which is complementary to the traditional electrophile/nucleophile cross-coupling reactions. Besides alcohol or amine-derived nucleophiles, the substrate scope has been extended to other heteroatom nucleophiles such as thiols, sulfinates, diaryl diselenides, H-phosphonate diesters and halides.[46-52] With these advantages, Chan–Lam coupling has become an important tool in medicinal drug discovery and complex molecule synthsis.[39, 53-55]

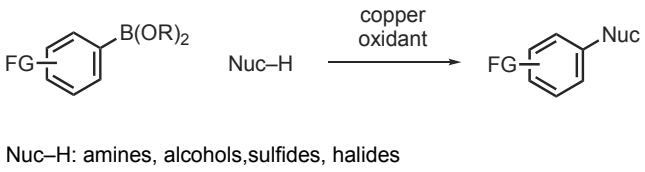


Figure 1-13 Coupling of aryl boronic acids and heteroatom nucleophiles: Chan-Lam reaction.

A mechanistic study of the Chan–Lam coupling for methoxylation of *p*-tolylboronic ester has been reported by Stahl and co-workers (Figure 1-14).[56-59] Based on kinetic, EPR spectroscopic and ^{11}B-NMR studies, the catalyst resting state consists of a Cu(II) species with weak anionic ligands, such as acetate or methoxide. Transmetallation from arylboron to the Cu(II) catalyst is the

turnover-limiting step. The aryl-Cu(II) intermediate generated from transmetallation could undergo disproportionation to form an aryl-Cu(III) complex and a Cu(I) complex. The coupling is produced by C–O reductive elimination of the aryl-Cu(III) intermediate. The Cu(II) catalyst is regenerated from the oxidation of Cu(I) by O_2.

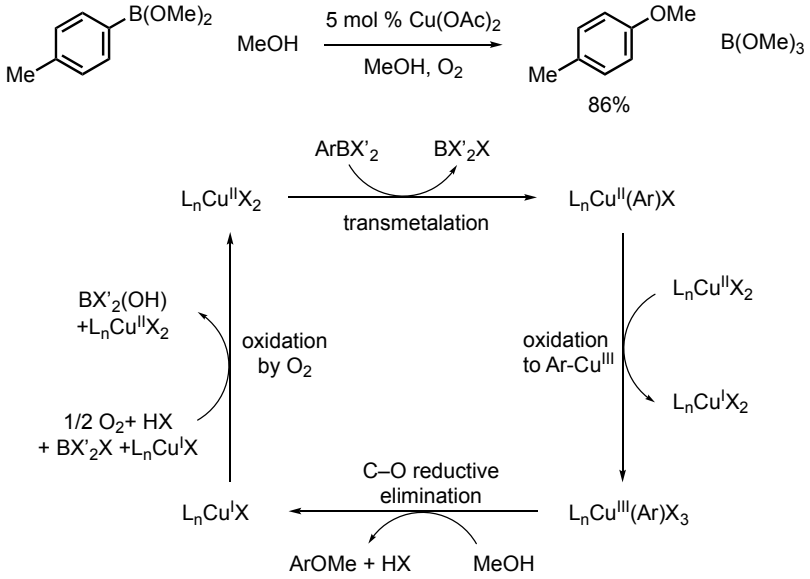


Figure 1-14 Proposed mechanism of Chan-Lam reaction

Despite the success of Chan–Lam coupling for carbon heteroatom bond formation, there are limited examples of copper promoted arylation with carbon-based nucleophiles. Zhu and co-workers reported synthesis of indoles by copper-catalyzed heteroannulation of 2-aminophenylboronic esters and β-keto esters (Figure 1-15).[60] This heteroannulation reaction is proposed to occur through an enamine intermediate from the condensation of an aniline with the β-keto ester. The phenylboronic ester could then transmetalate to copper, followed by oxidation and reductive elimination to deliver the product. The reaction scope is limited to phenylboronic esters with an unprotected *ortho* amine group.

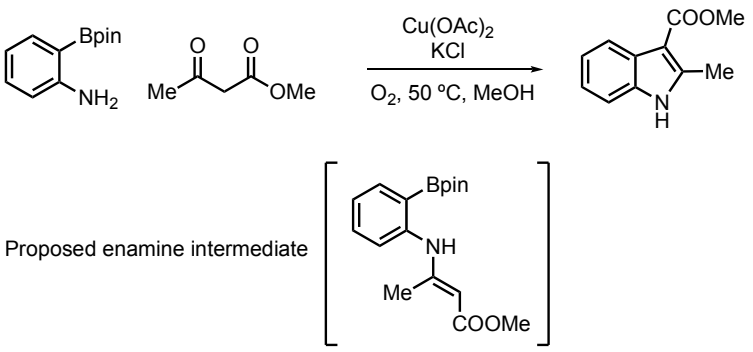


Figure 1-15 Cu-catalyzed heteroannulation of 2-aminophenylboronic esters and β-keto esters

In 2013, MacMillan and Stevens reported Cu/chiral amine catalyzed enantioselective α-alkenylation of aldehydes with boronic acids (Figure 1-16).[61] In their proposed mechanism, the boronic acid substrate undergoes transmetalation with a copper(II) catalyst which then can be oxidized to give an alkenylcopper(III) complex. The enamine generated from the chiral amine catalyst then intercepts the alkenylcopper(III) intermediate to form a chiral enamine−organocopper complex. This chiral enamine−organocopper complex could undergo reductive elimination to deliver the enantioenriched α-alkenyl aldehyde product. This mild reaction uses readily available boronic acids as starting materials and O_2 as the oxidant, which is a greener reaction compared with the group's pervious reported α-alkenylation of aldehydes reaction with vinyl iodonium salts or ceric ammonium nitrate as oxidants.[62, 63]

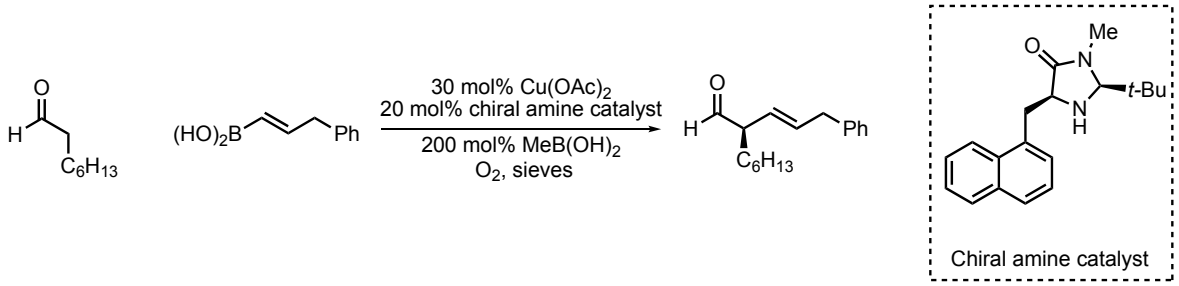


Figure 1-16 Enantioselective α-alkenylation of aldehydes with boronic acids

Arylation of unstabilized acetates can be achieved under harsh conditions. One method involves to use *in situ* enolization under strongly basic conditions, which is incompatible with protic or electrophilic functionalities and limit the control of stereochemistry (Figure 1-17 a).[64, 65] Instead of strongly basic alkali metal enolates, preformed silyl or transition metal enolates can be used as less basic surrogates (Figure 1-17 b).[66, 67] However, these strategies significantly reduce synthetic efficiency and utility in complex molecule synthesis.

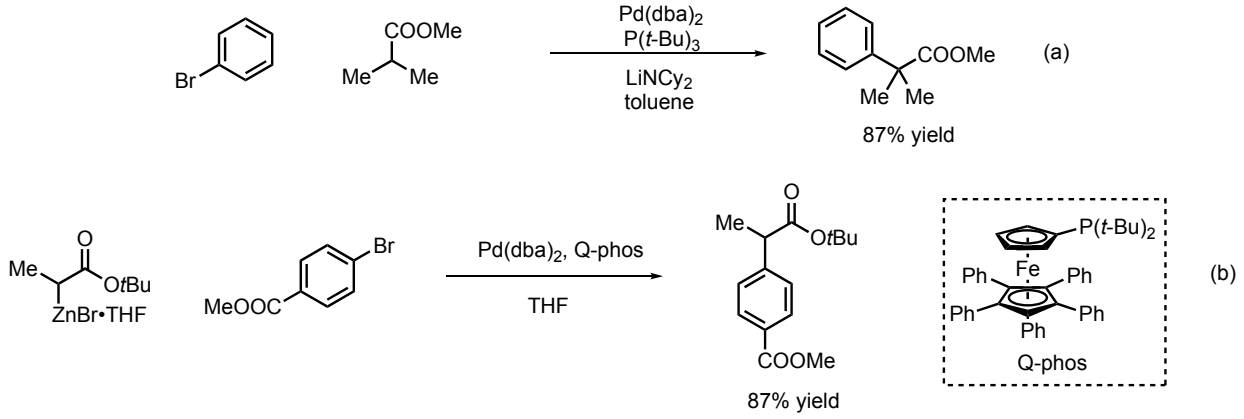


Figure 1-17 Pd-catalyzed arylation of enolates

In 2016, our group reported the oxidative coupling reaction between aryl boron reagents and a variety of stabilized sp^3-carbon nucleophiles (Figure 1-18).[68, 69] In this reaction, the combination of $Cu(OTf)_2$ and CsOAc in a 1:2 ratio provided excellent yields of cross-coupled product with aryl boroxines. Pinacol boronic esters also gave good yields, while aryl boronic acid mainly gave protodeborylation side products. This oxidative arylation reaction is chemoselective in the presence of aryl halides. Aryl boron reagents with electron-withdrawing substituents, bulky *ortho* substituents and potentially reactive ester, ketone and silyl functionality were tolerated. For electron-rich aryl boroxines, such as 4-OMe aryl boroxine and 4-NMe_2 aryl boroxine, low yields were observed. Heteroaryl boron nucleophiles such as pyridyl boroxines and dibenzofuran

boroxines also gave moderate to good yields. For the sp^3-carbon nucleophiles, amides, sulfonyls and phosphonyls can be used as reaction partners. Quaternary carbon centers can also be generated using this reaction.

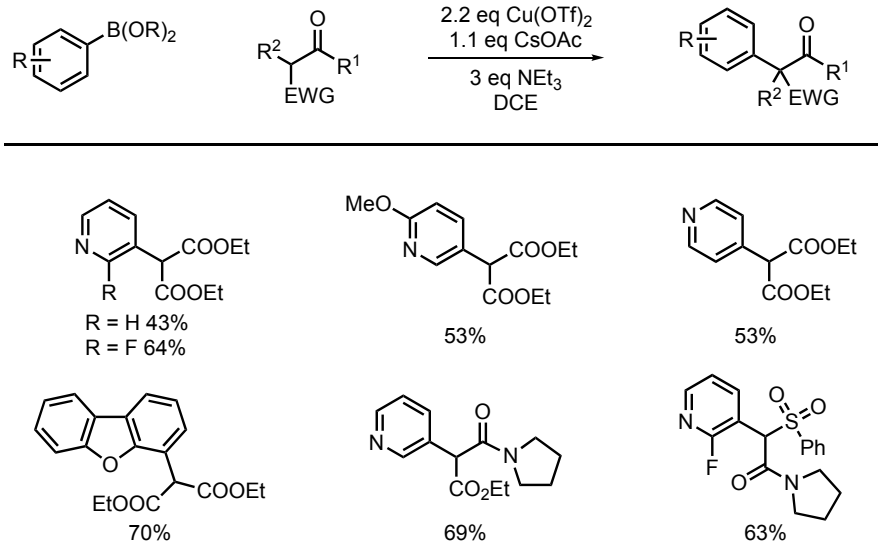
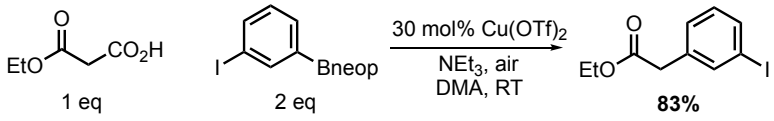


Figure 1-18 Oxidative coupling of aryl boron reagents with enolates (selected heteroarylation scope examples)

1.2 Optimization of decarboxylative arylation with pyridine additive

The α-aryl carbonyl unit is commonly encountered scaffold in pharmaceuticals. As a result, new methods for synthesizing functionalized aryl acetates are highly desirable. By the combination of two strategies, the decarboxylative functionalization of malonate derivatives and the copper mediated oxidative coupling of aryl boron nucleophiles, a solution for the synthesis of α-aryl carbonyl compounds could be achieved. Patrick Moon in our group found that malonate half esters could undergo decarboxylative coupling with aryl boron nucleophiles using a catalytic amount of $Cu(OTf)_2$ under air.



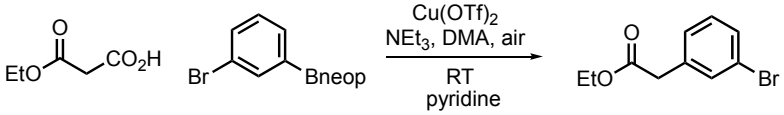
Entry	Deviation from standard conditions	Conv. (%)	Yield (%)
1	$(ArBO)_3$	98	68
2	$ArB(OH)_2$	59	19
3	ArBpin	99	40
4	$Cu(OAc)_2$	74	14
5	CuI	99	70
6	O_2 instead of air	99	31
7	no Et_3N	0	0
8	1.2 eq Ar-Bneop	99	74

Table 1-1 Overview of decarboxylative arylation optimization

The key reaction parameters of this decarboxylative coupling between malonate half esters and aryl boron reagents are summarized in Table 1-1. Neopentylglycol boronic esters were superior to pinacol esters, boroxines, or free boronic acids in this reaction. CuI could be used as catalyst in this reaction while $Cu(OAc)_2$ is not productive. Pure oxygen led to significantly reduced yields. Triethylamine is necessary for the product formation. With a slight excess amount of aryl boron reagent (1.2 eq), the reaction still generated the product in good yield (74%).

The application of this decarboxylative arylation reaction to achieve α-carbonyl heteroaromatic compound synthesis could provide valuable heteroaromatic acetates. Instead of optimizing the reaction with a specific heteroaryl boron reagent, a 1:1 pyridine and aryl boron nucleophile mixture was used in the reaction as a simplified model for heteroarylation optimization.

It is clear that the pyridine additive had a deleterious effect on the standard decarboxylative arylation (Table 1-2 Entry 1 vs Entry 2). A significant yield increase was observed with 50 mol% $Cu(OTf)_2$ loading, compared with 30 mol% $Cu(OTf)_2$. There was no yield improvement when the amount of boron nucleophile was increased to two equivalents.

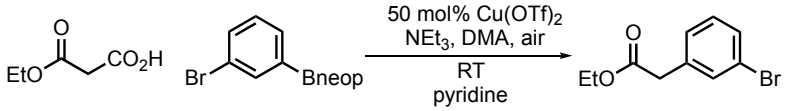


Entry	Conditions	Yield (%)
1	30 mol% [Cu], 2.0 eq ArBneop, no pyridine	89
2	30 mol% [Cu], 2.0 eq ArBneop, 2.0 eq pyridine	36
3	30 mol% [Cu], 1.5 eq ArBneop, 1.5 eq pyridine	55
4	50 mol% [Cu], 1.5 eq ArBneop, 1.5 eq pyridine	71
5	50 mol% [Cu], 2.0 eq ArBneop, 2.0 eq pyridine	72

0.2 mmol, 0.2 M, 46 h.
Yields determined by calibrated ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.

Table 1-2 Optimization of stoichiometry on the decarboxylative arylation with pyridine additive

In contrast to the standard arylation in Table 1-1, the arylation with the pyridine additive were found to be time sensitive (Table 1-3). The product decomposed overtime under arylation condition with the pyridine additive. This observation suggested that the heteroarylation must be stopped at an appropriate time in order to get highest yield. With more pyridine additive, the product formation is much slower and the product decomposition is much faster.



Entry	Conditions	Reaction time	Yield (%)
1	1.5 eq ArBneop, 1.5 eq pyridine	21h	84
2		46h	72
3		120h	60
4	2.0 eq ArBneop, 2.0 eq pyridine	21h	65
5		46h	71
6		120h	44

0.2 mmol, 0.2 M, 46 h.
Yields determined by calibrated ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.

Table 1-3 Effect of time on the decarboxylative arylation with high pyridine loading

Based on these results, we decided to use 50 mol% $Cu(OTf)_2$ catalyst and 1.5 equivalents of heteroaryl boron nucleophile as the standard condition for the decarboxylative heteroarylation scope study.

1.3 Reaction scope for decarboxylative heteroarylation

The reaction scope for decarboxylative heteroarylation is summarized in Figure 1-19. Under optimized reaction conditions, heteroaryl boronic esters such as substituted pyridines (**1.11**-**1.15**), quinolones (**1.16**) and pyrimidines (**1.17**, **1.18**, **1.19**), underwent oxidative coupling reaction with malonic monoesters smoothly. Both electron withdrawing groups including halogens and electron donating groups were tolerated. Malonate half amides including aryl−alkyl amides (**1.21**) could also be employed. Of note, Weinreb amide, a ketone surrogate, also gave the desired product in good yield with heteroaryl boronic reagents (**1.22**, **1.23**).

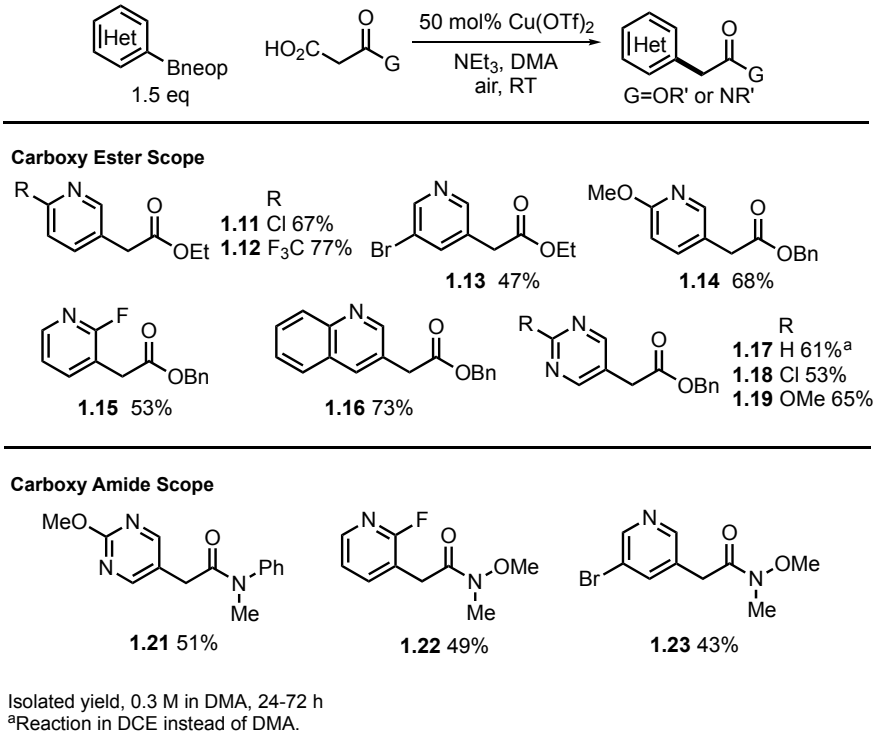
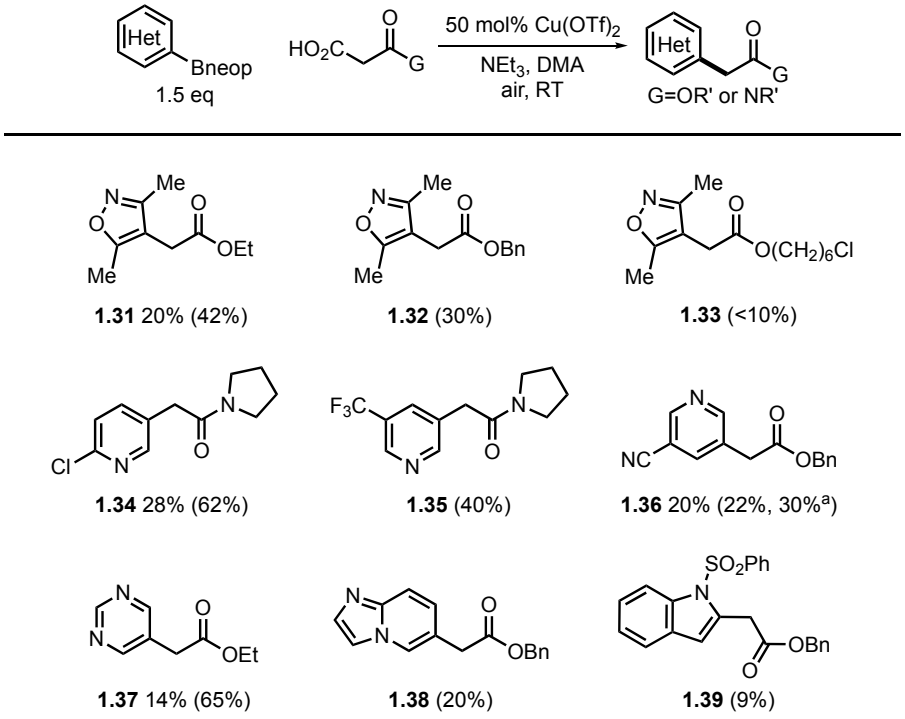


Figure 1-19 Reaction scope for decarboxylative heteroarylation

Other decarboxylative heteroarylation reactions with reduced amounts of product formation are listed in Figure 1-22. 3,5-Dimethylisoxazole boronic ester (**1.31**) can be coupled with mono-ethyl malonate in 42% yield. The purification of this product is difficult and loss of yield under reduced pressure was observed. Lower yields (30%) were also observed when mono-benzyl malonate was used (**1.32**). Increasing the loading of $Cu(OTf)_2$ to one equivalent in the benzyl acetate formation reaction did not improve the yield. Only trace amounts of isoxazole product (**1.33**) (<10%) with long alkyl chain in ester group was formed. The major side reaction is protodeborylation with all three half ester malonate substrates (>65%) studied.



Isolated yield.
Yields in parentheses determined by calibrated ^{1}H-NMR spectro with 1,3,5-trimethoxybenzene internal standard.
[a]Bpin (boronic acid pinacol ester) was used.

Figure 1-20 Decarboxylative heteroarylation with low isolated yields

A chloro-substituted pyridinyl boronic ester (**1.34**) underwent oxidative coupling reaction with dialkyl amides in a good yield. This product is water soluble and is difficult to isolate the pure product. While using a trifluoromethyl-substituted pyridinyl boronic ester coupling with dialkyl amides (**1.35**), rapid product decomposition was observed after 26 h.

In the reaction of a cyano-substituted pyridine substrate (**1.36**), the pinacol boronic ester (Bpin) worked better than the standard neopentylglycol boronic ester (Bneop). This is consistent with the general trend observed in our group that pinacol boronic esters attached to electron deficient aromatic rings could give better yields than neopentylglycol boronic esters due to a reduction in protodeborylation.

A pyrimidine substrate (**1.37**) can be coupled with mono-ethyl malonate in 65% yield. This pyrimidine acetate product is soluble in water. The same as the compound **1.34**, loss of yield was observed during the purification. Good isolated yield was achieved for the synthesis of similar compound **1.17** with 1,2-dichloroethane as solvent. Thus, using 1,2-dichloroethane as solvent could be the solution for the synthesis of these water-soluble products.

1.4 Summary

A new oxidative coupling method for the construction of α-heteroaryl carbonyl units was developed. With a simple copper catalyst and stable arylboronic esters, the decarboxylative α-heteroarylation of malonic half-esters and amides proceeds at room temperature in air under mildly basic conditions. In contrast with existing enolate (hetero)arylation, this reaction is compatible with electrophilic functional groups such as heteroaryl halides, which could be used for further functionalization. The late-stage modification of Nicergoline, a drug molecule used to treat senile dementia, has been demonstrated. The ethyl acetate derivative of Nicergoline was synthesized in

good yield (Figure 1-23).[70] This biomimetic decarboxylative heteroarylation method provides a new route to modify heteroaryl cores of drug molecules.

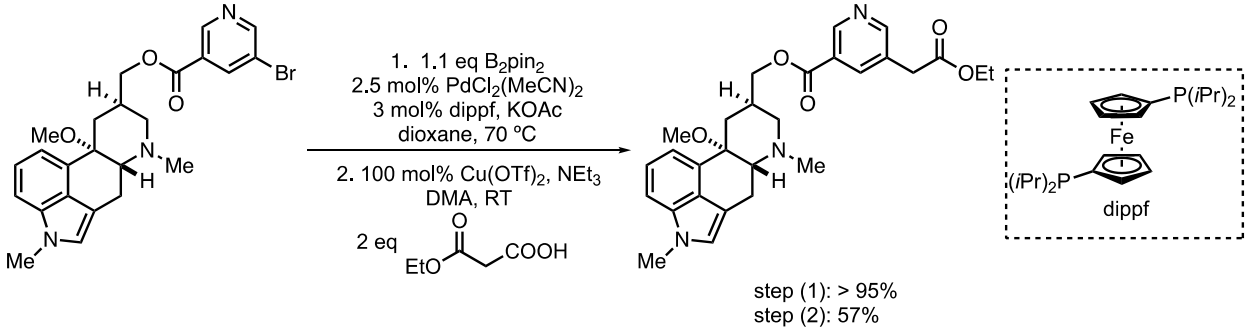


Figure 1-21 Applications of Cu-catalyzed decarboxylative malonate heteroarylation in the late-stage modification of Nicergoline

1.5 Procedures and Characterization

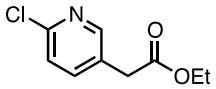
All glassware and vials were oven-dried prior to use. Flash chromatography was performed on silica gel with the indicated eluents (SiliaFlash P60, 40-63μm, 60A silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL or Ultra SNAP silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC - Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied. Boronic esters leading to **1.11-1.19**, **1.21-1.23**, **1.31-1.39** were synthesized according to a literature procedure from the corresponding boronic acid.[71] Benzyl malonate half-ester was synthesized according to the literature procedure from malonic acid.[72] 3-Oxo-3-(methoxy(methyl)amino)propanoic acid leading to **1.22** and **1.23** was synthesized according to a literature procedure from Meldrum's acid.[73] Other malonyl mono-amide and malonate half-ester substrates were synthesized according to a literature procedure.[70]

1.5.1 General procedure for decarboxlative heteroarylation reaction

In a N_2-filled glovebox, $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.50 eq) and arylboronic ester (0.750 mmol, 1.5 eq) were added sequentially to a 1 dram vial charged with a stirbar. The carboxylic acid (0.500 mmol, 1.00 eq) was added as a solution in anhydrous DMA (0.6 mL). Additional DMA (2 x 0.3 mL) was used to quantitatively transfer the solution to the reaction mixture. The mixture was stirred until a pale blue solution was formed (approximately 2 minutes, partially heterogeneous mixtures obtained when using increased Cu loadings), followed by the addition of triethylamine (0.42 mL, 3.0 mmol, 6.0 eq). The vial was sealed with a PTFE-lined cap, removed from the glovebox, exposed to air via a 20-gauge needle, and gently stirred at room

temperature. Upon completion of the reaction (24 to 72 h), the reaction mixture was diluted with EtOAc (40 mL), and washed sequentially with 1 M NH_4Cl solution (15 mL), 0.5 M NaOH (2 x 20 mL) and brine (15 mL). The organic layer was dried with Na_2SO_4, concentrated *in vacuo,* and purified by silica gel chromatography. No difference was observed if reactions were prepared in an atmosphere-controlled glovebox, then exposed to ambient air or if the entire reaction was set up in air.

1.5.2 Product Characterization

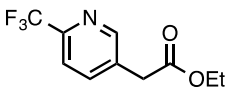


1.11 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (169.1 mg, 0.750 mmol, 1.50 eq) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 70 h. Isolated in 67% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.29 (s, 1H), 7.62 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H) 4.17 (q, *J* = 7.0 Hz, 2H), 3.60 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.4, 150.5, 150.2, 139.8, 128.9, 124.2, 61.5, 37.8, 14.3;

HRMS (LCMS ESI): calcd for $C_9H_{11}ClNO_2$ $[M+H]^+$: 200.0473. Found 200.0469.



1.12 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (194.3 mg, 0.750 mmol, 1.50 eq) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 eq) using

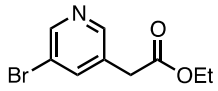
$Cu(OTf)_2$ (90.4 mg, 0.25 mmol, 0.500 eq), 44 h. Isolated in 77% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.64 (s, 1H), 7.83 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.71(s, 2H), 1.27 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 150.7, 147.2 (q, *J* = 34.8 Hz), 138.3, 133.3, 121.7 (q, *J* = 274.5 Hz) 120.4, 61.7, 38.4, 14.3;

^{19}F NMR ($CDCl_3$, 377 MHz) δ -68.0;

HRMS (LCMS ESI): calcd for $C_{10}H_{11}F_3NO_2$ $[M+H]^+$: 234.0736. Found 234.0737.

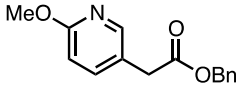


1.13 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (202.4 mg, 0.750 mmol, 1.50 eq) and mono-ethyl malonate (66.1 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 70 h. Isolated in 47% yield after purification by column chromatography (2:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.60 (br s, 1H), 8.44 (br s, 1H), 7.81 (t, *J* = 2.1 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.60 (s, 2H), 1.27 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.2, 149.8, 148.6, 139.6, 131.6, 120.8, 61.6, 38.1, 14.3;

HRMS (LCMS ESI): calcd for $C_9H_{11}BrNO_2$ $[M+H]^+$: 243.9968. Found 243.9965.



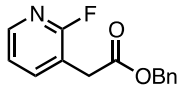
1.14 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (165.8 mg, 0.750 mmol, 1.50 eq) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 eq) using

$Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 46h. Isolated in 68% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.05 (d, *J* = 2.1 Hz, 1H), 7.52 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.29 –7.38 (m, 5H), 6.72 (d, *J* = 9.1 Hz, 1H), 5.14 (s, 2H), 3.92 (s, 3H), 3.59 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.2, 163.6, 147.1, 139.8, 135.8, 128.7, 128.5, 128.4, 122.4, 110.9, 67.0, 53.6, 37.7;

HRMS (LCMS ESI): calcd for $C_{15}H_{16}NO_3$ $[M+H]^+$: 258.1125. Found 258.1127.



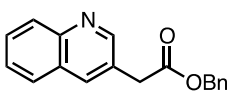
1.15 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (156.8 mg, 0.750 mmol, 1.50 eq) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 53 h. Isolated in 53% yield after purification by column chromatography (4:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.15 (d, *J* = 4.9 Hz, 1H), 7.71 (m, 1H), 7.31 – 7.38 (m, 5H), 7.16 (m, 1H), 5.17 (s, 2H), 3.72 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.8, 162.0 (d, *J* = 238.8 Hz), 146.8 (d, *J* = 14.8 Hz), 142.0 (d, *J* = 4.8 Hz), 135.5, 128.7, 128.5, 128.4, 121.6 (d, *J* = 4.4 Hz), 116.6 (d, *J* = 31.1 Hz), 67.2, 34.3(d, *J* = 1.9 Hz);

^{19}F NMR ($CDCl_3$, 376 MHz) δ -71.6;

HRMS (LCMS ESI): calcd for $C_{14}H_{13}FNO_2$ $[M+H]^+$: 246.0925. Found 246.0921.

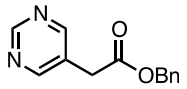


1.16 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (180.8 mg, 0.750 mmol, 1.50 eq) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 51 h. Isolated in 73% yield after purification by column chromatography (Hexane/EtOAc gradient with 6% NEt_3) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.85 (d, *J* = 2.1 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.07 (br s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.70 (m, 1H) 7.55 (m, 1H), 7.30 – 7.37 (m, 5H), 5.17 (s, 2H), 3.86 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.7, 151.8, 147.5, 136.0, 135.6, 129.5, 129.4, 128.8, 128.6, 128.5, 128.0, 127.7, 127.0, 126.9, 67.2, 38.8;

HRMS (LCMS ESI): calcd for $C_{18}H_{16}NO_2$ $[M+H]^+$: 278.1176. Found 278.1171.

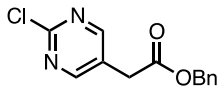


1.17 Prepared according to the General Procedure, with the modification of using 1,2-DCE as the solvent, from the corresponding neopentyl boronic ester (144.0 mg, 0.750 mmol, 1.50 eq) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 31h. The solvent was removed *in vacuo*. The crude residue was purified by silica gel chromatography (25:1 DCM/MeOH). Isolated in 61% yield as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 9.14 (s, 1H), 8.680 (s, 2H), 7.38 – 7.32 (m, 5H), 5.16 (s, 2H), 3.67 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.0, 157.8, 157.5, 135.3, 128.8, 128.7, 128.5, 127.9, 67.5, 36.0;

HRMS (LCMS ESI): calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$: 229.0972. Found 229.0972.

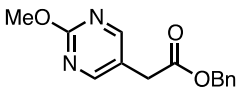


1.18 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (169.9 mg, 0.750 mmol, 1.50 eq) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 48 h. Isolated in 53% yield after purification by column chromatography (10:1 CH_2Cl_2/Et_2O) as a pale yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.57 (s, 2H), 7.32 – 7.39 (m, 5H), 5.17 (s, 2H), 3.67 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.3, 160.6, 160.2, 135.1, 128.9, 128.9, 128.6, 126.4, 67.7, 35.2;

HRMS (LCMS ESI): calcd for $C_{13}H_{12}ClN_2O_2$ $[M+H]^+$: 263.0582. Found 263.0578.

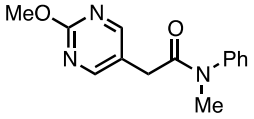


1.19 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (166.5 mg, 0.750 mmol, 1.50 eq) and mono-benzyl malonate (97.1 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 48 h. Isolated in 65% yield after purification by column chromatography (1:1 Hexane/EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.44 (s, 2H), 7.32 – 7.37 (m, 5H), 5.15 (s, 2H), 4.00 (s, 3H), 3.59 (s, 2H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.3, 165.1, 159.8, 135.4, 128.8, 128.7, 128.5, 120.8, 67.4, 55.1, 35.1;

HRMS (LCMS ESI): calcd for $C_{14}H_{15}N_2O_3$ $[M+H]^+$: 259.1077. Found 259.1080.

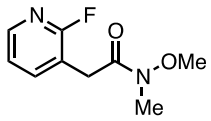


1.21 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (166.5 mg, 0.750 mmol, 1.50 eq) and 3-(methyl(phenyl)amino)-3-oxopropanoic acid (96.6 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.150 mmol, 0.500 eq), 43 h. Isolated in 49% yield after purification by column chromatography (1:4 Hexane/EtOAc) as a white solid.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.23 (s, 2H), 7.46 – 7.48 (m, 2H), 7.40 – 7.42 (m, 1H), 7.18 (d, *J* = 7.7 Hz, 2H), 3.97 (s, 3H), 3.33 (s, 2H), 3.28 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.7, 164.8, 159.7, 143.6, 130.3, 128.6, 127.6, 122.2, 55.0, 37.8, 34.8;

HRMS (LCMS ESI): calcd for $C_{14}H_{16}N_3O_2$ $[M+H]^+$: 258.1237. Found 258.1237.



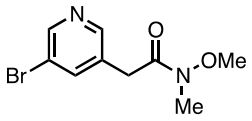
1.22 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (159.8 mg, 0.750 mmol, 1.50 eq) and 3-(methoxy(methyl)amino)-3-oxopropanoic acid (73.6 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 48 h. Isolated in 51% yield after purification by column chromatography (Hexane/EtOAc gradient with 1% NEt_3) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.12 (d, *J* = 3.5 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.15 – 7.17 (m, 1H), 3.80 (s, 2H), 3.73 (s, 3H), 3.22 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.3, 161.2 (d, *J* = 237.7 Hz), 146.3 (d, *J* = 15.0 Hz), 142.3 (d, *J* = 5.1 Hz), 121.6 (d, *J* = 3.7 Hz), 117.4 (d, *J* = 31.0 Hz), 61.4, 32.3, 31.8;

^{19}F NMR ($CDCl_3$, 376 MHz) δ -72.5;

HRMS (LCMS ESI): calcd for $C_9H_{12}FN_2O_2$ $[M+H]^+$: 199.0877. Found 199.0879.



1.23 Prepared according to the General Procedure from the corresponding neopentyl boronic ester (202.4 mg, 0.750 mmol, 1.50 eq) and 3-(methoxy(methyl)amino)-3-oxopropanoic acid (73.6 mg, 0.500 mmol, 1.00 eq) using $Cu(OTf)_2$ (90.4 mg, 0.250 mmol, 0.500 eq), 44h. Isolated in 43% yield after purification by column chromatography (Hexane/EtOAc gradient with 1% NEt_3) as a colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.57 (d, *J* = 2.1 Hz, 1H), 8.42 (s, 1H), 7.82 (m, 1H), 3.75 (s, 2H) 3.70 (s, 3H), 3.21 (s, 3H);

^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.7, 149.6, 148.8, 139.8, 132.4, 120.7, 61.6, 35.9, 32.5;

HRMS (LCMS ESI): calcd for $C_9H_{12}BrN_2O_2$ $[M+H]^+$: 259.0077. Found 259.0079.

Chapter 2. Rh-Catalyzed Olefination of Diazo Esters and Iodonium Electrophiles

2.1 Introduction

Carbenes and related metal-carbenoids are versatile synthetic intermediates in organic chemistry. The carbon atom of a free carbene has only six valence electrons. In order to complete the valence shell of eight electrons, carbenes can insert into σ-bonds or π-bonds or form metal carbon bonds. Free carbenes are highly reactive and usually undergo non-selective insertion reactions. In the pioneering studies of carbene reactivity, Doering and Dvoretzky reported that methylene ($:CH_2$) generated by solution photolysis of diazomethane is an indiscriminate reagent for alkane C–H insertion reactions and gave a statistical isomer mixture of insertion products (Figure 2-1).[74, 75] This non-selective insertion reaction arises from the singlet carbene intermediate. Since this initial work, extensive efforts have been made to develop synthetically useful transformations via carbene intermediates.

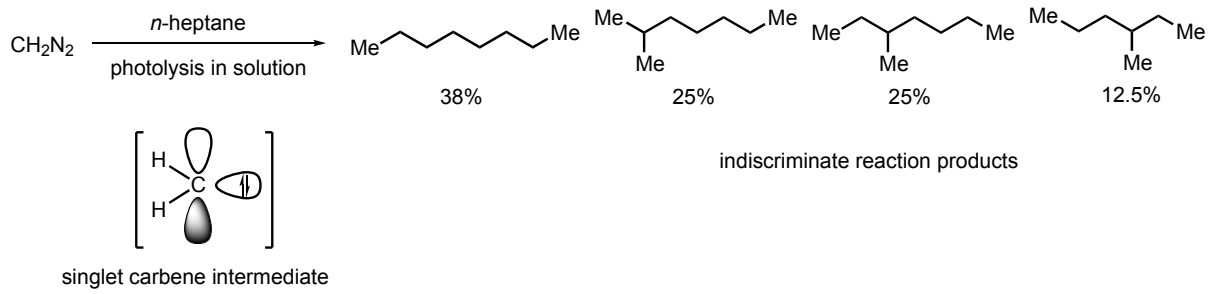


Figure 2-1 Indiscriminate methylene insertion into C–H bonds of *n*-heptane

The reactivity and selectivity profile of carbenes can be modulated by altering the substituents about the carbene center or binding the carbene to a transition metal. Two extremes of metal carbene complexes are known as Fischer carbenes and Schrock carbenes (Figure 2-2).[76] Fischer carbenes are electrophilic at the carbene carbon. They contain a π-donor substituent on the

carbene carbon, which competes for the π-bonding to the carbene carbon. Schrock carbenes are nucleophilic at the carbene carbon, which can be explained by the stronger π-electron back donation from the metal center.[77]

Figure 2-2 Two extremes of metal carbene complexes: Fischer carbene and Schrock carbene

A common method to generate metal-carbene intermediates is the transition metal catalyzed extrusion of dinitrogen from diazo compounds. Dirhodium complexes are the most utilized catalysts for selective transformations in carbene chemistry. Dirhodium(II) tetraacetate, $Rh_2(OAc)_4$, was first used as an efficient catalyst for diazo decomposition by the Teyssie group, initially for O–H insertion reactions.[78] Subsequent studies demonstrated broad applicability for dirhodium catalysts in carbene chemistry. Chiral dirhodium catalysts were developed by replacing the acetate ligand of dirhodium(II) tetraacetate with chiral carboxylates or related analogues such as carboxamidates. Rh-catalyzed carbene transformations provide efficient tools for the construction of C−C bonds and C−X (X = heteroatom) bonds, including X−H insertion reactions[79-82] (X = C, N, O, S, Si, B), cyclopropanation,[83] and ylide formation reactions[84] (Figure 2-3).

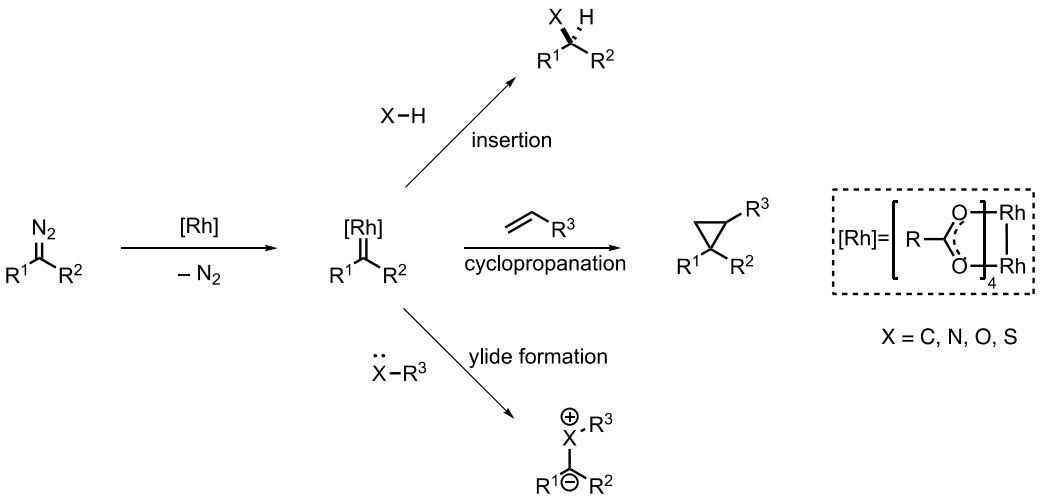


Figure 2-3 Typical Rh-catalyzed reactions via carbene intermediates

The generally accepted mechanism of metal carbene formation from diazo compounds was originally proposed by Yates in 1952 (Figure 2-4).[85] The nucleophilic carbon of the diazo compound first binds to the axial site of the Rh(II) catalyst. The resulting diazonium ion intermediate releases dinitrogen to form a Rh(II) carbene complex. This diazonium ion intermediate has been characterized with optical and NMR spectroscopy.[86] The extrusion of N_2 is the rate-limiting step, which is support by kinetic studies[87] and ^{15}N kinetic isotope effect (KIE).[88]

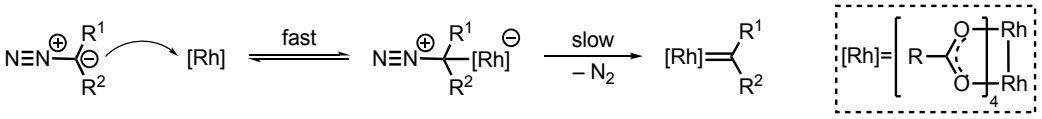


Figure 2-4 Mechanism for Rh-carbene formation

Highly selective C–H functionalization via rhodium-carbene transformations have been achieved through catalyst design and the choice of suitably substituted carbenes. The key challenge in C–H functionalization is how to precisely target the desired C–H bond in unactivated substrates. Davies and co-workers have demonstrated that rhodium carbenes containing both an electron

donor and an acceptor group are ideal reagents for selective C–H functionalization of hydrocarbons.[89-91] The chiral dirhodium catalyst systems developed by the Davies group can distinguish the slight differences between various C–H bonds of pentane (Figure 2-5).[92] These reactions proceed in high yield with good diastereoselectivity and enantioselectivity. Functional groups such as halides, silanes and esters are compatible in this reaction.

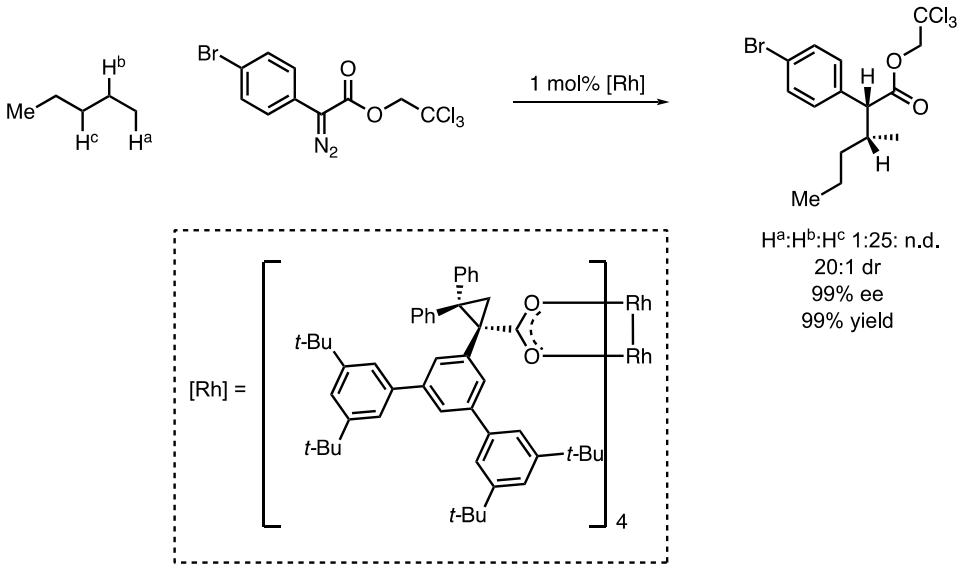


Figure 2-5 Selective carbene insertion of C–H bond catalyzed by dirhodium compounds

Carbenes with β-hydrogen atoms can undergo β-hydride migration to give alkene products. *Z*-alkene products are formed in the rhodium catalyzed decomposition of α-alkyl substituted α-diazo compounds.[93] A general method for the preparation of (*Z*)-α,β-unsaturated carbonyl compounds through β-hydride migration from a carbene was developed by Taber and co-workers.[94] Based on the favored perpendicular orientation of hydrogen for 1,2-hydrogen shift of free carbene,[95, 96] Ikota proposed a model for rationalizing the stereoselectivity of the alkene formation (Figure 2-6).[93] The stereoselectivity of alkene formation is influenced by the bystander

group on the carbene. In the presence of a β-methoxy group, *E*-methoxy enone product was obtained as the major isomer (Figure 2-7).[97]

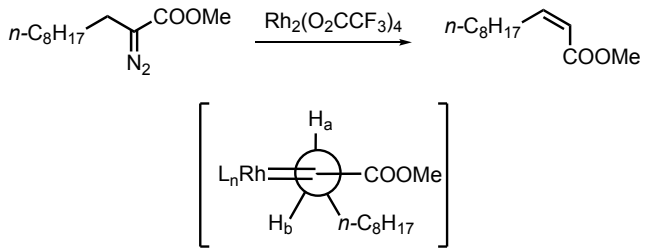


Figure 2-6 Rh-catalyzed *Z*-alkene formation via β-hydride migration

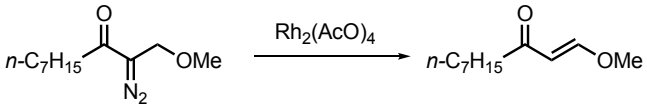


Figure 2-7 Rh-catalyzed *E*-methoxy enone formation via β-hydride migration

Intermolecular insertion reactions with alkyl-substituted carbenes are typically precluded due to the propensity for β-hydride migration under Rh-catalyzed conditions. Fox and co-workers found that bulky carboxylate ligands and low reaction temperatures could promote the intermolecular reaction of α-alkyl substituted diazoesters.[98] Cyclic diazocarbonyl compounds are more efficient carbene precursors than acyclic α-diazoesters for intermolecular cyclopropanation (Figure 2-8).[99] Attempted cyclopropanation of acyclic α-diazoesters only gave alkene product from β-hydride migration. The ring constraints of cyclic diazocarbonyl compounds would allow for a less hindered approach of substrate, thus the relative rate of the intermolecular insertion reaction to β-hydride migration was accelerated.

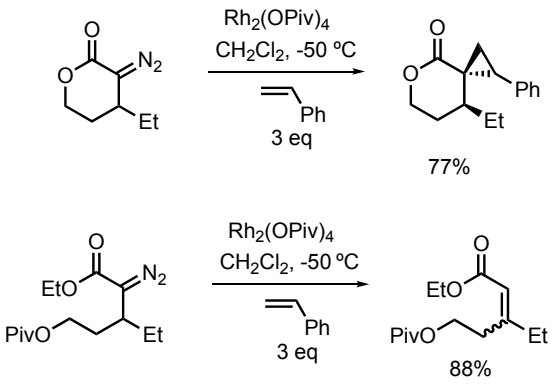


Figure 2-8 Rh-catalyzed cyclopropanation with cyclic α-diazocarbonyl compounds and attempted cyclopropanationan with an acyclic analogue

Other than the classic rhodium-catalyzed carbene insertion reactions, new patterns of carbene reactivity have been explored by integrating metal carbene intermediates with other well documented organometallic transformations. The rich reactivity of palladium makes it an attractive metal for new catalytic carbene based reactions. In traditional Pd-catalyzed cross-coupling reactions, electrophiles such as organohalides or pseudo halides can be coupled with nucleophilic partners like organometallic reagents for new carbon–carbon bond formation. In metal carbene cross-coupling reactions, electrophiles or nucleophiles can be coupled with carbene precursors. In this type cross-coupling reaction, carbene migratory insertion process is the key step for the construction of carbon–carbon bonds.

In the Pd-catalyzed cross-coupling reaction of methyl diazopropionate and iodobenzene (Figure 2-9),[100] the reaction begins with the oxidative addition of iodobenzene to the Pd(0) catalyst. This aryl palladium intermediate could react with the diazo compound to afford a palladium carbene intermediate. Migratory insertion of the aryl group to the carbenic carbon leads to the alkyl Pd(II) species, which undergoes β-hydride elimination to give the alkene product, in this case with 4:1 *E/Z* selectivity. With the help of base, the Pd(0) catalyst is regenerated from the Pd-hydride

species similar to a Heck-type reaction. The *E*-alkene products are favored under the reaction condition and the *E*/*Z* selectivity is moderate. A model for explaining the stereoselectivity in the β-hydride elimination step was proposed by Barluenga and co-workers (Figure 2-10).[101] Similar to the classical Heck-type reaction, they proposed that the alkene product was generated through *syn* β-hydride elimination.[102] The bulky groups would end up in a *trans* arrangement to minimize the steric hindrance of the species undergoing elimination. α-Diazoketones also proceed in related cross-coupling reactions smoothly with silver carbonate as an additive.

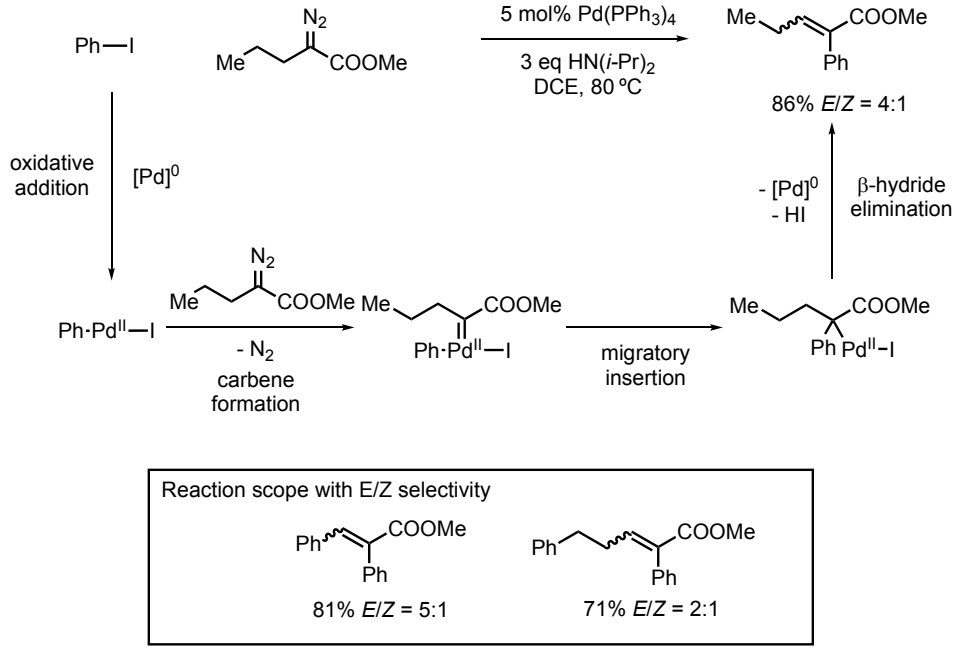


Figure 2-9 Pd-catalyzed reaction of methyl diazopropionate and iodobenzene

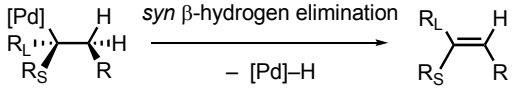


Figure 2-10 Proposed mechanism for *E*-selectivity for alkene product

N-tosylhydrazones, another commonly used carbene precursor, can also be coupled with aryl bromides promoted by Pd(0) catalysts (Figure 2-11).[101] It is well established that in presence of alkoxide base, *N*-tosylhydrazones decompose to generate diazo compounds eventually leading to metal carbene formation. Both aryl bromides and chlorides can be employed as coupling partners with *N*-tosylhydrazone carbene precursors. The *E*-alkene isomer of trisubstituted alkene product is favored in the reaction.

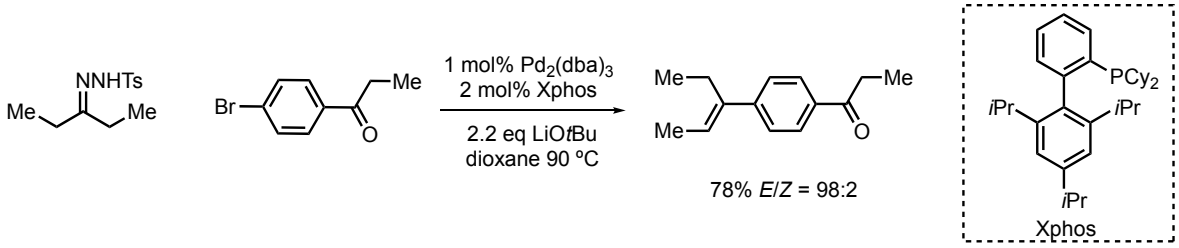


Figure 2-11 Pd-catalyzed cross-coupling of *N*-tosylhydrazones with aryl bromides

The stereoselective palladium-catalyzed cross-coupling reactions of diazo compounds was developed by Yu and co-workers (Figure 2-12).[103] Instead of using alkyl diazo compounds to provide the β-hydrogen containing intermediate, benzyl bromides were used as the β-hydrogen containing substrates. Notably, a bromo substituent on the aromatic ring of either the benzyl bromide or the diazoactate is tolerated. An excess of diazo compound (3 eq) and 40 mol% PPh_3 are required for good yield. The stereoselectivity for *E*-trisubstituted alkene is consistent with previously reported results in Perkin aldol condensation[104] and Heck reactions with aryl diazonium salts.[105]

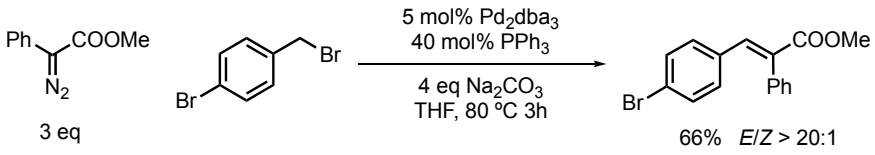


Figure 2-12 Stereoselective Pd-catalyzed cross-coupling of benzyl bromides with diazoesters

The coupling reaction between arylboronic acids and α-diazocarbonyl compounds leads to trisubstituted olefin products under oxidative Pd catalysis (Figure 2-13).[106] Compared with the cross-coupling of α-diazoesters with iodobenzene (Figure 2-9), the direct oxidative addition step is replaced by benzoquinone oxidation and arylboronic acid transmetalation steps. The resulting aryl palladium intermediate would follow the same series of steps to give the polysubstituted olefin product. The *E*/*Z* selectivity is also moderate (~2.5:1) in this reaction.

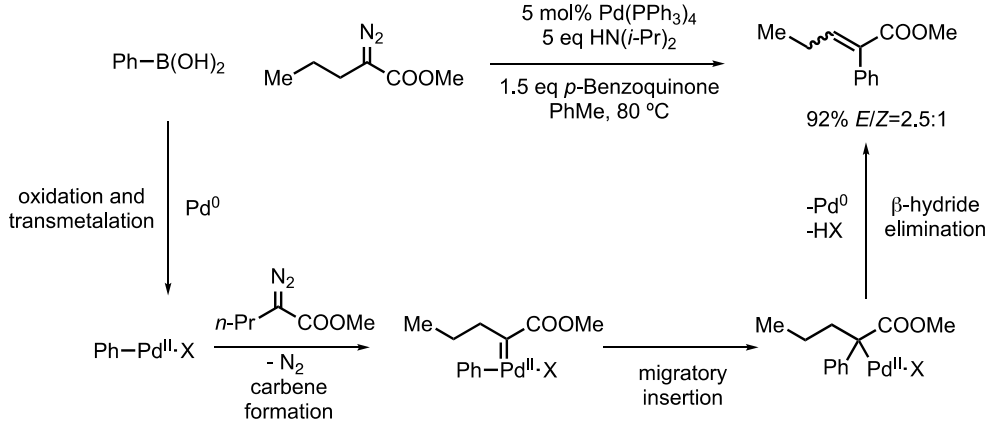


Figure 2-13 Pd-catalyzed cross-coupling of α-diazocarbonyl compounds with arylboronic acids

A stereoselective version of the oxidative cross-coupling reaction between arylboronic acids and α-diazoesters was developed by Yu and co-workers (Figure 2-14).[107] Unlike their previous reported stereoselective cross-coupling of benzyl bromide and α-diazoesters, there is no need for excess ligand and reactive benzyl bromides in this oxidative catalytic reaction; molecular oxygen was used as sole oxidant. However, the diazo esters need to be added by syringe pump over 31 hours to achieve good yield.

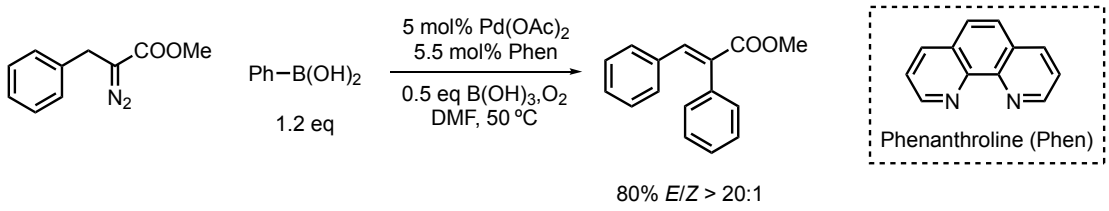


Figure 2-14 Stereoselective Pd-catalyzed cross-coupling of α-diazoesters with arylboronic acids

While Rh(II) compounds are catalysts for the classic carbene insertion reactions, Rh(I) compounds have been proved to be efficient catalysts for carbene cross-coupling reactions. In 2011, Yu and co-workers reported the first Rh(I) catalyzed three-component coupling reaction with a carbene precursor (Figure 2-15).[108] With $[Rh(COD)OH]_2$ as the catalyst, quaternary carbon centers were formed by the coupling reaction of arylboronates, α-diazoesters and alkyl halides. The diazo compound couples with an organorhodium(I) species to generate a Rh(I) carbene intermediate, which can undergo carbene migratory insertion. In the related palladium carbene cross-coupling reaction, β-hydride elimination prevents further functionalization. In the Rh(I) reaction, the resulting oxa-π-allylrhodium intermediate can be trapped by alkyl halides. In the stoichiometric reaction between oxa-π-allylrhodium complex and alkyl halides, KO*t*Bu was found essential for the second C–C bond formation, probably because the oxa-π-allylrhodium intermediate undergoes transmetalation to generate the potassium enolate for the tandem alkylation reaction.

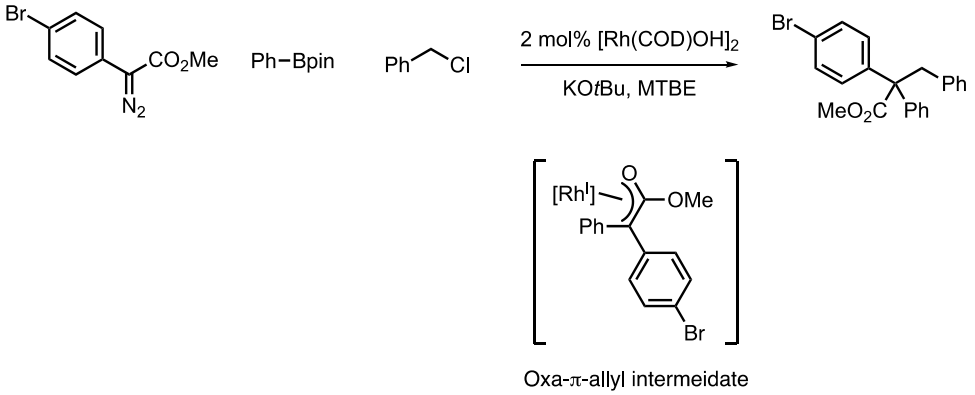


Figure 2-15 Rh-catalyzed cross-coupling of arylboronates and α-diazoesters and tandem alkylation

The Wang group reported the rhodium-catalyzed cross-coupling of arylsiloxanes with α-diazoesters (Figure 2-16).[109] A similar oxa-π-allylrhodium intermediate proposed to be generated after transmetalation and carbene insertion. The coupling product was delivered by protonating the oxa-π-allylrhodium intermediate with H_2O. Heteroaryl diazo compounds such as 3-pyridinyl and 3-thienyl diazoesters are compatible with this reaction. This reaction provided a new method for the formation of $C(sp^3)$–$C(sp^2)$ bonds.

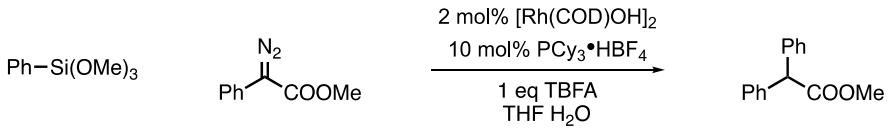


Figure 2-16 Rh-catalyzed cross-coupling of arylsiloxanes and α-diazoesters

Rh(I) catalyzed three-component reactions of *tert*-propargyl alcohols, α-diazoesters and alkyl halides (Figure 2-17) have been reported by the Wang group.[109] In the presence of a Rh(I) catalyst, *tert*-propargyl alcohol undergoes selective β-carbon elimination to generate an alkynyl Rh(I) species. This alkynyl Rh(I) intermediate undergoes similar tandem alkylation as the above

described Rh(I) three-component reactions. Both activated and unactivated alkyl halides are suitable substrates for this reaction. The diazo compounds bearing halogen substituents on the aromatic ring are compatible with the transformation. Attempted enantioselectivity control by placing chiral ligands on the rhodium center was not successful. This indicated that the alkylation step could occur from the sodium enolate, similar as Yu and co-workers' previous report. The reaction provided a straightforward way to construct all-carbon quaternary centers from readily available materials.

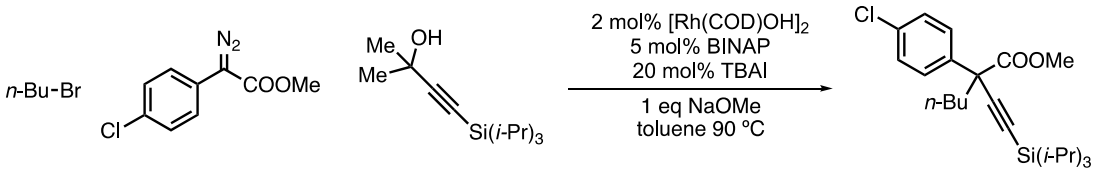


Figure 2-17 Rh-catalyzed sequential C(sp)–C(sp^3) and C(sp^3)–C(sp^3) bond formation

Metal carbene migratory insertion has also been combined with Rh(III) catalyzed C–H activation. Rh(III)-catalyzed *ortho* alkenylation of *N*-phenoxyacetamides with α-diazoesters or *N*-tosylhydrazones has been reported by Wang and co-workers (Figure 2-18).[110] The $[Cp^*RhCl_2]_2$ catalyst promotes directing group assisted C–H activation, followed by metal carbene formation. Migratory insertion of the Rh(III) carbene intermediate is proposed to give a cyclic Rh(III) intermediate. The cyclic Rh(III) intermediate could undergo β-hydride elimination to afford the alkene product. The Rh(III) catalyst is regenerated with the aid of the oxidizing directing group (-ONHAc), through oxidative addition to an N–O bond. After protonation, the desired *ortho*-alkenyl phenols are formed. *E*-alkene isomers were isolated as the exclusive product when α-diazoesters were used in this reaction.

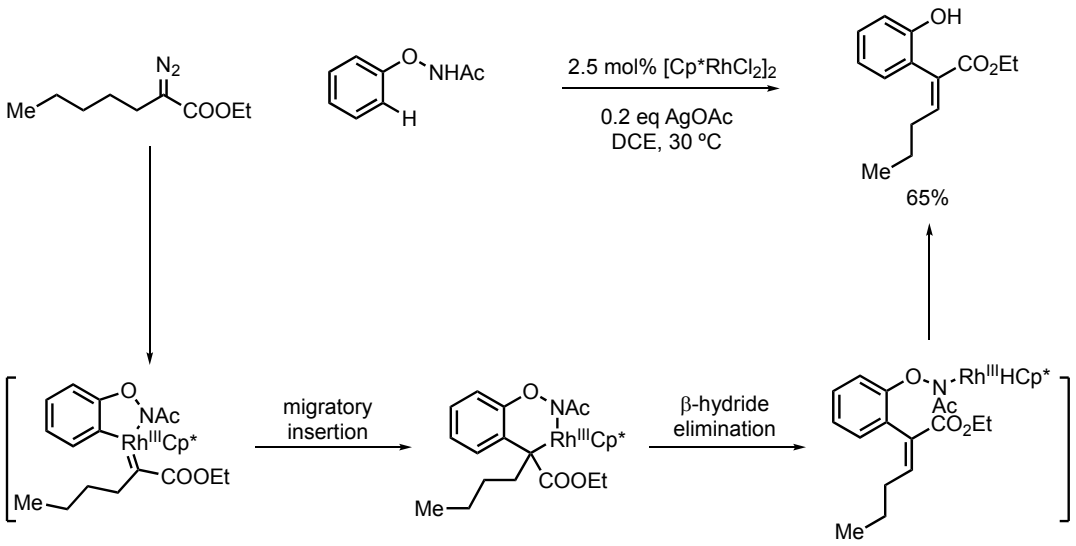


Figure 2-18 Rh-catalyzed *ortho* alkenylation through carbene migratory insertion

Iodine(III) compounds are commonly used reagents for oxidative functional group transfer. In 2016, Waser and Hari reported copper-catalyzed oxy-alkynylation of diazo compounds with ethynylbenziodoxolone (EBX) reagents (Figure 2-19).[111] Both the alkynyl moiety and the iodobenzoate moiety of an EBX reagent are coupled with a copper carbene intermediate in one reaction. $Cu(CH_3CN)_4BF_4$ was found to be the best catalyst for this reaction. Other transition metal catalysts such as $Rh_2(OAc)_4$, $PdCl_2(PPh_3)_2$ and $Cu(OAc)_2$ only provided trace amounts of product. The use of a diimine ligand is important to achieve high yield in this oxy-alkynylation. The reaction shows a broad scope of both diazo compounds and EBX reagents. When vinyl diazo compounds were used in the reaction, only vinylogous product was obtained. In Waser's proposed mechanism (Figure 2-20), copper carbene intermediate was formed by extrusion of N_2 from the diazo compound. The nucleophilic carboxylate group will add to the copper carbene intermediate first, then followed by the alkynylation step. There are two possible mechanisms for the alkynylation step which are consistent with experimental observations. The alkynylation could occur either through α-addition of alkyne or through oxidative alkyne transfer to copper.

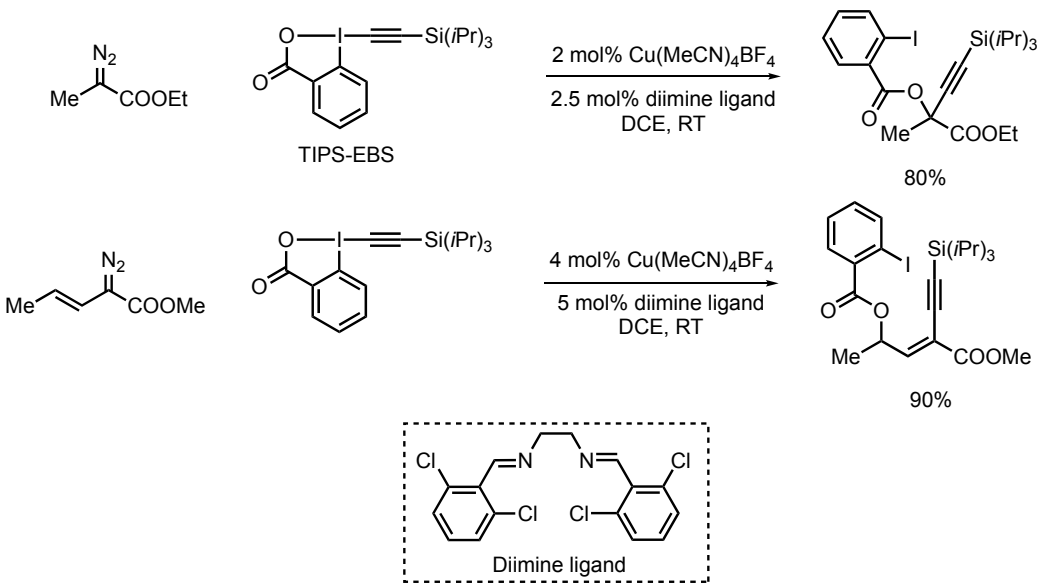


Figure 2-19 Cu-catalyzed oxy-alkynylation of diazo compounds with hypervalent iodine reagents

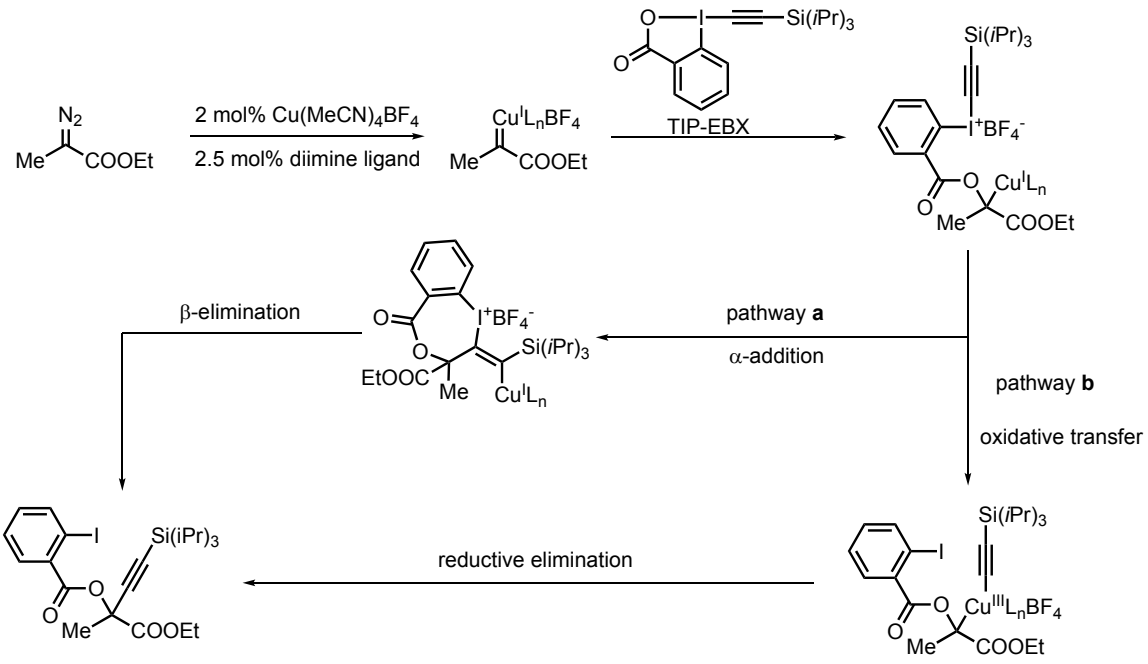


Figure 2-20 Proposed mechanism for Cu-catalyzed oxy-alkynylation

Recently our group developed an Ir-catalyzed *Z*-selective cross-coupling of allylic carbonates and α-diazoesters (Figure 2-21). In contrast to the preference of *E,E*-dienes in the Pd-catalyzed carbene cross-coupling reactions,[112-114] this Ir-catalyzed cross-coupling reaction provides *Z,E*-dieneoates in up to 90:10 selectivity. Improved *Z*-selectivity of the reaction was observed by increasing the steric demand of the ester substituent of the diazo coupling partner. The allylic leaving group can also influence the stereoselectivity of this Ir-catalyzed carbene cross-coupling reaction. Due to the large coordination sphere of the catalyst, the *Z*-selective product formation could occur from an otherwise disfavored conformer undergoing β-hydride elimination, or alternatively base-induced E2-type elimination.

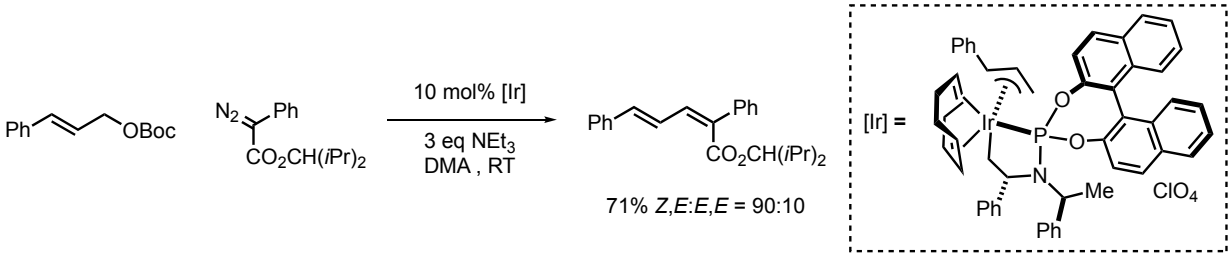
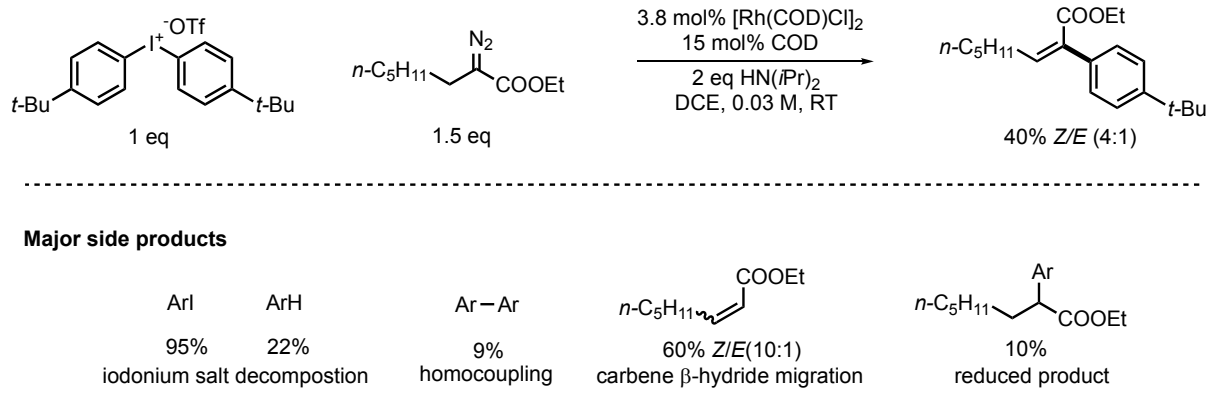


Figure 2-21 Ir-catalyzed *Z*-selective cross-coupling of allyic carbonates and α-diazoesters

2.2 Development of Rh-catalyzed olefination of diazo esters and diaryliodonium salts

Rh(I)-catalyzed olefination between diazo compounds and iodonium electrophiles could show different reactivity from well-established Pd(0) catalyzed olefination with carbene precursors. Owing to the highly electron deficient hypervalent bonds and the excellent leaving-group ability of aryl iodides, diaryliodonium salts are widely used for electrophilic arylations.[115] Under our current best condition (Figure 2-22), diaryliodonium salts and diazo compounds can be coupled in 40% yield with about 4:1 *Z*/*E* ratio. The stereoselectivity of this reaction is different

from the previous reported Pd(0) catalyzed olefination reactions with diazo compounds and iodobenzene, which gives *E*-alkene products as the major isomer.[100] Undesirable decomposition of both starting materials currently limit the yields of the reaction under the best identified conditions.



Product yield and side products distribution determined by calibrated ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.
Z/*E* ratio confirmed by GC

Figure 2-22 Rh(I)-catalyzed cross coupling of α-diazoesters and diaryliodonium salts

A potential mechanism for the Rh(I)-catalyzed olefination reaction of α-diazo esters and diaryliodonium salts is depicted in Figure 2-23. The reaction is initiated by oxidative addition of a diaryliodonium salt to the Rh(I) catalyst. The resulting aryl Rh(III) intermediate reacts with the diazo compound to give a Rh(III) carbene intermediate. Then a new C(sp^2)–C(sp^3) bond is formed by the migratory insertion of the aryl group to the carbenic carbon. In the presence of amine base, the β-hydride elimination step occurs to deliver the olefination product and the Rh(I) catalyst is re-generated.

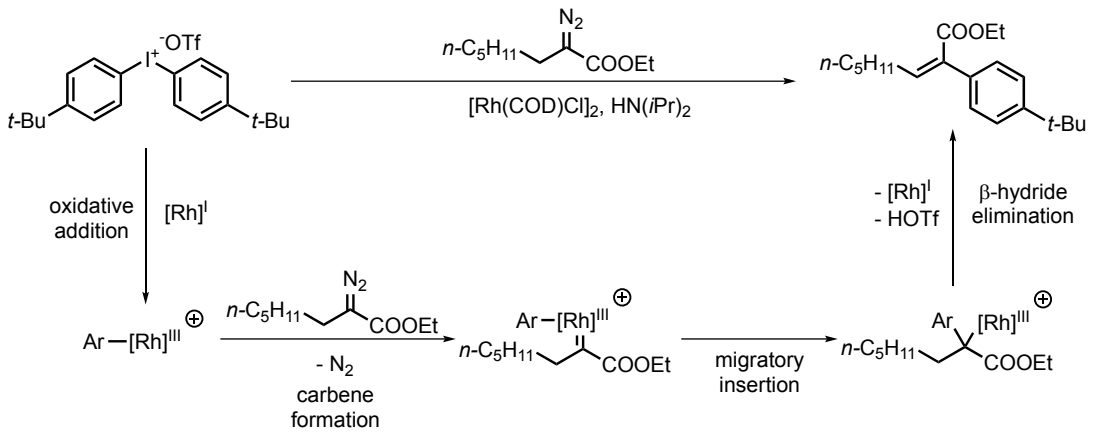


Figure 2-23 A potential mechanism of Rh(I)-catalyzed cross coupling of α-diazoesters and diaryliodonium salts

The typical side reactions are aryl-aryl homocoupling, iodonium salt decomposition and β-hydride migration of the diazo compounds. About 50% of the diazo precursor and iodonium salts decomposed unproductively under our best condition. The reaction was monitored by ^{1}H-NMR spectroscopy (Figure 2-24 and Figure 2-25). It is about 70% conversion after 1 hours and the reaction completed within 6 hours. The ratio of the side products to olefin product was consistent during the course of the reaction, which indicates the side reactions and the desired reaction occur at the same time and there is no significant catalyst decomposition in the reaction.

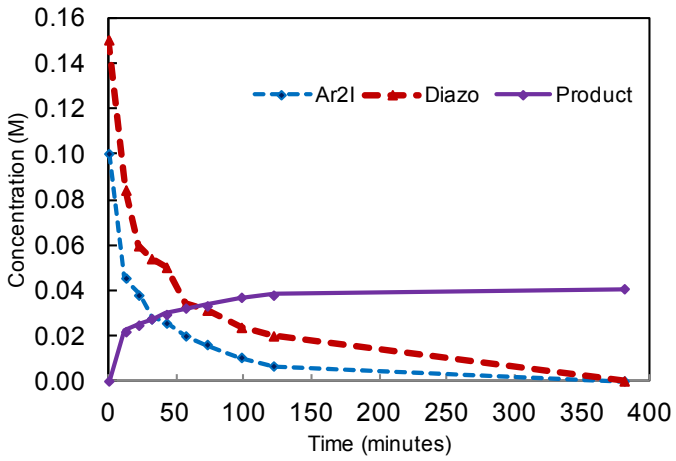


Figure 2-24 Starting materials and product concentrations variations of Rh(I)-catalyzed olefination with diaryliodonium salts

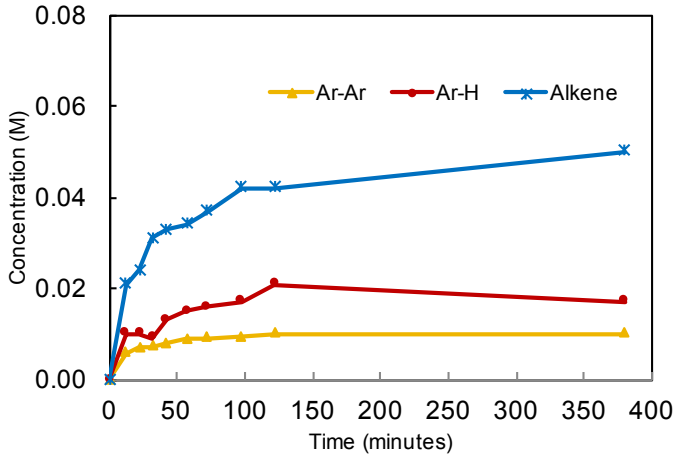
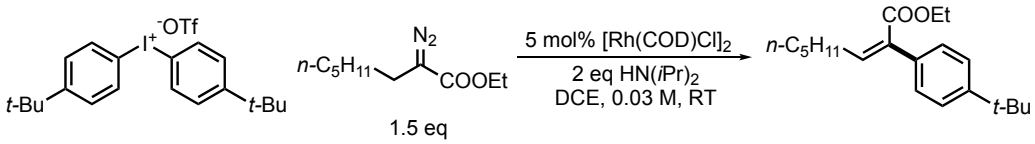
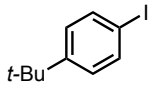
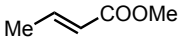


Figure 2-25 Side products concentrations variations of Rh(I)-catalyzed olefination with diaryliodonium salts

In control experiments (Table 2-1), $[Rh(COD)Cl]_2$ could catalyze the decomposition of diazo compound via facile β-hydride migration in DCE. 10% iodonium salts decomposition was observed in absence of diazo compounds under the reaction condition. No product was formed when aryl iodide or olefin was used. To reduce the side reaction of diazo compound

decomposition, the diazo reagent was added last into the reaction and the reaction was conducted under relative dilute concentration (0.03 mol/L) to minimize the unproductive diazo decomposition.



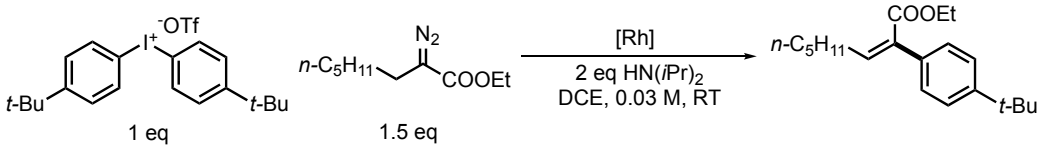
Entry	Conditions	Results
1	no [Rh]	no conversion of both diazo and Ar_2IOTf
2	no base	< 5% product
3	diazo + [Rh]	> 95% β-hydride migration
4[a]	no diazo	10% conversion of Ar_2IOTf
5	 instead of Ar_2IOTf	no product
6	 instead of diazo	no product

Side products distribution determined by calibrated ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.
[a]7.5 mol% RhCODCl + 15 mol% COD, 3h

Table 2-1 Control experiments of Rh(I)-catalyzed olefination with diaryliodonium salts

Different rhodium catalyst systems have been examined at different stages of reaction optimization (Table 2-2). The 1,5-cyclooctadiene (COD) ligand is essential for high conversion of diaryliodonium salts. The catalyst loading can be decreased to 3.8% with additional COD ligand. *In situ* generation of $[Rh(COD)Cl]_2$ from $[Rh(C_2H_4)_2Cl]_2$ and COD ligand is also an effective catalyst for this reaction (entry 5). Norbornadiene (NBD), a widely-used diene ligand in rhodium chemistry, is not the effective ligand for this reaction (entry 7). Excess diazo compound led to a higher yield for the olefination reaction (entry 3 vs entry 4). Other rhodium catalysts including $Rh_2(OAc)_4$, $[RhCp^*Cl_2]_2$, cationic $Rh(COD)_2BF_4$, $[Rh(COE)_2Cl]_2$ and $Rh(PPh_3)_3Cl$ did not

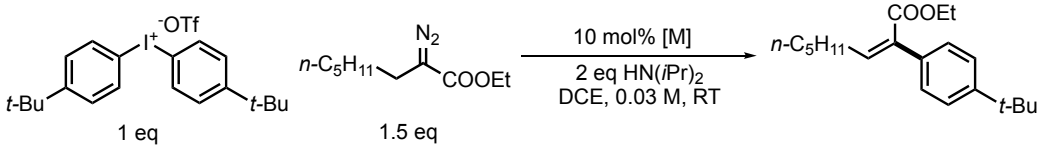
provide better yields of product. Except $[RhCp^*Cl_2]_2$, diazo compounds were mainly consumed by unproductive β-hydride migration with these rhodium catalysts.



Entry	Conditions	Converstion of Ar_2IOTf (%)	Yield (%) *Z*/*E*
1	3.8 mol% $[Rh(COD)Cl]_2$ + 15 mol% COD	95	43 (78:22)
2	3.8 mol% $[Rh(COD)Cl]_2$	66	25 (76:24)
3	5 mol% $[Rh(COD)Cl]_2$	100	42 (78:22)
4[a]	5 mol% $[Rh(COD)Cl]_2$	100	30 (78:22)
5	3.8 mol% $[Rh(C_2H_4)Cl]_2$ + 15 mol% COD	89	37 (76:24)
6	3.8 mol% $[Rh(C_2H_4)Cl]_2$	73	9 (76:24)
7	3.8 mol% $[Rh(COD)Cl]_2$ + 15 mol% NBD	86	12 (68:32)
8	3.8 mol% $Rh_2(OAc)_4$	67	13 (77:23)
9[b]	3.8 mol% $[RhCp^*Cl_2]_2$	11	0
10[a]	10 mol% $Rh(COD)_2BF_4$	55	17 (76:24)
11[a]	5 mol% $[Rh(COE)_2Cl]_2$	80	12 (78:22)
12[a]	10 mol% $Rh(PPh_3)_3Cl$	29	< 3

0.075 mmol, 18h, yields determined by calibrated ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard, *Z*/*E* ratio confirmed by GC.
[a]1 eq diazo compound
[b]No conversion of diazo compound

Table 2-2 Effect of Rh catalysts and diene ligands on olefination with diaryliodonium salts



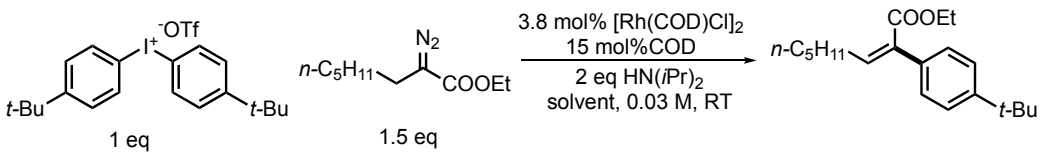
Entry	Conditions	Converstion of Ar_2IOTf (%)	Yield (%) *Z*/*E*
1[a]	$[Ir(COD)Cl]_2$	90	< 5
2[a]	$[Ir(COE)_2Cl]_2$	59	12 (78:22)
3	CuI	30	9 (12:88)
4	$Cu(MeCN)_4PF_6$	15	8 (12:88)
5	$Cu(OTf)_2$	23	< 3
6	$Pd(PPh_3)_4$	100	93 (20:80)

0.075 mmol, 18h, product yields determined by H-NMR with 1,3,5-trimethoxybenzene as internal standard, *Z*/*E* ratio confirmed by GC
[a]1 eq diazo compound used

Table 2-3 Effect of other transition metal catalysts on olefination with diaryliodonium salts

Other commonly used transition metal complexes for carbene chemistry have also been investigated (Table 2-3). Iridium catalysts are less effective for this reaction and these species give *Z*-olefin as the major products. Only trace amounts of product were observed with different copper salts. Use of $Pd(PPh_3)_4$ leads to high yield of product with the preference of *E* isomer, which is consistent with previously reported examples.[100]

Highest yield of the Rh(I)-catalyzed olefination was achieved with DCE as solvent (Table 2-4). A screen of solvents revealed that other solvents such as DCM, toluene, PhCl, THF and dioxane also worked for this reaction, but less effective compared with DCE. Diaryliodonium salt is not fully soluble in the non-polar solvent like toluene, which gave lower yield of desired product. No product formation was observed with more polar and potentially coordinative solvents such as MeCN and DMA.



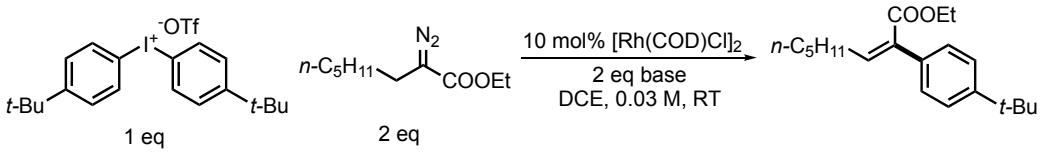
Entry	Solvent	Converstion of Ar_2IOTf (%)	Yield (%) *Z*/*E*
1	DCE	100	43 (78:22)
2	DCM	100	30 (75:25)
3	toluene	95	31 (77:23)
4	PhCl	100	34 (77:23)
5	THF	97	23 (68:33)
6	dioxane	59	23 (71:29)

0.075 mmol, 18h, product yields determined by ^{1}H-NMR with 1,3,5-trimethoxybenzene as internal standard, *Z*/*E* ratio confirmed by GC

Table 2-4 Effect of solvent on Rh(I)-catalyzed olefination with diaryliodonium salts

A significant base effect on both yield and stereoselectivity of the target reaction was observed (Table 2-5). $(i\text{Pr})_2\text{NH}$ was found to be the most suitable base for the *Z*-alkene product formation. Et_3N gave very similar result in yield, but was less selective for the *Z*-isomer. Other bulky amine bases are less efficient for the olefination. The use of DABCO led to the *E* alkene

product as the major isomer in a low yield (11%). Lower conversion of diazo compound (< 20%) was observed in the reaction with DABCO as the base. Inorganic bases such as K_2CO_3, LiO*t*Bu are not effective under the standard conditions.

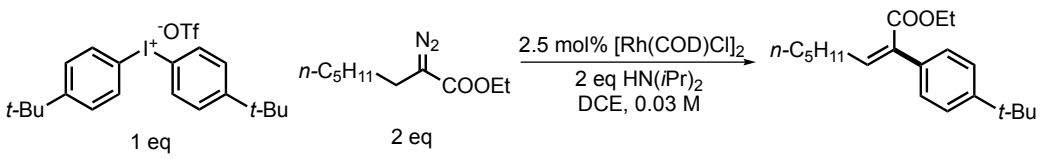


Entry	Base	Converstion of Ar_2IOTf (%)	Yield (%) *Z*/*E*
1	$(iPr)_2NH$	100	42 (78:22)
2	Et_3N	100	40 (60:40)
3	$(iPr)_2NEt$	68	32 (70:30)
4	HTMP	75	37 (78:22)
5[a]	Cy_2NH	90	36 (77:23)
6[a]	Cy_2NMe	96	30 (65:35)
8	DABCO	13	12 (10:90)
9	K_2CO_3	71	0
10	LiO*t*Bu	N/A	<10 (*Z*)[b]

0.075 mmol, 18h, product yields determined by calibrated ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard, *Z*/*E* ratio confirmed by GC.
[a]1.5 eq diazo compound used
[b]*E*-product ^{1}H-NMR signal overlap with other compounds

Table 2-5 Effect of base on Rh(I)-catalyzed olefination with diaryliodonium salts

No obvious temperature effect was observed in the coupling reaction (Table 2-6). Higher temperature (40 ºC) led to rapid β-hydride migration of the diazo compound. Much slower consumption of diaryliodonium salt was observed at 0 ºC, however no improvement of product formation was observed by changing the reaction temperature.

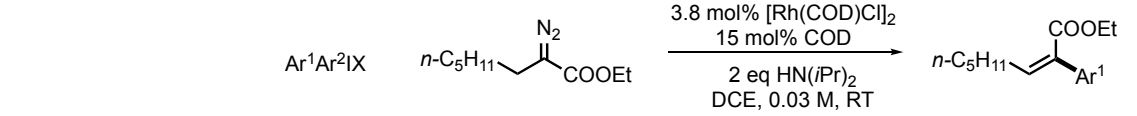


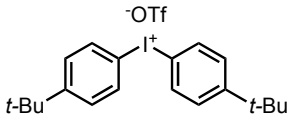
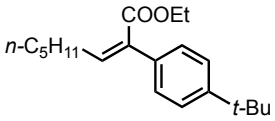
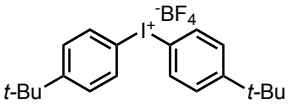
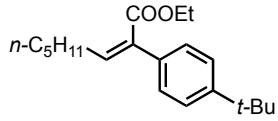
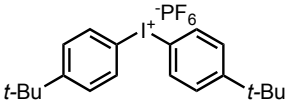
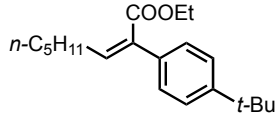
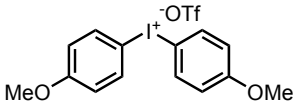
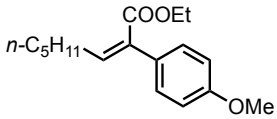
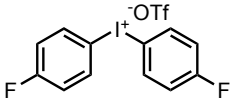
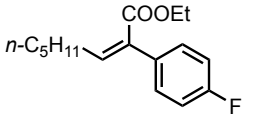
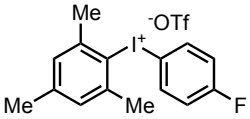
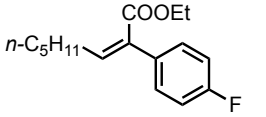
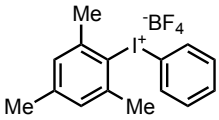
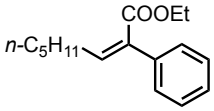
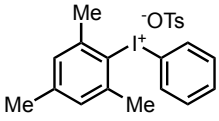
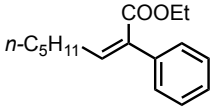
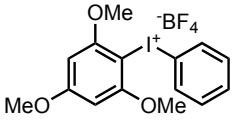
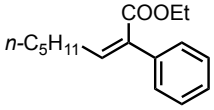
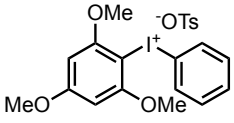
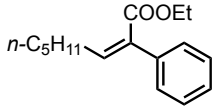
Entry	Temperature	Converstion of Ar_2IOTf (%)	Yield (%) *Z*/*E*
1	room temperature	99	37 (68:32)
2	30 ºC	100	35 (71:29)
3	40 ºC	100	28 (68:32)
4	0 ºC	64	29 (73:27)
5[a]	0 ºC	88	35 (77:23)

0.075 mmol, 3h, product yields determined by H-NMR with 1,3,5-trimethoxybenzene as internal standard, *Z*/*E* ratio confirmed by GC
[a]36h

Table 2-6 Effect of temperature on Rh(I)-catalyzed olefination with diaryliodonium salts

Other than bis(4-*tert*-butylphenyl) iodonium triflate, the model substrate in the standard reaction, different iodonium salts were also tested in the olefination reaction (Table 2-7). Diaryliodonium salts with other counter ions (entry 2, 3) led to the very similar results to the standard diaryliodonium triflate (30% yield). Aryl groups bearing the electron donating substituent (entry 4) or the electron withdrawing substituent (entry 5) are tolerated favoring the formation of the *Z*-isomer. Unsymmetrical diaryliodonium salts with inert auxiliary aryl group are also suitable substrates in the reaction,[116] where only one aryl group selectivity transferred to the olefin product (entry 6, 7, 8). Compared with iodonium salts bearing the mesitylene auxiliary group, aryl(2,4,6-trimethoxyphenyl)iodonium salts gave slightly lower yield. Using unsymmetrical iodonium salts with a tosylate counter ion led to decreased yields (entry 8 and 10).

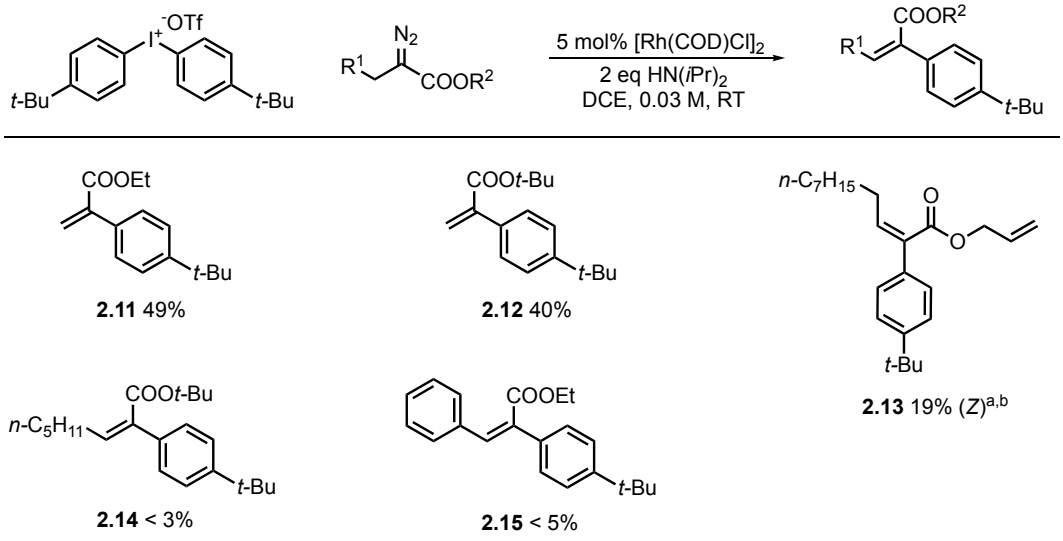


Entry	Diaryliodonium salts	Product	Yield (%) *Z*/*E*
1[a]			30 (76:24)
2[a]			26 (75:25)
3[a]			30 (76:24)
4[b]			40 (60:40)
5			28 (75:25)
6			30 (79:21)
7			21(*Z*)[c]
8			< 5
9			18 (*Z*)[c]
10			10 (*Z*)[c]

1.5 eq diazo compound,18h, product yields determined by calibrated ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.
[a]5% $[Rh(COD)Cl]_2$, 1 eq diazo compound; [b]5% $[Rh(COD)Cl]_2$, 2 eq diazo compound ; [c]*E*-product H-NMR signal overlap with other compounds

Table 2-7 Effect of iodonium electrophiles on Rh(I)-catalyzed olefination

The nature of the diazo coupling partner has a great impact on the olefination (Table 2-8). The terminal olefin product (**2.11**) derived from the methyl-substituted α-diazo ester was obtained in good yield (49%). A bulky ester group of the diazo compound led to slightly decreased yield (40%) for terminal olefin product (**2.12**). Allylic ester groups (**2.13**) were tolerated in olefination and gave a 19% yield of the *Z*-olefin product. Only a trace amount of the trisubstituted olefin product (**2.14**) was formed with the diazo compound containing a *tert*-butyl ester group, while β-phenyl substituted diazo reagents (**2.15**) are not the effective coupling partner under the currently explored conditions.



1.5 eq diazo compound,18h, product yields determined by calibrated ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.
[a]3.8 mol% $[Rh(COD)Cl]_2$, 15 mol% COD
[b]*E*-product H-NMR signal overlap with other compounds

Figure 2-26 Effect of diazo compounds on Rh(I)-catalyzed olefination with diaryliodonium salts

2.3 Summary and future work

A *Z*-favored Rh-catalyzed olefination between diazo esters and iodonium electrophiles was discovered. This Rh-catalyzed olefination exhibits complementary stereoselectivity to the Pd-catalyzed carbene cross-coupling reaction. Under the current best conditions, the olefination

product can be obtained in about 40% yield in 4:1 *Z*/*E*. Approximately 50% of the starting materials are consumed by undesirable side reactions which appear to proceed at similar rates to product formation. Electron-rich and electron-poor aryl groups of diaryliodonium salts are tolerated in this reaction. However, the Rh-catalyzed olefination is sensitive to different substituents of diazoester coupling partner by the preliminary results. The stereoselectivity is influenced by the amine base, which indicates that the amine base is involved in the selectivity determining elimination step.

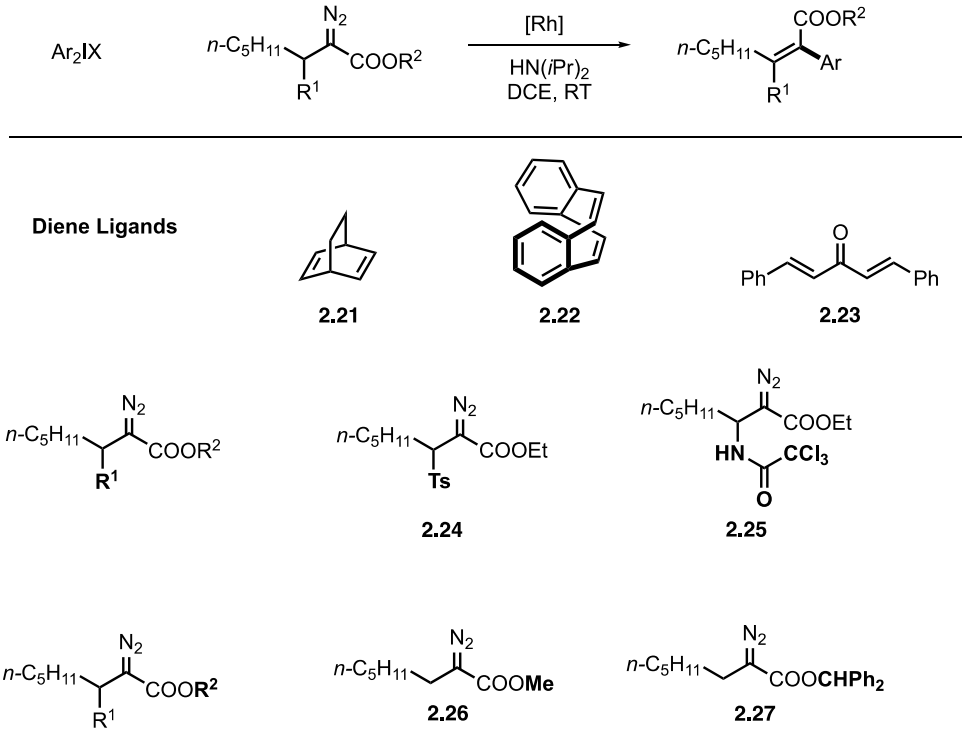


Figure 2-27 Selected future works

Future work on this reaction will focus on the control of side reactions and maximizing the product yield. Diene ligands have a significant impact on this reaction. More stable Rh-diene complexes could be better catalysts. With electron withdrawing substituents like p-toluenesulfonyl group and trichloroacetyl amino group on the diazo esters (**2.24** and **2.25**), β-hydride migration of

the Rh-carbene intermediate could be suppressed. Diazo compounds with both small and bulky ester groups will also be tested (**2.26** and **2.27**).

2.4 Procedures and characterization

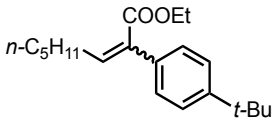
All glassware and vials were oven-dried prior to use. Flash chromatography was performed on silica gel with the indicated eluents (SiliaFlash P60, 40-63μm, 60A silica gel, Silicycle) or by automated flash chromatography (Isolera, HP-SIL or Ultra SNAP silica cartridges, Biotage). Analytical thin-layer chromatography was performed using glass plates pre-coated with silica (SiliaPlate G TLC-Glass-Backed, 250μm, Silicycle). TLC plates were visualized by UV light and/or staining with aqueous basic potassium permanganate. Unless otherwise noted, all reagents were obtained from commercial vendors and used as supplied. The Alkyl α-diazoesters were synthesized according to the literature procedures from the corresponding β-ketoesters.[106, 107] Diaryliodonium triflates were synthesized according to literature procedures reported by the Olofsson group.[117, 118] Diaryliodonium tetrafluoroborates and hexafluorophosphates were synthesized form corresponding diaryliodonium triflate through anion exchange with an aqueous $NaBF_4$ solution or an aqueous $NaPF_6$ solution.[119] Diaryliodonium tosylates were synthesized according to a procedure reported by the Stuart group.[116]

2.4.1 General Procedure

All reactions were prepared in a nitrogen-filled glovebox. 1.4 mg (0.0028 mmol) of $[RhCODCl]_2$, (0.011 mmol), 1.2 mg of COD (0.017 mmol), 4.2 mg of 1,3,5-trimethoxybenzene (0.025 mmol), 40.7 mg (0.075 mmol) bis(4-*tert*-butylphenyl)iodonium triflate and a stir bar were added to a 1-dram vial. 2 mL 1,2-dichloroethane and 15.2 mg (0.15 mmol) diisopropylamine was

added by pipet. The mixture was stirred until a clear solution was formed. Then 0.30 mL (0.50 mol/L) ethyl α-diazooctanoate 1,2-dichloroethane stock solution was added. The reactions were capped, taken out of the glovebox, and stirred at room temperature. Upon completion of the reaction (usually about 4 hours), the reaction mixture was filtered through celite and concentrated *in vacuo*, and purified by silica gel chromatography.

2.4.2 Product Characterization



2.11 Prepared according to the General Procedure. *Z*-olefin product was isolated in 31% yield after purification by Prep TLC (20:1 Hexane/EtOAc) as a colorless oil.

Z-isomer

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 – 7.33 (m, 2H), 7.27 – 7.26 (m, 2H), 6.15 (t, *J* = 7.5 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 2.39 (q, J = 7.5 Hz, 2H), 1.51 – 1.48 (m, 2H), 1.34 – 1.31 (m, 16H), 0.92 – 0.90 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 150.6, 138.6, 135.1, 134.6, 126.8, 125.4, 60.8, 34.7, 31.6, 31.4, 30.2, 29.2, 22.7, 14.5, 14.2;

HRMS (LCMS ESI): calcd for $C_{20}H_{31}O_2$ $[M+H]^+$:303.2319 Found 303.2317.

E-isomer

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 – 7.35 (m, 2H), 7.11 – 7.09 (m, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 2.11 (q, J = 7.5 Hz, 2H), 1.44 – 1.41 (m, 2H), 1.34 – 1.24 (m, 16H), 0.87 – 0.84 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 150.1, 145.0, 133.8, 132.5, 129.5, 124.9, 60.9, 34.7, 31.6, 31.5, 29.6, 28.8, 22.6, 14.4, 14.1

HRMS (LCMS ESI): calcd for $C_{20}H_{31}O_2$ $[M+H]^+$:303.2319 Found 303.2321.

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