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Palladium-catalyzed decarbonylative cross-coupling of cinnamic esters with silicon-based
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enolate precursors

A Thesis submitted in partial satisfaction of the requirements
for the degree Master of Science

in

Chemistry

by

SangHyun Lee

Committee in charge:

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      Professor Emmanuel Theodorakis

2018

The Thesis of SangHyun Lee is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

2018

Dedication

Dedicated to my beloved family who has supported me

with their unmeasurable love and faith

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LIST OF ABBREVIATIONS

α	alpha
Ac	acetyl
Ad	adamantyl
Ar	aryl
Atm	atmospheres
β	beta
Bipy	2'2-bipyridine
Bu	butyl
n-Butyl	*normal*-butyl
t-Butyl	*tert*-butyl
°C	degrees Celcius
CO	carbon monoxide
CO_2	carbon dioxide
CO_3	carbonate
COD	1,5-cyclooctadiene
CF_3	trifluoromethyl
Cy	cyclohexyl
dba	Bis(dibenzylideneacetone)
dcype	1,2-Bis(dicyclohexylphosphino)ethane
dcypb	1,2-Bis(dicyclohexylphosphino)butane
dmpe	1,1-Bis(dimethylphosphino)ethane
DCM	dichloromethane
DFT	density functional theory

DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	dimethyl sulfoxide
E	entgegen (*trans*)
equiv	equivalence
Et	ethyl
Et$_3$N	triethylamine
EtO	ethoxy
γ	gamma
GC	gas chromatography
h	hour
HMPA	hexamethylphosphoramide
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazolinium
IPr	1,3-bis(2,6-diisopropylphenyl)imidazolium
M	molarity
Me	methyl
MHz	mega hertz
MS	mass spectrometry
NHC	*N*-heterocyclic carbene
N.D.	not detected
NMR	nuclear magnetic resonance
o	*ortho*
OAc	acetate

OMe	methoxy
O*t*Bu	*tert*-butoxide
p	*para*
Ph	phenyl
PO$_4$	phosphate
PhMe	toluene
r.t.	room temperature
*t*Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	Thin-layer chromatography
Tol	Tolyl
Ts	*p*-toluenesulfonyl
UV	ultraviolet
Z	zusammen (*cis*)

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ACKNOWLEDGEMENTS

Chapter 1: Introduction to transition metal-catalyzed cross-coupling strategies

1.1 Advancement in traditional methods of cross-coupling

Transition metal-catalyzed cross-coupling is a powerful methodology for strategic carbon-carbon and carbon-heteroatom bond formation. Its significance has been highlighted with the 2010 Nobel Prize in chemistry, to Professors Richard Heck, Ei-ichi Negishi, and Akira Suzuki for their dedicated work in the development of palladium-catalyzed cross-couplings with different substrates; Heck with alkenes, Negishi with organozinc reagents, and Suzuki with organoboron reagents.[1] The nucleophilic partners in traditional cross-coupling have been expanded to a variety of organometallic reagents (Mg-, Sn-, Si-based) (Figure 1.1).
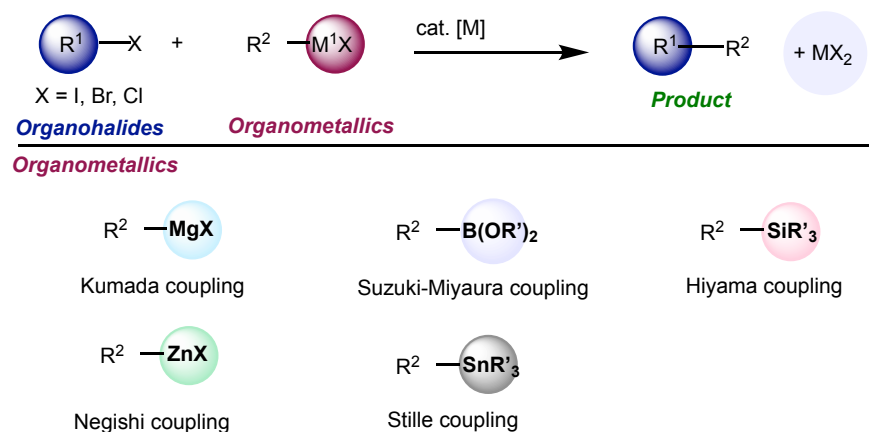
Figure 1.1 Traditional cross-coupling strategies

A general cross-coupling mechanism is outlined in Figure 1.2.
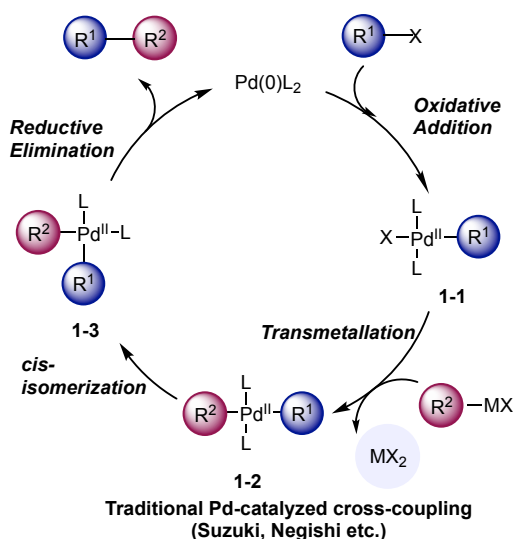
Figure 1.2 Generally accepted catalytic cycle of traditional cross-couplings

Beginning with a Pd(0)L$_2$ species, oxidative addition of the organohalide electrophile

forms a Pd(II)XR^1 species (**1-1**). The R^{1}Pd(II)XL$_2$ intermediate (**1-1**) undergoes transmetallation

with the added organometallic nucleophile followed by reductive elimination of R^{1}Pd(II)R^{2}L$_2$ (**1-2**)

to release the R^{1}R^2 (**1-3**) cross-coupled product and regenerate Pd(0)L$_2$.

Early cross-couplings were often carried out using toxic organometallic reagents such as

organostannes and highly reactive Grignard reagents.[2] In the necessity of stable organometallic

reagents for high chemoselectivity and stereoselectivity, organosilicons were considered by

their highly stable C-Si bond and usage of non-toxic silicon.[2] In fact, various organosilicon

reagents are commercially available and are cost-efficient due to the high natural abundance of

silicon.[2] With these advantages of organosilicons over other organometallics, the cross-coupling

strategy using organosilicon was pioneered by Hiyama and co-workers in 1988. This cross-

coupling variant now bears his name.

Previously, Kumada and co-workers reported cross-coupling reactions between organo-

(pentafluoro)silicates and aryl or alkenyl halides in 1978 (Figure 1.3).[3]

Kumada, M. *Organometallics*, **1982**, *1*, 542–549.

Figure 1.3 Kumada's cross-coupling strategy with organo(pentafluoro)silicates

It is proposed that formation of hypervalent, hexacoordinate silicate species is significant in the transmetallation step of the cross-coupling cycle with organosilicon reagents.[2] Hiyama and co-workers devised a cross-coupling strategy utilizing commercially available silanes via generation of *in-situ* hypervalent silicates upon activation with a fluoride source. In 1989, Hiyama and co-workers demonstrated Pd-catalyzed alkenylation and arylation coupling fluorinated vinyl silane and aryl silane in presence of TASF and KF (Figure 1.4).[4,5]

Hiyama, T. *J. Org. Chem.*, **1989**, *54*, 268–270.

Hiyama, T. *Chem. Lett.*,**1989**, *18*, 1711–1714.

Figure 1.4 Hiyama's cross-coupling strategy with organosilanes

The proposed general catalytic cycle of Hiyama couplings (Figure 1.5) suggests that the tetracoordinate organosilane is activated by a fluoride ion to yield pentacoordinate silicate (**1-4**) and, upon its coordination with XPd(II)R[2] complex, transmetallation occurs to generate R[1]Pd(II)R[2] species via formation of *in-situ* hexacoordinate organosilicate (**1-5**).[2]

Figure 1.5 Proposed general catalytic cycle of Hiyama coupling

With fluoride-assisted activation, Hiyama coupling has been extensively developed with diverse

organosilicon reagents: organo(alkoxy)silane (Tamao and Ito[6]; Shibata[7]), organosilanols

(Hiyama[8] and Denmark[9]), organosilanolates (Denmark[10]), and tetraorganosilanes (Hiyama and

Hatanaka[11]).

1.1.1. Development in oxygenated electrophiles

Another wave in cross-coupling evolved with development of alternative electrophiles.

While various aryl halides are commercially available, the preparation of non-commercially

available aryl halides requires multiple-step-synthesis and harsh reaction conditions, and

production of unwanted waste.[12,13] Since the 1980s, phenol-driven aryl sulfonates were

attractive alternatives of aryl halides in cross-coupling and the scope of electrophiles has been

expanded to aryl sulfonates, which include aryl triflates[14], fluorosulfonates[15], nonaflates[16],

tosylates[17,18] and mesylates[19,20] (Figure 1.6).
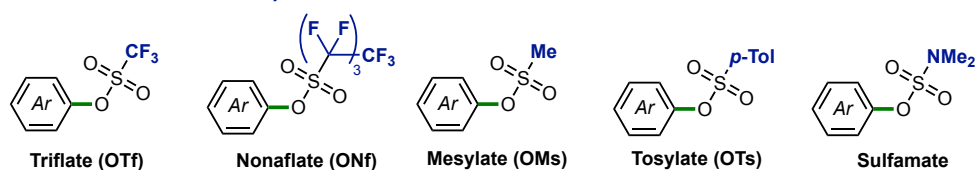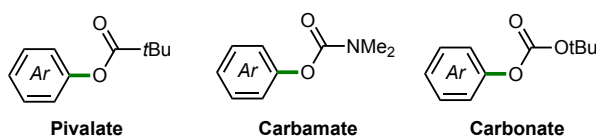
Figure 1.6 Examples of oxygenated electrophiles

Though C(aryl)-O bond is considered to be difficult to activate, development in ligands and

catalysts enabled aryl tosylates and mesylates to be coupled in cross-coupling reactions.[12] In

2008 and 2009, Garg and co-workers demonstrated that acylated phenols (Figure 1.6), such as

aryl pivalates[21], carbamates[22], carbonates[22] and sulfamates[22], can also be used as electrophiles

with organoboron reagents and amines under Ni-based catalyst system.

1.2 Development in decarboxylative cross-coupling

As introduced in Chapter 1.1, the transition metal-catalyzed cross-coupling is a well-

developed area that has benefited in syntheses of pharmaceuticals and agrochemicals by its

high catalyst efficiency and powerful functionalization.[23] However, traditional cross-coupling

generates a stoichiometric amount of metallic-halides wastes, which can result in difficult

purifications. As an alternative of expensive organometallic reagents, widely available carboxylic

acids and carboxylates were used to make carbon nucleophiles in the cross-coupling reaction,

which is known as decarboxylative cross-coupling.[29] The significance of decarboxylative cross-

coupling was highlighted with its equivalent functionalization by generating stoichiometric

amount of CO_2 as a waste. As synthetic equivalents of organohalides or of organometallic

reagents, carboxylic acids and their derivatives present some clear advantages as substrates:

1) inexpensive, 2) commercially available, 3) easily synthesized, 4) high stability under ambient

conditions. These benefits have sparked the development of a variety of decarboxylative cross-coupling strategies.[24]

1.2.1 Palladium-catalyzed decarboxylative cross-coupling with carboxylic acids/ carboxylates as nucleophilic partner

The first example of a decarboxylative cross-coupling reaction using carboxylic acid was reported by Nilsson in 1966 (Figure 1.7).[24,25]

Nilsson' decarboxylative biaryl synthesis

Nilsson *ActaChem. Scand.,* **1966**, 423
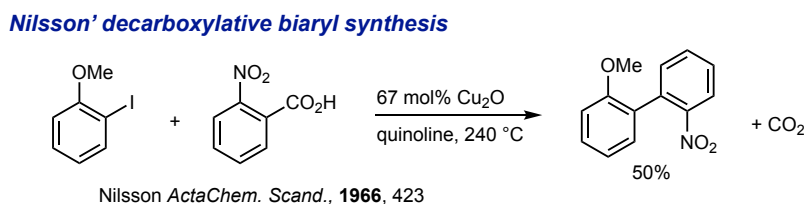
Figure 1.7 Original decarboxylative cross-coupling reactions (Nilsson)

Through this work, Nilsson disclosed that this Cu-catalyzed decarboxylative biaryl synthesis forms the same intermediate as that in an Ullmann biaryl coupling reaction.[24,25] However, decarboxylative cross-coupling requires extremely high reaction temperatures, limiting its applicability in complex molecule synthesis. Since Nilsson' pioneering work, Pd/Cu-catalyzed biaryl synthesis was thoroughly investigated by Gooßen and co-workers.[24]

Gooßen and co-workers first hypothesized that, upon decarboxylation of carboxylate salts, organocopper or organosilver species could cross-couple with aryl halides if there is a metal catalyst that can transmetallate with.[24] Their hypothesis is illustrated in their proposed mechanism of Pd/Cu-catalyzed decarboxylative biaryl synthesis shown in Figure 1.8.[26]

CO$_2$

Decarboxylation

[M]⎯Ar^1

1-7

Oxidative Addition

Ar^2⎯X

Ar^2
Pd^{II}L$_2$
X

Pd^{0}L$_2$

Transmetallation

[M]$^+$ $^-$O⎯C(=O)⎯Ar^1

1-6

Anion Exchange

K$^+$ $^-$O⎯C(=O)⎯Ar^1

[M]$^+$X$^-$

Ar^2
Pd^{II}L$_2$
Ar^1

Reductive Elimination

Ar^1⎯Ar^2

[M]$^+$ = [Cu^{II}F$^-$]$^+$, [Cu^{I}L$_2$]$^+$, Ag$^+$,…; X = I, Br, Cl
L = phosphine, phenanthroline, solvent,…
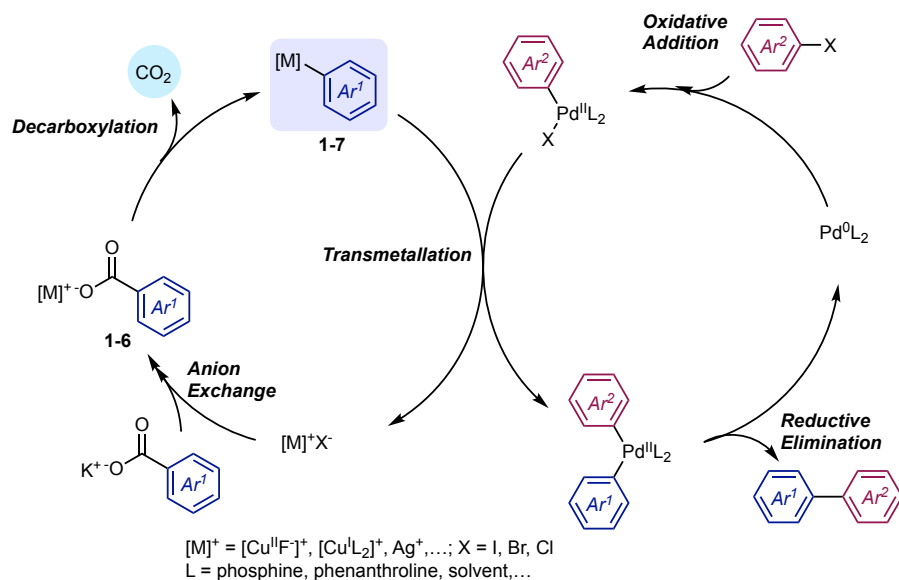
Figure 1.8 Catalytic cycle of Gooßen's Pd/Cu-catalyzed decarboxylative biaryl synthesis

Through extrusion of CO_2, metal-carboxylative salts (**1-6**) form organometallic species (**1-7**), which serve as nucleophiles that transmetallate with Ar^{2}Pd(II)X complex after oxidative addition of Ar^{1}X. The Ar^{1}Pd(II)Ar^2 complex generated after transmetallation undergoes reductive elimination to furnish cross-coupled biaryl product, Ar^1-Ar^2, and regenerate Pd(0)L$_2$, which re-enters the catalytic cycle. According to the proposed mechanism (Figure 1.8), *in-situ* organometallic species, as **1-7** in Figure 1.8, can be made from carboxylic acids and their derivatives. By using this strategy of generating *in-situ* organometallic nucleophiles, Gooßen and co-workers demonstrated Pd/Cu-catalyzed decarboxylative arylation and vinylation can be achieved (Figure 1.9).[26,27]
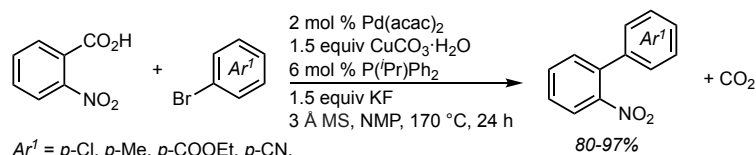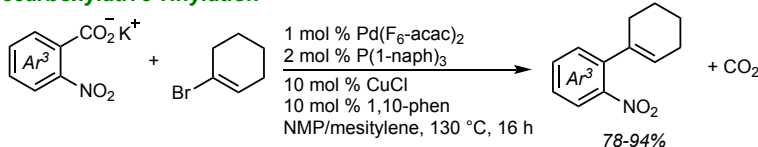
Figure 1.9 Gooßen's decarboxylative cross-coupling reactions

Based on the scope of the reactions, above, explored by Gooßen and co-workers, carboxylic acid or carboxylates with *ortho*-NO_2 substituent were coupled smoothly with various *para*-substituted aryl or alkenyl bromides. However, the substrates with other substituents (2-Ac, 2-OMe, 2-F and etc.) were still cross-coupled but resulted in poor to moderate yields.[26,27]

1.2.2 Nickel-catalyzed decarboxylative cross-coupling with redox-active esters as electrophilic partner

While Gooßen and co-workers have focused on developing Pd-catalyzed decarboxylative couplings of carboxylic acids with aryl[26]-, alkenylhalides[28], and alkenes[27], decarboxylative cross-coupling strategies using redox-active esters, such as Barton esters (**1-8**) and *N*-hydroxyphthalimide (NHPI) esters (**1-9**), have been developed by Barton[29] and Baran[30,31] (Figure 1.10).

Barton's decarboxylation strategy was broadly used in recent total syntheses of natural products, such as (-)-Ilimaquinone.[32] While Barton decarboxylation marked a significant finding, the strategy requires photochemical setup for activation of esters and often uses toxic reductants, such as Bu_3SnH.[31] In 2016, Baran and co-workers reported that Barton esters react with aryl-Ni complexes in the absence of light.[31] They initially hypothesized that aryl-Ni

complexes serve as single-electron oxidants to the pyridothione group and screened various

redox-active esters in this Ni-mediated-coupling.[30] Baran and co-workers subsequently

developed a Ni-catalyzed decarboxylative cross-coupling of alkyl NHPI-esters and organozinc

nucleophiles.[30] While decarboxylation occurred thermally and photochemically with Barton

esters, NHPI-esters undergo decarboxylation thermally.[30,31]

Barton decarboxylation

1-8
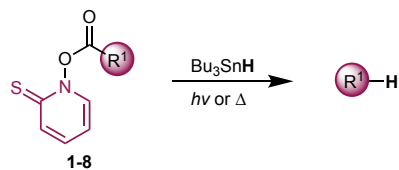
Barton *J. Chem. Soc. Chem. Commun.* **1983**, 939
Barton *Tetrahedron.* **1985**, *41*, 3901

Baran's general Ni- or Fe-catalyzed decarboxylative cross-coupling strategy

1-9
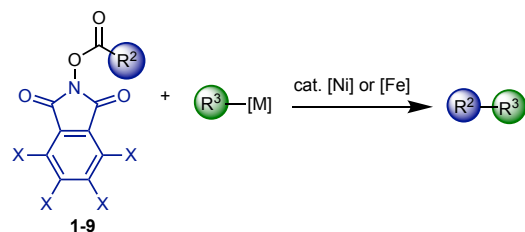
X = H, Cl
[M] = SiPhH$_2$, MgCl, ZnCl, Bpin

R^2 = alkyl,
R^3 = alkenyl, alkynyl, aryl, Het-aryl, Bpin, H

Figure 1.10 Barton's and Baran's decarboxylative coupling reactions

Baran and co-workers also expanded this strategy to decarboxylation[31], Giese

reaction[31], and various decarboxylative alkylation reactions (alkyl-alkyl[33], alkyl-aryl[30,34], alkyl-(*N*-

hetero)-aryl[35], alkyl-boryl[36], alkyl-alkenyl[37], and alkyl-alkynyl[38]) under Ni- or Fe-based condition

(Figure 1.10, Bottom). Furthermore, Baran and co-workers clearly revealed that alkyl-(*N*-

hetero)-aryl cross-coupling with conventional organometallic reagents, such as

organomagnesium (Kumada), organozinc (Negishi), and boronic acids (Suzuki) reagents, are

also applicable to decarboxylative coupling by using NHPI- or TCNHPI- or HATU esters as a

surrogate of alkyl halides under Ni- or Fe-based catalytic conditions.[35]

1.2.3 Development in radical-catalyzed oxidative decarboxylative cross-coupling reactions

However, decarboxylative cross-coupling with cinnamic acids and their derivatives often requires high reaction temperature and has limited scope of substrates. As Gooßen and co-workers demonstrated with decarboxylative cross-coupling between *trans*-cinnamic acid and *p*-Tol-Br, elevated temperatures of 170 °C were necessary to yield the cross-coupled product, *p*-methyl-stilbene (Figure 1.11).[24]

Gooßen *J. Am. Chem. Soc.* **2007**, 4824-4833.
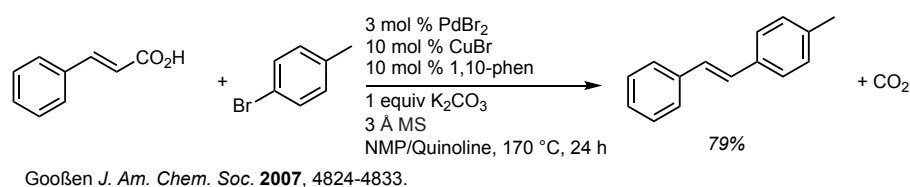
Figure 1.11 Gooßen's decarboxylative cross-couplings with cinnamic acids

Thus, previous decarboxylative cross-coupling reactions often requires: 1) harsh reaction condition and 2) transition-metal mediator. To overcome the limitations of decarboxylative cross-coupling with cinnamic acids, oxidative decarboxylative cross-coupling strategy, that uses stoichiometric amount of oxidants, was developed to improve reaction condition by lowering reaction temperature and, ultimately broaden the scope of carboxylic acids.[24] Particularly, the oxidative decarboxylative cross-coupling with cinnamic acids has been further explored with various substrates, such as alcohols, vinyl halides, and aryl boronic acids by Liu, Miura, and their co-workers (Figure 1.12).[43-45]

Liu's decarboxylative alkylation
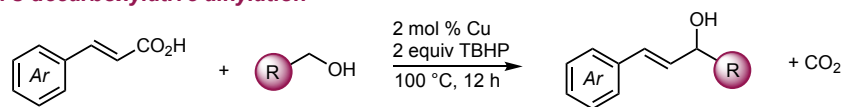
Liu *Chem. Sci.*, **2012**, 2853.

Miura's decarboxylative alkenylation
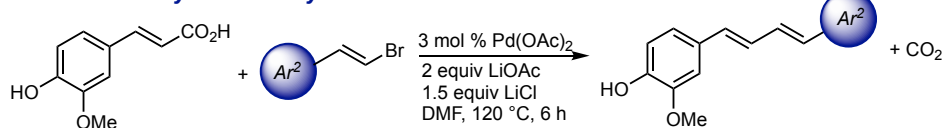
Miura *Org. Lett.*, **2010**, 592.

Miura's decarboxylative arylation
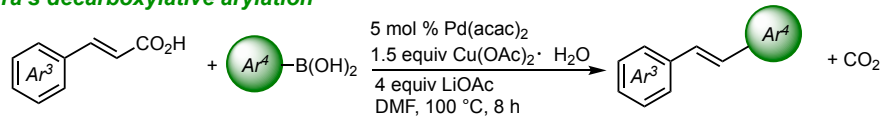
Miura *Chem. Lett.*, **2010**, 68.

Figure 1.12 Decarboxylative cross-couplings with cinnamic acids

Liu and co-workers demonstrated that alcohols can be used as alkylating reagents in the presence of catalytic amount of Cu and stoichiometric amount of TBHP as an oxidant.[39] While many Cu- or Fe-mediated decarboxylative $C(sp^2)$-$C(sp^3)$ cross-coupling strategies have been developed, $C(sp^2)$-$C(sp^2)$ cross-coupling strategies are less explored.[40]

In 2010, Miura and co-workers reported decarboxylative alkenylation and arylation of cinnamic acids under Pd-catalyzed or Pd/Cu-mediated reaction conditions (Figure 1.13).[41,42] By coupling organoboron nucleophile, Miura and co-workers demonstrated Suzuki-Miyaura type decarboxylative arylation can also be achieved via Pd/Cu-mediated catalytic cycle (Figure 1.13).
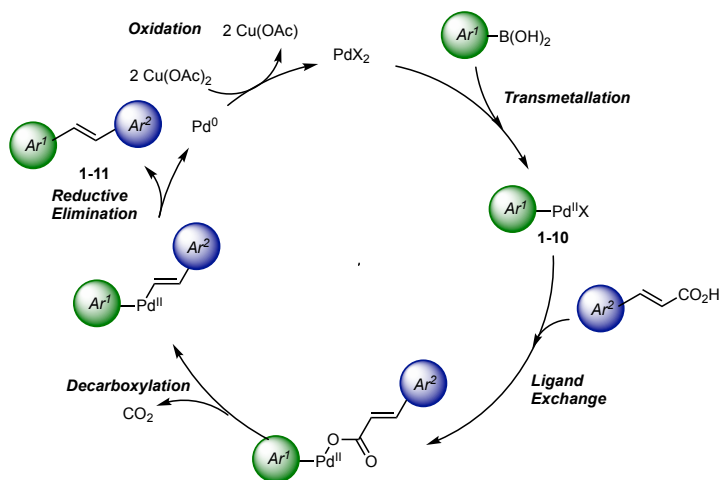
Figure 1.13 Catalytic cycle of Pd/Cu-mediated decarboxylative arylation

This reaction was proposed to proceed via an initial transmetallation of the intermediate Pd(II) species with the aryl boronic acid substrate to give an Pd(II)-aryl species (**1-10**), which undergoes ligand exchange with the aryl cinnamate. Decarboxylation and subsequent reductive elimination, yields the observed stilbene product (**1-11**) and Pd(0) species, which is oxidized by $Cu(OAc)_2$.

1.3 Development in decarbonylative cross-coupling

Following the trend of development in decarboxylative cross-couplings, decarbonylative cross-coupling strategy that couples aromatic esters and amides was developed due to their advantages in easy handling and facile preparation.[43] Investigated by Gooßen and co-workers, Rh-catalyzed decarbonylative Suzuki-Miyaura type coupling of aromatic acid anhydrides, was successfully demonstrated via activation of C(acyl)-O bond and serial extrusion of CO gas.[43] Since 2012, Itami, Yamaguchi, and their co-workers have further developed Ni- or Pd-catalyzed decarbonylative cross-coupling reactions to the extent of C-H arylation, Suzuki-Miyaura type reaction, Sonogashira type reaction, and etherification by using aromatic phenyl esters as electrophiles.[43] Through screening of ligands, Yamaguchi, Itami and co-workers revealed that electron-rich monodentate phosphine ligands such as PCy_3 and $Pn\text{-}Bu_3$ enable Ni-catalyzed

decarbonylative Suzuki-Miyaura coupling. However, limitations of the phenyl esters exclude

phenyl 2-pyridinecarboxylate from the reaction scope.[43] With the effort of the Yamaguchi and

Itami groups, the scope of aryl esters as electrophiles could encompass phenyl 2-

pyridinecarboxylate through the discovery of Pd and dcype reaction conditions.[43] While it is

known that decarbonylation occurs most preferentially at highly elevated temperature (>150 °C)

to dissociate CO from metal carbonyl complex, Yamaguchi/Itami's Pd-catalyzed decarbonylative

Suzuki-Miyaura coupling occurs at 130 °C when phenyl 2-pyridinecarboxylate was coupled. As

outlined in Figure 1.14, corresponding aryl phenyl ester undergoes oxidative addition with

LPd(0) through activation of C(acyl)-O, followed by transmetallation with boronic acid and

release of PhOH. According to their mechanistic studies, following decarbonylation is the rate-

determining step in overall catalytic cycle with high energy barrier and decarbonylated

intermediate (**1-14**) undergoes reductive elimination to give cross-coupling product (**1-15**).[44]
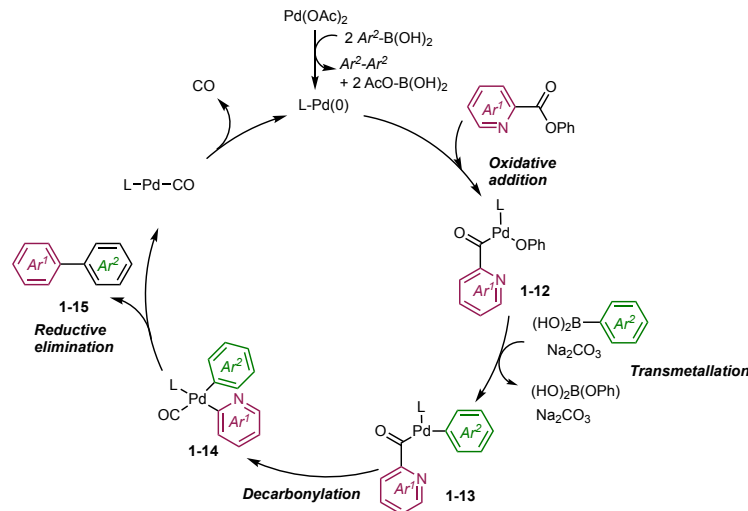
Figure 1.14 Catalytic cycle of decarbonylative Suzuki-type coupling

Further development in decarbonylative cross-coupling with phenyl esters was

accomplished with the efforts of other researchers: both the Shi[45] and the Rueping[46] groups

achieved Ni- or Ni/Cu-catalyzed borylation and silylation, respectively; the Rueping group

accomplished Ni-catalyzed hydrogenation[47] and amination[43]; Itami/Yamaguchi and Gade developed C-H arylation of benzoxazole[48].

Amides were analogously investigated as an ester alternative. In 2008 and 2010, phthalimides were first used for decarbonylative addition of phthalides with alkynes and 1,3-dienes by Matsubara and Kurahashi (Figure 1.15).[49]

Decarbonylative addition of phthalimides with alkynes

Kurahashi, T.; Matsubara, S.. *J. Am. Chem. Soc.,* **2008**, *130*, 6058

10 examples
13-92% yields

Decarbonylative addition of phthalimides with 1,3-dienes

Kurahashi, T.; Matsubara, S. *Org. Lett.*, **2010**, *12*, 4548.

major regioisomer
9 examples
31-99% yields
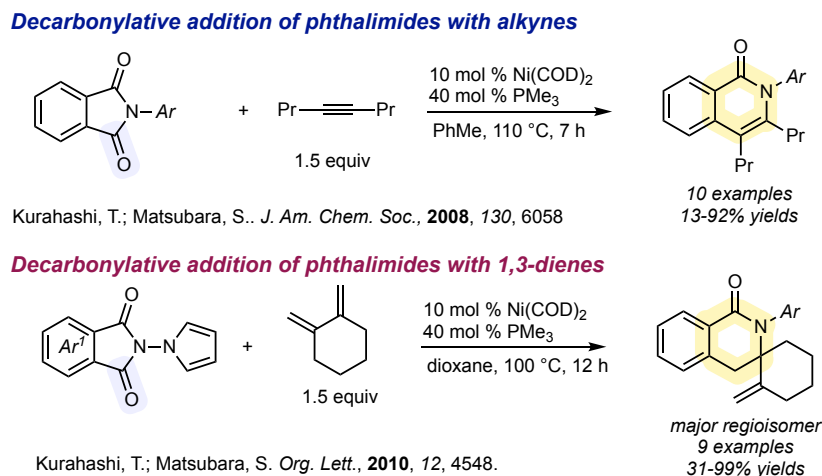
Figure 1.15 Decarbonylative addition of phthalimides with alkynes and 1,3-dienes

With the efforts of Johnson, Szostak and Rueping, there was immense development in decarbonylative cross-coupling with amides with rich examples as following: decarbonylative Suzuki-Miyaura type (Szostak), Negishi type (Johnson), C-H arylation (Szostak), and Amination (Rueping) reactions.[43] In non-decarbonylative cross-coupling with amides, with the absence of extrusion of CO, Garg and Szostak and their co-workers expanded it to non-decarbonylative Negishi type coupling (Garg and Szostak), transamidation (Garg), Suzuki-Miyaura type (Szostak) reactions and etc.[43]

1.4 Summary and goals of the project

We were primarily interested in developing a synthetic method to access β,γ-unsaturated carbonyl groups, which is an interesting synthetic motif found in molecules with a wide variety of biological activities (**1-16, 1-17, 1-18, 1-19**) (Figure 1.16).
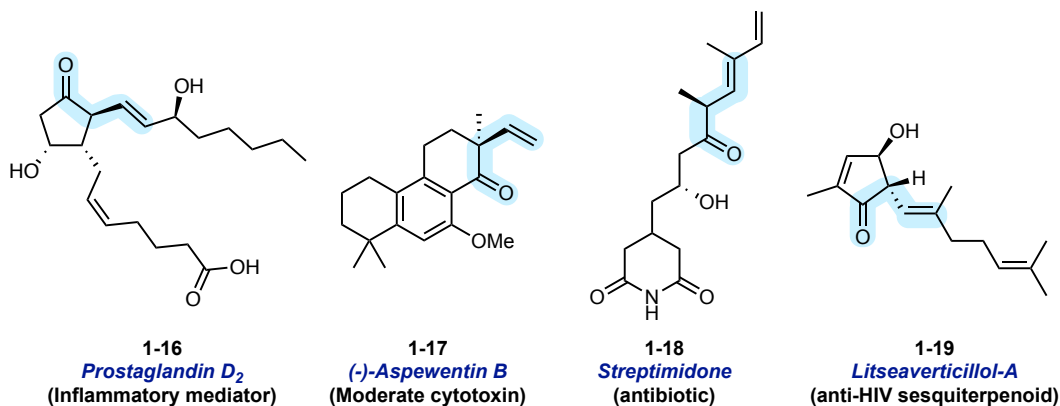
Figure 1.16 β,γ-unsaturated ketones in bioactive molecules

1-16	1-17	1-18	1-19
Prostaglandin D$_2$	*(-)-Aspewentin B*	*Streptimidone*	*Litseaverticillol-A*
(Inflammatory mediator)	(Moderate cytotoxin)	(antibiotic)	(anti-HIV sesquiterpenoid)

While prior α-vinylation methods have been reported by Buchwald[50], MacMillan[51], and others[52] researchers, our approach in decarbonylative/decarboxylative α-vinylation is unique because it does not require the usage of highly reactive/unstable organometallic reagents or organohalide-derived substrates.

Inspired by pioneering work done by Itami[43] and Yamaguchi[43], we approached α-vinylations via decarbonylative cross-coupling by using cinnamates as electrophiles. As introduced in 1.1.3, Itami[43], Yamaguchi[43] and their co-workers investigated decarbonylative cross-coupling reactions using aryl-boronic acids and terminal alkynes as nucleophiles, but there are no general methods using enoic acid derived esters as electrophilic partner.

In an alternative pathway, we hypothesized α-vinylation can be achieved via decarboxylative cross-coupling by using commercially available and relatively inexpensive *trans*-cinnamic acids as source of olefins. We assumed that diverse carbonyls sources could be coupled with various *trans*-cinnamic acids via decarboxylative pathway upon generation of alpha-carbonyl radicals, which is a well-established area developed by Snider and co-workers and will be introduced in Chapter 3.

15

1.5 References

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Chapter 2: Oxidative decarboxylative cross-coupling of cinnamic acids with ketones

2.1 Recent progress in oxidative decarboxylative cross-coupling of cinnamic acids

Transition-metal catalyzed decarboxylative cross-coupling of carboxylic acids and carboxylates has been well-developed as it was introduced in Chapter 1.2.1.[1] In contrast with traditional cross-coupling that requires sometimes expensive pre-synthesized organometallic reagents, decarboxylative cross-coupling represents a milestone in the history of cross-coupling by using inexpensive and widely available carboxylic acids and their derivatives as alternative coupling substrates. However, the scope of decarboxylative cross-coupling was mostly focused in the use of aryl carboxylic acids with organohalides. The pioneering work in Ni- or Fe-catalyzed cross-coupling of redox-active esters by Baran[2] and co-workers demonstrated that the scope of decarboxylative cross-coupling can be expanded to alkyl esters with successful coupling with various nucleophilic partners (organozinc, organomagnesium, and organoboron reagents).

The substitute for organohalides and organometallic reagents evolved another wave in cross-coupling strategy, which is an oxidative decarboxylative cross-coupling. With recent investigation done by Liu[3], Mao[4], Wang[5], Han[6] and Pan[5], decarboxylative oxidative cross-couplings between cinnamic acid and alkyl substrates with abstractable C-H bonds (e.g. alcohols, ethers, and alkanes) were well understood that the coupling undergoes radical process. In the presence of either TBHP and DTBP, hydrogen atom abstraction forms a carbon-radical, which adds into the carbon of cinnamic acid. The resulted benzylic radical then undergoes β-cleavage to lose CO_2 and it forms the final unsaturated product, but alkylated.

Among the examples of oxidative decarboxylative cross-coupling reaction with cinnamic acids, Zhang and co-workers' work report a divergent approach that formed furanyl products (**2-1**) (Figure 2.1).[7] Through the outlined mechanism, Zhang and co-workers proposed that an *in-*

situ α-carbon radical of the ketone forms. Its formation is vital in making a furan via radical-promoted decarboxylative process.
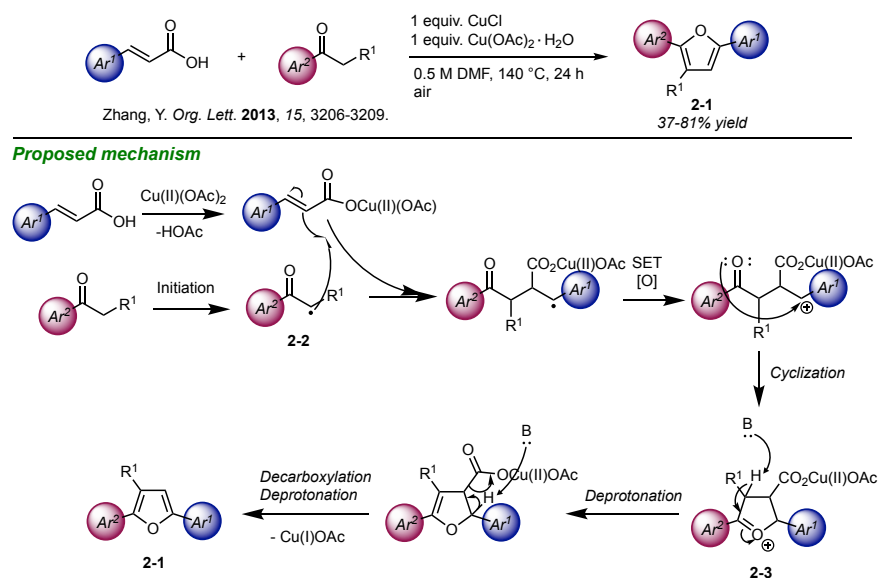
Figure 2.1 Zhang's Cu-mediated decarboxylative furan synthesis

In the proposed mechanism, an enolate-like radical **2-2** adds into the α-position of Cu(II)-cinnamate. The β-keto carboxylate cyclizes into heterocyclic intermediate **2-3** upon single-electron transfer. Subsequent deprotonation and decarboxylation of intermediate **2-3** furnishes furanyl product **2-1**. We were interested in this *in-situ* enolate-like radical by surveying well-established work in Mn-mediated enolate radical cyclization developed by Snider.

2.2 Mn(III)-mediated enolate radical-cyclization

The Mn(III)-mediated enolate radical cyclization via deprotonation-oxidation is a well-investigated area by Snider and co-workers.[8] Generally, Snider and co-workers demonstrated the Mn(III)-mediated enolate radical cyclization by using β-keto esters, such as **2-4**, with acidic α-protons (Figure 2.2).

Snider, B. *Chem. Rev.*, **1996**, 341
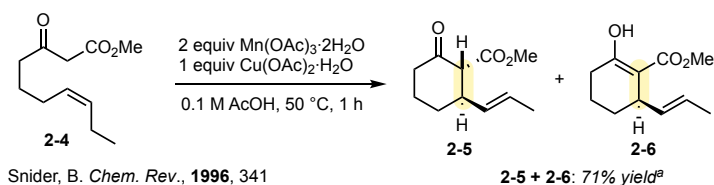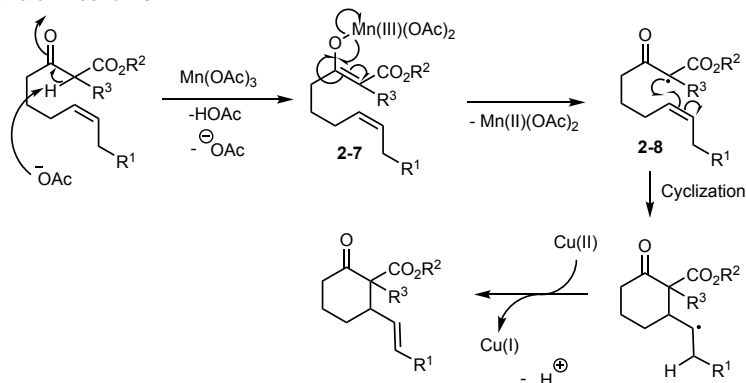
Generally works well with

1) *β-keto ester with pKa ≤ 12[b]*   2) *5-exo, 6-exo, or 6-endo*-cyclization model

[a]Mixture of tautomers **2-5** and **2-6**. [b]pKa in water

Figure 2.2 Snider's Mn(III)-mediated enolate radical-cylization

In the proposed mechanism, upon the deprotonation of acidic α-proton of **2-4** and

coordination with Mn(III), Mn(III)-enolate **2-7** is formed, which then oxidizes into enolate-like

radical **2-8**. Subsequent cyclization into the tethered alkene followed by Cu(II)-mediated

oxidative elimination resulted in 71% yield of cyclized products **2-5** and **2-6** as a mixture of

tautomers.[9] With the strategy of producing an *in-situ* α-carbon radical by utilizing

Mn(OAc)$_3$•2H$_2$O, Snider and co-workers established a rich history in Mn(III)-mediated oxidative

cyclization.

According to Snider, the nature of the Mn(III)-mediated oxidative cyclization depends on

the rate of formation of Mn(III)-coordinated enolate, which is governed by pKa and the ease of

single-electron oxidation of the enolate.[8,9,10] While the enolization step is rate-determining step

for most ketones, for very acidic compounds with pKa ~12 or less (in water), oxidation of the

enolate is slow.[9,10] With a slow enolate oxidation step, type of alkenes and length of tether affect

the rate of cyclization.[9,10] Through their investigation with β-keto esters with different lengths of tether, Snider and co-workers determined the rate of 6-exo cyclization to be faster than the rate of 5-endo cyclization.

2.3 Objective of this work

As an alternative pathway to β,γ-unsaturated ketones, we were interested in using an oxidative decarboxylative cross-coupling strategy, which was introduced in Chapter 2.1. Prior to beginning our investigations, we set out to replicate five oxidative decarboxylative reaction conditions using four different coupling partners: a) 1,4-dioxane by Liu[3] and Wang[5] b) toluene-derivatives by Mao[4] c) cycloalkanes by Han[5]&Pan[5] and d) ketones by Zhang[7].
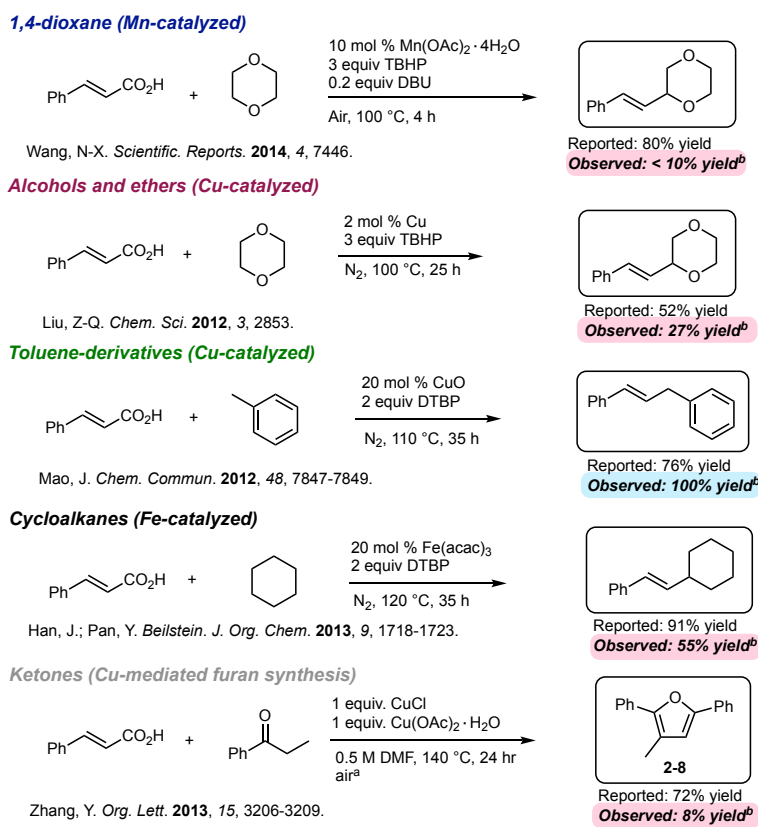
Figure 2.3 Replication of oxidative decarboxylative coupling reactions from literature

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However, not all of these reports could be replicated with the advertised yields reported in literature. The exception was Mao[4]'s Cu-catalyzed oxidative decarboxylative coupling between cinnamic acid and toluene (Figure 2.3, entry 3). Although we attempted replication of Wang[5]'s Mn-catalyzed oxidative decarboxylative coupling between cinnamic acid and 1,4-dioxane in various approaches, we could not successfully replicate their work as they reported the reactions were successful in air. To the other extent, the unsuccessful results of replications indicated that oxidative decarboxylative coupling strategy has a room for development. While others primarily coupled cinnamic acid with electron-rich C(sp^3)-H-containing substrates, Zhang[7] and co-workers demonstrated that ketones, such as propiophenone, can also be coupled with cinnamic acid, but forming furanyl products **2-1** in 37-81% yields (Figure 2.1). We were particularly interested in the synthesis of these furanyl products because, from the proposed mechanism of their formation, it invokes the generation of enolate-like radicals **2-2** of ketones. Zhang[7]'s work inspired us to question whether oxidative decarboxylative cross-coupling between cinnamic acid and a ketone could be achieved without furanyl product formation.

Intriguingly, Wang[12], Xing[12], and co-workers observed the formation of 1,4-dione product (**2-9**) with the best result earned when dual-metal additives (Cu[II]/Mn[II]), super-stoichiometric amount of TBHP, and non-nucleophilic amine base (DBU) were added to the system.
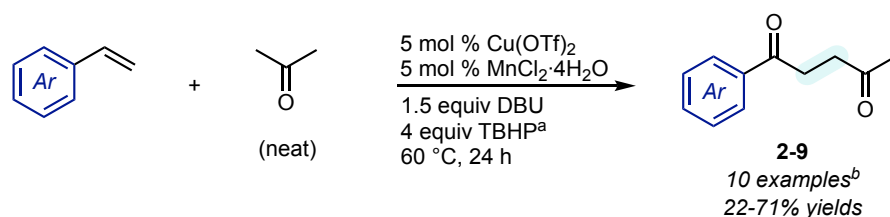
Wang, N-X.; Xing, Y. *Org Lett.* **2015**, *17*, 4460-4463

[a]70 wt% in water. [b]Excludes 4-CF_3, 4-NO_2-, and 4-NH_2-products **2-9**

Figure 2.4 Oxidative coupling of styrenes with ketones

Furthermore, the scope of styrenes explored by Wang[12], Xing[12], and co-workers indicated that the electronics of the styrene governs the coupling reactions. No corresponding

1,4-dione products (**2-9**) were detected or were produced in poor yields (< 20%) when electron-deficient styrenes (4-CF$_3$, 4-NO$_2$) were used.

By merging the strategies in oxidative decarboxylative cross-coupling of cinnamic acids and Mn(III)-mediated oxidative cyclizations, we hypothesized, if an *in-situ* α-carbon radical could be generated, upon deprotonation of ketone, we can potentially achieve α-vinylation by suppressing oxidative cyclization.

2.4 Results

We initially anticipated the formation of a β,γ-unsaturated ketone product if: 1) an electrophilic enolate-like radical forms, and 2) an alkene reforms followed by decarboxylation. To test our hypothesis, we initially designed a screening of reaction conditions based on metal additives, oxidants, and non-nucleophilic amine bases. To maximize concentration of α-carbon radicals of ketones, we chose acetone as a model ketone and solvent.

^{a}Reactions run by following General Method 2-A. ^{b}With DBU, instead of DABCO, 1,4-dione **2-10** observed in 4% yield
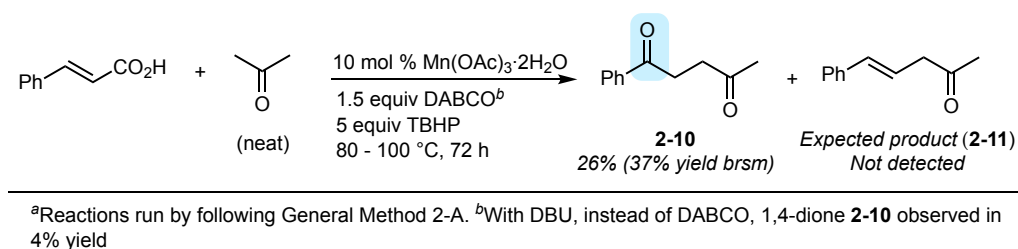
Figure 2.5 Initial screening of oxidative decarboxylative cross-coupling with acetone^a

In contrast to our initial hypothesis that β,γ-unsaturated ketones could be formed via an oxidative decarboxylative cross-coupling, we did not observe this expected product (**2-11**). Rather 1,4-dione product (**2-10**) was isolated in 26% yield (37% yield brsm) using 10 mol % Mn(OAc)$_3$•2H$_2$O, 5 equivalences of TBHP (in 70 wt% in water), and 1.5 equivalence DABCO at 80-100 °C for 72 hours. Formation of a 1,4-dione suggests that, under the reaction conditions, a decarboxylative coupling between cinnamic acid and acetone occurred with concomitant oxidation of the benzylic position. Although the desired functionality of β,γ-unsaturated ketone

was not observed, the functionality of 1,4-dione product was interesting enough by being a

polarity-mismatched product in terms of Aldol chemistry. Therefore, we proceeded to investigate

this reactivity via optimization of reaction conditions based on metal additives, bases, initiators,

and solvent.

Table 2.1 Optimization of cinnamic acid and acetone decarboxylative coupling[a]

Entry	Deviation from "standard" condition	2-10 Yield[c]
1	None	26% (37% brsm)
2	DLP, instead of TBHP	N.D.[d]
3	DTBP, instead of TBHP	N.D.[d]
4	K_2CO_3, instead of DABCO	<5%
5	NaOAc, instead of DABCO	20%
6	80 °C, instead of 100 °C	<5%
7	20 equiv acetone in AcOH(0.2 M), instead of neat	10%
8	20 equiv acetone in DMSO(0.2 M), instead of neat	<5%
9[e]	100 mol % Mn(OAc)$_3$·2H$_2$O, instead of 10 mol % Mn(OAc)$_3$·2H$_2$O	11%
10	2 mol % Mn(OAc)$_3$·2H$_2$O and 2 mol % NiBr$_2$, instead of 10 mol % Mn(OAc)$_3$·2H$_2$O	32%

[a]Reactions run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield. [d]Not detected. [e]Mn(OAc)$_3$·2H$_2$O (50 mol %), DABCO (1.5 equiv), TBHP (1 equiv) at 100 °C for 2 h, added TBHP (1 equiv) and heated for 2 h, added Mn(OAc)$_3$·2H$_2$O (50 mol %) and heated for another 2 h.

Though other initiators, including DLP, DTBP, BPO, and AIBN, were investigated, none

resulted in a higher yield of **2-10** than TBHP (Table 2.1, entry 2-3; Appendix 2.10.1). We then

turned our focus to other reaction parameters. We began examining the effect of base added.

However, with other non-nucleophilic amine bases (DBU and Et$_3$N) and inorganic bases

(K_2CO_3, NaOAc, K_3PO_4 and etc.) used in place of DABCO, the yield of **2-10** did not exceed

20%. Experiments carried out at temperatures below 100 °C resulted in only trace amount of

1,4-dione formation.

Instead of using acetone as solvent, we attempted analogous reactions with excess acetone (20 equiv) in a variety of organic solvents (MeCN, DMF, DMSO, AcOH, CHCl$_3$, DCE). However, no solvent was effective than the neat conditions.

We then began to explore the effect of various metal additives in 1,4-dione formation. Through the extensive screening of metal additives, the 1,4-dione product was observed, also with nickelous-, cuperous-, and ferrous-metal salts. Conversely when Cu(acac)$_2$, CuOAc, and CoCl$_2 \bullet$ 6H$_2$O were used, the reactivity of 1,4-dione was no longer observed, but only consumption of starting material was observed. These studies revealed that experiments using 10 mol % Mn(OAc)$_3 \bullet$ 2H$_2$O resulted in higher yields than with 100 mol % Mn(OAc)$_3 \bullet$ 2H$_2$O, added in two portions (50 mol % each) (Table 2.1, entry 9; Appendix 2.10.2). Following this trend, we found that the yield of 1,4-dione **2-10** was increased from 26% to 32% when a mixture of two metal additives, Mn(OAc)$_3 \bullet$ 2H$_2$O and NiBr$_2$, in 2 mol % each were added instead of 10 mol % Mn(OAc)$_3 \bullet$ 2H$_2$O (Table 2.1, entry 10). Among the combinations of metals assessed, the combination of Mn(OAc)$_3 \bullet$ 2H$_2$O and NiBr$_2$ gave the highest yield of 1,4-dione product **2-10**, 32% (Appendix 2.10.6). Through rigorous screening of reaction condition (metal additive, base, single-electron oxidants, solvent, concentration, equivalence of base), we concluded that the most effective reaction condition that yields 1,4-dione **2-10** the most is as outlined in Table 2.1 above. (Appendix 2.10.1-2.10.4)

During the optimization of the reaction condition, we observed that the yield of 1,4-dione decreases or increases when certain metal salts are added with Mn(OAc)$_3 \bullet$ 2H$_2$O. Therefore, we were intrigued to investigate what factors play as significant roles in producing 1,4-dione product by carrying out control experiments as below (Table 2.2).

Table 2.2 Control experiments[a]
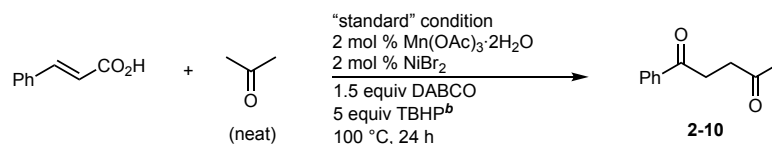
Entry	Deviation from "standard" condition	2-10 Yield[c]
1	None	32%
2	No Mn(OAc)$_3$·2H$_2$O/NiBr$_2$ and no TBHP	N.D.[d]
3	No DABCO and no TBHP	N.D.[d]
4	No TBHP	< 5%
5	No DABCO	< 5%
6	No Mn(OAc)$_3$·2H$_2$O/NiBr$_2$ and DABCO	< 5%
7	44 equiv water + No Mn(OAc)$_3$·2H$_2$O/NiBr$_2$, DABCO and TBHP	< 5%

[a]Reactions run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield. [d]Not detected.

These control experiments revealed that the formation of 1,4-dione product was only produced when TBHP in water was added with a combination of Mn(OAc)$_3$•2H$_2$O and NiBr$_2$, and base. Removing any one of these reaction components failed to result in any appreciable amount of the 1,4-dione product.

The importance of water observed from these control experiments prompted us, next, to investigate the reaction sensitivity to air and water (Table 2.3).

Table 2.3 Air- and water sensitivity of the oxidative decarboxylative coupling reaction[a,b]
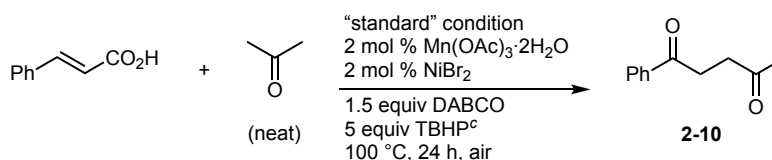
Entry	Deviation from "standard" condition	2-10 Yield[d]
1	None	32%
2[b]	N$_2$, instead of air	12% (14% brsm)
3	TBHP[c] + 60 µL water, instead of TBHP[c]	15%
4	TBHP[e] in dodecane, instead of TBHP[c]	<5%
5	TBHP[e] in dodecane + 60 µL water, instead of TBHP[c]	10%
6	60 µL water, instead of TBHP[c]	<5%

[a]Reactions run by following General Method 2-A. [b]Reactions run by following General Method 2-B. [c]70 wt% in water. [d]Isolated yield. [e]5.0-6.0 M dodecane.
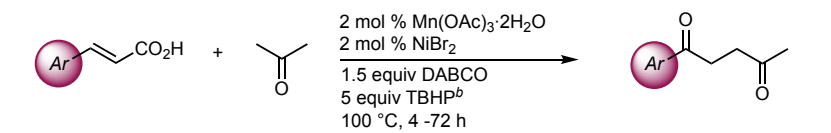
The results summarized in Table 2.3 show that the yield of **2-10** decreased from 32% to 12% (14% brsm) by sparging the reaction with a N_2-filled balloon prior to heating. This suggests that the reaction benefits from an aerobic atmosphere.
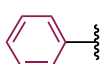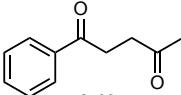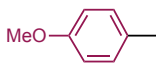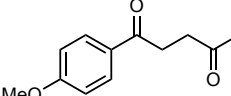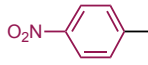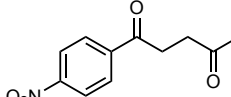
To test the effect of water, we added water in the amount equivalent to the amount present in aqueous TBHP (70 wt%) in addition to aqueous TBHP or TBHP in dodecane. While additional water added along with aqueous TBHP did not enhance yield of **2-10**, but it increased the yield of **2-10** from less than 5% to 10% when additional water was added with TBHP in dodecane (Table 2.3 entries 3-5). Water used in place of TBHP resulted less than 5% of 1,4-dione **2-10**. We concluded that aqueous TBHP is essential, but water alone does not promote the observed reaction, however, we expected the presence of water is significant in increasing solubility.

We next questioned whether other oxidants instead of TBHP would similarly produce 1,4-dione product. However, less than 5% yield of 1,4-dione or no product obtained when H_2O_2, mCPBA, DDQ, peracetic acid, and benzoquinone were added (Appendix 2.10.3). Through carrying out control experiment and single-electron oxidant screening, we could conclude that both water and TBHP play key roles in making 1,4-dione functionality. We hypothesize that water may be important in maintaining concentration of hydroxyl radical, which could potentially: 1) abstract a ketone α-hydrogen or 2) oxidize Mn(II) into Mn(III) to make Mn(III)-enolates.

We then turned our focus to further exploration of the scope of enoic acids (Table 2.4) and enolate precursors (Table 2.5).

Table 2.4 Enoic acids scope[a]

Entry	Ar—§	Product	Yield[c]
1	(phenyl)	**2-10**	32%
2[d]	MeO—(phenyl)	**2-12**	18%
3	O₂N—(phenyl)	**2-13**	N.D.[e,f]

[a]Reactions were run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield.
[d]Reaction condtion: Mn(OAc)₃·2H₂O (2 mol %), TBHP[b] (3 equiv), DABCO (1.5 equiv), 4 h, 100 °C.
[e]Confirmed by ¹H-NMR. No corresponding m/z of 1,4-dione **2-13** observed. [f]Not detected.

We attempted oxidative coupling acetone with aryl cinnamic acids, substituted with different functional groups (4-OMe, 4-NO₂) at the para-position. While we observed **2-10** with highest yield (32%) under the optimized reaction condition, corresponding 1,4-dione product **2-12** from 4-methoxycinnamic acid was observed with less than 5%. We achieved, however, oxidative coupling between acetone and *trans*-4-methoxy-cinnamic acid, producing 18% yield of the corresponding 1,4-dione when only Mn(OAc)₃•2H₂O and 3 equivalences of TBHP were used instead of 5 equivalences (Table 2.4, entry 2). Since we observed no oxidative coupling between acetone and electron-deficient enoic acid, we could understand oxidative coupling requires electron-rich enoic acids to produce 1,4-dione product. As we initially hypothesized the formation of electrophilic α-carbon radical of acetone in the presence of metal/base/initiator and the addition of α-carbon radical added on the α-position of enoic acid, enoic acid needs to be electronically matched with electrophilic enolate-like radical by being electron-rich enoic acids. Based on our exploration in the scope of enoic acids, electronically neutral enoic acids were

coupled with acetone most successfully by generating highest yield of 1,4-dione product, but electron-rich enoic acids were also successful in oxidative decarboxylative coupling reaction.

By choosing *trans*-cinnamic acid as an enoic acid substrate, we explored the scope of enolate precursors, including ketones, isopropenyl acetate, and silyl enol ethers, in this oxidative coupling reaction as outlined in Table 2.5.

Table 2.5 Enolate precursors scope[a]

Entry	Enolate precursor	Product	Yield[c]
1		2-10	32%
2		2-10	< 5%
3[d]		2-14	10%
4[d]		2-15	Not isolated[e]
5[f]		2-16	N.D.[g]
6[h]	2-17	2-18	N.D.[g]
7[h]	2-19	2-20	N.D.[g]
8[h]	2-21	2-22	N.D.[g]

[a]All reactions run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield.
[d]Reaction condition: cinnamic acid (0.54 mmol, 1 equiv), ketones (0.4 M, 1.35 mL), Mn(OAc)$_3$·2H$_2$O (2 mol %), NiBr$_2$ (2 mol %), DABCO (1.5 equiv), TBHP (5 equiv, 70 wt% water) in open-tube at 100 °C for 24 h. [e]Formation was only confirmed by GC-MS, could not be isolated.[f]Reaction condition: 4-Methoxy cinnamic acid (0.54 mmol, 1 equiv), ketones (10 equiv, 5.4 mmol), metal additives (50 mol %), DABCO (1.5 equiv), TBHP (2 equiv, 70 wt% water), PhCl (0.2 M) in closed-tube at 100 °C for 24 h. (See appendix 2.10.9) [g]Not detected. [h]Reaction condition: cinnamic acid (0.54 mmol, 1 equiv), silyl enol ethers (2.7 mmol, 5 equiv), Mn(OAc)$_3$·2H$_2$O (2 mol %), NiBr$_2$ (2 mol %), DABCO (1.5 equiv), TBHP (5 equiv, 70 wt% water) in closed-tube at 100 °C for 24 h.

Under the best reaction condition optimized by using acetone as enolate precursor, we observed formation of 1,4-dione products (**2-10, 2-14**) when isopropenyl acetate and cyclohexanone were chosen. As it is demonstrated in Table 2.5, the isopropenyl acetate, being an enol acetate derived from acetone, was able to be coupled with *trans*-cinnamic acid by producing 1,4-dione product **2-10** in less than 5% yield. While the isopropenyl acetate coupled with *trans*-cinnamic acid by yielding poor yield, we demonstrated the oxidative coupling between isopropenyl acetate and 4-MeO-*trans*-cinnamic acid can make 1,4-dione product **2-12** (Table 2.4) in 13% yield (Appendix 2.10.5). We were also delighted to achieve oxidative coupling of *trans*-cinnamic acid with cyclohexanone by successfully isolating 1,4-dione product **2-14** in 10% yield. We've noticed cyclohexanone has very close pKa (26.4 in DMSO) to that of acetone (26.5 in DMSO). However, when other enolate precursors (acetophenone, dimethyl malonate), having low pKa (< 20), or silyl enol ethers (**2-17**, **2-19**, **2-21**) were used, the corresponding 1,4-dione products (**2-18**, **2-20**, **2-22**) were not detected. With dimethyl malonate, we observed methylation of 4-methoxy cinnamic acid, which formation was not mechanistically understood. Other carbonyl sources, such as acetic acid and *tert*-butyl acetate, were also attempted, however, only the consumption of 4-methoxy-cinnamic acid was observed (Appendix 2.10.10).

Throughout the development in an oxidative decarboxylative coupling strategy to achieve α-vinylation of enolate precursors, we did not observe formation of β,γ-unsaturated ketones, but observed the formation of 1,4-dione product. Based on our experimental results, we proposed four different mechanisms to understand the formation of 1,4-dione products (Figure 2.7-2.10). Prior to those mechanistic proposals, we initially proposed two pathways of making enolate-like radicals via: 1) Mn(III)-mediated oxidation or 2) hydrogen abstraction of acetone (Figure 2.6).
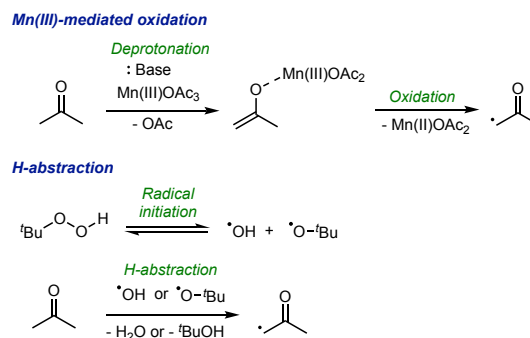
Figure 2.6 The mechanistic hypotheses for enolate-like radical formation

As our first hypothesis, we proposed that enolate-like radical is generated when Mn-enolate of acetone is oxidized by reducing Mn(III) to Mn(II). We also proposed that the generation of enolate-like radicals is achieved via hydrogen abstraction of acetone. However, Mn(III)-mediated oxidation was not likely based on our experimental results that do not require stoichiometric amount of metal additives. Furthermore, we observed some metal additives inhibit or promote the formation of 1,4-dione products. Therefore, we identified hydrogen abstraction of acetone is most likely to occur to generate the enolate-like radical.

We proposed four possible mechanisms based on generation of enolate-like radical via hydrogen abstraction as follows (Figure 2.7-2-10).
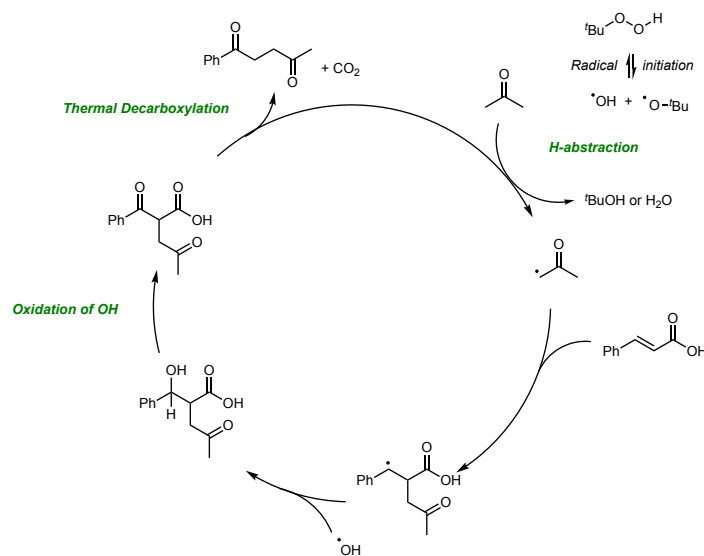
Figure 2.7 The mechanistic proposal 1 for 1,4-dione formation

In the mechanistic proposal 1 (Figure 2.7), we proposed that the enolate-like radical adds into α-position of cinnamic acid to generate a resonance-stabilized benzylic radical. The benzylic radical can be terminated by hydroxyl radical, generated after initiation of TBHP, to produce β-hydroxy carboxylic acid intermediate. We then proposed oxidation of β-hydroxy carboxylic acid into β-keto carboxylic acid and the subsequent thermal decarboxylation of β-keto carboxylic acid generates 1,4-dione product. However, oxidation of secondary alcohol into ketone requires high-valent metal oxidants, such as Cr(VI), and the absence of such oxidant in the system supports the oxidation is unlikely to occur. It is also known that allylic alcohol and benzylic alcohol can be oxidized into ketone in the presence of MnO_2, however, we observed the formation of 1,4-dione products even occurs in the absence of metal additives. Therefore, this mechanistic proposal 1 is unlikely to occur.

As identified in the previous mechanisms, we expected the same intermediate with a benzylic radical will preferentially form due to stabilization through resonance. We then proposed mechanistic proposal 2 (Figure 2.8) as below.
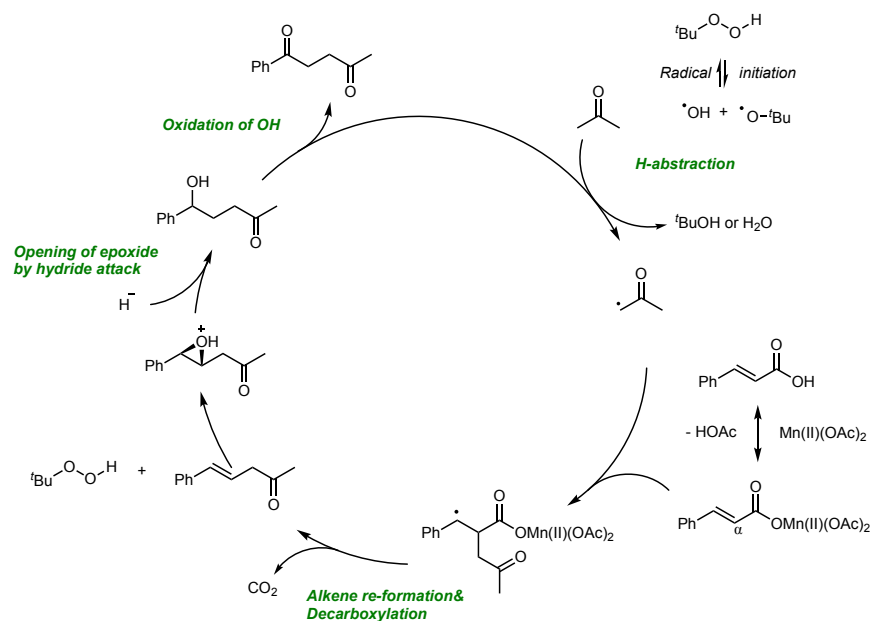
Figure 2.8 The mechanistic proposal 2 for 1,4-dione formation

In the mechanistic proposal 2, we proposed that the benzylic radical undergoes alkene re-formation and decarboxylation to yield β,γ-unsaturated ketone. The β,γ-unsaturated ketone undergoes epoxidation in the presence of TBHP. Subsequently, this epoxide could be opened by a hydride attack by generating a secondary alcohol, which oxidizes into ketone to generate the 1,4-dione product. However, we identified this mechanistic proposal 2 is also unlikely to occur due to several reasons: 1) we could not capture the formation of β,γ-unsaturated ketone 2) hydride attack of epoxide is extremely unlikely under highly oxidizing reaction condition and 3) the absence of high-valent metal oxidants for oxidation of secondary alcohol into ketone. In similar reason we ruled out the mechanistic proposal 1, the generation of 1,4-dione products did not even require the addition of metal additives. Therefore, this mechanistic proposal 2 is unlikely to occur.

We then proposed the mechanistic proposal 3 as below (Figure 2.9).
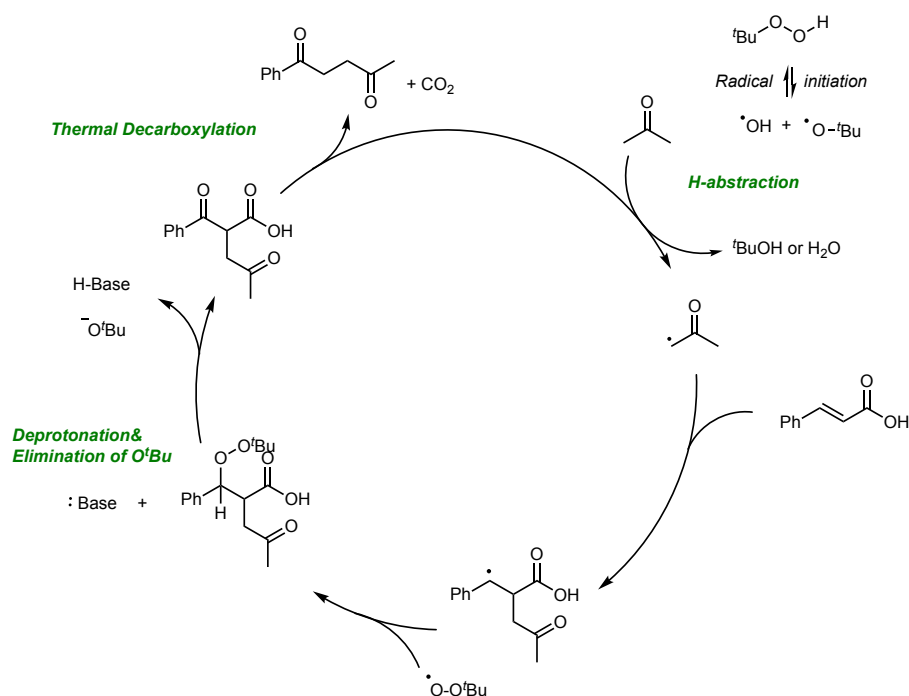
Figure 2.9 The mechanic proposal 3 for 1,4-dione formation

We anticipated the benzylic radical can also be terminated by a *tert*-butyl peroxy radical

to generate a β-*tert*-butyl peroxy carboxylic acid as an intermediate. Upon deprotonation by

DABCO, the β,γ-diketo carboxylic acid initially forms and the β,γ-diketo carboxylic acid

decarboxylates readily at elevated temperature. This elimination is analogous to Kornblum-

DeLaMare rearrangement.[11] This mechanistic proposal supports the need of stoichiometric

amount of base and we also observed the yield of 1,4-dione product increased when

equivalence of base increased (Appendix 2.10.5). In this mechanistic proposal 3, it proposes

radical-radical termination and the radical termination of such reactive radicals is not likely to

occur, therefore, this led us to the mechanic proposal 4, which is the most likely to be operative

(Figure 2.10).
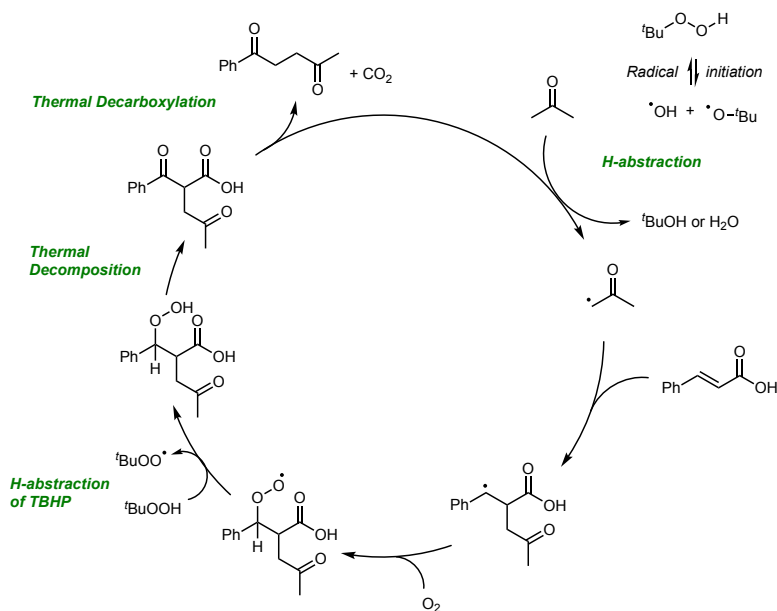
Figure 2.10 The mechanistic proposal 4 for 1,4-dione formation

We also proposed that the benzylic radical can be trapped by a molecular oxygen in

solution by generating a peroxy radical. The corresponding peroxy radical then abstracts

hydrogen from TBHP and the thermal decomposition of alkyl hydroperoxide gives β,γ-diketo

carboxylic acids. At elevated temperature, we anticipated thermal decarboxylation of β,γ-diketo

carboxylic acids occurs readily. Unlike most diatomic molecules are singlet at ground state, molecular oxygen is triplet at ground state. Interaction between organic radical and molecular oxygen occurs in diffusion-controlled rate. At such elevated temperature, we expected facile thermal decarboxylation of β,γ-diketo carboxylic acid will occur. As we obtained higher yield of 1,4-dione products in the presence of air, compared to nitrogen, the mechanistic proposal 4 well supports the importance of air in formation of 1,4-dione products and it is most likely to occur.

2.5 Summary and future outlook

We developed a decarboxylative oxidative coupling of cinnamic acids and ketones (acetone, isopropenyl acetate, and cyclohexanone) to produce 1,4-dione products in low to moderate yields (5 - 32%). We initially anticipated a ketone α-vinylation pathway would result in β,γ-unsaturated carbonyls via decarboxylative oxidative coupling. However, we observed the formation of 1,4-dione. The scope of enoic acids has been explored and the result indicated that electronics of enoic acid dictate the formation of 1,4-dione product by being only made when a neutral or electron-rich cinnamic acids were used (4-H- and 4-MeO-*trans*-cinnamic acids). The scope of enolate precursors was less broad than we anticipated by observing 1,4-dione products (**2-10**, **2-14**) when enolate precursors, such as isopropenyl acetate and cyclohexanone, were chosen. Based on our experimental results, we were able to propose four possible mechanisms to understand the formation of 1,4-dione product and, among them, the mechanistic proposal 4 was most likely to occur. However, our work-up procedure was not sufficiently acidic enough to capture the formation of the β,γ-diketo carboxylic acid. The future work can involve the validation of the mechanistic proposal by monitoring the formation of 1,4-dione products with the addition of β,γ-diketo carboxylic acid under our reaction condition.

2.6 Substrate preparation

Silyl enol ethers (**2-17**[12] and **2-19**[11]) were prepared by using the method reported in the

literature. All physical and analytical data were in good agreement with the values reported in

the literature.[11]

2.7 Experimental data

2.7.1. General Experimental Information

All oxidative decarboxylative coupling reactions were set-up on the benchtop. Solvents

(Acetone, DMF, DMSO and etc.) were used as received. All commercially available reagents

(excluding silyl enol ethers **2-17, 2-19, 2-21**) were purchased and were used as received.

Ketones (cyclohexanone and acetophenone) were distilled prior to use. Progress of reactions

was monitored by analytical TLC on silica gel 60-F_{254} (Merck EMD Millipore) and GC-MS

(Agilent 7890B GC/5977B MSD). Reactions were purified via short-column chromatography

packed with silica (Silicycle SilicaFlash® P60).

2.7.2. General method 2-A

In a 1-dram vial, Mn(OAc)$_3$ · 2H$_2$O (7 mg, 27 µmol, 0.10 equiv), DABCO (45 mg, 0.40 mmol, 1.5

equiv), *trans*-cinnamic acid (40 mg, 0.27 mmol, 1 equiv) were weighed and added along with a

magnetic stir bar. To the vial with reagents, acetone (1.35 mL, 0.2 M) was added and,

subsequently, aqueous TBHP in 70 wt% water (190 µL, 1.3 mmol, 5 equiv) was added, followed

by capping the vial. The reaction mixture was stirred and heated at 100 °C for 24 hours. The

reaction was monitored by TLC and GC-MS. Once reaction was completed, the reaction was

diluted with DCM (4 mL) and was added with DI H$_2$O (8 mL) for aqueous wash. After extracting

the organic layer with DCM (4 mL) for 5 times, collected organic layer was washed with brine.

After concentrating the organic layer, the crude mixture was purified via column chromatography

charged with silica gel (solvent system was used in gradient; 100% hexanes, 10% EtOAc in

hexane, 20% EtOAc in hexanes, and 30% EtOAc in hexanes) to yield light-yellow oil (15 mg, 32%). The identity of 1,4-dione product was confirmed by comparing ^{1}H NMR chemical shifts with literature value.[12]

2.7.3. General method 2-B

In a 1-dram vial, $Mn(OAc)_3 \cdot 2H_2O$ (7 mg, 27 μmol, 0.10 equiv), DABCO (45 mg, 0.40 mmol, 1.5 equiv), *trans*-cinnamic acid (40 mg, 0.27 mmol, 1 equiv) were weighed and added along with a magnetic stir bar. To the vial with reagents, acetone (1.35 mL, 0.2 M) was added and, subsequently, aqueous TBHP in 70 wt% water (190 μL, 1.3 mmol, 5 equiv) was added. Through septum cap, the reaction vial was sparged by using N_2-filled balloon for 2 minutes prior to heating and stirring. The reaction mixture was stirred and heated at 100 °C for 24 hours. The reaction was monitored by TLC and GC-MS. Once reaction was completed, the reaction was diluted with DCM (4 mL) and was added with DI H_2O (8 mL) for aqueous wash. After extracting the organic layer with DCM (4 mL) for 5 times, collected organic layer was washed with brine. After concentrating the organic layer, the crude mixture was purified via column chromatography charged with silica gel (solvent system was used in gradient; 100% hexanes, 10% EtOAc in hexane, 20% EtOAc in hexanes, and 30% EtOAc in hexanes) to yield light-yellow oil (15 mg, 32%). The identity of 1,4-dione product was confirmed by comparing ^{1}H NMR chemical shifts with literature value.[12]

2.8. Acknowledgement

2.9 Reference

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2.10 Appendix: Supplemental figures and tables

Appendix 2.10.1 Oxidants screening[a]
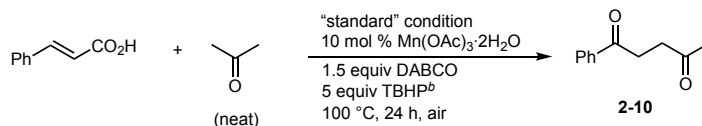
Entry	Deviation from "standard" condition	2-10 Yield[c]
1	None	26% (37% brsm)
2	DLP, instead of TBHP	N.D.[d]
3	DTBP, instead of TBHP	N.D.[d]
4	BPO, instead of TBHP	N.D.[d]
5	AIBN, instead of TBHP	N.D.[d]

[a]Reactions run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield. [d]Not detected.

Appendix 2.10.2 Metal additive screening (Mn-, Cu-, Fe-, Co-based)[a]
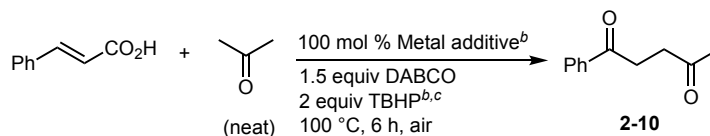
Entry	Metal additive	2-10 Yield[d]
1	$Mn(OAc)_3 \cdot 2H_2O$	11%
2	$Mn(OAc)_2 \cdot 4H_2O$	4%
3	$Cu(acac)_2$	N.D.[e]
4	CuBr	<5%
5	CuOAc	N.D.[e]
6	$Fe(acac)_3$	8%
7	$FeCl_3 \cdot 6H_2O$	10%
8	$CoCl_2 \cdot 6H_2O$	N.D.[e]
9	$Co(OAc)_2 \cdot 4H_2O$	N.D.[e]

[a]Reactions run by following General Method 2-A. [b]50 mol % metal additives and 1 equiv TBHP were added initially; additional 1 equiv TBHP was added after 2 h; another 50 mol % metal additives were added after 2 h. [c]70 wt% in water. [d]Isolated yield. [e]Not detected

Appendix 2.10.3 Metal additive screening (Ni-, Cu-, Fe-based)[a]
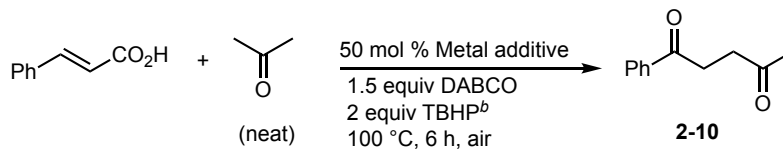
Entry	Metal additive	2-10 Yield[c]
1	$NiBr_2$	20%
2	$Ni(OAc)_2 \cdot 4H_2O$	<5%
3	$Ni(acac)_2 \cdot 4H_2O$	<5%
4	CuO	10%
5	$FeCl_2$	5%
6	$Fe(OAc)_2 \cdot 4H_2O$	<5%
7	$FeCl_3 \cdot 6H_2O$	10%

[a]Reactions run by following General Method 2-A. [b]70 wt% in water.
[c]Isolated yield.

Appendix 2.10.4 Single-electron oxidants screening[a]
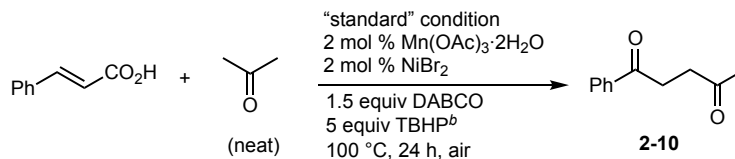
Entry	Deviation from "standard" condition	2-10 Yield[c]
1	None	32%
2	benzoquinone, instead of TBHP[a]	N.D.
3	H_2O_2, instead of TBHP[a]	<5%
4	mCPBA, instead of TBHP[a]	<5%
5	peracetic acid, instead of TBHP[a]	<5%
6	DDQ, instead of TBHP[a]	N.D.
7	3 equiv benzoquinone + 3 equiv TBHP[a], instead of 5 equiv TBHP[a]	N.D.
8	3 equiv H_2O_2	<5%
9	3 equiv mCPBA	<5%
10	3 equiv peracetic acid	<5%
11	3 equiv DDQ	N.D.

[a]Reactions run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield.

Appendix 2.10.5 The effect of concentration and equivalence of base[a]
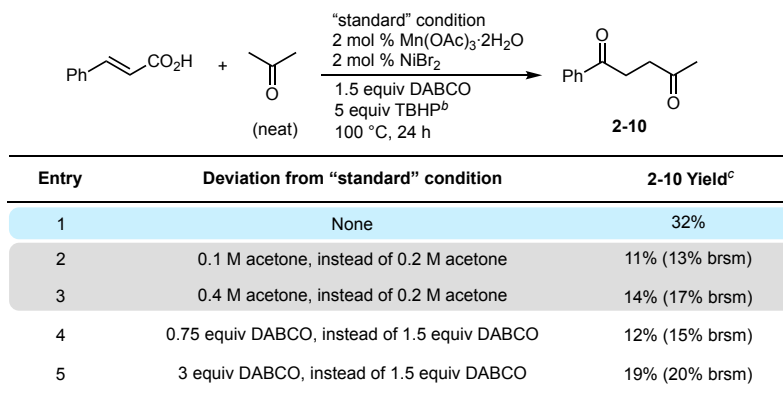
Entry	Deviation from "standard" condition	2-10 Yield[c]
1	None	32%
2	0.1 M acetone, instead of 0.2 M acetone	11% (13% brsm)
3	0.4 M acetone, instead of 0.2 M acetone	14% (17% brsm)
4	0.75 equiv DABCO, instead of 1.5 equiv DABCO	12% (15% brsm)
5	3 equiv DABCO, instead of 1.5 equiv DABCO	19% (20% brsm)

[a]Reactions run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield.

Appendix 2.10.6 Combination of metals (5 equiv TBHP)[a]
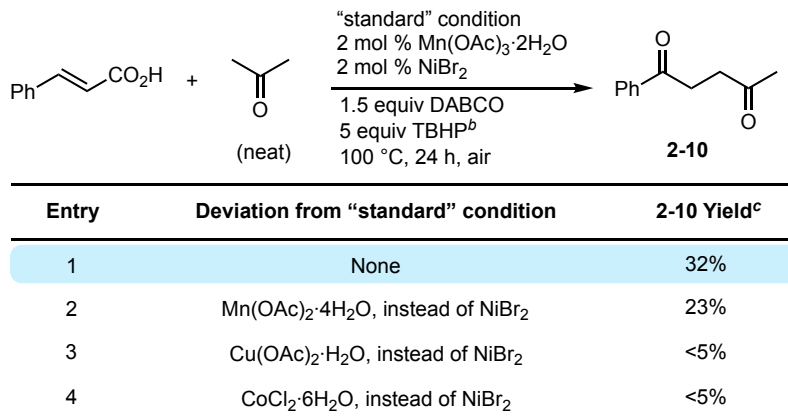
Entry	Deviation from "standard" condition	2-10 Yield[c]
1	None	32%
2	Mn(OAc)$_2$·4H$_2$O, instead of NiBr$_2$	23%
3	Cu(OAc)$_2$·H$_2$O, instead of NiBr$_2$	<5%
4	CoCl$_2$·6H$_2$O, instead of NiBr$_2$	<5%

[a]Reactions run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield.

Appendix 2.10.7 Combination of metals (3 equiv TBHP)[a]
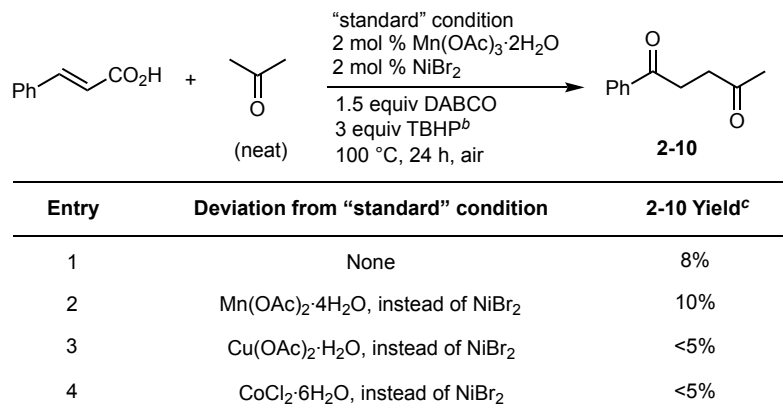
Entry	Deviation from "standard" condition	2-10 Yield[c]
1	None	8%
2	Mn(OAc)$_2$·4H$_2$O, instead of NiBr$_2$	10%
3	Cu(OAc)$_2$·H$_2$O, instead of NiBr$_2$	<5%
4	CoCl$_2$·6H$_2$O, instead of NiBr$_2$	<5%

[a]Reactions run by following General Method 2-A. [b]70 wt% in water. [c]Isolated yield.

Appendix 2.10.8 Oxidative decarboxylative coupling of 4-MeO-cinnamic acid with isopropenyl acetate
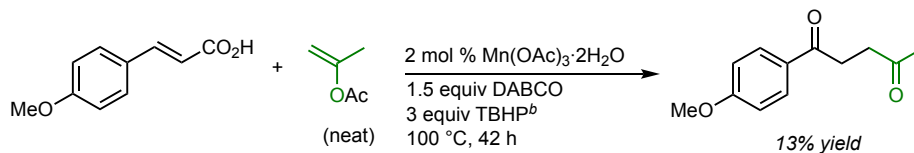
Appendix 2.10.9 Oxidative decarboxylative coupling of 4-MeO-cinnamic acid with dimethyl malonate
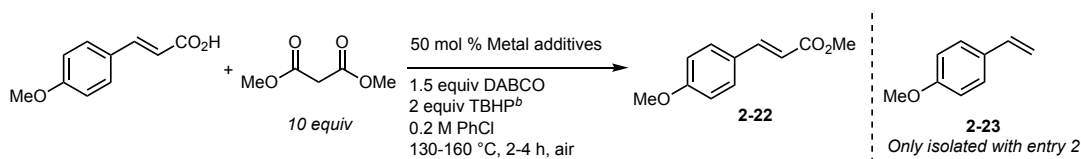
Entry	Metal additive	2-22 Yield[c]
1	Mn(OAc)$_3$·2H$_2$O	19%
2[d]	Mn(OAc)$_2$·4H$_2$O	25%
3	Cu(acac)$_3$	6%
4	CuBr	19%
5	CuOAc	8%
6	CuO	15%
7	Fe(acac)$_3$	39%
8	FeCl$_3$·6H$_2$O	19%
9	FeCl$_2$	<5%
10	Fe(OAc)$_2$·4H$_2$O	19%
11	CoCl$_2$·6H$_2$O	20%
12	Co(OAc)$_2$·4H$_2$O	N.D.[d]
13	Ni(OAc)$_2$·4H$_2$O	39%
14	Ni(acac)$_2$·4H$_2$O	19%
15	NiBr$_2$	<5%

[a]Reactions run by following General Method 2-A. [b]70 wt% in water.
[c]Isolated yield. [d]Styrenyl product **2-23** was also isolated with 7% yield.

Appendix 2.10.10 Oxidative decarboxylative coupling of 4-MeO-cinnamic acid with acetic acid and *tert*-butyl acetate
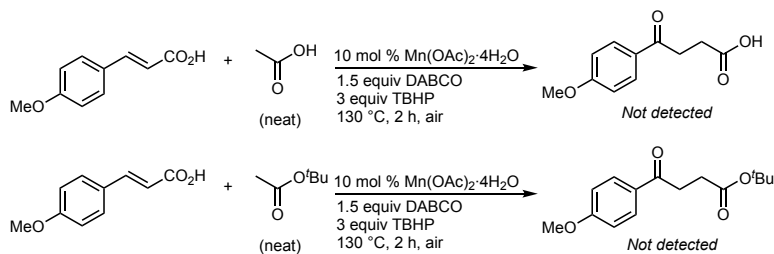
Chapter 3: Palladium-catalyzed decarbonylative cross-coupling strategy with silicon-based nucleophiles and enolates

3.1 Recent progress in decarbonylative cross-coupling reactions and α-C-C bond formations of silyl enol ethers

As introduced in Chapter 1.3, decarbonylative cross-coupling is an evolving cross-coupling strategy that uses acid anhydrides, enol ether esters, aryl esters, and amides as electrophiles in cross-coupling reactions. Work from the Itami and Yamaguchi groups has demonstrated that a decarbonylative cross-coupling strategy with phenyl esters can be applied to Suzuki-Miyaura type arylation[1], C-H arylation[2], and Sonogashira-type alkynylation[3] (Figure 3.1).

Ni-catalyzed decarbonylative Suzuki-Miyaura type arylation
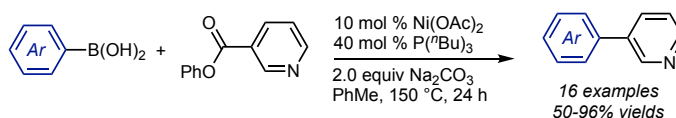
Itami, K. *Nature. Commun.* **2015**, *6*, 1-6.

Ni-catalyzed decarbonylative C-H arylation/alkenylation of 1,3-azoles
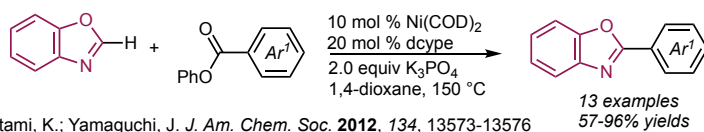
Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2012**, *134*, 13573-13576
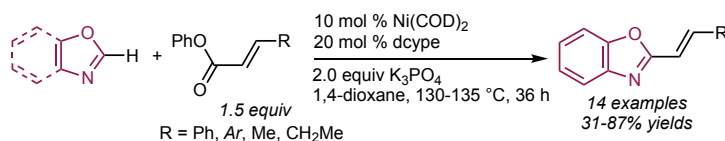
Yamaguchi, J.; Itami, K.; *Angew. Chem.* **2013**, *125*, 10232-10235

Pd-catalyzed decarbonylative Sonogashira type alkynylation
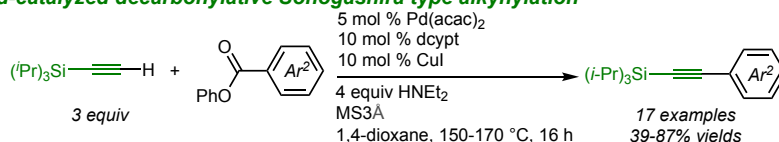
Itami, K.; Yamaguchi, J. *Chem. Lett.* **2017**, *46*, 218-220

Figure 3.1. Itami's and Yamaguchi's decarbonylative coupling reactions with various nucleophiles

Using a Ni-catalyzed procedure, Itami, Yamaguchi and co-workers demonstrated 16 examples of Suzuki-Miyaura type biaryl synthesis with phenyl esters and aryl boronic acids.[1] Non-functionalized nucleophiles, such as oxazoles, were also successfully coupled with phenyl esters (Figure 3.1, Middle) by using catalytic amount of $Ni(COD)_2$, dcype, and K_3PO_4 as base.[2] In the subsequent year, they also demonstrated that decarbonylative alkenylation can be achieved via coupling with enoic esters and their work in C-H alkenylation of 1,3-azoles with phenyl cinnamate was the first example that uses enoic esters as electrophiles (Figure 3.1, Middle).[4] In 2017, Pd-catalyzed decarbonylative Sonogashira-type alkynylation using a particular silyl acetylene was reported by the same group (Figure 3.1, Bottom).[3] Additional discussion and background information about decarbonylative cross-coupling reactions is found in Chapter 1.3.3.

Decarbonylative cross-coupling methods continue to be an area of interest with current work focusing on expanding the scope of viable nucleophilic partners. However, decarbonylative coupling using silicon-based nucleophiles is under-developed and, therefore, we set out to understand transmetallation with silicon-based nucleophiles, silanes and silyl enol ethers, in decarbonylative cross-coupling reaction. We were primarily interested in organosilicons as nucleophiles because organosilicons are: 1) commercially available with a variety of organosilicons, 2) generally regarded as less-expensive organometallics due to rich abundance of silicon on the earth, 3) stable organometallics, which can be stored in ambient condition while some organometallics, such as Grignard reagent, are highly sensitive to air and moisture.[5] As introduced in Chapter 1.1, the Hiyama cross-coupling reaction is a well-developed strategy using organosilane nucleophiles. A common theme with most reported Hiyama coupling conditions is the inclusion of super-stoichiometric amounts of fluoride additives such as TBAF, TASF, CsF, CuF_2 and etc.[5]

We initially envisioned that α-vinylation of ketones could be achieved via a decarbonylative cross coupling of an enoate ester and an enolate or enolate surrogate. In particular, developing methods using silyl enol ethers as the nucleophilic partners. Prior reports from Hartwig and coworkers demonstrate that silyl enol ethers and silyl ketene acetals can be coupled with aryl and vinyl halides using a Pd-catalyzed protocol.[6,7]

α-arylation of silyl ketene acetals with aryl halides

Hartwig, J.F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.
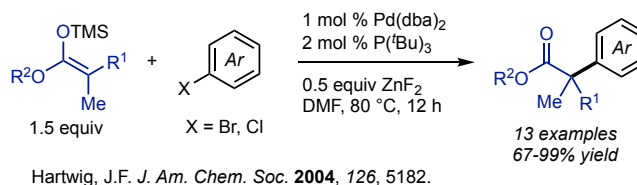
α-alkenylation&arylation of silyl enol ethers with aryl halides

Verkade, J.G.; Hartwig, J.F. *Angew. Chem. Int. Ed.* **2006**, *45*, 5852.
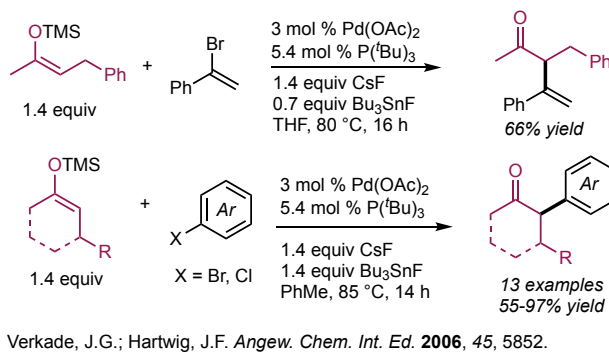
Figure 3.2 Hartwig's α-arylation and α-alkenylation of silyl enol ethers and

silyl ketene acetals

When comparing these silyl ketene acetal and silyl-enol ether α-arylation strategies, the common usage of a Pd pre-catalyst, tri-*tert*-butylphosphine, and fluoride additives (ZnF$_2$ or CsF/Bu$_3$SnF) is clear (Figure 3.2). While there were 13 examples of α-arylation of silyl-ketene acetals and silyl-enol ethers coupling with various aryl halides, under the similar reaction condition (Figure 3.2, Bottom), α-vinylation of silyl-enol ethers was reported with only one example with a single silyl enol ether. The proposed role of the metal-fluorides additives is to promote the *in-situ* formation of metal-enolates via desilylation of the silyl enol ether or silyl ketene acetal. While Hartiwig and Verkade found the need of CsF and Bu$_3$SnF for activating silyl

enol ethers into nucleophilic *in-situ* enolate, Sulikowski[8] and Chobanian[9] have analogously proposed formation of either Cu(II)- or Zn(II)-enolates in the mechanisms of α-arylation of silyl ketene acetals (Figure 3.3, Top) and α-arylation of silyl enol ethers (Figure 3.3, Bottom).

Silyl ketene acetal arylation

2-5 mol % PdCl$_2$[P(*o*-Tol)$_3$]$_2$
2 equiv CuF$_2$
THF, 70 °C, 9 h

4 equiv

Sulikowski, G. A. *Tetrahedron. Lett.* **1998**, *39*, 8807-8810.

Silyl enol ether arylation

7 mol % Pd$_2$(dba)$_3$
20 mol % SPhos
1.1 equiv ZnF$_2$
DMF, 150 °C, Microwave, 15 min

1.5 equiv

Chobanian, H. R. *Tetrahedron. Lett.* **2007**, *48*, 1213-1216.
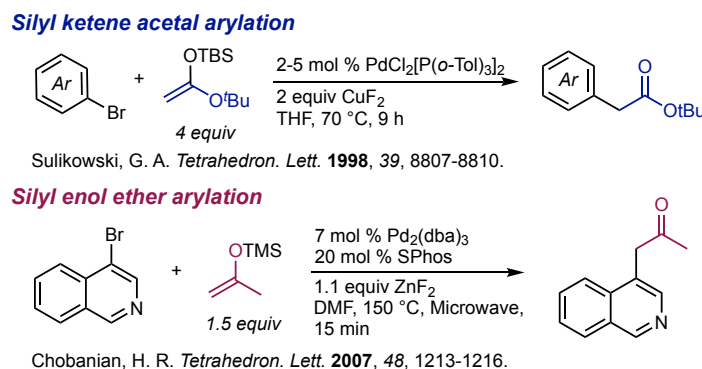
Figure 3.3 Sulikowski's and Chobanian's α-arylation of silyl ketene acetals and

silyl enol ethers

Similar to Hartwig's strategies (Figure 3.2), Sulikowski and Chobanian achieved α-arylation of silyl ketene acetals and silyl enol ethers using Pd-catalysis and bulky monodentate phosphine ligands (P(*o*-Tol)$_3$ and SPhos). As they proposed *in-situ* formation of metal(II)-enolates in their catalytic cycle, it suggested that fluoride additives (CuF$_2$ and ZnF$_2$) are necessary for making *in-situ* metal(II)-enolates and for transmetallation between aryl-Pd(II)-Br complex and *in-situ* metal(II)-enolates to give Pd(II)-complex, which then undergo reductive elimination to furnish α-arylated product.[7,8]

3.2 Objective of this work

Herein we present work towards expanding the scope of silicon-based nucleophiles viable in decarbonylative cross-couplings of aryl cinnamates electrophiles.

Prior to this work, Itami, Yamaguchi and co-workers successfully coupled 16 different aryl boronic acids with phenyl esters using Ni-catalyzed conditions to enable versatile biaryl synthesis.[10] However, they also discovered that a Pd-dcype combination was successful at

coupling phenyl esters and aryl boronic acids via a decarbonylative pathway. We were

interested in understanding the scope of decarbonylative cross-coupling in terms of nucleophilic

partners by replacing boron-based nucleophiles with silicon-based nucleophiles, such as

triethoxyphenyl silane and silyl enol ethers (Figure 3.4).
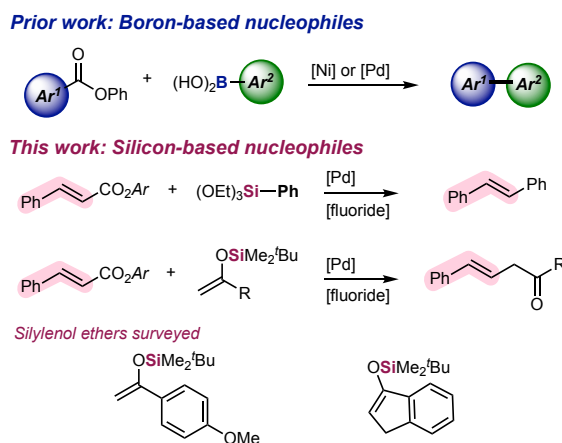
Figure 3.4 Comparison between prior work (Itami) and this work

As introduced in Chapter 1.4, our ultimate goal was developing methods for α-vinylation

of carbonyls and, therefore, we hypothesized that α-vinylation could be achieved via

decarbonylative cross-coupling between aryl cinnamates and silyl enol ethers. As Hiyama

cross-coupling reactions have been well studied, we first decided to develop a decarbonylative

Hiyama-type reaction and study the transmetallation step as a stepping stone towards

analogous couplings using other silicon-based nucleophiles.

3.3 Results

As introduced in Chapter 3.2, we began developing a decarbonylative Hiyama-type

cross-coupling using triethoxyphenyl silane as a model silicon-based nucleophile and various

Pd-sources as pre-catalysts. We also surveyed ligand scaffolds, such as phosphine-, NHC-,

bipyridal ligands, that have been successful with the Pd-sources. Among cinnamates, 2-

nitrophenyl cinnamate was selected due to its most effective reactivity toward decarbonylative

Suzuki-type coupling, which was determined by Alyssa F. Jones, another group member in the lab.[11] While there are multiple variables in decarbonylative cross-coupling conditions, we first investigated optimal ligand for the proposed decarbonylative coupling (Figure 3.5).
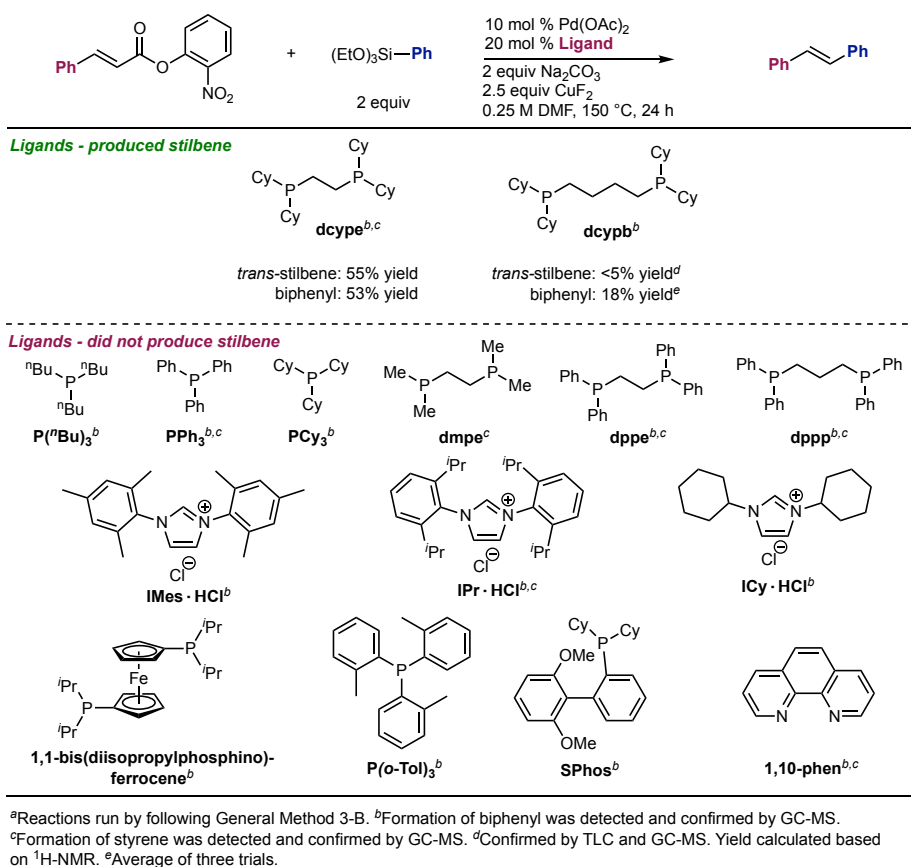
Figure 3.5 Ligands screened for decarbonylative coupling reaction[a]

These experiments revealed that only bidentate alkylphosphine ligands, such as dcype and dcypb, resulted in the formation of the desired product, *trans*-stilbene. Alternative ligands assessed, resulted in the formation of homodimerized product, biphenyl, and/or decarbonylated product, styrene, as detected by GC-MS. From the assessment, we determined that bidentate ligands (dmpe, dppe, dppp, dcype, dcypb, 1,10-phen) produce a stryne, decarboxylated product from cinnamate, while the formation of biphenyl was observed with no specificity in ligands. Throughout ligand screening discussed in Figure 3.5, we identified the best ligand among the ligands screened as 1,2-bis-(dicyclohexylphosphino)ethane (dcype) was identified as the ligand

that delivered the desired *trans*-stilbene product in the highest isolated yield, 55% yield. When

dcypb was used in place of dcype, we observed the formation of *trans*-stilbene product, but the

yield of product was less than 5%. However, biphenyl was also formed as a undesired by-

product in 53% yield, which we hypothesized was the result of rapid homodimerization of

triethoxyphenylsilane.

As discussed previously, we observed the formation of homodimerized product of

triethoxyphenylsilane in significant amount under the reaction condition we found. Therefore, we

initially hypothesized that the cross-coupling can be selective over homo-coupling if we could

tune fluoride additive, solvent, temperature, and even addition of silane (Table 3.1 and 3.9

Appendix).

Table 3.1 Optimization of decarbonylative cross-coupling of 2-NO$_2$-phenyl cinnamate and

triethoxyphenyl silane[a]
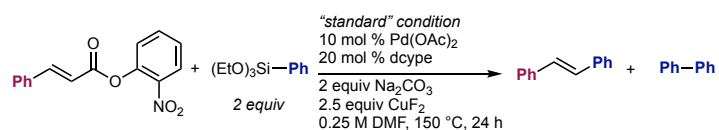
Entry	Deviation from "standard" condition	*Trans*-stilbene[d]	Biphenyl[d]
1	None	55%	53%
2	CsF, instead of CuF$_2$	-	-
3	TBAF, instead of CuF$_2$	-	-
4	CuBr$_2$, instead of CuF$_2$	-	-
5	CuBr$_2$ + CsF, instead of CuF$_2$	-	-
6	CuBr$_2$ + TBAF, instead of CuF$_2$	-	-
7	DMA, instead of DMF	28%	34%
8	DMSO, instead of DMF	9%	13%
9	100 °C, instead of 150 °C	<5%	<5%
10	Slow-addition of silane for 3 h[b]	<5%	<5%
11	Portion-wise addition of silane for 1 h[c]	55%	-

[a]Reactions run by following General Method 3-B. [b]Slow-addition was carried by using syringe-pump
(2.08 μl/min). [c]Reaction run by following General Method 3-C. [d]Isolated yields

Among the fluorides sources we investigated, copper(II) fluoride, CuF$_2$, emerged to be

the only fluoride source that produced cross-coupled product, *trans*-stilbene, in 55% yield (Table

3.1, entry 1). Via optimization of reaction condition, we found that there is a significant effect of

fluoride additives as other fluoride additives (CsF and TBAF), which were previously successful

in Hiyama-type couplings, did not give neither cross-coupling products nor homodimerized

products (Table 3.1, entry 2-3).

We also hypothesized that CuF_2 might play a role as a subsidiary metal additive that

promotes/increases the rate of transmetallation. An initial test of this hypothesis was to

substitute $CuBr_2$ for CuF_2. However, this experiment did not produce any *trans*-stilbene or

biphenyl, suggesting that a Cu(II) source alone does not facilitate either coupling pathway

observed with CuF_2. Instead adding Cu(II) source alone, we came up with another hypothesis

that it needs both Cu(II) source and fluoride source to activate triethoxyphenyl silane and

facilitate transmetallation step by adding $CuBr_2$ with CsF or TBAF instead of CuF_2 (Table 3.1,

entry 5-6). However, none of cross-coupled product and homdimerized product was not

observed in those reaction conditions and this supported a significant role of CuF_2 in

transmetallation with silane.

While additional bases, including alkoxide and other carbonate bases, were evaluated in

place of sodium carbonate, Na_2CO_3 remained the most effective base and this finding was in

good agreement with previous work of Itami and Yamaguchi (Appendix 3.9.3)

Reaction temperature and solvent can also affect the relative rates of elementary steps

of a cross-coupling reaction. As a result, we sought to potentially minimize the formation of the

undesired biphenyl by-product while maximizing the yield of *trans*-stilbene by judicial choice of

reaction solvents at various temperatures. With the effort of determining the most effective

solvent, we concluded that DMF is the best solvent among other solvents screened by

furnishing the highest yield of cross-coupled product (Table 3.1, entry 4-5; Appendix 3.9.4-

3.9.5). Initially, we investigated Pd-based conditions in non-polar solvent, such as PhMe, but we

only observed formation of biphenyl in 50% yield. After we found previous Hiyama-type

reactions have been successful in polar solvents, we moved our attention to high-boiling polar

solvents (DMA, HMPA, 1,4-dioxane, DMPU, 'BuOH, DMI, DMSO) (Appendix 3.9.4). Through

screening, we found highly polar amide-based solvents, such as DMA and DMF, are ideal for

this Pd-catalyzed cross-coupling reaction by producing 28% yield and 55% yield of *trans*-

stilbene, respectively. With other high boiling polar solvents (1,4-dioxane, DMPU, DMSO), it

only generated *trans*-stilbene in less than 10% yield. Therefore, we concluded polar amide-

based solvents are better in this Hiyama-type Pd-catalyzed cross-coupling reactions than other

high boiling polar solvents.

Interestingly, if the reaction temperature was below or equal to 100 °C, there were no

coupling products observed, and the result indicated that decarbonylative cross-coupling

doesn't occur at relatively low temperature like 100 °C. When we surveyed Itami's and

Yamaguchi's decarbonylative cross-coupling reactions of phenyl esters, most of the

decarbonylative cross-coupling reactions were successful at very high temperature (≥ 150 °C).[10]

To address the substantial amounts of biphenyl being produced, we rationalized that the

rate of homo-coupling may be decreased if the concentrations of triethoxyphenyl silane were

kept low, relative to 2-nitrophenyl cinnamate throughout the course of the reaction. We initially

attempted to keep the amount of $(EtO)_3SiPh$ low by adding it slowly via syringe pump over the

course of 3 hours. However, this rate of addition combined with the elevated reaction

temperatures did not result in the production of either *trans*-stilbene or biphenyl. Instead of

introducing the silane at a slow, consistent rate, we found that portion-wise addition every 10

minutes for 1 hour, produced trans-stilbene exclusively (Table 3.1, entry 9).

Throughout optimization study in decarbonylative cross-coupling, we found the reaction

condition that gives most successful reaction outcome when silane was added in portion-wise

for 1 hour by giving 55% yield of *trans*-stilbene (Table 3.1, entry 11). However, we could not

improve the yield of cross-coupled product than 55% because we observed consumption of 2-

nitrophenyl cinnamate, in the presence of catalytic amount of Pd/dcype in DMF solvent, and

generation of amide byproduct (Appendix 3.9.6). Since decarbonylative coupling reactions were taken place at very high temperature, DMF thermally disproportionate into dimethyl amine, which acts as a nucleophile attacking 2-nitrophenyl cinnamate to generate *N,N*-dimethyl cinnamide. With this optimized, and selective reaction protocol, we began exploring the scope of ester and silane substrates in this decarbonylative Hiyama-type cross-coupling.

Table 3.2 Scope of reaction – Electrophilic Partners[a]

Entry	Esters	Product	Yield
1	R = OMe, NO$_2$		R = OMe (**3-1**), yield: < 5% = NO$_2$ (**3-2**), yield: < 5%
2	**3-3**		N.D.
3	**3-4**		N.D.
4	**3-5**		N.D.
5	**3-6**		N.D.
6	**3-7**		N.D.

[a]Reactions run by following General Method 3-C. [b]2 equiv of silane was added in 6 portions for 1 h (Each portion was 0.3 equiv; 0.3 equiv every 10 min)

According to our colleague's finding in the scope of decarbonylative Suzuki type cross-coupling reactions, substituted aryl cinnamates with electron-withdrawing groups (3,5-CF$_3$, 2-NO$_2$, 4-NO$_2$) on phenol-moiety are most effective among other cinnamates, but, among them, highest yield of

cross-coupled product was obtained when 2-nitrophenyl cinnamate was chosen. However,

when other cinnamates (**3-1 – 3-7**) were used in replacement of 2-nitrophenyl cinnamate, we did

not observe versatile cross-coupled products (Table 3.2, entry 1-6). Due to the limited versatility

of reaction condition, we moved our attention to altering nucleophilic partners to other silanes

and silyl enol ethers (Table 3.3, entry 1-3).

**Table 3.3** Scope of reaction – Nucleophilic Partners[a]
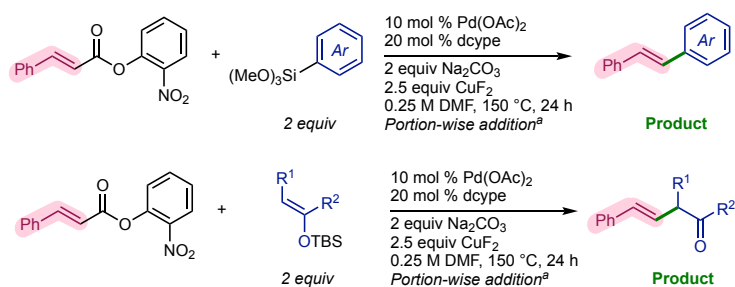
Entry	Silane/Silyl-enol ethers	Product	Yield[e]
1	**3-8**		N.D.
2	**3-9**[c]		N.D.
3	**3-10**[c]		N.D.
4	**3-11**[d]		N.D.

[a]Reaction run by following General Method 3-C. [b]2 equiv of silane/silyl-enol ethers was added in 6 portions for 1 h (Each portion was 0.3 equiv; 0.3 equiv every 10 min). [c]Silyl-enol ethers (**3-9, 3-10**) were prepared by following Method B. [d]Silyl-enol ethers (**3-11**) were prepared by following Method C. [e]N.D. stands for 'Not detected'.

Under the best reaction condition, however, expected cross-coupling products were not

observed when silane **3-8** and pre-synthesized silyl enol ethers (**3-9, 3-10, 3-11**) were added as

nucleophilic partner (Table 3.3, entry 1-4). While we initially hypothesized that, if the

transmetallation step in decarbonylative cross-coupling with silanes could be well-understood,

then we can possibly couple pre-synthesized silyl enol ethers (**3-9, 3-10, 3-11**) under the same

reaction condition, but the reaction outcomes indicated that the transmetallation, with silyl enol

ethers, is mechanistically different from the transmetallation with silanes in decarbonylative

cross-coupling. Therefore, it required us to trace back to the previous α-vinylation, and even α-

arylation, of silyl enol ethers and *in-situ* enolates to refine our reaction condition that could

possibly couple silyl enol ethers. According to the examples reported by Verkade[5] and Hartwig[5,6]

(Figure 3.2), α-arylation of silyl enol ethers and silyl ketene acetals can be achieved under Pd-

catalyzed reaction condition with bulky monodentate trialkylphosphine, such as P(^{t}Bu)$_3$. Also, to

activate silyl enol ethers into nucleophiles, it needed fluoride additives, such as CsF and

Bu$_3$SnF, while solvents could be either polar or non-polar solvents.

Through reviewing the previous examples in α-arylation/alkenylation of silyl enol ethers

and silyl ketene acetals, we could fill out our screening list with various Pd-catalysts (Pd(OAc)$_2$,

Pd(PPh$_3$)$_4$, Pd(IPr)(allyl)Cl, [Pd(π-cinnamyl)Cl]$_2$), bulkyl monodentate phosphine ligands (P^{t}Bu$_3$,

PCy$_3$, SPhos, etc.), fluoride additives (CsF, CuF$_2$, ZnF$_2$, CsF/ZnF$_2$), and solvents (DMF, THF,

PhMe). We also tested trialkyl bidentate ligand, such as dcypb, that can possibly work as a

mono-binding ligand due to long tether in between phosphines. With the knowledge that

arylation is more facile than vinylation, we screened reaction condition for α-arylation of silyl

enol ethers by choosing phenyl 4-fluorobenzoate as electrophile (Figure 3.6).
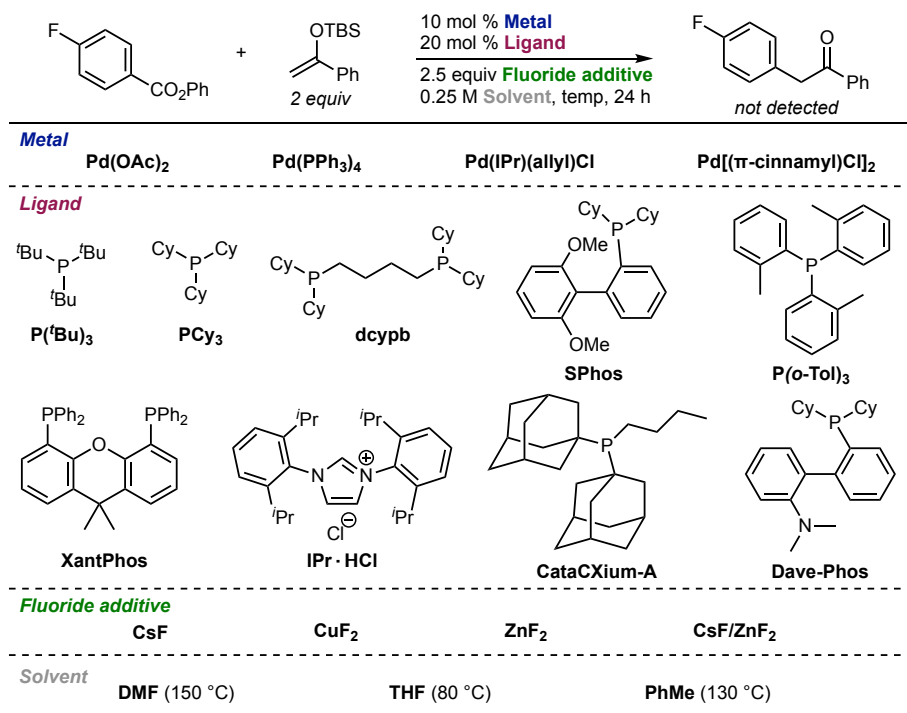
Figure 3.6 Screening of decarbonylative arylation with silyl enol ethers of acetophenone[a]

Despite the effort in screening reactions conditions designed based on the literature survey, we did not observe the corresponding α-arylated product, but only desilylation of silyl enol ethers or consumption of ester was observed by GC-MS.

Herein, we propose a plausible mechanism for Pd-catalyzed decarbonylative coupling reaction between aryl cinnamate and triethoxyphenyl silane (Figure 3.7).
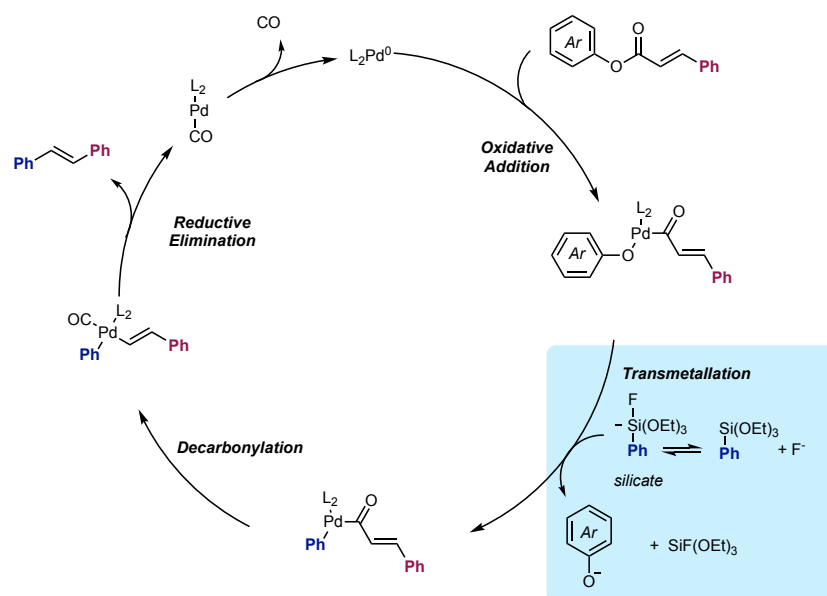
Figure 3.7 Proposed mechanism for Pd-catalyzed decarbonylative Hiyama-type coupling

Similarly with Itami's proposed mechanism for Pd-catalyzed decarbonylative Suzuki-type coupling, our proposed mechanism initiates with oxidative addition of aryl cinnamate into $L_2Pd(0)$ complex to produce Pd(II)-acyl species. Subsequently, the Pd(II)-acyl species undergo transmetallation with penta-coordinated silicate upon activation of triethoxyphenyl silane with fluoride additive to result in a new Pd(II)-acyl species. Decarbonylation of the Pd(II)-acyl species followed by reductive elimination generates *trans*-stilbene, as cross-coupled product, and L_2Pd-CO, which is converted to $L_2Pd(0)$ after extrusion of CO as gas.

3.4 Summary and future outlook

Herein, we found decarbonylative cross-coupling reaction condition that couples 2-nitrophenyl cinnamate and triethoxyphenyl silane by giving moderate (55%) yield of cross-coupled product with successful suppression of homo-coupling between silanes. The scope of esters found to be viable in this reaction was less broad than anticipated. Although α-arylation of silyl enol ethers was attempted by screening previously reported α-arylation and α-vinylation reaction conditions that used aryl halides as electrophiles, we did not observe this type of

reactivity. Lastly, we proposed a possible mechanism of Pd-catalyzed decarbonylative Hiyama-type coupling.

3.5 Substrate preparation

Silyl enol ethers (**3-9**[12], **3-10**[12], **3-11**[13]) were prepared by using the method reported in the literature. All physical and analytical data were in good agreement with the values reported in the literature.[12,13]

3.6 Experimental data

3.6.1. General Experimental Information

All catalytic reactions were set-up inside air- and moisture-free glovebox (M-Braun). Solvents (DMF, DMSO, DMA) were dried over CaH_2 for 2-3 days, freeze-pump-thawed, vacuum-transferred, and brought into a nitrogen filled glovebox. All commercially available reagents were purchased and were used as received. Progress of reactions was monitored by analytical TLC on silica gel 60 F_{254} (Merck EMD Millipore) and GC-MS (Agilent 7890B GC/5977B MSD). Reactions were purified by column chromatography packed with silica (Silicycle SilicaFlash® P60).

3.6.2. Method 3-A: General procedure for the synthesis of 2-nitrophenyl cinnamate

2-nitrophenyl cinnamate
60% yield
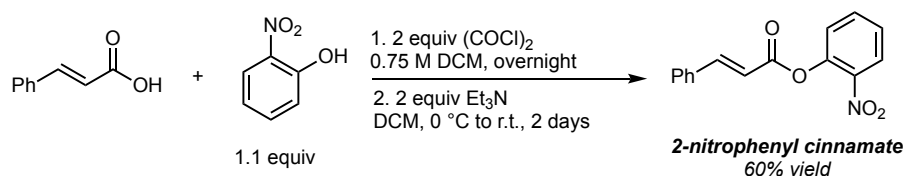
In a 100-mL round-bottom flask, trans-cinnamic acid (3.04 g, 20.5 mmol, 1 equiv) was dissolved in DCM (27 mL) dried over Na_2CO_3. After reaction flask was placed in an ice-bath under positive flow of nitrogen gas, oxalyl chloride (3.5 mL, 41 mmol, 2 equiv) was added dropwise and the reaction mixture was stirred overnight. Additional oxalyl chloride (2 mL, 20 mmol,1 equiv) was added as well as catalytic amount of DMF (100 μL). Upon the addition of DMF, bubbling in

reaction mixture was observed. Reaction was monitored by TLC after 24 hours of stirring. To

crude cinnamoyl chloride, after evaporation of solvent, 2-NO_2 phenol (3.16 g, 22.7 mmol, 1.1

equiv) was added with freshly dried DCM. At 0 °C, triethylamine (5.7 mL, 41 mmol, 2 equiv) was

added in drop-wise to the reaction mixture and, after addition, reaction flask was stirred at the

room-temperature overnight. Subsequently, the crude product was diluted with DCM and was

washed with aqueous K_2CO_3 and brine to give 2-nitrophenyl cinnamate (3.31 g, 60% yield). The

spectral values (^{1}H-NMR) were in good agreement with those reported in literature.[14]

Decarbonylative cross-coupling reaction

3.6.3. Method 3-B: *General procedure for the "standard" decarbonylative coupling reaction with*

silane

All decarbonylative cross-coupling reactions were set up under air-free condition inside

glovebox. After Pd(Oac)$_2$ (1 mg, 5.6 μmol, 0.1 equiv), dcype (4 mg, 11 μmol, 0.2 equiv), Na_2CO_3

(14 mg, 0.11 mmol, 2 equiv), CuF_2 (17 mg, 0.14 mmol, 2.5 equiv) were weighed in a 1-dram vial

inside the glovebox, the vial was added with rigorously dried DMF (250 μL) and magnetic stir-

bar. Before bringing outside of glovebox, the vial was capped with septum cap and sealed with

electrical tape. After the subsequent addition of triethoxyphenyl silane (27 μL, 0.11 mmol, 2

equiv) through septum cap via syringe, the reaction mixture was heated and stirred in metal pi-

block set at 150 °C for 24 hours. Next, the reaction vial was removed from the hot plate and was

cooled to the r.t. After cooling, the reaction mixture was diluted with CH_2Cl_2 (4 × 2 mL) and was

added with DI H_2O (8 mL) for aqueous wash. After the extraction of organic layer with CH_2Cl_2 (4

× 8 mL) and evaporation of solvent, the crude product was purified via short column

chromatography on silica gel (solvent system was in gradient; 100% Hexanes, and then 10%

EtOAc in Hexanes). The cross-coupled product, *trans*-stilbene, and homo-coupled product,

biphenyl, were isolated with 55% yield and 53% yield, respectively. The identity of products was

confirmed by ^{1}H-NMR and GC-MS after comparison with NMR chemical shift and GC retention times of commercially available *trans*-stilbene (103-30-0) and biphenyl (92-52-4).

3.6.4. Method 3-C: *Procedure for portion-wise addition of silane*

The catalytic reactions were prepared by following Method 3-B except addition of silane in one portion. Prior to heating at 150 °C, the one-sixth portion of triethoxyphenyl silane (4-5 µL, 0.2 mmol, 0.3 equiv) was added via syringe and, while heating and stirring, the remaining five one-sixth portions of triethoxyphenyl silane (4-5 µL, 0.2 mmol, 0.3 equiv) were added to the reaction vial every 10 minutes per portion. After the addition, reaction mixture was heated for another 18 hours and reaction progress was monitored by TLC and GC-MS.

3.7. Acknowledgement

3.8 Reference

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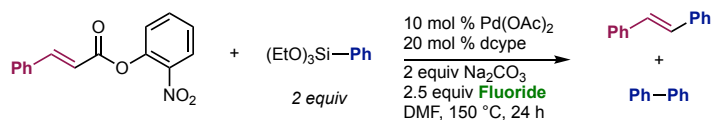
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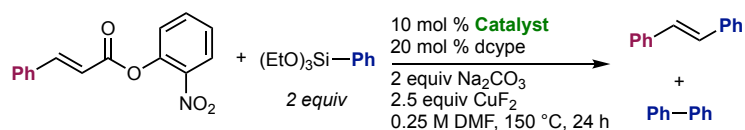
3.9 Appendix: Supplemental figures and tables

Appendix 3.9.1 Fluoride additives screening[a]

Entry	Fluoride	Trans-stilbene[b]	Biphenyl[b]
1	CsF	-	-
2	TBAF	-	-
3	CuF_2	55%	53%
4	CuF_2 + TBAF (0.5 equiv)	45%	18%
5	CuF_2 + CuBr (1 equiv)	30%	23%
6	CuF_2 + CuI (1 equiv)	43%	27%
7	$CuBr_2$	-	-

[a]Reactions run by following General Method 3-B. [b]Isolated yield.

Appendix 3.9.2 Catalyst screening[a]

Entry	Catalyst	Trans-stilbene[b]	Biphenyl[b]
1	$Pd(PPh_3)_4$	-	-
2	$PdCl_2$	-	-
3	$Pd(TFA)_2$	44%	24%
4	$Pd(acac)_2$	6%	28%
5	$Pd(OAc)_2$	55%	53%

[a]Reactions run by following General Method 3-B. [b]Isolated yield.

Appendix 3.9.3 Base screening[a]
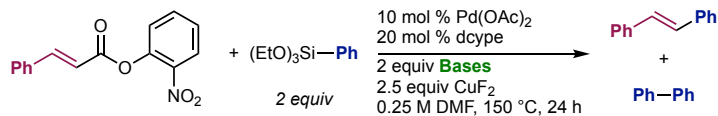
Entry	Base	Trans-stilbene
1[c]	K_2CO_3	< 5%
2[c]	Cs_2CO_3	< 5%
3[c]	NaOAc	< 5%
4[c]	KO^{t}Bu	-
5[c]	Na_2CO_3	55%

[a]Reactions run by following General Method 3-B. [b]Formation of *trans*-stilbene observed by GC-MS and TLC, but could not be isolated. [c]Formation of biphenyl observed by GC-MS.
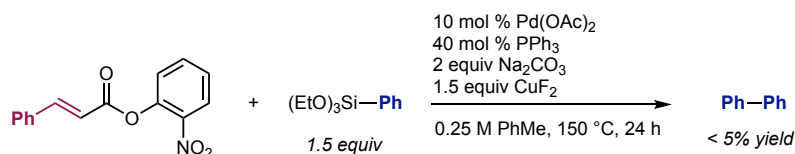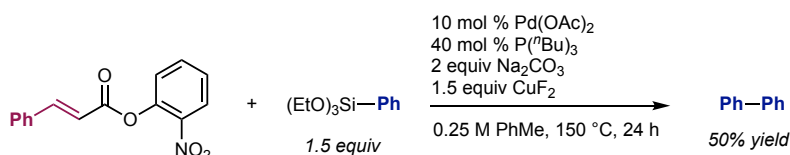
Appendix 3.9.4 Solvent screening[a]
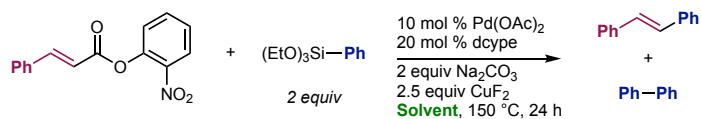
Entry	Solvent	Trans-stilbene[b]
1[c]	[t]BuOH	-
2[c]	HMPA	-
3[c]	1,4-dioxane	6%
4[d]	DMPU	<5%
5[c]	DMSO	9%
6	DMI	-
7[c]	DMA	28%
8[c]	DMF	55%

[a]Reactions run by following General Method 3-B. [b]Isolated yield. [c]Formation of biphenyl observed by GC-MS. [d]Reactions run by following General Method 3-C.
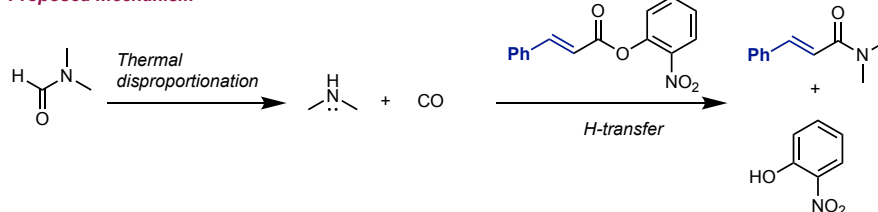
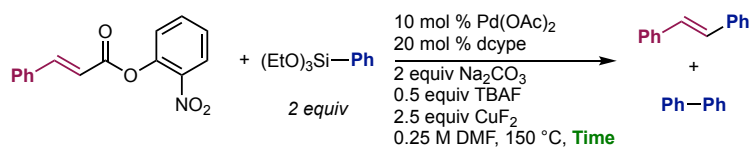## Appendix 3.9.5 Additional Pd-based reactions in non-polar solvent

Appendix 3.9.6 Amide byproduct formation
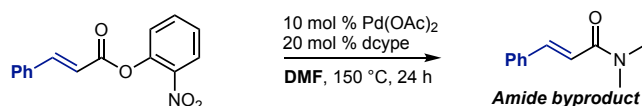
Proposed mechanism

Appendix 3.9.7 Reaction time monitoring[a]

Entry	Time (h)	GC ratio[b] (*Trans*-stilbene : Biphenyl)
1	0.5	38 : 62
2	1.5	46 : 54
3	2	41 : 59
4	24	40 : 60

[a]Reactions run by following General Method 3-B. [b]GC ratio was calculated based on integration of GC chromatogram.