CHEMICAL REVIEWS

pubs.acs.org/CR

Review

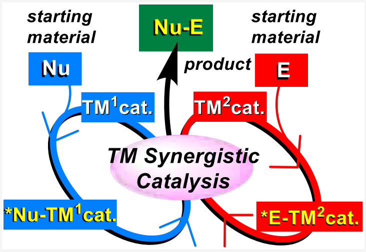
Synergistic Dual Transition Metal Catalysis

U Bin Kim, Da Jung Jung, Hyun Ji Jeon, Kris Rathwell, and Sang-gi Lee*

Cite This: *Chem. Rev.* 2020, 120, 13382−13433

Read Online

ABSTRACT: Synergistic catalysis, a type of plural catalysis which utilizes at least two different catalysts to enable a reaction between two separately activated substrates, has unlocked a plethora of previously unattainable transformations and novel chemical reactivity. Despite the appreciable utility of synergistic catalysis, specific examples involving two transition metals have been limited, as ensuring a judicious choice of reaction parameters to prevent deactivation of catalysts, undesirable monocatalytic event(s) leading to side products, or premature termination and other potentially troublesome outcomes present a formidable challenge. Excluding those driven by photocatalytic mechanisms, this review will highlight the reported examples of reactions that make use of two simultaneous catalytic cycles driven by two transition metal catalysts.



CONTENTS

Received: April 5, 2020
Published: November 29, 2020

https://dx.doi.org/10.1021/acs.chemrev.0c00245

1. INTRODUCTION

Synthetic organic chemistry is indebted to the power of transition metal-catalyzed reactions for key bond-forming events. During the last century, great strides were made in this field, where a single transition metal catalyst activates a substrate to promote a particular transformation. Even though this strategy has provided a wealth of new chemical reactions, some transformations are still challenging or nigh impossible using a sole catalyst. In addition, although a monocatalytic strategy utilizes substoichiometric amounts of the catalyst to activate one of the reactants, the second reactant of the reaction often requires further activation through the use of a stoichiometric (or greater) amount of an activating agent, and/or prior functional group manipulation in order to be amenable to the monocatalytic system. Concerns regarding the economic and environmental impact of such reactions have necessitated an investigation into processes that can further maximize the chemical usefulness and efficiency of catalyst-driven reactions while minimizing waste.[1] To address these challenges, different types of multicatalytic systems have been developed[2−4] such as bifunctional catalysis,[5−9] double activation catalysis,[10] cascade catalysis (and related tandem or domino catalysis),[11] and synergistic catalysis.[12]

Many recent works featuring synergistic catalysis, catalytic systems driven by two distinct catalysts acting on two different substrates to enable reaction between two activated intermediates, have focused on combining a transition metal catalyst with Lewis acids,[13] organocatalysts[14,15] (i.e., Lewis bases,[16−18] chiral amines,[19] Brønsted acids,[20] and *N*-heterocyclic carbenes[21,22]), combining of *N*-heterocyclic carbenes with Lewis acids,[23,24] and combining of transition metal catalysis with photocatalysis.[25−28] Dinuclear transition metal catalyzed reactions, where two of the same metals are placed in close proximity to each other to form active sites containing two metallic ions, are also known.[29,30] In contrast, combination of two different transition metals for synergistic dual catalysis has been far less explored until recently,[31−35] which is due in part to the difficulty in ensuring redox compatibility between the transition metal catalysts, and balanced kinetics between the two catalytic cycles, avoiding catalyst deactivation. In this review, we present the primary literature which features synergistic dual catalysis that utilize transition metals up to June 2020, excluding those driven by photocatalytic mechanisms, which are the subject of several excellent accounts and reviews.[25−28] Specifically, we will highlight catalyst pairings and their proposed catalytic cycles which are critical in enabling the reactivity of known and novel transformations.

For successful synergistic dual transition metal catalysis (Figure 1), each transition metal catalyst [cat.-M1] and [cat.-M2] must activate reactants [S^1] and [S^2] in a substrate selective manner with comparable and compatible activation rates (k_1 and k_2), as otherwise the high reactivity and prolonged presence of one of the activated species over the other could encourage decomposition or promote side reactions which diminish the reaction efficiency.

In this review, we have termed activated intermediates cat. M1···[$S^{1}*$] and cat. M2···[$S^{2}*$] as the (first and second) "catalytically activated reactive species". The two "catalytically activated reactive species" then must react with each other directly to afford the desired product with regeneration of the catalysts. As such, the near-simultaneous turnover of two metallic catalysts is important, and achieving this can be exceptionally challenging, as any particular reaction conditions suited for the one metal catalyst may not be compatible with the presence of the other. Often, undesirable conditions which are introduced by the increased number of variables inherent in such systems serve to imbue further difficulty in the refinement and optimization of these processes.

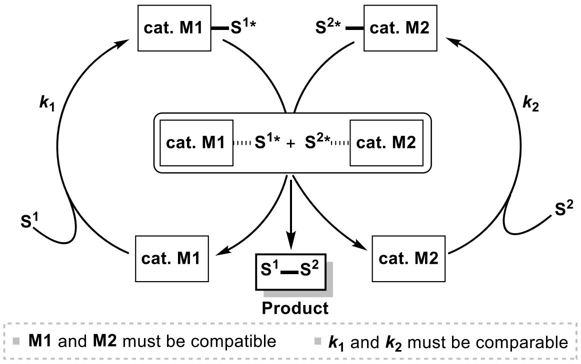


Figure 1. A schematic representation of synergistic dual transition metal catalysis.

In light of these constraints, understanding and surveying intercatalyst compatibility may be a helpful undertaking for the development of new synergistic dual transition metal catalysis. As depicted in Figure 2, an overview of the publications which utilize synergistic dual transition metal catalysis indicate that palladium catalysts (which generally activate an electrophile) show a broad range of catalyst cross-compatibility with various other transition metal catalysts such as copper, gold, ruthenium, rhodium, nickel, vanadium, and silver.

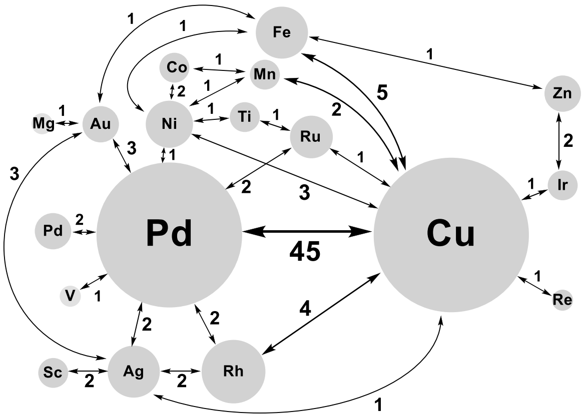


Figure 2. Compatible transition metals (indicated by double-headed arrows) in synergistic dual catalysis. The numbers represent frequency of the transition metal pairs taking part in synergistic catalysis as surveyed and featured by this review.

In addition, copper catalysts (which generally activate a nucleophile) can be largely compatible with iron, ruthenium, manganese, nickel, rhodium, and rhenium. Other reported combinations of transition metals include some rhodium and silver, ruthenium and titanium, gold and iron, and titanium and nickel catalysts. It must be highlighted that at this time, the most prominent catalytic metal pairing is between palladium and copper.

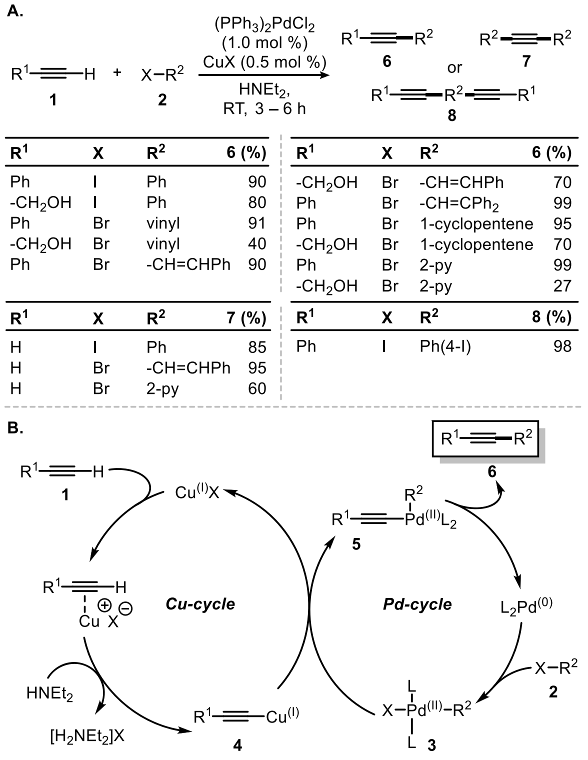
2. SYNERGISTIC Pd/Cu DUAL CATALYSIS

In the context of dual transition-metal synergistic catalysis, Pd/Cu catalytic pairing has received the greatest attention from the scientific community, which is well attested by the breadth and depth of methods attesting for it in the reported literature. The prominence of Pd/Cu parings also illustrates the general versatility and compatibility of Cu-derived nucleophilic intermediates and Pd-derived electrophilic intermediates in synergistic catalytic systems. During the final stages in preparation of this review, Zhang and co-workers published an overview focused on Pd/Cu synergistic catalysis, which can be further consulted by interested readers.[36]

2.1. Sonogashira and Modified Stille Reactions

2.1.1. Sonogashira Reaction. One of the earliest instances of synergistic dual transition metal catalysis was disclosed by Sonogashira to effect the alkynylation of aryl iodides under Pd(0)/Cu(I) dual catalytic conditions (Scheme 1).[37] This synergistic catalysis allowed for much milder conditions relative to the analogous alkynylations involving stoichiometric Cu[38] or monocatalytic Pd (Heck−Cassar reaction).[39,40]

Scheme 1. Sonogashira Cross-Coupling Reaction of Alkynes and Aryl Iodides



R^1	X	R^2	6 (%)
Ph	I	Ph	90
-CH$_2$OH	I	Ph	80
Ph	Br	vinyl	91
-CH$_2$OH	Br	vinyl	40
Ph	Br	-CH=CHPh	90
-CH$_2$OH	Br	-CH=CHPh	70
Ph	Br	-CH=CPh$_2$	99
Ph	Br	1-cyclopentene	95
-CH$_2$OH	Br	1-cyclopentene	70
Ph	Br	2-py	99
-CH$_2$OH	Br	2-py	27

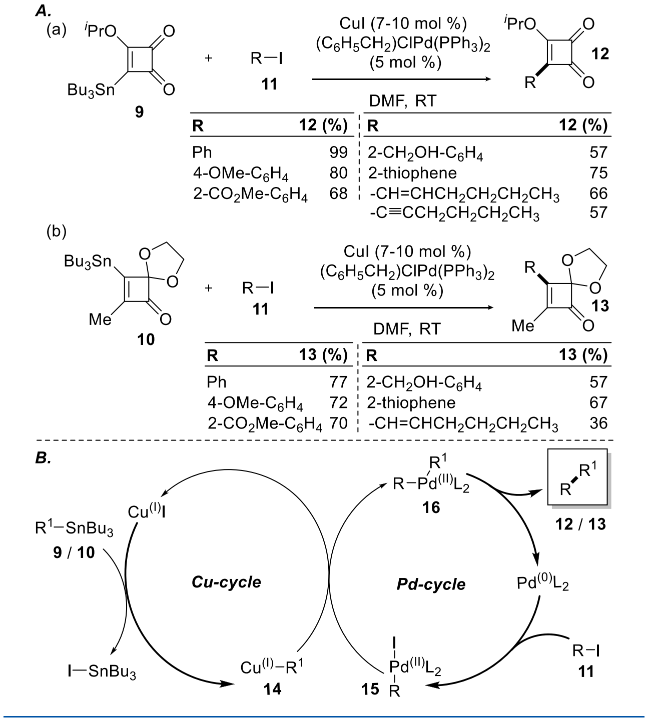
R^1	X	R^2	7 (%)
H	I	Ph	85
H	Br	-CH=CHPh	95
H	Br	2-py	60

R^1	X	R^2	8 (%)
Ph	I	Ph(4-I)	98

The Sonogashira reaction has now grown to encompass a vast range of substrates and different modes of reactivity. As such, Sonogashira reactions have been the focal subject of reviews elsewhere and will not be fully discussed here.[41] Briefly, the coupling reaction involves the substitution of an acetylenic hydrogen with an appropriately activated electrophile, mediated by catalytic Pd and Cu. The mechanistic details of the seminal report are as follows (Scheme 1B). First, the oxidative addition of Pd(0) into iodide **2** forms Pd(II) complex **3**. Meanwhile, simultaneous activation of **1** occurs through deprotonative coordination with the Cu(I) catalyst, and the resultant Cu(I)-acetylide **4** then undergoes transmetalation with **3** to generate Pd(II) complex **5**, along with regeneration of the Cu(I) catalyst. Reductive elimination yields the cross-coupled product **6** with regeneration of the Pd(0) catalyst. Using ethyne (**1**, R^1 = H) as the nucleophilic starting material, a series of symmetrical disubstituted alkyne **7** were prepared in good yield. Use of 1,4-diidobeneze as the electrophile **2** led to dialkynylation, affording diyne **8**. In addition to the original Pd/Cu procedure, synergistic Ni/Cu variants have also been developed.[42−44]

2.1.2. Modified Stille Coupling. While the traditional Stille cross-coupling employs a single Pd(0) catalyst to activate a vinyl halide (or pseudohalide) in reaction with stoichiometric organostannanes,[45] the use of both Pd and Cu catalysts were also documented as a footnote in Long's work on carbocyclic annulations, although without special emphasis.[46] This finding was further emphasized by Liebeskind and co-workers in the Stille reaction of 3-stannylcyclobutenediones **9** and monoacetals **10** with iodides **11**, where Pd(0)/Cu(I) dual catalysts enhanced the reaction to furnish substituted diones **12** and ketones **13** under mild conditions and in good yields (Scheme 2).[47] The proposed mechanism is shown in Scheme 2B. First, catalytically activated Cu(I) species **14** is derived from preliminary transmetalation of organostannane **9**/**10** with the copper catalyst. On the palladium catalytic cycle, oxidative addition of Pd(0) into iodide **11** affords Pd(II) complex **15**. Transmetalation of Cu(I)-**14** with Pd(II)-**15** furnishes Pd(II) complex **16**, which undergoes reductive elimination to yield the desired cross-coupled product **12**/**13**. This synergistic Pd/Cu catalytic methodology was investigated further by Baldwin and co-workers[48] in the coupling of 1-substituted vinyl stannanes, which are typically challenging substrates under traditional Pd monocatalysis.

Scheme 2. Synergistic Pd/Cu Dual Catalysis for Modified Stille Coupling



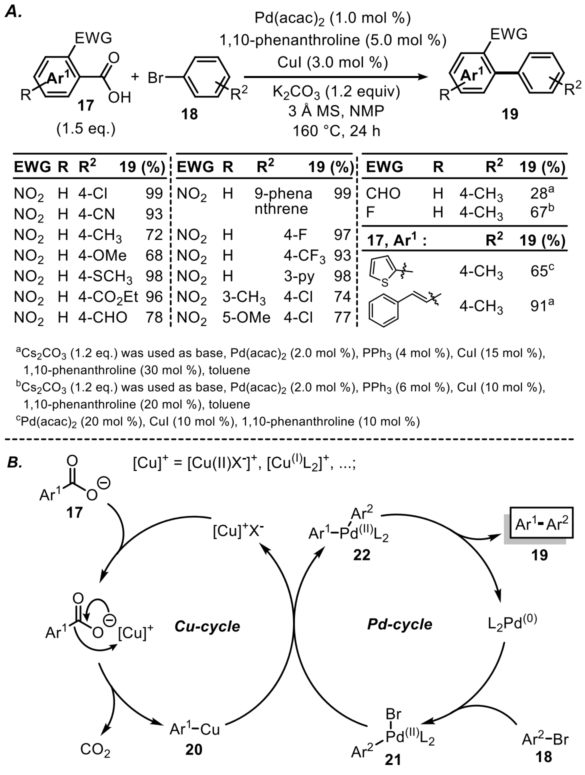
R	12 (%)
Ph	99
4-OMe-C$_6$H$_4$	80
2-CO$_2$Me-C$_6$H$_4$	68
2-CH$_2$OH-C$_6$H$_4$	57
2-thiophene	75
-CH=CHCH$_2$CH$_2$CH$_2$CH$_3$	66
-C≡CCH$_2$CH$_2$CH$_2$CH$_3$	57

R	13 (%)
Ph	77
4-OMe-C$_6$H$_4$	72
2-CO$_2$Me-C$_6$H$_4$	70
2-CH$_2$OH-C$_6$H$_4$	57
2-thiophene	67
-CH=CHCH$_2$CH$_2$CH$_2$CH$_3$	36

2.2. Cross-Coupling Reactions for the Synthesis of Biaryl Compounds

2.2.1. Decarboxylative Cross-Coupling. Inspired by enzymatic decarboxylation in nature as a means for carbanion generation,[49,50] Gooßen envisioned that copper catalysts would facilitate decarboxylative cupration of 2-nitrobenzoic acids to form a Cu bound nucleophilic complex which could undergo a coupling reaction with an electrophile. In this context, a decarboxylative coupling between 2-nitro benzoic acid **17** and aryl bromide **18** has been developed for the synthesis of biaryl compounds **19** through synergistic Pd(0)/Cu(I) catalysis (Scheme 3).[51,52] The initial coordination of the Cu(I) catalyst with the carboxylate oxygen of **17** allows for the decarboxylative insertion of Cu to form aryl-Cu(I) intermediate **20**. Meanwhile, oxidative addition of the Pd(0) catalyst into aryl bromide **18** produces aryl-Pd(II) complex **21**. Transmetalation between **20** and **21** forms **22**, which subsequently undergoes reductive elimination to furnish biaryl **19** with regeneration of Pd(0) catalyst. The use of 1,10-phenanthroline was important to promote binding of the Cu catalyst with carboxylate **17** over the free halide ions that are released during the transmetalation process.

Scheme 3. Synergistic Pd/Cu Dual Catalysis for the Decarboxylative Cross-Coupling Reaction



EWG	R	R^2	19 (%)
NO_2	H	4-Cl	99
NO_2	H	4-CN	93
NO_2	H	4-CH_3	72
NO_2	H	4-OMe	68
NO_2	H	4-SCH_3	98
NO_2	H	4-CO_2Et	96
NO_2	H	4-CHO	78
NO_2	H	9-phenanthrene	99
NO_2	H	4-F	97
NO_2	H	4-CF_3	93
NO_2	H	3-py	98
NO_2	3-CH_3	4-Cl	74
NO_2	5-OMe	4-Cl	77
CHO	H	4-CH_3	28[a]
F	H	4-CH_3	67[b]

17, Ar^1 :	R^2	19 (%)
	4-CH_3	65[c]
	4-CH_3	91[a]

[a] Cs_2CO_3 (1.2 eq.) was used as base, $Pd(acac)_2$ (2.0 mol %), PPh_3 (4 mol %), CuI (15 mol %), 1,10-phenanthroline (30 mol %), toluene

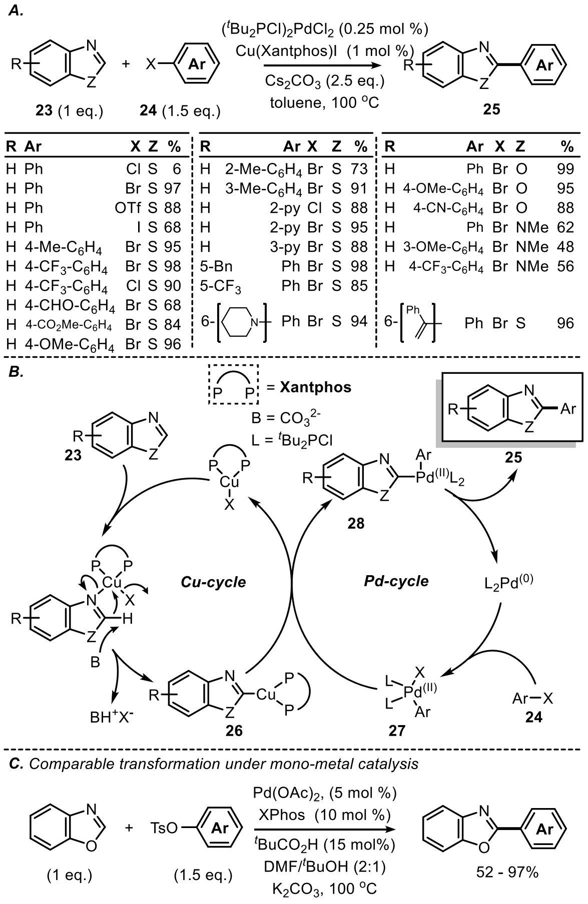
[b] Cs_2CO_3 (1.2 eq.) was used as base, $Pd(acac)_2$ (2.0 mol %), PPh_3 (6 mol %), CuI (10 mol %), 1,10-phenanthroline (20 mol %), toluene

[c] $Pd(acac)_2$ (20 mol %), CuI (10 mol %), 1,10-phenanthroline (10 mol %)

Gooßen and co-workers extended this synergistic Pd/Cu dual catalysis to make use of other electrophiles in place of aryl bromides such as aryl triflates,[53] tosylates,[54] mesylates,[55] and slightly different nucleophiles such as potassium carboxylates,[56−58] α-oxocarboxylates,[59,60] and picolinic acids.[61] The effect of microwave irradiation in facilitating this reaction was also explored.[61]

2.2.2. Arylation of Heteroarenes. Huang and co-workers utilized Pd(0)/Cu(I) dual catalysis to effect the direct C−H arylation of benzthiazoles **23** (Z = S) with aryl halides **24** to afford arylated heteroarenes **25** (Scheme 4).[62] Under Pd mediated monocatalysis, harsh conditions, high catalyst loadings, and strong bases are required to effect comparable transformations (Scheme 4C).[63] In contrast, under dual Pd/Cu catalysis, a catalyst loading of only 0.25 mol % Pd and 1.0 mol % Cu was required.

Scheme 4. Synergistic Pd/Cu Dual Catalysis for Arylation of Heteroarenes



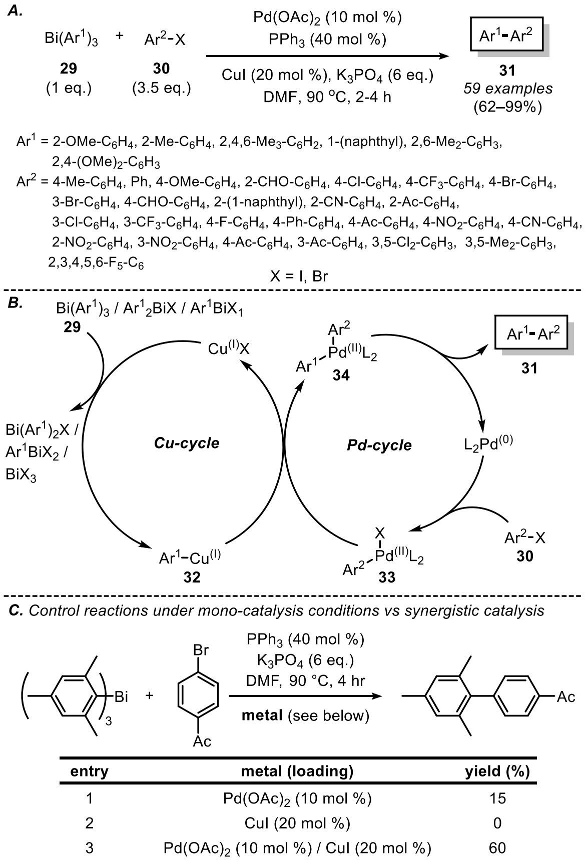
R	Ar	X	Z	%
H	Ph	Cl	S	6
H	Ph	Br	S	97
H	Ph	OTf	S	88
H	Ph	I	S	68
H	4-Me-C_6H_4	Br	S	95
H	4-CF_3-C_6H_4	Br	S	98
H	4-CF_3-C_6H_4	Cl	S	90
H	4-CHO-C_6H_4	Br	S	68
H	4-CO_2Me-C_6H_4	Br	S	84
H	4-OMe-C_6H_4	Br	S	96
H	2-Me-C_6H_4	Br	S	73
H	3-Me-C_6H_4	Br	S	91
H	2-py	Cl	S	88
H	2-py	Br	S	95
H	3-py	Br	S	88
5-Bn	Ph	Br	S	98
5-CF_3	Ph	Br	S	85
6-	Ph	Br	S	94
H	Ph	Br	O	99
H	4-OMe-C_6H_4	Br	O	95
H	4-CN-C_6H_4	Br	O	88
H	Ph	Br	NMe	62
H	3-OMe-C_6H_4	Br	NMe	48
H	4-CF_3-C_6H_4	Br	NMe	56
6-	Ph	Br	S	96

Benzoxazoles **23** (Z = O) could also be arylated by this procedure, while *N*-methylbenzoimidazoles **23** (Z = NMe), were less reactive, providing moderate yields.

In the proposed mechanism (Scheme 4B), coordination of Cu(I)(Xantphos) with the nitrogen atom of benzazole **23** facilitated deprotonation and rearrangement to yield Cu species **26**. Transmetalation with aryl-Pd(II) species **27**, derived from oxidative addition of Pd(0) into **24**, transfers the benzoxazole group onto Pd to yield intermediary Pd(II) complex **28**. Subsequent reductive elimination affords desired arylated product **25** with regeneration of the Pd(0) catalyst.

2.2.3. Cross-Coupling of Triarylbismuths with Aryl Halides. Rao and co-workers established a synergistic Pd(0)/Cu(I) dual catalytic system for cross-coupling sterically hindered *ortho*-substituted triarylbismuth reagents **29** and aryl halides **30** for the preparation of biaryl compounds **31** (Scheme 5).[64] A control reaction between **29** and **30** under monocatalytic Pd afforded low yields, while under monocatalytic Cu, no product was observed (Scheme 5C). However, under synergistic Pd/Cu dual catalysis, the cross-coupled biaryl **31** was produced in good yields. The proposed catalytic cycle is shown in Scheme

Scheme 5. Synergistic Pd/Cu Dual Catalysis for the Coupling of Triarylbismuths with Aryl Halides



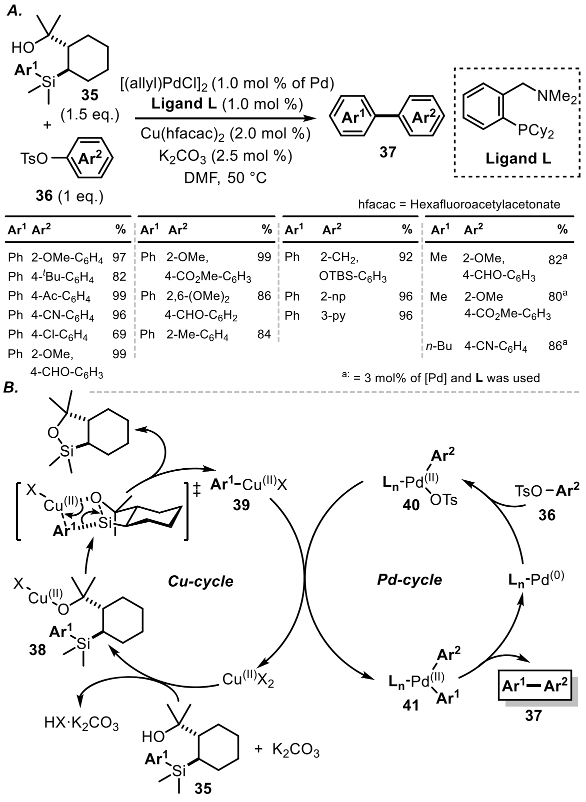
entry	metal (loading)	yield (%)
1	$Pd(OAc)_2$ (10 mol %)	15
2	CuI (20 mol %)	0
3	$Pd(OAc)_2$ (10 mol %) / CuI (20 mol %)	60

5B. First, reaction between the Cu(I) catalyst and triarylbismuth **29** affords monoaryl-Cu species **32**. Transmetalation with aryl-Pd(II) complex **33**, generated from oxidative addition of the Pd(0) into aryl halide **30**, affords bis-aryl Pd(II) complex **34**, which then undergoes reductive elimination to furnish the cross-coupled biaryl product **31**. Utilizing this process, various *ortho* functionalized biaryl compounds could be successfully accessed.

2.2.4. Cross-Coupling of Organosilanes with Aryl Tosylates.

Nakao and co-workers have previously disclosed a novel organosilicon reagent **35** which acts as a nucleophilic phenyl donor in reaction with aryl sulfonates mediated by Ni monocatalysis.[65,66] However, the monocatalytic system suffered from limited substrate scope, especially with compounds with *ortho*-substituents and sensitive functional moieties such as formyl groups. To address these limitations and improve the reactivity and scope of the reaction, they developed a novel synergistic Pd(0)/Cu(II) dual catalysis whereupon organosilicon reagent **35** underwent coupling with aryl tosylate **36** in the presence of allylPdCl and $Cu(hfacac)_2$ catalysts to afford the cross-coupled biaryl product **37** (Scheme 6).[67] In the proposed reaction mechanism (Scheme 6B), the Cu(II) catalyst reacts with arylsilicon **35** to form Cu-alkoxide intermediate **38**, which undergoes intramolecular rearrangement to transfer the aryl group from the silyl appendage to the Cu(II) center, affording copper complex **39** as the catalytically activated species. Meanwhile, the second catalytically active species **40** is derived from the oxidative addition of Pd(0) into **36**. Transmetalation between **39** and **40** yields Pd(II) complex **41**, which after reductive elimination, furnishes the desired product **37**.

Scheme 6. Synergistic Pd/Cu Dual Catalysis for the Cross-Coupling between Aryl Tosylates and Organosilanes



Ar^1	Ar^2	%
Ph	2-OMe-C_6H_4	97
Ph	4-^{t}Bu-C_6H_4	82
Ph	4-Ac-C_6H_4	99
Ph	4-CN-C_6H_4	96
Ph	4-Cl-C_6H_4	69
Ph	2-OMe, 4-CHO-C_6H_3	99
Ph	2-OMe, 4-CO_2Me-C_6H_3	99
Ph	2,6-$(OMe)_2$ 4-CHO-C_6H_2	86
Ph	2-Me-C_6H_4	84
Ph	2-CH_2, OTBS-C_6H_3	92
Ph	2-np	96
Ph	3-py	96
Me	2-OMe, 4-CHO-C_6H_3	82[a]
Me	2-OMe 4-CO_2Me-C_6H_3	80[a]
n-Bu	4-CN-C_6H_4	86[a]

[a]: = 3 mol% of [Pd] and **L** was used

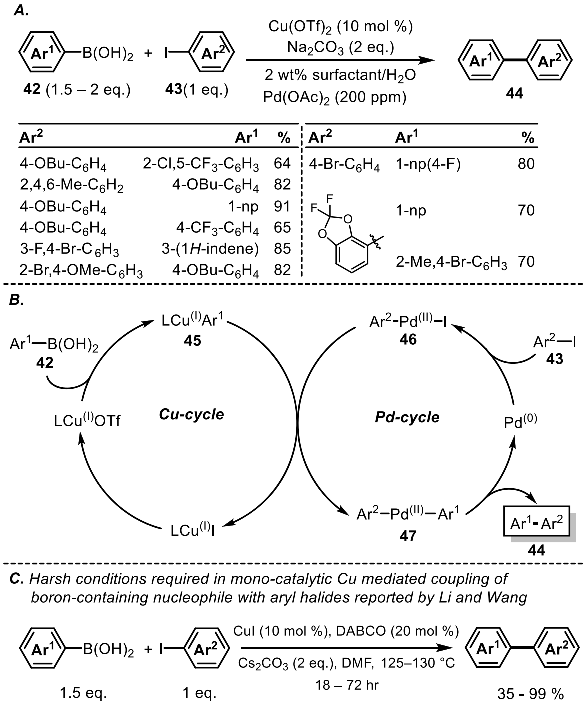
2.2.5. Cross-Coupling of Aryl Boronic Acids and Aryl Iodides.

Traditional monocatalytic Cu mediated coupling of boron-containing nucleophiles (such as boronic acid **42**) with aryl iodides (**43**) require harsh reaction conditions to necessitate the energetically demanding direct insertion of the LCu(I)Ar complex into the aryl iodide, forming the Cu(III) reaction intermediate (Scheme 7C).[68,69] To circumvent this reaction pathway, Lipshutz and co-workers reported milder synergistic Pd(0)/Cu(I) dual catalytic system, where LCu(I)Ar complex **45**, formed from boronic acid **42** in the presence of a Cu(I) catalyst, undergoes a facile transmetalation reaction with aryl-Pd(II) complex **46**, which is derived from oxidative addition of Pd(0) into an aryl iodide **43**. The resultant Pd(II) intermediate **47** underwent reductive elimination to yield desired biaryl product **44** in good yields (Scheme 7).[70]

The use of a surfactant (TPGS-750-M) allowed for ppm levels of Pd(0) loading. The authors also reported sequential cross-coupling reactions by utilizing dihalide compounds whereupon Cu(I)/ppm-Pd(0) mediated Suzuki coupling was followed by a second cross-coupling reaction mediated by either Fe/Pd nanoparticles[71] or other Pd catalysts to afford triaryl compounds. Similarly, Hoshi and co-workers reported a Cu(I)/Pd(0) mediated cross-coupling of aryl bromides **48** with pinacol boronic ester **49** for the synthesis of biaryl compounds **50** (Scheme 8).[72]

In desigining this reaction, it was rationalized that while the R-Phos ligand enhances the oxidative addition step of Pd(0) catalyst into aryl bromide **48**, it does not enhance the efficiency of the transmetalation of arylPd(II)-Br complex with boronic esters. To tune for the transmetalation, 5 mol % of Cu(I) cocatalyst was introduced, enabling very low catalytic Pd loadings (0.1 mol %).

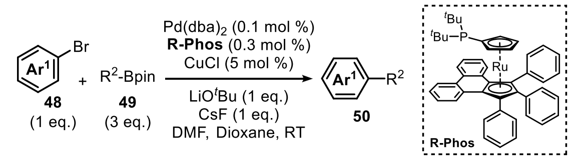
Scheme 7. Synergistic Pd/Cu Dual Catalysis for Modified Suzuki Coupling



Ar^2	Ar^1	%	Ar^2	Ar^1	%
4-OBu-C_6H_4	2-Cl,5-CF_3-C_6H_3	64	4-Br-C_6H_4	1-np(4-F)	80
2,4,6-Me-C_6H_2	4-OBu-C_6H_4	82			
4-OBu-C_6H_4	1-np	91		1-np	70
4-OBu-C_6H_4	4-CF_3-C_6H_4	65			
3-F,4-Br-C_6H_3	3-(1*H*-indene)	85			
2-Br,4-OMe-C_6H_3	4-OBu-C_6H_4	82		2-Me,4-Br-C_6H_3	70

C. Harsh conditions required in mono-catalytic Cu mediated coupling of boron-containing nucleophile with aryl halides reported by Li and Wang

Scheme 8. Pd/Cu Dual Catalysis for Suzuki Coupling of Pinacol Boronic Esters and Aryl Bromides



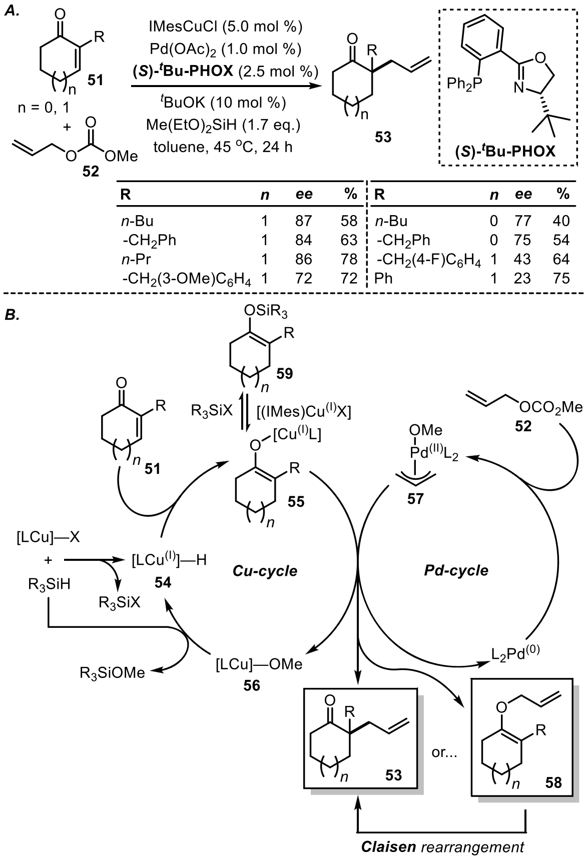
Ar^1	R^2	%	Ar^1	R^2	%	Ar^1	R^2	%
2,6-Me_2-C_6H_3	Ph	83	2,6-Et_2-C_6H_3	Ph	84	2-Me-C_6H_4	2-OMe-C_6H_4	100
2,6-Me_2-C_6H_3	2-OMe -C_6H_4	75	4-COMe-C_6H_4	Ph	91	4-OMe-C_6H_4	Ph	95
			-CH_2=CHPh	Ph	76	4-Me-C_6H_4	2,4-F_2-C_6H_4	100
2-py	Ph	73	4-Me-C_6H_4	2-furan (5-Me)	94	Bn	4-OMe-C_6H_4	83
4-Me-C_6H_4	2-py	36				4-Me-C_6H_4	3-thiophene	62

2.3. *α*-Allylation of Carbonyl Compounds

Riant and co-workers utilized synergistic Pd(0)/Cu(I) dual catalysis for enantioselective *α*-allylation of *α*,*β*-unsaturated ketones **51** with allyl carbonates **52** to afford optically active allylated ketone **53** (Scheme 9).[73]

In this process, copper hydride **54** is generated *in situ* from Cu(I) catalyst and silane. The conjugated hydride addition reaction of **54** with *α*,*β*-unsaturated ketone **51** affords Cu(I) enolate **55**, which can then react with *π*-allylPd(II) complex **57**, derived from oxidative addition of Pd(0) catalyst into carbonate **52**, to form either the *O*-allylation product **58** at room temperature or the *α*-allylated **53** at slightly elevated temperatures. The copper hydride **54** could be generated by reaction of **56** with silane. It was shown that the silyl enolate **59** would not react with *π*-allylPd(II) complex **57** without addition of a co-Cu catalyst, demonstrating that copper enolate **55** was the specifically required catalytically activated species. Studies on converting the *O*-allylation product **58** to the desired *α*-allylated product **53** showed that the conversion could be promoted with either a Pd(0) or a Pd(II) catalyst, suggesting that both an oxidative addition pathway and Claisen-type [3,3]-sigmatropic rearrangement pathway are plausible.

Scheme 9. Synergistic Pd/Cu Dual Catalysis for Enantioselective *α*-Allylation of *α*,*β*-Unsaturated Ketones

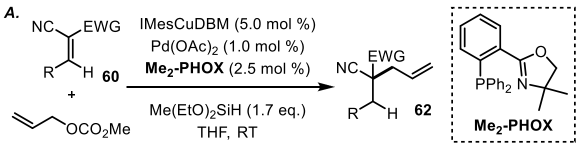


R	*n*	*ee*	%	R	*n*	*ee*	%
n-Bu	1	87	58	*n*-Bu	0	77	40
-CH_2Ph	1	84	63	-CH_2Ph	0	75	54
n-Pr	1	86	78	-CH_2(4-F)C_6H_4	1	43	64
-CH_2(3-OMe)C_6H_4	1	72	72	Ph	1	23	75

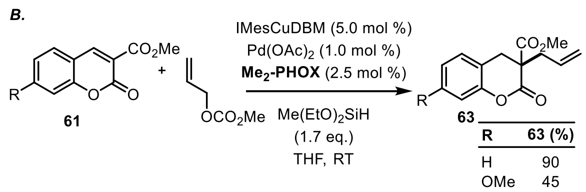
In addition, this dual catalytic reaction was further developed for the *α*-allylation of *α*,*β*-unsaturated malonates **60** and coumarins **61** to afford allylated **62** and **63**, respectively (Scheme 10).[74]

Recently, Shibasaki and co-workers disclosed enantioselective *α*-allylation of CF_3-containing azaindoline amide **64** with allylic carbonate **65** that affords allylated **66** under synergistic Pd(0)/Cu(I) dual catalysis conditions (Scheme 11).[75] Treatment of

Scheme 10. Synergistic Pd/Cu Dual Catalysis for *α*-Allylation of Malonates (A) and Coumarins (B)

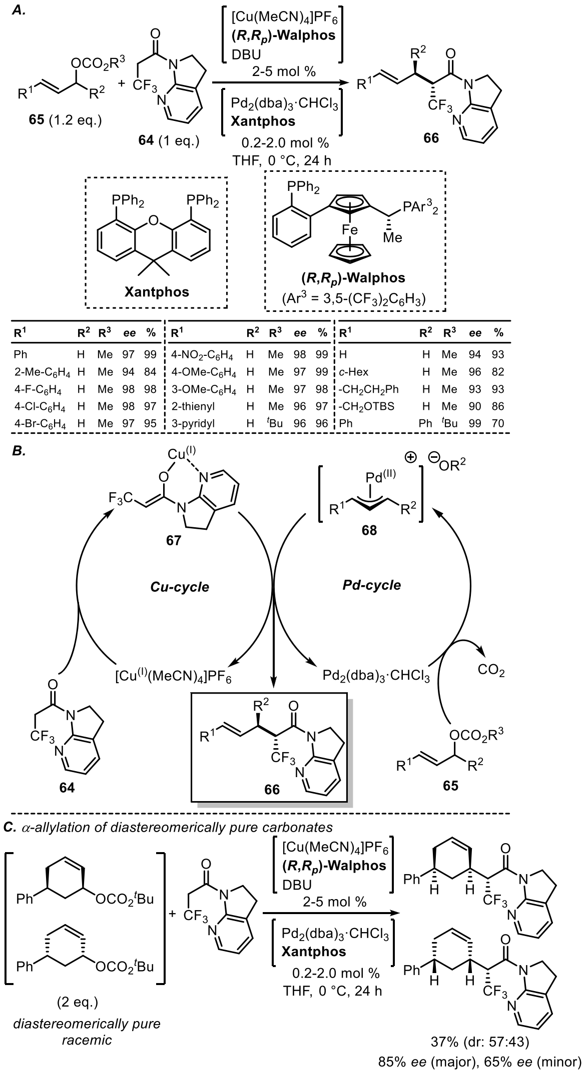


R	EWG	62 (%)	R	EWG	62 (%)	R	EWG	62 (%)
Ph	CO_2Me	83	4-F-C_6H_4	CO_2Me	79	4-py	CO_2Me	40
4-OMe-C_6H_4	CO_2Me	78	4-CF_3-C_6H_4	CO_2Me	43	*c*-hex	CO_2Me	81
2-Me-C_6H_4	CO_2Me	71	4-CN-C_6H_4	CO_2Me	60	4-OMe-C_6H_4	CN	86
						2-OTBS-C_6H_4	CO_2Me	56



R	63 (%)
H	90
OMe	45

Scheme 11. Synergistic Pd/Cu Dual Catalysis for α-Allylation of α-CF_3 Amides

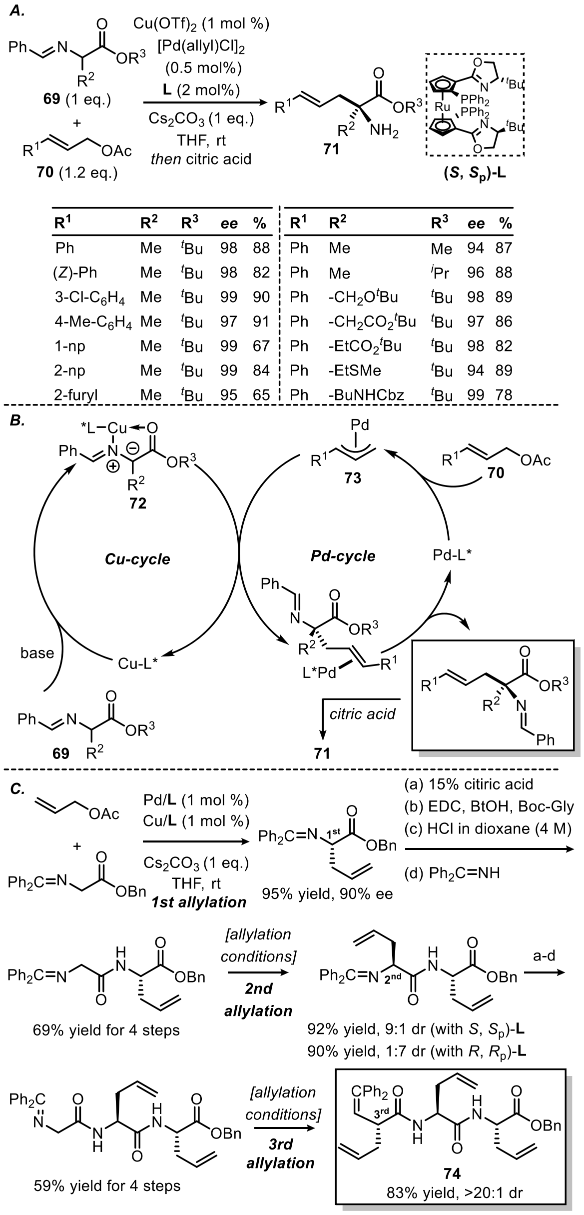


R^1	R^2	R^3	*ee*	%	R^1	R^2	R^3	*ee*	%	R^1	R^2	R^3	*ee*	%
Ph	H	Me	97	99	4-NO_2-C_6H_4	H	Me	98	99	H	H	Me	94	93
2-Me-C_6H_4	H	Me	94	84	4-OMe-C_6H_4	H	Me	97	99	*c*-Hex	H	Me	96	82
4-F-C_6H_4	H	Me	98	98	3-OMe-C_6H_4	H	Me	97	98	-CH_2CH_2Ph	H	Me	93	93
4-Cl-C_6H_4	H	Me	98	97	2-thienyl	H	Me	96	97	-CH_2OTBS	H	Me	90	86
4-Br-C_6H_4	H	Me	97	95	3-pyridyl	H	^{t}Bu	96	96	Ph	Ph	^{t}Bu	99	70

amide **64** with Cu(I) in the presence of base generated a chelated Cu enolate **67**, which was resistant toward the otherwise often observed β-elimination of fluoride. The Cu enolate **67** intercepts the π-allylPd(II) complex **68** generated from allylic carbonate **65** to afford the α-allylated product **66** with regeneration of both Pd(0) and Cu(I) catalysts. Stereocontrol is exerted by the (R,R_p)-Walphos chiral ligand to achieve excellent level of asymmetric induction. Reaction with diastereomerically pure, *syn* carbonates lead to exclusive formation of *syn* products stereospecifically, which suggests that catalytic reaction may proceed through outer-sphere mechanism without a distinct transmetalation step (Scheme 11C).

Zhang and co-workers modified the known, Pd(0) catalyzed asymmetric allylation of aldimine Schiff base **69** by introducing a Cu(II) cocatalyst (Scheme 12).[76] Under these synergistic dual catalysis conditions, formation of a stable, Cu-bound *N*-metalated azomethine ylide **72** is realized. Reaction of **72** with π-allylPd(II) complex **73** furnished the desired allylated product **71** in high yield with excellent enantioselectivities. Use of same chiral ligand **L** for both Pd and Cu catalysts mitigated problems arising from ligand exchange. The authors demonstrated the utility of this method by performing sequential asymmetric allylations after successive peptide couplings to prepare a triallylated peptide **74**, illustrating the potential for general, site specific, and enantioselective allylic alkylation of whole peptides (Scheme 12C). Furthermore, the same authors have also reported allylation on glycine-based aldimine esters.[77] Wang and co-workers reported a similar transformation utilizing synergistic catalysis between a chiral Cu(I) complex derived from aldimine Schiff base **76** and an achiral Pd(0) complex derived from allyl carbonates **75** to furnish chiral allylation products **77** (Scheme 13).[78] Recently, an updated account was published by the same authors utilizing glycine and cyclic ketamine esters to access various nonproteinogenic α-allyl α-amino acids.[79] The cooperative allylation reactions were recognized in its own topical review.[34] Similarly, The allylations of aldimine esters[80−82] and azaaryl acetamides[83] were also enabled under synergistic Cu/Ir dual catalytic conditions.

Scheme 12. Synergistic Pd/Cu Dual Catalysis for Asymmetric Allylic Alkylation of Amino Acids

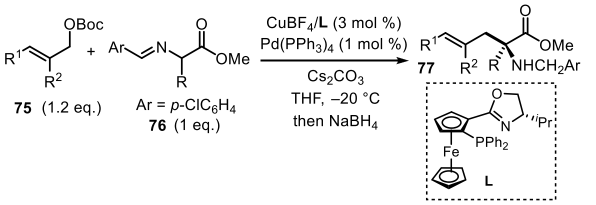


R^1	R^2	R^3	*ee*	%	R^1	R^2	R^3	*ee*	%
Ph	Me	^{t}Bu	98	88	Ph	Me	Me	94	87
(Z)-Ph	Me	^{t}Bu	98	82	Ph	Me	^{i}Pr	96	88
3-Cl-C_6H_4	Me	^{t}Bu	99	90	Ph	-CH_2O^tBu	^{t}Bu	98	89
4-Me-C_6H_4	Me	^{t}Bu	97	91	Ph	-$CH_2CO_2{}^t$Bu	^{t}Bu	97	86
1-np	Me	^{t}Bu	99	67	Ph	-$EtCO_2{}^t$Bu	^{t}Bu	98	82
2-np	Me	^{t}Bu	99	84	Ph	-EtSMe	^{t}Bu	94	89
2-furyl	Me	^{t}Bu	95	65	Ph	-BuNHCbz	^{t}Bu	99	78

2.3.1. Carboallylation of Alkenes.

Recently, Nakao and co-workers reported a three-component Pd/Cu mediated

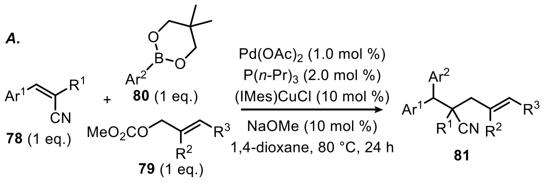
Scheme 13. Synergistic Pd/Cu Dual Catalysis for Allylic Alkylation of Amino Acids



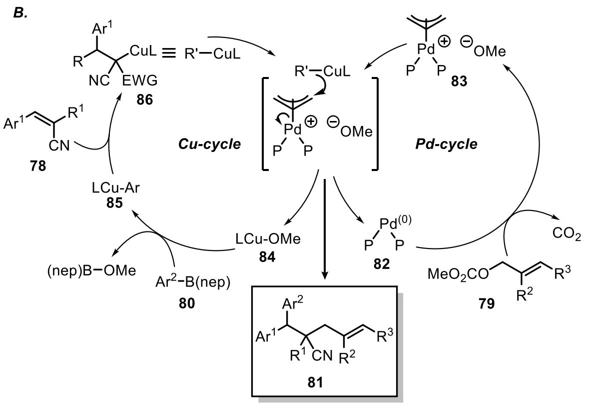
R^1	R^2	R	*ee*	%	R^1	R^2	R	*ee*	%	R^1	R^2	R	*ee*	%
Ph	H	Bn	95	91	2-thienyl	H	Bn	96	97	Ph	H	*n*-Pr	96	81
4-Me-C$_6$H$_4$	H	Bn	94	96	3-(1-tosyl-1*H*-indolyl)	H	Bn	88	84	Ph	H	*n*-Bu	98	81
3-Me-C$_6$H$_4$	H	Bn	96	91						Ph	H	*i*-Bu	97	85
2-Me-C$_6$H$_4$	H	Bn	80	92	-CH=CHPh	H	Bn	98	83	Ph	H	-CH$_2$CH$_2$SMe	98	89
4-OMe-C$_6$H$_4$	H	Bn	94	81	Me	H	Bn	90	84					
4-Cl-C$_6$H$_4$	H	Bn	92	94	H	H	Bn	90	92	Ph	H	Ph	99	86
3-Cl-C$_6$H$_4$	H	Bn	-91	81	H	Me	Bn	88	70	Ph	H	4-F-C$_6$H$_4$	94	79

carboallylation of electron-deficient alkenes **78** with allylic carbonates **79** and aryl boronic acid neopentylglycol esters **80** to furnish addition products **81** (Scheme 14).[84] The reported reaction is an update of a similar carboallylation reaction which employs tandem Pd/Cu catalysis, disclosed by the same authors utilizing tetraorganosilicon reagents.[85] Unlike other dicarbofunctionalizations for *α*,*β*-unsaturated compounds, synergistic Pd/Cu dual catalysis enables use of bench-stable reagents in place of moisture and O_2 sensitive reagents. Alkyl-allylation is also possible when using alkyl-9-BBN derivatives, which are prepared *in situ via* hydroboration of corresponding olefins with H-9-BBN. In the proposed reaction mechanism (Scheme 14B), Pd(0) **82** first undergoes oxidative addition into allylic carbonate **79** to generate *π*-allylPd(II) intermediate **83**. In the copper catalytic cycle, the interaction between Cu methoxide **84** and organoboron reagent **80** yields organocopper **85**. Addition of organocopper **85** across the electron-deficient alkene **78** affords alkyl copper **86** as the catalytically active species. Final reaction between **83** and **86** furnishes the allylated product **81** and return of the Pd and Cu catalysts to their respective cycles.

Scheme 14. Synergistic Cu/Pd Dual Catalysis for Three-Component Carboallylation



Ar^1	R^1	Ar^2	R^2	R^3	%	Ar^1	R^1	Ar^2	R^2	R^3	%
Ph	CN	4-Me-C$_6$H$_4$	H	H	48	4-OMe-C$_6$H$_4$	CN	4-Me-C$_6$H$_4$	H	H	67
Ph	CN	Ph	H	H	62	4-F-C$_6$H$_4$	CN	4-Me-C$_6$H$_4$	H	H	54
Ph	CN	4-Br-C$_6$H$_4$	H	H	61	Ph	CO$_2$Me	Ph	H	H	71
Ph	CN	4-Ac-C$_6$H$_4$	H	H	47	Ph	CO$_2$Me	Ph	H	Ph	63



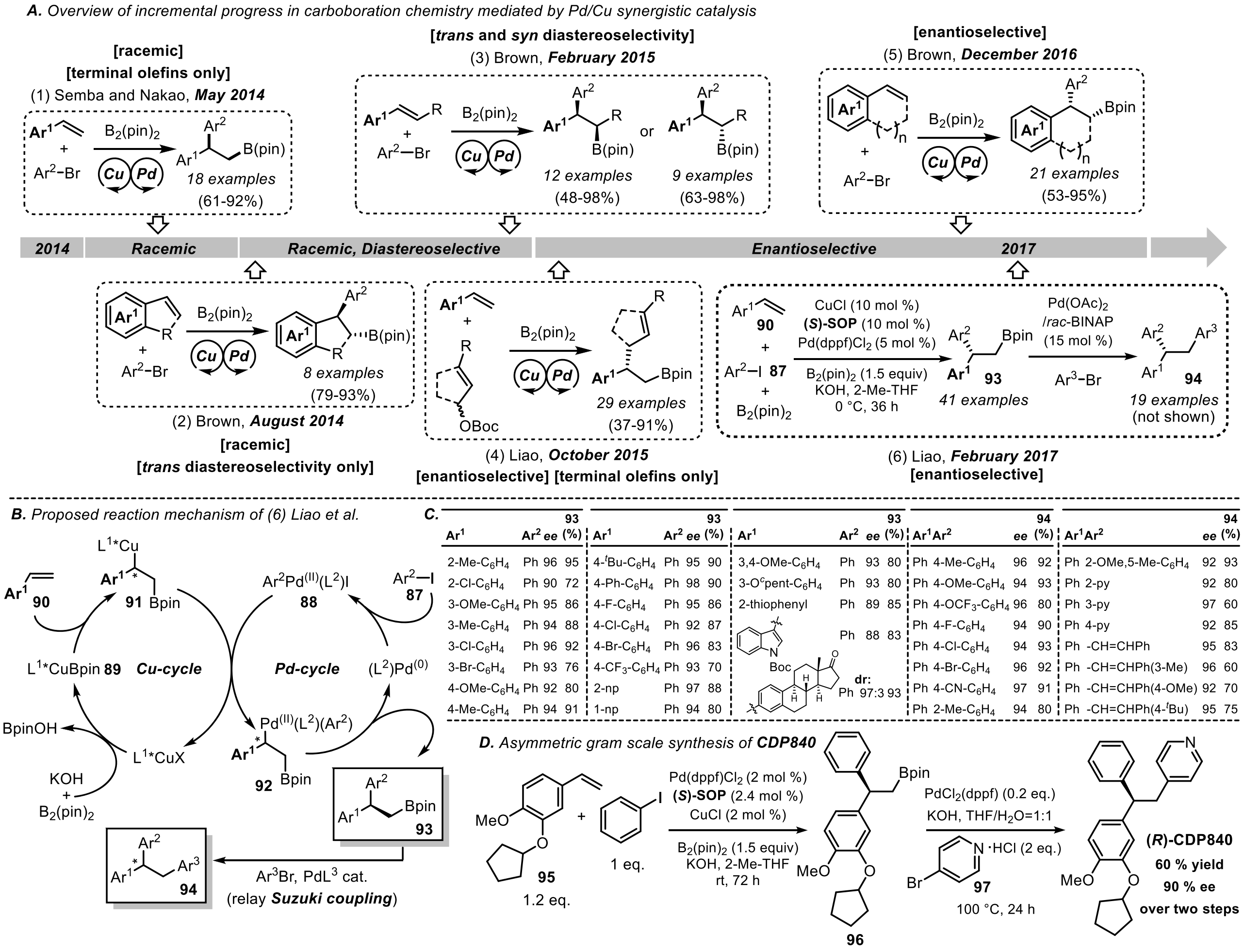
2.4. Carboboration of Alkenes

Synergistic Pd/Cu dual catalysis for three-component couplings between alkene, electrophile (aryl/allylic halides, or carbonates) and $B_2(pin)_2$ afford a highly functionalized boronic ester (Scheme 15). Advances on these transformations have been surveyed by Fananas-Mastral and co-workers, which should be consulted for an in-depth look of the field.[86] The seminal study in this direction was published by Nakao and co-workers where aryl bromide and $B_2(pin)_2$ were added across terminal aryl olefins to afford 2-boryl-1,1-diarylethanes (Scheme 15A-1).[87] Brown and co-workers extended this method to realize addition across 1,2-disubstituted cyclic olefins, where *anti* aryl-borylation was observed (Scheme 15A-2).[88] Further refinements and judicious choice of solvent and ligand then enabled both *syn* and *anti*-diastereoselective additions across acyclic 1,2-disubstitued olefins (Scheme 15A-3).[89] Liao and co-workers reported the first example of an enantioselective arylborylation reaction across terminal olefins (Scheme 15A-4).[90]

Brown and co-workers achieved enantio- and diastereoselective *syn* addition across cyclic and noncyclic 1,2-disubstituted olefins (Scheme 15A-5),[91] and finally, Liao and co-workers reported enantioselective preparation of 1,1,2-triarylethanes, which was realized with Cu/Pd mediated arylborylation followed by a tandem Pd catalyzed Suzuki reaction (Scheme 15A-6).[92] The mechanistic details of synergistic Pd/Cu dual catalysis for carboboration are generally applicable across the range of reactions featured above. The reaction reported by Liao and co-workers can serve as a typical example (Scheme 15B). First, aryl iodide **87** undergoes oxidative addition into Pd(0) catalyst, generating aryl-Pd(II) species **88**. In the Cu catalytic cycle, Cu(I) catalyst in the presence of base and $B_2(pin)_2$ undergoes transmetalation to furnish boryl copper intermediate **89**. Addition of **89** across olefin **90** yields *β*-borylorganocopper **91**, which undergoes transmetalation with **88** to deliver *β*-borylated alkyl moiety onto the Pd(II) center, forming **92** and regeneration of Cu(I) catalyst. Finally, reductive elimination affords 1,1-diaryl-2-borylalkane product **93** with regeneration of the Pd(0) catalyst. The products were amendable for further Suzuki coupling, affording triarylated **94** in good yields. The utility of the catalytic arylborylation was demonstrated in the gram scale asymmetric synthesis of phosphodiesterase IV inhibitor (*R*)-CDP840 by coupling vinylarene **95** with iodobenzene and $B_2(pin)_2$, followed by a subsequent Suzuki-coupling reaction of **96** with **97** (Scheme 15D).

Isoprene is a versatile and abundant starting material,[93] and considerable effort has been invested in functionalizing this feedstock chemical.[94] In this context, Brown and co-workers applied synergistic Pd/Cu dual catalysis to selectively introduce an aryl and a boronic acid pinacol ester moiety onto the isoprene backbone **98** (Scheme 16).[95] The problems associated with nonregioselective copper-boration and unselective transmetalation of the two alkene sites could be mitigated by increasing the steric factor of NHC-Cu catalyst. In this context, using $[(I^tBu)CuBr]$[96] and Pd-QPhos catalysts proved optimal in affording 1,4-arylborated **99** as the major geometric regioisomer (Scheme 16A top). Interestingly, 1,2-arylborated regioisomer **100** could be accessed by addition of DMAP in the reaction and with use of a bulkier trialkylphosphine ligand (Scheme 16A, bottom). The exact mechanistic role of DMAP in redirecting the regioselectivity remains unknown. Brown extended this strategy

Scheme 15. Three-Component Coupling of Alkene, Electrophile, and $B_2(pin)_2$



Ar^1	Ar^2	ee	93 (%)
2-Me-C_6H_4	Ph	96	95
2-Cl-C_6H_4	Ph	90	72
3-OMe-C_6H_4	Ph	95	86
3-Me-C_6H_4	Ph	94	88
3-Cl-C_6H_4	Ph	96	92
3-Br-C_6H_4	Ph	93	76
4-OMe-C_6H_4	Ph	92	80
4-Me-C_6H_4	Ph	94	91

Ar^1	Ar^2	ee	93 (%)
4-^{t}Bu-C_6H_4	Ph	95	90
4-Ph-C_6H_4	Ph	98	90
4-F-C_6H_4	Ph	95	86
4-Cl-C_6H_4	Ph	92	87
4-Br-C_6H_4	Ph	96	83
4-CF_3-C_6H_4	Ph	93	70
2-np	Ph	97	88
1-np	Ph	94	80

Ar^1	Ar^2	ee	93 (%)
3,4-OMe-C_6H_4	Ph	93	80
3-O^{c}pent-C_6H_4	Ph	93	80
2-thiophenyl	Ph	89	85
Boc	Ph	88	83
	Ph	dr: 97:3	93

Ar^1	Ar^2	ee	94 (%)
Ph	4-Me-C_6H_4	96	92
Ph	4-OMe-C_6H_4	94	93
Ph	4-OCF_3-C_6H_4	96	80
Ph	4-F-C_6H_4	94	90
Ph	4-Cl-C_6H_4	94	93
Ph	4-Br-C_6H_4	96	92
Ph	4-CN-C_6H_4	97	91
Ph	2-Me-C_6H_4	94	80

Ar^1	Ar^2	ee	94 (%)
Ph	2-OMe,5-Me-C_6H_4	92	93
Ph	2-py	92	80
Ph	3-py	97	60
Ph	4-py	92	85
Ph	-CH=CHPh	95	83
Ph	-CH=CHPh(3-Me)	96	60
Ph	-CH=CHPh(4-OMe)	92	70
Ph	-CH=CHPh(4-^{t}Bu)	95	75

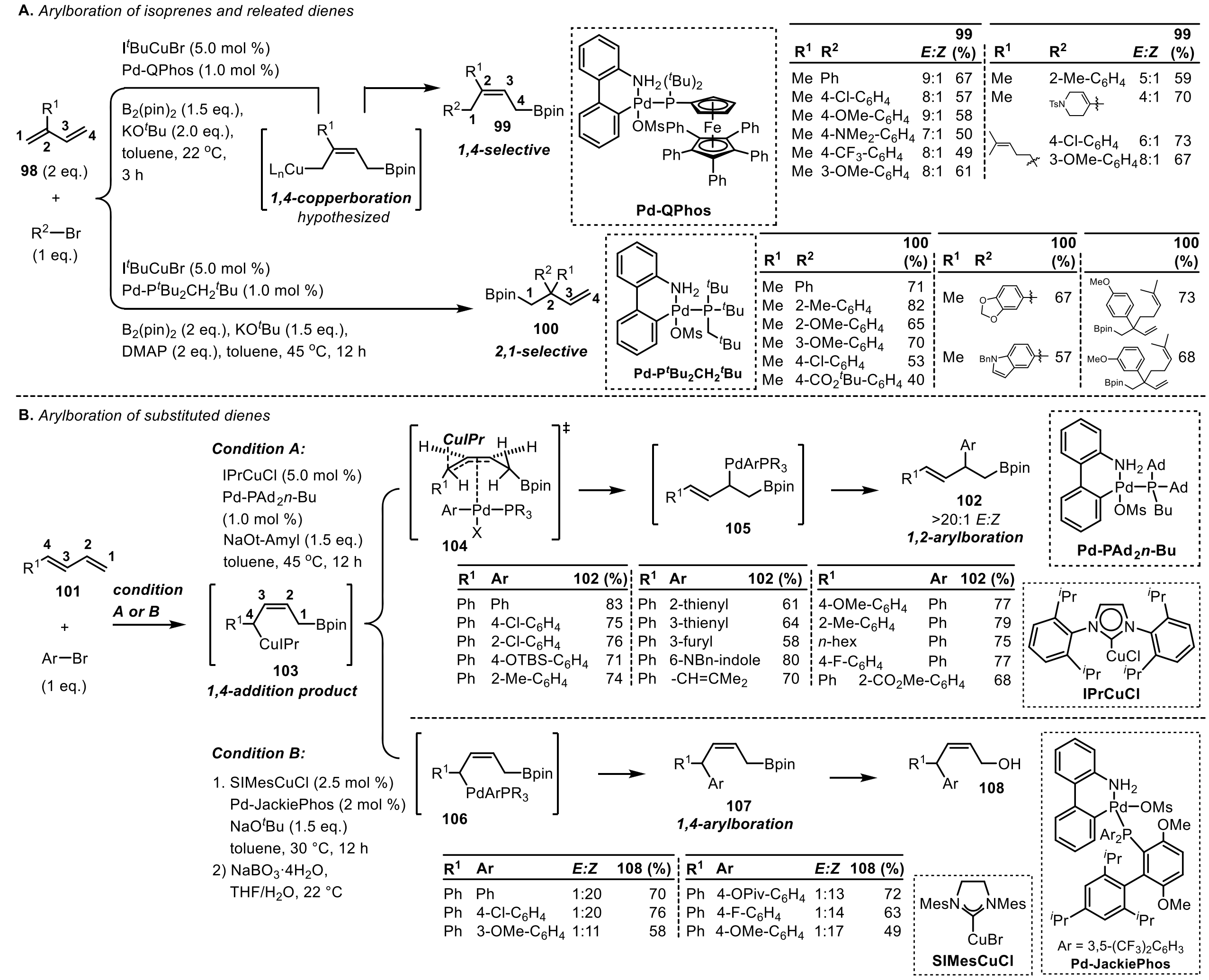
to functionalize another type of monosubstituted 1,3-diene (**101**, $R^1 \neq H$, Scheme 16B).[97] It was found that the use of sterically demanding [(IPr)CuCl][98,99] and Pd-PAd$_2$*n*-Bu complexes enabled facile 1,2-regioselectivity in the arylboration event, affording 1,2-arylborylated **102** with *E* geometry as the major product (Scheme 16B, top). Proposed mechanistic explanation for regioselective functionalization of **101** is as follows. First, borylcupration of diene **101** leads to regioselective boration at the terminal C(1) position and cupration at the C(4) position, yielding the 1,4-addition intermediate **103**. Then, transmetalation takes place between **103** and ArPd(II)BrL$_n$ *via* transition state **104** (Scheme 16B, top) where the Pd complex approaches the C(2)−C(3) double bond with the steric bulk of the ligands shielding the C(4)−Cu position, furnishing intermediate **105**. Subsequent reductive elimination affords 1,2-arylborated product **102**. On the basis of these results, it was rationalized that to access the 1,4-regioisomer, use of non-hindered ligands would allow for direct transmetalation at the C(4) position of **103** and afford the 1,4-palladated intermediate **106** (Scheme 16B, bottom). This outcome could be promoted by employing an exceptionally electrophilic palladium complex. Thus, the use of SIMesCuCl and PdJackiePhos under modified conditions enabled the selective arylboration of **101** by ArBr and $B_2(pin)_2$ to yield **107**, which after oxidation furnished allylic alcohol **108** in good yields.

2.5. Carboboration of Alkynes

2.5.1. Arylboration of Alkynes.

The development of regio- and stereoselective methods for tri- and tetrasubstituted olefins are considered highly valuable in organic synthesis.[100,101] Elaborating upon the initial report by Semba and Nakao describing the arylboration of diphenylacetylenes with *p*-bromoanisole,[87] Cazin and co-workers disclosed arylboration of unsymmetrical, disubstituted alkyl(aryl)acetylenes **109** with aryl halides **110** and $B_2(pin)_2$ under synergistic Pd(0)/Cu(I) dual catalysis to afford the tetrasubstituted alkenylboryl compounds **111** in high yields and regioselectivities (Scheme 17).[102] The mechanistic considerations diverge according to solvent used. In aprotic solvents (Scheme 17B), the reaction proceeds with NHC-Cu complex **112**, which reacts with NaO^{t}Bu then with $B_2(pin)_2$ to afford boryl-Cu(I) complex **113**. Borylcupration of alkyne **109** with **113** affords alkenyl-Cu(I) species **114** with high regioselectivity, where Cu is placed on the α-position to the aryl group of the unsymmetrical alkyne. For the Pd cycle, oxidative addition of the Pd(0) catalyst into aryl halide **110** affords Ar-Pd(II)X **115**, which upon transmetalation with **114** transfers alkenylboron moiety onto the Pd(II) center, affording intermediate **116** with liberation of Cu(I) catalyst **112**. Reductive elimination affords the desired product **111** with regeneration of the Pd(0) catalyst. Interestingly, this reactivity could be altered significantly by the use of a protic solvent such as EtOH, shutting down the synergistic process in favor of relay catalysis (Scheme 17C).

Scheme 16. Synergistic Pd/Cu Dual Catalysis for Arylboration of Isoprene and Related Dienes



R^1	R^2	E:Z	**99** (%)
Me	Ph	9:1	67
Me	4-Cl-C_6H_4	8:1	57
Me	4-OMe-C_6H_4	9:1	58
Me	4-NMe_2-C_6H_4	7:1	50
Me	4-CF_3-C_6H_4	8:1	49
Me	3-OMe-C_6H_4	8:1	61
Me	2-Me-C_6H_4	5:1	59
Me		4:1	70
	4-Cl-C_6H_4	6:1	73
	3-OMe-C_6H_4	8:1	67

R^1	R^2	**100** (%)
Me	Ph	71
Me	2-Me-C_6H_4	82
Me	2-OMe-C_6H_4	65
Me	3-OMe-C_6H_4	70
Me	4-Cl-C_6H_4	53
Me	4-$CO_2{}^t$Bu-C_6H_4	40
Me		67
Me		57
		73
		68

R^1	Ar	**102** (%)
Ph	Ph	83
Ph	4-Cl-C_6H_4	75
Ph	2-Cl-C_6H_4	76
Ph	4-OTBS-C_6H_4	71
Ph	2-Me-C_6H_4	74
Ph	2-thienyl	61
Ph	3-thienyl	64
Ph	3-furyl	58
Ph	6-NBn-indole	80
Ph	-CH=CMe_2	70
4-OMe-C_6H_4	Ph	77
2-Me-C_6H_4	Ph	79
n-hex	Ph	75
4-F-C_6H_4	Ph	77
Ph	2-CO_2Me-C_6H_4	68

R^1	Ar	E:Z	**108** (%)
Ph	Ph	1:20	70
Ph	4-Cl-C_6H_4	1:20	76
Ph	3-OMe-C_6H_4	1:11	58
Ph	4-OPiv-C_6H_4	1:13	72
Ph	4-F-C_6H_4	1:14	63
Ph	4-OMe-C_6H_4	1:17	49

With ethanol as the solvent, protonation of alkenyl-Cu(I) **114** affords protonated trisubstituted boryl alkenyl species **117**, which then reacts with Ar-Pd(II)-X **115**, akin to standard Suzuki coupling, to afford intermediate **118**, and subsequent reductive elimination affords trisubstituted olefin **119**. Following this work, Semba and Nakao reported the arylboration of alkynes with expanded scope, reacting diarylacetylenes, alkyl(aryl)-acetylenes, and dialkylacetylenes with aryl chlorides or bromides under synergistic Pd/Cu catalysis.[103]

2.5.2. Alkenyboration of Alkynes.

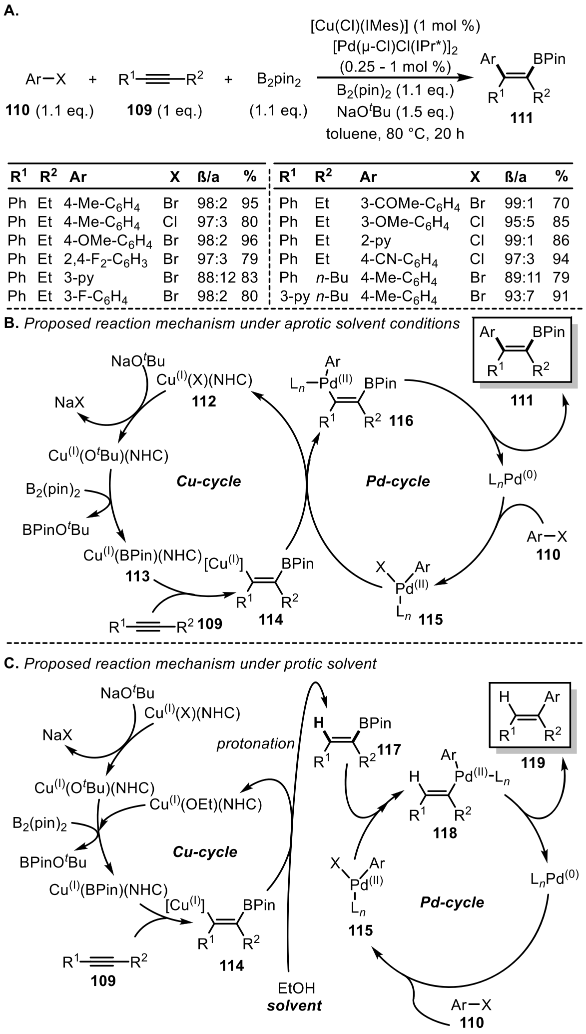
Inspired by Pd/Cu catalyzed arylborations described above, Fañanás-Mastral and co-worker envisioned using an alkenyl (pseudo)halide electrophile **120** for Pd/Cu catalyzed alkyne boration of **121** in the presence of (B_2 pin_2), giving access to *syn*-1-boron-1,3-dienes **122** (Scheme 18).[104]

Mechanistically, the use of co Pd-catalyst to activate **120** under mild conditions mitigates the potentially problematic, competitive migratory insertion of LCu-Bpin intermediate across alkenyl bromide. Thus, oxidative addition of Pd(0) into **120** furnishes catalytically active species **123**. LCu-Bpin **124** is generated by transmetalation of Cu(I) catalyst in the presence of base and $B_2(pin)_2$, which undergoes subsequent reaction across the acetylene **121** to yield β-boryl-substituted alkenyl copper **125**. Electrophilic trapping of **125** with Pd(II) complex **123** yields regeneration of Cu(I) catalyst and Pd(II)-complex **126**, whereupon subsequent reductive elimination yields borylated 1,3-diene product **122** and return of the Pd(0) catalyst.

2.5.3. Arylsilylation of Alkynes.

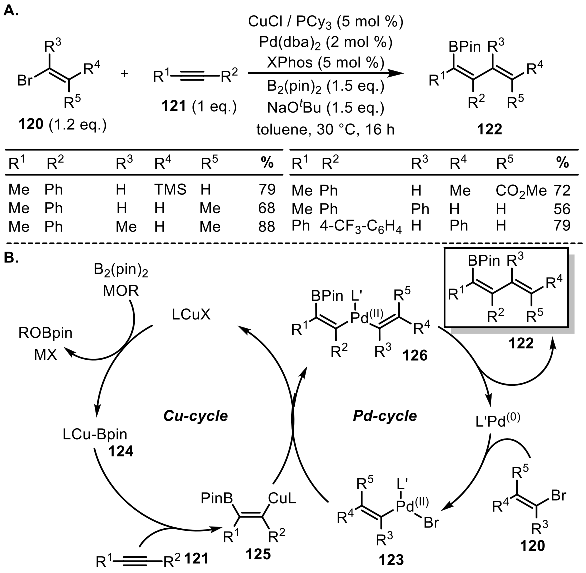
Nozaki and co-workers developed a three component intermolecular arylsilylation reaction of alkynes **127** with silylboronate **128** and aryl bromide **129** under synergistic Pd/Cu dual catalysis to prepare tetrasubstituted alkenylsilanes **130** in moderate to good yields (Scheme 19).[105] In this reaction, the silylCu(I) complex **131** was formed by reaction of Cu(I) catalyst with B(pin)-$SiMe_2$Ph **128** in the presence of NaO^{t}Bu. Addition of **131** across alkyne **127** allows for the formation of alkenyl Cu(I)-complex **132**, which then undergoes transmetalation with ArPd(II) complex **133** generated by oxidative addition of Pd(0) into **129**, producing vinylsilylPd(II) complex **134** along with regeneration of the Cu(I) catalyst. Reductive elimination of Pd(II) complex **134** afforded the desired arylsilylated product **130** with regeneration of the Pd(0) species. Alkylsilylation was also possible by using alkyl bromide in place of aryl bromide **129**, although in such reactions the yield was depressed. Use of an unsymmetrical alkyne (R^1 = Ph, R^2 = Me) led to moderate regioselectivity (76:24). Most examples utilized symmetrical alkynes (R^1 = R^2), where both diaryl acetylenes and dialkyl acetylenes afforded the desired product in moderate to good yields. Additionally, tetrasubstituted alkenyl silane products

Scheme 17. Synergistic Pd/Cu Dual Catalysis for Aryl-Boration of Disubstituted Alkynes



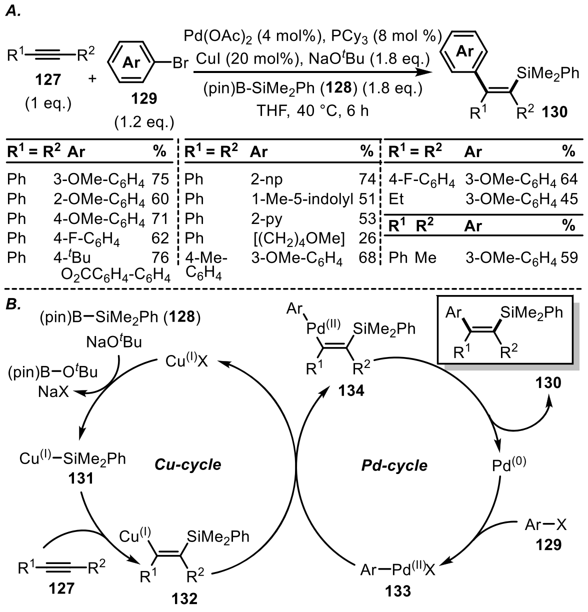
R^1	R^2	Ar	X	ß/a	%
Ph	Et	4-Me-C_6H_4	Br	98:2	95
Ph	Et	4-Me-C_6H_4	Cl	97:3	80
Ph	Et	4-OMe-C_6H_4	Br	98:2	96
Ph	Et	2,4-F_2-C_6H_3	Br	97:3	79
Ph	Et	3-py	Br	88:12	83
Ph	Et	3-F-C_6H_4	Br	98:2	80
Ph	Et	3-COMe-C_6H_4	Br	99:1	70
Ph	Et	3-OMe-C_6H_4	Cl	95:5	85
Ph	Et	2-py	Cl	99:1	86
Ph	Et	4-CN-C_6H_4	Cl	97:3	94
Ph	*n*-Bu	4-Me-C_6H_4	Br	89:11	79
3-py	*n*-Bu	4-Me-C_6H_4	Br	93:7	91

Scheme 18. Synergistic Pd/Cu Dual Catalysis for Alkenyl-Boration of Disubstituted Alkynes



R^1	R^2	R^3	R^4	R^5	%
Me	Ph	H	TMS	H	79
Me	Ph	H	H	Me	68
Me	Ph	Me	H	Me	88
Me	Ph	H	Me	CO_2Me	72
Me	Ph	Ph	H	H	56
Ph	4-CF_3-C_6H_4	H	Ph	H	79

Scheme 19. Synergistic Pd/Cu Dual Catalysis for Aryl-Silylation of Disubstituted Alkynes



$R^1 = R^2$	Ar	%
Ph	3-OMe-C_6H_4	75
Ph	2-OMe-C_6H_4	60
Ph	4-OMe-C_6H_4	71
Ph	4-F-C_6H_4	62
Ph	4-^{t}Bu $O_2CC_6H_4$-C_6H_4	76
Ph	2-np	74
Ph	1-Me-5-indolyl	51
Ph	2-py	53
Ph	$[(CH_2)_4OMe]$	26
4-Me-C_6H_4	3-OMe-C_6H_4	68
4-F-C_6H_4	3-OMe-C_6H_4	64
Et	3-OMe-C_6H_4	45

R^1	R^2	Ar	%
Ph	Me	3-OMe-C_6H_4	59

could undergo desilylative bromination to afford the corresponding alkenyl bromides in good yields.

2.5.4. Allylboration of Alkynes.

Fañanás-Mastral and coworkers reported synergistic Pd/Cu dual catalysis for allylboration of alkynes **135** with allyl carbonate **136** and $B_2(pin)_2$ to afford borylated 1,4-dienes **137** in good yield with high stereoselectivity (Scheme 20).[106] In the proposed reaction mechanism, Cu(I) catalyst undergoes transmetalation sequentially with alkoxide and B_2Pin_2 to afford LCu(I)Bpin complex **138**, which effects borylcupuration onto alkyne **135**, furnishing *β*-borylalkenylcopper complex **139** (Scheme 20B).

Regarding the synergistic event, although direct interaction of **139** with the Pd cycle can be suspected, it was proposed that **139** would react with an additional *tert*-butoxide anion to formate complex **140**, a more reactive intermediate and thereby rationalizing the stoichiometric amount of *tert*-butoxide required, even when Boc-allyl carbonates are used.[107,108] In the Pd catalytic cycle, oxidative addition of carbonate **136** into Pd(0) catalyst affords *π*-allylPd(II) complex **141**. Transmetalation between intermediates **140** and **141** furnishes 1,4-diene **137** with regeneration of the original Cu(I) and Pd(0) catalysts.

The synthetic utility of this method was demonstrated with total synthesis of (*Z*,*E*)-*α*-homofarnesene (fire-ant pheromone)[109] and formal synthesis of merochlorins A−D (antibiotic marine natural product),[110,111] where key borylated 1,4-diene intermediates were prepared in good yields (Scheme 20C).

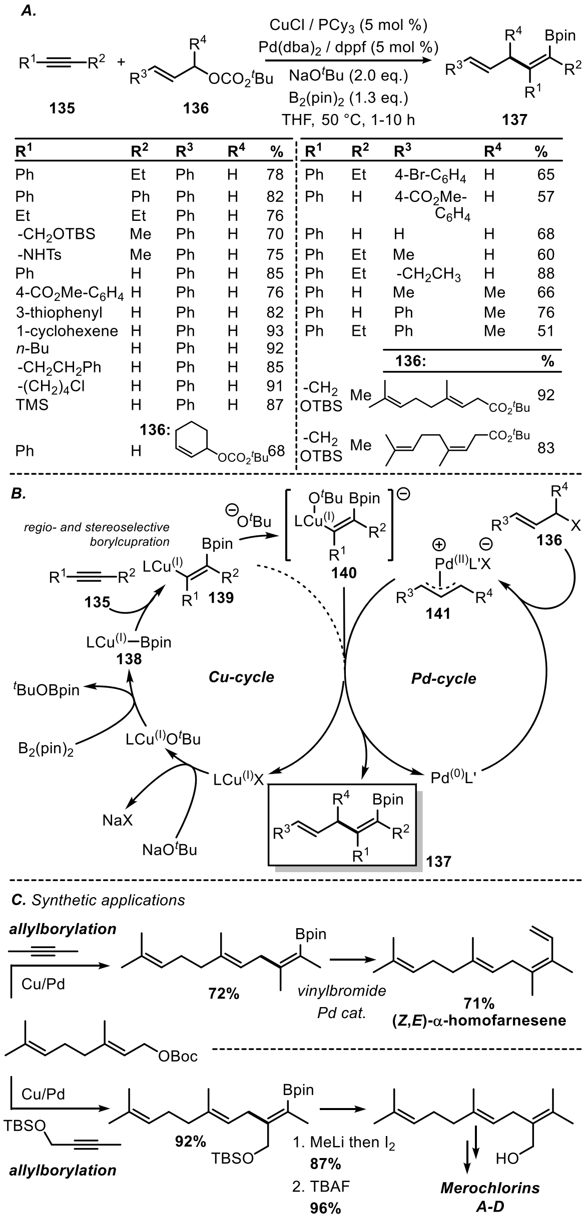
2.6. Hydroarylation of Alkenes

2.6.1. Hydroarylation of Arylalkenes.

Nakao and coworkers recently accomplished a reductive-cross-coupling between aryl alkenes **142** and aryl bromides **143** by utilizing stoichiometric amounts of hydrosilane **144** as a reducing agent under Pd/Cu dual catalysis, affording 1,1-diarylalkanes **145** with high regioselectivity (>20:1 dr) (Scheme 21).[112]

The proposed reaction mechanism begins with reaction of (NHC)Cu(I)Br with LiO^{t}Bu to generate Cu(I) alkoxide salt **146**, which is reduced with $HSi(OEt)_3$ (**144**) to furnish Cu(I) hydride species **147**. A regioselective hydrocupration reaction

Scheme 20. Synergistic Pd/Cu Dual Catalysis for Allyl-Boration of Disubstituted Alkynes



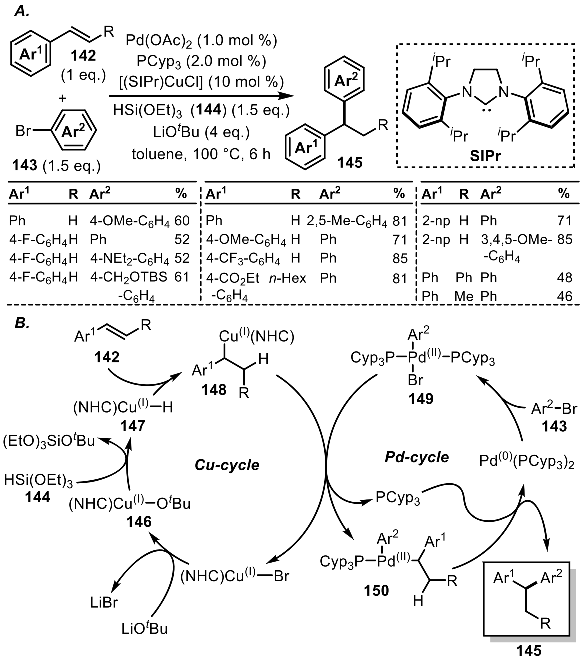
R^1	R^2	R^3	R^4	%
Ph	Et	Ph	H	78
Ph	Ph	Ph	H	82
Et	Et	Ph	H	76
$-CH_2OTBS$	Me	Ph	H	70
-NHTs	Me	Ph	H	75
Ph	H	Ph	H	85
$4-CO_2Me-C_6H_4$	H	Ph	H	76
3-thiophenyl	H	Ph	H	82
1-cyclohexene	H	Ph	H	93
n-Bu	H	Ph	H	92
$-CH_2CH_2Ph$	H	Ph	H	85
$-(CH_2)_4Cl$	H	Ph	H	91
TMS	H	Ph	H	87
Ph	H	136:		68

R^1	R^2	R^3	R^4	%
Ph	Et	$4-Br-C_6H_4$	H	65
Ph	H	$4-CO_2Me-C_6H_4$	H	57
Ph	H	H	H	68
Ph	Et	Me	H	60
Ph	Et	$-CH_2CH_3$	H	88
Ph	H	Me	Me	66
Ph	H	Ph	Me	76
Ph	Et	Ph	Me	51
		136:		%
$-CH_2OTBS$	Me			92
$-CH_2OTBS$	Me			83

across conjugated arylalkene **142** affords the more stable α-bound Cu(I) complex **148**,[113] which upon transmetalation with Ar-Pd(II)-Br **149** transfers the arylalkane moiety onto the Pd(II) center, along with one molecular disassociation of $PCyp_3$ ligand to form Pd(II) complex **150**, which is an unusual tricoordinated catalytic intermediate. Final reductive elimination affords the desired product **145** with regeneration of Pd(0) catalyst.

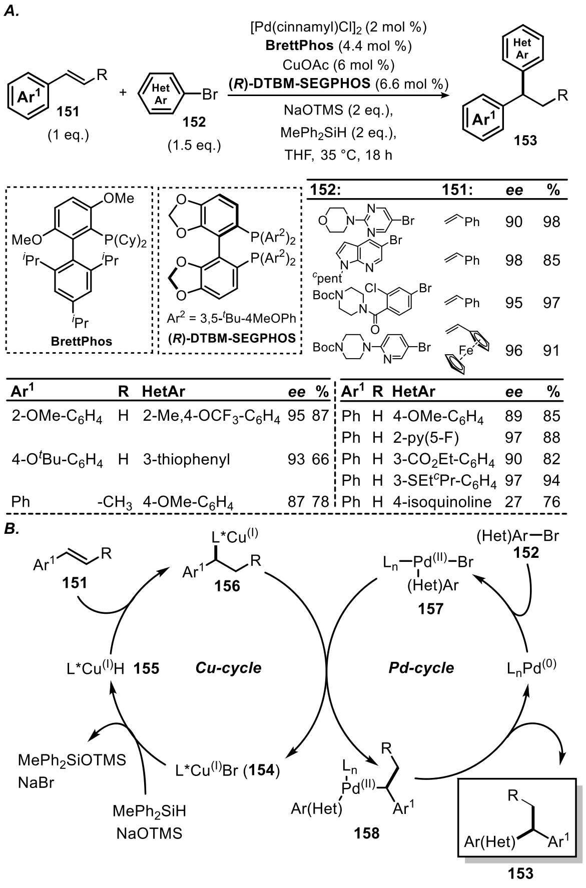
2.6.2. Asymmetric Reductive Cross-Coupling. Buchwald and co-workers reported an asymmetric hydroarylation of vinylarenes **151** utilizing hydrosilane reagent $MePh_2SiH$ and aryl bromides **152** under synergistic Pd(0)/Cu(I) dual catalysis to afford chiral 1,1-diarylalkanes **153** (Scheme 22).[114] The mechanistic details are similar to the one proposed by Nakao and co-workers in which asymmetrically ligated-Cu complex **154** reacts with $MePh_2SiH$ to afford chiral Cu(I) hydride species **155** (Scheme 22B).

Scheme 21. Synergistic Pd/Cu Dual Catalysis for Reductive Cross-Coupling of Aryl Alkenes and Aryl Bromides



Ar^1	R	Ar^2	%
Ph	H	$4-OMe-C_6H_4$	60
$4-F-C_6H_4$	H	Ph	52
$4-F-C_6H_4$	H	$4-NEt_2-C_6H_4$	52
$4-F-C_6H_4$	H	$4-CH_2OTBS-C_6H_4$	61
Ph	H	$2,5-Me-C_6H_4$	81
$4-OMe-C_6H_4$	H	Ph	71
$4-CF_3-C_6H_4$	H	Ph	85
$4-CO_2Et-C_6H_4$	n-Hex	Ph	81
2-np	H	Ph	71
2-np	H	$3,4,5-OMe-C_6H_4$	85
Ph	Ph	Ph	48
Ph	Me	Ph	46

Scheme 22. Synergistic Pd/Cu Dual Catalysis for Asymmetric Reductive Cross-Coupling of Aryl Alkenes and Aryl Bromides



152:	151:	ee	%
		90	98
		98	85
		95	97
		96	91

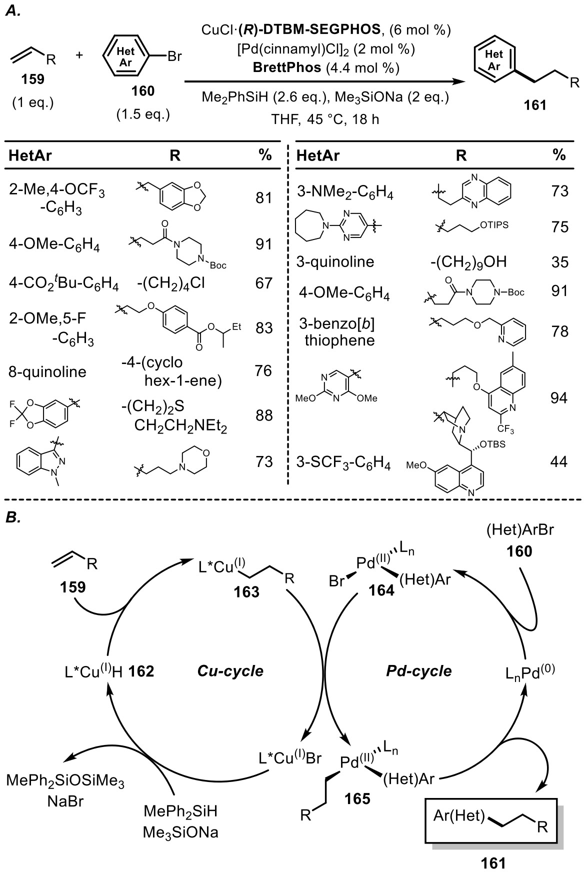
Ar^1	R	HetAr	ee	%
$2-OMe-C_6H_4$	H	$2-Me,4-OCF_3-C_6H_4$	95	87
$4-O^tBu-C_6H_4$	H	3-thiophenyl	93	66
Ph	$-CH_3$	$4-OMe-C_6H_4$	87	78
Ph	H	$4-OMe-C_6H_4$	89	85
Ph	H	2-py(5-F)	97	88
Ph	H	$3-CO_2Et-C_6H_4$	90	82
Ph	H	$3-SEt^cPr-C_6H_4$	97	94
Ph	H	4-isoquinoline	27	76

Hydrocupration of **151** with Cu(I) hydride **155** affords Cu(I) activated species **156**, which undergoes transmetalation with Ar-

Pd(II)-Br complex **157** to furnish **158**. Subsequent reductive elimination affords enantioenriched product **153**.

2.6.3. Hydroarylation of α-Olefins. Suzuki–Miyaura cross-coupling is a versatile reaction for forging a bond between an aryl halide and alkylboron reagents, with the latter often derived from the hydroboration of an olefin.[115] However, manipulation of boron reagents entail handling and stability issues. In this context, coupling of olefins **159** with aryl halides **160** to yield **161** represent a more direct approach to cross-coupled products, and this vision was realized by Buchwald and co-workers *via* a synergistic Pd(0)/Cu(I) dual catalytic system (Scheme 23).[116]

Scheme 23. Synergistic Pd/Cu Dual Catalysis for the Reductive Cross-Coupling of α-Olefins and Aryl Bromides

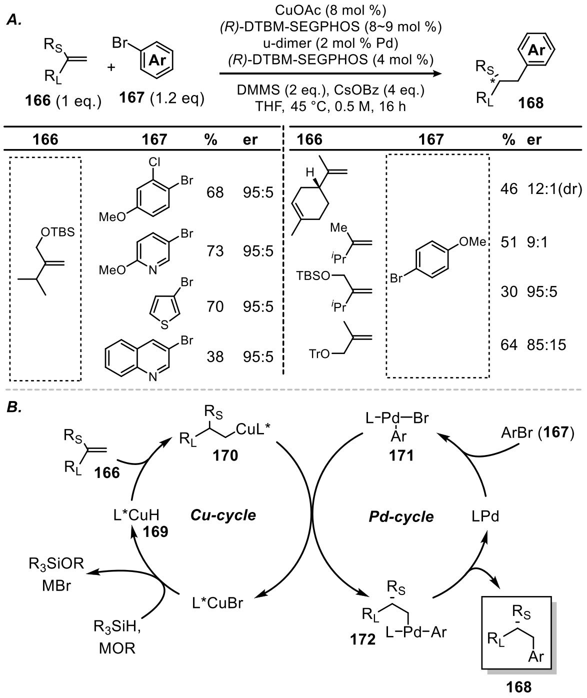


As shown in Scheme 23B, the reaction postulates the generation of a chiral Cu(I) hydride species **162** *via* action of silyl hydride with copper(I) catalyst, which then inserts into the alkene **159**. This *anti*-Markovnikov regioselectivity is driven by the favorable formation of the sterically less hindered Cu complex, affording catalytically activated alkyl Cu(I) intermediate **163**. For the palladium catalytic cycle, oxidative addition of the Pd(0) catalyst into aryl halide **160** affords Pd(II) complex **164**. Transmetalation between **163** and **164** transfers the alkyl moiety onto the Pd(II) center to form Pd(II) complex **165** with regeneration of the Cu(I) catalyst. The subsequent reductive elimination affords the desired product **161** with the regeneration of Pd(0) catalyst. In cases where the olefin coupling partner featured both a terminal and internal double bond, the more reactive terminal olefin reacted preferentially to selectively afford monocross-coupled product.

2.6.4. Hydroarylation of 1,1-Disubstituted Olefins. A long-standing problem in organic chemistry involved installation of β-stereogenic centers *via* functionalization of 1,1-disubstitued olefins, a class of substrates which feature barely prochiral enantiotopic faces.

Aggarwal termed asymmetric hydroboration on such substrates as "notoriously difficult".[117] This problem however has been met with some advances; beginning with Soderquist's disclosure of 9-borabicyclo[3.3.2]decane derived borohydrides[118] and, more recently, with Yun's discovery of Cu-catalyzed asymmetric hydroboration reaction.[119] Yun's hydroboration reaction was driven by the generation of a key, monocatalytic chiral Cu–H species in the presence of a chiral DTBM-SEGPHOS phosphine ligand that undergoes asymmetric hydrocupration across the double bond to yield a chiral Cu intermediate, which is intercepted by boron species to yield β-chiral alkylboronates. Quite recently, Buchwald and co-workers disclosed synergistic Pd/Cu catalysis to hydroarylate 1,1-disubstitued olefin **166** with aryl bromide **167** to afford chiral product **168** with high asymmetric induction at the β-stereogenic center (Scheme 24).[120] Mechanistically, this reaction is highly related to Yun's hydroboration work, utilizing the same DTBM-SEGPHOS phosphine ligand and Cu–H species.

Scheme 24. Synergistic Pd/Cu Dual Catalysis for Hydroarylation of 1,1-Disubstituted Olefins

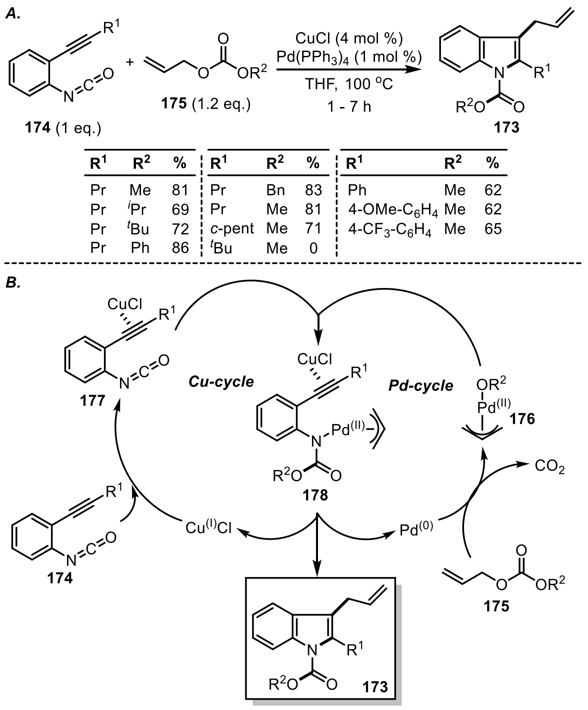


First, the required copper hydride **169** was generated from the reaction of copper acetate with Me(OMe)$_2$SiH (DMMS) in the presence of DTBM-SEGPHOS. Subsequently the known, anti-Markovnikov hydrocupration of chiral Cu–H across 1,1-disubstituted olefin **166** delivered chiral Cu(I) alkyl intermediate **170** as the catalytically activated species. Meanwhile, aryl bromide **167** was activated *via* oxidative addition of Pd(0) catalyst to yield aryl-Pd(II) intermediate **171**. Transmetalation of **170** with **171** returns the Cu catalyst to the catalytic cycle while forming the β-chiral Pd(II) alkyl complex **172**. Final reductive elimination furnishes the enantioenriched **168** while regenerating the Pd catalyst. This work notably exemplifies the potential of synergistic catalysis to powerfully expand the scope of important, monocatalytic reaction through the creative deployment of a second catalyst and reaction partner.

2.7. Miscellaneous Synergistic Pd/Cu Dual Catalysis

2.7.1. Synthesis of Indoles *via* Intramolecular Cyclization of (2-Alkynyl)phenylisocyanate. Yamamoto and co-workers initially envisioned monocatalytic, Pd(0)-catalyzed synthesis of indole **173** from (2-alkynyl)-phenylisocyanate **174** and allyl carbonate **175**. During the reaction discovery process, it was realized that coaddition of Cu(I) catalyst promotes the formation of the desired indole, presumably by acting as a π-coordinative Lewis acid to activate the alkyne (Scheme 25).[121]

Scheme 25. Synergistic Pd/Cu Dual Catalysis for Indole Synthesis

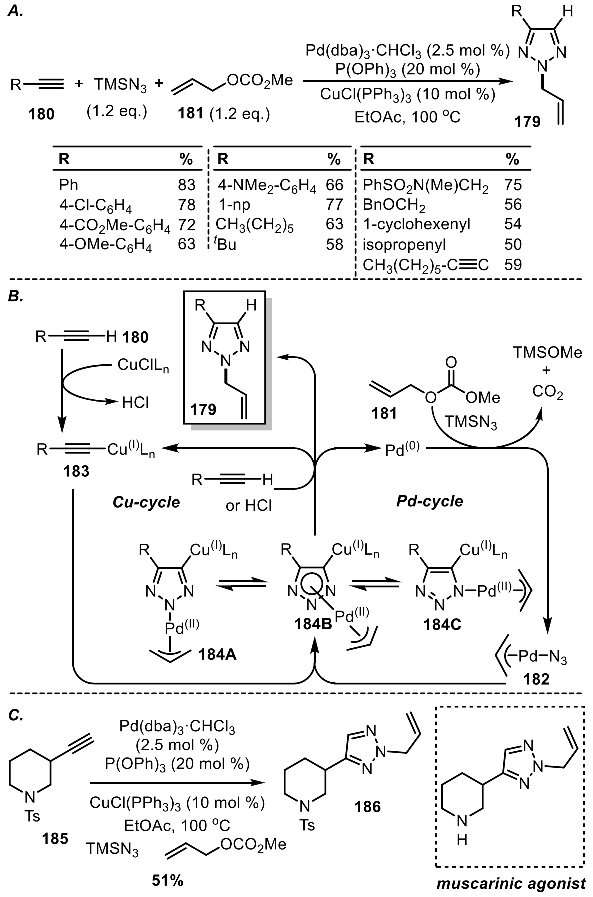


R^1	R^2	%	R^1	R^2	%	R^1	R^2	%
Pr	Me	81	Pr	Bn	83	Ph	Me	62
Pr	^{i}Pr	69	Pr	Me	81	4-OMe-C_6H_4	Me	62
Pr	^{t}Bu	72	*c*-pent	Me	71	4-CF_3-C_6H_4	Me	65
Pr	Ph	86	^{t}Bu	Me	0			

The detailed mechanistic rationale is described in Scheme 25B. First, the π-allylPd(II) alkoxide complex **176** is formed from decarboxylative oxidative addition of Pd(0) into allyl carbonate **175**. Subsequent reaction with the Cu(I)-coordinated isocyanate **177**, generated from **174** and Cu(I) catalyst, affords Pd(II)-carbamate complex **178**, which effectively furnish the allylated indole **173** through 5-endo cyclization followed by allylation. It was also suggested by the authors that the catalytic roles may be reversed and π-allylPd(II) species might activate the acetylene while the Cu(I) catalyst interacts with the nitrogen nucleophile.

2.7.2. Synthesis of Triazoles *via* Three Component Coupling. In many cases, the [3 + 2] cycloaddition between an alkyne and an azide generally require activation *via* presence of an electron withdrawing group on one of the starting substrates.[122−125] To realize the triazole forming reaction using nonactivated alkynes, Yamamoto and co-workers disclosed a synergistic Pd(0)/Cu(I) dual catalysis for three component synthesis of 2-allyl-1,2,3-triazole **179** starting from terminal alkyne **180**, azidotrimethylsilane ($TMSN_3$), and allyl carbonate **181** (Scheme 26).[126]

Scheme 26. Synergistic Pd/Cu Dual Catalysis for the Preparation of 2-Allyltriazoles



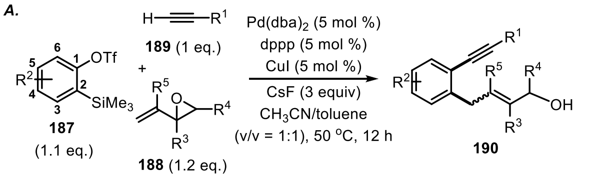
R	%	R	%	R	%
Ph	83	4-NMe_2-C_6H_4	66	$PhSO_2N(Me)CH_2$	75
4-Cl-C_6H_4	78	1-np	77	$BnOCH_2$	56
4-CO_2Me-C_6H_4	72	$CH_3(CH_2)_5$	63	1-cyclohexenyl	54
4-OMe-C_6H_4	63	^{t}Bu	58	isopropenyl	50
				$CH_3(CH_2)_5$-C≡C	59

In the proposed catalytic cycle, trimethylsilyl azide, and allyl carbonate **181** reacts with the Pd(0) catalyst to form π-allyl Pd(II) azide species **182** with extrusion of CO_2 gas and TMSOMe (Scheme 26B). A [3 + 2] cycloaddition of Pd(II)-azide **182** with copper acetylide **183** affords triazole-Pd(II) complex **184**, in which **184A−C** is in equilibrium. Reductive elimination of Pd(II) and protonolysis of the C−Cu bond affords the desired 2-allyltriazole **179**. Subsequent Ru-catalyzed isomerization followed by ozonolysis liberated *N*-unsubstituted 1,2,3-triazoles. Utilizing this methodology, piperidine substituted alkyne **185** was used to prepare **186**, a precursor for triazole containing muscarinic agonist (Scheme 26C).[127]

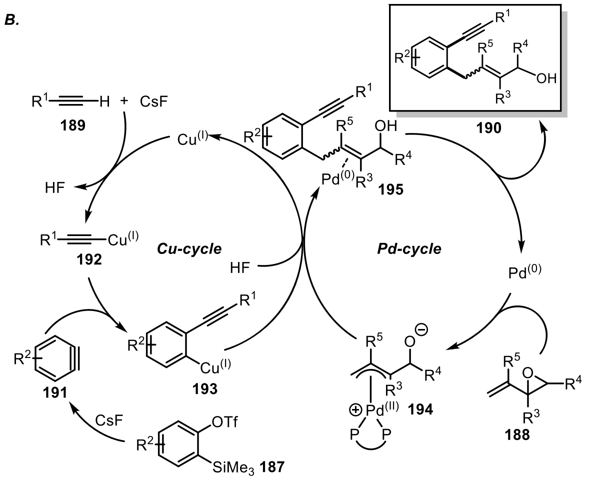
2.7.3. Three Component Coupling *via* Benzyne Intermediate. Cheng and co-workers reported synergistic Pd(0)/Cu(I) dual catalysis for the three component coupling of *O*-silyl triflate **187**, allylic epoxide **188**, and terminal alkyne **189** to produce 1,2-disubstituted arenes **190** through a benzyne intermediate (Scheme 27).[128]

As shown in Scheme 27B, benzyne **191**, formed *in situ via* action of CsF on *O*-silyl triflate **187**, undergoes alkynylcupration with copper acetylide **192**, generated from the Cu(I) catalyst and terminal alkyne **189** to afford Cu(I) species **193**. The π-allylPd(II) intermediate **194**, meanwhile, is generated by the oxidative addition of the Pd(0) catalyst into allylic epoxide **188**. The reaction of Cu(I) species **193** with π-allylPd(II)

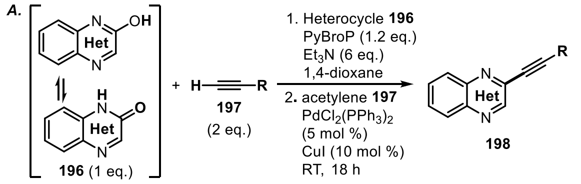
Scheme 27. Synergistic Pd/Cu Dual Catalysis for Three Component Synthesis of 1,2-Disubstituted Arenes

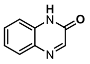
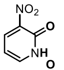
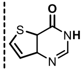
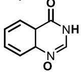
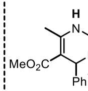
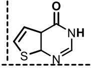


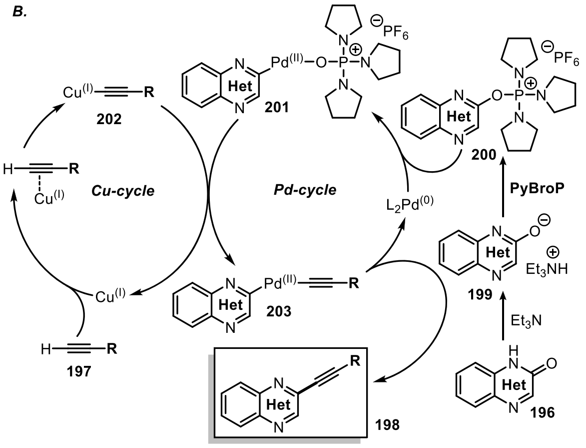
R^1	R^2	R^3	R^4	R^5	% (*E*:*Z*)	R^1	R^2	R^3	R^4	R^5	%
n-Bu	4,5-Me	H	H	H	87	*n*-Bu	4,5-Me	H	Ph	H	74
n-Bu	4,5-(dioxole)	H	H	H	77	Ph	H	H	H	H	87
n-Bu	4,5-F	H	H	H	63	4-OMe-C_6H_4	H	H	H	H	92
n-Bu	4-Me	H	H	H	85	3-(thiophene)	H	H	H	H	72
n-Bu	H	Me	H	H	79 (85:15)	^{t}Bu	H	H	H	H	83
n-Bu	H	Ph	H	H	75 (80:20)	CH_2OMe	H	H	H	H	79
n-Bu	H	H	H	Me	69 (82:18)	-$C(CH_3)=CH_2$	H	H	H	H	82



Scheme 28. Synergistic Pd/Cu Dual Catalysis for Alkynylation of Tautomerizable Heterocycles



196: (Het)	R	%	196: (Het)	R	%	196: (Het)	R	%
	Ph	78		4-Me-C_6H_4	74		4-Me-C_6H_4	72
	4-OMe-C_6H_4	80		4-Me-C_6H_4	66		4-Me-C_6H_4	73
	4-CF_3-C_6H_4	49		4-Me-C_6H_4	70			
	2-thiophene	72						
	1-cyclohexene	68						
	-*n*-hex	70						
	-$(CH_2)_4Cl$	82						
	-CH_2OH	72						
	-$C(Me)_2OH$	75						
	-$(CH_2)_4OH$	70						



intermediate **194** occurs at the least hindered position to produce the Pd bound species **195**. Dissociation of Pd(0) catalyst provides the desired 1,2-disubstituted arene **190**.

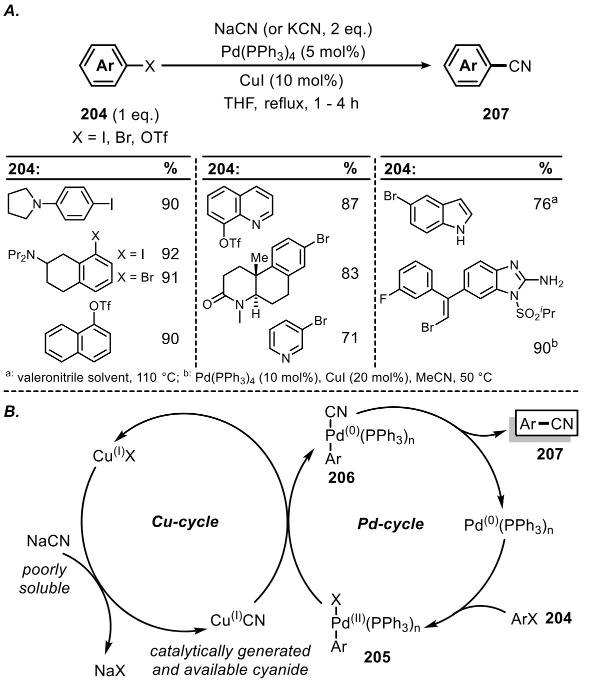
2.7.4. Dehydrative Cross-Coupling of Tautomerizable Heterocycles and Alkynes. Kang and co-workers demonstrated synergistic Pd/Cu dual catalysis for dehydrative cross-coupling of 2-quinoxalinone derived tautomerizable heterocycle **196** and alkyne **197** *via* C(sp)−H/C−O activation using a phosphonium peptide coupling reagent PyBroP[129] for preparation of alkynylated heterocycle **198** in good yields (Scheme 28).[130]

In the proposed reaction mechanism, **196** (Scheme 28B) first reacts with trimethylamine to form enolate **199**, which, in the presence of PyBroP, was trapped as C−O activated phosphonium intermediate **200**. Oxidative addition of the Pd(0) into the C−O bond of **200** produced catalytically activated heteroaryl-Pd(II) complex **201**. Upon formation of the Cu(I) acetylide species **202** from alkyne **197** and Cu(I) catalyst, transmetalation reaction with **201** transfers the alkynyl moiety from Cu(I) onto the Pd(II) center, forming Pd(II) complex **203**. Final reductive elimination furnishes cross-coupled product **198** along with the regeneration of Pd(0) catalyst. Other tautomerizable heterocycles such as 2-hydroxy-3-nitropyridines and 4-quinazolinone derivatives could also undergo analogous C−O activation and subsequent synergistic catalysis when slightly stronger base and higher temperatures were utilized.

2.7.5. Cyanation of Aryl Halides/Pseudohalides. The known classical Rosenmund−von Braun reaction uses stoichiometric CuCN and aryl halide at elevated temperature to yield aryl nitriles.[131] Although the introduction of Pd catalyst allowed for milder reaction conditions,[132] the monocatalytic Pd method suffers from Pd catalyst deactivation inflicted by increased concentrations of soluble ionic cyanides. Anderson and co-workers thought to mitigate this problem *via* synergistic Pd(0)/Cu(I) dual catalysis, allowing poorly soluble cyanide sources to be used and thereby realizing efficient cyanation of aryl halide **204** (Scheme 29).[133] The key mechanistic hypothesis was that poorly soluble cyanide sources such as NaCN or KCN in THF under Cu catalysis could form small amounts of the more covalent Cu(I)CN species *in situ* and work to effectively transfer the cyanide moiety onto the aryl-Pd(II) complex **205**, formed by oxidative addition of Pd(0) into aryl halide **204**, thus furnishing cyanated Pd(II) complex **206** without generation of free cyanide ions in the reaction mixture. Subsequent reductive elimination of **206** furnishes the desired aryl cyanide **207** (Scheme 29B). A diverse array of aryl/heterocyclic halides/pseudohalides were amendable under the reaction conditions, including complex substrates derived from ergot alkaloids, indoles, pyridines, and quinolones.

2.7.6. Stereoselective Synthesis of Vinyl Silanes. Riant and co-workers envisioned the use of Pd/Cu dual catalysis for the stereoselective synthesis of vinyl silanes (*Z*)-**208A** and (*E*)-**208B** *via* cross-coupling of alkynoate **196** with allyl carbonate **210** (Scheme 30).[134] The disclosed synthetic strategy entailed initial Cu-mediated *syn* silyl-cupration across the internal alkyne followed by Pd catalyzed allylation. The reaction yielded (*Z*)-isomer when PPh_3 was added (method A) while (*E*)-isomer was formed when PPh_3 was not utilized (method B). The observed selectivity was attributed to the difference in reactivity between the π-allylPd(II) species formed under the two diverging

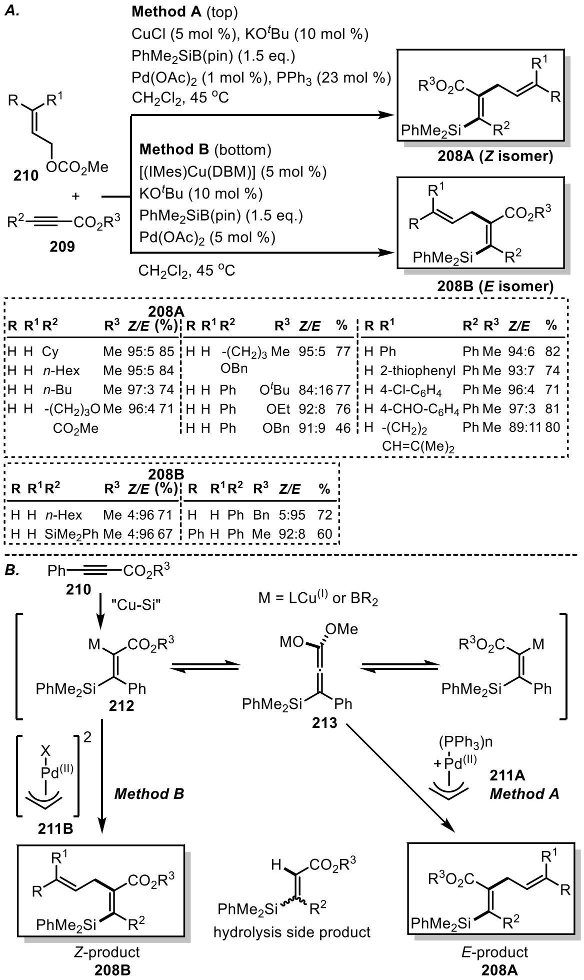
Scheme 29. Synergistic Pd/Cu Dual Catalysis for the Cyanation of Aryl Iodides



conditions As shown in Scheme 30B, without the phosphine ligand, dimeric π-allylPd(II)X species **211B** is formed from oxidative addition of Pd(0) into allylic carbonate, which undergoes direct transmetalation with alkenyl copper **212**, furnishing (*Z*)-isomer **208B** owing to the *syn*-geometric orientation of the silyl and copper appendage. In presence of PPh_3 however, π-allylPd(II)$[PPh_3]_n$ complex **211A** is formed from allyl carbonate, and the presence of the PPh_3 ligand inhibits the direct transmetalation pathway. Instead, alkenyl-Cu **212** initially isomerizes into allenoate **213**, which then reacts from the less hindered side with **211A** to produce (*E*)-isomer **208A**.

2.7.7. Boration of Propargylic Substrates. Szabó and co-workers developed Pd/Cu dual catalysis for net S_N2' boration of propargylic alcohols **214**, affording borated allenes **215** (Scheme 31A).[135] The reaction is comparable to monocatalytic CuO^{t}Bu procedure reported by Sawamura and co-workers.[136] For selected substrates, the use of Pd/CuCl over Pd/CuI resulted in formal S_N2 type displacement of carbonate, affording isomeric propargylic-borated products **216** (Scheme 31C). The proposed mechanistic explanation for S_N2' boration under Pd/CuI catalysis is as follows (Scheme 31B). First, Pd(0) initiated oxidative displacement of the carbonate group of propargylic ester **214** in the presence of iodide counteranion proceeds *via* S_N2' mechanism to afford catalytically activated allenyl-Pd(II) species **217**. The Cu(I) catalyst meanwhile undergoes transmetalation with $B_2(Pin)_2$ in the presence of KO^{t}Bu to afford Cu-Bpin complex **218** as the second catalytically activated species. The Bpin moiety could then be delivered onto the Pd center to yield **219**, and final reductive elimination affords the borated allene **215**. Divergent reactivity is realized in the presence of Cu(I)chloride as when carbonate **214** undergoes oxidative addition with Pd(0), the S_N2 mechanism is effected. This can be ascribed to the effect of the halide counterion on the η^1 and η^3 propargyl and allenyl palladium complexes, as chloride counteranions strongly stabilize the η^1 propargyl Pd species.[137] Thus, transmetalation

Scheme 30. Synergistic Pd/Cu Dual Catalysis for the Stereoselective Synthesis of Vinyl Silanes



208A

R	R¹	R²	R³	Z/E (%)	
H	H	Cy	Me	95:5	85
H	H	*n*-Hex	Me	95:5	84
H	H	*n*-Bu	Me	97:3	74
H	H	$-(CH_2)_3OCO_2Me$	Me	96:4	71

R	R¹	R²	R³	Z/E	%
H	H	$-(CH_2)_3OBn$	Me	95:5	77
H	H	Ph	O^{t}Bu	84:16	77
H	H	Ph	OEt	92:8	76
H	H	Ph	OBn	91:9	46

R	R¹	R²	R³	Z/E	%
H	Ph	Ph	Me	94:6	82
H	2-thiophenyl	Ph	Me	93:7	74
H	4-Cl-C_6H_4	Ph	Me	96:4	71
H	4-CHO-C_6H_4	Ph	Me	97:3	81
H	$-(CH_2)_2CH{=}C(Me)_2$	Ph	Me	89:11	80

208B

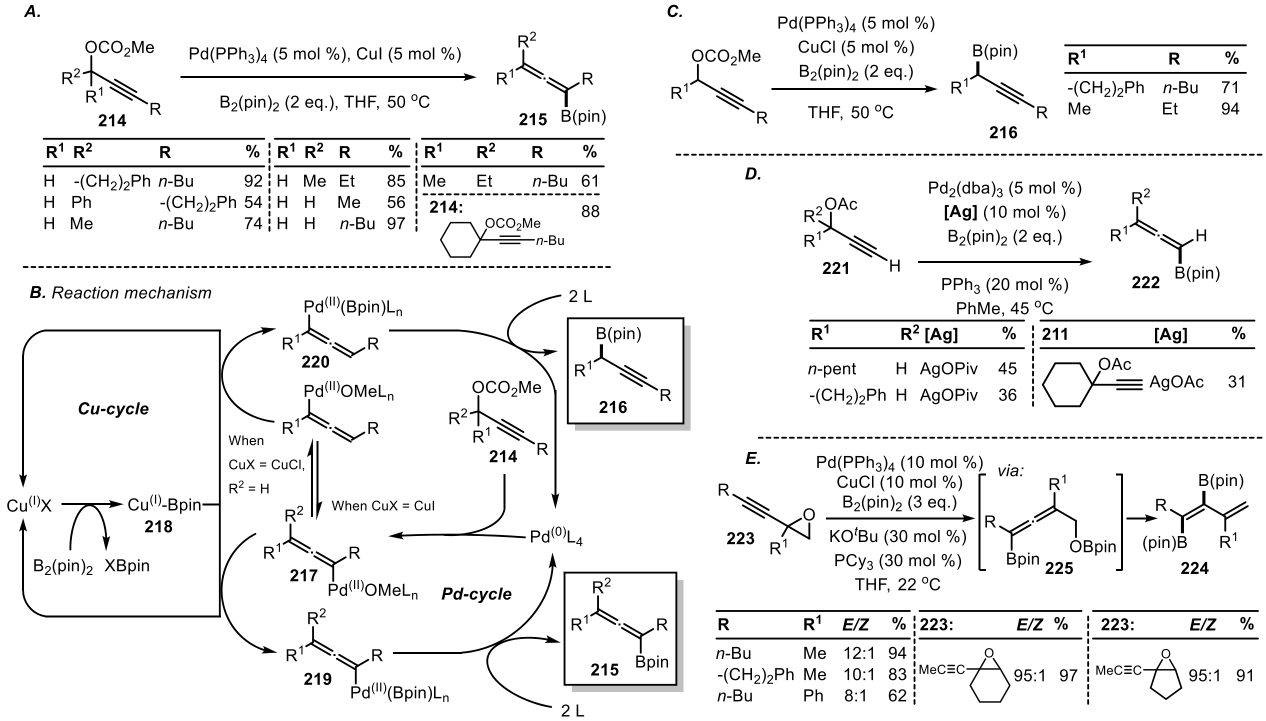
R	R¹	R²	R³	Z/E (%)	
H	H	*n*-Hex	Me	4:96	71
H	H	$SiMe_2Ph$	Me	4:96	67

R	R¹	R²	R³	Z/E	%
H	H	Ph	Bn	5:95	72
Ph	H	Ph	Me	92:8	60

with **218** affords Pd intermediate **220**, which after reductive elimination yields propargylic-borated **216**. Additionally, by substituting Cu catalyst with AgOAc or AgOPiv, terminal alkyne **221** could be used as substrates to give borated allene **222** in moderate yields (Scheme 31D). Propargyl epoxides **223** could also be used as starting substrates and under the reaction conditions gave rise to diborylated alkene **224**, derived from a second Cu-catalyzed S_N2' borylation event of the initially expected allyl-OBpin functionalized allenyl boronate **225** (Scheme 31E).

2.7.8. Cross-Coupling Reaction between Xanthenes and Electron Rich Aryls. Zhang and co-workers reported a synergistic Pd/Cu dual catalytic reaction between xanthenes **226** and electron-rich aryls **227** for the preparation of C-9 substituted **228** and C-9,9 disubstituted xanthene derivatives **229** *via* C−H activation/cross-dehydrogenative coupling sequence (Scheme 32).[138] By varying reaction time and temperatures, both mono- and double C−H activation at the C-9 position of the xanthene was possible, allowing access to C-9 or C-9,9 mono/diaryl xanthene derivatives **228** and **229**, respectively. The mechanistic pathway proposed is outlined in Scheme 32B: $Pd(OAc)_2$ activates C−H bond at C-9 position of xanthene **226** to produce activated Pd(II) intermediate **230**. The second activated Cu(II)-aryl complex **231** is generated by action of the copper catalyst with electron-rich aryl **227**. Transmetalation between **230** and **231** affords cross-coupled

Scheme 31. Synergistic Pd/Cu Dual Catalysis for the Boration of Propargylic Esters, Acetates, and Epoxides



Pd(II) species **232** and copper salt **233**, the latter of which is returned to its original catalytic form by the action of TfOH. Reductive elimination of **232** affords the monoarylated product **228** with regeneration of Pd(0) catalyst. The bis-arylated **229** was formed when the reaction was carried out at the higher reaction temperature and prolonged reaction time through further Pd-enabled C–H activation.

2.7.9. Synthesis of *Z*-Enedyines *via* Trimerization of Phenylacetylenes.

Serendipitously, Zhao and co-workers observed trimerization of phenylacetylenes **234** under synergistic Pd/Cu dual catalysis, furnishing *Z*-enediynes **235** in moderate yield (Scheme 33).[139] Recognizing the importance of this motif in anticancer drugs which work by facilitating Bergman cyclization and subsequent generation of radicals inside cancer cells,[140−142] the authors optimized the reaction to prepare *Z*-enediynes in good yields. During the reaction design, it was found that the use of molecular oxygen or inorganic oxidants promoted the generation of side product diynes **236** *via* oxidative homodimerization (route B in Scheme 33B), while exclusion of air greatly reduced the yield of the desired product.

The proposed reaction mechanism is as follows: The oxidatively generated Cu(II) catalyst oxidizes Pd(0) **237** to Pd(II) **238**. Complex **238** deprotonates alkyne **234** to form Pd(II)-acetylene complex **239**. Additional coordination of alkyne **234** results in 18-electron complex **240**, which undergoes carbopalladation to place Pd on the less substituted carbon, leading to the more stable 16-electron Pd(II)-complex **241** (route A in Scheme 33B). Meanwhile, reaction of the copper catalyst and starting alkyne **234** affords Cu(I) acetylide **242** as the catalytically activated species, which undergoes transmetalation with **241** to afford Pd(II) complex **243**. Subsequent reductive elimination affords desired product **235** with regeneration of Pd(0) complex **237**. The use of the bipyridine ligand in this system suppresses a undesired Pd(0)/Pd(II) monocatalytic pathway reported in a different study by Wu,[143] which leads to formation of **244** *via* alkenyl palladium intermediate **241**.

2.7.10. Synthesis of (3-Isoindazoyl)allenes.

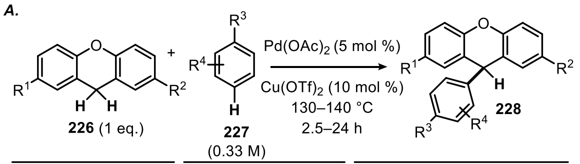
Yamane and co-workers reported synergistic Pd/Cu dual catalysis for the cross-coupling reaction between 2-alkynyl azobenzene **245** and terminal alkyne **246**, affording (3-isoindazolyl)allenes **247** (Scheme 34).[144] The proposed reaction mechanism comprises of two Cu-based catalytic cycles interacting with a concurrent Pd catalytic cycle. First, CuI catalyzes an intramolecular cyclization of **245** to yield isoindazolyl-appended copper carbenoid **248**. Then the transmetalation with the Pd(II) catalyst returns copper back to its catalytic cycle and forms Pd(II)-carbenoid **249**. In the second copper catalytic cycle, copper acetylide **250** is derived from deprotonation of terminal alkyne **246** with CuX and base. Subsequent transmetalation between **250** and Pd(II)-carbenoid **249** transfers the acetylene moiety onto the palladium center to form alkynyl palladium carbene **251**. Migratory insertion then affords **252**, which undergoes protonation to yield allene **247** with regeneration of the Pd(II) catalyst. In general, aromatic acetylenes yielded better results over aliphatic ones under the disclosed reaction conditions. The utility of the (3-isoindazolyl)-allene products were demonstrated by effecting a thermal cyclization reaction to afford indo[2,3-*a*]-quinolines, whose derivatives show antitumor activity.[145,146]

2.7.11. Modified Catellani Reactions Mediated by Pd/Cu Catalysis.

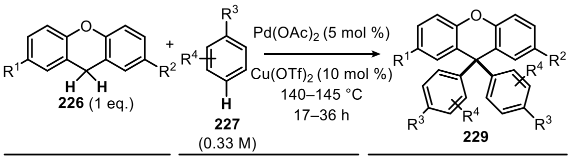
Liang and co-workers developed a variant of the Catellani reaction to react substituted aryl halides **253** with polyfluoroarenes **254**, affording polyfluoroarene- substituted benzofurans **255** (Scheme 35).[147]

The Cu/Pd dual catalysis was important in enabling inactivated polyfluoroarenes to be utilized as a terminal cross-coupling partner. The proposed reaction mechanism initially follows the known mode of the Catellani reaction.[148] Starting with aryl iodide **253**, oxidative addition of Pd catalyst and insertion of norbornene yields Pd complex **256** (Scheme 35B). Next, activation of *ortho* C–H bond leads to alkyl-aryl Pd-

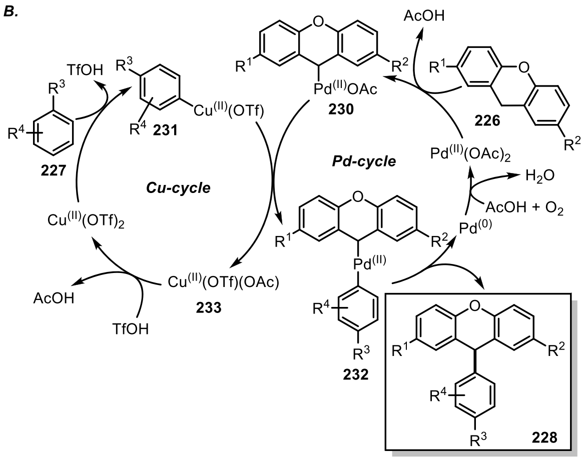
Scheme 32. Synergistic Pd/Cu Dual Catalysis for the Cross-Coupling Reaction *via* C−H Activation



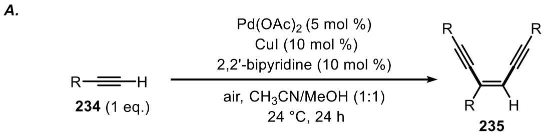
R^1	R^2	R^3	R^4	%
H	H	OMe	H	85
H	H	OEt	H	75
H	H	OPh	H	60
H	H	OMe	3-OMe	71
H	H	OMe	3-Me	32
H	H	OMe	3-Br	25
H	H	SMe	H	32
H	H	OH	H	-
H	H	NH_2	H	35
H	H	NH_2	3-Me	34
H	H	CN	H	-
H	H	OMe	3,5-OMe	45
H	C(O)Ph	OMe	H	85
H	C(O)Me	OMe	H	66
H	H	H	H	-
H	H	Me	H	-
H	H	NO_2	H	-



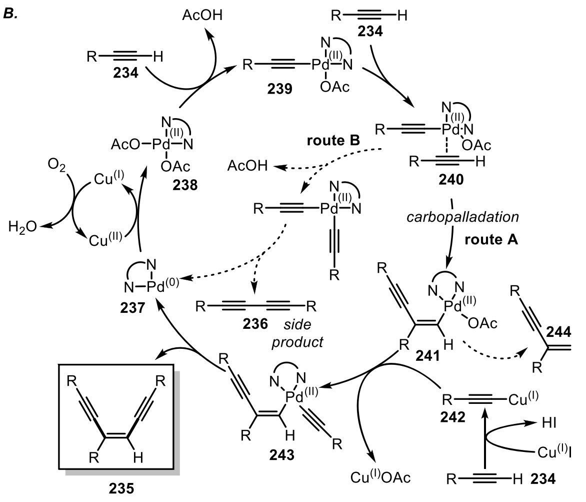
R^1	R^2	R^3	R^4	%
H	H	OMe	H	80
H	H	OEt	H	66
H	H	OPh	H	55
H	H	OMe	3-OMe	65
H	H	OH	H	76
H	H	NH_2	H	55
H	H	NH_2	3-Me	61
H	COPh	OMe	H	75
H	COMe	OMe	H	61



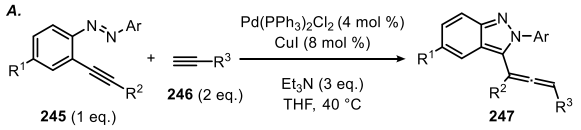
Scheme 33. Synergistic Pd/Cu Dual Catalysis for Trimerization of Alkynes



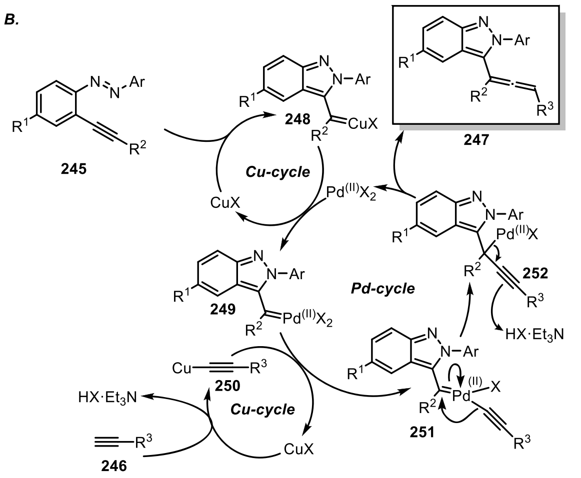
R	%
Ph	63
4-Et-C_6H_4	56
4-^{t}Bu-C_6H_4	55
4-OMe-C_6H_4	52
4-Br-C_6H_4	67
4-Cl-C_6H_4	70
4-F-C_6H_4	42
3-Me,4-F-C_6H_3	67
3-Me-C_6H_4	58
3-OMe-C_6H_4	52
3-Cl-C_6H_4	50
3-thiophenyl	40



Scheme 34. Synergistic Pd/Cu Dual Catalysis for the Preparation of (3-Isoindazolyl)allenes



R^1	R^2	Ar	R^3	%
H	Ph	Ph	Ph	81
H	Ph	Ph	4-Me-C_6H_4	82
H	Ph	Ph	2-Me-C_6H_4	62
H	Ph	Ph	4-OMe-C_6H_4	73
H	Ph	Ph	4-CO_2Et-C_6H_4	66
H	Ph	Ph	4-NO_2-C_6H_4	70
H	Ph	Ph	2-np	82
H	Ph	Ph	2-thienyl	79
H	Ph	Ph	*n*-Pr	50
H	Ph	Ph	$SiMe_3$	80
H	Ph	Ph	1-cyclohexene	65
OMe	Ph	4-CN-C_6H_4	Ph	49
OMe	Ph	4-OEt-C_6H_4	Ph	60
Me	Ph	Ph	Ph	85



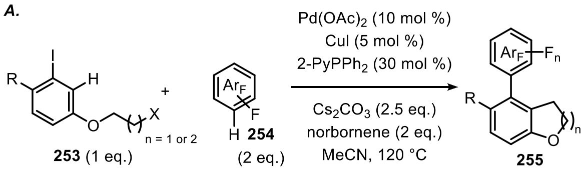
complex **257**, which undergoes intramolecular oxidative addition into the alkyl halide side chain, forming Pd(IV)-complex **258**. Reductive elimination and removal of norbornene ligand leads to catalytically activated Pd(II) species **259**. Critically, in the Cu catalytic cycle, the deprotonation of polyfluoroarene **254** occurs to give Cu complex **260**, which is able to transmetalate onto the Pd center of **259**, forming complex **261**. Final reductive elimination furnishes cross-coupled product **255** alongside the regeneration of the Pd catalyst.

Gu and co-workers reported a similar Pd/Cu mediated Catellani reaction of aryl iodide **262**, using thioester **263** as the terminal reagent to afford 2-(arylthio)aryl ketones **264** (Scheme 36).[149] However, the exact role of the copper cocatalyst was not specified, although it is hypothesized the Cu salt may coordinate and activate the C(O)-S thioester bond. Control experiments with radical scavengers ruled out a radical-based mechanism.

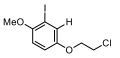
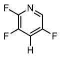
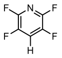
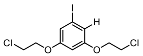
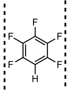
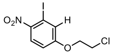
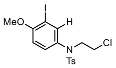
2.7.12. Hydroarylation of Internal Alkynes.

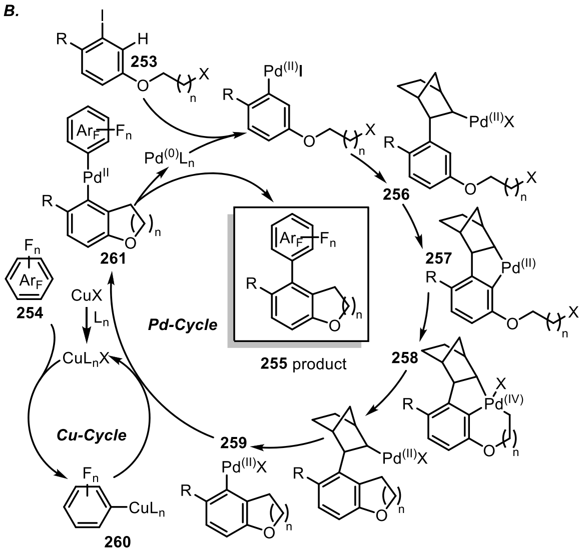
Utilizing synergistic Pd/Cu dual catalysis, Nakao and co-workers accomplished hydrogenative cross-coupling of internal alkynes **265** and aryl iodides **266** under H_2 atmosphere (Scheme 37).[150] Under the disclosed reducing conditions, it was found that unsaturated C−C bonds aptly survive to afford triaryl olefins **267** in good yield. In the proposed mechanism (Scheme 37B), the Cu catalyst first reacts with *tert*-butoxide to form copper alkoxide **268**, which is followed by hydrogenative reduction, leading to copper hydride **269**. Subsequent *syn* addition of copper hydride onto internal alkyne **265** furnishes catalytically

Scheme 35. Synergistic Pd/Cu Catalysis for the Preparation of Polyfluoroarene-Substituted Benzofuran Derivatives

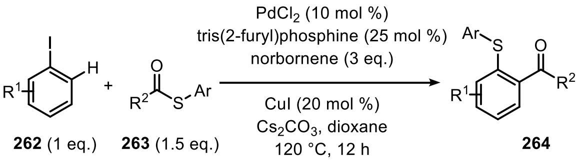


R	n	X	Ar_F-H	%
OMe	1	Cl	2,3,5,6-F_4	42
OMe	1	Cl	2,3,5,6-F_4,4-CF_3	77
OMe	1	Cl	2,3,5,6-F_4,4-(2,3,5,6-F_4)C_6H	58
OMe	2	Cl	2,3,4,5,6-F_5	28
Me	1	Cl	2,3,4,5,6-F_5	54

253:	Ar_F-H	%
		47
		52
		30
		-
		trace

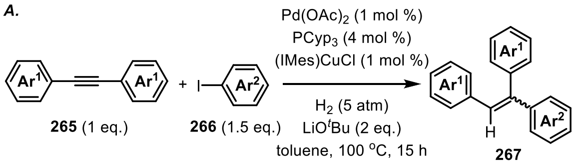


Scheme 36. Pd/Cu Dual Catalysis for the Preparation of 2-(Arylthio)aryl Ketones

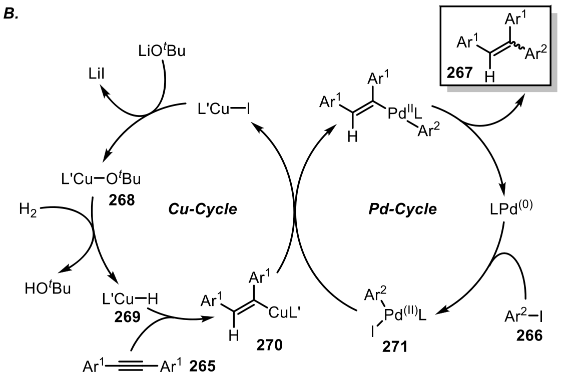


262: np(1-I)			262: np(1-I)						
R^2	Ar	Y%	R^2	Ar	Y%	R^1	R^2	Ar	Y%
Ph	2-Me-C_6H_4	66	3-NO_2-C_6H_4	Ph	78	6-Me-C_6H_4	Ph	Ph	76
Ph	2-Cl-C_6H_4	93	2-np	Ph	66	6-Me-C_6H_4	Ph(2,6-OMe)	4-Me-C_6H_4	94
Ph	2,5-Me_2-C_6H_3	46	4-F-C_6H_4	Ph	79				
Ph	2-np	83	4-Ph-C_6H_4	Ph	76	5-Me,6-OMe-C_6H_3	Ph	Ph	39
Ph	4-^{t}Bu-C_6H_4	66	2,6-$(OMe)_2$-C_6H_3	Ph	92				
Ph	4-Cl-C_6H_4	82	5-benzo[*d*][1,3]dioxole	Ph	61	5-F,6-Me-C_6H_3	Ph	Ph	78
Ph	4-OMe-C_6H_4	41	2-furyl	Ph	39				
Ph	4-F-C_6H_4	42	2-thiophenyl	Ph	53	5-Cl,6-Me-C_6H_3	Ph	Ph	72
Ph	4-py	68	Me	Ph	82				
Ph	2-thiophene	84	*n*-Bu	Ph	62	4-NO_2,6-Me-C_6H_3	Ph	Ph	53
2-Me-C_6H_4	Ph	94	^{i}Pr	Ph	87				
2-Cl-C_6H_4	Ph	81	-CH(CH_3)OPh	Ph	92	4-F,6-Me-C_6H_3	Ph	Ph	53

Scheme 37. Synergistic Pd/Cu Catalysis for Reductive Cross-Coupling of Internal Alkynes with Aryl Iodides



Ar^1	Ar^2	*E*:*Z*	%	Ar^1	Ar^2	*E*:*Z*	%
Ph	4-Me-C_6H_4	90:10	63	Ph	4-F-C_6H_4	93:7	42
Ph	Ph	-	54	Ph	4-Cl-C_6H_4	86:14	48
Ph	4-OMe-C_6H_4	90:10	65	Ph	3-CH_2OTBS-C_6H_4	90:10	66
Ph	3-NH_2-C_6H_4	92:8	70	4-Me-C_6H_4	4-Me-C_6H_4	-	67
4-OMe-C_6H_4	4-OMe-C_6H_4	-	73	4-Cl-C_6H_4	Ph	5:95	44



activated alkenyl copper **270**. Meanwhile, oxidative addition by Pd(0) catalyst into aryl iodide **266** affords arylPd(II) **271**. Transmetalation of **270** onto the Pd center delivers alkenyl moiety to Pd while regenerating the Cu catalyst. Finally, Pd complex undergoes reductive elimination to afford desired triaryl olefin **267** with regeneration of Pd(0) catalyst.

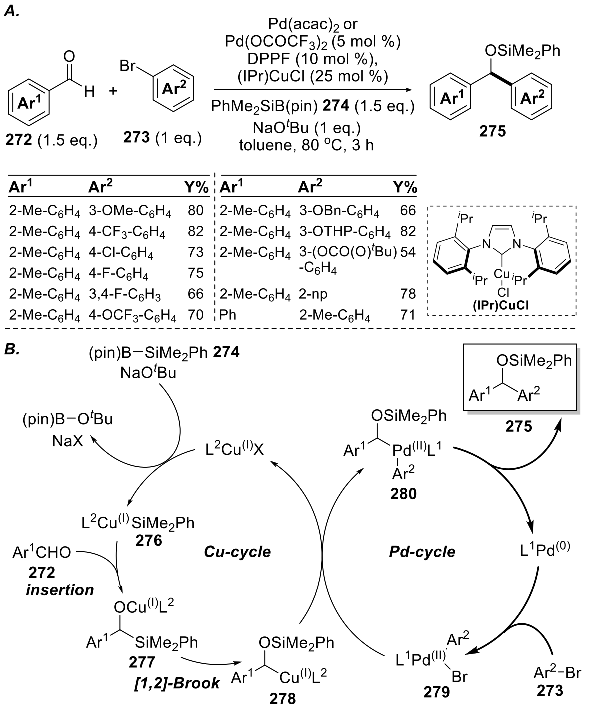
2.7.13. Three-Component Csp^3–Csp^2 Cross-Coupling of Aldehydes, Aryl Bromides, and Silylboronates.

Ohmiya and co-workers utilized aromatic aldehyde **272** as an α-alkoxyalkyl synthon in reaction with aryl bromide **273** and silylboronate **274** for formal three-component Pd/Cu mediated cross-coupling reaction to prepare silyl-protected benzhydrol derivatives **275** in good yields (Scheme 38).[151] Although the required intermediary α-silyloxybenzyl Cu(I) species derived from aldehydes were previously prepared in a stoichiometric manner,[152] in this reaction such species is realized *via* Cu catalysis. The reported reaction mechanism is as follows (Scheme 38B): IPr-coordinated silylCu(I) species **276** is first generated in the presence of Cu(I) catalyst, NaO^{t}Bu, and silylboron reagent **274**. The silyl Cu(I) complex **276** then inserts across the carbonyl of aryl aldehyde **272**, affording **277** which undergoes [1,2]-Brook rearrangement to furnish α-silyloxybenzylCu(I) species **278**. In the palladium catalytic cycle, activated species Ar^{2}Pd(II)X **279** (X = Br) is derived from oxidative addition of Pd(0) into aryl bromide **273**. Transmetalation between **278** and **279** delivers α-silyloxybenzyl moiety onto the Pd center to form **280** and return Cu(I) to its catalytic cycle. Reductive elimination of **280** leads to regeneration of the Pd(0) catalyst and yields silyl-protected benzhydrol **275**. The strategy of using aldehydes as latent α-alkoxyalkyl nucleophile such as in this example is an umpolung.[153]

2.7.14. Hydrocyanation of Olefins.

Olefin hydrocyanation is a conceptually straightforward method to introduce nitrile functionality. Known methods however generally rely on toxic hydrogen cyanide to produce racemic products. By utilizing synergistic catalysis, Buchwald and co-workers envisioned enantioselective coupling between activated aryl vinylic-olefin **281** and oxazole **282**, which serves as a benign

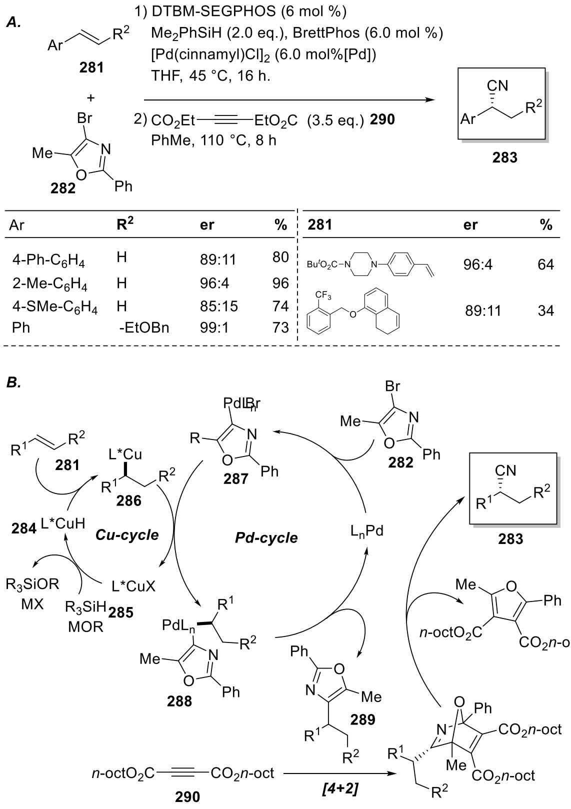
Scheme 38. Synergistic Pd(0)/Cu(I) Dual Catalysis for the Three-Component Cross-Coupling of Aryl Aldehydes, Silylboronates, and Aryl Bromides



Ar^1	Ar^2	Y%	Ar^1	Ar^2	Y%
2-Me-C_6H_4	3-OMe-C_6H_4	80	2-Me-C_6H_4	3-OBn-C_6H_4	66
2-Me-C_6H_4	4-CF_3-C_6H_4	82	2-Me-C_6H_4	3-OTHP-C_6H_4	82
2-Me-C_6H_4	4-Cl-C_6H_4	73	2-Me-C_6H_4	3-(OCO(O)^{t}Bu)-C_6H_4	54
2-Me-C_6H_4	4-F-C_6H_4	75			
2-Me-C_6H_4	3,4-F-C_6H_3	66	2-Me-C_6H_4	2-np	78
2-Me-C_6H_4	4-OCF_3-C_6H_4	70	Ph	2-Me-C_6H_4	71

nitrile surrogate, to produce Markovnikov hydrocyanation adducts **283** (Scheme 39).[154] This reaction works *via* initial Pd/Cu mediated hydroarylation, then undergoes a tandem [4 + 2] cycloaddition with an alkyne followed by a retro-[4 + 2] sequence to deliver the desired nitrile product **283**. The mechanistic details are as follows (Scheme 39B): Olefin **281** first undergoes enantioselctive hydrocupration by CuH species **284** generated from Cu(I) salt and silane **285** in the presence of chiral phosphine ligand to afford chiral Cu(I) alkyl intermediate **286**. For the Pd catalytic cycle, oxidative addition of ligated Pd(0) catalyst into 2-halo-oxazole **282** forms catalytically active species **287**. Stereospecific transmetalation between **287** and **286** furnishes alkyl Pd(II) complex **288**, which then undergoes reductive elimination to furnish enantioenriched oxazole **289**, which serves as an electron-rich aza-diene. The nitrile is then unmasked with use of alkyne **290** *via* thermal [4 + 2] cycloaddition followed by a retro-[4 + 2] sequence, affording desired nitrile **283**. Interestingly, use of inactivated, nonvinylic terminal olefins under similar reaction conditions lead to anti-Markovnikov hydrocynation, furnishing terminal nitriles (not shown).

Scheme 39. Synergistic Pd/Cu Dual Catalysis for Enantioselective Hydrocyanation of Olefins



Ar	R^2	er	%	281	er	%
4-Ph-C_6H_4	H	89:11	80		96:4	64
2-Me-C_6H_4	H	96:4	96			
4-SMe-C_6H_4	H	85:15	74		89:11	34
Ph	-EtOBn	99:1	73			

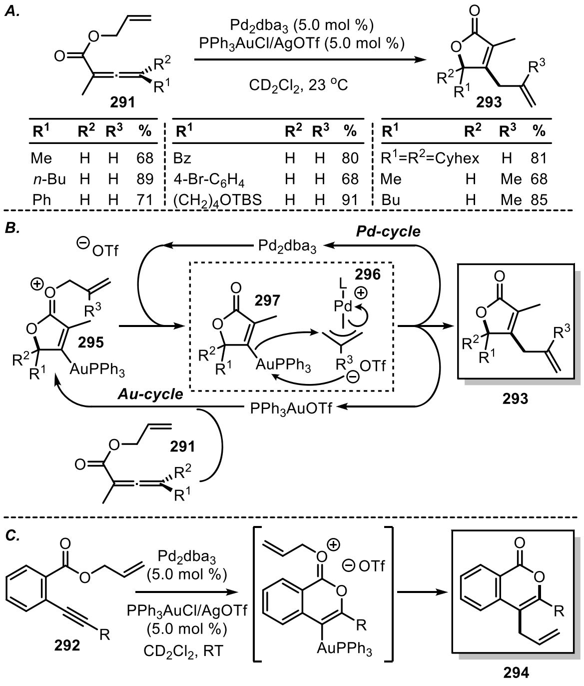
3. SYNERGISTIC Pd/Au DUAL CATALYSIS

As a soft Lewis acid, Au catalysts can often uniquely activate π-bond of various substrates such as allenes and alkynes. When Au catalysis is coupled with Pd catalysis, allylations, arylations, or stannylations of allenes and alkynes are possible.

3.1. Preparation of Allylated Butenolides and Isocoumarins

Blum and co-workers developed a Pd/Au dual catalytic system for a catalyst-catalyzed reaction, in which π-allylPd(II) intermediates were coupled with vinyl gold intermediates derived from allyl allenoates **291** or allyl benzoates **292** to afford allylated butenolides **293** (Scheme 40A) or isocoumarins **294** (Scheme 40C), respectively.[155] Proposed mechanistic details are as follows: the gold catalyst first prompted rearrangement of allenonate **291** to yield Au-butenolide **295**,

Scheme 40. Pd/Au Dual Catalysis for the Synthesis of Allylated Butenolides (A) and Isocoumarins (C)



R^1	R^2	R^3	%	R^1	R^2	R^3	%	R^1	R^2	R^3	%
Me	H	H	68	Bz	H	H	80	R^1=R^2=Cyhex		H	81
n-Bu	H	H	89	4-Br-C_6H_4	H	H	68	Me	H	Me	68
Ph	H	H	71	$(CH_2)_4$OTBS	H	H	91	Bu	H	Me	85

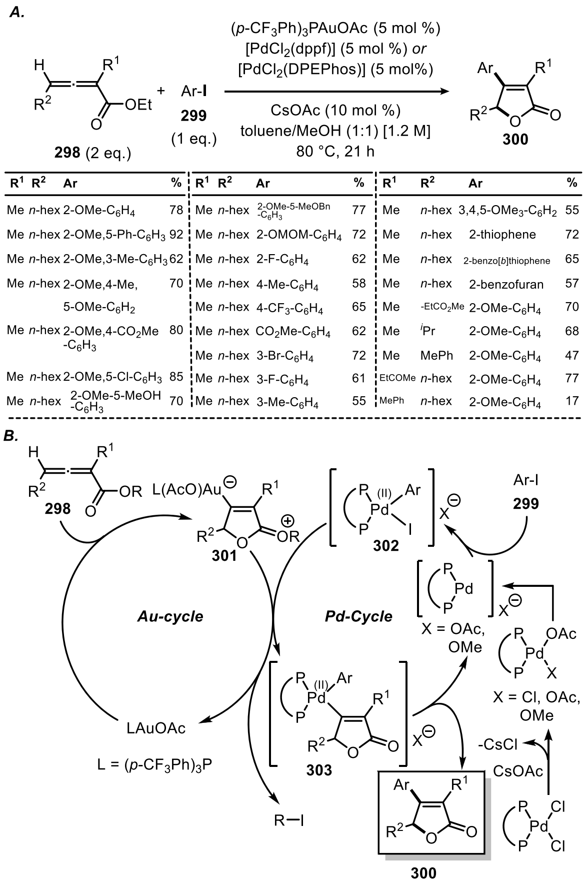
R = Ph (89%), *n*-Bu (83%), Ph(4-OMe) (86%)

which subsequently underwent Pd(0)-catalyzed deallylation reaction to generate π-allylPd(II) complex **296** and vinyl gold **297.** Reaction of **296** and **297** furnished the desired allylated product **293** (Scheme 40B).[156] The existence of both vinyl-Au **297** and π-allylPd complex **296** were confirmed in a crossover experiment using two different allenoates. Allyl benzoates **292** containing acetylene moiety were shown to react similarly in forming isocoumarins **294**. The scope of this isocoumarin forming process was further explored to prepare a wider range of fused lactone products.[157]

3.2. Preparation of Arylated Butenolides

Following Blum's work, Nevado and co-workers designed an intermolecular coupling of allenoates **298** and aryl or heteroaryl iodides **299** under Au/Pd dual catalysis for preparation of substituted butenolides **300** (Scheme 41).[158] In the gold catalytic cycle shown in Scheme 41B, substituted allenoate **298** is treated with $(p\text{-}CF_3Ph)_3PAuOAc$ to form zwitterionic lactone **301** *via* Au-carbophilic Lewis acid promoted rearrangement reaction. On the palladium cycle, the Pd(0) catalyst, generated from $[PdCl_2(dppf)]$ or $[PdCl_2(DPEPhos)]$, undergoes oxidative addition with aryl/heteroaryl iodide **299** to form catalytically activated Pd(II) species **302**. CsOAc is used as an addictive to sequester free anions and thereby prevent undesired catalyst poisoning *via* the formation of Au(I) halides. Transmetalation of **302** with vinylAu(I) **301** affords Pd(II) complex **303** with regeneration of the Au catalyst. Reductive elimination of **303** leads to desired substituted butenolide **300** and regeneration of Pd(0), closing the Pd catalytic cycle.

Scheme 41. Synergistic Pd/Au Dual Catalysis for the Synthesis of Butenolides

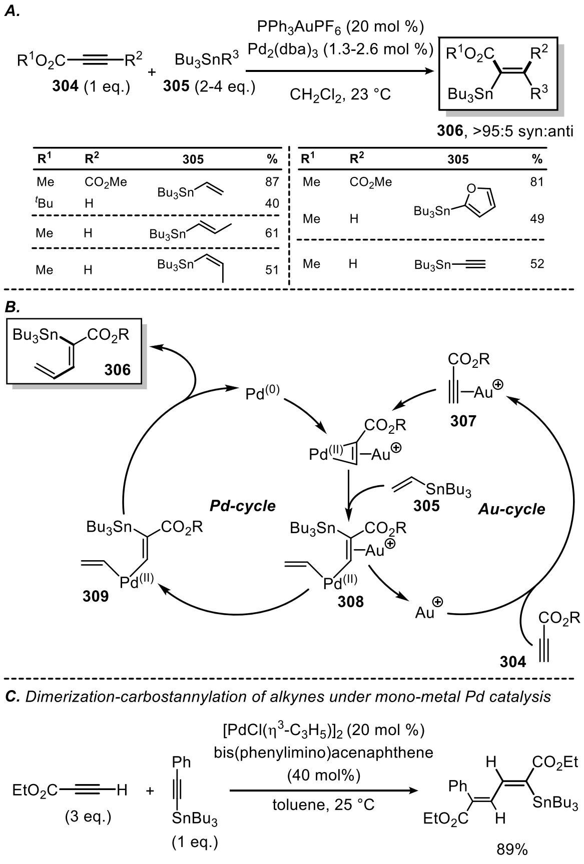


R^1	R^2	Ar	%	R^1	R^2	Ar	%	R^1	R^2	Ar	%
Me	*n*-hex	2-OMe-C_6H_4	78	Me	*n*-hex	2-OMe-5-MeOBn-C_6H_3	77	Me	*n*-hex	3,4,5-OMe_3-C_6H_2	55
Me	*n*-hex	2-OMe,5-Ph-C_6H_3	92	Me	*n*-hex	2-OMOM-C_6H_4	72	Me	*n*-hex	2-thiophene	72
Me	*n*-hex	2-OMe,3-Me-C_6H_3	62	Me	*n*-hex	2-F-C_6H_4	62	Me	*n*-hex	2-benzo[*b*]thiophene	65
Me	*n*-hex	2-OMe,4-Me, 5-OMe-C_6H_2	70	Me	*n*-hex	4-Me-C_6H_4	58	Me	*n*-hex	2-benzofuran	57
				Me	*n*-hex	4-CF_3-C_6H_4	65	Me	-$EtCO_2Me$	2-OMe-C_6H_4	70
Me	*n*-hex	2-OMe,4-CO_2Me-C_6H_3	80	Me	*n*-hex	CO_2Me-C_6H_4	62	Me	^{i}Pr	2-OMe-C_6H_4	68
				Me	*n*-hex	3-Br-C_6H_4	72	Me	MePh	2-OMe-C_6H_4	47
Me	*n*-hex	2-OMe,5-Cl-C_6H_3	85	Me	*n*-hex	3-F-C_6H_4	61	EtCOMe	*n*-hex	2-OMe-C_6H_4	77
Me	*n*-hex	2-OMe-5-MeOH-C_6H_3	70	Me	*n*-hex	3-Me-C_6H_4	55	MePh	*n*-hex	2-OMe-C_6H_4	17

3.3. Stille-like Cross-Coupling Reaction between Alkynes and Organostannanes

Monocatalytic Pd mediated vinylstannylation of alkynes predominantly afford double-addition products (Scheme 42C).[159] Blum and co-workers used synergistic Pd/Au catalysis to mediate a Stille-like reaction between alkyne **304** and organostane **305** to afford monoaddition products **306** with regio- and stereoselectivity, giving access to synthetically useful tri- and tetrasubstituted olefins (Scheme 42).[160] Notably, starting substrates do not require the presence of a carbon—halogen bond as the Au(I) catalyst serves to activate the alkyne and thereby promote oxidative addition of Pd(0) into it. The cross-coupled product displays retention of geometric configuration with respect to the organostannane used, although when sterically bulky *Z*-stannanes are utilized, moderate stereochemical leakage is observed. The proposed reaction mechanism is as follows (Scheme 42B): First, cationic Au(I) coordinates to the alkyne **304** to yield **307**, promoting oxidative addition of Pd(0) into it. Transmetalation of vinylstannane **305** results in intermediate **308**, which is the product of vinyl transfer to palladium and tin transfer to the nascent olefin. Au(I) is then dissociated, completing the Au cycle and final reductive elimination of Pd(II) complex **309** affords the desired cross-coupled product **306** and return of Pd to its catalytic cycle.

Scheme 42. Synergistic Pd/Au Dual Catalysis for Cross-Coupling Reaction between Alkynes and Organostannanes



4. SYNERGISTIC Pd/Ru DUAL CATALYSIS

Ruthenium catalysts are commonly utilized in directing group guided C—H activation.[161,162] Chang and co-workers exploit this chemistry by pairing Ru with Pd catalysis to achieve sequential C−H activation/arylation. Another unique chemistry enabled by ruthenium catalysis is the formation of Ru-carbenoid from diazo compounds.[163] Lautens and co-workers exploited this reactivity combining Ru-carbenoids with a Pd catalyst, enabling the synthesis of allylated heterocycles.

4.1. Formyl C−H Insertion/Arylation of Pyridine and Related Substrates

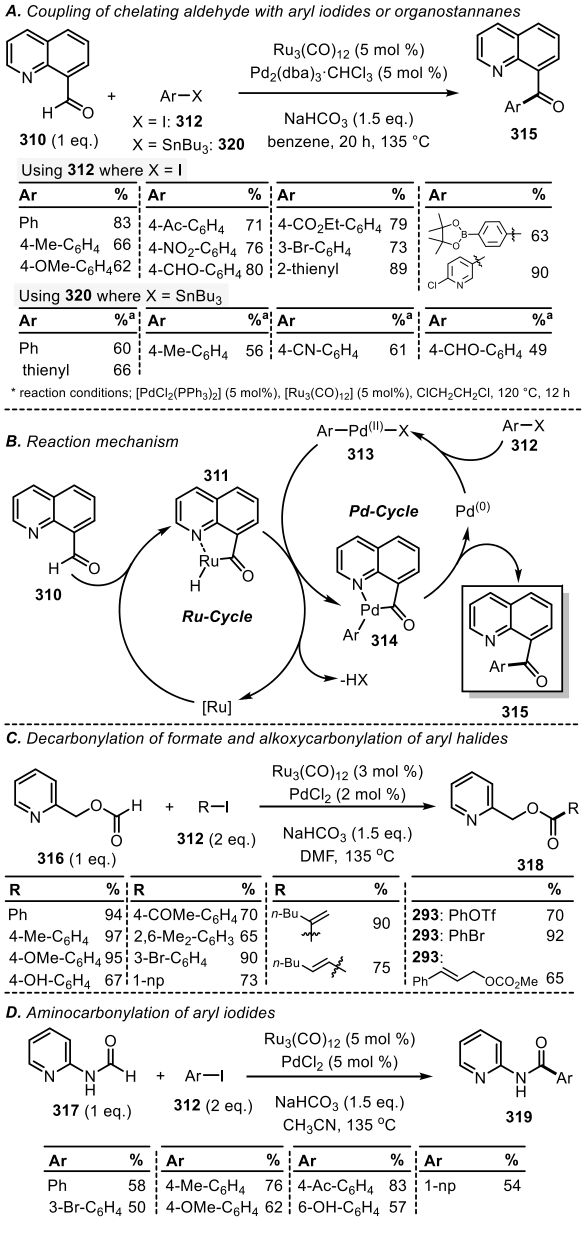
Chang and co-workers envisioned synergistic Pd/Ru dual catalysis for carbonyl arylation and vinylation *via* formyl C−H insertion process (Scheme 43).[164] Carbonyl arylation and vinylation both operate under a similar mechanism, making use of a directing group (Scheme 43B).

It is proposed that nitrogen atom of quinoline **310** chelate with Ru catalyst, bringing Ru in closer proximity to the formyl appendage, allowing a C−H insertion to take place to furnish intermediate **311**. Meanwhile, the Pd(0) catalyst undergoes oxidative addition into aryl iodide **312** to afford Ar−Pd(II) complex **313**. Transmetalation of **311** with **313** yields arylated Pd(II) complex **314**, which after reductive elimination, leads to product **315**. Similarly, aryl or vinyl iodides **312** were functionalized with pyridine-appended formates **316** and formamides **317** to give **318** and **319**, respectively (Schemes 43C,D).[165,166] Analogous to aryl iodides, organostannanes **320** could also undergo C−H insertions with 8-quinolinecarboxaldehydes **310** under Pd/Cu catalysis to yield ketone **315** (Scheme 43A).

4.2. C(sp^2)-H Insertion/Allylation

Inspired by intramolecular C(sp^2)-H insertion reaction of *N*-aryl diazoamides using Rh[167] or Ru[168] catalyst, Lautens and co-workers developed a synergistic Pd/Ru dual catalytic system wherein *N*-aryl diazoamide **321** react with allylic carbonate **322** to afford allylated 3-allyl-3-aryl oxindole derivatives **323** (Scheme 44).[169]

Scheme 43. Synergistic Pd/Ru Dual Catalysis for Formyl C−H Insertion/Arylation



Using **312** where X = I

Ar	%	Ar	%	Ar	%	Ar	%
Ph	83	4-Ac-C_6H_4	71	4-CO_2Et-C_6H_4	79		63
4-Me-C_6H_4	66	4-NO_2-C_6H_4	76	3-Br-C_6H_4	73		90
4-OMe-C_6H_4	62	4-CHO-C_6H_4	80	2-thienyl	89		

Using **320** where X = $SnBu_3$

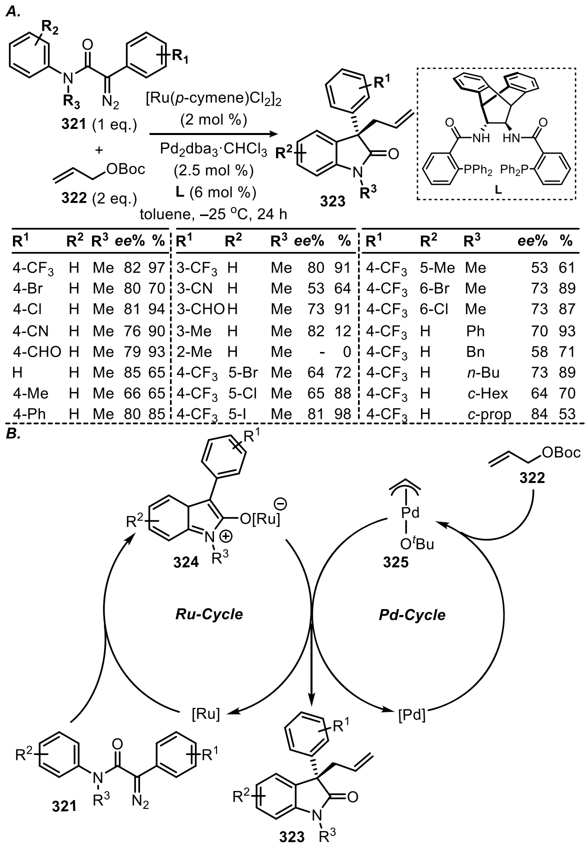
Ar	%^{a}	Ar	%^{a}	Ar	%^{a}	Ar	%^{a}
Ph	60	4-Me-C_6H_4	56	4-CN-C_6H_4	61	4-CHO-C_6H_4	49
thienyl	66						

* reaction conditions; $[PdCl_2(PPh_3)_2]$ (5 mol%), $[Ru_3(CO)_{12}]$ (5 mol%), $ClCH_2CH_2Cl$, 120 °C, 12 h

R	%	R	%	R	%		%
Ph	94	4-COMe-C_6H_4	70	*n*-Bu	90	**293**: PhOTf	70
4-Me-C_6H_4	97	2,6-Me_2-C_6H_3	65	*n*-Bu	75	**293**: PhBr	92
4-OMe-C_6H_4	95	3-Br-C_6H_4	90			**293**: Ph OCO_2Me	65
4-OH-C_6H_4	67	1-np	73				

Ar	%	Ar	%	Ar	%	Ar	%
Ph	58	4-Me-C_6H_4	76	4-Ac-C_6H_4	83	1-np	54
3-Br-C_6H_4	50	4-OMe-C_6H_4	62	6-OH-C_6H_4	57		

Scheme 44. Synergistic Ru/Pd Dual Catalysis for Intramolecular C−H Insertion and Intermolecular Allylation of Aryl α-Diazoamides



R^1	R^2	R^3	*ee*%	%	R^1	R^2	R^3	*ee*%	%	R^1	R^2	R^3	*ee*%	%
4-CF_3	H	Me	82	97	3-CF_3	H	Me	80	91	4-CF_3	5-Me	Me	53	61
4-Br	H	Me	80	70	3-CN	H	Me	53	64	4-CF_3	6-Br	Me	73	89
4-Cl	H	Me	81	94	3-CHO	H	Me	73	91	4-CF_3	6-Cl	Me	73	87
4-CN	H	Me	76	90	3-Me	H	Me	82	12	4-CF_3	H	Ph	70	93
4-CHO	H	Me	79	93	2-Me	H	Me	-	0	4-CF_3	H	Bn	58	71
H	H	Me	85	65	4-CF_3	5-Br	Me	64	72	4-CF_3	H	*n*-Bu	73	89
4-Me	H	Me	66	65	4-CF_3	5-Cl	Me	65	88	4-CF_3	H	*c*-Hex	64	70
4-Ph	H	Me	80	85	4-CF_3	5-I	Me	81	98	4-CF_3	H	*c*-prop	84	53

Mechanistically, treatment of aryl α-diazoamide **321** with a Ru catalyst generates a ruthenium carbenoid which undergoes a C(sp^2)−H bond insertion to afford ruthenium-bound oxindole enolate **324**. The second catalytically active species **325** is derived from oxidative addition of the Pd(0) catalyst into **322** in the presence of chiral ligand **L6**, which was previously utilized for asymmetric allyl alkylation of 3-aryl oxindoles.[170] The reaction between **324** and **325** furnishes allylated chiral oxindole **323** while returning the Pd and Ru catalysts to their respective catalytic cycles.

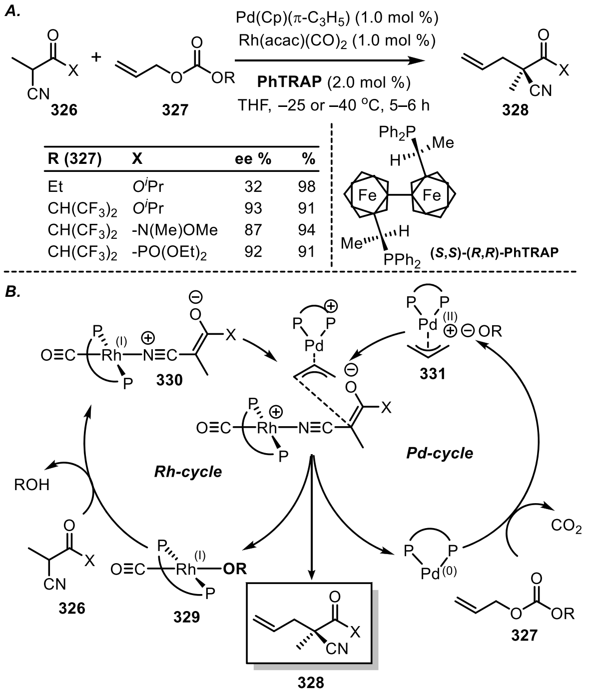
5. SYNERGISTIC Pd/Rh DUAL CATALYSIS

The redox-sensitivity relatively expensive nature of rhodium catalysts has limited its use in synergistic catalysis. Nevertheless, among the earlier reported examples of dual metal synergistic catalysis stands the work by Ito and co-workers, which describes the asymmetric allylation of α-carbonyl compounds enabled by Pd(0)/Rh(I) catalysis. Lee and co-workers meanwhile utilize synergistic Pd(0)/Rh(II) catalysis differently, pairing known rhodium-iminocarbenes derived from *N*-sulfonyl-1,2,3-triazoles[171,172] with Pd-catalyzed allylic alkylations, in which the traditionally wasted leaving group is incorporated into the final product.

5.1. Allylation of α-Cyano Esters, Weinreb Amides, and Phosphonates

Ito and co-workers reported a synergistic Rh(I)/Pd(0) dual catalytic system for the stereoselective allylation of α-cyano esters **326** with allylic carbonates **327** to prepare allylated α-cyanoesters **328** (Scheme 45).[173] The dual catalytic system was found to be critical for asymmetric induction. Mechanistically, the Rh(I) catalyst **329**, which is ligated to chiral phosphine ligand PhTRAP, forms a complex with α-cyano functionality of **326**. Elimination of the alkoxide ligand through hydrogen exchange provides enolate **330** as the catalytically active species (Scheme 45B).

Scheme 45. Synergistic Pd/Rh Dual Catalysis for Enantioselective α-Allylation of α-Cyanoesters



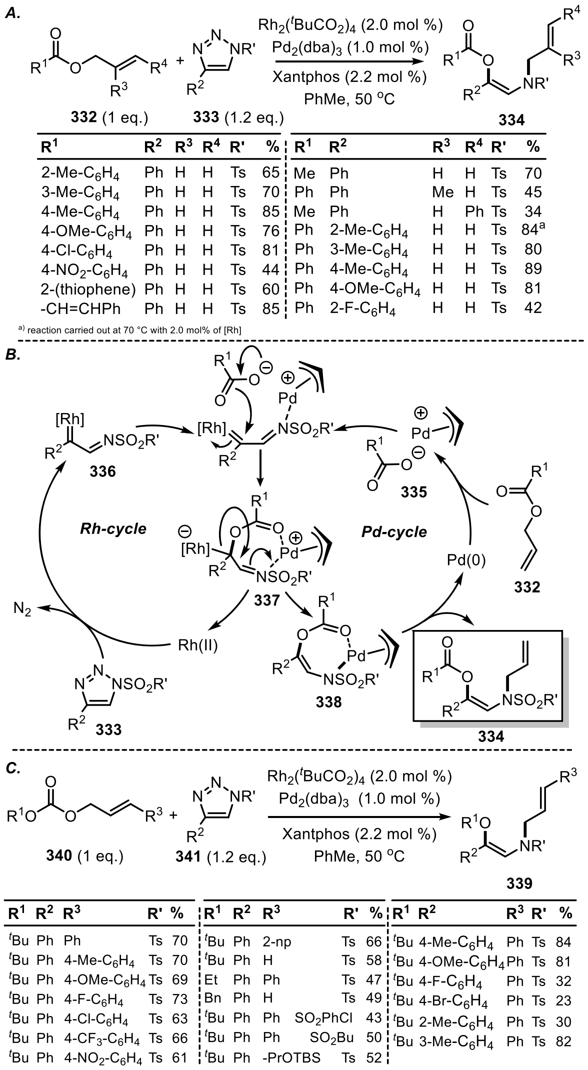
R (327)	X	ee %	%
Et	O^{i}Pr	32	98
CH(CF$_3$)$_2$	O^{i}Pr	93	91
CH(CF$_3$)$_2$	-N(Me)OMe	87	94
CH(CF$_3$)$_2$	-PO(OEt)$_2$	92	91

The enolate **330** reacts with π-allylPd(II) species **331** derived from allyl carbonate **327** to produce the α-allylated product **328**. When the reaction was mediated *via* monocatalytic Pd in the presence of chiral ligand, the racemic product was readily formed in high yield, showing that the Rh(I)-chiral ligand complex is required for stereoselectivity. In the absence of the Pd catalyst, the reaction fails to take place entirely, underlining the synergistic nature of this dual-catalytic system. The disclosed methodology was also applicable for α-allylation of α-cyano Weinreb amides and α-cyano phosphonate esters.

5.2. Atom-Economical Preparation of Z-Amino Vinyl Carbonates

Lee and co-workers developed a synergistic Rh(II)/Ph(0) dual catalytic system for the synthesis of *Z*-amino vinyl carbonates **334** from *N*-sulfonyl-1,2,3-triazole **333** and allylic carbonate **332** (Scheme 46).[174]

Scheme 46. Synergistic Pd/Rh Dual Catalysis for Stereocontrolled Synthesis of (*Z*)-Amino Vinyl Carboxylates



R^1	R^2	R^3	R^4	R'	%	R^1	R^2	R^3	R^4	R'	%
2-Me-C$_6$H$_4$	Ph	H	H	Ts	65	Me	Ph	H	H	Ts	70
3-Me-C$_6$H$_4$	Ph	H	H	Ts	70	Ph	Ph	Me	H	Ts	45
4-Me-C$_6$H$_4$	Ph	H	H	Ts	85	Me	Ph	H	Ph	Ts	34
4-OMe-C$_6$H$_4$	Ph	H	H	Ts	76	Ph	2-Me-C$_6$H$_4$	H	H	Ts	84[a]
4-Cl-C$_6$H$_4$	Ph	H	H	Ts	81	Ph	3-Me-C$_6$H$_4$	H	H	Ts	80
4-NO$_2$-C$_6$H$_4$	Ph	H	H	Ts	44	Ph	4-Me-C$_6$H$_4$	H	H	Ts	89
2-(thiophene)	Ph	H	H	Ts	60	Ph	4-OMe-C$_6$H$_4$	H	H	Ts	81
-CH=CHPh	Ph	H	H	Ts	85	Ph	2-F-C$_6$H$_4$	H	H	Ts	42

[a] reaction carried out at 70 °C with 2.0 mol% of [Rh]

R^1	R^2	R^3	R'	%	R^1	R^2	R^3	R'	%	R^1	R^2	R^3	R'	%
^{t}Bu	Ph	Ph	Ts	70	^{t}Bu	Ph	2-np	Ts	66	^{t}Bu	4-Me-C$_6$H$_4$	Ph	Ts	84
^{t}Bu	Ph	4-Me-C$_6$H$_4$	Ts	70	^{t}Bu	Ph	H	Ts	58	^{t}Bu	4-OMe-C$_6$H$_4$	Ph	Ts	81
^{t}Bu	Ph	4-OMe-C$_6$H$_4$	Ts	69	Et	Ph	Ph	Ts	47	^{t}Bu	4-F-C$_6$H$_4$	Ph	Ts	32
^{t}Bu	Ph	4-F-C$_6$H$_4$	Ts	73	Bn	Ph	H	Ts	49	^{t}Bu	4-Br-C$_6$H$_4$	Ph	Ts	23
^{t}Bu	Ph	4-Cl-C$_6$H$_4$	Ts	63	^{t}Bu	Ph	Ph	SO$_2$PhCl	43	^{t}Bu	2-Me-C$_6$H$_4$	Ph	Ts	30
^{t}Bu	Ph	4-CF$_3$-C$_6$H$_4$	Ts	66	^{t}Bu	Ph	Ph	SO$_2$Bu	50	^{t}Bu	3-Me-C$_6$H$_4$	Ph	Ts	82
^{t}Bu	Ph	4-NO$_2$-C$_6$H$_4$	Ts	61	^{t}Bu	Ph	-PrOTBS	Ts	52					

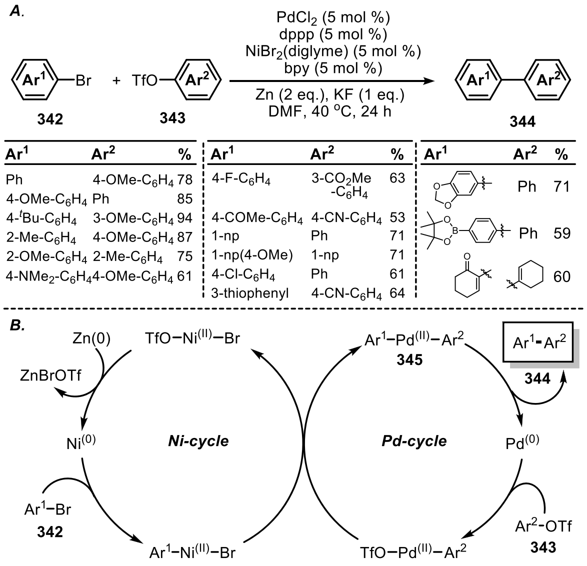
This process combined α-imino rhodium(II)-carbenoid **336**, formed catalytically *via* action of Rh(II) on *N*-sulfonyl triazole **333**, with catalytically generated π-allylPd(II) complex **335** and its associated carboxylate counteranion (derived from allylic carbonate **332**), to form (*Z*)-amino vinyl carboxylates **334** (Scheme 46B). The ambivalent nature of the Rh(II)-carbenoid **336** allows it to react with both the nucleophilic carboxylate counteranion and the electrophilic π-allylPd(II) moiety to generate the metal-associated zwitterionic intermediate **337**. Disassociation of Rh and reductive elimination of Pd affords the desired (*Z*)-amino vinyl carboxylate **334** alongside regeneration of Rh(II) and Pd(0) catalysts. The coordination of the cationic Pd species with the carbonyl appendage and nitrogen atom as shown in intermediate **338** to Pd was thought to be a crucial factor in the formation of the (*Z*)-product. In a similar manner, (Z)-amino vinyl ether **339** were prepared by using allyl carbonate starting material **340** and triazole **341** in good yields (Scheme 46C).

6. SYNERGISTIC Pd/Ni DUAL CATALYSIS

6.1. Cross-Ullmann Reaction of Aryl Bromides and Aryl Triflates for Biaryl Synthesis

Metal-catalyzed selective cross-coupling between aryl halides and/or pseudo halides presents a formidable challenge due to facile formation of homocoupling side products. Weix and co-workers developed a synergistic Pd(0)/Ni(0) dual catalysis strategy to effect a cross-Ullmann reaction between aryl bromides **342** and aryl triflates **343** for preparation of biaryl compounds **344** (Scheme 47).[175]

Scheme 47. Synergistic Pd/Ni Dual Catalysis for Aryl−Aryl Cross-Coupling



Ar^1	Ar^2	%
Ph	4-OMe-C_6H_4	78
4-OMe-C_6H_4	Ph	85
4-^{t}Bu-C_6H_4	3-OMe-C_6H_4	94
2-Me-C_6H_4	4-OMe-C_6H_4	87
2-OMe-C_6H_4	2-Me-C_6H_4	75
4-NMe_2-C_6H_4	4-OMe-C_6H_4	61
4-F-C_6H_4	3-CO_2Me-C_6H_4	63
4-COMe-C_6H_4	4-CN-C_6H_4	53
1-np	Ph	71
1-np(4-OMe)	1-np	71
4-Cl-C_6H_4	Ph	61
3-thiophenyl	4-CN-C_6H_4	64
	Ph	71
	Ph	59
		60

The success of the coupling is based on the elegant recognition of the orthogonal reactivity of two transition metals toward aryl bromides and aryl triflates. Oxidative addition of the two catalysts, Ni(0) into bromide **342** and Pd(0) into triflate **343**, occurs in a chemoselective manner, and transmetalation between the two catalytically activated species give rise to Pd(II) complex **345**. Reductive elimination forms the desired biaryl compound **344** while returning Pd(0) back to the catalytic cycle. Following the transmetalation event, the nickel catalytic cycle is assisted by the use of zinc metal to readjust the oxidation state of the Ni(II) to Ni(0), allowing the catalytic cycle to continue.

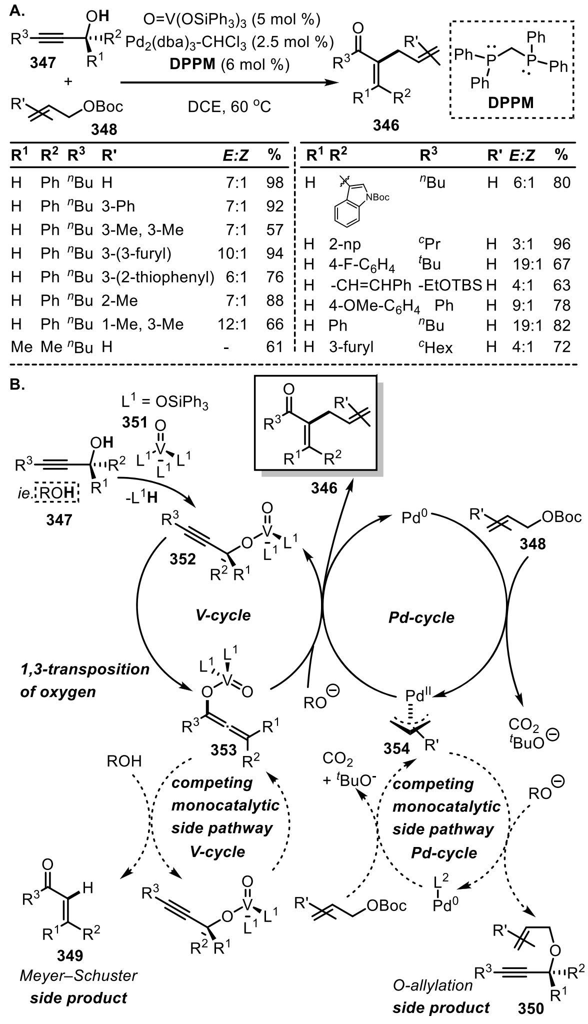
7. SYNERGISTIC Pd/V DUAL CATALYSIS

7.1. Allylation of Propargyl Allenonates

It is known that vanadium enolate/allenonate could react with aldehyde.[176,177] Trost and co-workers reasoned that allenoate intermediate could intercept an electrophilic π-allylPd(II) intermediate to establish the Pd/V synergistic catalysis for the production of α-allylated α,β-unsaturated carbonyl compounds **346** from reaction between propargyl alcohols **347** and allylic carbonates **348** (Scheme 48).[178−180]

Conceptually, this reaction is comprised of the vanadium(V)-catalyzed 1,3-transposition of propargyl alcohol coupled with Pd-mediated allylation reaction. A significant challenge was overcoming monocatalysis derived side reactions such as the vanadium(V) mediated Meyer−Schuster rearrangement of the allenoate, which yields undesired **349** and palladium(0) mediated O-allylation of the propargyl alcohol, yielding undesired **350**. Initial studies under monocatalysis respectively furnished both side products. Critically, when both vanadium and palladium catalysts are used concurrently, the desired α-allylated α,β-unsaturated ketone **346** could be accessed. Neither the Meyer−Schuster product **349** nor the O-allylation product **350** could be converted to the desired product under dual catalysis conditions, demonstrating that a two-step relay process was not involved. The proposed Pd/V mediated mechanism involves transesterification of propargyl alcohol **347** with the vanadium(V) catalyst **351**, yielding the vanadium ester **352** which, upon rearrangement, affords vanadium allenoate **353** as the catalytically activated species. Reaction of allenoate **353** with the π-allyl palladium species **354** formed from allyl carbonate **348** provides the desired α-allylated α,β-unsaturated product **346**. This synergistic dual catalysis was also extended to the production of α-allylated α,β-unsaturated esters and amides from vanadium-ketene acetals and aminals generated from the ether and amine appended acetylenes.

Scheme 48. Synergistic Pd/V Dual Catalysis for the Synthesis of α-Allylated α,β-Unsaturated Ketones



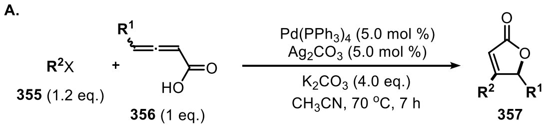
R^1	R^2	R^3	R'	E:Z	%
H	Ph	^{n}Bu	H	7:1	98
H	Ph	^{n}Bu	3-Ph	7:1	92
H	Ph	^{n}Bu	3-Me, 3-Me	7:1	57
H	Ph	^{n}Bu	3-(3-furyl)	10:1	94
H	Ph	^{n}Bu	3-(2-thiophenyl)	6:1	76
H	Ph	^{n}Bu	2-Me	7:1	88
H	Ph	^{n}Bu	1-Me, 3-Me	12:1	66
Me	Me	^{n}Bu	H	-	61
H		^{n}Bu	H	6:1	80
H	2-np	^{c}Pr	H	3:1	96
H	4-F-C_6H_4	^{t}Bu	H	19:1	67
H	-CH=CHPh	-EtOTBS	H	4:1	63
H	4-OMe-C_6H_4	Ph	H	9:1	78
H	Ph	^{n}Bu	H	19:1	82
H	3-furyl	^{c}Hex	H	4:1	72

8. SYNERGISTIC Pd/Ag DUAL CATALYSIS

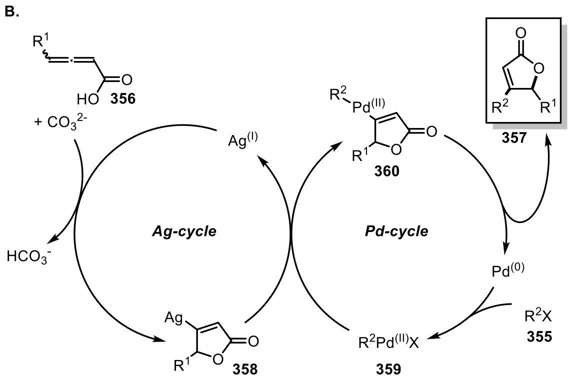
8.1. Pd/Ag Mediated Preparation of Butenolides

Ma and co-workers developed a synergistic Pd(0)/Ag(I) dual catalysis to react aryl and alkenyl halides **355** with allenylic carboxylic acids **356** for the synthesis of butenolides **357** (Scheme 49).[181] Initially, a monocatalytic reaction under Pd catalysis was attempted and only low yields of the desired product was obtained. Incorporation of Ag(I) as a cocatalyst significantly increased the yields (Scheme 49C). Mechanistically, in the presence of a carbonate base, Ag(I) catalyst promoted initial intramolecular cyclization of allenylic carboxylic acid **356** to form silver butenolide **358** (Scheme 49B). Transmetalation with the aryl/alkenyl-Pd(II) **359**, produced from the oxidative addition of Pd(0) into aryl/alkenyl halides **355**, transferred the butenolide moiety onto the Pd center to form **360**, and upon reductive elimination the desired product **357** could be accessed. In view of the low yields obtained under monocatalytic Pd catalysis, an alternative nonsynergistic reaction mechanism involving intermolecular carbopalladation of allene followed by intramolecular allylic substitution was also proposed.

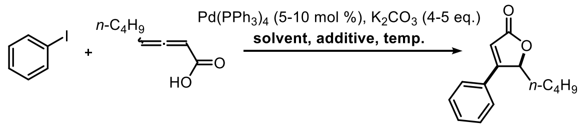
Scheme 49. Synergistic Pd(0)/Ag(I) Dual Catalysis for the Synthesis of Aryl and Vinyl Butenolides



R^1	R^2	X	%	R^1	R^2	X	%	R^1	R^2	X	%
n-Bu	Ph	I	79	*n*-Bu	1-np	Br	-	*n*-Hep	$4\text{-}NO_2\text{-}C_6H_4$	Br	63
n-Bu	$4\text{-}Me\text{-}C_6H_4$	I	73	*n*-Bu	1-np	I	69	*n*-Hep	1-np	I	72
n-Bu	$4\text{-}NO_2\text{-}C_6H_4$	Br	64	*n*-Hep	Ph	I	77	*n*-Bu	-CH=CH COOMe	I	77



C. Mono-metal catalytic conditions (entries 1-3) vs synergistic catalysis (entry 4)

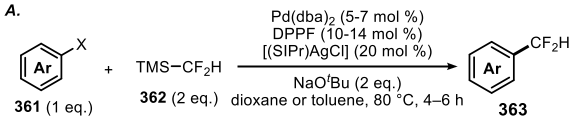


entry	solvent, additive, temp.	yield (%)
1	DMF, none, 80 °C	0
2	DMF, EtOH (10 eq.), 80 °C	15
3	MeCN, EtOH (10 eq.), 80 °C	49
4	**MeCN, Ag_2CO_3 (0.05 eq.), 70 °C**	**79**

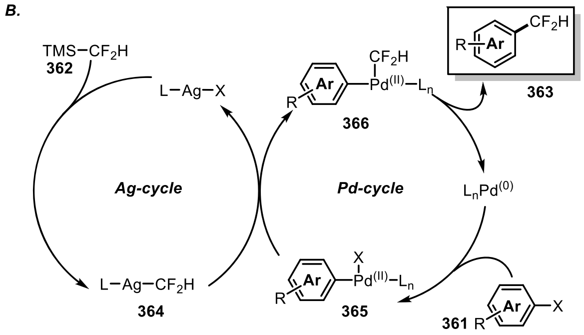
8.2. Preparation of Difluoromethyl Arenes

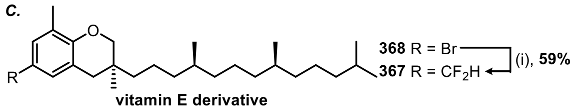
Shen and co-workers developed a synergistic Pd(0)/Ag(I) dual catalysis strategy for the difluoromethylation of aryl halides **361** utilizing trifluoromethyltrimethyl silane ($TMS\text{-}CF_3H$, **362**) to afford difluoromethyl arenes **363** in a single step (Scheme 50).[182] In the proposed mechanism (Scheme 50B), silver difluoromethyl complex **364** is first generated from action of silver catalyst on reagent **362**. Subsequent transmetalation with arylPd(II) **365** produced from oxidative addition of Pd(0) into halide **361** yields difluoromethyl-Pd(II) complex **366**. Reductive elimination furnishes the desired difluoromethyl arenes **363** in good yield. This mild synergistic catalysis could be utilized for the synthesis of difluoromethylated vitamin E derivate **367** from bromide **368** (Scheme 50C).

Scheme 50. Synergistic Pd(0)/Ag(I) Dual Catalysis for the Synthesis of Difluoromethyl Arenes



Ar	X	%	R	X	%	R	X	%
$4\text{-}Ph\text{-}C_6H_4$	I	86	*n*-Pr(4-morpholine)	I	76	$4\text{-}{}^{n}Oct\text{-}C_6H_4$	Br	92
$4\text{-}OBn\text{-}C_6H_4$	I	84	$3,4,5\text{-}(OMe)_3\text{-}C_6H_2$	I	60	$3\text{-}OPh\text{-}C_6H_4$	Br	78
$4\text{-}{}^{t}Bu\text{-}C_6H_4$	I	74	$3\text{-}OBn\text{-}C_6H_4$	I	71	1-np	Br	73
$4\text{-}CO_2{}^{t}Bu\text{-}C_6H_4$	I	76	$4\text{-}Ph\text{-}C_6H_4$	Br	90	2-np	Br	83
$4\text{-}CONEt_2\text{-}C_6H_4$	I	71	$2\text{-}F,5\text{-}Ph\text{-}C_6H_4$	Br	88	4-[2-benzo[*d*] thiazole]-C_6H_4	Br	77
$4\text{-}CH_2NEt_2\text{-}C_6H_4$	I	74	$4\text{-}OBn\text{-}C_6H_4$	Br	70			
1-pyrrole	I	83	$4\text{-}CO_2{}^{t}Bu\text{-}C_6H_4$	Br	73	(4-[9*H*-carbazole])-C_6H_4	Br	90
$4\text{-}Br\text{-}C_6H_4$	I	96	$4\text{-}CONEt_2\text{-}C_6H_4$	Br	77			
$4\text{-}OCH_2c\text{-}prop\text{-}C_6H_4$	I	61	$4\text{-}NPh_2\text{-}C_6H_4$	Br	70	3-(Py[5-OBn])	Br	58





(i) $Pd(dba)_2$ (7 mol %), DPPF (14 mol %), [(SIPr)AgCl] (20 mol %), NaO^tBu (2.4 eq.), $TMSCF_2H$, toluene, 80 °C, 48 h.

9. SYNERGISTIC Pd/Pd DUAL CATALYSIS

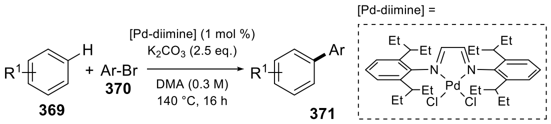
Generally, it is believed that transition metal synergistic catalysis involves catalytic systems based on two different metals. However, synergistic catalytic systems using a sole Pd catalyst in two catalytic cycles have been developed.

9.1. C−H Arylation

Hong and co-workers disclosed a Pd-catalyzed C−H arylation reaction utilizing unactivated arenes **369** and aryl bromides **370** under monocatalytic Pd catalysis to furnish biaryl products **371** (Scheme 51).[183] Interestingly, the authors contend that the single Pd catalyst participates in a synergistic catalysis-type mechanism with and by itself, where Pd catalyst activates the arene **369** *via* C−H activation and its aryl bromide coupling partner **370** by oxidative addition (Scheme 51B). The two intermediates then undergo a transmetalation step to deliver the penultimate intermediate **372**, which affords desired biaryl compound **371** by reductive elimination. The reaction is mediated in the presence of a rigid, nonflexible diimine ligand,

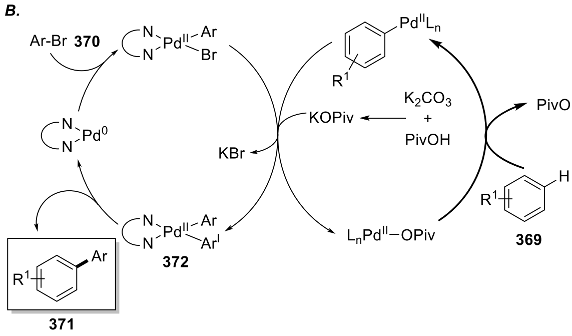
Scheme 51. Putative Synergistic Pd/Pd Dual Catalysis for Synthesis of Biaryl Compounds

A. *Putative synergistic Pd/Pd dual catalysis for synthesis of biaryl compounds.*



R^1	Ar	(*o*:*m*:*p*)	%
H	Ph	73	73
H	4-Me-C_6H_4	78	78
H	4-^{t}Bu-C_6H_4	79	79
H	Ph	79	79

R^1	R^2	R^3	%
8-F	4-Me-C_6H_4	H	83
H	Ph	3-^{t}Bu	64
H	Ph	3-Br	64
H	Ph	4-OMe	55



which coordinates in a bidentate manner to the Pd center, which shuts down the possibility of a traditional, pivalate-promoted concerted metalation deprotonation (CMD) process. Various mechanistic and kinetic studies by the authors further supported the synergistic catalysis type mechanism. This reaction tolerated nitro-, fluoro-, and cyano- substituents on the simple arene, yielding ortho-substituted diaryls. The reaction was also general with respect to the substituted aryl bromide coupling partner, although an electron withdrawing group at the para position afforded a decreased yield.

9.2. "Copper-Free" Sonogashira Reaction *via* Synergistic Pd/Pd Catalysis

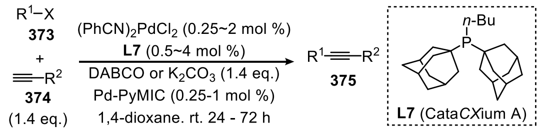
In the traditional Sonogashira reaction, the palladium catalyst activates aryl or vinyl halide while copper cocatalyst activates the acetylene to yield a cross-coupled product *via* classical, synergistic catalysis (*vide supra*). Although the use of copper catalyst alongside palladium enables mild reaction conditions, complications such as unwanted Cu-catalyzed acetylene homocoupling (Glaser coupling) necessitates the strict exclusion of oxygen in the reaction mixture.[184] The presence of Cu can also be incompatible with certain functional groups such as azides, amines, and alkynes in various situations. In this context, monocatalytic Pd driven alkynation (Heck and Cassar coupling)[39,40,185] can provide a complementary alternative. Recently, however, Kosmrlj and co-workers disclosed an intriguing "copper-free" variant of the Sonogashira reaction that made use of two distinct palladium catalysts to fulfill the traditional role of Pd (to activate the aryl halide **373**) and Cu (to activate the acetylene **374**).[186]

In this fully synergistic, Pd/Pd catalysis, cross-coupled product **375** are furnished in good yields (Scheme 52).

The mechanistic considerations played an important role in the development of this system, although superficially, the details are similar to the known Sonogashira reaction. For the first Pd cycle, Pd(0) species undergoes oxidative addition to furnish catalytically active Pd(II) specie **376**. In the second Pd cycle, Pd(II)X in the presence of base and acetylene yields Pd(II)-acetylene complex **377** as the second catalytically active species. Ideally, first and second catalytically active species should be at equimolar concentration as favoring the formation of one intermediate over the another leads to either biaryl homocoupling or 1,3-diyne/enyne homocoupling side products *via* unwanted mono-Pd catalysis. Upon transmetalation of **376** and **377**, arylated-Pd(II)-acetylene complex **378** is furnished, which undergoes reductive elimination to yield **375.** To facilitate the first Pd cycle, $(PhCN)_2PdCl_2$ precatalyst and phosphine ligand CataCXium A were chosen due to their ability to form active Pd(0) species and undergo subsequent oxidative addition—reductive elimination in cross-coupling systems. For the second Pd cycle, Pd-PyMIC complex was chosen as related NHC-Pd(II)-acetylene complexes have been characterized and Pd-PyMIC has been proven stable in Cu-free alkynylation reaction.[187]

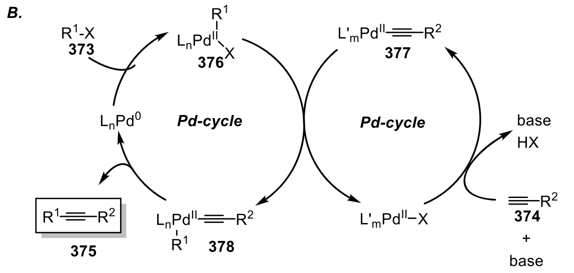
Scheme 52. Synergistic Pd/Pd Dual Catalysis for Coupling of (Hetero)aryl Bromides with Terminal Alkyne

A.



R^1	R^2	base	%
4-Me-C_6H_4	Ph	K_2CO_3	63
2-Me-C_6H_4	Ph	DABCO	35
4-CHO-C_6H_4	4-CF_3-C_6H_4	DABCO	85
2,3-Me_2-C_6H_3	4-OMe-C_6H_4	DABCO	32

R^1	R^2	base	%
4-CF_3-C_6H_4	cyclohexyl	DABCO	51
4-CF_3-C_6H_4	-TMS	DABCO	80
4-CHO-C_6H_4	-$(CH_2)_4$Cl	DABCO	70
4-CF_3-C_6H_4	4-CF_3-C_6H_4	DABCO	46



Under this judicious catalytic combination, Pd/Pd synergistic catalysis takes place at room temperature with potentially exceptionally low Pd loadings (up to 0.25 mol %).

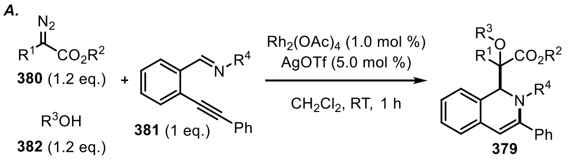
10. SYNERGISTIC Rh/Ag DUAL CATALYSIS

Rh/Ag synergistic catalysis exploit unique reactivity of the two metals; propensity of rhodium to activate -diazo compounds or highly strained carbocyclic moieties and silver to act as soft Lewis acids to activate π-bonds.

10.1. Rh/Ag Mediated Preparation of 1,2-Dihydroisoquinolines

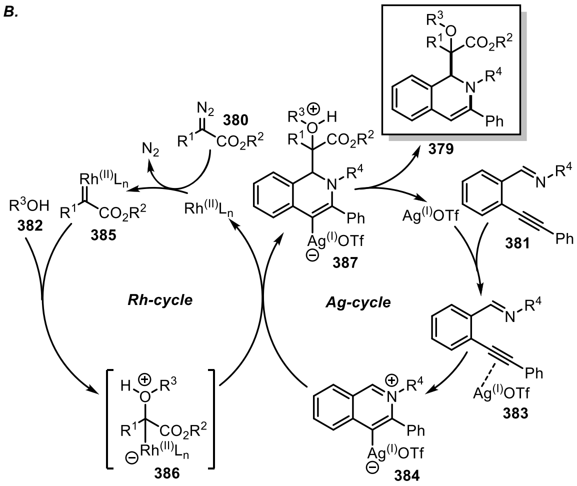
Hu and co-workers envisioned a synergistic Rh(II)/Ag(I) dual catalysis for production of 1,2-dihydroisoquinolines **379** *via* three component coupling reaction between α-diazo ester **380**, 2-(1-alkynyl)arylaldimine **381**, and water or simple alcohols **382** (Scheme 53).[188] Under monocatalytic environment with Rh catalyst, the desired 1,2-dihydroisoquinonlines were afforded in low yields. When AgOTf was used as a cocatalyst, the yields were significantly increased to enable facile access to 1,2-dihydroisoquinolines (Scheme 53C). As shown in Scheme 53B, the coordination of AgOTf with acetylene **381** *via* **383** promoted intramolecular cyclization, forming the Ag-bound intermediate **384** as the catalytically active species. Meanwhile, action of

Scheme 53. Synergistic Rh/Ag Dual Catalysis for the Three Component Synthesis of 1,2-Dihydroisoquinolines

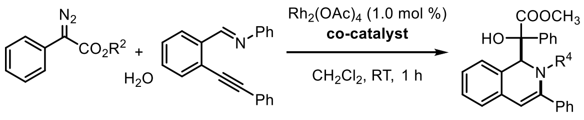


R^1	R^2	R^3	R^4	dr	%	R^1	R^2	R^3	R^4	dr	%
Ph	Me	H	Ph	60:40	83	Ph	Me	H	4-Br-C_6H_4	59:41	60
4-OMe-C_6H_4	Me	H	Ph	56:44	90	Ph	Me	H	4-NO_2-C_6H_4	-	-
4-Me-C_6H_4	Me	H	Ph	58:42	84	Ph	Me	H	2-OH-C_6H_4	-	-
3-Br-C_6H_4	Me	H	Ph	52:48	80	H	Et	H	Ph	49:51	92
3-Cl-C_6H_4	Me	H	Ph	53:47	85	H	Et	H	4-OMe-C_6H_4	54:46	93
4-Br-C_6H_4	Me	H	Ph	57:43	65	H	Et	H	3-Cl-C_6H_4	55:45	73
4-NO_2-C_6H_4	Me	H	Ph	-	-	H	Et	H	4-Br-C_6H_4	76:24	71
Ph	Me	H	3-Cl-C_6H_4	56:44	65	H	Et	Me	Ph	46:54	60[a]
Ph	Me	H	4-Cl-C_6H_4	56:44	67	H	Et	^{i}Pr	Ph	50:50	55[a]

[a] 4 Å molecular sieves were added.



C. Mono-metal catalysis (entry 1) vs synergistic catalysis (entry 2)



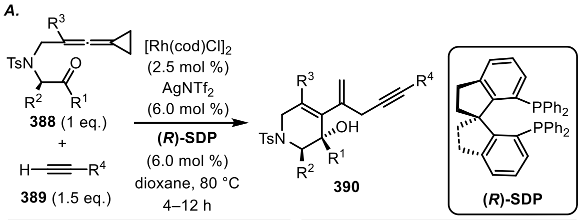
entry	co-catalyst	yield (%)	dr
1	none	9	50:50
2	**AgOTf (5 mol %)**	**83**	**60:40**

Rh(II) catalyst on α-diazo ester **380** effects extrusion of nitrogen gas and irreversible generation of Rh-carbenoid **385**. Nucleophilic attack of alcohol **382** onto electrophilic carbenoid carbon in **385** yields Rh-oxonium complex **386** as the second catalytically active species. A Mannich-type reaction between **384** and **386** could furnish penultimate Ag(I) intermediate **387** with regeneration of Rh(II) catalyst. Upon subsequent protodemetalation, the desired 1,2-dihydroisoquinoline product **379** is formed and Ag(I) is regenerated.

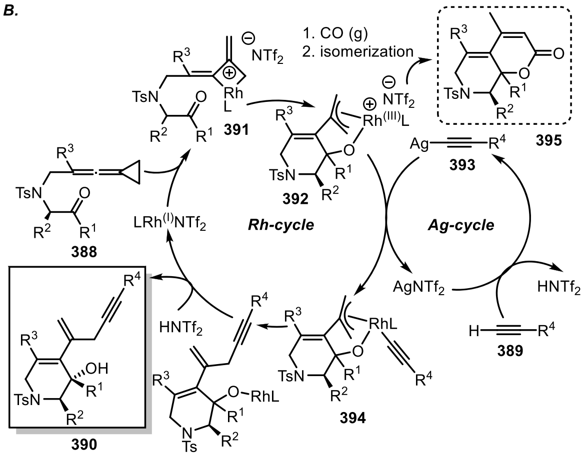
10.2. Rh/Ag Mediated Tetrahydropyridine-3-ol Tethered 7,4-Enynes

Recently, Shi and co-workers described synergistic Rh(I)/Ag(I) dual catalysis for cycloisomerization/cross-coupling reaction of keto-vinylidencyclopropanes **388** with terminal alkynes **389** for the regio- and enantioselective preparation of tetrayhydropyridin-3-ol tethered 1,4-enynes **390** (Scheme 54).[189] In this reaction, the highly strained structural moiety of vinylidenecyclopropane **388** was exploited in the presence of Rh(I) catalyst, which undergoes oxidative addition into the weaker C−C bond of the three membered ring to form rhodacyclobutene **391** (Scheme 54B). The subsequent isomerization *via* intramolecular ketone carbometalation yields the catalytically activated *oxa*-rhodacyclic intermediate **392**. Meanwhile, alkyne **389** reacts with Ag(I) catalyst to form Ag-alkynyl intermediate **393** as the second catalytically activated species. Transmetalation of **393** with **392** furnishes Rh-alkynyl intermediate **394** with regeneration of the Ag catalyst. Subsequent reductive elimination and protonolysis yields the desired cross-coupling product **390**. To firmly implicate intermediate **392** in the proposed reaction mechanism, a control experiment was conducted under a CO atmosphere where Rh intermediate **392** was made to undergo carbonylation followed by reductive elimination and double-bond isomerization to yield a lactone derivative **395**, which was characterized. The authors could not rule out, however, an alternative reaction mechanism involving alkynyl migratory insertion.

Scheme 54. Synergistic Rh/Ag Dual Catalysis for the Preparation of Tetrahydropyridin-3-ol Tethered 1,4-Enynes



R^1	R^2	R^3	R^4	*ee*	%	R^1	R^2	R^3	R^4	*ee*	%
Ph	H	Me	Ph	99	85	Ph	H	Bn	Ph	99	95
4-Ph-C_6H_4	H	Me	Ph	99	80	Ph	H	Ph	Ph	99	62
4-Me-C_6H_4	H	Me	Ph	99	81	Ph	H	Me	Ph	93	85
4-OMe-C_6H_4	H	Me	Ph	99	84	Ph	H	Me	Ph	93	34
4-F-C_6H_4	H	Me	Ph	98	77	Ph	H	Me	4-Me-C_6H_4	99	87
4-Cl-C_6H_4	H	Me	Ph	99	76	Ph	H	Me	4-OMe-C_6H_4	99	95
4-Br-C_6H_4	H	Me	Ph	99	82	Ph	H	Me	4-^{n}Bu-C_6H_4	99	82

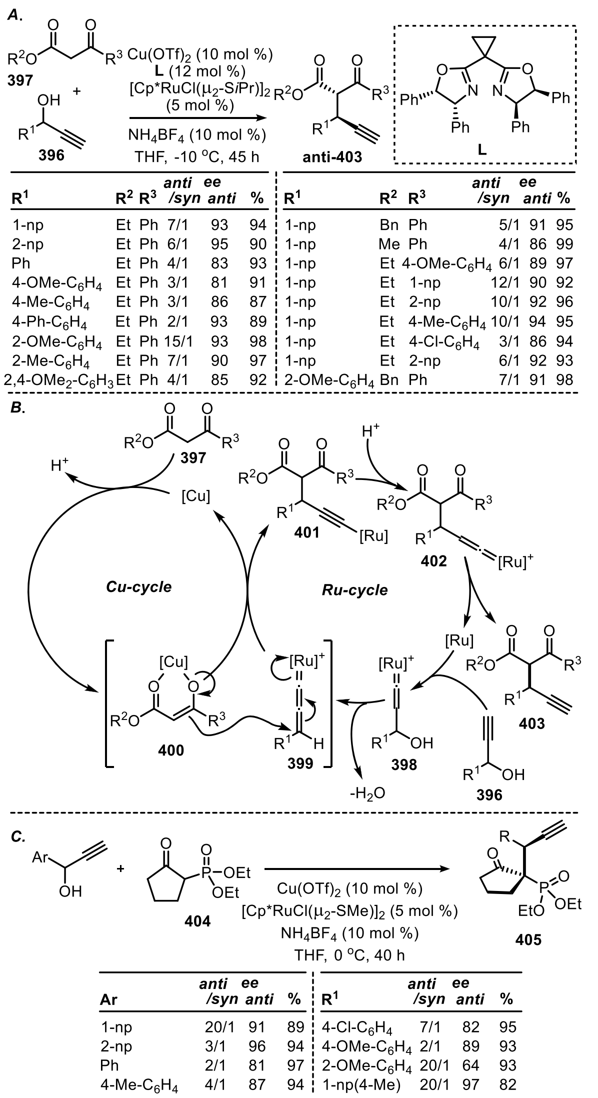


11. SYNERGISTIC Ru/Cu DUAL CATALYSIS

11.1. Enantioselective Propargylic Alkylation of β-Ketoesters

Although there are plethora of transition-metal catalyzed allylation substitution reactions,[190] corresponding enantioselective propargylic substitution reactions are limited to ruthenium-catalyzed examples reported by Nishibayashi and co-workers, which are driven by formation of ruthenium allenylidene complexes.[191−193] The same authors extend this methodology by intercepting aforementioned allenylidene intermediate with Cu-enolate complex to achieve Ru/Cu synergistic catalysis. To this end, propargyl alcohol **396** was envisioned to be activated by Ru catalyst to produce an electrophile susceptible to nucleophilic attack by copper enolate of β-ketoesters **397** (Scheme 55).[194]

Scheme 55. Synergistic Ru/Cu Dual Catalysis for the Propargylic Alkylation of β-Ketoesters



R^1	R^2	R^3	*anti/syn*	*ee anti*	%
1-np	Et	Ph	7/1	93	94
2-np	Et	Ph	6/1	95	90
Ph	Et	Ph	4/1	83	93
4-OMe-C_6H_4	Et	Ph	3/1	81	91
4-Me-C_6H_4	Et	Ph	3/1	86	87
4-Ph-C_6H_4	Et	Ph	2/1	93	89
2-OMe-C_6H_4	Et	Ph	15/1	93	98
2-Me-C_6H_4	Et	Ph	7/1	90	97
2,4-OMe$_2$-C_6H_3	Et	Ph	4/1	85	92

R^1	R^2	R^3	*anti/syn*	*ee anti*	%
1-np	Bn	Ph	5/1	91	95
1-np	Me	Ph	4/1	86	99
1-np	Et	4-OMe-C_6H_4	6/1	89	97
1-np	Et	1-np	12/1	90	92
1-np	Et	2-np	10/1	92	96
1-np	Et	4-Me-C_6H_4	10/1	94	95
1-np	Et	4-Cl-C_6H_4	3/1	86	94
1-np	Et	2-np	6/1	92	93
2-OMe-C_6H_4	Bn	Ph	7/1	91	98

Ar	*anti/syn*	*ee anti*	%
1-np	20/1	91	89
2-np	3/1	96	94
Ph	2/1	81	97
4-Me-C_6H_4	4/1	87	94

R^1	*anti/syn*	*ee anti*	%
4-Cl-C_6H_4	7/1	82	95
4-OMe-C_6H_4	2/1	89	93
2-OMe-C_6H_4	20/1	64	93
1-np(4-Me)	20/1	97	82

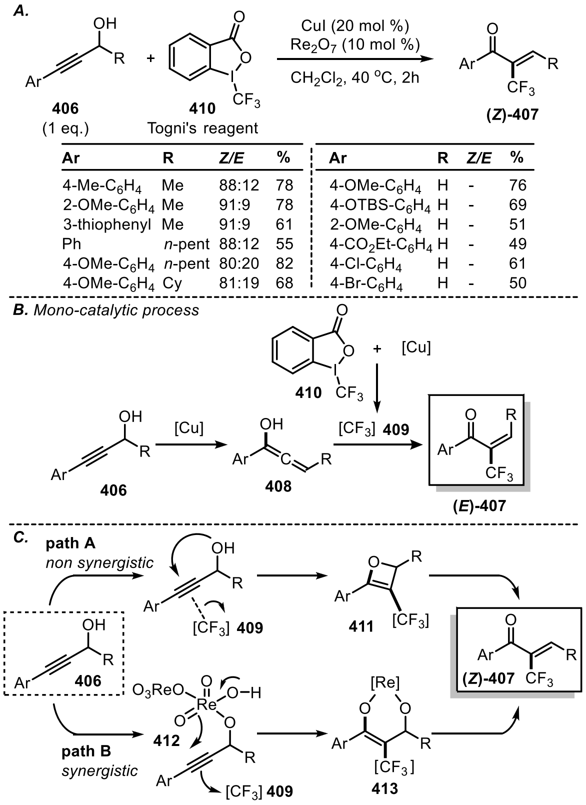
The initial complexation of Ru catalyst and propargyl alcohol **396** gave rise to ruthenium vinylidene complex **398** and upon elimination of water, the ruthenium allenylidene **399** was formed as the first catalytically activated species. Meanwhile, interaction of Cu catalyst and β-ketoester **397** affords Cu enolate **400** as the second catalytically activated species. Attack of the **400** at the terminal carbon of **399** forms alkynyl complex **401**, which further undergoes acid-catalyzed rearrangement to afford vinylidene **402**. Formation of the alkyne and final ligand exchange furnishes the desired product **403** as a mixture of the major *anti* and minor *syn* products. The *anti* product was formed with high enantioselectivity *via* attack on the *Si*-face of ruthenium allenylidene complex **399** by the *Re*-face of the copper enolate **400**. Internal alkynes did not react under the optimized reaction conditions, lending support for the presence of a key ruthenium allenylidene intermediate. This work was extended to include the propargylic alkylation of cyclic β-ketophosphonates (Scheme 55C).[195] In this context, using 2-oxocyclopentylphosphonates **404** under slightly modified reaction conditions provided high yields of alkynated **405**.

12. SYNERGISTIC Cu/Re DUAL CATALYSIS

12.1. Trifluoromethylation of Propargyl Alcohols

The Cu/Re catalyzed trifluoromethylation of propargyl alcohol **406** may or may not proceed by synergistic catalysis and was reported by Sodeoka and co-workers (Scheme 56).[196]

Scheme 56. Cu/Re Catalyzed Synthesis of *E*-α-Trifluoromethylated Enones



Ar	R	*Z/E*	%
4-Me-C_6H_4	Me	88:12	78
2-OMe-C_6H_4	Me	91:9	78
3-thiophenyl	Me	91:9	61
Ph	*n*-pent	88:12	55
4-OMe-C_6H_4	*n*-pent	80:20	82
4-OMe-C_6H_4	Cy	81:19	68

Ar	R	*Z/E*	%
4-OMe-C_6H_4	H	-	76
4-OTBS-C_6H_4	H	-	69
2-OMe-C_6H_4	H	-	51
4-CO_2Et-C_6H_4	H	-	49
4-Cl-C_6H_4	H	-	61
4-Br-C_6H_4	H	-	50

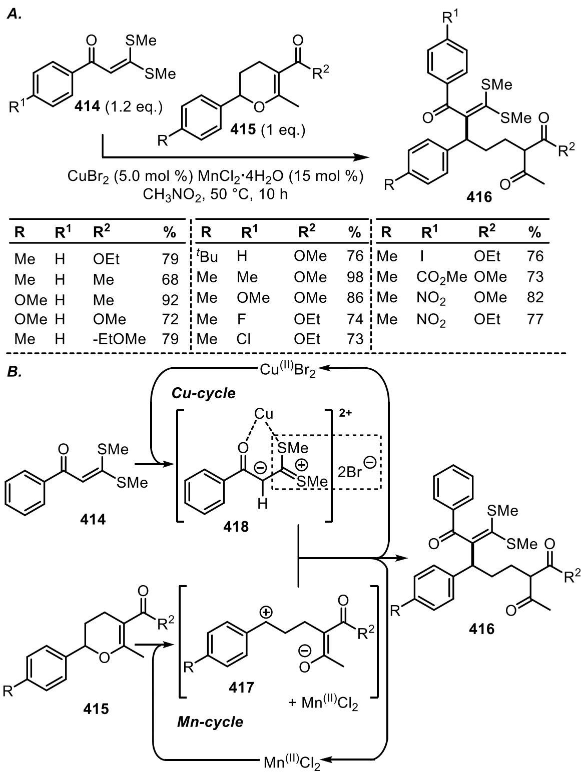
The dual catalysis method affords *Z*-α-trifluoromethylated enones (*Z*)-**407**, while a related Cu monocatalytic method reported by Tan and Liu and co-workers yields (*E*)-**407** (Scheme 56B).[197] The copper-catalytic process is believed to proceed *via* Meyer–Schuster rearrangement, affording an intermediary allenol **408**, which is then trifluoromethylated by a Cu containing trifluoromethyl species **409**,[198] generated from Togni's reagent **410**. The dual Cu/Re catalytic process differed from the monocatalytic process in a few key ways. First, the dual catalysis process produces the *Z*-isomer as the major product. Second, subjecting the *Z*-isomer to further copper and rhenium catalysis leads to isomerization, suggesting that the *Z*-isomer formed under kinetic conditions. Third, a control experiment using an allenol-silyl ether produced the *E*-isomer as the major product when subjected to the reaction conditions. On the basis of these results, two possible pathways were hypothesized (Scheme 56C). The first mechanism involves a nonsynergistic dual catalytic process where 4-*endo-dig* cyclization and trifluoromethylation by a copper/rhenium-Togni reagent complex provides cyclic intermediate **411** (path **A**, Scheme 56C). Subsequently, a ring-opening event while minimizing the steric interactions followed by reductive elimination providing the observed Z-isomer (Z)-**407**. The second proposed mechanism involves synergistic dual catalysis (path **B**, Scheme 56C), wherein copper activated trifluoromethyl species **409** would react with rhenium species **412** with rearrangement of the propargyl alcohol to provide intermediate **413**, which, upon fragmentation and reductive elimination, would afford (Z)-**407**. The authors suggested both reaction pathways were equally possible and that further studies were needed to ascertain which mechanism was correct.

13. SYNERGISTIC Cu/Mn DUAL CATALYSIS

13.1. Nucleophilic Addition of α-Oxoketene Dithioacetals into 2-Substituted 3,4-Dihydropyrans

Gu and co-workers utilized Cu(II)/Mn(II) dual catalysis to react α-oxoketene dithioacetal **414** with 2-substituted-3,4-dihydropyrans **415** to furnish ring-opened adducts **416** (Scheme 57).[199] The reaction is initiated by the $MnCl_2{\cdot}4H_2O$ mediated pyran ring-opening of **415**, producing carbonium intermediate **417**. Meanwhile, action of $CuBr_2$ and α-oxoketene dithioacetal **414** furnished Cu-nucleophile **418**, which reacts to trap carbonium intermediate **417**, furnishing adduct **416** in good yield alongside regeneration of Cu(II) and Mn(II) catalysts. In support of Cu(II) catalyzed formation of nucleophile **418**, UV−vis spectrum analysis after addition of $CuBr_2$ showed disruption of superconjugation present in the dithioacetal **414**.

Scheme 57. Synergistic Cu/Mn Dual Catalysis for Trapping of Ring Opened Pyrans with a Weak Nucleophile

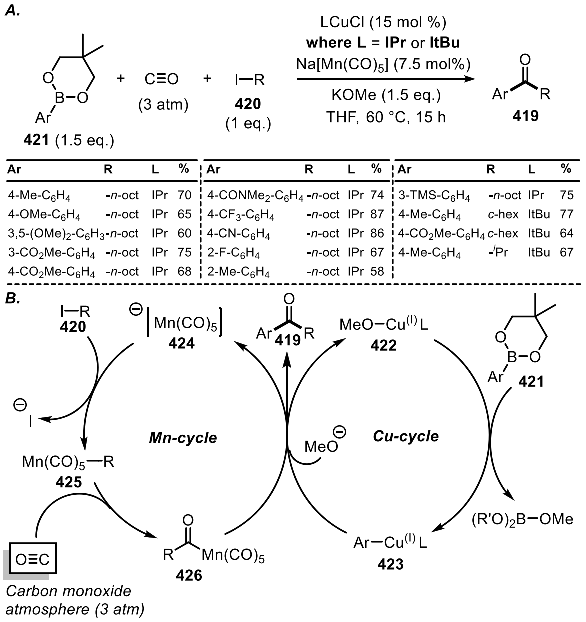


R	R1	R2	%	R	R1	R2	%	R	R1	R2	%
Me	H	OEt	79	^{t}Bu	H	OMe	76	Me	I	OEt	76
Me	H	Me	68	Me	Me	OMe	98	Me	CO_2Me	OMe	73
OMe	H	Me	92	Me	OMe	OMe	86	Me	NO_2	OMe	82
OMe	H	OMe	72	Me	F	OEt	74	Me	NO_2	OEt	77
Me	H	-EtOMe	79	Me	Cl	OEt	73				

13.2. Carbonylative C−C Coupling of Aryl Boronic Acids with Alkyl Halides

Although Pd-catalyzed carbonylations of aryl or vinyl halides are known, analogous Pd-catalyzed carbonylation for Csp^3-hybridized electrophiles such as alkyl halides are problematic due to alkyl-palladium intermediates undergoing undesirable β-hydride elimination.[200] Mankad and co-workers reasoned such complications could be avoided by using Mn catalyst in place of Pd. In this context, aryl ketone **419** was accessed *via* Mn/Cu mediated carbonylative C−C coupling between alkyl halide **420** and aryl boronic acid **421**, operating under CO atmosphere (Scheme 58).[201] In the optimized reaction conditions, aryl boronic acid **421** reacts with copper alkoxide complex **422** to afford cuprate nucleophile **423** as the catalytically activated species (Scheme 58B). Meanwhile, the Heck−Breslow mechanism is effected where anionic manganese complex **424** reacts with alkyl halide **420** to afford alkyl manganese **425**. Carbon monoxide is then incorporated to yield manganese metal-acyl electrophile **426**, which as the catalytically activated species, reacts with nucleophilic aryl cuprate **423** to furnish ketone **419** with regeneration of the manganese and copper catalysts. The authors were astute in conducting a Glorius robustness screen,[202] where it was shown that the disclosed method was inert toward aryl bromide additives, which is a unique advantage over Pd-catalyzed systems where undesired oxidative addition of Pd(0) into the C−Br bond might prove problematic.

Scheme 58. Synergistic Cu/Mn Dual Catalysis for Carbonylative C−C Coupling of Aryl Boronic Acids with Alkyl Halides



Ar	R	L	%	Ar	R	L	%	Ar	R	L	%
4-Me-C_6H_4	-*n*-oct	IPr	70	4-CONMe$_2$-C_6H_4	-*n*-oct	IPr	74	3-TMS-C_6H_4	-*n*-oct	IPr	75
4-OMe-C_6H_4	-*n*-oct	IPr	65	4-CF$_3$-C_6H_4	-*n*-oct	IPr	87	4-Me-C_6H_4	*c*-hex	ItBu	77
3,5-(OMe)$_2$-C_6H_3	-*n*-oct	IPr	60	4-CN-C_6H_4	-*n*-oct	IPr	86	4-CO$_2$Me-C_6H_4	*c*-hex	ItBu	64
3-CO$_2$Me-C_6H_4	-*n*-oct	IPr	75	2-F-C_6H_4	-*n*-oct	IPr	67	4-Me-C_6H_4	-^{i}Pr	ItBu	67
4-CO$_2$Me-C_6H_4	-*n*-oct	IPr	68	2-Me-C_6H_4	-*n*-oct	IPr	58				

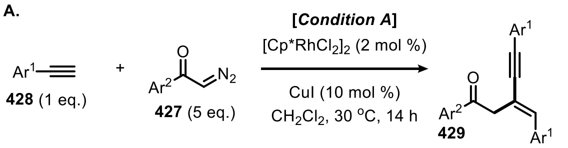
14. SYNERGISTIC Cu/Rh DUAL CATALYSIS

14.1. Cu/Rh Dual Catalysis with Alkynyl Nucleophiles

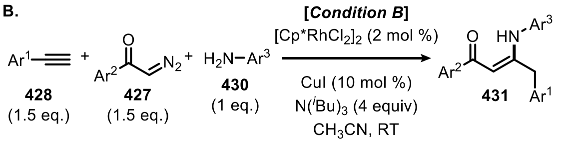
14.1.1. Preparation of 1,3-Enynes and *N*-Aryl Enaminones. Jiang and co-workers utilized Cu(I)/Rh(III) dual catalysis to react α-diazoketones **427** with nucleophilic terminal alkynes **428** to effect a C−H insertion of carbenoid, affording functionalized 1,3-enynes **429**. A similar three component reaction mediated by Cu(I)/Rh(III) catalysts was also realized in which α-diazoketones **427**, terminal alkynes **428**, and aryl amines **430** furnished *N*-aryl enaminones **431** (Scheme 59).[203]

In the proposed mechanism (Scheme 59C), α-diazoketone **427** first interacts with Rh(III) catalyst to form Rh-carbene **432**. Transmetalation with Cu-acetylide **433** derived from terminal alkyne **428** and Cu(I) catalyst transfers the alkyne moiety onto

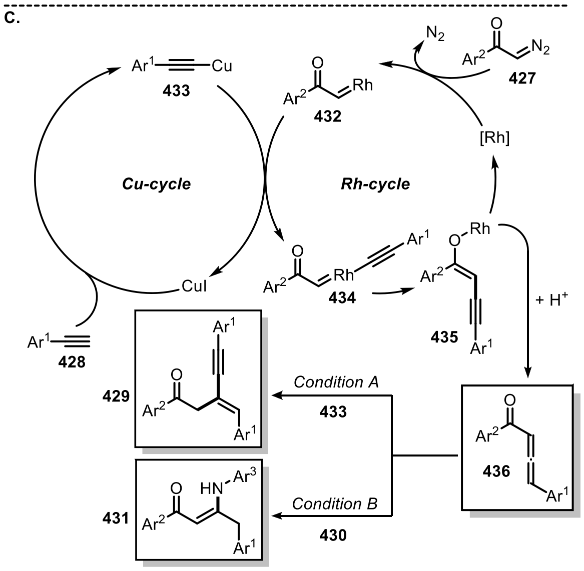
Scheme 59. Synergistic Cu/Rh Dual Catalysis for the Synthesis of 1,3-Enynes and *N*-Aryl enaminones



Ar^1	Ar^2	%	Ar^1	Ar^2	%	Ar^1	Ar^2	%
4-Me-C_6H_4	4-Me-C_6H_4	62	4-Cl-C_6H_4	Ph	55	4-Me-C_6H_4	4-Br-C_6H_4	66
Ph	4-Me-C_6H_4	45	4-Cl-C_6H_4	4-F-C_6H_4	45	Ph	4-Br-C_6H_4	52
4-F-C_6H_4	4-Me-C_6H_4	52	4-Me-C_6H_4	4-Cl-C_6H_4	65	4-F-C_6H_4	4-Br-C_6H_4	46
4-Cl-C_6H_4	4-Me-C_6H_4	54	Ph	4-Cl-C_6H_4	64	4-Cl-C_6H_4	4-Br-C_6H_4	53
4-Me-C_6H_4	Ph	53	4-F-C_6H_4	4-Cl-C_6H_4	47	Ph	4-NO_2-C_6H_4	55
4-F-C_6H_4	Ph	51	4-Cl-C_6H_4	4-Cl-C_6H_4	50	4-F-C_6H_4	4-NO_2-C_6H_4	57
						3-Me-C_6H_4	4-NO_2-C_6H_4	60



Ar^1	Ar^2	Ar^3	*Z/E*	%	Ar^1	Ar^2	Ar^3	*Z/E*	%
4-Me-C_6H_4	4-Me-C_6H_4	4-Me-C_6H_4	20:1	85	4-Me-C_6H_4	Ph	4-F-C_6H_4	11:1	67
4-OMe-C_6H_4	4-Me-C_6H_4	4-Me-C_6H_4	14:1	71	4-Me-C_6H_4	Ph	4-Cl-C_6H_4	7:1	63
3-OMe-C_6H_4	4-Me-C_6H_4	4-Me-C_6H_4	26:1	65	4-Me-C_6H_4	4-F-C_6H_4	4-Me-C_6H_4	20:1	64
Ph	4-Me-C_6H_4	4-Me-C_6H_4	50:1	74	4-Cl-C_6H_4	4-F-C_6H_4	4-Me-C_6H_4	25:1	60
4-F-C_6H_4	4-Me-C_6H_4	4-Me-C_6H_4	35:1	70	4-Me-C_6H_4	4-Me-C_6H_4	4-F-C_6H_4	3:1	63
4-Cl-C_6H_4	4-Me-C_6H_4	4-Me-C_6H_4	99:1	67	OMe-C_6H_4	4-Me-C_6H_4	4-Cl-C_6H_4	11:1	67
4-Me-C_6H_4	Ph	4-Me-C_6H_4	26:1	74	4-F-C_6H_4	4-Cl-C_6H_4	4-Me-C_6H_4	50:1	63
4-Cl-C_6H_4	Ph	4-Me-C_6H_4	50:1	80	4-Cl-C_6H_4	4-Cl-C_6H_4	4-Me-C_6H_4	35:1	61
4-Me-C_6H_4	4-Cl-C_6H_4	4-Me-C_6H_4	2:1	67	Ph	4-Br-C_6H_4	4-Me-C_6H_4	16:1	58



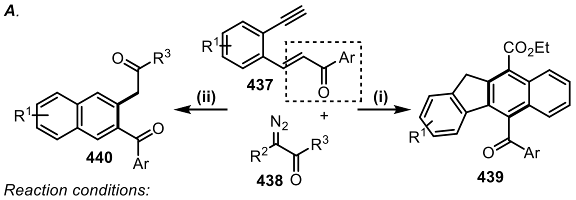
the Rh center, affording **434**. Subsequent enolization yields *O*-Rh enolate **435**, which can be protonated to furnish allene **436**. Allene **436** can react with another equivalent of Cu-acetylide **433** to yield enynes **429** (condition A) or with aryl amine **430** to produce *N*-aryl enaminone **431** (condition B).

14.1.2. Preparation of Benzo[*b*]fluorenes and 2-Naphthalenylmethanones.

Following previous work, Jiang and co-workers extended this chemistry to use *ortho*-propenone arylalkynes **437** with α-aryldiazoesters **438** under Cu/Rh catalysis to afford tetracyclic benzo[*b*]fluorenes **439** and 2-naphthalenylmethanones **440** (Scheme 60A).[204]

In the initial stages, the mechanism of this chemistry is similar to one previously described, where **438** and Rh catalyst first generates Rh(II)-carbenoid **441**, which subsequently undergoes transmetalation with Cu acetylene **442**, derived from terminal alkyne **437** in the presence of Cu catalyst and base to yield complex **443**. Subsequent enolization and H-abstraction affords allene intermediate **444**. From this point, however, the *ortho*-propenone starting material enables a differentiated mode of reactivity depending on the substitution pattern and reaction parameters. When the aryl-substituted allene is used (R^2 = Ph, 4-MePh, 4-FPh) with DMF as solvent and at elevated temperatures (60 °C), an intramolecular [4 + 2] cycloaddition takes place to afford **445** (route I in Scheme 60B). In the presence of PhI(OAc)$_2$, **445** undergoes oxidative aromatization to afford tetracyclic benzo[*b*]fluorene product **439**. Naphthalene **440**

Scheme 60. Synergistic Cu/Rh Dual Catalysis for Synthesis of Benzo[*b*]fluorenes and 2-Napthalenylmethanones



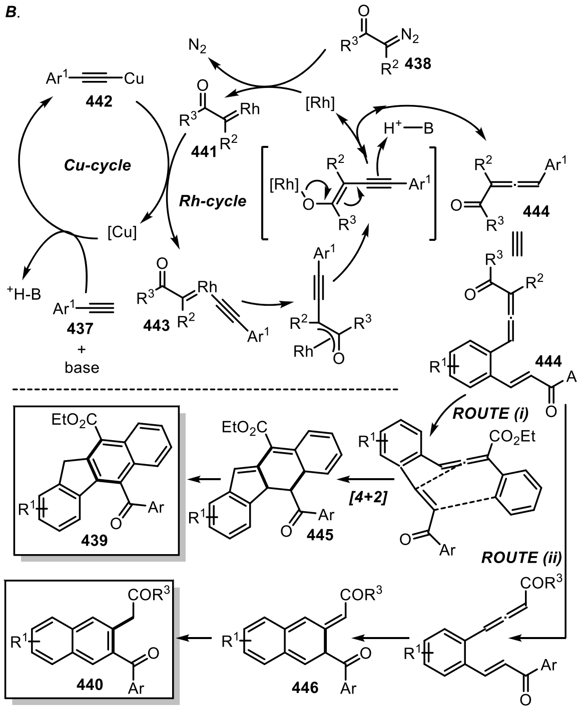
Reaction conditions:
CuI (10 mol %), [Cp*RhCl$_2$]$_2$ (1.5 mol %), PhI(OAc)$_2$ (1 eq.), TIBA (4 eq.), **(i)** : DMF, 60 °C / **(ii)** CH$_3$CN, 40 or 90 °C

(i) For **439**, R^3 = OEt

Ar	R^1	R^2	%	Ar	R^1	R^2	%
4-Br-C_6H_4	H	Ph(4-Me)	60	4-Cl-C_6H_4	H	Ph(4-F)	45
3-Br-C_6H_4	H	Ph(4-Me)	46	4-F-C_6H_4	H	Ph(4-F)	40
2-Br-C_6H_4	H	Ph(4-Me)	41	Ph	H	Ph(4-F)	35
4-Cl-C_6H_4	H	Ph(4-Me)	47	4-Cl-C_6H_4	3-F	Ph(4-F)	47
4-FPh-C_6H_4	H	Ph(4-Me)	59	Ph	3-F	Ph(4-F)	39
4-N_2OPh-C_6H_4	H	Ph(4-Me)	54	4-Me-C_6H_4	3-F	Ph(4-F)	48
Ph	H	Ph(4-Me)	51	4-Cl-C_6H_4	3-F	Ph(4-Me)	56
4-Me-C_6H_4	H	Ph(4-Me)	52	4-F-C_6H_4	3-F	Ph(4-Me)	51
4-Br-C_6H_4	H	Ph	35	Ph	3-F	Ph(4-Me)	39
				4-Me-C_6H_4	3-F	Ph(4-Me)	46

(i) For **440**, R^2 = H

Ar	R^1	R^3	%	Ar	R^1	R^3	%
4-Br-C_6H_4	H	OEt	81	4-F-C_6H_4	3-F	OEt	71
2-Br-C_6H_4	H	OEt	50	4-Me-C_6H_4	3-F	OEt	82
4-Cl-C_6H_4	H	OEt	70	4-OMe-C_6H_4	3-F	OEt	76
4-F-C_6H_4	H	OEt	70	4-Br-C_6H_4	H	Ph(4-Me)	44
Ph	H	OEt	92	4-Cl-C_6H_4	H	Ph(4-Me)	50
4-Me-C_6H_4	H	OEt	96	4-F-C_6H_4	H	Ph(4-Me)	45
4-OMe-C_6H_4	H	OEt	98	Ph	H	Ph(4-Me)	52
4-NO_2-C_6H_4	H	OEt	76	4-Me-C_6H_4	H	Ph(4-Me)	70
4-Cl-C_6H_4	3-F	OEt	67	1-np	H	Ph(4-Me)	40

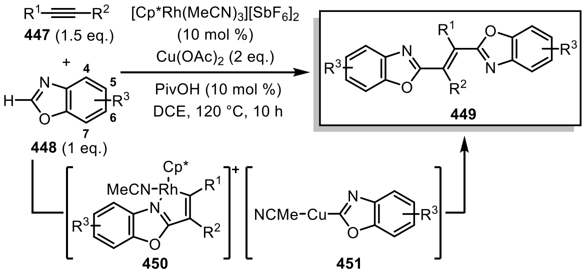


could also be accessed by utilizing **438** with different electronic properties (where $R^2 = H$) or with a sterically more demanding 1-naphthyl component. In this context, under CH_3CN solvent and reaction temperature maintained at 40 or 90 °C, pericyclic cyclization of aryl allene **444** is effected, affording **446**, which then tautomerizes to yield 2-naphthalenylmethanones **440** (route ii in Scheme 60B).

14.1.3. *trans*-Dihetroarylation of Internal Alkynes.

Recently, You and co-workers reported *trans*-dihetroarylation of internal alkynes **447** with azole **448** under stoichiometric Cu/monocatalytic Rh system to prepare *trans*-diazole substituted tetraarylethylene **449** (Scheme 61).[205]

Scheme 61. Synergistic Cu/Rh Dual Catalysis for *trans*-1,2-Diheteroarylation of Alkynes



R^1	R^2	R^3	%	R^1	R^2	R^3	%
Ph	$=R^1$	H	91	3-thiophene	$=R^1$	H	82
4-Me-C_6H_4	$=R^1$	H	73	2-dibenzo[*b*,*d*]furan	$=R^1$	H	68
3-Me-C_6H_4	$=R^1$	H	86	5-benzo[*b*]thiophene	$=R^1$	H	73
4-OMe-C_6H_4	$=R^1$	H	76	5-(1-benzyl-1*H*-indole)	$=R^1$	H	78
4-^{t}Bu-C_6H_4	$=R^1$	H	85	4-*N*,*N*-diphenylaniline	$=R^1$	H	79
4-F-C_6H_4	$=R^1$	H	49	4'-(*N*,*N*-diphenyl-[1,1'-biphenyl]-4-amine)	$=R^1$	H	78
2-F-C_6H_4	$=R^1$	H	40				
4-Cl-C_6H_4	$=R^1$	H	87	Ph	Ph(3,4-OMe)	H	93
4-Br-C_6H_4	$=R^1$	H	68	Ph	5-benzo[*b*]thiophene	H	74
3-Br-C_6H_4	$=R^1$	H	61	Ph	5-benzo[*d*]thiazole	H	59
4-CF_3-C_6H_4	$=R^1$	H	60	Ph	5-(1-phenyl-1*H*-indole-3-carbaldehyde)	H	81
4-COMe-C_6H_4	$=R^1$	H	50				
4-CO_2Et-C_6H_4	$=R^1$	H	91	4-NO_2-C_6H_4	3,4-OMe-C_6H_3	H	83
3-CN-C_6H_4	$=R^1$	H	46	4-OMe-C_6H_4	4-CO_2Et-C_6H_4	H	83
2-np	$=R^1$	H	64	*n*-pr	*n*-pr	H	72

Although the required Cu reagent is utilized stoichiometrically, an *in situ* formation of a key Cu-intermediate is implicated and the reaction is synergistic with respect to the two transition metal activated substrates. Mechanistically, it is proposed that Rh catalyst activates starting azole **448** and reacts further with alkyne **447** to yield rhodacycle **450** as the first catalytically activated species. Meanwhile, key Cu(I) complex arising from disproportionation of $Cu(OAc)_2$ reacts with azole to form second catalytically active species **451**. In the ensuing reaction between the two activated intermediates, the azole moiety on Cu is transferred on to the Rh and upon formation of the product **449**, Rh catalyst is regenerated. Under mono-Rh catalysis, monoarylated adduct is yielded upon protonation of intermediate **450**. The detailed mechanism and *trans*-selectivity of the reaction were supported by computational studies and control experiments.

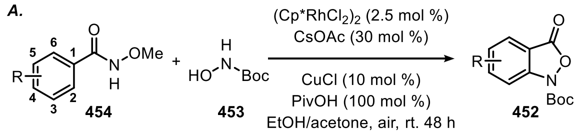
14.2. Miscellaneous Synergistic Cu/Rh Dual Catalysis

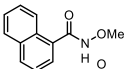
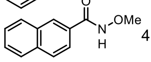
14.2.1. Cooperative Cu/Rh Dual Catalysis for Preparation of *N*-Hydroxycarbamates.

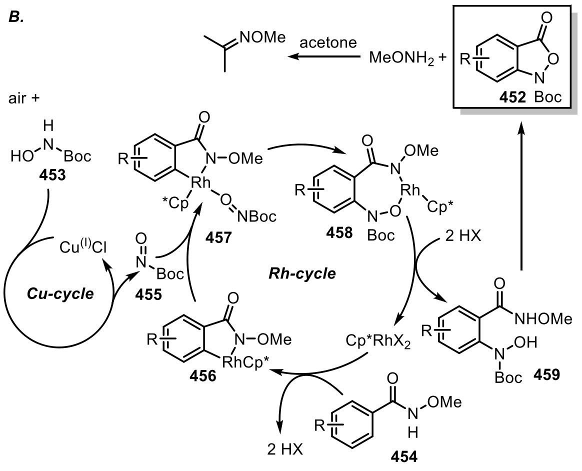
Zhang and co-workers reported preparation of *N*-hydroxycarbamate **452** from *N*-Boc-hydroxyamine **453** and *N*-methoxy benzamide **454** *via* Cu/Rh catalysis (Scheme 62).[206]

The disclosed chemistry exploit the ability of Rh(III) complexes facilitate C−H activation and intercepting it with electrophiles derived from nitrosocarbonyl compounds, formed *via* Cu catalysis. The reaction mechanism is as follows: First, Cu-catalyzed aerobic oxidation of **453** yields catalytically activiated nitrosocarbonyl intermediate **455**. Meanwhile, rhodacyclic intermediate **456** is derived from reversible C−H bond cleavage of **454** with Rh catalyst (Scheme 62B). The reaction between **455** and **456** yields Rh-intermediate **457**, which undergoes nucleophilic addition to form seven-membered rhodacycle **458**, followed by a protonolysis to afford intermediate **459**. Final nucleophilic intramolecular substitution reaction furnishes desired product **452** with displacement of $MeONH_2$.

Scheme 62. Synergistic Cu/Rh Catalysis for Preparation of Benzo[*c*]isoxazol-3(1*H*)-ones



R	%	R	%	R	%	**454:**	%
H	88	4-Br	59	4,5-Me	83		
4-Me	77	4-I	55	5,6-OMe	57		63
4-Et	73	4-CF_3	58	4-OMe	75		
4-^{i}Pr	76	5-Me	85	4-Cl	67		
4-^{t}Bu	82	5-OMe	95	6-Me	65		49



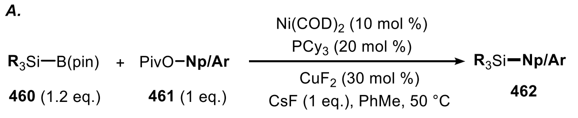
15. SYNERGISTIC Cu/Ni DUAL CATALYSIS

The catalysis based on nickel can be viewed in a similar manner to the more well-known palladium catalysis.[207] This general trend continues for synergistic catalysis; for example, arylboration reported below mediated by Cu/Ni catalysis finds directly analogues example in Cu/Pd catalysis.

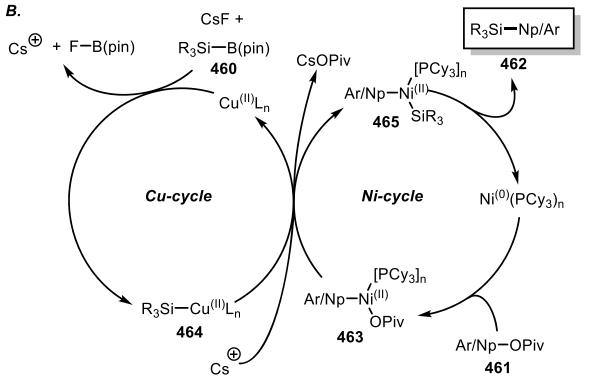
15.1. Silylation of C−O Electrophiles

Martin and co-workers developed silylation of aryl/naphthyl pivalates **461** with borylsilane **460** *via* Cu/Ni dual catalysis (Scheme 63).[208] Both phenyl and naphthyl pivalates could undergo the transformation under mild conditions to afford silylated aromatic **462** in good yields. In the proposed mechanism, oxidative addition of the Ni(0) catalyst into aryl pivalate **461** activiates the C−O bond to form aryl-Ni(II) complex **463**. Transmetalation with Cu(II)-silane **464**, derived from reaction of borylsilane and Cu(II) catalyst in the presence of CsF transfers the silyl moiety onto the Ni center to yield Ni(II) complex **465**. Subsequent reductive elimination affords the desired aryl silane **462** in good yield. In addition, this dual catalysis was also capable of converting primary and secondary benzylic pivalates into benzylic silanes.

Scheme 63. Synergistic Cu/Ni Dual Catalysis for Synthesis of Aryl Silanes



R	Ar/Nap	%	R	Ar/Np	%	R	Ar/Np	%
Et	2-np	90	Et	2-np(8-NHpiv)	55	Et	4-CO^{t}Bu-C_6H_4	85
Me_2Ph	2-np	51	Et	2-np(3-CO_2Me)	58	Et	3-OMe-C_6H_4	79
Et	2-np(7-OMe)	99	Et	2-np(7-OTIPS)	91	Et	3-NMe_2-C_6H_4	74
Et	1-np	74	Et	4-quinoline(2-Me)	57	Et	2,5-Me-C_6H_4	56
Et	1-np(4-OMe)	86	Et	4-^{t}Bu-C_6H_4	70	Et	2-Ph-C_6H_4	68
Et	2-np(6-CO_2Me)	86	Et	4-CF_3-C_6H_4	68	Et	4-Bpin-C_6H_4	89

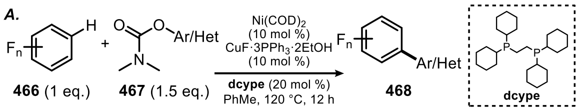


15.2. Coupling of Polyfluoroarenes with Aryl Carbamates

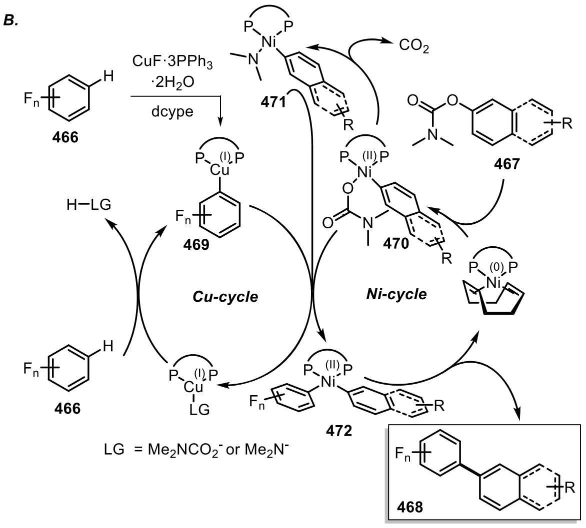
Shi and co-workers disclosed a cross-coupling reaction between polyfluoroarene **466** and heteroaryl/naphthyl carbamate **467** *via* aryl sp^2 C−O/C−H cleavage to prepare various biaryl **468** under synergistic Ni/Cu dual catalysis (Scheme 64).[209]

Preliminary investigation focused on realizing a Ni monocatalytic system, as Ni-catalyzed C−H activation of pentafluorobenzene was previously known.[210] However, undesired reductive coupling *via* Ni mediation of C−F bond activated species necessitated a dual catalytic approach. The proposed mechanism of the dual-catalytic reaction is detailed in Scheme 64B. First, the deprotonation of polyfluoroarene **466** with Cu catalyst afforded the nucleophilic Cu(I) species **469**. Meanwhile, oxidative addition of Ni(0) into carbamate **467** furnishes Ni(II) complex **470**. Further decarboxylation of **470** may take place to afford **471**. Subsequent transmetalation between **469** and nickel complex **470** or **471** would deliver the polyfluoroarene moiety onto the Ni center forming complex **472**. Reductive elimination of **472** affords coupled product **468** with regeneration of the Ni catalyst. Additionally, it was shown that terminal alkynes could undergo alkynylation reaction with carbamates in place of polyfluoroarenes, and with slight modification to the reaction conditions benzothiazoles were also shown to be an amendable reaction partner.

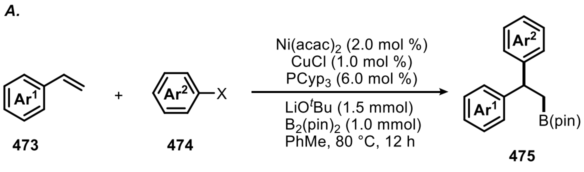
Scheme 64. Synergistic Cu/Ni Dual Catalysis for C−O/C−H Coupling between Polyfluoroarenes and Aryl Carbamates



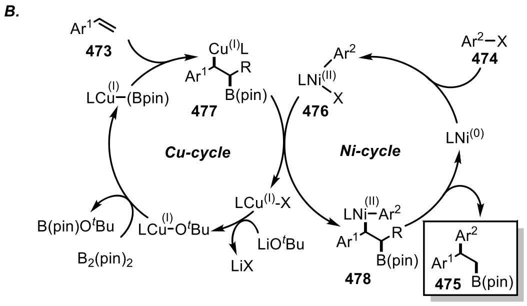
F_n	Ar/Het	%	F_n	Ar/Het	%	F_n	Ar/Het	%
2,3,4,5,6-F_5	2-np	68	2,3,4,5,6-F_5	6-quinoline	83	2,3,4,5,6-F_5	Ph(4-[2-pyridine])	62
2,3,4,5,6-F_5	2-np(6-Me)	86	2,3,4,5,6-F_5	3-quinoline	65	2,3,4,5,6-F_5	2-np(7-OPiv)	-
2,3,4,5,6-F_5	2-np(6-TMS)	30	2,3,4,5,6-F_5	2-np(6-prOMe)	85	2,3,5,6-F_4,4-CF_3	2-np(7-OMe)	72
2,3,4,5,6-F_5	2-np(7-NMe_2)	82	2,3,4,5,6-F_5	2,7-np	41	2,3,5,6-F_4,4-Me	2-np(7-OMe)	97
2,3,4,5,6-F_5	2-np(6-CO_2Me)	76	2,3,4,5,6-F_5	2-np (6-Ph[3,4-OMe])	78	2,3,5,6-F_4,4-OMe	2-np(7-OMe)	54
2,3,4,5,6-F_5	2-np(6-OMe)	50				2,3,5,6-F_4	2-np(7-OMe)	56
2,3,4,5,6-F_5	2-np(7-OMe)	76	2,3,4,5,6-F_5	Ph(4-COPh)	51	2,3,4,5-F_4	2-np(7-OMe)	60
						2,3,4,6-F_4	2-np(7-OMe)	57



Scheme 65. Synergistic Cu/Ni Dual Catalysis for Arylboration of 1-Arylalkenes



Ar^1	Ar^2	X	%	Ar^1	Ar^2	X	%	Ar^1	Ar^2	X	%
Ph	4-Me-C_6H_4	Cl	61	Ph	4-CON[^{i}Pr]$_2$ -C_6H_4	Cl	62	Ph	4-Me-C_6H_4	OTs	47
Ph	4-OMe-C_6H_4	Cl	57					Ph	4-OMe-C_6H_4	OTs	22
Ph	4-CH_2OTBS -C_6H_4	Cl	65	Ph	4-CF_3-C_6H_4	Cl	65	Ph	4-CO_2Et -C_6H_4	OTs	55
				Ph	2-Me-C_6H_4	Cl	35				
Ph	4-Cl-C_6H_4	Cl	70	Ph	4-Me-C_6H_4	Br	70	4-OMe-C_6H_4	4-Me-C_6H_4	Cl	62
Ph	4-CO_2Et-C_6H_4	Cl	67	Ph	4-Me-C_6H_4	OTf	20	4-F-C_6H_4	4-Me-C_6H_4	Cl	62



15.3. Arylboration of 1-Arylalkenes under Ni/Cu Catalysis

Although the group of Semba and Nakao previously disclosed Pd/Cu catalyzed racemic arylboration of 1-aryl and vinyl alkenes with aryl halides (*vide supra*),[87] the expensive cost of Pd was recognized as a limitation. The reliance on Pd also generally precludes the use of chlorides and tosylates. In this context, a more economical dual catalysis was disclosed wherein analogous three-component coupling between 1-arylalkene **473**, $B_2(pin)_2$, and aryl chloride/tosylate **474** was mediated byCu/Ni catalysts to afford 2-boryl-1,1-diarylalkane **475** (Scheme 65).[211] Proposed mechanistic details of the dual catalytic cycle is outlined in Scheme 65B. In the Ni cycle, Ni(0) catalyst undergoes oxidative addition with **474** (X = Cl, OTs) to afford catalytically activated Ni(II) complex **476**. In the Cu catalytic cycle, LCuCl is treated with LiO^{t}Bu to form LCu-O^{t}Bu species in a salt metathesis reaction, followed by reaction with $B_2(pin)_2$

to furnish LCu-(Bpin). Borylcupration of LCu-(Bpin) across the double bond of **473** affords alkylCu(I) complex **477**, the second catalytically active species. Transmetalation between **476** and **477** affords Ni(II) complex **478**, which undergoes reductive elimination to form desired product **475** and the regenerated LNi(0) catalyst. Electron donating or withdrawing groups on the *para* position of aryl chlorides **474** were well tolerated, however, substituents on the *ortho* position proved suboptimal. Aryl tosylates were able to react in lieu of aryl halides, although the yields were diminished. Although excellent regioselectivity is observed with terminal olefins, the use of 1,2-disubstituted olefins afforded products with moderate to poor stereoselectivity.

16. SYNERGISTIC Cu/Fe DUAL CATALYSIS

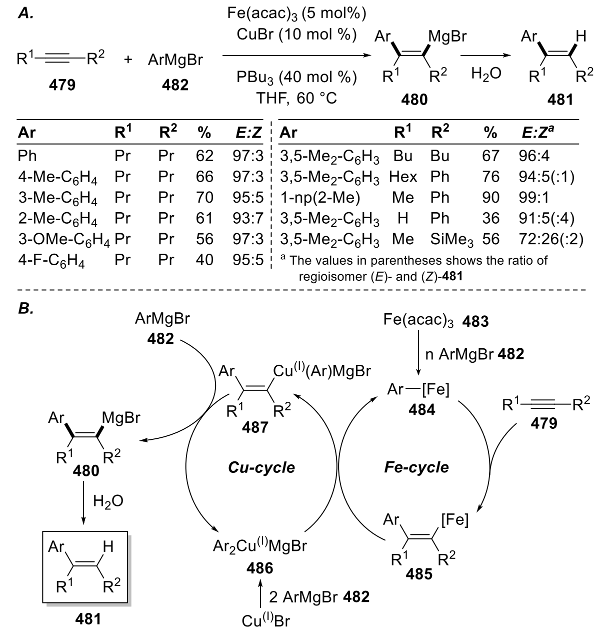
In context of dual catalysis, Cu and Fe metals represent an attractive catalytic pairing as they are inexpensive and relatively insensitive to air and moisture. A general review by Jiao and co-workers give excellent details on bimetallic-Cu/Fe catalytic systems based on tandem and relay mechanisms.[212] In this review, we give overview on Cu/Fe mediated systems which are clearly synergistic in nature, comprising the work disclosed by Hayashi and co-workers which describe Cu/Fe mediated arylmagnesiation of alkynes[213] and isomerization of secondary Grignard reagents,[214] which cumulate in a one-pot relay containing two distinct synergistic catalysis systems.[215] Work by Chavant and co-workers on borylation of aryl bromides under Cu/Fe catalysis is also detailed,[216] followed by application of Cu/Fe catalysis in synthetic nucleoside chemitry.[217]

16.1. One-Pot Relay of Two Synergistically Active Catalysis System

16.1.1. Arylmagnesiation of Disubstituted Acetylenes. Carbometalation of alkynes yields an alkenyl metal intermediate which is often amendable for further functionalization. Although palladium is ubiquitous in enabling such transformations, it is relatively expensive. Shirakawa and Hayashi and co-workers disclosed a strategy for effecting aryl magnesiation of alkyne **479** using synergistic dual Cu/Fe catalysis (Scheme 66).[213]

The utility of the resultant alkenyl magnesium product **480** was demonstrated further by reacting them with aldehydes, alkyl bromides, or water to afford *syn*-selective addition products **481**, where aryl and Mg-derived functionalized groups are placed across the triple bond. The proposed mechanistic details are shown in Scheme 66B. First, interaction of ArMgBr **482** with Fe catalyst **483** affords aryl-Fe complex **484**. Subsequent addition of **484** across alkyne **479** forms alkenyl-Fe complex **485** as the catalytically activated species. Meanwhile, ArMgBr **482** also reacts with Cu(I)Br to furnish diaryl-Cu **486**. Transmetalation between alkenyl-Fe complex **485** and **486** transfers alkenyl group onto Cu center, forming alkenyl(Ar)Cu **487** alongside regeneration of the Fe catalyst. The desired aryl magnesiation product **480** is released by the final transmetalation reaction between cuprate **487** and ArMgBr reagent **482**, which also regenerates diaryl-Cu **486** and completes the catalytic cycle. Although aliphatic and aromatic substituted alkynes are tolerated, the use of terminal alkynes with inherently acidic acetylenic protons proved problematic, as these reagents were expectedly incompatible with the basic character of an arylmagnesium Grignard reagent. Alkynes demonstrated in the study were mostly symmetrical ($R^1 = R^2$), although in some cases where unsymmetrical alkynes were deployed (where R^2 was much more sterically hindered than R^1), excellent regioselectivity was observed.

Scheme 66. Synergistic Cu/Fe Dual Catalysis for Arylmagnesiation of Internal Alkynes



Ar	R^1	R^2	%	*E*:*Z*
Ph	Pr	Pr	62	97:3
4-Me-C_6H_4	Pr	Pr	66	97:3
3-Me-C_6H_4	Pr	Pr	70	95:5
2-Me-C_6H_4	Pr	Pr	61	93:7
3-OMe-C_6H_4	Pr	Pr	56	97:3
4-F-C_6H_4	Pr	Pr	40	95:5

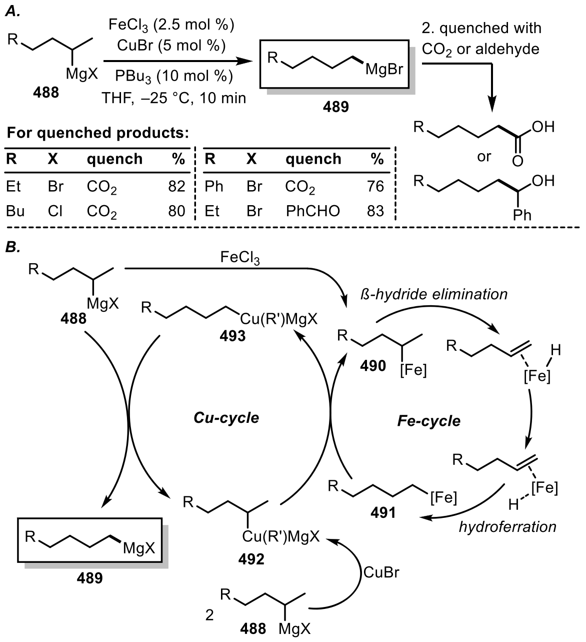
Ar	R^1	R^2	%	*E*:*Z*[a]
3,5-Me_2-C_6H_3	Bu	Bu	67	96:4
3,5-Me_2-C_6H_3	Hex	Ph	76	94:5(:1)
1-np(2-Me)	Me	Ph	90	99:1
3,5-Me_2-C_6H_3	H	Ph	36	91:5(:4)
3,5-Me_2-C_6H_3	Me	$SiMe_3$	56	72:26(:2)

[a] The values in parentheses shows the ratio of regioisomer (*E*)- and (*Z*)-**481**

16.1.2. Isomerization of Secondary Alkyl Grignard Reagents. Following aforementioned work, Shirakawa and Hayashi and co-workers reported Cu/Fe mediated isomerization of secondary alkyl Grignard reagents **488** into primary Grignard reagents **489** (Scheme 67).[214]

Although Ti(IV)[218] or Ni(II)[219] mediated monocatalytic isomerization of secondary Grignard reagents into primary ones are known (*via* β-hydride elimination/hydrometalation), such reactions typically proceed with low conversion. It was found that synergistic Fe/Cu dual catalysis was effective in yielding

Scheme 67. Synergistic Cu/Fe Dual Catalysis for Isomerization of Secondary Alkyl Grignard Reagents



For quenched products:

R	X	quench	%
Et	Br	CO_2	82
Bu	Cl	CO_2	80

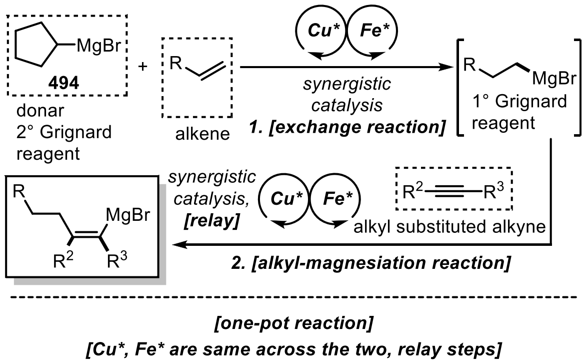
R	X	quench	%
Ph	Br	CO_2	76
Et	Br	PhCHO	83

489, which was further reacted with CO_2 to afford carboxylic acids or with aldehydes to afford secondary alcohols or with D_2O to afford deuterated primary alkanes. In the proposed mechanism (Scheme 67B), the reaction of secondary Grignard reagent **488** with $FeCl_3$ affords 2-alkyliron complex **490**, which undergoes *β*-hydride elimination/hydroferration sequence to afford the 1-alkyl iron **491**. Meanwhile, interaction of the original Grignard reagent **488** with CuBr catalyst affords cuprate **492**. The transmetalation between **491** and **492** affords 1-alkylcupurate complex **493** with regeneration of **490** to continue the iron catalytic cycle. Final transmetalation of **493** with Grignard **488** ultimately affords primary alkyl Grignard reagent **489** in good yield alongside regeneration of cuprate **492**.

16.1.3. A Relay Reaction of Two Synergistically Catalytic System in a Single Pot.

Hayashi and co-workers envisioned an exchange reaction between a secondary Grignard reagent **494** and alkene under synergistic Cu/Fe dual catalysis to prepare primary Grignard reagents (Scheme 68). This process is mechanistically related to the aforementioned isomerization reported by Hayashi (Scheme 67, *vide supra*). In addition to the exchange reaction, a subsequent alkyl-magnesiation of alkynes in a tandem reaction was also engineered, which is mechanistically related to aforementioned Hayashi's aryl-magnesiation of disubstituted alkynes **479** (Scheme 66, *vide supra*). The two processes could be effected by the same Cu/Fe species present in the flask and, in effect, a tandem reaction of the two synergistic catalysis was achieved, an unprecedented undertaking.[215]

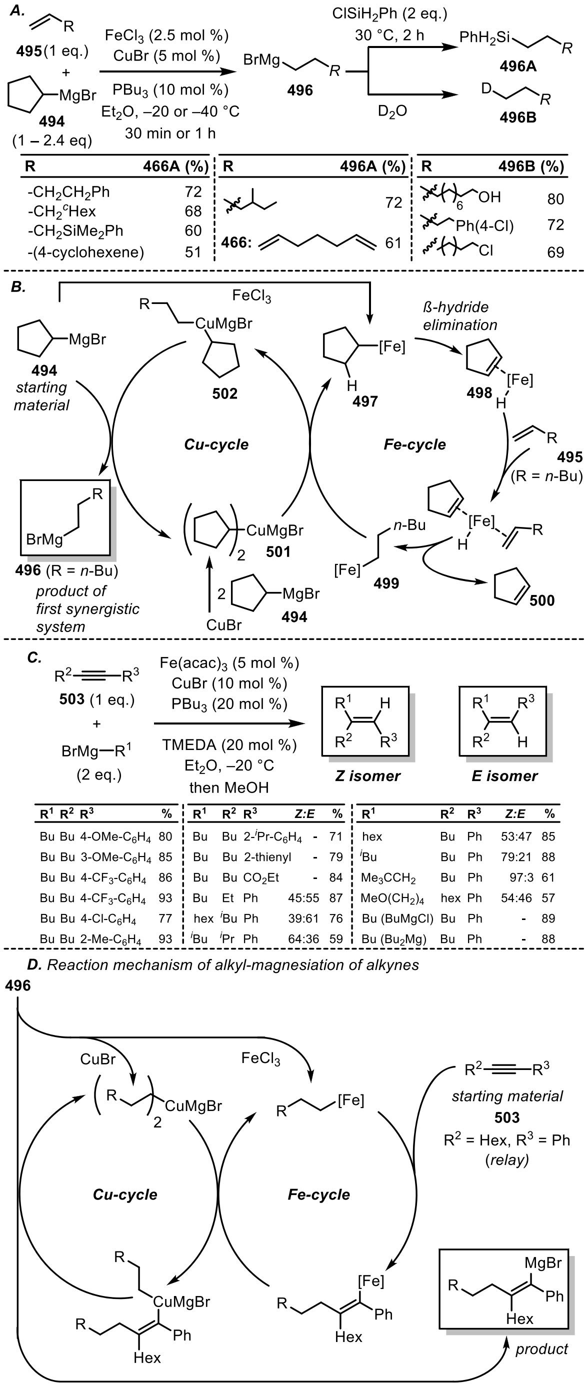
Scheme 68. Synergistic Cu/Fe Dual Catalysis for One-Pot Tandem Grignard-alkene Exchange/Alkyl-magnesiation Reaction



16.1.4. Exchange Reaction between Donor Grignard Reagent and Terminal Olefins.

Using cyclopentylmagnesium bromide **494** as secondary Grignard reagent/Mg donor, the reaction between it and terminal olefin **495** under synergistic Cu/Fe dual catalysis afforded corresponding primary alkyl-Grignard reagent **496** in good yield, which was quantified by quenching the Grignard products with $ClSiH_2Ph$ or D_2O (Scheme 69).

Scheme 69. Exchange Reaction with Alkenes and Alkyl-Magnesiation of Alkynes under Cu/Fe Catalysis



R	466A (%)
$-CH_2CH_2Ph$	72
$-CH_2{}^cHex$	68
$-CH_2SiMe_2Ph$	60
-(4-cyclohexene)	51

R^1	R^2	R^3	%
Bu	Bu	4-OMe-C_6H_4	80
Bu	Bu	3-OMe-C_6H_4	85
Bu	Bu	4-CF_3-C_6H_4	86
Bu	Bu	4-CF_3-C_6H_4	93
Bu	Bu	4-Cl-C_6H_4	77
Bu	Bu	2-Me-C_6H_4	93

R^1	R^2	R^3	*Z:E*	%
Bu	Bu	2-^{i}Pr-C_6H_4	-	71
Bu	Bu	2-thienyl	-	79
Bu	Bu	CO_2Et	-	84
Bu	Et	Ph	45:55	87
hex	^{i}Bu	Ph	39:61	76
^{i}Bu	^{i}Pr	Ph	64:36	59

R^1	R^2	R^3	*Z:E*	%
hex	Bu	Ph	53:47	85
^{i}Bu	Bu	Ph	79:21	88
Me_3CCH_2	Bu	Ph	97:3	61
$MeO(CH_2)_4$	hex	Ph	54:46	57
Bu (BuMgCl)	Bu	Ph	-	89
Bu (Bu_2Mg)	Bu	Ph	-	88

It is striking that in this reaction, the presence of otherwise Grignard-incompatible functional groups such as alkyl/aryl halides and alcohols are tolerated. With the regards to the mechanism, the authors considered that secondary alkyl-iron species could be derived from a reaction between a donor Mg-compound such as **493** and $FeCl_3$, which would then intercepted by a different terminal alkene introduced into the reaction. Thus, the previously reported intramolecular isomerization process would be made into an intermolecular one. The details are as follows (Scheme 69B): Donor Grignard reagent **494** is treated with $FeCl_3$ to form secondary alkyl-iron **497**. Subsequent *β*-hydride elimination forms transient, iron-coordinated disubstituted olefin **498**. Interaction of **498** with the newly introduced, monosubstituted terminal olefin **495** leads to the hydrometalation of the terminal olefin to afford more stable alkyl iron **499** as the catalytically activated species, with the accompanying extrusion of cyclopentene **508**. Alkyl iron **499**, the first catalytically activated species, then undergoes synergistic catalysis with the Cu cycle (as described previously and below). In brief, copper catalyst reacts with Grignard reagent **494** to afford alkyl copper **501** as the second catalytically active species. Transmetalation between alkyl copper **501** and

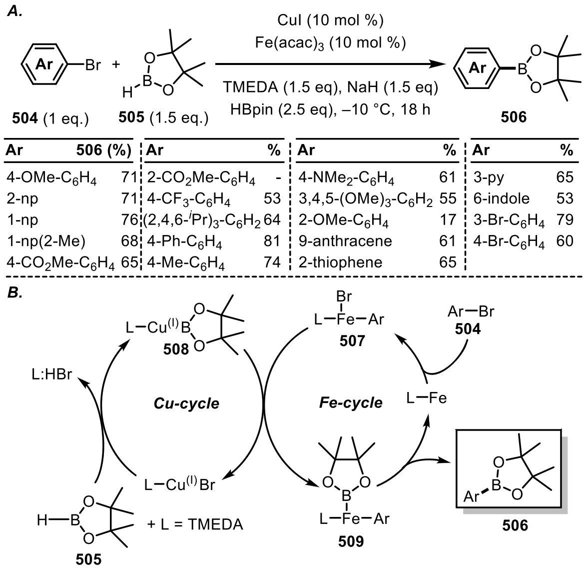
499 leads to copper complex **502**, which undergoes further transmetalation with the Grignard reagent to afford desired 1° alkyl Grignard reagent **496**.

16.1.5. Tandem Alkyl Magnesiation of Alkynes. To enable a tandem alkyl magnesiation reaction after preparation of primary alkyl-Grignard reagent, the exchange reaction detailed above is allowed to run for 10 min before alkyne **503** is introduced. This enables chemistry disclosed in the previous report (Scheme 66) to take place; the addition of the Grignard reagent across the alkyne (Scheme 69C). The mechanistic details (Scheme 69D) are the same as given in Scheme 66B (*vide supra*). In the current report, it is remarkable that no additional changes other than the introduction of the alkyne reagent into the reaction pot is able to effect the exchange reaction, illustrating the perfect compatibility between these two catalytic systems. In all, it was shown that two distinct synergistic catalysis can be run in a relay manner utilizing a single pair of transition metal catalysts in a single pot.

16.2. Miscellaneous Synergistic Cu/Fe Dual Catalysis

16.2.1. Boration of Aryl Bromides with Pinacolborane. Cyclic arylboronic esters can be prepared *via* Cu-catalyzed boration of aryl iodides with pinacolborane (HBpin) at room temperature.[220] However, use of aryl bromides require expensive Pd catalysts and higher reaction temperatures.[221] To overcome this limitation, Chavant and co-workers disclosed Fe/Cu-catalyzed boration reaction of aryl bromide **504** with pinacolborane **505**, yielding cyclic boronic ester **506** under exceptionally mild conditions, which even allowed for the selective monoboration of substrates such as *m*- and *p*-dibromobenzene (Scheme 70).[216]

Scheme 70. Synergistic Cu/Fe Dual Catalysis for Boration of Aryl Bromides with Pinacolborane

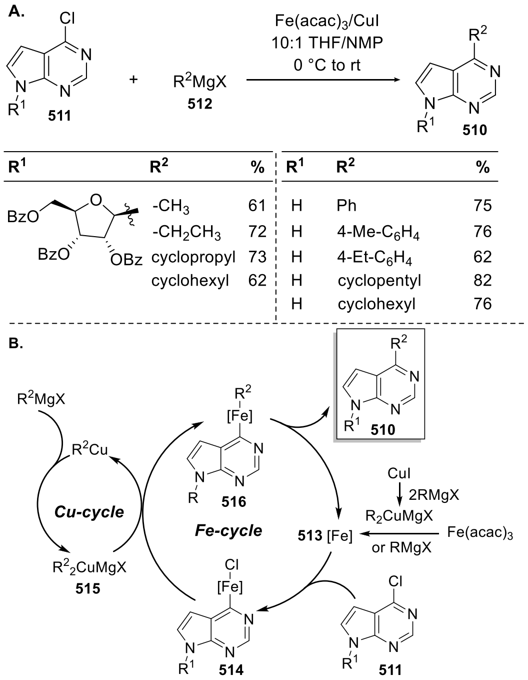


Ar	506 (%)	Ar	%	Ar	%	Ar	%
4-OMe-C_6H_4	71	2-CO_2Me-C_6H_4	-	4-NMe_2-C_6H_4	61	3-py	65
2-np	71	4-CF_3-C_6H_4	53	3,4,5-$(OMe)_3$-C_6H_2	55	6-indole	53
1-np	76	(2,4,6-^{i}Pr)$_3$-C_6H_2	64	2-OMe-C_6H_4	17	3-Br-C_6H_4	79
1-np(2-Me)	68	4-Ph-C_6H_4	81	9-anthracene	61	4-Br-C_6H_4	60
4-CO_2Me-C_6H_4	65	4-Me-C_6H_4	74	2-thiophene	65		

Mechanistically, the authors proposed a low-valent Fe, generated by reduction of Fe(acac)$_3$ with HBpin, inserting into aryl-bromide bond of **504** results in formation of catalytically activated Fe complex **507** (Scheme 70B). Meanwhile, the interaction between Cu catalyst and HBpin **505** in the presence of strong base leads to the deprotonation of HBpin followed by the attack of the boron onto the Cu center generating boryl-copper intermediate **508**. Transmetalation between **507** and **508** results in the regeneration of Cu catalyst along with the formation of Fe complex **509**, which following reductive elimination affords the desired product **506** with regeneration of the Fe catalyst.

16.2.2. Synthesis of 6-Substituted 7-Deazapurines and the Corresponding Nucleosides. Purine nucleoside derivative, 6-substituted 7-deazapurines are classically prepared from its aryl halide precursors *via* Suzuki–Miyaura cross-coupling reaction with boronic acids under Pd (or Ni) catalysis. These metals in trace amounts however, compromise vital antiviral or antitumoral activity which are associated with nucleoside derivatives of purine bases. Herdewijn and co-workers therefore envisioned a cross-coupling process utilizing nontoxic and cheap Cu/Fe catalysts to prepare 6-chloro-7-deazapurines and its ribonucleosides **510** *via* reaction of aryl halides **511** with Grignard reagent **512**, reasoning erroneous biological data due to trace Pd or Ni contamination can then be avoided (Scheme 71).[217] In the reported reaction mechanism, starting 6-chloro-7-deazapurine **511** undergoes oxidative addition into low-valent Fe species **513** to form alkenyliron species **514**. Transmetalation with organocopper **515** forms diorganointermediate **516**, which upon reductive elimination, affords the desired product **510** and regeneration of the low-valent iron species. The authors screened selected 6-substituted 7-deazapurine nucelosides against various cancer cell lines, where some compounds displayed up to deca-nanomolar cell proliferation inhibitory activity.

Scheme 71. Synergistic Cu/Fe Dual Catalysis for C-6 Alkylation of 6-Chloro-7-deazapurines



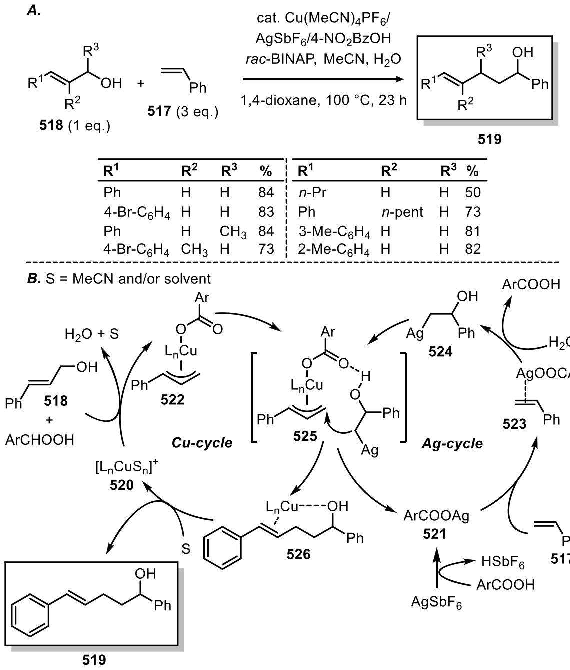
R^1	R^2	%	R^1	R^2	%
	-CH_3	61	H	Ph	75
	-CH_2CH_3	72	H	4-Me-C_6H_4	76
	cyclopropyl	73	H	4-Et-C_6H_4	62
	cyclohexyl	62	H	cyclopentyl	82
			H	cyclohexyl	76

17. SYNERGISTIC Cu/Ag DUAL CATALYSIS

17.1. Carbohydroxylation of Arylalkenes with Allylic Alcohols

Use of two different coinage metals to accomplish synergistic catalysis is highly attractive as they are relatively inexpensive and abundant. Recently, Bao and co-workers reported direct carbohydroxylation of aryl alkenes **517** with allylic alcohol **518**, adding an olefin and a hydroxyl moiety across the double bond (Scheme 72).[222] This unprecedented transformation was realized through Cu/Ag synergistic catalysis, which to our knowledge is notably rare in the scientific literature. The reaction yields synthetically useful 4,5-unsaturated alcohol **519** in good yields. Because of the nature of the metal catalysts, the reaction tolerates presence of Cl, Br, and functional groups such as carbonyl and chloromethyl. The authors propose the following reaction mechanism (Scheme 72B): first, the active Cu catalytic species $[L_nCu(I)S_n]^+$ **520** and active Ag catalytic species [ArCOOAg] **521** is generated from precatalysts $Cu(MeCN)_4PF_6$ and $AgSbF_6$, respectively. The reaction of Cu catalyst **520** with allylic alcohol **518** in the presence of Bronsted acid yields η^3-allyl copper(III) carboxylate **522** as the catalytically active species. In the silver cycle, **521** coordinates to arylalkene **517** to give intermediate **523**, which undergoes hydration reaction to furnish catalytically active silver species **524**. Key intermolecular hydrogen-bond interaction between **522** and **524** gives rise to intermediate **525**, which undergoes intramolecular nucleophilic substitution-like reaction to give Cu complex **526** with the newly forged C−C and C−O bond. Final ligand exchange regenerates the Cu catalyst while yielding the desired 4,5-unsaturated alcohol **519**. The prepared 4,5-unsaturated alcohols can potentially be utilized as synthons to access heterocycles such as tetrahydrofurans and tetrahydropyranes.

Scheme 72. Synergistic Cu/Ag Dual Catalysis for Direct Carbohydroxylation of Arylalkenes with Allylic Alcohols



R^1	R^2	R^3	%	R^1	R^2	R^3	%
Ph	H	H	84	*n*-Pr	H	H	50
4-Br-C_6H_4	H	H	83	Ph	*n*-pent	H	73
Ph	H	CH_3	84	3-Me-C_6H_4	H	H	81
4-Br-C_6H_4	CH_3	H	73	2-Me-C_6H_4	H	H	82

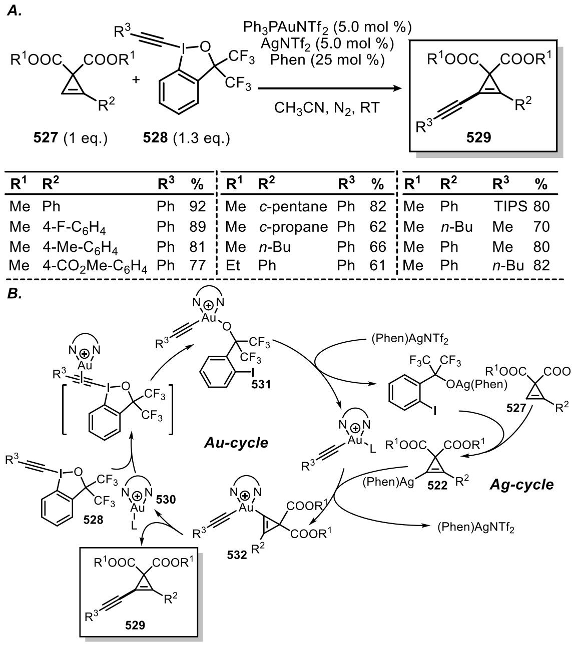
18. SYNERGISTIC Au/Ag DUAL CATALYSIS

The pairing of gold catalysis with silver catalysts can be imagined as silver salts are commonly employed as halogen scavengers in Au(I)/Au(III) catalysis, showing that such gold-based systems at least tolerate the presence of silver. In some cases, Recent studies turned out silver act as a catalyst, achiving synergistic catalytic system.

18.1. Alkynylation of Cyclopropenes

Hashmi and co-workers reported a direct alkynylation of cyclopropene **527**, utilizing alkynyl hypervalent iodine reagent **528** under Au/Ag synergistic catalysis to afford coupled product **529** (Scheme 73).[223]

Scheme 73. Synergistic Au/Ag Dual Catalysis for Alkynylation of Cyclopropenes Using Alkynyl Hypervalent Iodine Reagents



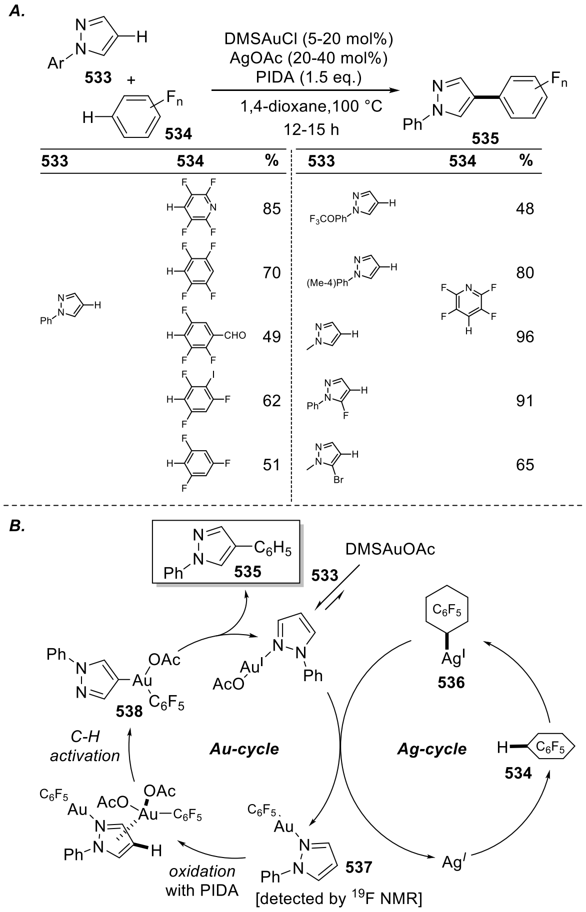
R^1	R^2	R^3	%	R^1	R^2	R^3	%	R^1	R^2	R^3	%
Me	Ph	Ph	92	Me	*c*-pentane	Ph	82	Me	Ph	TIPS	80
Me	4-F-C_6H_4	Ph	89	Me	*c*-propane	Ph	62	Me	*n*-Bu	Me	70
Me	4-Me-C_6H_4	Ph	81	Me	*n*-Bu	Ph	66	Me	Ph	Me	80
Me	4-CO_2Me-C_6H_4	Ph	77	Et	Ph	Ph	61	Me	Ph	*n*-Bu	82

The stated impetus of this work is the rarity of Au/Ag cocatalyzed reactions. In this context, mechanistic studies have been carried out to implicate a clear, Au-bound intermediate alongside an Ag-bound intermediate which undergoes a transmetalation reaction. Reported substrates are restricted to diester containing cyclopropenes. The proposed reaction mechanism is as follows: First, the active gold catalyst **530** undergoes coordination-oxidative addition into hypervalent idodine **528** to afford **531**. Subsequently, the alkoxy anion is transferred onto the silver in a ligand-exchange reaction, which activiates the C−H bond of cyclopropene **527** to afford silver-bound cyclopropene salt **522** as the catalytically active species. Cyclopropene is then transferred onto the gold, yielding **532** and thereby completing the silver catalytic cycle. Final reductive elimination of gold complex **532** affords the alkynated product **529**.

18.2. Dehydrogenative Cross-Coupling Reaction between Pyrazoles and Fluoroarenes

Although pyrazole derivatives find importance in drug discovery, realization of site-selective C−C coupling *via* traditional catalysis is difficult due to highly coordinating ability of the nitrogen atom. Recently, Zhu and co-workers thought to exploit the unique functional group tolerance of gold toward hetroatoms such as nitrogen to realize a highly selective cross-dehydrogenative coupling reaction between pyrazole **533** and fluoroarene **534** to yield cross-coupled product **535**. Critically, it was found that use of Ag(I) cocatalyst was essential in activating the C−H bond of the electron-poor arene (Scheme 74).[224]

Scheme 74. Synergistic Au/Ag Dual Catalysis for Dehydrogenative Cross-Coupling



As shown in Scheme 74B, silver salts are used to catalyze the activation of the most acidic C−H bond of the fluoroarene **534** *via* silver-promoted, concerted metalation−deprotonation mechanism, selectively furnishing Ag−Ar^{Fn} species **536**. Transmetalation between **536** and [AcOAu-pyrazole] then takes place, affording Ar^{Fn}-Au(I) intermediate **537** (detected by ^{19}F NMR) and completing the silver catalytic cycle. Ar^{Fn}-Au(I) **537** is oxidized by PIDA to form Ar^{Fn}-Au(III) intermediate, which then activates C−H bond of *N*-phenylpyrazole, furnishing Ar^{Fn}-Au(III)-Ar complex **538**. Subsequent reductive elimination completes the gold catalytic cycle and produces the desired biaryl product **535**.

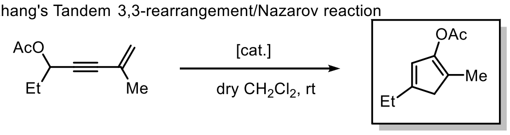
18.3. Synergistic Au/Ag Dual Catalysis Previously Thought to Be Operating under Monocatalysis

Traditionally, it was often thought that use of silver salts in gold catalysis was required to generate the active [L-Au]$^+$ species from [L-AuCl]. The side product AgCl was thought as an innocent bystander.

Shi and co-workers however removed the AgCl "side product" from reaction mixtures operating under Au catalysis and showed that without the silver species, the reactions are often disadvantaged or severely retarded.[225] The authors therefore suggest that many of the reaction mechanisms involving homogeneous gold(I) catalysis should be revised to include actions of silver. In this provocative report, four previously reported monocatalytic Au catalysis are shown to be operating under Au/Ag "bimetallic catalysis" (termed synergistic catalysis in this review), although the exact nature of the intermediates or metal complexes are not proposed (Scheme 75). In all cases, the synergistic nature of Au/Ag dual catalysis was validated experimentally by carefully removing either the Au or Ag species and showing that without the copresence of both species, the reaction fails to take place in its entirety, which is contrary to the original mechanistic hypothesis put forward with the reported reactions. The reactions reviewed which undergoes a form of Au/Ag catalysis are Zhang's cyclopentenone synthesis (Scheme 75A),[225,226] Toste's cyclopentene synthesis (Scheme 75B),[225,227] Toste's olefin cyclopropanation (Scheme 75C),[225,228] Toste's 1,5-enyne isomerization into bicyclo[3.1.0]hexanes (Scheme 75D).[225,229] This report serves to highlight not only the power of synergistic catalysis but also the importance of being prudent and unassuming when elucidating catalytic cycles and reaction mechanisms of novel systems.

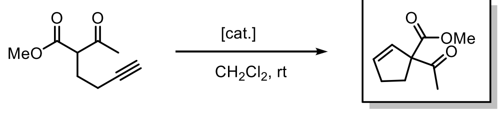
Scheme 75. Synergistic Au/Ag Dual Catalysis for Reactions Previously Considered to Be Operating under Au Monocatalysis

A. Zhang's Tandem 3,3-rearrangement/Nazarov reaction



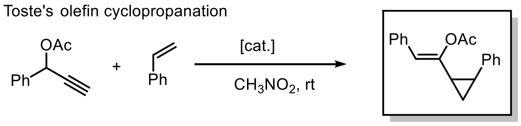
	only gold	only silver	gold + silver	
cat.	1% $[PPh_3Au]^+\cdot SbF_6^-$	5% $AgSbF_6$	1% $PPh_3AuCl/AgSbF_6$	1% $[PPh_3Au]^+\cdot SbF_6^-$ + 1% $AgSbF_6$
yield	24 h, 0%	24 h, 0%	0.5 h, 74%	4 h, 64%

B. Toste's 5-*endo-dig* carbocyclization of acetylenic dicarbonyl compounds



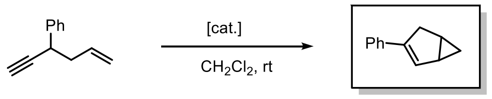
	only gold	only silver	gold + silver	
cat.	1% $[PPh_3Au]^+\cdot SbF_6^-$	5% $AgSbF_6$	1% $PPh_3AuCl/AgSbF_6$	1% $[PPh_3Au]^+\cdot SbF_6^-$ + 1% $AgSbF_6$
yield	24 h, 0%	24 h, 0%	0.5 h, 88%	4 h, 73%

C. Toste's olefin cyclopropanation



	only gold	only silver	gold + silver	
cat.	5% $[PPh_3Au]^+\cdot SbF_6^-$	10% $AgSbF_6$	5% $PPh_3AuCl/AgSbF_6$	5% $[PPh_3Au]^+\cdot SbF_6^-$ + 5% $AgSbF_6$
yield	24 h, 0%	24 h, 0%	0.5 h, 67%	4 h, 65%

D. Toste's Isomerization of 1,5-Enyne into Bicyclo[3.1.0]hexenes



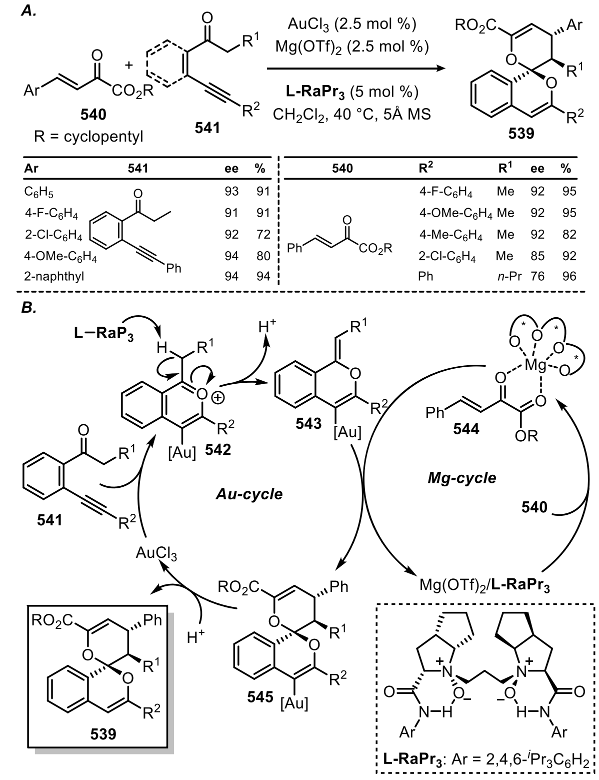
	only gold	only silver	gold + silver	
cat.	1% $[PPh_3Au]^+\cdot BF_4^-$	5% $AgBF_4$	1% $PPh_3AuCl/AgBF_4$	1% $[PPh_3Au]^+\cdot SbF_6^-$ + 1% $AgBF_4$
yield	4 h, 0%	4 h, 0%	10 min, 95%	30 min, 92%

19. SYNERGISTIC Au/Mg DUAL CATALYSIS

19.1. Asymmetric Synthesis of 6,6-Spiroketals

6,6-Spiroketal is an important motif commonly found in natural products.[230,231] It is also considered a "privileged scaffold" in medicinal chemistry.[232] Despite its importance, until recently there were limited methods known for enantioselective construction of the spirocenter found in sprioketals, which at this time are (a) use of chiral acids in cyclization of diol containing ketones[233] or (b) use of chiral iridium complexes from allylic-containing alcohols.[234] Recently, Feng and co-workers disclosed Au/Mg synergistic catalysis for enantioselective synthesis of 6,6-spiroketal **539** from β,γ-unsaturated α-ketoester **540** and β-alkynyl ketone **541**. This reaction hinged on the intermolecular, asymmetric [4 + 2] cycloaddition between achiral gold-containing dienophile and chiral N,N'-dioxide-Mg^{II} complex, which enables excellent asymmetric induction (Scheme 76).[235] In the proposed reaction mechanism, β-alkynyl ketone **541** first undergoes Au^{III} mediated 6-*endo-dig* oxo-cyclization to afford Au-containing carbonyl ylide **542**, which undergoes deprotonation to generate gold-bound alkene **543**. Meanwhile, α-ketoester **540** undergoes complexation with chiral Mg(OTf)$_2$/L-RaPr$_3$ to afford second catalytically activated species **544**. Subsequent [4 + 2] cycloaddition and affords gold-bound spiroketal intermediate **545**, which upon final protonation furnishes desired product **539**. A slightly different reaction mechanism involving [4 + 2] cycloaddition between enol derived from Au-activiated alkyne and **544** followed by intramolecular cycloisomerization was also proposed by the authors.

Scheme 76. Synergistic Au/Mg Dual Catalysis for Asymmetric Synthesis of 6,6-Spiroketals



Ar	541	ee	%
C_6H_5		93	91
4-F-C_6H_4		91	91
2-Cl-C_6H_4		92	72
4-OMe-C_6H_4		94	80
2-naphthyl		94	94

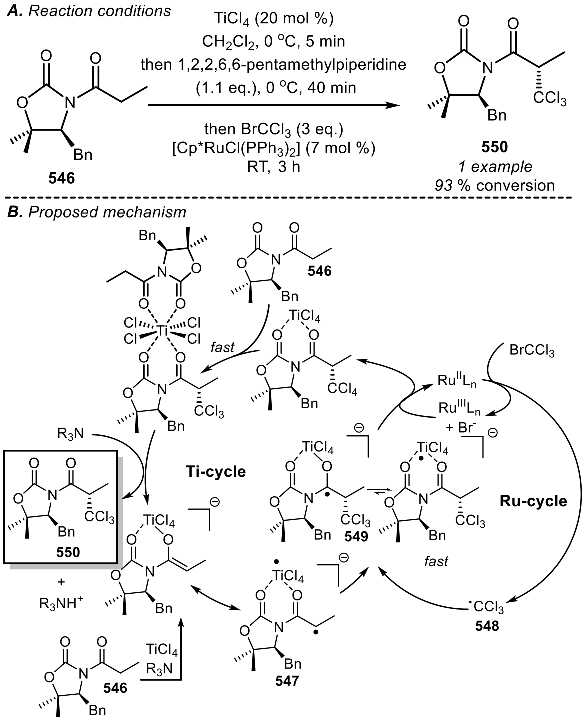
540	R^2	R^1	ee	%
	4-F-C_6H_4	Me	92	95
	4-OMe-C_6H_4	Me	92	95
	4-Me-C_6H_4	Me	92	82
	2-Cl-C_6H_4	Me	85	92
	Ph	*n*-Pr	76	96

20. SYNERGISTIC Ti/Ru DUAL CATALYSIS

20.1. Trichloromethylation of *N*-Acyl Oxazolidinones

Zakarian and co-workers developed stereoselective trichloromethylation of titanium oxazolidinone enolates using trichloromethyl radicals generated by a ruthenium catalyst (Scheme 77).[236] Traditionally, titanium complexes are preformed stoichiometrically before reaction with an amine base as it was thought that the irreversible formation of an inactive titanium−amine complex must be prevented. Following this reasoning, Zakarian and co-workers established a stoichiometric titanium/catalytic ruthenium process for the successful direct chloroalkylation of titanium enolates and applied this technology in the synthesis of halogenated natural products.[237,238] While performing mechanistic studies on this process, it was discovered that this process could also occur while using substoichiometric quantities of the titanium catalyst.

Scheme 77. Synergistic Ti/Ru Dual Catalysis for Trichloromethylation of *N*-Acyl Oxazolidinones



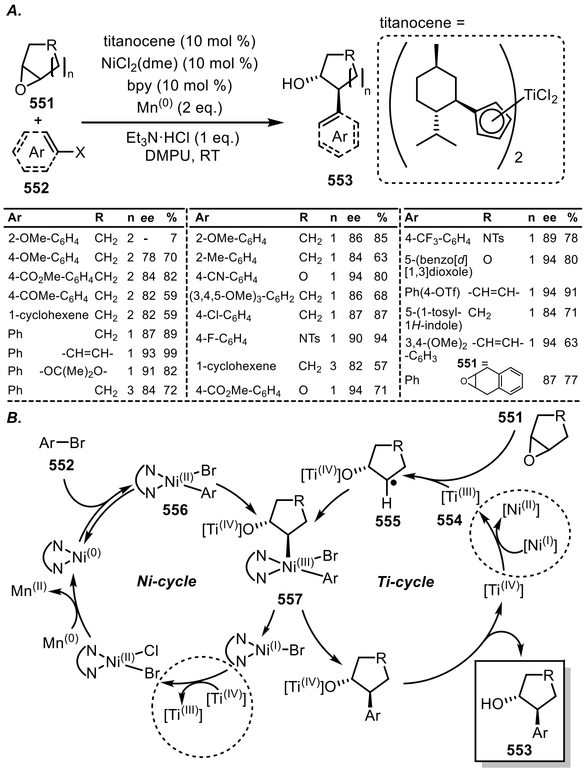
Although NMR studies suggested that the degree of enolization was significantly reduced when using substoichiometric amounts of titanium, the crossover experiments showed that the titanium catalyst could be rapidly exchanged between two different *N*-acyl oxazolidinones, implicating catalyst turnover without the formation of the feared inactivating titanium−amine complex. Additionally, when examining different amine bases, the inhibitory effects of the amine base was observed to be confined to Hünig's base; both sterically less hindered triethylamine and the more sterically hindered 1,2,2,6,6-pentamethylpiperidine (PMP) did not show the presumed inhibitory effect. Further studies where the amine base and the titanium catalyst were deliberately premixed demonstrated that while the titanium−amine complex can decrease the conversion of the reaction, its formation is reversible. As such, following mechanism for this synergistic dual transition metal process was proposed (Scheme 77B). Complexation of the titanium catalyst with *N*-acyl oxazolidinone **546** followed by enolization forms biradical titanium-enolate species **547** as the catalytically activated species. Meanwhile, single electron transfer (SET) from ruthenium(II) catalyst to $BrCCl_3$ provides the trichloromethyl radical **548** as the second catalytically activated species. Radical addition of **548** to titanium enolate **547** furnishes titanium(III) complex **549**. After the rapid transfer of the titanium to another molecule of substrate, single electron transfer between titanium(III) and ruthenium(III) would regenerate the catalysts and liberate trichloromethylated product **550**.

21. SYNERGISTIC Ti/Ni DUAL CATALYSIS

21.1. Asymmetric Ring-Opening Reaction of Epoxides with Aryl Halide Derived Nucleophiles

Building upon their previous work on regiodivergent (racemic) epoxide openings mediated by Ni monocatalysis,[239] Weix and co-workers utilized Ti/Ni dual catalysis for enantioselective ring-opening of *meso*-epoxide **551** with aryl/vinyl halide **552** to form chiral aryl/vinyl alcohol **553** (Scheme 78).[240]

Scheme 78. Synergistic Ti/Ni Dual Catalysis for Preparation of Aryl-epoxide Cross-Coupled Product



Ar	R	n	ee	%
2-OMe-C_6H_4	CH_2	2	-	7
4-OMe-C_6H_4	CH_2	2	78	70
4-CO_2Me-C_6H_4	CH_2	2	84	82
4-COMe-C_6H_4	CH_2	2	82	59
1-cyclohexene	CH_2	2	82	59
Ph	CH_2	1	87	89
Ph	-CH=CH-	1	93	99
Ph	-OC(Me)$_2$O-	1	91	82
Ph	CH_2	3	84	72

Ar	R	n	ee	%
2-OMe-C_6H_4	CH_2	1	86	85
2-Me-C_6H_4	CH_2	1	84	63
4-CN-C_6H_4	O	1	94	80
(3,4,5-OMe)$_3$-C_6H_2	CH_2	1	86	68
4-Cl-C_6H_4	CH_2	1	87	87
4-F-C_6H_4	NTs	1	90	94
1-cyclohexene	CH_2	3	82	57
4-CO_2Me-C_6H_4	O	1	94	71

Ar	R	n	ee	%
4-CF_3-C_6H_4	NTs	1	89	78
5-(benzo[*d*][1,3]dioxole)	O	1	94	80
Ph(4-OTf)	-CH=CH-	1	94	91
5-(1-tosyl-1*H*-indole)	CH_2	1	84	71
3,4-(OMe)$_2$-C_6H_3	-CH=CH-	1	94	63
Ph	551 =		87	77

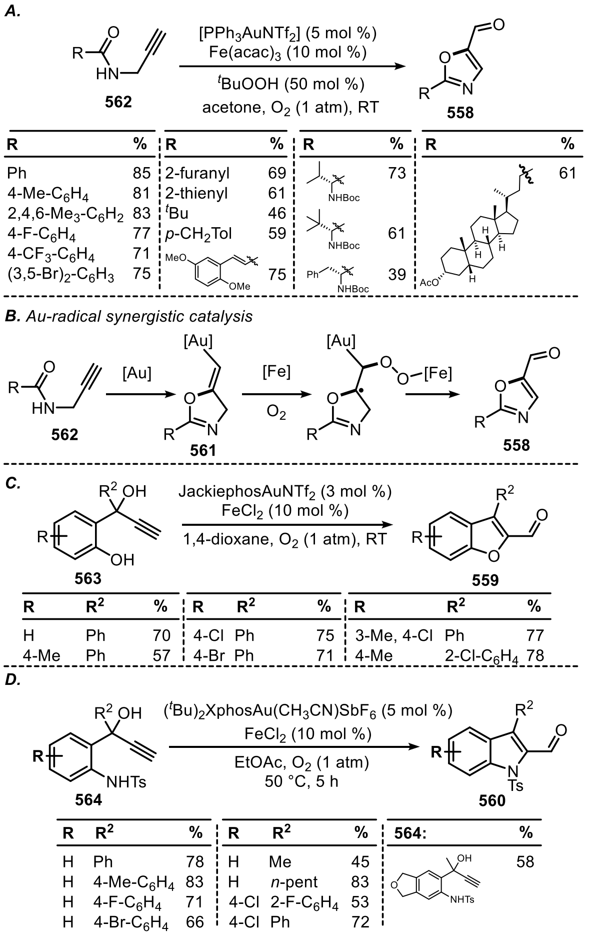
This coupling is facilitated by stoichiometric Mn(0), and unlike typical enantioselective methods for *meso*-epoxide opening which involve harsh conditions and aryl lithium reagents, the title process tolerates a range of sensitive functionalities such as ketals, tosylates, trifluoromethyl groups, aryl chlorides, and nitriles. Vinyl bromides and triflates can also be used to afford cross-coupled products in moderate to good yield. In the proposed mechanism, the two catalysts interact not only to bring together their activated intermediates but also to adjust each other's oxidation state to maintain the catalytic cycle with the manganese, affording the overall reducing environment. The details follow: Initial enantioselective reaction of the Ti(III) catalyst **554** with the epoxide **551** affords *β*-Ti(IV)oxy-carbon radical **555**, which can react with Ar–Ni(II) species **556** derived from oxidative addition of Ni^0 into **552** to form the Ti(IV)oxy-organo-Ni(III) species **557**. Reductive elimination of the nickel and protonolysis of the titanium affords the desired product **553**. Following the reduction of Ti(IV) by Ni(I), and Ni(II) by the manganese, the catalytic cycles can continue.

22. SYNERGISTIC Fe/Au DUAL CATALYSIS

22.1. Preparation of Heterocycles from Propargyl Substrates under Fe/Au Catalysis

Gold complexes are widely known to catalytically activate alkynes. Shi and co-workers utilized Fe/Au catalysis for the synthesis of aldehyde appended oxazoles **558**, benzofurans **559** , and indoles **560** from monosubstituted propargyl substrates (Scheme 79).[241]

Scheme 79. Synergistic Fe/Au Dual Catalysis for Synthesis of Heterocycles with Aldehyde Appendages



R	%	R	%	R	%	R	%
Ph	85	2-furanyl	69		73		61
4-Me-C_6H_4	81	2-thienyl	61				
2,4,6-Me_3-C_6H_2	83	^tBu	46		61		
4-F-C_6H_4	77	*p*-CH_2Tol	59				
4-CF_3-C_6H_4	71						
(3,5-Br)$_2$-C_6H_3	75		75		39		

R	R^2	%	R	R^2	%	R	R^2	%
H	Ph	70	4-Cl	Ph	75	3-Me, 4-Cl	Ph	77
4-Me	Ph	57	4-Br	Ph	71	4-Me	2-Cl-C_6H_4	78

R	R^2	%	R	R^2	%	564:	%
H	Ph	78	H	Me	45		58
H	4-Me-C_6H_4	83	H	*n*-pent	83		
H	4-F-C_6H_4	71	4-Cl	2-F-C_6H_4	53		
H	4-Br-C_6H_4	66	4-Cl	Ph	72		

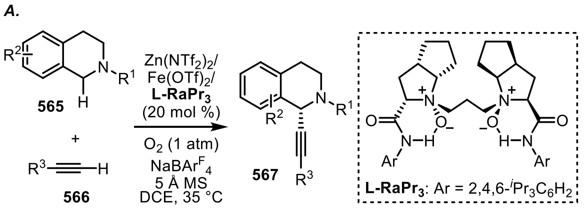
While the exact mechanism for these processes are unknown, experiments using $^{18}O_2$ demonstrated that the gaseous oxygen from the atmosphere is incorporated into the aldehyde, and studies on the reaction kinetics ruled out the possibility of a tandem process, suggesting a synergistic interaction between vinyl gold intermediate **561** and an iron/O_2 radical species. In this manner, various propargyl amides **562** were reacted with oxygen gas to form the desired oxazole aldehydes **558** while releated *ortho*-propargyl phenols **563** furnished benzofurans **559** and *ortho*-propargyl anilines **564** produced indoles **560**.

23. SYNERGISTIC Fe/Zn DUAL CATALYSIS

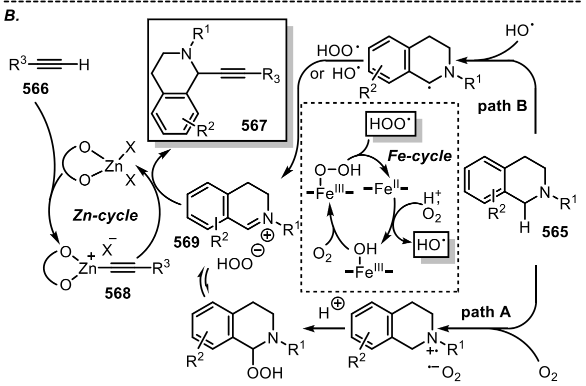
23.1. Asymmetric Cross-Coupling of Tetrahydroisoquinolines with Alkynes

Feng and co-workers developed a Fe(II)/Zn(II) catalyzed aerobic oxidative coupling of tetrahydroisoquinoline **565** with terminal alkyne **566** to afford α-alkynyl substituted chiral tetrahydroisoquinolines **567** (Scheme 80).[242]

Scheme 80. Synergistic Zn/Fe Dual Catalysis for Cross-Coupling of Tetrahydroisoquinolines and Alkynes



R^1	R^2	R^3	*ee*	%	R^1	R^2	R^3	*ee*	%	R^1	R^2	R^3	*ee*	%
PMB	H	Ph	93	70	PMB	H	3-Cl-C_6H_4	99	72	Ph	H	Ph	94	65
PMB	H	4-Cl-C_6H_4	96	74	PMB	H	3-Me-C_6H_4	98	76	4-Me-C_6H_4	H	Ph	95	66
PMB	H	4-Br-C_6H_4	99	73	PMB	H	3-OMe-C_6H_4	93	82	4-Et-C_6H_4	H	Ph	97	63
PMB	H	4-Me-C_6H_4	92	74	PMB	H	3-NO_2-C_6H_4	95	45	4-Ph-C_6H_4	H	Ph	94	60
PMB	H	4-Et-C_6H_4	95	76	PMB	H	3,5-F_2-C_6H_3	88	69	3,4-Me_2-C_6H_3	H	Ph	94	63



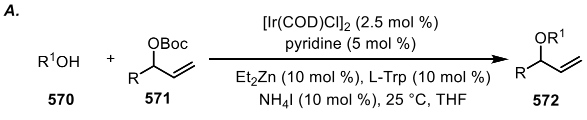
Although previously disclosed Cu-catalyst/O_2 system enabled racemic aerobic oxidative coupling of tetrahydroisoquinolines with select nucleophiles,[243] the acetylene coupling partner proved problematic with Cu(I) or Cu(II) mono- or cocatalysis, resulting in unsatisfactory yields and low asymmetric induction. In synergistic Zn/Fe dual catalytic system shown in Scheme 80B, it was rationalized that selective action of zinc catalyst on deprotonated alkyne **566** could furnish chiral zinc acetylene **568** separate from the Fe-mediated oxidative process. In this context, iron-mediated aerobic oxidation of tetrahydroisoquinoline **565** afforded iminium intermediate **569** through the path A and/or path B. The enantioselective alkynylation of **569** is mediated by the chiral *N*,*N*′-dioxide ligand **L-RaPr₃** on the Zn(II) complex **568**, furnishing the desired α-alkynyl substituted cross-coupled tetrahydroisoquinoline **567** with good asymmetric induction. Further transformations on **567** were demonstrated such as selective reductions of the alkyne bond and deprotection of the *N*-PMB group, showing potential synthetic utility.

24. SYNERGISTIC Ir/Zn DUAL CATALYSIS

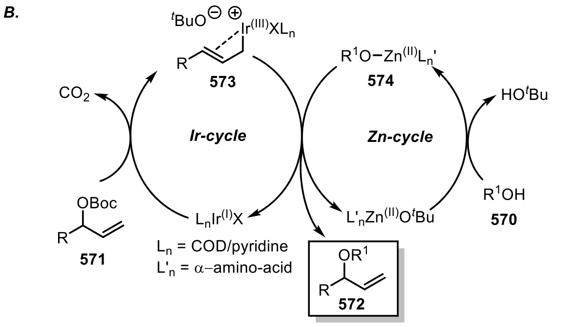
24.1. Allylic Etherification

Iridium catalysis can complement palladium-mediated Tsuji−Trost allylation reaction by offering access to branched regioisomers. Lee and co-workers reported allylic etherification of aliphatic alcohol **570** with allylic carbonate **571** under Ir/Zn catalysis for preparation of allylic ether **572** (Scheme 81).[244] It is notable that, in the absence of Zn(II) and Ir(I) catalysts, these starting materials are normally considered inert to each other. The proposed reaction mechanism is as follows: In the presence of $[Ir(COD)Cl)]_2$ catalyst, the allylic *tert*-butyl carbonate **571** reacts to generate allyl Ir complex **573**, alongside extrusion of carbon dioxide and *tert*-butoxide counteranion. Aliphatic alcohol **570** meanwhile reacts with zinc catalyst to afford zinc alkoxide **574**, the formation of which is driven by a pK_a dependent equilibrium between **570** and zinc *tert*-butoxide. The nucleophilic addition of **574** onto **573** affords the desired product **572**. The *tert*-butoxide counteranion regenerates zinc *tert*-butoxide to return Zn to its catalytic cycle. The poor direct reactivity of zinc *tert*-butoxide toward Ir complex **573** is essential in allowing the desired cross-coupling event to take place. For 1,2-disubstitued allylic carbonates, stoichiometric amounts of the zinc reagent was required, rendering such process monocatalytic. It was found that the use of enantiopure allylic carbonates led to significant scrambling of chirality, indicating a fast enantiofacial interconversion of the iridium intermediate relative to the nucleophilic addition of zinc alkoxide. In contrast to the disappointing stereochemical outcome, the reaction consistently displayed high regioselectivity.

Scheme 81. Synergistic Ir/Zn Dual Catalysis for Allylic Etherification



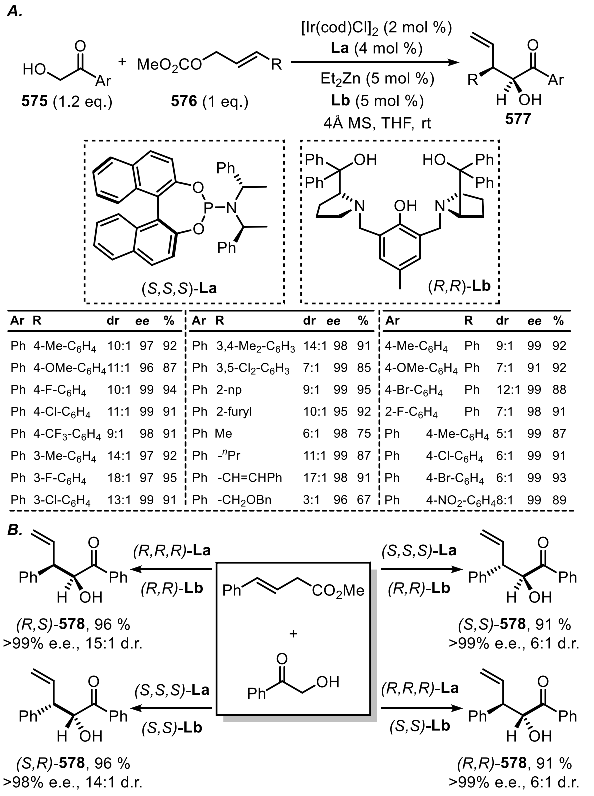
R^1	R	%	R^1	R	%
-CH_2Ph(4-OMe)	*n*-Pr	66	-CH$(Ph)_2$	Ph$(CH_2)_2$-	61
-CH_2Ph(4-NO_2)	*n*-Pr	71	-CH_2COPh	Ph$(CH_2)_2$-	46
-CH_2Ph(4-I)	*n*-C_5H_{11}	81	-CH_2CH(NHCbz)CO_2Me	Ph$(CH_2)_2$-	69
-CH_2Ph(2-Br)	-EtPh	75	2-(2,3-dihydro-1*H*-indene)	Ph	80
-CH_2CH_2TMS	Ph	73	-CH_2CH_2OCO(C)CH_3=CH	Ph	73



24.2. α-Allylation of α-Hydroxyketones

The enantioselective and diastereoselective construction of contiguous stereocenters are as useful as inherently challenging. Zhang and co-workers accomplished α-allylation of unprotected α-hydroxyketone **575** with allyl carbonate **576** to establish two new contiguous stereocenters of allylated **577** in a single step with high enantio- and diastereoselectivities, enabling access to all four possible stereoisomers (Scheme 82).[245] Mechanistically, chiral iridium complex prepared derived from $[Ir(cod)Cl]_2$ and the optically active phosphoramidite ligand **La** undergoes oxidative addition into allylic carbonate **576** to generate catalytically activated π-allyl Ir-complex, which independently sets the absolute configuration of C(2) stereocenter in **577**.[246] The second catalytically activated species is formed from the reaction of α-hydroxyketone **575** with the chiral zinc complex derived from Et_2Zn and chiral ligand **Lb**,[247] which avails itself as a zinc enolate, setting the stereogenic configuration at the C(3) position. Subsequent allylation of the zinc enolate with the aforementioned electrophilic π-allyl Ir-complex affords α-hydroxyketone **577** and regeneration of the catalysts. The

Scheme 82. Synergistic Ir/Zn Dual Catalysis for Allylic Alkylation of *α*-Hydroxyketones



Ar	R	dr	ee	%	Ar	R	dr	ee	%	Ar	R	dr	ee	%
Ph	4-Me-C_6H_4	10:1	97	92	Ph	3,4-Me_2-C_6H_3	14:1	98	91	4-Me-C_6H_4	Ph	9:1	99	92
Ph	4-OMe-C_6H_4	11:1	96	87	Ph	3,5-Cl_2-C_6H_3	7:1	99	85	4-OMe-C_6H_4	Ph	7:1	91	92
Ph	4-F-C_6H_4	10:1	99	94	Ph	2-np	9:1	99	95	4-Br-C_6H_4	Ph	12:1	99	88
Ph	4-Cl-C_6H_4	11:1	99	91	Ph	2-furyl	10:1	95	92	2-F-C_6H_4	Ph	7:1	98	91
Ph	4-CF_3-C_6H_4	9:1	98	91	Ph	Me	6:1	98	75	Ph	4-Me-C_6H_4	5:1	99	87
Ph	3-Me-C_6H_4	14:1	97	92	Ph	-^{n}Pr	11:1	99	87	Ph	4-Cl-C_6H_4	6:1	99	91
Ph	3-F-C_6H_4	18:1	97	95	Ph	-CH=CHPh	17:1	98	91	Ph	4-Br-C_6H_4	6:1	99	93
Ph	3-Cl-C_6H_4	13:1	99	91	Ph	-CH_2OBn	3:1	96	67	Ph	4-NO_2-C_6H_4	8:1	99	89

authors highlighted their work by showcasing a selective synthesis of all four possible diastereoisomers of 2-hydroxy-1,3-diphenylpent-4-en-1-one **578** through systematically varying the chirality of ligands (Scheme 82B).

Recently, the same group effected similar allylation mediated by synergistic Ir/Zn dual catalysts upon unprotected *α*-hydroxy indanones, with similar mechanistic considerations.[248] By effectively installing two stereocenters independently from two distinctive, catalytically activated chiral species, an exceedingly powerful exploitation of dual transition metal synergistic catalysis have been demonstrated to effect asymmetric synthesis.

25. SYNERGISTIC Ag/Sc DUAL CATALYSIS

Recently, Jiang and co-workers reported reaction between *β*-alkynyl ketone **579** and various reaction partners such as *o*-hydroxybenzyl alcohol **580**,[249] *p*-quinone methide **581**, and quinone imine ketal **582** under synergistic Ag/Sc dual catalysis to effect different cyclization cascades,[250] selectively affording five different end products (Scheme 83 and Scheme 84). In the first instance, *β*-alkynyl ketone **579** was treated with *o*-hydroxybenzyl alcohol **580** in the presence of AgTFA and Sc(OTf)$_3$ at 50 °C to afford 6,6-benzannulated spiroketals **583**, a motif found in a wide class of natural products (Scheme 83).[251] As shown in Scheme 83B, it was proposed that *o*-hydroxybenzyl alcohol **580** undergoes a dehydration reaction in the presence of [Sc] catalyst to afford *o*-quinone methine intermediate **584**. Meanwhile, *o*-alkynylated ketone **579** undergoes [Ag]-catalyzed 6-*endo-dig* cyclization to yield silver species **585**, which upon proton transfer and release of the silver catalyst affords isochromene intermediate **586**. A [4 + 2] cycloaddition between **584** and **586** furnishes 6,6-benzannulated spiroketals **583**. It was recognized that spiroketal product **583** could undergo a second [4 + 2] cycloaddition with **584** to furnish the polycyclic compound **587**. To effect this transformation, an excessive amount of starting *o*-hydroxybenzyl alcohol **580** was used and reaction temperature of the reaction was elevated to 80 °C. This facilitated the second [4 + 2] process with intermediate **584** to afford a wide range of end products represented by **587**. Meanwhile, in the aforementioned reaction between **579** and **580**, it was unexpectedly found that increased catalyst loading of [Sc] to 20 mol % and elevated reaction temperature of 100 °C led to formation of benzo[*c*]xanthenes **588**. Under these reaction conditions, a wide range of benzo[*c*]xanthenes were prepared in good yield. Under the modified reaction conditions, a different synergistic Ag/Sc catalysis on starting *o*-alkynylated ketone **579** was enabled to effect a 6-*endo-dig* cyclization affording intermediate **589**. Further proton-transfer and tautomerization yields key intermediate **590**, which undergo [4 + 2] cycloaddition with the intermediate **584**, followed by dehydration to afford polycyclic **588**.

The authors postulated that intercepting intermediate **590** with *p*-quinone methides **581** and quinone imine **582** would furnish benzo[*c*]xanthenes **591** and naphtho[1,2-*b*]benzofurans **592**, respectively (Scheme 84).[250] From aforementioned intermediate **590** prepared from synergistic Ag/Sc dual catalysis, [Sc]-catalyzed 1,6-addition of **581** yields intermediate **593**. Subsequent proton transfer and intramolecular oxo-nucleophilic addition affords **594**. Final deprotonation and dehydration sequence yields benzo[*c*]xanthenes **591**. For preparation of naphtho[1,2-*b*]benzofurans **592**, similar mechanistic considerations are in effect. [Sc]-catalyzed 1,4-addition of key intermediate **590** onto quinone imine **582** affords intermediate **595**. Subsequent proton-transfer yields species **596**, which undergoes *oxo*-cyclization followed by dehydration and disassociation of [Sc] to afford desired product **592**.

26. SYNERGISTIC Ni/Co DUAL CATALYSIS

Unlike in examples of Ni/Pd catalysis described above, Ni/Co catalysis give witness to Ni(I) and Ni(III) species and modes of reactions mediated by radical chemistry.

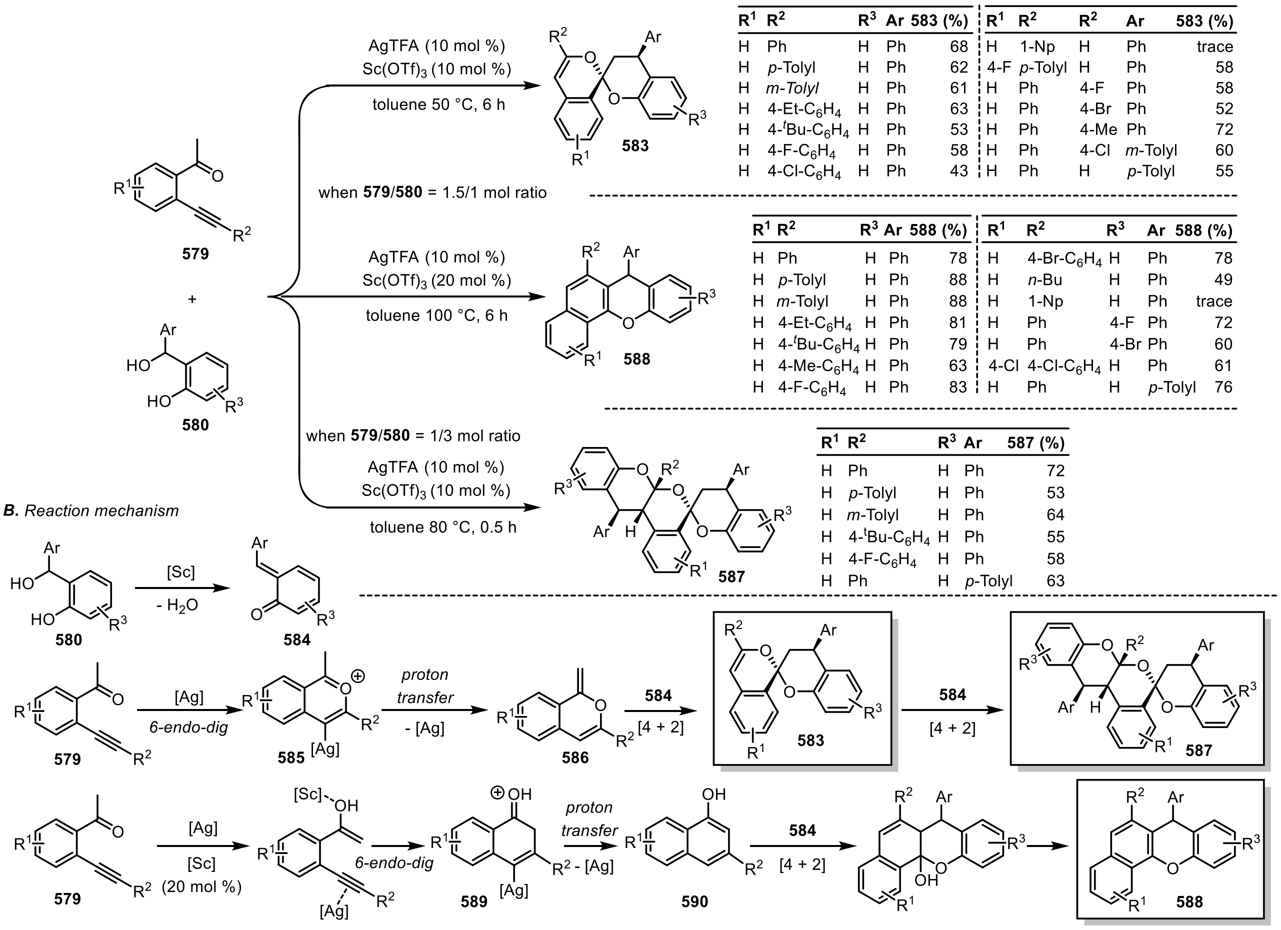
26.1. Hydroarylation of Olefins Using Iodoarenes

In 2016, Shenvi and co-workers disclosed a Markovnikov-selective hydroarylation of terminal olefin **597** using iodoarenes **598** under Ni/Co dual catalysis to yield branch-selective cross-coupled product **599** (Scheme 85).[252] Although the reaction was designed with the rationale to create a carbon centered radical which was to be captured with an catalytically generated organonickel species, further mechanistic studies clarified that while an alkyl radical is generated from the olefin **597**, it is likely recaptured by the cobalt to form a cobalt intermediate **600**, which then reacts with the nickel intermediate **601** in a transmetalation process to furnish **602**, giving rise to an unambiguously conventional synergistic catalysis (Scheme 85B).[253]

The reaction readily tolerated presence of thiophenes and sulfides, which are functional moieties with the potential to arrest other types of metal catalysis typically seen in cross-coupling reactions. The authors do show that hydroalkylation is also possible when using iodopentane in place of iodoarenes, although the yield is poor. Later, a more effective hydroalkylation procedure was disclosed by the authors, which relied on Ni/Mn dual catalysis (*vide supra*).[254] A limitation of this study was that only monosubstituted terminal olefins were tolerated due to disubstituted olefins readily undergoing

Scheme 83

A. Reaction conditions and substrate scope for preparation of 6,6-benzannulated spiroketals **583**, *hexacyclic spiroketals* **587**, *and benzo[c]xanthenes* **588**.



R^1	R^2	R^3	Ar	583 (%)
H	Ph	H	Ph	68
H	*p*-Tolyl	H	Ph	62
H	*m-Tolyl*	H	Ph	61
H	4-Et-C_6H_4	H	Ph	63
H	4-^{t}Bu-C_6H_4	H	Ph	53
H	4-F-C_6H_4	H	Ph	58
H	4-Cl-C_6H_4	H	Ph	43
H	1-Np	H	Ph	trace
4-F	*p*-Tolyl	H	Ph	58
H	Ph	4-F	Ph	58
H	Ph	4-Br	Ph	52
H	Ph	4-Me	Ph	72
H	Ph	4-Cl	*m*-Tolyl	60
H	Ph	H	*p*-Tolyl	55

R^1	R^2	R^3	Ar	588 (%)
H	Ph	H	Ph	78
H	*p*-Tolyl	H	Ph	88
H	*m*-Tolyl	H	Ph	88
H	4-Et-C_6H_4	H	Ph	81
H	4-^{t}Bu-C_6H_4	H	Ph	79
H	4-Me-C_6H_4	H	Ph	63
H	4-F-C_6H_4	H	Ph	83
H	4-Br-C_6H_4	H	Ph	78
H	*n*-Bu	H	Ph	49
H	1-Np	H	Ph	trace
H	Ph	4-F	Ph	72
H	Ph	4-Br	Ph	60
4-Cl	4-Cl-C_6H_4	H	Ph	61
H	Ph	H	*p*-Tolyl	76

R^1	R^2	R^3	Ar	587 (%)
H	Ph	H	Ph	72
H	*p*-Tolyl	H	Ph	53
H	*m*-Tolyl	H	Ph	64
H	4-^{t}Bu-C_6H_4	H	Ph	55
H	4-F-C_6H_4	H	Ph	58
H	Ph	H	*p*-Tolyl	63

B. Reaction mechanism

unproductive allylic isomerization of the olefin. The authors rectified this shortcoming by disclosing a Fe/Ni dual catalysis strategy for hydroarylations of disubstituted olefins (*vide infra*).[255]

26.2. C(sp^3)−C(sp^3) Cross-Coupling Reactions of Alkyl halides and Alkyl Tosylates

Given the ubiquitous and prevalent nature of C(sp^3)−C(sp^3) linkages in organic molecules, many methods have been developed to forge such bonds, which traditionally involved organometallic reagents and monotransition metal catalysis.[256] Recently, modern methodologies such as C−H activation,[257] metallaphotoredox catalysis,[258] and creative use of radical chemistry have also been reported.[259] In this context, Osaka, Komeyama, and co-workers disclosed Ni/Co synergistic catalysis to react alkyl halides **603** with alkyl tosylates **604** to produce cross-coupled products **605** in the presence of a Mn reductant[260] (Scheme 86).

Although exact and detailed mechanism for the transformation are unknown, the following mechanism is proposed by the authors (Scheme 86B). First, the cobalt catalyst is derived from reduction of vitamin B_{12}, yielding a highly nucleophilic planar-cobalt species **606**, which activates tosylate in an S_N2-type oxidative addition reaction to give alkyl-[Co] intermediate **607**. Meanwhile, [Ni^I]-X catalyst is reduced by Mn to furnish zerovalent Ni species **608**. Transmetalation between **608** and **607** is triggered by a SET event from Ni to Co, which further leads to spontaneous cleavage of the Co−C bond and generation of the alkyl radical, which is captured by ther Ni, affording alkyl-[Ni^{II}] **609**. Reduction of it by Mn affords alkyl-[Ni^I] intermediate **610**, and subsequent oxidative addition into alkyl halide **603** affords dialkyl-[Ni^{III}] **611**. Final rapid reductive elimination event forms cross-coupled product **605** and regeneration of the [Ni^I]-X catalyst **612**. Combination of halide and tosylate reaction partners were found to be essential compared to utilizing different halides such as bromide and a chloride, as in such cases homocoupling reaction were prevalent.

27. SYNERGISTIC Ni/Fe DUAL CATALYSIS

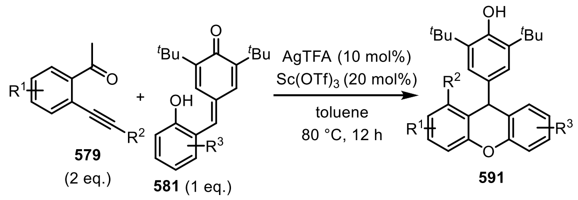
27.1. Hydroarylation of Alkenes

Extending the previously disclosed Ni/Co mediated hydroarylation of monosubstituted terminal olefins, the authors recently disclosed novel Ni/Fe dual catalysis to effect hydroarylation on trisubstituted and nonterminal olefins **613** with aryl iodide **614** to furnish arylated **615**, significantly expanding the utility of the transformation (Scheme 87).[255]

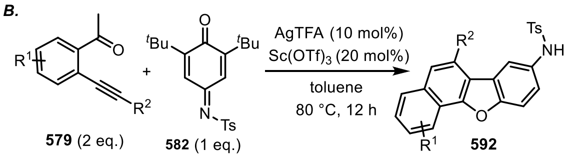
Iron catalyst **616** reacts with the silane **617** to generate an iron-hydride specie **618**. Hydrogen atom is then transferred to the olefin to furnish a key, carbon-centered radical intermediate **619**, which is trapped by the Ni catalyst **620** to afford **621**, which then undergoes oxidative addition into an aryl iodide **614** followed by reductive elimination of **622** to yield the desired cross-coupled product **615**. Presence of a catalytically active, radical species was confirmed by TEMPO adduct trapping experiments. Substrate scope of the reaction includes natural

Scheme 84. Synergistic Ag/Sc Dual Catalysis for Preparation of Benzo[*c*]xanthenes and Naphtho[1,2-*b*]benzofurans

A. Reaction conditions and substrate scope for preparation of benzo[c]xanthenes and naphtho[1,2-b]benzofurans.

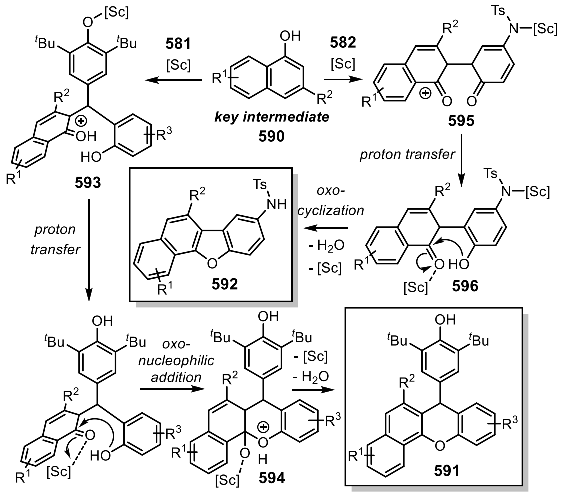


R^1	R^2	R^3	%	R^1	R^2	R^3	%	R^1	R^2	R^3	%
H	Ph	H	73	H	PMP	H	74	8-F	4-Me-C_6H_4	H	83
H	3-Me-C_6H_4	H	76	H	4-F-C_6H_4	H	80	H	Ph	3-Me	57
H	4-Me-C_6H_4	H	78	H	4-Cl-C_6H_4	H	73	H	Ph	3-^{t}Bu	64
H	4-Et-C_6H_4	H	83	H	4-Br-C_6H_4	H	66	H	Ph	3-F	80
H	4-^{t}Bu-C_6H_4	H	79	H	2-thineyl	H	68	H	Ph	3-Br	64
				H	*n*-Bu	H	66	H	Ph	4-OMe	55



R^1	R^2	%	R^1	R^2	%	R^1	R^2	%
H	Ph	52	H	4-^{t}Bu-C_6H_4	50	H	4-Cl-C_6H_4	50
H	4-Me-C_6H_4	55	H	PMP	62	H	4-Br-C_6H_4	49
H	4-Et-C_6H_4	46	H	4-F-C_6H_4	57	H	*n*-Bu	52
						8-F	4-Me-C_6H_4	51

C. Reaction mechanism



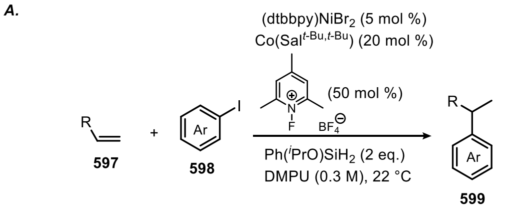
products and substrates usually not amendable for regioselective Fridel−Crafts or Minisci reactions. In addition to trisubstituted olefins, terminal mono and disubstituted olefins were also amendable under slightly modified reaction conditions to deliver the hydroarylated product.

28. SYNERGISTIC Ni/Mn DUAL CATALYSIS

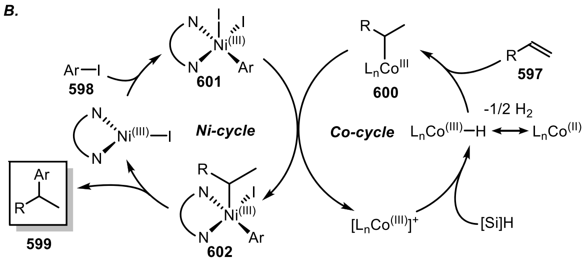
28.1. Markovnikov Hydroalkylation of Olefins

Recently, Shenvi and co-workers disclosed hydroarylation of unactivated alkenes *via* Ni/Co dual catalysis.[252] Attempted Ni/Co mediated hydroalkylation under the same conditions delivered desired alkylated product in low yields. To rectify this limitation, Shenvi disclosed a novel Ni/Mn dual catalytic strategy, which accomplished hydroalkylation of unactivated olefins **623** with alkyl iodide **624** in Markovnikov selectivity to yield **625** in good yields (Scheme 88).[254]

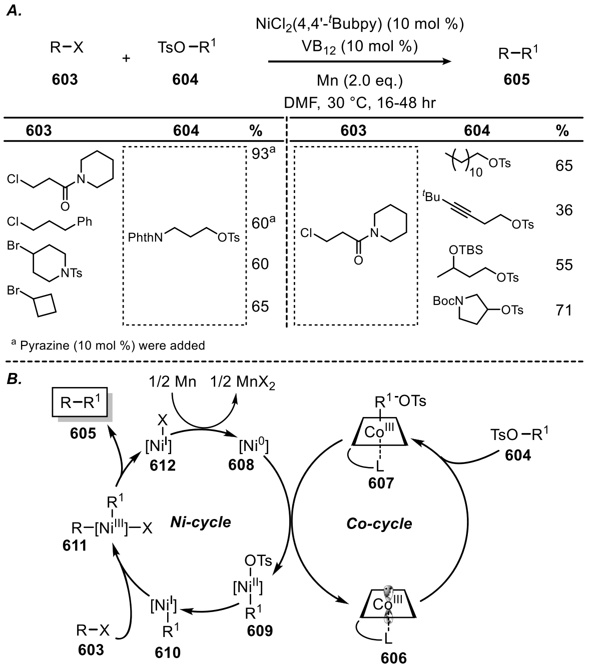
Scheme 85. Synergistic Ni/Co Dual Catalysis for Markovnikov Hydroarylation of Olefins



Ar/Het	R	%	Ar/Het	R	%
4-CF_3-C_6H_4	cyclohexane	78	4-CN-C_6H_4	*n*-octane	79
4-CF_3-C_6H_4	-$CH_2CH_2CH_2Br$	66	4-CO_2Me-C_6H_4	*n*-octane	65
4-CF_3-C_6H_4	-CH_2OTBS	43	3,5-F_2-C_6H_3	*n*-octane	70
4-CF_3-C_6H_4	-SPh	42	2-thiophene	*n*-octane	62

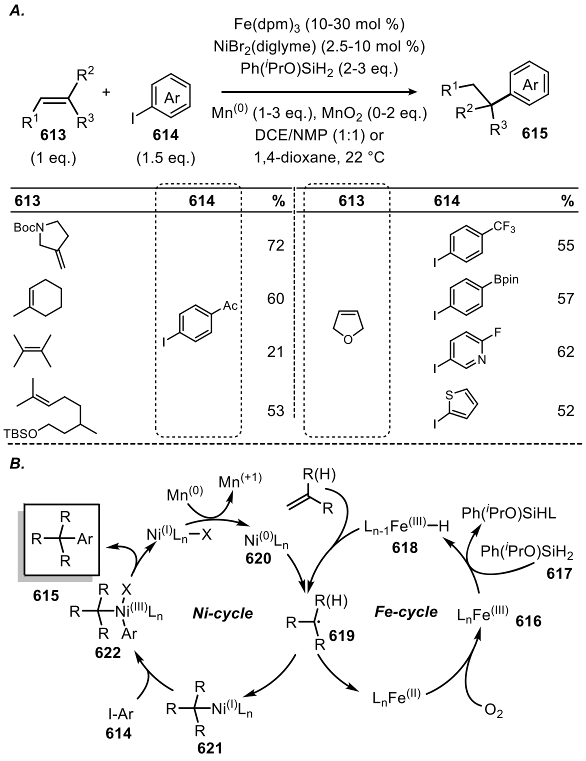


Scheme 86. Synergistic Ni/Co Dual Catalysis for Cross-Coupling of Alkyl Halides with Alkyl Tosylates

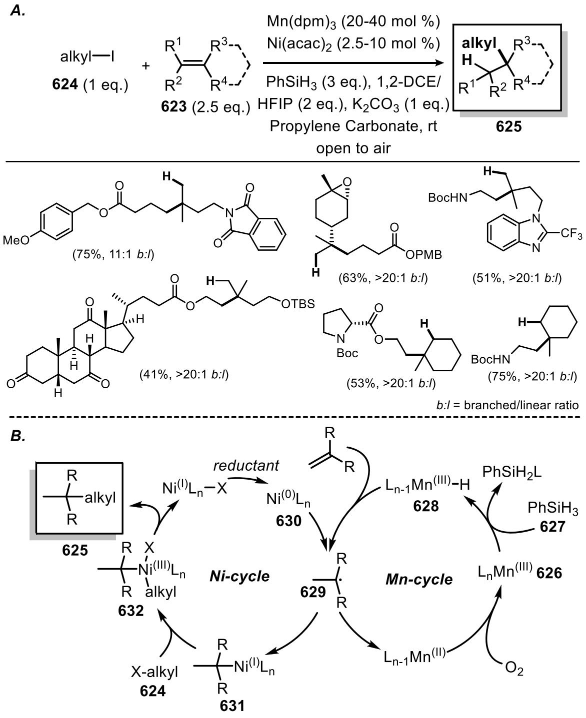


The reaction is based on metal-catalyzed hydrogen atom transfer strategy,[261] where combination of a Mn catalyst **626** and silane **627** react to form a Mn-hydride **628** and transfers a hydrogen atom onto an olefin to generate an intermediary carbon centered radical **629**. Nickel catalyst **630** then traps the radical to afford Ni(I) species **631**, which upon further oxidative addition into alkyl halide **624** and following a subsequent reductive elimination sequence from **632** affords the desired alkylated compound **625**. Sterochemistry on alkyl iodides are well preserved and translated onto the product without racemization. Sterically congested alkyl halides, however, such as secondary alkyl iodides, proceed in the reaction with low yields due to competing protodehalogenation.

Scheme 87. Synergistic Ni/Fe Dual Catalysis for Hydroarylation of Cyclic and Acyclic Alkenes



Scheme 88. Synergistic Ni/Mn Dual Catalysis for Markovnikov Hydroalkylation of Olefins Using Alkyl Iodides



29. CONCLUSION AND OUTLOOK

From its beginnings in the Sonagashira reaction, synergistic dual transition metal catalysis have gained increasing prominence and importance. This has been especially evident in the past few years, where the new paradigm of using two different transition metal catalysts have been applied in an increasing number of novel (or improving previously known) chemical transformations, yielding increased reactivity, selectivity, and efficiency.

Although synergistic transition metal catalysis may be perceived to have inherent difficulties, such as ensuring catalyst compatibility and balanced kinetics in substrate selective activation, this review has illustrated these challenges could be overcome with the right combination of transition metal catalysts.

It is also clear that a vast array of different nucleophiles was inventively utilized in synergistic catalysis. However, the electrophiles are still limited to aryl/allylic halides and allylic carbonates. In this context, there may be significant areas of underexplored and underexploited reactivity which might be made accessible by the discovery of other electrophiles and methods of activation amendable to synergistic dual transition metal catalysis. Regardless, it is certain that many discoveries await, and the chemical community can look forward to many additional powerful transformations realized by dual transition metal synergistic catalysis.

AUTHOR INFORMATION

Corresponding Author

Sang-gi Lee − *Department of Chemistry and Nanoscience (BK 21 Plus), Ewha Womans University, Seoul 120-750, Korea;* orcid.org/0000-0003-2565-5233; Email: sanggi@ewha.ac.kr

Authors

U Bin Kim − *Department of Chemistry and Nanoscience (BK 21 Plus), Ewha Womans University, Seoul 120-750, Korea*
Da Jung Jung − *Department of Chemistry and Nanoscience (BK 21 Plus), Ewha Womans University, Seoul 120-750, Korea*
Hyun Ji Jeon − *Department of Chemistry and Nanoscience (BK 21 Plus), Ewha Womans University, Seoul 120-750, Korea*
Kris Rathwell − *Department of Chemistry and Nanoscience (BK 21 Plus), Ewha Womans University, Seoul 120-750, Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrev.0c00245

Notes

The authors declare no competing financial interest.

Biographies

U Bin Kim was born in Masan, South Korea. He studied at the University of Auckland (New Zealand) under the supervision of Distinguished Professor Margaret A. Brimble, where he received his B.Sc. (Honours 1st class, 2008) and Ph.D. (2014), working on the total synthesis of natural products with monoamine oxidase inhibitory activity. In 2015, he joined Professor Sang-gi Lee's laboratory as a postdoctoral researcher at Ewha Womans University (Seoul, South Korea), where he worked on synthesis of natural products with neurological significance.

Da Jung Jung was born in Seoul, South Korea. She studied at Ewha Womans University and received her B.Sc. (2013) and Ph.D. (2019) under the supervision of Professor Sang-gi Lee. Her doctoral research was focused on developing transition metal catalyzed one-pot tandem catalytic reactions including metal carbene transformations. In 2019, she joined National Research Foundation of Korea as a researcher.

Hyun Ji Jeon was educated at Ewha Womans University for B.Sc. (2013), M.Sc. (2015), and Ph.D. degrees (2019) under the direction of Prof. Sang-gi Lee. Her doctoral research focused on transition metal catalyzed synergistic divergent catalysis and asymmetric catalysis. In 2019, she joined Professor Sukbok Chang's group as a postdoctoral researcher at Institute of Basic Science in Korea Advanced Instituted of Science and Technology (Daejeon, South Korea).

Kris Rathwell grew up in Coronation, Alberta, Canada. He was educated at the University of Alberta (B.Sc. Honors Chemistry, 2005) and at the University of Auckland (Ph.D. Organic Chemistry, 2010). His doctoral research focused on the synthesis of analogues of the nanaomycin family of antibiotics. His postdoctoral research at Ewha Womans University focused on catalysis and the synthesis of polyketide-*N*-acetylcysteamine thioesters pertaining to the biosynthesis of polyketide natural products.

Sang-gi Lee graduated from Kyungpook National University (B.Sc. 1982) and the Korea Advanced Institute of Science and Technology (M.Sc. 1985) and worked at the Korea Institute of Science and Technology (KIST) as a Research Scientist (1990). After completing a Ph.D. from the University of Missouri at Columbia (1994), he joined KIST as a Principal Research Scientist until 2005. During this period, he did postdoctoral research at the Massachusetts Institute of Technology (1998). In 2006, he joined the Department of Chemistry and Nano Science at Ewha Womans University as a Professor. His major research interests are homogeneous and heterogeneous catalysts.

ACKNOWLEDGMENTS

This work was financially supported by the Samsung Science and Technology Foundation (SSTF-BA1401-10) and by the National Research Foundation (NRF-2019R1A2B5-B02069449). D. J. Jung thanks the Hyundai Motors Chung Mong-Koo Foundation for a scholarship. H. J. Jeon is supported by Global Ph.D. Fellowship Program of the National Research Foundation of Korea funded by the Ministry of Education (NRF-2015H1A2A1031486).

REFERENCES

(1) Sheldon, R. A. Fundamentals of green chemistry: efficiency in reaction design. *Chem. Soc. Rev.* **2012**, *41*, 1437−1451.

(2) Patil, N. T.; Shinde, V. S.; Gajula, B. A one-pot catalysis: the strategic classification with some recent examples. *Org. Biomol. Chem.* **2012**, *10*, 211−224.

(3) Lee, J. M.; Na, Y.; Han, H.; Chang, S. Cooperative multi-catalyst systems for one-pot organic transformations. *Chem. Soc. Rev.* **2004**, *33*, 302−312.

(4) *Dual Catalysis in Organic Synthesis Vol 1 and Vol 2, Science of Synthesis*. Molander, G. A., Ed.; Georg Thieme Verlag: Stuttgart, NY, 2020.

(5) Dub, P. A.; Gordon, J. C. Metal−Ligand Bifunctional Catalysis: The "Accepted" Mechanism, the Issue of Concertedness, and the Function of the Ligand in Catalytic Cycles Involving Hydrogen Atoms. *ACS Catal.* **2017**, *7*, 6635−6655.

(6) Robinson, A. M.; Hensley, J. E.; Medlin, J. W. Bifunctional Catalysts for Upgrading of Biomass-Derived Oxygenates: A Review. *ACS Catal.* **2016**, *6*, 5026−5043.

(7) Ramasamy, B.; Ghosh, P. The Developing Concept of Bifunctional Catalysis with Transition Metal *N*-Heterocyclic Carbene Complexes. *Eur. J. Inorg. Chem.* **2016**, *2016*, 1448−1465.

(8) Shibasaki, M.; Yoshikawa, N. Lanthanide Complexes in Multifunctional Asymmetric Catalysis. *Chem. Rev.* **2002**, *102*, 2187−2210.

(9) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. Recent Progress in Asymmetric Bifunctional Catalysis Using Multimetallic Systems. *Acc. Chem. Res.* **2009**, *42*, 1117−1127.

(10) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. Asymmetric Cooperative Catalysis of Strong Brønsted Acid−Promoted Reactions Using Chiral Ureas. *Science* **2010**, *327*, 986−990.

(11) Fogg, D. E.; dos Santos, E. N. Tandem catalysis: a taxonomy and illustrative review. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379.

(12) Allen, A. E.; MacMillan, D. W. C. Synergistic catalysis: A powerful synthetic strategy for new reaction development. *Chem. Sci.* **2012**, *3*, 633−658.

(13) Wang, C.; Xi, Z. Co-operative effect of Lewis acids with transition metals for organic synthesis. *Chem. Soc. Rev.* **2007**, *36*, 1395−1406.

(14) Shao, Z.; Zhang, H. Combining transition metal catalysis and organocatalysis: a broad new concept for catalysis. *Chem. Soc. Rev.* **2009**, *38*, 2745−2755.

(15) Du, Z.; Shao, Z. Combining transition metal catalysis and organocatalysis - an update. *Chem. Soc. Rev.* **2013**, *42*, 1337−1378.

(16) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. Catalytic Enone Cycloallylation via Concomitant Activation of Latent Nucleophilic and Electrophilic Partners: Merging Organic and Transition Metal Catalysis. *J. Am. Chem. Soc.* **2003**, *125*, 7758−7759.

(17) Schwarz, K. J.; Amos, J. L.; Klein, J. C.; Do, D. T.; Snaddon, T. N. Uniting C1-Ammonium Enolates and Transition Metal Electrophiles via Cooperative Catalysis: The Direct Asymmetric α-Allylation of Aryl Acetic Acid Esters. *J. Am. Chem. Soc.* **2016**, *138*, 5214−5217.

(18) Jiang, X.; Beiger, J. J.; Hartwig, J. F. Stereodivergent Allylic Substitutions with Aryl Acetic Acid Esters by Synergistic Iridium and Lewis Base Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 87−90.

(19) Afewerki, S.; Córdova, A. Combinations of Aminocatalysts and Metal Catalysts: A Powerful Cooperative Approach in Selective Organic Synthesis. *Chem. Rev.* **2016**, *116*, 13512−13570.

(20) Rueping, M.; Koenigs, R. M.; Atodiresei, I. Unifying Metal and Brønsted Acid Catalysis—Concepts, Mechanisms, and Classifications. *Chem. - Eur. J.* **2010**, *16*, 9350−9365.

(21) Bugaut, X.; Glorius, F. Organocatalytic umpolung: N-heterocyclic carbenes and beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511−3522.

(22) Wang, M. H.; Scheidt, K. A. Cooperative Catalysis and Activation with N-Heterocyclic Carbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912−14922.

(23) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. Employing homoenolates generated by NHC catalysis in carbon−carbon bond-forming reactions: state of the art. *Chem. Soc. Rev.* **2011**, *40*, 5336−5346.

(24) Cohen, D. T.; Scheidt, K. A. Cooperative Lewis acid/N-heterocyclic carbene catalysis. *Chem. Sci.* **2012**, *3*, 53−57.

(25) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **2016**, *116*, 10035−10074.

(26) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* **2017**, *1*, 0052.

(27) Hossain, A.; Bhattacharyya, A.; Reiser, O. Copper's rapid ascent in visible-light photoredox catalysis. *Science* **2019**, *364*, No. eaav9713.

(28) Zhang, H.-H.; Chen, H.; Zhu, C.; Yu, S. A review of enantioselective dual transition metal/photoredox catalysis. *Sci. China: Chem.* **2020**, *63*, 637−647.

(29) van den Beuken, E. K.; Feringa, B. L. Bimetallic catalysis by late transition metal complexes. *Tetrahedron* **1998**, *54*, 12985−13011.

(30) Stojcevic, G.; Kim, H.; Taylor, N. J.; Marder, T. B.; Collins, S. Methacrylate Polymerization using a Dinuclear Zirconocene Initiator: A New Approach for the Controlled Synthesis of Methacrylate Polymers. *Angew. Chem., Int. Ed.* **2004**, *43*, 5523−5526.

(31) Inamdar, S. M.; Shinde, V. S.; Patil, N. T. Enantioselective cooperative catalysis. *Org. Biomol. Chem.* **2015**, *13*, 8116−8162.

(32) Pérez-Temprano, M. H.; Casares, J. A.; Espinet, P. Bimetallic Catalysis using Transition and Group-11 Metals: An Emerging Tool for C−C Coupling and Other Reactions. *Chem. - Eur. J.* **2012**, *18*, 1864−1884.

(33) Pye, D. R.; Mankad, N. P. Bimetallic catalysis for C−C and C−X coupling reactions. *Chem. Sci.* **2017**, *8*, 1705−1718.

(34) Fu, J.; Huo, X.; Li, B.; Zhang, W. Cooperative bimetallic catalysis in asymmetric allylic substitution. *Org. Biomol. Chem.* **2017**, *15*, 9747−9759.

(35) Lorion, M. M.; Maindan, K.; Kapdi, A. R.; Ackermann, L. Heteromultimetallic catalysis for sustainable organic syntheses. *Chem. Soc. Rev.* **2017**, *46*, 7399−7420.

(36) Wu, Y.; Huo, X.; Zhang, W. Synergistic Pd/Cu Catalysis in Organic Synthesis. *Chem. - Eur. J.* **2020**, *26*, 4895−4916.

(37) Sonogashira, K.; Tohda, Y.; Hagihara, N. A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Lett.* **1975**, *16*, 4467−4470.

(38) Stephens, R. D.; Castro, C. E. The Substitution of Aryl Iodides with Cuprous Acetylides. A Synthesis of Tolanes and Heterocyclics. *J. Org. Chem.* **1963**, *28*, 3313−3315.

(39) Cassar, L. Synthesis of aryl- and vinyl-substituted acetylene derivatives by the use of nickel and palladium complexes. *J. Organomet. Chem.* **1975**, *93*, 253−257.

(40) Dieck, H. A.; Heck, F. R. Palladium catalyzed synthesis of aryl, heterocyclic and vinylic acetylene derivatives. *J. Organomet. Chem.* **1975**, *93*, 259−263.

(41) Chinchilla, R.; Najera, C. Recent advances in Sonogashira reactions. *Chem. Soc. Rev.* **2011**, *40*, 5084−5121.

(42) Beletskaya, I. P.; Latyshev, G. V.; Tsvetkov, A. V.; Lukashev, N. V. The nickel-catalyzed Sonogashira−Hagihara reaction. *Tetrahedron Lett.* **2003**, *44*, 5011−5013.

(43) Vechorkin, O.; Barmaz, D.; Proust, V.; Hu, X. Ni-Catalyzed Sonogashira Coupling of Nonactivated Alkyl Halides: Orthogonal Functionalization of Alkyl Iodides, Bromides, and Chlorides. *J. Am. Chem. Soc.* **2009**, *131*, 12078−12079.

(44) Yi, J.; Lu, X.; Sun, Y.-Y.; Xiao, B.; Liu, L. Nickel-Catalyzed Sonogashira Reactions of Non-activated Secondary Alkyl Bromides and Iodides. *Angew. Chem., Int. Ed.* **2013**, *52*, 12409−12413.

(45) Cordovilla, C.; Bartolomé, C.; Martínez-Ilarduya, J. M.; Espinet, P. The Stille Reaction, 38 Years Later. *ACS Catal.* **2015**, *5*, 3040−3053.

(46) Marino, J. P.; Long, J. K. New strategies for annulations: a highly convergent and stereoselective synthesis of an octahydronaphthalene synthon for dihydrocompactin. *J. Am. Chem. Soc.* **1988**, *110*, 7916−7917.

(47) Liebeskind, L. S.; Fengl, R. W. 3-Stannylcyclobutenediones as nucleophilic cyclobutenedione equivalents. Synthesis of substituted cyclobutenediones and cyclobutenedione monoacetals and the beneficial effect of catalytic copper iodide on the Stille reaction. *J. Org. Chem.* **1990**, *55*, 5359−5364.

(48) Mee, S. P. H.; Lee, V.; Baldwin, J. E. Stille Coupling Made Easier—The Synergic Effect of Copper(I) Salts and the Fluoride Ion. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132−1136.

(49) Heath, R. J.; Rock, C. O. The Claisen condensation in biology. *Nat. Prod. Rep.* **2002**, *19*, 581−596.

(50) Ward, O. P.; Singh, A. Enzymatic asymmetric synthesis by decarboxylases. *Curr. Opin. Biotechnol.* **2000**, *11*, 520−526.

(51) Gooßen, L. J.; Deng, G.; Levy, L. M. Synthesis of Biaryls via Catalytic Decarboxylative Coupling. *Science* **2006**, *313*, 662−664.

(52) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. Biaryl Synthesis via Pd-Catalyzed Decarboxylative Coupling of Aromatic Carboxylates with Aryl Halides. *J. Am. Chem. Soc.* **2007**, *129*, 4824−4833.

(53) Goossen, L. J.; Rodríguez, N.; Linder, C. Decarboxylative Biaryl Synthesis from Aromatic Carboxylates and Aryl Triflates. *J. Am. Chem. Soc.* **2008**, *130*, 15248−15249.

(54) Gooßen, L. J.; Rodríguez, N.; Lange, P. P.; Linder, C. Decarboxylative Cross-Coupling of Aryl Tosylates with Aromatic Carboxylate Salts. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111−1114.

(55) Song, B.; Knauber, T.; Gooßen, L. J. Decarboxylative Cross-Coupling of Mesylates Catalyzed by Copper/Palladium Systems with Customized Imidazolyl Phosphine Ligands. *Angew. Chem., Int. Ed.* **2013**, *52*, 2954−2958.

(56) Gooßen, L. J.; Zimmermann, B.; Knauber, T. Palladium/Copper-Catalyzed Decarboxylative Cross-Coupling of Aryl Chlorides with Potassium Carboxylates. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103−7106.

(57) Goossen, L. J.; Linder, C.; Rodríguez, N.; Lange, P. P. Biaryl and Aryl Ketone Synthesis via Pd-Catalyzed Decarboxylative Coupling of Carboxylate Salts with Aryl Triflates. *Chem. - Eur. J.* **2009**, *15*, 9336−9349.

(58) Gooßen, L. J.; Lange, P. P.; Rodríguez, N.; Linder, C. Low-Temperature Ag/Pd-Catalyzed Decarboxylative Cross-Coupling of Aryl Triflates with Aromatic Carboxylate Salts. *Chem. - Eur. J.* **2010**, *16*, 3906−3909.

(59) Gooßen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. Synthesis of Ketones from α-Oxocarboxylates and Aryl Bromides by Cu/Pd-Catalyzed Decarboxylative Cross-Coupling. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043−3045.

(60) Rudolphi, F.; Song, B.; Gooßen, L. J. Synthesis of Azomethines from α-Oxocarboxylates, Amines and Aryl Bromides via One-Pot Three-Component Decarboxylative Coupling. *Adv. Synth. Catal.* **2011**, *353*, 337−342.

(61) Hackenberger, D.; Weber, P.; Blakemore, D. C.; Goossen, L. J. Synthesis of 3-Substituted 2-Arylpyridines via Cu/Pd-Catalyzed Decarboxylative Cross-Coupling of Picolinic Acids with (Hetero)Aryl Halides. *J. Org. Chem.* **2017**, *82*, 3917−3925.

(62) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. A Highly Efficient Palladium/Copper Cocatalytic System for Direct Arylation of Heteroarenes: An Unexpected Effect of Cu(Xantphos)I. *J. Am. Chem. Soc.* **2010**, *132*, 3674−3675.

(63) Ackermann, L.; Althammer, A.; Fenner, S. Palladium-Catalyzed Direct Arylations of Heteroarenes with Tosylates and Mesylates. *Angew. Chem., Int. Ed.* **2009**, *48*, 201−204.

(64) Rao, M. L. N.; Dhanorkar, R. J. Rapid threefold cross-couplings with sterically bulky triarylbismuths under Pd−Cu dual catalysis. *RSC Adv.* **2016**, *6*, 1012−1017.

(65) Tang, S.; Li, S.-H.; Nakao, Y.; Hiyama, T. Aryl[2-(hydroxypro-2-yl)cyclohyxyl]dimethylsilane: A Robust Aryl(trialkyl)silane Reagent for Nickel-catalyzed Cross-coupling Reactions with Aryl Tosylates. *Asian J. Org. Chem.* **2013**, *2*, 416−421.

(66) Tang, S.; Takeda, M.; Nakao, Y.; Hiyama, T. Nickel-catalysed cross-coupling reaction of aryl(trialkyl)silanes with aryl chlorides and tosylates. *Chem. Commun.* **2011**, *47*, 307−309.

(67) Ohgi, A.; Semba, K.; Hiyama, T.; Nakao, Y. Silicon-based Cross-coupling of Aryl Tosylates by Cooperative Palladium/Copper Catalysis. *Chem. Lett.* **2016**, *45*, 973−975.

(68) Casitas, A.; Ribas, X. The role of organometallic copper(III) complexes in homogeneous catalysis. *Chem. Sci.* **2013**, *4*, 2301−2318.

(69) Li, J.-H.; Wang, D.-P. CuI/DABCO-Catalyzed Cross-Coupling Reactions of Aryl Halides with Arylboronic Acids. *Eur. J. Org. Chem.* **2006**, *2006*, 2063−2066.

(70) Handa, S.; Smith, J. D.; Hageman, M. S.; Gonzalez, M.; Lipshutz, B. H. Synergistic and Selective Copper/ppm Pd-Catalyzed Suzuki−Miyaura Couplings: In Water, Mild Conditions, with Recycling. *ACS Catal.* **2016**, *6*, 8179−8183.

(71) Handa, S.; Wang, Y.; Gallou, F.; Lipshutz, B. H. Sustainable Fe−ppm Pd nanoparticle catalysis of Suzuki-Miyaura cross-couplings in water. *Science* **2015**, *349*, 1087−1091.

(72) Hoshi, T.; Shishido, Y.; Suzuki, A.; Sasaki, Y.; Hagiwara, H.; Suzuki, T. Suzuki−Miyaura Coupling Reactions Using Low Loading of Ligand-activated Palladium Catalyst by Cooperative Copper Catalysis. *Chem. Lett.* **2018**, *47*, 780−783.

(73) Nahra, F.; Macé, Y.; Lambin, D.; Riant, O. Copper/Palladium-Catalyzed 1,4 Reduction and Asymmetric Allylic Alkylation of α,β-Unsaturated Ketones: Enantioselective Dual Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 3208−3212.

(74) Nahra, F.; Macé, Y.; Boreux, A.; Billard, F.; Riant, O. Versatile CuI/Pd0 Dual Catalysis for the Synthesis of Quaternary α-Allylated Carbonyl Compounds: Development, Mechanistic Investigations and Scope. *Chem. - Eur. J.* **2014**, *20*, 10970−10981.

(75) Saito, A.; Kumagai, N.; Shibasaki, M. Cu/Pd Synergistic Dual Catalysis: Asymmetric α-Allylation of an α-CF3 Amide. *Angew. Chem., Int. Ed.* **2017**, *56*, 5551−5555.

(76) Huo, X.; He, R.; Fu, J.; Zhang, J.; Yang, G.; Zhang, W. Stereoselective and Site-Specific Allylic Alkylation of Amino Acids and Small Peptides via a Pd/Cu Dual Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 9819−9822.

(77) Huo, X.; Fu, J.; He, X.; Chen, J.; Xie, F.; Zhang, W. Pd/Cu dual catalysis: highly enantioselective access to α-substituted α-amino acids and α-amino amides. *Chem. Commun.* **2018**, *54*, 599−602.

(78) Wei, L.; Xu, S.-M.; Zhu, Q.; Che, C.; Wang, C.-J. Synergistic Cu/Pd Catalysis for Enantioselective Allylic Alkylation of Aldimine Esters: Access to α,α-Disubstituted α-Amino Acids. *Angew. Chem., Int. Ed.* **2017**, *56*, 12312−12316.

(79) Wei, L.; Xiao, L.; Wang, C.-J. Synergistic Cu/Pd Catalysis for Enantioselective Allylation of Ketimine Esters: The Direct Synthesis of α-Substituted α-Amino Acids and 2H-Pyrrols. *Adv. Synth. Catal.* **2018**, *360*, 4715−4719.

(80) Wei, L.; Zhu, Q.; Xu, S.-M.; Chang, X.; Wang, C.-J. Stereodivergent Synthesis of α,α-Disubstituted α-Amino Acids via Synergistic Cu/Ir Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 1508−1513.

(81) Huo, X.; Zhang, J.; Fu, J.; He, R.; Zhang, W. Ir/Cu Dual Catalysis: Enantio- and Diastereodivergent Access to α,α-Disubstituted α-Amino Acids Bearing Vicinal Stereocenters. *J. Am. Chem. Soc.* **2018**, *140*, 2080−2084.

(82) Wei, L.; Zhu, Q.; Xiao, L.; Tao, H.-Y.; Wang, C.-J. Synergistic catalysis for cascade allylation and 2-aza-cope rearrangement of azomethine ylides. *Nat. Commun.* **2019**, *10*, 1594.

(83) Jiang, X.; Boehm, P.; Hartwig, J. F. Stereodivergent Allylation of Azaaryl Acetamides and Acetates by Synergistic Iridium and Copper Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 1239−1242.

(84) Semba, K.; Ohta, N.; Nakao, Y. Carboallylation of Electron-Deficient Alkenes with Organoboron Compounds and Allylic Carbonates by Cooperative Palladium/Copper Catalysis. *Org. Lett.* **2019**, *21*, 4407−4410.

(85) Semba, K.; Ohta, N.; Yano, Y.; Nakao, Y. Carboallylation of electron-deficient alkenes by palladium/copper catalysis. *Chem. Commun.* **2018**, *54*, 11463−11466.

(86) Rivera-Chao, E.; Fra, L.; Fañanás-Mastral, M. Synergistic Bimetallic Catalysis for Carboboration of Unsaturated Hydrocarbons. *Synthesis* **2018**, *50*, 3825−3832.

(87) Semba, K.; Nakao, Y. Arylboration of Alkenes by Cooperative Palladium/Copper Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 7567−7570.

(88) Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. Copper-Catalyzed Cross-Coupling of Boronic Esters with Aryl Iodides and Application to the Carboboration of Alkynes and Allenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 3475−3479.

(89) Logan, K. M.; Smith, K. B.; Brown, M. K. Copper/Palladium Synergistic Catalysis for the syn- and anti-Selective Carboboration of Alkenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 5228−5231.

(90) Jia, T.; Cao, P.; Wang, B.; Lou, Y.; Yin, X.; Wang, M.; Liao, J. A Cu/Pd Cooperative Catalysis for Enantioselective Allylboration of Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 13760−13763.

(91) Logan, K. M.; Brown, M. K. Catalytic Enantioselective Arylboration of Alkenylarenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 851−855.

(92) Chen, B.; Cao, P.; Yin, X.; Liao, Y.; Jiang, L.; Ye, J.; Wang, M.; Liao, J. Modular Synthesis of Enantioenriched 1,1,2-Triarylethanes by an Enantioselective Arylboration and Cross-Coupling Sequence. *ACS Catal.* **2017**, *7*, 2425−2429.

(93) Morais, A. R. C.; Dworakowska, S.; Reis, A.; Gouveia, L.; Matos, C. T.; Bogdał, D.; Bogel-Łukasik, R. Chemical and biological-based isoprene production: Green metrics. *Catal. Today* **2015**, *239*, 38−43.

(94) Bozell, J. J.; Petersen, G. R. Technology development for the production of biobased products from biorefinery carbohydrates—the US Department of Energy's "Top 10" revisited. *Green Chem.* **2010**, *12*, 539−554.

(95) Smith, K. B.; Brown, M. K. Regioselective Arylboration of Isoprene and Its Derivatives by Pd/Cu Cooperative Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 7721−7724.

(96) Díez-González, S.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Slawin, A. M. Z.; Nolan, S. P. [(NHC)CuX] complexes: Synthesis, characterization and catalytic activities in reduction reactions and Click Chemistry. On the advantage of using well-defined catalytic systems. *Dalton Trans.* **2010**, *39*, 7595−7606.

(97) Sardini, S. R.; Brown, M. K. Catalyst Controlled Regiodivergent Arylboration of Dienes. *J. Am. Chem. Soc.* **2017**, *139*, 9823−9826.

(98) Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. (NHC)CuI (NHC = N-Heterocyclic Carbene) Complexes as Efficient Catalysts for the Reduction of Carbonyl Compounds. *Organometallics* **2004**, *23*, 1157−1160.

(99) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds Catalyzed by a Copper Carbene Complex. *Org. Lett.* **2003**, *5*, 2417−2420.

(100) Alonso, F.; Beletskaya, I. P.; Yus, M. Transition-Metal-Catalyzed Addition of Heteroatom-Hydrogen Bonds to Alkynes. *Chem. Rev.* **2004**, *104*, 3079−3160.

(101) Flynn, A. B.; Ogilvie, W. W. Stereocontrolled Synthesis of Tetrasubstituted Olefins. *Chem. Rev.* **2007**, *107*, 4698−4745.

(102) Lesieur, M.; Bidal, Y. D.; Lazreg, F.; Nahra, F.; Cazin, C. S. J. Versatile Relay and Cooperative Palladium(0) N-Heterocyclic Carbene/Copper(I) N-Heterocyclic Carbene Catalysis for the Synthesis of Tri- and Tetrasubstituted Alkenes. *ChemCatChem* **2015**, *7*, 2108−2112.

(103) Semba, K.; Yoshizawa, M.; Ohtagaki, Y.; Nakao, Y. Arylboration of Internal Alkynes by Cooperative Palladium/Copper Catalysis. *Bull. Chem. Soc. Jpn.* **2017**, *90*, 1340−1343.

(104) Vázquez-Galiñanes, N.; Fañanás-Mastral, M. Stereoselective Synthesis of Borylated 1,3-Dienes by Synergistic Cu/Pd Catalysis. *ChemCatChem* **2018**, *10*, 4817−4820.

(105) Shintani, R.; Kurata, H.; Nozaki, K. Intermolecular Three-Component Arylsilylation of Alkynes under Palladium/Copper Cooperative Catalysis. *J. Org. Chem.* **2016**, *81*, 3065−3069.

(106) Mateos, J.; Rivera-Chao, E.; Fañanás-Mastral, M. Synergistic Copper/Palladium Catalysis for the Regio- and Stereoselective Synthesis of Borylated Skipped Dienes. *ACS Catal.* **2017**, *7*, 5340−5344.

(107) Yoshida, H. Borylation of Alkynes under Base/Coinage Metal Catalysis: Some Recent Developments. *ACS Catal.* **2016**, *6*, 1799−1811.

(108) Yoshida, H.; Kageyuki, I.; Takaki, K. Copper-Catalyzed Three-Component Carboboration of Alkynes and Alkenes. *Org. Lett.* **2013**, *15*, 952−955.

(109) Alvarez, F. M.; Vander Meer, R. K.; Lofgren, C. S. Synthesis of homofarnesenes: trail pheromone components of the fire ant, solenopsisinvicta. *Tetrahedron* **1987**, *43*, 2897−2900.

(110) Kaysser, L.; Bernhardt, P.; Nam, S.-J.; Loesgen, S.; Ruby, J. G.; Skewes-Cox, P.; Jensen, P. R.; Fenical, W.; Moore, B. S. Merochlorins A−D, Cyclic Meroterpenoid Antibiotics Biosynthesized in Divergent Pathways with Vanadium-Dependent Chloroperoxidases. *J. Am. Chem. Soc.* **2012**, *134*, 11988−11991.

(111) Meier, R.; Strych, S.; Trauner, D. Biomimetic Synthesis of (±)-Merochlorin B. *Org. Lett.* **2014**, *16*, 2634−2637.

(112) Semba, K.; Ariyama, K.; Zheng, H.; Kameyama, R.; Sakaki, S.; Nakao, Y. Reductive Cross-Coupling of Conjugated Arylalkenes and Aryl Bromides with Hydrosilanes by Cooperative Palladium/Copper Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 6275−6279.

(113) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. DFT Studies of Alkene Insertions into Cu-B Bonds in Copper(I) Boryl Complexes. *Organometallics* **2007**, *26*, 2824−2832.

(114) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 8372−8375.

(115) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457−2483.

(116) Friis, S. D.; Pirnot, M. T.; Dupuis, L. N.; Buchwald, S. L. A Dual Palladium and Copper Hydride Catalyzed Approach for Alkyl−Aryl Cross-Coupling of Aryl Halides and Olefins. *Angew. Chem., Int. Ed.* **2017**, *56*, 7242−7246.

(117) Thomas, S. P.; Aggarwal, V. K. Asymmetric Hydroboration of 1,1-Disubstituted Alkenes. *Angew. Chem., Int. Ed.* **2009**, *48*, 1896−1898.

(118) Gonzalez, A. Z.; Román, J. G.; Gonzalez, E.; Martinez, J.; Medina, J. R.; Matos, K.; Soderquist, J. A. 9-Borabicyclo[3.3.2]decanes and the Asymmetric Hydroboration of 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2008**, *130*, 9218−9219.

(119) Jang, W. J.; Song, S. M.; Moon, J. H.; Lee, J. Y.; Yun, J. Copper-Catalyzed Enantioselective Hydroboration of Unactivated 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 13660−13663.

(120) Lu, Z.; Buchwald, S. L. Enantioselective Preparation of Arenes with *β*-Stereogenic Centers: Confronting the 1,1-Disubstituted Olefin Problem Using CuH/Pd Cooperative Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 16128−16132.

(121) Kamijo, S.; Yamamoto, Y. A New Pd0−CuI Bimetallic Catalyst for the Synthesis of Indoles from Isocyanates and Allyl Carbonates. *Angew. Chem., Int. Ed.* **2002**, *41*, 3230−3233.

(122) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. Regiospecific synthesis of 2-allyl-1,2,3-triazoles by palladium-catalyzed 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2002**, *43*, 9707−9710.

(123) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari'i, F. M.; Ali, A. A.-S. Dipolar cycloaddition reactions of organic azides with some acetylenic compounds. *J. Heterocycl. Chem.* **1989**, *26*, 1461−1468.

(124) Huisgen, R.; Blaschke, H. 1.3-Dipolare Cycloadditionen, XX: 2-Äthoxy-oxazole aus Athoxycarbonyl-azen und Alkinen. *Chem. Ber.* **1965**, *98*, 2985−2997.

(125) Woerner, F. P.; Reimlinger, H. 1.5-Dipolare Cyclisierungen, II. *ν*-Triazole aus Vinylaziden sowie durch Addition des Azid-Ions an die CC-Dreifachbindung. *Chem. Ber.* **1970**, *103*, 1908−1917.

(126) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. Synthesis of Triazoles from Nonactivated Terminal Alkynes via the Three-Component Coupling Reaction Using a Pd(0)-Cu(I) Bimetallic Catalyst. *J. Am. Chem. Soc.* **2003**, *125*, 7786−7787.

(127) Moltzen, E. K.; Pedersen, H.; Boegesoe, K. P.; Meier, E.; Frederiksen, K.; Sanchez, C.; Lemboel, H. L. Bioisosteres of Arecoline: 1,2,3,6-Tetrahydro-5-pyridyl-Substituted and 3-Piperidyl-Substituted Derivatives of Tetrazoles and 1,2,3-Triazoles. Synthesis and Muscarinic Activity. *J. Med. Chem.* **1994**, *37*, 4085−4099.

(128) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. A Cooperative Copper- and Palladium-Catalyzed Three-Component Coupling of Benzynes, Allylic Epoxides, and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2009**, *48*, 391−394.

(129) Coste, J.; Frérot, E.; Jouin, P.; Castro, B. Oxybenzotriazole free peptide coupling reagents for N-methylated amino acids. *Tetrahedron Lett.* **1991**, *32*, 1967−1970.

(130) Kang, F.-A.; Lanter, J. C.; Cai, C.; Sui, Z.; Murray, W. V. Direct dehydrative cross-coupling of tautomerizable heterocycles with alkynes via Pd/Cu-catalyzed phosphonium coupling. *Chem. Commun.* **2010**, *46*, 1347−1349.

(131) Rosenmund, K. W.; Struck, E. Das am Ringkohlenstoff gebundene Halogen und sein Ersatz durch and ere Substituenten. I. Mitteilung: Ersatz des Halogens durch die Carboxylgruppe. *Ber. Dtsch. Chem. Ges. B* **1919**, *52*, 1749−1756.

(132) Anbarasan, P.; Schareina, T.; Beller, M. Recent developments and perspectives in palladium-catalyzed cyanation of aryl halides: synthesis of benzonitriles. *Chem. Soc. Rev.* **2011**, *40*, 5049−5067.

(133) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. Cooperative Catalyst Effects in Palladium-Mediated Cyanation Reactions of Aryl Halides and Triflates. *J. Org. Chem.* **1998**, *63*, 8224−8228.

(134) Vercruysse, S.; Cornelissen, L.; Nahra, F.; Collard, L.; Riant, O. CuI/Pd0 Cooperative Dual Catalysis: Tunable Stereoselective Construction of Tetra-Substituted Alkenes. *Chem. - Eur. J.* **2014**, *20*, 1834−1838.

(135) Zhao, T. S. N.; Yang, Y.; Lessing, T.; Szabó, K. J. Borylation of Propargylic Substrates by Bimetallic Catalysis. Synthesis of Allenyl, Propargylic, and Butadienyl Bpin Derivatives. *J. Am. Chem. Soc.* **2014**, *136*, 7563−7566.

(136) Ito, H.; Sasaki, Y.; Sawamura, M. Copper(I)-Catalyzed Substitution of Propargylic Carbonates with Diboron: Selective Synthesis of Multisubstituted Allenylboronates. *J. Am. Chem. Soc.* **2008**, *130*, 15774−15775.

(137) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. Synthesis, Structure, and Reactivity of Neutral *η* 3-Propargylpalladium Complexes. *J. Am. Chem. Soc.* **1998**, *120*, 1938−1939.

(138) Shen, G.; Zhao, L.; Wang, Y.; Xia, W.; Yang, M.; Zhang, T. Palladium−copper catalyzed $C(sp^3)-C(sp^2)$ bond C−H activation cross-coupling reaction: selective arylation to synthesize 9-aryl-9H-xanthene and 9,9-diaryl-xanthene derivatives. *RSC Adv.* **2016**, *6*, 84748−84751.

(139) Lee, J. T. D.; Zhao, Y. Access to Acyclic Z-Enediynes by Alkyne Trimerization: Cooperative Bimetallic Catalysis Using Air as the Oxidant. *Angew. Chem., Int. Ed.* **2016**, *55*, 13872−13876.

(140) Bergman, R. G. Reactive 1,4-dehydroaromatics. *Acc. Chem. Res.* **1973**, *6*, 25−31.

(141) Jones, R. R.; Bergman, R. G. p-Benzyne. Generation as an intermediate in a thermal isomerization reaction and trapping evidence for the 1,4-benzenediyl structure. *J. Am. Chem. Soc.* **1972**, *94*, 660−661.

(142) Gredičak, M.; Jerić, I. Enediyne compounds - new promises in anticancer therapy. *Acta Pharm.* **2007**, *57*, 133−150.

(143) Wu, Y.-T.; Lin, W.-C.; Liu, C.-J.; Wu, C.-Y. Palladium-Catalyzed Trimerizations of Terminal Arylalkynes: Synthesis of 1,3-Diaryl-2-arylethynyl-1,3-butadienes[1]. *Adv. Synth. Catal.* **2008**, *350*, 1841−1849.

(144) Zhu, C.; Feng, C.; Yamane, M. Pd/Cu cooperative catalysis: an efficient synthesis of (3-isoindazolyl)allenes via cross-coupling of 2-alkynyl azobenzenes and terminal alkynes. *Chem. Commun.* **2017**, *53*, 2606−2609.

(145) Sharples, D.; Hajós, G.; Riedl, Z.; Csányi, D.; Molnár, J.; Szabó, D. Ellipticine analogues and related compounds as inhibitors of reverse transcriptase and as inhibitors of the efflux pump. *Arch. Pharm.* **2001**, *334*, 269−274.

(146) Phillips, S. D.; Castle, R. N. Quino[1,2-c]quinazolines. I. Synthesis of quino[1,2-c]quinazolinium derivatives and the related indazolo[2,3-a]quinoline derivatives as analogs of the antitumor benzo[c]phenanthridine alkaloids. *J. Heterocycl. Chem.* **1980**, *17*, 1489−1495.

(147) Shen, Y.; Wu, X.-X.; Chen, S.; Xia, Y.; Liang, Y.-M. Synthesis of polyfluoroarene-substituted benzofuran derivatives via cooperative Pd/Cu catalysis. *Chem. Commun.* **2018**, *54*, 2256−2259.

(148) Catellani, M.; Frignani, F.; Rangoni, A. A Complex Catalytic Cycle Leading to a Regioselective Synthesis of o, o′-Disubstituted Vinylarenes. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119−122.

(149) Sun, F.; Li, M.; He, C.; Wang, B.; Li, B.; Sui, X.; Gu, Z. Cleavage of the C(O)−S Bond of Thioesters by Palladium/Norbornene/Copper Cooperative Catalysis: An Efficient Synthesis of 2-(Arylthio)aryl Ketones. *J. Am. Chem. Soc.* **2016**, *138*, 7456−7459.

(150) Semba, K.; Kameyama, R.; Nakao, Y. Hydrogenative Cross-coupling of Internal Alkynes and Aryl Iodides by Palladium/Copper Cooperative Catalysis. *Chem. Lett.* **2018**, *47*, 213−216.

(151) Takeda, M.; Yabushita, K.; Yasuda, S.; Ohmiya, H. Synergistic palladium/copper-catalyzed Csp^3-Csp^2 cross-couplings using aldehydes as latent *α*-alkoxyalkyl anion equivalents. *Chem. Commun.* **2018**, *54*, 6776−6779.

(152) Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M. Copper-Catalyzed 1,2-Addition of Nucleophilic Silicon to Aldehydes: Mechanistic Insight and Catalytic Systems. *Chem. - Eur. J.* **2011**, *17*, 13538−13543.

(153) Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−258.

(154) Schuppe, A. W.; Borrajo-Calleja, G. M.; Buchwald, S. L. Enantioselective Olefin Hydrocyanation without Cyanide. *J. Am. Chem. Soc.* **2019**, *141*, 18668−18672.

(155) Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. Catalyzed Catalysis Using Carbophilic Lewis Acidic Gold and Lewis Basic Palladium: Synthesis of Substituted Butenolides and Isocoumarins. *J. Am. Chem. Soc.* **2009**, *131*, 18022−18023.

(156) Al-Amin, M.; Roth, K. E.; Blum, S. A. Mechanistic Studies of Gold and Palladium Cooperative Dual-Catalytic Cross-Coupling Systems. *ACS Catal.* **2014**, *4*, 622−629.

(157) Al-Amin, M.; Johnson, J. S.; Blum, S. A. Selectivity, Compatibility, Downstream Functionalization, and Silver Effect in the Gold and Palladium Dual-Catalytic Synthesis of Lactones. *Organometallics* **2014**, *33*, 5448−5456.

(158) García-Domínguez, P.; Nevado, C. Au−Pd Bimetallic Catalysis: The Importance of Anionic Ligands in Catalyst Speciation. *J. Am. Chem. Soc.* **2016**, *138*, 3266−3269.

(159) Shirakawa, E.; Yoshida, H.; Nakao, Y.; Hiyama, T. Palladium-Catalyzed Dimerization-Carbostannylation of Alkynes: Synthesis of Highly Conjugated Alkenylstannanes. *J. Am. Chem. Soc.* **1999**, *121*, 4290−4291.

(160) Shi, Y.; Peterson, S. M.; Haberaecker, W. W.; Blum, S. A. Alkynes as Stille Reaction Pseudohalides: Gold- and Palladium-Cocatalyzed Synthesis of Tri- and Tetra-Substituted Olefins. *J. Am. Chem. Soc.* **2008**, *130*, 2168−2169.

(161) Lewis, L. N.; Smith, J. F. Catalytic carbon-carbon bond formation via ortho-metalated complexes. *J. Am. Chem. Soc.* **1986**, *108*, 2728−2735.

(162) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. Efficient catalytic addition of aromatic carbon-hydrogen bonds to olefins. *Nature* **1993**, *366*, 529−531.

(163) Maas, G. Ruthenium-catalysed carbenoid cyclopropanation reactions with diazo compounds. *Chem. Soc. Rev.* **2004**, *33*, 183−190.

(164) Ko, S.; Kang, B.; Chang, S. Cooperative Catalysis by Ru and Pd for the Direct Coupling of a Chelating Aldehyde with Iodoarenes or Organostannanes. *Angew. Chem., Int. Ed.* **2005**, *44*, 455−457.

(165) Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. Chelation-Accelerated Sequential Decarbonylation of Formate and Alkoxycarbonylation of Aryl Halides Using a Combined Ru and Pd Catalyst. *J. Org. Chem.* **2003**, *68*, 1607−1610.

(166) Ko, S.; Han, H.; Chang, S. Ru-Catalyzed Hydroamidation of Alkenes and Cooperative Aminocarboxylation Procedure with Chelating Formamide. *Org. Lett.* **2003**, *5*, 2687−2690.

(167) Qiu, H.; Li, M.; Jiang, L.-Q.; Lv, F.-P.; Zan, L.; Zhai, C.-W.; Doyle, M. P.; Hu, W.-H. Highly enantioselective trapping of zwitterionic intermediates by imines. *Nat. Chem.* **2012**, *4*, 733−738.

(168) Chan, W.-W.; Kwong, T.-L.; Yu, W.-Y. Ruthenium-catalyzed intramolecular cyclization of diazo-β-ketoanilides for the synthesis of 3-alkylideneoxindoles. *Org. Biomol. Chem.* **2012**, *10*, 3749−3755.

(169) Yamamoto, K.; Qureshi, Z.; Tsoung, J.; Pisella, G.; Lautens, M. Combining Ru-Catalyzed C−H Functionalization with Pd-Catalyzed Asymmetric Allylic Alkylation: Synthesis of 3-Allyl-3-aryl Oxindole Derivatives from Aryl α-Diazoamides. *Org. Lett.* **2016**, *18*, 4954−4957.

(170) Trost, B. M.; Frederiksen, M. U. Palladium-Catalyzed Asymmetric Allylation of Prochiral Nucleophiles: Synthesis of 3-Allyl-3-Aryl Oxindoles. *Angew. Chem., Int. Ed.* **2005**, *44*, 308−310.

(171) Chattopadhyay, B.; Gevorgyan, V. Transition-Metal-Catalyzed Denitrogenative Transannulation: Converting Triazoles into Other Heterocyclic Systems. *Angew. Chem., Int. Ed.* **2012**, *51*, 862−872.

(172) Gulevich, A. V.; Gevorgyan, V. Versatile Reactivity of Rhodium−Iminocarbenes Derived from N-Sulfonyl Triazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371−1373.

(173) Sawamura, M.; Sudoh, M.; Ito, Y. An Enantioselective Two-Component Catalyst System: Rh-Pd-Catalyzed Allylic Alkylation of Activated Nitriles. *J. Am. Chem. Soc.* **1996**, *118*, 3309−3310.

(174) Chen, Z.-S.; Huang, L.-Z.; Jeon, H. J.; Xuan, Z.; Lee, S.-g. Cooperative Pd(0)/Rh(II) Dual Catalysis: Interceptive Capturing of π-Allyl Pd(II) Complexes with α-Imino Rh(II) Carbenoids. *ACS Catal.* **2016**, *6*, 4914−4919.

(175) Ackerman, L. K. G.; Lovell, M. M.; Weix, D. J. Multimetallic catalysed cross-coupling of aryl bromides with aryl triflates. *Nature* **2015**, *524*, 454−457.

(176) Trost, B. M.; Oi, S. Atom Economy: Aldol-Type Products by Vanadium-Catalyzed Additions of Propargyl Alcohols and Aldehydes. *J. Am. Chem. Soc.* **2001**, *123*, 1230−1231.

(177) Trost, B. M.; Tracy, J. S. Catalytically Generated Vanadium Enolates Formed via Interruption of the Meyer−Schuster Rearrangement as Useful Reactive Intermediates. *Acc. Chem. Res.* **2020**, *53*, 1568−1579.

(178) Trost, B. M.; Luan, X. Contemporaneous Dual Catalysis by Coupling Highly Transient Nucleophilic and Electrophilic Intermediates Generated in Situ. *J. Am. Chem. Soc.* **2011**, *133*, 1706−1709.

(179) Trost, B. M.; Luan, X.; Miller, Y. Contemporaneous Dual Catalysis: Chemoselective Cross-Coupling of Catalytic Vanadium−Allenoate and π-Allylpalladium Intermediates. *J. Am. Chem. Soc.* **2011**, *133*, 12824−12833.

(180) Trost, B. M.; Luan, X. Synthesis of α-allylated α,β-unsaturated carbonyl compounds using vanadium/palladium contemporaneous dual catalysis. *Nat. Protoc.* **2012**, *7*, 1497−1501.

(181) Ma, S.; Shi, Z. Pd(0)/Ag+-Cocatalyzed Cyclization Reaction of 1,2-Allenic Carboxylic Acids with Aryl/Alkenyl Halides. An Efficient Synthesis of Butenolides. *J. Org. Chem.* **1998**, *63*, 6387−6389.

(182) Gu, Y.; Leng, X.; Shen, Q. Cooperative dual palladium/silver catalyst for direct difluoromethylation of aryl bromides and iodides. *Nat. Commun.* **2014**, *5*, 5405.

(183) Kim, J.; Hong, S. H. Ligand-Promoted Direct C−H Arylation of Simple Arenes: Evidence for a Cooperative Bimetallic Mechanism. *ACS Catal.* **2017**, *7*, 3336−3343.

(184) Elangovan, A.; Wang, Y.-H.; Ho, T.-I. Sonogashira Coupling Reaction with Diminished Homocoupling. *Org. Lett.* **2003**, *5*, 1841−1844.

(185) Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. Efficient and General Protocol for the Copper-Free Sonogashira Coupling of Aryl Bromides at Room Temperature. *Org. Lett.* **2003**, *5*, 4191−4194.

(186) Martek, B. A.; Gazvoda, M.; Urankar, D.; Košmrlj, J. Designing Homogeneous Copper-Free Sonogashira Reaction through a Prism of Pd−Pd Transmetalation. *Org. Lett.* **2020**, *22*, 4938−4943.

(187) Gazvoda, M.; Virant, M.; Pevec, A.; Urankar, D.; Bolje, A.; Kočevar, M.; Košmrlj, J. A mesoionic bis(Py-tzNHC) palladium(II) complex catalyses "green" Sonogashira reaction through an unprecedented mechanism. *Chem. Commun.* **2016**, *52*, 1571−1574.

(188) Guo, Z.; Cai, M.; Jiang, J.; Yang, L.; Hu, W. $Rh_2(OAc)_4$-AgOTf Cooperative Catalysis in Cyclization/Three-Component Reactions for Concise Synthesis of 1,2-Dihydroisoquinolines. *Org. Lett.* **2010**, *12*, 652−655.

(189) Yang, S.; Rui, K.-H.; Tang, X.-Y.; Xu, Q.; Shi, M. Rhodium/Silver Synergistic Catalysis in Highly Enantioselective Cycloisomerization/Cross Coupling of Keto-Vinylidenecyclopropanes with Terminal Alkynes. *J. Am. Chem. Soc.* **2017**, *139*, 5957−5964.

(190) Lu, Z.; Ma, S. Metal-Catalyzed Enantioselective Allylation in Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2008**, *47*, 258−297.

(191) Inada, Y.; Nishibayashi, Y.; Uemura, S. Ruthenium-Catalyzed Asymmetric Propargylic Substitution Reactions of Propargylic Alcohols with Acetone. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715−7717.

(192) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. Ruthenium-Catalyzed Enantioselective Propargylation of Aromatic Compounds with Propargylic Alcohols via Allenylidene Intermediates. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488−6491.

(193) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. Ruthenium-Catalyzed Enantioselective Carbon-Carbon Bond Forming Reaction via Allenylidene-Ene Process: Synthetic Approach to Chiral Heterocycles Such As Chromane, Thiochromane, and 1,2,3,4-Tetrahydroquinoline Derivatives. *J. Am. Chem. Soc.* **2008**, *130*, 10498−10499.

(194) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. Cooperative Catalytic Reactions Using Distinct Transition-Metal Catalysts: Ruthenium- and Copper-Catalyzed Enantioselective Propargylic Alkylation. *Chem. - Eur. J.* **2012**, *18*, 3321−3328.

(195) Motoyama, K.; Ikeda, M.; Miyake, Y.; Nishibayashi, Y. Ruthenium- and Copper-Catalyzed Enantioselective Propargylic

Alkylation of Propargylic Alcohols with β-Keto Phosphonates. *Organometallics* **2012**, *31*, 3426−3430.

(196) Egami, H.; Ide, T.; Fujita, M.; Tojo, T.; Hamashima, Y.; Sodeoka, M. Dual Catalysis with Copper and Rhenium for Trifluoromethylation of Propargylic Alcohols: Efficient Synthesis of α-Trifluoromethylated Enones. *Chem. - Eur. J.* **2014**, *20*, 12061−12065.

(197) Xiong, Y.-P.; Wu, M.-Y.; Zhang, X.-Y.; Ma, C.-L.; Huang, L.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. Direct Access to α-Trifluoromethyl Enones via Efficient Copper-Catalyzed Trifluoromethylation of Meyer−Schuster Rearrangement. *Org. Lett.* **2014**, *16*, 1000−1003.

(198) Ling, L.; Liu, K.; Li, X.; Li, Y. General Reaction Mode of Hypervalent Iodine Trifluoromethylation Reagent: A Density Functional Theory Study. *ACS Catal.* **2015**, *5*, 2458−2468.

(199) Liu, C.; Taheri, A.; Lai, B.; Gu, Y. Synergistic catalysis-induced ring-opening reactions of 2-substituted 3,4-dihydropyrans with α-oxoketene dithioacetals. *Catal. Sci. Technol.* **2015**, *5*, 234−245.

(200) Ishiyama, T.; Miyaura, N.; Suzuki, A. Palladium-catalyzed carbonylative cross-coupling reaction of iodoalkanes with 9-alkyl-9-BBN derivatives. A direct and selective synthesis of ketones. *Tetrahedron Lett.* **1991**, *32*, 6923−6926.

(201) Pye, D. R.; Cheng, L.-J.; Mankad, N. P. Cu/Mn bimetallic catalysis enables carbonylative Suzuki−Miyaura coupling with unactivated alkyl electrophiles. *Chem. Sci.* **2017**, *8*, 4750−4755.

(202) Collins, K. D.; Glorius, F. A robustness screen for the rapid assessment of chemical reactions. *Nat. Chem.* **2013**, *5*, 597−601.

(203) Wang, N.-N.; Huang, L.-R.; Hao, W.-J.; Zhang, T.-S.; Li, G.; Tu, S.-J.; Jiang, B. Synergistic Rhodium/Copper Catalysis: Synthesis of 1,3-Enynes and N-Aryl Enaminones. *Org. Lett.* **2016**, *18*, 1298−1301.

(204) Wu, Y.-N.; Xu, T.; Fu, R.; Wang, N.-N.; Hao, W.-J.; Wang, S.-L.; Li, G.; Tu, S.-J.; Jiang, B. Dual rhodium/copper catalysis: synthesis of benzo[b]fluorenes and 2-naphthalenylmethanones via de-diazotized cycloadditions. *Chem. Commun.* **2016**, *52*, 11943−11946.

(205) Tan, G.; Zhu, L.; Liao, X.; Lan, Y.; You, J. Rhodium/Copper Cocatalyzed Highly trans-Selective 1,2-Diheteroarylation of Alkynes with Azoles via C−H Addition/Oxidative Cross-Coupling: A Combined Experimental and Theoretical Study. *J. Am. Chem. Soc.* **2017**, *139*, 15724−15737.

(206) Yang, W.; Sun, J.; Xu, X.; Zhang, Q.; Liu, Q. Hydroxyamination of aryl C−H bonds with N-hydroxycarbamate by synergistic Rh/Cu catalysis at room temperature. *Chem. Commun.* **2014**, *50*, 4420−4422.

(207) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **2014**, *509*, 299−309.

(208) Zarate, C.; Martin, R. A Mild Ni/Cu-Catalyzed Silylation via C−O Cleavage. *J. Am. Chem. Soc.* **2014**, *136*, 2236−2239.

(209) Wang, Y.; Wu, S.-B.; Shi, W.-J.; Shi, Z.-J. C−O/C−H Coupling of Polyfluoroarenes with Aryl Carbamates by Cooperative Ni/Cu Catalysis. *Org. Lett.* **2016**, *18*, 2548−2551.

(210) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. Nickel-Catalyzed Alkenylation and Alkylation of Fluoroarenes via Activation of C-H Bond over C-F Bond. *J. Am. Chem. Soc.* **2008**, *130*, 16170−16171.

(211) Semba, K.; Ohtagaki, Y.; Nakao, Y. Arylboration of 1-Arylalkenes by Cooperative Nickel/Copper Catalysis. *Org. Lett.* **2016**, *18*, 3956−3959.

(212) Su, Y.; Jia, W.; Jiao, N. Inexpensive Copper/Iron-Cocatalyzed Reactions. *Synthesis* **2011**, *2011*, 1678−1690.

(213) Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. Arylmagnesiation of Alkynes Catalyzed Cooperatively by Iron and Copper Complexes. *J. Am. Chem. Soc.* **2005**, *127*, 17164−17165.

(214) Shirakawa, E.; Ikeda, D.; Yamaguchi, S.; Hayashi, T. Fe−Cu cooperative catalysis in the isomerization of alkyl Grignard reagents. *Chem. Commun.* **2008**, 1214−1216.

(215) Shirakawa, E.; Ikeda, D.; Masui, S.; Yoshida, M.; Hayashi, T. Iron−Copper Cooperative Catalysis in the Reactions of Alkyl Grignard Reagents: Exchange Reaction with Alkenes and Carbometalation of Alkynes. *J. Am. Chem. Soc.* **2012**, *134*, 272−279.

(216) Labre, F.; Gimbert, Y.; Bannwarth, P.; Olivero, S.; Duñach, E.; Chavant, P. Y. Application of Cooperative Iron/Copper Catalysis to a Palladium-Free Borylation of Aryl Bromides with Pinacolborane. *Org. Lett.* **2014**, *16*, 2366−2369.

(217) Li, Q.; Persoons, L.; Daelemans, D.; Herdewijn, P. Iron/Copper Co-Catalyzed Cross-Coupling Reaction for the Synthesis of 6-Substituted 7-Deazapurines and the Corresponding Nucleosides. *J. Org. Chem.* **2020**, *85*, 403−418.

(218) Ashby, E. C.; Ainslie, R. D. Hydrometallation of 1-octene with grignard reagents. Alkylmagnesiums and alkylmagnesium hydrides catalyzed by dicyclopentadienyltitanium dichloride. *J. Organomet. Chem.* **1983**, *250*, 1−12.

(219) Farády, L.; Markó, L. Transition metal alkyls and hydrides X. Structure of products formed in the reactions between olefins and grignard reagents in the presence of nickel chloride. *J. Organomet. Chem.* **1971**, *28*, 159−165.

(220) Zhu, W.; Ma, D. Formation of Arylboronates by a CuI-Catalyzed Coupling Reaction of Pinacolborane with Aryl Iodides at Room Temperature. *Org. Lett.* **2006**, *8*, 261−263.

(221) Billingsley, K. L.; Buchwald, S. L. An Improved System for the Palladium-Catalyzed Borylation of Aryl Halides with Pinacol Borane. *J. Org. Chem.* **2008**, *73*, 5589−5591.

(222) Ahmed, W.; Zhang, S.; Yu, X.; Feng, X.; Yamamoto, Y.; Bao, M. Direct Carbohydroxylation of Arylalkenes with Allylic Alcohols: Cooperative Catalysis of Copper, Silver, and a Brønsted Acid. *Angew. Chem., Int. Ed.* **2019**, *58*, 2495−2499.

(223) Yang, Y.; Antoni, P.; Zimmer, M.; Sekine, K.; Mulks, F. F.; Hu, L.; Zhang, L.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Dual Gold/Silver Catalysis Involving Alkynylgold(III) Intermediates Formed by Oxidative Addition and Silver-Catalyzed C-H Activation for the Direct Alkynylation of Cyclopropenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 5129−5133.

(224) Li, W.; Yuan, D.; Wang, G.; Zhao, Y.; Xie, J.; Li, S.; Zhu, C. Cooperative Au/Ag Dual-Catalyzed Cross-Dehydrogenative Biaryl Coupling: Reaction Development and Mechanistic Insight. *J. Am. Chem. Soc.* **2019**, *141*, 3187−3197.

(225) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. Silver Effect” in Gold(I) Catalysis: An Overlooked Important Factor. *J. Am. Chem. Soc.* **2012**, *134*, 9012−9019.

(226) Zhang, L.; Wang, S. Efficient Synthesis of Cyclopentenones from Enynyl Acetates via Tandem Au(I)-Catalyzed 3,3-Rearrangement and the Nazarov Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 1442−1443.

(227) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. Gold(I)-Catalyzed 5-endo-dig Carbocyclization of Acetylenic Dicarbonyl Compounds. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350−5352.

(228) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. Gold(I)-Catalyzed Stereoselective Olefin Cyclopropanation. *J. Am. Chem. Soc.* **2005**, *127*, 18002−18003.

(229) Luzung, M. R.; Markham, J. P.; Toste, F. D. Catalaytic Isomerization of 1,5-Enynes to Bicyclo[3.1.0]hexenes. *J. Am. Chem. Soc.* **2004**, *126*, 10858−10859.

(230) Gillard, R. M.; Brimble, M. A. Benzannulated spiroketal natural products: isolation, biological activity, biosynthesis, and total synthesis. *Org. Biomol. Chem.* **2019**, *17*, 8272−8307.

(231) Zhang, F.-M.; Zhang, S.-Y.; Tu, Y.-Q. Recent progress in the isolation, bioactivity, biosynthesis, and total synthesis of natural spiroketals. *Nat. Prod. Rep.* **2018**, *35*, 75−104.

(232) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Privileged scaffolds for library design and drug discovery. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347−361.

(233) Čorić, I.; List, B. Asymmetric spiroacetalization catalysed by confined Brønsted acids. *Nature* **2012**, *483*, 315−319.

(234) Hamilton, J. Y.; Rössler, S. L.; Carreira, E. M. Enantio- and Diastereoselective Spiroketalization Catalyzed by Chiral Iridium Complex. *J. Am. Chem. Soc.* **2017**, *139*, 8082−8085.

(235) Ge, S.; Cao, W.; Kang, T.; Hu, B.; Zhang, H.; Su, Z.; Liu, X.; Feng, X. Bimetallic Catalytic Asymmetric Tandem Reaction of β-Alkynyl Ketones to Synthesize 6,6-Spiroketals. *Angew. Chem., Int. Ed.* **2019**, *58*, 4017−4021.

(236) Gu, Z.; Herrmann, A. T.; Zakarian, A. Dual Ti−Ru Catalysis in the Direct Radical Haloalkylation of N-Acyl Oxazolidinones. *Angew. Chem., Int. Ed.* **2011**, *50*, 7136−7139.

(237) Beaumont, S.; Ilardi, E. A.; Monroe, L. R.; Zakarian, A. Valence Tautomerism in Titanium Enolates: Catalytic Radical Haloalkylation and Application in the Total Synthesis of Neodysidenin. *J. Am. Chem. Soc.* **2010**, *132*, 1482−1483.

(238) Gu, Z.; Zakarian, A. Concise Total Synthesis of Sintokamides A, B, and E by a Unified, Protecting-Group-Free Strategy. *Angew. Chem., Int. Ed.* **2010**, *49*, 9702−9705.

(239) Zhao, Y.; Weix, D. J. Nickel-Catalyzed Regiodivergent Opening of Epoxides with Aryl Halides: Co-Catalysis Controls Regioselectivity. *J. Am. Chem. Soc.* **2014**, *136*, 48−51.

(240) Zhao, Y.; Weix, D. J. Enantioselective Cross-Coupling of meso-Epoxides with Aryl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 3237−3240.

(241) Peng, H.; Akhmedov, N. G.; Liang, Y.-F.; Jiao, N.; Shi, X. Synergistic Gold and Iron Dual Catalysis: Preferred Radical Addition toward Vinyl−Gold Intermediate over Alkene. *J. Am. Chem. Soc.* **2015**, *137*, 8912−8915.

(242) Huang, T.; Liu, X.; Lang, J.; Xu, J.; Lin, L.; Feng, X. Asymmetric Aerobic Oxidative Cross-Coupling of Tetrahydroisoquinolines with Alkynes. *ACS Catal.* **2017**, *7*, 5654−5660.

(243) Boess, E.; Schmitz, C.; Klussmann, M. A Comparative Mechanistic Study of Cu-Catalyzed Oxidative Coupling Reactions with *N*-Phenyltetrahydroisoquinoline. *J. Am. Chem. Soc.* **2012**, *134*, 5317−5325.

(244) Roberts, J. P.; Lee, C. Allylic Etherification via Ir(I)/Zn(II) Bimetallic Catalysis. *Org. Lett.* **2005**, *7*, 2679−2682.

(245) Huo, X.; He, R.; Zhang, X.; Zhang, W. An Ir/Zn Dual Catalysis for Enantio- and Diastereodivergent α-Allylation of α-Hydroxyketones. *J. Am. Chem. Soc.* **2016**, *138*, 11093−11096.

(246) Teichert, J. F.; Feringa, B. L. Phosphoramidites: Privileged Ligands in Asymmetric Catalysis. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486−2528.

(247) Trost, B. M.; Bartlett, M. J. ProPhenol-Catalyzed Asymmetric Additions by Spontaneously Assembled Dinuclear Main Group Metal Complexes. *Acc. Chem. Res.* **2015**, *48*, 688−701.

(248) He, R.; Liu, P.; Huo, X.; Zhang, W. Ir/Zn Dual Catalysis: Enantioselective and Diastereodivergent α-Allylation of Unprotected α-Hydroxy Indanones. *Org. Lett.* **2017**, *19*, 5513−5516.

(249) Liu, S.; Chen, K.; Lan, X.-C.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Synergistic silver/scandium catalysis for divergent synthesis of skeletally diverse chromene derivatives. *Chem. Commun.* **2017**, *53*, 10692−10695.

(250) Chen, K.; Liu, S.; Wang, D.; Hao, W.-J.; Zhou, P.; Tu, S.-J.; Jiang, B. Silver/Scandium-Cocatalyzed Bicyclization of β-Alkynyl Ketones Leading to Benzo[c]xanthenes and Naphtho[1,2-b]-benzofurans. *J. Org. Chem.* **2017**, *82*, 11524−11530.

(251) Sperry, J.; Wilson, Z. E.; Rathwell, D. C. K.; Brimble, M. A. Isolation, biological activity and synthesis of benzannulated spiroketal natural products. *Nat. Prod. Rep.* **2010**, *27*, 1117−1137.

(252) Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A. Branch-Selective Hydroarylation: Iodoarene−Olefin Cross-Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 12779−12782.

(253) Shevick, S. L.; Obradors, C.; Shenvi, R. A. Mechanistic Interrogation of Co/Ni-Dual Catalyzed Hydroarylation. *J. Am. Chem. Soc.* **2018**, *140*, 12056−12068.

(254) Green, S. A.; Huffman, T. R.; McCourt, R. O.; van der Puyl, V.; Shenvi, R. A. Hydroalkylation of Olefins To Form Quaternary Carbons. *J. Am. Chem. Soc.* **2019**, *141*, 7709−7714.

(255) Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A. Iron−Nickel Dual-Catalysis: A New Engine for Olefin Functionalization and the Formation of Quaternary Centers. *J. Am. Chem. Soc.* **2018**, *140*, 11317−11324.

(256) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417−1492.

(257) Chen, Z.; Rong, M.-Y.; Nie, J.; Zhu, X.-F.; Shi, B.-F.; Ma, J.-A. Catalytic alkylation of unactivated C(sp^3)−H bonds for C(sp^3)−C(sp^3) bond formation. *Chem. Soc. Rev.* **2019**, *48*, 4921−4942.

(258) Smith, R. T.; Zhang, X.; Rincón, J. A.; Agejas, J.; Mateos, C.; Barberis, M.; García-Cerrada, S.; de Frutos, O.; MacMillan, D. W. C. Metallaphotoredox-Catalyzed Cross-Electrophile Csp^3−Csp^3 Coupling of Aliphatic Bromides. *J. Am. Chem. Soc.* **2018**, *140*, 17433−17438.

(259) Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. Radicals: Reactive Intermediates with Translational Potential. *J. Am. Chem. Soc.* **2016**, *138*, 12692−12714.

(260) Komeyama, K.; Michiyuki, T.; Osaka, I. Nickel/Cobalt-Catalyzed C(sp^3)−C(sp^3) Cross-Coupling of Alkyl Halides with Alkyl Tosylates. *ACS Catal.* **2019**, *9*, 9285−9291.

(261) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vásquez-Céspedes, S.; Shevick, S. L.; Shenvi, R. A. The High Chemofidelity of Metal-Catalyzed Hydrogen Atom Transfer. *Acc. Chem. Res.* **2018**, *51*, 2628−2640.