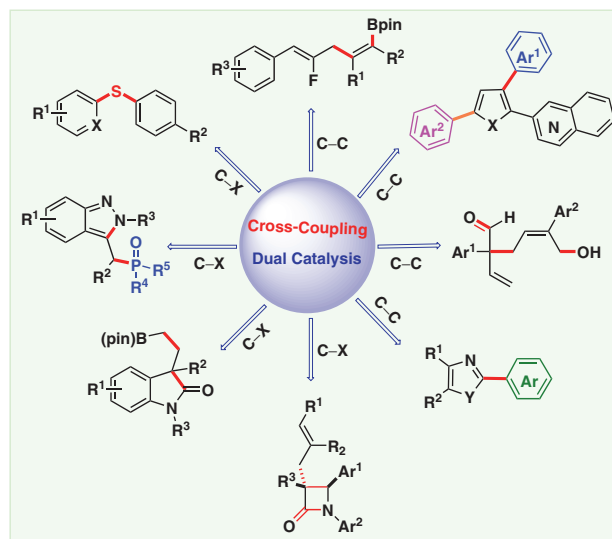THIEME
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Review

Recent Applications on Dual-Catalysis for C–C and C–X Cross-Coupling Reactions

Dakoju Ravi Kishore◊
Chinnabattigalla Sreenivasulu◊
Anil Balajirao Dapkekar
Gedu Satyanarayana* 🔳

Department of Chemistry, Indian Institute of Technology
Hyderabad, Kandi-502285, Sangareddy, Telangana, India
gvsatya@chy.iith.ac.in

◊ These authors contributed equally

Dedicated to Prof. Günter Helmchen on the occasion of his
81st birthday

Abstract Coupling reactions stand amid the most significant reactions in synthetic organic chemistry. Of late, these coupling strategies are being viewed as a versatile synthetic tool for a wide range of organic transformations in many sectors of chemistry, ranging from indispensable synthetic scaffolds and natural products of biological significance to novel organic materials. Further, the use of dual-catalysis in accomplishing various interesting cross-coupling transformations is an emerging field in synthetic organic chemistry, owing to their high catalytic performance rather than the use of a single catalyst. In recent years, synthetic organic chemists have given considerable attention to hetero-dual catalysis; wherein these catalytic systems have been employed for the construction of versatile carbon–carbon [C(sp^3)–C(sp^3), C(sp^3)–C(sp^2), C(sp^2)–C(sp^2)] and carbon–heteroatom (C–N, C–O, C–P, C–S) bonds. Therefore, in this mini-review, we are emphasizing recently developed various cross-coupling reactions catalysed by transition-metal dual-catalysis (i.e., using palladium and copper catalysts, but omitting the reports on photoredox/metal catalysis).

Key words dual-metal catalysis, cross-coupling reactions, Kinugasa reaction, palladium catalysis, heterocycles

1 Introduction

Cross-coupling reactions, which traditionally involve transition metals, are one of the most significant chemical processes in synthetic organic chemistry.[1–4] A cross-coupling reaction is specified as the substitution process of alkyl, vinyl, and aryl halides or pseudohalides by carbon as well heteroatom-based nucleophiles under transition-metal (TM) catalysis, leading to the efficient construction of new C–C and C–X (X = hetero atoms) bonds. Often, an electrophile (e.g., halide) and a nucleophile (e.g., organometallic regent) serve as coupling partners, forming new chemical bonds with the loss of activating groups. These routes are considered an important synthetic tool in various domains of chemistry to prepare a wide range of organic molecules, ranging from natural and unnatural products of biological relevance to novel organic materials. Almost for two decades, cross-coupling reactions have had a significant influence on drug discovery and medicinal chemistry.[5–7] Expanding the spectrum of coupling partners is one of the primary research aims in the cross-coupling field. For example, an organoborane nucleophile is used in the Suzuki–Miyaura reaction;[8,9] whereas the Stille reaction employs an organotin nucleophile.[10–12] The significant contribution to palladium cross-coupling reactions was acknowledged in 2010 with the award of the Nobel Prize in chemistry.[13,14] Over the years, several attempts have been made to activate a substrate with a single transition metal catalyst to enable a specific transformation. For example, palladium–phosphine-based complexes, are frequently used in cross-coupling reactions owing to their conventional oxidative addition, facilitating coupling, and reductive elimination cata-

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lytic cycle mechanism.[15–18] For decades, expensive phosphine ligands have been designed with improved reactivity. On the other hand, considerable attention has also been given to copper catalysis in the field of cross-coupling reactions during the last decade, owing the low cost of the catalysts, good functional group tolerance, high abundance, and low toxicity.[19–25] Besides which, copper plays a crucial role in cross-coupling reactions, and its scope and practicality in the bond formation processes of C–N, C–O, C–P, and C–C bonds has substantially grown. Most well-known catalytic processes use a single catalyst to achieve the de-

Biographical Sketches

Dakoju Ravi Kishore was born and brought up in Andhra Pradesh, India. He obtained his B.Sc. degree from V. S. M. College (Ramachandrapuram, Andhra Pradesh, India), affiliated with Andhra University. Subsequently, he pursued his M.Sc. in chemistry from the same college. He joined Prof. G. Satyanarayana's group in 2016 as a Ph.D. scholar in the Department of Chemistry, Indian Institute of Technology Hyderabad, where he is studying acid- and transition-metal-catalysed organic transformations.

Dr. Chinnabattigalla Sreenivasulu was born in Andhra Pradesh, India. He completed his B.Sc. in Chemistry from Viswam Degree and PG College, Angallu, Andhra Pradesh. Then he moved to Tirupati to pursue his M.Sc. in Chemistry from the Department of Chemistry, Sri Venkateswara University, Andhra Pradesh. After a brief research stay as an Internship Fellow at IISc, Bangalore, under the IAS Scheme, he received a Ph.D. from the Department of Chemistry, Indian Institute of Technology Hyderabad, under the supervision of Prof. G Satyanarayana, in May 2022. During his Ph.D., he worked on transition-metal-catalysed heterocyclic compounds synthesis.

Anil Balajirao Dapkekar was born in Maharashtra state, India. He completed his B.Sc. from Shivaji College Udgir, affiliated with SRTM University Nanded, Maharashtra. Subsequently, he pursued his M.Sc. in Chemistry at the School of Chemical Sciences, Swami Ramanand Teerth Marathwada University Nanded (MH, India). Later, in January 2021, he joined as a research scholar at the Indian Institute of Technology Hyderabad, under the guidance of Prof. G Satyanarayana. Presently, he is working on transition metal catalysis.

Prof. G. Satyanarayana received his Ph.D. from the Department of Organic Chemistry, Indian Institute of Science (Bangalore, Karnataka, India) in 2005, under the supervision of the late Prof. A. Srikrishna. Subsequently, he worked as a Research Associate in the same Department under the supervision of Prof. K. R. Prasad. He then moved to the Universität Tübingen, where he pursued his postdoctoral research as an Alexander von Humboldt (AvH) Fellow (2007–2008), under the guidance of Prof. Martin E. Maier. Afterwards, he joined the research group of Prof. Günter Helmchen, Institute of Organic Chemistry, University of Heidelberg (2008–2009). Subsequently, he joined the Department of Chemistry, IIT Hyderabad, as Assistant Professor in 2009, wherein he is currently working as Professor. His research interests include developing new methodologies and domino processes, transition metal-catalysis, remote C–H functionalization, and acid-driven reactions.
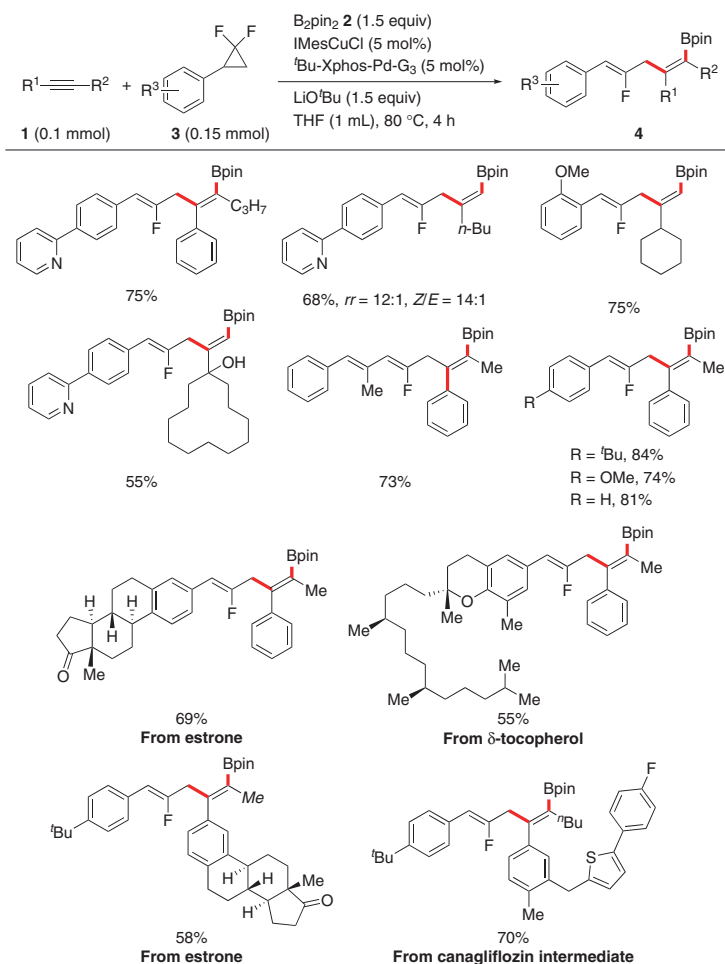
Scheme 1 Selected examples of boryl-substituted monofluoroalkenes **4** via *cis*-borylfluoroallylation of alkynes **1**

sired chemical transformation. On the other side, in a mono-catalytic approach, one of the reactants is activated by the use of sub-stoichiometric quantities of the catalyst, whereas the second reactant often needs an extra activa-
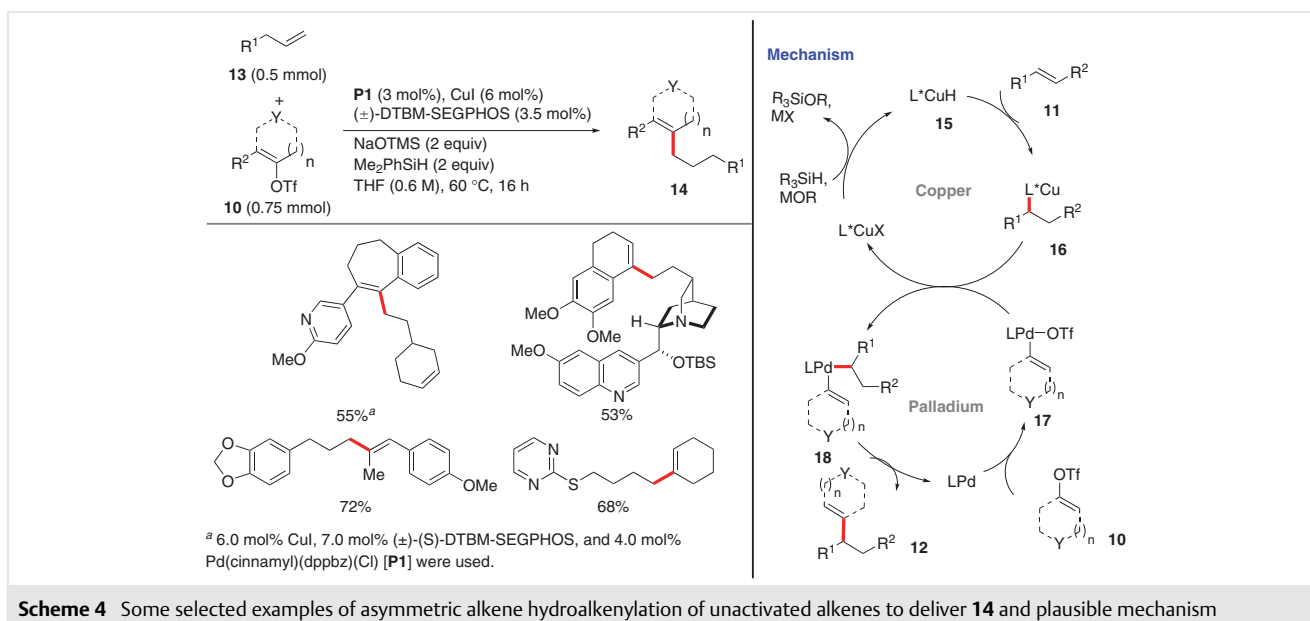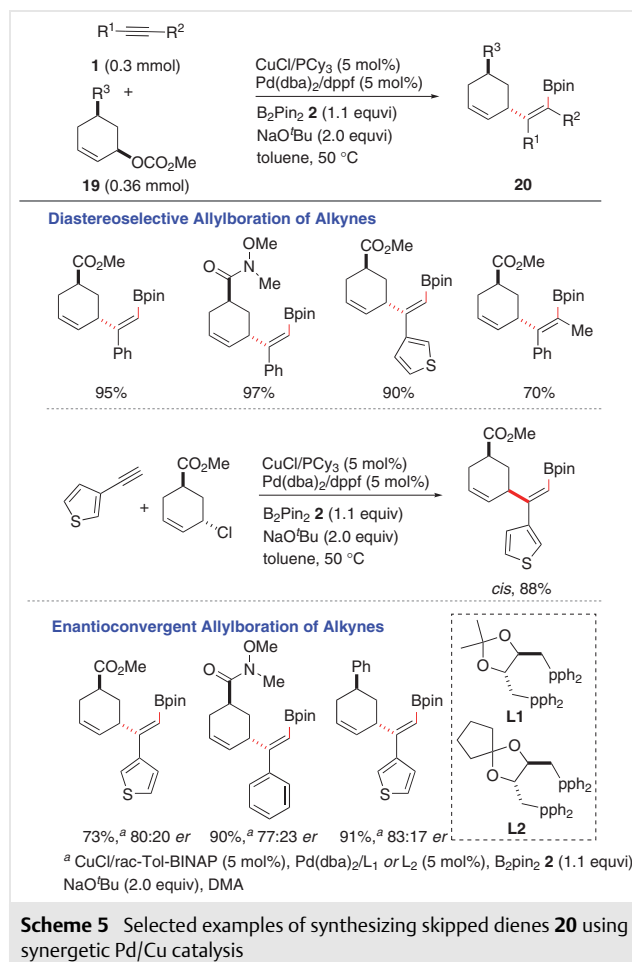
tion through a stoichiometric quantity of an activating agent/pre-functional group manipulation to facilitate the required transformation. Concerning environmental and economic aspects, it is desirable to develop chemical pro-
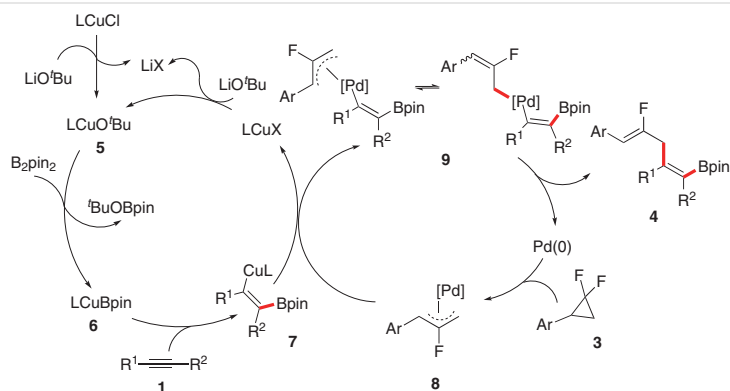
Scheme 2 Proposed mechanism for formation of monofluoroalkenes **4** via *cis*-borylfluoroallylation of alkynes **1**

Scheme 3 Some selected examples of asymmetric alkene hydroalkenylation **12**
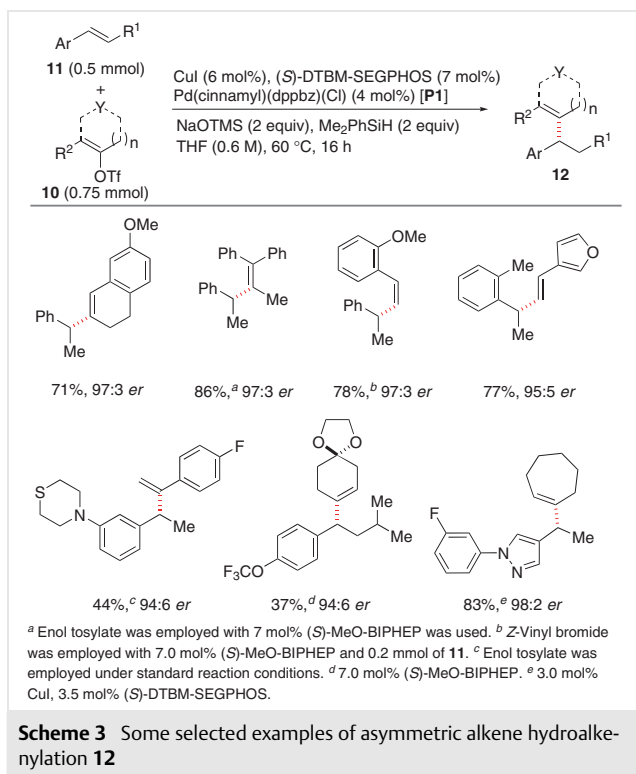
cesses that might improve the chemical utility and efficiency of catalyst-driven reactions while reducing waste. Chemical space diversity is generally limited to one-pot reactions catalysed by a single transition metal complex in order to access a wide range of reactions in a single vessel.[26–30] Thus, dual catalysis, where two catalysts can react with two substrates to produce active intermediates, has become popu-

Scheme 5 Selected examples of synthesizing skipped dienes **20** using synergetic Pd/Cu catalysis

Scheme 4 Some selected examples of asymmetric alkene hydroalkenylation of unactivated alkenes to deliver **14** and plausible mechanism

lar, allowing multi-transformation processes with high regioselectivity.[31–33] Such types of catalytic systems provide more opportunities, not only because they allow the successful delivery of a significant percentage of transformations in a single step, but also allow tailoring of each catalytic cycle to produce selective and divergent products. In particular, as a result of these factors, dual catalysis has started to develop as a research methodology of considerable interest, among various areas.[34–37] Of late, there has

been a surge of interest in combining distinct types of catalysis to enable novel chemical reactivity.[37–42] In that context, alternative catalytic approaches that go beyond the single-site method might lead to the discovery of alternative reactivity and selectivity regimes. Multicatalytic systems such as cascade catalysis (domino or tandem catalysis),[43,44] bifunctional catalysis,[45,46] double activation catalysis, and synergistic catalysis have been developed to date.[34,37,47–49] The use of dual-metal catalytic systems in the synthesis of new compounds has increased significantly during the past twenty years.[50–52] In addition to improving selectivity and reactivity, these novel methods can also greatly enhance the reaction processes that would not be feasible with a single metal catalyst, enabling the synthesis of novel compounds and molecular frameworks. Synergistic catalysis has often been studied by combining a transition metal catalyst with Lewis acids,[53,54] organocatalysts (e.g., Brønsted acids, N-heterocyclic carbenes, chiral amines, and Lewis bases),[55–67] or Lewis acids with N-heterocyclic carbenes.[68–70] The use of bimetallic catalysts for cross-coupling reactions is one such alternate strategy emphasized in this review.

2 Cu/Pd-Catalysed Bond Formation

2.1 Cu/Pd-Catalysed C(sp^3)–C(sp^2) Bond Formation

The research group of Gong and Fu has disclosed the synthesis of boryl-substituted monofluoroalkenes 4 via cis-borofluoroallylation using Pd/Cu dual catalysis, involving alkynes 1, B$_2$pin$_2$ 2, and gem-difluorocyclopropanes 3 as starting materials as shown in Scheme 1. Remarkably, the reported method gives easy and quick entry to a wide array of borylated monofluoroalkenes 4 with high regio- and stereoselectivities. Besides which, further studies were carried out to validate the applicability of this three-component coupling reaction, and late-stage transformations on complex molecules, such as δ-tocopherol, estrone, and canagliflozin derivatives, were examined. Furthermore, the silylation-fluoroallylation process proceeded efficiently, yielding the appropriate silyl monofluoroalkene product 4. Notably,
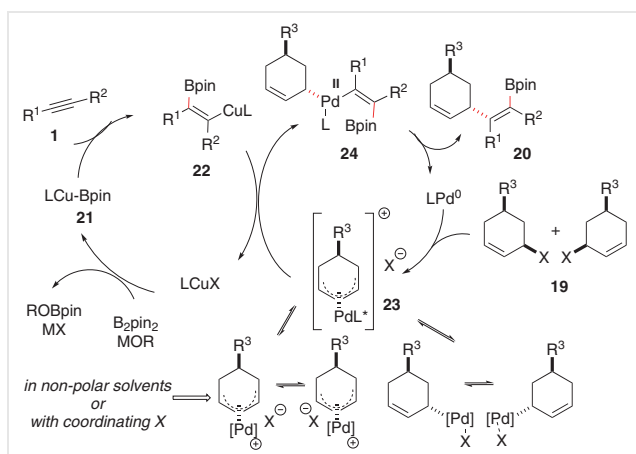
Scheme 6 Plausible reaction mechanism for generating skipped dienes 20
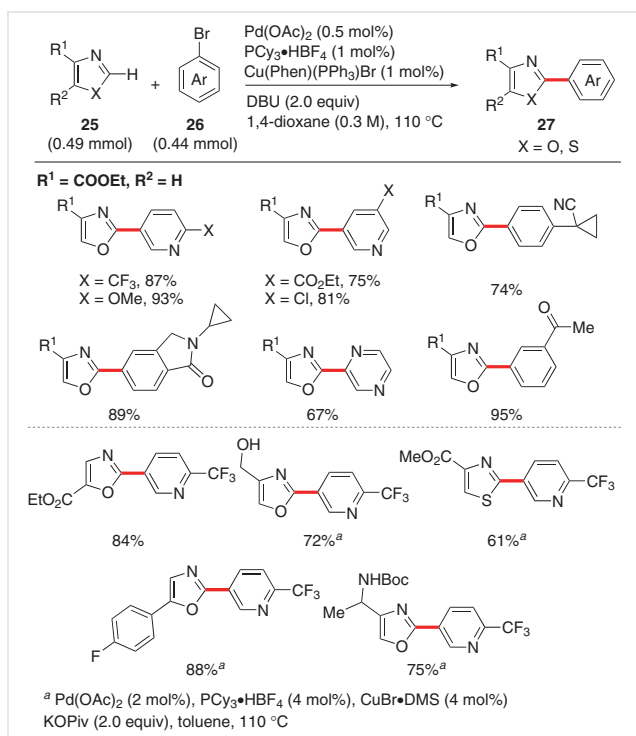
**Scheme 7** The C–2 arylation process to obtain azole derivatives 25 via Pd/Cu catalysis
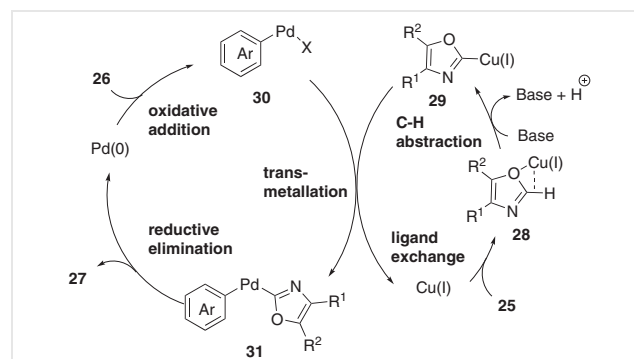
Scheme 8 Plausible reaction mechanism for C2 arylation to give 27

the use of Cu catalysts allows for the simple insertion of Cu–B into triple bonds via the intermediate LCuBpin. Concurrently, the use of palladium catalysts with sterically hindered phosphine ligands favors the ring-opening coupling of *gem*-difluorinated cyclopropanes, followed by transmetallation and reductive elimination to lead to the final monofluorinated alkenes **4** as shown in Scheme 2.[71]

In another report, Buchwald *et al.* reported an asymmetric olefin hydroalkenylation approach that enables the fabrication of various *α*-stereogenic olefins **12** and olefins **14** from easily accessible starting materials as depicted in Schemes 3 and 4.[72] This methodology has successfully coupled vinylarenes **11** and unactivated olefins **13** using CuH and Pd catalysis, from the easily accessible enol triflates **10** as coupling partners. This method made use of an *in situ* produced Cu(I)–alkyl species as well as readily accessible enol triflates. Notably, the activated olefins such as vinylarenes successfully delivered the asymmetric Markovnikov hydroalkenylation products **12** (Scheme 3), whereas the

anti-Markovnikov hydroalkenylation products **14** were obtained from unactivated olefins **13** (Scheme 4, left side); wherein the readily available enol triflates were utilized as alkenyl coupling partners. The suggested synergism involves the CuH and Pd catalytic cycles (Scheme 4, right side). Significantly, the combination of CuH and Pd catalysed reactions enabled access to tri- and tetrasubstituted alkene classes **12** and **14** that are difficult to synthesize using conventional methods.

Mastrel and his research group have disclosed a three-component coupling reaction involving alkynes **1**, bis(pinacolato)diborane **2**, and allyl carbonates **19** for the synthesis of skipped dienes using synergetic Cu/Pd catalysis via allylboration of alkynes **1** and racemic allyl carbonates **19**. Significantly, new $C(sp^2)$–B and $C(sp^3)$–$C(sp^2)$ bonds are formed in a single operation as shown in Scheme 5.[73] The addition of a Cu–Bpin complex across the alkyne catalyses the generation of a *β*-boryl-alkenylcopper species **22**, which undergoes transmetallation with **23** to furnish the
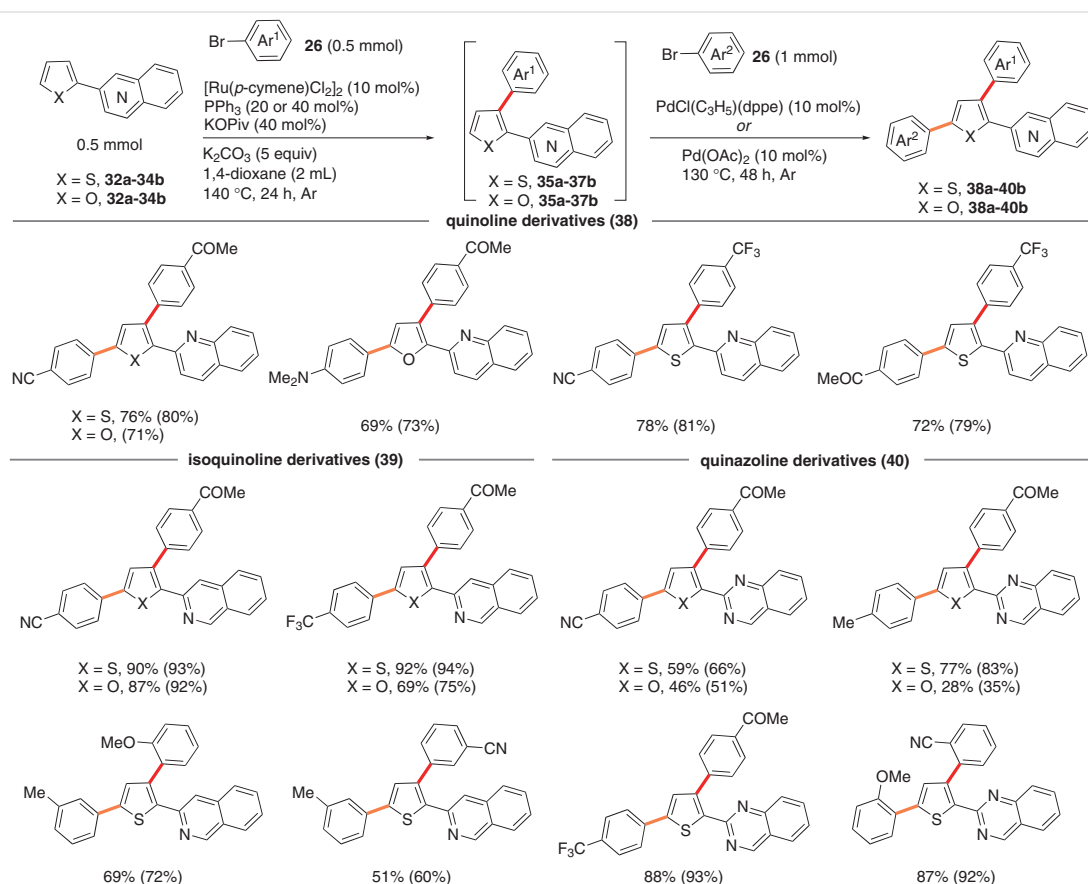
Scheme 9 Regioselective direct C–H arylation of five-membered heterocycles **32–34** via Ru/Pd catalysis

Scheme 10 Stereodivergent synthesis of alkenyl pyridines **42/42'** via pyridinium salts **41**
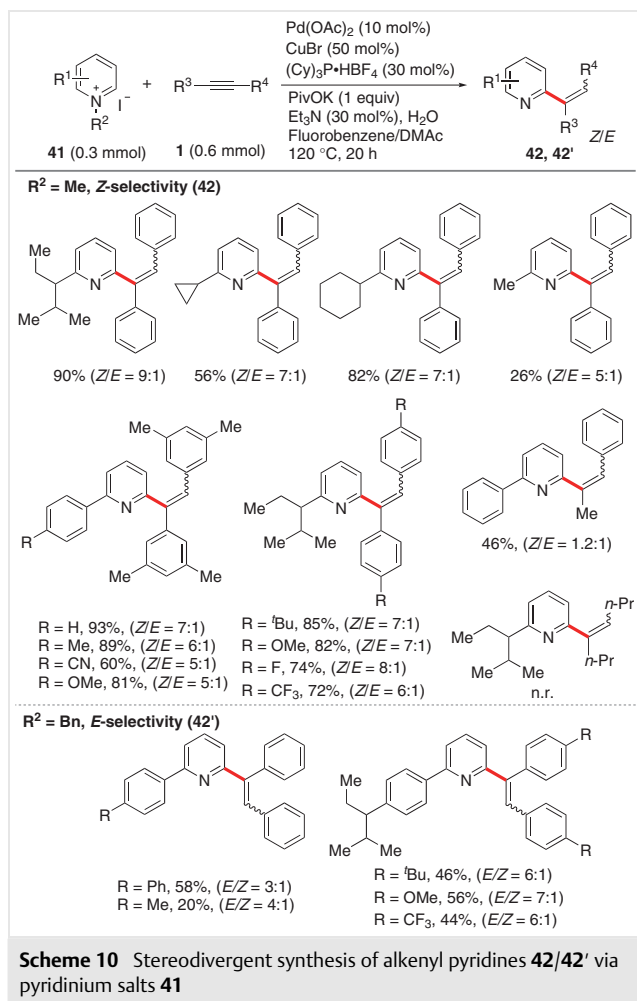
intermediate **24**. Subsequently, intermediate **24** undergoes reductive elimination to result in the final product **20** as depicted in Scheme 6.

## 2.2 Cu/Pd-Catalysed C(sp^2)–C(sp^2) Bond Formation

Similarly, the research group of Piou and Slutskyy has demonstrated C2-arylation of azole derivatives **25** using Pd/Cu dual catalytic systems. The optimization conditions revealed that a dual catalytic system of Pd(OAc)$_2$, PCy$_3$·HBF$_4$, and Cu(Phen)(PPh$_3$)Br allowed the formation of the coupling products **27** in fair to excellent yields. In addition, the reaction has been explored with alternative Cu co-catalysts, such as CuCl, CuBr, CuI, or Cu(NCMe)$_4$PF$_6$; however, these combinations resulted in poor yields. Using only 0.5–2 mol% of Pd catalyst, this dual-catalytic approach showed high catalyst turnover. Furthermore, control experiments showed that the Pd/Cu co-catalyst plays a crucial role to achieve maximum reaction efficiency, as both metallic species take part in the reaction cycle. The suggested mechanism involves a bimetallic catalytic system that operates si-

multaneously with Pd(0) and Cu(I) species. A variety of aryl bromides **26** and azoles **25** were examined and found to be amenable as shown in Scheme 7.[74] The key step in the mechanism includes the Cu intermediate **29**, which undergoes transmetallation with ArPd(II) complex **30** (generated via oxidative addition of Pd(0) to bromopyridine **26**), and liberates the Cu(I) catalyst and **31**. Subsequently, intermediate **31** undergoes reductive elimination to result in the final product **27** (Scheme 8).

Brodnik *et al.* have reported a direct arylation strategy on thiophenes and furans **32** using aryl bromides **26** as coupling partners, under Ru(II)/Pd(0) dual catalysis. Notably, the reported method was achieved regioselectively by carrying out the arylation reaction on thiophenes **32a–34a** and furans **32b–34b** in a sequential manner in a single flask, using nitrogen-based directing groups to achieve a Ru-catalysed C3 arylation followed by a Pd-catalysed C5 arylation, resulting in highly conjugated heterocycles **38–40** in excellent yields up to 93% (Scheme 9). An initial investigation was carried out with quinolone-catalysed C3 arylations on thiophene/furan derivatives. Following on from the Ru-catalysed functionalization, Pd-catalysed arylation was investigated, which occurred at C5 of the five-membered heterocycles. Subsequently, other azine compounds, such as isoquinoline and quinazoline derivatives were investigated as directing groups. Consequently, isoquinoline derivative **33a** was shown to be the most reactive, followed by the quinazoline **34a**, with quinoline **32a** as the least reactive substrate. Some selected examples are as illustrated in Scheme 9.[75]

Fu, Chen, and co-workers disclosed the first example of the stereodivergent synthesis of alkenylpyridines **42** using a Pd/Cu dual catalytic system through the activation of pyridinium salts **41** to alkenylate selectively at C2 of pyridines with internal alkynes **1**. Significantly, the configuration of the resulting alkenylpyridines could be tuned by choosing the appropriate *N*-alkyl groups of the pyridinium salts, enabling the synthesis of both *Z*- and *E*-alkenylpyridines **42** with high regio- and stereoselectivities (Scheme 10). Notably, the *Z*-enriched alkenylpyridines **42** were selectively synthesized using *N*-methylpyridinium salts, whilst the *E*-enriched alkenylpyridines **42'** were favored using *N*-benzylpyridinium salts; reportedly due to the differing de-alkylation abilities of the *N*-alkylpyridinium salts **41**. Overall, this approach has a broad substrate scope, excellent functional group compatibility, and is easily scalable. A plausible mechanism is depicted in Scheme 11.[76]

Minami, Hiyami *et al.* established a dual-metal catalytic system involving Pd/Cu catalysts for the cross-coupling of bromoarenes **26** with aryl(trialkyl)silanes **51**. Significantly, this method enabled the cross-coupling of various aryl(trialkyl)silanes [e.g., trimethyl, triethyl, triisopropyl, and *tert*-butyldimethyl aryl silanes] with various aryl bromides **26** to deliver the anticipated coupling products **52**. It was

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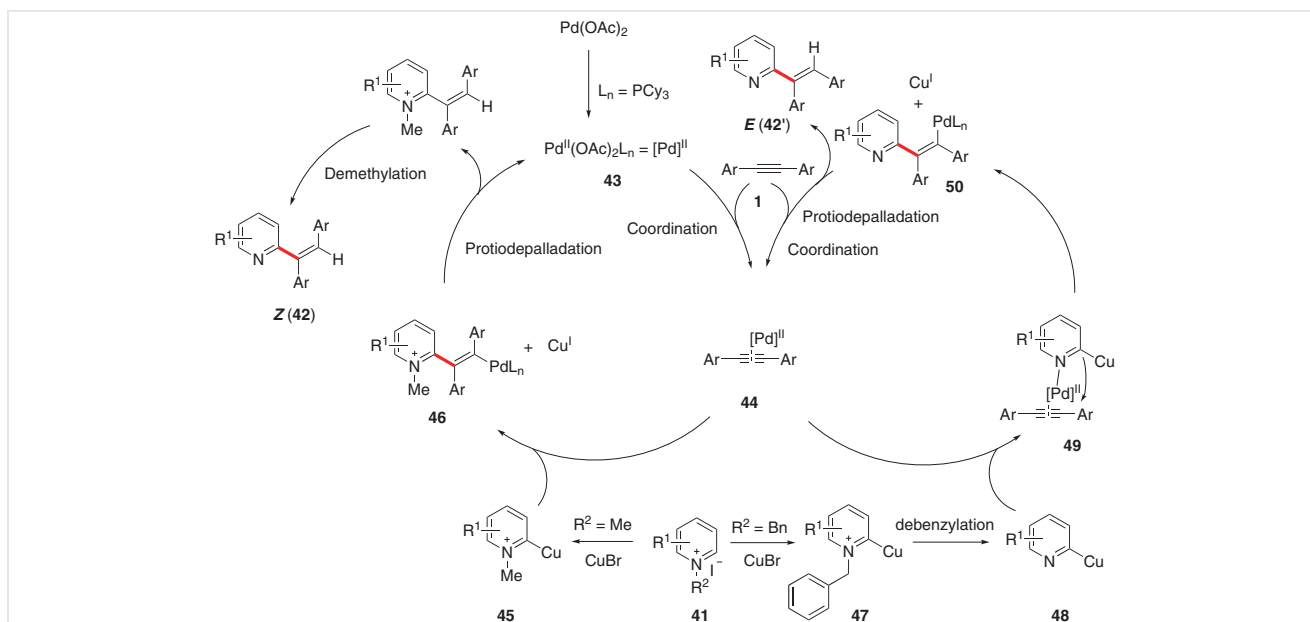
Scheme 11 Plausible reaction mechanism for constructing Z and E enriched alkenyl pyridines **42/42′**
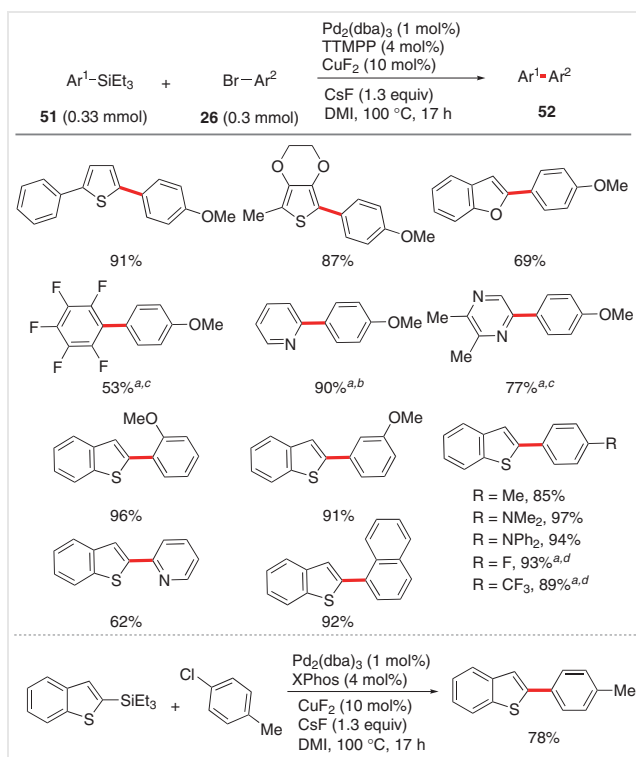
Scheme 12 Pd/Cu-catalysed cross-coupling of bromoarenes **26** and aryl(trialkyl)silanes **51**. [a] Reaction at 120 °C; [b] PPh$_2$(2-NMe$_2$C$_6$H$_4$) was used instead of TTMPP; [c] XPhos was used instead of TTMPP, heated at 120 °C; [d] JohnPhos was used instead of TTMPP.

found the combination of CuF$_2$, Pd$_2$(dba)$_3$/tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP), and CsF in DMI at 100 °C, gave the desired biaryl products **52** in excellent yields. Fur-

thermore, a less reactive aryl chloride was also coupled under the Pd/Cu^{II} catalysis, in the presence of the XPhos ligand, and yielded the corresponding product in 78% yield (Scheme 12).[77]

2.3 Cu/Pd-Catalysed C(*sp*)–C(*sp^2*) Bond Formation

Gandon, Roulland, *et al.* have reported the synthesis of *E*-1,3-enynes **55** in a stereoselective manner via alkyne hydrocarbation of allenes (AHA), using terminal alkynes **54** and allenes **53** under Pd and Cu cooperative dual catalysis. Significantly, the *E*-1,3-enynes **55** are furnished with high regio-/stereoselectivities, good atomic economy, and high yields. Based on DFT calculations and experimental observations, the authors suggested a non-traditional but coherent process. It was proposed that a Pd^{II}/Pd^{IV} catalytic cycle is involved, as well as transition states tightly structured by H-bonds with Pd counterions and an oxidative addition triggered by a stereodeterminant H$^+$ transfer (Scheme 13).[78]

2.4 Cu/Pd-Catalysed C(*sp^3*)–C(*sp^3*) Bond Formation

The asymmetric synthesis of products containing a quaternary stereocenter is a key construct in organic synthesis. Moreover, such prevalent motifs are widely present in bioactive natural substances. In 2021, Kleij *et al.* reported a dual metal-catalysed decarboxylative C(*sp^3*)–C(*sp^3*) bond-forming approach for the asymmetric synthesis of highly functionalized compounds bearing quaternary carbon center from cyclic vinyl carbonates **63**. In this protocol, the authors screened a broad range of ligands, bases, and chiral diphosphine ligands, under the influence of different con-
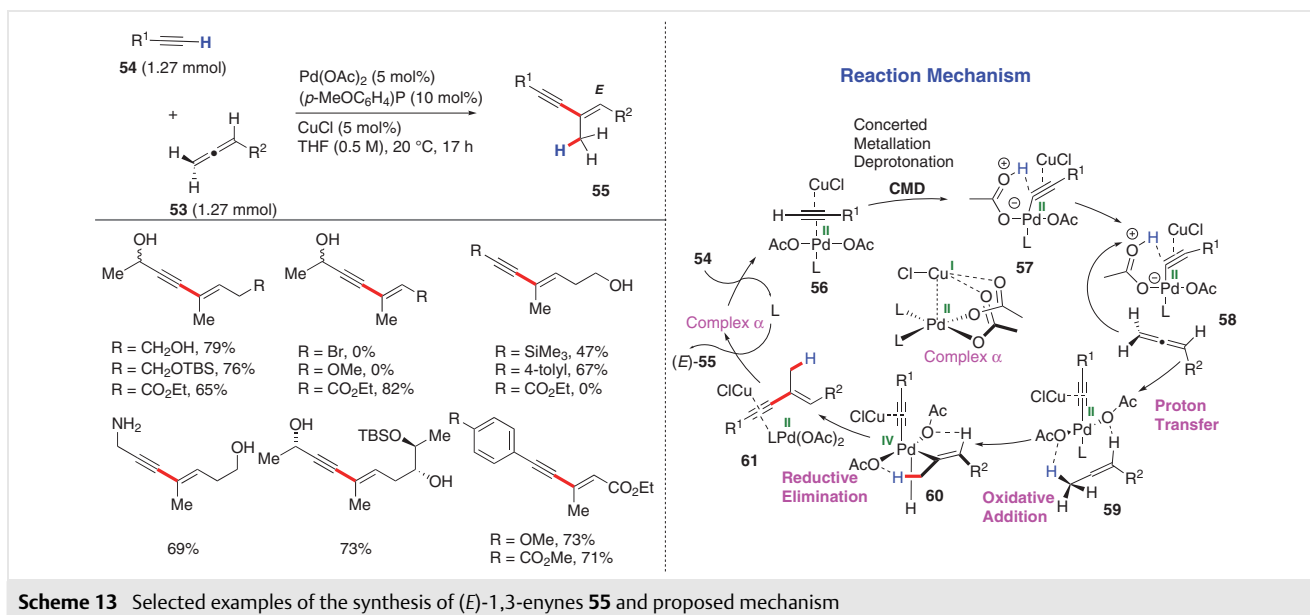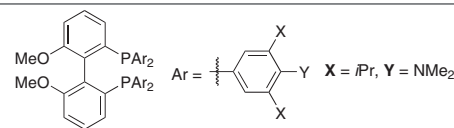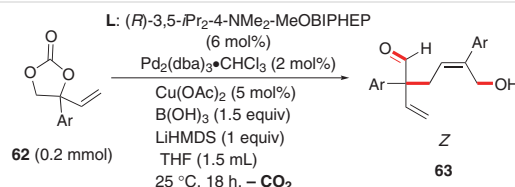
Scheme 13 Selected examples of the synthesis of (*E*)-1,3-enynes **55** and proposed mechanism

centrations and reaction temperatures to generate the cross-coupling products. The required Pd catalyst was synthesized from (*R*)-3,5-*i*Pr$_2$-4-NMe$_2$-MeOBIPHEP, which was proved to be effective to achieve good enantiomeric excess (*ee*), as depicted in Scheme 14.[79]
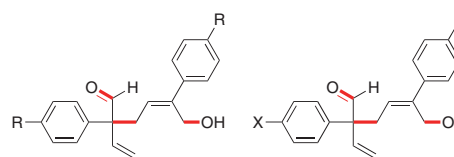
2.5 Cu/Pd-Catalysed C–X (X = B, N, P, S, Si) Bond Formation

The research group of Qu and Chen has reported the synthesis of borylated 3,3-disubstituted oxindoles **66** via domino cyclization/deborylation starting from 1,1-diborylmethane **65** and alkene-tethered carbamoyl chlorides **64** (Scheme 15, left side). Notably, the oxindole derivatives **66** with a C(*sp*^{3})–B bond, could be used for further functionalization via the formation of new C–C and C–X bonds. Since the products formed are versatile intermediates, they have been further elaborated synthetically due to the presence of the C(*sp*^{3})–B bond. Thus, transformations, such as halogenations (F, Br, and I), Cham–Lam coupling with *N*-methylaniline, and treatment of oxindoles with vinylmagnesium bromide under I$_2$, were successfully employed for late-stage transformations (Scheme 15, right side).[80] The mechanism for the formation of the borylated 3,3-oxindole derivatives **66** is shown in Scheme 16.

Lin *et al.* disclosed a protocol for the synthesis of phosphorated 2*H*-indazoles **74** via domino C–N and C–P bond formation using a Cu/Pd cooperative dual catalytic system, involving 2-alkynyl azobenzenes **72** and diarylphosphine oxides or phosphonates **73** (Scheme 17).[81] This method of-
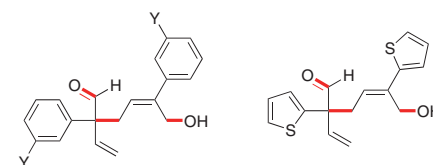

Scheme 14 Substrate scope for the synthesis of targets **63**
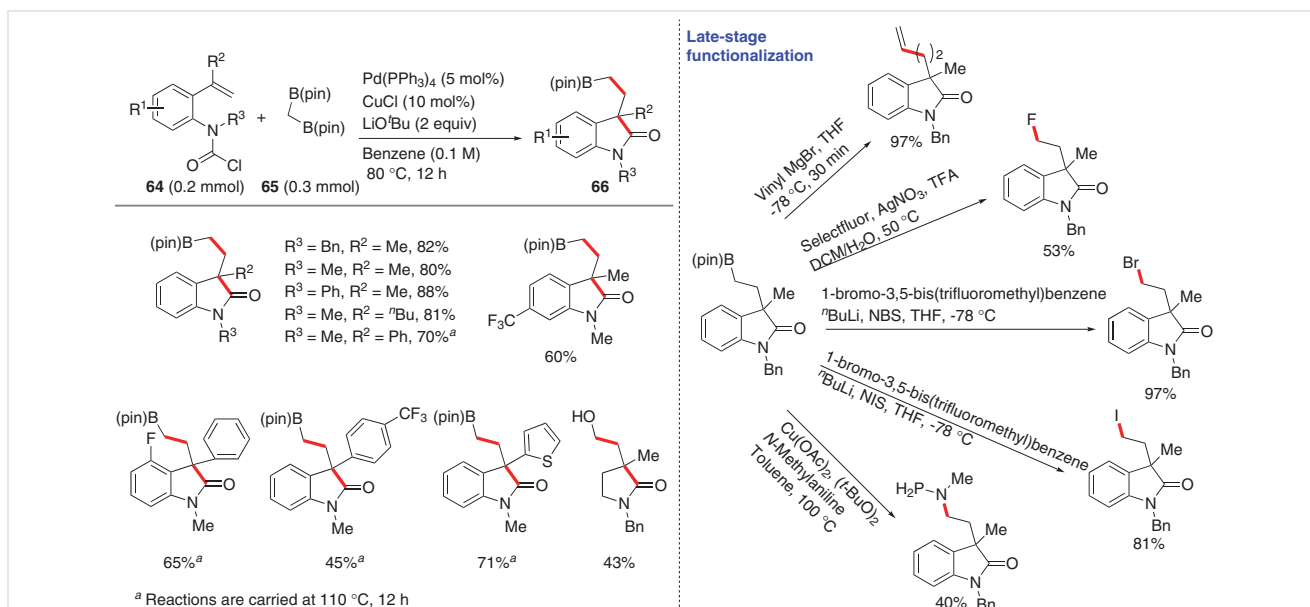
Scheme 15 Selected examples of borylated 3,3-disubstituted oxindole derivatives **66**
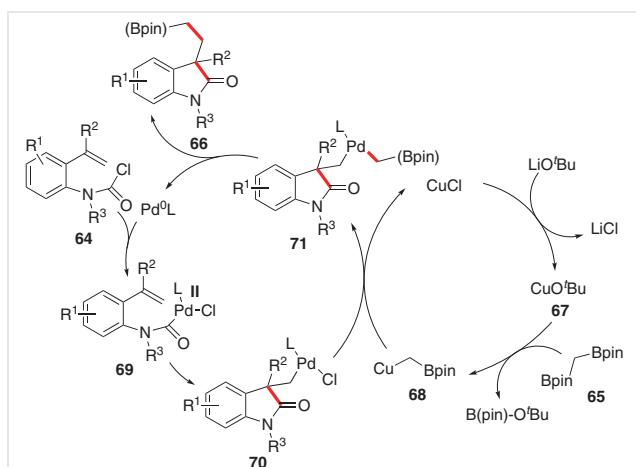
Scheme 16 Plausible mechanism for the synthesis of borylated 3,3-disubstituted oxindoles **66**

fered a practical approach to obtain several phosphorus 2H-indazoles **74** in moderate to good yields, and with good tolerance of functional groups. Based on control experiments, the mechanism is proposed to proceed via a copper carbene intermediate **75**, which further undergoes transmetallation with the palladium catalyst to deliver palladium carbene intermediate **76**. Subsequently, phosphinous acid **73′** (the tautomeric form of H-phosphonate) reacts with **76** to offer Pd(II) intermediate **77** in the presence of a base, which fur-

ther undergoes migratory insertion and delivers the intermediate **78**. Finally, the target product **74** is formed via protonation of the intermediate **78** as shown in Scheme 18.

An efficient dual catalysis strategy for the construction of unsymmetrical aryl sulfides **81** has been reported by Khakyzadeh *et al.* This method uses phenols **79**, arylboronic acids **80**, and S_8(II) as starting materials (Scheme 19). The designed palladium encapsulated on nano-silica-based (SiO₂@OL@Pd) catalyst and CuI were employed for this purpose. This method converted the free hydroxyl group of phenols **79** into phenolic compounds **82** (Scheme 20), which are more active as coupling partners in C–S bond-forming processes than aryl halides. Notably, nanomaterial-based catalysts have a relatively high surface area to volume ratio, which increases the interaction between the reactants and the catalyst and, as a result, increases catalytic activity.

After synthesizing and characterizing SiO₂@OL@Pd(II), the authors shifted their attention to developing and improving a dual metal catalytic system involving Pd and Cu for C–O bond cleavage and subsequent C–S bond formation under mild and efficient conditions. Initially, when the reaction is carried out in the absence of [SiO₂@OL@Pd(II)], a poor yield of the desired product (21%) was isolated. Similar results (25%) were obtained when the reaction was carried out in the absence of CuI. The reaction was further studied with activating groups such as toluenesulfonyl chloride and acetic anhydride. In general, the reactions proceeded smoothly and furnished the final products in good to excel-

Scheme 17 Synthesis of phosphorated 2*H*-indazoles **74** using Cu/Pd cooperative catalysis
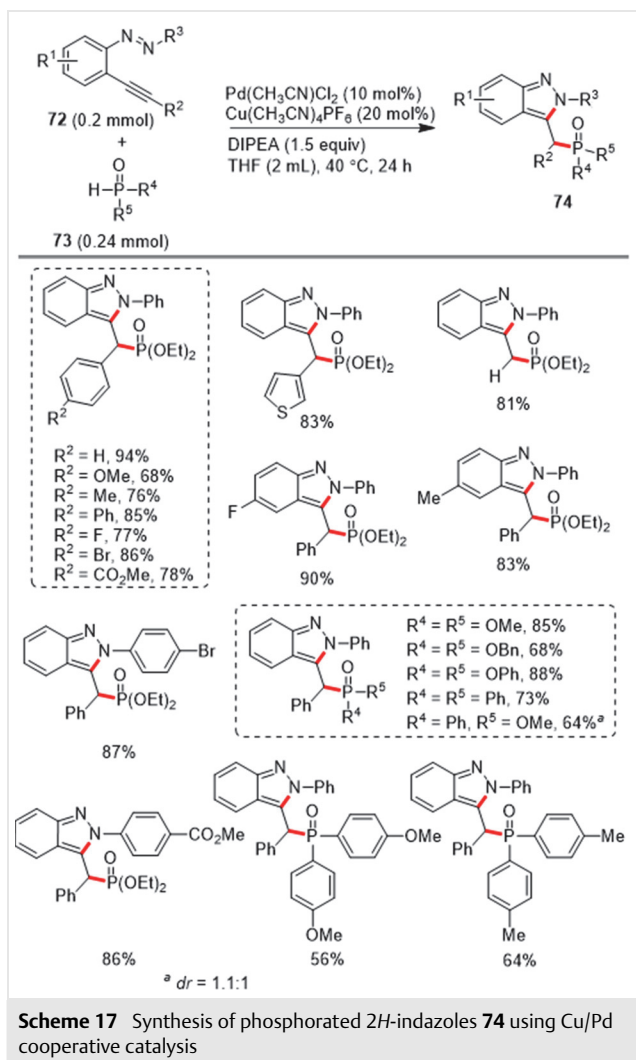
lent yields (70–96%) after activating the phenols **79** to form their active tosylates/acetates/triflates **82**. The studies revealed that the electronic properties of substituents flanking the phenols/arylboronic acids and steric effects pertaining to *ortho*-substituted substrates had a considerable impact on yields. Notably, most aromatic rings substituted with electron-withdrawing groups, such as CHO, CH_3CO, and NO_2, groups were effective in furnishing the desired products.[82]

The proposed reaction mechanism is as demonstrated in Scheme 20. Initially, the free phenol interacts with the activating agent (trifluoromethanesulfonyl chloride, toluenesulfonyl chloride, or acetic anhydride) to yield the phenolic intermediate **82**. Following the reaction of **82** with palladium, driven by oxidative addition and C–O bond dissociation, an aryl palladium species **83** is produced. Simultaneously, in another cycle, the reaction of arylboron-
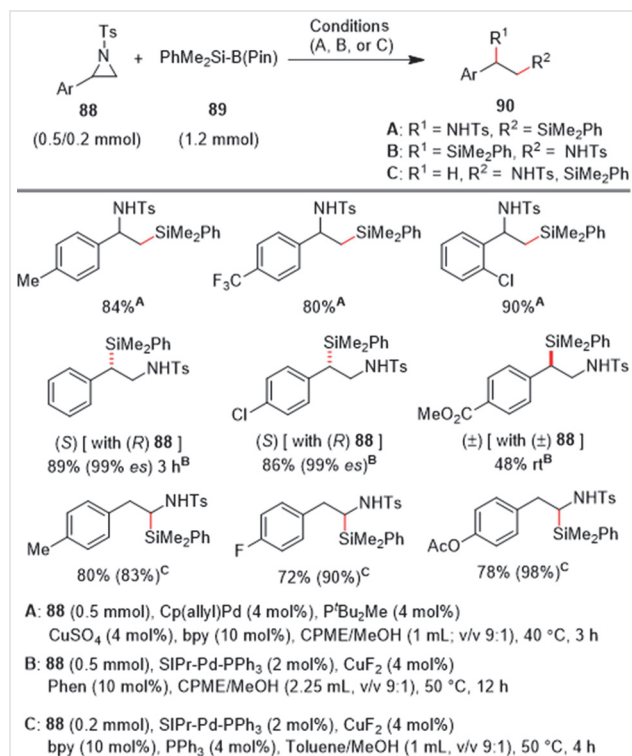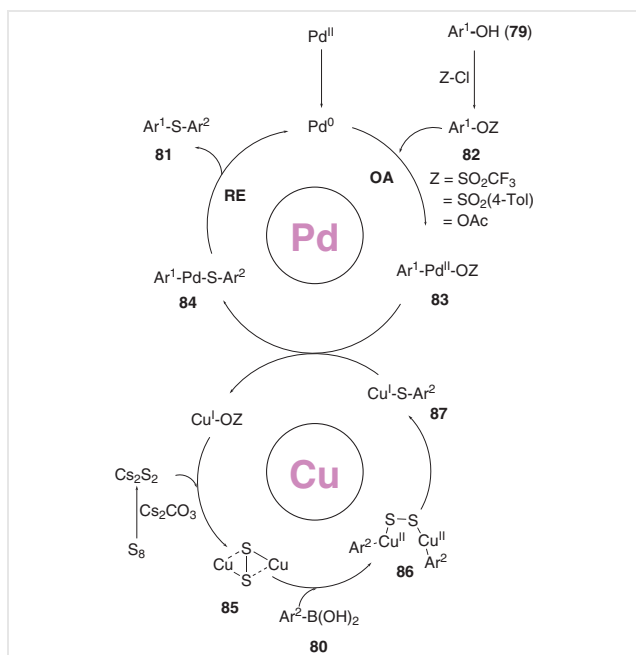

Scheme 18 Proposed mechanism for synthesis of **74**
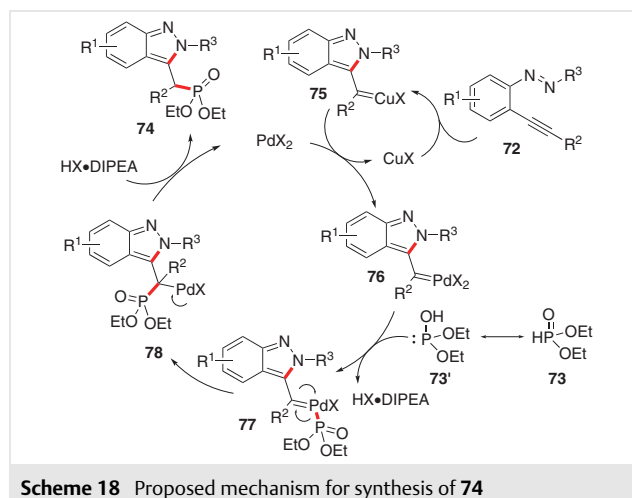
ic acid **80** with S_8 in the presence of CuI produces the organocopper thiolate intermediate **87**. Subsequently, intermediate **87** undergoes transmetallation with intermediate **83** to give intermediate **84**. In the final step, the targeted products **81** are obtained via reductive elimination of the intermediate **84**, thus, completing the catalytic cycle.

A synergistic Pd/Cu dual catalysis-controlled regioselective and stereospecific ring-opening C(*sp*³)–Si cross-coupling of 2-arylaziridines **88** using silylborane **89** was demonstrated for the synthesis of differently functionalized products **90** by Minakata *et al.* in 2019. The regioselectivity of the coupling is effectively controlled by choosing an appropriate combination of catalysts to produce two regioisomers of *β*-silylamines **90**, such as *β*-silyl-*α*-phenethylamines (condition A) and *β*-silyl-*β*-phenethylamines (condition C), in good to high yields. Furthermore, a slight variation in reaction conditions (conditions B) resulted in a significant shift in the reaction pathways, giving in an efficient and selective tandem reaction to yield *α*-silyl-*β*-phenethylamines. The detailed conditions and conversions are presented in Scheme 21.[83]

An efficient cooperative copper and palladium dual-catalysed (Cu/Pd) four-component borocarbonylation from readily available aryl iodides 92 or aryl triflates 93, vinylarenes 91, CO, and B2Pin2 2 for the formation of β-boryl ketones 94 and β-boryl vinyl esters 95 was demonstrated by Wu and co-workers in 2020. Incorporating a variety of electron-withdrawing or electron-donating groups at the meta/para-positions, aryl iodides were effectively converted into the required products 94/95 depending on the substrate and the conditions applied. This strategy enables the formation of various synthetically essential β-boryl ketones 94 with good to excellent yields. Furthermore, by applying appropriate p-tolyl triflates as the substrates instead of aryl halides, the reaction surprisingly generated β-boryl vinyl
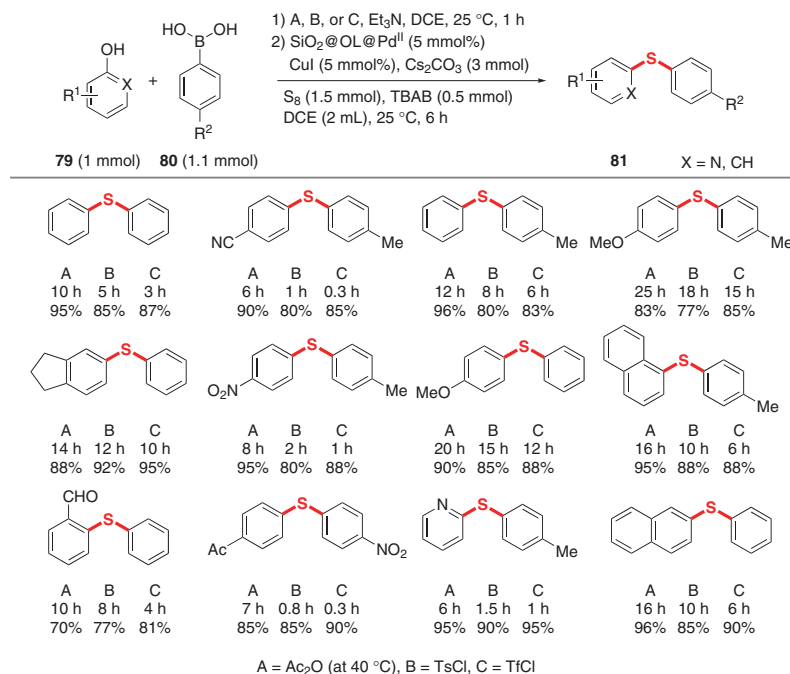
Scheme 19 Substrate scope for diaryl sulfide preparation

Scheme 20 Proposed mechanism for the synthesis of diaryl sulfides **81**

esters **95**, along with a trace of β-boryl ketone. The authors further optimized the reaction conditions for synthesizing β-boryl vinyl esters **95**. The substrate scope was investigated using the optimized reaction conditions for four-component borocarbonylation. As described in Scheme 22[84]
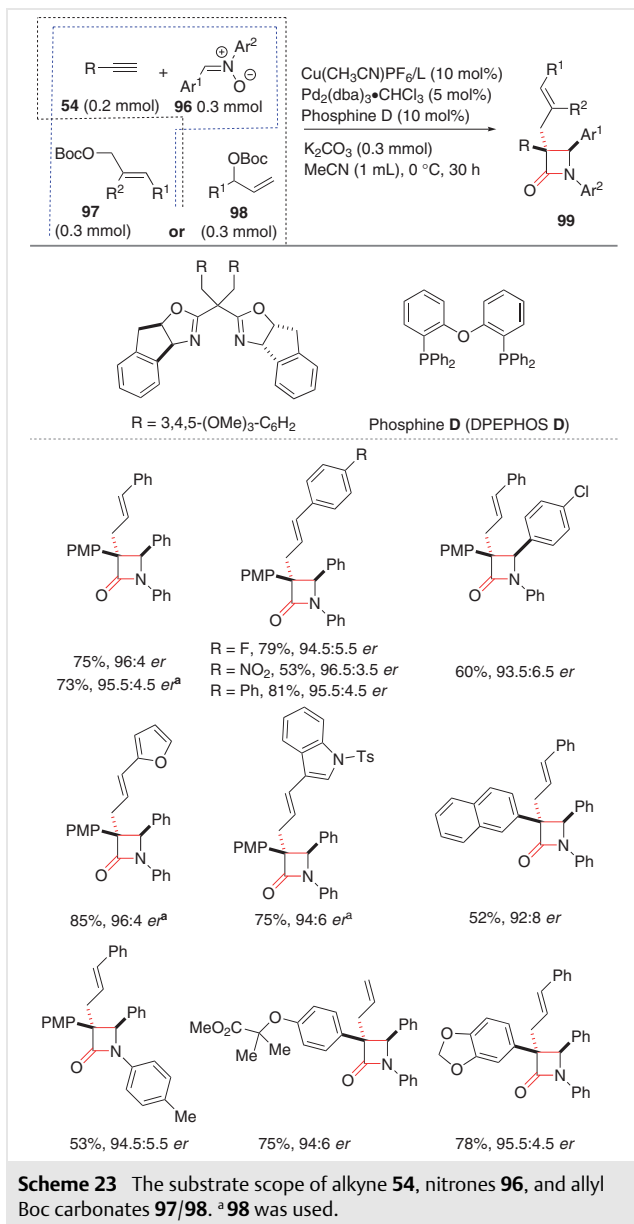

Scheme 21 Substrate scope of aziridines **88**

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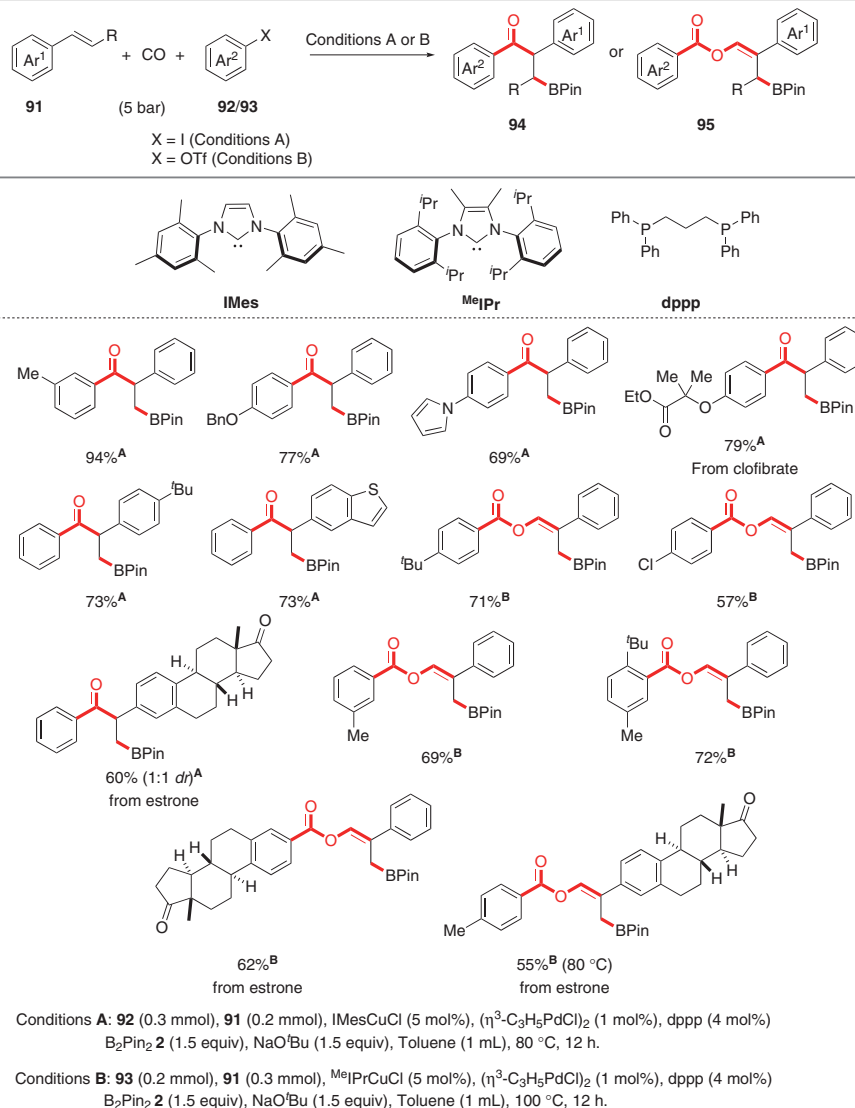
Scheme 22 Substrate scope of styrenes **91** and aryl iodides/triflates **92/93**

the reaction proceeded readily with a wide range of aryl triflates **93**, yielding the anticipated β-boryl vinyl esters **95** in moderate to excellent yields. Aryl triflates having either electron-withdrawing or electron-donating groups on the *para* position of the aromatic ring were amenable substrates and produced the products in 47–71% yields. Significantly, aryl triflates with *ortho*- or *meta*-substituents and more sterically hindered substituents such as isopropyl and *tert*-butyl groups provided the desired products in high yields. The triflate produced from estrone also resulted in the desired product in 62% yield.

The Kinugasa reaction provides a nitrone-alkene, which results in isoxazolines or isoxazolidines through a [3+2] cycloaddition reaction.[85–87] Kinugasa and Hashimoto discovered the direct synthesis of β-lactams **99** in 1972 when they reported that reacting a copper acetylide with a nitrone delivered β-lactams **99**. The Kinugasa reaction is an appealing alternative for the synthesis of β-lactams due to its efficient atom economy, and readily available starting materials. In this context, in 2021, Xu *et al.* demonstrated a synergistic Cu-catalysed Kinugasa mechanism and a Pd-catalysed allylic alkylation reaction for the synthesis of chiral β-lactams **99**. This asymmetric multicomponent, interrupted Kinugasa

allylic alkylation (IKAA) protocol successfully delivered chiral β-lactams **99** with a quaternary carbon center starting from **54**, **96**, and **97/98** in high yields and stereoselectivity; difficult to achieve using alternative synthetic approaches. An essential aspect of this reaction is the stereoselective coupling of two catalytic quantities of transitory organometallic intermediates produced *in situ*. The detailed reaction conditions and substrate scope for the selected examples are shown in Scheme 23.[88]

Scheme 23 The substrate scope of alkyne **54**, nitrones **96**, and allyl Boc carbonates **97/98**. [a] **98** was used.

Alkene difunctionalization allows rapid generation of molecular complexity from simple alkene precursors, with control of diastereo-, regio-, and enantioselectivity an inherent problem. In that context, Brown and Dorn reported a Pd/Cu-catalysed approach to alkene arylboration from alkenes **100** with (Bpin)$_2$ **2** and aryl halides **26**. In this protocol, the authors screened various alkene substrates, such as alkenylarenes **100** (Scheme 24, left side), 1,3-dienes **103** (Scheme 24, right side), and 1-substituted alkenylarenes **106** (Scheme 25, left side) resulting in good yields with excellent diastereoselectivities.[89] The authors proposed a reaction mechanism based on the literature and their previous experience with reactions of 1,1- and 1,2-disubstituted derivatives; the plausible mechanism has been presented in Scheme 25 (right side).

3   Conclusion

The significance of dual transition metal catalysis has had an increasing profile in recent years, as the new paradigm of combining two distinct transition metal catalysts has been implemented in an increasing number of novel chemical transformations, resulting in greater efficiency, selectivity, and reactivity. Bimetallic catalysis enables the formation of unique C–C and C–X bonds using a wide variety of nucleophiles in synergistic catalysis. The electrophiles, on the other hand, are still confined to allylic/aryl halides and carbonates. Nevertheless, there remains unexplored and unexploited reactivity that could be made available by the discovery of new electrophiles and activation mechanisms amenable to synergistic dual transition metal catalysis. Doubtless, further discoveries are on the way, and the chemical world may expect many more potent transformations enabled by dual transition metal synergistic catalysis.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information
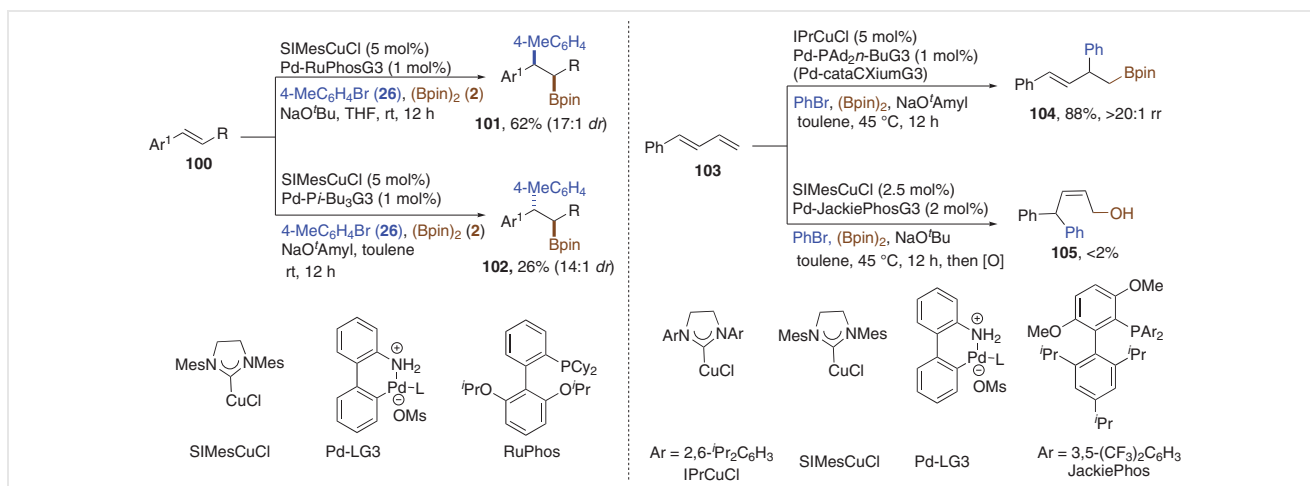
Scheme 24 Arylboration of alkenyl arenes **100** and 1,3-dienes **103**
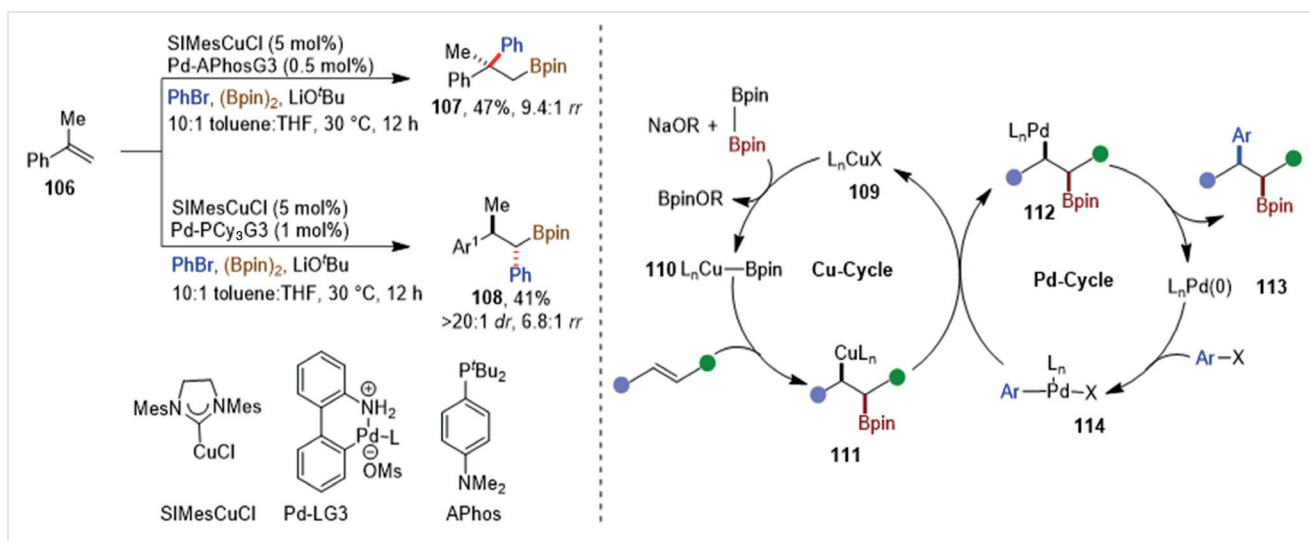
Scheme 25 Arylboration of 1-substituted alkenyl arenes **106** and arylboration reaction mechanism

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