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

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Dedicated to Prof. Günter Helmchen on the occasion of his 81\textsuperscript{st} 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 \( [\text{C}(\text{sp}^3)–\text{C}(\text{sp}^3)] \), \( \text{C}(\text{sp})–\text{C}(\text{sp}) \), \( \text{C}(\text{sp}^2)–\text{C}(\text{sp}^2) \) 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 photocatalytic/transition metal catalysis).

1 Introduction

Cross-coupling reactions, which traditionally involve transition metals, are one of the most significant chemical processes in synthetic organic chemistry.\textsuperscript{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.\textsuperscript{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,\textsuperscript{8,9} whereas the Stille reaction employs an organonitrogen nucleophile.\textsuperscript{10–12} The significant contribution to palladium cross-coupling reactions was acknowledged in 2010 with the award of the Nobel Prize in chemistry.\textsuperscript{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-
lytic cycle mechanism.\textsuperscript{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.\textsuperscript{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.

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**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.
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 activation 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 1 Selected examples of boryl-substituted monofluoroalkenes 4 via cis-borylfluoroallylation of alkynes 1

<table>
<thead>
<tr>
<th>R = Bu, 84%</th>
<th>R = OMe, 74%</th>
<th>R = H, 81%</th>
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<tbody>
<tr>
<td>75%</td>
<td>73%</td>
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From estrone

68%, r = 12:1, Z/E = 14:1

<table>
<thead>
<tr>
<th>R = Bu, 84%</th>
<th>R = OMe, 74%</th>
<th>R = H, 81%</th>
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<tr>
<td>75%</td>
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</table>

From estrone

69% From estrone

From canagliflozin intermediate

58% From estrone

70% From canagliflozin intermediate

Scheme 2 Proposed mechanism for formation of monofluoroalkenes 4 via cis-borylfluoroallylation of alkynes 1
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.\textsuperscript{26–30} Thus, dual catalysis, where two catalysts can react with two substrates to produce active intermediates, has become popu-
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., Bronsted 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(sp²)–C(sp²) Bond Formation

The research group of Gong and Fu has disclosed the synthesis of boryl-substituted monofluoroalkenes 4 via cisborofluoroallylation using Pd/Cu dual catalysis, involving alkyne 1, Bpin 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 γ-tocopherol, estrone, and canagliflozin derivatives, were examined. Furthermore, the silylation-fluoroallylation process proceeded efficiently, yielding the appropriate silyl monofluoroalkene product 4. Notably,
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 transmetalation and reductive elimination to lead to the final monofluorinated alkenes 4 as shown in Scheme 2.

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. 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 synergistic Cu/Pd catalysis via allylboration of alkynes 1 and racemic allyl carbonates 19. Significantly, new C(sp²)–B and C(sp³)–C(sp²) bonds are formed in a single operation as shown in Scheme 5. The addition of a Cu–Bpin complex across the alkyne catalyses the generation of a α-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
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(sp²)–C(sp²) Bond Formation

Similarly, the research group of Piou and Slutskyy has demonstrated C2-arylation ofazole derivatives 25 using Pd/Cu dual catalytic systems. The optimization conditions revealed that a dual catalytic system of Pd(OAc)₂, PCy₃·HBF₄, and Cu(Phen)(PPh₃)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)₂PF₆; 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 simultaneously 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. 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 thiophenones 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 thiophenones 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.

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.

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-butyl(dimethyl)aryl silanes] with various aryl bromides 26 to deliver the anticipated coupling products 52. It was...
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. Furthermore, 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($sp$) 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 PdII/PdIV 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($sp$)–C($sp$) 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 biologically active natural substances. In 2021, Kleij et al. reported a dual metal-catalysed decarboxylative C($sp$)–C($sp$) bond-forming approach for the asymmetric synthesis of highly functionalized compounds bearing quaternary carbon centers 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-
centrations and reaction temperatures to generate the cross-coupling products. The required Pd catalyst was synthesized from \((\text{R})\)-3,5-iPr2-4-NMe2-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-diboryl-methane 65 and alkene-tethered carbamoyl chlorides 64 (Scheme 15, left side). Notably, the oxindole derivatives 66 with a C(sp3)–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(sp3)–B bond. Thus, transformations, such as halogenations (F, Br, and I), Châm–Lam coupling with N-methylaniline, and treatment of oxindoles with vinylmagnesium bromide under I2, 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 2H-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 diarylposphine oxides or phosphonates 73 (Scheme 17). 81 This method of-
mechanism is proposed to proceed via a copper carbene intermediate, which further undergoes migratory insertion and delivers the intermediate \( \text{78} \). Finally, the target product \( \text{74} \) is formed via protonation of the intermediate \( \text{78} \) as shown in Scheme 18.

An efficient dual catalysis strategy for the construction of unsymmetrical aryl sulfides \( \text{81} \) has been reported by Khakyzadeh et al. This method uses phenols \( \text{79} \), arylboronic acids \( \text{80} \), and \( \text{S}_2(\text{II}) \) as starting materials (Scheme 19). The designed palladium encapsulated on nano-silica-based \( \text{SiO}_2@\text{OL@Pd} \) catalyst and \( \text{CuI} \) were employed for this purpose. This method converted the free hydroxyl group of phenols \( \text{79} \) into phenolic compounds \( \text{82} \) (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 reagents and the catalyst and, as a result, increases catalytic activity.

After synthesizing and characterizing \( \text{SiO}_2@\text{OL@Pd(II)} \), the authors shifted their attention to developing and improving a dual metal catalytic system involving \( \text{Pd} \) and \( \text{Cu} \) 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 \( [\text{SiO}_2@\text{OL@Pd(II)}] \), 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 \( \text{CuI} \). 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 15** Selected examples of borylated 3,3-disubstituted oxindole derivatives \( \text{66} \)

**Scheme 16** Plausible mechanism for the synthesis of borylated 3,3-disubstituted oxindoles \( \text{66} \)
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D. Ravi Kishore et al.

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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, CH₃CO, and NO₂, 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 arylboronic acid 80 with S₉ in the presence of Cul 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(sp³)–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 ketones.
esters 95, along with a trace of $\beta$-boryl ketone. The authors further optimized the reaction conditions for synthesizing $\beta$-boryl vinyl esters 95. The substrate scope was investigated using the optimized reaction conditions for four-component borocarbonylation. As described in Scheme 2284.

Scheme 19  Substrate scope for diaryl sulfide preparation

Scheme 20  Proposed mechanism for the synthesis of diaryl sulfides 81

Scheme 21  Substrate scope of aziridines 88
the reaction proceeded readily with a wide range of aryl triflates 93, yielding the anticipated $\beta$-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. Kinugasa and Hashimoto discovered the direct synthesis of $\beta$-lactams 99 in 1972 when they reported that reacting a copper acetylide with a nitrone delivered $\beta$-lactams 99. The Kinugasa reaction is an appealing alternative for the synthesis of $\beta$-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 $\beta$-lactams 99. This asymmetric multicomponent, interrupted Kinugasa
allylic alkylation (IKAA) protocol successfully delivered chiral β-lactams 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

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 with (Bpin)2 and aryl halides. In this protocol, the authors screened various alkene substrates, such alkenylarenes (Scheme 24, left side), 1,3-dienes (Scheme 24, right side), and 1-substituted alkenylarenes (Scheme 25, left side) resulting in good yields with excellent diastereoselectivities. 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.

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