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Recent advances in the synthesis of 1,1-diarylalkanes by transition-metal catalysis

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1,1-Diaryl moieties are core structures in a wide range of bioactive and pharmaceutical compounds. Transition-metal catalysis is a convenient approach to accessing these invaluable compounds affording high yields and enantioselectivities. This review summarizes 1,1-diarylalkanes synthesis through transition metal catalysis. Particular focus is given to recent developments, such as reductive cross-electrophile couplings, benzylic C–H bond arylation, transformations involving metal migration, asymmetric hydrogenation of 1,1-diarylalkenes and three-component coupling reactions.

transition metal, catalysis, 1, 1-diarylalkanes

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1 Introduction

Transition-metal-catalyzed reactions have proven to be useful in various organic transformations since last few decades. These methodologies provide facile synthetic access to molecules that would otherwise require multi-step traditional approaches [1]. Accordingly, development of reaction protocols for the synthesis of bioactive natural compounds exploiting transition metal catalysis has surged [2]. 1,1-Diarylalkanes are important organic moieties found in a wide range of naturally occurring compounds and are the core structures of many pharmaceuticals and building blocks for many important drugs. A slight variation in the aryl or amine moieties of the 3,3-diarylamines can lead to a different drug such as antiallergic-drug pheniramine and choleretic agent diisopromine (Figure 1) [3]. Further examples are antidepressant sertraline and antimuscarinic agents Detrol. The design of new and facile synthetic methods to access these molecules remains desirable. Synthetic chemists have shown great interest in 1,1-diarylalkanes owing to their biological importance and the interesting chemistry involved in their synthesis [4]. Among the transition metals, Pd, Ni, and Cu have played the most important roles in the synthesis of 1,1-diarylalkanes [5]. Although some reviews have been published on *gem*-diarylalkane synthesis, many recent important developments, particularly some new strategies are not included [6]. This review will mainly focus on the current strategies, both stereoselective and racemic, employed to synthesize 1,1-diarylalkanes. Current strategies can be divided into two- and three-component reactions. The two-component reactions are classical cross-couplings of benzylic halides, ethers and esters, migratory cross-coupling reactions, carbenes functionalization, benzylic C–H bond arylation, hydrogenation of 1,1-diarylalkenes, conjugate addition reactions and allylic arylation reactions. Furthermore, three-component reactions for 1,1-diarylalkanes synthesis include alkene hydroarylation, alkenyl arenes difunctionalization, alkene 1,1-diarylation and C–H bonds double arylation (Scheme 1).

This review outlines the evolution of different strategies

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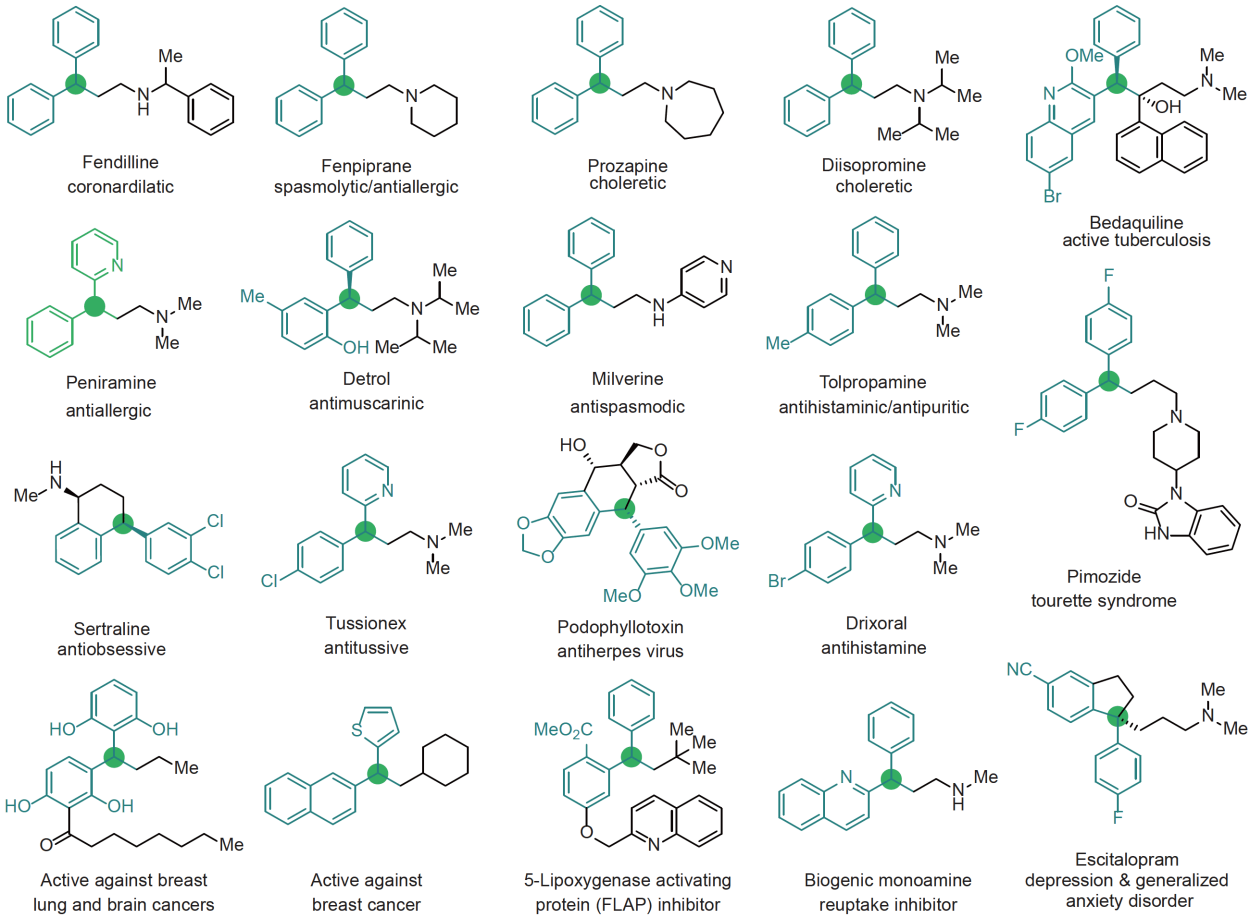


Figure 1 Represented bioactive molecules containing 1,1-diarylalkane moieties (color online).

for the synthesis of 1,1-diarylalkanes. The content is organized according to the transition-metal catalysis strategy used for preparation of these compounds.

2 Two-component reactions for synthesis of 1,1-diaryl alkanes

Transition metal-catalyzed two-component reaction is a classical strategy for 1,1-diarylalkanes synthesis, particularly the cross coupling reactions.

2.1 Transition metal-catalyzed cross coupling reactions

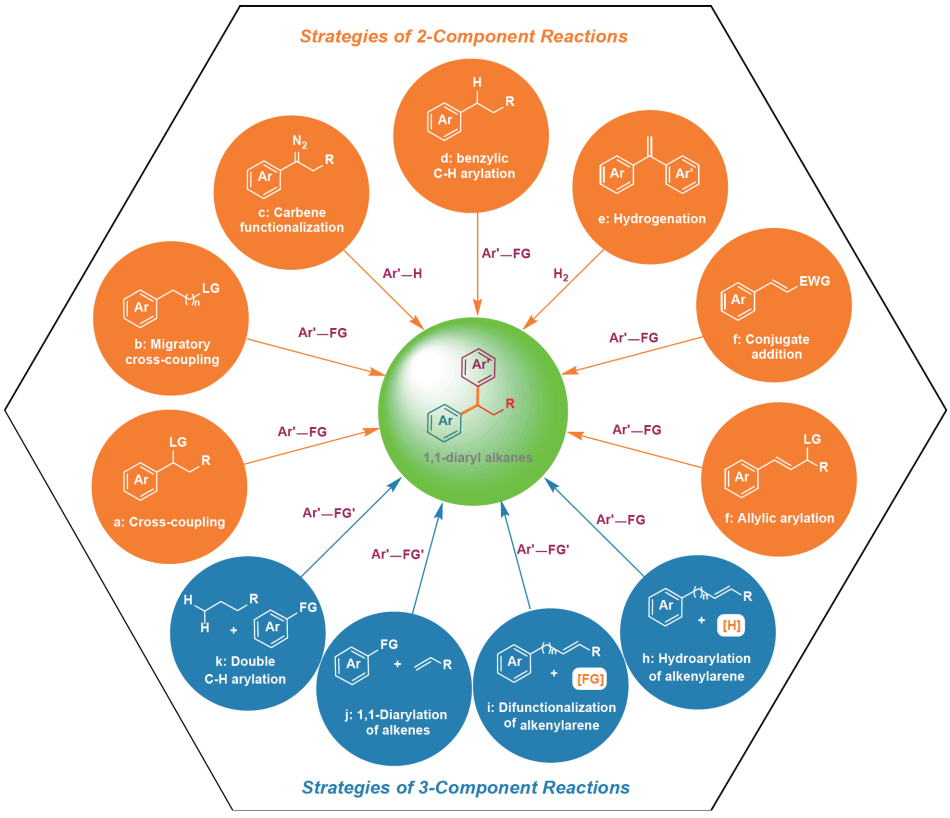
Transition metal-catalyzed cross-coupling reactions have caused a paradigm shift in the synthesis of invaluable organic compounds, including broadening the synthetic scope of 1,1-diaryl functionalized molecules. This section gives a brief account of the reaction strategies used to prepare 1,1-diarylalkanes by transition-metal catalyzed cross-coupling reactions (Scheme 2).

2.1.1 Cross coupling of benzyl halides

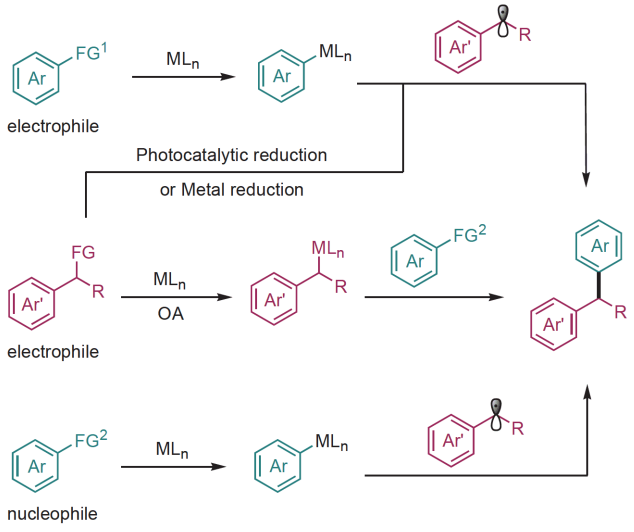
Benzyl halides as electrophiles can be transformed into 1,1-diarylalkanes using arylborate under redox neutral conditions. Furthermore, they readily react with aryl halides under reductive conditions to produce 1,1-diaryl structures in a straightforward manner. The main challenge in this approach is the fast homocoupling of benzyl halides. However, careful selection of reaction conditions has made this a successful strategy for 1,1-diarylalkanes synthesis.

Coupling benzyl halides with arylboronate is a convenient strategy for obtaining 1,1-diaryl products with Cu-catalyzed Suzuki-Miyuara cross-coupling having been widely explored (Scheme 3).

Accordingly, in 2014, the Fu's group [7] reported a Cu-catalyzed Suzuki-Miyuara cross coupling of benzyl halides (Cl, Br) and arylboronates using CuI (Scheme 3(a)). In this case, the nitrogen-based ligands showed low efficiency. However, the diketone-based ligands showed excellent performance improving the yield in *N*,*N*-dimethylformamide (DMF). Interestingly, the yield increased to 90% by using *N*-methylcaprolactam (NMCPL) as solvent. Various benzyl chlorides and bromides, as well as aryl boronates were



Scheme 1 Strategies for the synthesis of 1,1-diarylalkanes by transition-metal catalysis (color online).



Scheme 2 Cross-coupling strategies for 1,1-diarylakanes (color online).

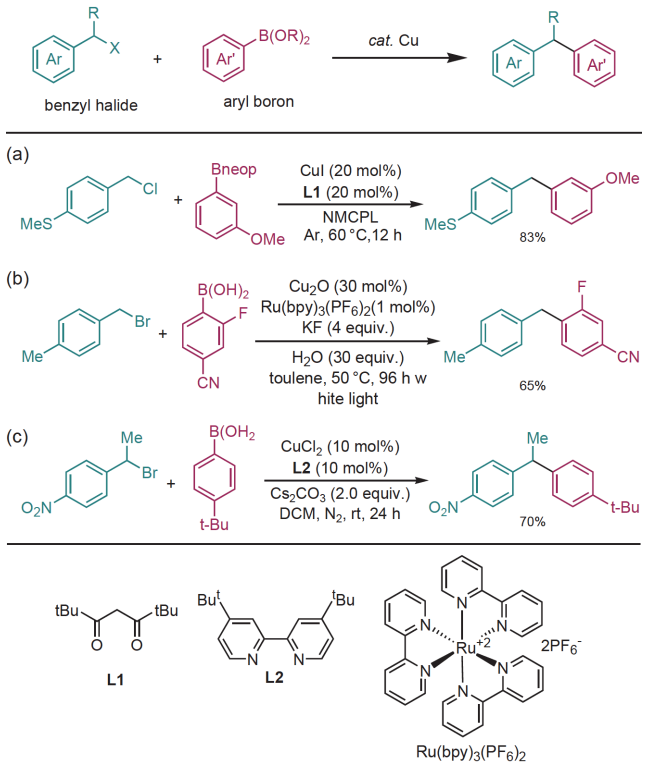
evaluated and good to excellent yields were achieved. This represents the first Suzuki-Miyaura coupling reactions using Cu-catalysis.

Later, Lee *et al.* [8] reported the synthesis of 1,1-diarylalkanes through a cross-coupling of benzyl bromides and aryl boronic acids by photoredox dual catalysis using Cu_2O and Ru(bpy)$_3$(PF$_6$) (Scheme 3(b)). This photoredox catalyst generates a benzyl radical that undergoes cross coupling with the Cu-Ar intermediate formed by *trans*-metalation of aryl boronic acid. This reaction protocol provides an alternative to existing of 1,1-diarylalkanes synthesis methods under mild reaction conditions. However, the reactions afforded diarylalkanes in low yields when electron-deficient benzyl bromides were used owing to their higher reduction potentials.

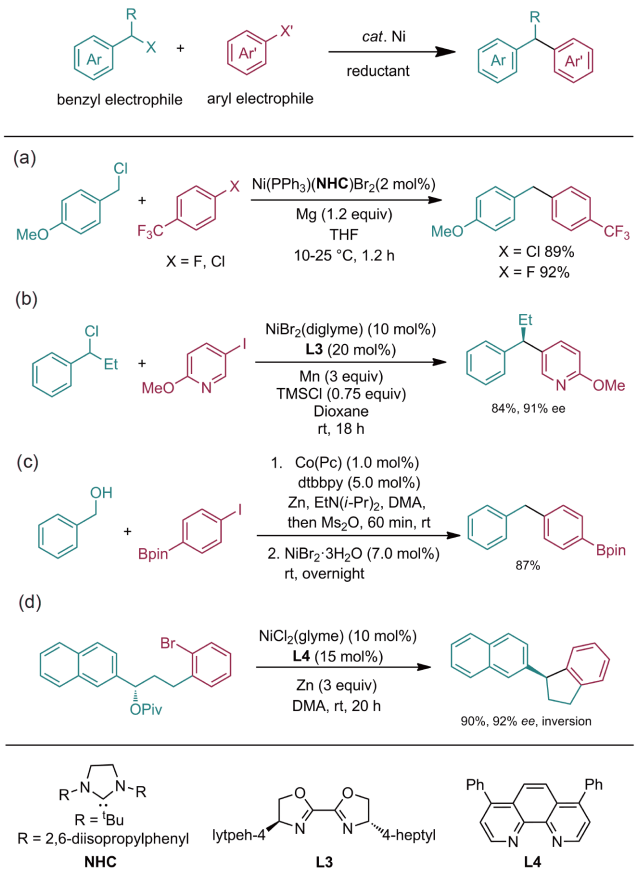
Recently, Li's group reported 1,1-diarylation using a secondary benzyl bromide and arylboronic acid in the presence of CuI and ligand dtbbpy. Several primary and secondary benzyl bromides and aryl boronic acids were evaluated, giving good to excellent yields. Both electron rich and electron deficient aryl bromides gave the 1,1-diaryl products in excellent yields. Even sensitive substituents on aryl bromides, such as NO_2 group, were also tolerated. Aryl boronic acids containing heteroatom such as N, S also reacted well under the optimized conditions (Scheme 3(c)) [9].

Reductive cross-coupling reactions have proven to be successful for cross-coupling electrophiles [10]. Several metal species are effective as reducing agents in the cross-coupling of electrophiles. The reductive cross-coupling of benzyl halides and aryl halides has also been developed into a versatile synthetic approach for preparing 1,1-diarylalkanes (Scheme 4).

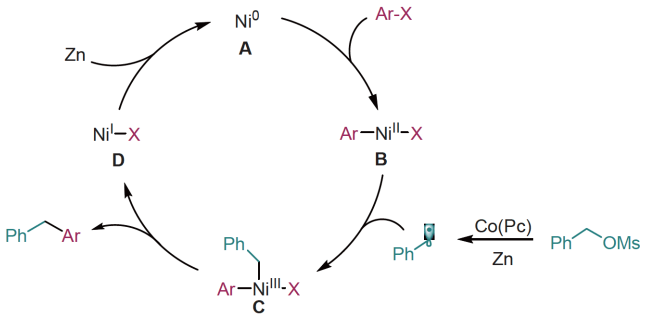
In this context, Sun *et al.* [11] reported the cross coupling of various benzyl chlorides and aryl chlorides/fluorides to



Scheme 3 Cu-catalyzed Suzuki-Miyaura cross coupling of benzyl halides and arylboronates, NMCPL=*N*-methylcaprolactam (color online).



Scheme 4 Ni-catalyzed reductive cross-coupling of benzyl halides and aryl halides (color online).



Scheme 5 Mechanism for Ni/Co dual catalysis for cross coupling of benzyl alcohol and aryl halides (color online).

synthesize diarylmethanes under reductive conditions using Mg as a reductant and mixed PPh_3/NHC Ni(II) complexes $Ni(PPh_3)(NHC)Br_2$ (Scheme 4(a)). Mg as a reducing agent is important in this reaction. The use of Zn or Mn as reductant dramatically decreased the overall yield by forming bibenzyl as the major product. Experiments suggested that a benzyl Grignard species formed by the reaction of Mg and benzyl chloride undergoes cross-coupling with a aryl chloride or fluoride.

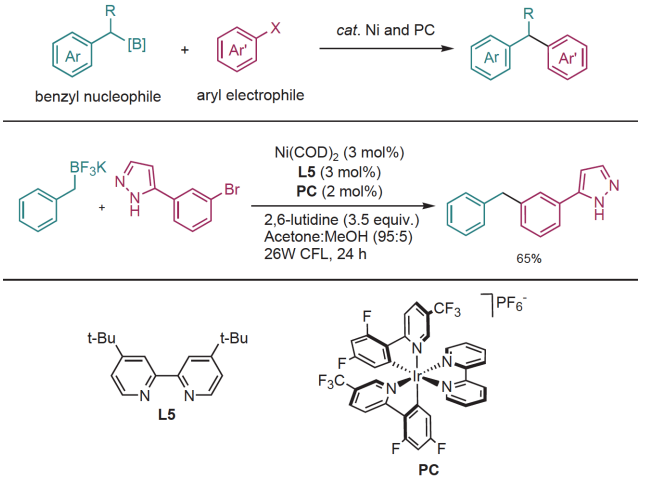
The Reisman's group [12] later achieved a Ni-catalyzed enantioselective reductive cross-coupling for 1,1-diarylalkanes synthesis using benzyl chlorides and aryl/heteroaryl iodides. Mn was used as a stoichiometric reductant to generate the nickel catalyst. Using 4-heptyl-BiOX, **L3** as ligand resulted high yields and *ee* value (Scheme 4(b)). The length of the alkane chain in the ligand was important. Several heteroaryl compounds were tolerated in this reaction in contrast to previously reported benzylic cross coupling for 1,1-diarylalkanes synthesis.

Radical generation for cross coupling reaction is generally achieved either by oxidation or reduction through single-electron transfer (SET). However, the Weix's group [13] reported a different approach to generating alkyl radical species using cobalt phthalocyanine Co(Pc) as co-catalyst in nickel-catalyzed cross-coupling of benzyl alcohol derivatives and aryl halides (Scheme 5). Co(Pc) generates radicals through a two-electron nucleophilic substitution rather than SET. Bibenzyl formation is very common in nickel-catalyzed reactions. Although the low reactivity of sulfonate esters of benzyl alcohols prevented bibenzyl formation, the yield of the cross coupled product was poor. Interestingly, Co(Pc) readily generates benzyl radical from sulfonate esters of benzyl alcohols (Scheme 4(c)). Therefore, combination Ni-catalyst with Co(Pc) proved to be an efficient strategy for diarylalkanes synthesis.

In 2016, the Jarvo's group [14] reported an intramolecular arylation of secondary benzylic ester with aryl halides to achieve cyclic 1,1-diarylalkanes (Scheme 4(d)). The

benzylic pivalate in the presence of $NiCl_2$·glyme (10 mol%), bathophenanthroline (Bphen, 15 mol%) and Zn as reductant furnished an array of cyclic 1,1-diarylalkanes in good to excellent yields. The absence of either the catalyst or ligand resulted in no desired product being obtained. An intermolecular version of this method appeared complement to the method reported by Weix's group. However, the inversion of stereochemistry showed that this transformation less likely to involve a radical pathway. Notably, only naphthyl pivalates were reactive, with simple benzylic esters failing to produce the desired products.

The cross-coupling of benzylic nucleophiles with aryl halides is another strategy to achieve 1,1-diarylalkanes. Molander and co-workers [15] introduced the cross-coupling of benzylic trifluoroborates with aryl bromides under photocatalytic dual catalysis (Scheme 6). Nucleophilic organoboron reagents undergo slow transmetalation in a two-electron transfer mechanistic cycle. This photocatalytic process enables the generation of benzylic radicals from nucleophilic organoboron species through an SET pathway.



Scheme 6 Ni-catalyzed cross-coupling of benzyl trifluoroborates and aryl halides (color online).

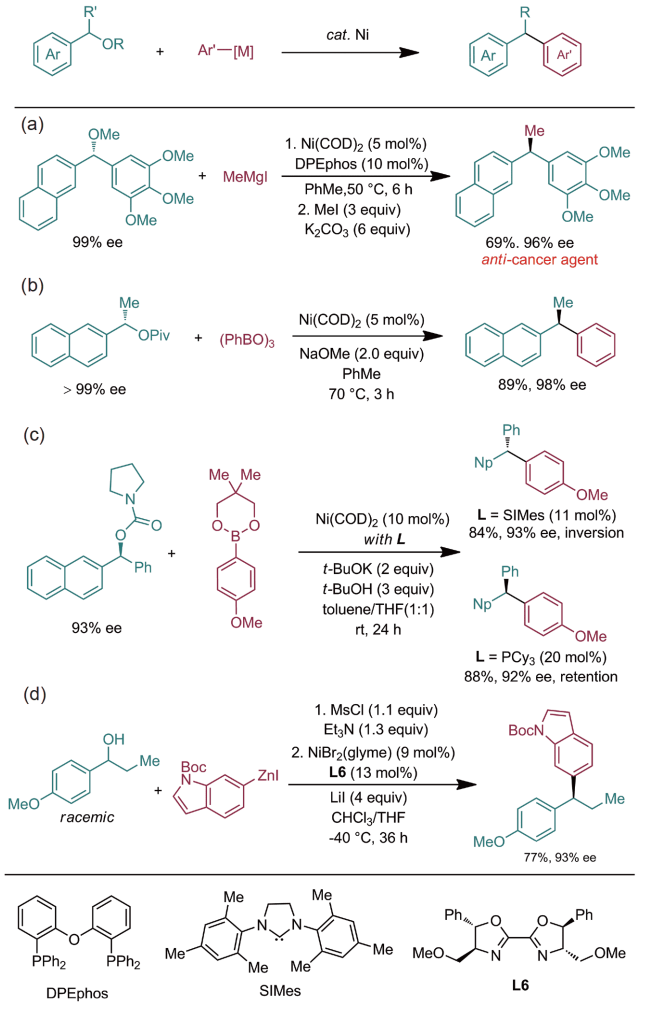
2.1.2 *Cross-coupling of benzylic ethers/esters*

Alkyl ethers, particularly benzyl ethers, readily undergo oxidative addition to Ni and are preferred substrates for achieving alkyl-aryl cross-coupling reactions owing to heterolytic cleavage of the ethers.

In this context, Jarvo *et al.* [16] conducted a stereospecific transformation of benzyl ethers into diarylalkanes using $Ni(COD)_2$ (5 mol%) and *rac*-BINAP (10 mol%). Several enantio-enriched benzyl ethers were transformed into 1,1-diarylethanes with inversion at the stereocenter using MeMgI as the coupling partner (Scheme 7(a)). However, this highly nucleophilic organometallic reagent is not compatible with several functional groups diminishing its synthetic potential. Organic synthesis involving Grignard reagents does not show promising selectivity. Therefore, a mild alternating approach to Grignard reagents is often desirable.

The Watson's group [17] reported a more convenient approach using benzylic pivalates and arylboroxine for cross coupling to achieve 1,1-diarylalkanes (Scheme 7(b)). Using arylboroxines as nucleophilic coupling partners, greatly expanded the substrate scope of this synthetic approach. NaOMe used in the reaction was key to improving the yield. The stereospecific reaction was initiated by oxidative addition of benzylic ethers to electron-rich Ni(0), and proceeded with retention of stereochemistry at the chiral center.

The Jarvo's group [18] showed that the stereospecificity of such reactions depends on their conditions. The authors used different ligands to show inversion and retention of the stereocenters. Using $Ni(COD)_2$ (10 mol%) and PCy_3 (20 mol%) as catalyst and ligand respectively, various 1,1-diaryl products were obtained with stereochemical retention at the chiral carbon. Replacing the ligand with SIMes, afforded the



Scheme 7 Synthesis of 1,1-diarylalkane using Ni-catalyzed cross coupling of alkyl ethers (color online).

products with stereochemical inversion (Scheme 7(c)). Using *t*-BuOH as an additive improved the enantioselectivity

of the reaction. Several naphthyl moieties and arylboroxines were evaluated affording excellent stereoselectivities and yields. However, electrophilic coupling partners other than naphthyl and benzhydryl groups did not afford comparable *ee* values.

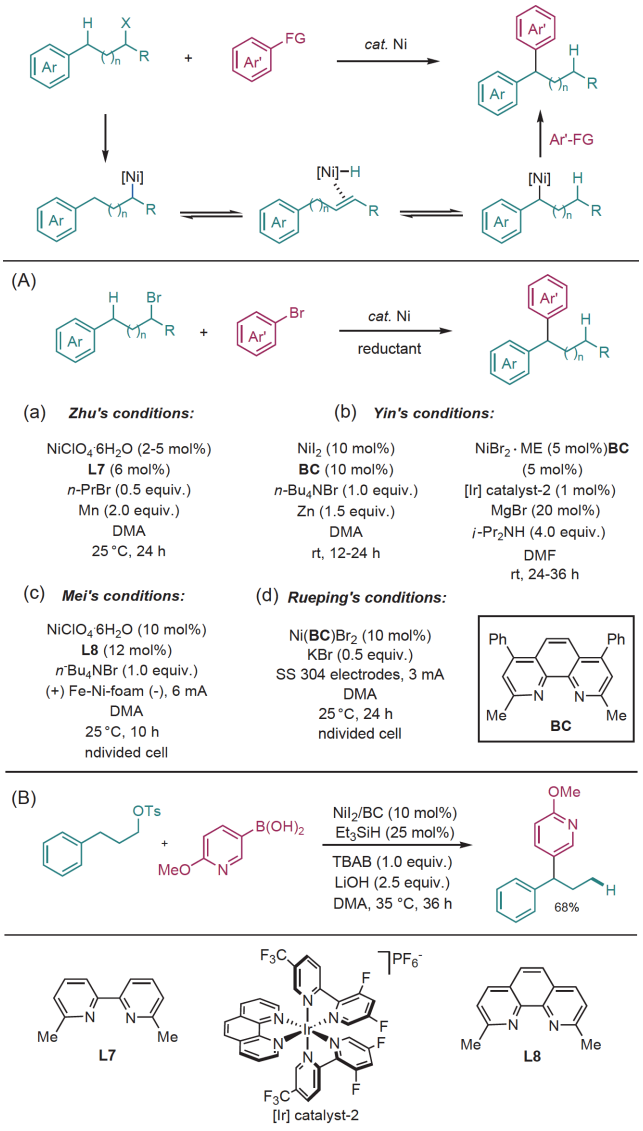
In all above methods enantiopure benzylethers/esters were used for stereospecific transformation into 1,1-diaryl products. However, in 2013, Fu and co-workers [19] converted racemic benzyl alcohols into benzyl mesylate *in situ* which were then transformed into enantioenriched 1,1-dairyalkanes by coupling with arylzinc reagents. The nickel-catalyzed asymmetric Negishi reaction using bisoxazoline **L6** ligand afforded various enantio-enriched 1,1-diarylalkanes (Scheme 7(d)). LiI was important for improving reaction yield. Using LiBr gave an improved *ee* but lower yield. Experimental evidences supported the *in-situ* generation of benzyl iodides, which undergo cross-coupling with aryl zinc reagents.

2.2 Metal-catalyzed migratory cross-coupling reactions

Recently, migratory cross-coupling reactions have emerged as a powerful tool for the remote functionalization of various organic scaffolds [20]. Unlike traditional transition-metal catalyzed cross coupling reactions which occur between two reactive sites, a migratory cross-coupling reaction occurs away from the reactive site, with one of the coupling partners able to undergo β-hydride elimination. Various sterically hindered nitrogen-based ligands play a crucial role in migratory reactions, wherein iterative β-hydride elimination/insertion of the metal-ligand complex across the alkyl chain leads to the thermodynamically stable intermediate, followed by coupling with aryl coupling partners to provide the diarylalkane products. Various protocols using migratory cross-coupling reactions have been developed in the last few years.

Zhu *et al.* [21] initially reported a remote cross electrophilic coupling of alkyl and aryl bromides (Scheme 8(A-a)). The reductive condition produced diaryl products under mild conditions. *n*-PrBr was used as an additive but no arylation of *n*-PrBr was observed. Mn was a better reductant compared to Zn and several aryl bromides with wide ranging substituents were tolerated in this reaction protocol. However, when an aryl iodide was used the biaryl was the major product.

Simultaneously, our group also reported a migratory cross electrophilic-coupling of alkyl and aryl bromides. Several 1,1-diaryl alkanes were synthesized using NiI_2 (10 mol%) and bathocuproine (10 mol%) under reductive conditions with *n*-Bu_4NBr as an additive (Scheme 8(A-b)) [22]. The nature of the ligand substituents was important with bpy or its 6,6′-dimethoxy derivative producing only traditional cross-coupling products. Later, our group reported a photocatalytic method using Ni/Ir dual catalysis for the migratory cross-coupling of non-activated alkyl- and aryl bromides



Scheme 8 Migratory cross coupling of alkyl halides and aryl partners (color online).

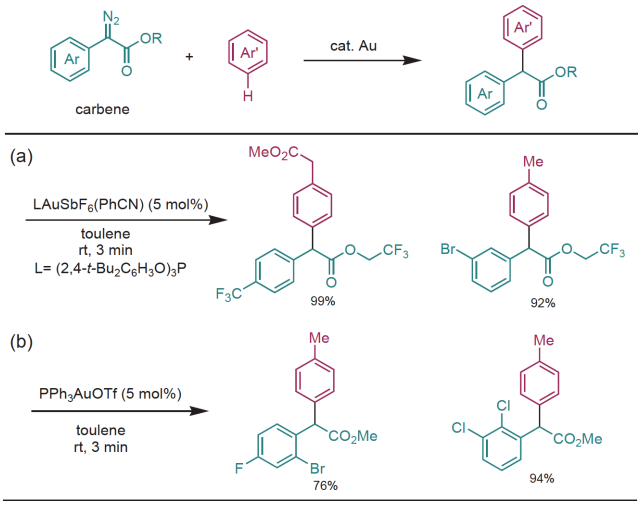
(Scheme 8(A-b)) [23]. Interestingly, diispropylamine was used as a reductant in this migratory reaction in contrast to earlier methods. Both primary and secondary alkyl bromides were successfully converted to diarylalkane products.

Mei and co-workers [24] developed an electrochemical reductive relay process for the migratory cross-coupling of electrophiles. Several 1,1-diarylalkanes were synthesized from alkyl and aryl halides under electrochemical reduction (Scheme 8(A-c)). This electrochemical process avoids the use of stoichiometric reductants such as Mn, Zn and circumvents the problems associated with their chemical reactivity.

Later, the Rueping's group [25] also demonstrated the migratory cross electrophilic coupling reactions under electrochemical reduction and extended the methodology to migratory hydroarylation of styrene (Scheme 8(A-d)).

Large-scale synthesis of the 1,1-diarylalkane product was also achieved under electrochemical reduction conditions.

Suzuki-Miyaura cross-coupling reactions are widely used in synthetic medicinal chemistry. However, the versatile migratory version is underdeveloped. Recently, our group reported a Ni-catalyzed migratory Suzuki-Miyaura cross-coupling with high regioselectivity for the benzylic position (Scheme 8(b)) [26]. Various unactivated alkyl electrophiles and aryl boronic acids were efficiently converted to diarylalkane derivatives under redox-neutral conditions. Interestingly, alkyl chlorides which are generally unreactive in cross-coupling reactions reacted well in this reaction in the presence of KI at a slightly elevated temperature (80 °C). Employing Et_3SiH assisted the generation of the active nickel catalyst. TBAB improved reaction yield possibly forming corresponding alkyl bromides from the tosylates.



Scheme 9 Gold-catalyzed cross-coupling of arenes and diazo compounds (color online).

2.3 Metal-catalyzed carbene functionalization

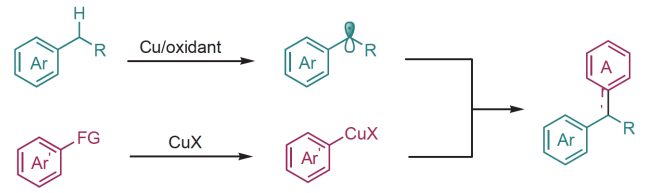
Carbenes are highly active unsaturated compounds that play important roles in organic synthesis. Transition-metal catalyzed carbene coupling reactions have greatly expanded the concept of cross-couplings [27]. Transition metal-catalyzed carbene insertion into C–H bonds has attracted much attention [28]. In this context, Zhang's group [29] reported a gold-catalyzed C–H activation of 2,2,2-trifluoroethyl α-aryl-α-diazoester, followed by para-regioselective arylation to afford various 1,1-diaryl products (Scheme 9(a)). CF_3 was important for enhancing stability of the gold carbocation species. Thus, a low nucleophilic aryl group easily reacts with a strong electrophilic partner. Catalyst $(2,4\text{-}tBu_2C_6H_3O)_3PAuPhCNSbF_6$ greatly improved the reaction yield. Other catalysts, such as Rh, Ru, Cu and Fe were much less selective. Various functional group were tolerated showing outstanding chemoselectivity and regioselectivity. Furthermore, synthesis of an ibuprofen analogue was demonstrated. The trifluromethyl group was necessary in the above transformation to increase the electrophilicity of the diazoester, which diminished the synthetic utility of this method. To circumvent this problem, the authors installed an electron withdrawing group at the ortho-position of the aryl ring in the diazo ester, which allowed to the simple methyl ester bearing an electron-withdrawing group on the aryl ring as the substrate. Interestingly, several 1,1-diaryl products were obtained using PPh_3AuOTf as catalyst (Scheme 9(b)) [30].

2.4 Transition metal-catalyzed benzylic C–H arylation

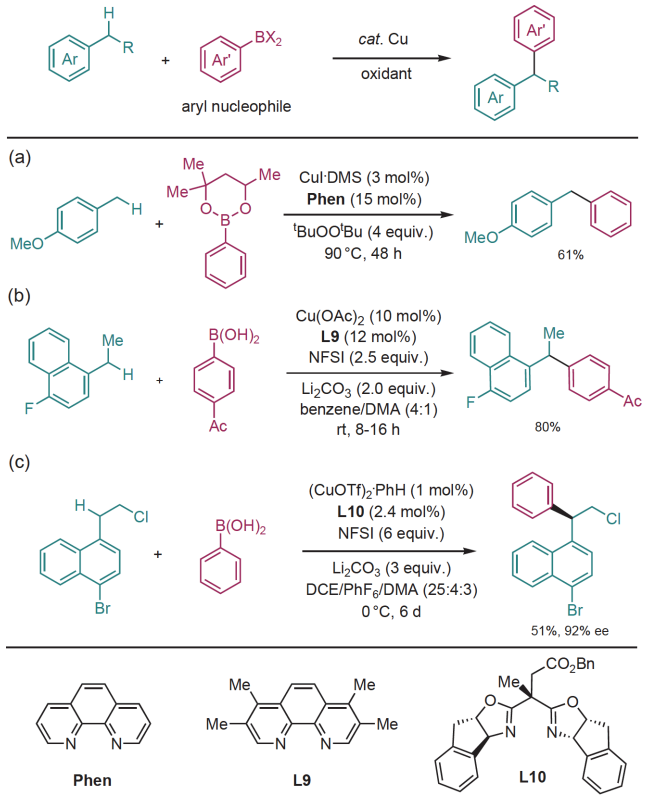
As alkyl benzenes are readily accessible and cheap feedstocks, their conversion into valuable products is desirable in industrial synthesis [31]. Conversion of alkyl benzenes into useful products has received much attention. The acidic benzylic C–H bonds in these compounds can be activated by transition-metal catalysis avoiding prefunctionalization to halides or other reactive functional groups.

Benzyl C–H bonds in the presence of a Cu salt and an external oxidant readily generate benzylic radicals through a hydrogen atom transfer (HAT) process. This can be coupled with Cu(II)-Ar formed from organoborons and Cu salt to synthesize 1,1-diarylalkanes (Scheme 10). In 2017, Stahl *et al.* [32] reported 1,1 diarylation by oxidative C–H arylation of various ethyl and methyl benzenes using CuI·DMS as catalyst and arylboronic esters as the aryl source (Scheme 11(a)). Phenanthroline was used as the ligand playing an important role in controlling unwanted biphenyl products. *t*-BuOOH (TBHP) was used as the oxidant assisting in benzylic radical generation. A library of diarylalkanes with diverse functional group patterns was synthesized by this method. Simultaneously, Liu *et al.* [33] reported a similar transformation using NFSI as the oxidant and HAT reagent (Scheme 11(b)). Benzylic compounds were used as limiting reagents in this transformation. Notably, these reactions are important for the downstream modification of pharmaceutically interesting, biologically active molecules. The synthesis of chiral 1,1-diarylalkanes is important because they are widely found in drug molecules. The enantioselective version of this reaction has been achieved by the Liu's group (Scheme 11(c)) [34]. Bioxazoline as ligand played an important role in the enantioselectivity-determining step. Introducing a carbonyl group into the ligand enhanced the transmetalation step preventing side reactions. Various arylboronic acids and alkyl naphthalenes were tolerated under the optimized conditions. However, alkyl benzenes did not react efficiently under these reaction conditions.

Another strategy for the 1,1-diarylation of arylalkanes involves benzylic C–H bond activation through directing-group-assisted transition-metal catalysis (Scheme 12). Palladium has been widely explored in directing-group-assisted



Scheme 10 Strategy for Cu-catalyzed oxidative arylation of C–H bonds (color online).



Scheme 11 Synthesis of 1,1-diaryalkanes through Cu-catalyzed oxidative arylation of C–H bonds (color online).

C–H activation to achieve C–H functionalization. Both directing groups and an external ligand are required for the Pd-catalyzed redox-neutral benzylic arylation reactions. In 2015, Duan's group [35] reported palladium-catalyzed enantioselective arylation of benzylic C–H bond using a carboxylic amide as the directing group. A chiral phosphoric amide played an important role in determining the enantioselectivity of the reaction (Scheme 12(a)). Later, Chen's group [36] reported a similar benzylic C–H arylation reaction of alkyl amines enabled by bidentate picolinamide (PA) as the directing group (Scheme 12(b)).

Strongly co-ordinating directing groups tethered to the substrate precluded the use of potential chiral bidentate ligands in Pd-catalyzed asymmetric C–H activation. Yu and co-workers [37] pioneered a weak coordinating-group-assisted asymmetric C–H functionalization, in which high enantioselectivity was achieved by chiral acetyl-protected aminoethyl quinoline (APAQ) ligand **L13** (Scheme 12(c)).

The problem with directing groups tethered to the substrate is that their installation and removal from the parent molecule is cumbersome. These two extra steps not only diminish the synthetic utility but also are often incompatible with functional group already present in the substrate. Accordingly, a transient directing group generated *in situ* is desirable.

In 2016, Yu's group [38] used amino acids to generate imines *in situ* to function as a transient directing group for C–H activation (Scheme 12(d)). Various aldehydes and ketones were functionalized at β or γ positions allowing many diarylalkane compounds to be synthesized. The method was also extended to the synthesis of various asymmetric 1,1-diaryl products using chiral amino acid L-*tert*-Leucine.

In addition to palladium, nickel catalyst can also promote benzylic C–H bond arylation reaction. Molander *et al.* [39] reported a Ni-catalyzed cross-coupling of (hetero)aryl bromides with activated α-heterosubstituted or benzylic C(sp^3)–H bonds using visible light phororedox catalysis.

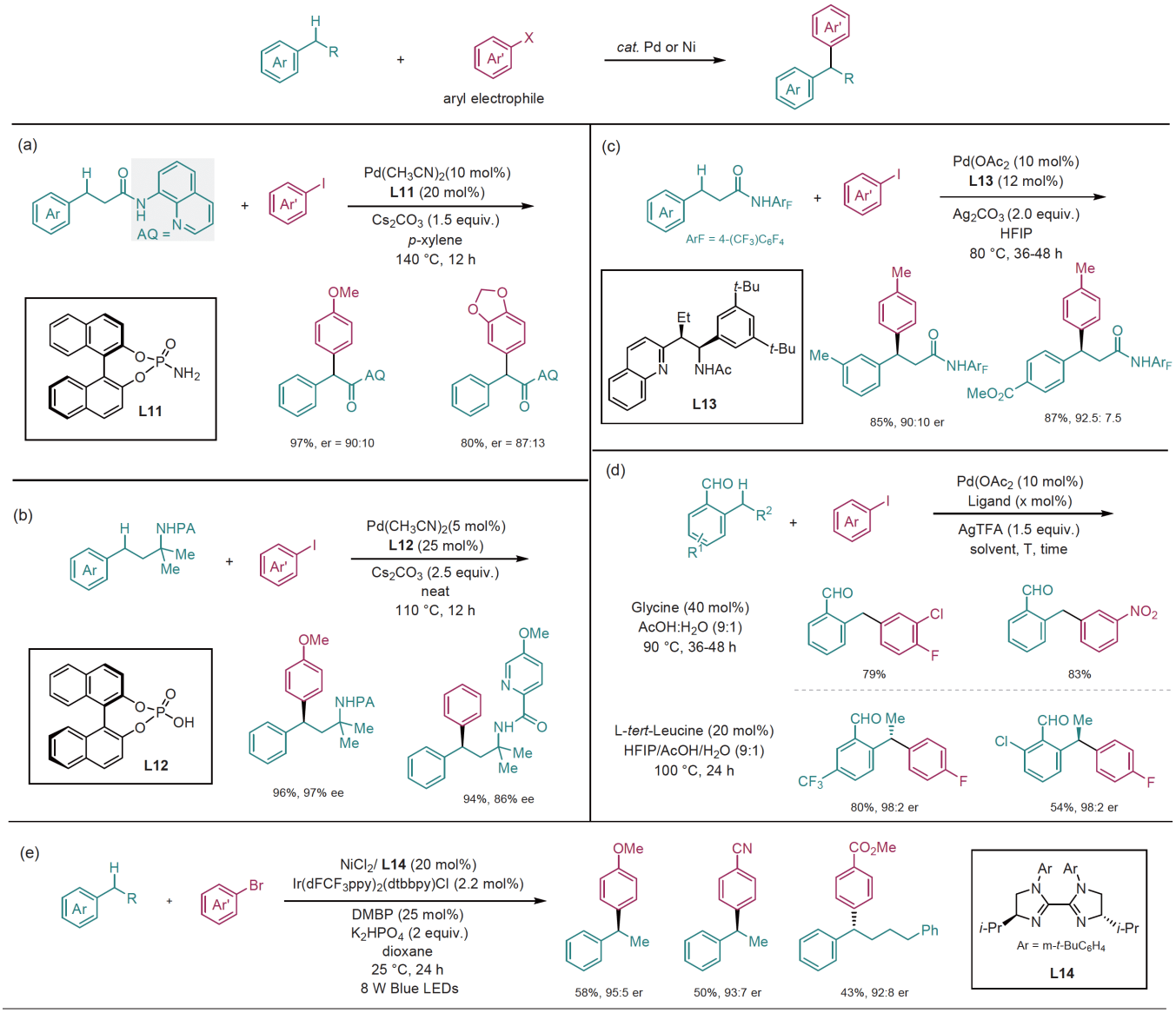
Later, Lu's group [40] reported an enantioselective benzylic C–H arylation of alkylbenzene with aryl bromides *via* photoredox and nickel dual catalysis (Scheme 12(e)). Chiral bisoxazoline based ligands, frequently used in cross-coupling reactions, were not effective in this dual photoredox catalytic method, while bisimidazole based chiral ligands were found to be efficient for this enantioselective transformation. Various enantioenriched 1,1-diarylalkenes were synthesized in good yields using $NiCl_2$ and Ir($dFCF_3ppy$)$_2$(dtbbpy)Cl as catalysts in the presence of light.

2.5 Hydogenation reactions for 1,1-diarylalkane synthesis

Hydrogenation reactions of alkenes represent one of the most atom-economic reactions. These reactions are operationally simple yet very challenging to achieve high enantioselectivity [41]. Several reaction protocols have been developed to synthesize 1,1-diarylethanes through transition metal-catalyzed hydrogenation of diarylethenes. Mostly, Rh- and Ir-complexes have been used for these reactions.

Andersson *et al.* [42] reported Iridium phosphite-oxazoline catalyzed enantioselective hydrogenation of 1,1-disubtituted alkenes and synthesized various 1,1-diarylalkanes with excellent *ee*s (Scheme 13(a)). Interestingly, the authors optimized various phosphite-oxazoline ligands, amongst **L15** gave the best results with more than 90% *ee* and 100% conversion. Moreover, various heteroaryl substituents on the alkanes were tolerated. The substituents on the oxazoline ring of the ligand affected the *ee*, with bulky substituent providing the best result.

Another important strategy to conduct hydrogenation of unactivated 1,1-disubstituted olefins is directing-group as-



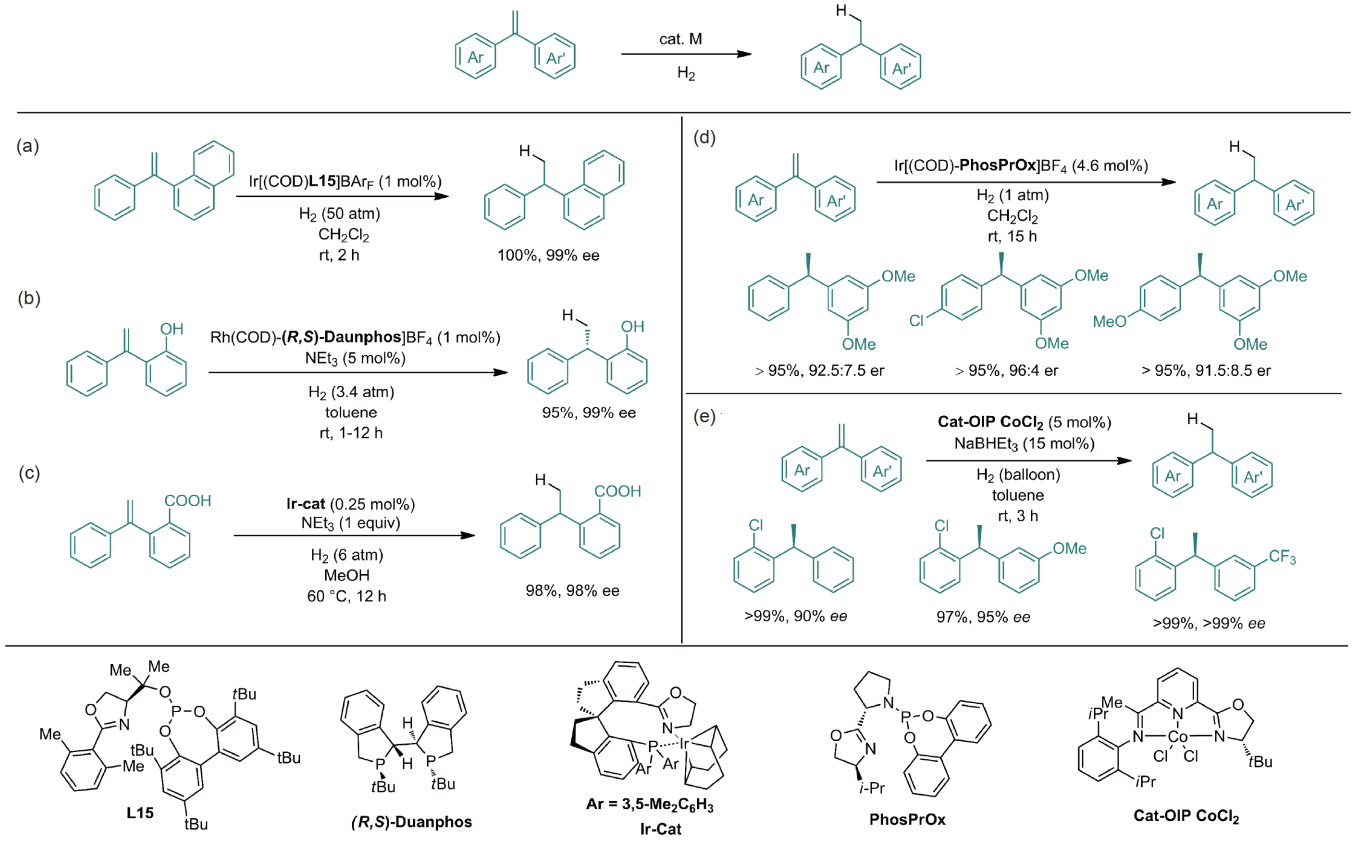
Scheme 12 Metal-catalyzed C–H arylation reactions under redox-neutral conditions (color online).

sisted hydrogenation. Wang *et al.* [43] disclosed a Rh-catalyzed asymmetric hydrogenation of 1,1-diarylethenes, which require a 2′-hydroxyl group attached to one of the phenyl rings acts as a directing group (Scheme 13(b)). Notably, the authors used an *E*/*Z* mixture of alkenes and high enantiopure 1,1-diarylalkanes were obtained. The presence of hydroxyl group was crucial for the enantioselectivity. This reaction is an improvement to the Ir(P-N) catalyst system, which requires a single isomer *E* or *Z* for high enantioselectivity.

Zhou *et al.* [44] reported a highly enantioselective iridium-catalyzed hydrogenation of 1,1-diarylethenes directed by an ortho carboxy group (Scheme 13(c)). Notably, use of base was essential for this hydrogenation reaction. Interestingly, carboxy group in the final products were easily transformed into acetyl and formyl group without altering the enantioselectivity. However, a carboxy group at *meta*-position could not give the desired hydrogenation product.

Later, Sigman and co-workers [45] reported an Ir-catalyzed hydrogenation of 1,1-disubstituted olefins using a phosphoramidite ligand, PhosPrOx. The MeO- groups at *meta*-position induced the enatioselectivity. Various 1,1-diarylalkanes were obtained with good enantioselectivity using a meta-directing group for first time in hydrogenation reactions (Scheme 13(d)).

Later, Lu and co-workers [46] reported an enantioselective hydrogenation of 1,1-diarylethenes employing a chiral oxazoline iminopyridine-cobalt complex as the precatalyst where a unique *o*-chloride effect was observed for high enantioselectivity (Scheme 13(e)). Various functional groups were well compatible in these mild reaction conditions. However, free alcohols diminished the efficiency of the catalyst.



Scheme 13 Hydrogenation reactions for 1,1-diarylalkane synthesis (color online).

2.6 Conjugate addition reactions

Transition-metal-catalyzed conjugate arylation of α, β-unsaturated aldehydes, ketones, diketone, nitroalkenes and sulfonyl compounds have been extensively studied. This is a powerful strategy to access organic molecules with 1,1-diary moiety. Although chiral and achiral both methods for conjugate arylation have been explored, more emphasis has been given to the asymmetric 1,4-conjugate arylation [6].

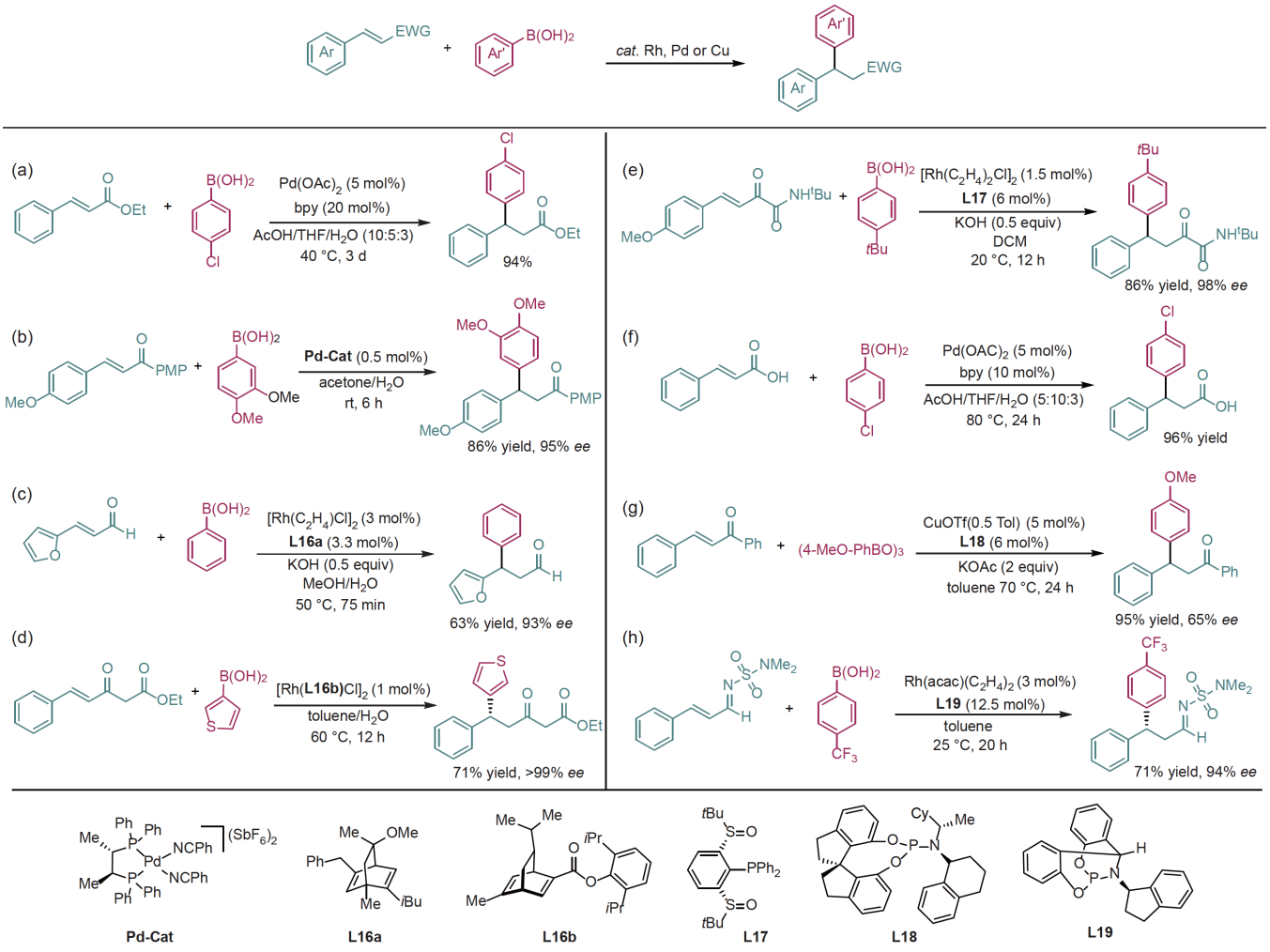
In 2005, Bedford *et al*. [47] reported various palladacyclic catalysts to study their efficiency in 1,4-conjugate addition reactions and synthesized several β-diaryl containing carbonyl compounds. Later, Lu and co-workers [48] disclosed a Pd(II)-catalyzed conjugate addition of arylboronic acid to α, β-unsaturated ketones, aldehydes and esters using 2,2′-bipyridine as ligand. The bipyridine ligands play important role in suppressing the β-hydride elimination (Scheme 14 (a)).

Several reactions protocols involving Pd(II) or Rh-catalyzed asymmetric conjugate arylation of α, β-unsaturated enones were reported by Miuriya and co-workers [49]. In 2008, the authors reported a Pd(II) catalyzed 1,4-addition of arylboronic acids to β-aryl-α,β-unsaturated ketones. The palladium/chiraphos complex afforded the diaryl esters up to 95% *ee* (Scheme 14(b)) [50]. Interestingly, the method has been used for the synthesis of muscarinic receptor antagonist, (R)-tolterodine.

Significant developments have been made in exploring chiral dienes in asymmetric conjugate arylation and several important 1,1-diary containing organic molecules have been synthesized by various groups [51]. In this regard, Carriera and co-workers [52] disclosed the synthesis of 3,3-diarylpropanals with chiral diene-Rhodium catalysts. This Rh(I)-catalyzed conjugate addition of arylboronic acids was not sensitive to the electronic nature of the arene nucleophile (Scheme 14(c)).

Conjugate arylation of α-unsubstituted γ,δ-unsaturated β-dicarbonyls is very challenging because of low electrophilicity of these enolizable dicarbonyl compounds and their nucleophilic character under basic conditions. Recently Hayashi *et al*. [53] reported asymmetric conjugate arylation of γ,δ-unsaturated β-dicarbonyl compounds using arylboronic acid as the source of aryl moiety in presence of Rh(I)-catalyst (Scheme 14(d)). Using chiral diene-rhodium (I) μ-chloro dimer as the catalyst, various β-dicarbonyls with 1,1-diaryl moiety was achieved in high yield and enantioselectivity.

Liao's group [54] has greatly contributed in the conjugate arylation of α,β-unsaturated compounds. Rh-catalyzed conjugate arylation and development of new chiral ligands were



Scheme 14 Conjugate arylation for synthesis of 1,1-diaryl structures (color online).

the important features of their reaction strategy. In 2014, the authors reported a Rhodium-catalyzed asymmetric arylation of α,β-unsaturated ketoamides using chiral ligand **L17** (Scheme 14(e)) [55]. The sulfinylphosphine ligand provided a convenient approach to access important chiral γ,γ-diarylsubstituted carbonyl compounds. This was the first reaction protocols to synthesize γ,γ-diarylsubstituted carbonyl compounds using conjugate arylation strategy. Interestingly, the authors demonstrated the applicability of the method by synthesizing sertraline, an anti-depressant agent.

In 2017, Lin *et al*. [56] reported Pd(II)/bipyridine-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carboxylic acids (Scheme 14(f)). Various arylboronic acids were tolerated in the reactions. However, acid sensitive groups such as 2-furylboronic acids underwent fast hydrolysis and did not provide the desired product.

Zhou *et al*. [57] reported a Cu-catalyzed conjugate arylation of acylic enones using phosphoramidites ligand **L18** (Scheme 14(g)). The mechanism was quite different from the previously reported conjugate arylation. A 1,4-insertion of the Cu-Ar complex was observed in this case. Various enones and arylboroxines, including heteroatom-containing ones were applicable in this method. However, α, β-unsaturated esters and aldehydes were unreactive.

Kim and co-workers [58] used a chiral bicyclic bridgehead phosphoramidite (briphos) in a Rh-catalyzed asymmetric conjugate arylation for *N*,*N*-dimethyl-sulfamoyl imino esters. Several enantioriched (*Z*)-γ,γ-diaryl-α,β-dehydroamino esters were obtained with excellent yields and enantioselectivities (Scheme 14(h)). The bicyclic secondary alkyl group in the chiral briphos structure was indispensable for the high stereoselectivity. Notably, the products can be further transformed to unnatural amino acids, hydroxy ketones and keto acids, which demonstrate the synthetic utility of the reaction.

2.7 Allylic arylation reactions

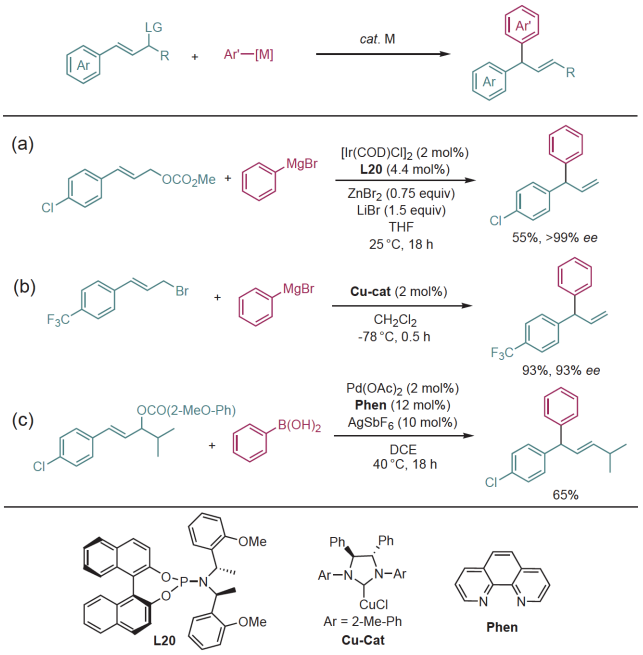
Transition metal-catalyzed allylic substitution reactions have

been one of the most versatile methods used to synthesize various 1,1-diarylalkanes. The nucleophilic organometallic reagents such as Grignard and boronic acids have been successful used in these C–C bond formation reactions.

Alexakis *et al*. [59] reported an Ir-catalyzed allylic arylation using aryl zinc as nucleophiles and several 1,1-diaryl substituted products were obtained under mild reaction conditions including synthesis of an intermediate, which was used in the preparation of (+)-sertraline (Scheme 15(a)). Although good enantioselectivities were achieved in this method, only moderate regioselectivities were obtained.

Tomioka's group [60] has been engaged in Cu-catalyzed allylic substitution reactions for quite long time. In 2009, the authors reported an enantioselective synthesis of diarylvinylmethanes using arylmagnesium bromides to cinnamyl-type substrates catalyzed by a chiral *N*-heterocyclic carbene (NHC)-copper(I) complex (Scheme 15(b)). High regioselectivities and excellent enantioselectivities were obtained in this reaction.

Sawamura [61] developed a palladium catalytic system consisting of $Pd(OAc)_2$, phenanthroline and $AgSbF_6$ for allylic arylation of acyclic (*E*)-allylic acetates with arylboronic acids. The reaction proceeded with excellent γ-selectivity to afford allyl-aryl coupling products with (*E*)-configuration (Scheme 15(c)). Various functional groups in both the allylic acetates and the arylboronic acids were compatible in these reaction conditions. The synthetic potential of the method was demonstrated by the efficient synthesis of an antidepressant agent (+)-sertraline.



Scheme 15 Allylic arylation for synthesis of 1,1-diaryl structures (color online).

3 Three-component reactions for synthesis of 1,1-diaryl alkanes

Three-component reactions are excellent for assembling complex molecular architectures. However, they are more challenging than two-component reactions owing to the possibility of unwanted side reactions. Hydroarylation and the difunctionalization of alkenylarenes and non-activated alkenes are important strategies in three-component reactions for the synthesis of 1,1-diarylalkanes.

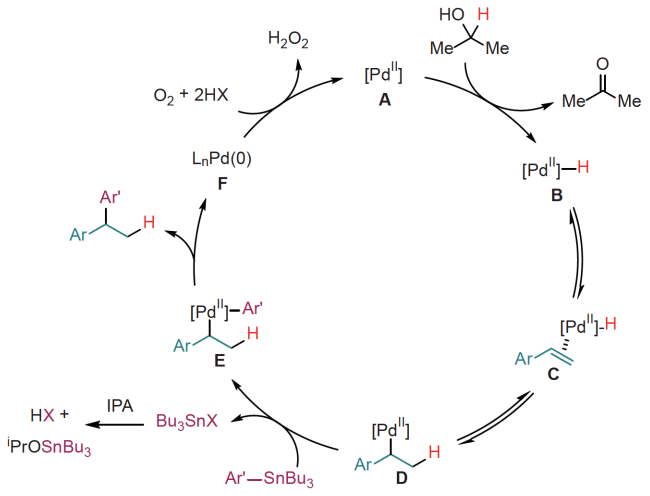
3.1 Hydroarylation of alkenylarenes

The hydroarylation of alkenylarenes is an efficient synthetic strategy for obtaining 1,1-diarylalkanes in which a metal-hydride species adds to the alkene double bond to generate an alkyl metal complex which is followed by arylation. Interestingly, many catalytic systems have been used to synthesize 1,1-diary alkanes using the above strategies with Pd, Cu and Cu/Pd co-operative catalysis. Furthermore, Ni-catalyzed hydroarylation reactions have recently being developed.

In 2007, Sigman and co-workers [62] reported the hydroarylation of styrenes under Pd catalysis. The Pd(II)-H was generated by the oxidation of isopropyl alcohol as shown in the mechanism (Scheme 16). The method applicable to the synthesis of various 1,1-diarylethanes. Both electron-donating and electron-withdrawing groups on each aryl ring were well tolerated (Scheme 17(a)). Later, the same group extended the reaction scope to arylboronic acids [63]. An enantioselective version was also achieved subsequently by using $Pd[(S\text{-}i\text{PrBox})]Cl_2$, *S*-*i*PrBox as ligand and molecular oxygen as oxidant (Scheme 17(b)) [64].

Hydroarylation reactions can also be achieved using organosilanes ([Si]-H) directly as hydride sources to couple with the aryl electrophiles. Semba *et al*. [65] pioneered this approach using Pd/Cu cooperative catalysis (Scheme 17(c)). In this system, the copper catalyst generated the Cu(I)-H species followed by styrene insertion to generate a benzyl copper species, which was then intercepted in the Pd-catalyzed cross-coupling with aryl halides to afford 1,1-diarylalkanes (Scheme 18). Buchwald *et al*. [66] reported an asymmetric version of this reaction using a chiral ligand for copper (Scheme 17(d)).

Interestingly, Buchwald's group [67] realized a Cu-catalyzed enantioselective hydroarylation of styrenes using important heterocycles such as pyridine, and pyridazines directly without introducing any reactive functional group into the heterocyclic ring. Dimethoxymethylsilane (DMMS) was used as the hydride source and (*S*,*S*)-Ph-BPE as the chiral ligand. The initial product was a 1,4-dihydropyridine compound, which subsequently oxidized to the crossponding



Scheme 16 Mechanism of palladium-catalyzed hydroarylation of vinylarenes (color online).

pyridine in a one-pot synthesis leading to 1,1-diarylethanes (Scheme 17(e)).

Recently, hydroarylation reactions have also been extended to nickel-catalysis. In 2019, Zhou *et al*. [68] reported the first Ni-catalyzed hydroarylation of styrenes (Scheme 17(f)). Intriguingly, MeOH was used as the proton source, which generates the Ni(II)-H species by oxidative addition with the Ni(0) species. Notably, using MeOH as the solvent and proton source led to the dimerization of styrene as the major product. This side reaction was circumvented by using a bulky phosphine ligand. Arylboronic acids with an electron-donating group provided higher yields than those with an electron-withdrawing group. However, internal styrenes such as *trans*-β-methylstyrene or indene and aliphatic alkenes, such as 1-hexene, failed to undergo this Ni-catalyzed hydroarylation reaction.

Soon after, Mei *et al*. [69] reported an asymmetric version of this reaction using bisoxazole **L21** as the ligand (Scheme 17(g)). Recently, Zhou's group [70] also achieved the enantioselective version of hydroarylation reaction using their developed chiral spiro-aminophosphine **L22** as the ligand (Scheme 17(h)). Several bioactive molecules were also synthesized using this methodology. Again, internal alkenylarenes were not effective under the optimized conditions.

More recently, Zhu's group [71] demonstrated a Ni-catalyzed highly regio-and enantioselective hydroarylation of styrenes using aryl iodide and DMMS. A new chiral bisimidazoline ligand **L23** was found to be very efficient in this enantioselective transformation. 1,1-Diarylalkanes with various functional groups on the aryl iodide and alkenylarenes moieties were synthesized under the mild reaction conditions (Scheme 17(i)). Importantly, internal styrenes could also smoothly convert to their corresponding products with this method.

β-Hydride elimination usually leads to undesired side products in metal-catalyzed cross-coupling reactions. However, the application of repeated β-hydride elimination/insertion processing changes the reaction site has attracted growing interest recently. In 2017, Zhu's group [72] reported the first Ni-catalyzed migratory hydroarylation reaction for the synthesis of 1,1-diarylalkanes (Scheme 17(j)). Polymethylhydrosiloxane (PMHS) was used as the hydride source. The advantages of this method include very good functional group tolerance and excellent regio-and chemoselectivities.

3.2 Difunctionalization of alkenylarenes

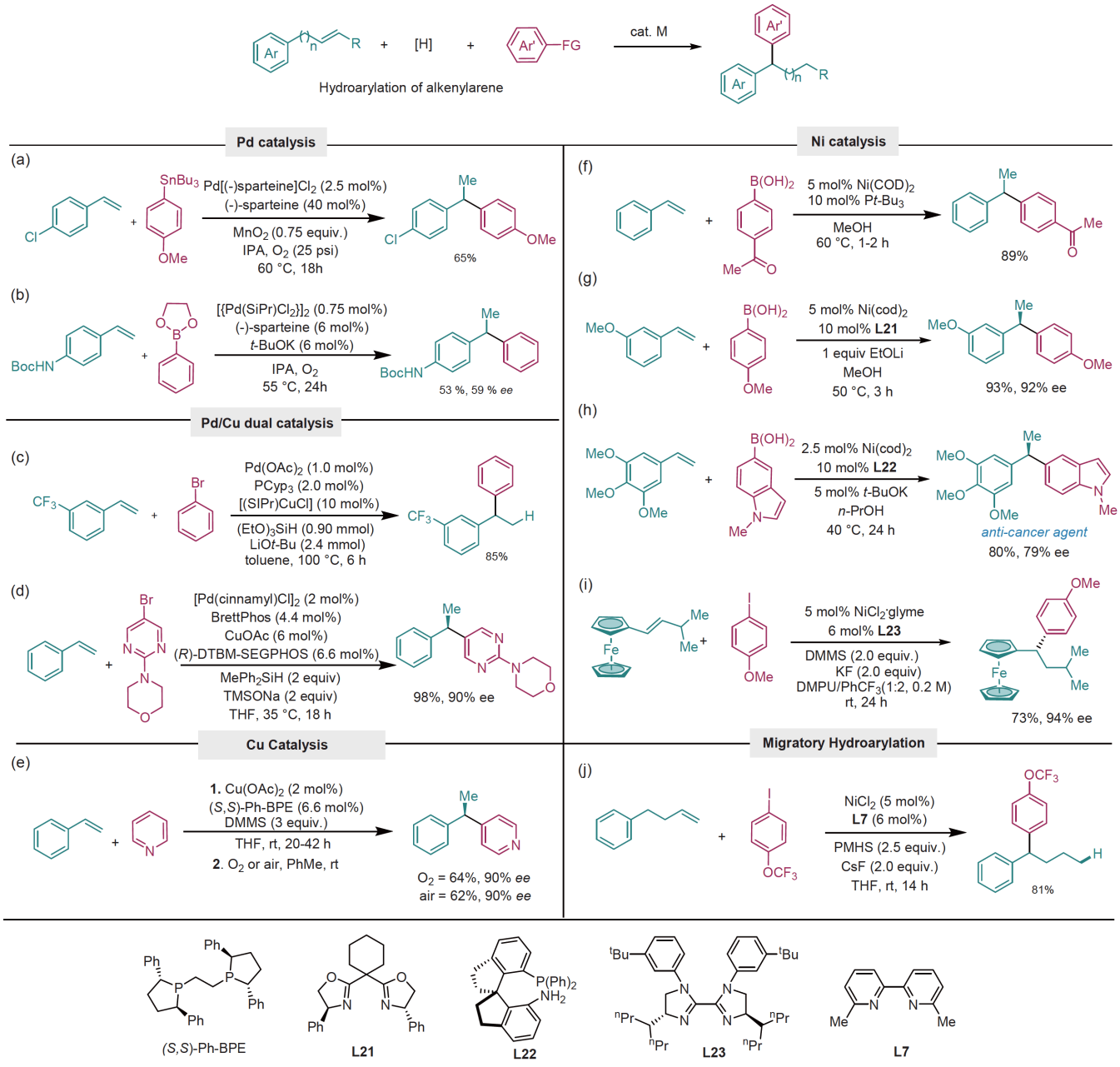
The difunctionalization of alkenylarenes is an intriguing strategy for accessing complex 1,1-diarylalkanes. Borylation/arylation, carbometalation/arylation and radical addition/arylation are among the most prominent pathways used to construct diverse important diarylalkane motifs from readily available starting materials.

3.2.1 Borometalation/arylation

Owing to the diverse transformations of organoboron compounds, the synthesis of boryl-containing 1,1-diarylalkanes has attracted much curiosity among the synthetic chemists [73]. In 2015, Semba and Nakao [74] initially reported Cu/Pd cooperative catalysis for arylboration of vinylarenes using aryl iodides and bis(pinacolato)diboron (B_2pin_2). Using this method, various β-boryl 1,1-diarylalkanes were obtained in good to excellent yield (Scheme 19(a)). The synthetic utility was demonstrated by the synthesis of biologically active compound CDP840. Simultaneously, Brown and co-workers [75] also reported a similar reaction. However, they extended the substrate scope to cyclic arylarenes obtaining the 1,1-diarylalkane products with good diastereoselectivities (Scheme 19(b)).

Later, Brown's group [76] reported Pd/Cu dual catalysis for an enantio- and diastereoselective arylborylation reaction for the synthesis of enantio-riched 1,1-diaryl products (Scheme 19(c)). Liao's group [77] also reported an enantioselective arylboration of styrene by Cu/Pd co-operative catalysis using a chiral sulofxide-phosphine (SOP) ligand in the enantioselective arylboration of styrene by Cu/Pd co-operative catalysis. The reaction conditions were highly selective for iodide as F, Cl and Br were non-competitive. Notably, β-substituted styrenes failed to afford the desired product. The aryl borylated product was further transformed into 1,1,2-triarylated product using a Suzuki-Miyaura cross-coupling reaction (Scheme 19(d)).

Brown *et al*. [78] further expanded the Cu/Pd cooperative catalysis to arylboration reactions of heteroarylarenes and heteroaryl bromides affording several heteroarylated borane compounds (Scheme 19(e)). The Cu-complex used was important for formation of the three-component products. Al-



Scheme 17 Metal-Catalyzed hydroarylation of alkenylarenes. DMMS=dimethoxymethylsilane; PMHS=polymethylhydrosiloxane; DMPU=*N*,*N*-dimethylpropyleneurea (color online).

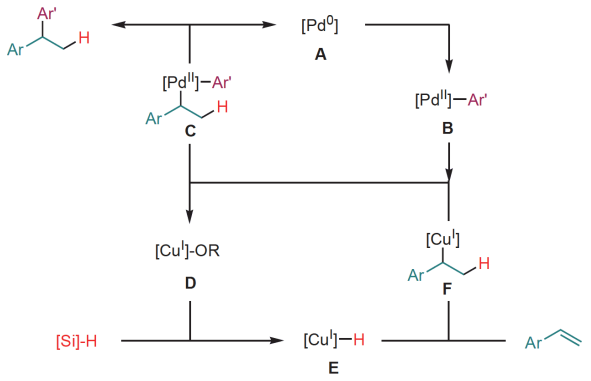
though, earlier reports using heteroaryl halides were not very effective, several important bioactive compounds were synthesized using this reaction.

Semba and Nakao [79] also developed a Ni/Cu cooperative catalysis for arylboration reaction allowing cheaper and more abundant metals to be used but challenging aryl chlorides are required as coupling partners (Scheme 19(f)).

In 2019, our group [80] reported a Ni-catalyzed arylboration of alkenylarenes for the synthesis of diarylalkanes (Scheme 19(g)). Good functional group tolerance has been shown in these mild reaction conditions. However, α or β-substituted styrenes were not effective.

Soon after, Brown's group [81] reported the arylboration of highly substituted alkenylarenes. The intriguing feature of this reaction was the formation of quaternary carbon centers (Scheme 19(h)).

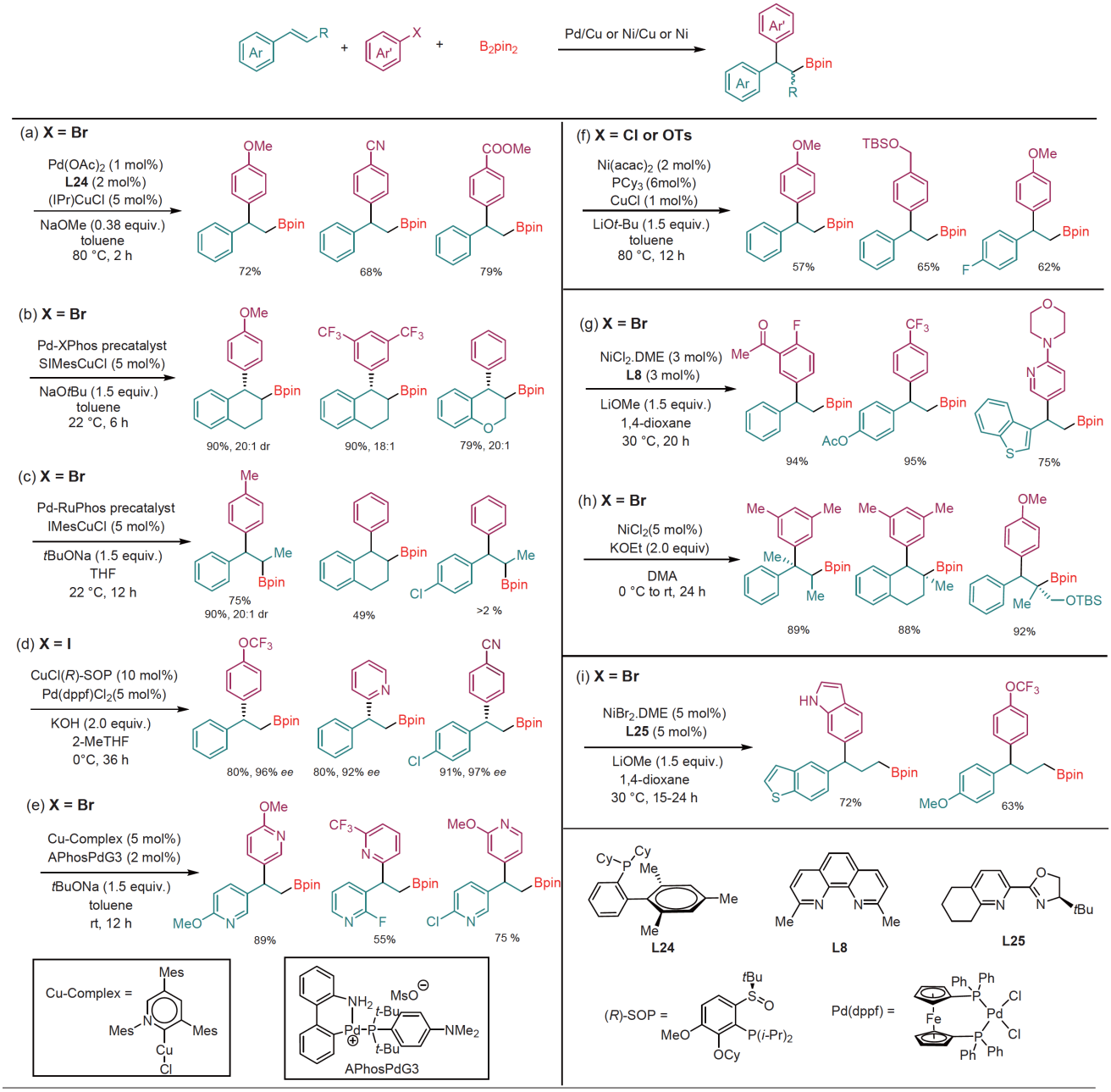
As a continuation of our interest in metal migration, our group discovered a Ni-catalyzed migratory arylboration reaction. The arylboration of unactivated alkenes using this protocols favoured 1,*n*-regioselectivity, which has not been explored previously (Scheme 19(i)) [82]. Notably, several drugs including fenpiprane, diisopromine, prozapine, and fendiline were synthesized by downstream modification of the borylated products.



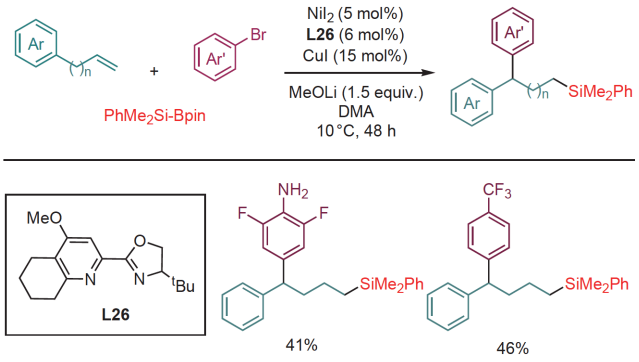
Scheme 18 Mechanism of Pd/Cu cooperative catalysis for hydroarylation of alkanes (color online).

3.2.2 *Migratory silylation/arylation*

Very recently, our group [83] reported silylation/arylation of electronically unbiased alkenes through Cu/Ni dual catalysis in a three-component reaction (Scheme 20). Several 1,1-diarylalkanes containing aliphatic silanes were synthesized from terminal alkenes, aryl halides and Suginome's reagent in moderate yields. PyrBox was used as ligand, which played an important role in suppressing β-hydride elimination, and the steric hinderance in the oxazoline ring of the ligand greatly influenced the chain walking process. Mechanistic studies suggested that copper co-catalyst promotes transmetaltion of Suginome's reagent.



Scheme 19 Synthesis of boryl-containing 1,1-diarylalkanes by metal-catalyzed arylboration of alkenylarene (color online).



Scheme 20 Ni/Cu catalyzed migratory arylsilyation of alkenylarenes (color online).

3.2.3 *Carbometalation/Arylation*

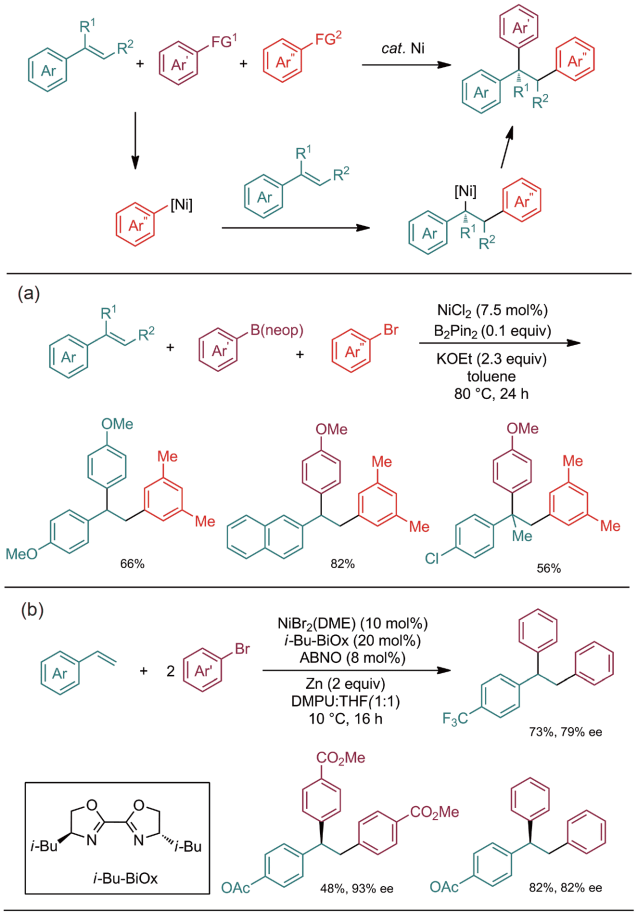
Brown and co-workers [84] reported a nickel-catalyzed 1,1-diarylation of styrenes using aryl bromides and aryl borons (Scheme 21(a)). Using B_2pin_2 in the reaction was important, with the combination of KOEt and B_2pin_2 presumably acting as a reductant for converting Ni(II) to Ni(0). Amine and phosphine base ligand favored the cross-coupling of aryl bromides and arylboron over 1,2-difunctionalization. Several styrene derivatives including 1,2-disubstituted arylarenes, arylboron and aryl bromides were well tolerated.

Diao's group [85] reported a nickel-catalyzed asymmetric 1,2-diarylation of styrene using aryl bromides as the only aryl source (Scheme 21(b)). Interestingly, using 9-azabicyclo [3.3.1]nonane *N*-oxyl radical (ABNO) as an additive was important for controlling enantioselectivity. A wide range of aryl substituted alkanes were prepared in good to excellent yield.

3.2.4 *Radical addition/arylation*

Radical addition to alkenylarenes is another strategy for generating benzylic radicals. The radicals are trapped by Ar-M species to deliver diarylalkanes, or oxidized by metal species to generate benzylic cation intermediates, which then react with nucleophilic arenes to afford biaryl structures. Copper catalysts play a major role in this chemistry. The synthesis of fluorine-containing 1,1-diarylalkanes would greatly expand the pool of drug candidates, as fluorine atoms enhance lipophilicity and permeability. Accordingly, Liu's group [86] reported a Cu-catalyzed trifluoromethylarylation of styrene using Togni's reagent as the trifluoromethyl radical precursor. Later the authors reported an enantioselective version of this reaction (Scheme 22(a)) [87]. Notably, adding EtOH improved the yields of this reaction.

The same group subsequently reported a Cu-catalyzed enantioselective aminoarylation of styrenes synthesizing various optically active 2,2-diarylethylamines with excellent enantioselectivity. *N*-Fluoro-*N*-alkylsulfonamides were used as nitrogen radical sources in this reaction (Scheme 22(b)) [88].

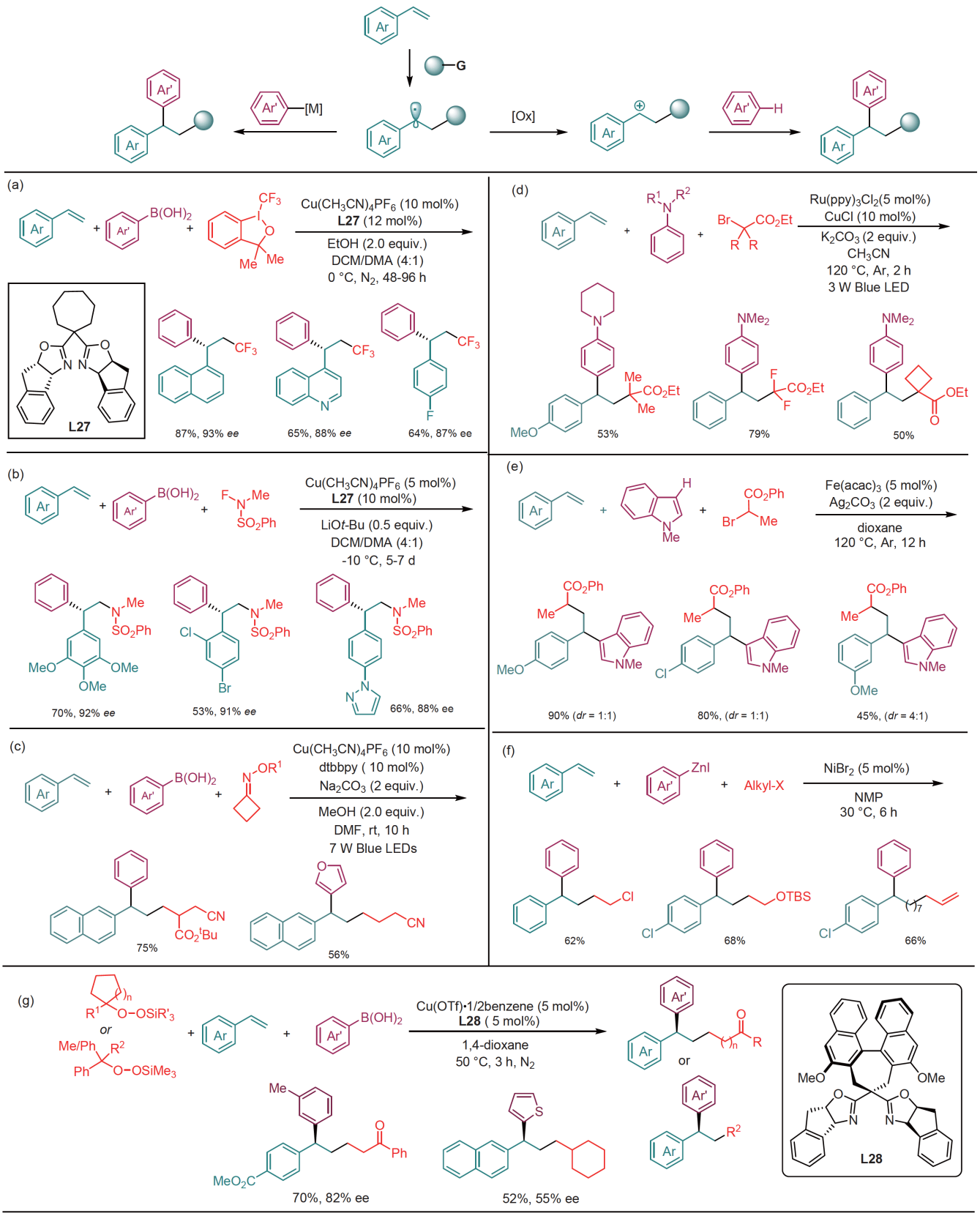


Scheme 21 Ni-catalyzed stereoselective diarylation of alkenylarenes (color online).

Among the various methods for generating alkyl radicals, photocatalysis is an important approach encompassing a broad range of challenging substrates and an alternative to traditional SET. Xiao's group [89] reported photoredox Cu-catalyzed three-component reactions of styrenes, oxime esters and boronic acids (Scheme 22(c)). In the above radical addition/arylation reactions, the aryl coupling partners were either aryl boronic acids or aryl zinc reagents. However, the cationic pathway provides an opportunity to use electron-rich (hetero)arenes as the aryl source.

Li *et al.* [90] reported alkylarylation of styrenes mediated by photoredox and copper cooperative catalysis (Scheme 22(d)). In this reaction, *N,N*-disubstituted anilines were used as arylating reagents with high *para*-selectivity. Various α-carbonyl alkyl bromides, including primary-, secondary- and tertiary-α-bromoalkyl ketone esters, malonic esters and cycloalkane were used for the synthesis of 1,1-diarylalkanes under mild reaction conditions.

The same group also reported an iron-catalzyed, silver-mediated alkylarylation of alkenylarenes, where electron-rich indoles were used as the aryl source (Scheme 22(e)) [91]. The free radical generated by α-bromo ester reacts



Scheme 22 Metal-catalyzed radical-involved arylfunctionalization of vinylarenes (color online).

with styrene to form benzyl radicals, which undergo oxidation to a benzylic carbocation in the presence of the silver salt. Notably, $Fe(acac)_3$ was used only to improve the yield.

In 2018, Giri's group [92] reported an alkylarylation of vinylarene using alkyl halides and aryl zinc reagents to synthesize 1,1-diarylalkanes (Scheme 22(f)). Alkyl iodides and bromides were both applicable in this reaction. Furthermore, tertiary alkyl halides also gave excellent yields under these reaction conditions.

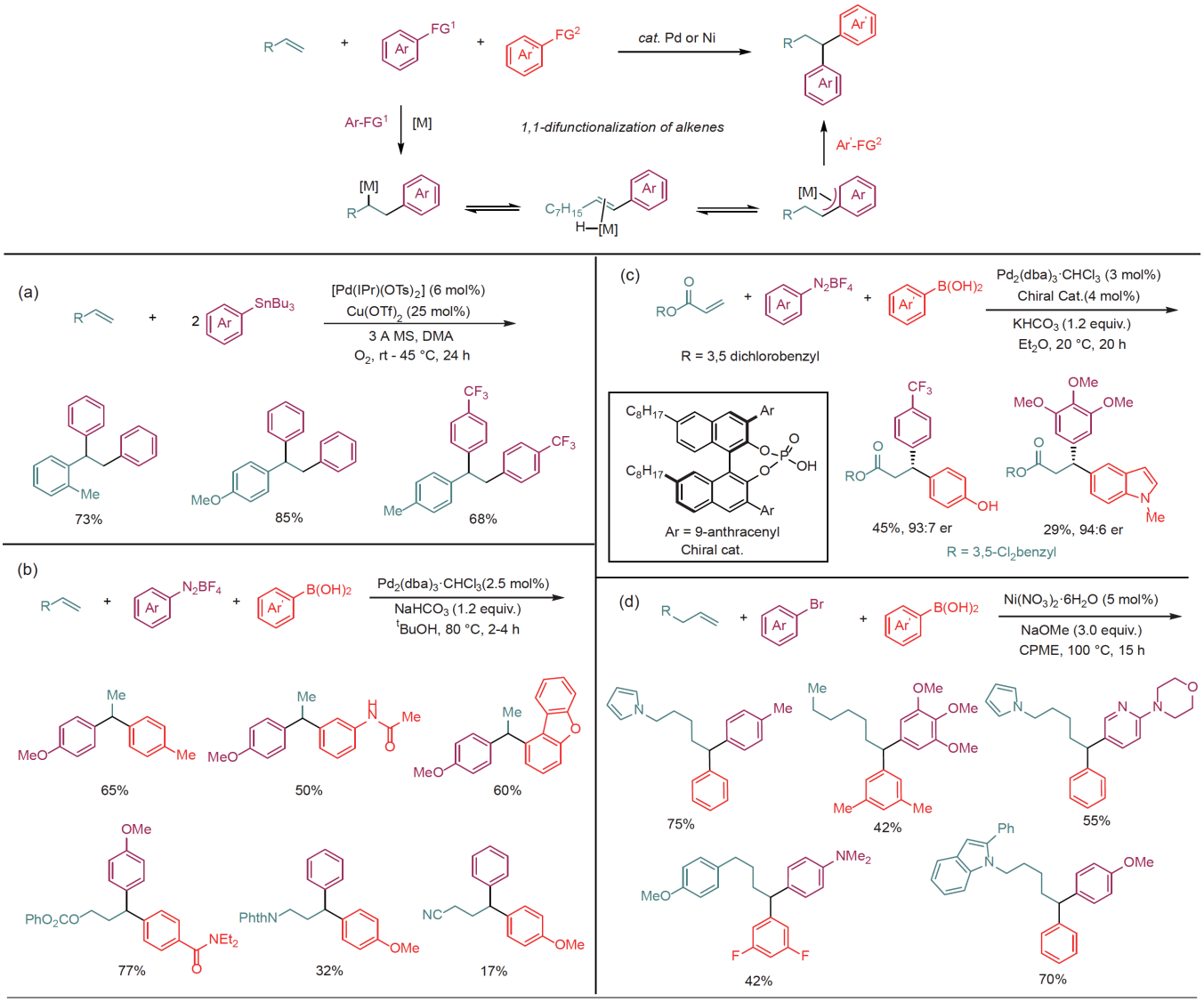
More recently, Marouka's group [93] reported a Cu-catalyzed enantioselective alkyl/arylation of styrenes using hybrid ligand **L28** comprising bisoxazoline and naphthyl motifs, and alkylsilyl peroxides was used as alkyl radical sources (Scheme 22(g)). This radical relay cross-coupling of alkylsilyl peroxides, styrenes and arylboronic acids provided various chiral 1,1-diarylalkane structures under mild reaction conditions.

3.3 1,1-Diarylation of alkenes

Classical palladium-catalyzed alkene difunctionalization has evolved from the Heck reactions, wherein β-hydride elimination is hampered. However, if β-hydride elimination followed migratory reinsertion of M-H generates a new thermodynamically stable benzylmetal species then subsequent bond formation affords the 1,1-difunctionalized product [20]. This technique was used by various groups to synthesize 1,1-diarylalkanes.

In 2008, Le Bras *et al.* [94] reported a protocol for the synthesis of 1,1-difurylated alkanes *via* Pd-catalyzed 1,1-difunctionalization of alkenes using benzoquinone (BQ) as oxidants. The main lacuna in this protocol was that aryl furan compounds other than 2-ethyl/2-methylfuran did not react.

Later, Sigman and coworkers [95] reported a Pd(II)-catalyzed oxidative difunctionalization of terminal alkenes using aryl tin reagents as aryl sources (Scheme 23(a)). Later,



Scheme 23 Metal-catalyzed 1,1-diarylation of terminal alkenes (color online).

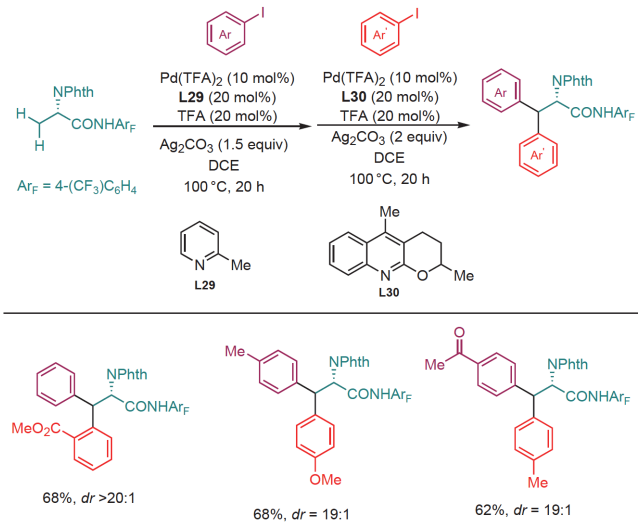
in another report further substrate scope was detailed [96]. The main limitation of this approach was that only identical aryl groups were incorporated in the alkenes.

Later, a redox-neutral palladium-catalyzed 1,1-diarylation approach was developed by the same authors, using aryldiazonium salts and arylboronic acids to introduce two distinct aryl group (Scheme 23(b)) [97]. Following these successes, in 2017, an asymmetric 1,1-diarylation of acrylate was reported by Sigman and Toste [98] using a chiral anion phase transfer (CAPT) process (Scheme 23(c)). Chirality was induced by the chiral phosphate ion.

As a continuation of our work on nickel-catalyzed migratory cross-coupling reactions, we developed a nickel-catalyzed 1,1-diarylation of unactivated alkenes providing a protocol for the synthesis of 1,1-diarylalkanes from unactivated alkenes, aryl bromides and aryl boronic acids (Scheme 23(d)) [99]. Small olefins such as ethylene and propylene also provided the 1,1-products under balloon pressure in this system.

3.4 Double arylation of C–H bonds

The direct functionalization of C–H bond has revolutionized traditional disconnections in organic synthesis. Double C–H bonds arylation is among the most convenient protocols for diarylalkanes synthesis. Accordingly, Yu's group [100] reported the sequential diarylation of alanine derivatives with two different aryl iodides to afford β-diarylated α-amino acids with excellent diastereoselectivities (Scheme 24). Notably, this fascinating strategy used two different ligands to introduce two aryl groups in a one-pot synthesis of diarylated amino acids. The authors found that a pyridine-based ligand promoted mono-arylation of primary β-C(sp^3)–H bonds exclusively and that a second, quinoline-based ligand directed another aryl group for secondary β-C(sp^3)–H activation.



Scheme 24 Ligand-controlled successive arylation of C–H bonds (color online).

4 Summary and outlook

1,1-Diarylalkanes skeletons are found in many naturally occurring compounds and important drugs. Many synthetic efforts have been devoted to the synthesis of these structures, thus many intriguing protocols have been developed, including their enantioselective versions. However, current methods still face challenges that restrict their synthetic utilities. For examples although reductive cross-electrophile couplings and direct arylation of benzylic C–H bonds are important recent advances in two-component reactions, their scope are quite limited with some heteroaryl partners suffering from low efficiency or/and low enantioselectivities. Furthermore, although three-component alkene functionalization reactions provide modular approach for assembling of complex diaryl structures, the olefin scope is limited to mono-substituted, terminal olefins, particularly in asymmetric versions. Additionally, metal migration provides new scope for alkene difunctionalization reactions, few successful examples have been reported for alkenes with substitutions on their carbon chain. Furthermore, asymmetric 1,1-diarylation of unactivated alkenes, double arylation of C–H bonds and the construction of quaternary carbon centers remains challenging. Finally, although the introduction of dual catalysis, such as dual metal cooperative catalysis, photo/metal cooperative catalysis and electric/metal cooperative catalysis has greatly advanced the scope of 1,1-diarylalkanes, only a few asymmetric examples have been reported. Therefore, further efforts are still required to overcome these limitations.

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