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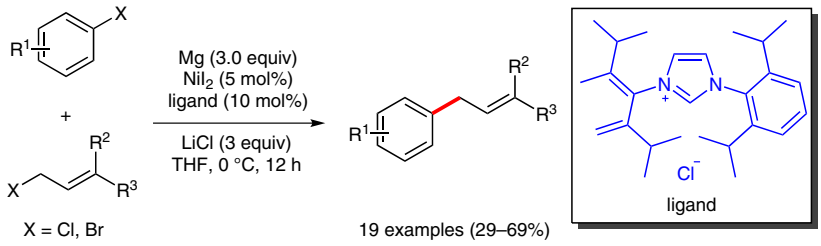
Nickel-Catalyzed Regioselective Reductive Cross-Coupling of Aryl Halides with Polysubstituted Allyl Halides in the Presence of Imidazolium Salts

Zhan Zhang
Lijun Xu
Zhengkai Chen
Zhubo Liu
Maozhong Miao
Jinyu Song
Hongjun Ren*

Department of Chemistry, Zhejiang Sci-Tech University, Hangzhou 310018, P. R. of China
renhj@zstu.edu.cn



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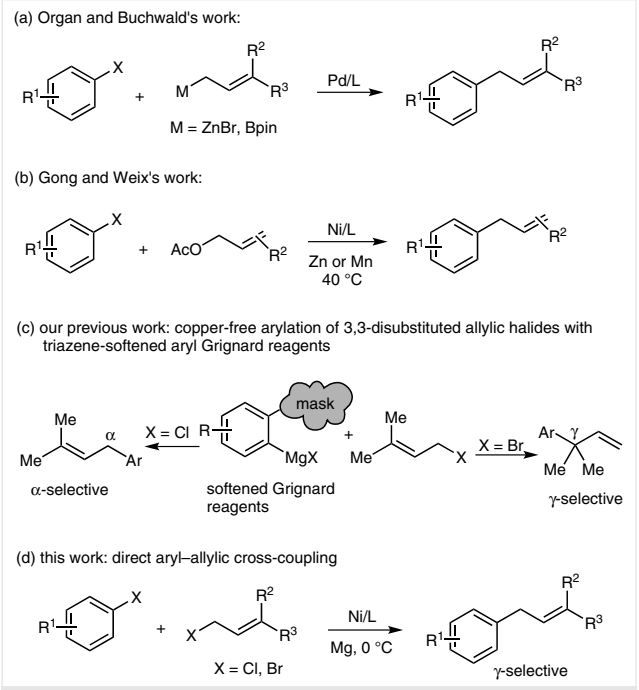
Abstract The nickel-catalyzed direct reductive cross-coupling of aryl halides with readily accessible polysubstituted allyl halides provides an efficient method for preparing diverse allylated arenes under mild conditions. Both allyl bromides and allyl chlorides are compatible with the transformation.

Key words nickel, catalysis, cross-coupling, aryl halides, allylarenes, imidazolium salts

Considerable attention has recently been paid to the synthesis of allylarene derivatives, which can serve as versatile synthetic intermediates and useful chemicals.[1] Among this important group of compounds are the prenylated arenes, which are especially worthy of attention because of their widespread distribution in synthetic and natural bioactive products and their privileged position in drug discovery.[2] Generally, the preparation of allylarenes, especially prenylated arenes, involves the introduction of prenyl or related 3,3-disubstituted allyl groups onto functionalized aromatic systems. In this context, the exclusive control of regioselectivity remains a great challenge.

Organ and co-workers developed cross-coupling reactions of 3,3-disubstituted allylboronates with aryl or hetaryl halides in the presence of N-heterocyclic carbene (NHC)-based palladium catalysts to give linear allylated products with high selectivity (Scheme 1, a).[3] Yang and Buchwald subsequently demonstrated a phosphine-ligand-controlled regiodivergent Suzuki–Miyaura coupling of allylboronates with (het)aryl halides (Scheme 1, a).[4] This elegant protocol provides an efficient approach to the highly selective construction of linear or branched allylated arenes. Buchwald and co-workers also reported a practical Negishi coupling reaction of 3,3-disubstituted allylzinc reagents with aryl, hetaryl, or vinyl halides with completely linear selectivity (Scheme 1, a).[5] Although these methods are efficient and highly selective, they have some drawbacks, especially in the case of the preparation of polysubstituted allyl–metal reagents, such as polysubstituted allylboronates[6a–c] or zinc reagents.[6d–e] The development of strategies for the synthesis of diverse allylated arenes that are more convenient and more economic is still desirable.



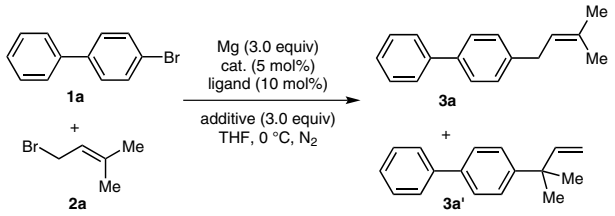
Scheme 1 Various strategies for the preparation of allylated aromatic compounds

From the point of view of environmental and economic sustainability, nickel catalysts are less expensive and more sustainable than palladium catalysts. Nickel has been widely used in organic synthesis as a catalyst for the formation of carbon–carbon and carbon–heteroatom bonds.[7] A nickel-catalyzed direct reductive cross-coupling reaction to construct C–C bonds has recently received significant attention.[8] Nickel catalyst have also been applied in a synthesis of various allylated arenes. Gong[9a,b] and Weix[9c] and their respective co-workers have individually disclosed general nickel-catalyzed selective coupling reactions of organic halides with allylic acetates under mild conditions (Scheme 1, b). Apart from these contributions, there are few reported examples of successful nickel- or cobalt-catalyzed transformations that generate allylated motifs.[10] The nickel-catalyzed direct reductive coupling of aryl halides with 3,3-disubstituted allyl halides remains rare, presumably due to issues of regioselectivity and, especially, homocoupling. We recently developed a copper-free arylation of 3,3-disubstituted allyl halides with triazene-softened aryl Grignard reagents, which provides an efficient way to construct both the α- and γ-isomers of prenylated arenes (Scheme 1, c).[11]

Here we report a nickel-catalyzed direct reductive cross-coupling reaction of aryl halides with readily accessible polysubstituted allyl halides for the rapid assembly of a wide range of allylated arenes under mild conditions (Scheme 1, d).

We began by examining the reaction of 4-bromobiphenyl (**1a**) with 1-bromo-3-methylbut-2-ene (prenyl bromide; **2a**) in the presence of magnesium in tetrahydrofuran with various nickel salts as catalysts (Table 1). When nickel(II) fluoride or bromide was chosen as the catalyst, none of the desired cross-coupling product was obtained (Table 1, entries 1 and 2). Gratifyingly, the use of nickel(II) iodide as a catalyst gave the linear coupling product **3a** in 25% yield (entry 3). Because of the significant effects of N-heterocyclic carbene on coupling reactions,[12] we surmised that an N-heterocyclic carbene precursor might improve the efficiency of our reaction. Unexpectedly, the reaction proceeded smoothly with nickel(II) fluoride or bromide as catalyst in the presence of imidazolium salt **L1** (Figure 1) to give the desired coupling product **3a** in 22 or 23% yield, respectively, demonstrating that the imidazolium salt has a positive effect on the transformation (entries 4 and 5). A combination of nickel(II) iodide (5 mol%) and **L1** (10 mol%) gave **3a** in 37% yield (entry 6). Note that the yield increased to 41% or 62% with the addition of LiI (10 mol%) or LiCl (3.0 equiv) to the reaction system (entries 7 and 8, respectively). Various imidazolium salts were tested, but the promoting effect of imidazolium salts **L2**–**L6** was found to be inferior to that of **L1** (entries 9–13). Screening of other commercially available metal salts, such as iron(III) chloride, tris(acetylacetonato)iron(III) [$Fe(acac)_3$], cobalt(II) chloride, or bis(acetylacetonato)cobalt(II), gave poor yields and poor regioselectivities, showing that their catalytic activity was inferior to that of nickel(II) iodide (entries 14–17).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Ligand	Additive	Yield[b] (%) of **3a**
1	NiF_2	–	–	–
2	$NiBr_2$	–	–	–
3	NiI_2	–	–	25
4	NiF_2	**L1**	–	22
5	$NiBr_2$	**L1**	–	23
6	NiI_2	**L1**	–	37
7	NiI_2	**L1**	LiI[c]	41
8	**NiI_2**	**L1**	**LiCl[d]**	**62**
9	NiI_2	**L2**	LiCl[d]	40
10	NiI_2	**L3**	LiCl[d]	28
11	NiI_2	**L4**	LiCl[d]	46
12	NiI_2	**L5**	LiCl[d]	46
13	NiI_2	**L6**	LiCl[d]	50
14	$FeCl_3$	**L1**	LiCl[d]	40[e]
15	$Fe(acac)_3$	**L1**	LiCl[d]	38[e]
16	$CoCl_2$	**L1**	LiCl[d]	39[e]
17	$Co(acac)_2$	**L1**	LiCl[d]	32[e]

[a] Reaction conditions: 4-bromobiphenyl (**1a**; 1.0 mmol), **2a** (3.0 mmol), catalyst (5 mol%), Mg (3.0 mmol), ligand (10 mol%), additive, THF (3.0 mL), under N_2, 0 °C, 12 h.
[b] Yield of the isolated product.
[c] 10 mol%.
[d] 3 equiv.
[e] The γ-selective product **3a**′ was also obtained in 5–10% yield.

Having identified the optimal reaction conditions, we examined the scope of nickel-catalyzed reductive cross coupling reaction with various aryl halides and allyl halides (Scheme 2). 2-Bromobiphenyl and 3-bromobiphenyl reacted well with bromide **2a** under the standard conditions to give the desired coupling products **3b** and **3c** in moderate yields (52 and 50%, respectively).[13] The reactivity of 1-bromo-4-methoxybenzene (**2d**) and 1-bromo-3-methoxybenzene (**2f)** was similar to that of 1-bromo-2-methoxybenzene (**2e**), indicating that the orientation of the substituents has only a weak effect on this transformation. 1-Bromo-2-(methoxymethyl)benzene (**2k**) and 4-bromo-2,5-dimethylbiphenyl (**2l**) also reacted to give the corresponding coupling product **3k** and **3l** in 49 and 54% yield,

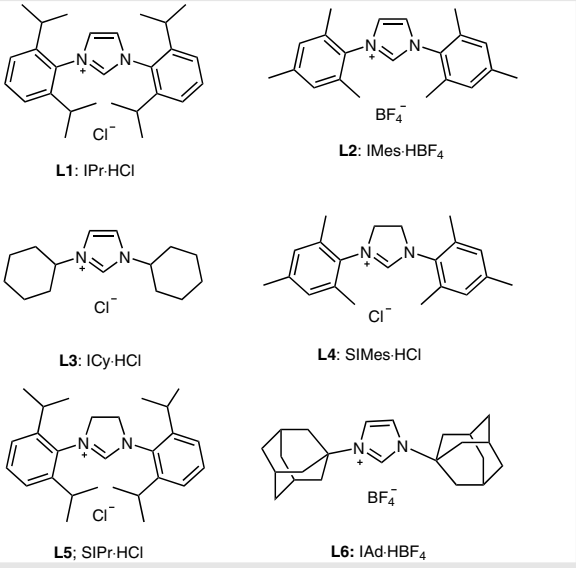
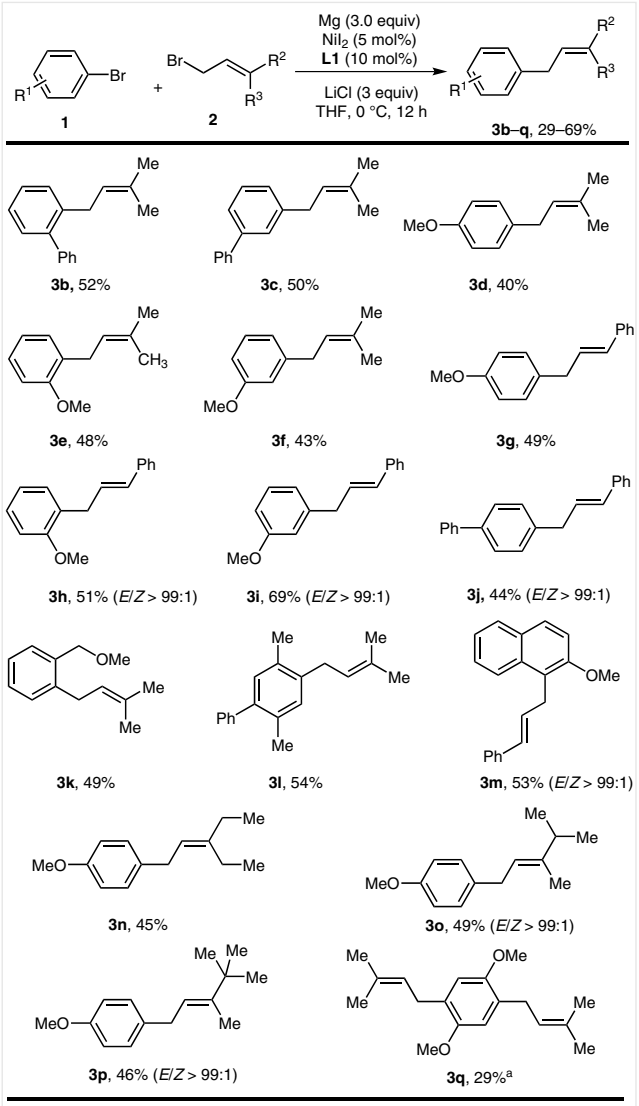


Figure 1 NHC ligands **L1**–**L6**

respectively. Notably, [(1*E*)-3-bromoprop-1-en-1-yl]benzene reacted with various aryl halides to give the corresponding coupling products **3g**–**j** and **3m** in 44–69% isolated yield. It is worth mentioning that the reaction also proceeded smoothly with the series of substituted allyl bromides **2n**–**p**, and that the configuration of the alkenes was retained in the corresponding products **3g**–**j**, **3m**, and **3o**–**p**. Furthermore, the dicoupling product **3q** was successfully obtained with the current catalytic system, albeit in a lower yield.

To extend the applicability of the reaction, we next turned our attention to the possibility of using cyclic allylic chlorides in the nickel-catalyzed reductive cross-coupling reaction (Scheme 3). To our delight, when we used 1-bromo-4-methoxybenzene or 1-bromo-3-methoxybenzene with 3-chloro-1,5,5-trimethylcyclohex-1-ene (**4**) as substrates under the nickel-catalyzed reductive cross-coupling conditions, we obtained the desired α-selective coupling product **5a** and **5b**, respectively, albeit with relatively low yields. However, the desired product **5c** was not obtained from 1-bromo-2-methoxybenzene, indicating that steric interference between the *ortho*-substituent and the bulky 3-chloro-1,5,5-trimethylcyclohex-1-ene (**4**) had an obvious influence on the reactivity of the substrate in this case.

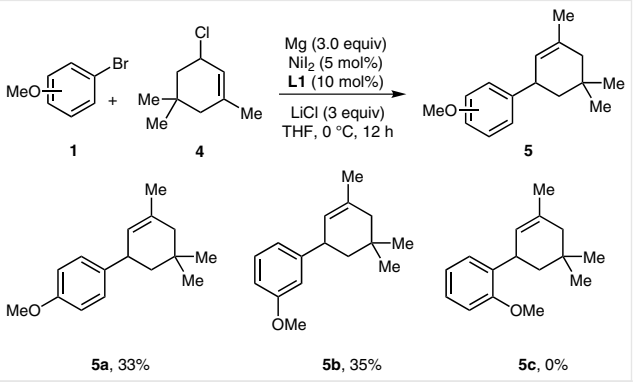
Next, we attempted to exploit the full potential of our nickel-catalyzed reductive cross-coupling by synthesizing a complex molecule. The diprenyl derivative of curcumin (PCRM) is a useful probe for investigating the antioxidant pharmacophore of natural curcuminoids, and it possesses excellent anticarcinogenic and antiinflammatory properties.[14] The usual synthesis of diprenylated curcumin required intricate procedures for the installation of the prenyl moiety.[15] By using our method, we obtained the key PCRM



Scheme 2 The scope of nickel-catalyzed reductive cross-coupling. *Reagents and conditions*: aryl bromide **1** (1.0 mmol), allyl bromide **2** (3.0 mmol), NiI_2 (5 mol%), Mg (3.0 mmol), **L1** (10 mol%), LiCl (3.0 equiv), THF (3.0 mL), stirring, under N_2, 0 °C, 12 h. The yields refer to the isolated products. [a] *Reagents and conditions*: aryl bromide **1** (1.0 mmol), allyl bromide **2** (5.0 mmol), NiI_2 (5 mol%), Mg (5.0 mmol), **L1** (10 mol%), LiCl (5.0 equiv), THF (3.0 mL), stirring, under N_2, 0 °C, 12 h.

precursor **6e** smoothly from readily available starting materials, thereby providing straightforward access to the useful bioactive molecule (Scheme 4).

In summary, we have developed an efficient pathway for the preparation of a range of allylated arenes by nickel-catalyzed reductive cross-coupling of aryl halides with polysubstituted allyl halides. Notable features of this transformation include the mild reaction conditions, the readily available starting materials, and a broad substrate scope.



Scheme 3 The coupling reaction of a cyclic allylic chloride with various aryl bromides. *Reagents and conditions*: aryl bromide **1** (1.0 mol), 1,5,5-trimethylcyclohex-1-ene (**4**; 3.0 mol), NiI_2 (5 mol%), Mg (3.0 mol), **L1** (10 mol%), LiCl (3.0 equiv), THF (3.0 mL), stirring, under N_2, 0 °C, 12 h. Yields are those of the isolated products.

Further studies to elucidate the mechanism of the reaction and to extend the range of practical applications of this method are in progress in our laboratory.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560531.

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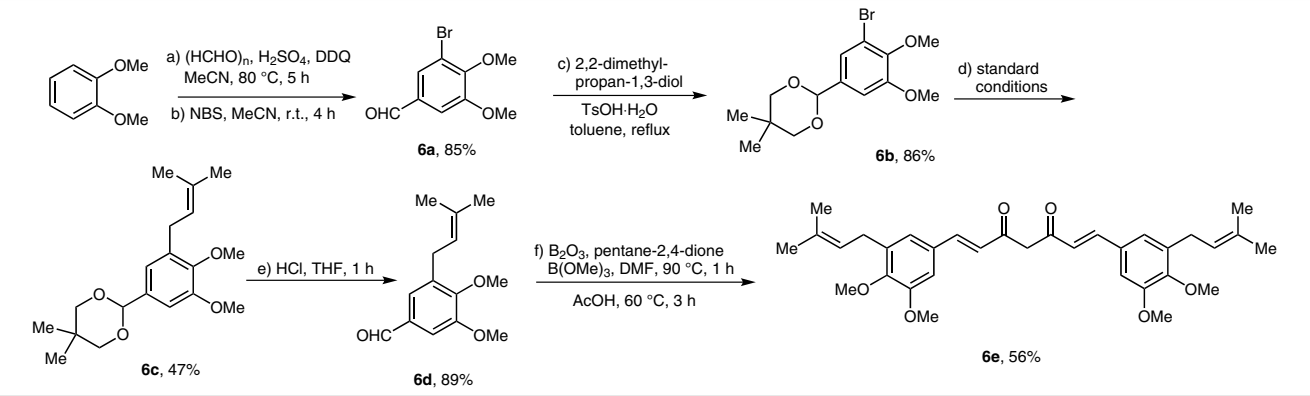

Scheme 4 Application in the synthesis of a diprenyl derivative of curcumin. *Reagents and conditions*: (a) $(HCHO)_n$ (4.0 equiv), H_2SO_4 (cat.), DDQ (2.0 equiv), MeCN, 80 °C, 5 h; (b) NBS (2.0 equiv), MeCN, r.t., 4 h; (c) 2,2-dimethylpropane-1,3-diol (1.05 equiv), $TsOH·H_2O$ (0.1 equiv), toluene, reflux, 12 h; (d) standard Ni-catalyzed conditions; (e) concd aq HCl (2.0 equiv), THF, r.t., 1 h; (f) B_2O_3 (0.47 equiv), pentane-2,4-dione (0.5 equiv), $B(OMe)_3$ (3.3 equiv), DMF, 90 °C, 1 h, then AcOH (0.05 equiv), 60 °C, 3 h.

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(13) **2-(3-Methylbut-2-en-1-yl)biphenyl (3b); Typical Example**
A dry, N_2-flushed, 25 mL Schlenk tube equipped with a magnetic stirrer was charged with Mg (3.5 mmol, 3.5 equiv) and anhyd LiCl (3 mmol, 3.0 equiv), which were covered with anhyd THF (3 mL) and activated by the addition of a few drops of TMSCl. The mixture was stirred for 30 min, then ligand **L1** (0.1 mmol, 0.1 equiv) and NiI_2 (0.05 mmol, 0.05 equiv) were added, and the mixture was stirred at 0 °C. A solution of 4-bromobiphenyl (**1b**; 1.0 mmol, 1.0 equiv) and bromide **2a** (3.0 mmol, 3.0 equiv) in THF (2 mL) was slowly added from a syringe pump at 0 °C (flow rate: 3 mL/h). The resulting mixture was stirred under N_2 at 0 °C for 12 h. Sat. aq NH_4Cl (10 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4), concentrated in vacuo, and purified by chromatography [silica gel (200–300 mesh), PE] to give a colorless oil; yield: 115 mg (52%); R_f = 0.58 (PE). IR (ATR–FTIR): 2969, 1479, 1047, 738, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 2 H), 7.36–7.29 (m, 5 H), 7.25–7.21 (m, 2 H), 5.19 (t, *J* = 7.2 Hz, 1 H), 3.28 (d, *J* = 7.2 Hz, 2 H), 1.68 (s, 3 H), 1.51 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.84, 141.76, 139.2, 131.9, 130.0, 129.33, 129.25, 128.0, 127.4, 126.7, 125.7, 123.7, 32.0, 25.7, 17.7. MS (ES^+): *m/z* (%) = 223 (8) $[M + H]^+$, 195 (28), 177 (21), 168 (25), 133 (100), 117 (35), 105 (12). HRMS (ES^+–TOF): *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}$: 223.1487; found: 223.1474.

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