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Nickel-catalyzed allyl–allyl coupling reactions between 1,3-dienes and allylboronates†

Ding-Wei Ji, [ID] [ab] Gu-Cheng He, [ID] [a] Wei-Song Zhang,[a] Chao-Yang Zhao,[a] Yan-Cheng Hu [ID] [a] and Qing-An Chen [ID] *[a]

A regiospecific allyl–allyl coupling reaction between 1,3-dienes and allylboronates has been demonstrated under nickel catalysis. Salient features of this method include the earth-abundant metal catalyst, excellent regioselectivity and good functional group tolerance. Notably, even congested allyl substrates can also be applied to this protocol, thus allowing for the rapid preparation of a series of valuable 1,5-dienes.

Owing to the diverse reactivity of the allyl and vinyl groups, 1,5-diene fragments and their derivatives often serve as useful building blocks in organic synthesis.[1] Besides, the 1,5-diene unit itself is widely found in biologically active molecules and natural products.[2] Therefore, their synthesis has attracted considerable attention over the past few decades and some efficient strategies have been established.[3] Among them, transition metal-catalyzed cross-coupling between allyl electrophiles and allyl nucleophiles represents one of the simplest and most straightforward tools.[4] However, two inherent challenges limit the applications of this classic strategy (Scheme 1a). First, the requirement for pre-installation of a leaving group onto the starting allyl electrophiles may diminish the synthetic economy. Second, several difficulties such as the poor regioselective control of products or the competing formation of side product 1,3-dienes derived from β-hydride elimination may arise when utilizing internal allyl electrophiles as the coupling partners.[4l,o] In this context, developing a general and regioselective allyl–allyl coupling reaction to access 1,5-dienes from non-activated precursors is still highly demanded.

As 1,3-dienes are easily accessible and versatile synthons in organic synthesis, the employment of 1,3-dienes as greener allyl precursors *via* catalytic hydrofunctionalization is becoming an attractive method for the buildup of molecular complexity.[5,6]

Despite the fact that reductive allyl–allyl cross-coupling of allenes or alkynes has been developed by Hoveyda,[7] Tsuji,[8] Zhang[9] and our group,[10] the direct utilization of 1,3-dienes in allyl–allyl coupling for the synthesis of 1,5-dienes has been rarely realized. Very recently, Meek and co-workers reported a seminal work on the rhodium-catalyzed hydroallylation of 1,3-dienes with allyltrifluoroborates.[11] Due to undesired alkene isomerization, a mixture of 1,5- and 1,4-dienes was obtained in most cases (Scheme 1b). In light of the excellent performance of a nickel catalyst in 1,3-diene hydrofunctionalization,[12] we envisioned that the relatively cheap and earth-abundant nickel could also serve as an attractive alternative to noble rhodium catalysts in hydroallylation of 1,3-dienes. As an extension of our studies on catalytic functionalization of dienes,[13] herein we report this regiospecific reductive allyl–allyl cross-coupling between 1,3-dienes and allylboronates under nickel-hydride catalysis (Scheme 1c).
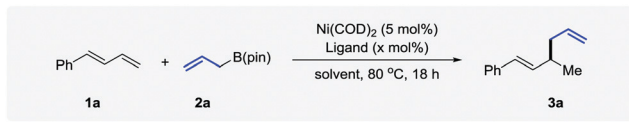
[a] *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China. E-mail: qachen@dicp.ac.cn; Web: http://www.lbcs.dicp.ac.cn*
[b] *University of Chinese Academy of Sciences, Beijing 100049, P. R. China*
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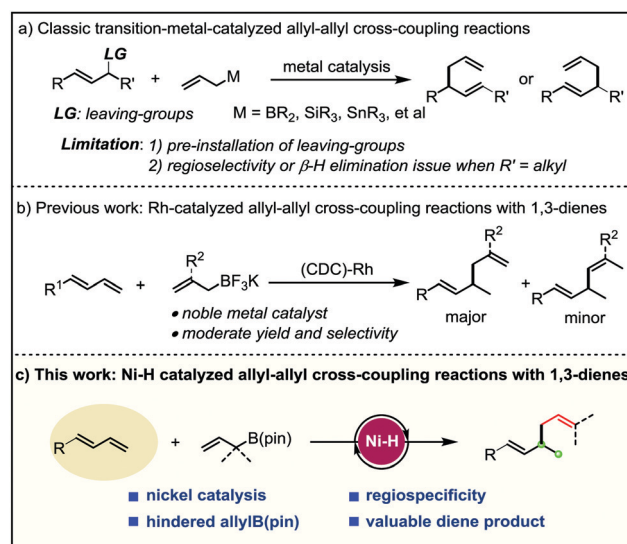
Scheme 1   Transition metal-catalyzed allyl–allyl coupling reactions.

Table 1 Optimization for hydroallylation of 1,3-diene[a]
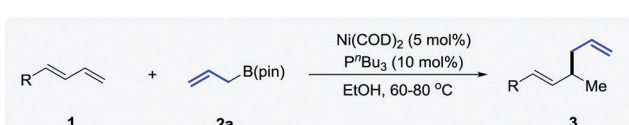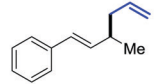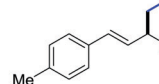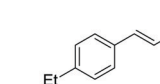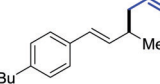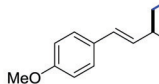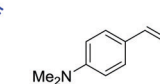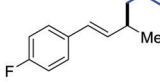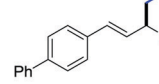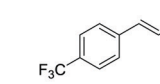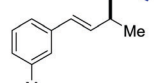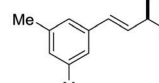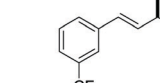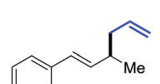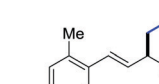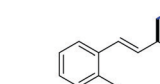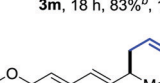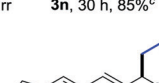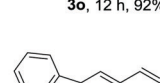
Entry	Ligand (x mol%)	Solvent	Yield[b] (%)
1	PPh$_3$ (10)	MeOH	50
2	PPh$_3$ (10)	EtOH	58
3	PPh$_3$ (10)	^{n}PrOH	51
4	PPh$_3$ (10)	^{i}PrOH	55
5	PPh$_3$ (10)	^{t}BuOH	45
6	PCy$_3$ (10)	EtOH	22
7	P(^{t}Bu)$_3$ (10)	EtOH	Trace
8	P(^{n}Bu)$_3$ (10)	EtOH	83
9	dppp (5)	EtOH	2
10	dppb (5)	EtOH	50
11	dppf (5)	EtOH	5
12[c]	P(^{n}Bu)$_3$ (10)	EtOH	42
13[d]	P(^{n}Bu)$_3$ (10)	EtOH	74
14[e]	**P(^{n}Bu)$_3$ (10)**	**EtOH**	**93 (85)[g]**
15[f]	P(^{n}Bu)$_3$ (10)	EtOH	75

[a] Reaction conditions: **1a** (0.20 mmol), **1b** (0.40 mmol), Ni(COD)$_2$ (5 mol%), ligand (5–10 mol%), solvent (0.4 M), 80 °C, 18 h. [b] Determined by GC-FID with 1,3,5-trimethoxybenzene as the internal standard. [c] 60 °C. [d] 100 °C. [e] EtOH (0.8 M). [f] EtOH (0.2 M). [g] Isolated yield.

We initiated our research with 1-phenyl-1,3-butadiene **1a** and allylB(pin) **2a** as the model substrates (Table 1). Pleasingly, the expected 1,5-diene **3a** was observed as a sole product in the presence of Ni(COD)$_2$ (5 mol%) and PPh$_3$ (10 mol%) in MeOH at 80 °C (entry 1). The evaluation of the solvent suggested that the yield of **3a** could be improved to 58% when the reaction was performed in ethanol (entries 2–5). After examining various ligands, we obtained an increased yield of **3a** with P(^{n}Bu)$_3$ (entries 6–11). While lowering or raising the temperature resulted in decreased yields (entries 12 and 13), increasing the reaction concentration successfully led to **3a** in an excellent yield (93%, entry 14).

With the optimal reaction conditions in hand, we shifted our attention to explore the substrate scope of this nickel-catalyzed allyl–allyl coupling reaction. As shown in Table 2, we generally obtained various 1,5-dienes in good yields and selectivities. The 1,3-dienes with alkyl substituents on the phenyl ring such as methyl, ethyl and butyl all gave desirable products in good to excellent yields (**3b–3d**, **3j**, **3k**). Strong electron-donating substrates (*e.g.* OMe, NMe$_2$) were comparatively sluggish in this reaction (**3e** and **3f**). A fluoro group was also well tolerated, delivering the 1,5-diene **3g** in 80% yield. Electron-withdrawing Ph and CF$_3$ groups exhibited higher reactivity and offered good yields of 1,5-dienes even at lower temperature (**3h**, **3i** and **3l**). Notably, *ortho*-substituted substrates **1m** and **1n** also proceeded smoothly, regardless of their steric hindrance, generating the corresponding products in 83% and 85% yields, respectively. On replacing the phenyl group with a 1-naphthalenyl group, the substrate was transformed into product **3o** in an excellent yield. Heterocyclic substrates **3p–3r** were also compatible in the current protocol and afforded the products in 21–60% yields.

Table 2 Hydroallylation of 1,3-diene

Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), Ni(COD)$_2$ (5 mol%), P^{n}Bu$_3$ (10 mol%), EtOH (0.8 M), 80 °C, 18 h, isolated yields were given. The rr values refer to the ratio of **3** to 1,4 adducts and determined by ^{1}H NMR analysis. Unless note that the rr is more than 20:1. [a] Accompanied by a small amount of inseparable diene **1**, the yield of the product has been adjusted accordingly. [b] 70 °C. [c] 60 °C.

Transition-metal catalyzed allyl–allyl couplings with congested allylboronates are a challenging task and very limited studies have been successfully realized.[4j,o] Satisfactorily, although linear substrate **2b** was unreactive under the current reaction conditions, the prenylative product **3s** could be obtained in an acceptable yield with branched prenyl-B(pin) (Table 3). Moreover, geranyl-B(pin) **2d** also reacted well with **1a** and gave the product **3t** in 42% yield. These results complement the Rh-catalyzed hydroallylation method for the synthesis of 1,5-dienes.[11]

To further verify the synthetic utility of this protocol, a scale-up reaction (5.0 mmol) was performed, delivering 1,5-diene product **3a** in 88% yield (762 mg, Scheme 2). Besides, further synthetic transformation of **3a** with phenyl acrylate under cross olefin-metathesis conditions furnished the unsaturated ester **4**
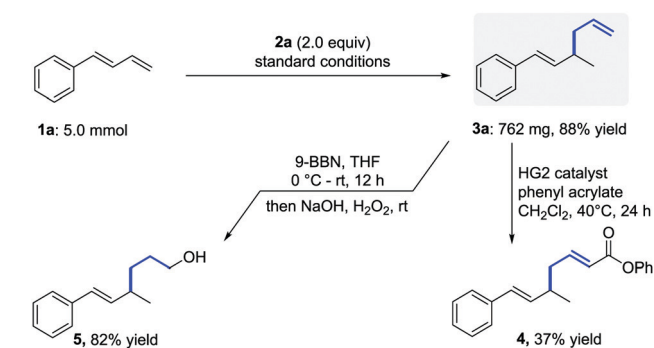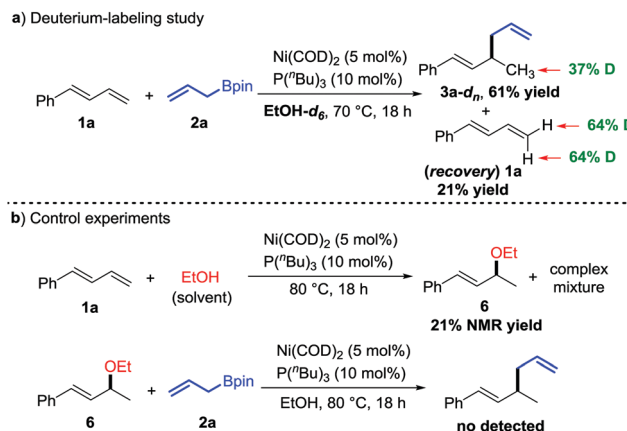
Table 3 The scope of allylborons

2	Product	Yield (%)
2b	3s	< 5%
2c	3s	43%
2d	3t	42% Z/E mixture, 1/1.6[a]

Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), Ni(COD)$_2$ (5 mol%), P^{n}Bu$_3$ (10 mol%), EtOH (0.8 M), 80 °C, 18 h, isolated yields were given. Unless noted, the rr > 20 : 1. [a] Determined by GC-FID.

in 37% yield. Moreover, the hydroboration/oxidation reactions of **3a** could proceed efficiently to give alcohol **5** in a good yield (82%).

To gain some insights into the mechanism, a deuterium-labeling experiment with 1-phenyl-1,3-butadiene **1a** and allyl-B(pin) **2a** was conducted with EtOH-d_6. As depicted in Scheme 3a, while 0.37 deuterium was incorporated into the methyl group of the 1,5-diene product, 0.64 deuterium was also exchanged into the terminal CH$_2$ of the recovered diene **1a**. This observation supports a reversible process of the migratory insertion between the 1,3-diene and the Ni-hydride. In the absence of **2a**, hydroalkoxylative product **6** could also be obtained in 21% NMR yield under the standard reaction conditions. However, the reaction between **6** and **2a** under standard conditions could not deliver 1,5-diene **3a** (Scheme 3b), thus excluding the possibility that **6** is an intermediate of the process.

While further studies are warranted, we tentatively proposed the following mechanism on the basis of the literature and our own observations (Fig. 1).[11,12f] First, the oxidative addition of the ethanol with a nickel(0) precursor **A** gives Ni(II)-hydride species **B**, which then undergoes migratory insertion with 1,3-diene **1** to afford allyl–Ni(II) intermediate **C** or **C′** in a reversible pathway. Through the transmetalation between the allyl–Ni(II) intermediate and allyl-B(pin) **2**, bis(allyl)Ni species **D** is produced.

Scheme 3 Deuterium-labeling and control experiments.

Finally, reductive elimination of **D** leads to terminal 1,5-diene product **3** and regenerates the nickel(0). It should be noted that the existence of allyl–Ni(II) intermediate **C/C′** was supported by the observation of **6** via a reductive elimination step. Therefore, the current mechanism was preferred over the reported transmetalation-alkene insertion pathway in previous Rh-catalyzed reactions.[11]

In summary, a nickel-catalyzed allyl–allyl cross-coupling reaction between 1,3-dienes and allyl-B(pin) was achieved via a hydroallylative protocol. This strategy exhibited good functional group tolerance, exclusive regioselectivity and high reactivity, thus complementing a facile route to access 1,5-dienes. Further studies on expanding the scope of unsaturated substrates and the detailed mechanism, as well as the asymmetric version, are now in progress in our laboratory.

Scheme 2 Scale-up synthesis and transformations of 1,5-diene **3a**.
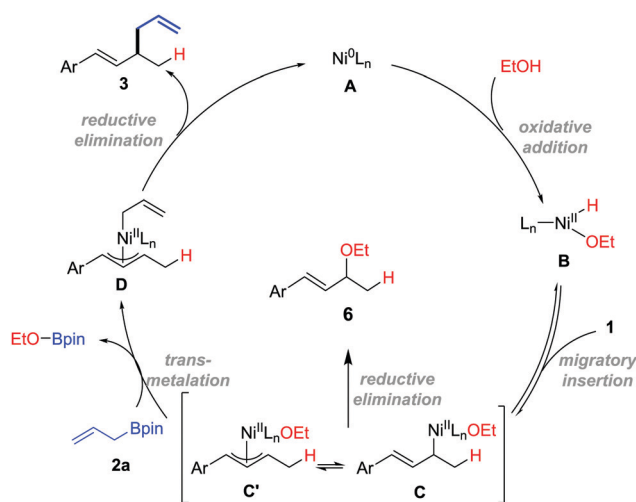
Fig. 1 Proposed mechanism for Ni-catalyzed hydroallylation.

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Conflicts of interest

There are no conflicts to declare.

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