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COMMUNICATION

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

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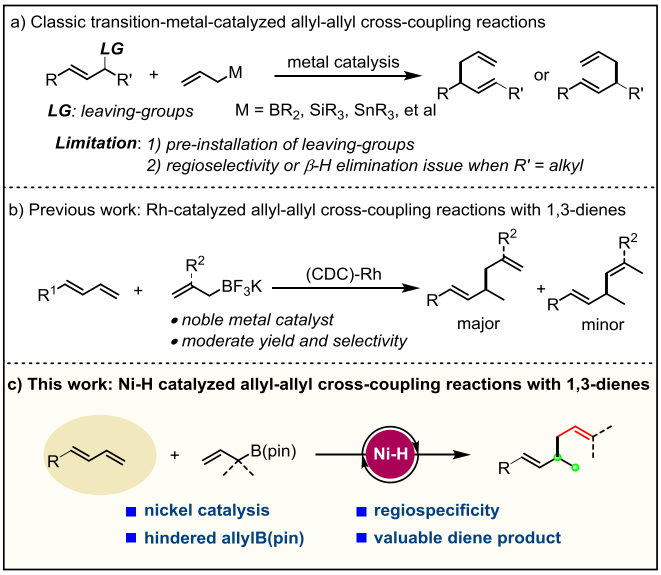
A regiospecific allyl-allyl coupling reaction between 1,3-dienes and allylboronates has been demonstrated under nickel catalysis. Salient features of this method include the earth-abundant metal catalyst, excellent regioselectivity and good functional group tolerance. Notably, even congested allyl substrates 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, 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 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,4o] 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 the catalytic hydrofunctionalization is becoming an attractive way for the buildup of molecular complexity.[5,6] Despite the fact that reductive allyl–allyl cross-coupling of allenes or alkynes have 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 was 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 were obtained in most cases (Scheme 1b). In light of excellent performance of 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 catalyst 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 1,4-dienes and allylboronates under nickel-hydride catalysis (Scheme 1c).



Scheme 1. Transition metal-catalyzed allyl–allyl coupling reactions

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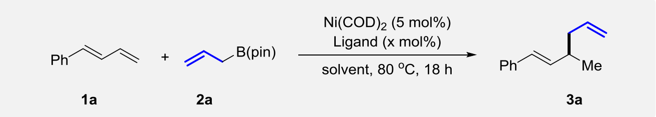
We initiated our research with 1-phenyl-1,3-butadiene **1a** and allylB(pin) **2a** as the model substrates (Table 1). Pleasingly, the expected 1,5-diene **3a** was observed as sole product in the presence of Ni(COD)$_2$ (5 mol%) and PPh$_3$ (10 mol%) in MeOH at 80 °C (entry 1). The evaluation of solvent 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 temperature resulted in decreased yields (entries 12-13), increasing the reaction concentration successfully led to **3a** in an excellent yield (93%, entry 14).

Table 1. Optimization for hydroallylation of 1,3-diene

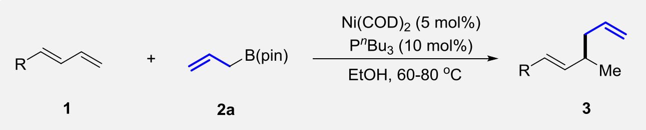


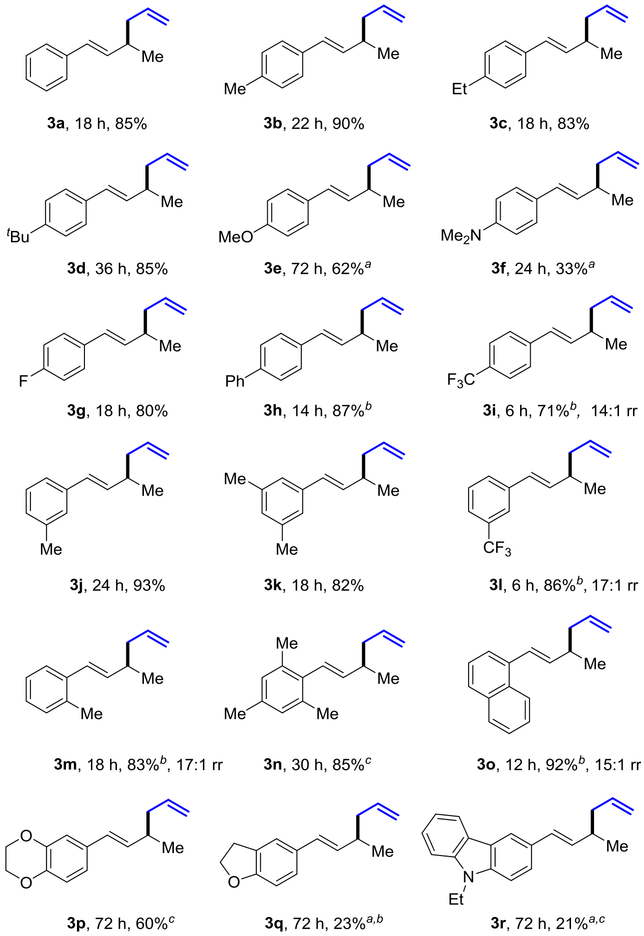
entry	ligand (x mol%)	solvent	yield (%)[b]
1	PPh$_3$ (10)	MeOH	50
2	PPh$_3$ (10)	EtOH	58
3	PPh$_3$ (10)	^{n}PrOH	51
4	PPh$_3$ (10)	^{i}PrOH	55
5	PPh$_3$ (10)	^{t}BuOH	45
6	PCy$_3$ (10)	EtOH	22
7	P(^{t}Bu)$_3$ (10)	EtOH	trace
8	P(^{n}Bu)$_3$ (10)	EtOH	83
9	dppp (5)	EtOH	2
10	dppb (5)	EtOH	50
11	dppf (5)	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.

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 phenyl ring such as methyl, ethyl and butyl all gave desirable products in good to excellent yields (**3b**-**3d**, **3j**, **3k**). The 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% yield, respectively. On replacing the phenyl group with 1-naphthalenyl group, the substrate was transformed into product **3o** in an excellent yield. Heterocyclic substrates **3p**-**3r** were also compatible in current protocol and afforded the products in 21-60% yields.

Table 2. Hydroallylation of 1,3-diene





3a, 18 h, 85% — **3b**, 22 h, 90% — **3c**, 18 h, 83%

3d, 36 h, 85% — **3e**, 72 h, 62%[a] — **3f**, 24 h, 33%[a]

3g, 18 h, 80% — **3h**, 14 h, 87%[b] — **3i**, 6 h, 71%[b], 14:1 rr

3j, 24 h, 93% — **3k**, 18 h, 82% — **3l**, 6 h, 86%[b], 17:1 rr

3m, 18 h, 83%[b], 17:1 rr — **3n**, 30 h, 85%[c] — **3o**, 12 h, 92%[b], 15:1 rr

3p, 72 h, 60%[c] — **3q**, 72 h, 23%[a,b] — **3r**, 72 h, 21%[a,c]

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

The transition-metal catalyzed allyl–allyl couplings with congested allylboronates is a challenging task and very limited works have been successfully realized.[4j,4o] Satisfactorily, although linear substrate **2b** was unreactive under 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]

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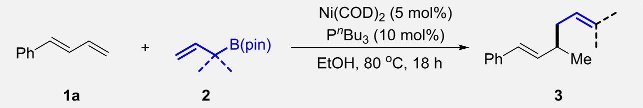
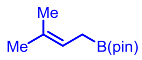
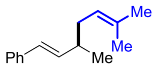
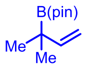
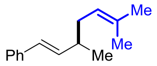
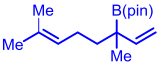
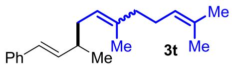
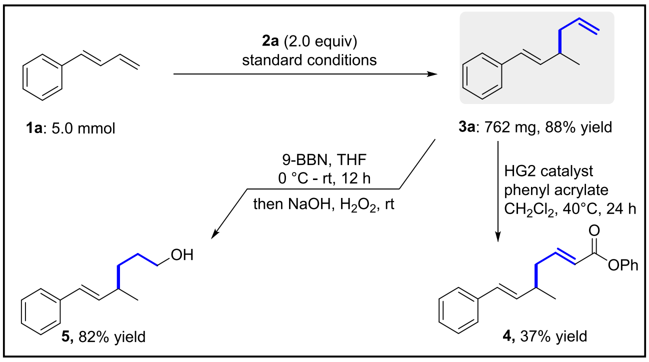
Table 3. The scope of allylborons



2	product	yield (%)
 **2b**	 **3s**	< 5%
 **2c**	 **3s**	43%
 **2d**	 **3t**	42% Z/E mixture, 1/1.6^a

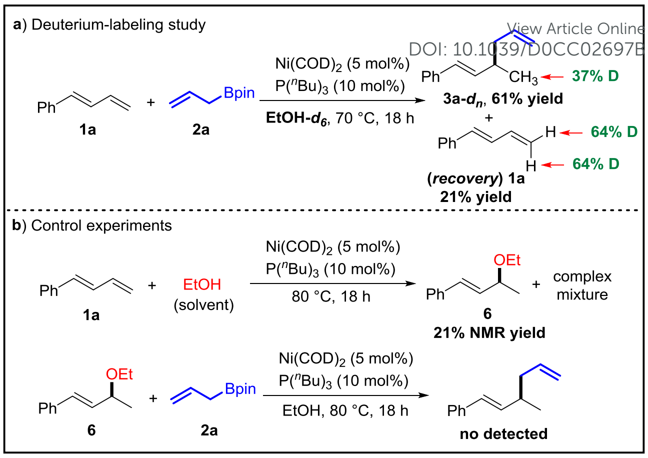
Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), Ni(COD)$_2$ (5 mol%), P^{n}Bu$_3$ (10 mol%), EtOH (0.8 M), 80 °C, 18 h, isolated yields were given. unless noted, the rr > 20:1. ^{a}determined by GC-FID.

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



Scheme 2. Scale-up synthesis and transformations of 1,5-diene **3a**

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 1,5-diene product, 0.64 deuterium was also exchanged into terminal CH$_2$ of the recovered diene **1a**. This observation supports a reversible process of the migratory insertion between the 1,4-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 condition. However, the reaction between **6** and **2a** under standard condition could not deliver 1,5-diene **3a** (Scheme 3b), thus excluding the possibility that **6** is an intermediate of the process.



Scheme 3. Deuterium-Labeling and Control Experiments

While further studies are warranted, we tentatively proposed the following mechanism on the basis of literature and our own observations (Figure 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 allyl-Ni(II) intermediate and allyl-B(pin) **2**, bis(allyl)Ni species **D** is produced. 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'** were supported by the observation of **6** *via* a reductive elimination step. Therefore, current mechanism was preferred over the reported transmetalation-alkene insertion pathway in previous Rh-catalyzed reactions.[11]

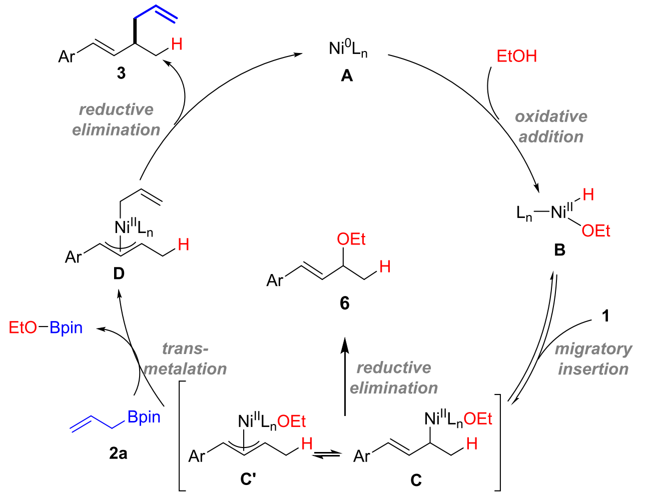


Figure 1. Proposed mechanism for Ni-catalyzed hydroallylation

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, detailed mechanism as well as the asymmetric version are now in progress in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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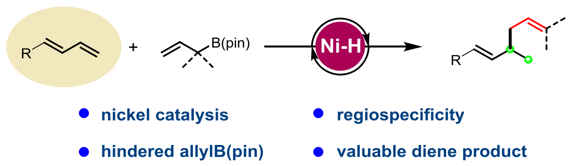
Graphical Abstracts (Table of Contents Entry)



A nickel-hydride catalysis has been developed to facilitate the allyl–allyl cross-coupling reactions between 1,3-dienes and allyl-B(pin) in excellent regioselectivity.