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Nickel-Catalyzed Regioselective Arylboration of Conjugated Dienes

Haoyang Li,[a] Jiao Long,[a] Yuqiang Li,[a] Wang Wang,[a] Hailiang Pang,[a] and Guoyin Yin*[a]

The nickel-catalyzed arylboration of conjugated dienes is reported. Good 1,4-regioselectivity and (*E*)-stereoselectivity were obtained using isoprene, together with very good 1,2-regioselectivity and (*E*)-stereoselectivity using 1-arylbutadienes. The high reactivity and selectivity of this process were dependent on the use of the appropriate nitrogen-based ligand. Moreover, wide functional group tolerance was observed under mild reaction conditions. This protocol provides a path to allyl or homoallyl boronic ester derivatives starting from 1,3-dienes, aryl bromides, and B_2pin_2. The downstream transformation of allyl boronic esters was also achieved, suggesting a strategy for the diastereoselective 1,2-difunctionalization of isoprene and demonstrating the potential for the synthesis of complex molecules.

The transformations of 1,3-dienes have attracted much attention in the field of organic synthesis, partly because these substrates are readily available. As a consequence, significant advances have been achieved based on both transition metal and metal-free catalysis over the past several decades.[1] The incorporation of boron-based moieties increases the translatability of a molecule, and so the synthesis of boron-containing compounds from 1,3-dienes is of particular interest.[2] The carboboration of 1,3-dienes with the one-step addition of carbon- and boron-based groups greatly increases the complexity of the products that can be obtained as well as the efficiency of the synthesis.[3] However, it is challenging to perform such reactions with both regioselectivity and stereoselectivity at the double bonds (Figure 1a).[4] Currently, such syntheses are primarily performed on the basis of copper catalysis.[3a] As an example, the Oestreich group demonstrated the use of ketone electrophiles to quench copper-based intermediates,[5] while Cao and Liao demonstrated the reactions of imine electrophiles to generate homoallylic amines.[6] Procter et al.[7] and Meng et al.[8] independently reported the borylcyanation of 2-substituted 1,3-dienes. Moreover, the Brown group combined the use of copper intermediates with palladium-catalyzed cross-coupling[9] to achieve the arylboration of conjugated dienes.[10] However, significant progress, including the regiodivergent arylboration of isoprene derivatives, is possible through the use of palladium catalysts (Figure 1b).[11] Regiodivergent products can also be obtained from 1-aryl-substituted butadienes by employing alternate catalysts and bases[12] (Figure 1c). Intriguingly, the (Z)-isomer is always favored when the arylboration reactions proceed in a 1,4-regioselective fashion.

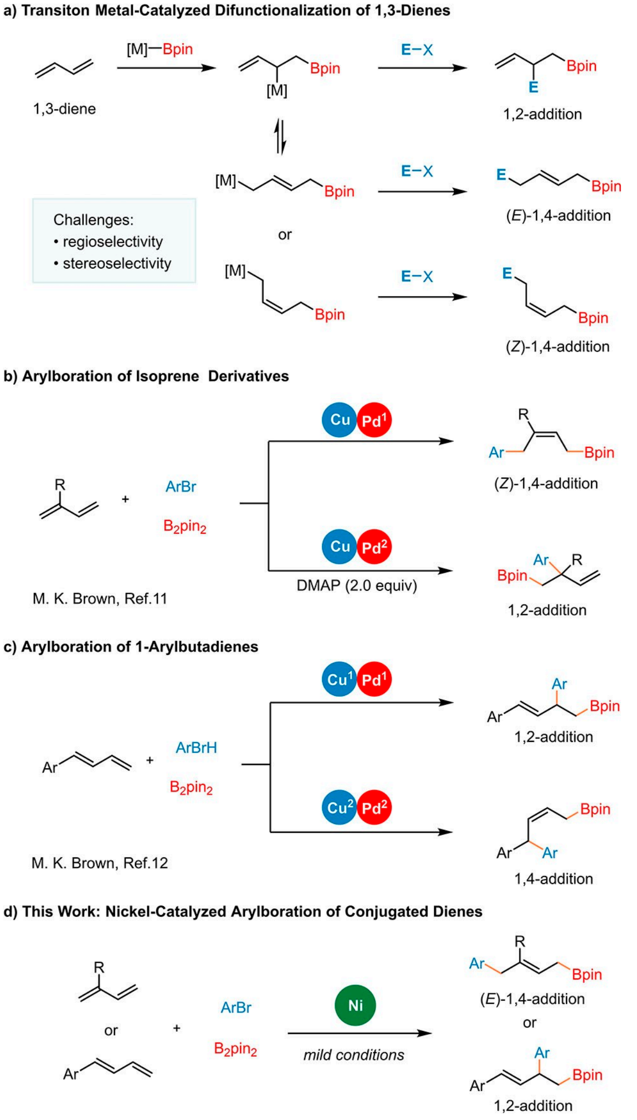

Figure 1. Arylboration of Conjugated Dienes.

Herein, we report the nickel-catalyzed arylboration of conjugated dienes (Figure 1d) with high reactivity resulting

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[a] H. Li, J. Long, Y. Li, Dr. W. Wang, Dr. H. Pang, Prof. Dr. G. Yin
The Institute for Advanced Studies
Wuhan University
299 Bayi Road, Wuhan, Hubei province, China
E-mail: yinguoyin@whu.edu.cn

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from the use of nitrogen-based ligands. Both excellent regioselectivity and stereoselectivity were obtained from this system.[13] In particular, in contrast to dual metal catalytic systems, (*E*)-1,4-addition products were obtained using isoprene as the substrate in conjunction with nickel-based catalysis.

On the basis of our continued interest in the nickel-catalyzed carboboration of alkenes[14] and asymmetric hydroamination of conjugated dienes,[15] we assessed the extension of these concepts to conjugated dienes, especially with regard to the regioselectivity and stereoselectivity of the reactions. In addition, we examined a new single catalyst system so as to provide an operationally simple option. On this basis, we explored the arylboration of isoprene. Considering that the reactivity of conjugated dienes might be similar to that of styrenes, the standard reaction conditions employed during the 1,2-arylboration of styrenes in our prior work were selected for the initial trial (Table 1, entry 1).[16] Surprisingly, only a trace amount of products **4a** incorporating all three reagents was obtained. We speculated that modification of the ligand could promote the reaction, so a series of ligands was evaluated. Table 1 demonstrates that ligands based on 1,10-phenanthroline or 2,2′-bipyridine frameworks (**L2**-**L5**) were ineffective in this reaction (entry 2). The pyridine-oxazoline (PyrOx) ligand **L6** was also not useful.[17] In contrast, the 6-methyl-substituted PyrOx ligand **L7** provided the 1,4-addition product (*E*)-**4a** in a 73% yield (as determined by gas chromatography) with excellent stereoselectivity ($E/Z > 20:1$). Incorporating ligand **L8**, with slightly modified steric hindrance associated with the pyridine moiety (entries 4 and 5), also afforded a better yield. A subsequent survey of solvents in conjunction with **L8** (entries 7–12) showed that dimethoxyethane (DME) was optimal, and gave an improved yield of 93% without reducing the stereoselectivity (entry 9). Notably, no other regioisomers were detected when applying these reaction conditions. Control experiments demonstrated that no arylboration products were observed in the case of ligand-free reactions (entries 13 and 14) or in the absence of the nickel catalyst (entry 15). Additionally, none of the desired product was obtained when the reaction was performed under air, demonstrating that the process is very sensitive to oxygen (entry 16).

With the optimal reaction conditions in hand, we next turned our attention to the scope of this process. As

Haoyang Li was born in Henan Province, China. He received his B.Sc. degree from Northwest A&F University in 2019. Subsequently, he pursued his master's degree under the guidance of Prof. Guoyin Yin at the Institute for Advanced Studies of Wuhan University.

Yuqiang Li was born in Anhui Province, China. He received his B.Sc. degree from Central South University in 2016. Subsequently, he pursued his Ph.D. degree under the guidance of Prof. Guoyin Yin at the Institute for Advanced Studies of Wuhan University.

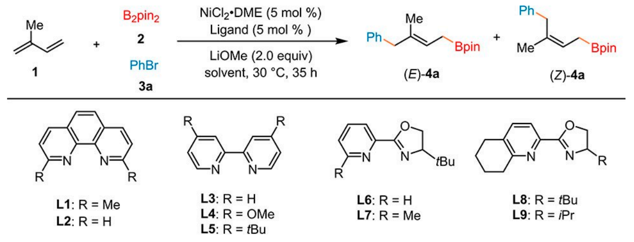
Jiao Long was born in Hunan Province, China. She received her B. Sc. Degree from Nanchang University in 2015. In the same year, she joined The College of Chemistry and Molecular Sciences of Wuhan University for her master's degree, supervised by Prof. Xumu Zhang. From 2018, she pursued her Ph.D. under the guidance of Prof. Guoyin Yin at the Institute for Advanced Studies of Wuhan University.

Wang Wang was born in Anhui Province, China. He received his Bachelor's degree from Huainan Normal University in 2014 and a Master's degree from Zhejiang University of Technology in 2017. Subsequently, he pursued his Ph.D. degree under the supervision of Prof. Guoyin Yin at Wuhan University. Currently, he is a postdoc under the supervision of Prof. Xin-Yuan Liu at South University of Science and Technology of China.

Hailiang Pang is from Shandong Province, China. He had completed his Master's degree in 2017 from Beijing University of Technology. He joined the Institute For Advanced Studies, Wuhan University in September 2017 for his doctoral studies. He completed his Ph.D. under the supervision of Prof. Guoyin Yin in June 2020.

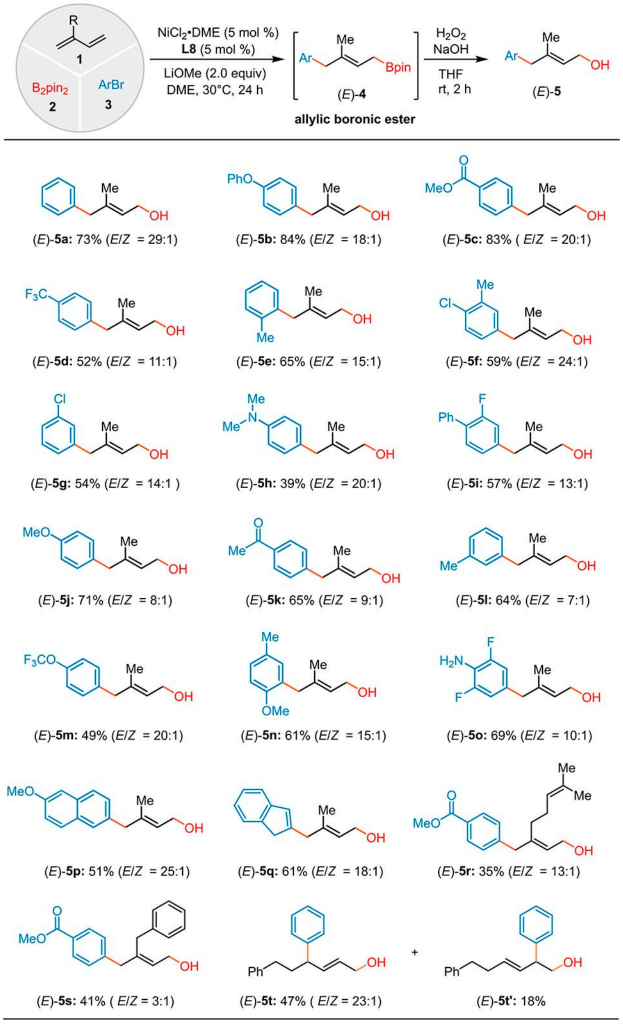
Prof. Dr. Guoyin Yin received his Ph.D. from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences in 2011, under the supervision of Prof. Guosheng Liu. He conducted postdoctoral research at the Technical University of Munich with Prof. Thorsten Bach, at RWTH Aachen University with Prof. Franziska Schoenebeck, and at the University of Delaware with Prof. Donald A. Watson. In 2016, he began his independent career at the Institute for Advanced Studies at Wuhan University. His research interest focuses on transformations involving metal migration.

Table 1. Optimization of Arylboration of Isoprene.



Entry	Ligand	Solvent	E/Z[a]	Yield of (E)-4a [%][b]
1	**L1**	1,4-dioxane	nd	< 5
2	**L2–L5**	1,4-dioxane	nd	< 5
3	**L6**	1,4-dioxane	nd	< 5
4	**L7**	1,4-dioxane	23:1	73
5	**L8**	1,4-dioxane	19:1	82
6	**L9**	1,4-dioxane	24:1	72
7	**L8**	NMP	14:1	33
8	**L8**	DMA	15:1	35
9	**L8**	DME	27:1	93(73)[c]
10	**L8**	THF	24:1	53
11	**L8**	toluene	18:1	53
12	**L8**	CH_3CN	6:1	8
13	**no**	DME, DMA, NMP	–	0
14	**no**	CH_3CN, DMSO	–	0
15[d]	**L8**	DME	–	0
16[e]	**L8**	DME	–	0

[a] The ratio of E/Z was determined by GC-MS analysis. [b] Yield was determined by gas chromatography analysis with naphthalene as internal standard. [c] The number in parenthesis is isolated yield of the corresponding alcohol after oxidation on 0.5 mmol scale. [d] The reaction was conducted without nickel catalyst. [e] The reaction was performed under air.



(E)-**5a**: 73% (E/Z = 29:1)
(E)-**5b**: 84% (E/Z = 18:1)
(E)-**5c**: 83% (E/Z = 20:1)
(E)-**5d**: 52% (E/Z = 11:1)
(E)-**5e**: 65% (E/Z = 15:1)
(E)-**5f**: 59% (E/Z = 24:1)
(E)-**5g**: 54% (E/Z = 14:1)
(E)-**5h**: 39% (E/Z = 20:1)
(E)-**5i**: 57% (E/Z = 13:1)
(E)-**5j**: 71% (E/Z = 8:1)
(E)-**5k**: 65% (E/Z = 9:1)
(E)-**5l**: 64% (E/Z = 7:1)
(E)-**5m**: 49% (E/Z = 20:1)
(E)-**5n**: 61% (E/Z = 15:1)
(E)-**5o**: 69% (E/Z = 10:1)
(E)-**5p**: 51% (E/Z = 25:1)
(E)-**5q**: 61% (E/Z = 18:1)
(E)-**5r**: 35% (E/Z = 13:1)
(E)-**5s**: 41% (E/Z = 3:1)
(E)-**5t**: 47% (E/Z = 23:1)
(E)-**5t'**: 18%

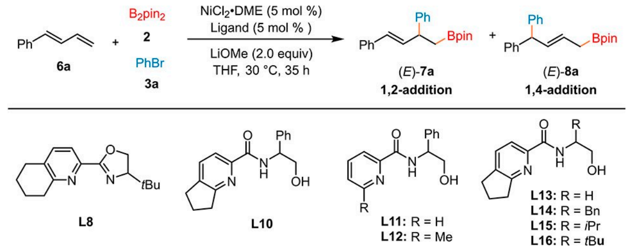
Figure 2. Scope of the Arylboration of Isoprene and Its Analogues.

summarized in Figure 2, various aryl bromides bearing different functional groups were initially examined. To simplify the isolation step, the boron-containing products were converted to their corresponding alcohols by *in situ* oxidation. Overall, both electron-deficient and electron-rich aryl bromides, as well as bromonaphthalene (**5p**) and 2-bromoindene (**5q**), gave the regioselective 1,4-addition products in good yields with suitable (*E*)-selectivity. The use of aryl bromides bearing *ortho*-substituents, such as methyl (**5e**) and methoxyl (**5n**) groups, also did not affect the efficiency or selectivity. A variety of functional groups, including ether (**5b**, **5j**, **5m**, and **5n**), ester (**5c**), chloride (**5f** and **5g**), fluoride (**5i** and **5o**), amine (**5h**), ketone (**5k**) and unprotected aniline (**5o**) moieties, were all highly compatible with these mild reaction conditions. However, some heteroaryl bromides, such as bromopyridine and bromoquinoline, did not react efficiently, likely as a result of their strong coordinating characteristics (see Supporting Information for details). Isoprene analogs also provided the desired arylboration products under the same reaction conditions (**5r** and **5s**), albeit with poor stereoselectivity. Finally, 1-alkyl-1,3-dienes primarily generated 1,4-addition products but 1,2- products were also obtained (**5t** and **5t'**).

Encouraged by the results described above, we subsequently examined the reactions of 1-aryl-1,3-dienes, which represent another type of conjugated diene widely used in organic synthesis.[18] The thermodynamically favored 1,2-addition product (*E*)-**7a** was isolated in 13% yield with good stereo- and regioselectivity under the same reaction conditions (Table 2, entry 1). Optimization of this system led to the identification of the pyridylcarboamide ligand **L10** as the most successful promoter,[19] with a 75% isolated yield (Table 2, entry 2). It should be noted that there was no 1,4-addition product (*E*)-**8a** was detected in these reaction conditions.

The generality of these reaction conditions was investigated next, with the results presented in Figure 3. Varying the substituents on the aryl group, and even replacing this moiety with a furyl group, did not greatly affect the reactivity. Both 1,1- and 1,2-disubstituted alkenes were found to generate the corresponding arylboration products under the same reaction conditions (**9f** and **9g**), although the latter afforded a lower yield. More importantly, a quaternary carbon center could also be constructed using this arylboration reaction (**9h**).[20] Notably, when 1-alkyl-1,3-diene was used, the 1,2-addition product (**5t'**) was still favored under these reaction conditions. The reverse regioselectivities were obtained by employing two different sets of reaction parameters, indicating that the choice of ligands could modify the regioselectivity of the arylboration. Addition-

Table 2. Optimization of the Arylboration of 1-Phenyl-1,3-diene.



Entry	Ligand	Solvent	(*E*)-**7a**/(*E*)-**8a**[a]	Yield of (*E*)-**7a** [%][b]
1	**L8**	DME	>99:1	13
2	**L10**	THF	>99:1	81(75)[c]
3	**L11**	THF	nd	<5
4	**L12**	THF	>99:1	27
5	**L13**	THF	>99:1	73
6	**L14**	THF	>99:1	47
7	**L15**	THF	>99:1	67
8	**L16**	THF	>99:1	19

[a] The ratio of (*E*)-**7a**/(*E*)-**8a** was determined by GC-MS analysis. [b] Yield was determined by gas chromatography analysis with naphthalene as internal standard. [c] The number in parenthesis is isolated yield of the corresponding alcohol after oxidation on 0.4 mmol scale.

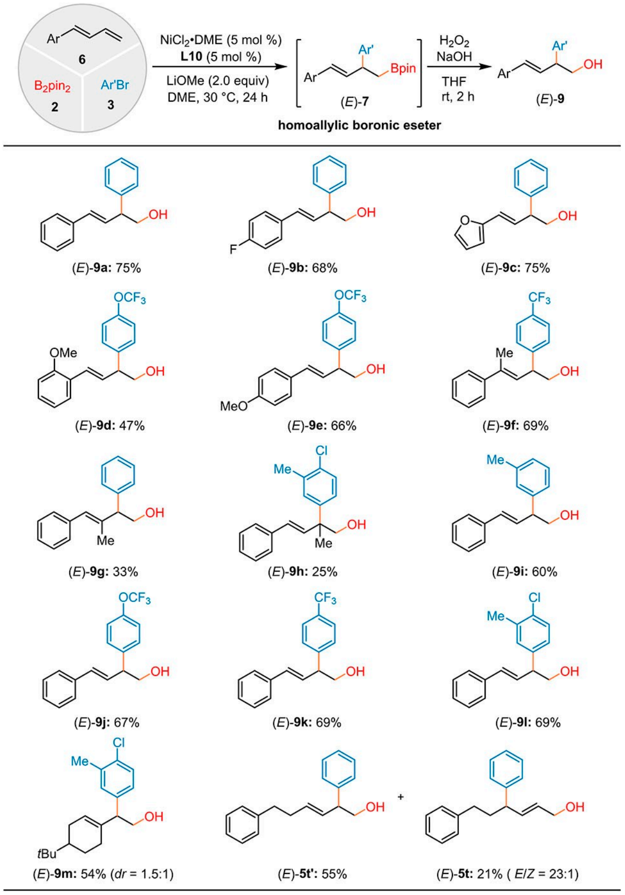
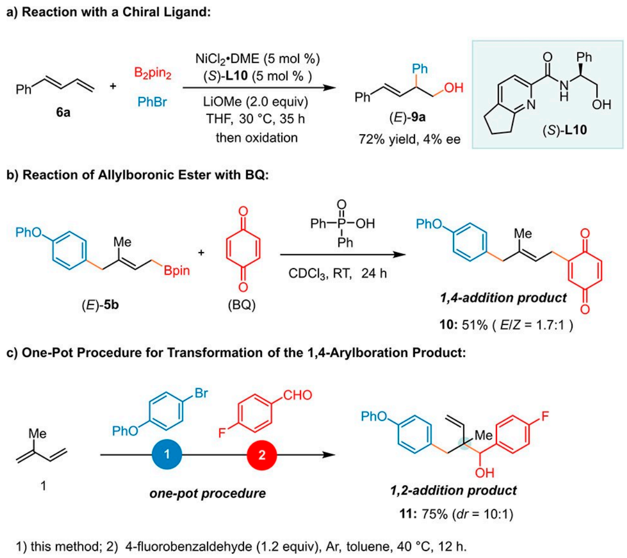


Figure 3. Scope of the Arylboration of 1-Aryl-1,3-dienes.



1) this method; 2) 4-fluorobenzaldehyde (1.2 equiv), Ar, toluene, 40 °C, 12 h.

Figure 4. Attempted Development of an Asymmetric Variant and Transformations of Arylboration Products.

ally, only a very small degree of enantioisomeric excess (4% *ee*) was observed (Figure 4a) when the chiral ligand (S)-**10** was used. This result suggests that pyridylcarboamide ligands are likely not a good choice with regard to controlling the enantioselectivity.

Transformations of the arylboration products were also assessed. The allylboronic ester **5b** was found to react with benzoquinone to formally produce the 1,4-addition product **10** in 51% yield (Figure 4b).[21] In addition, the allylboronic ester obtained from the arylboration of isoprene could be converted to the homoallylic alcohol **11** bearing a quaternary carbon center with a 75% isolated yield and good diastereoselectivity (*dr* = 10:1). This reaction, therefore, represents a strategy for the 1,2-difunctionalization of isoprene (Figure 4c).[22] This efficient one-pot procedure has potential applications to the synthesis of complex molecules.

In summary, this work demonstrated the nickel-catalyzed arylboration of conjugated dienes, thus providing a route to the formation of allyl and homoallyl boronic ester derivatives from 1,3-dienes, aryl bromides, and B_2pin_2. The reactivity and selectivity of this synthetic procedure were found to be governed by the nitrogen-based ligand. Further research regarding the synthetic applications and reaction mechanism of this technique is ongoing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: nickel catalysis · arylboration · allylboronic esters · 1,3-dienes · regioselectivity

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