A Journal of the Gesellschaft Deutscher Chemiker

Angewandte

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International Edition

Chemie

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Accepted Article

Title: Nickel(0)-Catalyzed Hydroarylation of Styrenes and 1,3-Dienes with Organoborons

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201710735
Angew. Chem. 10.1002/ange.201710735

Link to VoR: http://dx.doi.org/10.1002/anie.201710735
http://dx.doi.org/10.1002/ange.201710735

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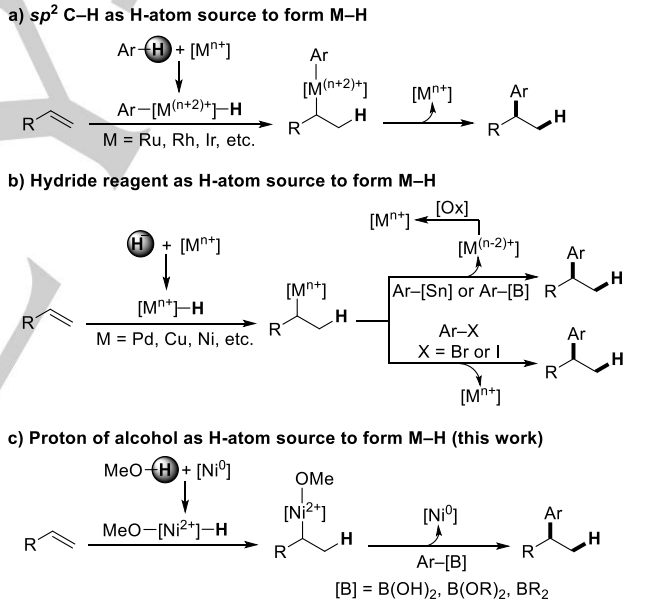
Nickel(0)-Catalyzed Hydroarylation of Styrenes and 1,3-Dienes with Organoborons

Li-Jun Xiao,[a] Lei Cheng,[a] Wei-Min Feng,[a] Mao-Lin Li,[a] Jian-Hua Xie,[a,b] Qi-Lin Zhou*[a,b]

Abstract: The Ni-catalyzed hydroarylation of styrenes and 1,3-dienes with organoborons has been developed. The reaction offers a highly selective approach to the diarylalkanes and allylarenes under redox-neutral condition. In this hydroarylation reaction, a new strategy that uses easily available proton of methanol to generate active catalyst species Ni–H was developed. The Ni-catalyzed hydroarylation, combining with a Ir-catalyzed C–H borylation, affords a very efficient and straightforward access to retinoic acid receptor agonist.

Transition-metal-catalyzed functionalization of alkenes is a highly efficient C−C bond forming reaction using abundant feedstocks to produce value-added products and has received increasing attention.[1] Hydroarylation, the addition of hydrogen and aryl to alkenes offers a straightforward method for the synthesis of alkylarenes. Among the hydroarylations, the reaction with styrenes could produce 1,1-diarylalkanes, which often show biological activity.[2] To date, two strategies have been developed for achieving hydroarylation of alkenes, which are characterized by using different way to generate active catalyst species M−H. One uses C−H bond activation of arenes to form M−H (Scheme 1a),[3] and other uses hydride reagents to form M−H (Scheme 1b).[4] The former strategy usually required the arenes having a directing group or heteroarenes. The latter strategy worked only under reductive conditions. As a part of our efforts on the development of earth-abundant nickel catalysis,[5] we herein report the hydroarylation of alkenes under redox-neutral condition. In our hydroarylation reaction, proton of methanol was used to react with Ni^0 to generate active catalyst species Ni−H (Scheme 1c), which represents a unique example in which the catalytic process is initiated by the protonation of a low-valent metal.[6]

We began our study by investigating the hydroarylation of styrene (**1a**) with (4-methoxyphenyl)boronic acid (**2a**) in the presence of a Ni catalyst generated in situ from $Ni(COD)_2$ and a monophosphine ligand. The complex Ni^0/PCy_3 was found to catalyzed the reaction of **1a** with **2a** at 80 °C in THF or toluene, giving branched hydroarylation product **3a**, however, in low yield (Table 1, entries 1 and 2). Adding H_2O and MeOH into toluene increased the yields of **3a** to 64% and 36% yield, respectively (entries 5 and 6). The reaction can also be performed in pure alcohols, with MeOH giving best result (**3a**: 70%, b/l >99:1, entry 7). However, under these reaction conditions, a competitive styrene dimerization reaction occurred, producing **5a** in up to 84% yield. To prevent this side reaction and improve the yield of the hydroarylation product, various monophosphine ligands were evaluated. It was delighted to find that the bulky and electron-rich phosphine ligand P^tBu_3 not only prevented styrene dimerization but also allowed the reaction to occur at a lower temperature. When the reaction was carried out at 60 °C for 1 h, the hydroarylation product **3a** was obtained in 88% yield (entry 14). It is worth mentioning that the uses of Ni(II) catalysts or chelating diphosphine ligands give no reaction (see SI).



Scheme 1. Transition-metal-catalyzed hydroarylations of alkenes

A variety of alkenes **1** and arylboronic acids **2** were investigated under the aforementioned optimal reaction conditions. As shown in Table 2, all reactions of styrene **1a** with different arylboronic acids gave hydroarylation products **3a**–**3g** in moderate to high yields (50–92%) with excellent regioselectiviity (b/l >99:1). Both electronic and steric properties of the arylboronic acids affected the yield of the reaction. Arylboronic acids having an electron-donating group afforded higher yields than those having an electron-withdrawing group (**3a** vs **3d**). The arylboronic acid with a 2-methyl group exhibited only a moderate yield (**3e**, 61%) because of the steric effect of the 2-methyl on the phenyl ring of arylboronic acid. Notably, the reaction tolerated a wide range of functional groups in arylboronic acids, including ketone (**3i**),

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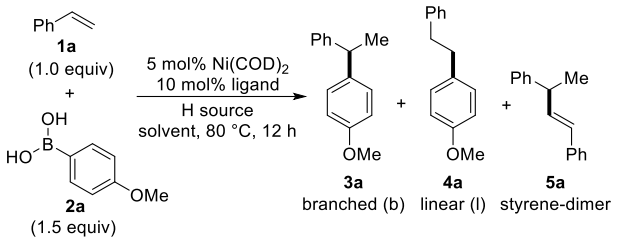
Table 1. Optimization of reaction conditions[a]



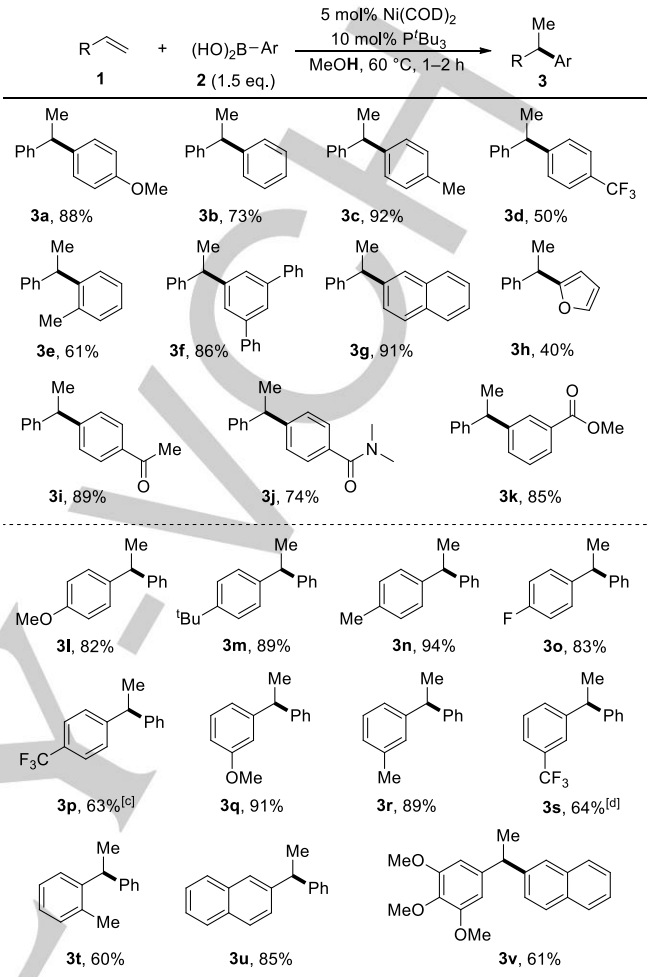
entry	ligand	solvent	H source	yield of **3a** (%)[b]	b/l[b]	yield of **5a** (%)[b]
1	PCy_3	THF	none	14	93:7	84
2	PCy_3	toluene	none	21	95:5	76
3[c]	PCy_3	toluene	AcOH	trace	–	6
4[c]	PCy_3	toluene	PhOH	13	99:1	32
5[c]	PCy_3	toluene	H_2O	64	96:4	22
6[c]	PCy_3	toluene	MeOH	36	99:1	42
7	PCy_3	MeOH	MeOH	70	>99:1	20
8	PCy_3	EtOH	EtOH	45	>99:1	21
9	PCy_3	^{i}PrOH	^{i}PrOH	31	>99:1	27
10	PCy_3	^{t}BuOH	^{t}BuOH	32	>99:1	20
11	P^nBu_3	MeOH	MeOH	4	>99:1	27
12	$PCyp_3$	MeOH	MeOH	45	>99:1	37
13	PPh_3	MeOH	MeOH	11	>99:1	0
14[d]	**P^tBu_3**	**MeOH**	**MeOH**	**90 (88)**	**>99:1**	**trace**

[a] Reaction conditions: styrene **1a** (0.5 mmol), (4-methoxyphenyl)boronic acid **2a** (0.75 mmol), $Ni(COD)_2$ (0.025 mmol), ligand (0.050 mmol), solvent (1.0 mL). [b] Yields and b/l ratio were determined by GC with internal standard; isolated yield is given in parenthesis. [c] H source: 2.0 equiv. [d] At 60 °C for 1 h.

amide (**3j**), and ester (**3k**). The boronic acid with a furyl ring also underwent hydroarylation reaction with **1a** albeit the yield was relatively low (**3h**, 40%). Next, we carried out hydroarylation reactions of various styrenes with phenylboronic acid or naphthylboronic acid. High yield (82–94%) and excellent regioselectivity (b/l > 99:1) were obtained for the most of tested styrenes. However, styrenes having a strongly electron-withdrawing CF_3 group afforded only moderate yield and lower regioselectivity (**3p** and **3s**). Styrenes with sterically bulky 2-methyl and 3,4,5-trimethoxyl groups still reacted with phenylboronic acid and naphthylboronic acid, but gave only moderate yields (**3t** and **3v**). The internal aromatic alkenes such as trans-β-methylstyrene or indene and aliphatic alkenes such as 1-hexene were inert in the Ni-catalyzed hydroarylation reaction with arylboronic acid.

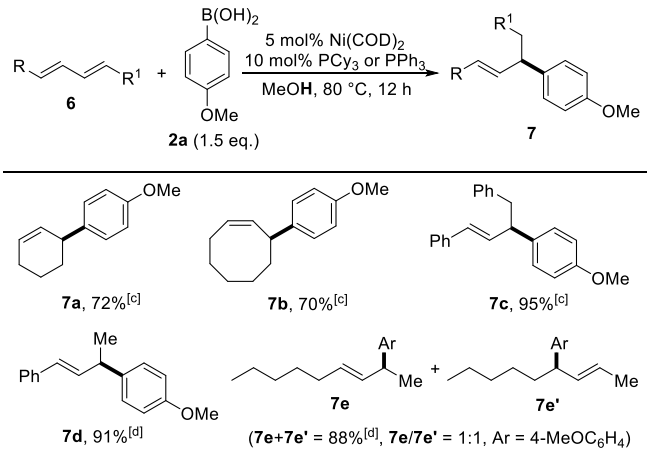
We also examined Ni-catalyzed hydroarylation reactions of 1,3-dienes **6** with (4-methoxyphenyl)boronic acid (**2a**) (Table 3). For these dienes, Ni/PCy_3 or Ni/PPh_3 catalyst provided better results than the Ni/P^tBu_3 catalyst. The aromatic 1,3-dienes and cyclic 1,3-dienes reacted with **2a** at 80 °C, giving exclusively allylic arylation product in good to high yields (70−95%). However, the aliphatic 1,3-diene **6e** provided a mixture of hydroarylation products at C2 and C4 in a 1:1 ratio.

Table 2. Hydroarylation of alkenes with arylboronic acids[a,b]



[a] Reaction conditions: alkenes **1** (0.5 mmol), boronic acid **2** (0.75 mmol), $Ni(COD)_2$ (0.025 mmol), P^tBu_3 (0.050 mmol), MeOH (1.0 mL) for 1–2 h; the ratio of b/l >99:1 unless otherwise noted. [b] Isolated yields. [c] b/l = 87:13. [d] b/l = 89:11.

Table 3. Hydroarylation of 1,3-dienes[a,b]



[a] Reaction conditions: diene **6** (0.5 mmol), boronic acid **2a** (0.75 mmol), $Ni(COD)_2$ (0.025 mmol), PR_3 (0.050 mmol), MeOH (1.0 mL) for 12 h. [b] Isolated yield. [c] Performed with PCy_3. [d] Performed with PPh_3.

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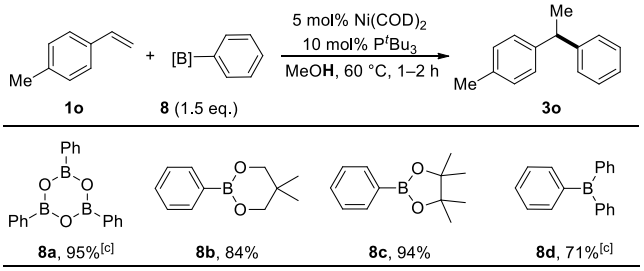
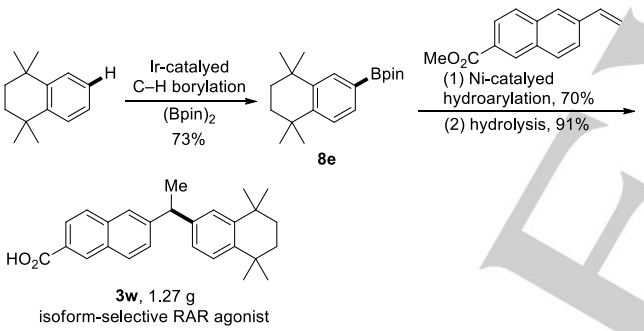
In addition to arylboronic acids, arylboroxines, arylboronic esters, and boranes could also be used as hydroarylation reagent in this Ni-catalyzed hydroarylation reaction (Table 4). For example, arylboronic esters **8a**–**8c** and triphenylborane **8d** reacted with 4-methylstyrene (**1n**), giving hydroarylation product **3n** in good to excellent yields (71–95%) with excellent regioselectivity (b/l > 99:1). Encouraged by these results, we applied this Ni-catalyzed hydroarylation protocol to the synthesis of 1,1-diarylethane **3w**, which is a retinoic acid receptor agonist.[7] The combination of our Ni-catalyzed hydroarylation with an Ir-catalyzed C–H borylation reaction[8] afforded a very efficient and straightforward access to **3w** in good yield on a gram scale.

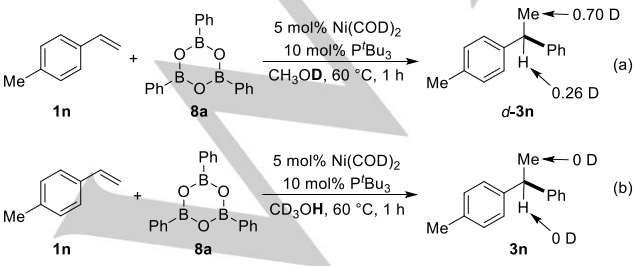
Table 4. Arylboron reagent scope and the synthesis of retinoic acid receptor agonist[a,b]



[a] As for Table 2, unless otherwise noted. [b] Isolated yield. [c] Performed using 0.5 equiv arylboron reagent.

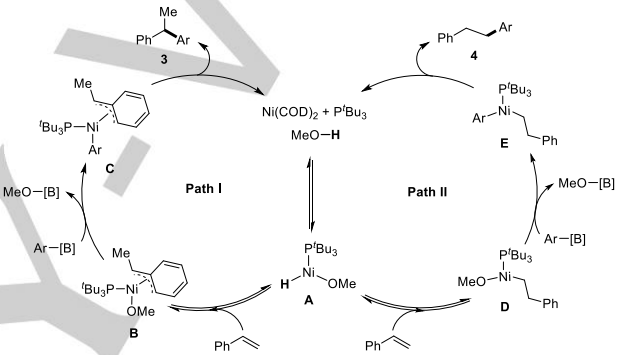


To gain some mechanistic insight on the hydroarylation reaction, deuterium-labeling experiments using CH_3OD and CD_3OH were conducted. As shown in Scheme 2, the ^1H NMR spectroscopic analysis of the products revealed that the Ni−**H** intermediate was generated from methanol O−**H**, instead of C−**H** bond of alcohol like that in the previous work.[4a-c] The observation of H/D scrambling at methyl and benzyl of the hydroarylation product suggested that the reaction involves reversible formations of methoxyl-nickel–hydrogen and methoxyl-nickel–benzyl intermediates.



Scheme 2. Deuterium-labeling experiment.

A mechanism was proposed based on the aforementioned experimental results and previous reports (Scheme 3).[9] First, oxidative addition of the O–H bond of methanol to the nickel atom yields methoxyl-nickel-hydride intermediate **A**. The hydride of Ni–H was transferred to the terminal carbon of the double bond of styrene to form a benzylic nickel intermediate **B** in path I. The resulting methoxyl-Ni-benzyl intermediate underwent transmetalation with arylboron to generate intermediate **C**.[10] Finally, reductive elimination of **C** provided the hydroarylation product **3**. Similar steps were involved in path II, with the hydride of Ni–H being transferred to the internal carbon of the double bond of styrene and afforded linear product **4**. Because the methoxyl-nickel-benzylic intermediate **B** is stabilized by forming a η^3-ally nickel complex,[11] the branched product (path I) was expected as a main product.



Scheme 3. Proposed mechanism.

In summary, we have developed a highly selective Ni-catalyzed hydroarylation of styrenes and 1,3-dienes with arylboron compounds under redox-neutral conditions. This reaction offers a new approach to the selective preparation of diarylalkanes and allylarenes. In this hydroarylation reaction, a new strategy that uses easily available proton of methanol to generate active catalyst species Ni–H has been developed. These results shed light on the origins of the reactivity and the regioselectivity of the reaction and may be useful for the development of new functionalization reaction of alkenes catalyzed by nickel or other transition metals.

Experimental Section

In an argon-filled glove-box, an oven-dried sealed tube was charged with a stir bar, catalyst precursor $Ni(COD)_2$ (7.0 mg, 0.025 mmol), and (4-methoxyphenyl)boronic acid (**2a**, 114 mg, 0.75 mmol). A solution of P^tBu_3 in toluene (25 μL, 0.050 mmol, 50 wt%), styrene **1a** (58 μL, 0.50 mmol), and methanol (1.0 mL) was injected into the tube under argon. The mixture was heated at 60 ºC for one hour, and then cooled down to room temperature. The resulting mixture was passed through a short silica gel column eluted with ethyl acetate, and analyzed branched/linear ratio of product **3a** by GC using *n*-dodecane as an internal standard. The pure product was obtained by column chromatography on silica gel (PE/EA = 40:1, v/v) in 88% yield as a colorless oil.

Acknowledgements

We thank the National Natural Science Foundation of China (Nos. 21325207, 21421062, 21532003) and the “111” project (B06005) of the Ministry of Education of China for financial support.

Keywords: Nickel Catalyst • Coupling • Hydroarylation• Alkene • Organoboron

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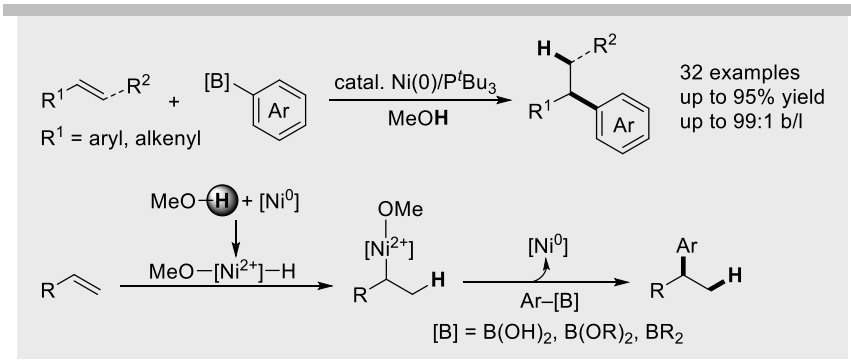

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A nickel(0)-catalyzed hydroarylation of alkenes with organoborons using alcohol O−H as H-atom source is reported. The reaction offers a highly selective approach to the diarylalkanes and allylarenes under redox-neutral conditions.