



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

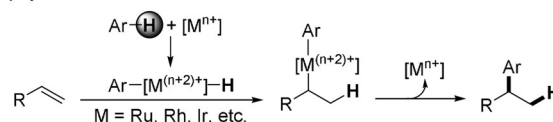
Li-Jun Xiao, Lei Cheng, Wei-Min Feng, Mao-Lin Li, Jian-Hua Xie, and Qi-Lin Zhou*

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

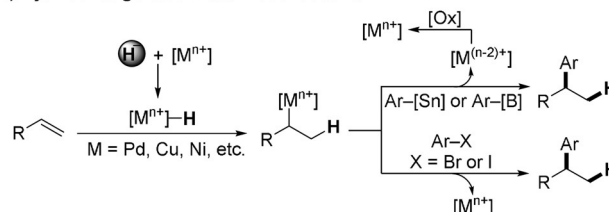
Transition-metal-catalyzed functionalization of alkenes is a highly efficient C–C bond forming reaction that makes use of abundant feedstocks to produce value-added products and it has received increasing attention.^[1] Hydroarylation, the addition of hydrogen and an aryl group to alkenes offers a straightforward method for the synthesis of alkylarenes. Among hydroarylations, reaction with styrenes can produce 1,1-diarylalkanes, which often show biological activity.^[2] To date, two strategies have been developed for achieving the hydroarylation of alkenes, and they 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 1 a),^[3] and the other uses hydride reagents to form M–H (Scheme 1 b).^[4] The former strategy usually requires arenes with a directing group or heteroarenes. The latter strategy works only under reductive conditions. As a part of our efforts toward the development of catalysis based on earth-abundant nickel,^[5] we herein report the hydroarylation of alkenes under redox-neutral conditions. In our hydroarylation reaction, the proton of methanol was used to react with Ni⁰ to generate the active catalyst species Ni–H (Scheme 1 c), which represents a unique example in which the catalytic process is initiated by the protonation of a low-valence 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 Ni⁰/PCy₃ was found to catalyze the reaction of **1a** with **2a** at 80 °C in THF

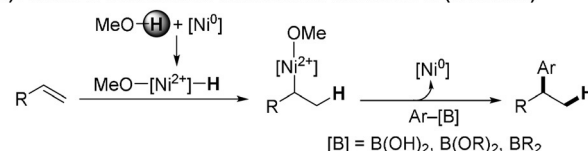
a) sp² C–H as H-atom source to form M–H



b) Hydride reagent as H-atom source to form M–H



c) Proton of alcohol as H-atom source to form M–H (this work)



Scheme 1. Transition-metal-catalyzed hydroarylations of alkenes.

or toluene, giving branched hydroarylation product **3a**, albeit in low yield (Table 1, entries 1 and 2). Adding H₂O and MeOH into toluene increased the yields of **3a** to 64% and 36%, respectively (entries 5 and 6). The reaction can also be performed in pure alcohols, with MeOH giving the 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. We were delighted to find that the bulky and electron-rich phosphine ligand P^tBu₃ 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 gave no reaction (see the Supporting Information).

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 regioselectivity (b/l > 99:1). Both the electronic and steric properties of the arylboronic acids affected the yield of the reaction. Arylboronic acids with an electron-donating group afforded higher yields than those with an electron-withdraw-

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Table 1: Optimization of reaction conditions.^[a]

Entry	Ligand	Solvent	H source	Yield 3a [%] ^[b]	b/l ^[b]	Yield 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 ₂ O	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 ^t Bu 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 ^t Bu 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 an internal standard; yield of isolated product is given in parenthesis. [c] H source: 2.0 equiv. [d] At 60 °C for 1 h.

ing 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**), amide (**3j**), and ester (**3k**) groups. The boronic acid with a furyl ring also underwent hydroarylation with **1a** although 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 most of the tested styrenes. However, styrenes with a strongly electron-withdrawing CF₃ group afforded only moderate yield and lower regioselectivity (**3p** and **3s**). Styrenes with sterically bulky 2-methyl and 3,4,5-trimethoxy groups still reacted with phenylboronic acid and naphthylboronic acid, but gave only moderate yields (**3t** and **3v**). 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 of 1,3-dienes **6** with (4-methoxyphenyl)boronic acid (**2a**; Table 3). For these dienes, Ni/PCy₃ or Ni/PPh₃ catalysts provided better results than the Ni/P^tBu₃ catalyst. The aromatic 1,3-dienes and cyclic 1,3-dienes reacted with **2a** at 80 °C, giving exclusively the allylic arylation product in good to high yields (70–95 %). However, the aliphatic 1,3-diene **6e** provided a mixture of products from hydroarylation at C2 and C4 in a 1:1 ratio.

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

Product	Yield [%]
3a	88%
3b	73%
3c	92%
3d	50%
3e	61%
3f	86%
3g	91%
3h	40%
3i	89%
3j	74%
3k	85%
3l	82%
3m	89%
3n	94%
3o	83%
3p	63% ^[c]
3q	91%
3r	89%
3s	64% ^[d]
3t	60%
3u	85%
3v	61%

[a] Reaction conditions: alkenes **1** (0.5 mmol), boronic acid **2** (0.75 mmol), Ni(COD)₂ (0.025 mmol), P^tBu₃ (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]

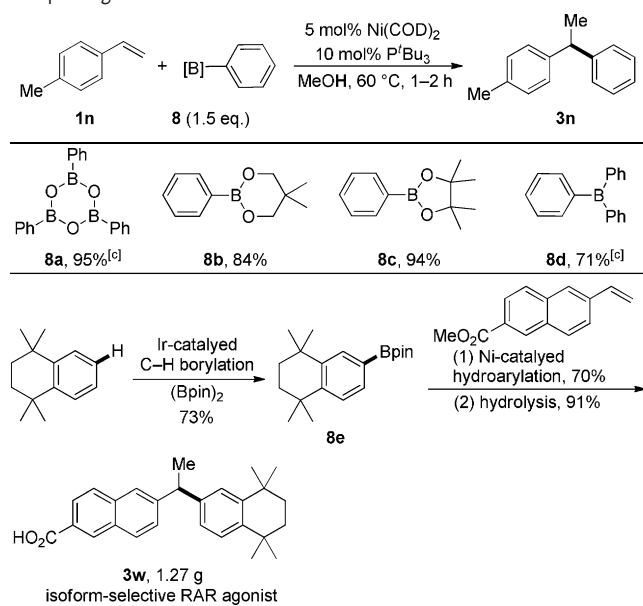
Product	Yield [%]
7a	72% ^[c]
7b	70% ^[c]
7c	95% ^[c]
7d	91% ^[d]
7e	88% ^[d]
7e'	88% ^[d]

(7e+7e' = 88%^[d], 7e/7e' = 1:1, Ar = 4-MeOC₆H₄)

[a] Reaction conditions: diene **6** (0.5 mmol), boronic acid **2a** (0.75 mmol), Ni(COD)₂ (0.025 mmol), PR₃ (0.050 mmol), MeOH (1.0 mL) for 12 h. [b] Yield of isolated product. [c] Performed with PCy₃. [d] Performed with PPh₃.

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).

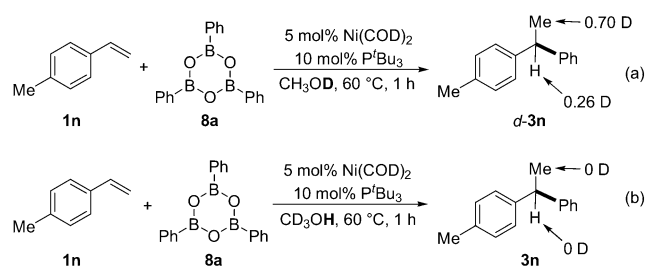
Table 4: Arylboron reagent scope and the synthesis of retinoic acid receptor agonist.^[a,b]



[a] As for Table 2 unless otherwise noted. [b] Yield of isolated product. [c] Performed using 0.5 equiv arylboron reagent.

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 method to the synthesis of 1,1-diarylethane **3w**, which is an agonist of the retinoic acid receptor.^[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.

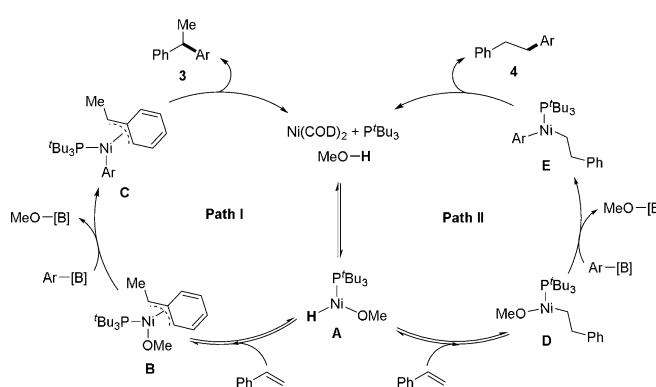
To gain some mechanistic insight into the hydroarylation reaction, deuterium-labeling experiments using CH₃OD and CD₃OH were conducted. As shown in Scheme 2, ¹H NMR spectroscopic analysis of the products revealed that the Ni–H intermediate was generated from methanol O–H group instead of the C–H bond of the alcohol as in the previous work.^[4a–c] The observation of H/D scrambling at the methyl



Scheme 2. Deuterium-labeling experiment.

and benzyl groups of the hydroarylation product suggested that the reaction involves reversible formation of methoxyl nickel hydrogen and methoxyl nickel benzyl intermediates.

A mechanism was proposed based on the aforementioned experimental results and previous reports (Scheme 3).^[9] First,



Scheme 3. Proposed mechanism.

oxidative addition of the O–H bond of methanol to the nickel atom yields methoxyl nickel hydride intermediate **A**. The hydride of Ni–H is transferred to the terminal carbon of the double bond of styrene to form benzylic nickel intermediate **B** in path I. The resulting methoxyl nickel benzyl intermediate undergoes transmetalation with arylboron to generate intermediate **C**.^[10] Finally, reductive elimination of **C** provides the hydroarylation product **3**. Similar steps are involved in path II, with the hydride of Ni–H being transferred to the internal carbon atom of the double bond of styrene to afford linear product **4**. Because the methoxyl nickel benzylic intermediate **B** is stabilized by forming a η³-allyl nickel complex,^[11] the branched product (path I) is expected as a main product.

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 the proton of methanol to generate active catalyst species Ni–H was developed. These results shed light on the origins of the reactivity and regioselectivity of the reaction and may be useful for the development of new functionalization reactions 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^tBu₃ 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 °C for one hour, and then cooled down to room temperature. The resulting mixture was passed through a short silica gel column and eluted with ethyl acetate, and the branched/linear ratio of product **3a** was analyzed 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

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · coupling reactions · hydroarylation · nickel · organoboron reagents

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