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Nickel-catalyzed Diastereoselective Reductive Coupling Reaction of Norbornene with Aldehydes in the Presence of Triethylborane

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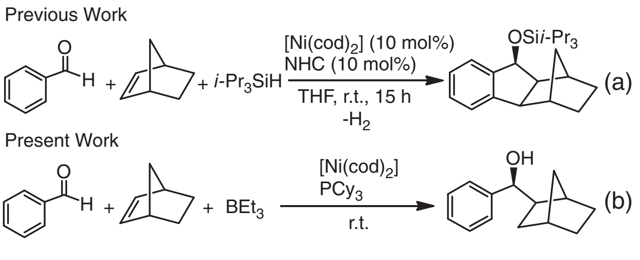
Highly diastereoselective reductive coupling reaction was achieved between an aldehyde and a norbornene to afford an alcohol compound using a nickel/phosphine catalyst system in the presence of a reducing agent. The combination of a PCy$_3$ ligand and triethylborane as the reducing agent proved effective for the reaction. A wide range of aldehydes were found to participate in the reaction with high diastereoselectivities.

Nickel-catalyzed reductive coupling reaction between an aldehyde and an unsaturated compound in the presence of a reducing agent is one of the most effective methods for C–C bond formation.[1] Although the majority of reports are based on the use of alkynes as unsaturated compounds,[2] reactions involving alkene compounds such as α-olefins,[3] 1,3-dienes,[4] allenes,[5] and methylenecyclopropanes[6] have also been studied. Our research group recently reported the first example of a reductive coupling reaction between an aryl aldehyde and a norbornene to afford a silylated indanol derivative by the activation of aromatic C–H bonds of aryl aldehydes using triisopropylsilane as the reducing agent in the presence of a nickel/NHC catalyst system (Scheme 1a).[7] Although many examples of nickel-catalyzed reductive coupling reactions using aryl aldehydes have been reported, there has been no report of the herein presented transformation through aromatic C–H bond activation of an aryl aldehyde.[8] It should also be noted that this reaction proceeded with excellent diastereoselectivities. We assumed that this aromatic C–H bond activation was caused by a combination of an NHC ligand with the silane compound used as a reducing agent, and reductive coupling reactions that did not involve the C–H bond activation probably proceeded by a combination of a different type of ligand with the reducing agent. To test our hypothesis, we examined this reductive coupling reaction using various catalysts and reducing agents. Herein, we describe a highly diastereoselective reductive coupling reaction of aldehydes and norbornenes using triethylborane in the presence of a nickel/phosphine catalyst system, in which the aromatic C–H bond activation did not occur (Scheme 1b).

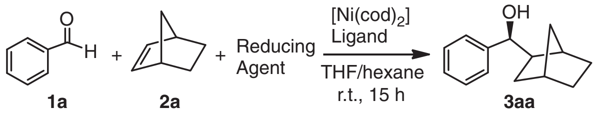


Scheme 1. Reductive coupling reactions using norbornene.

First, various ligands and reducing agents were screened in the nickel-catalyzed reductive coupling reaction between benzaldehyde (**1a**), norbornene (**2a**), and a reducing agent, as shown in Table 1. In the presence of the [Ni(cod)$_2$]/PCy$_3$ catalyst, the reductive coupling reaction proceeded smoothly at room temperature to afford **3aa** in high yield with excellent diastereoselectivity using triethylborane as the reducing agent (Entry 1).[9] When 1 equiv of **2a** was used, the reaction resulted in a lower yield of **3aa** (Entry 2). Using other reducing agents such as diethylzinc and triethylsilane, the coupling reaction resulted in an extremely low yield of **3aa** (Entries 3 and 4). In the case of the reaction using diethylzinc, other reductive coupling products involving ethylation were also isolated.[10] As compared to PCy$_3$, **3aa** was obtained in a lower yield using P*n*-Bu$_3$ and PPh$_3$ (Entries 5 and 6). The reductive coupling reaction was not observed when a NHC was used as the ligand (Entry 7). In all case of Table 1, indanol product via C–H bond activation was not formed. On the basis of this screening of ligands and reducing agents, the highest yield of product **3aa** was found using triethylborane as a reducing agent in the presence of a [Ni(cod)$_2$]/PCy$_3$ catalyst system.

Next, the nickel-catalyzed diastereoselective reductive coupling reaction using norbornene was examined using various aldehydes as shown in Table 2. The use of monosubstituted aryl aldehydes bearing electron-donating or electron-withdrawing groups also afforded **3** in good to high yields with good to excellent diastereoselectivities (Entries 1–6). Furthermore, 2,6-dimethylbenzaldehyde (**1h**) participated in the reaction and gave the corresponding product **3ha** (Entry 7). Although reaction of 2-furaldehyde (**1i**) resulted in low diastereoselectivity (Entry 8), reactions of **1j** and **1k**, which possess 2-thienyl and 3-pyridyl

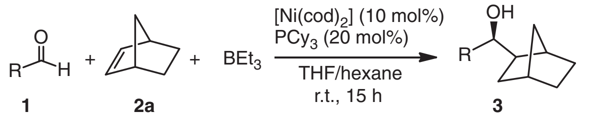
Table 1. Screening of ligands and reducing agents[a]



Entry	Ligand	Reducing agent	Yield of **3aa**/%[b]
1	PCy$_3$	BEt$_3$	87
2[c]	PCy$_3$	BEt$_3$	66
3	PCy$_3$	ZnEt$_2$	10
4	PCy$_3$	Et$_3$SiH	0
5	P*n*-Bu$_3$	BEt$_3$	68
6	PPh$_3$	BEt$_3$	10
7	IMes	BEt$_3$	0

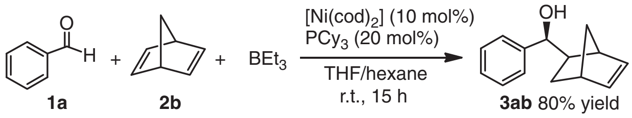
[a] Reaction conditions: [Ni(cod)$_2$] (0.10 mmol), ligand (0.20 mmol), **1a** (1.0 mmol), **2a** (2.0 mmol), reducing agent (2.0 mmol), THF (3 mL), and hexane (2 mL) were employed. [b] GC yield. [c] **2a** (1.0 mmol).

Table 2. Nickel-catalyzed reductive coupling reaction of **1b**–**1m** with **2a** in the presence of triethylborane[a]



Entry	1	R	3, yield/%[b]	dr[c]
1	**1b**	p-MeC$_6$H$_4$	**3ba** (92)	99:<1
2	**1c**	p-MeOC$_6$H$_4$	**3ca** (71)	99:1
3	**1d**	p-ClC$_6$H$_4$	**3da** (76)	97:3
4	**1e**	p-FC$_6$H$_4$	**3ea** (68)	95:5
5	**1f**	p-MeO$_2$CC$_6$H$_4$	**3fa** (87)	99:<1
6	**1g**	o-MeC$_6$H$_4$	**3ga** (73)	99:<1
7[d]	**1h**	2,6-Me$_2$C$_6$H$_3$	**3ha** (52)	99:<1
8	**1i**	2-furyl	**3ia** (82)	81:19
9	**1j**	2-thienyl	**3ja** (80)	93:7
10	**1k**	3-pyridyl	**3ka** (56)	93:7
11	**1l**	Cy	**3la** (52)	99:<1
12	**1m**	Hexyl	**3ma** (78)	99:<1

[a] Reaction conditions: [Ni(cod)$_2$] (0.10 mmol), PCy$_3$ (0.20 mmol), **1** (1.0 mmol), **2a** (2.0 mmol), BEt$_3$ (2.0 mmol, 1.0 M hexane solution), and THF (3 mL) were employed.[12] [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Reaction temperature: 50 °C.



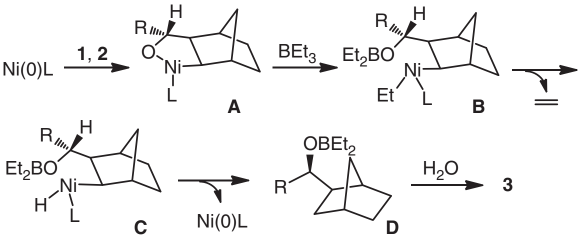
Scheme 2. Nickel-catalyzed reductive coupling reaction using norbornadiene.

groups, also succeeded in forming the corresponding products **3ja** and **3ka** with high diastereoselectivities (Entries 9 and 10). In addition to aryl aldehydes, alkyl aldehydes **1l** and **1m** were also effective in affording the corresponding products **3la** and **3ma** with excellent diastereoselectivities (Entries 11 and 12).

Furthermore, norbornadiene was also used in the reaction and gave the corresponding product **3ab**, with retention of one of the double bonds in the bicyclic ring (Scheme 2).[9] In contrast, other six-membered cyclic alkenes such as cyclohexene and 1,4-epoxy-1,4-dihydronaphthalene could not participate in this reaction.

A possible mechanism which would account for the diastereoselective reductive coupling reaction is shown in Scheme 3. First, the nickelacycle intermediate **A** is formed by the reaction of the nickel(0) complex with an aldehyde and a norbornene. In this step, the substituent (R) of the aldehyde may prefer to be located away from the methylene group of the norbornene unit in order to avoid steric hindrance. This is followed by a σ bond metathesis involving triethylborane through its coordination with the oxygen of nickelacycle,[11] which leads to intermediate **B**. Next, β-hydrogen elimination from **B** occurs, generating the hydride intermediate **C**. Finally, reductive elimination from **C**, followed by hydrolysis of **D**, occurs to afford the reductive coupling product **3**.

In summary, we have demonstrated a reductive coupling reaction between an aldehyde and a norbornene using triethylborane in the presence of a [Ni(cod)$_2$]/PCy$_3$ catalyst system.



Scheme 3. A possible pathway of the reductive coupling reaction using norbornene.

This reaction proceeded to afford alcohol products with high diastereoselectivities. Further efforts are under way to explain the different reactions caused by various combinations of ligands and reducing agents.

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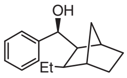
9 Structure of compound **3** was determined by X-ray crystallographic analysis of **3ab**.[12] The supplementary crystallographic data of **3ab** (CCDC number, 854135) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10 Ethylation product **4aa** was also isolated in 14% yield.



4aa

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