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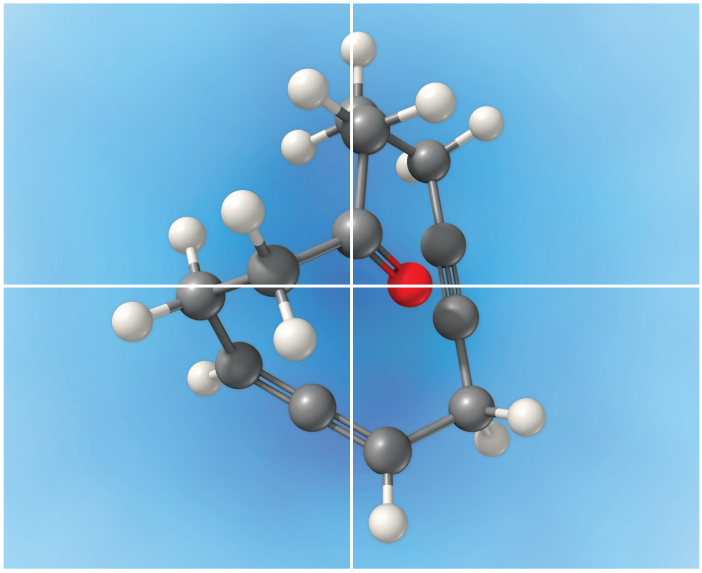

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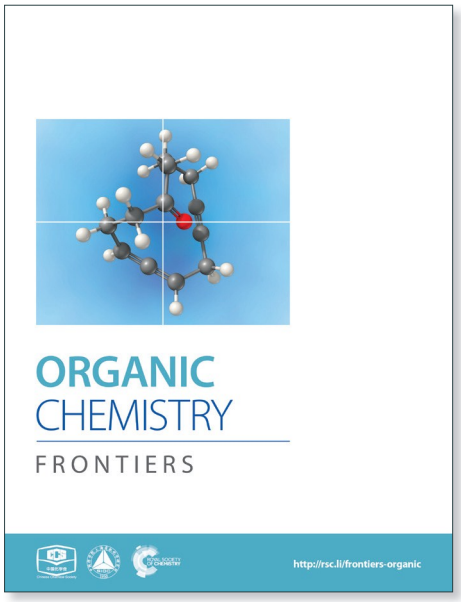

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Organic Chemistry Frontiers

Method

Nickel Catalyzed Reduction of Arenols under Mild Conditions

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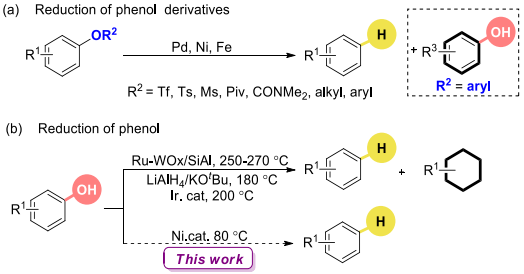
Nickel catalyzed reduction of arenols has been developed with mutual activation strategy under mild conditions. The reduction featured as broad substrate scopes, non-sensitive to steric hindrance and non-over-reduction of aromatic rings.

The industry has commonly forced on the oil as the carbon source of chemical feedstocks.[1] Compared to this non-renewable resource, the utilization of renewable and abundant biomass opens another door. Many efficient catalytic systems have been developed to degrade the biomass into valuable chemicals.[2] The recent flourishing developments on the C-O bond activations shed light on selective and efficient transformation of oxygen-rich lignocellulosic plant biomass to the commercial chemicals.[3] One of the most important achievements is the catalytic reduction of arenols and their derivatives,[4-6] especially the deoxygenated analogues of phenol-based natural products.[7] Traditionally, the reduction process of arenols and their derivatives includes three steps: 1) hydrolysis to their corresponding arenols, 2) conversion to the sulfonates, and 3) deoxygenation *via* Pd catalysis with H resources.[8] Direct reduction of phenols and their derivatives is highly appealed by avoiding tedious procedures and the use of costly and unfriendly fluorinated reagents. Obviously, the desirable processes can lead further utilization of electron-donating oxygen-based functionalities as a temporary removable directing group to achieve regioselective functionalization of arenes.[9-10] In this field, heterogeneous catalysis showed its beauty and power while the reactions usually ran under harsh conditions, companying with the over reduction of aromatic rings.[11]

Recently, impressive progress in homogeneous catalysis has been made to reduce the C-O bonds of arenol derivatives, including the esters,[5] and ethers (**Scheme 1a**).[4] To the best of our knowledge, the in-situ generated arenols as byproduct has never been reduced into the desired arenes under mild conditions (under 100 °C). Under high temperature, the Ru/W bifunctional catalyst,[5a] the stoichiometric $LiAlH_4/KO^tBu$ combination system,[5b] and the hydroxycyclopentadienyl iridium complexes[5c] could promote the reduction of arenols. However, aromatic rings were hydrogenated to form cyclohexanes, cyclohexanol and others in many cases.

Major challenges for direct and selective reduction of arenols rely on the stability of C-OH moiety: (1) the high bond dissociation energy (BDE) of its C-O bond; (2) the poor leaving ability of its hydroxyl group; (3) the deactivation of catalyst by bonding with phenolic anion; (4) the further enhancement of BDE by the p-π conjugative effect of its anion.[3c, 12] Based on our previous progress on mutual activation of arenols, we envisioned that the deoxygenation of arenols with suitable reducing reagents assisted by proper Lewis acid should be possible.[3c, 12] Herein we describe novel nickel catalyzed reduction of arenols under mild conditions.



Scheme 1. The reduction of phenol and its derivatives.

We began our investigations by examining the reactivity of naphthalen-2-ol (**1a**) with several hydride sources in the combination of $Ni(cod)_2/PCy_3$/NaH in toluene. (**Table 1**) The nature of reductants was critical, and HBPin, BH_3•SMe_2, $HSi(OEt)_3$, $HSiEt_3$, ^{i}PrMgCl, $LiAlH_4$, $NaBH_4$, Zn, H_2, were all ineffective, even when in company with a stoichiometric amount of $AlMe_3$[4g] or BEt_3[12a] (entry 1). Based on our experience in Suzuki-type coupling of arenols,[12a] we considered the important interaction between arenol and boron reagents. After extensive screenings, we found that a cocktail containing $Ni(cod)_2/PCy_3/B_2Pin_2/K_3PO_4$ promoted the targeted reaction in 91% yield and other diboron reagents did not show better results (entries 2-3). The inclusion of different ligands had a profound influence on the transformation (entry 4). Strikingly, the utilization of base with regime basicities had deleterious effects on the reactivity (entry 5). The yield slightly decreased in the absence of base (entry 6). The air and moisture-stable nickel catalyst could also catalyze the reaction (entry 7). Moreover, a difference in the reactivity was found in the diverse solvents (entries 8-9). Amazingly, the reaction

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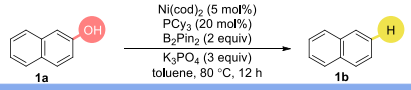
occurred at room temperature (entry 10), although the yield was sacrificed (entry 11). The addition of 1.5 equivalent of B_2Pin_2 delivered the product in excellent yields (entry 12). Notably, the reaction was efficient while the catalyst loading was decreased to 2.5 mol%. Indeed, this is a relative low catalyst loading in Ni catalyzed C-O bond activations, which was considered as one of major challenges in this field (entry 13). Importantly, no any over-reduction of aromatic ring was observed.

Table 1. Optimization of reaction conditions.[a]



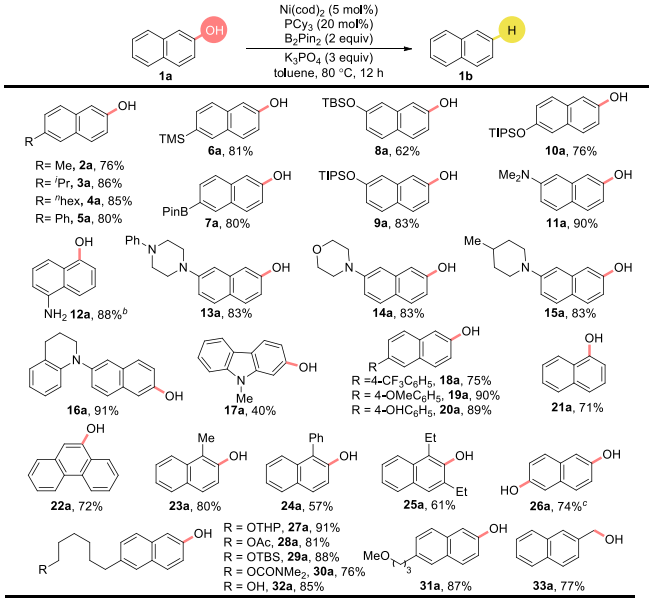
1a 1b

Entry	Ligand	Reductant	Base	Solvent	Yield (%)
1[b]	PCy_3	$HSiEt_3$ *etc*	K_3PO_4	toluene	< 5
2	PCy_3	$B_2(nep)_2$	K_3PO_4	toluene	45
3	PCy_3	B_2Pin_2	K_3PO_4	toluene	91 (80)[c]
4[d]	Dcype *etc*	B_2Pin_2	K_3PO_4	toluene	< 5
5[e]	PCy_3	B_2Pin_2	Cs_2CO_3 *etc*	toluene	< 5 ~ 85
6	PCy_3	B_2Pin_2	-	toluene	84
7[f]	PCy_3	B_2Pin_2	K_3PO_4	toluene	65
8	PCy_3	B_2Pin_2	K_3PO_4	THF	53
9	PCy_3	B_2Pin_2	K_3PO_4	DMF	< 5
10[g]	PCy_3	B_2Pin_2	K_3PO_4	toluene	15
11[h]	PCy_3	B_2Pin_2	K_3PO_4	toluene	65
12[i]	PCy_3	B_2Pin_2	K_3PO_4	toluene	87
13[j]	PCy_3	B_2Pin_2	K_3PO_4	toluene	72
14[k]	PCy_3	B_2Pin_2	K_3PO_4	toluene	< 5

[a] Conditions: **1a** (0.2 mmol), reductant (0.4 mmol), Ni catalyst (5 mol%), ligand (20 mol%), base (0.6 mmol), solvent (0.5 mL), 80 °C, 12 h and the yield was determined by GC analysis. [b] $HSiEt_3$, $HSi(OEt)_3$, BH_3•SMe_2, HBPin, Zn, ^{i}PrMgCl, $NaBH_4$, $LiAlH_4$, H_2 were used. [c] Isolated yield. [d] Dcype, IPr•HCl, phen were used.[e] Cs_2CO_3, K_2HPO_4, KH_2PO_4, NaH, DABCO were used. [f] $Ni(acac)_2$ was used. [g] The reaction was performed at 20 °C. [h] The reaction was performed at 60 °C. [i] B_2Pin_2 (1.5 equiv)/K_3PO_4 (2.5 equiv) was used. [j] $Ni(cod)_2$ (2.5 mol%)/PCy_3 (10 mol%) was used. [k] No $Ni(cod)_2$.

With the delightful conditions in hand, we found that the substrate scope encompassed electron-neutral (**2a-4a**), electron-poor (**25a**) and electron-rich naphthols (**26a**). The chemoselective character of this reduction was nicely illustrated by the good tolerance of diverse substituents in good yields (**Table 2**). Notably, excellent yield was obtained with the silyl group (**6a**),[14] which could be easily converted to other functionalities.[15-18] Importantly, the boronic ester group survived well (**7a**).[19] Silyloxyl groups in different positions of aromatic ring showed competing reactivities (**8-10a**). *N*,*N*-dimethylamino and free amine functionalities were tolerated well (**11-12a**). Substrates with nitrogen containing heterocycles, such as piperazinyl (**13a**), morpholinyl (**14a**), piperidinyl (**15a**) and tetrahydroquinolinyl (**16a**) produced the corresponding arenes in excellent yields. A worthy reactivity was found for the carbazole structural unit as a novel building block in pharmaceuticals, natural products and materials science (**17a**).[20] The reduction took place smoothly for the substrate bearing trifluoromethyl group, which was highly valuable for widely application in material and pharmaceutical molecules (**18a**).[21] Survival of methoxyl and hydroxyl groups on the phenyl ring was achieved by the control of the amount of B_2Pin_2 (**19-20a**). The reaction proceeded efficiently with α-naphthol (**21a**) and fused-aromatic substrates (**22a**). Notably, the *ortho* substituted groups did not have an obviously effect on the efficiency, as exemplified by **23-24a** in good yields. Most importantly, the highly steric hindered 1,3-diethylnaphthalen-2-ol (**25a**) showed a great reactivity. In addition, the dihydroxyl groups gave efficient conversion to the product of mono reduction (**26a**). Luckily, the successful preparation of **27-32a** illustrated both the selectivity profile among different C-O bonds, showing the practical utility of this method for further transformations in late-stage modification of biological compounds. Unfortunately, cyano, ester, halides and ether groups on the naphthyl ring could not be survived. Luckily, benzyl hydroxyl group could also be deoxygenized in a high yield (**33a**). Noteworthy, over-reduction products of aromatic ring were not observed.

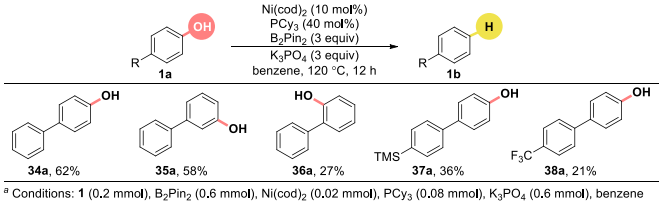
Table 2. Substrate scope of naphthols.[a]



[a] Conditions: **1** (0.2 mmol), B_2Pin_2 (0.4 mmol), $Ni(cod)_2$ (0.01 mmol), PCy_3 (0.04mmol), K_3PO_4 (0.6 mmol), toluene (0.5 mL) at 80 °C, 12 h. [b] K_3PO_4 (1.0 mmol) was used. [c] Conditions: $Ni(cod)_2$ (0.02 mmol), PCy_3 (0.08 mmol), B_2Pin_2 (0.8 mmol), K_3PO_4 (1.2 mmol), toluene (0.5 mL) at 80 °C, 12 h.

A closer look into the literatures indicated that the inclusion of π-extended systems strongly enhanced the reactivity of C–O bond.[22] Encouraged by the result in **Table 2**, we extended the substrate scope to the simple, yet, challenging phenols without the utilization of ortho-directing groups under the finely modified conditions (**Table 3**). Substrate bearing an *ortho* phenyl group generated the product, albeit in a relative lower yield, comparing to its *meta* and *para* analogues (**34-36a**). Both electron-poor (**37a**) and electron-rich (**38a**) groups were tolerated. Unfortunately, other π-extended system, such as (*E*)-4-styrylphenol was fully recovered. Further efforts to extend this chemistry to general phenol are underway.

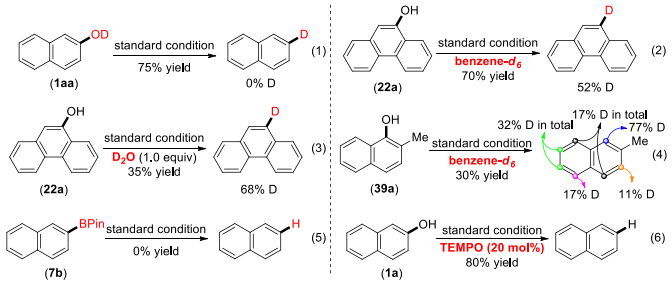
Table 3. Substrate scope of arenols.[a]



[a] Conditions: **1** (0.2 mmol), B_2Pin_2 (0.6 mmol), $Ni(cod)_2$ (0.02 mmol), PCy_3 (0.08 mmol), K_3PO_4 (0.6 mmol), benzene (0.5 mL) at 120 °C, 12 h.

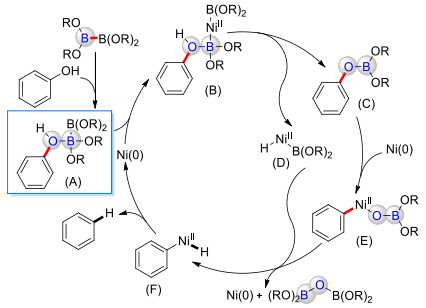
To further understand this reduction, we conducted preliminary mechanistic experiments (**Scheme 3**). Firstly, when the deuterated naphthalen-2-ol (**1aa**) was subjected to the standard conditions (Eq 1), no deuterium incorporation in product ruled out the direct deoxygenation pathway. The use

of benzene-d^6 or toluene together with 1 equivalent D_2O only afforded 52% and 68% deuterium incorporation of the reduction product (Eqs 2 and 3). Those results indicated that the solvent was at least one of hydrogen atom source in accordance with the literature report.[23] An unsymmetrical substrate was subjected to the standard conditions with benzene-d^6 as the solvent. And a H/D exchange occurred because the deuterium incorporated was observed at different aryl C-H bonds in the final product (Eq 4). This result indicated the C-H bonds in the naphthalene rings could be another source of hydrogen atom, since C-H bonds could be cleavaged by low valent metal catalysts with boron reagents,[24] which made the labeling experiments complicated. Moreover, according to the result that the reduction was very sensitive to the basicity of base, we speculated whether the reduction product would be originated from aryl boronic pinacol ester since the arylboronate product in the borylation of C(sp^2)-H was reported to be possibly decomposed in the present of K_3PO_4.[25] The starting marital was recovered when we subjected **7b** to the standard reaction conditions (Eq 5), resulting that the borylated product was not the precursor in this transformation. Finally, we found that the catalytic reduction product of **1a** was generated in 80 % GC yield by the addition of 20 mol% TEMPO (Eq 6). This observation indicated that single electron transfer process might not come into play. Finally, the unique effect of B_2Pin_2 stimulated us to investigate its role in this reduction under such a mild condition. From the ^{11}B NMR spectrums in **Scheme S1**, no doublet peaks of HBPin were detected,[26] when a mixture of **1a**, B_2Pin_2, $Ni(cod)_2$ and PCy_3 in toluene was stirred at 80 ° C for 30 min, while a new singlet peak at δ = 22.50 ppm[27] indicated that Nap-OBPin intermediate was formed. And in this reaction, a very low conversion to naphthalene was observed. Since naphthyl boronic acid ester was very prone to hydrolyze, we failed to isolate this intermediate, but it was confirmed by GC-MS. (**Scheme S2**) When B_2Pin_2 was replaced by 4 equivalent of HBPin under the standard conditions, **1a** was highly converted into trace amount of **1b** and the major product was Nap-OBPin, which was confirmed by GC-MS. (**Scheme S3**)



Scheme 3. Investigation of the mechanism.

Based on the literature report and current mechanism studies, we proposed the catalytic cycle as **Scheme 4**. Arenol was coordinated with diboronic acid pinacol ester to form the key intermediate **A**. With a mutual activation strategy, phenolic oxygen atom worked as a Lewis base to weaken the B-B bond, thus enhancing the transmetallation of B_2Pin_2. Meanwhile, the Lewis acidic B atoms decreased the electron density of the C-O bond, reducing the energy barrier of oxidation addition step. After oxidative addition of B-B bond to the low-valent Ni species,[28] the intermediate **B** was transformed *in situ* to the nickel species **D** and a relatively active naphthyl boronic pinacol ester **C**, which was oxidized to generate the nickel species **E**. The reductive elimination of **F** generated from the transmetallation between two nickel species **D** and **E** afforded the final product and regenerated the nickel catalyst.[29]



Scheme 4. Proposed mechanism.

In summary, the efficient nickel catalyzed reduction of C-O bonds of arenols under mild conditions with mutual activation strategy was reported. This new transformation was featured as a good group tolerance and non-sensitivity to the steric hindrance. Over-reduction of arene ring was not observed. The vital role of B_2Pin_2 was the key to this successful transformation of arenols, which would be utilized for the further design of interesting transformations of C-O bonds.

Experimental section

A representative procedure (**Table 2**): To an oven-dried schlenk tube with a stirring bar was added 2-naphthol (**1a**) (28.8 mg, 0.20 mmol), B_2Pin_2 (101.6 mg, 0.40 mmol) in the air, and then K_3PO_4 (127.2 mg, 0.60 mmol), PCy_3 (11.2 mg, 0.04 mmol) and $Ni(cod)_2$ (2.8 mg, 0.01 mmol) were added, followed by the injection of toluene (0.50 mL) in glove box. The tube was sealed up and the mixture was stirred at 80 °C for 12 h. The mixture was then cooled to room temperature and directly purified by column chromatography to afford compound **1b** as a white solid (20.5 mg, 80%).

Acknowledgements

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