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Nickel-Catalyzed Cross-Electrophile Coupling between Benzyl Alcohols and Aryl Halides Assisted by Titanium Co-reductant

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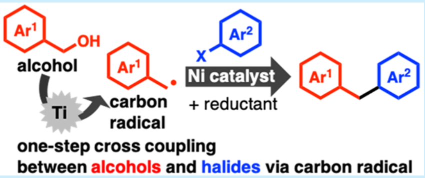
Supporting Information

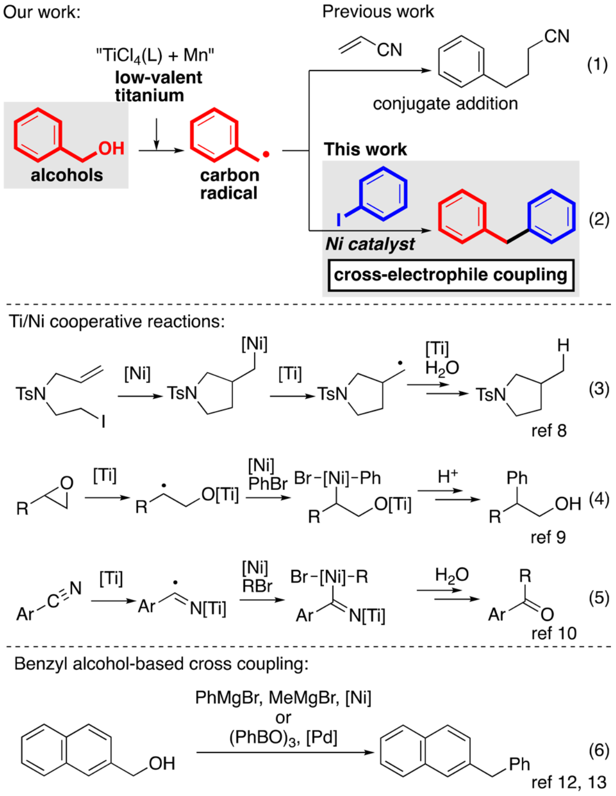
ABSTRACT: A nickel-catalyzed cross-electrophile coupling reaction between benzyl alcohols and aryl halides has been developed using a homolytic C−O bond cleavage protocol that has recently been established. The treatment of a benzyl alcohol and aryl halide with a nickel catalyst and low-valent titanium reagent generated from $TiCl_4$(lutidine) (lutidine = 2,6-lutidine) and manganese powder afforded the cross-coupled product in high yield. A mechanistic study indicated the intermediacy of the benzyl radicals that originate from the benzyl alcohols.



Alcohols, although ubiquitous, have found limited direct use as partners in transition-metal-catalyzed reactions, except in processes such as allylic alcohol activation[1] and hydrogen-autotransfer catalysis.[2] The development of an alternative method that could replace esters, halides, or carbonyl compounds with their precursor alcohols in catalytic C−C bond-forming reactions would be a desirable advancement and could exponentially extend the use of alcohols. Very recently, we have discovered a concise protocol for generating benzyl radicals in one step from benzyl alcohols by using an inexpensive low-valent titanium reagent; this reaction was successfully applied to radical conjugate additions (Scheme 1, eq 1).[3] Encouraged by this discovery, we proposed that our protocol could offer an unexploited radical route toward transition-metal-catalyzed alcohol transformations.[4−7] In this report, we describe the nickel-catalyzed radical cross-electrophile coupling reaction[4,7] between alcohols and aryl halides (Scheme 1, eq 2). Although uncommon in the literature, low-valent titanium reagents have been used for incorporating carbon radicals into transition-metal catalysis. Cuerva has discovered that low-valent titanium reagents can react with alkylnickel complexes to generate carbon radicals (Scheme 1, eq 3).[8] Weix has introduced the low-valent titanium-mediated reduction of epoxides into the nickel-catalyzed radical cross-electrophile coupling (Scheme 1, eq 4).[9] Similarly, Rahaim has merged the reduction of benzonitrile and the cross-electrophile coupling very recently (Scheme 1, eq 5).[10] In this context, our present work newly unlocks alcohols for such titanium/nickel cooperative reactions.

Only two previous diarylmethane syntheses via cross-coupling reactions using benzyl alcohols have been reported.[11] Shi has recently described a hydroxy-Kumada−Tamao−Corriu coupling[12] and hydroxy-Suzuki−Miyaura coupling (Scheme 1, eq 6).[13] These reactions exhibited excellent performance when the substrates were benzyl alcohols that have extended π-conjugation systems at the arene moieties (e.g., 2-naphthalenemethanol). However, monocyclic alcohols were likely to be less suitable. We expected that the broad alcohol scope of our radical generation protocol would overcome this limitation.[3]

Scheme 1. Background of This Study



We found that the desired cross-coupling took place when a nickel catalyst and aryl halide were introduced into our typical conditions[3] for homolytic C−OH bond cleavage (Table 1).

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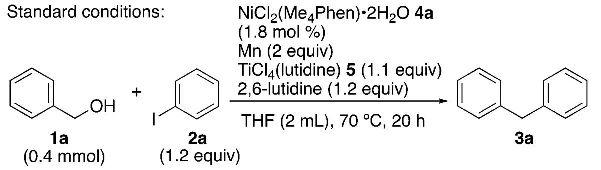
Table 1. Optimization of Reaction Conditions[a]



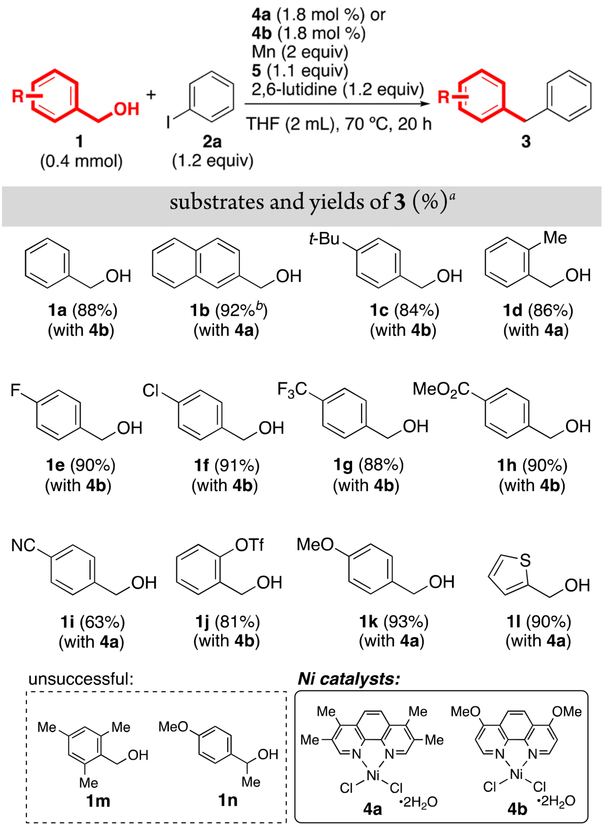
entry	deviations from standard conditions	3a[b] (%)
1	none	86
2	w/o **4a**	0
3	Me_4Phen instead of **4a**	0
4	$NiCl_2(PPh_3)_2$ instead of **4a**	9
5	$NiBr_2$(dme) instead of **4a**	25
6	w/o $TiCl_4$(lutidine)	0
7	$TiCl_4$(tmeda) instead of **5**	42
8	Cp_2TiCl_2 instead of **5**	62
9	benzene instead of THF	>5
10	DMA instead of THF	>5
11	w/o Mn	0
12	Zn instead of Mn	28
13	w/o added 2,6-lutidine	78
14[c]	$NiBr_2$(dme) (1 mol %) + Me_4Phen instead of 1.8 mol % of **4a**	77
15[c]	$NiBr_2$(dme) (1 mol %) + $(MeO)_2$Phen instead of 1.8 mol % of **4a**	81
16	$NiCl_2((MeO)_2Phen)\cdot 2H_2O$ **4b** (1.8 mol %) instead of 1.8 mol % **4a**	88[d]

[a] Abbreviations: lutidine = 2,6-lutidine; Me_4Phen = 3,4,7,8-tetramethylphenanthroline; $(MeO)_2$Phen = 4,7-dimethoxyphenanthroline; tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; dme = 1,2-dimethoxyethane. [b] ^{1}H NMR yield unless otherwise noted. [c] Catalyst was prepared by premixing 1 mol % $NiBr_2$(dme) and 1.2 mol % ligand in THF. [d] Isolated yield.

For example, the treatment of benzyl alcohol **1a** and 1.2 equiv of iodobenzene **2a** with 1.8 mol % of $NiCl_2(Me_4Phen)\cdot 2H_2O$ **4a**, $TiCl_4$(lutidine)[14] **5** (lutidine = 2,6-lutidine), manganese powder, and 2,6-lutidine in THF at reflux temperature afforded the cross-coupling product **3a** in 86% yield (Table 1, entry 1). To prove the necessity of each component, several control experiments were conducted. No coupling product was observed in the absence of the nickel catalyst (Table 1, entries 2 and 3). The advantage of the phenanthroline ligand was obvious, but other ligands worked to some extent (Table 1, entries 4 and 5). Without the titanium coreductant **5**, again, no coupling reaction took place (Table 1, entry 6). The reaction using $TiCl_4$(tmeda) and Cp_2TiCl_2 also afforded **3a**, albeit with decreased yields (Table 1, entries 7 and 8). The reaction in benzene or *N*,*N*-dimethylacetamide only resulted in the recovery of **1a** (Table 1, entries 9 and 10). A reductant was indispensable for the reaction (Table 1, entry 11). The use of zinc instead of manganese decreased the yield of **3a** (Table 1, entry 12). The effect of the added 2,6-lutidine was not apparent for **1a** and **2a**, but an obvious positive effect was observed for several other substrates (Table 1, entry 13) (see also Table S2). The yield did not drop significantly, even with 1 mol % of nickel catalysts prepared from $NiBr_2$(dme) and ligands. Me_4Phen (Table 1, entry 14) and $(MeO)_2$Phen (Table 1, entry 15) exhibited the best performance of all of the ligands that we tested. Isolated $NiCl_2((MeO)_2Phen)\cdot 2H_2O$ **4b** was as reactive as **4a**, giving the coupling product in 88% isolated yield (Table 1, entry 16). The results of the further ligand screening are summarized in Table S3.

The range of tolerated benzyl alcohols **1** was investigated using iodobenzene **2a** as a coupling partner and either **4a** or **4b** as a catalyst (Table 2). Similar to the simplest benzyl alcohol **1a**, polycyclic 2-naphthalenemethanol **1b** afforded the coupling product in high yield. An alkyl substituent at the *para*- or *ortho*-position did not affect the yield (**1c** and **1d**). Various functional groups were tolerant of the reaction conditions. 4-Fluoro- and 4-chlorobenzyl alcohol were suitable (**1e** and **1f**). Electron-deficient benzyl alcohols such as 4-(trifluoromethyl), 4-(methoxycarbonyl), and 4-cyanobenzyl alcohol afforded the desired products in good to high yields (**1g**–**i**). Trifluoromethanesulfonate **1j** retained its functionality through the reaction. An electron-donating methoxy group did not interfere in the reaction significantly (**1k**). Heteroaromatic 2-thiophenemethanol **1l** also underwent the coupling reaction efficiently. Unfortunately, in sharp contrast to our previous radical conjugate addition reaction,[3] sterically demanding alcohols **1m** and **1n** were not suitable.

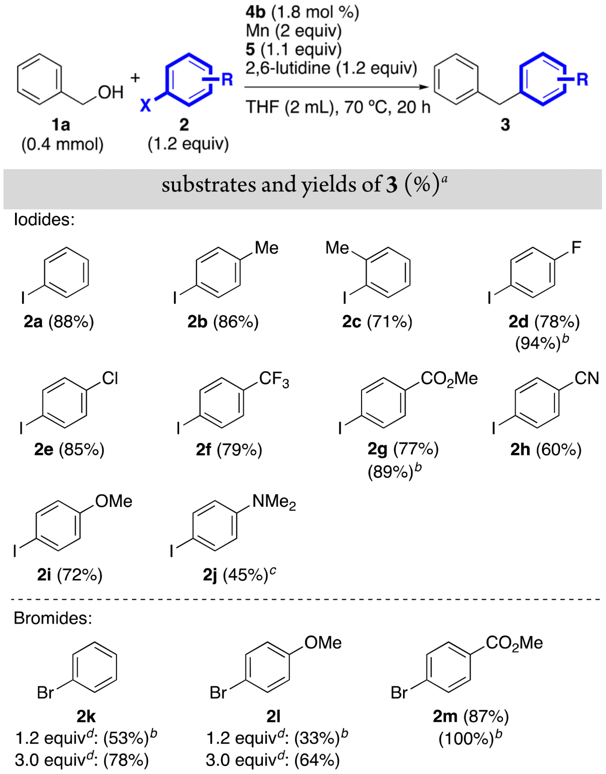
Table 2. Scope of Benzyl Alcohols



[a] Isolated yield. The catalyst used is shown parenthetically. [b] 1.0 mmol scale.

The scope of the aryl halides is provided in Table 3. In cases of technical difficulty during isolation, NMR yields are also given. The reaction accepted many representative aryl iodides other than iodobenzene (**2a**). Both 4- and 2-methyliodobenzene **2b** and **2c** afforded coupling products in good yields. 4-Fluoro- and 4-chloroiodobenzene **2d** and **2e** were also good substrates. Aryl iodides bearing either electron-withdrawing (4-trifluoromethyl, 4-methoxycarbonyl, and 4-cyano) or electron-donating (4-methoxy and 4-dimethylamino) groups underwent

Table 3. Scope of Aryl Halides

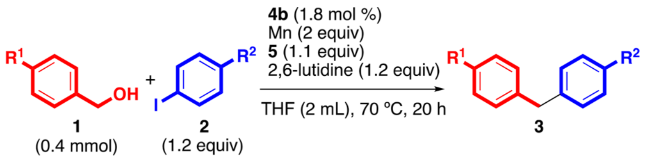


[a]Isolated yield. [b]^{1}H NMR yield before isolation. [c]Considerable amount of 1,2-diphenylethane was obtained (23% NMR yield). [d]Amount of aryl halide.

the desired reaction, although the presence of cyano and dimethylamino groups decreased the yields (**2f**–**j**). Aryl bromides were also suitable substrates. Higher loadings (3 equiv) of the bromides were necessary to obtain satisfactory yields for bromobenzene and 4-bromoanisole **2k** and **2l**, while methyl 4-bromobenzoate **2m** afforded the product quantitatively even with 1.2 equiv. To further ensure the utility of this reaction, we examined all combinations of electron-deficient/electron-rich substrates by employing 4-methoxy/methoxycarbonyl alcohols/iodobenzenes (Scheme 2). Fortunately, all combinations afforded the coupling products in good to high yields, regardless of the electronic natures of the substrates (63–89% yields).

We conducted several mechanistic studies to rule out the possible two-electron oxidative addition of the C–O[Ti] bond to Ni^0. First, the time-course dependence of alcohol consumption was compared between reactions with or without nickel catalyst **4b** using 4-*tert*-butylbenzyl alcohol **1c** (Figure 1). In both cases, the reactions began after 1–2 h induction periods,[15] followed by the gradual consumption of starting material **1c** at similar rates. Compound **1c** was converted to a mixture of the corresponding dimer of the benzyl radical and the deoxygenated product in the absence of **4b** and iodobenzene **2a** (hashed line). Meanwhile, **3c** was nearly the sole product obtained in the presence of **4b** and **2a** (solid line). We also found that an increased catalyst loading did not accelerate the reaction (Scheme 3). For example, reactions with either 1.8 or 9 mol % catalyst loadings afforded the coupling product in ca. 40% yield after 4 h. These results clearly indicate that the reaction rate is dependent only on the self-decomposition of the benzyl titanate intermediate ($ArCH_2O[Ti]$) to generate the benzyl radical, and the Ni catalyst does not participate in the C–O bond-cleavage step.

Scheme 2. Cross Couplings between Both Functionalized Benzyl Alcohols and Iodobenzenes



Isolated yields of 3 (%)		R² –OMe (**2i**)	–CO$_2$Me (**2g**)
R¹	–OMe (**1k**)	81 (**3o**)	89 (**3p**)
	–CO$_2$Me (**1h**)	63 (**3p**)	84 (**3q**)

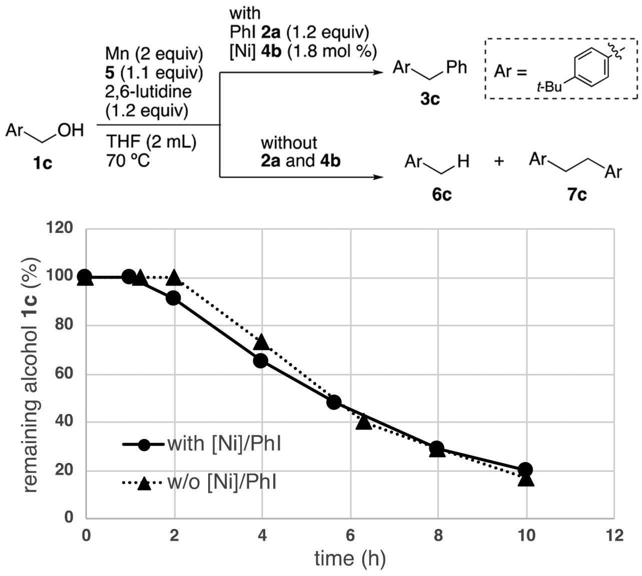
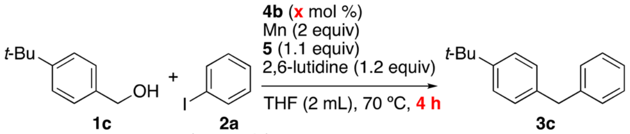


Figure 1. Time-course dependence of alcohol consumption. The reaction conditions were as follows: **1c** (0.4 mmol), Mn (2.0 equiv), and **5** (1.1 equiv) in THF (2 mL) at 70 °C (oil bath temperature). For the solid line, **2a** (1.2 equiv) and **4b** (1.8 mol %) were added. The reactions were carried out in separate batches for each point. The yields were estimated by ^{1}H NMR. The detailed data are given in Figure S2.

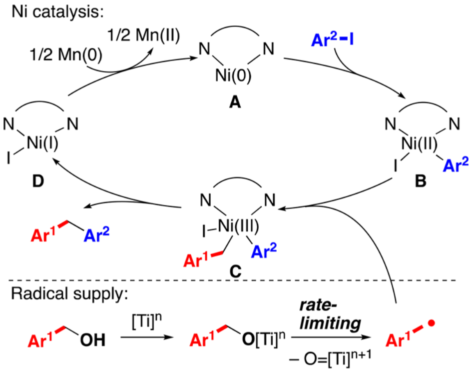
Scheme 3. Effect of Catalyst Loading



	NMR yield (%)	
x	1c	3c
1.8	65	40
9	65	35

The proposed reaction mechanism is depicted in Scheme 4.[5] Ni^0 **A** reacts with iodobenzene to generate arylnickel **B**, followed by the one-electron oxidative addition of the benzyl radical to give **C**. Reductive elimination of the product furnishes **D**, and **D** is further reduced to **A** to close the catalytic cycle. The benzyl radical is supplied from the outside of the

Scheme 4. Proposed Reaction Mechanism



catalytic cycle by low-valent titanium-mediated homolytic C−O bond cleavage.[16]

In summary, we have established a cross-electrophile coupling reaction between benzyl alcohols and aryl halides through titanium-mediated homolytic C−O bond cleavage. This reaction has broad scope for both coupling fragments, and no large excesses of substrates are required, except in the cases of some aryl bromides. Mechanistic studies indicated that the reaction proceeds via a benzyl radical, as we expected. This work provides a new use for alcohols in transition-metal catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03367.

Experimental details, analytical data for new compounds, and additional experimental results (PDF)

^{1}H, ^{13}C, and ^{19}F NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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