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One-Shot Radical Cross Coupling Between Benzyl Alcohols and Alkenyl Halides Using Ni/Ti/Mn System

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Abstract. A “one-shot” cross coupling between benzyl alcohols and alkenyl halides has been established. A combination of low-valent Ti-mediated C–OH homolysis and the prominent chemistry of Ni-based radical catalysis afforded the desired cross-coupled product with good efficiency. The reaction proceeded regardless of the electronic property of benzyl alcohols, and Ar–B bond remained intact throughout the reaction. Alkenyl bromides with various substitution patterns were applicable to this reaction. Attempts for utilizing sterically demanding tri-substituted alkenes indicated that the steric hinderance mainly inhibited the radical-trapping by Ni species. This reaction can be a simple and efficient strategy for synthesizing densely substituted allylbenzene derivatives.

Keywords: Cross-coupling; Radicals; Alcohols; Titanium; Nickel

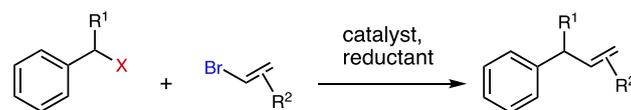
Ni-catalyzed radical cross-coupling is emerging as a powerful tool for realizing coupling reactions using nontraditional reactants. Mechanistic studies of the seminal discoveries on the cross-coupling reactions between aryl bromides and alkyl bromides^[1] revealed the participation of alkyl radical species derived from the alkyl bromides.^[2] These studies triggered intense collaborations of the single-electron redox reaction of various carbon radical precursors (borates, carboxylic acids, oxalates, etc.) and Ni-catalyzed reactions.^[3,4] However, the direct use of alcohol C–OH bonds as carbon radical precursors in such cross couplings was largely underexplored because of the lack of reliable methods for C–OH homolysis, till before our previous work.^[5]

Alcohols constitute a large part of our chemical feedstocks, and thus, its direct application to organic transformations is indeed desirable.^[6] In particular, their use in cross-coupling reactions could replace the conventional organometallic reagent-based synthetic

schemes with simpler and less expensive alcohol-based schemes.^[7] We have been tackling this challenge and have recently resolved it in part by combining the low-valent Ti-mediated C–OH homolysis and Ni-catalyzed radical cross coupling.^[5] For instance, the reaction between benzyl alcohols and aryl halides successfully afforded the corresponding coupling products in the Ni/Ti/Mn reaction system.^[8] However, the product, diarylmethane, has a narrow scope for application in organic synthesis because of the relative difficulties in undergoing further transformations. We herein report a one-shot cross-coupling between benzyl alcohols and alkenyl halides for preparing allylbenzenes, that can be derivatized by known facile transformations of alkenes.

Scheme 1. Cross-coupling between Bn–X and Alkenyl Bromides.

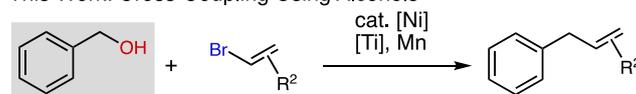
Known Methods:



catalyst(s)/reductant	X	reference
Pd/Zn	Cl	Lipshutz (ref. 12)
Co/Mn	Cl	Gosmini (ref. 13)
Ni+Co/Zn	OMs	Weix (ref. 14) ^a
Ni/Zn	Cl	Gong (ref. 15) ^a
Ni(+Co)/Mn, etc.	Cl	Reisman (ref.16)

a) Only one example is reported in the reference.

This Work: Cross-Coupling Using Alcohols

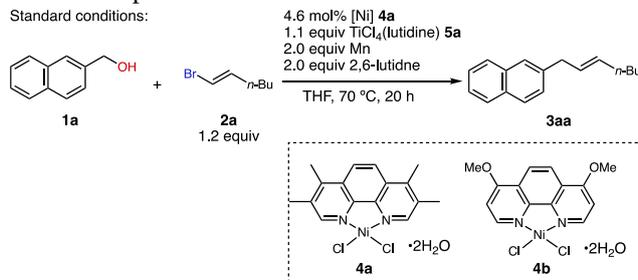


The reductive C–C bond formation reaction between Bn–X (X = heteroatom) and alkenyl halides commonly involves multiple steps that include the preparation of organometallic reagents.^[9,10] In contrast,

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a simplified “one-shot” cross coupling approach has also been developed.^[11] Lipshutz reported the Pd-catalyzed coupling between benzyl chlorides and alkenyl halides.^[12] Gosmini reported the Co-catalyzed coupling,^[13] while Ni-catalyzed reactions were reported by Weix^[14], Gong^[15] and Reisman.^[16] Although benzyl (pseudo)halides have been widely employed as described, benzyl alcohol, their common precursor, is not used for this purpose.

Table 1. Optimization of Reaction Conditions.^a



Entry	Deviation	Yield/% ^b
1	None	70
2	TiCl ₄ (collidine) 5b and collidine instead of 5a and lutidine	38
3	TiCl ₄ (tmeda) 5c instead of 5a	40
4	[Ni] 4b instead of 4a	50
5	No Mn	0
6	No 2,6-lutidine	6

^aReactions were performed at 0.20 mmol scale. Abbreviations: lutidine = 2,6-lutidine, collidine = 2,4-collidine, tmeda = *N,N',N',N'*-tetramethylethylenediamine.

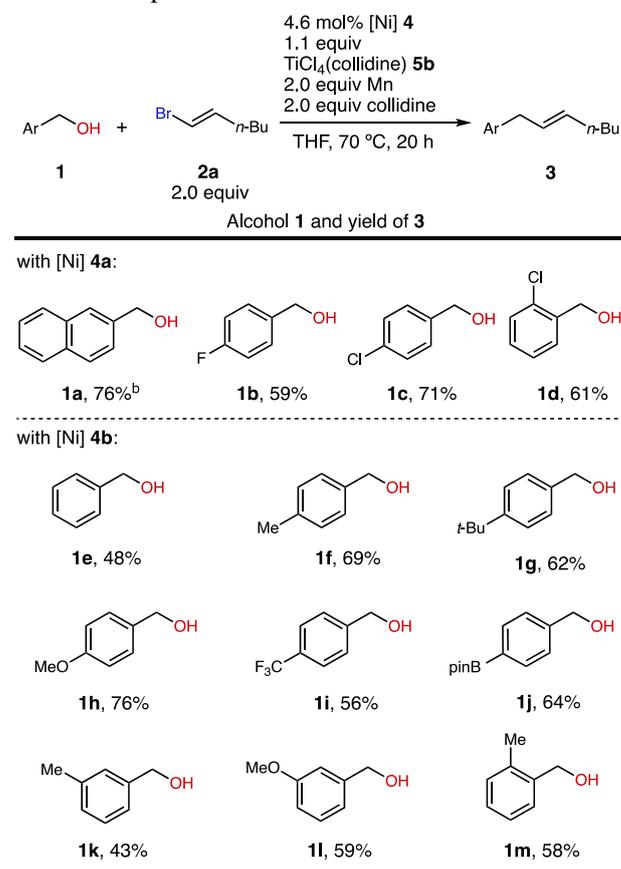
^bNMR yields of **3aa**.

The optimum conditions were determined using 2-naphthalenemethanol **1a** and (*E*)-1-bromo-1-hexene **2a** as substrates (Table 1). The highest yield (70%) was obtained when TiCl₄(lutidine) **5a**, 4.6 mol% Ni catalyst **4a**, Mn powder, and additional 2,6-lutidine were used in THF at 70 °C (entry 1). Gratifyingly, no positional isomerization of the alkene moiety was observed in any reactions, including those in the later studies. Other Ti reagents such as TiCl₄(collidine) **5b** and TiCl₄(tmeda) **5c** could also be used for this reaction, although the yields were low (entries 2 and 3). The use of Ni catalyst **4b** also resulted in a low yield (entry 4). The combination of Ni catalyst **4** and Ti reagent **5** was optimized as described, but further investigation revealed that the best combination depended on alcohols **1** and alkenyl bromides **2** (see Table S1 and S2 in ESI for details). The control experiments clearly demonstrated the need for Mn and the added 2,6-lutidine (entries 5 and 6).

The scope of alcohol was tested using alkenyl bromide **2a** (Table 2). For all the reactions studied, the isolated yields of the products were mostly in a relatively narrow range of 50% to 70%, establishing that the reaction efficiency remained nearly constant regardless of the substituents on the aromatic moiety. In addition to naphthalene derivative **1a**, various substituted benzyl alcohols were suitable for this

reaction. The presence of electron-donating or electron-withdrawing substituents did not affect the yield significantly (**1h** and **1i**). It is notable that boronic ester **1j** was neatly converted to the desired product with retention of the boronic ester moiety, despite its known reactivity in cross-coupling reactions (64% yield).^[17]

Table 2. Scope of Alcohols.^a



^aReactions were performed at 0.4 mmol scale. Isolated yields of **3** are shown. ^b**5a** and lutidine were used instead of **5b** and collidine.

Our major interest was to investigate the scope of alkenes in the Ni/Ti/Mn systems, as there is only a handful of detailed information on the effect of substitution patterns on the Ni-catalyzed radical cross-coupling.^[11a, 15, 18] For this purpose, a series of mono-, di-, and tri-alkyl-substituted alkenyl bromides were examined (Table 3). To better understand the correlation between the steric hindrance around the C-Br bond and the reaction efficiency, the amount of alkene (except volatile alkenes **2c** and **2f**) was reduced (1.2 equiv). All the mono- and di-substituted alkenyl bromides reacted to give satisfactory yields. For obtaining higher yields, increasing the alkene loadings can be helpful to some extent. For example, increasing the amount of **2d** from 1.2 to 3.0 equiv improved the yield by 17%. Linear alkenyl bromide **2f** with *E/Z* = 30/70 was converted to the product with *E/Z* = 37/63. The virtual retention of the *E/Z* ratio in the presence of excess **2f** (3.0 equiv) indicated that the (*E*)-isomer was only slightly more reactive than the (*Z*)-isomer. In

contrast, the (*Z*)-isomer of **2d** was apparently less reactive than the (*E*)-isomer. Further comparison between the *E/Z* isomers is provided in the ESI. Alkenyl iodides **2i** and **2j** as well as the corresponding bromides reacted when Ni catalyst **4b** was used (71% and 82% yield, respectively). Although most of the tested alkenes reacted efficiently, the most sterically demanding tri-substituted alkenyl bromide **2h** was exceptionally unsuitable, similar to that reported by Gong (18% yield).^[15] These similar observations suggest that this is a common difficulty in Ni-catalyzed radical cross-coupling reactions. To overcome this, we further investigated the factors that could improve the yield.

Table 3. Scope of Alkenes.^a

alkene 2	x/equiv	yield (<i>E:Z</i>)	alkene 2	x/equiv	yield (<i>E:Z</i>)
2a	1.2	63% ^b	2f	3.0	73% (37:63)
	2.0	76%			
2b	1.2	60%	2g	1.2	87%
2c	3.0	81%	2h	1.2	18% ^{b,c,d}
2d	1.2	69% ^b (93:7)	2i	1.2	71% ^d
	3.0	86% (94:6)			
2e	1.2	68%	2j	1.2	82% ^d

^aReactions were performed at 0.40 mmol scale. Isolated yields of **3** are shown unless otherwise stated. ^bNMR yield. ^c**5b** and collidine were used instead of **5a** and lutidine. ^d[Ni] **4b** was used instead of **4a**.

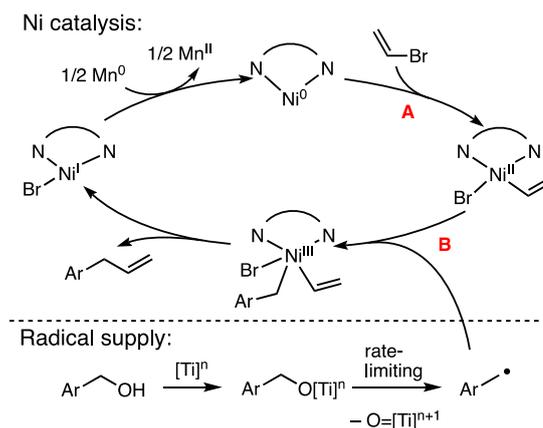
The low yield (18%) with tri-substituted alkenyl bromide **2h** was accompanied by the substantial formation of radical dimer **6** (45% yield) and deoxygenated product **7** (26% yield, Table 4, entry 1). We have previously shown that such a Ni/Ti/Mn system consists of two independent processes—Ti-mediated C–O bond homolysis and Ni-catalyzed cross-coupling, while the reaction rate is controlled by the radical-formation step (Scheme 2).^[5] The reaction of **2h** in this catalytic cycle can be influenced by a couple of factors. In the Ni-catalyzed process, it is possible that the oxidative addition step is reasonably

Table 4. Optimization of Reaction Conditions for Tri-Substituted Alkene **2h**.^a

Entry	2h		Temp. /°C	Yield/% ^b		
	x/equiv	y/mol %		3ah	6	7
1	1.2	4.6	70	18	45	26
2	3.0	4.6	70	26	21	48
3	1.2	9.2	70	40	31	28
4	3.0	9.2	70	47	21	32
5	1.2	9.2	50	54 ^c	4	16

^aReactions were performed at 0.40 mmol scale. ^bNMR yields, unless otherwise stated. ^cIsolated yield.

Scheme 2. Proposed Mechanism and Possible Yield-Limiting Steps (A and B).



slower than the C–O bond homolysis, because of which the Ni species is not ready for trapping the radical (step A). In light of the reaction kinetics, increase in both alkene **2h** and catalyst **4a** loadings should improve the yield; else, the radical-trapping step can be affected by the steric hindrance (step B). In this case, only an increase in catalyst **4a** loading improves the yield.

To rationalize these hypotheses, we increased either or both the alkene and Ni catalyst loadings. Increasing the alkene **2h** loading from 1.2 to 3.0 equiv improved the yield only slightly (entry 2, 26% yield), indicating that the concentration of **2h** is not critical for the efficiency. In contrast, doubling the Ni catalyst loading (9.2 mol%) almost doubled the yield of the cross-coupling product (entry 3, 40% yield). A simultaneous increase in the **2h** and **4a** loadings further increased the reaction yield, but incremental (entry 4, 47% yield). This indicates that the oxidative addition step (step A) is not necessarily critical even with a small excess of alkenes, while an inefficient radical-trapping step (step B) is mainly responsible for the poor yield.^[19] Lowering the reaction temperature

could suppress the formation of dimer **6**, because dimerization is sensitive to the concentration of the radical species in comparison to the other reaction pathways. Indeed, at 50 °C, the yield of **6** dramatically decreased to 4% while that of **3ah** increased to 54% (entry 5).

In conclusion, we have developed a Ni-catalyzed radical cross-coupling between benzyl alcohols and alkenyl bromides. The reaction tolerates various benzyl alcohols, including those with bromo and boronic ester groups. The low sensitivity to the substitution pattern of the alkene moiety in alkenyl bromides promises a broad scope of alkenes. An attempt with the tri-substituted alkenyl bromide provided new insights into the challenging and sterically demanding cross-coupling reaction. We hope that this study will lead to the development of an alcohol-based radical strategy for transition metal-catalyzed alkenylation.

Experimental Section

General procedure for cross-coupling: The representative procedure using **1a** and **2a** is as follows; to a dried test tube, Mn powder (44 mg, 0.80 mmol) and NiCl₂(Me₄Phen)•2H₂O (7.3 mg, 0.018 mmol) were added under air atmosphere, and the gaseous phase was replaced with argon. Next, TiCl₄(lutidine) (131 mg, 0.44 mmol), THF (1.0 mL) and 2,6-lutidine (92 μL, 0.80 mmol) were added, and the mixture was stirred for 10 min. To this, THF (1.0 mL) solution of 2-naphthalenemethanol (**1a**, 63 mg, 0.40 mmol) and (*E*)-1-bromo-1-hexene (**2a**, 65 μL, 0.48 mmol) were added dropwise while stirring the mixture vigorously. Following this, the mixture was stirred at 70 °C for 20 h. After cooling, hexane/ethyl acetate (1/1 (v/v), ca. 2 mL) was added. The mixture was stirred under air until the black color almost disappeared. The gray precipitate formed was filtered with a short plug of silica gel (hexane/ethyl acetate 1/1 (v/v) as an eluent), and the resulting solution was concentrated under reduced pressure. The crude product was purified by preparative TLC (hexane) to afford the coupling product **3aa** as a pale-yellow oil (68.2 mg, 76% yield).

Acknowledgements

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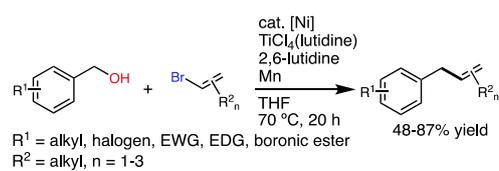
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Takuya Suga*, Yuuki Takahashi, Yutaka Ukaji*



Ti-mediated homolytic C–OH cleavage
for direct cross-electrophile coupling
between **alcohols** and **alkenyl bromides**

