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Nickel catalyzed deoxygenative cross-coupling of benzyl alcohols with arylbromides

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Nickel catalyzed deoxygenative cross- coupling of benzyl alcohols with aryl-	Leave this area blank for abstract info.	
bromides		
Vinoth Kumar Chenniappan, Devin Peck, and Ronald J. Ra	ahaim <sup>†</sup> *	
$\mathbf{R}^{1} \underbrace{\mathbf{R}^{2}}_{\text{DMA, r.t., 12 h}} \mathbf{R}^{2} \underbrace{\begin{array}{c} 5 \text{ mol}\% \text{ Ni(phen)Cl}_{2} \\ 2.5 \text{ equiv TMS-Cl} \\ 2 \text{ equiv Mn} \\ \text{DMA, r.t., 12 h} \end{array}}_{\mathbf{R}^{1}} \mathbf{R}^{1} \underbrace{\mathbf{H}^{2}}_{\mathbf{R}^{2}} + \underbrace{\mathbf{H}^{2}}_{\mathbf{R}^{2}} \mathbf{R}^{2} + \underbrace{\mathbf{H}^{2}}$	Ho $1 = \frac{5 \text{ mol% Ni(phen)Cl}_2}{2.5 \text{ equiv TMS-Cl}_2}$ $2 = \frac{2 \text{ equiv Mn}}{DMA, r.t., 12 \text{ h}} R^1$	



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# Nickel catalyzed deoxygenative cross-coupling of benzyl alcohols with aryl-bromides

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#### ARTICLE INFO

# ABSTRACT

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Keywords: nickel cross-coupling cross-electrophile coupling alcohol diarylmethane Keyword\_5 A nickel-catalyzed cross-electrophile coupling of benzyl alcohols with aromatic bromides has been developed. This deoxygenative cross-coupling occurs under mild reaction conditions at ambient temperature affording diarylmethanes, or 1,3-diarylpropenes from benzyl allyl alcohols. The system demonstrated good chemoselectivity tolerating an assortment of reactive functional groups.

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Alcohols are a ubiquitous functional group that is a versatile handle in bond forming reactions. They are readily available, can be prepared in chiral nonracemic form, and are typically bench stable. The ability to directly utilize alcohols in cross-coupling reactions is highly desirable for this would greatly expand the pool of available coupling partners. Several challenges face this approach, namely overcoming the strong C-O bond strength, the hydroxyl group being a poor leaving group, and potential undesirable pathways being competitive such as ether formation or oxidation of the alcohol through  $\beta$ -hydride elimination. To circumvent these issues the alcohol is typically derivatized to a carbonate<sup>1</sup>, carbamate<sup>2</sup>, ester<sup>3</sup>, ether<sup>4</sup>, or sulfonate<sup>5</sup> for application in cross-coupling or cross-electrophile<sup>6</sup> reactions. While progress on the cross-coupling of derivatized alcohols has occurred, the direct coupling of alcohols is far less developed. Only a few examples exist where benzyl alcohols have been coupled with boron<sup>7</sup> and Grignard reagents<sup>8</sup>, and a single example for a crosselectrophile coupling with aryl iodides.9

Recently our group developed a dual catalytic crosselectrophile coupling of nitriles in which titanium was used to generate a putative imidoyl radical.<sup>10</sup> As a continuation of developing dual catalytic methods for the cross-coupling of in situ generated carbon radicals, we became interested in extending the Ni/Ti system to alcohols. Stoichiometric amounts of titanium(III) reagents have been shown to promote alcohol deoxygenation through formation of a carbon radical.<sup>11</sup> It was speculated that a Ni/Ti catalytic system could facilitate the coupling of alcohols with aryl halides. While in the process of developing this dual catalytic coupling, Suga and Ukaji reported a nickel-catalyzed cross-electrophile coupling of benzyl alcohols and aryl iodides that is promoted by a stoichiometric low-valent titanium reagent through homolytic C-O bond cleavage.9 While optimizing our Ni/Ti catalyzed cross-coupling of benzyl alcohols we found in control reactions that the coupling occurred in the

absence of titanium (Table 1, entry 2). Based on this result and Suga and Ukaji's overlapping study we choose to determine the generality of this nickel catalyzed deoxygenative cross-coupling. Initial optimization studies focused on coupling of 4methoxybenzyl alcohol with 4-bromotoluene while using titanocene dichloride as a co-catalyst (entry 1). Control reactions established, for this substrate combination, that the titanium catalyst was not needed, but the chlorotrimethylsilane (TMS-Cl) additive to turn over the titanium catalyst was essential. No coupling occurred in the absence of TMS-Cl (entry 3). Examination of the TMS-Cl concentration showed as little as 0.2 equivalents could be used to promote product formation (entry 4). Increasing the concentration to 1.5 equivalents (entry 5) dramatically improved the yield, but the maximal yield was obtained with 2.5 equivalents (entry 6). Standard screening of solvents, nickel salts, ligands, and metal reductants was performed, where it was found that two nickel catalysts efficiently promoted the coupling each in a separate solvent, Ni(phen)Cl<sub>2</sub> in DMA and Ni(di-OMe-bpy)Cl<sub>2</sub> in DMF (entry 6). For further studies, we opted to use the precomplexed Ni(phen)Cl<sub>2</sub> for consistency, even though NiCl<sub>2</sub>•glyme plus phenanthroline (entry 5) afforded similar results, and because phenanthroline is more cost effective than 4,4'-dimethoxy-2,2'bipyridine. Mono and bidentate phosphine ligands, along with carbene ligands were ineffective. It was found that a slight excess of 4-methoxybenzyl alcohol to 4-bromotoluene produced the highest yield versus a 1 to 1 ratio or a slight excess of the arylbromide (entry 10). This is in part do to with electron neutral and rich aryl bromides homocoupling of the 4-methoxybenzyl alcohol occurred in the background to a minor extent.

To establish the scope of the coupling reaction under the optimized conditions we first varied the aryl bromide component (Table 2, 1-17). Both electron donating and withdrawing groups were tolerated in the meta and para positions, whereas ortho

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bromonaphthalene (2) afforded the desired product. The system demonstrated good chemoselectivity with substituted aryl bromides tolerating halogens (9-10), silyl ethers (5), esters (7 & 13), amides (6), sulfonamides (17), nitriles (12), ketones (14), furans (15), thiophenes (16), and indoles (17). Additionally, a chloride<sup>12</sup> (9), triflate (8), and pivalate ester (7) were also tolerated leaving a handle for iterative cross-couplings. For aryl bromides containing electron withdrawing groups, homocoupling became competitive. To address this the equivalences of the coupling partners were flipped to using an excess (2 equivalence) of the aryl bromide. Variation of the benzyl alcohol was conducted next, where movement of the methoxy group (18-20) from the para position resulted in lower yields with meta (19) being the lowest. The methoxy group could be replaced with a dimethylamine (21) but was lower yielding potentially due to the amine reacting with the TMS-Cl. Electron deficient benzyl alcohols (22, EWG = F, CF<sub>3</sub>, and  $CO_2Me$ ) were found to be completely unreactive.

Table 1. Optimization and control reactions

OH + OMe 1.5 equiv	Srol% Ni(phen)Cl <sub>2</sub> 2.5 equiv TMS-Cl 2 equiv Mn DMA, r.t., 12 h 1.0 equiv	Me
Entry	Deviation from above	%Yield <sup>a</sup>
1	+ 10 mol% Cp <sub>2</sub> TiCl <sub>2</sub>	97
2	none	96
3	No TMS-Cl	0 <sup>b</sup>
4	0.2 equiv TMS-Cl	25
5	1.5 equiv TMS-Cl	82
6°	NiCl₂•dme + phen	99
7°	NiCl₂●dme + di-OMe-bpy in DMF	95
8	1 equiv Mn	42
9	Zn instead of Mn	62
10	1 equiv PMB-OH & 1.5 equiv 4-MeAr-Br	42

a) Isolated yield after flash chromatography, run on a 0.5 mmol scale

b) %conversion by GC/MS

c) 10 mol% nickel source + 10 mol% ligand

Based on the trend with the methoxy group (meta < ortho < para), it was questioned if further activation of the C-O bond would enable the coupling of electron deficient benzyl alcohols. To accomplish this, it was reasoned that modifying the alcohol to a 1-arylprop-2-en-1-ol, a secondary benzyl allyl alcohol, would weaken the C-O bond facilitating coupling of benzyl alcohols that would otherwise be unreactive. The premise for this modification was further supported by a recent dual Ni/Zr catalytic system that directly cross-coupled allylic alcohols.13 It had already been determined that simple benzyl alcohol was not a competent coupling partner with less than 10% conversion to product (Table 4, entry 3). As such, to test the feasibility of this activation we initially reacted 1-phenylprop-2-en-1-ol to the conditions, where this activated alcohol was fully consumed affording 23 in 65% (Table 3). This modification increased the yield for ortho substituted substrates (Table 2, 18 vs Table 3, 24), and enabled the coupling of benzyl alcohols containing electron withdrawing groups (25-27). The reaction was regioselective favoring bond formation at the least substituted carbon of the 1Table 2. Substrate scope of nickel-catalyzed benzyl alcohol cross-coupling<sup>a,b</sup>



a) Conditions: benzyl alcohol (0.75 mmol), aryl bromide (0.5 mmol), Ni(phen)Cl<sub>2</sub> (0.025 mmol), TMS-Cl (1.25 mmol), Mn (1.0 mmol) in 2 mL of DMA, at r.t. for 12 hours.

b) isolated yields after flash chromatography

c) isolated as an inseparable mixture with 1,2-bis(4-methoxyphenyl)ethane

d) 0.5 mmol benzyl alcohol to 1.0 mmol aryl bromides was used.

e) yield determined by GC/MS with internal standard

Control reactions were run to gain further insight into the mechanism of this coupling. It has been established that nickel can undergo oxidative addition into benzyl ethers.<sup>4</sup> As TMS-Cl is

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occurring through a silyl ether. Subjection of the silyl protected PMB-OH to the reaction conditions with and without added chlorotrimethylsilane afforded none of the product (Scheme 3). Additionally, only trace amounts of the silvl ether were seen by GC/MS when monitoring the couplings. It is established that chlorotrimethylsilane can convert benzyl alcohols to benzyl chlorides, as such, we investigated the potential of TMS-Cl to convert the alcohol to a chloride under our reaction conditions.<sup>14</sup> We saw full conversion of 4-methoxybenzyl alcohol, 4methylbenzyl alcohol, and benzyl alcohol to the benzyl chlorides with 1.5 equivalents of TMS-Cl in DMA (Scheme 2). To further examine the possibility that the coupling was occurring through an in situ generated benzyl chloride we subjected a variety of benzyl chlorides to the reaction conditions (Table 3). A similar trend was seen where electron rich benzyl chlorides coupled (entry 1) but electron deficient ones were unreactive (entries 4 & 5). The discrepancy occurs in entries 2 and 3, where 4methylbenzyl chloride and benzyl chloride efficiently coupled but there alcohol counter parts afforded less than 10% of the product. Additionally, when the coupling of these alcohols was monitored by GC/MS the resultant benzyl chlorides were not detected and the alcohols were isolated back (>80%). These results indicate that, in the presence of the nickel catalyst and manganese metal, the TMS-Cl is not converting the alcohol to a chloride. Nickel catalyzed cross-electrophile couplings have been shown to occur through radical intermediates, as such the coupling was performed in the presence of 1 equivalent of TEMPO (Table 5, entry 1) which inhibited the reaction indicating the possibility of radical intermediates. It has been demonstrated that zinc metal in DMA can convert benzyl chlorides to benzyl radicals.15 To examine if this was occurring the coupling was setup in the absence of the nickel catalyst, with and without 1 equivalent of TEMPO (Table 5, entries 2 & 3). As expected, in both cases none of the product was formed. Examination of these reaction mixtures by GC/MS did not show the presence of any of the anticipated radical coupling byproducts. More detailed mechanistic studies are needed to gain a better picture.

Table 3. Cross-coupling benzyl allyl alcohols with aryl bromides<sup>a,b</sup>



Ni(pnen)Cl<sub>2</sub> (0.025 mmol), 11vi5-Cl (1.25 mmol), ivin (1.0 mmol) in 2 mL of DMA, at r.t. for 12 hours.

b) isolated yields after flash chromatography.

c) E:Z = 88:12, linear:branched = >95:5

d) E:Z = >95:5, linear:branched = >95:5

e) E:Z = >95:5, linear:branched = 87:13



Scheme 1. Control reactions to probe if a silyl ether is the active cross-coupling partner



Scheme 2. Examination of the reaction conditions to generate a benzyl chloride from the alcohol

Table 4. Comparison of benzyl alcohols versus benzyl chlorides <sup>a,b</sup>

×	+ + Mo Mo Mo Mo Mo Mo Mo Mo	6 Ni(phen)Cl <sub>2</sub> quiv TMS-Cl equiv Mn A, r.t., 12 h	R	Me
к 1.5 equiv	we		1, 20	-31
Entry	R	X = OH	X = C1 c	Product ID
1	OMe	96%	95%	1
2	Me	<10%	93% <sup>d</sup>	28
3	Н	<10%	94%	29
4	CO <sub>2</sub> Me	0%	0%	30
5	CF <sub>3</sub>	0%	0%	31

- a) 0.5 mmol scale
- b) isolated yields after flash chromatography
- c) No TMS-Cl was used
- d) isolated as an inseparable mixture with 1,2-di-p-tolylethane

able 5. Radical scavenging experiments with TEMPO

	Br x mol% Ni(phen 2.5 equiv TMS	)Cl <sub>2</sub> -Cl	EMPO
• + OMe 1.5 equiv	Me 2 equiv Mn x equiv TEMP DMA, r.t., 12	O → MeO	Me
Entry	x mol% Ni(phen)Cl <sub>2</sub>	x equiv TEMPO	%Yield
1	5	1	<4%
2	0	1	0
3	0	0	0

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Ni/Ti cross-coupling of benzyl alcohols is was found that chlorotrimethylsilane promotes the nickel catalyzed deoxygenative cross-coupling of methoxy substituted benzyl alcohols at room temperature. The system tolerated a variety of functionalized aryl bromides, affording diarylmethanes in 44% to 99%. Expansion of the alcohol coupling partner was achieved by modifying the alcohol to a secondary benzyl allyl alcohol affording 1,3-diarylpropenes with good selectivity.

### **General Procedure**

In an argon filled glovebox an oven dried 10-20 mL microwave vial was charged with Ni(phen)Cl<sub>2</sub> (0.025 mmol, 0.008 g) and -325 mesh manganese powder (1 mmol, 0.055 g). The vial was sealed with a septa crimp cap and removed from the glove box. To the vial was sequentially injected aryl bromide (0.5 mmol), benzyl alcohol (0.75 mmol), and TMS-Cl (1.25 mmol, 0.159 mL).<sup>16</sup> The mixture was stirred for 5 minutes followed by the injection of degassed DMA (2 mL) and stirring the reaction for 12 hours at room temperature. The reaction mixture was poured into a separatory funnel containing water, which was

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#### **Supplementary Material**

<sup>1</sup>H and <sup>13</sup>C NMR spectra for all products (PDF).

### **References and notes**

# **Declaration of interests**

 $\boxtimes$  The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

□The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

were washed with water then brine, dried over magnesium sulfate, filtered, and concentrated down. The crude material was purified by flash chromatography.

Note – For compound 1, the coupling was setup outside of the glovebox, with all reagents weighed out on a bench top and the reaction placed under an argon atmosphere through three vacuum-purge cycles. This afforded the desired product in only a slight diminished yield, 91% vs. 99%

1.

2.

- The direct nickel catalyzed cross-coupling of benzyl alcohols
- Cross-electrophile coupling of aryl bromides with benzyl alcohols under mild conditions
- 3) Synthesis of diarylmethanes and 1,3diarylpropenes from alcohols

# **Graphical Abstract**

# Nickel catalyzed deoxygenative crosscoupling of benzyl alcohols with arylbromides

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<sup>16</sup> When the TMS<sup>2</sup> Clewily TMS<sup>2</sup> Cl<sup>1</sup> last, after DMA TMS profective the next accord was obtained R<sup>1</sup> addition, only the -R<sup>2</sup> DMA, r.t., 12 h

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