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Nickel-Catalyzed Reductive Cross-Coupling of Benzyl Chlorides with Aryl Chlorides/Fluorides: A One-Pot Synthesis of Diarylmethanes

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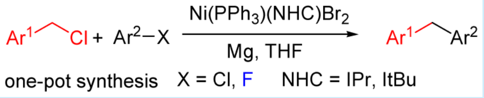
S *Supporting Information*

ABSTRACT: The first nickel-catalyzed, magnesium-mediated reductive cross-coupling between benzyl chlorides and aryl chlorides or fluorides is reported. A variety of diarylmethanes can be prepared in good to excellent yields in a one-pot manner using easy-to-access mixed PPh_3/NHC Ni(II) complexes of $Ni(PPh_3)(NHC)Br_2$ (NHC = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene, IPr, **1a**; 1,3-di-*tert*-butylimidazol-2-ylidene, ItBu, **1b**) as catalyst precursors. Activation of polychloroarenes or chemoselective cross-coupling based on the difference in catalytic activity between **1a** and **1b** is used to construct *oligo*-diarylmethane motifs.



Transition-metal-catalyzed Grignard cross-coupling reactions have been developed over the past few decades to become some of the most powerful tools for C–C bond formation in organic synthesis.[1] In particular, versatile copper-,[2] palladium-,[3] nickel-,[4] and iron[5]-catalyzed cross-couplings of aryl Grignard reagents with benzylic electrophiles or vice versa have been applied for the synthesis of diarylmethanes. Diarylmethanes are important structural motifs of several classes of functional molecules such as pharmaceuticals, drugs, and dyes[6] and are frequently found as subunits in supramolecules.[7] The use of Grignard reactions in syntheses traditionally requires the presynthesis of Grignard reagents as nucleophiles. Despite their synthetic advantages (i.e., ready availability, relatively low cost, and being environmentally benign[8]), the direct use of stoichiometric amounts of Grignard reagents is constrained by the safe processing and cost-efficiency of these inherently moisture-sensitive and hazardous compounds. These issues often hamper their application for large-scale reactions. The development of alternative protocols for the synthesis of diarylmethanes that obviate the need for the presynthesis and intricate handling of stoichiometric amounts of Grignard reagents is of great interest.

Recent developments of the reductive cross-coupling reactions between two stable electrophiles offer an attractive alternative strategy to Grignard reactions.[9] In this context, the first reductive cross-coupling of aryl bromides with alkyl bromides was reported by Jacobi von Wangelin et al.[10a] using stoichiometric amounts of magnesium turnings as the reductant and a catalytic system of $FeCl_3$/*N,N,N′,N′*-tetramethylethylenediamine. Jacobi von Wangelin's group also discovered that $CoCl_2$/*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane is catalytically capable of the same reductive cross-coupling.[10b] Both reactions featured the in situ generation of Grignard reagents and exhibited high selectivity for the cross-coupling product in a one-pot synthesis, lowering hazard potential and cost while simplifying the process operations. Very recently, we have described the extension of this intermolecular reductive cross-coupling to an intramolecular version.[10d] Copper-catalyzed couplings of aryl bromides with alkyl tosylates or mesylates are also notable examples of magnesium-mediated cross-couplings.[10c] While these reactions are efficient for aryl–alkyl couplings, their expansion to the selective one-pot coupling between benzyl and aryl halides remains challenging because of homocoupling of the benzyl halides.[10c,d] Thus, catalytic systems with improved cross-coupling selectivity are in high demand to broaden the scope of these reactions for the successful formation of diarylmethanes.[11]

Substantial advances have been made over the past five years in nickel-catalyzed reductive cross-coupling reactions between aryl and alkyl electrophiles with manganese or zinc as a reductant.[12] Surprisingly, until now, only two papers report the use of this approach for the synthesis of diarylmethanes. Peng et al.[12g] reported the coupling of benzyl bromide with 4-iodoanisole using a catalytic mixture of Zn/$NiCl_2$/pyridine/ethyl crotonate. Weix et al.[12l] showed that the use of Zn/$NiBr_2 \cdot 3H_2O$/bipyridine in combination with a cobalt cocatalyst (cobalt phthalocyanine) promoted the coupling of benzyl mesylates with aryl iodides or bromides. However, applying the latter catalytic system to the coupling of benzyl bromides with aryl halides resulted primarily in the formation of bibenzyl. Undertaking this cross-coupling reaction with a nickel–based catalyst and a magnesium reductant has not been reported to date. Furthermore, to the best of our knowledge, nickel-catalyzed magnesium-mediated reductive cross-coupling reactions remain poorly explored.[9c]

We recently described the easy synthesis of mixed phosphine/*N*-heterocyclic carbene (NHC) Ni(II) complexes, i.e., $Ni(PPh_3)(IPr)Br_2$ (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, **1a**) and $Ni(PPh_3)(ItBu)Br_2$ (ItBu = 1,3-di-*tert*-butylimidazol-2-ylidene, **1b**) (Scheme 1), via controlled ligand substitution reactions of easily obtainable Ni(II) complexes

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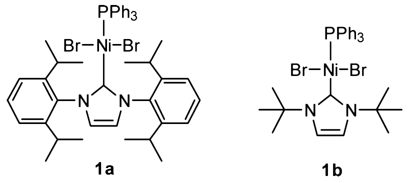
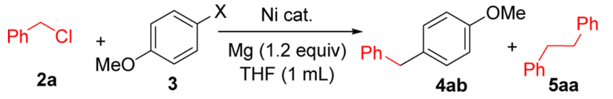
Scheme 1. Mixed Phosphine/NHC Ni(II) Complexes



$[NEt_4][Ni(PPh_3)X_3]$. We demonstrated the efficient application of **1a** and **1b** as catalyst precursors for the cross-coupling between aryl Grignard reagents and aryl chlorides or fluorides.[13f] We continue our studies[13] by reporting herein the application of **1a** and **1b** to the synthesis of diarylmethanes using readily available and low-cost benzyl chlorides and aryl chlorides or fluorides with reductive magnesium in a simple one-pot procedure. To the best of our knowledge, this is the first example of a nickel-catalyzed reductive cross-coupling of two organohalides using magnesium turnings as the reductant.

We began our study by examining the reductive cross-coupling reaction of benzyl chloride (**2a**) and 4-chloroanisole (**3b**) with catalytic **1a** or **1b** and reductive magnesium turnings. These initial experiments revealed extremely high selectivity for the desired products (Table 1). In the presence of 2 mol % of **1a** loading and 1.2 equiv of magnesium turnings, the desired product **4ab** was obtained in almost quantitative yield, with only a trace amount of homocoupling byproduct **5aa** observed (Table 1, entry 1). Lowering the loading of **1a** to 1 mol % still gave a high yield of **4ab** (98%) but required an extended reaction time (1 h) to reach reaction completion (entry 3). The reaction was also catalyzed by **1b**, giving **4ab** in 99% yield with 2 mol % catalyst loading and 1 h reaction time (entry 2). The catalytic activity of **1b** dropped dramatically when the dosage was lowered to 1 mol % to give 8% yield of **4ab** (entry 4).[14]

Table 1. Ni-Catalyzed Reductive Cross-Coupling of $C_6H_5CH_2Cl$ with 4-$MeOC_6H_4X$[a]



entry	X	cat. (mol %)	reductant	time[b] (h)	yield **4ab**/**5aa** (%)
1	Cl	**1a** (2)	Mg	0.5[b]	99 (95[c])/3
2	Cl	**1b** (2)	Mg	1	99/3
3	Cl	**1a** (1)	Mg	1	98/3
4	Cl	**1b** (1)	Mg	1	8/3
5	Cl	**1a** (2)	Zn	12[d]	9/24
6	Cl	**1a** (2)	Mn	12[b]	0/3
7	Cl	**1a** (2)	Mn	12[d]	15/27
8	F	**1a** (2)	Mg	9[b]	22/4
9	F	**1b** (2)	Mg	9[b]	99 (96[c])/3

[a] Reaction conditions: **2a** (0.6 mmol), **3** (0.5 mmol), magnesium turnings (0.6 mmol), THF (1.0 mL), 10 min at 0 °C, then 1 h at 25 °C, GC yields using *n*-dodecane as an internal standard. [b] At 25 °C. [c] Isolated yield. [d] At 45 °C.

Replacing magnesium turnings with widely used zinc dust or magnesium powder resulted in the primary formation of the homocoupling byproduct **5aa** with a 2 mol % loading of **1a** (entries 5−7). These results are similar to those previously reported with a nickel/cobalt cocatalytic system.[12b] The different selectivity of these reactions indicates that magnesium turnings are a reductant worthy of further investigation in nickel-catalyzed reductive cross-couplings.

The increasing attention given to transition-metal-catalyzed activation and transformation of C−F bonds[15] captivated our interest as to whether **1a** and **1b** could activate an aryl C−F bond in the reaction shown in Table 1. Aryl fluorides have been little involved in nickel-catalyzed reductive cross-coupling reactions.[16] The coupling of **2a** and 4-fluoroanisole was effectively promoted by a 2 mol % loading of **1b**, resulting in the desired product **4ab** in an almost quantitative yield (entry 9). The IPr-based analogue **1a** exhibited poor activity and furnished merely a 22% yield of **4ab** under the same conditions (entry 8). The reason for the difference in catalytic behavior between **1a** and **1b** is not apparent.[17]

The one-pot protocol proved to have quite broad generality, and a variety of diarylmethanes were easily synthesized from benzyl chlorides and aryl chlorides or fluorides (Scheme 2). Effective coupling of 4-methoxybenzyl chloride with different aryl chlorides or fluorides bearing a range of electron-donating groups or electron-withdrawing groups afforded the corresponding products with yields from 89% to 95% (**4ba−bf**). It is worth noting that 1,4-difluorobenzene and its 1,2-derivative and 1-fluoro-4-(trifluoromethyl)benzene can be selectively monofunctionalized via a sp^2 C−F bond activation using **1a** as a catalyst, affording fluorinated diarylmethanes **4bd**, **4bd′**, and **4be** in 81%−92% yields. The reaction of sterically hindered aryl chlorides did not result in lower product yields (**4bf**, **4bg**, and **4cg**). Highly hindered 2,4,6-trimethylbenzyl chloride provided the desired product **4dg** in 78% yield when subjected to a longer reaction time. Both electron-rich and electron-poor benzyl chlorides react smoothly with comparable yields of the desired diarylmethanes **4bb**, **4eb**, **4fb**, and **4gb**, respectively. These results are quite similar to those reported previously for a palladium-catalyzed, zinc-mediated approach.[18] Notably, a number of functional groups on the coupling partners survived, including vinyl (**4bh**), amine (**4aj**), ketal (**4ak**), ester (**4al**), and even ketone groups (**4am**).[19] Moreover, 2-chloronaphthalene or its fluoro analogue, *N*-methyl-6-chloroindole, 2-chlorothiophene, 2-chloropyridine, 2-chloro-5-methoxypyridine, 5-chloro-3-methylbenzothiophene, and *N*-ethyl-3,6-dichlorocarbazole are suitable reactants, affording the desired products (**4ai**, **4an**, **4fn**, **4bo**, **4bp**, **4aq**, **4br**, and **4as**, respectively) in 40−98% yields. A 50 mmol scale reaction of 2-chloronaphthalene gave a yield similar to that of the smaller scale experiment, producing **4ai** in 90% yield.

The present scope was further extended to the reaction of polychloroarenes such as 1,3-dichloro-5-methoxybenzene and 1,3,5-trichlorobenzene. As far as we are aware, such substrates have not been coupling partners in nickel-catalyzed reductive cross-couplings. The precursor of naturally occurring 2,4-bis(4-hydroxybenzyl)phenol,[20] **4bt**, was obtained in 80% yield, and **4bu**, which can be used to synthesize hexacata-hexabenzocoronenes,[21] was isolated in 71% yield using enhanced conditions. These results show the potential of this protocol in polyfunctionalization syntheses because the sp^2 C−OMe bond survives the reaction and can further undergo cross-coupling with different nucleophilic reagents.[4c,d]

The difference in catalytic activity between **1a** and **1b** was used to chemoselectively activate the sp^2 C−Cl bond or the sp^2 C−F bond on aryl halides to construct *oligo*-diarylmethane structures in the *para* (**4bd** and **4abd**), *meta* (**4gb** and **4agb**), and *ortho* (**4bd′** and **4abd′**) positions (Scheme 3).

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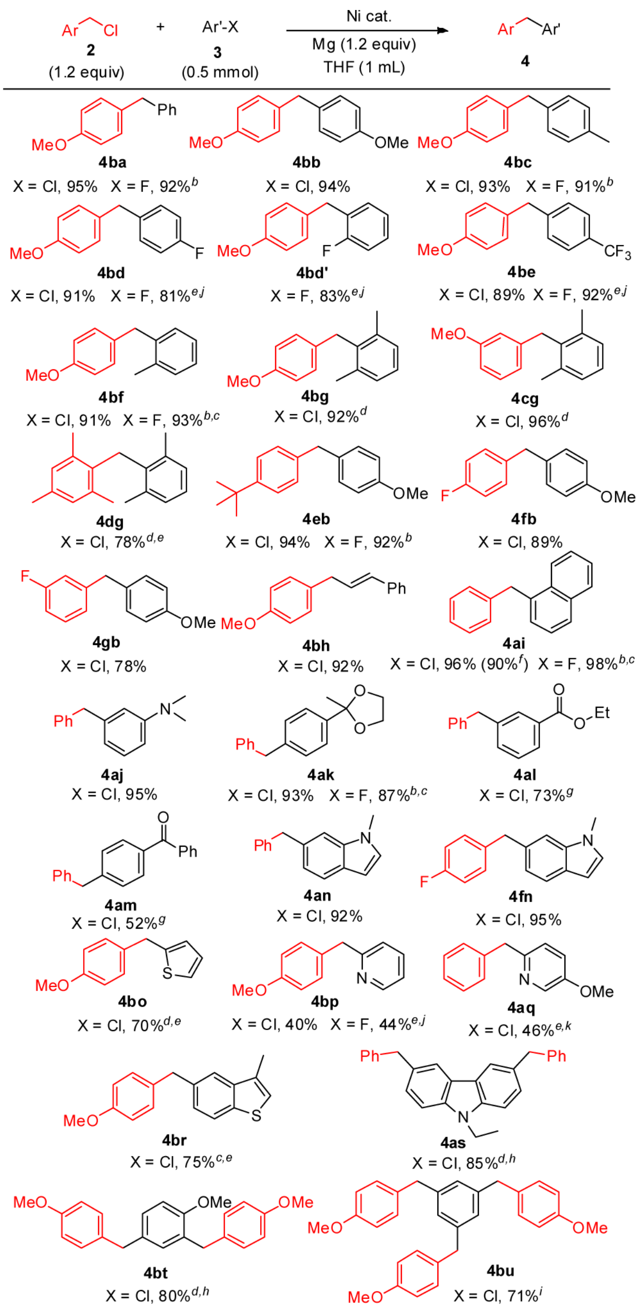
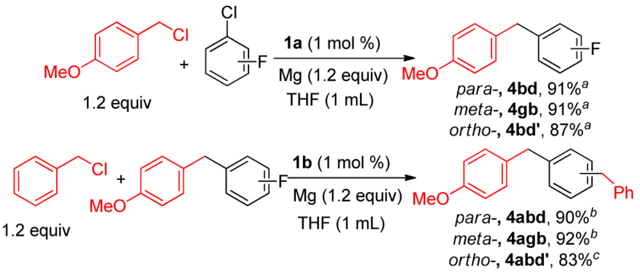
Scheme 2. Representative Benzyl–Aryl Couplings[a]



[a] Reaction conditions: benzyl chloride (0.6 mmol), aryl halide (0.5 mmol), magnesium turnings (0.6 mmol), **1a** (1 mol %), THF (1 mL), 10 min at 0 °C, then 1 h at 25 °C, isolated yields. [b] **1b** (2 mol %) instead of **1a**, 12 h at 25 °C. [c] 12 h at 35 °C. [d] 8 h at 25 °C. [e] **1a** (2 mol %). [f] 50 mmol scale. [g] **1a** (3 mol %), benzyl chloride (0.7 mmol), $ZnCl_2$ (0.7 mmol), LiCl (0.8 mmol), magnesium turnings (0.75 mmol), THF (2.5 mL), 1 h at 0 °C, then 24 h at 35 °C. [h] **1a** (2 mol %), benzyl chloride (1.2 mmol), magnesium turnings (1.2 mmol), THF (2.0 mL). [i] **1a** (3 mol %), benzyl chloride (1.8 mmol), magnesium turnings (1.80 mmol), THF (5.0 mL), 20 min at 0 °C, then 8 h at 35 °C. [j] 12 h at 25 °C. [k] THF (2.0 mL), 3 h.

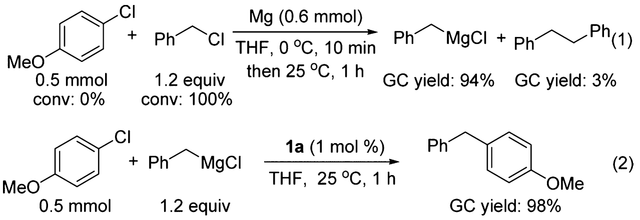
Our current experimental investigations (Scheme 4, eqs 1 and 2) suggest that the reaction proceeds by initial in situ generation of a benzyl Grignard reagent, which then couples with the aryl halide catalyzed by **1a** or **1b** through a catalytic cycle involving oxidative addition, transmetalation, and reductive elimination.

Scheme 3. Chemoselective Benzyl–Aryl Cross-Coupling Strategy To Synthesize *oligo*-Diarylmethanes



[a] Reaction conditions: benzyl chloride (0.6 mmol), aryl halide (0.5 mmol), Mg turnings (0.60 mmol), **1a** (1 mol %), THF (1 mL), 10 min at 0 °C, then 1 h at 25 °C, isolated yield, [b] **1b** (2 mol %), 9 h at 25 °C, [c] **1b** (2 mol %), 24 h at 45 °C.

Scheme 4. Reactions Relevant to Mechanism



This hypothetical mechanism closely resembles the magnesium-mediated reductive cross-coupling reactions using iron(III)[10a,b,d] or copper(I) catalysts.[10c] In considering that a metathesis reaction of **1a** or **1b** may take place to form bisphosphine and biscarbene Ni (II) complexes,[22] respectively, the reductive cross-coupling reaction of benzyl chloride (**2a**) and 4-chloroanisole (**3b**) with 1 mol % of $Ni(PPh_3)_2Br_2$ or $Ni(IPr)_2Br_2$ was conducted under the conditions shown in Table 1. It is noteworthy that each of the two Ni(II) complexes showed very low catalytic activity, affording the desired product in merely 27% and 10% yields, respectively. These results indicate that there is a possibly synergic effect between the two kinds of ligands on the catalytic active nickel species. However, establishing a detailed mechanism requires further investigation.

In summary, our process is the first nickel-catalyzed, magnesium-mediated reductive cross-coupling reaction for the direct synthesis of diarylmethanes using stable, low-cost, and widely available benzyl chlorides and aryl chlorides or inert aryl fluorides in place of traditional Grignard reagents. Our one-pot procedure utilizes catalytic amounts of a mixed PPh_3/NHC Ni(II) complex **1a** or **1b** and stoichiometric amounts of magnesium turnings to cross-couple two organohalides in a highly selective manner, avoiding the homocoupling of benzyl chlorides and the presynthesis and handling of stoichiometric amounts of sensitive Grignard reagents. Our reaction is a practical protocol to synthesize a wide variety of diarylmethanes. Very efficient chemoselective reductive cross-couplings were developed to construct *oligo*-diarylmethane structures by exploiting the difference in catalytic activity between **1a** and **1b**. The present study shows the great potential of nickel-catalyzed, magnesium-mediated reductive cross-coupling in C–C bond formation. Further investigation to extend this method to other substrates and a detailed mechanistic study are ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Detailed experimental procedures and details pertaining to the characterization of the products (PDF)

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Notes

The authors declare no competing financial interest.

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(14) The extremely low yield of the corresponding product with 1 mol % loading of **1b** might be because of the relatively instability of **1b** in THF solution compared with that of **1a**; see ref 13f.

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(17) In the presence of a 2 mol % loading of **1b**, time−yield plots illustrate that the induction period for the coupling of benzyl chloride with 4-chloroanisole was twice as long as that observed with **1a**. On the contrary, the induction time of **1b** for the coupling of 4-floroanisole is much shorter than that of **1a**, resulting in a relatively fast reaction. See the Supporting Information.

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