JOC*Note*

Palladium-Catalyzed Cross-Coupling Reactions of Benzyl Indium Reagents with Aryl Iodides

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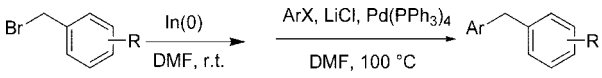

Herein described is an operationally simple procedure for generating benzyl indium species from readily available benzyl bromides and indium metal followed by *in situ* palladium-catalyzed coupling with aryl halides. The procedure provides diarylmethanes in modest to excellent yield and tolerates a variety of functional groups in both coupling partners.

As part of a drug discovery program, we required diarylmethanes as synthetic intermediates. We sought a simple procedure with broad functional-group compatibility. Our goal was to have a method that was compatible with parallel-synthesis techniques, tolerant of most functional groups, and avoided using highly reactive organometallic intermediates. In particular, our synthetic targets had to contain an ester or nitro group on one of the aryl rings.

To the best of our knowledge, there are three useful methods for making diarylmethanes: (1) reduction of diarylketones or diarylcarbinols; (2) Friedel−Crafts alkylation; and (3) transition-metal-catalyzed couplings of either a benzyl halide with an aryl metal species or an aryl halide with a benzyl metal species. Reduction protocols do not address the carbon−carbon bond formation, often require the presence of electron-rich aromatic rings, and lack the broad functional-group compatibility we required. While hydride donors are the typical reductants, recently Provot and co-workers[1] described a high-yield disproportionation reaction of diarylmethylisopropyl ethers under acid catalysis. The authors demonstrated the selective reduction of a diarylcarbinol in the presence of a diaryl ketone. This method did not meet our criteria because the diarylcarbinols were formed from aryl Grignards or aryllithium intermediates. Recently, Roy reported a milder version of the Friedel−Crafts alkylation using benzyl alcohol to produce diarylmethanes. The authors described a bimetallic catalyst consisting of $[Ir(COD)Cl]_2$ and $SnCl_4$[2] that promotes the reaction of aldehydes with electron-rich benzenes. The resulting benzyl alcohol continues to react giving substituted diarylmethanes. The reaction worked best with electron-donating groups in the arene and electron-withdrawing groups in the aldehyde. We targeted compounds that would contain electron-withdrawing groups in both aromatic rings. Furthermore, we could not rely on classical directing-group effects to control regiochemistry due to the varying substitution patterns in our substrates.

Transition-metal catalysis has become a powerful tool for the formation of diarylmethanes from aryl zinc or aryl boronic acids. A recent report for coupling aryl zincs with benzyl halides showed excellent tolerance of functional groups on the aryl rings and on the benzylic position.[3] The only drawback to this method was the requirement for *in situ* zinc activation. The most promising methods for diarylmethane synthesis are the Suzuki−Miyaura-type couplings of benzylic halides,[4a] benzylic carbonates,[4] or benzylic phosphates.[4] These methods show excellent functional-group tolerance, proceed under mild conditions, and provide predictable connectivity regardless of the aryl substitution pattern. The only limitation is the availability of the desired aryl boronic acids. This limitation is rapidly fading as more aryl boronic acids become commercially available. [5] We sought a simple procedure that would take advantage of the many benzyl halides and aryl halides that are commercially available.

We chose to prepare a benzyl metal species from a benzyl halide and couple it with an aryl halide. Benzyl Grignard,[6a] benzyl zinc,[6b] or benzyl indium[6c] reagents can be coupled with aryl halides to provide diarylmethanes. Benzyl Grignards couple in high yields with aryl and heteroaryl iodides under copper catalysis. Unfortunately, sensitive functional groups are not compatible with these conditions. Organozinc and organoindium reagents are well-known for having excellent functional group compatibility, but these reagents are often prepared from more reactive benzyl metal species.[7] Knochel described the use of zinc dust and lithium chloride to generate reactive benzyl zinc chlorides directly from the benzyl chlorides.[6b] These organozinc reagents were used in a variety of palladium-catalyzed coupling reactions. Minehan described a lithium chloride-promoted insertion of indium into aryl halides that avoids using more

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(1) L'Hermite, N.; Giraud, A.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron* **2006**, *62*, 11994, and references cited therein.

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(5) A current SciFinder search shows 1797 commercially available phenylboronic acids.

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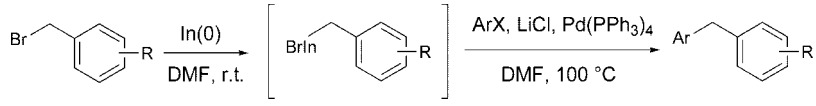
TABLE 1. Pd-Catalyzed Cross-Coupling Reactions of Aryl Halides with Benzyl Indiums derived from Benzyl Halides



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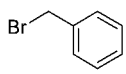
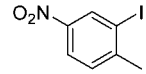
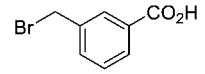
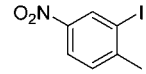
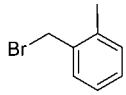
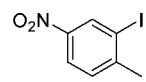
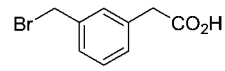
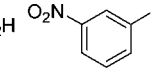
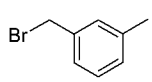
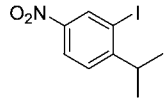
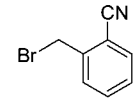
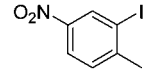
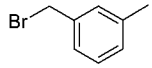
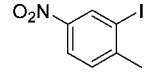
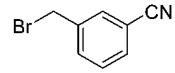
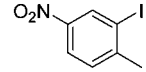
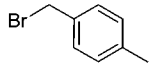
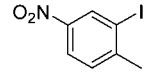
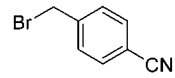
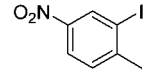
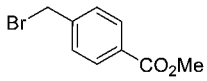
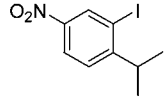
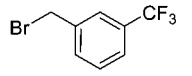
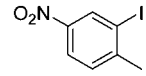
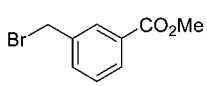
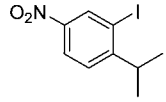
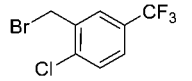
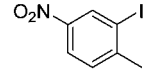
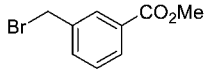
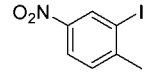
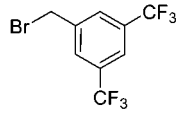
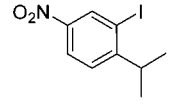
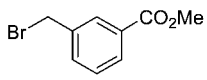
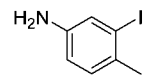
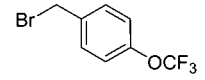
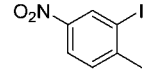
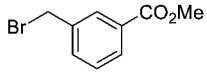
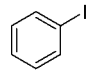
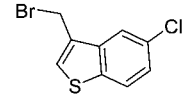
1			58%	13			43%
2			64%	14			63%
3			51%	15			59%
4			66%	16			57%
5			57%	17			23%
6			33%	18			85%
7			82%	19			87%
8			76%	20			93%
9			16%	21			81%
10			54%	22			39%
11			35%	23			9%
12			21%	24			0%

reactive organometallic precursors. The resulting aryl indium species react under palladium catalysis with a variety of electrophiles.[8]

To the best of our knowledge, diarylmethanes have not been prepared by the insertion of unactivated indium into a benzyl halide followed by palladium-catalyzed coupling. Here we report our results using unactivated indium metal in the absence of additives to generate benzyl indium species. Our simple procedure generates benzyl indium reagents containing ester, carboxylic acid, and cyano groups from readily available benzyl bromides. Palladium-catalyzed coupling with aryl halides produced diarylmethanes that contained the desired ester or nitro groups.

Our best results followed the procedure of Lee for the cross-coupling of allyl halides with aryl halides.[7a] In our adaptation of this procedure, unmodified, commercially available indium powder was added to a DMF solution of the desired benzyl halide. Disappearance of the benzyl halide was monitored by partitioning a reaction aliquot between diethyl ether and water followed by thin-layer chromatography of the diethyl ether portion. This analysis showed that the reaction was rapid and usually complete in less than 1 h. No precautions to exclude air or moisture were taken during the formation of the benzyl

(8) Papoian, V.; Minehan, T. *J. Org. Chem.* **2008**, *73*, 7376.

indium. After the benzyl halide was consumed, the reaction mixture was added to the remaining reactants under nitrogen and heated at 100 °C until the aryl halide was consumed, usually overnight. We did not attempt to modify or optimize the reaction when low yields were obtained. Also, we did not attempt to optimize the catalyst because of our initial success with tetrakis(triphenylphosphine)palladium(0). It should be noted that in the absence of any palladium catalyst no product was observed.

The examples in Table 1 show that a wide variety of functional groups are compatible with this procedure. For example, electron-withdrawing groups are tolerated in both partners as evidenced by the reaction of 2-iodo-4-nitrocymene and 3,5-bis(trifluoromethyl)benzyl bromide in 93% yield (entry 20). Electron-donating groups in the aryl halide tended to give modest yields (entries 9 and 11). The reaction was not sensitive to steric bulk in the aryl halide coupling partner. An isopropyl group in the aryl halide ortho position gave a range of yields from 33% to 93% (entries 3, 6, 7, and 20). The electron-rich *o*- and *m*-methoxy-substituted benzyl bromides failed to couple as did *p*-methoxybenzyl chloride (not shown). In contrast, *p*-trifluoromethoxybenzyl bromide, in which the electron-donating ability of the oxygen has been attenuated, reacted to provide the desired product in 81% yield (entry 21). The presence of a carboxylic acid resulted in slightly reduced yields compared to the parent ester (compare entries 10 and 13). The cross-coupling also worked when basic groups were present, but the yields were significantly reduced (entries 9 and 12), although in entry 12 the low yield may be due to the use of an aryl bromide instead of an aryl iodide as the electrophile. Surprisingly, para-substituted benzyl bromides consistently coupled in lower yields than their meta or ortho isomers. This reduced yield was particularly apparent for *p*-cyanobenzyl bromide, which cross-coupled in only 23% yield (entry 17). We identified several side products for this reaction that accounted for a portion of the starting materials. The homo-coupled aryl iodide (2,2′-dimethyl-4,4′-dinitrobiphenyl, 16% yield), reduced benzyl bromide (4-methylbenzonitrile, 4% yield), reduced aryl iodide (1-methyl-3-nitrobenzene, 8% yield), and recovered 1-iodo-2-methyl-4-nitrobenzene (2% yield) were isolated by chromatography on silica gel. The *o*- and *m*-cyanobenzyl bromides gave the desired products in 59% and 57% yield, respectively. Sulfur-containing heterocycles also cross-coupled, but in low yields (entries 22 and 23). A final limitation was the failure of α-methylbenzyl bromide to react under the standard conditions (entry 24) to give α-methyldiaryl-methane. In this instance, the benzyl bromide was consumed in the reaction with indium metal, but failed to couple with the iodobenzene. This failure was a surprising disappointment in light of the fact that sterics seemed to have little impact on the reaction when the bulky group was in the electrophile. Such α-methyldiarylmethanes have been prepared from the reaction of α-methylbenzyl chloride with an arylzinc by using $CoBr_2$ as the catalyst.[3]

In summary, a simple procedure for generating benzyl indium species from readily available benzyl bromides and indium metal followed by in situ palladium-catalyzed coupling with aryl halides was developed. The method compares favorably with existing methods in that it uses readily available starting materials, is compatible with a variety of functional groups, and is simple to perform. Many benzyl and aryl halides are commercially available or easily prepared. Access to these starting materials is an advantage for our method when the corresponding aryl boronic acids are unavailable, unstable, or expensive. We have shown that carboxylic acid, ester, cyano, and amino groups are compatible with the reaction conditions. The yields were highest when both coupling partners contained electron-withdrawing groups. This result compares well with the Friedel−Crafts alkylation where at least one partner must contain an electron-donating group. While the examples presented here are limited by our choice of medicinal chemistry targets, our method provided diarylmethanes containing a variety of functional groups in useful yields. The reaction is simple to perform because we prepared the benzyl indium intermediates without the use of more reactive benzyl metal intermediates. A detailed, general procedure is given in the Experimental Section.

Experimental Section

Representative Procedure for the Synthesis of (2-Methyl-5-nitrobenzyl)benzene (Table 1, Entry 1). To 5 mmol of benzyl bromide (855 mg, 5 mmol) in 5 mL of DMF was added indium (861 mg, 7.5 mmol). The reaction mixture was stirred at room temperature until the disappearance of starting material as assessed by TLC. To a separate flask were sequentially added 2-iodo-1-methyl-4-nitrobenzene (526 mg, 2 mmol), LiCl (170 mg, 4 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol), and the benzyl indium solution. Additional dimethylformamide (5 mL) was used to complete the transfer of the benzyl indium to the reaction. The resulting reaction mixture was placed under a nitrogen atmosphere and stirred at 100 °C until no starting aryl iodide was observed by TLC. After dilution with Et_2O (100 mL), the reaction mixture was washed with 3 N HCl (5 × 20 mL), water (3 × 20 mL), and brine (1 × 20 mL). The organic portion was dried over $MgSO_4$ and filtered, and the solvents were removed by rotary evaporation. Chromatography of the residue on SiO_2 with 1:3 ethyl acetate:hexanes provided the title compound (265 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.04 (s, 2H), 7.10 (d, 7.5 Hz, 2H), 7.20−7.25 (m, 1H), 7.27−7.31 (m, 3H), 7.99 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.2, 36.9, 121.7, 124.1, 126.7, 127.2, 129.2, 131.1, 131.2, 136.7, 136.8, 140.6, 145.0, 146.9. LC/MS 3.0 min. FAB HRMS calcd for $C_{14}H_{13}NO_2$ (M^+) 228.1024, found 228.1036.

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Supporting Information Available: Characterization data for all compounds and X-ray crystallography for entry 14 in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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