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Palladium-Catalyzed Cross-Coupling Reaction of Tricyclopropylbismuth with Aryl Halides and Triflates

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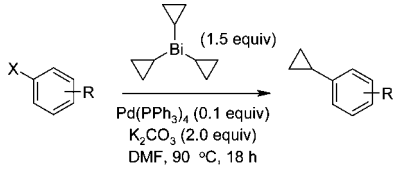

The palladium-catalyzed cross-coupling reaction of tricyclopropylbismuth with aryl and heterocyclic halides and triflates is reported. The reaction tolerates numerous functional groups and does not require anhydrous conditions. The method was successfully extended to the cross-coupling of triethylbismuth.

Cyclopropanes are commonly found in pharmaceutically active compounds since they provide unique structural and electronic properties.[1] In addition, cyclopropyl fragments are generally metabolically more stable toward microsomal oxidation than other aliphatic groups.[2,3] Consequently, cyclopropanes are often part of structure–activity relationship studies[2,4].

In the course of our ongoing medicinal chemistry programs, we required a simple, general, and expedient method to introduce unsubstituted cyclopropyl groups onto highly functionalized aryl and heteroaryl scaffolds. Historically, functionalized arylcyclopropanes were prepared by radical substitution on arenes using cyclopropyl radicals[5] or by halogenation of arylcyclopropanes followed by further derivatization.[6] More recently, arylcyclopropanes have been accessed via cyclopropanation of the corresponding vinylarenes under Simmons−Smith conditions[4b,7] or through the use of diazomethane,[4a,c] sulfonium ylides,[8] or ferrocenyl carbenes.[9] However, this approach necessitates the preparation of a styrenyl intermediate which is usually obtained from an aryl halide. For this reason, arylcyclopropanes are more commonly prepared directly from the corresponding halides via cross-coupling reactions with a cyclopropyl metal. However, cross-coupling of cyclopropylzinc halides under Negishi conditions[2,10] requires strict exclusion of water, whereas the use of cyclopropylmagnesium bromide in a Kumada-type coupling[4e,11] precludes the presence of numerous functional groups. Further, due to the lack of reactivity, the Stille coupling of cyclopropyltin reagents has been utilized only in limited cases.[12] Recently, the transfer of unsubstituted cyclopropyl units has been efficiently achieved through Suzuki coupling employing cyclopropylboronic acid,[13] but no reaction was observed with aryl triflates. Finally, the cross-coupling of tricyclopropylindium has also allowed the transfer of unsubstituted cyclopropyl fragments on arenes, but the reagent has to be prepared in situ and used as a stock solution.[14]

The chemistry of organobismuth reagents has found wide application in numerous C−C, C−O, and C−N bond-forming reactions, in part due to the low toxicity of bismuth salts.[15] Although the palladium-catalyzed cross-coupling reaction of triarylbismuth reagents has been extensively documented,[16]

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(14) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.

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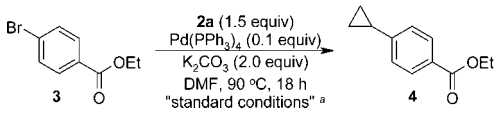
TABLE 1. Optimization of the Palladium-Catalyzed Cross-Coupling Reaction Conditions Using Tricyclopropylbismuth 2a

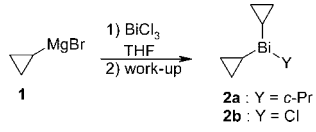


entry	change from "standard conditions"	isolated yield of **4** (%)
1	no change[b]	80
2	toluene instead of DMF, 100 °C	63
3	Na_2CO_3 instead of K_2CO_3	83
4	K_3PO_4 instead of K_2CO_3	80
5	No K_2CO_3	39
6	$PdCl_2$(dppf) instead of $Pd(PPh_3)_4$	65
7	$Pd(PPh_3)_4$ 0.05 equiv instead of 0.1 equiv	77
8	H_2O (5.0 equiv) added	82
9	reagent **2a** generated in situ (1.0 equiv)[21]	89
10	reagent **2a** generated in situ (0.50 equiv)	70

[a] Standard conditions: ethyl 4-bromobenzoate **3** (0.30 mmol), reagent **2a** (1.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), K_2CO_3 (2.0 equiv), DMF (3 mL, 0.1 M), degassed solution, 90 °C (oil bath temperature), 18 h. [b] The number of equivalents for **2a** was calculated assuming that pure reagent is used.

surprisingly, *no report could be found for the corresponding coupling of trialkylbismuth reagents*.[17] Based on the fact that cyclopropyl carbons have a partial sp^2 character,[18] we hypothesized that tricyclopropylbismuth could undergo palladium-catalyzed cross-coupling reaction with aryl halides, similarly to triarylbismuth reagents, allowing access to arylcyclopropanes.

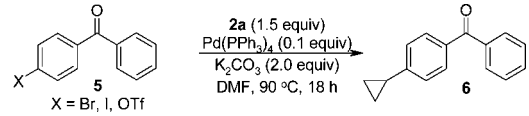
We recently reported the synthesis of tricyclopropylbismuth and its use in the direct *N*-cyclopropylation of azoles and cyclic amides.[19] Tricyclopropylbismuth **2a** is easily prepared by the addition of commercially available cyclopropyl magnesium bromide **1** to bismuth chloride (eq 1). The presence of chloro derivative **2b** was suspected based on elemental analysis and neutronic activation of the crude reagent. We report herein our studies in the palladium-catalyzed cross-coupling reaction of tricyclopropylbismuth with aryl and heteroaryl halides and triflates.



(1)

Utilizing ethyl 4-bromobenzoate **3** as a test substrate, we explored the reactivity of reagent **2a** in the context of palladium-catalyzed cross-coupling reaction (Table 1). In the event, the desired product **4** was obtained in 80% isolated yield using standard conditions for cross-coupling reactions (entry 1). Optimization of the reaction protocol showed that other solvents such as toluene gave lower yields of the desired product (entry 2) and that the base could be replaced by sodium carbonate (entry 3) or potassium phosphate (entry 4). Interestingly, the reaction proceeded even in the absence of base (entry 5), although at much lower efficiency. Changing the catalyst for dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) resulted in a considerable decrease in the yield of the reaction (entry 6), whereas reducing the catalyst loading to 5 mol % had no impact on the efficiency of the transformation (entry 7). The presence of ca. 5.0 equiv of water had no consequence on the outcome of the reaction (entry 8), showing that strict exclusion of moisture is unnecessary. Although we chose to pursue our studies with isolated crude tricyclopropylbismuth, we demonstrated that the use of 1.0 equiv of reagent **2a** generated in situ leads to excellent yield of coupling product **4** (entry 9).[20] In order to address the ability of the second cyclopropyl group to transfer, 0.50 equivalent of reagent was used (entry 10). The result indicates that more than one cyclopropyl group is transferred in the course of the reaction but also suggests that the reactivity of the second cyclopropyl group is slightly lower than the first one.

TABLE 2. Impact of the Nature of the Halogen on the Outcome of the Cross-Coupling Reaction with Tricyclopropylbismuth 2a



entry	X	isolated yield of **6** (%)
1	**5a**, OTf	66
2	**5b**, Br	73
3	**5c**, I	79

Aryl triflates are an important class of electrophiles in palladium-catalyzed cross-coupling reactions due to their ease of preparation from phenols. Therefore, we compared the reactivity of 4-trifluoromethanesulfonyl benzophenone **5a** to that of the corresponding bromide **5b** and iodide **5c**. In the event, the reaction proceeded smoothly in all cases, giving 4-cyclopropylbenzophenone **6** in similar yields (Table 2). This is in contrast with the Suzuki reaction involving cyclopropylboronic acid where no reaction was observed with aryl triflates.[13]

We then embarked on establishing the scope of the method using various aryl bromides, iodides, and triflates (Table 3). As a general observation, the reaction proceeded smoothly with ortho- (entry 2), meta- (entry 3), and para-substituted (entry 4) aryl halides. Again, iodides, bromides, and triflates gave comparable yields of the corresponding coupling products (**7a** vs **3** and **7d** vs **7e**). The presence of an electron-donating group such as a phenoxy (entry 7), an amine (entry 9), an alkyl thiolate (entry 10), or a dioxolane (entry 11) had little impact on the outcome of the reaction. Moreover, functional groups such as nitriles (entry 6), acetals (entry 12), indanones (entry 13), and phthalides (entry 14) were unaffected during the transformation.

Due to the ubiquity of heterocycles in medicinal chemistry, we expanded our studies to heterocyclic halides (Table 4). In the event, 3-, 4-, and 5-bromothiophenes **9a**, **9b**, and **9c** gave good yields of the corresponding coupling products (entries 1, 2, and 3, respectively). 5-Iodothiophene **9d** gave slightly higher yield of **10c** than the corresponding bromide **9c** (entry 4 vs 3). Further, modest to good yields of coupling products were observed for thiophene **9e**, furan **9f**, thiazole **9g**, pyrrole **9h**, indole **9i**, and bromopyridine **9j**. Interestingly, 2-chloropyridine **9k** was found to react smoothly under the current conditions to give the desired cross-coupling compound **10k** (entry 11) in moderate yield.

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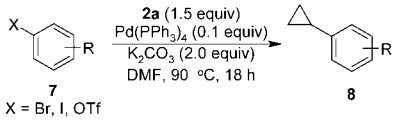
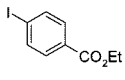
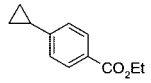
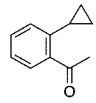
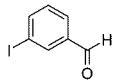
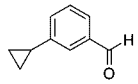
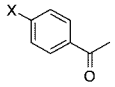
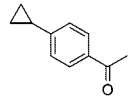
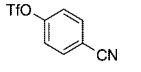
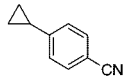
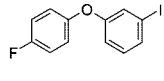
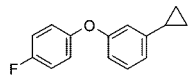
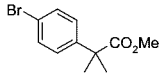
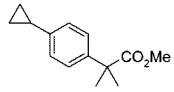
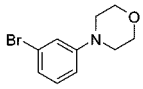
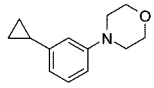
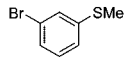
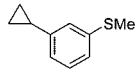
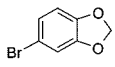
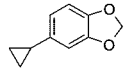
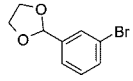
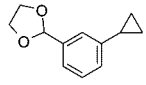
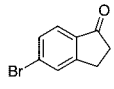
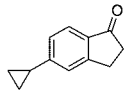
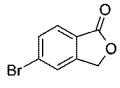
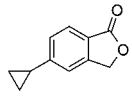
(20) A control experiment using only cyclopropylmagnesium bromide (no bismuth chloride) gave recovered aryl bromide **3**.

TABLE 3. Cross-Coupling Reaction of Tricyclopropylbismuth 2a with Aryl Bromides, Iodides, and Triflates

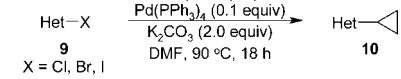


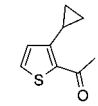
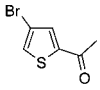
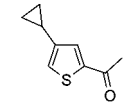
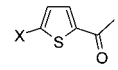
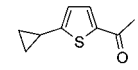
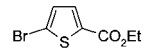
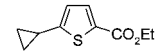
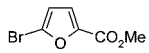
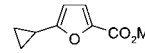
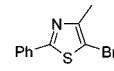
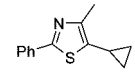
Entry	Substrate		Product	Isolated yield (%)
1		**7a**		**4**, 85
2		**7b**		**8b**, 79[a]
3		**7c**		**8c**, 64
4		**7d**, X = I		**8d**, 77
5		**7e**, X = OTf		**8d**, 77
6		**7f**		**8f**, 74
7		**7g**		**8g**, 77
8		**7h**		**8h**, 69
9		**7i**		**8i**, 65
10		**7j**		**8j**, 75
11		**7k**		**8k**, 78
12		**7l**		**8l**, 83
13		**7m**		**8m**, 58
14		**7n**		**8n**, 75

[a] Contains 5% of dehalogenated product.

Having demonstrated the scope of the cross-coupling reaction using reagent **2a**, we wondered if other trialkylbismuth reagents could be used for the transfer of acyclic aliphatic groups. Keeping in mind the propensity of linear aliphatic groups to undergo β-hydride elimination during palladium-catalyzed cross-coupling reaction and being aware of the absence of examples involving trialkylbismuth reagents, we elected to test the reaction conditions with triethylbismuth. When generated and used in situ, triethylbismuth **11** smoothly underwent cross-coupling with ethyl 4-bromobenzoate **3** under standard conditions to give ethyl

TABLE 4. Cross-Coupling Reaction of Tricyclopropylbismuth 2a with Heterocyclic Halides



Entry	Substrate		Product	Isolated yield (%)
1		**9a**		**10a**, 76
2		**9b**		**10b**, 77
3		**9c**, X=Br		**10c**, 74
4		**9d**, X=I		**10c**, 82
5		**9e**		**10e**, 76
6		**9f**		**10f**, 59
7		**9g**		**10g**, 71
8		**9h**		**10h**, 55
9		**9i**		**10i**, 52
10		**9j**		**10j**, 80
11		**9k**		**10k**, 65

4-ethylbenzoate **12** in excellent isolated yield (eq 2).[21] Gratifyingly, *the transfer of one ethyl group proceeded smoothly under simple conditions and did not require additives or complex ligands.*[22] A full account of our work involving the cross-coupling of other aliphatic groups will be reported in due course.

In summary, we have reported the palladium-catalyzed cross-coupling reaction of tricyclopropylbismuth **2a** with aryl and heterocyclic halides and triflates. The reaction tolerates numerous functional groups and proceeds efficiently under standard conditions for cross-coupling reactions, without requiring strict anhydrous conditions. The reaction can be performed with

(21) See the Supporting Information for experimental details.

(22) Less than 4% of dehalogenated product was observed by ^{1}H NMR. For other methods allowing the transfer of an ethyl group, see: (a) Bumagin, N. A.; Luzikova, E. V. *J. Organomet. Chem.* **1997**, *532*, 271. (b) Shenglof, M.; Gelman, D.; Molander, G. A.; Blum, J. *Tetrahedron Lett.* **2003**, *44*, 8593. (c) Fardis, M.; Mertzman, M.; Thomas, W.; Kirschberg, T.; Collins, N.; Polniaszek, R.; Watkins, W. J. *J. Org. Chem.* **2006**, *71*, 4835. (d) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997. (e) Kondolff, I.; Doucet, H.; Santelli, M. *Organometallics* **2006**, *25*, 5219.

isolated reagent **2a** or with less than 1.0 equivalent of reagent **2a** generated in situ. The protocol was extended to the coupling of triethylbismuth **11**, allowing the transfer of a linear aliphatic group with hydrogens in β-position. To the best of our knowledge, this work constitutes the first report of cross-coupling reactions involving trialkylbismuth reagents.

Experimental Section

Preparation of Tricyclopropylbismuth (2a). Bismuth chloride (2.50 g, 7.93 mmol) was dissolved in anhydrous THF (100 mL) and cooled to −10 °C (ice−acetone bath). The bismuth chloride is not entirely soluble at this temperature, and a white solid may be observed. Cyclopropylmagnesium bromide (77.1 mL, 26.2 mmol, 0.34 M in THF) was slowly added dropwise under argon via syringe pump over 1 h. The reaction mixture was stirred at room temperature for 1 h and heated at 70 °C for 30 min, at which time a black precipitate was observed. After being cooled to room temperature, the solution was cannulated under argon over a degassed biphasic solution of brine (200 mL) and ether (200 mL). The heterogeneous solution was stirred for 5 min, transferred in a separatory funnel, and diluted with ether (100 mL). The organic phase was collected, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford a yellow oily solid. Ether (50 mL) was added, followed by hexanes (50 mL). The mixture was sonicated, cooled to 0 °C, and filtered over a Buchner funnel to afford **2a** as a white solid (1.75 g, 72%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (s (br), 3H), 1.57 (s (br), 6H), 1.22 (s (br) 6H); HRMS (EI) calcd for $C_9H_{15}Bi$ (M) 332.0978, found 332.0973 (M), 291.0584 (M − *c*-Pr), 250.0191 (M − 2(*c*-Pr)), 208.9808 (Bi). *The reagent should not be pumped under high vacuum for more than a few minutes. The solid should be placed immediately under argon in the freezer after use. The reactivity will remain essentially the same for a few weeks if stored appropriately.* CAUTION: *On a larger scale, a pyrophoric material is sometimes obtained.*

General Procedure for Palladium-Catalyzed Cross-Coupling Reaction with Reagent 2a. In a sealed tube, the starting iodide, bromide, chloride, or triflate (0.30 mmol) was dissolved in *N*,*N*-dimethylformamide (3 mL). Potassium carbonate (83 mg, 0.60 mmol) was added, followed by tetrakis(triphenylphosphine) palladium (35 mg, 0.030 mmol) and cyclopropylbismuth reagent **2a** (150 mg, 0.45 mmol). Argon was bubbled in the reaction mixture for 15 min. The tube was sealed and heated at 90 °C for 18 h. The reaction mixture was cooled to rt, diluted with saturated aqueous sodium bicarbonate (50 mL), and extracted with ether (2 × 50 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and brine (2 × 50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using 10% ether in hexanes to afford the desired pure aryl or heteroaryl cyclopropane.

Acknowledgment. We thank our colleagues at Boehringer Ingelheim (Canada) Ltd. for valuable help during manuscript preparation and Sylvain Bordeleau for his help with compound characterization.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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