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Construction of Di(hetero)arylmethanes Through Pd-Catalyzed Direct Dehydroxylative Cross-Coupling Benzylic Alcohols and Aryl Boronic Acids Mediated by Sulfuryl Fluoride (SO_2F_2)

Chuang Zhao,[a] Gao-Feng Zha,[a] Wan-Yin Fang,[a] K. P. Rakesh,[a] and Hua-Li Qin*[a]

Abstract: A practical Pd-catalyzed direct dehydroxylative coupling of (hetero)benzylic alcohols with (hetero)arylboronic acids for the constructions of di(hetero)arylmethane derivatives under SO_2F_2 was described. This new method provided a strategically distinct approach to di(hetero)arylmethane derivatives from readily available and abundant benzylic alcohols under mild condition.

Introduction

The di(hetero)arylmethane derivatives are ubiquitous and important structures present in biologically active molecules and notable pharmaceuticals for treatment of a wide range of diseases (Figure 1),[1] supramolecules and materials,[2] organic synthesis and chemical industry,[3] and pigments and dyes.[4] Currently, there are two major strategies for the construction of di(hetero)arylmethane derivatives: the Friedel-Crafts type of reactions,[5] and transition metal-catalyzed coupling reactions.[6] Because Friedel-Crafts reactions have significant electronic and steric limitations, the transition metal-catalyzed coupling reactions, especially, the Suzuki-Miyaura type of cross-coupling of organoboronic acids (or esters) with organohalides has been predominately employed for di(hetero)arylmethanes synthesis with high practicality and effectiveness.[7]

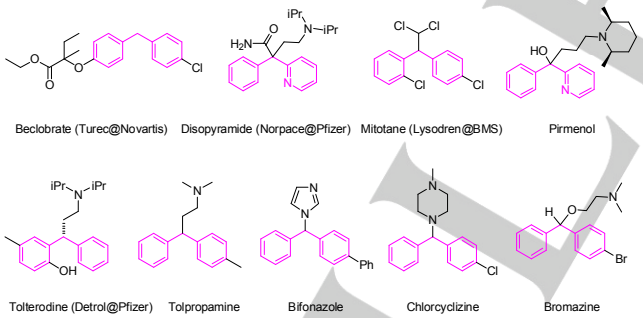
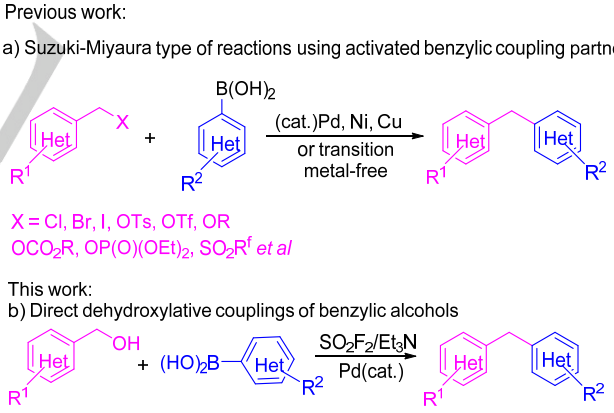


Figure 1. Representative drugs containing di(hetero)arylmethane derivatives

The available Suzuki-Miyaura type of reactions for the assembly of di(hetero)arylmethanes (Scheme 1, a), mainly relied on the use of either benzyl halides, which are not environment-friendly and require tedious preparation;[8] or benzylic alcohol derived active species of sulfonates (tosylates, mesylates, triflates);[7p,9] or relatively inert still active benzylic alcohol derivatives such as carboxylates (esters, carbamates, carbonates),[7h,r,10] ethers,[11] phosphates;[12] or other activated benzyl derivatives.[13] However, ironically, the direct utilization of benzylic alcohols for dehydroxylative couplings has rarely been achieved and still remained as a challenging and significant goal,[14] despite the natural abundance, availability, and environmentally benign advantages of alcohols.[15] To the best of our knowledge, there is no general method for synthesis of biologically more valuable, *N*-heterocycle-containing diarylmethane derivatives accomplished from the corresponding *N*-heteroaryl boronic acids and/or *N*-hetero benzylic alcohols. Therefore, it is highly desirable and of great significance to develop methods for the synthesis of diarylmethanes, especially, diheteroarylmethanes, from heteroaryl methanols and/or heteroaryl boronic acids because of the great importance of diheteroarylmethane products and the superiority of benzylic alcohols as the starting materials.



Scheme 1. Synthesis of diarylmethane derivatives through the Suzuki-Miyaura type of cross-coupling reactions

Sulfuryl fluoride (SO_2F_2),[16] an inexpensive (about 1$/kg),[16a] abundant (millions-kilograms annual production),[16a] and relatively inert gas (stable up to 400 °C when dry) has recently attracted significant attention for SuFEx click chemistry and other transformations.[17] Based on the success of application of SO_2F_2 as an electrophile to react with hydroxy groups of phenols for generating fluorosulfates to participate in nucleophilic substitutions and SuFEx click chemistry (scheme 2, a),[16a,18] we envision that the hydroxy groups of benzylic alcohols would also proceed nucleophilic attack to SO_2F_2 to generate the ammonium salts to undergo further coupling with boronic acids to generate

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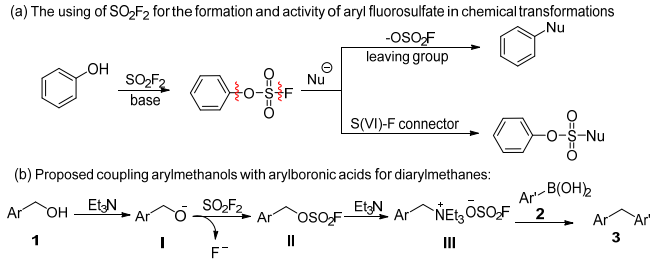
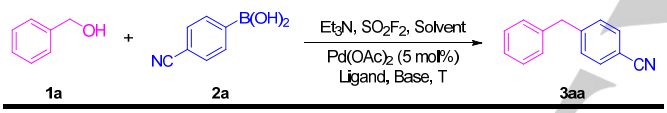
the desired diarylmethanes (Scheme 2, b). Herein, we report a practical and effective Pd-catalyzed, SO_2F_2 mediated direct dehydroxylative coupling (hetero)benzylic alcohols with (hetero)arylboronic acids for the constructions of di(hetero)arylmethane derivatives (Scheme 1, b) as our continuing research on application of SO_2F_2 for organic transformations.[18e-j]



Scheme 2. The proposed direct coupling of arylmethanols with arylboronic acids mediated by SO_2F_2

Results and Discussion

Table 1. Optimization of the Reaction Conditions[a]

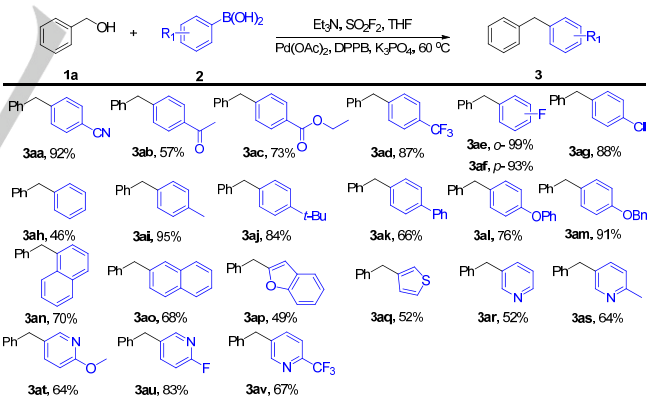


Entry	Ligand (10 mol %)	Base (3.0 eq.)	Solvent (2.0 ml)	T (°C)	Yield (**3aa**, %)[b]
1	PPh_3	K_3PO_4	THF	50	11
2	X-Phos	K_3PO_4	THF	50	15
3	DPPE	K_3PO_4	THF	50	34
4	DPPP	K_3PO_4	THF	50	82
5	DPPB	K_3PO_4	THF	50	93
6	DPPB	Cs_2CO_3	THF	50	92
7	DPPB	K_2CO_3	THF	50	54
8	DPPB	K_3PO_4	MeCN	50	85
9	**DPPB**	**K_3PO_4**	**THF**	**60**	**99**
10[c]	DPPB	K_3PO_4	THF	60	29

[a] Reaction conditions: a mixture of benzyl alcohol (**1a**, 0.2 mmol), Et_3N (0.4 mmol, 2.0 eq.), Solvent (2.0 mL) was added to a reaction flask (25 mL), before SO_2F_2 was introduced into the stirred reaction mixture by slowly bubbling from a balloon (degassed with SO_2F_2 for 10-30 seconds), and the mixture was allowed to stir at room temperature for 1 h before (4-cyanophenyl)boronic acid (**2a**, 0.24 mmol, 1.2 eq.), $Pd(OAc)_2$ (5 mol%), Ligand (10 mol%), Base (3.0 eq.) and Solvent (2.0 mL) were added into the mixture to react for an additional 12 h under Ar atmosphere at corresponding temperature. [b] The yield was determined by HPLC using **3aa** as the external standard (t_R = 8.2 min, λ_{max} = 237.0 nm, water/methanol = 30 : 70 (v / v)). [c] Reaction was operated under air.

Initially, benzyl alcohol 1a and (4-cyanophenyl)boronic acid **2a** were used as a model substrate to test the feasibility of the direct dehydroxylative coupling of benzylic alcohols with arylboronic acids, and the results were illustrated in Table 1. After screening a variety of conditions (see supporting information for details), we were pleased to find that the combination of $Pd(OAc)_2$ and DPPB was the most efficient catalyst system for this coupling reaction. It was worth noting that the use of monodentate phosphine ligands, such as PPh_3 and X-Phos, provided only a trace amount of the desired products (Table 1, entries 1 and 2), while the use of the bidentate phosphine ligands such as DPPE, DPPP and DPPB assisted the Pd-catalyzed coupling more efficiently to generate the desired product 3aa in improved yields (Table 1, entries 3-5), which could be attributed to the greater stability and stronger coordination ability of the bidentate phosphine ligands.[19] Cesium carbonate was found to be another ideal base for this transformation providing a 92% yield of **3aa** (Table 1, entry 6), while the use of potassium carbonate generated the desired product in a moderate yield (54%, Table 1, entry 7). When the CH_3CN was chosen as solvent instead of THF, the yield was slightly decreased (Table 1, entry 8 *vs* entry 5). To our delight, when the temperature was elevated to 60 °C, the yield was improved to quantitative (Table 1, entry 9). However, under an air atmosphere, the yield was significantly decreased (Table 1, entry 10) due to the homo-coupling of phenylboronic acid. Accordingly, the reaction condition of Table 1, entry 9 was chosen as the standard operating condition for further examination of substrate scope and functional group tolerance.

Table 2. Screening of substrate scope of boronic acids.[a,b]

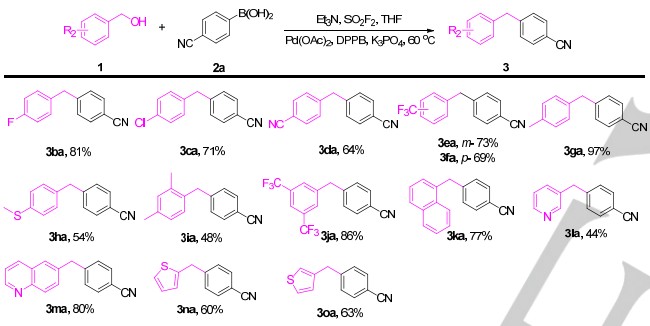


[a] Reaction conditions: a mixture of benzyl alcohol (**1a**, 1.0 mmol), Et_3N (2.0 mmol, 2.0 eq.), THF (2.0 mL) was added to a reaction flask (50 mL), before SO_2F_2 was introduced into the stirred reaction mixture by slowly bubbling from a balloon (degassed with SO_2F_2 for 10-30 seconds), and the mixture was allowed to stir at room temperature for 1 h before aryl boronic acid (**2**, 1.2 mmol, 1.2 eq.), $Pd(OAc)_2$ (5 mol%), DPPB (10 mol%), K_3PO_4 (3.0 eq.) and THF (8.0 mL) were added into the mixture to react for an additional 12 h under Ar atmosphere at 60 °C. [b] Isolated yields.

With the optimized reaction conditions in hand, we next set out to evaluate the generality of boronic acids **2** using benzyl alcohol **1a** as a model substrate. As shown in Table 2, a broad substrate scope of boronic acids were examined for the dehydroxylative coupling process. It was worth highlighting the substrates functionalized with both electron-withdrawing groups,

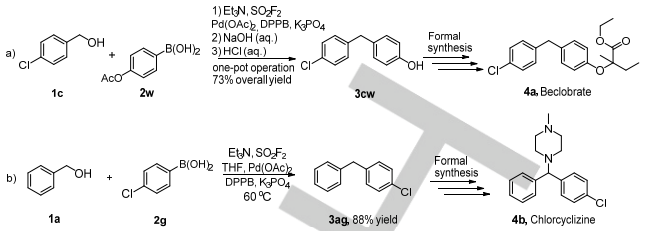
such as cyano groups (**2a**), acyl groups (**2b** and **2c**), trifluoromethyl groups (**2d**), and halogens (**2e**-**2g**); and electron-donating groups, such as alkyl groups (**2i** and **2j**), aryl groups (**2k**), ethers (**2l** and **2m**), tolerated smoothly under the reaction conditions and the products **3aa-3am** were obtained in good to quantitative yields (yield 57% to 99%). Due to the high volatility of diarylmethanes, the isolated yields are not high, especially for products with very low boiling points (**3ab**, **3ah**). Naphthalene boronic acid (**2n** and **2o**) were also examined to provided their products (**3an** and **3ao**) in 68% and 70% respectively. Most importantly, the syntheses of diarylmethanes containing aromatic heterocycle such as furan (**3ap**), thiophene (**3aq**), especially pyridines (**3ar**-**3av**) were achieved from the corresponding heteroaryl boronic acids in 49% to 83% yields, which indicated the potential authentic value of this method for the synthesis of bioactive heterocycles-containing molecules. Because heteroaryl boronic acids may be coordinated with metal catalyst to deactivate the catalyst, the coupling reaction between heteroaryl methanols and boronic acid was found to be sluggish with lower efficiency.

Table 3. Screening of substrate scope of benzylic alcohols.[a,b]



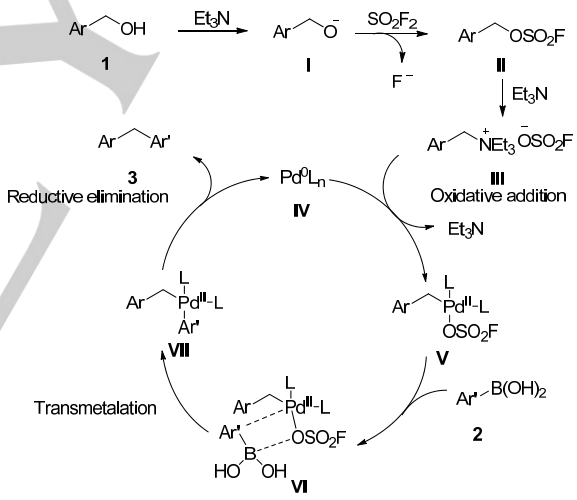
[a] Reaction conditions: a mixture of alcohol (**1**, 1.0 mmol), Et_3N (2.0 mmol, 2.0 eq.), THF (2.0 mL) was added to a reaction flask (50 mL), before SO_2F_2 was introduced into the stirred reaction mixture by slowly bubbling from a balloon (degassed with SO_2F_2 for 10-30 seconds), and the mixture was allowed to stir at room temperature for 0.5-3 h before (4-cyanophenyl)boronic acid (**2a**, 1.2 mmol, 1.2 eq.), $Pd(OAc)_2$ (5 mol%), DPPB (10 mol%), K_3PO_4 (3.0 eq.), THF (8.0 mL) were added into the mixture to react for an additional 12 h under Ar atmosphere at 60 °C. [b] Isolated yields.

The substrate scope of benzylic alcohols **1** has also been investigated and the results were summarized in Table 3. It was noted that a series of functional groups such as halogens (**3ba** and **3ca**), cyano groups (**3da**), trifluoromethyl groups (**3ea** and **3fa**), alkyl groups (**3ga**) and thioether group (**3ha**) were compatible (yield 54% to 97%). Furthermore, multi-functionalized benzylic alcohols and 1-naphthylmethanol were also successfully converted to their corresponding products in moderate to excellent yields (**3ia, 3ja** and **3ka;** yield 48%, 86%, 77%). Excitingly, although heteroaryl methanols may be coordinated with metal catalyst to decrease the efficiency of the coupling reaction, *S*-heterobenzylic alcohols and *N*-heterobenzylic alcohols were still successfully transformed to their diarylmethanes (**3la**-**3oa**) in moderate to excellent yields (44% to 80%).



Scheme 3. Application of the Developed Method to Formal Synthesis Beclobrate and Chlorcyclizine.

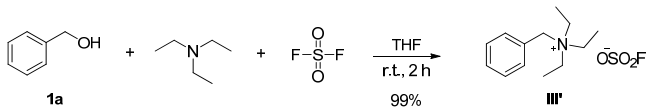
Furthermore, to demonstrate the synthetic utility of this protocol, formal synthesis of beclobrate **4a**, a potent cholesterol and triglyceride lowering drug for the treatment of hyperlipidemia was achieved.[20] The key precursor, 4-(4-chlorobenzyl)phenol **3cw,** was synthesized through a one-pot process from (4-chlorophenyl)methanol **1c** and (4-acetoxyphenyl)boronic acid **2w** in 73% over all yield on gram-scale (Scheme 3, a). In addition, the synthesis of 1-benzyl-4-chlorobenzene **3ag**, the key intermediate for the preparation of Chlorcyclizine **4b**,[21] an effective antihistamine drug treating allergic diseases and anti-inflammatory, was accomplished through dehydroxylative coupling of benzyl alcohol **1a** and (4-chlorophenyl)boronic acid **2g** using this developed method in 88% yield (Scheme 3, b).



Scheme 4. Proposed reaction mechanism.

A plausible reaction mechanism was proposed in Scheme 4. The benzylic alcohols **1** were initially deprotonated by the base (Et_3N) to generate alkoxides **I**. The alkoxides **I** subsequently reacted with SO_2F_2 to form the fluorosulfonate esters **II** and generate fluoride anion. The fluorosulfonate esters **II** intermediate reacted rapidly with Et_3N to generate the benzyltriethylammonium salts **III**, which underwent an oxidative addition to provide metal complex Pd^0L_n **IV** *in situ*. The benzyltriethylammonium salts **III** subsequently produced intermediate **V** with simultaneous releasing Et_3N.[22] When the intermediate **V** coordinated with boronic acids **2**, complex **VI** was formed, which proceeded a transmetalation to generate the

intermediate **VII**.[13b,d,14a] The reductive elimination of intermediate **VII** afforded the desired product **3** and started another catalytic cycle after regenerating the active catalytic Pd^0L_n **IV**.



Scheme 5. Experiments for verifying the formation of benzyltriethylammonium sulphofluoridate **III'**.

To testify whether this transformation was proceeded through the formation benzyltriethylammonium salt **III'** intermediate, benzyl alcohol **1a** and Et_3N was allowed to react in THF under a SO_2F_2 atmosphere (Scheme 5). Excitingly, after stirring for an hour, a white solid was crystallized, which was identified as the proposed ammonium salt. Further research indicated that 2.0 equivalent of Et_3N was essential for completely converting benzylic alcohol to the corresponding ammonium salt (see the ESI, Table S5).

Conclusions

In summary, a mild and practical method for dehydroxylative coupling of benzylic alcohols with aryl boronic acids for the formation of widely useful diarylmethanes was developed. This Pd-catalyzed reaction displayed exceptional functional group tolerance and substrate scope for both alcohols and boronic acids. Notably, this novel protocol enabled the efficient cross coupling of heteroaromatic benzylic alcohols and heteroaromatic boronic acids for the construction of bioactive heterocycles-containing diarylmethane-derivatized molecules. The application of this method for formal synthesis of drugs of Beclobrate and Chlorcylizine was also achieved.

Experimental Section

General procedure for synthesis of di(hetero)arylmethane derivatives (3).

A mixture of alcohol (**1**, 1.0 mmol), Et_3N (2.0 mmol, 202.4 mg, 2.0 eq.), THF (2.0 mL) was added to a reaction flask (50 mL), before SO_2F_2 was introduced into the stirred reaction mixture by slowly bubbling from a balloon (degassed with SO_2F_2 for 10-30 seconds), and the mixture was allowed to stir at room temperature for 0.5-3 h before a mixture of boronic acid (**2**, 1.2 mmol, 1.2 eq.), $Pd(OAc)_2$ (5 mol %, 11.2 mg), DPPB (10 mol %, 42.6 mg), K_3PO_4 (3.0 mmol, 636 mg, 3.0 eq.) and THF (8.0 mL) was added. The mixture was allowed to react for an additional 12 h under Argon atmosphere (balloon) at 60 °C. Subsequently, the mixture was diluted with water (50 mL) and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by silica gel chromatography through gradient elution with EtOAc / Petroleum ether to afford pure products (**3**).

Procedure for gram-scale synthesis of 4-(4-chlorobenzyl)phenol (3cw).

A mixture of alcohol (**1c**, 10 mmol, 1.43 g), Et_3N (20 mmol, 2.02 g, 2.0 eq.), THF (20 mL) was added to a reaction flask (250 mL), before SO_2F_2 was introduced into the stirred reaction mixture by slowly bubbling from a balloon (degassed with SO_2F_2 for 10-30 seconds), and the mixture was allowed to stir at room temperature for 2 h before the mixture of (4-acetoxyphenyl)boronic acid (**2w**, 12 mmol, 2.16 mg, 1.2 eq.), $Pd(OAc)_2$ (5 mol %, 112 mg), DPPB (10 mol %, 426 mg), K_3PO_4 (30 mmol, 6.36 mg, 3.0 eq.) and THF (80 mL) was added. The reaction mixture was allowed to for an additional 12 h under Argon atmosphere (an Ar balloon) at 60 °C. When the reaction was complete, 30 mL 1 N NaOH (aq.) was added to the reaction mixture and continued stirring for 10 min before diluted with 50 mL 1 N HCl (aq.) and extracted with EtOAc (3×30 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by silica gel chromatography through gradient elution with EtOAc / Petroleum ether to afford pure products (**3cw**, 1.59 g, 73%) as a light yellow solid.

Procedure for synthesis of benzyltriethylammonium sulfofluoridate III'.

A mixture of benzyl alcohol (**1a**, 1.0 mmol, 108.13 mg), Et_3N (2.0 mmol, 202.4 mg, 2.0 eq.), THF (2.0 mL) were added to a reaction flask (50 mL), before SO_2F_2 was introduced into the stirred reaction mixture by slowly bubbling from a balloon (degassed with SO_2F_2 for 10-30 seconds), and the mixture was allowed to stir at room temperature for 2 h. The precipitate was washed with THF (2 mL × 3) and dried in vacuo to yield the title compound (**III'**, 189 mg, 99%) as a white solid.

Acknowledgments

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Keywords: Alcohols • Cross-coupling • Palladium

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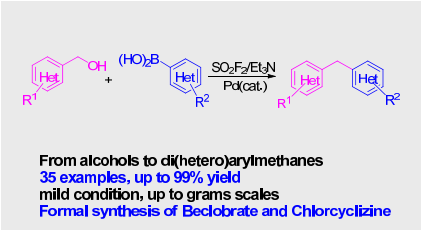
A practical Pd-catalyzed direct dehydroxylative coupling of (hetero)benzylic alcohols with (hetero)arylboronic acids for the constructions of di(hetero)arylmethane derivatives under SO_2F_2 was described. This new method provided a strategically distinct approach to di(hetero)arylmethane derivatives from readily available and abundant benzylic alcohols under mild condition.



Cross-coupling

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Construction of Di(hetero)arylmethanes Through Pd-Catalyzed Direct Dehydroxylative Cross-Coupling Benzylic Alcohols and Aryl Boronic Acids Mediated by Sulfuryl Fluoride (SO_2F_2)