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Synthesis of the Benzhydryl Motif via a Suzuki−Miyaura Coupling of Arylboronic Acids and 3-Chloroacrylonitriles

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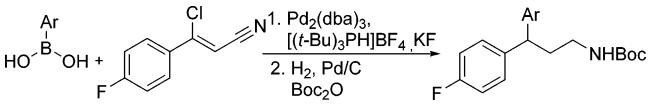
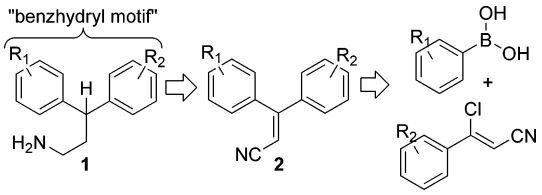


A simple two-step procedure for synthesizing functionalized benzhydrylamines is described. The first step involves a Suzuki−Miyaura coupling reaction between arylboronic acids and 3-chloro-3-arylacrylonitriles at 45 °C. A variety of boronic acids and substituted acrylonitriles can be used for the reaction. The resulting 3,3-diaryl-substituted acrylonitriles can be converted into their corresponding Boc-protected amines by catalytic hydrogenation.

The benzhydryl (diarylmethyl) structural motif is an important substitution pattern in many pharmaceuticals and biologically active small molecules (Scheme 1).[1] Specifically, drugs containing the benzhydryl motif either in preclinical testing or in clinical applications include antihypertensives,[2] anti-allergics,[3] hypolipidemics,[4] anti-Parkinson agents,[5] opioid agonists,[6] anticoagulants,[7] and others.[8] Typical syntheses of such motifs (Scheme 1, **1**) involve conjugate addition to enones[9] or Horner−Wadsworth−Emmons reactions with ketone precursors, in both cases followed by reduction of the resulting olefin moieties (Scheme 1, **2** and **1**).[10] Additionally, compounds similar to **2** have demonstrated differential reactivity under a variety of conditions,[11] making them useful intermediates in diversity-oriented synthesis.[12] Recent reports have described that 3,3-diarylacrylonitriles can be accessed via Heck couplings involving 2−3 equiv of an aryl iodide or bromide and temperatures ranging between 80 and 120 °C.[13] Additionally, β-aryl/alkylarylidene malonates are readily synthesized from β-chloro/alkylarylidene malonates, 1.5 equiv of a boronic acid, and a palladium catalyst at 100 °C in a microwave reactor.[14] Herein we report a modular two-step procedure that generates the benzhydryl motif precursor **2** via a Suzuki−Miyaura cross-coupling reaction between arylboronic acids and β-substituted 3-chloroacrylonitriles. The resulting 3,3-diaryl-substituted acrylonitriles can be reduced to a protected amine by catalytic hydrogenation yielding the diarylalkyl motif.

SCHEME 1



We envisioned that the 3,3-diaryl-substituted acrylonitriles could be accessed by way of a metal-catalyzed reaction between a boronic acid and a 3-chloro-3-arylacrylonitrile (Scheme 1). This method allows for the rapid synthesis of analogues to quickly determine the structure−activity relationship (SAR) of these motifs in a drug discovery program. Substituted acrylonitriles were conceived as optimal starting materials due to their commercial availability and the presence of an olefinic carbon−halogen bond capable of undergoing metal-catalyzed coupling reactions.[15] Additionally, these substrates are key intermediates in the synthesis of various COX-2 inhibitors[16] and can be readily

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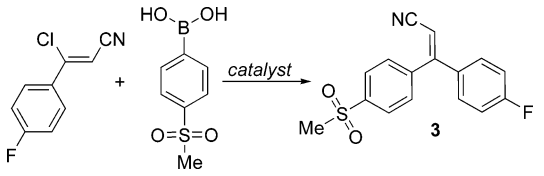
TABLE 1. Efficiency of Cross-Coupling with Various Catalyst Systems[a]



entry	catalyst	base	temp °C	% yield[f]
1[c]	$Pd(PPh_3)_4$	Cs_2CO_3	80	0
2[c]	$Pd(PPh_3)_4$	Cs_2CO_3	150[b]	0
3[d]	$Pd(OAc)_2$	K_2CO_3	45	0
4[d]	$Pd(OAc)_2$	K_2CO_3	90	40
5[e]	$Pd_2(dba)_3$	$[(t\text{-}Bu)_3PH]BF_4$	KF	rt	57
6[e]	$Pd_2(dba)_3$	$[(t\text{-}Bu)_3PH]BF_4$	KF	45	76

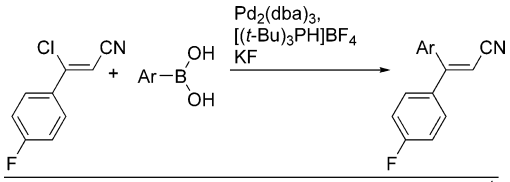
[a] See Supporting Information for experimental details. [b] Performed under microwave heating for 20 min. [c] 10 mol % catalyst, 3 equiv of base. [d] 5 mol % catalyst, 3 equiv of base. [e] 2.5 mol % catalyst, 5 mol % ligand, 3 equiv of base. [f] Isolated yield of purified material. Base selection based upon the optimization of each catalyst system as described in the literature. Yields based upon the average of a minimum of two runs; all compounds isolated as a single stereoisomer (determined by ROESY experiments).

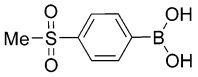
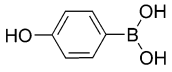
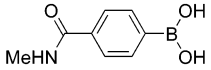
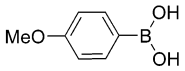
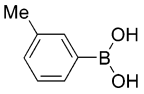
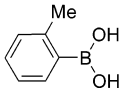
accessed from the corresponding ketones in DMF in the presence of $POCl_3$ and $NH_2OH{\cdot}HCl$.[17]

Our initial attempts at performing the cross-coupling reaction focused on catalysts known to promote the coupling reaction of similar substrates (Table 1).[18] When using tetrakis(triphenylphosphine) palladium as a catalyst, no product was observed and only starting material was recovered (entry 1). Additional heating of the reaction in a microwave (150 °C) led solely to decomposition of the starting materials (entry 2). Employing a more reactive "ligandless" palladium catalyst system (entries 3 and 4) resulted in product formation, although high temperatures and extended reaction times were necessary.[19] To our satisfaction, addition of a sterically hindered electron-rich tertiary phosphine (tri-*t*-butylphosphine) to a palladium(0) source and KF resulted in the formation of **3** in 57% yield, as well as 25% recovery of the starting nitrile (entry 5). At slightly elevated temperatures (45 °C), complete conversion to the desired diaryl compound **3** was achieved. The use of the air-stable tetrafluoroborate salt precursor of tri-*tert*-butylphosphine simplifies reaction setup and thus increases the throughput that can be obtained with this procedure,[20] making it amenable to parallel synthesis techniques. Also, the reaction can be performed at temperatures more moderate than those required for the ligandless system, giving superior yields of the desired diaryl product.

The general applicability of the catalyst system was determined by examining boronic acids with varying electronic properties and steric demand (Table 2). Boronic acids with electron-withdrawing substituents in the 4-position readily react, producing the diaryl product in good yields (entries 1 and 3).

TABLE 2. Catalytic Cross-Coupling Reaction Employing Various Boronic Acids[a]



entry	Boronic Acid	% yield[b]
1		75 82[c]
2		89
3		79
4		90
5		96
6		95

[a] Reagents and conditions: 1.0 equiv of 3-chloro-3-(4-fluorophenyl)-acrylonitrile), 1.1 equiv of boronic acid, 3.1 equiv of KF, 5 mol % $[(t\text{-}Bu)_3PH]BF_4$, 2.5 mol % $Pd_2(dba)_3$, 45 °C, 16 h. [b] Isolated yield of purified material. Yields based upon the average of a minimum of two runs; all compounds isolated as a single stereoisomer (determined by ROESY experiments). [c] Reaction performed with 1.5 g of acrylonitrile; product purified by recrystallization.

Boronic acids with electron-donating groups in the 4-position undergo the coupling to produce product in equally good yields (entry 4). The catalytic system tolerates substrates containing both hydrogen bond donors and acceptors. Boronic acids with a hydroxyl group (entry 2) or an amide (entry 3) in the 4-positions are tolerated. The methodology is not solely limited to boronic acids with substitution in the 4-position. For example, boronic acids bearing a methyl substituent in the 2- and 3-positions (entries 5 and 6) undergo reaction in nearly quantitative yield. Additionally, the reaction can be performed on a gram scale, generating the desired biaryl product without erosion in yield (entry 1).

For further assessment of the reaction scope, we examined various substituted 3-chloro-3-arylacrylonitriles in the coupling reaction (Table 3). The reaction was found to tolerate both electron-withdrawing (entry 2) and electron-donating (entry 3) groups in the 4-position, providing the corresponding biaryl compounds in 75 and 63% yield, respectively. When α-chlorobenzylidenemalonitrile was employed in the reaction, the corresponding tetrasubstituted olefin was obtained, albeit in lower yield than the trisubstituted olefin products (entry 3 versus entries 1 and 2). On the basis of this result, we then employed a coumarin-like substrate (4-chloro-3-cyano-6-fluoro-2*H*-benzopyran)[21] in the reaction, which generated product in 27% yield (entry 4).

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(20) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. $[(t\text{-}Bu)_3PH]BF_4$ is commercially available; see the Supporting Information for details. Alternatively, the Buchwald catalyst system (S-PHOS, 100 °C, $Pd(OAc)_2$) can be used to obtain similar results: Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew Chem., Int. Ed.* **2004**, *43*, 1871.

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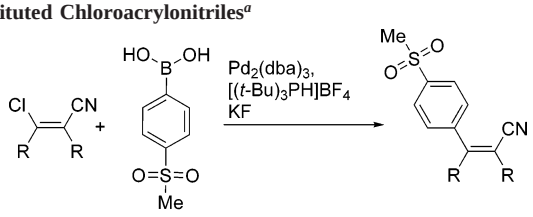
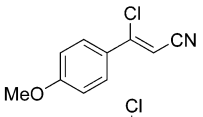
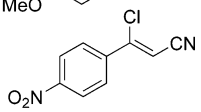
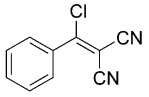
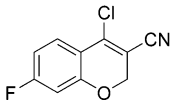
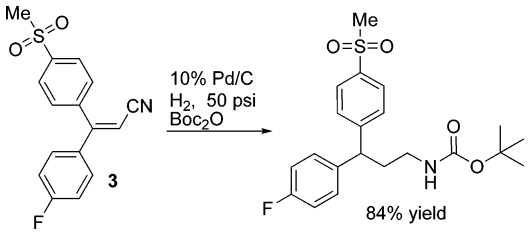
TABLE 3. Catalytic Cross-Coupling Employing Various Substituted Chloroacrylonitriles[a]



entry	chloroacrylonitrile	% yield[b]
1		75
2		63
3		35[c]
4		27[c]

[a] Reagents and conditions: 1.0 equiv of chloroacrylonitrile, 1.1 equiv of boronic acid, 3.1 equiv of KF, 5 mol % $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$, 2.5 mol % $\text{Pd}_2(\text{dba})_3$, 45 °C, 16 h. [b] Isolated yield of purified material. Yields based upon the average of a minimum of two runs; all compounds isolated as a single stereoisomer (determined by ROESY experiments). [c] Yields not optimized.

SCHEME 2[a]



[a] Reaction performed at room temperature for 24 h. Isolated yield of purified material, based upon the average of two runs.

With a simple method developed to generate compounds containing the diaryl motif, we then examined whether the products could be directly reduced to the corresponding propylamines, thereby generating the benzhydryl product. When compound **3** was subjected to catalytic hydrogenation at 50 psi at room temperature, in the presence of Boc anhydride, the corresponding Boc-protected amine was produced in 84% yield (Scheme 2).[22] Importantly, no partially hydrogenated product or dialkylamine side products were observed under these reaction conditions.

In summary, a simple method to synthesize the diarylmethyl (benzhydryl) motif is outlined that employs a mild Suzuki−Miyaura cross-coupling reaction followed by catalytic hydrogenation. The cross-coupling reaction occurs between a variety of boronic acids, including substituents that are electron-rich and electron-poor and contain hydrogen bond donors or acceptors. Trisubstituted chloroacrylonitriles can be employed in the reaction, as well as coumarin analogues, both of which highlight the feasibility of generating differentially functionalized tetrasubstituted olefins. The method allows for the rapid synthesis of analogues of the benzhydryl motif in drug discovery programs. The intermediates from the Suzuki−Miyaura reaction are useful substrates for a number of transformations[7] including catalytic reduction, producing the corresponding protected benzhydrylpropylamines.

(22) Boc_2O had to be used to avoid the formation of dialkylamine side products. Similar hydrogenations have been performed with Ni catalysts: (a) Schultz, H. *Pharmazie* **1967**, *22*, 19. With Pt catalysts: (b) Atwal, K. S.; O'Reilly, B. C.; Ruby, E. P.; Turk, C. T.; Aberg, G.; Asaad, M. M.; Bergey, J. L.; Moreland, S.; Powell, J. R. *J. Med. Chem.* **1987**, *30*, 627.

Experimental Section

General Procedure for Cross-Coupling Reactions. A 2.5-mL oven-dried glass vial was charged with 4-(methanesulfonyl)-benzeneboronic acid (181 mg, 0.91 mmol), 3-chloro-3-(4-fluorophenyl)acrylonitrile (150 mg, 0.83 mmol), $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$ (12.2 mg, 0.042 mmol), and $\text{Pd}_2(\text{dba})_3$ (19.0 mg, 0.021 mmol). The vial was sealed with a Teflon-lined septum cap and then purged with nitrogen for 3 min. The cap was removed, and then KF was added quickly in one portion. The reaction cap was replaced, and the vial was flushed with nitrogen for 3 min. Dry THF (1.7 mL) was introduced into the vial via syringe, and the reaction vessel was sealed with Teflon tape. The vial was then immersed at 45 °C in an oil bath and then was stirred overnight. After 16 h, the vial was removed from the oil bath and cooled to room temperature. The mixture was filtered through a plug of silica gel, and the silica gel was washed with copious amounts of tetrahydrofuran and diethyl ether. The combined washings were evaporated in vacuo to give a solid that was immediately purified via flash chromatography (7:1 to 1:1 hexanes/ethyl acetate) to yield 208 mg (0.69 mmol, 76%) of **3** as a solid.

(3) (*Z*)-3-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)acrylonitrile. Yield 76% TLC R_f 0.3 (1:1 hexanes/ethyl acetate) ^{1}H NMR δ: 7.99 (m, 2H), 7.55 (m, 2H), 7.19 (m, 2H), 7.04 (m, 2H), 5.78 (s, 1H), 3.06 (m, 3H) ppm. ^{13}C NMR δ 164.3 (d, $^1J_{\text{C-F}}$ 253 Hz), 159.9, 142.2, 141.9, 133.8, 130.5, 130.3 (d, $^3J_{\text{C-F}}$ 8.7 Hz), 127.9, 116.9, 116.2 (d, $^2J_{\text{C-F}}$ 22 Hz), 96.6, 44.4 ppm. HRMS Calcd for $C_{16}H_{12}FNO_2S$, 302.0645 $(M + H)^+$; found, 302.0646.

(9) (*Z*)-3-(4-Methanesulfonylphenyl)-3-(4-methoxyphenyl)-acrylonitrile. Yield 91%. TLC R_f 0.3 (3:1 hexanes/ethyl acetate) ^{1}H NMR δ: 7.97 (m, 2H), 7.55 (m, 2H), 7.12 (m, 2H), 6.83 (m, 2H), 5.74 (s, 1H), 3.78 (s, 3H), 3.06 (s, 3H) ppm. ^{13}C NMR δ: 162.0, 160.6, 142.8, 141.6, 131.4, 130.5, 129.8, 127.7, 117.5, 114.2, 94.8, 55.5, 44.4 ppm. HRMS Calcd for $C_{17}H_{15}NO_3S$, 314.0845 $(M + H)^+$; found, 314.0845.

(13) Synthesis of Boc-3-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)propylamine. A 500-mL glass Parr shaker vessel was charged with 500 mg of **3** (1.66 mmol), 1.11 g (5.1 mmol) of di-*tert*-butyl dicarbonate, and 1 g of palladium on carbon (10% wet). Methanol (25 mL) was added to the solution, and then the reaction vessel was attached to a hydrogenation apparatus, purged 3× with hydrogen gas, and pressurized to 50 psi of hydrogen. The reaction was shaken overnight for a total of 24 h. After completion, the reaction mixture was poured though a pad of Celite and washed with copious amounts of methanol. The filtrate was evaporated in vacuo to give a clear oil that was immediately purified via silica gel chromatography (20:1 dichloromethane/methanol) to yield 570 mg (1.4 mmol, 84%) of compound **13** as an oil. TLC R_f 0.32 (1:1 hexanes/ethyl acetate) ^{1}H NMR δ: 7.85 (m, 2H), 7.42 (m, 2H), 7.28 (m, 2H), 7.02 (m, 2H) 4.58 (brs, 1H), 4.07 (t, J = 7.8 Hz, 3H), 3.07 (m, 2H), 3.06 (s, 3H), 2.27 (brq, 7.4 Hz, 2H), 1.44 (s, 9H) ppm. ^{13}C NMR δ: 161.6 (d, $^1J_{\text{C-F}}$ 246 Hz), 155.8, 150.7, 138.6, 138.4, 129.2 (d, $^3J_{\text{C-F}}$ 7.9 Hz), 128.6, 127.8, 115.7 (d, $^2J_{\text{C-F}}$ 21 Hz), 79.4, 47.9, 44.5, 39.0, 35.6, 28.4 ppm. HRMS Calcd for $C_{21}H_{26}FNO_4S$, 430.1458 $(M - \text{BOC} + \text{Na})^+$; found, 430.1457.

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Supporting Information Available: Experimental details, full characterization including ^{1}H NMR, ^{13}C NMR, HMBC, and HMQC for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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