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Copper-Mediated Cross-Coupling of Aryl Boronic Acids and Alkyl Thiols

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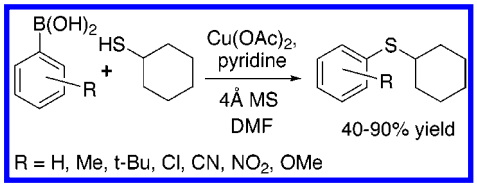
ABSTRACT



The cross-coupling of aryl boronic acids and alkanethiols mediated by copper(II) acetate and pyridine in anhydrous dimethylformamide affords aryl alkyl sulfides in good yield with a wide variety of substituted aryl boronic acids. The method is applicable to the synthesis of aryl sulfides of cysteine.

Alkyl aryl sulfides have a long and rich history as intermediates in organic synthesis.[1] Numerous methods exist for synthesizing these sulfides, typically involving the condensation of activated aryl halides with thiols under strongly basic conditions.[2] However, such methods are not applicable to the synthesis of sulfides containing readily epimerizable stereocenters. The recent advent of nelfinavir (Figure 1, **1**), a potent inhibitor of HIV protease,[3] has highlighted the need for more gentle methods for the production of these compounds. This need is further underscored by the presence of such linkages in several other biologically interesting molecules such as kynureninase inhibitors[4] and the toxins produced by *Amanita phalloidies*.[5] Recently, the conversion of unactivated aryl halides to aryl alkyl sulfides has been accomplished with stoichiometric amounts of copper[6] or catalysis by palladium.[7] However, both methods still require a strong inorganic base and an aryl halide. In the case of the copper-mediated reaction, yields are low.

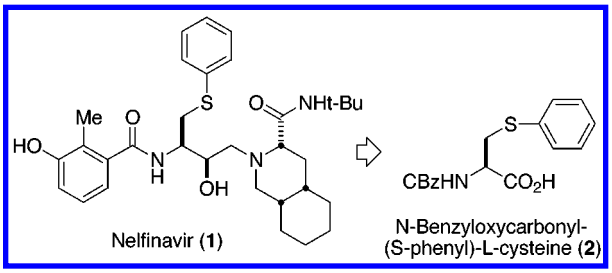


Figure 1. HIV protease inhibitor Nelfinavir (**1**).

We were recently faced with the need to form an alkyl sulfide from a π rich heterocycle and the thiol group of

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(1) Tiecco, M. *Synthesis* **1988**, 749.
(2) Sasaki, N. A.; Hashimoto, C.; Potier, P. *Tetrahedron Lett.* **1987**, *28*, 6069.
(3) Kaldor, S. W.; Kalish, V. J.; Davies, J. F., II; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.
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(7) (a) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133. (b) Arnould, J. C.; Didelot, M.; Cadilhac, C.; Pasquet, M. J. *Tetrahedron Lett.* **1996**, *37*, 4523. (c) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D., III; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606. (d) Belokon, Y. N.; Sagyan, A. S.; Djamgaryan, S. M.; Bakhmutov, V. I.; Belikov, V. M. *Tetrahedron* **1988**, *44*, 5507.

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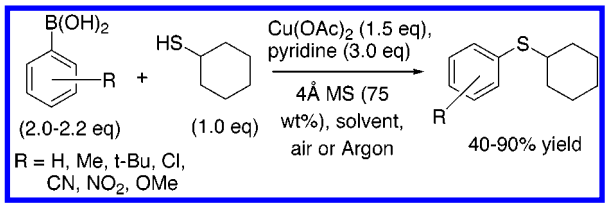
cysteine. Such heterocyclic iodoarenes can prove capricious in their tendency to decompose before undergoing productive reaction. Therefore, we set out to develop a method for the formation of alkyl aryl sulfides that both involved a more stable precursor and was suitable for application in racemization-sensitive chiral systems.

Recent work in the Chan,[8] Cundy,[9] and Evans[10] laboratories has revealed the efficacy of copper(II) acetate in mediation of the cross-coupling of aryl boronic acids and phenols or amines to give biaryl ethers and aryl alkylamines. We sought to develop a similar procedure for the formation of aryl alkyl sulfides and report herein the success of this approach. In general, this reaction (Scheme 1) proceeds as

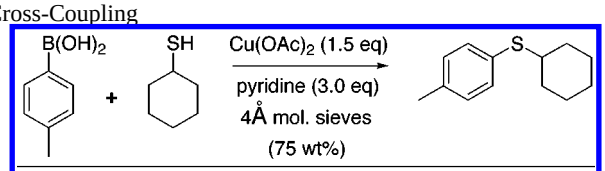
Scheme 1. Cross-Coupling of Cyclohexane Thiol with Aryl Boronic Acids



follows: Aryl boronic acids (2−2.2 equiv) are allowed to react with a limiting quantity of alkanethiols (1 equiv) with the mediation of copper(II) acetate and pyridine in anhydrous DMF to give alkyl sulfides in 40−90% yield. The reaction proceeds facilely with a variety of aryl boronic acids.

Initially, we began with the Evans conditions for the formation of biaryl ethers. In this case, the reaction proceeds in methylene chloride at 25 °C and is accelerated by the presence of oxygen. In the cross-coupling of *p*-toluene boronic acid and cyclohexane thiol (Table 1, entry 1), these

Table 1. Optimization of Reaction Conditions for Cross-Coupling

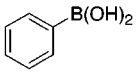
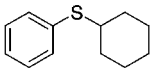
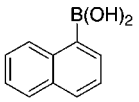
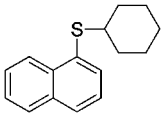
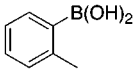
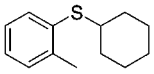
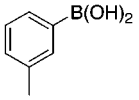
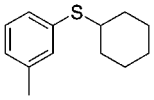
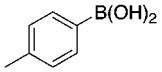
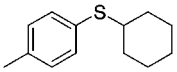
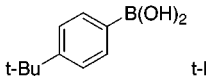
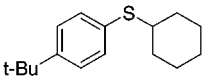
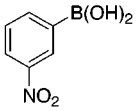
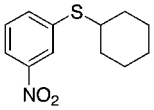
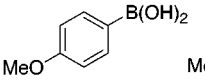
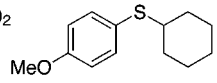
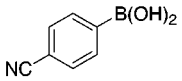
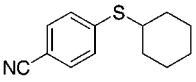
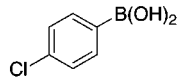
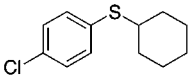


entry	atmosphere	solvent	T (°C)	time (h)	% yield
1	Air	CH_2Cl_2	25	96	49
2	Ar	CH_2Cl_2	45	96	50
3	Air	THF	70	96	55
4	Ar	THF	70	96	68
5	Ar	DMF	155	3	88

conditions did yield the expected product, but the rate of reaction was very sluggish and progression was hindered by the oxidation of free thiol to dithiane. However, other than the competitive oxidation of thiol to dithiane, the reaction proceeded very cleanly, giving only the desired product.[11] Carrying out the reaction under an atmosphere of argon abated the formation of dithiane but did not significantly enhance the rate, even at 45 °C in a sealed tube (entry 2). Switching to a more polar solvent and higher temperatures did increase the reaction rate (entries 3 and 4), but failure to exclude oxygen continued to lower the overall yield as a result of sequestration of the thiol by dithiane formation (entry 3). In each case, no significant side reactions were observed other than dithiane formation, and the problem seemed to be a slow reaction rate. The use of refluxing DMF as solvent allowed the rapid formation of the desired product with no observable side products (entry 5). These studies revealed that the optimal conditions for the reaction were 2 equiv of aryl boronic acid, 3 equiv of pyridine, 1.5 equiv of copper(II) acetate, and 75 wt % of 4 Å molecular sieves in DMF under argon.

We set out to explore the scope of the methodology with respect to the substitution of the aryl ring (Table 2). In general, the reaction is unaffected by electronic factors but moderately affected by steric hindrance of the reaction center.

Table 2. Substituent Effects in the Cross-Coupling of Cyclohexane Thiol with Aryl Boronic Acids

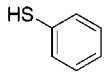
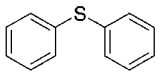
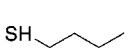
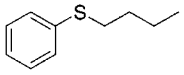
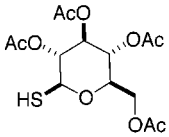
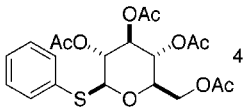
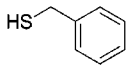
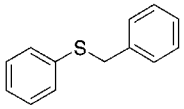
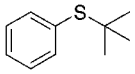
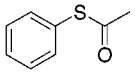
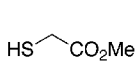
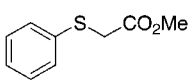
entry	aryl boronate	product	time (h)	% yield
1			3	88
2			16	41
3			16	70
4			4	85
5			3	83
6			6	75
7			4	65
8			5	66
9			5	74
10			5	85

Conditions: $Cu(OAc)_2$ (1.5 eq), pyridine (3.0 eq), 4Å molecular sieves (75 wt%), DMF, reflux , Argon.

The unsubstituted phenyl boronic acid undergoes the reaction with equal facility as the *p*-toluene boronic acid used in the initial studies (entry 1). The reaction is sensitive to sterics surrounding the boronic acid as demonstrated by the lengthened reaction times and reduced yields for the naphthalene (entry 2) and *o*-toluene (entry 3) boronic acids. However, more distal steric bulk has, as expected, little effect upon reactivity as demonstrated by the *m*-toluene (entry 4), *p*-toluene (entry 5), and *p*-*tert*-butylbenzene (entry 6) boronic acid cases. More strongly electron-donating or electron-withdrawing substitutions do not significantly affect the reaction rates or overall yields, with *m*-nitro (entry 7), *p*-methoxy (entry 8), *p*-cyano (entry 9), and *p*-chloro (entry 10) benzene boronic acids all producing good yield of the expected product within a reasonable time. Thus, the reaction is applicable to the synthesis of a wide variety of substituted phenyl sulfides and does not seem to be extremely sensitive to electronic effects. These results are at odds with the trends observed in the palladium-catalyzed cross-coupling of aryl iodides with thiols, where both strongly electron-withdrawing and electron-donating groups (*p*-methoxy and *p*-nitro) significantly inhibited the reaction.[7c] Therefore, the conditions reported herein provide advantage for such substrates.

We also examined the scope of the methodology with respect to the nature of the thiol nucleophile. These studies revealed that most thiols would enter into cross-coupling with phenyl boronic acid under the standard conditions (Table 3). Thus, this method can afford the diphenyl sulfide (entry 1), the product of coupling of a primary thiol (entry 2), and the product of coupling of a chiral secondary thiol with retention of chirality at the sulfur center (entry 3). The method can also be used with substrates that can be viewed as a protected thiol (entry 4), thus giving access to thiophenols. However, the method does not work well with tertiary thiols (entry 5), giving some product but in very low yields. The method is also inapplicable to the cross-coupling of thio acids (entry 6) or to the production of α-carboxy thiols (entry 7). Thus, the conditions reported herein tolerate a wide variety of thiols as nucleophiles but cannot be applied to the generation of tertiary alkyl aryl sulfides or aryl thioesters. Of particular note is the preservation of chirality at the sulfur containing stereocenter.

Table 3. Substituent Effects in the Cross-Coupling of Thiols with Phenyl Boronic Acid

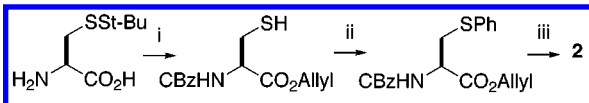
entry	thiol	product	time (h)	% yield
1			4	72
2			4	71
3			4	51
4			5	55
5			4	2
6			5	0
7			4	0

Conditions: $Cu(OAc)_2$ (1.5 eq), pyridine (3.0 eq), 4Å molecular sieves (75 wt%), DMF, reflux , Argon.

We next turned our attention to applying this method to the synthesis of *S*-aryl cysteine derivatives. As a convenient test case, we targeted the synthesis of *N*-benzyloxycarbonyl-(*S*-phenyl)-L-cysteine **2**, a key intermediate in the synthesis of Nelfinavir (Figure 1, **1**).[12]

Toward this end, *S*-*tert*-butylthio-L-cysteine (Scheme 2, **3**) was orthogonally protected by sequential blocking of the amino functionality as a carboxybenzoate and the acid functionality as an allyl ester to afford **4**. Compound **4** reacted cleanly under our standard conditions to afford the phenyl sulfide **5** in 79% yield. Selective removal of the allyl group using palladium catalysis afforded *N*-benzyloxycarbonyl-(*S*-phenyl)-L-cysteine **2**. The optical rotation of this material revealed that the reaction proceeded without epimerization of the α-carbon of the amino acid. Thus, this method is readily applicable to the synthesis of optically enriched cysteine sulfides.

Scheme 2. Synthesis of *N*-Benzyloxycarbonyl-(*S*-phenyl)-L-cysteine



3 **4** **5**

Conditions:

i) (a) Benzyloxycarbonyl chloride (1.2 eq), 10% $NaHCO_3$ in water, 1,4-dioxane (3 h, 0 °C-rt, 78%), (b) Allyl alcohol (1.3 eq), TsOH (0.2 eq), benzene (18 h, 80-100 °C, 86%), (c) Dithiothreitol (15 eq), 10% NH_4HCO_3 in water, DMF (3 h, rt, 68%); ii) Phenylboronic acid (2 eq), $Cu(OAc)_2$ (1.5 eq), pyridine (3 eq), 4Å mol sieves, DMF (2 h, reflux-110°C, 79%); iii) $Pd(PPh_3)_4$ (0.1 eq), piperidine (10 eq), PPh_3 (0.3 eq), THF (2 h, rt, 58%).

In conclusion, we have discovered a copper-mediated method for the formation of alkyl aryl sulfides from thiols

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and aryl boronic acids that proceeds in good to excellent yield with most substrates. The method is tolerant of all substitutions on the aryl ring with only modest changes in rate being attributable to steric effects. Additionally, this method works well with a variety of thiols including potentially sensitive chiral thiols and is directly applicable to the synthesis of cysteine sulfides. This new method nicely complements the existing methodologies based upon the coupling of aryl halides to thiols.

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Supporting Information Available: A complete experimental procedure for a typical coupling reaction and annotated spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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