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Exploring New Uses for C–H Amination: Ni-Catalyzed Cross-Coupling of Cyclic Sulfamates

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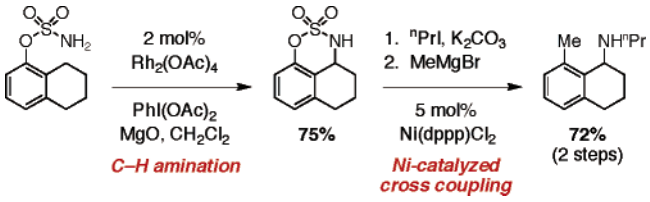
ABSTRACT



Benzene-fused cyclic sulfamates are prepared from *ortho*-substituted phenolic starting materials through selective C–H amination or olefin aziridination. These unique heterocycles will engage in Ni-catalyzed cross-coupling reactions with aryl- and alkyl-Grignard reagents. Application of modern tools for C–N and C–C bond formation thus makes readily available functional amine derivatives and augments the possible uses for C–H amination in synthesis.

The advent of new methods for the selective amination of C−H and C═C bonds has facilitated the synthesis of unique heterocyclic structures.[1] 1,2,3-Oxathiazinane-2,2-dioxides represent one such class of products that are assembled efficiently and stereoselectively through oxidative cyclization of primary sulfamate esters.[2] The strong bias for six-membered ring formation is a distinguishing feature of this process. The same reaction conditions that promote insertion at sp^3 centers, however, do not effect the amination of aryl C−H bonds. Consequently, we have been able to develop a high yielding preparation of benzo-fused oxathiazinane heterocycles **2** from *ortho*-substituted phenolic sulfamates **1** (Figure 1). Such compounds, although not without precedent, have received little attention in synthesis.[3,4] As highlighted in this report, 3,4-dihydro-1,2,3-benzoxathiazine-2,2-dioxides **2** and related cyclic structures can serve as effective starting materials for cross-coupling reactions with Grignard reagents.[5] The combination of modern catalytic tools for C−H amination and C−C bond formation thereby affords rapid entry to important functionalized amines, constituents of both natural and synthetic products.

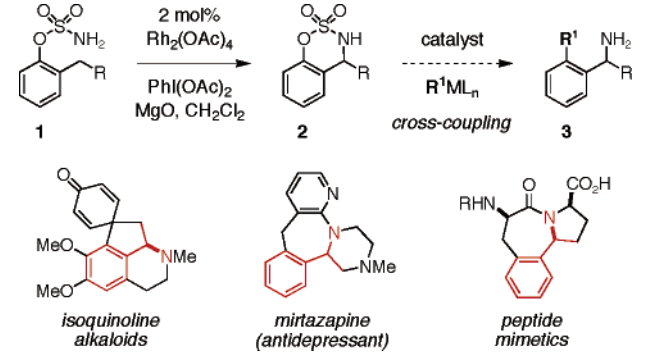


Figure 1. Applications in cross-coupling for products of C−H amination.

(1) (a) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 379−416. (b) Halfen J. A. *Curr. Org. Chem.* **2005**, *9*, 657−669. (c) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2920. (d) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586.

(2) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936.

(3) (a) Peters, R. H.; Chao, W.-R.; Sato, B.; Shigeno, K.; Zaveri, N. T.; Tanabe, M. *Steroids* **2003**, *68*, 97−110. (b) Dhar, D. N.; Bag, A. K. *Indian J. Chem.* **1983**, *22B*, 627−631. (c) Stokker, G. E.; Deana, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Russo, H. F.; Watson, L. S. *J. Med. Chem.* **1982**, *25*, 735−742.

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Phenolic sulfamates **1** may be conveniently prepared by either of two protocols using $ClSO_2NCO$ or $ClSO_2NH_2$.[6] These crystalline compounds react with $PhI(OAc)_2$, MgO, and 2 mol % $Rh_2(OAc)_4$ to give the desired benzoxathiazine products (e.g., **4**−**6,** Figure 2) in high yield. In all cases that

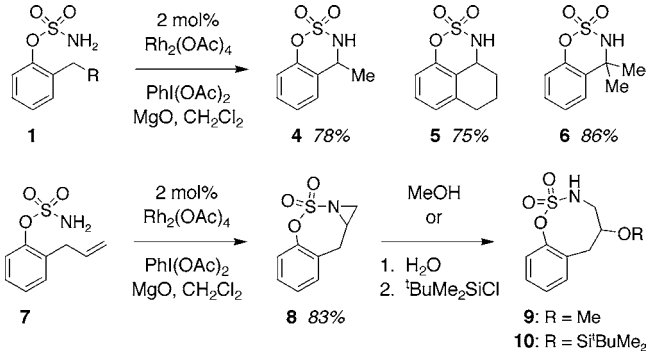
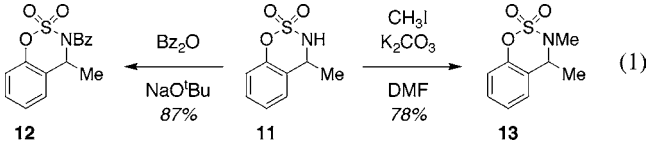


Figure 2. Oxidative methods for the preparation of benzo-fused cyclic sulfamates.

we have examined, no products resulting from aryl C−H insertion are observed. Alternatively, unsaturated sulfamates, as exemplified by **7**, will cyclize under oxidizing conditions to furnish bicyclic aziridines (e.g., **8**).[7,8] Subsequent nucleophilic addition of alcohols or H_2O to **8** occurs selectively to furnish the rather unusual eight-membered ring structures **9** and **10**.[9]

Despite their structural homology to triflates and tosylates, sulfamate esters and oxathiazines had, to our knowledge, never been described as partners in cross-coupling reactions.[10] An initial screen of catalysts and nucleophiles examined the use of various Ni and Pd salts with Grignard reagents, boronic acids, and mono- or dialkyl zinc reagents. To minimize potential side reactions, benzoxathiazine **11** was chosen as the test substrate for investigation (eq 1). We

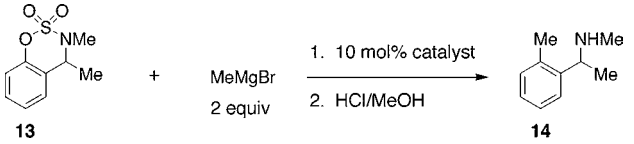


(1)

reasoned that *N*-acylation of **11** might facilitate oxidative addition of the reduced metal species into the C−O bond.[11] This modification proved ineffective, however, as almost all cross-coupling conditions employed led simply to cleavage of the acyl moiety and returned the parent heterocycle. Our subsequent efforts thus turned to the *N*-methylated derivative **13**, which was easily prepared following a standard protocol.[12]

A preliminary test of **13** against several Ni and Pd salts revealed $Ni(dppp)Cl_2$ as an optimal catalyst for cross-coupling of MeMgBr (entries 5 and 9, Table 1).[13,14]

Table 1. Screen of Reaction Conditions for Cross-Coupling



entry	catalyst	solvent	% conversion[a]
1	$Ni(dppe)Cl_2$	Et_2O	<5
2	$Ni(PPh_3)Cl_2$	Et_2O	20
3	$Ni(acac)_2$	Et_2O	70
4	$Ni(dppf)Cl_2$	Et_2O	100[b]
5	$Ni(dppp)Cl_2$	Et_2O	100
6	Ni(cod) + dppp	Et_2O	<5
7	$Ni(dppp)Cl_2$	THF	<5
8	$Ni(dppp)Cl_2$	$C_6H_5CF_3$	40
9	$Ni(dppp)Cl_2$	C_6H_6	100
10[c]	$Pd(dppf)Cl_2$	C_6H_6	<5

[a] Reactions performed at 25 °C; conversion based on ^1H NMR analysis of the unpurified reaction mixture. [b] The desired product was formed in addition with other unidentified materials. [c] Reaction performed at 55 °C.

Somewhat surprisingly, however, the combination of $Ni(cod)_2$ and dppp failed to give any of the amine product **14**, as only starting material was recovered (entry 6). Reactions conducted with alternative Ni^{2+} phosphine adducts typically afforded some of the desired compound, although consumption of benzoxathiazine **13** was incomplete. Palladium catalysts, on the other hand, showed very little activity regardless of the ligand employed. The choice of solvent also proved critical for successful cross coupling. Weakly coordinating (Et_2O) or noncoordinating (C_6H_6) solvents were

(4) Contemporaneous work by Fruit and Müller has also demonstrated oxidative cyclization reactions of phenolic sulfamates; see: Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019−1026.

(5) We refer to such heterocycles as benzoxathiazines for short.

(6) With $ClSO_2NCO$, see: Kamal, A.; Rao, A. B.; Sattur, P. B. *J. Org. Chem.* **1988**, *53*, 4112−4114. The method using $ClSO_2NH_2$ is generally preferred. For a representative procedure, see ref 2.

(7) For examples of intramolecular aziridination of homoallyl sulfamate esters, see: (a) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823−4826. (b) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481−2483.

(8) The product of benzylic C−H insertion is formed in trace amounts (<5%).

(9) We and others have observed aziridine ring opening in these types of bicyclic sulfamates to be strongly biased for nucleophilic attack at the internal C−N bond; see ref 7 for examples. Wehn, P. M.; Du Bois, J. Unpublished results.

(10) A very recent report by Snieckus highlights Ni-catalyzed cross-coupling reactions of *N*,*N*-diethyl-*O*-phenylsulfamates with ArMgX reagents; see: Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519−2522.

(11) *N*-Acylation of aliphatic oxathiazinanes increases dramatically the rate of nucleophilic displacement of the C−O bond; see ref 2.

(12) These conditions have also been employed to synthesize *N*-^{n}Pr, ^{i}Pr, ^{i}Bu, allyl, Bn, and PMB derivatives,

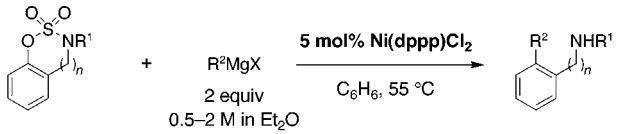
(13) Related conditions were described by Snieckus for Kumada-type reactions with aryl carbamates and aryl triflates; see: Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066−4068. Also see: (a) Milburn, R. R.; Snieckus, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 888−891. (b) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428−2432. (c) Cho, C.-H.; Yun, H.-S.; Park, K. *J. Org. Chem.* **2003**, *68*, 3017−3025. (d) Dallaire, C.; Kolber, I.; Gingras, M. *Org. Synth.* **2000**, *78*, 42−50.

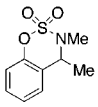
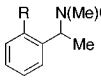
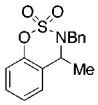
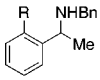
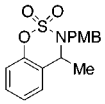
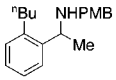
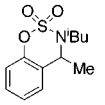
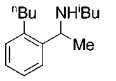
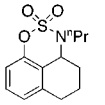
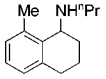
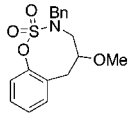
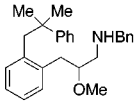
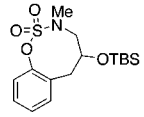
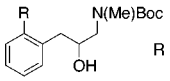
(14) We have tested both PhLi and ^{n}BuLi with $Ni(dppp)Cl_2$ but have observed none of the cross-coupled products. A small amount (∼10%) of biaryl material was obtained when 3 equiv of PhZnBr was employed.

superior to 1,2-dimethoxyethane (DME), dioxane, and THF, the latter of which appears to greatly inhibit the reaction and gives isolable amounts of the product arising formally from C−O bond reduction (vide infra).[15]

The protocol for Ni(dppp)Cl_2-catalyzed cross-coupling of benzoxathiazine **13** now established, variation of both the *N*-alkyl group on **11** and the Grignard reagent was explored. Replacement of the *N*-Me group with either ^{n}Pr, ^{i}Bu, or benzyl (Bn) did not adversely affect the reaction performance (Table 2). Conversely, the use of ^{i}Pr, CH_3OCH_2 (MOM), and allyl as N-blocking groups either decreased product yield or inhibited the reaction altogether. The lack of reactivity observed with the *N*-allylated benzoxathiazine is not surprising given that the allyl moiety is rapidly cleaved under the reaction conditions. Both benzyl and *p*-methoxybenzyl (PMB) groups can be employed, however, and thus conveniently removed if desired from the amine product.

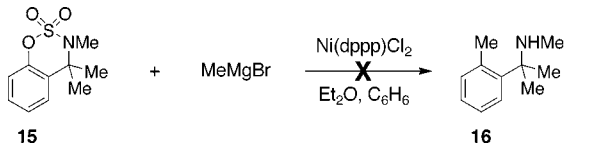
Table 2. Cross-Coupling of Cyclic Sulfamates with RMgX



entry	substrate	R^2MgX	product		yield[a]
1		MeMgBr		R = Me	72[b]
		^{c}HxMgCl		^{c}Hx	75[b]
		Me_3SiCH_2MgCl		Me_3SiCH_2	80[b,c]
2		^{i}BuMgCl		R = ^{i}Bu	95
		^{t}BuMgCl		H	91[d]
3		^{n}BuMgCl			94
4		^{n}BuMgCl			86[e]
5		MeMgBr			75
6		RCH_2MgCl			84
7		PhMgBr		R = Ph	88[f]
		BnMgCl		Bn	81[f]

[a] Reactions performed with 5 mol % Ni(dppp)Cl_2 and 2 equiv RMgX at 0.1 M in substrate. [b] Product isolated following treatment of the unpurified amine with $(CF_3CO_2)_2O$. Yield is reported for two steps. [c] Reaction performed with 10 mol % catalyst. [d] Reaction performed at 25 °C. [e] Reaction performed with 2 mol % catalyst. [f] TBS = ^{t}BuMe_2Si; product isolated following treatment of the unpurified amine with $(Boc)_2O$. Yield is reported for two steps.

Kumada-type coupling of *N*-alkyl cyclic sulfamates against a variety of Grignard reagents demonstrates the versatility of this method (Table 2). As a general rule, both alkyl- and arylmagnesium salts may be employed with 5 mol % of the Ni catalyst. In one notable exception (entry 2), use of ^{t}BuMgBr as a cross-coupling partner led to reduction of the C−O bond. This latter result is in accord with other observations we have made that show the considerable influence of steric factors on reaction performance. Accordingly, attempts to cross-couple oxathiazine **15** (eq 2) with



MeMgBr using Ni catalysts have proven unsuccessful.[16] Nevertheless, the current state of the art makes available a large number of structurally disparate amine derivatives from readily available components. The desired products are obtained following a requisite acid workup to cleave the sulfated amine intermediate.[17] In many cases, products are then purified by chromatography; alternatively, isolation of highly polar compounds is facilitated by acylating the impure material with $(CF_3CO_2)O$ or Boc_2O. Finally, as a demonstration of the overall ease of operation and utility of this protocol, the cross-coupling reaction shown in entry 4 (Table 2) was conducted on a 1 g scale with 2 mol % Ni(dppp)Cl_2 and 1.3 equiv of ^{n}BuMgCl. Under these conditions, the secondary amine is furnished in 86% yield.

The ineffectiveness of the cross-coupling reaction in THF and the isolation of the C−O reduced product (e.g., **18**, Figure 3) prompted an investigation of the reaction mechanism. Such findings are suggestive of a pathway involving the intermediacy of aryl radical species.[18] An experiment conducted with **17** in d_8-THF, however, gave no incorpora-

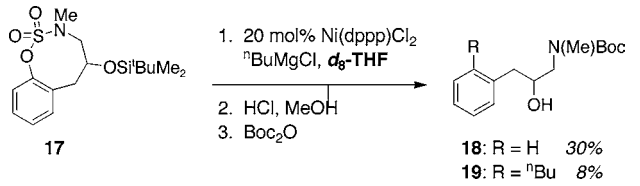


Figure 3. Experimental test confirms β-hydride elimination of Ni^{2+}-alkyl intermediate.

(15) Similar findings have been observed in Ni-catalyzed cross-coupling when THF was used as solvent; see: Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958−1969.

(16) Starting material was recovered quantitatively.

(17) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655−658.

tion of a deuterium label. Presumably, the reduced product **18** follows from β-hydride elimination of the Ni-alkyl species, [(dppp)Ni(aryl)(^{n}Bu)]. For reasons not entirely transparent, this side reaction is promoted in a more polar solvent such as THF. We speculate that the pendant SO_3^- group may play a role in stabilizing the Ni^{2+} intermediate and that THF could promote its dissociation from the metal, thereby triggering the unproductive β-hydride elimination.

Selective amination of sp^3 C−H bonds enables the preparation of a large and varied number of benzo-fused heterocyclic sulfamate structures. These compounds, interesting in their own right, can function as electrophilic partners with Ni-catalyzed cross-coupling reaction of Grignard reagents.[19] Such chemistry thus offers easy access to value-added, aryl-substituted amines and expands the number of possible uses for Rh-mediated C−H amination in synthesis.

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Supporting Information Available: General experimental protocols 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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(18) A mechanism involving a Ni^+/Ni^{3+} cycle has been discussed for related Kumada couplings; see: (a) Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003**, *68*, 1190−1199. (b) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547−7560.

(19) Initial investigations have demonstrated coupling of $ArB(OH)_2$ to benzoxathiazines with both $Ni(IMes)Cl_2$ and certain Pd catalysts.