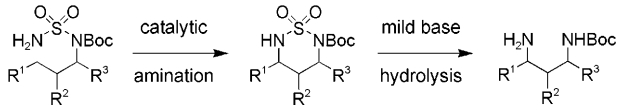
Synthetic Methods

DOI: 10.1002/anie.200806192

Synthesis of 1,3-Diamines Through Rhodium-Catalyzed C–H Insertion**

*Toshiki Kurokawa, Mihyong Kim, and J. Du Bois**

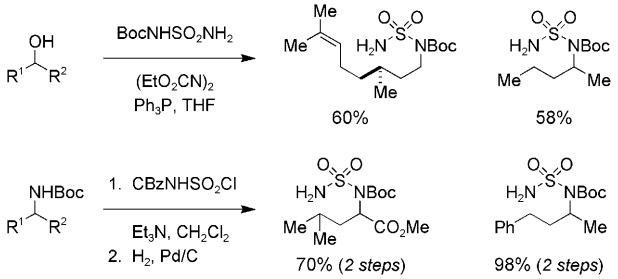
Amination of C–H bonds continues to gain prominence as a general and selective method for chemical synthesis.[1] Our research group has devised such processes using dimeric rhodium catalysts to enable the oxidative cyclization of carbamate, sulfamate, sulfonamide, urea, and guanidine substrates.[2,3] The universal nature of this C–H insertion reaction may be further exploited with reactions of alkylsulfamides (Scheme 1).[4–6] These unique starting materials



Scheme 1. A C–H amination strategy for the synthesis of cyclic sulfamides and 1,3-diamines. Boc = *tert*-butoxycarbonyl.

furnish selectively six-membered-ring heterocyclic products that are of interest as medicinal agents and as precursors to substituted 1,3-diamines, the latter transformation having been made possible under mild reaction conditions by using chemistries described herein.[7] The union of these methods represents a decided advance for C–H amination technology.

Given our success with developing sulfamate ester insertion reactions, we anticipated that *N*-alkylsulfamides would perform with similar effectiveness as substrates for oxidative cyclization. We observed, however, that simple *N*-alkylsulfamides are degraded when treated with $PhI(OAc)_2$. Prior work by our research group has demonstrated that incorporation of an electron-withdrawing group into the substrate design can mitigate this type of background reaction.[2a] Accordingly, *N*-acyl- and *N*-sulfonyl-*N*-alkylsulfamides were tested and were found to engage in the amination reaction, the *N*-Boc derivative proving superior to all others.[8] As an added benefit, this type of substituted sulfamide is made readily available from either an alcohol or a Boc-protected amine (Scheme 2). The former protocol utilizes $BocNHSO_2NH_2$, as a nucleophile for the Mitsunobu



Scheme 2. Two preparative methods for the assembly of *N*-Boc-*N*-alkylsulfamides. CBz = benzyloxycarbonyl.

reaction with either primary or secondary alcohols.[9] Alternatively, *N*-sulfamoylation of a secondary *tert*-butylcarbamate using $CBzNHSO_2Cl$ and subsequent hydrogenolytic removal of the CBz group furnishes the desired substrate. Each of the necessary reagents for these respective processes can be prepared in a single step from $ClSO_2NCO$, an inexpensive commodity chemical. Having both methods available greatly increases the number and structural diversity of *N*-Boc-*N*-alkylsulfamide derivatives that can be accessed.

Successful oxidative cyclization of *N*-Boc-*N*-alkylsulfamides is due in part to the superior performance of $[Rh_2(esp)_2]$ as a catalyst for C–H amination.[10,11] Early studies revealed that 1 mol% of this dirhodium complex in combination with $PhI(OAc)_2$, MgO, and toluene could promote C–N bond formation in modest yields. Following a recent report, we have tested isopropyl acetate (*i*PrOAc) as a solvent for this reaction and have noted improved catalyst turnover numbers in this medium.[12] The results from cyclization reactions of various sulfamide substrates under these optimized reaction conditions are summarized in Table 1. Insertion into tertiary, benzylic, and even unfunctionalized secondary C–H bonds is quite efficient, affording the six-membered-ring heterocyclic products with outstanding chemoselectivity.[13] Perhaps not surprisingly, many of the observed reactivity trends parallel reactions of sulfamate esters.[2b,14] Oxidation of optically active tertiary C–H centers is stereospecific (entry 3), thereby enabling formation of enantiopure tetrasubstituted amine derivatives. Functional groups including ester, arenesulfonyl, and azole groups are compatible with the reaction conditions. Alkene units, if positioned remote to the sulfamide moiety, are left intact (entry 3). Olefin aziridination outcompetes C–H insertion, however, in homoallyl and bis(homoallyl) derivatives (entries 9, 10). Nucleophilic opening of the aziridine ring in either of these products gives the seven-membered-ring heterocyclic sulfamide (i.e. 1,4-diamines).

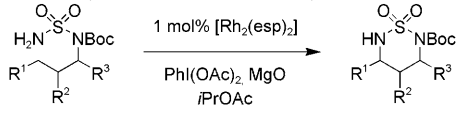
High levels of substrate-based diastereocontrol are evidenced in reactions of chiral sulfamide starting materials

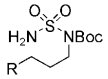
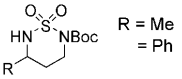
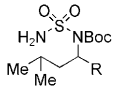
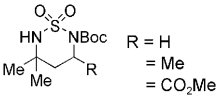
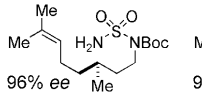
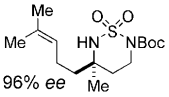
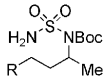
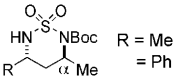
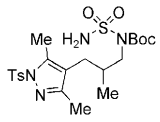
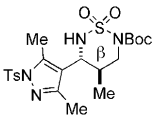
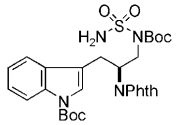
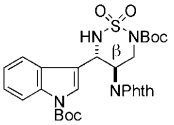
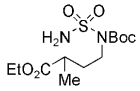
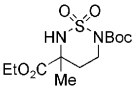
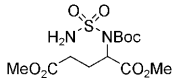
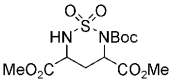
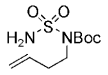
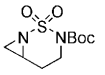
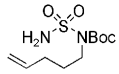
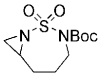
[*] Dr. T. Kurokawa, Dr. M. Kim, Prof. J. Du Bois
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0259
E-mail: jdubois@stanford.edu

[**] We are grateful to Eisai Pharmaceuticals for sponsoring T.K. as a visiting scientist. This work has been supported by the National Institutes of Health and by generous gifts from Pfizer, Amgen, GlaxoSmithKline, and Eisai.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200806192.

Table 1: Oxidative cyclization of *N*-Boc-*N*-alkylsulfamides.

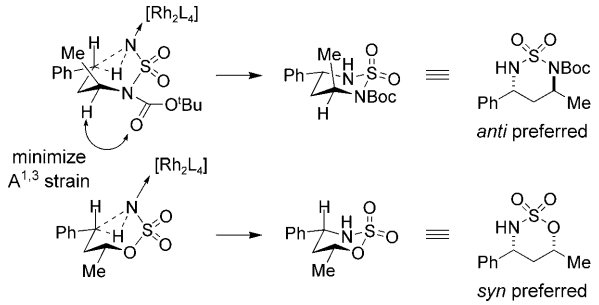


Entry	Substrate	Product[a]	*anti*/*syn*[b]	Yield [%]
1		 R = Me = Ph		93 88
2		 R = H = Me = CO_2Me		99 97[c] 94[c]
3				99
4		 R = Me = Ph	1.4:1 20:1	73[c] 82[c]
5			20:1	79
6			7:1	75
7				99
8			_[d]	10[c,e]
9				86
10				51[f]

[a] Reactions were performed with 1 mol% of $[Rh_2(esp)_2]$, 1.1 equivalents of $PhI(OAc)_2$, and 2.3 equivalents of MgO in *i*PrOAc. [b] Diastereoselectivity was determined by integration of the ^1H NMR spectra. [c] 2.5 mol% of catalyst was used. [d] Stereochemistry was not determined. [e] 30% of the five-membered-ring C–H insertion product was also obtained. [f] 29% of the six-membered-ring C–H insertion product was also obtained. Phth = phthalimide, Ts = 4-toluenesulfonyl.

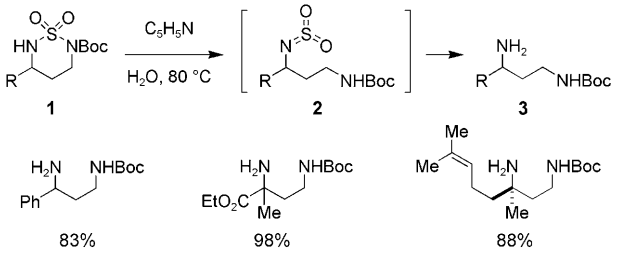
(entries 4–6). The *anti* diastereomer is favored in all cases examined irrespective of the substitution pattern (i.e., α- or β-branching) of the acyclic substrate. Results obtained with α-branched sulfamides contrast those with analogous sulfamate esters, which favor *syn* products (Scheme 3).[15] The preference for the *anti* isomer in the sulfamide oxidation may be rationalized as a minimization of $A^{1,3}$ strain in the developing product. As with sulfamate ester insertion, the responsiveness of this reaction to substituent effects is rather striking.

Hydrolytic ring opening of cyclic sulfamides has been described in rare instances and only under the most forcing of conditions.[5,16] We have found, however, that *N*-Boc derivatives react smoothly in warm, aqueous pyridine to afford the



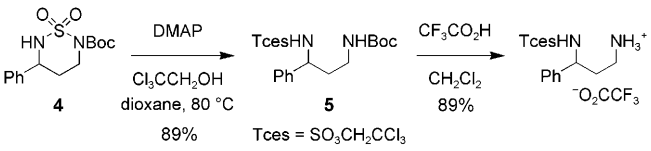
Scheme 3. A proposed stereochemical model for C–H insertion.

corresponding *N*-Boc-protected 1,3-diamines in excellent yields (Scheme 4). To our knowledge, this observation is unprecedented. It is likely that pyridine induces elimination to form an intermediate species such as **2**.[17,18] Accordingly,



Scheme 4. Facile ring-opening reactions to afford protected 1,3-diamines.

use of Cl_3CCH_2OH (20 equiv) in place of H_2O furnishes the Tces-protected amine **5** (Scheme 5). The Tces-group is stable to the acidic conditions used to effect removal of the Boc moiety. Thus, the two methods for ring opening of the cyclic sulfamides are very much complementary and provide easy access to differentially N-blocked 1,3-diamines.



Scheme 5. An alternative ring-opening sequence. DMAP = 4-dimethylaminopyridine.

Substituted cyclic sulfamides are made available through the power of rhodium-catalyzed intramolecular C–H amination. Substrates for this reaction can be easily prepared using one of two different methods. Oxidative cyclization is both chemo- and diastereoselective, in addition to being stereospecific. The combination of these features together with the discovery of a novel method for heterocyclic ring opening offers a significant tactical advance for accessing optically active 1,3-diamine products.[19]

Received: December 19, 2008
Published online: March 6, 2009

Keywords: amination · C–H insertion · diamines · rhodium · sulfamides

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[8] Acetyl, methoxycarbonyl, CBz, and *p*-methoxybenzenesulfonyl derivatives were tested.

[9] a) Y. Nishino, T. Komurasaki, T. Yuasa, M. Kakinuma, K. Izumi, M. Kobayashi, S. Fujiie, T. Gotoh, Y. Masui, M. Hajima, M. Takahira, A. Okuyama, T. Kataoka, *Org. Process Res. Dev.* **2003**, *7*, 649–654; b) Y. Iso, T. Irie, T. Iwaki, M. Kii, Y. Sendo, K. Motokawa, Y. Nishitani, *J. Antibiot.* **1996**, *49*, 478–484.

[10] $[Rh_2(esp)_2]$ is sold by the Aldrich Chemical Co. as dirhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionate)$_2$. For the initial report of this catalyst, see Ref. [3].

[11] Use of 4–5 mol% of $Rh_2(OAc)_4$ is needed to effect modest product yields with high performing substrates, see: C. G. Espino, Ph. D. Thesis, Stanford University (USA), **2004**.

[12] J. Chan, K. D. Baucom, J. A. Murry, *J. Am. Chem. Soc.* **2007**, *129*, 14106–14107.

[13] As observed for all rhodium-catalyzed C–H amination reactions, insertion into electron-deficient C–H bonds (e.g., α-carbonyl secondary C–H bonds; Table 1, entry 8) is generally marred by low product yields.

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[15] P. M. Wehn, J. Lee, J. Du Bois, *Org. Lett.* **2003**, *5*, 4823–4826.

[16] S. V. Pansare, A. N. Rai, S. N. Kate, *Synlett* **1998**, 623–624.

[17] If the *N*-Boc group is first removed from the cyclic sulfamide, then ring opening under these reaction conditions does not occur.

[18] In some cases, the isolation of the monoamine product is most easily accomplished as the oxalate salt (see the Supporting Information for details.

[19] We have recently disclosed a method for the synthesis of 1,2-diamines, see: D. E. Olson, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 11248–11249.

