Synthesis of 1,3-Difunctionalized Amine Derivatives through Selective C−H Bond Oxidation

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Amination reactions of saturated C−H bonds hold great potential as methods for the synthesis of amines and amine derivatives.[1,2] We have recently delineated one such process that makes possible the conversion of 1° carbamates to oxazolidin-2-ones using dinuclear Rh carboxylate catalysis.[2] Further explorations of this chemistry have guided us to sulfamate esters **1** (Figure 1). This uniquely reactive class of compounds affords six-membered ring insertion products **2** through exclusive γ-C−H bond amination.[3] Such findings contrast distinctly the reactions of carbamates and serve to define a new, exceptionally versatile strategy for the preparation of 1,3-amino alcohols and related β-amino acids.[4] Additionally, we have demonstrated that these seldom described oxathiazinane heterocycles **2** can be converted following *N*-carbamoylation into reactive alkylating agents. Nucleophilic displacement reactions of these electrophiles afford 1,3-difunctionalized compounds with marked efficiency. The chemistry described herein thus offers powerful methodology for the construction of myriad amine-derived materials through selective, intramolecular C−H oxidation.

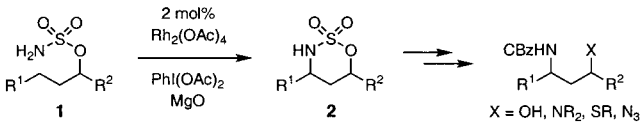
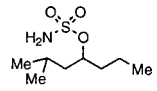
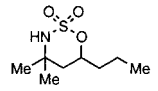
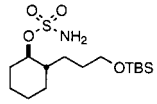
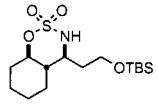
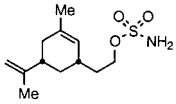
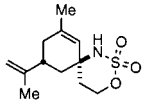
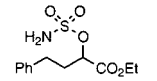
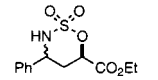
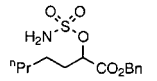
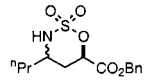
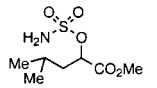
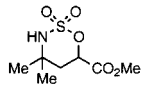
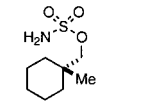
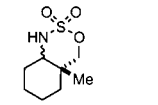
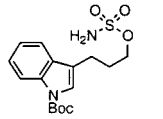
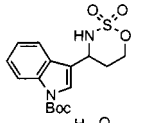
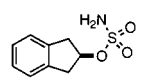
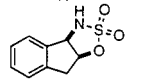


Figure 1. Rh-catalyzed oxidative cyclization of sulfamate esters.

Reported protocols for the synthesis of sulfamate esters typically employ sulfamoyl chloride, $ClSO_2NH_2$, a convenient reagent for preparative scale use made easily from inexpensive $ClSO_2NCO$ and formic acid.[5] Condensation of $ClSO_2NH_2$ with most 1° and 2° alcohols (pyridine, CH_2Cl_2) furnishes the target sulfamates in 65−75% yield.[6] These substrates react rapidly (<2 h) at 40 °C with $PhI(OAc)_2$, MgO, and 2 mol % $Rh_2(OAc)_4$ to afford the corresponding six-membered ring insertion products through selective γ-C−H insertion (Table 1).[7,8] The strong bias for oxathiazinane formation is presumably accounted for by the elongated S−O and S−N bonds (1.58 Å) and the obtuse N−S−O angle (103°) of the sulfamate, which match closely the metrical parameters of the heterocycle.[9] Nonetheless, it is possible to generate efficiently the five-membered sulfamidate in systems for which no alternative cyclization pathway is available (entry 9).

C−H amination under Rh-catalysis has general applicability with a range of structurally disparate starting materials. High product yields are obtained for sulfamates possessing 3° and benzylic C−H centers nearly without exception. Although 3° C−H bonds react in preference to 2° $-CH_2$ units (entry 1), amination of unactivated $-CH_2$ groups is catalyzed effectively.

Table 1. Oxidative Cyclization of Sulfamate Esters[a]

Entry	Substrate	Product	Catalyst[a]	Yield[b]
1			A	90[c]
2			B	75[d]
3			A	80[c]
4			B	91[e]
5			B	78[f]
6			A	86
7			A	85[g]
8			A	78[h]
9			A	60[h]

[a] (a) Catalyst: **A** = $Rh_2(OAc)_4$, **B** = $Rh_2(oct)_4$. (b) Reactions conducted for ~2 h with 2 mol % catalyst, 1.1 equiv $PhI(OAc)_2$, and 2.3 equiv MgO in CH_2Cl_2 at 40 °C; in two cases (entries 5 and 8), 5 mol % catalyst loading was employed. (c) Exclusive product as determined by ^{1}H NMR of the unpurified reaction mixture. (d) Exclusive product as determined by ^{1}H NMR of unpurified reaction mixture; stereochemistry established by nOe experiments. (e) 13:1 syn/anti by ^{1}H NMR. (f) 4:1 syn/anti by ^{1}H NMR. (g) 8:1 cis/trans by ^{1}H NMR. (h) Product isolated by crystallization; conversion is >97% from ^{1}H NMR of the unpurified reaction mixture.

(1) For leading references, see: (a) Müller, P. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press Inc.: Greenwich, 1997; Vol. 2, pp 113−151. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. (c) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120−9132. (d) Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858−7864.

(2) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600.

(3) Compound **2** is named as a 1,2,3-oxathiazinane 2,2-dioxide or as a 2,2-dioxo-tetrahydro-1,2,3-oxathiazine. We refer to such structures as oxathiazinanes for convenience. For a leading reference on the little known chemistry of these compounds, see: Riddell, F. G.; Royles, B. J. L. In *Comprehensive Heterocyclic Chemistry II*; Boulton, A. J., Ed.; Pergamon Press: Oxford, 1996; Vol. 6, pp 825−859.

(4) For recent advances in β-amino acid synthesis, see: (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (c) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411−6417. (d) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960. (e) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635−3638.

(5) (a) Benson, G. A.; Spillane, W. J. *The Chemistry of Sulfamic Acids, Esters, and their Derivatives*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: Chichester, 1991; pp 947−1036. (b) Timberlake, J. W.; Ray, W. J., Jr.; Stevens, E. D.; Klein, C. L. *J. Org. Chem.* **1989**, *54*, 5824−5826.

(6) For an alternative procedure using $ClSO_2NH_2$, see: Okada, M.; Iwashita, S.; Koizumi, N. *Tetrahedron Lett.* **2000**, *41*, 7047−7051.

(7) As determined by ^{1}H NMR of the unpurified reaction mixture.

(8) $Rh_2(OAc)_4$ and $Rh_2(oct)_4$ can be employed interchangeably with no apparent difference to the reaction outcome.

(9) An X-ray structure of the product from entry 4 has S−O and S−N bond lengths of 1.59 Å and an N−S−O angle of 105°. Conversely, the N−S−O angle in sulfamidates is 95°, see: Gritsonie, P.; Pilkington, M.; Wallis, J. D.; Povey, D. C. *Acta Crystallogr.* **1994**, *C50*, 763−765.

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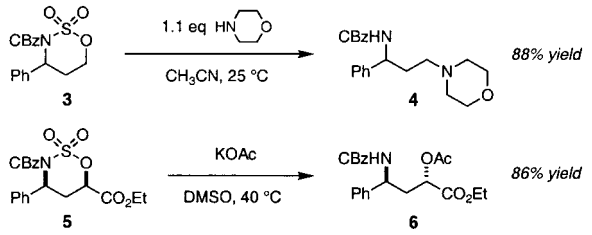
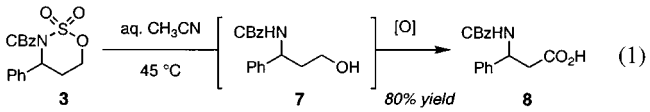


Figure 2. Representative oxathiazinane ring-opening reactions.

Notably, good to excellent levels of 1,3-diastereoselective induction are recorded for substrates derived from 2° alcohols having prochiral $-CH_2$ centers (entries 2, 4, 5, 7).[10] Preference for the 1,3−*syn* isomer ranges from 4 to >20:1, as evidenced in entries 2, 4, and 5, and is consistent with the cyclization event proceeding through a chairlike transition state.[11] 1,3-Asymmetric induction in systems such as these can be exploited for the purpose of establishing stereogenic amine centers from remote alcohol groups. Importantly, reactions with chiral substrate probes (entry 3) confirm that sulfamate insertion is stereospecific.[2,12] Thus, C−H amination is suited ideally for the *enantiospecific* preparation of quaternary stereocenters given the challenges associated with the asymmetric synthesis of such functional units.[13]

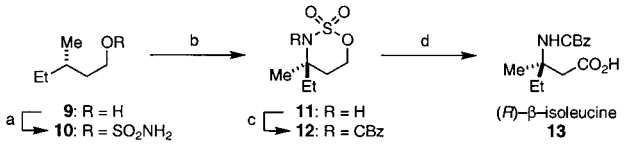
The structural homology between oxathiazinanes **2**, cyclic sulfates, and sulfamidates suggested to us that the former compounds could serve as useful electrophiles.[14] To our knowledge, only two prior reports have demonstrated that nucleophilic ring-opening of these heterocycles is indeed possible. In both examples, however, vigorous reaction conditions were employed (e.g., NaCN, DMF, 130 °C).[15] We reasoned that carbamoylation of the −NH moiety might improve the electrophilic reactivity of **2**. Accordingly, *N*-CBz oxathiazinanes **3** and **5** were synthesized using CBzCl and NaO^{t}Bu (80−90%). Ring-opening of these compounds occurs smoothly with 1° and 2° amines, thiolates, AcO^-, and N_3^- nucleophiles (Figure 2).[16] At slightly elevated temperatures (45 °C), even weakly reactive species such as water, 1° and 2° alcohols add to **3** and **5**.[17] The remarkably facile displacement reactions of *N*-CBz oxathiazinanes vis-à-vis **2** raise considerably the utility of these heterocycles for synthesis.



(1)

The effectiveness of the hydrolytic ring-opening of *N*-CBz oxathiazinane **3** in aqueous CH_3CN has enabled the development of a single-step method for the conversion of **3** to the corresponding *N*-CBz-*β*-amino acid **8** (eq 1).[4c] Addition of H_2O to **3** followed by treatment of the resulting alcohol **7** with catalytic TEMPO, NaOCl, and $NaClO_2$ (phosphate buffer, pH ≈ 3−4) produces the target compound, *N*-CBz-*β*-phenylalanine **8**, in 80% yield without recourse to intermediate purification steps.[18] By conjoining sulfamate ester cyclization with this oxathiazinane ring opening-oxidation protocol, we have further advanced a concise, asymmetric synthesis of (*R*)-*N*-CBz-*β*-isoleucine **13** (Scheme 1).[19] Synthesis of **13** (1.8 g) is thus accomplished in four straightforward and readily scalable steps from (*S*)-3-methyl-1-pentanol **9**.[20] The multigram preparation of **13** illustrates the salient potential of our C−H insertion reaction for the efficient assembly of chiral *β*-amino acids and optically pure quaternary centers.[21]

Scheme 1[a]



[a] (a) $ClSO_2NH_2$, C_5H_5N, CH_2Cl_2, 70%; (b) 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 91%; (c) CBzCl, NaO^{t}Bu, 75%; (d) aq CH_3CN, then cat. TEMPO, NaOCl, $NaClO_2$, 81%.

Intramolecular C−H amination using commercial Rh-catalysts, $PhI(OAc)_2$, and MgO offers a practical solution for the controlled oxidation of saturated C−H bonds. Reactions of sulfamates with 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$, and MgO yield selectively six-membered ring oxathiazinanes. These novel heterocycles are shown to have exceptional value as precursors for 1,3-amino alcohols, *β*-amino acids, and numerous other 1,3-difunctionalized amine derivatives. In addition, asymmetric quaternary centers are constructed with absolute stereocontrol. As such, these new chemistries should find broad application in synthesis.

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Supporting Information Available: General experimental protocols and characterization data for all new compounds including azide and thiolate ring-opened products not shown in Figure 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Stereochemical assignment is based on ^{1}H NMR coupling constants and an X-ray crystal structure for entry 4. Product ratios are determined by ^{1}H NMR integration of the unpurified reaction mixture.

(11) A similar proposal has been made by Yang to account for the observed levels of diastereoselectivity in intramolecular oxidation reactions of dioxiranes, see: Yang, D.; Wong, M.-K.; Wang, X.-C.; Tang, Y.-C. *J. Am. Chem. Soc.* **1998**, *120*, 6611−6612.

(12) Stereospecific C−H insertion has been shown in Rh-catalyzed reactions of diazoalkanes, see: Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196−199. Also, see: Taber, D. F.; Stiriba, S.-E. *Chem. Eur. J.* **1998**, *4*, 990−992 and references therein.

(13) For a leading review on the synthesis of 4° stereocenters, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.

(14) For recent references on the chemistry of cyclic sulfates and sulfamidates, see: (a) Lohray, B. B.; Bhushan, V. *Adv. Heterocycl. Chem.* **1997**, *68*, 89−180. (b) Boulton, L. T.; Stock, H. T.; Raphy, J.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1421−1429 and references therein. (c) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051−7091.

(15) (a) Lyle, T. A.; Magill, C. A.; Pitzenberger, S. M. *J. Am. Chem. Soc.* **1987**, *109*, 7890−7891. (b) Meunier, N.; Veith, U.; Jäger, V. *Chem. Commun.* **1996**, 331−332. Our findings show that compounds such as **2** (Figure 1) react with NaN_3 in DMF only at temperatures >110 °C.

(16) CH_3CN is employed as solvent with **3** and reactions are typically conducted at 25 °C. Nucleophilic additions with **5** perform most efficiently in DMSO at 40 °C.

(17) Alternatively, hydrolysis of the parent oxathiazinane is possible in aq CH_3CN at ∼100 °C (20 h).

(18) Alcohol oxidation using catalytic TEMPO as described by Merck is an extremely effective method, see: Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564−2566.

(19) For a racemic preparation of **13**, see: Dobrev, A.; Ivanov, C. *Monatsh. Chem.* **1968**, *99*, 1050−1055.

(20) Optically pure **10** is available from TCI or may be prepared conveniently following a reported protocol, see: Nakamura, Y.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2175−2182.

(21) (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13−18. (b) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1−15.