ORGANIC LETTERS

2003
Vol. 5, No. 25
4823−4826

Stereochemical Models for Rh-Catalyzed Amination Reactions of Chiral Sulfamates

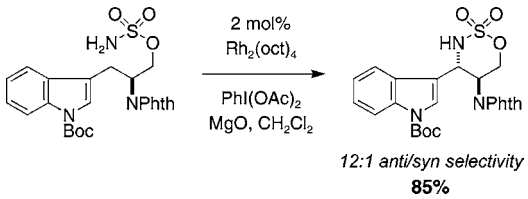
Paul M. Wehn, Jihee Lee, and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080

jdubois@stanford.edu

Received September 15, 2003

ABSTRACT



Oxidative C–H amination of chiral sulfamate esters using achiral Rh-carboxylate catalysts, $PhI(OAc)_2$, and MgO occurs in high yield and with good to excellent diastereocontrol. A number of examples are included to support a proposed transition state model that accounts for the observed stereoinduction. In addition, stereoselective intramolecular aziridination with substituted homoallyl sulfamates is demonstrated and is rationalized through an analogous stereochemical construct.

Selective methods for saturated C−H bond amination continue to evolve as general tools for synthesis.[1] We have described one such process in which sulfamate esters **1** are used in combination with a dimeric Rh(II)-carboxylate catalyst, $PhI(OAc)_2$, and MgO to give heterocyclic oxathiazinane products **2**.[2,3] A strong bias for oxidation of the γ-C−H center is observed in almost all of the examples that we have tested to date. Importantly, oxathiazinanes **2** react as electrophiles with an exceptional range of disparate agents to generate 1,3-difunctionalized amine products.[2,4] Ready access to stereochemically pure oxathiazinanes would make such compounds available for asymmetric synthesis. Herein, the first systematic study of diastereoselective C−H amination using chiral sulfamate esters is reported (Figure 1).[5] Our findings demonstrate that high levels of stereocontrol can be obtained using commercially available, achiral Rh-catalysts. The sense of induction in these reactions is predictable and can be rationalized by a simple transition state model. Accordingly, the power to employ C−H amination for diastereoselective synthesis should augment greatly the practical import of this process.

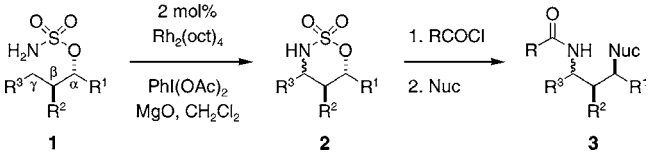


Figure 1. Diastereoselective C−H amination with chiral sulfamate esters.

The sulfamate ester prepared from 2-pentanol (entry 1, Table 1) was chosen as an initial test substrate to measure

(1) (a) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919. (c) Watson, I. D. G.; Yudin, A. K. *Curr. Opin. Drug Discov. Dev.* **2002**, *5*, 906−917. (d) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, pp 607−618.

(2) (a) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. (b) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950−12951.

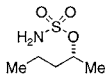
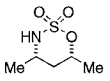
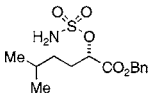
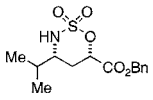
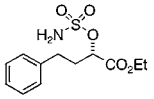
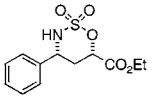
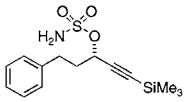
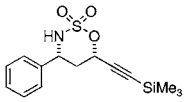
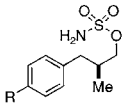
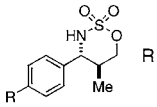
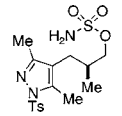
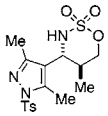
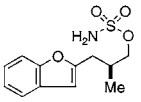
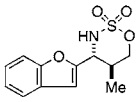
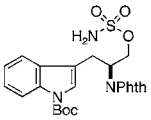
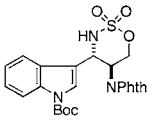
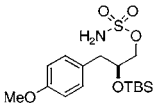
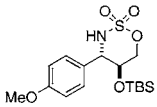
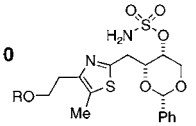
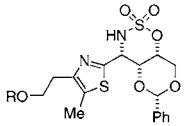
(3) For a related procedure using carbamate esters, see: Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600.

(4) For a comprehensive review, see: Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581−2616.

(5) Enantioselective sulfamate insertion using a chiral Ru-porphyrin catalyst has been described, see: Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465−3468.

10.1021/ol035776u CCC: $25.00
Published on Web 11/08/2003

Table 1. Diastereoselective C−H Amination with α- and β-Substituted Sulfamates

entry	substrate	major product	selectivity[a]	yield[b]
1			3:1	88[c]
2			8:1	55[d]
3			15:1	91
4			20:1	62[e]
5			R = CF_3 20:1 = OMe 20:1	70 85
6			20:1	84
7			20:1	65[c]
8			12:1	85[f]
9			10:1	77
10			20:1	92[c]

R = OSi^tBuPh_2

[a] Reactions performed with 2 mol % $Rh_2(oct)_4$, 1.1 equiv of $PhI(OAc)_2$, and 2.3 equiv of MgO at 40 °C, except where indicated. Product diastereoselectivity was determined by ^1H NMR integration. [b] Reported yields are of product mixtures. [c] Reaction performed with 4 mol % $Rh_2(oct)_4$. [d] Reaction performed with 8 mol % $Rh_2(oct)_4$. A 25% isolated yield of the tertiary C−H insertion product was also obtained. [e] Reaction performed with 4 mol % $Rh_2(oct)_4$ between 0 and 25 °C. [f] NPhth = phthalamide.

reaction diastereoselectivity. Following a standard protocol of $PhI(OAc)_2$, MgO, and catalytic $Rh_2(oct)_4$, a modest 3:1 *syn*/*anti* product ratio was measured.[6] Further experiments using analogous secondary alcohol-derived sulfamates (entries 2−4, Table 1) indicated that *syn*/*anti* selectivity could be influenced significantly by the steric size of groups on the sulfamate backbone. In these cases, preference for the *syn* isomer was always observed. As shown in Table 1 diastereoselection improves to levels exceeding 15:1 for amination of benzylic centers (entries 3 and 4). Reactions with such substrates are efficient and to our minds remarkably selective given the nature of this oxidation process.

To explore in greater detail stereoselective C−H insertion, a series of substituted 3-arylpropan-1-ol sulfamates was prepared (entries 5−10). These compounds afforded uniformly high stereocontrol (12−20:1), with all examples strongly favoring the *anti* oxathiazinane isomer. Notably, substrates of this type produced only trace amounts of the five-membered sulfamidate despite the intrinsic reactivity of tertiary and α-ethereal C−H bonds toward oxidative amination (entries 5−7, 9).[2,7] In addition, the reaction conditions are found to be tolerant of differing heteroaromatic and other more common functional groups.

The observed diastereoinduction in experiments with α- and β-branched sulfamates has allowed us to formulate a predictive stereochemical model (Figure 2). Placement of

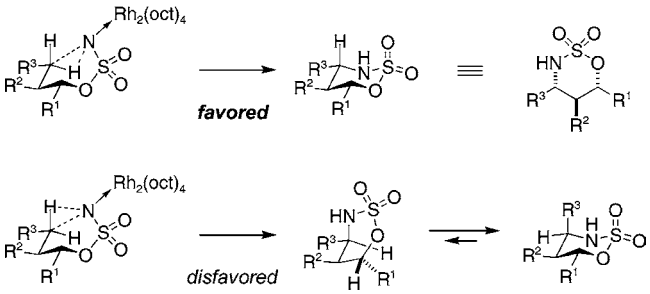


Figure 2. Proposed stereochemical model for C−H insertion.

the sulfamate group in a cyclohexane chairlike arrangement staggers groups at R^1, R^2, and R^3, thus minimizing gauche interactions between the substituents.[8] Accordingly, metallonitrene insertion into the equatorially aligned C−H bond generates a product in a low-energy chair conformation, the stereochemistry of which is consistent with the favored reaction pathway.[9] By contrast, oxidation of the axially disposed C−H center is seemingly destabilized by torsional strain induced in the developing product. Though speculative, this model provides a rationale for the *syn* and *anti* preference recorded with α,γ- and β,γ-substituted sulfamates, respectively.

We have examined further the proposed stereochemical mnemonic with sulfamates **4**, **6**, **8**, and **11** (eqs 1−4), and

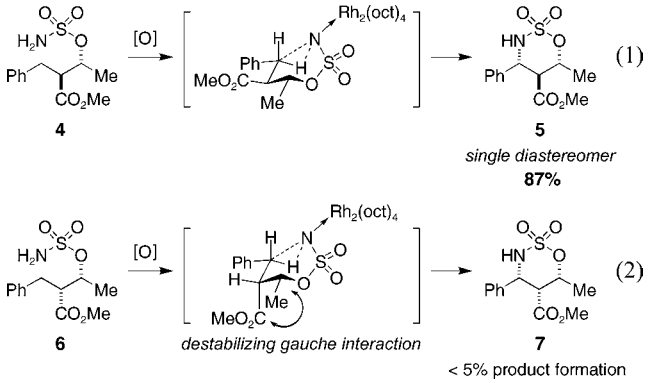
(6) Diastereomeric ratios were determined by ^1H NMR integration. Coupling constant and NOE analysis were used to assign relative stereochemistry.

(7) (a) Fleming, J. J.; Fiori, K. W. Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028−2029. (b) Fiori, K. W.; Du Bois, J. Unpublished results.

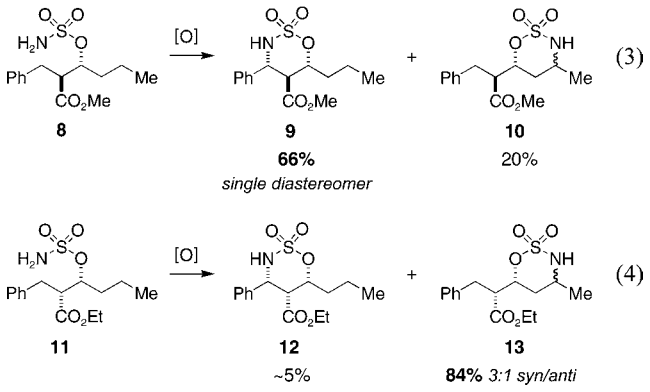
(8) For a related discussion of transition state geometries in intramolecular C−H hydroxylation reactions with dioxirane-based oxidants, see: Wong, M.-K.; Chung, N.-W.; He, L.; Wang, X.-C.; Yan, Z.; Tang, Y.-C.; Yang, D. *J. Org. Chem.* **2003**, *68*, 6321−6328 and references therein.

(9) For studies on reaction diastereoselectivity in Rh-carbene C−H insertion, see: (a) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717−3721. (b) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8, 8837−8846. (c) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547−556.

the findings from these experiments are in accord with prediction. The consonant relationship of the stereochemical elements in **4** results in excellent product diastereocontrol, furnishing oxathiazinane **5** with >20:1 selectivity (eq 1). Conversely, the *syn* isomer **6** gives <5% of insertion product **7** and returns mostly starting material (eq 2). Similar observations are made for poorly reactive substrates where catalyst oxidation is thought to compete with the desired insertion event.[3] It would appear that the dissonant stereochemical groups in **6** sufficiently reduce the rate of C−N bond formation such that catalyst deactivation arrests reaction turnover.



Our findings with sulfamates **4** and **6** suggested to us the possibility of exploiting different stereochemical substitutions to direct regioselectivity in these amination reactions. Such a concept has been highlighted using compounds **8** and **11**. Reaction of sulfamate **8** furnished 66% of oxathiazinane **9** with >20:1 diastereoselectivity (eq 3). A lesser amount of



the isomeric product **10** was also isolated as a 3:1 *syn*/*anti* mixture. The analogous experiment with **11**, however, yielded principally oxathiazinane **13** (eq 4). In this case, C−H insertion takes place distal to the attached ester group and affords the product with a 3:1 *syn*/*anti* ratio. These two complementary results underscore the effect of stereochemical substitutions on positional selectivity in C−H oxidation reactions and provide further support to the proposed TS‡ model.

Concurrent with our studies in C−H amination, we wished to determine if a similar stereochemical construct could be extended to intramolecular olefin azirdination reactions.[1,10−12]

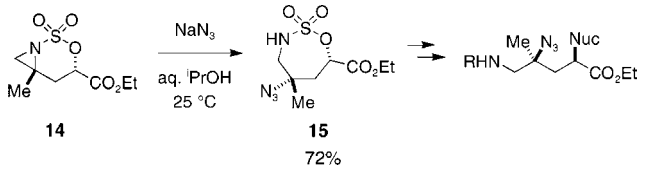
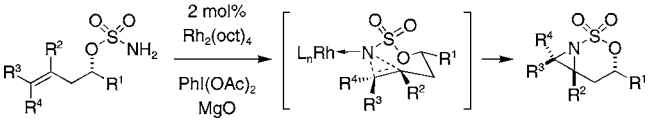
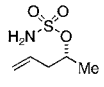
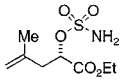
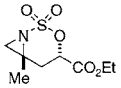
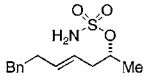
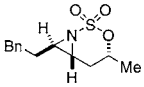
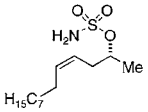
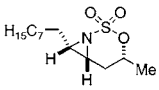


Figure 3. Nucleophilic addition to bicyclic aziridine **14**.

Bicyclic products (e.g., **14**) generated from this process are versatile precursors to polyfunctionalized amines, thus warranting further efforts to investigate their stereoselective preparation (Figure 3).[13] To this end, reactions with chiral homoallyl sulfamates were conducted using 2 mol % $Rh_2(oct)_4$, $PhI(OAc)_2$, and MgO (Table 2).[14] Results from these

Table 2. Diastereoselective Alkene Aziridination



entry	substrate	major product	selectivity[a]	yield[b]
1			4:1	84
2			4:1	92
3			2.5:1	88
4			10:1	84

[a] Reactions performed with 2 mol % $Rh_2(oct)_4$, 1.1 equiv $PhI(OAc)_2$, and 2.3 equiv of MgO in CH_2Cl_2 at 25 °C. Product diastereoselectivity was determined by ^1H NMR integration. [b] Reported yields are of product mixtures.

preliminary studies indicate that alkene azirdination occurs efficiently and with moderate levels of diastereocontrol (2.5−

(10) For Rh-catalyzed intermolecular aziridinations, see: (a) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673. (b) Müller, P.; Baud, C.; Jacquier, Y. *Can. J. Chem.* **1998**, *76*, 738−750.

(11) For Rh-catalyzed intramolecular aziridination using sulfonamides, see: Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507−4510. Using carbamates, see: (a) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137−2139. (b) Levites-Agababa, E.; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863−865.

(12) Intramolecular Cu-catalyzed aziridination with sulfamate and sulfonamide substrates has been described; see: (a) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481−2483. (b) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707−7708.

(13) Dauban and Dodd have previously demonstrated ring opening of a seven-membered cyclic sulfamidate; see ref 12a.

10:1 ds). Substrates containing terminal, 1,1-disubsituted, *trans* and *cis* olefins (entries 1−4, respectively) furnish bicyclic aziridines, each having the same sense of induction for the major isomer.[6,15] The favored formation of these products is consistent with a TS‡ in which R^1 is placed in a sterically open pseudoequatorial site and R^4 is positioned to minimize $A_{1,3}$ strain (Table 2). Analogous arguments have been presented for transition-metal-directed epoxidation and cyclopropanation reactions.[16,17] Although the magnitude of the selectivity differences between entries 1−4 is not entirely resolved from this picture,[18] such a model offers a useful, qualitative predictor of relative stereochemistry. The close parallel between this TS‡ construct and that conjectured for C−H amination is intriguing as well. Additional experiments are in progress to examine further the influence of differing stereochemical elements and catalyst structure on these reactions.

Sulfamate ester C−H and π-bond amination reactions have been established as stereoselective tools for C−N bond formation. Simple transition state models are advanced to rationalize product stereochemistry in these processes. The ability to make stereochemical predictions with a high degree of certainty confers added value to each of these unique methods.

Acknowledgment. Dedicated to our friend and mentor Professor Erick Carreira on the occasion of his 40th birthday. P.M.W is the recipient of an Eli Lilly graduate fellowship. This work was funded by grants from the NSF and the Beckman Foundation, and with generous gifts from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson Matthey, Merck, and Pfizer.

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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(14) In one example (entry 2, Table 1), a reaction performed with 0.1 mol % $Rh_2(oct)_4$ showed >95% conversion to the desired aziridine.

(15) It is of note that the substrate in entry 1 reacts with PhI═O under Cu^+ catalysis to give the aziridine as a 1:1 *cis*/*trans* mixture; see ref 12a.

(16) For a leading reference, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(17) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763−5775.

(18) We have observed that the catalyst structure can influence product diastereoselectivity in both insertion and amination reactions. Such findings suggest that the catalyst is involved in the product-forming step. A more detailed picture of the reactive substrate−catalyst complex is thus needed to account for quantitative differences in selectivity recorded for these processes.