ORGANIC LETTERS

2002
Vol. 4, No. 13
2137−2139

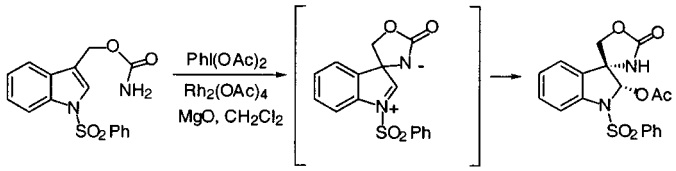
Stereochemical Aspects of the Iodine(III)-Mediated Aziridination Reaction of Some Cyclic Allylic Carbamates

Albert Padwa* and Thomas Stengel

Department of Chemistry, Emory University, Atlanta, Georgia 30322
chemap@emory.edu

Received March 29, 2002

ABSTRACT



The iodine(III)-mediated aziridination reaction of an indolyl-substituted carbamate requires a Rh(II) catalyst and proceeds by a metallonitrene intermediate. Stepwise addition across the indole π-bond followed by Rh(II) detachment generates a metal-free zwitterion, which ultimately leads to the observed products. In contrast, intramolecular aziridination of several cycloalkenyl carbamates does not require a Rh(II) catalyst and occurs via an iminoiodinane intermediate.

Vicinal amino alcohols are found in a substantial number of bioactive compounds[1] and are also utilized for asymmetric synthesis[2] and as ligands for transition metal catalyzed processes.[3] This functionality not only is of importance in the chemistry of aminosugars, carbohydrates, and nucleosides[4] but also has varied applications in organic synthesis.[5] Considering the enormous potential of the β-amino alcohol moiety for chemistry, it is not surprising that numerous synthetic routes have been reported.[6] Cyclic carbamates, readily available from cyclocarbamation of allylic or homoallylic amines and alcohols,[7] have often been used as crucial intermediates for highly stereoselective construction of both 1,2- and 1,3-amino alcohol structures. Another useful strategy is the ring opening of aziridines with oxygen nucleophiles.[8]

Although the transition metal catalyzed oxygen[9] and carbon transfer[10] to olefins is a highly developed process, significantly fewer reagents and procedures are available for the analogous nitrogen atom transfer.[11] On the basis of our

(1) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359. Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305.

(2) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. Ghosh, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937.

(3) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley-Interscience: New York, 1994. Gomez, M.; Muller, G.; Rocamora, M. *Coord. Chem. Rev.* **1999**, *193*−*195*, 769. Seyden-Pene, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley-Interscience: New York, 1995.

(4) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C. H. *Chem. Rev.* **1996**, *96*, 443. Banoub, J.; Boullanger, P.; LaFont, D. *Chem. Rev.* **1992**, *92*, 1167.

(5) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179. Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354.

(6) Williams, D. R.; Osterhout, M. H.; Reddy, J. P. *Tetrahedron Lett.* **1993**, *34*, 3271. Barrett, A. G. M.; Seefeld, M. A. *J. Chem. Soc., Chem. Commun.* **1993**, 339. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449. Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798. Marshall, J. A.; Gill, K.; Seletsky, B. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 953.

(7) Wang, T.; Izawa, S.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. Georges, M.; Mackay, D.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1982**, *104*, 1101. Bartlett, P. A.; Tauzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619.

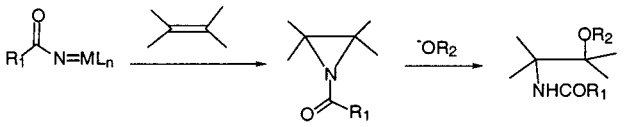
(8) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243. Pirrung, M. C.; Nunn, D. S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1489. Dehmlow, H.; Mulzer, J.; Seilz, C.; Strecker, A. R.; Kohlmann, A. *Tetrahedron Lett.* **1992**, *33*, 3607. Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59.

(9) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2. Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123.

10.1021/ol0259490 CCC: $22.00
Published on Web 05/29/2002

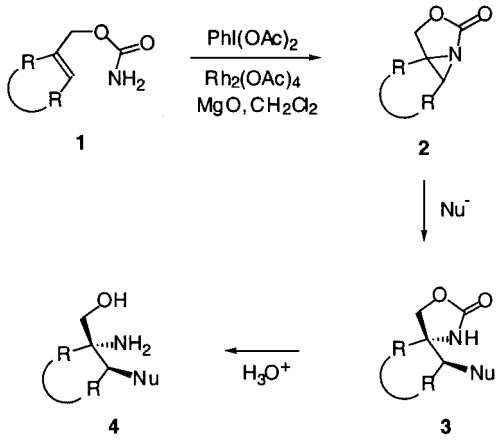
long-standing involvement with metallo carbenoids derived from α-diazocarbonyl compounds,[12] we naturally became interested in the chemistry of the corresponding acyl nitrenoids. Addition of a metallo nitrene to an olefin followed by aziridine ring opening (Scheme 1) represents an attractive approach to a variety of medicinally important vicinal amino alcohols.[13]

Scheme 1



Inspired by Du Bois' recently discovered Rh(II)-directed intramolecular nitrogen C−H insertion reaction of carbamates to oxazolidinones,[14] we wondered whether this procedure could be used for delivery of a nitrogen atom to a tethered π-bond. When we started our studies in this area, the transition metal catalyzed delivery of nitrogen from a carbamoyl nitrene to an olefin had not been described in the literature.[15] Our plan was to utilize an intramolecular primary carbamate cyclization to provide for the directed aziridination reaction shown in Scheme 2. Nucleophilic ring opening would

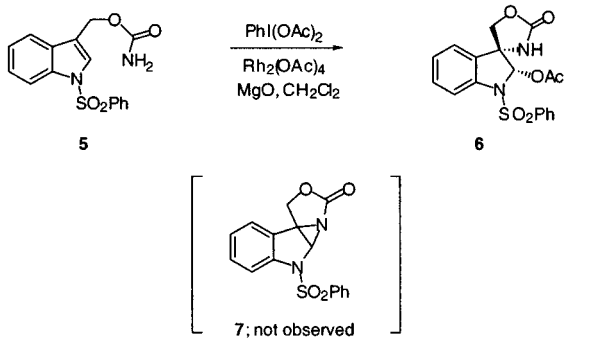
Scheme 2



generate oxazolidinone **3**, which we intended to use for the stereospecific preparation of a variety of 1,2-amino alcohol derivatives (**3** → **4**). Herein we describe the iodine(III)-mediated aziridination reaction of a carbamoyl nitrene[16] with an indole π-bond, as well as a detailed study of this reaction with several other cyclic alkenes.

Our initial studies involved the protected indolyl carbamate **5**, which was synthesized in three steps[17] [tosylation (82%), reduction (77%), and carbamoylation (71%)] starting from indole-3-carboxaldehyde. In a recent report, Du Bois and Espino described the use of iodobenzene diacetate [PhI(OAc)$_2$], MgO, and catalytic Rh$_2$(OAc)$_4$ for acyl nitrenoid generation from primary carbamates.[14] Application of these conditions to indole **5** provided oxazolidinone **6** as a single diastereomer in 85% yield (Scheme 3). The expected

Scheme 3



aziridine **7** was not observed. Rather, simultaneous spirocyclization of C$_3$ and stereoselective acylation at C$_2$ occurred, leading to compound **6**. The stereochemical assignment of **6** was unequivocally established by an X-ray crystallographic study. The stereochemical outcome of the reaction was totally unexpected and certainly incompatible with an S$_N$2 opening of a transient aziridine intermediate (i.e., **7**), since nucleophilic attack of an acetate group on the three-membered ring would lead to an *anti*-configuration of the substituent groups.[18] The experimental observations suggest a close interaction of the acetate moiety with the metal fragment, thereby favoring formation of the oxazolidinone with the *syn*-configuration of substituents. Without the addition of the Rh(II) catalyst, only recovered starting material was obtained. Interestingly, when the above reaction was carried out using iodosobenzene (PhI=O) rather than PhI(OAc)$_2$ as the oxidant[19] in the presence of 5 equiv of an added alcohol, indolines **12**, **13**, and **14** were formed in 64%, 65%, and 50% isolated yield as single diastereomers (Scheme 4).[20] Again,

(10) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1997. Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. Davies, H. M. L. *Curr. Org. Chem.* **1998**, *2*, 463. Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.

(11) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844. Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2001**, *42*, 1037. Evans, D. A.; Faul, M. M.; Bilodeau, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2742. Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707. Müller, P. Transition Metal-Catalyzed Nitrene Transfer. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2, pp 113−151.

(12) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.

(13) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897. Dauban, P.; Dod, R. H. *J. Org. Chem.* **1999**, *64*, 5304.

(14) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598.

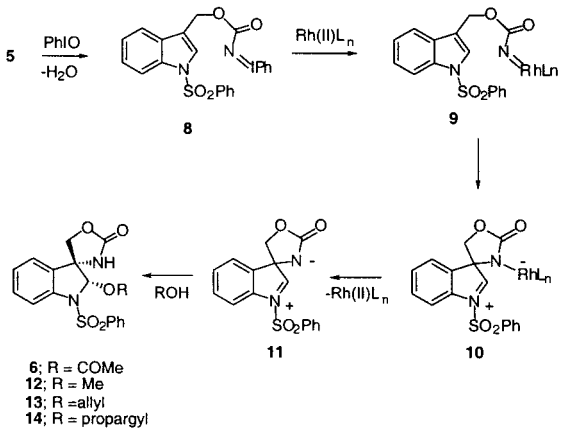
(15) While this work was in progress, Rojas and co-workers have described the amidoglycosylation of allal 3-carbamates using metallo acyl nitrenoids; see: Levites-Agababa, E.; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863.

(16) For a recent report of a transition metal catalyzed reaction of an alkenylcarbonyl azide, see: Bach, T.; Schlummer, B.; Harms, K. *Chem. Eur. J.* **2001**, *7*, 2581.

(17) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

(18) Padwa, A.; Woolhouse, A. D. *Comprehensive Heterocyclic Chemistry*, Lwowski, W., Ed.; Pergamon: Oxford, 1983; Vol. 7, pp 47−93.

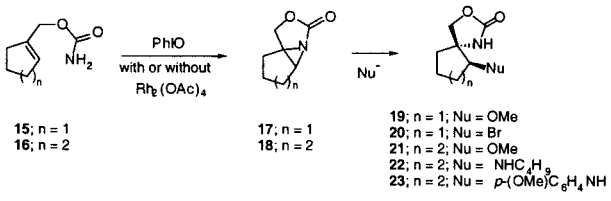
Scheme 4



without the addition of the Rh(II) catalyst, only recovered starting material was obtained. A reasonable mechanism that accounts for the experimental findings involves initial formation of an iminoiodinane intermediate (i.e., **8**) followed by catalyst (Rh(II))-promoted loss of iodobenzene to give the metallonitrene **9** (Scheme 4).[8] Stepwise addition across the indole π-bond followed by Rh(II) detachment generates the metal-free zwitterionic intermediate **11**. Attack of the neutral nucleophile will then occur on the side of the amide anion because deprotonation of the nucleophile and nucleophilic attack on the *N*-sulfonyl iminium ion can occur simultaneously to deliver indolines **12**−**14**.

With the intention of exploring the scope, generality, and synthetic opportunities of this metal-mediated nitrenoid cyclization reaction, we extended our studies to include several carbocyclic systems containing an allylic carbamate subunit. When either of the two procedures used with the indolyl system were applied to cycloalkenes **15** and **16**, tricyclic aziridines **17** and **18** were obtained in 71% and 75% yield, respectively (Scheme 5). No ring-opened products were

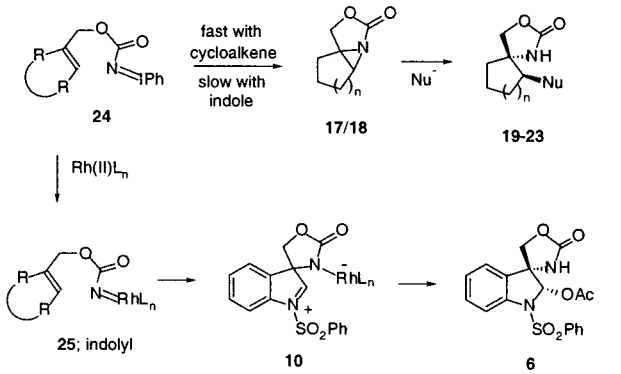
Scheme 5



observed with these systems. Although both aziridines were stable to silica gel chromatography, they did undergo reaction with various nucleophiles at room temperature in the presence of either *p*-TsOH or $LiClO_4$. In most cases the addition of 1−5 equiv of the nucleophile was used. The smooth and efficient reaction with aliphatic and aromatic amines is potentially very useful since 1,2-diamines represent an important subunit in many biological compounds.[21]

Notably, the ring-opened products (i.e., **19**−**23**) were completely anti-stereoselective;[20] only the *trans*-isomers were formed (ca. 80% yield) as expected for nucleophilic attack at the three-membered ring. This stands in marked contrast to the results encountered with indole carbamate **5** where the reaction proceeded with complete *syn*-selectivity. A clue to the differing behavior of these systems was gleaned when it was noted that the reactions of **15** and **16** proceeded smoothly in the absence of the Rh(II) catalyst. This would suggest that the initially formed iminoiodinane **24** readily reacts with the electron rich π-bond present in the cycloalkene ring (Scheme 6). In the case of the indole system,

Scheme 6



however, addition of iminoiodinane **24** to the π-bond is much slower, presumably as a result of its heteroaromatic character. It's only when **24** reacts with the Rh(II) catalyst that stepwise addition to the indole π-bond occurs, eventually producing acetate **6**.

In summary, the iodine(III)-mediated aziridination reaction of an indolyl substituted carbamate requires a Rh(II) catalyst and proceeds in a stepwise manner via a metal-free zwitterionic intermediate. In contrast, the intramolecular aziridination of several cycloalkenyl carbamates does not require a Rh(II) catalyst and proceeds via an iminoiodinane intermediate. The full scope and limitations of this novel methodology are currently under investigation.

Acknowledgment. This research was supported by the National Science Foundation (grant CHE-0132651). We thank our colleague, Dr. Kenneth Hardcastle, for his assistance with the X-ray crystallographic studies.

Supporting Information Available: Complete description of the synthesis and characterization of all compounds prepared in this study and ORTEP drawings of compounds **6**, **14**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0259490

(19) Willgerodt, C. *Chem. Ber.* **1892**, *25*, 3494. White, R. E. *Inorg. Chem.* **1987**, *26*, 3916.

(20) The stereochemical assignment of **14** (and **19**, vide infra) was unequivocally established by X-ray crystallography.

(21) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hubel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103.