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# 1,7-Asymmetric Induction in a Nitrogen Ring Expansion Process Facilitated by in Situ Tethering

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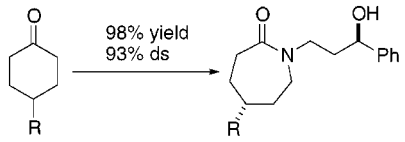
## ABSTRACT




**There are only a few methods for the asymmetric ring expansion of prochiral ketones. Symmetrically substituted cyclohexanones can be converted to the corresponding ring-expanded caprolactam with excellent 1,7-diastereoselectivity (≥93% ds) and yields (≥86%), using a chiral hydroxy azide-mediated Schmidt reaction.**

Synthetically important ring-expansion reactions include those that add the elements of carbon, oxygen, or nitrogen to an existing carbocyclic unit. To date, only a few such reactions have addressed the issues of asymmetric induction or remote regiochemical control. Most of this work has concentrated on biochemically mediated Baeyer−Villiger reactions,[1] although some progress has been recorded on nonbiological ring expansions leading to lactams,[2] lactones,[3] and carbocycles.[4] Our own interest in nitrogen-insertion reactions has largely dealt with enabling modes of stereoselectivity unavailable to traditional routes such as the Beckman or Schmidt reactions.[5] This work, which resulted in the first nonresolving method for the group-selective conversion of ketones to chiral lactams, used a three-pot protocol that featured the stereoselective photochemical rearrangement of oxaziridines as first described by Lattes et al.[6] Overall, the selectivities obtained in this scheme topped out at ca. 7:1 (88% diastereoselectivity (ds)), although enantiomerically pure lactams could be obtained by separating the diastereomerically pure N-substituted lactams prior to removing the chiral group on nitrogen.

(1) (a) Ouazzani-Chadhi, J.; Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1987**, *28*, 1109−1112. (b) Taschner, M. J.; Black, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 6892−6893. (c) Alphand, V.; Archelas, A.; Furstoss, R. *Tetrahedron Lett.* **1989**, *30*, 3663−3664. (d) Alphand, V.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1990**, *55*, 437−350. (e) Taschner, M. J.; Chen, Q.-Z. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 535−538. (f) Taschner, M. J.; Black, D. J.; Chen, Q.-Z. *Tetrahedron: Asymmetry* **1993**, *4*, 1387−1390. (g) Kelly, D. R.; Knowles, C. J.; Mahdi, J.; Taylor, I. N.; Wright, M. A. *J. Chem. Soc., Chem. Commun.* **1995**, 729−730. (h) Adger, B.; Bes, M. T.; Grogan, G.; McCague, R.; Pedragosa-Moreau, S.; Roberts, S. M.; Villa, R.; Wan, P. W. H.; Willetts, A. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1563−1654. (i) Lebreton, J.; Alphand, V.; Furstoss, R. *Tetrahedron Lett.* **1996**, *37*, 1011−1014. (j) Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1996**, *37*, 7583−7586. (k) Mazzini, C.; Lebreton, J.; Alphand, V.; Furtoss, R. *Tetrahedron Lett.* **1997**, *38*, 1195−1196. (l) Bolm, C.; Luong, T. K. K.; Schlingloff, G. *Synlett* **1997**, 1151−1152. (m) Stewart, J. D.; Reed, K. W.; Zhu, J.; Chen, G.; Kayser, M. M. *J. Org. Chem.* **1996**, *61*, 7652−7653. (n) Stewart, J. D.; Reed, K. W.; Martinez, C. A.; Zhu, J.; Chen, G.; Kayser, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 3541−3548. (o) Kayser, M. M.; Chen, G.; Stewart, J. D. *J. Org. Chem.* **1998**, *63*, 7103−7106.

(2) (a) Lyle, R. E.; Lyle, G. G. *J. Org. Chem.* **1959**, *24*, 1679−1684. (b) Lyle, G. G.; Pelosi, E. T. *J. Am. Chem. Soc.* **1966**, *88*, 5276−5279. (c) Toda, F.; Akai, H. *J. Org. Chem.* **1990**, *55*, 4973−4974.

(3) (a) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848−1849. (b) Bolm, C.; Luong, T. K. K.; Schlingloff, G. *Synlett* **1997**, 1151−1152.

(4) (a) Nemoto, H.; Ishibashi, H.; Magamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707−1712. (b) Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74−79. (c) Nemoto, H.; Tanabe, T.; Fukumoto, K. *Tetrahedron Lett.* **1994**, *35*, 6499−6502. (d) Nemoto, H.; Tanabe, T.; Fukimoto, K. *J. Org. Chem.* **1995**, *60*, 6785−6790.

(5) Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269−277.

(6) (a) Lattes, A.; Oliveros, E.; Rivière, M.; Belzecki, C.; Mostowicz, D.; Abramskj, W.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 3929−3934. (b) Aubé, J.; Burgett, P. M.; Wang, Y. *Tetrahedron Lett.* **1988**, *29*, 151−154. (c) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879−4891. (d) Aubé, J.; Hammond, M.; Gherardini, E.; Takusagawa, F. *J. Org. Chem.* **1991**, *56*, 499−508; 4086 (correction). (e) Aubé, J.; Wang, Y.; Ghosh, S.; Langhans, K. L. *Synth. Commun.* **1991**, *21*, 693−701.

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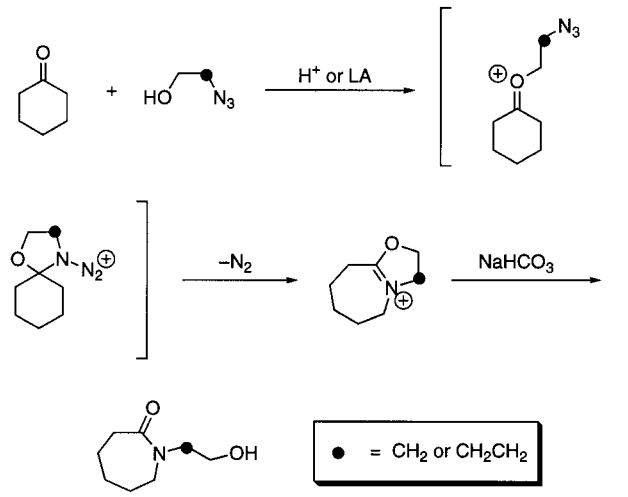
More recently, this laboratory has been exploring the utilization of 1,2- and 1,3-hydroxy azides as nitrogen ring-expansion reagents.[7] This technique allows for the high-yield synthesis of N-substituted lactams from ketones in a one-pot, two-reaction protocol. The key reaction is enabled by the initial formation of a hemiketal, dehydration to an oxonium ion, intramolecular attack by the now-attached azido group, and rearrangement along with the loss of nitrogen (Scheme 1). Notably, the intermolecular reaction of simple

**Scheme 1**

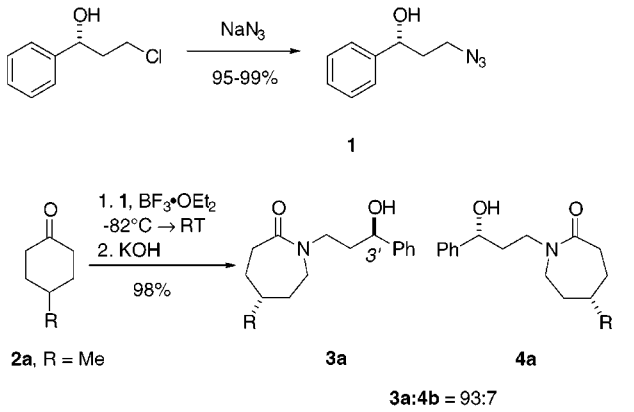



(non-hydroxy) azides fails under the same conditions.[8] A hydrolytic workup then releases a lactam identical to that which would have resulted from direct reaction of the azide portion of the molecule. This procedure is described as "in situ tethering" because the carbon−oxygen linkage is formed and released without additional synthetic operations.

The use of chiral hydroxy azides would permit the extension of this chemistry to the synthesis of chiral lactams in enantiomerically pure form. A few such examples were noted in the original disclosure; thus, 2-phenyl-2-azidoethanol combined with 4-*tert*-butylcyclohexanone to afford lactam having ds = ca. 88%.[7] Still more promising results (90% yield, 97.5% ds) were obtained when a single example of a chiral 1,3-azido alcohol was used with the same substrate, but the particular reagent used ((2*S*,4*R*)-2-azido-4-hydroxypentane) was expensive to prepare. We now wish to present a 1,3-hydroxy azide that is trivially obtained from a commercially available chiral starting material, gives superior reactions over the previously published examples (with respect to rate, yield, and selectivity), and leads to a remarkable level of 1,7-diastereomeric control in lactam formation.

As shown in Scheme 2, (*R*)-3-chloro-1-phenylpropanol reacts with sodium azide to provide azide **1** in excellent yield and ≥99% ee (HPLC; Chiracel OD-H). $BF_3$·$OEt_2$ was added to a mixture of **1** and 4-methylcyclohexanone in $CH_2Cl_2$ at

**Scheme 2**




−82 °C, and the reaction allowed to warm to room temperature. Hydrolysis of the resulting iminium ether with KOH afforded a mixture of lactams **3a**/**4a** in 98% yield and 93% ds (HPLC). In contrast, the corresponding reaction of 4-methylcyclohexanone with 2-phenyl-2-azidoethanol in ca. 20:1 cyclohexanone/$CH_2Cl_2$ proceeded only in 74% ds (81% yield) and required temperatures of about −5 °C for satisfactory conversions (reaction not shown).[9] A survey of reactions of **1** with a variety of substituted ketones shows that excellent selectivity is preserved for substituted cyclohexanones but that there is room for improvement with four-

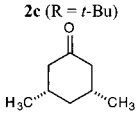
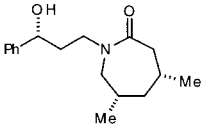
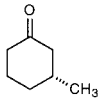
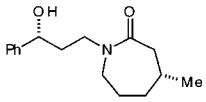
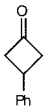
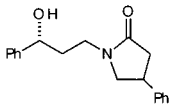
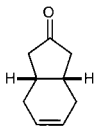
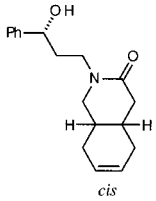
(7) (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047−8048. (b) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 10−11. (c) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241−16252. (d) For an application of this methodology to an attempted alkaloid synthesis, see: Vidari, G.; Tripolini, M.; Novella, P.; Allegraucci, P.; Garlaschelli, L. *Tetrahedron: Asymmetry* **1997**, *8*, 2893−2903.

(8) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637.

(9) **Representative Procedure.** A solution of (*R*)-3-azido-1-phenylpropanol (205 mg, 1.15 mmol) and 4-methylcyclohexanone (188 mg, 1.68 mmol) in 3 mL of $CH_2Cl_2$ was cooled to −82 °C (ether/dry ice bath), and $BF_3$·$OEt_2$ (0.56 mL, 4.48 mmol) was added dropwise. The reaction was allowed to come to room temperature over a period of 48 h. The resulting crude iminium ether was diluted with $Et_2O$ (5 mL) and hydrolyzed with 50% KOH (1 mL) added dropwise over 5 min. The solution was stirred for 30 min and partitioned between $CH_2Cl_2$ (20 mL) and $H_2O$ (10 mL). The layers were separated, and the water layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were washed with $NH_4Cl$ (5 mL), dried ($MgSO_4$), filtered, and concentrated. HPLC analysis of the crude reaction mixture showed a 93:7 ratio of diastereomeric lactams. Flash chromatography (1:1 → 9:1 EtOAc/MeOH) gave **3a** and **4a** as transparent oils in a combined yield of 296 mg (98%). TLC (1:1 hexane/EtOAc): $R_f$(**3a**) = 0.15, $R_f$(**4a**) = 0.20; HPLC $t_R$ major (**3a**) = 19.9 min, $t_R$ minor (**4a**) = 18.2 min (Chirobotic T; 90% hexane/EtOH; flow rate 1 mL/min; UV 254 nm). Major diastereomer (**3a**): $[\alpha]_D$ = −4.2 (*c* 1.02, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.99 (d, *J* = 6.6, 3H), 1.12−1.31 (m, 3H), 1.62−1.75 (m, 1H), 1.76−1.98 (m, 4H), 2.42−2.61 (m, 2H), 3.12 (dt, *J* = 14.2, 4.4 Hz, 1H), 3.24 (dd, *J* = 6.5, 15.2 Hz, 1H), 3.51 (dd, *J* = 10.9, 15.2 Hz, 1H), 4.09−4.19 (m, 1H), 4.62 (m, 1H), 7.21−7.28 (m, 1H), 7.31−7.39 (m, 4H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 22.6, 31.4, 35.7, 36.1, 37.2, 37.7, 45.7, 49.3, 69.8, 125.5, 127.0, 128.3, 144.1, 177.1; MS (EI) *m/e* 262 ($M^+$ + 1), 244(100); HRMS *m/e* calcd for $C_{16}H_{24}NO_2$ ($M^+$ + 1) 262.1807, found ($M^+$ + 1) 262.1798. Minor diastereomer (**4a**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.97 (d, *J* = 6.5 Hz, 3H), 1.18−1.30 (m, 2H), 1.65−1.95 (m, 5H), 2.50−2.56 (m, 2H), 3.01 (m, 1H), 3.32 (dd, *J* = 15.1, 5.9 Hz, 1H), 3.47 (*J* = 15.1, 11.0 Hz, 1H), 4.10−4.25 (m, 1H), 4.53 (br d, *J* = 10.4 Hz, 1H), 4.75−4.85 (m, 1H), 7.21−7.29 (m, 1H), 7.29−7.39 (m, 4H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 22.6, 31.3, 35.7, 35.8, 36.3, 37.5, 44.9, 48.4, 69.6, 125.7, 127.0, 128.2, 144.1, 177.2; MS (EI) *m/e* 262 ($M^+$ + 1), 244; HRMS *m/e* calcd for $C_{16}H_{24}NO_2$ ($M^+$ + 1) 262.1807, found ($M^+$ + 1) 262.1797.

or five-membered rings (Table 1). In most cases, an enantioselective lactam synthesis is effected by this process. However, the conversion of (*R*)-3-methylcyclohexanone to the corresponding 4-methylcaprolactam (Table, entry 5) is a relatively rare example of *overall regiochemical* control as effected by an *locally enantioselective* process.[6,10]

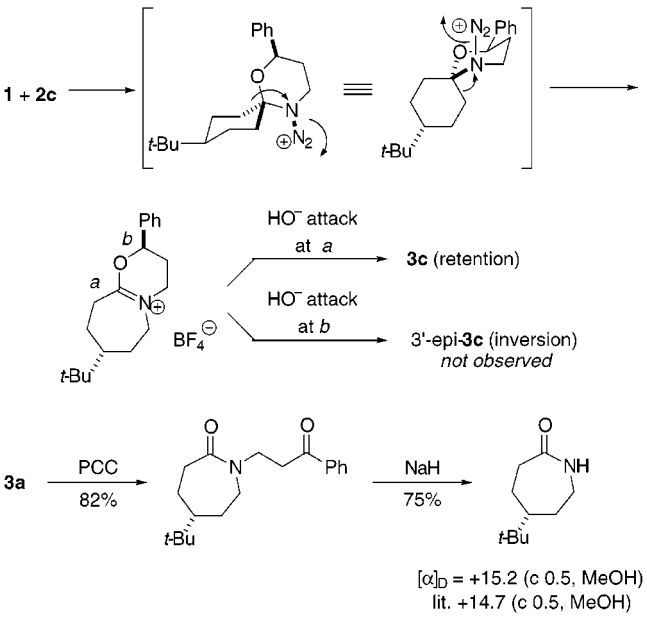
**Table 1.** Reactions of (*R*)-3-Azido-1-phenylpropanol (**1**) with Ketones

| entry | ketone | major product | ds (%) | yield (%) |
|---|---|---|---|---|
| 1 | **2a** | **3a** | 93 | 98 |
| 2 | **2b** (R = Ph) | **3b** | 96 | 99 |
| 3 | **2c** (R = *t*-Bu) | **3c** | 95 | 100 |
| 4 |  |  | 98 | 86 |
| 5 |  |  | 96 | 90 |
| 6 |  |  | 65[a] | 82[b] |
| 7 |  |  *cis* | 60[a] | 57[b] |

[a] Stereochemistry of major product was not determined. [b] Yield not optimized for this example.

The structures of the major isomers obtained from the reactions in entries 1, 3, and 5 were proven by removal of the nitrogen substituent by PCC oxidation, $\beta$-elimination with NaH (ca. 62% overall yield), and comparison of specific rotations with known lactams[6] (Scheme 3). In addition, the structure of compound **3c** was directly determined by X-ray crystallographic analysis (see Supporting Information). This precaution was required to ensure that the hydrolysis of the iminium ether intermediate did not effect inversion at the benzylic stereocenter. The other products resulting from cyclohexanone-derived ketones were assigned by analogy. From this information, we propose that the observed stereochemistry results from the following sequence of events (Scheme 3).[11] (1) The temporarily tethered alkyl azide group

**Scheme 3**




approaches the substituted cyclohexane ring from an equatorial direction (presuming that the 4-substituent is also equatorially aligned). (2) The phenyl group of the hydroxy azide chain also adopts a pseudoequatorial position. (3) The reaction proceeds by C → N migration occurring antiperiplanar to a pseudoaxial $N_2^+$ leaving group to afford the iminium ether shown. Antiperiplanar migration has long been presumed to be a feature of such bond migrations[12] and has recently been experimentally supported in the Baeyer−Villiger reaction as well.[13] (4) Hydroxide ion attack at position *a* (Scheme 3) leads to the observed product **3c**. At this point, events 2−4 are either on firm theoretical ground or have been experimentally verified, whereas the equatorial attack of the azide upon the oxonium ion (event 1 above) is proposed on the basis of the observed stereochemical course of the reaction. Further experiments to support this mechanism are currently planned.

There are several noteworthy features of this protocol. The enhanced selectivity related to previously reported versions of this reaction are undoubtedly due to the greater reactivity of this alkyl azide due to a combination of its 1,3-relationship to the hydroxyl group and the fact that the azido group itself is primary and not secondary. The overall course of the reaction allows the control of two stereogenic centers having a 1,7 relationship to one another; this is made possible by the intermediacy of the spiro species depicted in Scheme 3.

**Acknowledgment.** We thank the National Institutes of Health for support of this work (GM-49093) and Lawrence Seib for the X-ray crystallographic determination.

**Supporting Information Available:** Details of X-ray crystallographic determination of **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Aubé, J.; Hammond, M. *Tetrahedron Lett.* **1990**, *31*, 2963−2966.
(11) The transition structure given in ref 7b was incorrectly drawn (the stereocenters on the side chain were inadvertently inverted relative to the starting materials and product); it should have also indicated equatorial attack.
(12) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley & Sons: New York, 1963; Vol. 1, pp 457−591.
(13) (a) Chandreasekhar, S.; Deo Roy, C. *Tetrahedron Lett.* **1987**, *28*, 6371−6372. (b) Goodman, R. M.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9392−9393.