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Use of Optically Active Cyclic *N*,*N*-Dialkyl Aminals in Asymmetric Induction

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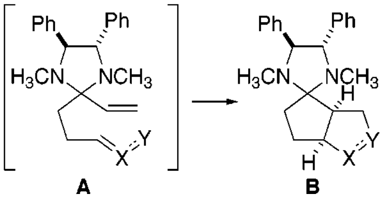
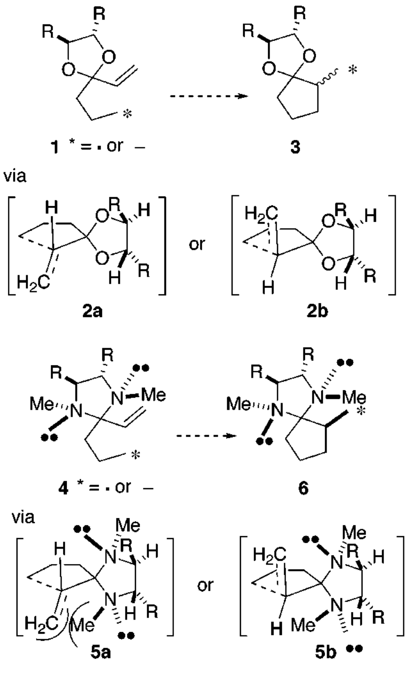
ABSTRACT



Cyclization of the optically active ketone *N*,*N*-dialkyl aminals A affords the diastereomer B as the major product with diastereoselectivities ranging from nearly 1:1 to essentially 100:0 depending on the cyclization studied.

There are many good methods available today for the preparation of optically active compounds using chiral auxiliaries.[1] Although optically active ketals are easily prepared, they have not found extensive use as chiral auxiliaries in asymmetric induction processes.[2,3] For example, if one examines the transition states for the cyclization of either the radical or anion onto the alkene, one does not find any significant energy differences between the diastereomeric transition states for cyclization, **2a**,**b**, and one would expect a nearly equimolar mixture of the two diastereomers of **3** to be formed (Scheme 1). This is due to the fact that the alkyl groups on the ketal are too far from the site of reaction to have much influence. However, optically active *N*,*N*-dimethyl aminals **4** such as those prepared by Alexakis and Mangeney[4]

Scheme 1



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[1] For a good review, see: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

[2] (a) For example, Alexakis observed that the cyclization of the anion **1** (R = Me) gave a product with a de of 52% in 29% isolated yield. A. Alexakis, personal communication. See also: Nirouël, V. Diplôme d'Etude Approfondi, Université Pierre et Marie Curie, Paris, 1993. For other examples, see: (b) Mash, E. A.; Nimkar, K. S.; Baron, J. A. *Tetrahedron* **1997**, *53*, 9043. (c) Fujioka, H.; Kitagawa, H.; Nagatomi, Y.; Kita, Y. *J. Org. Chem.* **1996**, *61*, 7309. (d) Jung, M. E.; Lew, W. *Tetrahedron Lett.* **1990**, *31*, 623. (e) For a good review, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

[3] The Alexakis group has been able to prepare substituted aminals of ketones (but not enones) under fairly harsh conditions. A. Alexakis, personal communication. See also: Tranchier, J.-P. Ph.D. Thesis, Université Pierre et Marie Curie, Paris, 1995. Londez, A. Diplôme d'Etude Approfondi, Université Pierre et Marie Curie, Paris, 1995.

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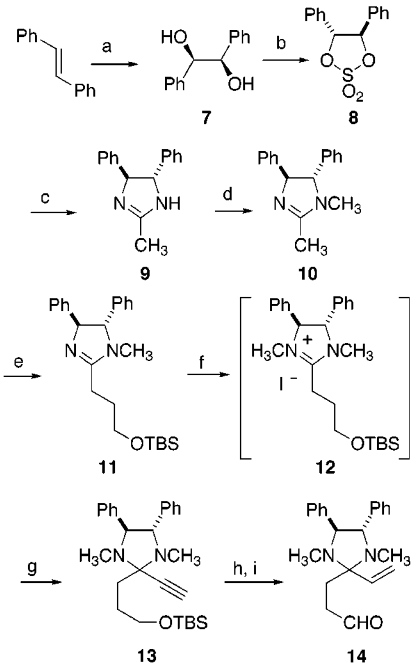
are perfectly suited to this problem, since the chirality at carbon forces the *N*-methyl groups to exist primarily in one of the two possible conformations and thus effectively moves the chirality one atom closer to the reaction site. Now the two diastereomeric transition states, **5a**,**b**, are somewhat dissimilar in energy, with the former experiencing steric hindrance from the *N*-methyl group while the latter lacks this interaction. Thus, one would expect to achieve reasonable asymmetric induction favoring the isomer **6** as shown. We now report the preparation of such fully substituted optically active aminals by an interesting route and their use in achieving good asymmetric induction.

It has been reported that *N*,*N*-dialkyl-1,2-diamines react well with aldehydes but do not react with ketones (presumably due to steric hindrance) although the simple 1,2-diamines do.[3,4] Therefore, we devised a different strategy for the preparation of the very hindered aminals **4**, as shown in Scheme 2. The readily available optically active diol **7** (prepared by Sharpless asymmetric dihydroxylation of (*E*)-stilbene) was converted into the known optically active cyclic sulfate **8**[5] and then reacted with acetamidine[6] to give the imidazoline **9** in 54% overall yield. Monomethylation of the lithium anion of **9** with 1 equiv of methyl iodide gave a quantitative yield of **10**.[7] Formation of the anion of the *C*-methyl group of **10** and alkylation (by the method of Jones)[8] with 2-iodoethanol TBS ether gave the imine **11** which was converted into the imidazolinium salt **12** on treatment with methyl iodide. After several failed attempts to add various nucleophiles to **12**, we found that the simple silylated acetylide anion added extremely well to give, after desilylation, the acetylene **13**.[9] This step forms the required hindered quaternary center and represents a new way to prepare fully substituted aminals of ketones. The aldehyde **14** was then prepared from **13** in two steps, catalytic hydrogenation and then Swern oxidation, in nearly quantitative yield.

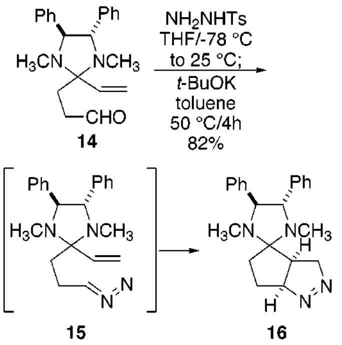
Scheme 2^{a-i}



[a] (a) Reaction conditions: (a) K_2OsO_4 $(H_2O)_2$, (DHQD) $_2$Phal, NMO, H_2O, *t*-BuOH, 100%, 92% ee; (b) $SOCl_2$, Et_3N, $CCl_4/H_2O/CH_3CN$, then $RuCl_2{\cdot}3(H_2O)$ $_2$ (cat.), $NaIO_4$, 81%; (c) acetylamidine, toluene, reflux, 16 h, 54.2%; (d) *n*-BuLi, MeI, THF, −78 °C, 99%; (e) *n*-BuLi, ICH_2CH_2OTBS, THF, −78 °C, 93%; (f) MeI, THF, 100%; (g) LiCCTMS, THF, −78 °C to rt, then 1 equiv of TBAF, 85%; (h) 5% Pd/$BaSO_4$ (cat.), H_2 (1 atm) TBAF, THF, 20 h, 98%; (i) DMSO, (COCl) $_2$, Et_3N, THF, −78 °C, 100%.

With aldehyde **14** in hand, we began to examine various intramolecular cyclizations to determine whether one could observe good asymmetric induction in this system. Thus, treatment of **14** with tosylhydrazide followed by reaction with *tert*-butoxide at 50 °C afforded an 82% yield of the pyrazoline **16** as the only isomer isolated (Scheme 3). The structure of **16** was proven by a single-crystal X-ray determination.[10] Thus, the intermediate diazo compound **15** undergoes intramolecular dipolar cycloaddition only from the bottom side of the alkene to give solely the isomer with the α ring juncture hydrogens in agreement with the picture shown in **5a**,**b**.[11] However, the difference in diastereomeric transition states is not always so clear-cut. For example, cyclization of the nitrone **17** derived from **14** is not very stereoselective (Scheme 4). Reaction of **14** with *N*-benzyl hydroxylamine afforded a 91% yield of a 1:1.2 mixture of

Scheme 3



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(4) (a) Alexakis, A.; Mangeney, P.; Lensen, N.; Tranchier, J. P.; Gosmini, R.; Raussou, S. *Pure Appl. Chem.* 1996, *68*, 531. (b) Alexakis, A.; Tranchier, J. P.; Lensen, N.; Mangeney, P. *J. Am. Chem. Soc.* 1995, *117*, 10767. (c) Alexakis, A.; Lensen, N.; Tranchier, J. P.; Mangeney, P.; Feneaudupont, J.; DeClercq, J. P. *Synthesis* 1995, 1038. (d) Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* 1993, *4*, 2431. (e) Commerçon, M.; Mangeney, P.; Tejero, T.; Alexakis, A. *Tetrahedron: Asymmetry* 1990, *1*, 287. (f) For a good review, see: Alexakis, A.; Mangeney, P. In *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed., Chapman and Hall: London, 1996; Chapter 5, pp 93−110.

(5) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999.

(6) Perrin, C. L.; Nuñez, O. *J. Am. Chem. Soc.* **1987**, *109*, 522.

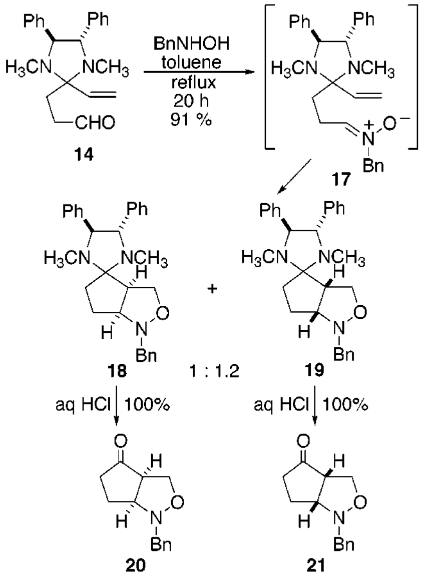
(7) Gruseck, U.; Heuschmann, M. *Chem. Ber.* **1987**, *120*, 2053.

(8) (a) Anderson, M. W.; Jones, R. C. F. *Tetrahedron Lett.* **1981**, *22*, 261. (b) Anderson, M. W.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 205. (c) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 2681.

(9) Jones reported the addition of nucleophiles to such salts to give the products of hydrolysis of the presumed dialkylated imidazolidines. Anderson, M. W.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1995.

(10) We thank Dr. Saeed Khan for his assistance in obtaining this crystal structure.

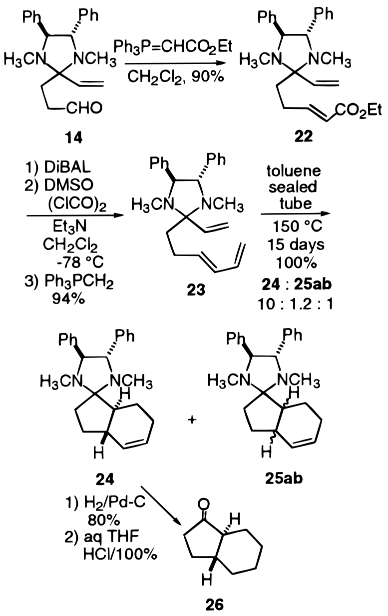
Scheme 4



the two isoxazolidines **18** and **19** which could be separated by chromatography. The structures of the two products were assigned by careful NOE experiments on both the products themselves and the ketones **20** and **21** (which are enantiomers) produced by acidic hydrolysis. Thus, the two diastereomeric transition states for cyclization of the nitrone **17** are nearly equivalent in energy.[12]

Finally, we examined a cyclization that produces a six-membered ring, namely an intramolecular Diels–Alder reaction. The substrate **23** was prepared as follows (Scheme 5). Wittig olefination of the aldehyde **14** afforded the *E* α,*β*-unsaturated ester **22** which was converted into the desired triene **23** by reduction, Swern oxidation, and a second Wittig reaction. Cyclization of the triene required high temperature for a long period but gave a quantitative yield of a 10:1.2:1 mixture of the Diels–Alder products, the expected trans compound **24**, and two other compounds **25a**,**b**, the exact structures of which could not be determined. The relative stereochemistry of the major product **24** was assigned by hydrogenation of the alkene and hydrolysis to produce the known ketone **26**.[13] The spectral data of our material, especially the ^{13}C NMR data, matched that in the literature for **26**.[13a] The absolute configuration of **26** was proven by the positive Cotton effect ($\Delta\epsilon \sim +0.8$) in its CD spectra, which is that expected for **26** due to the well-known octant rule.[14] Thus, the Diels–Alder reaction of **23** also shows a high degree of asymmetric induction due to the aminal group. It should also be pointed out that the trans ring juncture would be expected for this cyclization since earlier work had shown that the analogous ketals gave the products with the trans ring juncture as the major products.[15]

Scheme 5



Therefore, we have shown that an optically active *N*,*N*-dimethyl aminal is effective in inducing asymmetry in the formation of a carbon–carbon bond to an adjacent double bond. Further reactions in this area are currently underway in our laboratories. This novel preparation of optically active aminals of ketones opens up the possibility of their general use in diastereoselective synthesis, which would be quite useful to the field of organic synthesis.

Acknowledgment. We thank the National Institutes of Health for financial support and the National Science Foundation for a Travel Grant.

Supporting Information Available: Experimental procedures and full spectral data for compounds **9–14**, **16**, and **18–24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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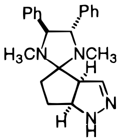
[11] In one experiment when a larger amount of potassium *tert*-butoxide was used, the 1*H* pyrazoline **i** was isolated in essentially quantitative yield. This compound is presumably formed by isomerization of the initially formed pyrazoline **16**.



i

[12] Although the ratio of products is dependent on the relative energies of the transition states leading to them, one can often estimate the differences by examining the energies of the products. Calculations (PM3) of close models (with hydrogen in place of benzyl) indicate that the two products **18** and **19** are essentially equivalent in energy (**19**-H is favored by 0.28 kcal/mol over **18**-H) while the two pyrazolines (**16** and epi-**16**, the other cis diastereomer) are very different in energy with **16** being favored by 2.6 kcal/mol.

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[14] (a) Lightner, D. A.; Gurst, J. E. *Organic Conformational Analysis and Stereochemistry from Circular Dichroism*; Wiley-Interscience: New York, 2000. (b) Lightner, D. A. The Octant Rule. *Circular Dichroism: Principles and Applications*, 2nd ed.; Nakanishi, K., Berova, N., Woody, R. W., Eds.; Wiley-Interscience: New York, 2000; Chapter 10.

[15] (a) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 3929. (b) Bal, S. A.; Helquist, P. *Tetrahedron Lett.* **1981**, *22*, 3933. (c) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1984**, *25*, 2121.