Tetrahedron Letters, Vol.31, No.25, pp 3633-3636, 1990
Printed in Great Britain

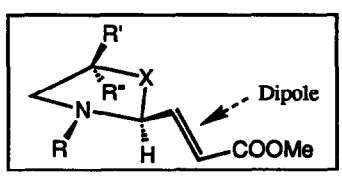
0040-4039/90 $3.00 + .00
Pergamon Press plc

ASYMMETRIC 1,3-DIPOLAR CYCLOADDITIONS OF AZOMETHINE YLIDES WITH A CHIRAL ELECTRON-DEFICIENT OLEFINIC DIPOLAROPHILE

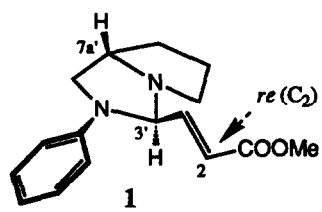
Shuji KANEMASA* and Hidetoshi YAMAMOTO†
Institute of Advanced Material Study (†Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences), Kyushu University, Kasugakoen, Kasuga 816, Japan

Summary The first example of efficient asymmetric 1,3-dipolar cycloadditions of azomethine ylides is presented, where reactive *N*-metalated azomethine ylides and the α,β-unsaturated ester with a chiral perhydropyrrolo[1,2–*c*]imidazol-3-yl moiety at the β-position have been employed. The exclusive participation of thermodynamically less stable 3-H/3'-H synperiplanar conformer is based on its sterical preference in the frontier orbital- and chelation-controlled rigid transition state.

Asymmetric version of Diels-Alder reaction now offers a powerful and reliable synthetic methodology for constructing stereochemically complex framework of organic molecules.[1] High diastereo- or enantioselectivities are frequently observed when the six-membered ring-forming process is performed at a low reaction temperature in the presence of an effective Lewis acid catalyst which works not only to activate dienophiles and/or dienes but also to tighten the transition state by chelate formation.[2]



Chiral Dipolarophiles

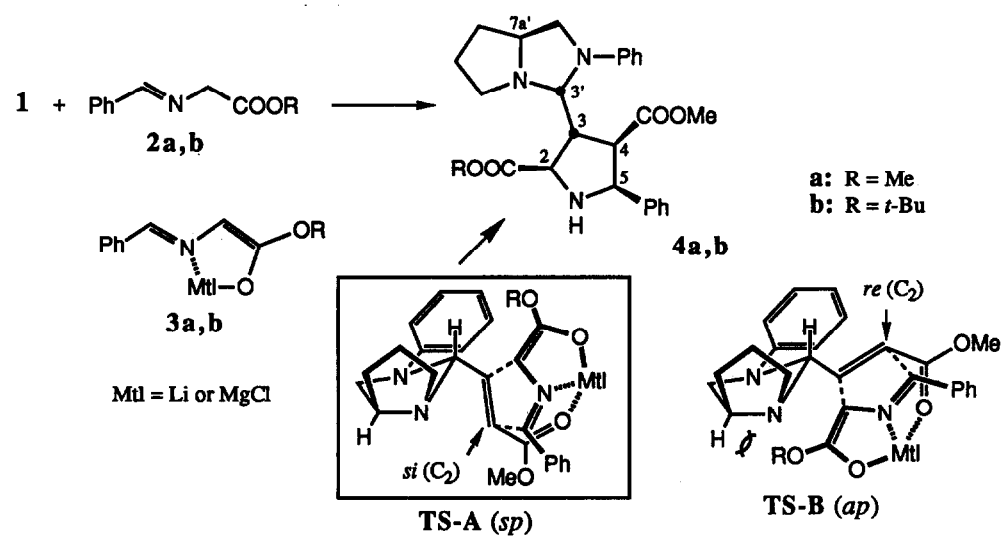


1

Unlike Diels-Alder reactions, the successful control of stereo- and regioselectivities by use of Lewis acid is unknown in the field of 1,3-dipolar cycloaddition reactions,[3] and most of the hitherto reported asymmetric 1,3-dipolar cycloadditions have been carried out without catalyst by using chiral dipoles or dipolarophiles;[4] the level of diastereoselectivity achieved is rather low, depending upon the proper choice or combination of 1,3-dipoles and dipolarophiles. We expected that α,β-unsaturated carbonyl compounds bearing a 2-pyrrolidinyl chiral controller, or heteroanalog (X: heteroatom), would serve effectively as chiral dipolarophiles of activated types since the approach of dipole from one side of the olefin face would be sterically hindered by the extruding *N*-substituent R. However, there is no example reported for the use of such chiral olefins in asymmetric cycloadditions.

The present communication describes the first example of efficient asymmetric cycloadditions of azomethine ylides,[5] where highly reactive *N*-metalated ylides and an α,β-unsaturated ester bearing a bicyclic aminal type chiral controller at the β-position are used.

Methyl (3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazole-3-(*E*)-propenoate (**1**), was selected as chiral dipolarophile of the above mentioned type since **1** can be readily prepared in a diastereomerically pure form from (*S*)-2-(*N*-phenylaminomethyl)pyrrolidine and methyl (*E*)-4-oxobutenoate,[6] and can be employed in the subsequent cycloaddition without further purification.[7] The predominant involvement of thermodynamically more stable 3-H/3'-H antiperiplanar conformer (*ap*) of **1**, rather than 3-H/3'-H synperiplanar isomer (*sp*), in the cycloaddition is expected,[8] so that the *re*–face (C_2) would be open to the attack of dipole because of the critical steric hindrance caused by the *N*-phenyl substituent.



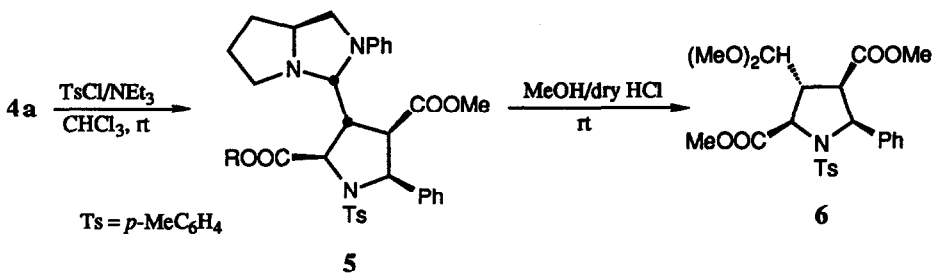
Scheme 1.

The reaction of methy (benzylideneamino)acetate (**2a**) with **1** smoothly took place, at –78 °C for 5 h in tetrahydrofuran (THF), in the presence of lithium bromide (1.5 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.2 equiv.) to give 82% yield of cycloadduct **4a** as a single diastereomer (Scheme 1). The structural assignment of **4a** was accomplished on the basis of spectral data.[9] Relative stereochemistry of the newly formed pyrrolidine ring was based on ^{1}H NMR analysis,[10] where the strong magnetic shielding of 4-COOMe (δ 2.90) by both 5-Ph and *N*-Ph substituents and the notable NOE observed between 7a'-H and 4-H definitively determined the absolute configuration of **4a**.

Although the exclusively high stereoselectivity creating four new chiral centers on the pyrrolidine ring was not surprising,[10] the absolute diastereofacial selectivity should be emphasized. Absolute configuration of **4a** was not the one derived from the anticipated transition state **TS-B** (R: Me) which involves an attack of *N*-lithiated azomethine ylide **3a** (Mtl: Li) to the thermodynamically more favored 3-H/3'-H antiperiplanar

conformation of **1** from the side opposite to the 2-phenyl obstacle. The actually involved transition state producing **4a** is **TS-A** (R: Me) where ylide **3a** attacked the *si*-face (C_2) of 3-H/3'-H synperiplanar conformation of **1**. Existence of serious steric hindrance between the ester moiety (R: Me) of **3a** and 7a'-H of **1**, or between the ester moiety and the bridgehead nitrogen, would be a major stereoselectivity-determing factor as shown in **TS-B**.

Removal of the heterocyclic chiral controller from **4a** was performed by a sequence of *N*-tosylation and acetal exchange reaction (Scheme 2). Thus, cycloadduct **4a** was allowed to react with *p*-toluenesulfonyl chloride and triethylamine in chloroform at room temperature to give tosylate **5** in 66% yield, and **5** was treated with methanol saturated with dry hydrogen chloride at room temperature. No epimerization was observed during the above transformation, and the resulting polyfunctionalized 2,4-pyrrolidinedicarboxylate **6** showed $[\alpha]_D$ = -40.9° [c = 1.0, $CHCl_3$].



Scheme 2.

The absolutely diastereoselective formation of **4a** mentioned above was not affected in the reaction at room temperature (**4a**: 79% yield), where ylide **3a** (Mtl: Li) was generated by treating **2a** with lithium bromide and triethylamine. In the case of *t*-butyl ester **3b**, 96% yield of **4b** was obtained under the equivalent conditions. *N*-Magnesioazomethine ylide **3a** (Mtl: MgCl), generated from **2a** and *t*-butylmagnesium chloride at –78 °C, slowly reacted with **1** at the same temperature to give 30% yield of **4a** as a single diastereomer.

Cycloadditions of **1** and related olefins with azomethine ylides and other 1,3-dipoles are now under investigation in our laboratory; the full details will be soon published elsewhere.

References

1. Review: L. A. Paquette, "Asymmetric Cycloaddition Reactions," in "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., New York (1984), Vol. 3, Chap. 7, pp. 455-501. Recent papers: A. Pouilhes, E. Uriarte, C. Kouklovsky, N. Langlois, Y. Langlois, A. Chiaroni, and C. Riche, *Tetrahedron Lett.*, **30**, 1395 (1989); M. E. Jung, W. D. Vaccaro, and K. R. Buszek, *ibid.*, **30**, 1893 (1989); R. F. Menezes, C. A. Zezza, J. Sheu, and M. B. Smith, *ibid.*, **30**, 3295 (1989); P. G. McDougal, J. M. Jump, C. Rojas, and J. G. Rico, *ibid.*, **30**, 3897 (1989).

2. D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988); K. Furuta, S. Shimizu, Y. Miwa, and H. Yamamoto, *J. Org. Chem.*, **54**, 1481 (1989); I. Alonso, J. C. Carretero, and J. L. G. Ruano, *Tetrahedron Lett.*, **30**, 3853 (1989); H. Walsmann and M. Dräger, *ibid.*, **30**, 4227 (1989); K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989); E. J. Corey, R. Imwinkelried, S. Pikul, and Y. B. Xiang, *ibid.*, **111**, 5493 (1989); T. Poll, A. F. A. Hady, R. Karge, G. Linz, J. Weetman, and G. Helmchen, *Tetrahedron Lett.*, **30**, 5595 (1989).

3. A. Padwa, "1,3-Dipolar Cycloaddition Chemistry," A Wiley-Interscience Publication, New York (1984), Vols. 1 and 2.

4. M. D. Amici, C. D. Micheli, A. Ortisi, G. Gatti, R. Gandolfi, and L. Toma, *J. Org. Chem.*, **54**, 793 (1989); S. F. Martin, M. S. Dappen, B. Dupé, C. J. Murphy, and J. A. Colapret, *ibid.*, **54**, 2209 (1989); K. Kasahara, H. Iida, and C. Kibayashi, *ibid.*, **54**, 2225 (1989); A. Brandi, P. Cannavò, K. M. Pietrusiewicz, M. Zablocka, and M. Wieczorek, *ibid.*, **54**, 3073 (1989); J. A. White, R. A. Badger, H. S. Kezar III, A. J. Pallenberg, and G. A. Schiehser, *Tetrahedron*, **45**, 6631 (1989).

5. T. Takahashi, K. Kitano, T. Hagi, H. Nihonmatsu, and T. Koizumi, *Chem. Lett.*, **1989**, 597; P. Garner, K. Sunitha, W.-B. Ho, W. J. Youngs, V. O. Kennedy, and A. Djebli, *J. Org. Chem.*, **54**, 2041 (1989); J. Rouden, J. Royer, and H.-P. Husson, *Tetrahedron Lett.*, **30**, 5133 (1989).

6. M. Asami and T. Mukaiyama, *Chem. Lett.*, **1970**, 569; M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **51**, 1869 (1978).

7. Although monocyclic 2-oxazolidinyl chiral controllers are readily accessible from chiral 2-amino alcohols and α,β-unsaturated aldehydes, low stereoselectivity at the 2-position and chemical instability discouraged us to use them in the present research.

8. F. D. Lewis, J. D. Oxman, and J. C. Huffman, *J. Am. Chem. Soc.*, **106**, 466 (1984); R. J. Loncharich, T. R. Schwartz, and K. N. Houk, *ibid.*, **109**, 14 (1987).

9. **4a**: IR (KBr) 3200 and 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.69 (1H, ddt, *J* = 12.4, 7.8, and 4.6 Hz, one of 7'-H), 1.8 - 1.9 (2H, m, 6'-H), 2.15 (1H, ddt, *J* = 12.4, 7.8, and 4.6 Hz, the other of 7'-H), 2.78 (1H, dt, *J* = 8.8 and 7.1 Hz, one of 5'-H), 2.90 (3H, s, 4-COOMe), 3.02 (1H, dd, *J* = 8.8 and 7.1 Hz, one of 1'-H), 3.2 - 3.3 (2H, m, 3-H and the other of 5'-H), 3.36 (1H, dd, *J* = 8.1 and 5.5 Hz, 4-H), 3.72 (1H, dd, *J* = 8.8 and 7.3 Hz, the other of 1'-H), 3.91 (3H, s, 2-COOMe), 3.98 (1H, m, 7a'-H), 4.06 (1H, d, *J* = 8.1 Hz, 2-H), 4.72 (1H, d, *J* = 8.1 Hz, 5-H), 4.74 (1H, d, *J* = 3.2 Hz, 3'-H), and 6.6 - 7.4 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 25.40, 31.40, 50.88, 51.29, 52.08, 52.30, 54.73, 57.09, 62.62, 63.01, 65.31, 82.57, 113.01, 116.84, 126.69, 127.28, 128.02, 129.10, 139.15, 146.10, 172.67, and 173.51; MS *m/z* (rel intensity, %) 449 (M^+, 5), 448 (16), 264 (15), 188 (16), 187 (base peak), 159 (40), 158 (15), 117 (12), 108 (10), 107 (12), and 104 (16).

10. O. Tsuge, S. Kanemasa, and M. Yoshioka, *J. Org. Chem.*, **53**, 1384 (1988); S. Kanemasa, M. Yoshioka, and O. Tsuge, *Bull. Chem. Soc. Jpn.*, **62**, 869 and 2196 (1989).

(Received in Japan 7 May 1990)