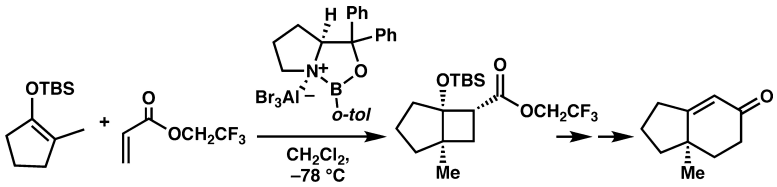
Communication

Highly Enantioselective [2+2]-Cycloaddition Reactions Catalyzed by a Chiral Aluminum Bromide Complex

Eda Canales, and E. J. Corey

J. Am. Chem. Soc., **2007**, 129 (42), 12686-12687• DOI: 10.1021/ja0765262 • Publication Date (Web): 27 September 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 12 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 09/27/2007

Highly Enantioselective [2+2]-Cycloaddition Reactions Catalyzed by a Chiral Aluminum Bromide Complex

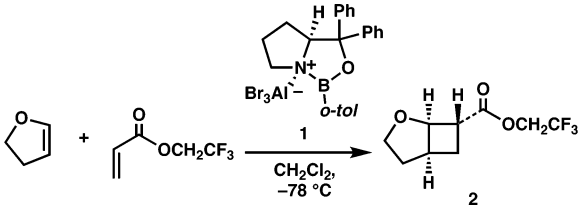
Eda Canales and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received August 29, 2007; E-mail: corey@chemistry.harvard.edu

There are just a few reported examples of catalytic enantioselective [2+2]-cycloaddition reactions of achiral components. Narasaka et al. described the application of chiral TADDOL−$TiCl_2$ catalyst to the cycloaddition of allenyl thioethers and *N*-fumaryl-1,3-oxazolidinone.[1] Later, Engler et al. used the same catalyst for the cycloaddition of methoxy-1,4-benzoquinones to a few styrenes.[2] The products of these specialized reactants were not utilized for synthetic objectives. Here we describe the positive results of a project aimed at developing a new and useful methodology for the synthesis of chiral cyclobutanes starting from the known Lewis acid-catalyzed reaction of vinyloxysilanes and α,β-unsaturated esters to form racemic [2+2]-adducts.[3] The present approach was stimulated by our recent finding that the oxazaborolidine−aluminum bromide complex **1** is exceedingly effective as a chiral catalyst for many Diels−Alder reactions of achiral components.[4]

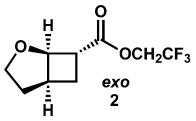
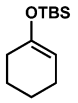
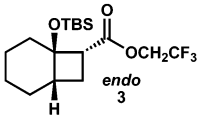
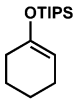
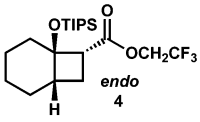
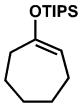
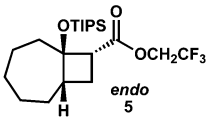
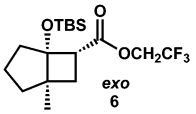
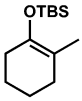
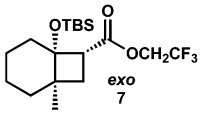
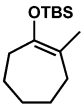
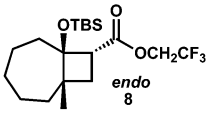
Catalyst **1** is conveniently generated in situ by the addition of a commercially available solution of aluminum bromide in CH_2Br_2 (Aldrich) to a cold (<−20 °C) CH_2Cl_2 solution of the known oxazaborolidine component[5,6] (ratio of $AlBr_3$ to oxazaborolidine, 0.8:1). In a typical example, the slow addition of 1 equiv of 2,3-dihydrofuran to a solution of 0.1 equiv of catalyst **1** and 5 equiv of trifluoroethyl acrylate in CH_2Cl_2 at −78 °C and further reaction at −78 °C for 3 h produced after isolation the *exo*-[2+2]-cycloadduct **2** in 87% yield and with 99% ee.[7,8] This process represents a very direct and practical route to this previously unknown chiral cyclobutane.[9]



We next tested the catalytic [2+2]-cycloaddition process with enol silyl derivatives of various ketones since, if operable, this operation might be broadly useful. The reaction of the *tert*-butyldimethylsilyl (TBS) and triisopropylsilyl (TIPS) enol ethers of cyclohexanone with trifluoroethyl acrylate (the most reactive acrylate ester[6k]) and 0.1 equiv of catalyst **1** in CH_2Cl_2 at −78 °C proceeded smoothly to give [2+2]-cycloaddition products. The results for these two reactions are summarized in Table 1. Although the *endo* ester predominated in each case, the selectivity (97:3) was greater for the TIPS-enol ether (**4**) than for the TBS-enol ether (**3**) (82:18) (entries 2 and 3 in Table 1). A 96:4 enantioselectivity was determined for the predominating *endo* ester, the absolute configuration of which was ascertained by reduction of $CO_2CH_2CF_3$ to CH_2OH in **3** and comparison of optical rotation with the known bicyclic primary alcohol.[10]

Entries 4−7 in Table 1 summarize the results for four other substrates. Excellent yields and enantioselectivities were found in each instance for the adducts **4**−**8**. The absolute configurations of the products **6** and **7** in entries 5 and 6 were established by the chemical correlations described below.[14] The absolute configuration of adduct **5** was ascertained by reduction of the carboxylic ester function to the corresponding primary alcohol, conversion to the 4-bromophenylurethane with 4-bromophenylisocyanate-triethylamine, desilylation with Bu_4NF, crystallization, and X-ray diffraction analysis.[14] The absolute configuration of **8** was determined by conversion to the bicyclic ketone **12** as described below and X-ray diffraction analysis.[14]

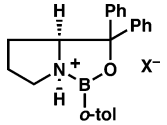
Table 1. Enantioselective [2+2]-Cycloaddition of Trifluoroethyl Acrylate to Enol Ethers with 10 mol % of Catalyst **1** in CH_2Cl_2 at −78 °C

entry	enol ether	product	time	yield % *(endo : exo)*	ee %
(1)		 *exo* **2**	3	87 (1:>99)	99[a]
(2)		 *endo* **3**	6	97 (82:18)	92[a]
(3)		 *endo* **4**	12	99 (97:3)	92[b]
(4)		 *endo* **5**	6	99 (99:1)	99[b]
(5)		 *exo* **6**	0.5	99 (1:99)	98[a]
(6)		 *exo* **7**	16	99 (10:90)	98[a]
(7)		 *endo* **8**	4	91 (96:4)	98[c]

[a] See ref 7 for determination of enantioselectivity. [b] Enantioselectivity was determined by reduction of $COOCH_2CF_3$ to CH_2OH, conversion to the Mosher ester, and ^1H NMR analysis. [c] Enantioselectivity was determined by GC analysis of enone **12**.

10.1021/ja0765262 CCC: $37.00

The protonated oxazaborolidinium cation **9**, X = $CF_3SO_3^-$ or $(CF_3SO_2)_2N^-$,[6] was decidedly inferior to the $AlBr_3$ complex **1** in catalyzing the [2+2]-cycloadditions shown in Table 1, apparently due to side reactions involving the enol ether component.

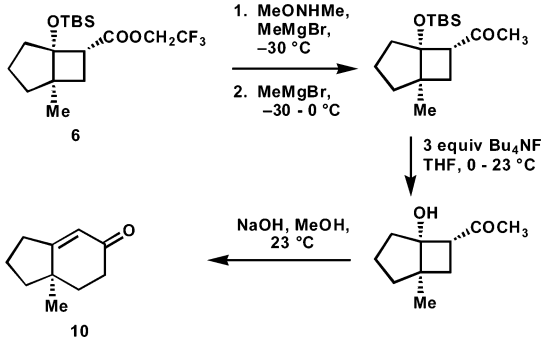


9

The silyl enol ethers in entries 5[11] and 6[12] of Table 1 were prepared by the procedures described previously for these compounds. The silyl enol ether in entry 7[13] of Table 1 was made by the conversion of 2-methylcycloheptanone to the potassium enolate by stirring with KH in THF at ambient temperature (23 °C) for 5.5 h and reacting subsequently with TBSCl at 23 °C for 8 h.

The bicyclic [2+2]-adducts shown in Table 1 are very useful chiral intermediates for further synthetic elaboration. For instance, the adduct **6** from 2-methylcyclopentanone enol silyl ether and trifluoroethyl acrylate can be transformed efficiently into the bicyclic α,β-enone **10** as shown in Scheme 1. Reaction of **6** with the magnesium amide from *O*,*N*-dimethylhydroxylimine in THF at −30 °C produced in 1 h the Weinreb amide which was treated in the same flask with methylmagnesium bromide at −30 to 0 °C for 5 h to give, after column chromatography on silica gel, the corresponding methyl ketone (80% overall). Desilation of this intermediate followed by treatment with 5% methanolic NaOH gave the known (*R*)-bicyclo[3,2,1]nonenone **10** in 80% yield; $[\alpha]^{24}_D$ −94 (*c* 1, EtOH).[15] The [2+2]-cycloadducts **7** and **8** were transformed in the same way into the known α,β-enones **11** and **12**, respectively.[16]

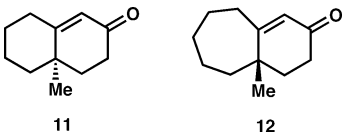
Scheme 1. Conversion of [2+2]-Cycloadduct **6** to (*R*)-1,2,3,6,7,7a-Hexahydro-7a-methyl-5H-indene-5-one



6 **10**

The absolute configuration of **12** was established unambiguously by conversion to the crystalline thiosemicarbazone and X-ray diffraction analysis,[14] thereby confirming the absolute configurational assignment for **8** that is shown in Table 1.

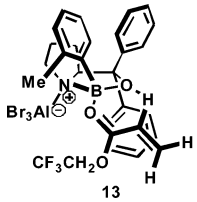
Since the absolute configurations of all of the [2+2]-cycloadducts (**2**−**8**) listed in Table 1 have been established, we are in position to discuss the mechanistic pathways for their formation. It is clear that in every case attack by the vinyl ether occurs at the same face of the acrylate ester (*si* face), exactly as predicted from our mechanistic model for the *S*-proline-derived catalyst **1**.[6a−c] The face selectivity for the silyl enol ether partner is not invariable, however.



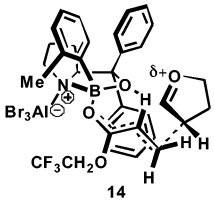
11 **12**

The predominating diastereomer for the cyclic vinyl ethers in entries 2−7 of Table 1 depends on the bulk of the silyloxy group, on further substitution at the vinyl group (H vs CH_3), and on ring size. This variability is probably the result of differing steric interactions for the series of vinyl ether substrates.

In our judgment, a reasonable working hypothesis is that the [2+2]-cycloaddition occurs by an asynchronous process involving the same type of α-CH hydrogen-bonded complex of catalyst **9** with trifluoroethyl acrylate that has previously been proposed[6b] for Diels−Alder reactions of this dienophile, i.e., **13**. The reaction of this complex with 2,3-dihydrofuran, for example, would then proceed via the pretransition-state assembly **14** in which the bonding is principally between the β-carbon of trifluoroethyl acrylate and C(3) of 2,3-dihydrofuran, as described earlier for [2+3]-cycloaddition reactions of 2,3-dihydrofuran and benzoquinones.[6j]



13



14

Acknowledgment. E.C. is the recipient of a Pfizer postdoctoral fellowship.

Supporting Information Available: Experimental procedures and characterization data; X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hayashi, Y.; Nihata, S.; Narasaka, K. *Chem. Lett*. **1990**, 2091−2094.
(2) Engler, T. A.; Letavic, M. A.; Iyengar, R.; LaTessa, K. O.; Reddy, J. P. *J. Org. Chem.* **1999**, *64*, 2391−2405.
(3) (a) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 253−255. (b) Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 517−521. (c) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668−3669.
(4) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498−1499.
(5) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.
(6) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808−3809. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992−9993. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388−6390. (d) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800−4802. (e) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708−13713. (f) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979−3982. (g) Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 740−742. (h) Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 1346−1352. (i) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310−6311. (j) Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 11958−11959. (k) Ryu, D. H.; Zhou, G.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1633−1636.
(7) Enantiomeric purity was determined by gas chromatographic analysis using a J&W Scientific Cyclosil-B column.
(8) The absolute configuration of **2** was determined by conversion to the crystalline 4-bromoanilide followed by single-crystal X-ray diffraction analysis (see SI).
(9) For a recent review on chiral cyclobutanes, see Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449−1483.
(10) Takasu, K.; Nagao, S.; Ueno, M.; Ihara, M. *Tetrahedron* **2004**, *60*, 2071−2078. This paper describes diastereoselective cycloaddition reactions of vinyl ethers with 8-phenylmenthyl acrylate in the presence of $EtAlCl_2$.
(11) Saraber, F. C. E.; Baronovsky, A.; Jansen, B. J. M.; Posthumus, M. A.; de Groot, A. *Tetrahedron* **2006**, *62*, 1726−1742.
(12) Takasu, K.; Ishii, T.; Inanaga, K.; Ihara, M. *Org. Synth*. **2006**, *83*, 193.
(13) Ikura, K.; Ryu, I.; Ogawa, A.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1989**, *30*, 6887−6890.
(14) See Supporting Information for details.
(15) Pfau, M.; Revial, G.; Guigant, A.; Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273−274.
(16) (a) Doering, W. E.; Birladeanu, L.; Sarma, K.; Shao, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 6660−6665. (b) Goubaud, V.; Azerad, R. *Synth. Commun.* **1996**, *26*, 915−922.

JA0765262