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Enantioselective Synthesis of Bridged- or Fused-Ring Bicyclic Ketones by a Catalytic Asymmetric Michael Addition Pathway

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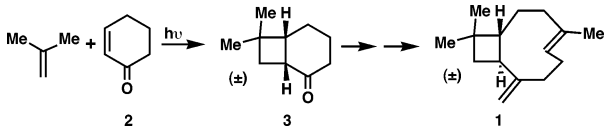
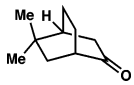
The generation of bicyclic structures by a cycloaddition reaction of simpler unsaturated precursors is a major entryway to complex naturally occurring structures. Despite recent advances in enantioselective methodology, asymmetric versions of many such reactions have yet to be devised. For instance, the total synthesis of (±)-caryophyllene (**1**), developed several decades ago,[1] employed an initial [2+2] photocycloaddition reaction that has not been put

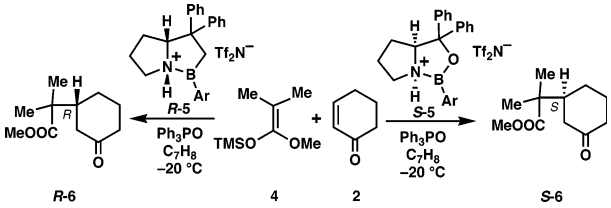


in enantioselective form for lack of applicable methodology. We describe herein an effective enantioselective route to **3** that bypasses photochemistry and that also has the versatility to produce the isomeric bicyclo[2.2.2]-octanone system. The approach that has been used takes advantage of chiral cationic oxazaborolidinium



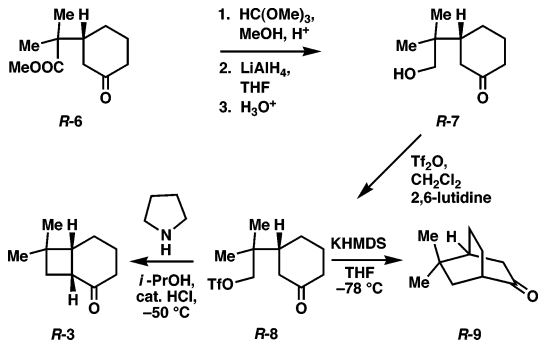
reagents as catalysts for enantioselective Michael reactions. These catalysts have previously been applied principally to effect enantioselective Diels−Alder reactions across a broad range of substrates,[2] including additions to 2-cycloalkenones as dienophiles.

Our initial studies were carried out with 2-cyclohexenone (**2**) and 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (**4**, Lancaster or Aldrich Co.) in the presence of the triflimide catalyst *S*-**5** or the *R*-enantiomer, *R*-**5**. After a few experiments in which the usual reaction variables were examined, we found that the reaction proceeded with high efficiency and enantioselectively when conducted in toluene solution at −20 °C for 16 h, in the presence of 0.25 equiv of triphenylphosphine oxide[3] as a trap for any electrophilic (i.e., catalytically active) Me_3Si species formed during the reaction, to give the desired Michael adduct **6**. With 0.2 equiv of the catalyst *S*-**5**, Michael adduct *S*-**6** was obtained in 91% yield and with about 20:1 enantioselection (90% ee).[4−6] Similarly, the catalyst *R*-**5** provided the Michael adduct *R*-**6** with the same



efficiency and enantioselectivity. The chiral keto ester *R*-**6** was transformed into the chiral bicyclo[4.2.0]octanone **3**, as shown in Scheme 1. Temporary masking of **6** as the dimethyl ketal, ester

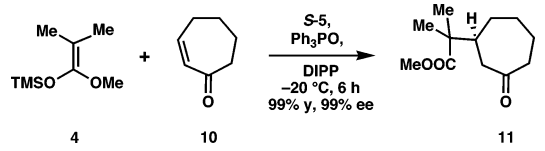
Scheme 1



reduction, and acidic ketal hydrolysis provided the hydroxy ketone *R*-**7** (91%), which was then transformed into the corresponding triflate *R*-**8** (73%).

Treatment of the keto triflate *R*-**8** with potassium hexamethyldisilazane in THF at −78 °C for 15 min produced the bicyclo[2.2.2]octanone **9** in 80% yield, along with only a few percent of the isomeric bicyclo[4.2.0]octanone *R*-**3**. On the other hand, when triflate *R*-**8** was allowed to react with a solution of pyrrolidine (3 equiv) and a catalytic amount of HCl in *i*-PrOH at −50 °C, the major product was the bicyclo[4.2.0]octanone *R*-**3** (72%) with 10:1 selectivity over the bridged isomer **9**. The enantioselective synthesis of *R*-**3** effectively converts the original synthesis of caryophyllene[1] (and isocaryophyllene) into an enantioselective version and demonstrates the first enantioselective route to the bicyclo[4.2.0]-octanone system. Clearly, numerous applications of this methodology to enantioselective synthesis are possible.

We have also extended this new enantioselective process to a variety of other substrates. An initial experiment with ketene acetal **4** and 2-cycloheptenone (**10**) under the conditions that were found to be effective with 2-cyclohexenone, resulted in definitely lower enantioselectivity and yield. However, when 1 equiv of 2,6-diisopropylphenol (DIPP)[7] was added as an additional scavenger of electrophilic Me_3Si species, the reaction proceeded well. Thus, the reaction of 2-cycloheptenone, 0.2 equiv of catalyst *S*-**5**, 3 equiv of ketene acetal **4**, 0.25 equiv of Ph_3PO, and 1.0 equiv of DIPP in toluene at −20 °C for 6 h produced the Michael adduct **11** in 99%



yield with 99% ee. The same conditions (and 0.1 M enone concentration) were then applied to various 2-cycloalkenones and silyl ketene acetals to give the Michael products **12**−**15** in the indicated yields and ee (all using catalyst *S*-**5**).[6,8,9] The reaction of 2,6-dimethylbenzoquinone (**16**; 0.02 M) with the methyl silyl ketene

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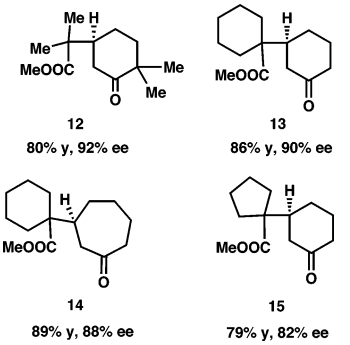
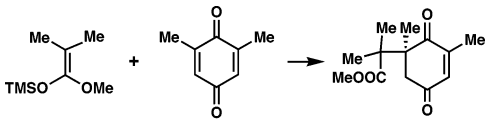
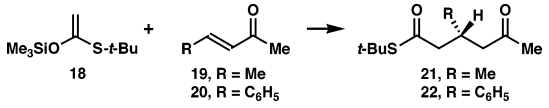


acetal **4**, 0.2 equiv of catalyst *S*-**5**, 0.25 equiv of Ph_3PO, and 1.5 equiv of DIPP in toluene at −20 °C for 24 h produced the Michael adduct **17** in 87% yield and 90% ee. This reaction was also regioselective and followed the selection rules for [2+4] cycloaddition reactions of 1,4-dienes to 1,4-benzoquinones that have been described elsewhere.[2d] Effectively, the regiochemistry follows from the pathway involving favored coordination of catalyst *S*-**5** to the sterically less-screened carbonyl oxygen at C(4) of the quinone **16**.



We also examined the reactions of the silyl *tert*-butylthio ketene acetal **18** with the acyclic α,*β*-enones **19** and **20** as compared to the cyclic α,*β*-enones discussed above. Under the standard conditions (0.2 equiv *S*-**5**, 0.25 equiv of Ph_3PO, 3 equiv of DIPP), with a reaction time of 24 h, the Michael adducts **21** (94% yield, 90% ee) and **22** (99% yield, 84% ee) resulted. The chiral Michael



products **21** and **22** had previously been described and the absolute configurations had been determined by correlation with the corresponding methyl esters.[7] Thus, the absolute configurations of **21** and **22** obtained using catalyst *S*-**5** followed from comparison by chiral-phase HPLC analysis with reported data.[7]

The absolute stereochemical course of the enantioselective Michael addition of 2-cyclohexenone (**2**) and 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (**4**) in the presence of the catalyst *S*-**5** can be rationalized by the pre-transition-state assembly, shown in Figure 1. The mode of complexation of the α,*β*-enones **2** is the same that has previously been shown to be reliably predictive of the absolute configuration of Diels−Alder products from α,*β*-enones, α,*β*-unsaturated esters and lactones, and 1,4-benzoquinones with 1,3-dienes under catalysis by *S*-**5**. Because of shielding the rear face of the α,*β*-enones, as depicted in Figure 1, attack by the silyl ketene acetal **4** on the *re* face of C(*β*) of the coordinated α,*β*-enones (i.e, the front face in Figure 1). A parallel analysis successfully predicts the absolute configurations of the products **21** and **22**.

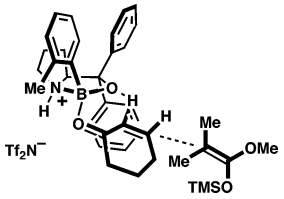


Figure 1. Pre-transition-state assembly for the reaction of **2**, **4**, and *S*-**5** leading to *S*-**6**.

Although there have been several studies of enantioselective Michael reactions of silyl ketene acetals catalyzed by chiral Lewis acids,[7,10] the cases reported herein represent the first examples of such reactions with α,*β*-cycloalkenones, as far as we are aware. The enantioselective methodology described herein is illustrated by the application to the synthesis of *R*-**3**, a key intermediate for the enantioselective synthesis of caryophyllene, and also to the synthesis of the chiral bridged-ring product *R*-**9**. Further research on new applications is in progress.

Supporting Information Available: Experimental procedures for the reactions described herein and characterization data (13 pp). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1963**, *85*, 362−363. (b) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485−492. (c) Corey, E. J.; Bass, J. D.; Le Mahieu, R. E.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570−5583.

(2) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388. (d) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800. (e) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708. For selected examples of enantioselective, intramolecular Diels−Alder reactions, see: (f) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979. (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.

(3) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384−5387.

(4) The reaction was considerably slower at −78 °C, but the enantioselectivity was the same. Distinctly lower enantioselectivity was observed in the absence of Ph_3PO or in CH_2Cl_2 as solvent.

(5) The absolute configuration of the product using the catalyst *S*-**5** was shown to be *S*-**6** by application of the octant rule and also by comparison of optical rotation with *S*-**6** that had been made by a different method and correlated with a known standard. See Chordia, M. D.; Harman, W. D. *J. Am. Chem. Soc.* **2000**, *122*, 2725−2736.

(6) The use of $Me_2C{=}C(OEt)$ (OTMS) instead of $Me_2C{=}C(OMe)$ (OTMS) (**4**) in this and the other Michael reactions described herein led to the same yields and ee's of the corresponding ethyl esters of the Michael products.

(7) Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A. *Org. Lett.* **2001**, *3*, 2101−2103. The rates of the various Michael additions to α,*β*-enones (including 2-cyclohexenone) are accelerated by DIPP.

(8) The absolute configurations of the Michael adducts **11**−**15** were assigned by analogy with the proven stereochemical course for the formation of *R*-**6** and *S*-**6** from **2** and **4**. Enantioselectivities of all the enantioselective Michael reactions of α,*β*-enones reported herein were determined by HPLC analysis using a Chiral Technologies Chiralpak IA, OD-H, OJ, or AD analytical column with hexane-2-propanol (99:1) for elution.

(9) In the reaction leading to the Michael adduct **15**, best results were obtained by slow addition (syringe drive over 3−4 h) of a solution in toluene of DIPP and 2-cyclohexenone to the other reactants at −20 °C in toluene.

(10) (a) Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97−100. (b) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921−8924. (c) Bernardi, A.; Karamfilova, K.; Sanguinetti, S.; Scolastico, C. *Tetrahedron* **1997**, *53*, 13009−13026. (d) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, 17015−17028. (e) Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165−1170. (f) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142.

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