J|A|C|S
COMMUNICATIONS

Published on Web 07/22/2003

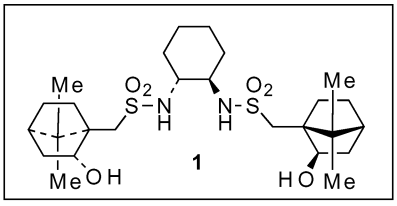
Asymmetric Addition of Alkylzinc Reagents to Cyclic α,β-Unsaturated Ketones and a Tandem Enantioselective Addition/Diastereoselective Epoxidation with Dioxygen

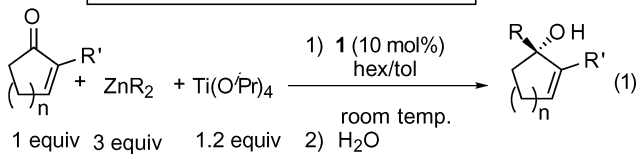
Sang-Jin Jeon and Patrick J. Walsh*

P. Roy and Diane T. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

Received May 23, 2003; E-mail: pwalsh@sas.upenn.edu

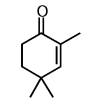
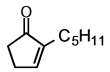
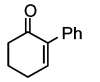
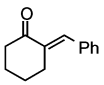
We recently reported the asymmetric addition of alkylzinc reagents to ketones using an easily prepared constrained-geometry catalyst.[1] A noteworthy aspect of this study is that it offers a solution to a long-standing problem in synthetic organic chemistry: the catalytic synthesis of tertiary alcohols from acetophenone derivatives with high enantioselectivity. In contrast to related addition reactions with aldehyde substrates, which are promoted by hundreds of catalysts,[2,3] only a handful of systems will promote additions to ketones,[1,4−7] and most of these require high catalyst loadings and long reaction times.[5−7] Despite significant effort in this area, we are not aware of successful reports of the enantioselective addition of alkyl groups to conjugated cyclic enones. In this Communication, we report the results of an investigation into the efficient and highly enantioselective 1,2-addition reactions of cyclic α,β-unsaturated ketones. The resulting tertiary allylic alcohols are valuable intermediates that can be further elaborated via directed epoxidation reactions with excellent diastereoselectivities. The resulting epoxy alcohols undergo Lewis acid promoted semipinacol rearrangement to give β-hydroxy-α,α-disubstituted ketones. Furthermore, we have developed a tandem, one-pot protocol for the enantioselective addition/diastereoselective epoxidation simply by capping the reaction with a balloon of dioxygen when the asymmetric addition is complete.





Initial evaluation of ligand **1** in the asymmetric addition reaction (eq 1) with $ZnMe_2$ and $ZnEt_2$ indicated that 2-substituted enones are excellent substrates. Thus, as shown in Table 1, treatment of enone **2** with 10 mol % ligand **1**, 3 equiv of $ZnMe_2$, and 1.2 equiv of $Ti(O^iPr)_4$ at room temperature leads to the tertiary allylic alcohol in 84% yield and 99% enantioselectivity after chromatography on silica gel. Likewise, use of $ZnEt_2$ under identical conditions provided the allylic alcohol in 76% yield and 98% enantioselectivity (entry 2). It is significant that the titanium catalyst is chemoselective, giving only carbonyl addition and no conjugate addition. In contrast, copper-catalyzed additions of dialkylzinc reagents to enones give conjugate addition products.[8] In a related titanium-BINOL-catalyzed asymmetric addition of alkylzinc reagents to aldehydes, it has recently been definitively demonstrated that the alkyl group is transferred from titanium, and not zinc.[9] Thus, the oxophilic Ti-alkyl adds in a 1,2-fashion, and the soft Cu-alkyl adds in a 1,4-fashion.

Table 1. Asymmetric Addition of Alkyl Groups to Cyclic Enones

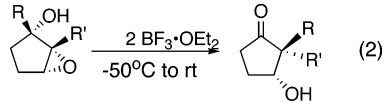
entry	substrates		ZnR_2	time (h)	yield (%)	ee[a] (%)
1		**2**	R = Me	40	84	99
2			R = Et	40	76	98
3		**3**	R = Me	40	55	98
4			R = Et	37	65	96
5		**4**	R = Me	40	62	99
6			R = Et	40	50	99
7		**5**	R = Me	40	54	95
8			R = Et	40	40	95
9		**6**	R = Me	38	20	99
10			R = Et	38	32	99
11		**7**	R = Et	19	75	52
12		**8**	R = Et	80	50	61

[a] See Supporting Information for ee determination protocol.

The scope of the asymmetric ketone alkylation is illustrated in Table 1. Addition of $ZnMe_2$ and $ZnEt_2$ to 2-methyl cyclopentenone exhibits 98% and 96% enantioselectivity in 55% and 65% yield, respectively. Increasing the length of the 2-substituent to pentyl led to an increase in the enantioselectivities to 99% for both $ZnMe_2$ and $ZnEt_2$. Aryl-substituted substrates also underwent alkylation with high enantioselectivity, but with diminished yields due to aldol/dehydration side reactions.

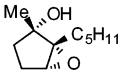
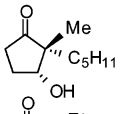
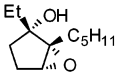
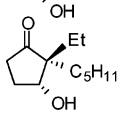
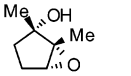
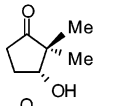
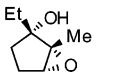
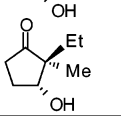
Reactions of 2-phenyl cyclohexenone with $ZnMe_2$ and $ZnEt_2$ both generated allylic alcohol products with 95% enantioselectivity, albeit in 54% and 40% yield. Decreased yields were observed with the exocyclic enone **6**, which gave 20% and 32% yield with 99% enantioselectivity in each case. Enones devoid of alkyl substituents α to the carbonyl group are not particularly good substrates, giving 52% and 61% enantioselectivity (entries 11 and 12). Because of

10.1021/ja036302t CCC: $25.00 © 2003 American Chemical Society



(2)

Table 2. Semipinacol Rearrangement Products

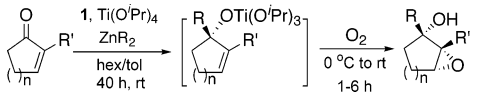
entry	substrates	products	yield (%)	ee (%)
1			70	99
2			89	99
3			75	98
4			73	97

the similar steric environments of the oxygen lone pairs, discrimination of the enantiotopic carbonyl faces of these substrates is quite challenging.

The allylic alcohols in eq 1 are valuable chiral building blocks that contain chiral quaternary centers. Such centers are difficult to access, and, therefore, methods to synthesize them have attracted considerable attention.[10,11] The Lewis acid-promoted semipinacol rearrangement of α-hydroxy epoxides is another useful method to establish chiral quaternary centers.[12,13] Thus, diastereoselective epoxidation of selected allylic alcohols was examined using *m*-CPBA. The desired *syn*-epoxy alcohols were obtained in >90% yield. Treatment of the epoxy alcohols with BF_3•OEt_2, as shown in eq 2, resulted in semipinacol rearrangement cleanly providing new β-hydroxy-α,α-disubstituted ketones in good yields (Table 2). The ketone products are formed as single diastereomers with no loss of ee in the epoxidation/rearrangement sequence. These densely functionalized products contain chiral all-carbon stereocenters (entries 1, 2, and 4).

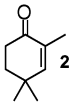
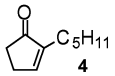
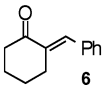
We next investigated the possibility of performing a tandem one-pot enantioselective ketone alkylation/diastereoselective epoxidation sequence. Dialkylzinc reagents readily react with dioxygen to provide metal peroxides.[14,15] In the presence of titanium tetraisopropoxide, hydroperoxides are known to catalyze olefin epoxidation with high diastereoselectivity.[16] Performing the addition reaction with $ZnEt_2$ followed by exposure of the reaction mixture to dioxygen (1 atm) resulted in complete conversion to the *syn*-epoxy alcohol in under 4 h. Epoxidations in the presence of $ZnMe_2$ were very slow. In these reactions, 2 equiv of $ZnEt_2$ was added before exposure to dioxygen. The yields and enantioselectivities of the epoxy alcohols (Table 3) are essentially identical to those of the addition reactions reported in Table 1. Interestingly, the epoxidation reaction outlined here is very different than the Sharpless asymmetric epoxidation in that our reaction is conducted under basic, aprotic conditions.[17]

An effective protocol for the enantioselective addition of alkyl groups to cyclic conjugated enones is disclosed. This transformation



(3)

Table 3. One-Pot Synthesis of Epoxy Alcohol Products with Oxygen

entry	substrates	ZnR_2[a]	yield (%)	ee (%)
1	 **2**	R = Me	82	99
2		R = Et	80	99
3	**3**	R = Me	50	98
4		R = Et	60	97
5	 **4**	R = Me	67	99
6		R = Et	60	99
7	 **6**	R = Et	34	96

[a] For reactions with $ZnMe_2$, 1.5−2 equiv of $ZnEt_2$ was added after complete ketone consumption.

can be coupled with a diastereoselective epoxidation in which the ultimate oxidant is generated from dioxygen. Rearrangement of the resulting epoxy alcohols provides highly functionalized aldol type products with excellent ee that are not accessible through traditional aldol chemistry. We are currently investigating the mechanism of the asymmetric addition and the epoxidation reaction.

Acknowledgment. This work was supported by the NIH (GM58101).

Supporting Information Available: Procedures and full characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971.
(2) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.
(3) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.
(4) Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 2291−2293.
(5) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239−1242.
(6) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651−5666.
(7) Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103−1114.
(8) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756.
(9) Balsells, J.; Davis, T. J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336−10348.
(10) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597.
(11) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.
(12) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1987**, *28*, 5891−5894.
(13) Tu, Y. Q.; Fan, C. A.; Ren, S. K.; Chan, A. S. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3791−3794.
(14) Yamamoto, K.; Yamamoto, N. *Chem. Lett.* **1989**, 1149−1152.
(15) Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1725−1728.
(16) Katsuki, T. In *Epoxidation of Allylic Alcohols*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Comprehensive Asymmetric Catalysis; Springer: Berlin, 1999; Vol. 2, pp 621−648.
(17) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5776.

JA036302T