JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Desymmetrizing Asymmetric Ring Expansion of Cyclohexanones with α-Diazoacetates Catalyzed by Chiral Aluminum Lewis Acid

Takuya Hashimoto, Yuki Naganawa, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Supporting Information

ABSTRACT: Chiral aluminum Lewis acid catalyst composed of Me_3Al and 3,3′-bis(trimethylsilyl)-BINOL in a 2:1 ratio was found to promote novel catalytic asymmetric ring expansion of cyclohexanone with α-substituted α-diazoacetates to give seven-membered rings with an all-carbon quaternary center. Application of this strategy to 4-substituted cyclohexanones opened up a novel way for the catalytic desymmetrizing asymmetric construction of cycloheptanones bearing remote α,δ-chiral centers.

Acid-catalyzed ring expansion of cyclohexanones with α-diazoacetates or diazoalkanes has been known for more than half a century as a practical strategy to synthesize seven-membered carbocycles.[1,2] Recent innovative studies by our group and Kingsbury et al. revealed that this method could be extended to the incorporation of an all-carbon quaternary center by use of α-substituted α-diazoacetates or internal diazoalkanes under the influence of Lewis acid catalysts.[3−5]

The daunting challenge remaining in this research field is the development of a catalytic asymmetric procedure which would be achieved using chiral acid catalysts. Although chiral acid catalysis has become a mature field owing to its extensive development in the past decades,[6] asymmetric ring expansion of cyclohexanones with α-substituted α-diazoacetates poses a problem distinct from these conventional acid catalyses: namely, cyclohexanone to which chiral acid coordinates is not a prochiral substrate unlike aldehydes,[7] and the prochirality resides only on α-substituted α-diazoacetates. Accordingly, the catalyst complexed with cyclohexanone must discriminate the prochiral face of the approaching α-diazoacetates relying only on the steric factor. In addition, the pertinent problem of the formation of a quaternary stereogenic center from sterically less biased and less reactive substrates also remains as a laborious task.[8,9]

We report herein a breakthrough toward this end which has culminated in the realization of highly enantioselective catalytic ring expansion of cyclohexanones with α-substituted α-diazoacetates using chiral aluminum Lewis acid with 3,3′-bis(trimethylsilyl)-BINOL as an effective ligand,[10] providing an unprecedented pathway for asymmetric formation of seven-membered rings with an all-carbon quaternary center (Figure 1). More importantly, the reaction system could be successfully applied to catalytic desymmetrizing asymmetric ring expansion of symmetrically substituted cyclohexanones, giving seven-membered rings with an additional stereogenic center.

In the preliminary experiments to identify a chiral acid catalyst of choice, we examined some chiral boron and aluminum Lewis acids, given the fact that the use of strong, hard Lewis acid was

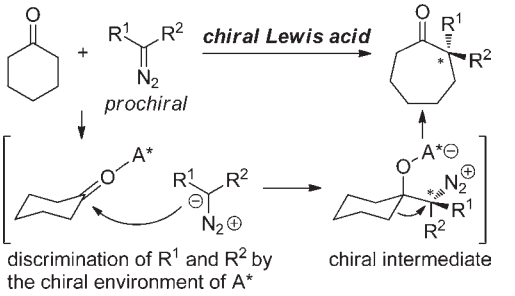


Figure 1

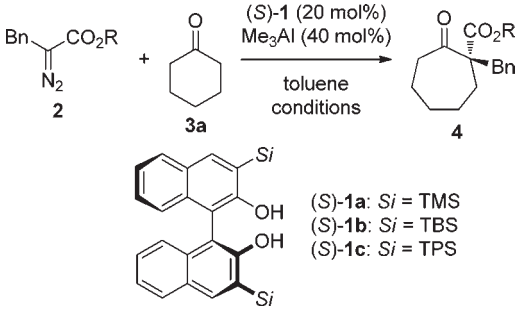
necessary to facilitate the ring expansion. Among the various catalysts screened, we identified a chiral aluminum Lewis acid composed of Me_3Al and 3,3′-disilyl-BINOL in a ratio of 2:1 as having promise.[11] The active bis-aluminum Lewis acid was prepared by stirring a solution of 3,3′-bis(trimethylsilyl)-BINOL (*S*)-**1a** (20 mol %) and Me_3Al (40 mol %) in toluene at room temperature for 1 h, and this catalyst promoted the reaction of methyl α-benzyl-α-diazoacetate and cyclohexanone at −40 °C to give cycloheptanone in 97% yield with 76% ee (Table 1, entry 1). Replacement of the silyl substituents had a significant impact on the selectivity, wherein even the sense of chirality was inverted by use of the triphenylsilyl-substituted BINOL (*S*)-**1c** as ligand (entries 2 and 3). For the successful implementation of the catalysis, a 2:1 complex of Me_3Al and BINOL was found to be indispensable, as the 1:1 complex failed to promote the reaction under the identical reaction conditions (entry 4).[10,12,13] Use of α-diazoacetates bearing a different ester moiety resulted in a decrease in enantioselectivities, proving the importance of the steric factor to control the stereoselectivity (entries 5 and 6). Further optimization revealed the drastic effect of the temperature, as the enantioselectivity reached 90% when the reaction was carried out at −78 °C (entries 7 and 8).

With these optimized conditions in hand, we investigated the scope of this catalytic asymmetric ring expansion (Table 2). In the variation of the α-benzyl group attached to the diazoacetate, use of 3- and 4-methylbenzyl-substituted α-diazoacetates **2e** and **2f** was tolerated to give ring-expanded products with 81% and 84% ee, respectively, whereas α-(2-methylbenzyl)-α-diazoacetate **2d** was poorly reactive under this reaction condition (entries 2−4). The electronic property of the benzylic moiety did not affect the reactivity or selectivity of the reaction (entries 5 and 6). 2-Naphthylmethyl-substituted α-diazoacetate **2i** could also be

Received: March 7, 2011
Published: May 09, 2011

ACS Publications © 2011 American Chemical Society

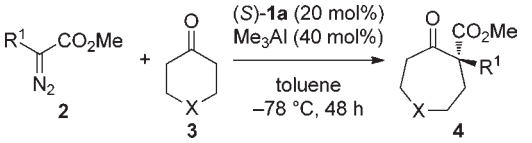
Table 1. Optimization of the Reaction Conditions[a]



entry	R	1	temp (°C), time (h)	yield (%)[b]	ee (%)[c]
1	Me (**2a**)	**1a**	−40, 24	97 (**4a**)	76
2	Me	**1b**	−40, 24	91	58
3	Me	**1c**	−40, 24	99	−40
4[d]	Me	**1a**	−40, 24	no reaction	
5	Bn (**2b**)	**1a**	−40, 15	76 (**4b**)	58
6	*t*-Bu (**2c**)	**1a**	−40, 15	90 (**4c**)	54
7	Me	**1a**	−60, 24	84	86
8	Me	**1a**	−78, 48	72	90

[a] Reactions were performed with cyclohexanone (0.20 mmol) and α-benzyl-α-diazoacetate (0.22 mmol) in the presence of 20 mol % chiral bis-aluminum catalyst (0.04 mmol) in toluene (2.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Performed with a catalyst composed of 20 mol % (*S*)-**1a** and 20 mol % Me_3Al.

Table 2. Catalytic Asymmetric Ring Expansion[a]

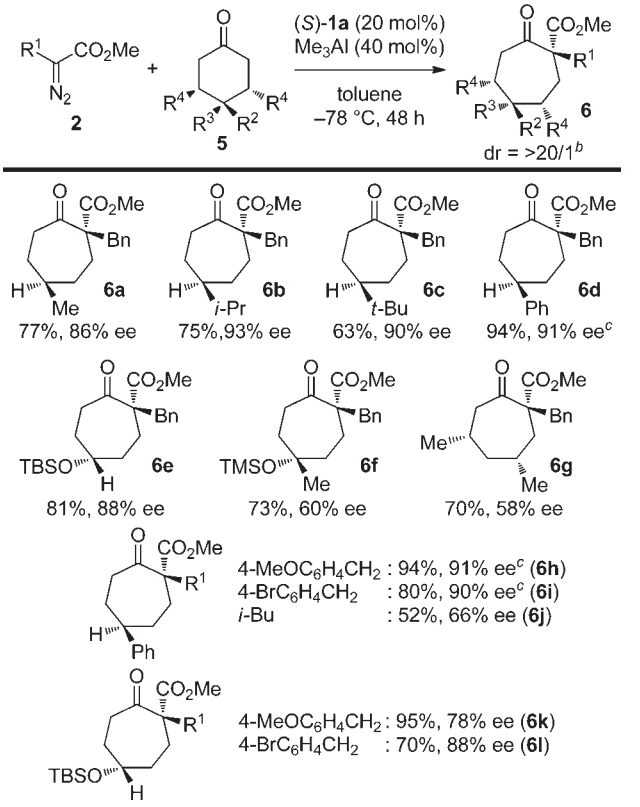


entry	R^1	X	yield (%)[b]	ee (%)[c]
1	Bn (**2a**)	CH_2 (**3a**)	72 (**4a**)	90
2[d]	2-$MeC_6H_4CH_2$ (**2d**)	CH_2	24 (**4d**)	71
3	3-$MeC_6H_4CH_2$ (**2e**)	CH_2	72 (**4e**)	81
4	4-$MeC_6H_4CH_2$ (**2f**)	CH_2	94 (**4f**)	84
5	4-$MeOC_6H_4CH_2$ (**2g**)	CH_2	93 (**4g**)	84
6	4-$BrC_6H_4CH_2$ (**2h**)	CH_2	50 (**4h**)	89
7	2-$NpCH_2$ (**2i**)	CH_2	58 (**4i**)	80
8	Me (**2j**)	CH_2	92 (**4j**)	14
9[e]	*i*-Bu (**2k**)	CH_2	69 (**4k**)	43
10	Bn (**2a**)	O (**3b**)	67 (**4l**)	80
11[d]	Bn (**2a**)	S (**3c**)	74 (**4m**)	77

[a] Reactions were performed with cyclohexanone (0.20 mmol) and methyl α-substituted α-diazoacetate (0.22 mmol) in the presence of 20 mol % chiral aluminum catalyst (0.04 mmol) in toluene (2.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Performed at −60 °C for 24 h. [e] Performed for 66 h.

employed (entry 7). Application of this strategy to α-diazoacetates bearing an aliphatic side chain was found to be even more challenging, as the reaction furnished the product with poor to modest enantioselectivity (entries 8 and 9). Not only cyclohexanone but also its oxa and thia analogues **3b** and **3c** could be

Table 3. Catalytic Desymmetrizing Asymmetric Ring Expansion[a]



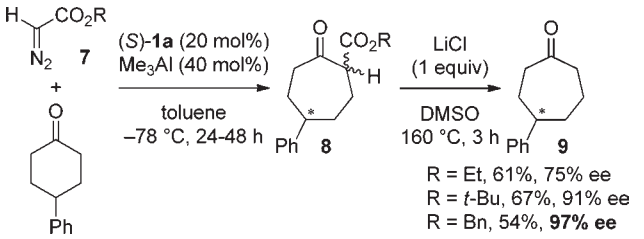
[a] Reactions were performed with cyclohexanone (0.20 mmol) and methyl α-substituted α-diazoacetate (0.22 mmol) in the presence of 20 mol % chiral aluminum catalyst (0.04 mmol) in toluene (2.0 mL). Yields reported were isolated. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Determined by ^1H NMR of the crude mixture. [c] Performed at −60 °C for 24 h.

utilized for this ring expansion, affording seven-membered rings containing a heteroatom with good enantioselectivities (entries 10 and 11). As for the other cycloalkanones, cyclobutanone was found to be a potentially viable substrate, although the yield and ee remained low under our reaction conditions (<25% yield, 19% ee, data not shown).

Our recent study disclosed that achiral Lewis acid-catalyzed ring expansion of 4-alkyl- or 4-arylcyclohexanones with α-substituted α-diazoacetates gave cylcoheptanones projecting two functionalities in a cis fashion with high diastereoselectivity. This moved our focus to the use of 4-substituted cyclohexanones in this catalytic asymmetric ring expansion, as it would provide seven-membered carbocycles having an additional stereocenter via the stereoselective desymmetrization of the pendant functionality. As shown in Table 3, this catalytic desymmetrizing asymmetric ring expansion of 4-substituted cyclohexanones with methyl α-benzyl-α-diazoaceate provided the corresponding seven-membered carbocycles **6a**−**d** as an essentially single diastereomer. Irrespective of the 4-substituents of the corresponding cyclohexanones, the enantioselectivities of these heptanones were remarkably high, ranging from 86% to 93% ee. In contrast to 4-alkyl- and 4-arylcyclohexanones, use of 4-silyloxycyclohexanones is known to give cycloheptanones bearing the α-substituent of diazoacetates and the siloxy group in a trans fashion,

dx.doi.org/10.1021/ja202070j |*J. Am. Chem. Soc.* 2011, 133, 8834–8837

Scheme 1. Use of α-Unsubstituted α-Diazoacetate for Traceless Catalytic Desymmetrizing Asymmetric Expansion



presumably due to the tendency of these cyclohexanones to project their silyloxy group in an axial fashion. Accordingly, this catalytic desymmetrizing asymmetric ring expansion with 4-(*tert*-butyldimethyl)silyloxycyclohexanone furnished the cycloheptanone **6e** as the single expected isomer with 88% ee. In the reaction with cyclohexanone having 4-alkyl- and 4-silyloxy groups, a considerable decrease of the enantioselectivity was observed, although the product **6f** was obtained as a single diastereomer. This strategy could be extended to the use of 3,5-*cis*-dimethylcyclohexanone to give **6g** having three stereogenic centers with 58% ee. At last, we also examined the variation of the α-substituent of diazoacetates, as exemplified in the reaction with 4-phenylcyclohexanone and 4-silyloxycyclohexanone. Irrespective of the substituents attached at the benzylic position of α-diazoacetates, the ring expansion proceeded to give the corresponding carbocycles **6h**, **6i**, **6k**, and **6l**, respectively, with high enantioselectivities. It should be noted that α-alkyl-α-diazoacetate could be utilized as well, giving the cycloheptanone **6j** with moderate enantioselectivity.

As a unique application of this catalytic desymmetrizing asymmetric ring expansion, we turned our attention to the use of simple α-unsubstituted α-diazoacetate **7** as a substrate (Scheme 1).[3b] Ring expansion of 4-phenylcyclohexanone with ethyl diazoacetate **7a** under the identical reaction conditions furnished seven-membered cyclic β-keto ester having an α-hydrogen. While the stereocenter at the α-position generated by the primary action of the chiral catalyst easily disappeared via the epimerization, it is strongly anticipated that the stereogenic center at the remote δ-position imparted by the desymmetrization would be retained. To confirm this, decarboxylation of this cyclic β-keto ester **8** (R = Et) was implemented to give 4-phenylcycloheptanone **9** with 75% ee, offering a novel route for the traceless asymmetric one-carbon homologation of 4-substituted cyclohexanones. Further optimization revealed that use of benzyl diazoacetate **7** (R = Bn) drastically improved the enantioselectivity of this desymmetrization, giving cycloheptanone **9** with 97% ee.

In conclusion, we have succeeded in developing the chiral bis-aluminum Lewis acid-catalyzed asymmetric ring expansion of cyclohexanones by controlling the stereochemistry of approaching α-substituted α-diazoacetates. By combining this catalytic asymmetric ring expansion with the desymmetrization of 4-substituted cyclohexanones, seven-membered carbocyles having two remote functionalities could be synthesized as a single isomer with high enantioselectivities. This procedure could also be extended to the reaction with α-unsubstituted α-diazoacetate, which led to the establishment of a novel traceless procedure for the desymmetrization of 4-substituted cyclohexanone via one-carbon homologation.[14]

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
maruoka@kuchem.kyoto-u.ac.jp

■ ACKNOWLEDGMENT

This work was partially supported by a Grant-in-Aid for Scientific Research from MEXT (Japan). T.H. and Y.N. thank a Grant-in Aid for Young Scientists (B) and the Research Fellowships of JSPS for Young Scientists, respectively.

■ REFERENCES

(1) For reviews, see: (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.(b) Doyle, M. P.; Ye, T.; McKervey, M. A. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998.

(2) (a) House, H. O.; Grubbs, E. J.; Gannon, W. F. *J. Am. Chem. Soc.* **1960**, *82*, 4099. (b) Müller, E.; Bauer, M. *Liebigs Ann. Chem.* **1962**, *654*, 92. (c) Tai, W. T.; Warnhoff, E. W. *Can. J. Chem.* **1964**, *42*, 1333. (d) Mock, W. L.; Hartman, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 5767. (e) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459. (f) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 466. (g) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725. (h) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283. (i) Liu, H.-J.; Yeh, W.-L.; Browne, E. N. C. *Can. J. Chem.* **1995**, *73*, 1135. (j) Yang, S.; Hungerhoff, B.; Metz, P. *Tetrahedron Lett.* **1998**, *39*, 2097.

(3) (a) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 6614. (b) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *Chem. Commun.* **2010**, *46*, 6810.

(4) For our related works, see: (a) Hashimoto, T.; Miyamoto, H.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 11280. (b) Hashimoto, T.; Naganawa, Y.; Kano, T.; Maruoka, K. *Chem. Commun.* **2007**, 5143. (c) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434. (d) Hashimoto, T.; Nakatsu, H.; Watanabe, S.; Maruoka, K. *Org. Lett.* **2010**, *12*, 1668. (e) Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Watanabe, S.; Maruoka, K. *Chem. Asian J.* **2011**, *6*, 607.

(5) (a) Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 878. (b) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202.

(6) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, 2008.

(7) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532.

(8) (a) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.

(9) (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (b) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.

(10) (a) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (b) Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7791. (c) Maruoka, K.; Banno, H.; Yamamoto, H. *Tetrahedron: Asymmetry* **1991**, *2*, 663. (d) Maruoka, K.; Yamamoto, H. *Synlett* **1991**, 793. (e) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3501.

(11) (a) Ishihara, K.; Kobayashi, J.; Inanaga, K.; Yamamoto, H. *Synlett* **2001**, 394. (b) Li, P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 16628. (c) Son, A. J. R.; Thorn, M. G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **2003**, *22*, 2318.

(12) For the use of other bis-aluminum Lewis acid catalysts, see: (a) Ooi, T.; Takahashi, M.; Maruoka, K. *J. Am. Chem. Soc.* **1996**, *118*, 11307.

(b) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1150.

(13) For a discussion on the active species based on the NMR experiments, see the Supporting Information.

(14) After the submission of this paper, a study on asymmetric ring expansion of cycloalkanones with terminal diazoalkanes was reported by Kingsbury and co-workers: Rendina, V. L.; Moebius, D. C.; Kingsbury, J. S. *Org. Lett.* **2011**, *13*, 2004.