Asymmetric Synthesis of 3-Substituted 2-*exo*-Methylenealkanones by Addition–Elimination Reaction Using a Chiral Leaving Group and Organometallic Nucleophiles

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A novel diastereodifferentiating addition–elimination reaction of (*S*)-2-[[2-(methoxymethyl)-1-pyrrolidinyl]methyl]-2-alken-1-ones with organometallic reagents such as organocuprates and organozincates afforded optically active 3-substituted 2-methylenealkanones with high enantiomeric purity. The enantiomeric excess (ee) of the products in this asymmetric induction reaction involving 1,5-transfer of stereogenicity was highly dependent on the structure of the enone substrates and the type of organometallic reagents, chiral auxiliaries, and added Lewis acids: (i) the use of lithium diorganocuprates (R_2CuLi) led to the highest ee's, (ii) in the reaction with R_2CuLi the ee decreased in the following order by varying their structure of the main framework of the enones, cycloheptenones (96–97% ee) > cyclohexenones (95% ee) > cyclopentenones (82–85% ee) > acyclic enones (55–70% ee), (iii) the addition of LiBr as the external Lewis acid in the reaction with R_2CuLi did not affect the ee, whereas that of $ZnBr_2$ or $MgBr_2$ decreased the ee by 5% or considerably more, respectively, and (iv) the existence of the methoxy oxygen atom in the chiral auxiliary was essential to achieve high ee's. The origin of the observed high and low ee's was rationalized by considering plausible transition state models.

Introduction

Enantio- and diastereoselective conjugate addition reactions of carbon nucleophiles such as enolates and organometallic reagents to α,β-unsaturated carbonyl compounds and their analogues have been the subject of much recent development and provide potent methodology for asymmetric C–C bond formation.[1-3] These asymmetric induction reactions can be classified into three types: (1) diastereoselective addition of achiral nucleophiles to chiral substrates,[1] (2) diastereoselective addition of chiral nucleophiles, preformed or generated in situ, to prochiral substrates,[2] and (3) enantioselective addition of achiral nucleophiles to prochiral substrates in the presence of chiral catalysts.[3] Although reactions of types 1 and 2 can very often lead to high enantiomeric purity of products with high reproducibility, the synthetic utility of the individual reaction is dependent on efficient removal and recovery of the chiral auxiliary from the product, as well as the extent of enantiomeric purity of the product. In this regard, highly diastereoselective asymmetric induction using a chiral auxiliary as a leaving group can offer a direct and efficient route to an enantiomer, but only two schemes using this strategy have resulted in considerable success. Wilson and Cram synthesized chiral binaphthyls (up to 95% ee) by nucleophilic aromatic substitution involving ipso addition of arylmetal reagents and the subsequent elimination of the chiral group.[4] Fuji et al. reported the reaction of chiral nitro enamines with zinc enolates of α-substituted δ-lactones affording chiral α,α-disubstituted δ-lactones (up to 96% ee) through an addition–elimination process.[5] In this context, we have recently reported a novel diastereodifferentiating addition–elimination reaction with 1,5-transfer of stereogenicity as high as 90% ee, which involves eventual allylic S_N2' substitution of a chiral amine auxiliary by organocuprates (R_2CuLi), leading directly to optically active 3-substituted 2-*exo*-methylenecyclohexanones (eq 1).[6] Because of the ready accessibility

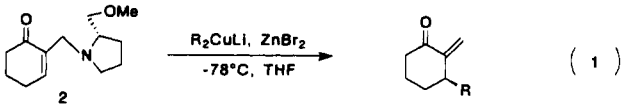

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Table I. Preparation of Chiral Amino Enones 1–5 (eqs 2 and 3)

entry	leaving group (X)	reaction condns[a]	time (h)	product	yield (%)
1	NO_2	A	1.0	**1a**	55
2	SO_2Ph	A	96	**1a**	73
3	SO_2Ph	B	24	**1b**	60
4	SO_2Ph	A	48	**1c**	87
5	NO_2	A	1.0	**2**	91
6	NO_2	A	1.0	**3**	97
7	NO_2	A	1.0	**4**	100
8	NO_2	A	1.0	**5a**	97
9	NO_2	A	1.0	**5b**	100
10	NO_2	A	1.0	**5c**	88

[a] A: CH_3CN, 25 °C. B: CH_3CN, 80 °C.

of the designed chiral substrate[7] and the simple experimental procedure,[6] this methodology will turn out to be

(1) For reviews, see: (a) Tomioka, K.; Koga, K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, pp 201–224. (b) Posner, G. H. *Ibid.* 1983, Vol. 2, pp 225–241. (c) Posner, G. H. *Acc. Chem. Res.* 1987, *20*, 72. (d) Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley: New York, 1989; Vol. 19, pp 227–407. For recent examples, see: (e) Oppolzer, W.; Moretti, R.; Bernardinelli, G. *Tetrahedron Lett.* 1986, *27*, 4713. (f) Oppolzer, W.; Schneider, P. *Helv. Chim. Acta* 1986, *69*, 1817. (g) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* 1988, *110*, 4718. (h) Oppolzer, W.; Kingma, A. J. *Helv. Chem. Acta* 1989, *72*, 1337. (i) Asaoka, M.; Aida, T.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* 1989, *30*, 7075. (j) Yoda, H.; Naito, S.; Takabe, K.; Tanaka, N.; Hosoya, K. *Tetrahedron Lett.* 1990, *31*, 7623. (k) Yoshino, T.; Okamoto, S.; Sato, F. *J. Org. Chem.* 1991, *56*, 3205. Also see refs 4–6.

(2) For reviews, see refs 1a and 1d. For recent examples using chiral organocopper or -zinc reagents, see: (a) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* 1986, *108*, 7114. (b) Yamamoto, K.; Kanoh, M.; Yamamoto, N.; Tsuji, J. *Tetrahedron Lett.* 1987, *28*, 6347. (c) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* 1987, *109*, 2040. (d) Scholkopf, D.; Petting, D.; Schule, E.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* 1988, *27*, 1194. (e) Dieter, R. K.; Lagu, B.; Deo, N.; Dieter, J. W. *Tetrahedron Lett.* 1990, *31*, 4105. (f) Doi, T.; Shimizu, K.; Takahashi, T.; Tsuji, J.; Yamamoto, K. *Tetrahedron Lett.* 1990, *31*, 3313. (g) Takahashi, T.; Nakazawa, M.; Kanoh, M.; Yamamoto, K. *Tetrahedron Lett.* 1990, *31*, 7349. (h) Rossiter, B. E.; Eguchi, M. *Tetrahedron Lett.* 1990, *31*, 965. (i) Rossister, B. E.; Eguchi, M.; Hernandez, A. E.; Vickers, D. *Tetrahedron Lett.* 1991, *32*, 3973. (j) Tanaka, K.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* 1991, 101. For recent examples using chiral enamides, see: (k) Tomioka, K.; Yasuda, K.; Koga, K. *J. Chem. Soc., Chem. Commun.* 1987, 1345. (l) Enders, D.; Rendenbach, B. E. M. *Chem. Ber.* 1987, *120*, 1223. (m) Enders, D.; Demir, A. S.; Rendenbach, B. E. M. *Chem. Ber.* 1987, *120*, 1731. (n) Tomioka, K.; Yasuda, K.; Koga, K. *J. Chem. Soc, Chem. Commun.* 1987, 1345. (o) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* 1989, *111*, 8266.

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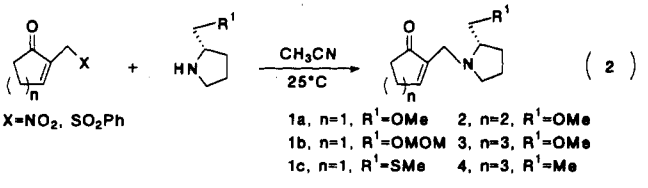
a powerful tool for asymmetric synthesis of various 3-substituted 2-*exo*-methylene carbonyl compounds, a fragment that is incorporated in a number of natural products and biologically active compounds as well.[8] Thus, we undertook exploring the scope and limitations of this asymmetric induction reaction by using cyclic and acyclic chiral enones and organometallic nucleophiles and by searching for optimum conditions via the judicious choice of chiral auxiliaries and Lewis acids. We have achieved high ee's (>95%) in several cases with lithium organocuprates with high reproducibility, and the rationale for the origin of the resulting high ee was obtained on the basis of plausible transition-state models proposed. Here we describe these new experimental results including assignment of absolute configuration and enantiomeric purity of the products.

Results and Discussion

Preparation of Chiral Enones. Requisite chiral amino enones **1a–1c**, **2**, **3**, **4**, and **5a–5c** were obtained by the reaction of the corresponding α-(nitromethyl)- or α-[(phenylsulfonyl)methyl]enones with (*S*)-2-(methoxymethyl)-,[9] (*S*)-2-[[(methoxymethyl)oxy]methyl]-, (*S*)-2-[(methylthio)methyl]-,[10] or (*R*)-2-ethylpyrrolidine[11] in acetonitrile as reported earlier[7] (eqs 2 and 3 and Table I).



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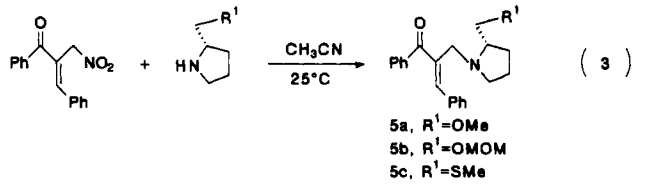


(3)

(3) For a review, see ref 1d. For recent examples, see: (a) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025. (b) Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175. (c) Schionato, A.; Paganelli, S.; Botteghi, C. *J. Mol. Catal.* **1989**, *50*, 11. (d) Soai, K.; Hayasaka, T., Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516. (e) Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1990**, *55*, 4168. (f) Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011. (g) Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95.

(4) (a) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881. (b) Wilson, J. M.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930.

(5) (a) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Terada, S. *J. Am. Chem. Soc.* **1986**, *108*, 3855. (b) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Taga, T.; Machida, K.; Snatzke, G. *J. Am. Chem. Soc.* **1989**, *111*, 7921. (c) Fuji, K.; Node, M.; Abe, H.; Itoh, A.; Masaki, Y.; Shiro, M. *Tetrahedron Lett.* **1990**, *31*, 2419. (d) Fuji, K.; Node, M. *Synlett* **1991**, 603.

(6) Tamura, R.; Watabe, K.; Katayama, H.; Suzuki, H.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 408.

(7) Tamura, R.; Katayama, H.; Watabe, K.; Suzuki, H. *Tetrahedron* **1990**, *46*, 7557.

(8) For examples: (a) Carmely, S.; Kashman, Y. *J. Org. Chem.* **1983**, *48*, 3517. (b) Endo, M.; Nakagawa, M.; Hamamoto, Y.; Nakanishi, T. *J. Chem. Soc., Chem. Commun.* **1983**, 322 and 980. (c) Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001. (d) Matsumoto, T.; Usui, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 491. (e) Matsumoto, T.; Imai, S.; Yoshinari, T.; Matsuno, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3103. (f) Piers, E.; Marais, P. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1222. (g) Gonzalez, A. G.; Rodriguez, P.; Elsa, M.; Diaz, J. G.; Bermejo Barrera, J. *J. Nat. Prod.* **1991**, *54*, 609. (h) Froissant, J.; Vidal, J.; Guibe-Jampel, E.; Huet, F. *Tetrahedron* **1987**, *43*, 317. (i) Page, P. C. B.; Jennens, D.; Porter, R. A.; Baldock, A. N. *Synlett* **1991**, 472. (j) Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5590.

(9) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173.

(10) We could not obtain this compound in a high state of purity by the procedure reported in ref 2c. Therefore, an alternative synthetic procedure was used; see the Experimental Section.

(11) Blarer, S.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.

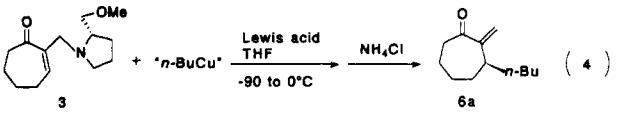
Table II. Reaction of 3 with Various Butylcopper Reagents (eq 4)

entry	butylcopper reagent (equiv)	added salt (equiv)	6a, yield (%)	6a, % ee
1	*n*-Bu_2CuLi·LiBr (2.0)	none	74	96
2	*n*-Bu_2CuLi·LiBr (2.0)	LiBr (1.0)	91	96
3	*n*-Bu_2CuLi·LiBr (1.0)	LiBr (2.0)	90	96
4	*n*-Bu_2CuLi·LiBr (1.0)	LiBr (1.0)	73	96
5	*n*-Bu_2CuLi·LiBr (2.0)	$ZnBr_2$ (1.0)	90	90
6	*n*-BuCu·LiBr (2.0)	LiBr (1.0)	91	92
7	*n*-BuCu(CN)Li (2.0)	LiBr (1.0)	73	86
8	*n*-Bu_2CuLi·LiCN (2.0)	LiBr (1.0)	86	93
9	*n*-Bu_2CuMgCl·MgClBr (2.0)	LiBr (1.0)	99	15

However, reaction of C_2 symmetric (2*S*,5*S*)-2,5-bis(methoxymethyl)pyrrolidine[12] with α-(nitromethyl)- and α-[(phenylsulfonyl)methyl]enones failed, giving substitution products in only low yields (10–20%) even under forcing conditions using a Pd(0) catalyst, probably due to the severe steric hindrance.

Reaction with Organocuprates. In our preliminary report, we showed that lithium diorganocuprates exerted high asymmetric induction (90% ee) in the reaction of the six-membered enone **2**.[6] Therefore, we investigated the reaction of various chiral amino enones with organocuprates to optimize reaction conditions for obtaining the maximum ee and chemical yield in our system. We first undertook the reaction of the seven-membered enone **3** because of the considerable stability of the product 3-substituted 2-methylenecycloheptanones and the ease with which their ee's are determined (see the accompanying section).

The chiral enone **3** was allowed to react with butylcopper reagents with varied composition in THF at −90 °C in the presence of the Lewis acid, and the reaction mixture was slowly warmed to 0 °C during 1 h. After saturated aqueous NH_4Cl solution was added followed by the usual extraction,[13] the product **6a** was purified by chromatography on silica gel (eq 4). The results are summarized in Table II.



(4)

Among the butylcopper reagents examined (e.g., *n*-BuCu·LiBr, *n*-Bu_2CuLi·LiBr, *n*-BuCu(CN)Li, *n*-Bu_2CuLi·LiCN, and *n*-Bu_2CuMgCl·MgClBr), *n*-Bu_2CuLi·LiBr led to the highest enantiomeric purity (96% ee), whereas *n*-Bu_2CuMgCl·MgClBr resulted in a considerable decrease of ee of **6a** (15% ee). With *n*-Bu_2CuLi·LiBr, addition of LiBr did not affect the ee of **6a** (96% ee), but the chemical yield (ca. 90%) was improved, while $ZnBr_2$ slightly reduced the ee of **6a** to 90%. The use of stronger Lewis acids such as $TiCl_4$ and $SnCl_4$ did not give **6a**, but led to the isomerization of the double bond of **6a** to the endocyclic position to afford the achiral isomer. As can be seen in Table II, the use of *n*-Bu_2CuLi·LiBr together with LiBr (entries 2 and 3) can be regarded as the best choice with respect to both chemical yield and ee; the 1:2 ratio of the cuprate vs LiBr is recommended from the economical standpoint. Thus, under these optimized conditions, 2-*exo*-methylenecycloheptanones **6b–6e** bearing

(12) Yamamoto, Y.; Ohmori, H.; Sawada, S. *Synlett* **1991**, 319.

(13) Deamination reaction of β-amino ketones, Mannich bases, proceeds under acidic conditions to provide α,β-unsaturated ketones, see: (a) Tramontini, M. *Synthesis* **1973**, 703. (b) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791.

Table III. Reaction of 2 and 3 with $R^2_2CuLi \cdot LiBr$ (eq 5)

entry	enone	R^2	added salt (equiv)	product	yield (%)	$[\alpha]_D$[a]	% ee[b]
1	3	*n*-Bu	LiBr (2.0)	**6a**	93	−15.1[c]	96
2	3	Me	LiBr (2.0)	**6b**	87	−60.2[d]	96
3	3	Et	LiBr (2.0)	**6c**	89	−28.0[e]	97
4	3	Ph	LiBr (2.0)	**6d**	60	+20.2[f]	97
5	3	$CH{=}CH_2$	LiBr (2.0)	**6e**	52	−6.1[g]	96
6	2	*n*-Bu	LiBr (2.0)	**7a**	81	+51.3[h]	95
7	2	*n*-Bu	$ZnBr_2$ (1.0)	**7a**	87	–	90
8	2	Me	LiBr (2.0)	**7b**	81	+34.3[i]	95
9	2	Me	$ZnBr_2$ (1.0)	**7b**	84	–	90
10	2	Et	LiBr (2.0)	**7c**	80	+41.2[j]	95
11	2	Et	$ZnBr_2$ (1.0)	**7c**	82	–	90

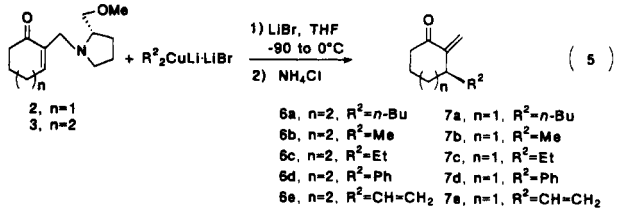
[a] Measured in $CHCl_3$ at 25 °C. [b] Determined by HPLC analysis after conversion into **11a–11d** or **17a–17c**. [c] *c* 2.92. [d] *c* 1.34. [e] *c* 1.04. [f] *c* 1.06. [g] *c* 1.48. [h] *c* 1.42. [i] *c* 1.44. [j] *c* 1.35.

Table IV. Reaction of 1a–1c with $R^2_2CuLi \cdot LiBr$ (eq 6)

entry	R^1	R^2	added salt (equiv)	**8**, yield (%)	**9**, yield (%)	$[\alpha]_D$[a]	% ee[b]
1	OMe	*n*-Bu	LiBr (2.0)	**8a**, 82	**9a**, 78	−18.2[c]	82
2	OMOM	*n*-Bu	LiBr (2.0)	**8a**, 78	**9a**, 43	–	82
3	SMe	*n*-Bu	LiBr (2.0)	**8a**, 99	**9a**, 82	–	10
4	OMe	*n*-Bu	$ZnBr_2$ (1.0)	**8a**, 86	**9a**, 80	–	28
5	OMe	Et	LiBr (2.0)	**8b**, 74	**9b**, 70	−32.1[d]	85
6	OMe	Ph	LiBr (2.0)	**8c**, 80	**9c**, 45	+6.67[e]	47
7	OMe	$CH_2{=}CH$	LiBr (2.0)	**8d**, 99	**9d**, 68	−81.5[f]	79

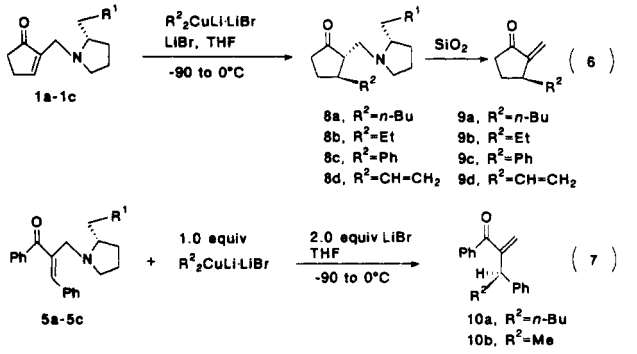
[a] Measured in $CHCl_3$ at 25 °C. [b] Determined by HPLC analysis after conversion into **15a–15c**. [c] *c* 1.26. [d] *c* 1.12. [e] *c* 1.17. [f] *c* 1.70.

various 3-substituents were prepared in high ee's (eq 5 and Table III).



(5)

The identical procedure was applied to asymmetric induction with the six-membered enone **2**, leading to the formation of **7a**, **7b**, and **7c** (R^2 = *n*-Bu, Me, and Et) in 95% ee (eq 5 and Table III). In contrast to the case with the seven-membered homologues, **7d** (R^2 = Ph) and **7e** (R^2 = $CH{=}CH_2$) were not isolated due to its thermal instability. Distinctly, addition of $ZnBr_2$ somewhat lowered the ee (90%) of **7a**, **7b**, and **7c**.[6]



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(7)

Five-membered enone **1a** was also subjected to the reaction with *n*-$Bu_2CuLi \cdot LiBr$ in the presence of additional LiBr (eq 6). Since workup with aqueous saturated NH_4Cl solution resulted in partial isomerization of the double bond in the product **9a** to the endocyclic position, the 1,4-addition product **8a** was isolated under neutral conditions and then was passed through a silica gel column to remove the chiral amine.[13] As shown in Table IV, **9a** was obtained in 90% yield with slightly low ee (82%). Similarly, $Et_2CuLi \cdot LiBr$ and $(CH_2{=}CH)_2CuLi \cdot LiBr$ led to 85 and 79% ee of **9b** and **9d**, respectively, but unexpectedly the use of $Ph_2CuLicLiBr$ resulted in fairly reduced ee (47% ee) of **9c** (Table IV). In order to achieve the high ee's comparable to those of six- and seven-membered homologues, we attempted to identify appropriate chiral auxiliaries, Lewis acids, and other reaction conditions (Table IV). However, we could not improve the ee of **9a**; e.g., the use of chiral enones **1b** and **1c** resulted in comparable ee (82%) and greatly diminished ee (10% ee), respectively, and $ZnBr_2$ largely lowered the ee (28%) of **9a** (entries 2–4). The use of ether as the reaction solvent decreased the ee (71%) of **9a**.

Table V. Reaction of 5a–5c with $R^2_2CuLi \cdot LiBr$ (eq 7)

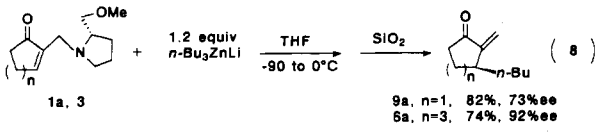
entry	R^1	R^2	product	yield (%)	$[\alpha]_D$[a]	% ee[b]
1	OMe	*n*-Bu	**10a**	90	−5.7[c]	62
2	OMOM	*n*-Bu	**10a**	63	–	70
3	SMe	*n*-Bu	**10a**	93	–	41
4	OMe	Me	**10b**	90	−3.9[d]	55

[a] Measured in $CHCl_3$ at 25 °C. [b] Determined by HPLC analysis. [c] *c* 1.46. [d] *c* 1.40.

Acyclic chiral enones **5a–5c** were also subjected to the asymmetric reaction with 1 equiv of *n*-$Bu_2CuLi \cdot LiBr$ and $Me_2CuLi \cdot LiBr$ in the presence of 2 equiv of LiBr to yield the products **10a** and **10b** directly upon workup by simple addition of water. The chemical yields and ee's of **10a** from **5a**, **5b**, and **5c** were 90% (62% ee), 63% (70% ee), and 93% (41% ee), respectively (eq 7 and Table V). Similarly, **10b** was obtained in 90% yield (55% ee).

Reaction with Organozincates and Other Nucleophiles. It is known that triorganozinclithiums possess lower basicity and effect 1,4-addition to conjugated enones under milder conditions than the corresponding organocuprates.[14] With a view to obtaining higher ee in our system, we attempted the reaction of the chiral enones **1a** and **3** with tributylzinclithium (*n*-Bu_3ZnLi) (eq 8). This reaction was accompanied by the 1,2-addition product to the carbonyl function in the presence of external LiBr or

(14) (a) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679. (b) Tuckmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581. (c) Watson, R. A.; Kjonaas, R. A. *Tetrahedron Lett.* **1986**, *27*, 1437. (d) Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809.



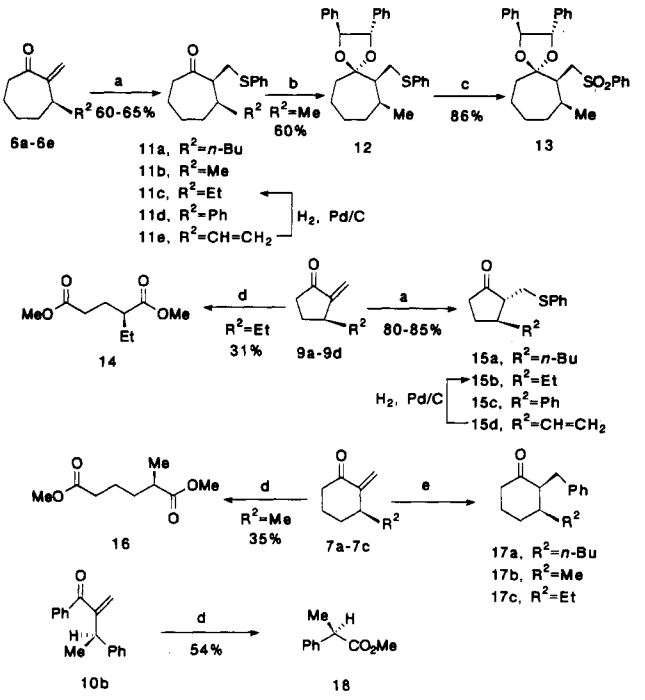
(8)

$ZnBr_2$. The use of a slight excess (1.2 equiv) of n-Bu_3ZnLi alone led to a much improved yield of the 1,4-adduct. Evidently, the use of n-Bu_3ZnLi was inferior to that of n-Bu_2CuLi·LiBr with respect to the enantiomeric purity of **9a** and **6a**, but superior to the n-Bu_2CuLi·LiBr/$ZnBr_2$ system.

Attempted asymmetric induction reactions of chiral enones **1a** or **3** with enolates such as CH_2=C(OMe)OLi, CH_2=C(OMe)OSiMe_2-t-Bu and CH_2=C(Ph)OSiMe_3 in the presence of the Lewis acids like LiBr, $ZnCl_2$, $SnCl_4$, $TiCl_4$, Ti(i-PrO)$_2Cl_2$, BF_3·OEt_2, and R_3SiOTf failed to give appreciable 1,4-addition product and resulted in the recovery of substantial amounts (more than 50%) of the starting chiral enones and a mixture of unidentified products.

Determination of Absolute Configuration and Enantiomeric Purity. Chemical transformations for determining the absolute configuration and enantiomeric purity of the optically active products obtained are summarized in Scheme I. The S configuration of the cycloheptanone (−)-**6b** (R^2 = Me) was unequivocally established by an X-ray analysis of a single crystal of **13**,[15] which was obtained as a single enantiomer from (−)-**6b** via **11b** and **12** by successive phenylthiolation, acetalization with (*S*,*S*)-(−)-hydrobenzoin, and oxidation with *m*-CPBA, followed by recrystallization. The ee's of **6a**–**6d** were determined by HPLC analysis of the *cis*-2-[(phenylthio)methyl]cycloheptanone derivatives **11a**–**11d**[15] with a chiral stationary phase (CSP) column (Daicel chiralcel OJ, hexane/2-propanol (97:3)). The S configuration of **6a** (R^2 = n-Bu) and **6c** (R^2 = Et) and the R configuration of **6d** (R^2 = Ph) were established by the comparison of the HPLC behavior (elution pattern) of **11a**, **11c**, and **11d** with that of **11b** (R^2 = Me) and as well on the basis of the transition-state model (see the next section). The R configuration and 96% ee for **6e** (R^2 = CH=CH_2) were determined upon hydrogenation (H_2, Pd/C) of **11e** into **11c** (R^2 = Et). The *S*, *S*, and *R* configurations were assigned to the five- and six-membered products (−)-**9b** (R^2 = Et) and (+)-**7b** (R^2 = Me), and the acyclic product (−)-**10b** by ozonolysis of them followed by esterification with methanol into known diesters **14**[16] and **16**[17] and monoester **18**,[18] respectively. The ee's of **9a**–**9c** and **7a**–**7c** were determined by HPLC analyses on the same CSP column of the *trans*-2-[(phenylthio)methyl]cyclopentanone derivatives **15a**–**15c** (97:3 hexane/2-propanol as the eluent)[16] and the *cis*-2-benzylcyclohexanone derivatives **17a**–**17c** (9:1 hexane/2-propanol),[19] while those of **10a** and **10b** were directly performed by analyzing themselves on the CSP column (97:3 hexane/2-propanol). The S configuration of **9a** (R^2 = n-Bu), **7a** (R^2 = n-Bu), and **7c** (R^2 = Et) and the R configuration of **9c** (R^2 = Ph) were established on the basis of the HPLC behavior of **15a**, **17b**, **17c**, and **15c** by comparison with that of **15b** and **17a**. Further, the CD spectra of **17a**, **17b**, and **17c** uniformly showed a negative Cotton effect near 295 nm ($[\theta]_{295}$ −4850, −3990, and −3290 deg cm^2 dmol^{-1} in acetonitrile, respectively), indicating the same

Scheme I[a]



[a] Key: (a) PhSH, Et_3N, CH_3CN; (b) (*S*,*S*)-(−)-hydrobenzoin, PPTS, PhH; (c) *m*-CPBA, CH_2Cl_2; (d) (1) O_3, AcOEt; (2) MeOH, PTS; (e) Ph_2CuLi, THF.

Table VI. Selected ^{1}H and ^{13}C NMR Spectral Data of 2 in the Presence of the Lewis Acids

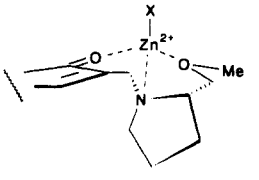
Lewis acid	^{1}H NMR (δ)[a] C=CH–	^{1}H NMR (δ)[a] OCH_3	^{13}C NMR (δ)[a] C=O
none	6.90	3.26	197.7
LiBr	6.94	3.27	198.3
$ZnBr_2$	7.45	3.40	201.6

[a] Measured in THF-d_8 (0.8 mL) at 25 °C using **2** (0.20 mmol) and the Lewis acid (0.20 mmol) and recorded in δ (ppm).

S configuration of **7a** and **7c** as **7b**.[6] Similarly, the *R* configuration was assigned to **10a** by comparison of its HPLC behavior with that of **10b**.

Furthermore, the ee values were reconfirmed with diastereomeric cyclic acetals prepared by the reaction of **11b**, **15b**, and **17a** with (2*R*,3*R*)-(−)-2,3-butanediol. The de's of these acetals analyzed by capillary GC and HPLC showed good accordance with those obtained above.

Transition-State Models. As described in the previous sections, when organocopper nucleophiles and chiral pyrrolidine derivatives are used, the composition of the organocopper reagents and the nature of the endogeneous and external Lewis acids affect the enantiomeric purity of the products. To explore the actual role of the Lewis acid, NMR studies on the complexation between **2** and Lewis acids were carried out. The ^{1}H and ^{13}C NMR spectra of **2** alone and a mixture of equimolar amounts of **2** and LiBr or **2** and $ZnBr_2$ were recorded in THF-d_8 at 25 °C, and selected chemical shifts are summarized in Table VI. Apparently, $ZnBr_2$ forms a tight complex **19** with **2**,

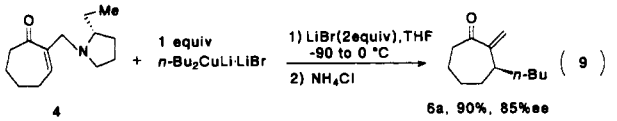


19

(15) See the following paper in this issue.
(16) Berner, E.; Leonardsen, R. *Liebigs Ann. Chem.* **1939**, *538*, 1.
(17) Kawasaki, I.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1482.
(18) Angres, I.; Zieger, H. E. *J. Org. Chem.* **1975**, *40*, 1457.
(19) Correction: The assumed trans geometry of **17a**–**17b** reported in our preliminary communication (ref 6) was wrong. For more details, see the following paper in this issue.

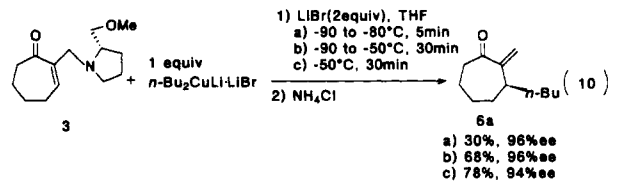
leading to precipitation of a small amount of a white solid, and an NMR spectrum of the solution showed appreciable deshielding of the vinylic proton, methoxymethyl protons, and carbonyl carbon more than LiBr, which did not form any precipitation with **2**.[20] $MgBr_2$ immediately produced much white precipitate with **2** in THF at 25 °C, and hence an NMR measurement was infeasible. Since LiBr is a more suitable Lewis acid than $ZnBr_2$ and MgX_2 with respect to enantiomeric purity (Table II–IV), the formation of a strong complex between **2** and the Lewis acid is not a pivotal cause of the observed high ee's.[21]

We investigated the importance of a methoxy functionality in the chiral 2-(methoxymethyl)pyrrolidinyl group. The chiral enone **4** (R^1 = Me) bearing no oxygen atom was subjected to the reaction with *n*-Bu_2CuLi·LiBr under the optimum conditions (vide supra), giving **6a** in a reduced ee (85%), compared with 96% ee in the case of **3** (R^1 = OMe) (eq 9). Further, as shown in Table IV, the



(9)

reaction of the five-membered enone **1c** (R^1 = SMe) with *n*-Bu_2CuLi·LiBr led to the greatly decreased ee (10%) of **9a** (entry 3), compared with those of **1a** (R^1 = OMe) and **1c** (R^1 = OMOM) (82% ee each) (entries 1 and 2). Similarly, the reaction of acyclic enones **5a** (R^1 = OMe) (62% ee), **5b** (R^1 = OMOM) (70% ee), and **5c** (R^1 = SMe) (41% ee) with *n*-Bu_2CuLi·LiBr indicated the importance of the oxygen atom in the C(2) side chain of the pyrrolidinyl group (entries 1–3 in Table V). These results imply the significance of complexation between the organocopper species and the three heteroatoms in **3**. Next, we examined temperature effects on the reaction of **3** with *n*-Bu_2CuLi·LiBr in the presence of LiBr. The reaction was conducted at −90 °C and was slowly warmed to −80 °C during 5 min, or to −50 °C during 30 min. The chemical yield and ee of **6a** at each temperature, and the same data obtained from the reaction performed at −50 °C for 30 min, are shown in eq 10. Apparently, between −90 and −80 °C

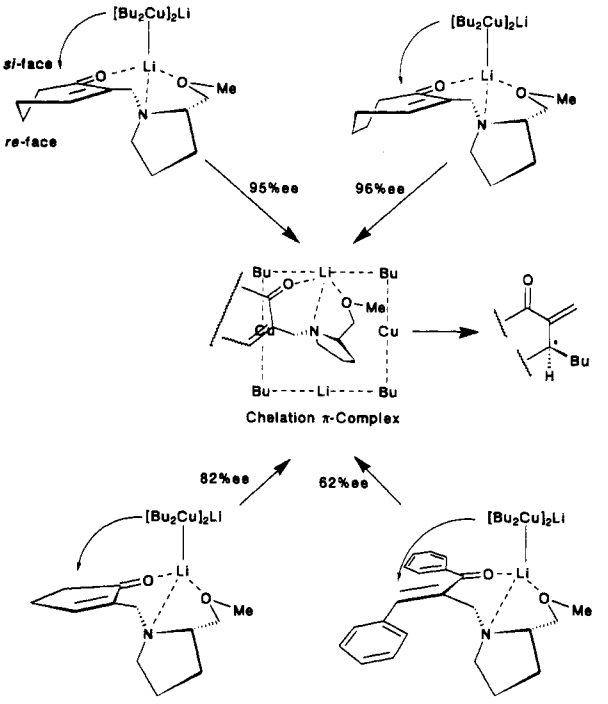


(10)

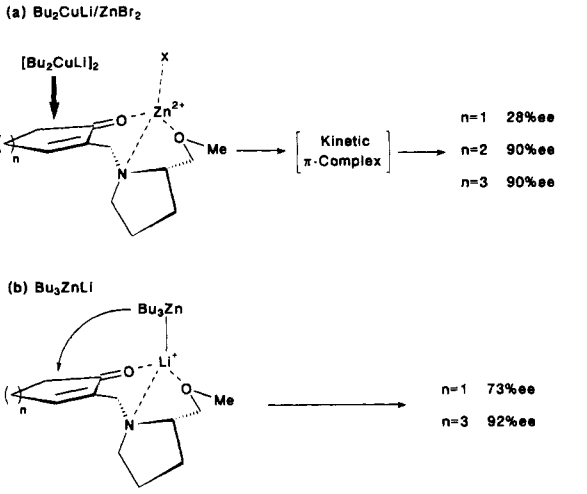
the reaction rate was slow, and the ee of **6a** was slightly better in the reaction started at −90 °C (96% ee) than in that at −50 °C (94% ee).

These experimental results permit us to account for the observed high and low ee's in terms of the formation of chelation π-complex[22] between *n*-Bu_2CuLi and the structurally different chiral enones **1a**, **2**, **3**, and **5a** as shown

Scheme II. Transition-State Model (Bu_2CuLi/LiBr)



Scheme III. Transition-State Model



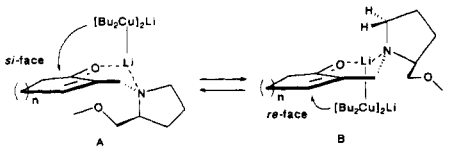
in Scheme II. The chiral enone initially forms a weak tridentate chelation complex with *n*-Bu_2CuLi by coordination of three heteroatoms to the lithium,[23] followed by additional d–π* complexation between the copper atom and the conjugated enone moiety.[24] This chelation d–π* complexation occurs at the *Si* face, since the *Re* face is shielded by the extruding pyrrolidine ring. The *Si* face oriented chelation π-complex might be in equilibrium with

(20) For diastereodifferentiating asymmetric conjugate addition which takes advantage of Zn^{2+}-chelation to the chiral β-keto sulfoxide substrates, see refs 1b and 1c.

(21) Both Li^+ and Zn^{2+} can assume a tetrahedral coordination state, while Mg^{2+} can assume up to hexacoordination; see: (a) Mukaiyama, T.; Sakito, Y.; Asami, M. *Chem. Lett.* **1978**, 1253; (b) *Ibid.* **1979**, 705. (c) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1. (d) Fujisawa, T.; Funabara, M.; Ukaji, Y.; Sato, T. *Chem. Lett.* **1988**, 59. (e) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256.

(22) (a) Alexakis, A.; Sedrani, R.; Mangeney, P. *Tetrahedron Lett.* **1990**, *31*, 345. (b) Christenson, B.; Hallnemo, G.; Ullenius, C. *Tetrahedron* **1991**, *47*, 4739.

(23) The formation of a bidentate chelation complex between Li^+ of *n*-Bu_2CuLi and the oxygen (C=O) and nitrogen atoms in the chiral enone seemed reasonable. However, there are two possible conformations for the bidentate chelate; one (**A**) favors nucleophilic addition to the *si*-face and the other (**B**) does the *re*-face addition.



(24) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063; (b) *Tetrahedron Lett.* **1985**, *26*, 6015.

the Re face oriented one to some extent at temperatures as low as −90 °C. Consequently, the interplay between the steric distortion of the six- and seven-membered ring skeletons and *Re* face shielding by the pyrrolidine ring should favor the less sterically hindered, stable *Si* face complexation. This arrangement should lead to high ee's (95 and 96% ee) compared with the cases of flat five-membered and acyclic enones (82 and 70% ee) (Tables II–V and Scheme II). In the presence of $ZnBr_2$ (Scheme IIIa), the formation of tight chelation complex between Zn^{2+} and **3** prevented the Li^+-directed chelation π-complexation between *n*-Bu_2CuLi and **3**, instead leading to fast 1,4-addition via a kinetic or nonchelated d–π^* complex due to the strong Lewis acidity of $ZnBr_2$. Thus, 28% ee of **9a** from **1a** and 90% ee of **7a** and **6a** from **2** and **3** reflect such a kinetic addition in the presence of $ZnBr_2$, although addition occurs from the *Si* face, too (Tables II–IV and Scheme IIIa).

n-Bu_3ZnLi exhibited better stereoselectivity than the *n*-Bu_2CuLi·LiBr/$ZnBr_2$ system, giving 73% ee of **9a** from **1a** and 92% ee of **6a** from **3** (eq 8 and Scheme IIIb). Probably, in this case, Li^+-directed chelation of *n*-Bu_3ZnLi to three heteroatoms in the enones would be responsible for the relatively high ee's, partly similar to the case of the *n*-Bu_2CuLi·LiBr/LiBr system described in Scheme II, since d–π^* complexation between zinc and the double bond is infeasible.

Conclusions

A highly diastereodifferentiating addition–elimination type of asymmetric induction was accomplished by reacting chiral 2-[[2-(methoxymethyl)-1-pyrrolidinyl]-methyl]-2-cyclohexen-1-one and -cyclohepten-1-one with lithium diorganocuprates (R_2CuLi) to give directly 3-substituted 2-methylenecyclohexanones and -heptanones in 95 and 96–97% ee, respectively. From the comparison of the experimental results obtained with structurally different substrates, organometallic reagents and chiral auxiliaries, and external Lewis acids, the observed high diastereoselectivity was accounted for in terms of the formation of thermodynamically more stable chelation d–π^* complexes between R_2CuLi and the chiral amino enones in the transition state at lower temperature. The simple experimental procedure with high reproducibility described here can offer a convenient synthetic method for optically active 3-substituted 2-methylenecycloalkanones with high enantiomeric purity.

Experimental Section

General. Infrared spectra were recorded as liquid films on NaCl plates. ^1H NMR spectra were recorded at 270 MHz, and ^{13}C NMR were recorded at 67.8 MHz. All reactions were run under argon. HPLC analyses were carried out by using a chiral stationary phase column (Daicel chiralcel OJ, 0.46 cm × 25 cm).

THF and ether were distilled from sodium benzophenone ketyl. DMF and acetonitrile were distilled over calcium hydride and phosphorus pentoxide, respectively. Ethyllithium (pentane suspension) was prepared by a published procedure.[25] Vinyllithium (ether solution) was prepared by the reaction of triphenylvinyltin with an equimolar amount of phenyllithium in ether at 25 °C for 1 h, followed by filtration. *n*-Bu_2CuLi·LiBr, *n*-$Bu_2CuMgCl$·MgClBr, Me_2CuLi·LiBr, Et_2CuLi·LiBr, and Ph_2CuLi·LiBr were prepared by adding dropwise the corresponding organolithium or the Grignard reagent (2.0 mmol) to a suspension of CuBr·Me_2S (1.0 mmol) in THF (10 mL) at −78 °C and warming the resulting solution to −30–0 °C during 1 h. $(CH_2{=}CH)_2CuLi$·LiBr was prepared in ether by the analogous procedure. *n*-BuCu·LiBr and *n*-BuCu(CN)Li were prepared from *n*-BuLi (1.0 mmol) and CuBr·Me_2S (1.0 mmol) or CuCN (1.0 mmol), respectively, in THF. *n*-Bu_2CuLi·LiCN was prepared from *n*-BuLi (2.0 mmol) and CuCN (1.0 mmol) in THF. *n*-Bu_3ZnLi was prepared according to a published procedure.[14] 2-(Nitromethyl)- and 2-[(phenylsulfonyl)methyl]-2-alken-1-ones were prepared by our procedure;[7] α-[(phenylsulfonyl)methyl]chalcone was obtained from α-(nitromethyl)chalcone, which was synthesized in four steps from 1,3-diphenyl-2-propanone. (*S*)-2-(Methoxymethyl)pyrrolidine[9] and (*R*)-2-ethylpyrrolidine[11] were prepared by literature methods. (*S*)-2-[[(Methoxymethyl)oxy]methyl]-pyrrolidine was synthesized in overall 40% yield from (*S*)-proline according to the method for preparation of (*S*)-2-(methoxymethyl)pyrrolidine,[9] except that diisopropylethylamine and chloromethyl methyl ether were employed for methoxymethylation of (*S*)-(−)-1-formyl-2-(hydroxymethyl)pyrrolidine.

α-(Nitromethyl)chalcone: IR (neat) 1655, 1560, 1360, 735, 700 cm^{-1}; ^1H NMR δ 7.89–7.26 (m, 11 H), 5.59 (s, 2 H); ^{13}C NMR δ 196.0, 148.3, 137.0, 133.4, 132.7, 130.2, 130.1, 129.7, 129.2, 128.9, 128.5, 71.8. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.79; H, 5.23; N, 5.50.

(*S*)-2-[[(Methoxymethyl)oxy]methyl]pyrrolidine: bp 82–84 °C (10 Torr); $[\alpha]_D$ +6.6 (*c* 1.30, $CHCl_3$); IR (neat) 3380, 3190, 1215, 1150, 1110 cm^{-1}; ^1H NMR δ 4.65 (s, 2 H), 3.37 (s, 3 H), 3.61–3.33 (m, 4 H), 3.05–2.82 (m, 2 H), 1.93–1.61 (m, 3 H), 1.53–1.47 (m, 1 H); ^{13}C NMR δ 77.5, 76.4, 60.9, 57.7, 46.2, 27.7, 25.0. Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.83; H, 10.64; N, 10.00.

Preparation of (*S*)-2-[(Methylthio)methyl]pyrrolidine.[10] To a solution of (*S*)-*N*-Boc-2-(hydroxymethyl)pyrrolidine[11] (10 mmol) and methanesulfonyl chloride (11 mmol) in CH_2Cl_2 (50 mL) was added dropwise triethylamine (22 mmol) at −50 °C. The reaction mixture was slowly warmed to room temperature during 1 h and stirred for an additional 2 h. Water (50 mL) was added to the mixture, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo to give crude (*S*)-*N*-Boc-2-[[(methylsulfonyl)oxy]methyl]pyrrolidine in 99% yield.

A solution of this crude material (9.9 mmol) in MeOH (70 mL) was added to CH_3SNa (59 mmol) in MeOH (70 mL) at rt. The reaction mixture was stirred for 10 d at the same temperature and then concentrated in vacuo. The residue was diluted with ethyl acetate (60 mL), and the organic phase was washed with water (2 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo to give crude (*S*)-*N*-Boc-2-[(methylthio)methyl]pyrrolidine in 80% yield. To a solution of this crude material (7.9 mmol) in THF (25 mL) was added trifluoroacetic acid (5.3 mL) at 0 °C during 15 min, and the reaction mixture was stirred at the temperature for 30 min. After addition of 2 N HCl (20 mL) and ether (30 mL), the solution was made basic with solid KOH and then saturated with NaCl. The organic phase was separated, and the aqueous phase was extracted with ether (2 × 30 mL). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to afford a 50% yield: bp 105–110 °C (10 Torr); $[\alpha]_D$ +9.2° (*c* 1.00, $CHCl_3$); IR (neat) 3370, 1200 cm^{-1}; ^1H NMR δ 3.28 (m, 1 H), 3.02 (m, 1 H), 2.89 (s, 1 H), 2.91 (m, 1 H), 2.60 (d, *J* = 6.1 Hz, 1 H), 2.59 (d, *J* = 7.0 Hz, 1 H), 2.14 (s, 3 H), 1.97–1.76 (m, 3 H), 1.48–1.40 (m, 1 H). Anal. Calcd for $C_6H_{13}NS$: C, 54.91; H, 9.98; N, 10.67. Found: C, 55.22; H, 10.32: N, 10.29.

General Procedure for Preparation of Chiral Amino Enones 1a–1c, 2, 3, 4, and 5a–5c. To the 2-(nitromethyl)- or 2-[(phenylsulfonyl)methyl]-2-alken-1-one (5.0 mmol) in acetonitrile (10 mL) was added the chiral pyrrolidine derivative (10.5 mmol) at 25 °C. The reaction mixture was stirred for the stated period of time (see Table I) and concentrated in vacuo. The oily residue was diluted with ethyl acetate (30 mL) and washed with water (30 mL). The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo to give the chiral aminoenone in a high state of purity: **1a** (73%),[7] **2** (91%),[7] **3** (97%).[7]

1b: IR (neat) 1700, 1640, 1445, 1150, 1110 cm^{-1}; ^1H NMR δ 7.48 (m, 1 H), 4.57 (s, 2 H), 3.58 (d, *J* = 14.6 Hz, 1 H), 3.51 (dd, *J* = 9.9, 5.2 Hz, 1 H), 3.40 (dd, *J* = 9.9, 5.8 Hz, 1 H), 3.30 (s, 3 H), 3.06 (d, *J* = 14.6 Hz, 1 H), 2.98 (m, 1 H), 2.68–2.50 (m, 2 H), 2.37–2.33 (m, 3 H), 2.16 (m, 1 H), 1.84 (m, 1 H), 1.74–1.52 (m, 3 H); ^{13}C NMR δ 175.2, 160.4, 143.7, 96.6, 76.5, 63.2, 55.1, 54.7,

(25) Bryce-Smith, D.; Turner, E. E. *J. Chem. Soc.* **1953**, 861.

48.7, 34.6, 28.2, 26.6, 22.8. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.60; H, 9.22; N, 5.49.

1c: IR (neat) 1700, 1635, 1440, 1115 cm^{-1}; ^1H NMR δ 7.57–7.55 (m, 1 H), 3.54 (m, 1 H), 3.10–3.03 (m, 2 H), 2.74 (dd, J = 12.2, 3.1 Hz, 1 H), 2.63 (m, 2 H), 2.50 (dd, J = 12.2, 8.6 Hz, 1 H), 2.45–2.41 (m, 3 H), 2.20 (m, 1 H), 2.13 (s, 3 H), 2.06 (m, 1 H), 1.75–1.64 (m, 3 H); ^{13}C NMR δ 209.3, 160.4, 143.4, 63.4, 54.4, 48.0, 39.0, 34.6, 30.3, 26.5, 22.3, 16.3. Anal. Calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.50; N, 6.22. Found: C, 64.30; H, 8.32; N, 6.01.

4: IR (neat) 1670, 1450 cm^{-1}; ^1H NMR δ 6.97 (t, J = 6.0 Hz, 1 H), 3.80 (d, J = 13.0 Hz, 1 H), 3.63–3.23 (m, 2 H), 3.03–2.90 (m, 2 H), 2.65–1.63 (m, 14 H), 0.91 (t, J = 6.4 Hz, 3 H). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.35; H, 10.77; N, 5.99.

5a: IR (neat) 1650, 1620, 1600, 1495, 1450, 1110, 720, 700 cm^{-1}; ^1H NMR δ 7.60 (m, 10 H), 7.18 (s, 1 H), 4.03 (dd, J = 12.2, 0.9 Hz, 1 H), 3.66 (d, J = 12.2 Hz, 1 H), 3.37 (dd, J = 9.5, 4.9 Hz, 1 H), 3.30 (s, 3 H), 3.26 (dd, J = 9.5, 6.1 Hz, 1 HI), 2.99 (m, 1 H), 2.67 (m, 1 H), 2.21 (m, 1 H), 1.85 (m, 1 H), 1.69–1.56 (m, 3 H); ^{13}C NMR δ 198.6, 141.9, 139.6, 138.0, 135.2, 132.0, 129.9, 129.6, 128.6, 128.2, 128.1, 75.6, 63.6, 58.9, 54.4, 51.1, 28.2, 22.8. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 79.00; H, 7.62; N, 3.99.

5b: IR (neat) 1650, 1620, 1600, 1495, 1450, 1150, 1110, 730, 700 cm^{-1}; ^1H NMR δ 7.59 (m, 10 H), 7.20 (s, 1 H), 4.58 (s, 2 H), 3.99 (dd, J = 12.2 Hz, 1 H), 3.67 (d, J = 12.2 Hz, 1 H), 3.31 (s, 3 H), 3.39–3.28 (m, 2 H), 2.97 (m, 1 H), 2.68 (m, 1 H), 2.26 (m, 1 H), 1.81 (m, 1 H), 1.68–1.62 (m, 3 H); ^{13}C NMR δ 198.6, 142.1, 139.6, 138.1, 135.3, 132.0, 129.9, 128.7, 128.2, 128.1, 96.6, 70.6, 63.6, 55.1, 54.4, 51.0, 28.5, 22.9. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 74.20; H, 7.77; N, 4.15.

5c: IR (neat) 1650, 1620, 1600, 1495, 1450, 720, 700 cm^{-1}; ^1H NMR δ 7.87–7.19 (m, 10 H), 7.21 (s, 1 H), 3.89 (d, J = 12.2 Hz, 1 H), 3.62 (d, J = 12.2 Hz, 1 H), 3.02 (m, 1 H), 2.73–2.63 (m, 2 H), 2.39 (m, 1 H), 2.26 (m, 1 H), 2.05 (s, 3 H), 2.04–1.98 (m, 1 H), 1.68–1.60 (m, 3 H); ^{13}C NMR δ 198.5, 142.3, 139.3, 137.9, 135.2, 132.1, 129.9, 129.6, 129.1, 128.7, 128.2, 64.1, 54.2, 50.2, 38.7, 30.5, 22.5, 16.3. Anal. Calcd for $C_{22}H_{25}NOS$: C, 75.17; H, 7.17; N, 3.98. Found: C, 75.45; H, 6.80; N, 4.35.

General Procedure for Asymmetric Conjugate Addition–Elimination Reaction of Organocopper Reagents to Chiral Amino Enones. A mixture of the chiral amino enone (1.0 mmol) and the Lewis acid (1.0–2.0 mmol) in THF (5 mL) was stirred at 25 °C for 10 min and cooled to −90 °C in a dry ice/methanol bath. A THF or ether solution of the organocopper reagent precooled to −90 °C was added to the THF solution of the aminoenone at −90 °C using a cannula. The resulting mixture was slowly allowed to warm to 0 °C during 1 h. The workup procedure was dependent on the substrate structure used; saturated aqueous NH_4Cl (10 mL) was added for the production of products **6a–6e** and **7a–7c**, while water (10 mL) was added to obtain products **8a–8d** and **10a**, **10b**. After extraction of the aqueous mixture with ether (3 × 30 mL), the combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude 2-methylene ketones **6a–6e**, **7a–7c**, and **10a**, **10b** were purified by column chromatography on Florisil. The adducts **8a–8d** were subjected to short flash column chromatography on silica gel (20:1 hexane/ethyl acetate) for both deamination and purification to afford **9a–9d**.

6a: IR (neat) 1690, 1605, 935 cm^{-1}; ^1H NMR δ 5.90 (d, J = 1.5 Hz, 1 H), 5.20 (dd, J = 1.5, 1.5 Hz, 1 H), 2.71–2.49 (m, 2 H), 2.37 (m, 1 H), 1.90–1.26 (m, 12 H), 0.89 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 205.7, 153.6, 119.9, 42.7, 41.9, 36.9, 33.2, 29.7, 28.7, 24.8, 22.7, 14.0. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.62; H, 11.55.

6b: IR (neat) 1690, 1610, 935 cm^{-1}; ^1H NMR δ 5.97 (dd, J = 1.5, 0.9 Hz, 1 H), 5.25 (dd, J = 1.5, 1.5 Hz, 1 H), 2.67–2.52 (m, 3 H), 1.94–1.26 (m, 6 H), 1.18 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 204.9, 153.7, 119.2, 42.7, 39.0, 35.6, 29.7, 24.9, 20.5. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.88; H, 10.52.

6c: IR (neat) 1690, 1610, 935 cm^{-1}; ^1H NMR δ 5.92 (d, J = 1.5 Hz, 1 H), 5.20 (dd, J = 1.5, 1.5 Hz, 1 H), 2.70–2.49 (m, 2 H), 2.29 (m, 1 H), 1.93–1.43 (m, 8 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 205.6, 153.3, 119.9, 43.7, 42.7, 36.5, 28.8, 26.3, 24.8, 12.1. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 79.22; H, 10.62.

6d: IR (neat) 1690, 1600, 1495, 930, 735, 700 cm^{-1}; ^1H NMR δ 7.35–7.12 (m, 5 H), 6.02 (dd, J = 1.5, 1.5 Hz, 1 H), 4.78 (dd, J = 1.5, 0.9 Hz, 1 H), 3.79 (d, J = 9.8 Hz, 1 H), 2.80–2.50 (m, 2 H), 2.22–1.52 (m, 6 H); ^{13}C NMR δ 204.3, 152.5, 143.6, 128.5, 127.9, 126.3, 123.8, 47.4, 42.9, 36.1, 29.5, 25.3. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.29; H, 7.99.

6e: IR (neat) 1695, 1645, 1610, 950, 920 cm^{-1}; ^1H NMR δ 6.01 (dd, J = 1.5, 0.9 Hz, 1 H), 5.92 (ddd, J = 16.8, 11.0, 6.7 Hz, 1 H), 5.27 (d, J = 1.5 Hz, 1 H), 5.16–5.01 (m, 2 H), 3.23 (m, 1 H), 2.64–2.55 (m, 2 H), 1.95–1.61 (m, 6 H); ^{13}C NMR δ 204.3, 150.9, 140.0, 122.6, 115.0, 45.4, 42.9, 35.4, 28.5, 24.9. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.33; H, 9.30.

7a: IR (neat) 1695, 1610, 940 cm^{-1}; ^1H NMR δ 5.77 (d, J = 1.5 Hz, 1 H), 5.10 (d, J = 1.5 Hz, 1 H), 2.69–2.41 (m, 3 H), 1.96–1.30 (m, 10 H), 0.90 (t, J = 6.4 Hz, 3 H); ^{13}C NMR δ 203.4, 150.3, 118.7, 41.7, 40.7, 33.1, 29.4, 22.7, 20.9, 14.0. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.08; H, 11.30.

7b: IR (neat) 1695, 1610, 940 cm^{-1}; ^1H NMR δ 5.81 (dd, J = 1.8, 1.5 Hz, 1 H), 5.15 (dd, J = 1.8, 2.1 Hz, 1 H), 2.62–2.48 (m, 2 H), 2.37 (m, 1 H), 2.05–1.75 (m, 4 H), 1.17 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 202.9, 151.3, 118.0, 40.6, 36.6, 32.6, 22.0, 19.4. Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 76.99; H, 10.01.

7c: IR (neat) 1695, 1610, 940 cm^{-1}; ^1H NMR δ 5.80 (dd, J = 1.5, 1.5 Hz, 1 H), 5.11 (dd, J = 1.5, 1.5 Hz, 1 H), 2.46–2.41 (m, 3 H), 1.98–1.78 (m, 4 H), 1.63–1.37 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 203.3, 149.9, 119.0, 43.4, 40.7, 29.0, 26.2, 20.9, 11.3. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.10; H, 10.58.

9a: IR (neat) 1730, 1640, 940 cm^{-1}; ^1H NMR δ 5.94 (d, J = 2.5 Hz, 1 H), 5.17 (dd, J = 2.5, 0.6 Hz, 1 H), 2.61 (m, 1 H), 2.39–2.04 (m, 2 H), 1.67 (m, 1 H), 1.50–1.18 (m, 7 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 207.7, 149.2, 116.4, 41.0, 37.1, 33.7, 29.0, 26.3, 22.7, 14.0. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.50; H, 10.95.

9b: IR (neat) 1730, 1640, 940 cm^{-1}; ^1H NMR δ 6.02 (dd, J = 2.8, 0.9 Hz, 1 H), 5.25 (dd, J = 2.8, 1.2 Hz, 1 H), 2.63 (m, 1 H), 2.46–2.12 (m, 2 H), 1.79 (m, 1 H), 1.58–1.32 (m, 3 H), 1.00 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 207.6, 148.9, 116.5, 42.6, 37.1, 26.7, 25.8, 11.1. Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.75; H, 9.53.

9c: IR (neat) 1720, 1640, 1098, 910, 700 cm^{-1}; ^1H NMR δ 7.39–7.15 (m, 5 H), 6.14 (dd, J = 3.1, 0.6 Hz, 1 H), 5.05 (dd, J = 3.1, 0.9 Hz, 1 H), 3.92 (m, 1 H), 2.59–2.33 (m, 3 H), 1.98 (m, 1 H); ^{13}C NMR δ 206.3, 148.9, 142.7, 128.7, 128.0, 126.9, 119.0, 48.1, 37.5, 29.8. Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.32; H, 7.33.

9d: IR (neat) 1720, 1640, 1630, 940, 910 cm^{-1}; ^1H NMR δ 6.00 (dd, J = 2.7, 0.6 Hz, 1 H), 5.67 (ddd, J = 17.4, 9.8, 7.6 Hz, 1 H), 5.19 (dd, J = 2.7, 0.9 Hz, 1 H), 5.12 (m, 1 H), 5.07 (m, 1 H), 3.30 (m, 1 H), 2.36–2.09 (m, 3 H), 1.62 (m, 1 H); ^{13}C NMR δ 206.2, 147.3, 139.0, 118.1, 116.5, 46.0, 37.1, 26.9. Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 79.0; H, 8.42.

10a: IR (neat) 1660, 1620, 1600, 1580, 1490, 730, 700 cm^{-1}; ^1H NMR δ 7.68–7.14 (m, 10 H), 5.78 (d, J = 1.5 Hz, 1 H), 5.61 (s, 1 H), 4.10 (dd, J = 7.3, 7.6 Hz, 1 H), 1.36–1.20 (m, 6 H), 0.85 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 198.2, 151.6, 142.4, 137.8, 132.1, 129.5, 128.4, 128.2, 128.0, 126.3, 123.5, 46.3, 33.6, 29.8, 22.6, 13.9. Anal. Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 85.99; H, 8.32.

10b: IR (neat) 1660, 1615, 1600, 1580, 1490, 735, 700 cm^{-1}; ^1H NMR δ 7.71–7.15 (m, 10 H), 5.76 (d, J = 1.5 Hz, 1 H), 5.64 (s, 1 H), 4.31 (q, J = 7.3 Hz, 1 H), 1.49 (d, J = 7.3 Hz, 3 H); ^{13}C NMR δ 198.0, 152.4, 143.8, 137.8, 132.2, 129.5, 128.4, 128.1, 127.6, 126.4, 123.5, 40.5, 20.0. Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.28; H, 7.11.

General Procedure for Asymmetric Conjugate Addition–Elimination Reaction of Tributylzinclithium to Chiral Amino Enones. To the chiral aminoenone (1.0 mmol) in THF (5 mL) was added a precooled (−90 °C) solution of n-Bu_3ZnLi (1.2 mmol) in THF (10 mL) at −90 °C via a cannula. The reaction solution was slowly allowed to warm to 0 °C during 1 h. For workup, saturated aqueous NH_4Cl (10 mL) was added to produce **6a**, while water (10 mL) was added to obtain **8a**. The aqueous mixture was extracted with ether (3 × 30 mL). The ether extract was washed with H_2O (2 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude **6a** was purified by column chromatography on Florisil (ether). The adduct **8a** was subjected

to flash column chromatography (20:1 hexane/ethyl acetate) for both deamination and purification to afford **9a**.

General Procedure for Conversion of 3-Substituted 2-Methylenecycloheptanones 6a–6e into 3-Substituted 2-[(Phenylthio)methyl]cycloheptanones 11a–11e. To the 2-methylene ketone (1.0 mmol) in THF (5.0 mL) was added a solution of thiophenol (1.5 mmol) and triethylamine (0.05 mmol) at 25 °C. The reaction mixture was stirred for 2–3 h and poured into water (30 mL). The aqueous mixture was extracted with ether (3 × 30 mL). The ether extract was washed with water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (9:1 hexane/ethyl acetate). The cis/trans ratio of the products was determined to be uniformly 96/4 according to ^1H NMR analysis.[15]

***cis*-11a**: 64% yield; IR (neat) 1700, 1585, 1480, 740, 680 cm^{-1}; ^1H NMR δ 7.40–7.15 (m, 5 H), 3.39 (dd, J = 13.4, 6.1 Hz, 1 H), 3.05 (ddd, J = 7.5, 6.1, 1.8 Hz, 1 H), 2.85 (dd, J = 13.4, 7.5 Hz, 1 H), 2.49 (m, 1 H), 2.34 (m, 1 H), 2.04–1.21 (m, 13 H), 0.86 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 213.2, 136.4, 129.4, 128.8, 126.0, 55.1, 43.9, 38.0, 33.5, 33.3, 29.9, 27.0, 23.8, 23.4, 22.6, 14.0. Anal. Calcd for $C_{18}H_{26}OS$: C, 74.43; H, 9.02. Found: C, 74.20; H, 9.33.

***cis*-11b**: 62% yield; IR (neat) 1700, 1585, 1480, 740, 695 cm^{-1}; ^1H NMR δ 7.35–7.16 (m, 5 H), 3.38 (dd, J = 13.1, 6.4 Hz, 1 H), 3.07 (ddd, J = 7.3, 6.4, 2.1 Hz, 1 H), 2.84 (dd, J = 13.1, 7.3 Hz, 1 H), 2.53–2.45 (m, 1 H), 2.38–2.25 (m, 2 H), 1.84–1.39 (m, 6 H), 0.79 (d, J = 7.3 Hz, 3 H); ^{13}C NMR δ 213.3, 136.4, 129.4, 128.9, 126.0, 54.6, 44.2, 37.2, 33.5, 32.8, 23.7, 23.5, 13.9. Anal. Calcd for $C_{15}H_{20}OS$: C, 72.53; H, 8.12. Found: C, 72.24; H, 8.44.

***cis*-11c**: 63% yield; IR (near) 1700, 1585, 1480, 740, 690 cm^{-1}; ^1H NMR δ 7.40–7.14 (m, 5 H), 3.40 (dd, J = 13.3, 6.3 Hz, 1 H), 3.06 (ddd, J = 7.5, 6.3, 2.1 Hz, 1 H), 2.86 (dd, J = 13.3, 7.5 Hz, 1 H), 2.49 (m, 1 H), 2.30 (m, 1 H), 2.04–1.25 (m, 9 H), 0.83 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 213.2, 136.4, 129.4, 128.9, 126.0, 55.1, 43.8, 39.9, 33.4, 32.6, 23.8, 23.4, 20.3, 12.3. Anal. Calcd for $C_{16}H_{22}OS$: C, 73.23; H, 8.45. Found: C, 73.54; H, 8.80.

***cis*-11d**: 60% yield; IR (neat) 1700, 1600, 1580, 1495, 1480, 740, 700 cm^{-1}; ^1H NMR δ 7.31–7.08 (m, 10 H), 3.32 (m, 1 H), 3.20 (m, 1 H), 3.16 (d, J = 12.2 Hz, 1 H), 2.72 (dd, J = 12.2, 4.0 Hz, 1 H), 2.64–2.60 (m, 2 H), 2.05–1.64 (m, 6 H); ^{13}C NMR δ 213.2, 142.0, 135.9, 129.1, 128.8, 128.3, 126.7, 126.0, 55.3, 45.3, 43.3, 33.9, 31.6, 25.8, 23.8. Anal. Calcd for $C_{20}H_{22}OS$: C, 77.38; H, 7.14. Found: C, 77.25; H, 7.38.

***cis*-11e**: 62% yield; IR (neat) 1700, 1580, 1480, 995, 920, 740, 690 cm^{-1}; ^1H NMR δ 7.35–7.16 (m, 5 H), 5.57 (ddd, J = 10.4, 11.0, 16.8 Hz, 1 H), 5.10–5.01 (m, 2 H), 3.33 (dd, J = 13.4, 6.0 Hz, 1 H), 3.05 (ddd, J = 6.0, 7.9, 2.4 Hz, 1 H), 2.82 (dd, J = 13.4, 7.9 Hz, 1 H), 2.53 (m, 1 H), 2.38 (m, 1 H), 1.92–1.43 (m, 7 H); ^{13}C NMR δ 212.7, 136.2, 136.1, 129.6, 128.9, 126.2, 117.6, 53.8, 44.2, 42.9, 36.1, 33.5, 24.3, 23.5. Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74. Found: C, 74.11; H, 7.85.

Hydrogenation of 11e into 11c. **11e** (0.5 mmol) was added to a mixture of ethanol (5 mL) and 10% Pd on carbon (30 mg). After being stirred under hydrogen atmosphere (1 atm) at 25 °C for 4 h, the mixture was filtered over Celite and the filtrate was concentrated to give **11c** quantitatively.

General Procedure for Conversion of 3-Substituted 2-Methylenecyclopentanones 9a–9c into 3-Substituted 2-[(Phenylsulfonyl)methyl]cyclopentanones 15a–15c. To a solution of thiophenol (1.1 mmol) in THF (3 mL) was added *n*-BuLi (1.1 mmol) at −78 °C. After being stirred at −78 °C for 10 min, the resulting lithium thiophenoxide solution was added to a precooled (−78 °C) solution of the 2-methylene ketone (1.0 mmol) in THF (2 mL) via a stainless cannula. The reaction mixture was stirred at −78 °C for 1 h and poured into water (30 mL). The aqueous mixture was extracted with ether (3 × 30 mL). The ether extract was washed with water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (10:1 hexane/ethyl acetate). The cis/trans ratio of the products was determined to be uniformly 5/95 by means of ^1H NMR analysis.

***trans*-15a**: 84% yield; IR (neat) 1740, 1580, 1480, 740, 690 cm^{-1}; ^1H NMR δ 7.38–7.14 (m, 5 H), 3.30 (dd, J = 13.1, 4.3 Hz, 1 H), 3.12 (dd, J = 13.1, 5.2 Hz, 1 H), 2.35 (m, 1 H), 2.20–2.04 (m, 4 H), 1.70 (m, 1 H), 1.42–1.19 (m, 6 H), 0.89 (t, J = 7.0 Hz, 3 H); ^{13}C NMR δ 218.5, 136.6, 129.3, 128.8, 126.0, 54.8, 41.3, 37.8, 34.2, 29.1, 26.8, 22.7, 14.0. Anal. Calcd for $C_{16}H_{22}OS$: C, 73.23; H, 8.45. Found: C, 72.95; H, 8.77.

***trans*-15b**: 80% yield; IR (neat) 1740, 1585, 1480, 740, 695 cm^{-1}; ^1H NMR δ 7.38–7.14 (m, 5 H), 3.31 (dd, J = 13.1, 4.3 Hz, 1 H), 3.11 (dd, J = 13.1, 5.2 Hz, 1 H), 2.36 (m, 1 H), 2.22–1.99 (m, 4 H), 1.81 (m, 1 H), 1.42–1.26 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 218.6, 136.5, 129.2, 128.8, 126.0, 54.3, 42.9, 37.7, 32.4, 27.1, 26.2, 11.2. Anal. Calcd for $C_{14}H_{18}OS$: C, 71.75; H, 7.74. Found: C, 71.35; H, 8.13.

***trans*-15c**: 82% yield; IR (neat) 1740, 1600, 1580, 1495, 1480, 740, 700 cm^{-1}; ^1H NMR δ 7.34–7.08 (m, 10 H), 3.30 (m, 1 H), 3.22 (dd, J = 13.4, 4.9 Hz, 1 H), 3.09 (dd, J = 13.4, 5.2 Hz, 1 H), 2.62–2.48 (m, 2 H), 2.34–2.19 (m, 2 H), 1.92 (m, 1 H); ^{13}C NMR δ 216.8, 141.4, 136.3, 129.5, 128.8, 128.6, 127.2, 126.9, 126.0, 56.0, 47.0, 38.3, 31.6, 29.6. Anal. Calcd for $C_{18}H_{18}OS$: C, 76.56; H, 6.42. Found: C, 76.79; H, 6.55.

***trans*-15d**: 69% yield; IR (neat) 1745, 1645, 1590, 920, 745, 695 cm^{-1}; ^1H NMR δ 7.38–7.14 (m, 5 H), 5.78 (ddd, J = 18.0, 10.4, 6.4 Hz, 1 H), 5.09–5.00 (m, 2 H), 3.21 (d, J = 4.9 Hz, 2 H), 2.75 (m, 1 H), 2.38 (m, 1 H), 2.27–2.09 (m, 3 H), 1.71–1.57 (m, 1 H); ^{13}C NMR δ 217.1, 139.6, 136.6, 129.5, 128.8, 126.1, 116.0, 54.6, 45.6, 37.7, 31.7, 27.4. Anal. Calcd for $C_{14}H_{16}OS$: C, 72.37; H, 6.94. Found: C, 72.03; H, 7.27.

Hydrogenation of 15d into 15b. **15d** (0.5 mmol) was added to a mixture of ethanol (5 mL) and 10% Pd on carbon (30 mg). After being stirred under hydrogen atmosphere (1 atm) at 25 °C for 4 h, the mixture was filtered over Celite and the filtrate was concentrated to give **15b** quantitatively.

General Procedure for Conversion of 3-Substituted 2-Methylenecyclohexanones 7a–7c into 3-Substituted 2-Benzylcyclohexanones 17a–17c. To the 2-methylene ketone (1.0 mmol) in THF (5 mL) was added at −78 °C a precooled (−78 °C) THF solution of Ph_2CuLi (1.5 mmol) via a cannula. The reaction mixture was stirred at −78 °C for 30 min, and saturated aqueous NH_4Cl solution (30 mL) was added. The aqueous mixture was extracted with ether (3 × 30 mL). The ether extract was washed with water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20:1 hexane/ethyl acetate). The cis/trans ratio of the products was determined by means of ^1H NMR analysis.[15]

***cis*-17a**: 69% yield; 96/4 cis/trans; IR (neat) 1710, 1605, 1495, 745, 700 cm^{-1}; ^1H NMR δ 7.28–7.13 (m, 5 H), 3.04 (dd, J = 14.0, 7.9 Hz, 1 H), 2.81 (dd, J = 14.0, 5.2 Hz, 1 H), 2.51–2.38 (m, 2 H), 2.29 (m, 1 H), 2.01–1.93 (m, 2 H), 1.73–1.61 (m, 2 H), 1.59–1.43 (m, 2 H), 1.34–1.16 (m, 5 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR δ 213.1, 140.7, 129.0, 128.2, 125.8, 57.6, 42.3, 41.0, 33.7, 33.4, 28.6, 28.5, 24.8, 22.8, 14.0. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.20; H, 10.23.

***cis*-17b**: 63% yield; 97/3 cis/trans; IR (neat) 1710, 1605, 1495, 745, 700 cm^{-1}; ^1H NMR δ 7.72–7.12 (m, 5 H), 3.06 (dd, J = 14.0, 7.9 Hz, 1 H), 2.80 (dd, J = 14.0, 4.0 Hz, 1 H), 2.43–2.21 (m, 3 H), 2.04–1.85 (m, 2 H), 1.80–1.61 (m, 3 H), 1.11 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 212.2, 141.2, 129.1, 128.1, 125.7, 59.6, 41.6, 38.7, 33.2, 32.7, 25.5, 20.9. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.28; H, 9.35.

***cis*-17c**: 72% yield; 93/7 cis/trans; IR (neat) 1710, 1605, 1495, 745, 700 cm^{-1}; ^1H NMR δ 7.28–7.13 (m, 5 H), 3.04 (dd, J = 14.0, 7.9 Hz, 1 H), 2.82 (dd, J = 14.0, 4.6 Hz, 1 H), 2.52–2.38 (m, 2 H), 2.26 (m, 1 H), 2.02–1.91 (m, 2 H), 1.75–1.31 (m, 5 H), 0.89 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 213.0, 140.8, 129.0, 128.2, 125.8, 57.3, 43.8, 41.1, 33.4, 28.1, 26.2, 24.8, 10.6. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.55; H, 9.19.

Preparation of (2*S*,3*S*)-3-Methyl-2-[(phenylsulfonyl)methyl]cycloheptane (*S*,*S*)-1,2-Diphenylethylene Acetal (13). A mixture of **11b** (0.85 mmol), (*S*,*S*)-hydrobenzoin (1.27 mmol), and PPTS (10 mg) in benzene (5 mL) was refluxed for 7 d, cooled, and diluted with ether (100 mL). The organic mixture was washed with 5% $NaHCO_3$ solution (3 × 30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (10:1 hexane/ethyl acetate) to afford **12** in 60% yield.

A mixture of **12** (0.3 mmol), *m*-CPBA (0.6 mmol), and K_2CO_3 (50 mg) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 1 h. After addition of triethylamine (0.9 mmol), the reaction mixture was diluted with CH_2Cl_2 (60 mL), washed with 10% $NaHSO_3$ solution (3 × 20 mL) and 5% $NaHCO_3$ solution (3 × 20 mL), dried over

$MgSO_4$, and concentrated in vacuo. The crude product was recrystallized from ether/hexane to give **13** in 86% yield.

13: mp 117-118 °C; IR (KBr) 1585, 1495, 1450, 1305, 1150, 1090, 750, 720, 700 cm^{-1}; ^1H NMR δ 7.97-7.14 (m, 15 H), 4.72 (s, 2 H), 3.60 (dd, J = 14.3, 1.8 Hz, 1 H), 3.34 (dd, J = 14.3, 7.9 Hz, 1 H), 2.85 (dd, J = 7.9, 1.8 Hz, 1 H), 2.52 (m, 1 H), 2.20 (m, 1 H), 1.87-1.42 (m, 7 H), 1.14 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 140.7, 136.7, 135.7, 133.3, 129.1, 128.4, 128.3, 128.2, 127.8, 127.1, 126.4, 112.5, 85.6, 85.4, 54.7, 47.8, 39.0, 31.4, 30.1, 25.3, 20.2, 19.5. Anal. Calcd for $C_{29}H_{22}O_4S$: C, 73.08; H, 6.77. Found: C, 72.88; H, 6.99.

General Procedure for Ozonolysis of 9b, 7a, and 10b and Esterification. A solution of the 2-methylene ketone (0.9 mmol) in ethyl acetate (50 mL) was cooled to -78 °C. A stream of ozone was bubbled through the solution until it was blue. The blue solution was warmed to rt, and nitrogen gas was bubbled through the mixture to expel surplus ozone. After concentration of the mixture in vacuo, the residue was dissolved in acetic acid (12 mL), and one drop of concd H_2SO_4 and 35% H_2O_2 (1.5 mL) were added. The mixture was stirred at 25 °C overnight and subjected to reduced distillation (50 °C (10 mm Hg)) to remove considerable amounts of acetic acid and water. The residue was dissolved in methanol (2 mL), and PTSA dihydrate (4 mg) was added. After being stirred at 25 °C for 2 h, methanol was removed in vacuo and the residue was dissolved in ether (30 mL). The ether solution was washed with water (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate).

14:[16] $[\alpha]^{25}_D$ +11.0° (c 1.00, $CHCl_3$) [lit. S-form: $[\alpha]^{20}_D$ +14.6 (neat)]; IR (neat) 1740, 1260, 1200, 1170 cm^{-1}; ^1H NMR δ 3.69 (s, 3 H), 3.67 (s, 3 H), 2.37-2.29 (m, 3 H), 1.94-1.82 (m, 2 H), 1.68-1.51 (m, 2 H), 0.90 (t, J = 7.3 Hz, 3 H).

16:[17] $[\alpha]^{25}_D$ +12.7° (c 1.20, EtOH) [lit. S-form: $[\alpha]^{23}_D$ +13.5 (c 1.48, EtOH)]; IR (neat) 1740, 1250, 1200, 1175 cm^{-1}; ^1H NMR δ 3.68 (s, 3 H), 3.67 (s, 3 H), 2.50-2.40 (m, 1 H), 2.35-2.29 (m, 2 H), 1.70-1.57 (m, 3 H), 1.52-1.40 (m, 1 H), 1.16 (d, J = 7.0 Hz, 3 H).

18:[18] $[\alpha]^{25}_D$ -39.4° (c 1.03, $CHCl_3$) [lit. R-form: $[\alpha]^{22}_D$ +103.5 (neat)]; IR (neat) 1740, 1600, 1495, 735, 700 cm^{-1}; ^1H NMR δ 7.31-7.27 (m, 5 H), 3.73 (q, J = 7.0 Hz, 1 H), 3.65 (s, 3 H), 1.50 (d, J = 7.0 Hz, 3 H).

Stereoselective Synthesis of Cis 2,3-Disubstituted Cycloheptanones by Kinetic Protonation

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The hitherto unknown stereochemistry concerning the formation of 2,3-disubstituted cycloheptanones by the Michael addition reaction was studied. The Michael addition of thiophenol to 3-substituted 2-methylenecycloheptanones in the presence of triethylamine in THF at ambient temperature produced 3-substituted 2-[(phenylthio)methyl]cycloheptanones with high cis selectivity (>96/4), which was unequivocally established by ^1H NMR and X-rays analyses. An isomerization experiment and theoretical calculations (AM1) suggest that the origin of the observed high stereoselectivity can be explained in terms of kinetic protonation of the corresponding enolate intermediate.

Introduction

The kinetic protonation of enolates is a useful technique for producing stereoisomers (diastereomers) with high stereoselectivity in synthetic organic chemistry.[1] The formation of the kinetic product has been well interpreted in terms of the concept of the least hindered approach of a proton donor to the enolates which usually leads to the thermodynamically less stable stereoisomers.[1] Thus, the deprotonation-kinetic protonation sequence is often used to obtain the less stable stereoisomer from its more stable counterpart via epimerization.[2]

The Michael addition of nucleophiles to substituted α,β-unsaturated carbonyl compounds and their analogues involves a protonation process of the resulting enolates and hence raises an issue of diastereoselectivity.[3-6] The resulting stereochemistry generally depends on the protonation conditions; protonation at low temperatures leads to the kinetic product, while the product of thermodynamic control is formed at higher temperatures. Recently, there have been several reports dealing with the stereochemistry of protonation of 2,3-disubstituted endocyclic enolates formed by the Michael addition of carbanions to 2-substituted 2-cyclopentenones and 2-cyclohexenones.[5,6] It was found that highly stereoselective protonation of 2,3-disubstituted cyclohexanone enolates was achieved under kinetic conditions to give cis products,[5,6] and the predom-

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