solubilized concomitant with expulsion of water. This is in accord with other studies that show that solubilization is due to a hydrophobic effect involving elimination of hydrocarbon–water interfaces similar to the micellization process itself.[18,19]

Acknowledgment. We are grateful to the National Science Foundation (Grant No. CHE7823126) for support of this work.

Registry No. (*E*)-**1**, 80631-72-7; (*Z*)-**1**, 80631-73-8; (*E*)-**2**, 80631-74-9; (*Z*)-**2**, 80631-75-0; (*E*)-**3**, 80631-76-1; (*Z*)-**3**, 80631-77-2.

(16) Russell, J. C.; Whitten, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 3219–3220.
(17) Foreman, T. K.; Sobol, W. M.; Whitten, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 533–5336.
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(19) Photochemical Reactivity in Organized Assemblies. Part 28.

High Diastereoselection in the Alkylation of Siloxy-Substituted Methyl Cyclopropanecarboxylates: Consequence of a Pyramidal Ester Enolate Anion?

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Received November 19, 1981

Recently we reported[1] on the reaction depicted in Scheme I, which to our best knowledge is the first example of a successful deprotonation and alkylation of an alkyl cyclopropanecarboxylate.[2] This transformation makes available a great variety of siloxy-substituted cyclopropanes of type **2**, which are useful building blocks in organic synthesis.[3] At first sight one would expect both diastereomers, (*E*)-**2** and (*Z*)-**2**, in the alkylation reaction (Scheme I). Yet we demonstrate here with suitable model compounds that (*E*)-**2** is formed in large excess or even exclusively.

A 1:1 mixture of (*E*)- and (*Z*)-methyl 2-phenyl-2-trimethylsiloxycyclopropanecarboxylate (**1a**) was deprotonated with LDA (1.5 equiv) in THF at −78 °C (2 h), and the resultant enolate was treated with iodomethane (Table I, entry 1).[4] Only (*E*)-**2a** could be detected by ^{1}H and ^{13}C NMR spectrometry in the reaction mixture. Similarly, addition of other electrophiles El–X, e.g., Me_2SO_4, *n*-BuI, $CH_2{=}CHCH_2Br$, and $PhCH_2Br$, to the enolate **1a** also resulted in the exclusive formation of the corresponding *E* isomers (*E*/*A* > 95:5) in excellent yields (73–89%).[5] Protonation of the enolate is less selective (NH_4Cl/H_2O: (*E*)-**1a**:(*Z*)-**1a** = 76:24).[7]

Deprotonation and methylation of the cyclopropanes **1c** and **1d** also gave only the *E* diastereomers (entries 3, 4). Since the same sequence applied to **1b**, **1e**, and **1f** led to 92:8, 90:10, and 90:10 *E*:*Z* mixtures, respectively (entries 2, 5, 7), the reaction of the enolate **1f** with other electrophiles was studied. Entries 6–13 show a large to moderate preference for (*E*)-**2f**α to (*E*)-**2f**ϵ in all cases.[8] The diastereoselectivity decreases with more reactive electrophiles (entries 7, 8, 11, 12) but also seems to be sensitive to the bulkiness of El–X (entries 7, 9, 10). As expected, the same *E*:*Z* mixture was obtained in the alkylation regardless of the diastereomeric composition of the starting material (entries 6, 7).

Table I. Diastereoselectivity in the Alkylation of 1 → 2 According to Scheme I

entry	educt	*E*:*Z*	El–X[a]	product(s)	*E*:*Z*[b]	yield,[c] %
1	1a	50:50	Me–I	2a	>97:3	84
2	1b	53:47	Me–I	2b	92:8	70
3	1c	52:48	Me–I	2c	>97:3	92
4	1d	58:42	Me–I	2d	>95:5	65
5	1e	75:25	Me–I	2e	90:10	85
6	1f	>98:2	Me–I	2fα	88:12	86
7	1f	75:25	Me–I	2fα	90:10	87
8	1f	75:25	$Me–OSO_3Me$	2fα	85:15	66
9	1f	75:25	Et–I	2fβ	88:12	90
10	1f	75:25	*n*-Bu–I	2fγ	81:19	77
11	1f	75:25	allyl–Br	2fδ	82:18	81
12	1f	75:25	allyl–I	2fδ	72:28	76
13	1f	75:25	benzyl–Br	2fϵ	65:35	81

[a] Reaction conditions: THF:hexane = 3:1; −78 °C; 6–40 h. [b] Ratio determined by ^{1}H and ^{13}C NMR spectrometry. Control experiments showed that the *E*:*Z* ratios are reproducible to within ±2%. [c] Isolated yield of purified product after bulb-to-bulb distillation. Satisfactory spectra and combustion analyses were obtained for all compounds.

No definitive explanation of the high *E* diastereoselectivity can be given; however, a number of interesting conclusions concerning the structure of the methyl cyclopropanecarboxylate anion may be drawn. Three limiting principal structures of the anion[9] are shown in Scheme II: (1) the "normal" planar ester enolate anion[10] **3**; (2) the pyramidal ester enolate anions[10] (*E*)-**4** and (*Z*)-**4**; (3) the pyramidal cyclopropyl anions (*E*)-**5** and (*Z*)-**5** with the carbomethoxy group in a bisected conformation.

If it is assumed that the reaction is governed only by steric effects,[11] entries 1–5 ($OSiMe_3 < R^1$) are in accordance with the type-**3** planar anions. However, the results of entries 6–13 ($OSiMe_3 > R^1 = H$), which show a marked preference for the electrophile to be introduced cis to the sterically more demanding group, imply that pyramidal species such as **4** and **5** are involved. On the other hand, the configurational instability of the anions concluded from all entries makes a cyclopropyl anion of type **5** unlikely. Furthermore, the changing product *E*/*Z* ratios arising from different electrophiles (entries 6–13) suggest a mobile equilibrium of the intervening anionic species. Probably (*E*)-**4** is the most reactive[12] among the postulated enolates affording (*E*)-**2** as main product.[13] In summary our present experimental data are best rationalized in terms of a configurationally labile pyramidal ester enolate **4** as intermediate.

†Liebig Fellow, 1979–1982.
(1) Böhm, I.; Hirsch, E.; Reissig, H.-U. *Angew. Chem.* **1981**, *93*, 593. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 574.
(2) For the deprotonation of cyclopropanecarboxylates and alkylation attempts see: Pinnick, H. W.; Chang, Y. H.; Foster, S. C.; Govindan, M. *J. Org. Chem.* **1980**, *45*, 4505 and literature cited therein.
(3) For a review see: Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. See also ref 1 and Reissig, H.-U. *Tetrahedron Lett.* **1981**, *22*, 2981 and literature cited therein.
(4) For description of a typical experiment see ref 1.
(5) The cis relationship of the carbomethoxy function and the phenyl group in (*E*)-**2a** derivatives is clearly demonstrated by the high-field methoxy singlet ($CDCl_3$, δ 3.18–3.40); see ref 6.
(6) Booth, H. "Progress in Nuclear Magnetic Resonance Spectroscopy"; Pergamon Press: Oxford, England, 1969; Vol. **5**, p 149.
(7) This result and a comparable product ratio in the protonation of the **1f** enolate (*E*/*Z* = 71/29) suggest at least partial *O*-protonation followed by nonstereoselective H shift to carbon.
(8) In isomers (*E*)-**2f**α to (*E*)-**2f**ϵ R^1 = H is shifted to lower field ($CDCl_3$, δ 3.57–3.85) due to the cis-located carbomethoxy group, whereas the respective protons in the *Z* isomers appear at higher field ($CDCl_3$, δ 2.87–3.23); see ref 6.
(9) As in most work dealing with carbanionic species one can only speculate about the role of the cation. Li^+ might be coordinated to oxygen in **3** and **4** and to carbon in **5**. Also the kind of ion pair involved and the degree of aggregation are not certain. These unknown factors, however, should not distract from our argumentation regarding the geometry of the reacting anion.
(10) Only one of the two possible isomers concerning the enolate C–C bond is shown. We see no obvious mechanism showing how this factor could control the diastereoselectivity.
(11) The E_s value for $OSiMe_3$ should be in the order of that of *O*-alkyl ≈ 0.55; for E_s values see: Fujita, T.; Nishioka, T. *Progr. Phys. Org. Chem.* **1976**, *12*, 49. For empirical substitutent parameters see: Knorr, R. *Chem. Ber.* **1980**, *113*, 2441.
(12) If the cation is coordinated to the carbonyl oxygen of the enolate, favorable complexation to the siloxy group seems possible in (*Z*)-**4** but not in (*E*)-**4**, which might be the reason for its higher reactivity; however, see footnote 9.
(13) Retention of configuration with respect to the nucleophilic carbon, as mostly observed in electrophilic substitution, is assumed. Also, (*E*)-**4** can be regarded as a system with a nonplanar C–C double bond interacting with El-X via its larger orbital lobe and finally giving (*E*)-**2**.

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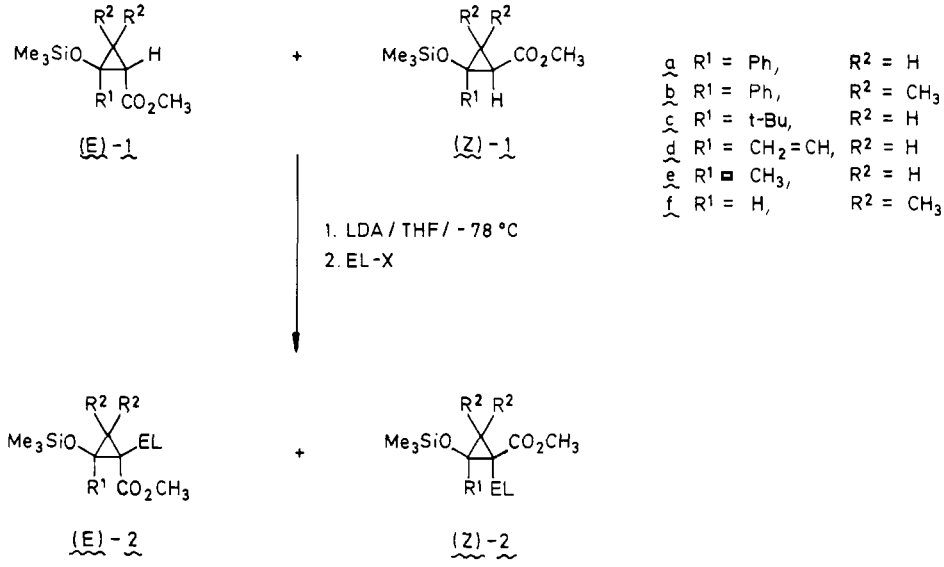
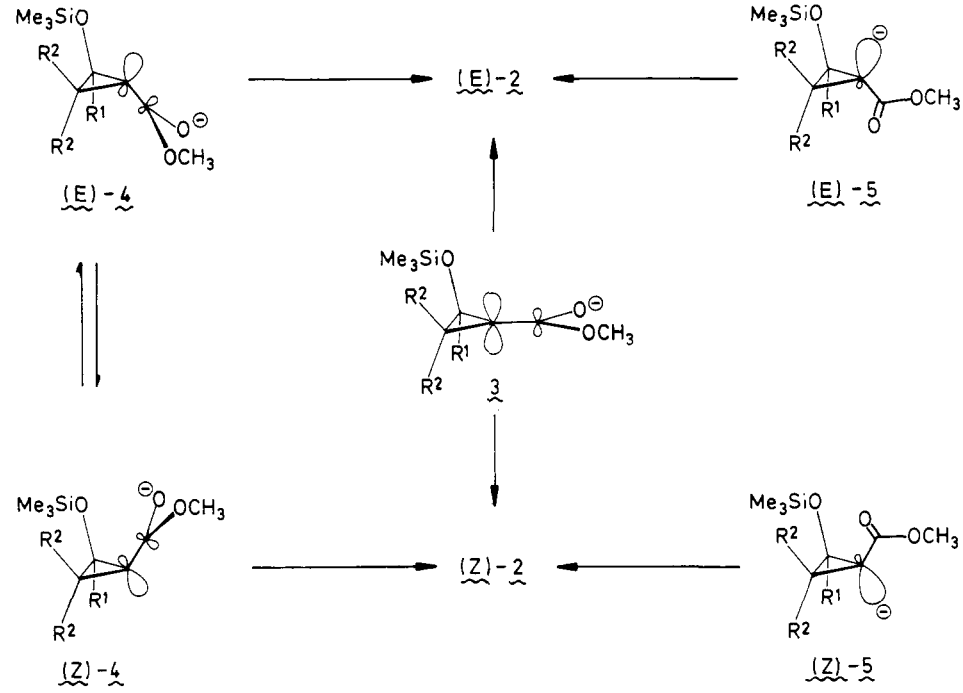
Scheme I



Scheme II



This interpretation is further strengthened by estimating the relative energies of the three proposed anion structures, which give **4** < **3** ~ **5**. Enolate **3** is destabilized due to the strain caused by the exocyclic enolate double bond, while **5** lacks conjugative stabilization by the carbomethoxy function. It is reasonable that the intermediary anion should adopt a pyramidal structure such as **4**, thereby considerably diminishing angle strain while still preserving conjugation with the carbonyl group. Similar conclusions have been drawn for other cyclopropyl anions bearing electron-accepting groups[14] and for the isoelectronic aziridine derivatives.[15] Our system, however, provides the first example of a pyramidal cyclopropyl anion with a carbonyl function.[16]

We are actively pursuing the attractive possibility of transmitting the high diastereoselectivities reported here to the ring-opened products of these cyclopropanes.

Acknowledgment. Support of this work by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft is gratefully appreciated.

Registry No. (*E*)-**1a**, 80737-53-7; (*Z*)-**1a**, 80737-54-8; (*E*)-**1b**, 80737-55-9; (*Z*)-**1b**, 80737-56-0; (*E*)-**1c**, 75032-06-3; (*Z*)-**1c**, 75032-05-2; (*E*)-**1d**, 80737-57-1; (*Z*)-**1d**, 80737-58-2; (*E*)-**1e**, 80737-59-3; (*Z*)-**1e**, 80737-60-6; (*E*)-**1f**, 75032-08-5; (*Z*)-**1f**, 75032-07-4; (*E*)-**2a**, 80737-61-7; (*E*)-**2b**, 80737-62-8; (*Z*)-**2b**, 80753-72-6; (*E*)-**2c**, 80737-63-9; (*E*)-**2d**, 80737-64-0; (*E*)-**2e**, 80737-65-1; (*Z*)-**2e**, 80737-66-2;

(14) Phenylsulfonyl group: Ratajczak, A.; Anet, F. A. L.; Cram, D. J. *J. Am. Chem. Soc.* **1967**, *89*, 2072. Nitrile group: Walborsky, H. M.; Motes, J. M. *Ibid.* **1970**, *92*, 2445. Acetylene group: Köbrich, G.; Merkel, D.; Imkampe, K. *Chem. Ber.* **1973**, *106*, 2017. Isonitrile group: Walborsky, H. M.; Periasamy, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 3711.

(15) A rapidly inverting pyramidal species has been established for *N*-carbomethoxyaziridine: Anet, F. A. L.; Osyany, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 352.

(16) A pyramidal anion has been proposed for certain α-chloroesters: Roux-Schmitt, M.-C.; Seyden-Penne, J.; Wolfe, S. *Tetrahedron* **1972**, *28*, 4965.

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(*E*)-**2f**α, 80737-67-3; (*Z*)-**2f**α, 80737-68-4; (*E*)-**2f**β, 80737-69-5; (*Z*)-**2f**β, 80737-70-8; (*E*)-**2f**γ, 80737-71-9; (*Z*)-**2f**γ, 80737-72-0; (*E*)-**2f**δ, 80737-73-1; (*Z*)-**2f**δ, 80737-74-2; (*E*)-**2f**ϵ, 80737-75-3; (*Z*)-**2f**ϵ, 80737-76-4; iodomethane, 74-88-4; dimethyl sulfate, 77-78-1; iodoethane, 75-03-6; 1-iodobutane, 542-69-8; 3-bromo-1-propene, 106-95-6; 3-iodo-1-porpene, 556-56-9; (bromomethyl)benzene, 100-39-0; methyl *trans*-1-butyl-2-phenyl-2-[(trimethylsilyl)oxy]cyclopropanecarboxylate, 80737-77-5; methyl *trans*-2-phenyl-1-(2-propanyl)-2-[(trimethylsilyl)oxy]cyclopropanecarboxylate, 80737-78-6; methyl *trans*-2-phenyl-1-(phenylmethyl)-2-[(trimethylsilyl)oxy]cyclopropanecarboxylate, 80737-79-7.

Asymmetric Alkylation Reactions of Chiral Imide Enolates. A Practical Approach to the Enantioselective Synthesis of α-Substituted Carboxylic Acid Derivatives[1]

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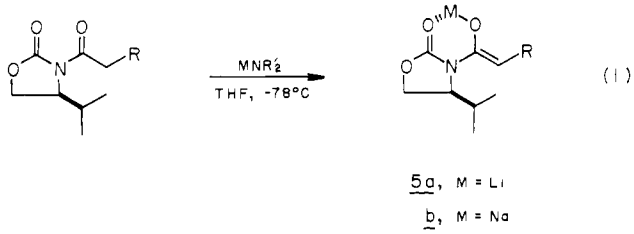
Received November 23, 1981

The development of chiral enolate synthons and their practical utility in bond construction have been the subject of intensive investigation,[2] and recently several enolate systems have been reported to exhibit high levels of diastereoselection in alkylation reactions.[3] The purpose of this communication is to report our observations on the utility of the enolates derived from *N*-acyl oxazolidones **1** and **2**[4] in complementary diastereoselective alkylation processes (Scheme I). In a recent communication we disclosed the general procedures for the synthesis of imides **1** and **2**, which are readily derived from (1*S*,2*R*)-norephedrine and (*S*)-valinol, respectively.[4,5]

In direct analogy with earlier studies, we have found that either lithium or sodium amide bases (1.1 equiv) [$LiN(i\text{-}C_3H_7)_2$ or $NaN(SiMe_3)_2$, −78 °C, THF] cleanly transform imides **1** and **2** to their respective (*Z*)-metal enolates.[6] From the ensuing results, *enolization stereoselectivity under these conditions must be* >100:1 *(eq 1) if chelated (Z)-enolates such as* **5** *are involved in the*

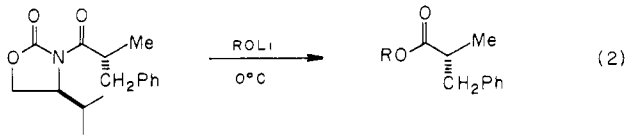


(1)

5a, M = Li
b, M = Na

creation of a diastereofacial bias in the alkylation process. For the alkylation studies summarized in Table I, lithium enolates were employed except for entries K and M–P. General reaction conditions involved treatment of a 0.2–0.5 M solution of the lithium enolate in THF with 3 equiv of alkylating agent at 0 °C (2–4 h).[7] In several instances we have scaled these alkylations up to the 0.3 M level without loss in yield. Diastereomer analysis (**3**:**4**) was carried out by capillary gas chromatography.[8] A number of general trends are evident from the data in the table. First, complementary levels of diastereoface selection can be anticipated from the enolates derived from **1** and **2**, with the latter system exhibiting somewhat greater selectivity. For example, in the reactions of the lithium enolates derived from **1** and **2** with benzyl bromide (entries A, B), the kinetic diastereoselection (**3**:**4**) was found to be 49:1 for **1** (R = Me) and 1:120 for **2** (R = Me), respectively. These data provide an important calibration for the stereoselectivities encountered in *both* the enolization and alkylation processes. Second, we have found that, as anticipated, electrophile structure plays a significant role in dictating reaction stereoselectivity.[3] Qualitatively, "small" alkyl halides are *less* stereoselective than their more sterically demanding counterparts (cf. $PhCH_2Br$ vs. MeI). In general, enolate methylations (entries M–P) with methyl iodide have been the least stereoselective processes encountered to date. In surveying conditions for optimizing this particular process, we have found that alkylation of the sodium enolates (−78 °C) is superior to the analogous reactions of the corresponding lithium enolates (0 °C). One unanticipated benefit encountered in the development of these imide enolate systems has been the ease with which the diastereomeric alkylation products **3** and **4** may be resolved by column chromatography.[9] Overall, the major limitation encountered with the lithium and sodium enolates derived from **1** and **2** is highlighted in entries K and L in the table. One must employ alkylating agents that will react at a convenient rate at temperatures ≤0 °C.[7] The counterpoint to this limitation is the superb diastereoface selection noted for these systems in both alkylations and aldol condensations[4] and the ease with which these chiral oxazolidones may be synthesized and recycled. In all of the alkylation reactions carried out during the course of this study, the sense of asymmetric induction is readily interpreted by assuming a metal-chelated (*Z*)-enolate (see **5**) where diastereoface selection is dictated by the C_4-substituent on the oxazolidone ring.

During the course of this study we have developed a number of useful transformations that nondestructively remove the chiral auxiliaries from the desired chiral synthon. *For example, the alkylated imides may be transformed into benzyl esters with* <0.2% *racemization (eq 2).* The reaction of **6a** (**4**:**3** = 99.9:0.1)[8]



(2)

6a

(*R*)-**7a**, R = CH_2Ph
b, R = H
c, R = CO_2Et

in THF (0.2 M) with $PhCH_2OLi$–$PHCH_2OH$ (prepared from 2.0 equiv of benzyl alcohol and 1.5 equiv of *n*-C_4H_9Li) at 0 °C (1 h) afforded the *R* ester **7a** in 93% yield ($[\alpha]_D$ −26.9° (*c* 6.12, CH_2Cl_2)) along with recovered oxazolidone. Catalytic hydrogenolysis of **7a** afforded (*R*)-**7b** ($[\alpha]_D$ −25.1° (neat) [lit., −25.4° (neat)]).[10] A rigorous racemization assay for this transesterification process was accomplished via the reacylation of the (4*S*)-(2-propyl)oxazolidone with **7c** to give **6a** (**4**:**3** = 99.8:0.2).[8] In more than ten cases that were studied with either chiral aux-

(1) Presented at the 12th International Symposium on the Chemistry of Natural Products, Tenerife, Canary Islands, Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *J. Pure Appl. Chem.* **1981**, *53*, 1109–1127.

(2) For recent reviews see: (a) ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797–2842. (b) Meyers, A. I. *J. Pure Appl. Chem.* **1979**, *51*, 1255–1268. (c) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329–356.

(3) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236. (b) Meyers, A. I.; Yamamoto, Y.; Mihelich, E. D.; Bell, R. A. *J. Org. Chem.* **1980**, *45*, 2792–2796. (c) Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 207–208.

(4) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(5) The optical purities of the oxazolidone chiral auxiliaries employed in this study were determined to be >99% by GLC analysis of the imides derived from the Mosher acid chloride: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(6) The assignment of the (*Z*)-enolate geometry to these systems has not been rigorously established; however, it is fully consistent with an interpretation of the results obtained in this and related studies (see ref 3a, 4).

(7) At temperatures >0 °C the lithium enolates will decompose via a ketene pathway. The corresponding sodium enolates exhibit reasonable stability at <−20 °C.

(8) Gas chromatographic analyses employed a Hewlett-Packard instrument (Model 5880A) and 30 m × 0.32 mm WCOT columns (column types: Carbowax 20 M, methyl silicone, SE-54, DB-1).

(9) Diastereomer resolution was carried out either by medium-pressure chromatography using Merck Lobar silica gel columns or by the flash method: Still, W. C.; Kahn, M.; Miltra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(10) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 63–65.

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