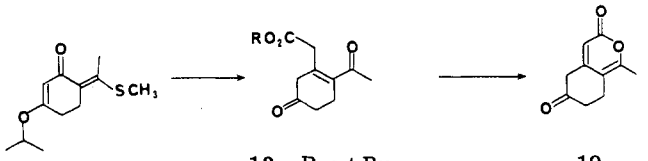
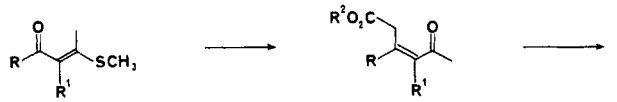
or substituted acetic acid unit and can, in principle, be effected with *tert*-butyl, methyl, and trimethylsilyl ester enolate anions[17,18] or carboxylic acid dianions.[18] These various nucleophiles were examined in an effort to maximize the efficiency of the synthetic sequence. Dilithioacetate[19] afforded low yields of addition products (entry 3) and carboxylic acid dianions were not examined further. Trimethylsilyl lithioacetate underwent smooth addition to cyclic ketones (entries 2, 8, and 10) but afforded poor



7 13a, R = *t*-Bu; b, R = H 19

yields of addition products upon reaction with acyclic ketones (entries 12 and 14). *tert*-Butyl lithioacetate, however, underwent smooth addition[20] to both cyclic and acyclic ketones (entries 1, 6, 7, 9, 11, and 13) although diminished yields were observed for *tert*-butyl lithiopropionate (entry 5). Addition of methyl lithioacetate to **4** (87%) requires subsequent alkaline hydrolysis of the methyl ester and enol lactonization of the resulting δ-keto acid. The alkaline hydrolysis of **10c** [10% aqueous KOH, CH_3OH] was quantitative, and the resulting δ-keto acid **10b** was converted to α-pyrone **16a** (88%) upon treatment with trifluoroacetic anhydride. These results indicate that the enolate anions of the *tert*-butyl and methyl esters are generally the more reliable nucleophiles in the 1,2-nucleophilic addition reaction.

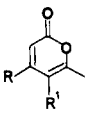
The reaction conditions required to effect *tert*-butyl ester hydrolysis and subsequent enol lactonization were remarkably dependent upon substrate structure. The cyclic δ-keto esters **10a,d**, **12a**, and **13a** were isolated upon quenching the Rathke-type Reformatsky reactions[17] and then converted into the corresponding α-pyrones upon treatment with trifluoroacetic acid in trifluoroacetic anhydride. The acyclic substrates **14a** and **15a** were more susceptible to ester hydrolysis and enol lactonization. α-Pyrones **20** (76%) and **21** (77%) were formed directly



8a, R = *i*-Pr; R^1 = H; b, R = Et; R^1 = Me

14a, R^2 = *t*-Bu; R^1 = H; R = *i*-Pr; b, R^2 = R^1 = H; R = *i*-Pr

15a, R^2 = *t*-Bu; R^1 = Me; R = Et; b, R^2 = H; R^1 = Me; R = Et



20, R^1 = H; R = *i*-Pr; 21, R^1 = Me; R = Et

in a one-pot process when the reaction of **8** and **9**, respectively, with *tert*-butyl lithioacetate was quenched with HBF_4 (10% v/v aqueous HBF_4/THF, 1:2, v/v) and the resulting solution allowed to stir at room temperature for 12 h.[21] Interestingly, δ-keto ester **10a** was recovered unchanged when treated with HBF_4 under the same reaction conditions. Finally, although the acyclic δ-keto esters **14a** and **15a** existed as a mixture of *E* and *Z* geometrical isomers,[22] good yields of α-pyrones were obtained.

In summary, cyclic and acyclic ketones can be efficiently converted into α-pyrones in four steps through the intermediacy of α-oxoketene dithioacetals. The method provides for the systematic introduction of alkyl substituents at all four olefinic carbon atoms of the α-pyrone ring and is the most general synthetic route to alkyl-substituted α-pyrones.

Acknowledgment. We are pleased to acknowledge the partial support of this investigation by Research Corporation, NSF (Grant CHE-8219093), and Boston University for seed grants from the Graduate School and Department of Chemistry.

Supplementary Material Available: Detailed spectroscopic data (IR and NMR) for compounds **10a,d**, **11**, **12a,b**, and **14a,b** (2 pages). Ordering information is given on any current masthead page.

(17) Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.

(18) For a review, see: Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521.

(19) (a) Ellison, R. A.; Bhatnagar, P. K. *Synthesis* **1974**, 719. (b) Lawson, J. A.; Colwell, W. T.; Degraw, J. I.; Peters, R. H.; Dehn, R. L.; Tanabe, M. *Ibid.* **1975**, 729.

(20) Utilization of *tert*-butyl lithioacetate (i) in THF at −78 °C afforded higher yields of addition products than the alternative procedure involving 1 M solutions of i in toluene at 25 °C (e.g., reaction of **4** with i afforded, after quenching with 2 N HCl a 55% yield of **10a** and a 31% yield of unreacted **4**): Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050.

(21) Under these reaction conditions trans olefinic δ-keto esters **14a** and **15a** did not undergo ester hydrolysis or isomerization to the cis isomers. Treatment of pure *trans*-**15a** with HBF_4 for 24 h afforded only recovered ester. The crude products were a mixture of α-pyrones **20** and **21**, trans δ-keto esters **14a** and **15a**, and uncyclized cis δ-keto acids **14b** and **15b**, respectively. Exposure of the initial 1,2-addition product to HBF_4 for shorter periods of time (2–4 h) afforded larger quantities of δ-keto acid **14b**. Attempted separation of these product mixtures by chromatography on silica gel afforded pure α-pyrones **20** and **21** in yields that were unaffected by the quantity of δ-keto acids **14b** and **15b** present in the original mixture. Similarly, δ-keto acid **11** underwent cyclization to α-pyrone **17** when subjected to medium-pressure liquid chromatography (MPLC) on silica gel.

(22) When the reaction of **8** with *tert*-butyl lithioacetate was quenched with 1.2 equiv of 10% HBF_4 **14a** was isolated as a 5:1 *Z*/*E* mixture of stereoisomers. The structures of these stereoisomers were assigned on the basis of proton NMR chemical shifts for the methylene protons ($CDCl_3$; *E* δ 3.01, *Z* 3.53). A methyl substituent cis to the carbonyl functionality in β-methyl-α,β-unsaturated carbonyl compounds resonates downfield in the NMR spectrum relative to the trans methyl substituent: Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: London, 1969; pp 222–224.

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Asymmetric Diels–Alder Reaction: Applications of Chiral Dienophiles

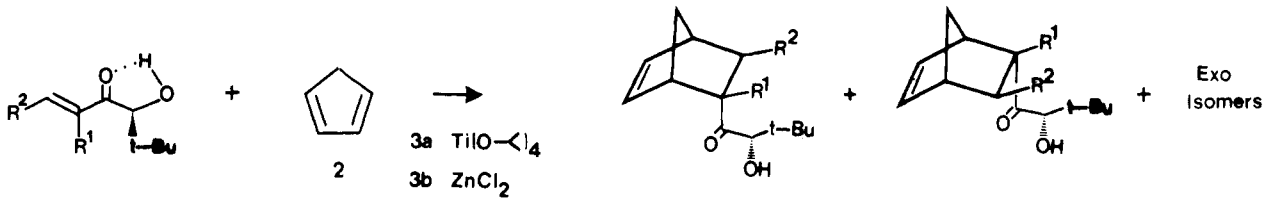
Summary: The chiral dienophile recently designed and its related compounds react highly diastereoselectively with a wide variety of both achiral and chiral dienes, and the stereochemical outcome of these Diels–Alder reactions is predictable.

Sir: The asymmetric Diels–Alder reaction continues to attract keen attention.[1] Our recent efforts in this area were directed toward the design of new chiral dienophiles

(1) For recent reviews, see: (a) Mori, Y. *J. Synth. Org. Chem., Jpn.* **1982**, *40*, 321. (b) Paquette, L. A. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press; New York, in press.

0022-3263/83/1948-4441$01.50/0

Scheme I



1: $R^1 = R^2 = H$ 4: $R^1 = R^2 = H$ 4a: $R^1 = R^2 = H$ 5

6: $R^1 = Me, R^2 = H$ 8: $R^1 = Me, R^2 = H$ 8a. $R^1 = Me, R^2 = H$ 9

7: $R^1 = H, R^2 = Me$ 10: $R^1 = H, R^2 = Me$ 10a: $R^1 = H, R^2 = Me$ 11

Table I.[a] Diels-Alder Reaction of 1, 6, or 7 with 2

entry	reactants	time, h	temp, °C	solvent	products	ratio of endo diastereomers[b]	endo:exo	yield,[d] %
1	1 + 2	24	−20	$PhCH_3$	4 + 4a + 5	4:4a = 100:1	4/4a:5 = 8:1	90
2	1 + 2 + 3a	3	−43	$PhCH_3$	4 + 4a + 5	4:4a = >100:1	4/4a:5 = 10:1	91
3	1 + 2 + 3b	<1	−43	$PhCH_3$	4 + 4a + 5	4:4a = >100:1	4/4a:5 = 15:1	95
4	1 + 2 + 3c (0.25 equiv)	0.25	−85	CH_2Cl_2	4 + 4a + 5	4:4a = 35:1	4/4a:5 = 35:1	100
5	6 + 2 + 3b	24	0	CH_2Cl_2	8 + 8a + 9	8:8a = 12:1	8/8a:9 = c	100
6	7 + 2	72	rt[e]	$PhCH_3$	10 + 10a + 11	10:10a = 75:1	10/10a:11 = 5:1	84
7	7 + 2 + 3b	16	−20	$PhCH_3$	10 + 10a + 11	10:10a = >100:1	10/10a:11 = 15:1	90

[a] For catalysts other than 3a-c, see supplementary material. [b] Product ratios were determined by integration of comparable sets of signals in the 250- or 270-MHz NMR spectrum of the crude reaction mixture. [c] Could not be determined. [d] Combined yield of endo and exo adducts. [e] Room temperature.

and have brought about the enone 1, which reacts highly diastereoselectively with cyclopentadiene (2) even in the absence of a Lewis acid catalyst. (See Scheme I and Table I, entry 1).[2] Encouraged with this finding, we have further pursued this asymmetric reaction in order to define its scope and limitations in terms of (1) effects of the catalyst on both the reaction rate and stereoselectivity, (2) modifications of 1, (3) the reactivity of dienes (other than 2) with 1, and, finally, (4) double asymmetric induction.[2] The numerous results that have now accumulated reveal that 1 and its related enone(s) are indeed effective chiral inducers, and we present a succinct account of some important findings.

(1) Lewis Acid Catalyst. To a 0.05 M solution of 1 and a Lewis acid (1 equiv unless otherwise stated) in toluene or dichloromethane is added compound 2 (in excess) at −43 °C, and the resulting reaction mixture is stirred at the same temperature until the cycloaddition has been completed as indicated by thin-layer chromatography. The usual workup and product analysis demonstrate that, of the Lewis acids examined in this investigation,[3] three of them, $Ti(O\text{-}i\text{-}Pr)_4$ (3a), $ZnCl_2$ (3b), and $BF_3{\cdot}OEt_2$ (3c), bear a notable synthetic significance. Table I (entries 2–4) shows that with these catalysts both the ratio of the two diastereomeric endo adducts (4:4a) and the combined yield (4 + 4a + 5) are excellent.[3] As expected, the time required for completion of the cycloaddition is considerably shortened: without a catalyst, 24 h at −20 °C;[2] with 3b, <1 h at −43 °C; with 3c, 15 min even at −85 °C. Catalysts 3b or 3c appear to be the Lewis acids of choice (see below).

(2) Dienophiles. Treatment of 2-hydroxy-3,3-dimethylbutyric acid with vinyllithium (3.5 equiv) or 1.9 equiv of *n*-butyllithium followed by vinyllithium (1.5 equiv) provides 1. Therefore the selection of a proper lithium reagent in this reaction allows modification of 1 (yield ranging from 53 to 75%).[2,4,5] Although Diels–Alder reactions of only the α- and (*E*)-β-methyl-substituted enones 6[3] and 7[3] are described here, the general trend of the stereochemical outcome effected by this methyl substitution is apparent (Scheme I, Table I). While the reaction of 6 with 2 is considerably slower even with 3b (0 °C, 24 h) and the 8:8a[3] ratio decreases to 12:1 (entry 5), enone 7 remains as highly diastereoface selective[6] as 1 in the absence of a catalyst (entry 6) and becomes more so with 3b (entry 7). This last reaction (entry 7) is completed within 24 h at −43 to −20 °C. It seems that the diastereofacial selectivity of a dienophile depends highly on the ease with which it can attain the coplanar cisoid enone conformation.[2] Molecular models indicate that in 6 the steric interaction between the methyl and *tert*-butyl groups is certainly not negligible, in contrast with that in coplanar cisoid 7. Thus, enones 1 and 7 show high synthetic utility.

(3) Dienes. A variety of dienes react with 1 and 7. In each of the following three examples (Scheme II) the cycloaddition reaction provides a *single adduct* to the detection limits of ^1H NMR spectroscopy (270 MHz). Oxidative removal of the chiral auxiliary group from the adduct thus leads to an enantiomerically pure (homochiral) product (at minimum 98% ee), which serves as an intermediate for the synthesis of a natural product. **Example 1.** Reaction of 1 with excess butadiene 12 in the presence of 3b is completed within 2 h (−78 to −20 °C) to give rise to 13,[3] which is in turn transformed via three steps (Dibal, $NaIO_4$, and Dibal) to alcohol 14, $[\alpha]^{22}_D$ −100.4° (*c* 1.71, MeOH).[3,7a,b] Conversion of the enantiomer of 14 to natural sarkomycin 15 has already been documented.[7c] **Example 2.** Diacetoxybutadiene (16) and 1 are coupled with the aid

(2) Choy, W.; Reed, L. A., III; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137.

(3) Further information on this subject and the synthesis of 1 as well as structural and stereochemical assignments to new compounds are provided in the supplementary material. Spectral properties of these compounds are tabulated in footnote 17.

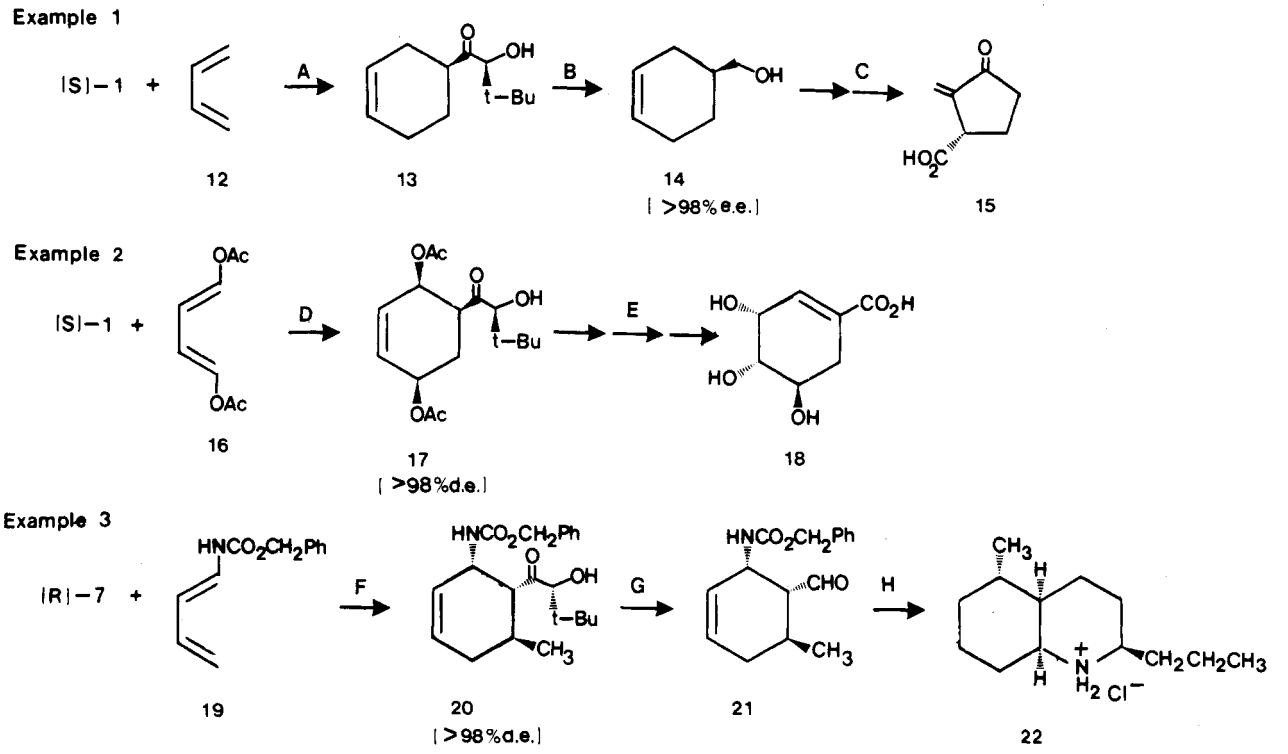
(4) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47.

(5) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

(6) For the definition of this phrase, see: Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523 (ref 16).

(7) *R* enantiomer reported as $[\alpha]^{22}_D$ +96.0° (*c* 3, MeOH). (a) Ceder, O.; Hansson, B. *Acta Chem. Scand.; Ser. B.* **1977**, *31*, 189. (b) Ceder, O.; Hansson, B. *Acta Chem. Scand.* **1970**, *24*, 2693. (c) Boeckman, R. K., Jr.; Naegly, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752.

Scheme II[a]



[a] A, 1 equiv of **3b**, −78 → 20 °C, 2 h, toluene (83%). B, (i) 3 equiv of Dibal, −43 °C, toluene; (ii) $NaIO_4$, $MeOH/H_2O$ (4:1), 24 h; (iii) 3 equiv of Dibal, −43 °C, toluene (58% overall). C, ref 7c. D, 0.5 equiv of **3c**, 2 equiv of **16**, −43 °C, 12 h, CH_2Cl_2 (72%). E, ref 9. F, 1 equiv of **3c**, 2 equiv of **19**, −78 °C, 0.5 h, toluene (95%). G, (i) $LiBH_4$, THF; (ii) $NaIO_4$, $MeOH/H_2O$, 12 h (75% overall). H, ref 10a

of **3c** (0.5 equiv). Product **17**[3] (which is the exclusive stereoisomer of this cycloaddition, 72% yield) is subjected to a series of six transformations analogous to those used earlier[8a,b] to provide shikimic acid **18**, $[\alpha]^{20}_D$ −160.1° (*c* 1.39, MeOH).[8,9] **Example 3.** A mixture of (*R*)-**7** (1 equiv) and **3c** (1 equiv) is allowed to react with excess diene **19**[10] to provide in 95% yield an adduct (**20**), $[\alpha]^{24}_D$ +22.2° (*c* 1.00 $CHCl_3$), which is in turn converted in two steps ($LiBH_4$ reduction and $NaIO_4$ oxidation) to the acid- and base-sensitive aldehyde **21**. Conversion of **21** to the hydrochloride of (+)-pumiliotoxin C **22** ($[\alpha]^{25}_D$ +16.2° (*c* 1.00 MeOH)[3,10c] follows the published procedure.[10a] Other examples will be documented in due course.

(4) Match and Mismatch Problem.[4,11] In contrast with all the above examples of single asymmetric induction,[2] the stereochemical course of the Diels–Alder reaction may become much more complex in the case of double asymmetric induction[2] where both diene and dienophile are the chiral partners.[4,11] Can our chiral dienophile **1** control the stereochemistry of such reactions? To answer this question we have selected, as chiral dienes, butadienyl (*R*)- and (*S*)-*O*-methyl mandelates ((*R*)-**23**, (*S*)-**23**), which are (moderately) effective in single asymmetric induction.[12]

Scheme III shows a set of experiments in which (*R*)-**23** or (*S*)-**23** is coupled with **1** under standard conditions [**1** in CH_2Cl_2 (0.05 M), **3c** (0.3 equiv), **23** (2 equiv), addition at −78 °C followed by stirring at −45 °C for 18 h]. The reaction of the *R* isomer with **1** provides a 35:1 mixture of the products **24a**[3] and **24b** in 73% yield, while the ratio of adducts **25a**[3] and **25b** obtained from the *S* isomer is 130:1 (70%). The ratios have been confirmed by converting the two mixtures (**24a** + **24b**, **25a** + **25b**) separately into the mixtures of (**26a** + **26b**)[3] and (**27a** + **27b**).[3,12] Further transformation of **26a** and **27a** into **28** of known absolute configuration[13] establishes the stereochemical assignments of the created chiral centers as shown in Scheme III.

Note that in both cycloadditions, the absolute configurations of the two major products **24a** and **25a** are the same at the C(1) and C(2) centers and are directly correlated with the chirality of **1**, thus the stereochemistry of these reactions is *controlled* through the selection of (*R*)- or (*S*)-**1**. This outcome reflects the overwhelmingly large diastereofacial selectivity of **1** as compared with that of **23**.[14] The different ratios (130:1 and 35:1) observed for this set of two cycloaddition reactions correspond to matched and mismatched pairs, respectively, as in the earlier cases of double asymmetric aldol reaction[15] and epoxidation.[16] Thus, with this and the above demon-

(8) (a) Smissman, E. E.; Suh, J. T.; Oxman, M.; Daniels, R. *J. Am. Chem. Soc.* **1959**, *81*, 2909; **1962**, *84*, 1040. Also see: (b) McCrindle, R.; Overton, K. H.; Raphael, R. A. *J. Chem. Soc.* **1960**, 560. (c) Smissman, E. E.; Li, P. J. *Tetrahedron Lett.* **1968**, 4601. (d) McCrindle, R.; Overton, K. H.; Raphael, R. A. *Ibid.* **1968**, 1847. (e) Hill, R. K.; Newkome, G. R. *Ibid.* **1968**, 1851. Reported $[\alpha]_D$ −161° (*c* 0.54, MeOH)[8b] and $[\alpha]_D$ −157° (*c* 0.97, MeOH).[8b]

(9) A detailed account of this synthesis will be prepared for publication.

(10) (a) Overman, L.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179. Also see: (b) Jessup, P. J.; Petty, B.; Roos, J.; Overman, L. *Org. Synth.* **1979**, *59*, 1. (c) For another enantioselective synthesis of **22** (reported to have $[\alpha]^{20}_D$ +16.4° (*c* 1.00, MeOH)), see: Oppolzer, W.; Flaskamp, E. *Helv. Chem. Acta* **1977**, *60*, *204*.

(11) For a detailed discussion of this subject, see: Masamune, S.; McCarthy, P. A. In "Macrolide Antibiotics"; Omura, S., Ed.; Academic Press; New York, in press.

(12) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7596.

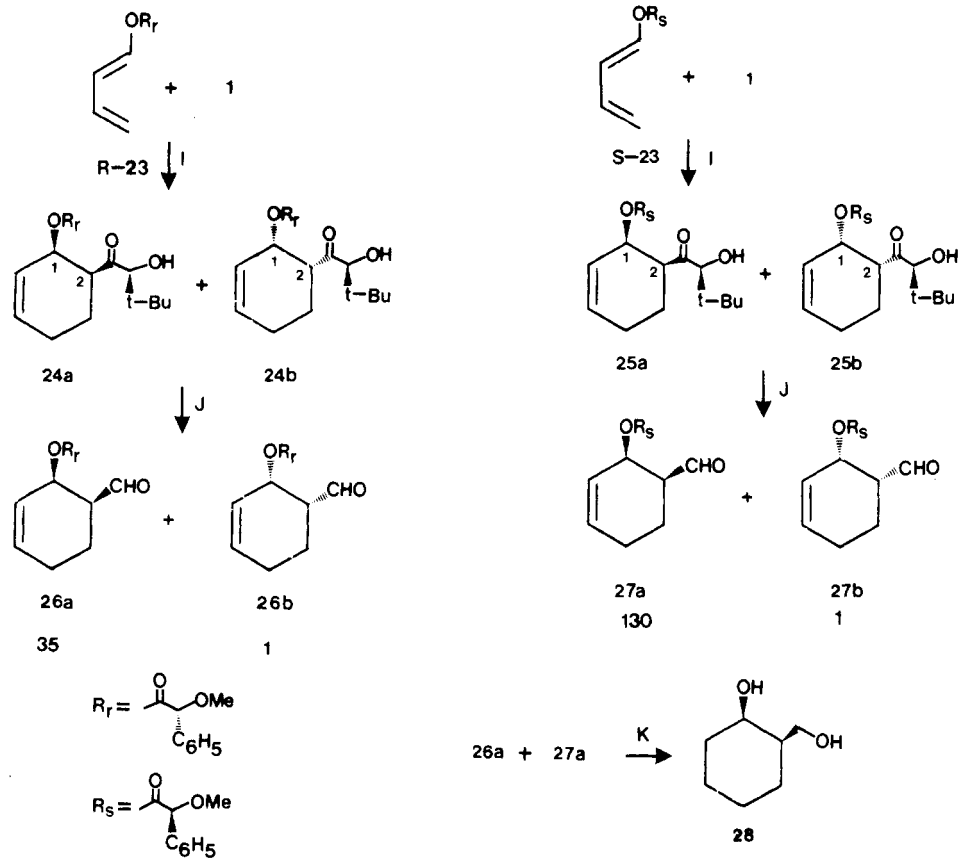
(13) Lemieux, R. U.; Brewer, J. T. *Adv. Chem. Ser.* **1973**, *117*, 121.

(14) The chiral center of **23** is close to the reaction site, and thus the diastereofacial selectivity of most chiral dienes normally encountered in the synthesis is smaller than that of **23**. Therefore, the chirality of **1** should control the stereochemistry of most double asymmetric reactions.

(15) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

(16) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III.; Sharpless, K. B.; Walker, F. J. *Science (Washington, D.C.)* **1983**, *220*, 949.

Scheme III[a]



[a] I, 0.3 equiv of **3c**, CH_2Cl_2, −78 → −45 °C (73% for **24a** + **24b**, 70% for **25a** + **25b**). J, (i) $BH_3 \cdot NH_3$, wet Et_2O, room temperature; (ii) $NaIO_4$, MeOH/H_2O, room temperature (90% for **26a** + **26b**, 95% for **27a** + **27b**). K, (i) $BH_3 \cdot NH_3$, wet Et_2O, room temperature; (ii) Dowex 1-X4, MeOH, room temperature; (iii) Ac_2O, C_5H_5N, room temperature; (iv) Rh/Al_2O_3, H_2(1 atm), EtOAc, AcOH; (v) Dowex 1-X4, MeOH, room temperature (60% overall yield).

stration we conclude that reagent **1** as well as **7** is capable of creating new chiral centers in the predictable manner on a variety of both achiral and chiral dienes and that the concept of matching and mismatching is also valid for the Diels–Alder reaction.[17,18]

Acknowledgment. We thank the National Institutes of Health (Grant CA 28337) and Kao Corporation, Japan, for financial support. High-resolution mass spectra were provided by the facility supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), for the Biotechnology Resources Branch, Division of Research Resources.

Supplementary Material Available: The synthesis of **1**, table on the effects of nine Lewis catalysts, and the structural and stereochemical assignments to new compounds (5 pages). Ordering information is given on any current masthead.

(17) Spectral data of new compounds. **6**: IR ($CHCl_3$) cm^{-1} 3500 b, 3025 w, 2980 s, 1665 s, 1625 w, 1260 s, 1040 m; ^1H NMR ($CDCl_3$) δ 0.92 (s, 9 H), 1.94 (dd, J = 0.9, 1.0 Hz, 3 H), 3.24 (d, J = 8.6 Hz, 1 H), 4.57 (d, J = 8.6 Hz, 1 H), 5.84 (m, 2 H); $[\alpha]^{20}_D$ +247.9° (*c* 1.83, $CHCl_3$). **7**: IR ($CHCl_3$) cm^{-1} 3480 b, 3025 m, 2980 m, 1685 m, 1660 w, 1625 s, 1260 s, 1050 m; ^1H NMR ($CDCl_3$) δ 0.95 (s, 9 H), 1.92 (dd, J = 1.5, 7.0 Hz, 3 H), 3.41 (d, J = 7.0 Hz, 1 H), 4.01 (d, J = 7.0 Hz, 1 H), 6.28 (dd, J = 1.5, 15.6 Hz, 1 H), 6.99 (dq, J = 7.0, 15.6 Hz, 1 H); $[\alpha]^{20}_D$ +178.1° (*c* 0.96, $CHCl_3$). **8**: IR ($CHCl_3$) cm^{-1} 3580 b, 3060 w, 2970 s, 2890 m, 1700 s, 1365 m, 1005 s; ^1H NMR ($CDCl_3$ (D_2O exchangeable)) δ 0.77 (dd, J = 2.8, 11.8 Hz, 1 H), 1.02 (s, 9 H), 1.13 (s, 3 H), 1.33 (m, 2 H), 2.44 (dd, J = 3.9, 11.8 Hz, 1 H), 2.82 (m, 1 H), 3.13 (m, 1 H), 4.22 (s, 1 H), 6.09 (dd, J = 3.1, 5.7 Hz, 1 H), 6.25 (dd, J = 3.1, 5.7 Hz, 1 H). **10**: IR ($CHCl_3$) cm^{-1} 3520 b, 3050 w, 1695 s, 1365 m, 1030 w, 1015 w; ^1H NMR ($CDCl_3$ (D_2O exchangeable)) δ 0.99 (s, 9 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.55 (m, 2 H), 2.07 (m, 1 H), 2.52 (m, 1 H), 2.75 (dd, J = 3.7, 3.9 Hz, 1 H), 3.18 (m, 1 H), 4.02 (s, 1 H), 5.72 (dd, J = 2.7, 5.6 Hz, 1 H), 6.31 (dd, J = 3.2, 5.6 Hz, 1 H); mp 85–86 °C. **13**: IR ($CHCl_3$) cm^{-1} 3400 b, 3025 m, 2940 s, 1700 s, 1650 m, 1360 w, 1075 w, 1020 w; ^1H NMR ($CDCl_3$ (D_2O exchangeable)) δ 1.00 (s, 9 H), 1.65–2.32 (m, 6 H), 2.87 (m, 1 H), 4.01 (s, 1 H), 5.70 (m, 2 H); $[\alpha]^{20}_D$ +75.18° (*c* 1.08, $CHCl_3$); mp 42 °C. **14**: IR ($CHCl_3$) cm^{-1} 3550 b, 3020 m, 2920 s, 1435 m, 1210 s, 1015 m; ^1H NMR ($CDCl_3$ (D_2O exchangeable)) δ 1.27 (m, 1 H), 1.78 (m, 3 H), 2.08 (m, 3 H), 3.52 (m, 2 H), 5.68 (m, 2 H); $[\alpha]^{20}_D$ −100.4° (*c* 1.71, MeOH) (lit. *R* isomer, $[\alpha]^{22}_D$ +96.0° (*c* 3, MeOH)).[7] **17**: IR ($CHCl_3$) cm^{-1} 3550 b, 3050 w, 2980 m, 1735 s, 1370 m, 1230 s, 1015 m; ^1H NMR ($CDCl_3$ (D_2O exchangeable)) δ 0.98 (s, 9 H), 1.95–2.19 (m, 2 H), 2.00 (s, 3 H), 2.09 (s, 3 H), 3.04 (ddd, J = 3.0, 3.7, 13.0 Hz, 1 H), 4.05 (s, 1 H), 5.34 (dd, J = 6.2, 10.6 Hz, 1 H), 5.61 (m, 1 H), 5.96 (m, 2 H); $[\alpha]^{25}_D$ −18.2° (*c* 1.0, $CHCl_3$); mp 113–114 °C. **18**: ^1H NMR (D_2O) δ 2.06 (dd, J = 18.1, 6.1 Hz, 1 H), 2.58 (dd, J = 18.1, 5.0 Hz, 1 H), 3.62 (dd, J = 8.1, 4.2 Hz, 1 H), 3.88 (m, 1 H), 4.29 (m, 1 H), 6.66 (m, 1 H); $[\alpha]^{20}_D$ −160.1° (*c* 1,39, MeOH); mp 185–186 °C mmp 186–187 °C. **20**: IR ($CHCl_3$) cm^{-1} 3680, 3620, 3540, 1705 b, 1505 s; ^1H NMR ($CDCl_3$) δ 0.96 (s, 9 H), 1.20 (d, J = 7 Hz, 3 H), 2.79 (dd, J = 11.4, 4 Hz, 1 H), 3.68 (d, J = 4 Hz, 1 H), 4.08 (d, J = 4 Hz, 1 H), 4.48 (m, 1 H), 4.72 (br s, 1 H, NH), 4.87 (d, J = 12.2 Hz, 1 H), 5.03 (d, J = 12.2 Hz, 1 H), 5.65 (m, 1 H), 5.82 (m, 1 H), 7.25 (m, 5 H); $[\alpha]^{24}_D$ +22.22° (*c* 1.0, $CHCl_3$). **22**: ^1H NMR ($CDCl_3$, D_2O) δ 0.88 (d, J = 6.3 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H), 1.20–2.50 (m, 17 H), 2.95 (m, 1 H), 3.30 (m, 1 H); $[\alpha]^{25}_D$ +16.2° (*c* 1.00, MeOH); mp 260–265 °C. **24a**: IR (neat) cm^{-1} 3550, 3035, 1748, 1715; ^1H NMR ($CDCl_3$ + D_2O) δ 0.89 (s, 9 H), 1.68–2.34 (m, 4 H), 2.88 (dt, J = 3.3, 11.8 Hz, 1 H), 3.39 (s, 3 H), 3.87 (s, 1 H), 4.69 (s, 1 H), 5.53 (m, 1 H), 5.88 (m, 1 H), 6.06 (m, 1 H), 7.27–7.40 (m, 5 H). **25a**: IR (neat) cm^{-1} 3600, 3035, 1750, 1715; ^1H NMR ($CDCl_3$ (D_2O exchangeable)) δ 0.98 (s, 9 H), 1.62–2.28 (m, 4 H), 2.94 (dt, J = 3.3, 11.6 Hz, 1 H), 3.41 (s, 3 H), 4.09 (s, 1 H), 4.67 (s, 1 H), 5.60–5.70 (m, 2 H), 5.97 (m, 1 H), 7.26–7.36 (m, 5 H). **26a**: IR (neat) cm^{-1} 3035, 2730, 1750, 1730; ^1H NMR ($CDCl_3$) δ 1.57–2.35 (m, 4 H), 2.49 (dt, J = 3.6, 11.2 Hz, 1 H), 3.39 (s, 3 H), 4.73 (s, 1 H), 5.65 (m, 1 H), 5.91 (m, 1 H), 6.04 (m, 1 H), 7.26–7.43 (m, 5 H), 9.24 (s, 1 H). **27a**: IR (neat) cm^{-1} 3035, 2725, 1750, 1730; ^1H NMR ($CDCl_3$) δ 1.60–2.24 (m, 4 H), 2.63 (dt, J = 3.3, 10.9 Hz, 1 H), 3.39 (s, 3 H), 4.71 (s, 1 H), 5.71–5.77 (m, 2 H), 5.95 (m, 1 H), 7.26–7.54 (m, 5 H), 9.71 (s, 1 H). **28**: IR (neat) cm^{-1} 3360; ^1H NMR (D_2O + $CDCl_3$) δ 0.98–1.82 (m, 9 H), 3.74 (m, 2 H), 4.14 (m, 1 H); $[\alpha]^{20}_D$ −36.4° (*c* 0.24, H_2O).

(18) After the submission of this manuscript, we learned from Professor Kagan that the concept of double asymmetric induction was first described briefly in Horeau, A.; Kagan, H.-B.; Vigneron, J.-P. *Bull. Soc. Chim. Fr.* **1968**, 3795.

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Received August 8, 1983