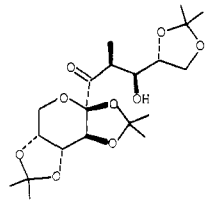
three aldols in a ratio of 5.5:2.5:1. The two major products were isolated by chromatography and shown to have the stereostructures **16** (61%) and **17** (28%) by a combination of ^{13}C



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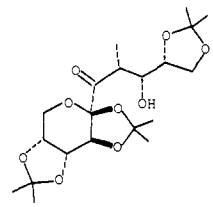

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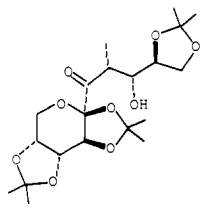

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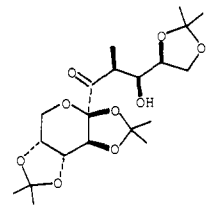

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NMR[10] and circular dichroism.[11] The minor isomer from this condensation must be a threo diastereomer from its ^{13}C NMR spectrum.[10]

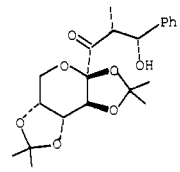
In contrast, the similar reaction of **13** with aldehyde **15** affords only two stereoisomers, in a ratio of 13:1. The major isomer was shown to have structure **18** by its ^{13}C NMR and CD spectra;[10,11] the minor isomer has the threo configuration. None of the alternate erythro isomer **19** could be detected under conditions where we could detect as little as 3% of a minor diastereomer.

Thus, the principle of double stereodifferentiation is vividly demonstrated; in this case the 1,2 diastereoselectivity exhibited by the aldehyde is increased from 2:1 to >30:1. We have observed similar results with another chiral ethyl ketone. Further application of the strategy in synthesis is reported in the following communication.

Acknowledgment. Support for this research was provided by a grant from the U.S. Public Health Service (NIH Grant AI-15027).

References and Notes

(1) For paper 4 in this series, see C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, *J. Org. Chem.*, in press.
(2) C. T. Buse and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 8109 (1977).
(3) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828, 5851 (1952).
(4) The term is defined in Y. Izumi and A. Tai, "Stereodifferentiating Reactions", Kodansha Ltd., Tokyo; Academic Press, New York, 1977. It is equivalent to "double asymmetric induction" [5] but has the advantage that it may be used without causing confusion even when all reactants are racemic.
(5) A. Horeau, H.-B. Kagan, and J.-P. Vigneron, *Bull. Soc. Chim. Fr.*, 3795 (1968).
(6) Reaction with acetone and H_2SO_4; oxidation of the primary hydroxyl with dimethyl sulfide–*N*-chlorosuccinimide (NCS); addition of ethylmagnesium bromide; oxidation of the secondary hydroxyl with dimethyl sulfide–NCS.
(7) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).
(8) S. B. Baker, *J. Am. Chem. Soc.*, **74**, 827 (1952). (*S*)-Arabinose was substituted for (*R*)-arabinose in the preparation to provide (*S*)-glyceraldehyde acetonide.
(9) We thank Mr. Steven Young for preparing aldehydes **14** and **15**.
(10) See ref 1. In brief, structure assignments may be made based on the ^{13}C NMR chemical shift of the methyl carbon resonance adjacent to the carbonyl group. In erythro diastereomers this resonance occurs in the range 8–13 ppm, while in threo diastereomers it is in the range 13–18 ppm.
(11) The CD method that we have employed to make these assignments may be summarized as follows. Condensation of ketone **13** with benzaldehyde affords two erythro diastereomers in a ratio of 3.7:1. The major isomer (mp 82–84 °C) was shown by single-crystal X-ray analysis to have structure **20**. Thus, the minor isomer (mp 105–107 °C) is the other erythro diastereomer **21**. The CD spectra of **13**, **20**, and **21** are as follows: **13**, $[\theta]_{295}$ +1500; **20**, $[\theta]_{300}$ +8900; **21**, $[\theta]_{313}$ −2500. Thus, the $\alpha R,\beta R$ configuration in the aldol results in a slight red shift in the absorption, accompanied by a large increase in $[\theta]$. On the other hand, the $\alpha S,\beta S$ configuration at these two centers results in a more pronounced red shift and a more negative $[\theta]$. The CD spectra of aldols **16**, **17**, and **18** follow: **16**, $[\theta]_{325}$ +460; **17**, $[\theta]_{297}$ +4000; **18**, $[\theta]_{300}$ +3250.



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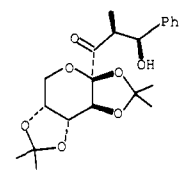

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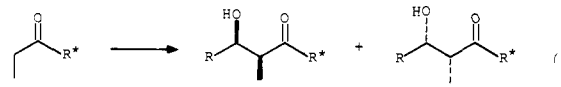
Acyclic Stereoselection. 6. A Reagent for Achieving High 1,2 Diastereoselection in the Aldol Conversion of Chiral Aldehydes into 3-Hydroxy-2-methylcarboxylic Acids

Sir:

In the accompanying communication[1] we demonstrate the utility of double stereodifferentiation for enhancing the 1,2 diastereoselectivity ("Cram's rule selectivity") of chiral aldehydes. In order for this strategy to be employed for the synthesis of β-hydroxy acids and aldehydes, we need a readily available ethyl ketone (**1**) which possesses several properties. First, the group R* must be large, so that the resulting enolate will show high erythro selectivity.[2] Second, R* must be easily convertible into OH or H. Finally, R* must be chiral and the resulting enolate must show substantial stereoselectivity (1,3 diastereoselectivity) in its reactions with achiral aldehydes, since the greater the ratio of **2** to **3** (eq 1), the more effective



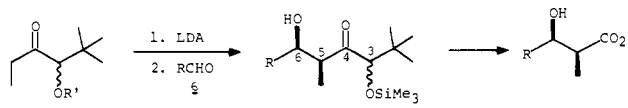
(1)

1 **2** **3**

1 will be in enhancing 1,2 diastereoselectivity in its reactions with chiral aldehydes. In this communication, we report the synthesis and some reactions of such a reagent.

Ketone **5** has been prepared by two routes. In one method, 1-lithio-1-methoxypropene[3,4] is added to pivaldehyde (pentane, −60 °C). After hydrolysis of the enol ether (0.1 N methanolic HCl, 30 min, 25 °C), hydroxy ketone **4** is produced in 54% yield. Alternatively, 5-methylhex-4-en-3-one[5] is allowed to react with lithium dimethylcopper (ether, 0 °C) and the resulting enolate mixture quenched with trimethylsilyl chloride and triethylamine to obtain a silyl enol ether. The crude ether is oxidized using *m*-chloroperoxybenzoic acid (CH_2Cl_2, 0 °C, 1 h),[6] and the oxidation product is hydrolyzed (1.2 N aqueous HCl–ether, 25 °C, 3 h) to obtain hydroxy ketone **4** in 56% yield. **4** is heated at 100 °C for 24 h with bis(trimethylsilyl)-acetamide[7] to obtain **5** (40% overall yield).

Ketone **5** is converted into its enolate by reaction with lithium diisopropylamide in THF (0.25 M, −70 °C, 2 h). Te-



4: R' = H
5: R' = $SiMe_3$

7

8

a: R = Ph_2CH
b: R = $PhCH_2$
c: R = $(CH_3)_2CH$
d: R = $(CH_3)_3C$
e: R = Ph

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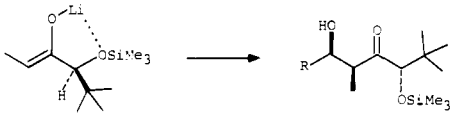
Table I. Condensation of Keto Ether **5** with Various Aldehydes **6**

aldehyde	reaction time, min	yield of **7**, %[a]	diastereomer ratio	mp, °C	yield of **8**, %	diastereomeric purity, %	mp, °C
6a	20	69	≥9:1	73-74	84	>98	146
6b	25	75	87:13	56-58	62	>98	119-120
6c	25	93	3:1	oil	45	>98	oil
6d	35	47	≥95:5	oil	57	>98	115-116
6e	5	75	3:1	oil	63	>98	oil

[a] Yield of LC-purified aldols. For **7b, 7c,** and **7e** the yield refers to the mixture of diastereomers.

tramethylethylenediamine is added (1.8 equiv), followed by an aldehyde. After an appropriate reaction time (see Table I), the reaction mixture is quenched by the addition of saturated $NaHCO_3$ solution (2 cm^3/mmol of aldehyde used). Diastereometer ratios were determined on the crude reaction mixture using ^{13}C NMR. Pure samples of products **7** were obtained by preparative high pressure liquid chromatography. The crude product **7** is oxidized by periodic acid in methanol (4 equiv of H_5IO_6, methanol-H_2O, 18-48 h) to obtain β-hydroxycarboxylic acid **8.**

Results for the condensation of **5** with a variety of achiral aldehydes are summarized in Table I. In all cases the two newly formed chiral centers have the erythro relative configuration, as shown by ^1H NMR[8] and ^{13}C NMR[9] spectroscopy. It may also be seen that substantial 1,3 diasteroselection is realized, from 3:1 to >19:1.[10] Although the experiments summarized in Table I were performed using racemic **5,** the diastereomer ratios obtained correspond to enantiomeric excesses in the ultimate acids **8** of 50-90%. The highest 1,3 diastereoselection which has previously been observed in the aldol condensation of a chiral ethyl ketone is 1.35:1, corresponding to an enantiomeric excess of 15%.[11] Although we have not rigorously established this point in every case, we propose that the major diastereomer has the 3*SR*,5*SR* configuration. This proposal is based on the hypothesis that the enolate of **5** has a chelated structure (**9**) and that the aldehyde approaches the less en-



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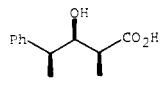
cumbered face of the double bond (the *re* face in the *S* enantiomer).[12] An X-ray determination of one adduct (vide infra) provides support for this hypothesis.

Thus, ketone **5** possesses the three properties which are necessary for it to be useful as a reagent for enhancing 1,2 diastereoselectivity in reactions with chiral aldehydes. The most exciting finding is our observation that **5** shows very high stereoselectivity in its condensations with chiral aldehydes, *even when both reactants are racemic.* For example, **5** reacts with 2-phenylpropanal to give, after oxidation, only acid **10,** in an overall yield for the crystalline acid (mp 142-143 °C) of 68%. Appropriate control experiments demonstrate that we could detect as little as 2% diastereomer **11;** that is, with enolate **9,**



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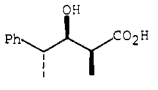

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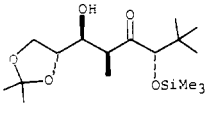

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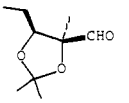
2-phenylpropanal exhibits a 1,2 diastereoselectivity of >45:1![13] A second example of high diastereoselectivity in such a "double racemic" condensation is the reaction of **5** with the acetonide of racemic glyceraldehyde. Again, only one racemic diastereomer, which we suppose to have stereostructure **12,**[14] results.

Finally, the special utility of **5** as a reagent for accomplishing stereoselective aldol condensations is strikingly demonstrated by the following example. Condensation of aldehyde **13** with ketone **14**[15] affords the erythro adducts **15** and **16** in a ratio of



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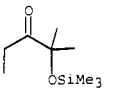

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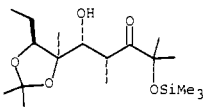

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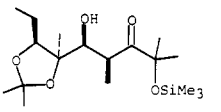

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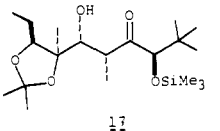

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~3:1. However, reaction of aldehyde **13** with a reagent **5** (both racemic) furnishes only one (racemic) adduct, **17** (mp 81.5-82.5 °C).[16] Further exploitation of these discoveries is underway.

Acknowledgment. Support for this research was provided by a grant from the U.S. Public Health Service (NIH Grant AI-15027). M.C.P. thanks the Fannie and John Hertz Foundation for a Fellowship.

References and Notes

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(2) W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Am. Chem. Soc.*, **99,** 247 (1977).
(3) J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96,** 7125 (1974).
(4) Although it is not specified in the communication,[3] Dr. Lever informs us that lithiation of 1-methoxypropene by *tert*-butyllithium and TMEDA must be done in pentane, rather than in THF.
(5) G. Malone and A. Meyers, *J. Org. Chem.*, **39,** 623 (1974).
(6) G. M. Rubottom, M. A. Vasquez, and D. R. Pelegrina, *Tetrahedron Lett.*, 4319 (1974).
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(8) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95,** 3310 (1973), and references cited therein.
(9) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, *J. Org. Chem.*, in press.
(10) In the case of aldehyde **6a,** the crude product is a 9:1 mixture of a single aldol and an α,β-unsaturated ketone. If we assume that *all* of this enone arises from another stereoisomeric aldol, then the selectivity is at least 9:1. With aldehyde **6d,** only one aldol may be detected.
(11) D. Seebach, V. Ehrig, and M. Teuschner, *Justus Liebigs Ann. Chem.*, 1357 (1976).
(12) The use of highly chelated lithium enolates to achieve stereochemical control in alkylation reactions has been reported; see inter alia, A. I. Meyers, G. Knaus, M. Ford, and K. Kamata, *J. Am. Chem. Soc.*, **98,** 567 (1976).
(13) At first sight, the high stereoselecitvity observed in this double racemic reaction is surprising, since it requires that (*R*)-enolate react with (*R*)-aldehyde almost to the exclusion of (*S*)-aldehyde. However, close analysis reveals that the extent of such "mutual kinetic stereodifferentiation" is simply a function of the inherent diastereoselectivity of the two reaction partners.
(14) The stereostructural assignment for **12** is tentative. It is known to have the C-3-C-4 erythro configuration from its ^{13}C NMR spectrum.[9] The C-4-C-6

relative configuration is assigned on the basis of the argument advanced in the text. The C-2–C-3 erythro configuration is assigned by analogy to the known stereochemical outcome of a related reaction of this aldehyde.[1]

(15) C. T. Buse and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 8109 (1977).
(16) The stereostructure of **17** was determined by single-crystal X-ray analysis: J. A. Bertrand and D. VanDerveer. That **15** and **17** have the same relative stereochemistry at the pertinent centers was shown by converting them into the same β-hydroxy aldehyde. The sequence of reactions for this conversion is reduction with lithium aluminum hydride in ether; removal of the trimethylsilyl group; cleavage of the resulting vicinal diol with $NaIO_4$ in aqueous ethanol. Full details fo the X-ray determination on **17** and on the correlation of **15** with **17** will be reported in a full paper.

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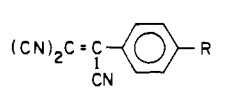
The Intermolecular π-Amphoteric Character of *p*-Tricyanovinyldimethylaniline

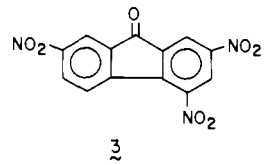
Sir:

While, in principle, any molecular species may behave as a "donor" or "acceptor" in complex formation, the behavior of a given species will depend not only on its own ionization potential (IP_g) and electron affinity (EA_g) but also on those of its complexing partner, as well as the specific experimental conditions under which the molecules interact. In this communication, we demonstrate for the first time that an organic *molecule, p*-tricyanovinyldimethylaniline[1] (TCVDMA, **1**),



1 R = $-N(CH_3)_2$

2 R = $-C(CN)_2^-$



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forms a *solid* complex with one molecular partner in which it behaves as a donor and a *solid* complex with another molecular partner in which it behaves as an acceptor.[2,5,6] Thus, this is also the first report of the isolation of solid complexes of TCVDMA. A previous report[7] indicates possible intermolecular complex formation in *solution.*

In the course of our[8] characterization of the donor properties of the *p*-tricyanovinylphenyldicyanomethide[9] (TCVPDM$^-$, **2**), we noted a molecular analogy in the electrochemical behavior of TCVDMA and TCVPDM$^-$. Since TCVPDM$^-$ forms a complex with 2,4,7-trinitrofluorenone (TNF, **3**),[8] we were prompted to prepare the TNF complex of TCVDMA, which crystallizes from ethanol solution as red plates of 1:1 stoichiometry, mp 151 °C dec.

We also attempted to prepare the TNF complex of TCVDMA in aromatic solvents where relatively large solvent shifts of the absorption maximum of TCVDMA have been observed.[1] To our surprise, we found that TCVDMA crystallized from a variety of aromatic solvents, including *N,N*-dimethylaniline (DMA), complexed with the solvent.[10] We established the stoichiometry of the purple DMA complex as DMA·4TCVDMA,[11] mp 138 °C dec, by solution spectrophotometry. Analytical and crystal data for the TCVDMA complexes of TNF and DMA are given in Table I. The observation of a lattice constant ~4.0 Å in DMA·4TCVDMA (Table I) is reminiscent of that found in uniform segregated stack structures of ion-radical salts;[3,12] we have also observed a comparable short lattice constant in the 1,2,4-trichlorobenzene complex of TCVDMA which also has a 1:4 stoichiometry.[10]

Table I. Analytical[a] and Crystal Data[b] for TCVDMA Complexes

	TCVDMA·TNF		DMA·4TCVDMA	
	calcd	obsd	calcd	obsd[c]
C	58.11	57.78	71.43	71.41
H	2.81	3.04	4.96	5.29
N	18.24	18.00	23.61	22.80
a, Å	7.467 (1)		3.992 (6)	
b, Å	11.992 (1)		16.315 (10)	
c, Å	14.405 (1)		20.562 (11)	
α, deg	107.02 (1)		90	
β, deg	102.49 (1)		90.27 (9)	
γ, deg	91.38 (1)		90	
V_{mc}[d,e], Å^3	1198.9		1339	
V_{add}[d,e], Å^3	1229.6		1411	
Z	2		1	
ρ_{calcd}	1.487		1.214	
ρ_{obsd}	1.49 (1)		1.23 (1)	

[a] Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. [b] Lattice constants were determined by Molecular Structure Corporation, College Station, Texas, using Cu Kα radiation. [c] Complexes of TCVDMA with volatile components such as DMA cannot be washed with solvents or vacuum dried without loss of the volatile component. [d] Reference 3. [e] Molecular volume of TCVDMA from Chetkina. L. A., Popova, E. G.; Kotov, B. V.; Ginzburg, S. L.; Smelyanska, E. M. *J. Struct. Chem.* **1976,** *17*, 902, Molecular volume of TNF from Dorset D. L.; Hybl, A.; Ammon, H. L. *Acta Crystallogr., Sect. B* **1972,** *28*, 3122. Molecular volume of DMA calculated from room temperature density.

Table II. Molecular Energy Levels and Redox Potentials

molecule	IP_g, eV	EA_g, eV	$E_{1/2}^{ox}$ [a]	$E_{1/2}^{red}$ [a]
DMA	7.45[b]	1.24[c]	+0.71[c]	<−1.0
TCVDMA	7.94[e]		+0.96[f]	−0.70[f]
TNF		2.1[g]	>+1.6	−0.42[h]

[a] Measured in acetonitrile solution in volts vs. a saturated calomel electrode. [b] Egdell, R.; Green, J. C.; Rao, C. N. R. *Chem. Phys. Lett.* **1975,** *33*, 600. [c] Jordan, K. D.; Barrow, P. D. *Acc. Chem. Res.* **1978,** *11*, 341. [d] Seo, E. T., et al. *J. Am. Chem. Soc.* **1966,** *88*, 3498. This value is the potential as half peak height for an irreversible anodic wave. [e] This value is reported in ref *b* for *p*-nitrodimethylaniline. [f] Kuder, J. E.; Limburg, W. W.; Pochan, J. M.; Wychick, D. *J. Chem. Soc., Perkin Trans. 2,* **1977,** 1643. [g] Chen, E. M. C.; Wentworth, W. E. *J. Chem. Phys.* **1975,** *63*, 3183. [h] Kuder, J. E.; Pochan, J. M.; Turner, S. R.; Hinman, D. T. *J. Electrochem. Soc.* **1978,** *125*, 1750.

Our designation of TCVDMA as the donor in its TNF complex and as the acceptor in its complex with DMA is in accord with the available data, summarized in Table II, concerning ionization energies, electron affinities, and redox potentials of these molecules. Thus, from Table II, TCVDMA is more easily oxidized and less readily reduced than TNF and it is less easily oxidized and more easily reduced than DMA. The data of Table II are necessary but not sufficient conditions for the isolation of the new complexes described herein. The tendency of TCVDMA to complex with aromatic solvents is a major reason for this statement. The presence of the strongly electron-attracting tricyanovinyl group in a molecule is not a sufficient condition for solid complex formation with DMA. Both 3-tricyanovinylindole (peak of irreversible cathodic wave at −0.60 V vs. SCE, conditions as in Table II) and 4-tricyanovinyl-2,6-dimethylphenol (peak of irreversible cathodic wave at −0.50 V vs. SCE, as above) crystallize unchanged from DMA, in contrast to the behavior of TCVDMA and TNF noted herein.

Distinct charge-transfer maxima separated from the absorption of the components are not observed for these com-

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