Communications

Catalytic Enantioselective Synthesis of Dihydropyrones *via* Formal Hetero Diels–Alder Reactions of "Danishefsky's Diene" with Aldehydes

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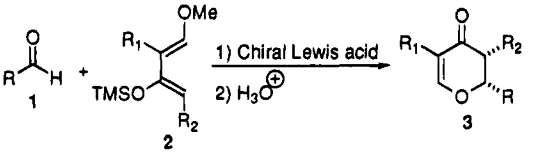
Recently, we reported the results of a study of catalytic enantioselective Mukaiyama aldol reactions between 1-(*tert*-butylthio)-1-[(trimethylsilyl)oxy]ethene and various aldehydes.[1] In this study, $Ti(O\text{-}i\text{-}Pr)_4$/BINOL catalysts originally employed by us for the catalytic asymmetric allylation of aldehydes[2] (CAA reaction) were found to give high levels of asymmetric induction, provided that the reactions were conducted using ether as solvent. Considerably lower levels of asymmetric induction were observed using dichloromethane, the usual solvent of choice for the allylation reactions.

In an attempt to extend these observations to reactions of other useful (silyloxy)alkene nucleophiles, and because of the relevance to certain synthetic targets of interest to us, we have examined reactions between a variety of simple aldehydes and 1-methoxy-3-[(trimethylsilyl)oxy]butadiene ("Danishefsky's diene"). Asymmetric catalysis of formal hetero-Diels–Alder reactions (either directly or *via* a two-stage process) of this type (note eq 1) has been previously reported by a number of investigators,[3] but very few reactions with the parent diene itself ($R_1 = R_2 = H$) have been recorded, these generally with benzaldehyde.[3] Most examples employ oxygenated dienes **2** in which R_1 and R_2 are alkyl groups, cases which were found to give higher enantiomeric excess in Danishefsky's original report.[3a] In fact, there appears to be only one general study of (formal) catalytic asymmetric hetero Diels–Alder reactions of Danishefsky's diene with aldehydes. Corey found that the tryptophan-derived oxazaborolidine catalyst[3e] gave "good yields and moderate enantioselectivities" for the reaction of Danishefsky's diene with representative aldehydes *via* a two step aldol–Michael sequence (note eq 2). We record herein results for this formal hetero Diels–Alder reaction using catalysts generated from (*R*)- or (*S*)-BINOL and $Ti(O\text{-}i\text{-}Pr)_4$, which leads to dihydropyrones with good to excellent enantiomeric excess.



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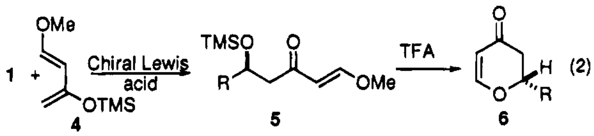


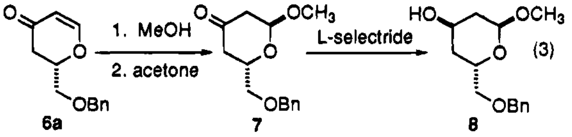
(2)

Selected results from these investigations are shown in Table 1. All reactions employed a BINOL-derived catalyst prepared from (*R*)-BINOL and $Ti(O\text{-}i\text{-}Pr)_4$ according to "method B" previously reported by us[2a] (catalyst prepared using 2:1 BINOL/$Ti(O\text{-}i\text{-}Pr)_4$ stoichiometry in the presence of 4 Å MS and 0.003 equiv of CF_3CO_2H in ether). Other catalyst preparations previously employed ("methods A, C, and D")[4] gave lower enantiomeric excesses, except for the case of benzaldehyde as substrate. This is quite surprising since "method A" (catalyst prepared at 1:1 stoichiometry in the presence of 4 Å MS) proved optimal in the previous Mukaiyama aldol study.[1]

Inspection of the results shown in Table 1 shows that this procedure gives useful levels of asymmetric induction in most cases; poor results were obtained only with benzaldehyde and cyclohexanecarboxaldehyde as substrates. Use of "method A" with benzaldehyde results in considerable improvement (83% yield, 75% ee), but the enantiomeric excess is still not in the synthetically useful range. Comparison to other known catalytic methods is thus not possible, except for the previously mentioned Corey procedure. In that study, benzaldehyde gave the *best* results (100% yield, 82% ee) of the substrates examined; reactions with furaldehyde, dihydrocinnamaldehyde, cyclohexanecarboxaldehyde, and cyclopropanecarboxaldehyde all displayed lower levels of asymmetric induction.[3e]

As in the Corey study, little, if any of the dihydropyrones were produced directly in the initial Lewis acid catalyzed event. The major products at this stage were the Mukaiyama aldol products **5** which were subsequently cyclized (after workup but without isolation) by exposure to CF_3CO_2H in CH_2Cl_2. For preparative purposes, isolation of the aldol intermediates is neither necessary nor desirable.

This formal hetero Diels–Alder process makes dihydropyrones of general structure **6** with reasonable optical purities quite readily available. The adduct derived from α-(benzyloxy)acetaldehyde (97% ee) is known to be an important intermediate en route to compactin and mevinolin.[5] As shown in eq 3 below, structural subunit **8** is available in just three steps using this chemistry.[6] Dihydropyrones derived from protected 3-hydroxypropa-



(3)

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[1] Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363.

[2] (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (c) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543.

[3] (a) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. (b) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (c) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951. (d) Giao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.;Yamamoto, H. *Tetrahedron* **1994**, *50*, 979. (e) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907.

[4] Designations for catalyst preparations as "methods A–D" are used to be consistent with our earlier reports.[1,2]

[5] (a) Heathcock, C. H.; Rosen, T. *Tetrahedron* **1986**, *42*, 4909. (b) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.*, **1986**, *51*, 2487.

[6] Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

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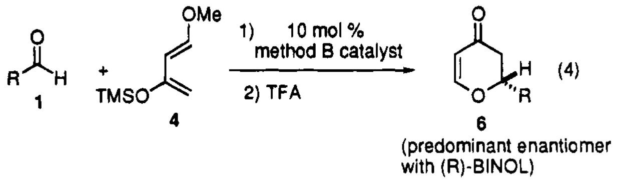
Table 1. Yields and ee's for Dihydropyrones 6



entry[a]	R	*T*, °C (time, h)	yield[b] (%)	% ee[c] (%)
1[d]	Ph	−20 (12)	83	75
2	Ph	−20 (40)	40	55
3	$TBSOCH_2CH_2$	−20 (72)	55	92
4	$BnOCH_2$	−20 (40)	60	97
5	furyl	−20 (40)	61	97
6	n-C_8H_{17}	−20 (72)	88	97
7	C_6H_{11}	−20 (72)	69	78
8	$CH_3CH{=}CH$	−20 (72)	50	86

[a] Unless otherwise specified, all reactions were carried out using 10 mol % of method B catalyst as detailed in the experimental procedure. [b] All yields are isolated yields. Satisfactory spectral data (^1H NMR, ^{13}C NMR, IR) and C, H combustion analyses were obtained for all new compounds. [c] In all cases ee was determined by HPLC using a chiral column (Chiracel OD-H). [d] This entry was conducted using 20 mol % of "method A" catalyst.

nal (note entry 3 in Table 1) are also known to be useful synthetic intermediates for the construction of dihydropyrans of the type found in the complex marine natural products swinholide and scytophycin C.[7]

The BINOL/Ti(O-*i*-Pr)$_4$-derived Lewis acids originally developed for the catalytic allylation of aldehydes are thus proving to be of considerable utility in other reaction types susceptible to catalysis by Lewis acidic metals.[8] A representative experimental procedure is summarized below.

Preparation of (*R*)-2-[(Phenylmethoxy)methyl]-2,3-dihydro-4*H*-pyran-4-one. A mixture of (*R*)-(+)-BINOL (28.6 mg, 0.1 mmol), 1 M Ti(O-*i*-Pr)$_4$ in CH_2Cl_2 (50 μL, 0.05 mmol), CF_3CO_2H (0.003 mL, 0.5 M in CH_2Cl_2), and oven-dried powdered 4 Å molecular sieves (200 mg) in ether (2.0 mL) was heated at reflux for 1 h. The red-brown mixture was cooled to rt, and 2-(benzyloxy)-acetaldehyde (75.0 mg, 0.5 mmol) was added. The mixture was stirred for 5 min and cooled to −78 ° C, Danishefsky's diene (103 mg, 0.59 mmol) was added, and the contents were stirred for 10 min and then placed in a −20 °C freezer for 40 h. Saturated $NaHCO_3$ (0.5 mL) was added, and the contents were stirred for 1 h and then filtered through a plug of Celite. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was dissolved in CH_2Cl_2 (6 mL) and cooled to 0 ° C. To this solution was added trifluroacetic acid (0.025 mL). After the mixture was stirred for 1 h, saturated $NaHCO_3$ (3 mL) was added, the contents were stirred for 10 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography, eluting with 10% acetone in hexanes, to afford 65.4 mg (60%) of product as an oil. The enantiomeric purity was 97% by HPLC analysis using a chiral column (Chiracal OD-H). The eluent was 10% 2-propanol in hexanes, with a flow rate of 0.5 mL/min; the t_R of the (*S*)-isomer (33.7 min) is shorter than that of the major (*R*)-isomer (39.9 min).

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Supporting Information Available: Spectral and analytical data (^1H NMR, ^{13}C NMR, IR, C,H analyses, and HPLC analyses) for the dihydropyrone products corresponding to entries 3 and 6 of Table 1 (12 pages).

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[8] We suggest the acronym "BITIP", from **BI**NOL/**Ti**tanium **i**so**p**ropoxide, for these catalysts.