J. Am. Chem. Soc. **1995,** *117,* 2363−2364 2363

Pronounced Solvent and Concentration Effects in an Enantioselective Mukaiyama Aldol Condensation Using BINOL−Titanium(IV) Catalysts

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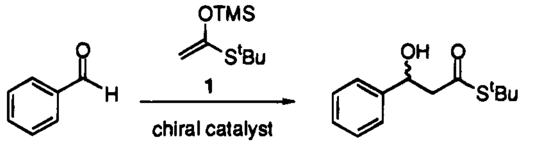
Received November 4, 1994

Recently we have reported reaction protocols for the catalytic asymmetric allylation (CAA reaction) of aldehydes using allylstannanes and chiral Lewis acid catalysts prepared from (*R*)- or (*S*)-BINOL and Ti(O-*i*-Pr)$_4$.[1] These procedures have proven remarkably efficient and especially convenient, since the chiral catalysts are prepared very simply in *ca.* 1 h from commercially available reagents. As the enantioselectivity exhibited in these reactions would appear to be derived solely from the structure of the chiral Lewis acid−aldehyde complex, it seemed obvious that other Lewis acid promoted reactions might be susceptible to enantioselective catalysis using the same procedures. We record herein the development of methodology using these catalysts for the catalytic enantioselective Mukaiyama aldol condensations[2] of 1-(*tert*-butylthio)-1-((trimethylsilyl)oxy)ethene with aldehydes to give β-hydroxy thiol esters in high yields and with excellent enantiomeric excesses.[3] In addition, surprisingly large and unexpected solvent effects on both rates and enantioselectivity are observed in this system which are *not* paralleled in the allylstannane addition reactions.

Results for the prototype reaction of benzaldehyde with **1** are summarized in Table 1 below.[4]

Table 1. Yields and Enantiomeric Excesses for Reaction of **1** with Benzaldehyde



(1)

entry	meth^a	solvent^b	mol % of catalyst	reactn conditns	yield (%)	ee (%)
1	A	CH_2Cl_2	10	0 °C, 16 h	27	36
2	D	CH_2Cl_2	10	0 °C, 16 h	45	62
3	D	$CHCl_3$	10	23 °C, 48 h	<10	43
4	D	toluene	10	0 °C, 16 h	54	89
5	D	toluene	20	0 °C, 16 h	54	95
6	D	toluene	50	0 °C, 16 h	36	87
7	D	toluene	10	23 °C, 16 h	36	70
8	D	ether	20	0 °C, 10 min	93	89
9	D	ether	10	0 °C, 16 h	82	65
10	*A*	*ether*	*20*	*−20 °C, 4 h*	*90*	*97*
11	A	ether	10	−20 °C, 16 h	71	97
12	A	ether	10^c	−20 °C, 16 h	45	92
13	A	ether	20	0 °C, 16 h	80	93
14	D	ether	20	−20 °C, 16 h	86	91

^{a} Descriptions of methods as A or D are used as consistent with our earlier reports.[1] ^{b} All reactions were 0.25 M in benzaldehyde unless otherwise indicated. ^{c} This reaction was 0.50 M in benzaldehyde.

We began by examining the reaction of **1** with benzaldehyde using the optimum conditions previously described for the corresponding allylstannane reaction, in which the catalyst was prepared by heating (*S*)-BINOL, Ti(O-*i*-Pr)$_4$, and 4 Å MS in refluxing CH_2Cl_2 for 1 h, with 1:1 stoichiometry of BINOL/Ti (method A).[1a,c] Reaction using 10 mol % of this catalyst at 0 °C for 16 h (entry 1) gave very low conversion (27% isolated yield) and also very low enantiomeric excess (30%) when compared to previous results using allyltri-*n*-butylstannane[1a] or methallyltri-*n*-butylstannane.[1c] Use of method D[1b,c] (catalyst prepared simply by stirring a solution of (*S*)-BINOL and Ti-(O-*i*-Pr)$_4$ at 2:1 stoichiometry for 1 h), again in CH_2Cl_2, improved both the yield and enantiomeric excess considerably. Attempts to further increase conversion and enantioselectivity using chloroform as solvent,[5] however, gave very poor results (entry 3).

With toluene as solvent and 10 mol % of catalyst, a dramatic improvement in ee was observed (to 89%, entry 4) but conversion (54% yield after 16 h at 0 °C) remained a problem. Increasing the amount of catalyst to 20 mol % (entry 5) in an attempt to increase conversion surprisingly had no effect on yield, but did significantly increase the ee, from 89 to 95%. However, a further increase in the mol % of catalyst employed (to 50%, entry 6) *diminished* both conversion and enantiomeric excess. Surprisingly, returning to the 10 mol % level and increasing the reaction temperature (to 23 °C, entry 7) also *decreased* conversion, as well as diminishing the ee.

Optimal conditions were established using ether as solvent. Using the 20 mol % of catalyst (which had proven optimal in toluene) prepared according to the simple method D protocol in ether at 0 °C resulted in an extremely rapid reaction *which was complete within 10 min.* Isolation and purification (entry 8) provided a 93% isolated yield of product with 89% ee. In view of this striking rate acceleration observed in ether, it seemed likely that considerably less catalyst could be used successfully. However, simply changing from 20 to 10 mol % of catalyst gave only 82% yield *after 16 h* at 0 °C (entry 9), and the reaction was still incomplete (benzaldehyde remaining) by TLC analysis. The enantiomeric excess was also considerably diminished.

However, very good success was achieved using method A in ether[6] at −20 °C with the amount of catalyst (20 mol %) which had proven optimal using method D. Thus, under these conditions (entry 10) a 90% isolated yield was achieved with a 4 h reaction time, and the product was formed with 97% enantiomeric excess. Decreasing the catalyst loading to the 10 mol % level resulted in the same enantiomeric excess, but with somewhat diminished yield (71% after 16 h, entry 11). The same reaction conducted at twice the concentration (entry 12)

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[1] (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.

[2] (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973,** 1011. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974,** *96,* 7503.

[3] (a) While our own work was in progress, Mikami and Matsukawa reported the use of the Mikami−Nakai ene catalyst[3b−e] (prepared from BINOL, $TiCl_2$(O-*i*-Pr)$_2$, and 4 Å MS) in asymmetric Mukaiyama reactions with **1** and the ethyl derivative corresponding to **1**: Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994,** *116,* 4078. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989,** *111,* 1940. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990,** *112,* 3949. (d) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992,** 255. (e) Mikami, K.; Shimuzu, M. *Chem. Rev.* **1992,** *92,* 1021. (f) Very recently, Carreira and co-workers reported catalytic symmetric Mukaiyama reactions using a new binaphthyl-based chiral Lewis acid and silyl enol ethers of methyl or ethyl acetate, with very high yields and enantiomeric excesses: Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994,** *116,* 8837. (g) The Carreira paper contains an excellent bibliography of recent efforts toward asymmetric catalysis of the Mukaiyama aldol reaction.

[4] The initial reaction products are generally TMS ethers; in some cases, mixtures of TMS ethers and the corresponding free alcohols were obtained. In all cases, the yield refers to the isolated yield of free alcohols obtained by hydrolysis of the crude reaction product (10% HCl−MeOH, 23 °C, 10 min) followed by chromatographic purification.

[5] Some reactions of methallyltri-*n*-butylstannane with aldehydes[1c] show a significant rate acceleration in chloroform as compared to the same reactions in CH_2Cl_2: Keck, G. E.; Krishnamurthy, D. Unpublished results.

[6] Use of method A in toluene (20 mol %, −20 °C) gave a very sluggish reaction with little conversion even after 72 h.

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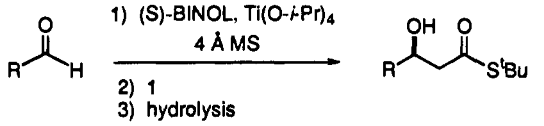
Table 2. Isolated Yields and Enantiomeric Excesses for Various Aldehydes



(2)

entry[a]	R	yield[b] (%)	ee[c] (%)
1	Ph	90	97
2	$PhCH_2CH_2$	80	97
3	n-C_8H_{17}	74	98
4	furyl	88	>98
5	c-C_6H_{11}	70	89
6	PhCH=CH	76	89
7	$PhCH_2OCH_2$	82	>98[d]

[a] All reactions used 20 mol % of catalyst prepared in ether according to method A, with reaction at −20 °C for *ca.* 12 h in ether (4 mL/mmol of substrate). [b] All yields are isolated yields of β-hydroxy thiol esters. [c] Enantiomeric excess was determined by ^{1}H NMR with Eu(hfc)$_3$. [d] ^{19}F NMR of the derived Mosher ester was employed in this case.

surprisingly gave even *lower* yield. As expected, reaction at 0 °C (entry 13) decreased the ee, while use of method D at the 20 mol % level at −20 °C (entry 14) also gave slightly poorer results than the optimal method A procedure represented by entry 10.

Having identified conditions which afforded high yield and enantiomeric excess with benzaldehyde, we then employed these conditions in catalytic asymmetric Mukaiyama aldols with a representative range of alkyl, aryl, and α,β-unsaturated aldehydes. The results are tabulated in Table 2 and can be seen to be uniformly excellent in terms of both isolated yield and enantiomeric excess. The enantiospecificity of the reaction was the same as previously observed for the stannane reactions; use of (*S*)-BINOL afforded *S* product with benzaldehyde.[7]

The results described herein allow for a facile and convenient preparation of β-hydroxy thiol esters with high enantiomeric excess directly from commercially available materials. This procedure nicely compliments the previously described allylation reactions in that aldehydes are accessible from the products *via* reduction, rather than oxidation. In addition, the results obtained in the development of this reaction offer several caveats:

(a) Dramatic and unpredictable solvent effects on both rate and enantioselectivity may be encountered using chiral Lewis acids of the BINOL−Ti^{IV} type. Optimal reaction conditions for one reaction type may not transfer even to reactions which may seem closely related.

(b) It appears that reactions using chiral Lewis acids of the BINOL−Ti^{IV} type operate most efficiently within a fairly narrow concentration range (*i.e.*, mol % of catalyst utilized). Unusual concentration effects (*e.g.*, decreased yields and/or ee's with higher mol % of catalyst) may be related to the nonlinear effects often observed with such catalyst systems.[1,8,9] Clearly, those interested in applications of such methodology should endeavor to employ the procedures precisely as described, paying particular attention to the concentrations used.[10,11]

Acknowledgment. Financial support was provided by the National Institutes of Health through Grant GM-28961.

Supplementary Material Available: Representative experimental procedures, ^{1}H NMR spectra for products, and ^{1}H NMR spectra used for determination of enantiomeric excess with Eu(hfc)$_3$ (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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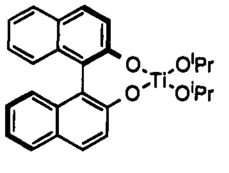
[7] The absolute configuration was determined by comparison of optical rotation with that previously reported: Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. Likewise it was verified that (*S*)-BINOL gave *R* product with nonanal and *S* product with α-(benzyloxy)acetaldehyde. The same sense of addition is assumed for the other cases.

[8] The reactions described herein, as expected from the unusual concentration effects noted, are also nonlinear. Use of (*S*)-BINOL of 50% ee with benzaldehyde and the optimum conditions represented by entry 10 of Table 1 gave a 50% yield of product with 91% ee.

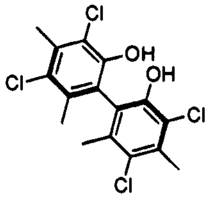
[9] (a) Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623. (b) Mikami, K.; Tereda, M. *Tetrahedron Lett.* **1992**, *48*, 5671. (c) Guillaneuse, D.; Zhao, S.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.

[10] (a) It should be noted that both the structures of the catalysts and the mechanisms involved in these reactions remain unknown. Nonetheless, the structure of one of the catalysts employed by us[1] has been represented[10b] as i, presumably for convenience. In the absence of definitive experimental data, we regard such structures as potentially useful shorthand for indicating the stoichiometry of reagents used to prepare the catalysts, but fear that such depictions may be confused with conventional chemical representations of real structures. The nonlinear effects observed by us[1c] and by Mikami and Nakai[9] cannot be accommodated on the basis of structures such as i alone. (b) Bach, T. *Angew Chem., Int. Ed. Engl.* **1994**, *33*, 417.



i

[11] (a) In a very recent publication, Corey has reported two very different X-ray crystallographic structures for materials prepared from bis(phenol) ii and TiCl$_4$ or Ti(O-*i*-Pr)$_4$. Both are dimeric structures containing two bis(phenol) units and two titaniums. With Ti(O-*i*-Pr)$_4$, both oxygens from one bis(phenol) bind to the same titanium atom, while *with TiCl$_4$, each phenolic oxygen from one bis(phenol) is bonded to a different titanium atom in a "criss-cross" arrangement.* (b) Corey, E. J.; Letavic, M. A.; Noe, M. C.; Sarsher, S. *Tetrahedron Lett.* **1994**, *35*, 7553. (c) The Corey findings should serve to reinforce our comments regarding catalyst structure[10] and may be relevant to the structure of the Mikami−Nakai catalyst[3a−e] (prepared using TiCl$_2$(O-*i*-Pr)$_2$) as compared to our own (prepared using Ti(O-*i*-Pr)$_4$).



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