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A Catalytic Asymmetric Vinylogous Mukaiyama Aldol Reaction

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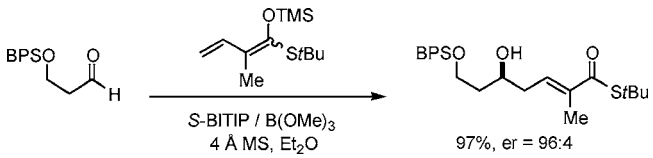
ABSTRACT



A vinylogous Mukaiyama aldol reaction, conducted using 10 mol % of a BITIP catalyst and $B(OMe)_3$ as an additive, effects an enantioselective four-carbon chain extension to give versatile *E*-α,*β*-unsaturated thiol esters.

The Mukaiyama aldol addition is a powerful method for asymmetric C−C bond construction especially in the field of polypropionate natural product synthesis. Stereoselectivity is typically obtained through substrate control in additions to aldehydes bearing α- or *β*-stereocenters or through the control of a chiral catalyst in cases using a facially unbiased substrate or in order to override an inherent facial selectivity.[1] A number of systems consisting of reactivity-matched nucleophile and chiral catalyst pairs have been developed for this type of addition,[2] and several catalytic methods have also been established for the vinylogous version of this reaction.[3]

The asymmetric additions of several functionalized and unfunctionalized allylstannanes utilizing a selection of BINOL/$Ti(O\text{-}i\text{-}Pr)_4$ (BITIP) systems, differing in the ligand to metal ratio and the method of preparation, have previously been developed in our laboratory.[4,5] In addition to allylstannane additions, the BITIP system has also been used as an efficient catalyst in the addition of thiol ester derived Mukaiyama reagents to aldehydes, giving rise to the products in high yield and excellent enantioselectivity.[6] We were hopeful that we could extend these asymmetric Mukaiyama aldol reactions to encompass vinylogous cases, which would afford access to *δ*-hydroxy-α,*β*-unsaturated thiolesters, potential intermediates of interest with respect to structures such as preswinholide and acutiphycin (Figure 1).[7]

We investigated the use of this direct method employing diene **4** (Scheme 1). Although preliminary experiments using this reagent afforded good yields in additions to aldehydes using $BF_3{\cdot}OEt_2$ as Lewis acid, the use of reagent **4** in catalytic asymmetric additions using BITIP catalysis was not promising. Reactions using this reagent were far more sluggish than typical allylation reactions using this catalyst, and yields were lower. Aliphatic aldehydes required extended

(1) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.

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(3) For recent reviews, see: (a) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (b) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43. (c) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

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(6) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363.

(7) For a related asymmetric BITIP-mediated vinylogous Mukaiyama addition developed by Ian Paterson and co-workers, see: (a) Paterson, I.; Findlay, A. D.; Florence, G. J. *Org. Lett.* **2006**, *8*, 2131. (b) Paterson, I.; Florence, G. J.; Heimann, A. C.; Mackay, A. C. *Angew. Chem., Int. Ed.* **2005**, *44*, *1130*. (c) Paterson, I.; Davies, R. D. M.; Heimann, A. C.; Marquez, R.; Meyer, A. *Org. Lett.* **2003**, *5*, 4477.

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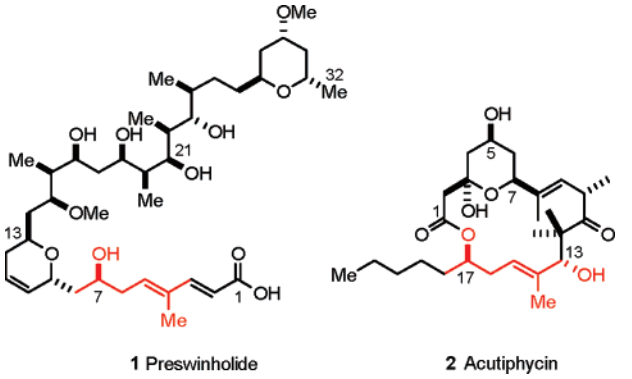
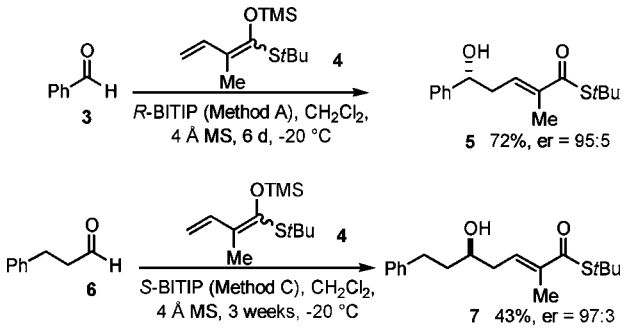


Figure 1. Structures of preswinholide and acutiphycin.

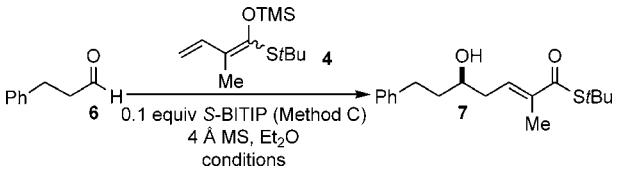
reaction times at −20 °C or ambient temperature (Table 1, entries 1 and 2). Reasonable results were obtained only with benzaldehyde.[8] Nonetheless, the formation of addition products with reasonable enantiomeric ratios (er's) encouraged us to investigate means to increase the reactivity between aliphatic aldehydes and reagent **4** without sacrificing enantioselectivity.

Scheme 1. Initial Catalyst-Controlled Additions Using Reagent **4**



A number of efforts have been made to gain insight into the mechanism of action of the BITIP catalyst system;[9−12] however, an understanding of the exact role of each individual component remains elusive. In addition, seemingly

Table 1. Conditions for Asymmetric Vinylogous Mukaiyama Additions



entry	$B(OMe)_3$ (equiv)	T (°C)	time	yield (%)	er
1[a]	-	rt	3 weeks	60	95:5
2[a]	-	−20	3 weeks	43	97:3
3	-	rt	4 d	8	91:9
4	0.05	rt	4 d	58	94:6
5	0.1	rt	4 d	51	94:6
6	0.2	rt	4 d	60	93:7
7	0.3	rt	4 d	49	92:8
8	0.4	rt	4 d	56	92:8
9	0.5	−20	4 d	36	95:5
10	0.5	0	4 d	79	92:8
11	0.5	rt	4 d	95	93:7

entry	$B(O\text{-}i\text{-}Pr)_3$ (equiv)	T (°C)	time	yield (%)	er
12	0.5	rt	4 d	37	93:7

[a] CH_2Cl_2 was used as solvent.

subtle changes in the ligand−metal stoichiometry or method of catalyst preparation can have dramatic effects on the reaction outcome, and some evidence for the formation of different catalytically active BITIP species has emerged.[4,5b,9−11] Despite the complexity of these systems and lack of detailed understanding of catalyst structures, overall reaction mechanisms, and solvent effects, a number of additives and BINOL derivatives have been explored by several groups in an attempt to enhance the performance of the parent BITIP system.[13] One of the additives used in

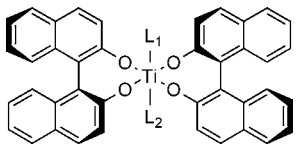


Figure 2. Simplified representation of an *S*-BINOL/titanium complex.

combination with the original BITIP catalyst is $B(OMe)_3$,[13b] which allowed for shorter reaction times while maintaining

(8) (a) Krishnamurthy, D. Ph.D. Thesis, University of Utah, Salt Lake City, UT, 1995. (b) Li, X.-Y. Ph.D. Thesis, University of Utah, Salt Lake City, UT, 1998.

(9) (a) Mikami, K.; Matsumoto, Y.; Xu, L. *Inorg. Chim. Acta* **2006**, *359*, 4159. (b) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267. (c) Terada, M.; Matsumoto, Y.; Nakumara, Y.; Mikami, K. *Chem. Commun.* **1997**, 281. (d) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639.

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(11) (a) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336. (b) Davis, T. J.; Balsells, J.; Carroll, P.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 699. (c) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233. (d) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585.

(12) (a) Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321. (b) Corey, E. J.; Letavic, M. A.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 7553.

(13) (a) For a recent review on the use of BINOL as a metal ligand, see: Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (b) Yu, Ch.-M.; Choi, H.-S.; Yoon, S.-K.; Jung, W.-H. *Synlett* **1997**, 889. (c) Yu, C.-M.; Choi, H.-S.; Jung, W.-H.; Kim, H.-J.; Shin, J. *Chem. Commun.* **1997**, 761. (d) Yu, Ch.-M.; Choi, H.-S.; Jung, W.-H.; Lee, S.-S. *Tetrahedron Lett.* **1996**, *37*, 7095. (e) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613. (f) Matsukawa, S.; Mikami, K. *Tetrahedron: Asymmetry* **1997**, *8*, 815.

high yields and er's in reactions using allyltributylstannane as the nucleophile.[13b]

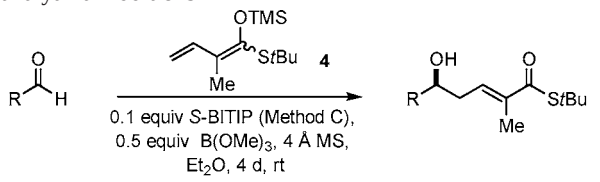
Given this precedent, we decided to examine the effect of $B(OMe)_3$ in the reactions of diene **4** with aliphatic aldehydes. After considerable optimization, reaction of diene **4** with hydrocinnamaldeyde **6** in the presence of *S*-BITIP (method C)[14] and $B(OMe)_3$ in ether as solvent provided addition product **7** in 95% yield and with a 93:7 er (Table 1, entry 11). Use of 0.5 equiv of $B(OMe)_3$ was established as the minimum amount necessary to achieve this reaction outcome; use of additional $B(OMe)_3$ did not have any other observable effects. The configuration of the new alcohol was established to be *R* by Mosher ester analysis;[15] this is the configuration expected for a BITIP-catalyzed addition using *S*-BINOL.[4−6] In these experiments, reaction times were standardized at 4 days for comparison purposes.

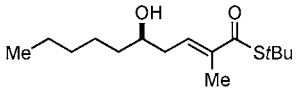
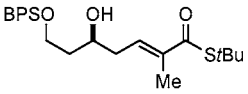
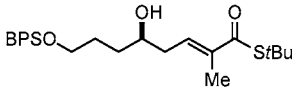
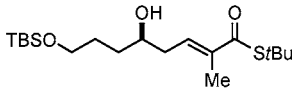
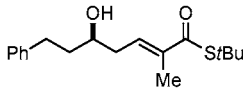
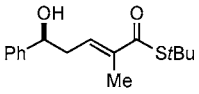
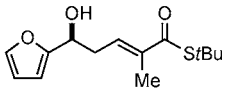
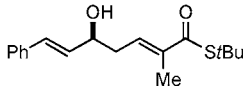
Table 2 summarizes the yields and er's obtained for the catalytic asymmetric addition of diene **4** to several other aldehydes. Again, reaction times were standardized at 4 days, although most of the additions appeared to be complete within 2 days. Aliphatic aldehydes generally gave high yields coupled with good enantioselectivity. Although the yields for aromatic aldehydes were high, the enantioselectivity was slightly lower. The most surprising result is that enantioselectivity was essentially lost with an α,β-unsaturated aldehyde, and the yield was also low (Table 2, entry 8). This stands in marked contrast to the allylation and Mukaiyama reactions, where the same substrate has been shown to afford 62% yield with 95:5 er[4b] and 76% yield with 95:5 er, respectively.[6]

The reason for the beneficial effect of $B(OMe)_3$ in this catalytic addition reaction is not obvious. A number of mechanistic possibilities in which $B(OMe)_3$ could participate as part of a catalytic cycle before, during, or after the addition can be envisioned. It has been suggested that $B(OMe)_3$ is simply a "turnover-reagent" which facilitates the dissociation of the product from the reaction complex.[13b] Numerous other alternatives include the formation of a catalytically active BINOL/boron or bimetallic BITIP/boron complex, the formation of a vinylogous boron enol ether by transmetalation of $B(OMe)_3$ with reagent **4**, and the generation of a reactive enolate through alkoxide assisted desilylation of reagent **4**. Another a priori possibility is that $B(OMe)_3$ complexes oxygen in the BINOL ligand and enhances the Lewis acidity, and hence reactivity, of the BITIP catalyst.

In an attempt to develop an understanding as to the role of the various catalyst components, we conducted additonal experiments which employed NMR spectroscopy as a tool. A brief survey of deuterated solvents established $CDCl_3$ as a suitable replacement solvent for ether in the preparation of the "active" catalyst system (Table 3).

Table 2. Isolated Yields and er's for Asymmetric Vinylogous Mukaiyama Additions



entry	product	yield (%)	er[a]
1		90	95:5
2		97	96:4
3		92	95:5
4		93	92:8
5		95	93:7
6		quant	91:9
7[b]		quant	91:9
8		31	70:30

[a] er determined by chiral HPLC. [b] er determined by ^1H and ^{19}F NMR analysis of the corresponding Mosher ester.[15]

Unfortunately, ^{11}B NMR offered little insight as to the role of $B(OMe)_3$ in the catalytic cycle. However, the use of ^1H NMR gave some intriguing results. Here all spectra had to be taken after removal of the molecular sieves; otherwise, no useful spectra could be obtained. The spectra for three cases are summarized here: (a) the normal reaction protocol without added $B(OMe)_3$, (b) the reaction protocol with added borate, and (c) the spectrum obtained when sieves are removed prior to addition of the borate.

While the signals in the ^1H NMR arising from BINOL and the "*i*-PrO" methyl groups resulted in complex multiplets, the methyl of the "MeO" and the methine of the "*i*-PrO"-containing species were diagnostic.[16] In the parent BITIP system, that is with no added $B(OMe)_3$, all "*i*-PrO" exists in the "protonated form", that is, as isopropyl alcohol (Figure 3a). For the case when $B(OMe)_3$ is present (and after

(14) (a) For details of BITIP preparation according to methods A−D, see ref 4. (b) Method A: Catalyst prepared from optically pure BINOL and Ti(O-*i*-Pr)$_4$ at 1:1 stoichiometry in the presence of 4 Å MS for 1 h at 38 °C. Method B: Catalyst prepared from optically pure BINOL and Ti(O-*i*-Pr)$_4$ at 2:1 stoichiometry in the presence of 4 Å MS and CF_3CO_2H (0.003 equiv relative to aldehyde) for 1 h at 38 °C. Method C: Catalyst prepared from optically pure BINOL and Ti(O-*i*-Pr)$_4$ at 2:1 stoichiometry in the presence of 4 Å MS for 1 h at 38 °C. Method D: Catalyst prepared from optically pure BINOL and Ti(O-*i*-Pr)$_4$ at 1:1 stoichiometry for 1 h at 25 °C.

(15) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *95*, 512. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.

(16) "*i*-PrO" and "MeO" designate the entirety of isopropoxide/isopropanol and methoxide/methanol species, respectively.

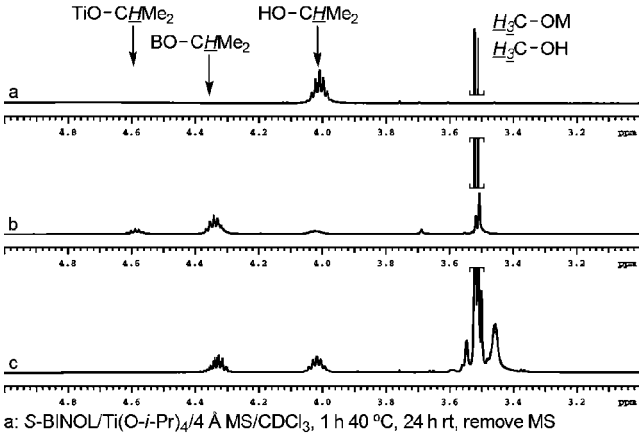
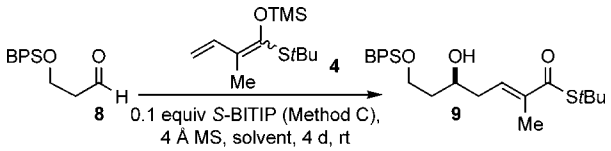


Figure 3. Effect of catalyst preparation and representative 300 MHz ^{1}H NMR Spectra.

the molecular sieves were removed) a minor fraction of the "*i*-PrO" is still protonated; however, the majority is bound to boron and another small fraction to titanium (Figure 3b). On the other hand, there is only a small signal corresponding to "MeO". When the molecular sieves were removed prior to addition of $B(OMe)_3$, "*i*-PrO" was found in equal amounts in the protonated form and bound to boron (Figure 3c); the "MeOH" signal, however, is large. These observations reveal a critical relationship between $B(OMe)_3$ and the 4 Å MS in the BITIP/$B(OMe)_3$ system. We suggest that the *i*-PrO groups observed on boron derive from exchange of free *i*-PrOH with $B(OMe)_3$. This exchange is facilitated by the presence of sieves (spectra b vs c). This reaction would liberate methanol, but essentially no methanol is observed if sieves are present (spectrum b). Hence the methanol is apparently sequestered by the 4 Å MS.[17] Hydrolysis of the methoxy borate by water contained in the sieves would also liberate methanol which would then be sequestered by the sieves. The ability of molecular sieves to act as a source of water and to facilitate the formation of titanium μ_3-oxo species has previously been demonstrated.[9]

The function of the 4 Å MS in this catalyst system is complex and also seems to extend beyond its role of capturing MeOH.[9−11] Reactions with diene **4** which parallel the procedures for catalyst preparation giving rise to spectra b and c above were also carried out. As expected, a low yield of addition product **9** was obtained when $B(OMe)_3$ was added *after* removing the molecular sieves from the BITIP catalyst prepared according to method C (Table 4, entry 1), and the enantioselectivity was also lowered. When $B(OMe)_3$ was added *before* the molecular sieves were removed, a good chemical yield was obtained (Table 4, entry 2); however, the er was again below any of those measured for this addition in the presence of molecular sieves. These data suggest that participation of the 4 Å MS is not limited to promoting formation of the active catalyst as in related systems,[9] but that the 4 Å MS may also play an important role during the progress of the reaction, as enantioselectivity is reduced significantly in their absence.

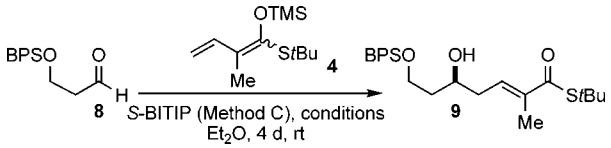
Table 3. Isolated Yields and er's for Asymmetric Vinylogous Mukaiyama Additions in Ether and Selected Deuterated Solvents



entry	solvent	$B(OMe)_3$ (equiv)	yield (%)	er
1	Et_2O	0.5	97	96:4
2	CD_2Cl_2	0.5	55	76:24
3	C_6D_6	0.5	60	94:6
4[a]	$CDCl_3$	0.5	61	97:3
5[a]	$CDCl_3$	-	<20	ND

[a] $CDCl_3$ was filtered through a plug of alumina stored at 110 °C prior to use.

Table 4. Effect of Catalyst Preparation on Isolated Yields and er's for Asymmetric Vinylogous Mukaiyama Additions



entry	catalyst preparation	yield (%)	er
1	*S*-BINOL/Ti(O-*i*-Pr)$_4$/4 Å MS/Et_2O, 1 h 40 °C, remove MS, add $B(OMe)_3$, 24 h rt, add **8** and **4**	11	80:20
2	*S*-BINOL/Ti(O-*i*-Pr)$_4$/4 Å MS/Et_2O, 1 h 40 °C, add $B(OMe)_3$, 24 h rt, remove MS, add **8** and **4**	90	87:13

In summary, we have developed a new catalytic asymmetric Mukaiyama aldol addition with reagent **4**. We believe that this reaction will prove to be a valuable synthetic method given its success with aliphatic aldehydes coupled with the extreme ease of catalyst preparation from commercially available and inexpensive BINOL (ca. $0.70/gram). In addition, our data reveal that *the additive B(OMe)$_3$ is not an unaffected participant in these reactions* but in fact is consumed during catalyst formation.

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Supporting Information Available: Full experimental details as well as spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701851F

(17) (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1968; Vol. 1, pp. 703. (b) Breck, D. W.; Eversole, W. G.; Milton, R. M.; Reed, T. B.; Thomas, T. L. *J. Am. Chem. Soc.* **1956**, *78*, 5963.