Apparent Catalytic Generation of Chiral Metal Enolates: Enantioselective Dienolate Additions to Aldehydes Mediated by Tol-BINAP·Cu(II) Fluoride Complexes

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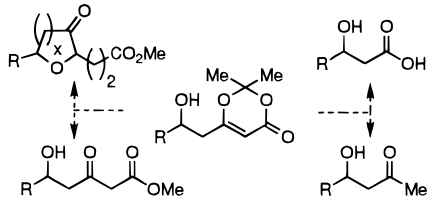
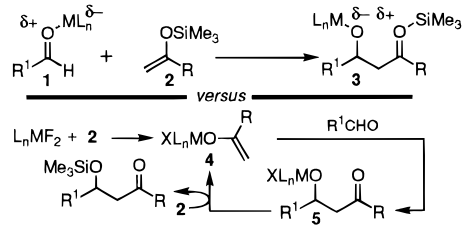
The development of catalytic, enantioselective methods for carbonyl addition reactions is an important intense area of investigation. The majority of approaches reported to date involve the use of chiral Lewis acids that activate the aldehyde component toward addition by enol silanes.[1,2] In contrast, the development and study of catalytic processes that recursively generate chiral enolates which participate in enantioselective addition to aldehydes has little precedence.[3−5] In this paper we report a process which appears to proceed by catalytic generation of a chiral metal dienolate initiated by a transition metal fluoride complex that is readily assembled in situ upon mixing (*S*)-Tol-BINAP,[6] $Cu(OTf)_2$, and $(Bu_4N)Ph_3SiF_2$ (TBAT) in THF. The adducts are isolated for a range of aldehydes in useful yields and up to 95% enantiomeric excess (ee) utilizing as little as 2 mol % catalyst. We have chosen to focus on the use of the silyl dienolate as nucleophile since the acetoacetate products isolated are versatile synthetic intermediates allowing access not only to δ-hydroxy β-keto esters but also acetone and acetate derived aldol adducts (Scheme 1).[7] Moreover, the hydroxy keto esters that may be prepared through this process have played an important role in the ongoing development of HMG-CoA reductase inhibitors and Vitamin D_3 analogues.[8]

In the most commonly exploited mechanism for catalytic enantioselective aldol addition reactions, an aldehyde is activated upon coordination to a Lewis acid to afford **1** (Scheme 2). The electrophilic complex is attacked by the enol silane **2** to produce intermediate **3** that must undergo silylation at a rate faster than the competing background rate of the silyl-catalyzed aldol addition reaction.[9]

Scheme 1



Scheme 2



We reasoned that the labile fluoride counterion in a soft-metal fluoride complex (Ag(I), Cu(II), or Ni(II)) would effect desilylation of an enol silane with concomitant generation of the corresponding enolate **4**.[10] The use of a chiral metal fluoride complex would provide a chiral enolate that might lead to an asymmetric aldol addition to afford **5**.[11] The completion of a catalytic cycle would depend on the metal alcoholate **5** undergoing rapid silylation by the starting enol silane **2**, a key step that would regenerate metal enolate and effect catalyst turnover. This contrasts extant processes involving Lewis acid mediated carbonyl additions wherein the corresponding metal alcoholate intermediate undergoes silylation by the activated silyl species **3**.

Our interest in examining soft-metal fluoride complexes as practical aldol addition catalysts led us to examine commercially available optically active diphosphines as ligands.[12] The synthesis of the desired optically active complexes requires access to anhydrous metal fluoride salt precursors. However, two well-known aspects of metal fluoride chemistry hampered our efforts: (1) preparative methods for the synthesis of simple metal fluoride salts are unwieldy, and, more importantly, (2) metal fluoride salts are difficult to solubilize in commonly employed organic solvents.[13] Thus, we examined a procedure employing the recently reported crystalline, anhydrous fluoride source $(Bu_4N)Ph_3SiF_2$ (TBAT) for the in situ generation of a soft-metal fluoride complex.[14]

We have observed that treatment of a solution of (*S*)-Tol-BINAP[15] with $Cu(OTf)_2$ and $(Bu_4N)Ph_3SiF_2$ produces a complex that effects the enantioselective addition of silyl dienolate **6** to a

(1) For a leading discussion, see: *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.

(2) For a recent discussion of a novel mechanistic model involving aldehyde binding and activation in Lewis acid mediated additions, see: Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 4351 and references therein.

(3) Recently, Denmark has reported a reaction process with dual activation of nucleophilic and electrophilic reaction partners, see: Denmark, S. E.; Wong, K. T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.

(4) (a) For a report in which the involvement of a Pd enolate is suggested, see: Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648 and references therein. (b) For a report in which the involvement of a Ln acetone enolate is suggested, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236.

(5) Related processes wherein putative chiral metal enolates are generated and undergo conjugate additions, isocyanoacetic ester aldol additions, nitroaldols, and enolate amination reactions, see: (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (c) Sasi, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (d) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452.

(6) (*S*)-Tol-BINAP is the accepted abbreviation for (*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl, a commercially available diphosphine derivative.

(7) (a) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435 and references therein. (b) Dritz, J. H.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 5579.

(8) (a) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347. (b) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877.

(9) (a) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323. (b) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570.

(10) For a study involving molybdenum, rhodium, and tungsten enolates, see: (a) Slough, G. A.; Bergman R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938. (b) Burkhardt, E. R.; Doney, J. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2022.

(11) Nakamura, E.; Yamago, S.; Machii, D.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 2207.

(12) For a report of Ag(I)·BINAP complexes that effect the addition of allyltributyltin and tin enolates to aldehydes, see: Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723. (b) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319. It is important to note that these systems prescribe high catalyst loading (10 mol %) and that the Ag(I) complex functions as a Lewis acid without metalation of the nucleophile.

(13) For a comprehensive review on the preparation and use of transition-metal fluoride complexes, see: Doherty, N. M.; Hoffman, N. W. *Chem. Rev.* **1991**, *91*, 553.

(14) Oilscher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.

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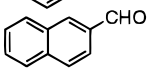
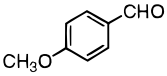
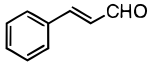
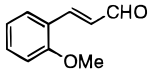
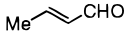
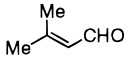
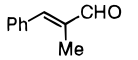
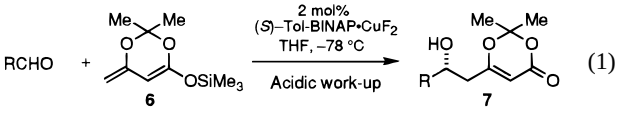
Table 1. Enantioselective Dienolate Additions

Entry	Aldehyde	Yield	ee[a,b]
1		92%	94%
2		86%	93%
3		98%	95%
4		91%	94%
5		93%	94%
6		83%	85%
7		82%	90%
8		48%	91%
9		81%	83%
10		74%	65%

[a] The enantiomeric excess was determined by HPLC analysis of the 2° alcohol product using a Chiralcel OD column or by conversion of the adduct to the corresponding Mosher ester upon treatment with (*R*)−(+)-MTPA-Cl and analysis by ^{1}H NMR spectroscopy, see Supporting Information for details. [b] The absolute configuration for the products was established by comparison to the known compounds or by conversion of each adduct to the corresponding β-hydroxy methyl ketones which were independently synthesized (see ref 17).

range of aldehydes (eq 1 and Table 1).[16] The process is quite

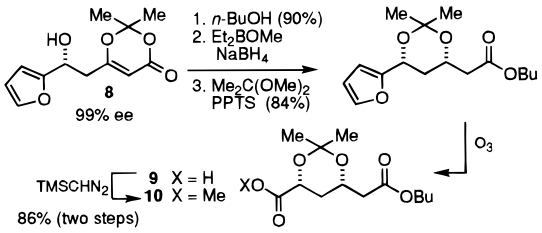


(1)

general for α,β-unsaturated, aromatic, and hetero-aromatic aldehydes; additionally, aliphatic aldehydes have been observed to serve as substrates in the dienolate addition reaction to give products with high levels of enantioselectivity, albeit poor yields (<40%).

The results of some additional experiments highlight the unique aspects of this process in comparison to other metal-catalyzed enol silane aldehyde addition reactions. In support of the hypothesis that a soft-metal enolate is an intermediate in the reaction, we have observed that the reaction can be successfully executed under conditions that directly promote transmetalation of the enol silane in the absence of fluoride. When a solution of enol silane **6** is successively treated with 10 mol % of either MeLi or $(Bu_4N)Ph_3SiF_2$ at 0 °C, followed by 5 mol % of (*S*)-BINAP•$Cu(OTf)_2$ at −78 °C and benzaldehyde, the aldol adduct was isolated in good yields and enantioselectivities. Thus, the fluoride counterion is only responsible for initiating the catalytic cycle and is not important in the generation of an active catalyst. The results of an additional control experiment are consistent with a model wherein the complex is involved in the generation of a metal enolate and not exclusively as a chiral Lewis acid. When the reaction is carried out by treatment of a solution of enol silane **6** and benzaldehyde (−78 °C) with 5 mol % (*S*)-BINAP•$Cu(OTf)_2$ in the absence of the fluoride additive, product formation is rapid at −78 °C; however, analysis of the adduct isolated revealed that it had been formed as a racemate.[18]

Scheme 3



The reaction process we have described may be carried out on preparative scale with as little as 0.5 mol % catalyst without deleterious effects on reaction rate or product enantioselectivity. We have conducted the addition reaction on multigram quantities of furfural (entry 4) to afford the corresponding adduct which is conveniently purified by a single crystallization yielding **8** in >99% ee as determined by HPLC. Following a short sequence of facile reactions, acid **9** and its corresponding methyl ester **10** were prepared (Scheme 3); such intermediates are important building blocks in the synthesis of HMG-CoA reductase inhibitors.[19]

A new catalytic, enantioselective aldehyde addition process is described which provides an efficient alternative to the well-established methods for conducting enantioselective Mukaiyama aldol reactions which have traditionally involved Lewis-acid mediated additions of *O*-silyl enolates and aldehydes. The salient features of this process include: (1) (*S*)-Tol-BINAP and $Cu(OTf)_2$ are available from commercial sources at a nominal price; (2) dienolate adducts are isolated in excellent yields and useful levels of enantioselectivity. We have demonstrated the utility of this efficient process in the synthesis of **9**, a key intermediate in the synthesis of HMG-CoA reductase inhibitors. Importantly, this study provides a new mechanistic model for the development of catalytic processes for aldehyde addition reactions wherein enol silanes and chiral metal fluoride complexes are used to generate, in a catalytic fashion, metal enolates that undergo enantioselective aldol addition reactions. Continuing investigations in this laboratory will attempt to elucidate the identity of the various intermediate transition-metal complexes and further expand the scope of the process.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (6 pages). See any current masthead page for ordering and Internet access instructions.

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(15) In our intial studies we observed that the use of (*S*)-BINAP as ligand affords the benzaldehyde aldol adduct in 88% ee and 90% yield. A brief examination of other commercially available diphosphines led to identifying (*S*)-Tol-BINAP as the ligand which provides optimal selectivities to date.

(16) The complexes prepared with AgOTf and $Ni(OTf)_2$ were observed to catalyze the addition of silyldienolates to aldehydes, albeit in diminished levels of asymmetric induction.

(17) The absolute configuration of the adducts was established upon hydrolysis of the dioxinones followed by decarboxylation and comparison of the resulting methyl ketones to the same compounds independently prepared using the method of Paterson: Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

(18) For pioneering developments of Cu(II) complexes as Lewis acids, see: Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (b) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.

(19) (a) Boberg, M.; Angerbauer, R.; Fey, P.; Kanhai, W.; Karl, W.; Kern, A.; Ploschke, J.; Radtke, M. *Drug Metab. Dispos.* **1997**, *25*, 321. (b) Konioke, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849.