Catalytic, Enantioselective Dienolate Additions to Aldehydes: Preparation of Optically Active Acetoacetate Aldol Adducts

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The synthesis of optically active β-hydroxy carbonyl compounds using catalytic aldol addition methods typically has utilized O-silyl enol ether derivatives of ketones, esters (ketene silyl acetals), and thioesters.[1,2] By contrast, only recently Sato and co-workers have investigated acetoacetate-derived O-silyl dienolates as nucleophiles.[3] The δ-hydroxy-β-ketoesters and the derived *syn-* and *anti-*β,δ-diol esters, which may be prepared from the adducts of dienolate additions to aldehydes, are ubiquitous structural subunits in biologically active natural products such as the polyene macrolide antibiotics (amphotericin, mycoticin), bryostatins, spongestatins, and compactin.[4-6] These structural subunits are also found in chemotherapeutics, most notably compactin analogs that have been studied as cholesterol-lowering agents.[7] The development of synthetic methods to effect enantioselective dienolate additions to aldehydes would significantly expand the scope of asymmetric aldol processes.[8-10] In this communication, we report a catalytic, enantioselective aldehyde addition reaction which provides direct access to protected acetoacetate aldol adducts. The addition of an O-silyl dienolate to aldehydes is catalyzed by 1–3 mol % of a chiral Ti(IV) complex (**1**) and affords carbinol adducts in 79–97% yields with up to 94% ee. The protected acetoacetate adducts isolated serve as versatile precursors for the preparation of optically active δ-hydroxy-β-keto esters, amides, and lactones.

We previously described enantioselective aldol reactions using chiral Ti(IV) catalyst **1** (0.5–2 mol %), which mediates the addition of aldehydes with the O-SiMe$_3$ ketene acetal of methyl
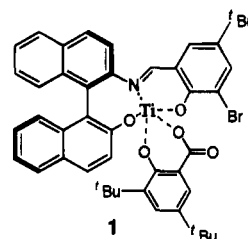

Figure 1. Ti(IV) catalyst for aldol addition reaction.

Table 1. Catalytic Asymmetric Aldol Additions of Dienolate **3**[a]

Entry	Aldehyde	Yield[b]	ee[c,d]
1	$^iPr_3Si$—≡≡—CHO	86%	91%
2	$^tBuMe_2SiO$—_/CHO	97%	94%
3	Ph—/═\\—CHO	88%	92% (99%)[d]
4	Me—/═\\—CHO	95%	92%
5	PhCHO	83%	84% (96%)[d]
6	Ph—_/CHO	97%	80%
7	Bu$_3$Sn—/═\\—CHO	79%	92%

[a] % ee's were determined by preparation of the derived (*S*)-MTPA ester, analysis by ^{1}H NMR spectroscopy, and comparison with authentic racemic material. [b] Yields are reported for two steps (addition and desilylation). [c] The absolute configuration of the adducts was established by comparison with authentic material prepared independently, see ref 16. [d] Optical purity after recrystallization from hexane/EtOAc.

acetate and produces adducts with 94–97% ee's (Figure 1).[11,12] We subsequently observed that the same Ti (IV) catalyst can be employed in aldehyde additions of O-SiMe$_3$ dienolates. After surveying a number of acetoacetate derivatives,[13] we have found that the dienolate derived from 2,2,6-trimethyl-4H-1,3-dioxin-4-one (**2**) (diketene + acetone adduct) is optimal (eq 1). The dioxinone **2** is commercially available at a nominal price; in addition, the silyl dienolate **3** is readily prepared (LDA, Me$_3$-SiCl),[14] purified by distillation, and stable to storage.

$$\text{(1)}$$
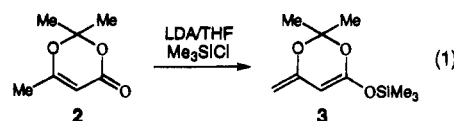
The addition reactions were conducted by dissolution of 1–3 mol % of catalyst **1** in Et$_2$O at 0 °C, followed by addition of 2,6-lutidine (0.4 equiv), aldehyde, and dienolate **3** (Table 1). After being stirred for 4 h at 0 °C, the reaction mixture was quenched and the unpurified product treated with a 10% trifluoroacetic acid/THF solution to effect desilylation.[15] As

(1) For recent developments, see the following, and references cited therein: (a) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995,** *117,* 2363. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994,** *116,* 8837. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994,** *116,* 4077.

(2) For the use of 2-methoxypropene as an enolate equivalent, see: Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995,** *117,* 3649.

(3) During the completion of this manuscript, we became aware of enantioselective additions of dienolates to aldehydes reported by Sato and co-workers. The reaction of the O-SiMe$_3$ enol ether prepared from 2,2,6-trimethyl-4H-1,3-dioxin-4-one with aldehydes in the presence of 20–100 mol % of chiral Ti·BINOL and CAB-derived catalysts/promoters afforded adducts in 10–84% yields and 33–88% ee's; see: (a) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995,** *41,* 1435. (b) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994,** *42,* 839. The work described herein was carried out independently of Sato's work.

(4) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 351–404.

(5) Pettit, G. R. *Pure Appl. Chem.* **1994,** *66,* 2271.

(6) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976,** *29,* 1346.

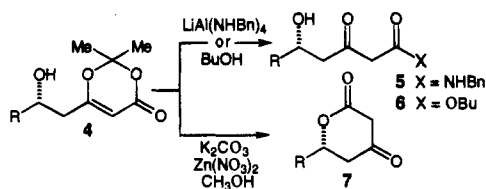(7) Lee, T.-J. *Trends Pharmacol. Sci.* **1987,** *8,* 442.

(8) Aldehyde addition reactions have been described employing 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene to yield upon acidic workup 2-substituted 2,3-dihydro-4H-pyran-4-ones, see: (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992,** *33,* 6907. (b) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995,** *60,* 5998.

(9) For a related heterocycloaddition reaction of adehydes and silyl dienolates, see: Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983,** *105,* 6968.

(10) Diastereoselective dienolate additions have been reported, for example: (a) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1986,** *860.* (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992,** *114,* 2260.

(11) Since our initial communication, we have observed that the aldol additions can be conducted with as little as 0.5 mol % catalyst in equally good yields and enantioselectivities.

(12) The illustrated structure of the Ti(IV) complex **1** is only intended as an heuristic model. Further studies on the solution structure of the complex are in progress.

(13) (a) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979,** *578.* (b) Brownbridge, P.; Chan, T.-H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983,** *61,* 688. (c) Chu, D. T. W.; Huckin, S. N. *Can. J. Chem.* **1980,** *58,* 138.

(14) Grunwell, J. R.; Karapides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991,** *56,* 91.

(15) The O-SiMe$_3$ adducts were isolated in good yields by omitting treatment with TFA/THF; analysis of the optical purity of the adducts was facilitated by conversion to the corresponding carbinols.

Scheme 1

Scheme 2

shown in Table 1, a variety of aldehydes serve as substrates and yield aldol adducts in 79—97% yields. In addition, for each adduct shown, preparation of the derived (*S*)-MTPA ester allowed the extent of asymmetric induction (80-94% ee's) to be assayed by ^{1}H NMR spectroscopy.[16] The absolute sense of induction parallels that which we have previously reported for the aldehyde additions of methyl acetate-derived silyl enol ethers and 2-methoxypropene.[1b,2] In addition, we have observed that some adducts were crystalline and readily enantiomerically enriched. For example, the cinnamaldehyde and benzaldehyde adducts (entries 3 and 5, Table 1) were isolated in >99% ee (60% yield) and 96% ee (73% yield), respectively, after a single recrystallization from 6:1 hexane/EtOAc.

The protected acetoacetate adducts are versatile precursors to optically active δ-hydroxy-β-keto esters, amides, and lactones (Scheme 1). For example, treatment of cinnamaldehyde adduct **4** (R = PhCH=CH—) with LiAl(NHBn)₄ afforded the crystalline (mp 86—87 °C) amide **5** (73%);[17] heating in *n*-BuOH converted **4** (R = PhCH=CH—) to ester **6** in 81% yield;[18] in alkaline MeOH, **4** (R = PhCH=CH—) yielded (79%) crystalline lactone **7** (mp 129—130 °C).[19,20] The synthetic utility of adducts such as **5** and **6** is highlighted by the reaction methods that have been developed for their reduction to the corresponding *syn*- and *anti*-diols.[21,22]

Application of known aldol methods for the construction of δ-hydroxy-β-keto esters and the derived 3,5-diol esters would require iterative carbonyl addition reactions with accompanying

adjustments of oxidation states to install two acetate fragments. Such sequential reactions of acetate subunits parallel the natural polyacetate biosynthetic pathways. The dienolate additions reported herein provide a convergent, enantioselective alternative to the synthesis of 1,3-polyols by appending a protected acetoacetate in a single step.

An important application of the methodology described herein is illustrated for keto ester **8** (Scheme 2), derived from the addition of dienolate **3** and 3-(tributylstannyl)-2-propenal using 1 mol % *ent*-**1**. The use of **8** in Pd⁰-mediated couplings provides access to a wide range of functionalized δ-hydroxy-β-keto esters from the same aldol adduct. Keto esters **11** and **12** and related aryl-substituted analogs have been converted to medicinally important HMG—CoA reductase inhibitors (eq 2).[23]

HMG—CoA Reductase Inhibitors
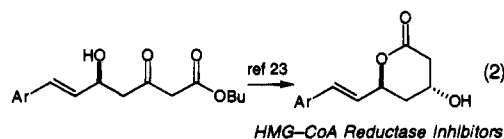
A new catalytic, enantioselective aldehyde addition process is described which employs readily available *O*-SiMe₃ dienolate **3** and as little as 1—3 mol % of Ti(IV) complex **1**, affording aldol adducts in good yields and useful levels of enantioselectivity. The reaction process we have delineated expands the scope of catalytic, enantioselective aldol addition methods by providing direct access to optically active acetoacetate adducts. These can be converted to the versatile δ-hydroxy-β-keto esters, amides, and lactones.[24]

(16) The absolute configuration of the products was established unambiguously by conversion of each of the adducts to the corresponding *n*-butyl δ-hydroxy-β-keto esters. These were compared to authentic samples prepared from the known optically active β-hydroxy esters[1b] via Claisen condensation with the lithium enolate of *n*-butyl acetate.

(17) Solladie-Cavallo, A.; Benchegroun, M. *J. Org. Chem.* **1992**, *57*, 5831.

(18) The *O*-SiMe₃—protected aldol adduct directly isolated from the addition reaction was converted quantitatively into the corresponding ketoester upon heating in *n*-BuOH.
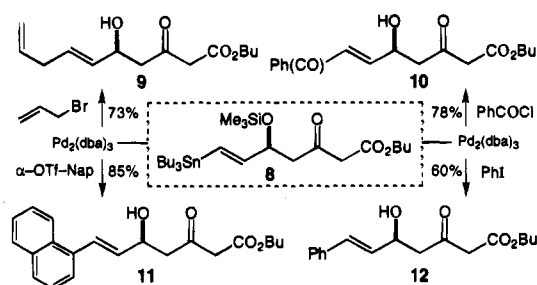
(19) Lactone formation was optimized in the presence of 0.4 equiv of Zn(NO₃)₂, which minimizes the formation of elimination byproducts, see: Buonora, P. T.; Rosauer, K. G.; Dai, L. *Tetrahedron Lett.* **1995**, *36*, 4009.

(20) The stereochemical integrity of the stereocenter in lactone products (for example, **7** (R = PhCH=CH—)) was determined by opening the lactone with benzyl amine to the corresponding β-keto amide **5** (R = PhCH=CH—) and comparison to authentic material prepared via an independent route.

(21) *Syn* reduction: Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419 and references therein.

(22) *Anti* reduction: Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447 and references therein.

(23) 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.

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