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# An *In Situ* Procedure for Catalytic, Enantioselective Acetate Aldol Addition. Application to the Synthesis of (*R*)-(-)-Epinephrine

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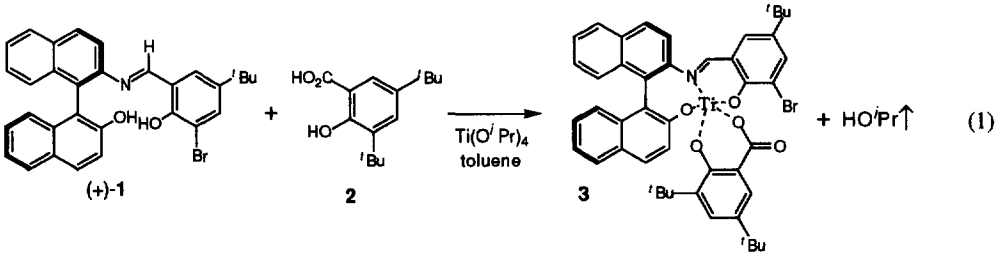
**Abstract.** We report an *in situ* preparation of catalyst **3** which substantially simplifies the experimental procedure for the enantioselective, catalytic acetate aldol addition reaction. The addition of $Me_3SiCl$ and $Et_3N$ circumvents the azeotropic removal of the released isopropanol upon treating ligands **1** and **2** with $Ti(O^iPr)_4$. Importantly, this new procedure maintains the salient features of the catalytic process we originally described: high yields and enantioselectivities, low catalyst loads, and convenient reaction times and temperatures. We have applied the new procedure to an efficient synthesis of (*R*)-(-)-epinephrine from commercially available reagents in an overall yield of 45%. © 1997, Elsevier Science Ltd. All rights reserved.

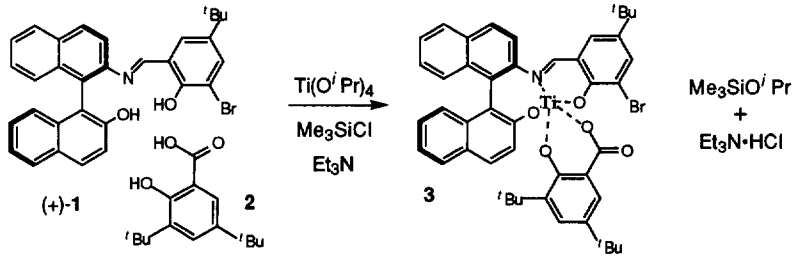
Catalytic, enantioselective processes are important in the development of environmentally benign and economically attractive reactions for the synthesis of optically active molecules. An ideal process must not only deliver products in high yield and optical purity, but must also satisfy a number of important criteria including ease of catalyst preparation and handling as well as practicality of the experimental procedure. We have recently reported a catalytic, enantioselective acetate aldol addition reaction employing tridentate ligand **1**, $Ti(O^iPr)_4$, and salicylic acid **2** (Eq 1 and Eq 2).[1,2] The reported catalyst preparation procedure prescribes the co-mixing of tridentate ligand **1**, salicylate **2**, and $Ti(O^iPr)_4$ in one pot followed by evaporation of solvent with concomitant azeotropic removal of isopropanol.[3] Using the catalyst prepared in this fashion, aldol adducts can be obtained from a wide range of substrates with up to 99% enantiomeric excess.[4] For example, this protocol has been applied on a preparative scale by Simon in an elegant total synthesis of the bacterial metabolite FR-901,228, which is capable of de-transforming tumorigenic cell lines.[5] In an effort to simplify the experimental procedure for generation and use of catalyst **3**, we have sought a procedure which would not require azeotropic removal of the isopropanol generated. In this letter we describe a simple experimental protocol for the preparation of the active catalyst. The addition of 20 mol% $Me_3SiCl$ and 1 equiv $Et_3N$ to a solution of 2 mol% **3** gives a catalyst solution which can be directly utilized in the aldol addition reaction.




(1)

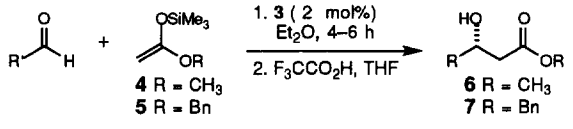
The addition of salicylimine **1** and salicylic acid **2** to $Ti(O^iPr)_4$ releases four equivalents of $^iPrOH$. Using the catalyst preparation procedure originally described, optimal enantioselectivities and yields were observed only when the isopropanol was removed prior to addition of aldehyde and silyl ketene acetal. This is conveniently carried out on the benchtop by concentrating the reaction mixture *in vacuo* with evaporation of the $^iPrOH$•toluene

azeotrope (bp = 80.6 °C). However, preparation of the catalyst on large scale in this transformation necessitates the removal of large volumes of toluene, a procedure which may be cumbersome and time-consuming. We have subsequently investigated alternative procedures for the catalyst preparation. Numerous reports in the literature cite the use of molecular sieves to sequester the isopropanol released from related ligand exchange processes involving $Ti(O^iPr)_4$.[6] However, in the preparation of the aldol catalyst **3**, the use of powdered molecular sieves did not provide an adequate solution. For example, in the presence of powdered 4 Å molecular sieves, the addition of the benzyl acetate derived silyl ketene acetal to cinnamaldehyde (2 mol% **3**, toluene, –20 – 23 °C) gave the aldol adduct in 5% yield and 80% ee. We have observed that the addition of $Me_3SiCl$ and $Et_3N$ to the reaction mixture was effective as an *in situ* trap for isopropanol. Importantly, the $Me_3SiO^iPr$ and $Et_3N$•HCl generated do not interfere with the salient features of the catalytic process we originally described: high yields and enantioselectivities, low catalyst loads, and convenient reaction times and temperatures.



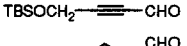
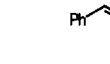

(2)

Using the *in situ* catalyst preparation procedure, silyl ketene acetals undergo addition with various aldehydes to give adducts in 93–99% ee and 89–98% yield (Table 1).[7] The aldol addition reactions can be carried out with as little as 2 mol% catalyst at –20 °C. In addition to the enol silane **4** derived from methyl acetate




(3)

**Table 1.** Aldol additions with the *in situ* catalyst preparation procedure.[a]

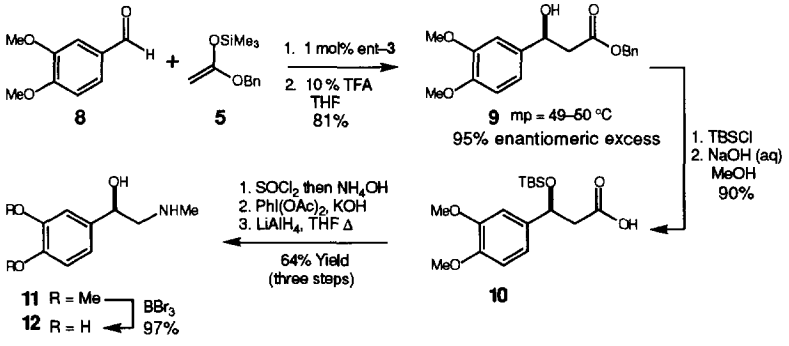
| Entry | Aldehyde | R = $CH_3$ Yield | R = $CH_3$ ee[a] | R = $CH_2Ph$ Yield | R = $CH_2Ph$ ee[a] |
|---|---|---|---|---|---|
| 1 |  | 95% | 98%[b] | 98% | 96%[b] |
| 2 |  | 98% | 93%[b] | 95% | 91%[b] |
| 3 |  | 91% | 99%[c] | 99% | 99%[c] |
| 4 |  | 89% | 97%[b] | 91% | 97%[b] |
| 5 | PhCHO | 94% | 96%[b] | 94% | 96%[b] |

[a] For each entry, the % ee was determined by comparison to an authentic racemic mixture; absolute configuration was established by comparison to known reference compounds (ref 1). [b] Optical purity was determined by HPLC using chiralcel OD column. [c] Optical purity assayed by preparation of the (*S*)-MTPA esters and analysis by $^1H$ NMR .

we have also examined the use of the benzyl acetate derived silyl ketene acetal **5**.[8] The use of **5** in the aldol addition reactions has noteworthy advantages over the use of **4**. For example, the isolation of **4** free of the *C*–silylated product and diisopropyl amine is possible only by careful distillation. In contrast, **5** was isolated in 70% yield upon simple distillation. Additionally, the decreased vapor pressure of **5** allows for easier handling and storage procedures.

As an application of the catalytic, enantioselective aldol addition employing the *in situ* catalyst preparation procedure, the synthesis of (*R*)–(–)–epinephrine **12** was carried out (Scheme 1). Epinephrine was chosen as a prototypical representative of the large class of optically active β–amino arylethanols such as albuterol, terbutaline, isoproterenol, and solatol.[9] These constitute an important class of bioactive molecules which have been developed as β–blockers and have been used in the treatment of glaucoma, cardiovascular disease, and asthma.[10] In general, the syntheses of these compounds have relied on enantioselective aryl ketone reductions.[11] We have developed a convenient seven–step synthesis from the commercially available veratraldehyde **8** ($ 0.08/gram). This commodity aldehyde undergoes aldol addition by silyl ketene acetal **5** in the presence of 1 mol% catalyst **3** to give adduct **9** (mp 49–50 °C) in 81% yield (two steps, aldol addition and desilylation) and 95% ee.

**Scheme 1**




Protection of the secondary alcohol ($^t$BuMe$_2$SiCl, imidazole, DMF) and subsequent saponification of the methyl ester gave acid **10.** The conversion of this acid to the protected aryl ethanolamine was effected by treatment of the corresponding carboxamide of **10** ($SOCl_2$ then $NH_4OH$) with $PhI(OAc)_2$ and KOH to give the *N*-methyl carbamate intermediate.[12] Reduction of this carbamate with $LiAlH_4$ afforded *N*–methyl amine **11** in 64% yield from **10.** Deprotection of the methyl aryl ethers was effected by treatment of **11** with $BBr_3$ to give (*R*)-(-)-epinephrine in 97% yield. The synthetic (*R*)–(–)–epinephrine isolated was identical with authentic material by $^1$H and $^{13}$C NMR spectroscopy as well as chromatographic behavior and optical rotation $[\alpha]_D^{19}$ = –53 °C (c = 2.2, 1N HCl).

The ability to prepare Ti(IV) catalyst **3** *in situ* substantially simplifies the procedure for the enantioselective, catalytic acetate aldol addition reaction. Importantly, the efficiency of the catalytic process (high % ee's and yields with low catalyst loads) is not jeopardized in the presence of the $Et_3NHCl$ and $Me_3SiO^iPr$ byproducts. Moreover, the *in situ* procedure described herein provides a useful alternative to the more commonly employed methods for the removal of isopropanol released in the preparation of Ti(IV) complexes with $Ti(O^iPr)_4$ (evaporation and addition of 4 Å sieves).

The enantioselective aldol addition can be employed for the efficient synthesis of β–arylethanol amines by combining the aldol addition reaction with a Hoffman rearrangement. The synthetic route we have delineated complements alternative processes previously described involving stereoselective ketone reductions. Using a seven–step sequence of reactions, epinephrine is prepared from commercially available reagents in an overall yield of 45%. Future applications of the catalytic aldol addition may be envisioned and are the subject of ongoing investigations.

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3. The azeotropic removal of released isopropanol is a common procedure in the preparation of Ti(IV) complexes, see: Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta.* **1992**, *75*, 2171 and references therein.
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7. A representative procedure: To a 5.5 mM solution of the chiral Schiff base ligand (0.044 equiv) in toluene at 23 °C was added $Ti(^iPrO)_4$ (0.020 equiv). The orange solution was stirred for 1 h at 23 °C prior to adding via cannula a 10 mM toluene solution of 3,5-di-*tert*-butylsalicylic acid (0.040 equiv, dried by dissolving in toluene and concentrating *in vacuo* twice). Stirring was continued for an additional hour at 23 °C and then the solution was cooled to -20 °C. To the cooled solution was added trimethylsilyl chloride (0.20 equiv) followed by triethylamine (1.0 equiv) and the aldehyde (1.0 equiv). After stirring the resulting solution for 15 min, the silyl ketene acetal (2.0 equiv) was added dropwise neat. The reaction was allowed to gradually warm to 23 °C over 6 h before it was quenched by pouring onto water. The mixture was extracted with $Et_2O$; the combined organic extracts were washed with saturated aqueous NaCl solution and dried over anhydrous $Na_2SO_4$. The organic extracts were concentrated *in vacuo* and the residue was dissolved in 10% $CF_3CO_2H$/THF. Once the reaction was complete, the solution was then partitioned between $Et_2O$ and water. The organic layer was washed with 1.0 M NaOH solution followed by brine. The separated organic layer was dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. Purification by chromatography on silica gel gave the β-hydroxy ester adduct.
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