

An air-stable, storable chiral zirconium catalyst for asymmetric aldol reactions

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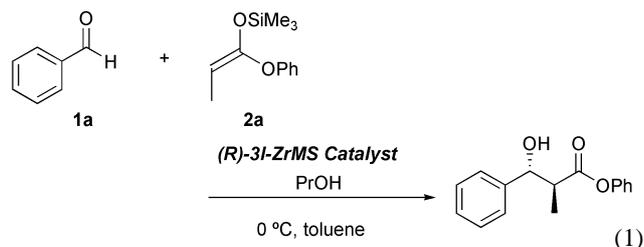
Asymmetric aldol reactions of ketene silyl acetals with aldehydes using an air-stable, storable chiral zirconium catalyst, which could be stored for at least 13 weeks at room temperature, proceeded smoothly to afford the desired adducts in high yields with high selectivity.

Catalytic asymmetric carbon–carbon bond-forming reactions with chiral catalysts provide powerful tools for construction of the basic skeletons of optically active compounds.¹ While several excellent chiral catalysts have been developed, chiral Lewis acids are among the most useful and promising.² However, these catalysts are often sensitive to moisture and/or oxygen even in air, and they decompose rapidly in the presence of a small amount of water. Accordingly, most chiral Lewis acids have to be prepared *in situ* under strictly anhydrous conditions just before use with often tedious handling. They can not be stored for extended periods, and therefore, development of air-stable and storable chiral Lewis acid catalysts is strongly desired.³ To address this issue, we have recently developed an air-stable, storable chiral zirconium catalyst (ZrMS) prepared from zirconium tetra-*tert*-butoxide (Zr(O^{*t*}Bu)₄), 6,6'-bis(pentafluoroethyl)-1,1'-binaphthalene-2,2'-diol (6,6'-(C₂F₅)₂-BINOL), *N*-methylimidazole (NMI), and powdered molecular sieves 5A (MS 5A). ZrMS was shown to be effective for highly enantioselective Mannich-type reactions.⁴ This catalyst was stable in air at room temperature and was easy to handle without requiring strict exclusion of moisture and oxygen, *etc.*†

On the other hand, catalytic asymmetric aldol reactions are powerful tools for preparation of optically active β-hydroxy carbonyl compounds, and are often successfully used in total synthesis of optically active natural products.⁵ Recently, we have developed highly *anti*-selective asymmetric aldol reactions of silicon enolates with aldehydes using a chiral zirconium catalyst, which was prepared from Zr(O^{*t*}Bu)₄, 3,3'-diiodo-1,1'-binaphthalene-2,2'-diol (3,3'-I₂BINOL), primary propanol (PrOH), and a small amount of H₂O *in situ*.⁶ While this catalyst has attained a high level of enantioselectivity with a wide scope of substrates, the catalyst was sensitive to water and even moisture in air. In this communication, we describe an air-stable and storable zirconium catalyst for practical and highly stereoselective asymmetric aldol reactions.

In the course of our investigations, we found that a combination of a chiral zirconium catalyst and powdered molecular sieves (MS) was important to realize storage of the catalyst for extended periods without loss of activity.⁷ The zirconium catalyst with MS (3I-ZrMS) was prepared according to the following procedure. First, a zirconium propoxide propanol complex (Zr(OPr)₄·PrOH),⁸ 3,3'-I₂BINOL, PrOH, and H₂O were combined in toluene at room temperature for 3 h, and then MS (2.5 g mmol⁻¹) was added, and the mixture was stirred for 5 min. After removal of the solvents under reduced pressure at room temperature for 1 h, the 3I-ZrMS catalyst was formed.

In the first trial, we used well-dried MS 5A as a support to prepare the 3I-ZrMS catalyst. The aldol reaction of benzaldehyde (**1a**) with ketene silyl acetal (**2a**), eqn. (1),



was carried out using 5 mol% of the 3I-ZrMS catalyst in toluene at 0 °C in the presence of PrOH (80 mol%). The reaction proceeded smoothly to afford the desired product in 74% yield with high diastereo- and enantio-selectivities (*syn/anti* = 9/91, 85% ee). The selectivities were improved by adding H₂O (10 mol%) (96% yield, *syn/anti* = 9/91, 93% ee). We then employed the 3I-ZrMS catalyst prepared from wet MS 5A which contained 10% (w/w) H₂O, and it was found that additional H₂O was not needed in any catalyst-preparation steps to obtain high yield and selectivities (quantitative yield, *syn/anti* = 5/95, 99% ee).⁹ We also investigated the effect of other molecular sieves, MS 3A and MS 4A; however, a slight decrease of the enantioselectivity was observed (MS 3A: *syn/anti* = 7/93, 91% ee; MS 4A: *syn/anti* = 7/93, 96% ee). The result obtained using 3I-ZrMS was almost comparable to that of the reaction using the zirconium catalyst prepared *in situ*. It is noteworthy that this 3I-ZrMS catalyst was remarkably stable to air and moisture, and that the catalyst could be stored for at least 13 weeks at room temperature without loss of reactivity or selectivity (Table 1).

The 3I-ZrMS catalyst was successfully applied to asymmetric aldol reactions of various substrates, and the results are summarized in Table 2. In the reactions of benzaldehyde with other silicon enolates (**2b** and **2c**), the 3I-ZrMS catalyst worked well, and excellent yields and enantioselectivities were obtained (entries 1–3). In the reactions with the ketene silyl acetal derived from phenyl propionate (**2a**), *anti*-aldol adducts were obtained with high diastereo- and enantio-selectivities (entry 4). The

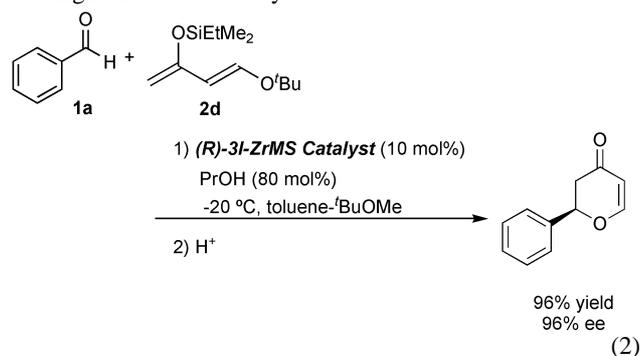
Table 1 Storage of a 3I-ZrMS catalyst in the reaction of benzaldehyde (**1a**) with ketene silyl acetal **2a**

| Entry | Storage time/weeks | Yield (%) (<i>syn/anti</i>) ^b | Ee (%) (<i>anti</i>) ^c |
|-------|--------------------|--|-------------------------------------|
| 1 | 0 | Quantitative (5/95) | 99 |
| 2 | 2 | Quantitative (5/95) | 99 |
| 3 | 6 | Quantitative (5/95) | 99 |
| 4 | 13 | Quantitative (5/95) | 99 |

^a All reactions were performed in toluene at 0 °C for 18 h in the presence of 5 mol% of 3I-ZrMS catalyst and 80 mol% of propanol. The concentration was 0.2 M. 3I-ZrMS catalyst was prepared from Zr(OPr)₄·PrOH, 3,3'-I₂BINOL in toluene, and then all solvents were evaporated in the presence of MS 5A containing 10% (w/w) H₂O. ^b Determined by ¹H-NMR. ^c Determined after acetylation.

reactions of *p*-methoxy- and *p*-chloro-benzaldehyde (**1b** and **1c**) as well as α,β -unsaturated aldehyde (**1d**) with **2a** also took place with high diastereo- and enantio-selectivities (entries 5–7). In the case of an aliphatic aldehyde (**1e**), a slight decrease of yield and selectivity was observed (entry 8). It is noted that a high level of stereocontrol was achieved in the reactions of several aldehydes, and that *anti*-aldol adducts were obtained with excellent diastereo- and enantio-selectivities.

We also found that the hetero Diels–Alder reaction of **1a** with Danishefsky's diene **2d**, eqn. (2), proceeded smoothly in the presence of 3I-ZrMS to afford the desired product in high yield with high enantioselectivity.¹⁰



In conclusion, we have developed an air-stable, storable chiral Lewis acid catalyst (3I-ZrMS) for highly stereoselective aldol reactions. This catalyst can be stored for more than three months in air at room temperature without loss of activity. This 3I-ZrMS-catalyzed asymmetric aldol reaction provides a practical way to prepare optically active β -hydroxy carbonyl compounds with high diastereo- and enantio-selectivities. Further investigation to utilize this catalyst in the total synthesis of a biologically important compound is now in progress.

Table 2 Asymmetric aldol reactions using the (*R*)-3I-ZrMS catalyst^a

| Entry | RCHO | Nucleophile | Yield (%) (<i>syn/anti</i>) ^b | Ee (%) (<i>anti</i>) ^c |
|----------------|-----------|-------------|---|--|
| 1 | | | Quantitative | 92 |
| 2 ^d | 1a | 2b | 97 | 94 |
| 3 | 1a | | 92 | 94 |
| 4 | 1a | | Quantitative (5/95) | 99 |
| 5 | | 2a | 80 (5/95) | 94 |
| 6 | | 2a | Quantitative (8/92) | 95 |
| 7 | | 2a | 94 (16/84) | 98 |
| 8 | | 2a | 65 (15/85) | 87 |

^a The reactions were performed in toluene at 0 °C for 18 h in the presence of 5 mol% of 3I-ZrMS and 80 mol% PrOH, unless otherwise noted. The concentration was 0.2 M. The 3I-ZrMS catalyst was prepared from Zr(OPr)₄-PrOH and 3,3'-I₂-BINOL with MS 5A containing 10% (w/w) of H₂O. ^b Determined by ¹H-NMR. ^c In the reaction with **2a**, the ee was determined after acetylation. ^d Catalyst (10 mol%) was used. The concentration was 0.1 M.

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Notes and references

† Preparation of the 3I-ZrMS catalyst: Zirconium propoxide propanol complex (Zr(OPr)₄-PrOH, 0.66 g, 1.55 mmol) was added to 3,3'-I₂-BINOL (1.0 g, 1.86 mmol) in toluene (3.5 mL) at room temperature, and the mixture was stirred for 3 h to form a catalyst solution. In the second vessel, MS 5A (3.87 g) was placed, and THF (10 mL) was added at room temperature. After stirring for 5 min at the same temperature, 10% (w/w) H₂O (0.387 g) in THF (4 mL) was added, and the mixture was stirred for a further hour. After the solvent was evaporated under reduced pressure, toluene (5 mL) was added. To this vessel was added the catalyst solution at room temperature, and the mixture was stirred for 5 min. The solvents were removed under reduced pressure at room temperature to afford the 3I-ZrMS catalyst (5.77 g). The 3I-ZrMS was treated in air and was stored in a sealed bottle with air.

A typical experimental procedure is described for the reaction of **1a** with **2a** using the 3I-ZrMS catalyst: To a suspension of the 3I-ZrMS (74.5 mg, 5 mol%) in toluene (0.9 mL) was added PrOH (19.2 mg, 0.32 mmol) in toluene (0.3 mL) at room temperature, and the mixture was stirred for 1 h at the same temperature. After cooling to 0 °C, **1a** (42.5 mg, 0.4 mmol) in toluene (0.4 mL) and **2a** (107 mg, 0.48 mmol) in toluene (0.4 mL) were successively added, and the whole was stirred for 18 h at the same temperature. The reaction was quenched with saturated aqueous sodium bicarbonate solution, and dichloromethane (CH₂Cl₂) was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The organic layers were combined and dried over anhydrous sodium sulfate. After filtration and concentration under reduced pressure, the crude mixture was purified by preparative thin-layer chromatography (SiO₂, benzene–ethyl acetate) to afford the desired aldol adduct (103 mg, quantitative yield). The diastereomer ratio was determined by ¹H NMR analysis, and the optical purity was determined by HPLC analysis using a chiral column after acetylation.

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