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# Direct Catalytic Asymmetric Aldol Additions of Methyl Ynones. Spontaneous Reversal in the Sense of Enantioinduction

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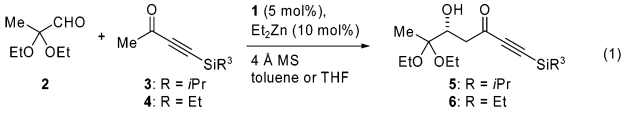
The direct catalytic asymmetric aldol addition reaction has emerged as a powerful tool for the rapid assembly of enantiomerically enriched $\beta$-hydroxy carbonyl compounds.[1] However, most of the examples reported to date are limited to rather simple nucleophiles, and hence development of processes which allow for the use of functionalized substrates is highly desirable. Although the synthetic value of ynones has long been appreciated, their ability to act as powerful Michael acceptors and the tendency of ynone-derived $\beta$-hydroxy ketones to undergo retro-aldol reactions has precluded the development of aldol addition methods with these substrates. Thus, the use of ynones in aldol additions is virtually unknown.[2] The lack of methods for enantioselective aldol reactions of ynones provided a fitting challenge for the further development of our dinuclear zinc catalyst (Scheme 1).[3] Herein, we report unusual effects in the asymmetric aldol addition of methyl ynones to pyruvaldehyde ketals, the products of which are well suited for structural elaboration.

Initially, we focused on the addition of TIPS-protected methyl ketone **3** to pyruvate-derived aldehyde **2** using ligand **1** and $Et_2Zn$ in toluene (eq 1, Table 1). Reactions were typically carried out using 2.5 equiv of the ketone in the presence of 4 Å M.S.



(1)

These preliminary studies were frustrated by low yield and/or enantioselectivity (entries 1 and 2). It is noteworthy that the absolute configuration changes with temperature in this system; formation of the (*R*)-enantiomer **5** is favored at 0 °C (44% ee, entry 1), whereas *ent*-**5** is the major product at −25 °C (72% ee, entry 2).[4] Using the more coordinating solvent THF led to a significant increase in enantioselectivity (entries 3−11), giving aldol **5** in good yield and synthetically useful levels of enantiomeric purity. The use of coordinating additives had no pronounced beneficial effect on the reaction outcome (entries 5−7). As in toluene, the sense of stereoinduction was found to be temperature-dependent (entry 3). Switching to ketone **4** (entries 8−11), a significant improvement in enantioselectivity was observed at ambient temperature. Indeed, in the presence of 5 mol % of catalyst, aldol **6** was isolated in 65% yield and 99% ee (entry 9). By lowering the catalyst loading to 2 mol % and the amount of ketone to 1.2 equiv, the yield increased to 75% without deterioration of optical purity, albeit at the expense of extended reaction times (entries 10 and 11).

To show the generality of the process, the use of variously substituted α,α-diethoxy aldehydes was investigated (Table 2). The addition process proceeded cleanly at 0 °C or at room temperature in the presence of allyl and methallyl substituents (entries 1−3), as well as with protected alcohols (84%, >95% ee, entries 4 and 5).

***Scheme 1.*** Generation of Dinuclear Zinc Catalyst

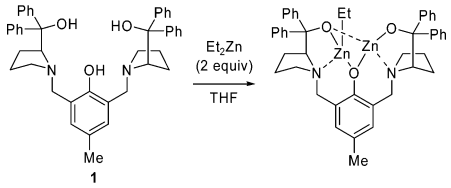
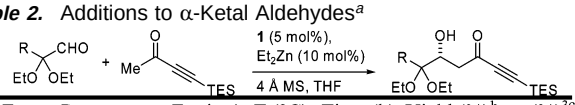



***Table 1.*** Optimization Studies[a]

| Entry | R | Solvent | Mol % of cat. | Additive | *T* (°C) | Time (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | *i*Pr | PhMe | 10 | none | 0 | 4 | 63 | (+)-44 |
| 2 | *i*Pr | PhMe | 10 | none | −25 | 4 | 27 | (−)-72 |
| 3 | *i*Pr | THF | 10 | none | −25 | 2 | | (−)-69 |
| 4 | *i*Pr | THF | 10 | none | 0 | 7.25 | 61 | (+)-83 |
| 5 | *i*Pr | THF | 10 | $Ph_3As{=}O$ | 0 | 7 | 85 | (+)-69 |
| 6 | *i*Pr | THF | 10 | $Ph_3P{=}S$ | 0 | 7 | 66 | (+)-75 |
| 7 | *i*Pr | THF | 10 | $F_6$-*i*PA | 0 | 7.25 | 69 | (+)-80 |
| 8 | Et | THF | 5 | none | 0 | 7.5 | 63 | (+)-84 |
| 9 | Et | THF | 5 | none | 25 | 2.5 | 65 | (+)-99 |
| 10[d] | Et | THF | 2 | none | 25 | 7.5 | 75 | (+)-99 |
| 11[d,e] | Et | THF | 2 | none | 25 | 19 | 72 | (+)-99 |

[a] All reactions were run 0.25 M in THF in the presence of 100 mg of 4 Å M.S./mmol of **2**. [b] Yields refer to isolated products. [c] Determined utilizing chiral HPLC. [d] 1.2 equiv of **4** was used. [e] The reaction was performed on 20 mmol scale. $F_6$-*i*PA = 1,1,1,3,3,3-hexafluoro-2-propanol.

***Table 2.*** Additions to α-Ketal Aldehydes[a]




| Entry | R | Equiv **4** | T (°C) | Time (h) | Yield (%)[b] | ee (%)[3c] |
|---|---|---|---|---|---|---|
| 1 |  | 2.5 | 0 | 17.5 | 76 | > 98 |
| 2 |  | 2.0 | 25 | 4 | 75 | > 98 |
| 3 |  | 2.5 | 0 | 14 | 79 | > 98 |
| 4 | $TBSOCH_2$ | 2.5 | 0 | 6 | 84 | > 95 |
| 5[d] | $TBSOCH_2$ | 1.2 | 25 | 5 | 73 | > 98 |
| 6 | $EtO_2C$ | 2.5 | 0 | 4.25 | 68 | 37 |

[a] All reactions were run 0.25 M in THF in the presence of 100 mg of 4 Å M.S./mmol of **2**. [b] Yields refer to isolated products. [c] Determined utilizing chiral HPLC. [d] 4 mol % of catalyst was used.

Amazingly, terminal alkyne **7** and alkyl ynone **9** were found to be viable reaction partners (eqs 2 and 3). Although the corresponding aldol adducts **8** and **10** were obtained in slightly decreased yield and enantioselectivity, this result is well-worth noting given the high propensity of these substrates to undergo conjugate addition.

During the course of our optimization studies of the addition of ketone **4** to aldehyde **2** (eq 4), a dramatic reversal of enantioselectivity over the course of the reaction was observed. When the reaction was carried out under standard conditions (THF, 4 Å M.S., 0 °C) using 2 equiv of ketone **4**, we found that at early time points, *ent*-**6** was the major product (69% ee after 5 min), but that the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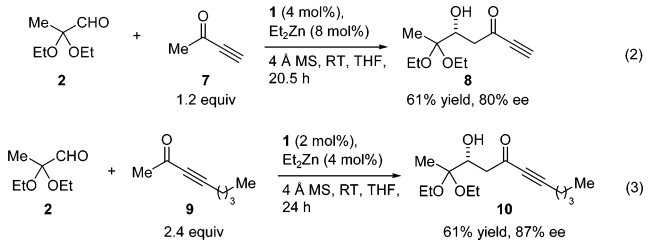
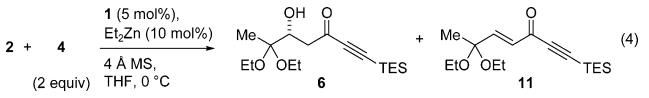



reaction became more and more selective for the opposite enantiomer, which was isolated in 96% enantiomeric excess after 22 h (Figure 1).




Although we observed kinetic resolution of the aldol product under the reaction conditions,[5] the relatively high yields of **6** precluded this effect from being solely responsible for the increase in optical purity; these data clearly suggest that a second catalytic species be formed as the reaction progresses. While the initially formed catalyst gives *ent*-**6** in at least 69% enantiomeric excess, this second catalyst is highly selective for the formation of the opposite enantiomer. We theorized that a new, highly selective catalyst is formed in situ and that this new species might incorporate the aldol product **6**. To test this hypothesis, ligand **1** (1 equiv) was treated with $Et_2Zn$ (2 equiv), and aldol **6** (1 equiv) was added. The resulting solution was stirred at 0 °C for 45 min and used as catalyst (5 mol %) for the aldol addition of **2** and **4** (Figure 1).

This modified catalyst led to consistently higher enantiomeric excesses throughout the course of the reaction. Moreover, the amount of elimination byproduct is significantly decreased, which is in agreement with the previously mentioned recalcitrance of **6** toward elimination.

This example of enantioselective autoinduction is remarkable and, to the best of our knowledge, unique, in that product incorporation into the catalyst not only leads to an increase in enantioselectivity, as has been reported previously,[7] but also to a change in the sense of enantioinduction.

In an attempt to find a readily available cocatalyst that mimics the beneficial effect of **6**, we discovered that addition of achiral

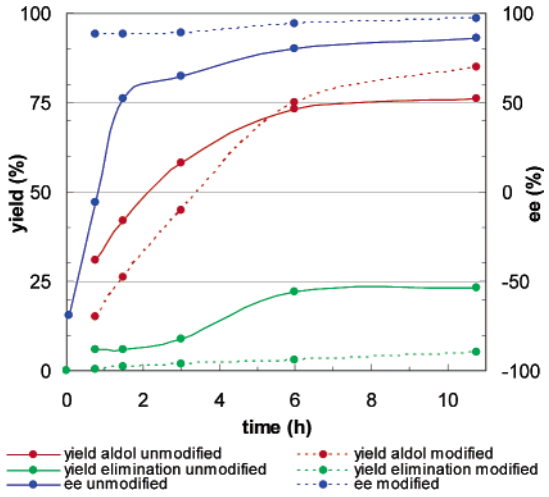
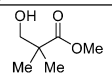
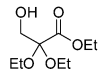



***Figure 1.*** Variation of enantioselectivity (blue line), yield of aldol product (red line), and yield of elimination product (green line) for both the standard catalyst (solid line) and the modified catalyst (dotted line).

***Table 3.*** Effect of Additives on Enantioselectivity after 45 min[a]

| Entry | Additive | Yield (%)[b] | ee (%) | Entry | Additive | Yield (%)[b] | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | None | 31 | (−)-6 | 4 |  | 14 | (+)-48 |
| 2 | **6** | 15 | (+)-88 | 5 |  | 16 | (+)-52 |
| 3 | *i*PrOH | 20 | (+)26 | | | | |

[a] Reactions were carried out 0.25 M in THF in the presence of 100 mg of 4 Å M.S./mmol of **2** at 0 °C for 45 min using 5 mol % of catalyst (**1**/$Et_2Zn$/additive 1/2/1). [b] Yields refer to isolated products.

alcohols to the ligand **1**/$Et_2Zn$ mixture followed by an incubation time of 45 min also allows for the preparation of new catalytic species which exhibit enhanced stereoselectivity as compared to the standard catalyst without additive (Table 3). While the effect of added 2-propanol was almost negligible (entry 1), addition of $\beta$-hydroxy esters had a more pronounced effect on enantioselectivity (entries 2 and 3), suggesting that coordination of the carbonyl oxygen to zinc be important.

In summary, we have reported the first enantioselective aldol additions of methyl ynones using our dinuclear zinc catalyst. The juxtaposition of functionality that is very nicely differentiated gives tremendous flexibility for further structural elaboration of the aldol adducts. Moreover, the recognition of a dramatic case of enantioselective autoinduction may prove to have important implications on related systems.

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**Supporting Information Available:** Experimental details and characterization data for all relevant compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) The absolute configuration was assigned by converting aldol **6** into its *O*-methyl mandelate ester. For details, see: Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202−4205.

(5) When *rac*-**6** was submitted to the reaction conditions, the enantioselectivity increased to 24% after 3.5 h. It could also be shown that only *ent*-**6** eliminates under the reaction conditions, while **6** is stable over extended periods of time (24 h).

(6) *ent*-**6** as additive had little effect on the reaction.

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