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# Development of Bifunctional Salen Catalysts: Rapid, Chemoselective Alkylations of α-Ketoesters

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We have found that bifunctional Lewis acid−Lewis base salen catalysts[1] are much more reactive compared to the Noyori DAIB[2] or the Nugent MIB[3] catalysts in the alkylation of aldehydes[2] (Figure 1). Indeed, these salen catalysts are among the fastest for this class of reactions. Separation of the Lewis acid and Lewis base sites in these salen catalysts, which is not possible in the DAIB-type catalyst, is proposed to account for this reactivity difference. We envisioned that these catalysts would also show enhanced reactivity in the addition of dialkylzincs to α-ketoesters. The α-hydroxyesters arising from such additions (eq 1) are versatile synthetic precursors.[4]

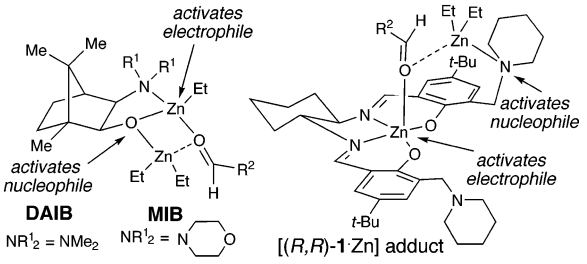



***Figure 1.***

For α-ketoesters, the development of a selective alkylation, is complicated due to competing reaction pathways. Two main products (reduction and addition) are encountered with organometallics containing a *β*-hydrogen (eq 1).[5,6]

Thus, several factors must be considered in developing enantioselective catalysts for the reaction in eq 1. First, the catalyst must accelerate addition faster than the uncatalyzed, racemic addition or reduction. *With aldeyhdes and ketones, this issue does not arise since there is no uncatalyzed reaction with $Et_2Zn$ even at room temperature*. In contrast, the uncatalyzed reaction of $Et_2Zn$ with α-ketoesters is rapid (Table 1, entries 1−2). Second, the catalyst must accelerate addition to a greater degree than reduction.

Despite their success in aldehyde alkylation, we found that DAIB-type catalysts such as MIB[3] performed poorly with α-ketoesters[7] (Table 1, entries 3−4). Thus, our investigation commenced with the piperidine salen−metal complexes (*R*,*R*)-**1**·M, which were prepared in four simple steps (Scheme 1).

In the absence of a catalyst, reduction is the principal product (86%) at 0 °C in the reaction of $Et_2Zn$ with ethyl oxo(phenyl)-acetate (Table 1, entry 1). In contrast, **1**·Zn[8] at 0 °C, affords 93% addition with very little reduction (Table 1, entry 5). This represents *a 120-fold change in selectivity* with respect to the uncatalyzed reaction; the salen catalysts clearly accelerate addition to a far greater degree than reduction. The Mg[9] and Ti(O*i*-Pr)$_2$[10,11] complexes proved even more reactive, providing complete conversion

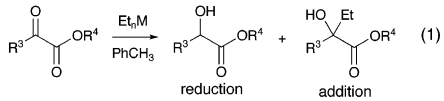
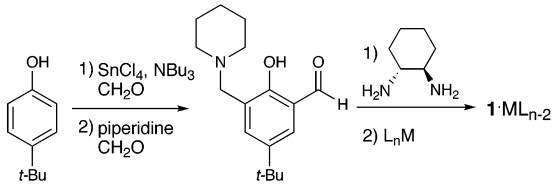



***Table 1.*** Addition of $Et_2Zn$ to $PhCOCO_2Et$ (eq 1, M = Zn, $n$ = 2, $R^3$ = Ph, $R^4$ = Et)[a]

| entry | cat.[b] | *T* (°C) | t (h) | reductionconv. (%)[c] | addition conv. (%)[c] |
|---|---|---|---|---|---|
| 1 | none | 0 | 24 | 86 | 11 |
| 2 | none | −40 | 2 | 45 | 23 |
| 3 | MIB·ZnEt | 0 | 24 | 43 | 30 (0) |
| 4 | MIB·ZnEt | −40 | 2 | 37 | 25 (5) |
| 5 | **1**·Zn | 0 | 24 | 6 | 93 (20) |
| 6 | **1**·Mg | −40 | 2 | 0 | 99 (34) |
| 7 | **1**·Ti(O*i*-Pr)$_2$ | −40 | 2 | 0 | 99 (56) |
| 8 | **1**·V(O)(O*i*-Pr) | 0 | 24 | 7 | 36 |
| 9 | **1**·Al(O*i*-Pr) | −40 | 2 | 2 | 92 (21) |
| 10 | **1**·Zr(O*i*-Pr)$_2$ | −40 | 2 | 3 | 45 |

[a] Addition of 1.2 equiv $Et_2Zn$ with 10 mol % cat. [b] Complexes with (*R*,*R*)-**1** prepared by stirring with $MR_2$ (M = Zn and Mg) or $MY(Oi\text{-}Pr)_n$ (M = Ti, V, Al, and Zr) for 5−30 min. For the O*i*-Pr sources, the released *i*-PrOH was removed in vacuo, and the catalyst was redissolved for the reaction. [c] Determined by GC (Cyclodex*β*). Enantiomeric excess (%) of the (*R*) enantiomer in parentheses.

***Scheme 1***




to the addition product within 2 h at −40 °C (Table 1, entries 6−7). The V(O)(*Oi*-Pr), Al(O*i*-Pr), and Zr(O*i*-Pr)$_2$ complexes are less reactive and less selective (Table 1, entries 8−10).

We propose that the piperidine group plays a critical role in this catalyst as a Lewis basic activating group. In line with this hypothesis, the structurally similar complexes **2**−**5** provide comparable reactivity and selectivity (Figure 2, Table 2, entries 2−5). More hindered amines are less effective for coordination of metal species (i.e., $Et_2Zn$) which is consistent with the decreased reactivity of 2,6-dimethylpiperidinyl **7** (Table 2, entry 7). If the amine base is distant from the Ti center, bifunctional activation is less likely. This conjecture is supported by the lesser reactivity and selectivity of quinolinyl **8** (Table 2, entry 8) compared to pyridinyl **6** (Table 2, entry 6). Replacement of the amine with nonbasic groups should change the catalytic activity if this Lewis base causes activation. The lesser reactivity of the Ti complex **9** (Table 2, entry 9) is consistent with this proposal. When 2 equiv of *N*-methyl morpholine are added for every equiv of **9** (Table 2, entry 10), similar results are observed as for **9** alone. By itself, the base is not a catalyst

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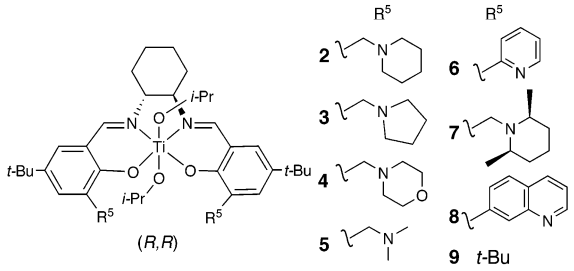



***Figure 2.***

***Table 2.*** Addition of $Et_2Zn$ to $PhCOCO_2Et$ (eq 1, M = Zn, $n = 2$, $R^3$ = Ph, $R^4$ = Et) Using the (*R,R*)-Salen−Ti(O*i*-Pr)$_2$ Complexes[a]

| entry | cat. | reduction conv. (%)[b] | addition conv. (%)[b] |
|---|---|---|---|
| 1 | none | 45 | 23 (0) |
| 2 | **2** | 0 | 99 (56) |
| 3 | **3** | 3 | 94 (54) |
| 4 | **4** | 9 | 72 (54) |
| 5 | **5** | 0 | 91 (44) |
| 6 | **6** | 0 | 91 (57) |
| 7 | **7** | 10 | 84 (20)[c] |
| 8 | **8** | 5 | 57 (7) |
| 9 | **9** | 20 | 56 (4)[c] |
| 10 | **9** + NMM[d] | 15 | 56 (2)[c] |
| 11 | NMM[e] | 30 | 14 (0) |

[a] Addition of 1.2 equiv of $Et_2Zn$ with 10 mol % cat. at −40 °C for 2 h. [b] Determined by GC (Cyclodex$\beta$ column). Enantiomeric excess (%) of the (*R*)-enantiomer in parentheses. [c] (*S*)-Enantiomer. [d] 2 equiv (relative to **9**) of *N*-methyl morpholine added. [e] Same amount as in entry 10.

***Table 3.*** Addition of $Et_2Zn$ to Ketoesters (eq 1, M = Zn, $n = 2$) Using (*R,R*)-**2**[a]

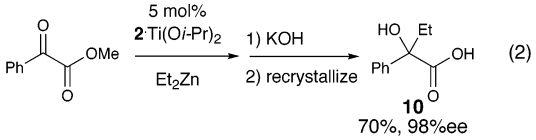
| entry | $R^3$ | $R^4$ | reduction conv. (%)[b] | addition conv. (%)[b] | isolated yield (%) |
|---|---|---|---|---|---|
| 1 | Ph | Et | 0 | 99 | 92 |
| 2 | *p*-MeO−$C_6H_4$ | Et | 0 | 99 | |
| 3 | *p*-Br−$C_6H_4$ | Et | 0 | 96 | |
| 4 | $\beta$-naphthyl | Et | 0 | 96 | |
| 5 | Me | Et | 0 | 92 | |
| 6 | *i*-Pr | Et | 0 | 98 | |
| 7 | Cy | Et | <4 | 84 | |
| 8 | *t*-Bu | Et | 13 | 57 | |
| 9 | Ph | Me | 0 | 99 | 93 |
| 10 | Ph | Me | 0 | 99 | 96[c] |
| 11 | Ph | Bn | 0 | 99 | |
| 12 | Ph | *t*-Bu | 0 | 99 | |

[a] Addition of 1.2 equiv $Et_2Zn$ with 10 mol % cat. at −40 °C for 2 h. [b] Determined by GC (Cyclodex$\beta$) or HPLC (Chiracel AD). [c] 5 mmol substrate, 5 mol % catalyst.

(Table 2, entry 1 vs 11). *The base and titanium salen in **2**−**6** (Table 2, entries 2−6) clearly act in a cooperative manner* as evidenced by their higher reactivity and enantioselectivity relative to entry 10 in Table 2.

We speculate that the mechanism involves ionization of an alkoxide group to provide a five-coordinate cationic Ti species.[10a,12] This hypothesis is supported by the identical results obtained when Ti(O*t*-Bu)$_4$ is used in place of Ti(O*i*-Pr)$_4$. The lack of a nonlinear effect (see Supporting Information) with enantioimpure **2** in this reaction is also consistent with the proposed bifunctional activation mechanism.

The scope of this reaction was examined with (*R,R*)-**2** (Table 3) since it affords the best combination of reactivity and selectivity. In all cases, the catalyst greatly accelerates the addition pathway. This catalyst also provides a moderate degree of stereochemical control (≤78% ee) in the approach of the $Et_2Zn$ to the prochiral α-ketoesters. The best selectivity was obtained with methyl oxo(phenyl)acetate (eq 2). With this substrate, the addition was performed on a 5 mmol scale using 5 mol % **2**. The α-hydroxyester was isolated in 96% yield (99% conv.) with 78% ee (*R*). After ester hydrolysis, the corresponding α-hydroxy acid **10** could be readily enriched to 98% ee (*R*) by recrystallization. For this two-step sequence, a 70% yield of α-hydroxy acid **10** with 98% ee is obtained.




In summary, Lewis acid−Lewis base salen complexes have been identified as effective catalysts for the addition of dialkylzincs to α-ketoesters while suppressing the accompanying reduction reaction. In addition, this represents the first example of the catalytic asymmetric addition of alkyls to α-ketoesters.[13] Further work is underway to investigate the mechanism of this reaction and to apply the concepts behind the amino-salen catalysts to the development of more reactive and more selective catalysts.

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**Supporting Information Available:** Full experimental procedures are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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