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Zn(salen)-Catalyzed Enantioselective Phenyl Transfer to Aldehydes and Ketones with Organozinc Reagent

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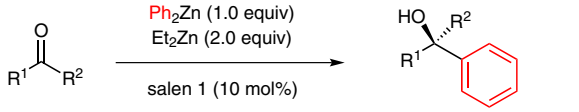

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Abstract A chiral zinc complex of salen was found to be an efficient catalyst for the phenyl transfer of organozinc reagent to aromatic aldehydes and ketones. High enantioselectivities were obtained in reactions of both aromatic aldehydes and ketones (up to 97% and 92% ee, respectively).

Key words Zn(salen) complex, asymmetric catalysis, phenyl transfer, aldehydes, ketones, diarylmethanol

Enantioselective aryl transfer to aromatic aldehydes or ketones is a current topic in synthetic organic chemistry. These reactions provide a useful method for the synthesis of chiral secondary or tertiary diarylmethanols, which are useful chiral building blocks for synthesizing pharmacologically active compounds.[1] Since Bolm et al. reported using an arylzinc reagent prepared from Ph_2Zn/Et_2Zn[2a,b] or $ArB(OH)_2/Et_2Zn$[2c,d] as a nucleophile, various chiral ligands have been developed that exhibit high enantioselectivity in aryl transfer to aldehydes.[3,4] However, a relatively small number of chiral ligands are effective for aryl transfer to ketones due to their lower reactivity and their difficulty in discriminating lone pairs of carbonyl oxygen.[5]

In 1998, Fu et al. reported the first enantioselective phenyl transfer to ketones using diphenylzinc with methanol as an additive.[6] Subsequently, Walsh et al.[7] and Yus et al.[8] independently reported that the use of titanium tetraisopropoxide greatly improves the effect of the addition of organozinc reagent to ketones and high enantioselectivities were obtained. However, to the best of our knowledge, only the zinc complex of a chiral phosphoramide ligand, a class of Lewis acid–Lewis base catalyst, developed by Ishihara et al.[4c,d,9] could efficiently catalyze the enantioselective phenyl transfer to both aldehyde and ketones with arylzinc reagent without the use of a titanium complex.[10] Thus, a new catalyst is still required for aryl transfer to both aldehydes and ketones.

The catalytic behaviors of Zn(salen) complexes with organozinc reagent have attracted our attention, because Zn(salen)-catalyzed enantioselective alkyl transfer to aldehyde and enantioselective alkynyl transfer to ketones have been reported, whereas enantioselective aryl transfer to aldehydes or ketones has not been reported. Cozzi et al. reported the first Zn(salen)-catalyzed ethyl transfer to aldehydes with diethylzinc using salen **1** (Figure 1) bearing *tert*-butyl groups at C3(3′) and C5(5′).[11a] This reaction was thought to proceed through a Lewis acid–Lewis base dual activation mode: The Lewis acidic central zinc ion captures the carbonyl oxygen of aldehyde, and the Lewis basic phenolic oxygen captures the diethylzinc. Later, a zinc complex of **1** was successfully utilized in an enantioselective alkynyl transfer with an alkynylzinc reagent to ketones.[11b,c] Kozlowski et al. developed the modified salen **2**, which bears more Lewis basic alkyl amino groups at C3(3′) on a salen ligand. The zinc complex of **2** exhibited high catalytic activity in the ethyl transfer to aldehydes or α-ketoesters and high enantioselectivities were obtained.[12] On the other hand, Katsuki et al. reported highly enantioselective alkynyl transfer to ketones using the zinc complex of **3** bearing a 2-substituted naphthyl group at C3(3′) on a salen ligand.[13] Although its precise reaction mechanism is unclear, they stated that the coordination of organozinc with the phenolic oxygen is unlikely due to the steric hindrance caused by a bulky 2-phenylnaphthyl group at C3(3′), and that the 2-phenylnaphthyl group makes it possible to discrimination of the enantioface of ketone coordinated with the central zinc ion.

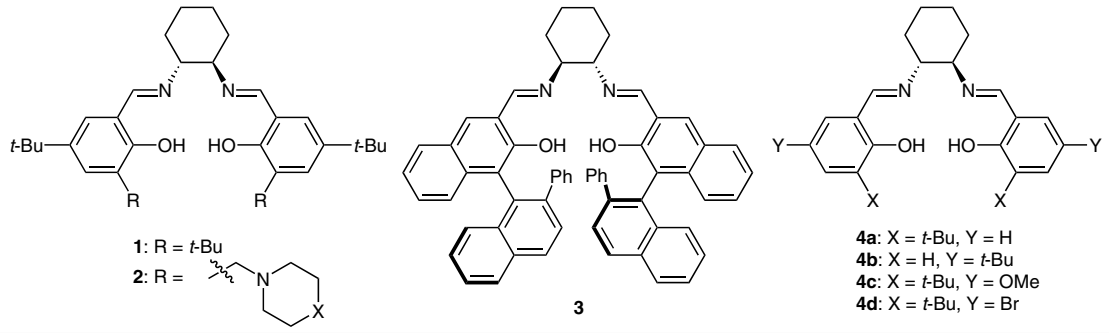
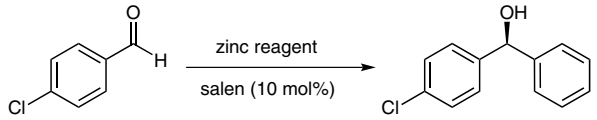


Figure 1

These reports suggested that the Lewis acidic zinc ion of a Zn(salen) complex could discriminate between the lone pairs of the carbonyl oxygen and efficiently activate not only aldehydes but also ketones. It is well-known that diarylzinc and alkylarylzinc reagents are more nucleophilic than dialkylzinc. Thus we expected that chiral Zn(salen) complexes bearing appropriate substituents at least at C3(3′) on a salen ligand would be an effective catalyst for phenyl transfer to both aldehydes and ketones with zinc reagent. Moreover, salen ligands have the advantage of high availability (some are commercially available) and modifiability.

On this basis, we first examined phenyl transfer using *p*-chlorobenzaldehyde as the test substrate at 0 °C with ethylphenylzinc in the presence of 10 mol% of Zn(salen) complexes prepared in situ from salen **1**, **4a**–**d** (Table 1). An ethylphenylzinc solution was prepared from phenylboronic acid and a hexane solution of diethylzinc according to Bolm's procedure.[2c,14] As expected, the reaction with a zinc complex of **1** proceeded smoothly, and the product was obtained with a good enantioselectivity of 83% ee (Table 1, entry 1). Reaction with a zinc complex of **4a** bearing the *tert*-butyl group only at C3(3′) also proceeded smoothly although the enantioselectivity was slightly diminished, while that with a zinc complex of **4b** bearing the *tert*-butyl group only at C5(5′) proceeded more slowly and poor enantioselectivity was obtained (Table 1, entries 2 and 3). Next, we examined the electronic nature of the C5(5′) substituents but the catalytic activity and enantioselectivity were not greatly affected (Table 1, entries 4 and 5). With a zinc complex of **1**, we also examined the effect of temperature, and a high enantioselectivity of 93% with a high chemical yield was obtained when the reaction was carried out at –40 °C (Table 1, entry 6). When we used an ethylphenylzinc reagent obtained by mixing diphenylzinc and diethylzinc,[2a,b,14] we could significantly increase the reaction rate without any deterioration in the enantioselectivity or the chemical yield (Table 1, entry 7).

Table 1 Enantioselective Phenyl Transfer to *p*-Chlorobenzaldehyde with a Zinc Complex of Salen Ligands[a,19]

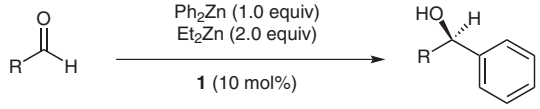


Entry	Salen	Time (h)	Yield (%)	ee (%)[b]
1	**1**	1	95	83
2	**4a**	1	95	71
3	**4b**	3.5	96	8
4	**4c**	1	98	80
5	**4d**	1	93	71
6[c]	**1**	5.5	94	93
7[c,d]	**1**	1	95	94

[a] All reactions were carried out with molar ratio of *p*-chlorobenzaldehyde/$PhB(OH)_2$/Et_2Zn/salen = 1:2.5:7.5:0.1 at 0 °C, unless otherwise indicated.
[b] Determined by HPLC analysis using chiral stationary-phase column (Daicel Chiralpak AD-H; hexane–*i*-PrOH, 90:10).
[c] Reaction was carried out at –40 °C.
[d] Reaction was carried out with molar ratio of *p*-chlorobenzaldehyde/Ph_2Zn/Et_2Zn/salen = 1.0:1.0:2.0:0.1.

To explore the scope of the present reaction, we next examined the reactions of various aldehydes under optimized reaction conditions (Table 2). The reactions of substituted aromatic aldehydes exhibited high enantioselectivities, irrespective of the electronic nature of the aryl substituent (Table 2, entries 1–8). The reaction of heteroaromatic aldehydes, such as 2-thiophenecarboxaldehyde, also exhibited high enantioselectivity while that of furfural showed some drop in enantioselectivity (Table 2, entries 9 and 10). In particular, poor enantioselectivity was obtained for the reaction of 2-pyridinecarboxaldehyde (Table 2, entry 11). This tendency is probably attributable to the fact that the nitrogen atom coordinates strongly with the Lewis acidic central zinc atom, which leads to the reaction having an undesired transition state (vide infra). In contrast, the reactions of aliphatic aldehydes showed moderate enantioselectivities (Table 2, entries 12–14).

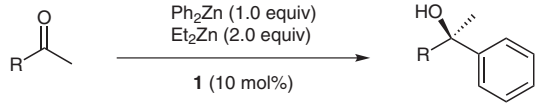
Table 2 Enantioselective Phenyl Transfer to Aldehydes with a Zinc Complex of **1**[a,19]



Entry	R in aldehyde	Time (h)	Yield (%)	ee (%)[b]
1	2-naphthyl	1	94	95
2	2-MeC_6H_4	1	95	97
3	2-$MeOC_6H_4$	1	95	89
4	2-BrC_6H_4	1.5	89	90
5	4-PhC_6H_4	1	91	94
6	4-MeC_6H_4	2	87	90
7	4-$MeOC_6H_4$	1.5	95	95
8	4-BrC_6H_4	1	92	95
9	2-thienyl	1	96	92
10	2-furyl	1	93	83
11	2-pyridyl	1	71	6
12	*c*-Hex	1	64	76
13	*i*-Pr	1	61	59
14	*n*-Hex	1	71	54

[a] All reactions were carried out at –40 °C with molar ratio of aldehyde/Ph_2Zn/Et_2Zn/salen = 1.0:1.0:2.0:0.1, unless otherwise indicated.
[b] Determined by HPLC analysis using chiral stationary-phase column according to the literature (ref. 4 and 10).

Table 3 Enantioselective Phenyl Transfer to Ketones with a Zinc Complex of **1**[a,19]

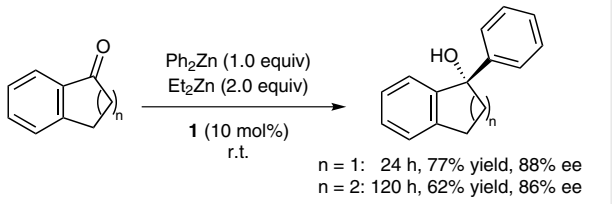


Entry	R in ketone	Temp	Time (h)	Yield (%)	ee (%)[b]
1	4-ClC_6H_4	r.t.	24	81	88
2	4-ClC_6H_4	0 °C	96	82	92
3	2-naphthyl	r.t.	30	80	85
4	2-naphthyl	0 °C	144	75	90
5	4-MeC_6H_4	r.t.	48	74	85
6	4-$MeOC_6H_4$	r.t.	60	52	87
7	4-BrC_6H_4	r.t.	20	77	86
8	4-BrC_6H_4	0 °C	96	80	92
9	2-thienyl	r.t.	42	72	90[c]
10	2-furyl	r.t.	30	60	71
11	2-pyridyl	r.t.	3.5	87	rac.
12	*c*-Hex	r.t.	65	74	–44
13	*i*-Pr	r.t.	48	59	–42
14	*n*-Hex	r.t.	24	87	rac.

[a] All reactions were carried out with molar ratio of ketone/Ph_2Zn/Et_2Zn/salen = 1.0:1.0:2.0:0.1.
[b] Determined by HPLC analysis using chiral stationary-phase column according to the literature (ref. 4c, 6–10, and 15).
[c] Absolute configuration was not determined.

We further examined the reactions of several ketones with a zinc complex of **1** as a catalyst using an ethylphenylzinc reagent derived from diphenylzinc and diethylzinc (Table 3). Due to the lower reactivity of ketones, all the reactions were carried out without the addition of toluene at room temperature. As expected, the reactions of the aromatic aldehydes exhibited good to high enantioselectivities (Table 3, entries 1–8). In these reactions, some ketones bearing electron-withdrawing groups proceeded smoothly, which enabled the reactions to be carried out at 0 °C, and high enantioselectivities were obtained (Table 3, entries 2, 4, and 8). The reactions of heteroaromatic aldehydes also showed good to high enantioselectivities except for the reaction of 2-acetylpyridine (Table 3, entries 9–11). Interestingly, the reactions of α-substituted aliphatic ketones gave opposite enantiomers with low enantioselectivities, and no asymmetric induction was observed in the reaction of 2-octanone (Table 3, entries 12–14).

We also examined the reactions of cyclic aromatic ketones and good enantioselectivities were obtained (Scheme 1). The absolute configurations of the products from the reactions of aromatic aldehydes or aromatic ketones were determined as *S* by comparison of their specific rotation or elution order of HPLC with reported values.[4,6–10,15] According to the transition-state model reported by Cozzi et al.,[11a] the observed stereochemistry can be explained by the transition-state model depicted in Figure 2, in which the *si* face of aldehyde (R^1 = Ar or Alk, R^2 = H) or ketone (R^1 = Ar, R^2 = Me) was preferentially attacked by the zinc reagent.[16] However, in the reaction of dialkyl ketone, the orientation of the zinc-bonded ketone was mainly dictated by the steric factor of the alkyl substituents, and the opposite enantiomer was produced as the result of a *re*-face attack by the zinc reagent (R^1 = Me, R^2 = α-substituted Alk).[18] Furthermore, the lone pairs of carbonyl oxygen of 2-octanone are difficult to discriminate, which meant there was no asymmetric induction of the reaction. However, further study is required to fully understand the mechanism of asymmetric induction.



Scheme 1 Enantioselective phenyl transfer to cyclic ketones using Zn(salen) complex

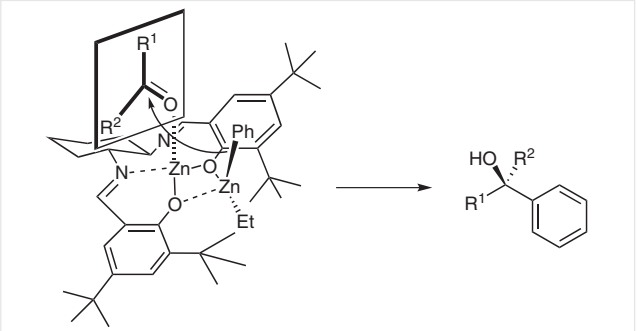


Figure 2 Possible mechanism for enantioselective phenyl transfer to aldehydes or ketones using a zinc complex of salen **1**

In conclusion, we have demonstrated that a zinc complex of salen **1** is an efficient catalyst for enantioselective phenyl transfer to both aromatic aldehydes and aromatic ketones. Further studies on the scope of the reaction and clarification of the reaction mechanism are under way in our laboratory.

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(18) At present, we do not have any evidence to explain the change-over of the stereoselectivity in the reactions of aliphatic ketones.
(19) **Typical Experimental Procedure is Exemplified by Enantioselective Phenyl Transfer to *p*-Chlorobenzaldehyde**
Diphenylzinc (43.9 mg, 0.2 mmol) was placed in a flask under nitrogen, and diethylzinc (0.38 mL, 1.06 mol·dm^{-3} in hexane) was added at r.t. and stirred for 30 min at the temperature. This suspension was added to a solution of salen **1** (10.9 mg, 0.02 mmol) in toluene (0.25 mL) and further stirred at the temperature for 30 min. After the mixture was cooled to –40 °C, *p*-chlorobenzaldehyde (28.1 mg, 0.2 mmol) was added. After being stirred for 1 h at the same temperature, the mixture was quenched with sat. aq NH_4Cl, allowed to warm to r.t., and extracted with Et_2O and then washed with sat. aq NaCl. The organic extract was dried over anhydrous Na_2SO_4 and concentrated. Silica gel chromatography of the residue (hexane–EtOAc, 19:1 to 9:1) gave the desired product (41.4 mg, 95%) as an oil. The ee of the product was determined to be 94% by HPLC using chiral stationary-phase column as described in the footnote b of Table 1. $[\alpha]_D^{13}$ +20.2 (*c* 0.45, $CHCl_3$) [lit.[10d] $[\alpha]_D^{23}$ +19.1 (*c* 0.83, $CHCl_3$) for 83% ee, (*S*)].
All spectral data of products in Tables 1–3 were in accordance with those reported in the literature.

Specific Rotation of some Compounds

(*R*)-Cyclohexylphenylmethanol
$[\alpha]_D^{26}$ +33.9 (*c* 0.2, $CHCl_3$) for 76% ee [lit.[10d] $[\alpha]_D^{23}$ +38.0 (*c* 0.4, $CHCl_3$) for 96% ee, (*R*)].

(*S*)-1-(4-Chlorophenyl)-1-phenylethanol
$[\alpha]_D^{13}$ +13.2 (*c* 0.2, $CHCl_3$) for 92% ee [lit.[15b] $[\alpha]_D^{22}$ +14.8 (*c* 6.5, $CHCl_3$) for 98% ee, (*S*)].

(*S*)-Phenylindan-1-ol
$[\alpha]_D^{17}$ +36.9 (*c* 1.6, $CHCl_3$) for 88% ee [lit.[15b] $[\alpha]_D^{24}$ –33.3 (*c* 1.05, $CHCl_3$) for 88% ee, (*R*)].

(*S*)-1-Cyclohexyl-1-phenylethanol
$[\alpha]_D^{13}$ –7.1 (*c* 0.75, CH_2Cl_2) for 44% ee [lit.[15a] $[\alpha]_D^{24}$ +17.9 (*c* 3.4, CH_2Cl_2) for 99% ee, (*R*)].