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Achiral phenolic *N*-oxides as additives: an alternative strategy for asymmetric cyanosilylation of ketones

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Abstract—The activation of chiral titanium(IV) complexes with additives, phenolic *N*-oxides, is found to provide an alternative strategy for asymmetric cyanosilylation of ketones in excellent yield with up to 82% ee.
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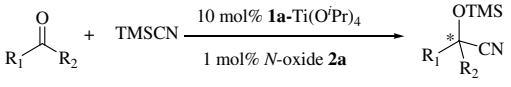
Recent years, there are a number of important observations made in regarding the effect of additives on asymmetric catalytic reactions.[1] The addition of suitable achiral additives and cocatalysts to support the asymmetric catalyst system, enhance the yield and surprisingly, in many cases also enhance the enantioselectivity efficiently.[2] Currently, asymmetric cyanosilylation of ketones is intensively studied due to the importance of cyanohydrins as the versatile synthons. Significant contribution was made by Belokon,[3] Shibasaki,[4] Deng,[5] Hoveyda and Snapper,[6] the latter also developed this reaction by employing MeOH and 3 Å molecular sieves as additives.

Furthermore, chiral *N*-oxides were extensively used in asymmetric synthesis such as allylation of aldehydes,[7] addition of Et_2Zn to aldehydes,[8] Strecker reaction,[9] aldol reaction,[10] and reduction of ketones.[11] However, there are only a few achiral *N*-oxides used as additives in asymmetric reactions.[12]

Recently, our group has reported the asymmetric cyanosilylation of ketones in which *N*-oxides play a key role for activation of TMSCN in the catalytic system.[13] We improved this reaction with a catalytic double-activation method (CDAM), in which salen-Ti(IV) complex acted as the Lewis acid and achiral *N*-oxide acted as the Lewis base to activate ketones and TMSCN, respectively.[13e]

We herein wish to describe our alternative strategy for the asymmetric cyanosilylation of ketones based on a chiral salen-Ti(O^iPr)$_4$ catalyst in combination with a suitable achiral *N*-oxide as an additive (Scheme 1).

Our studies started with acetophenone as a model substrate. In a preliminary study, we found ligand **1a** has the highest capability of asymmetric induction among **1a**–**f** (Fig. 1). Further searching for the suitable *N*-oxide additive (Fig. 1) revealed that the phenolic *N*-oxide **2a** is most promising in this catalytic system (Table 1, entries 5, 7–11). We also found that several parameters were important for both the reactivity and enantioselectivity. The best results were obtained when the molar ratio of *N*-oxide **2a** to acetophenone was 1% (Table 1, entries 1–4). The yield and enantioselectivity were also dependent on the temperature. The optimal temperature is −20 °C, increasing or further decreasing the reaction temperature leads to a reduction in enantioselectivity (Table 1, entries 3, 5, and 6). A study on the solvent effect showed that dichloromethane provided the best overall results.



Scheme 1. Asymmetric cyanosilylation of ketones.

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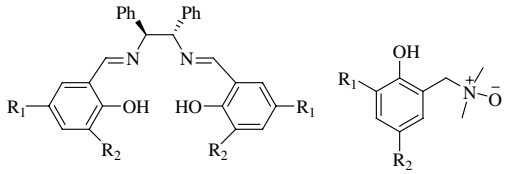

(1*S*, 2*S*)-**1a-f**

2a-f

1a R_1 = ^{t}Bu, R_2 = ^{t}Bu
1b R_1 = H, R_2 = Me
1c R_1 = H, R_2 = Ph
1d R_1 = H, R_2 = ^{t}Bu
1e R_1 = Me, R_2 = ^{t}Bu
1f R_1 = H, R_2 = H

2a R_1 = ^{t}Bu, R_2 = H
2b R_1 = Me, R_2 = H
2c R_1 = Ph, R_2 = H
2d R_1 = ^{t}Bu, R_2 = ^{t}Bu
2e R_1 = H, R_2 = ^{t}Bu
2f R_1 = H, R_2 = H

Figure 1. Screening of ligands and *N*-oxides.

Table 1. Asymmetric cyanosilylation of acetophenone catalyzed by **1a**-Ti(O^iPr)$_4$ complex and additives[a]

Entry	Additive	Amount of additive[b] (%)	Temp (°C)	Yield[c] (%)	Ee[d] (%)
1	**2a**	10	−20	94	70
2	**2a**	5	−20	89	76
3	**2a**	1	−20	94	81
4	**2a**	0.5	−20	83	80
5	**2a**	1	0	98	70
6	**2a**	1	−40	23	72
7	**2b**	1	0	73	68
8	**2c**	1	0	93	69
9	**2d**	1	0	88	69
10	**2e**	1	0	80	66
11	**2f**	1	0	73	60

[a] All the reactions were carried out under the following conditions: 10 mol% **1a**-Ti(O^iPr)$_4$ complex, concentration of acetophenone = 0.5 M in CH_2Cl_2, 96 h.
[b] The molar ratio of additive to acetophenone.
[c] Isolated yield.
[d] Determined by chiral GC analysis on Chirasil DEX CB.

Encouraged by the result obtained for acetophenone, we investigated a number of other ketones to probe their behavior under the current catalytic condition.[14] As shown in Table 2, observations accorded with those afforded by CDAM.[13e] While the *para*-substituents (methyl, methoxy, chloro or fluoro) on the aromatic ring lead to lower enantioselectivities and yields than acetophenone (Table 2, entries 1–5), the *meta*-chloro substituted ketone gives similar enantioselectivity and yield to acetophenone (Table 2, entry 6). α-Tetralone and 1-indanone afford products with similar enantioselectivities (Table 2, entries 7 and 8). Different from Snapper's report,[6] the α,β-saturated ketone gives a higher ee value than the α,β-unsaturated one (Table 2, entries 9 and 10). This is in agreement with Shibasaki's result.[4a]

Table 2. Asymmetric cyanosilylation of ketones catalyzed by **1a**-Ti(O^iPr)$_4$ complex and *N*-oxide additive **2a**[a]

Entry	Ketone	Yield[b] (%)	Ee[c] (%)
1	Acetophenone	94	81
2	4′-Methylacetophenone	68	71
3	4′-Methoxyacetophenone	81	74
4	4′-Chloroacetophenone	75	67
5	4′-Fluoroacetophenone	89	73
6	3′-Chloroacetophenone	93	82
7	α-Tetralone	73	77
8	1-Indanone	96	79
9	Benzylacetone	94	74[d]
10	*trans*-4-Phenyl-3-buten-2-one	77	52[d]

[a] All the reactions were carried out under the optimized conditions: 10 mol% **1a**-Ti(O^iPr)$_4$, 1 mol% **2a**, −20 °C, concentration of ketones = 0.5 M in CH_2Cl_2, 96 h.
[b] Isolated yield.
[c] Determined by chiral GC analysis on Chirasil DEX CB.
[d] Determined by HPLC on Chiralcel OD.

In conclusion, by introducing phenolic *N*-oxides as additives into the asymmetric cyanosilylation of ketones, we achieved the comparable results that afforded by CDAM. Moreover, the use of additives simplified the procedure and it is a method for the screening of efficient catalyst systems. The precise function of the *N*-oxide additive is not clear at present. To improve enantioselectivity, modification of the *N*-oxides can be rationally based and an investigation of the mechanism is underway.

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14. A representative procedure: To a solution of **1a** (32.2 mg 0.05 mmol) and *N*-oxide **2a** (1.1 mg, 0.005 mmol) in CH_2Cl_2 (1 mL) was added $Ti(O^iPr)_4$ (1 M in toluene, 50 μL, 0.05 mmol) at room temperature, and the mixture was stirred at 35 °C for 1 h under N_2 atmosphere. To this solution, acetophenone (58 μL, 0.5 mmol) was added at −20 °C, followed by the addition of TMSCN (137 μL, 1 mmol). After 96 h, the solution was concentrated and the residue was purified by silica gel column chromatography giving the product with 94% yield and 81% ee that was determined by Chiral GC analysis on Chirasil DEX CB.