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Asymmetric synthesis of cyanohydrins catalysed by a potassium Δ-bis[*N*-salicylidene-(*R*)-tryptophanato]cobaltate complex

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A chiral cobalt(III) complex of a Schiff base derived from (*R*)-tryptophan and salicylaldehyde catalysed asymmetric trimethylsilylcyanation of benzaldehyde at ambient temperature and a 20:1 substrate/catalyst ratio with the formation of enantiomerically enriched mandelonitrile (ee up to 77%).

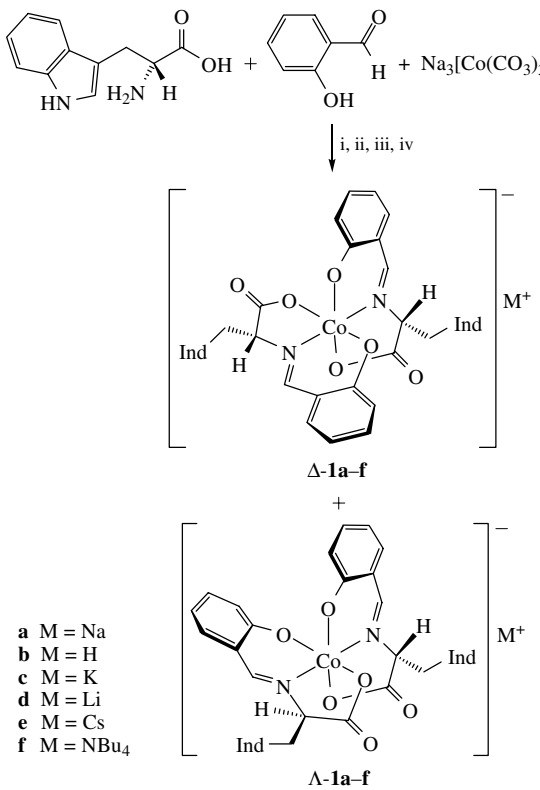
We report the design and development of a new catalytic system based on chiral cobalt(III) complex **1** and the use of this system for asymmetric trimethylsilylcyanation of benzaldehyde. Complex **1** was obtained from (*R*)-tryptophan, salicylaldehyde and $Na_3[Co(CO_3)_3]$[1] with a total yield of 60% (Scheme 1) as a mixture of diastereoisomers according to a procedure described earlier.[2]

The resulting mixture of diastereomeric complexes, Λ-bis[*N*-salicylidene-(*R*)-tryptophanato]cobaltate sodium (Λ-**1a**) and Δ-bis[*N*-salicylidene-(*R*)-tryptophanato]cobaltate sodium (Δ-**1a**), was separated by flash column chromatography (Al_2O_3, EtOH). The individual stereoisomers were additionally purified by chromatography on Sephadex LH-20 (EtOH/benzene, 1:3). Sodium countercations in complexes Δ-**1a** and Λ-**1a** were exchanged by other ions (Li^+, K^+, Cs^+, Bu_4N^+ and H^+) *via* ion-exchange chromatography.†

All of the complexes were tested as catalysts for the trimethylsilylcyanation of benzaldehyde (Scheme 2).

The results of these experiments are presented in Table 1. Although under conditions A complexes **1a–f** were catalytically active, some asymmetric induction (ee 19 and 6.5%, Table 1, conditions A, entries 5 and 7) was provided only by complexes Δ-**1c**,**d**.

Triphenylphosphine, 1,2-bis(diphenylphosphinoethane), *tert*-butanol, water, (*R*)-tryptophan and indole were tested as co-catalysts in the reaction catalysed by **1a–f** (Table 1, conditions B). The reaction catalysed by Δ-**1c** was most sensitive to the additives (Table 1, entry 5, conditions B). The most effective co-catalyst was triphenylphosphine (ee 77%, Table 1, conditions B, entry 5[c]). The chelating phosphine, DPPE, was less effective than triphenylphosphine (ee 45%, Table 1, conditions B, entry 5[d]). Indole was also effective in promoting the enantio-



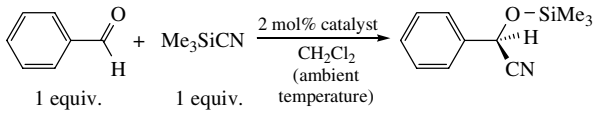
a M = Na
b M = H
c M = K
d M = Li
e M = Cs
f M = NBu_4

Scheme 1 *Reagents and conditions*: i, EtOH, reflux, 3 h; ii, chromatography on Al_2O_3 (EtOH); iii, ion exchange on DOWEX-50Wx8; iv, Sephadex LH-20 (C_6H_6/EtOH; 3:1).

† All the complexes had satisfactory analytical data.

Data for Λ-bis[*N*-salicyliden-(*R*)-tryptophanato]cobaltate potassium: $[\alpha]_D^{25}$ = +5281, $[\alpha]_{578}^{25}$ = +5506, $[\alpha]_{546}^{25}$ = +4893, (*c* 0.032, MeOH). ^{1}H NMR (D_2O) δ: 3.1–3.2 (m, 2H), 3.4–3.5 (m, 2H), 4.8–4.9 (m, 2H), 6.5–7.3 (m, 18H), 7.7 (s, 2H). Found (%): C, 60.26; H, 4.31; N, 7.14. Calc. for $C_{36}H_{28}N_4CoO_6K{\cdot}1^1/_2H_2O{\cdot}^1/_2C_6H_6$ (%): C, 60.31; H, 4.41; N, 7.21.

Data for Δ-bis[*N*-salicyliden-(*R*)-tryptophanato]cobaltate potassium: $[\alpha]_D^{25}$ = +3446, $[\alpha]_{578}^{25}$ = +3133, $[\alpha]_{546}^{25}$ = +473, (*c* 0.032, MeOH). ^{1}H NMR (D_2O) δ: 3.1–3.2 (m, 2H), 3.4–3.5 (m, 2H), 4.8–4.9 (m, 2H), 6.5–7.3 (m, 18H), 7.7 (s, 2H). Found (%): C, 60.58; H, 4.81; N, 7.21. Calc. for $C_{36}H_{28}N_4CoO_6K{\cdot}1^2/_3H_2O{\cdot}^2/_3C_6H_6$ (%): C, 60.60; H, 4.49; N, 7.07.



Scheme 2

selectivity of the reaction (ee 74%, Table 1, conditions B, entry 5[e]). The use of Bu^{t}OH, H_2O and (*R*)-tryptophane led to the complete disappearance of asymmetric induction (ee 0%, Table 1, conditions B, entry 5[f]). The change of the configuration of Co^{III} stereogenic centre from Δ-**1c** to Λ-**1c** brought about loss of the enantioselection (ee 0%, Table 1, conditions B, entry 6). Evidently, both the configuration of the complex and the nature of the countercation were the most important factors in determining the asymmetric efficiency of the catalysts, with the K^+ ion being much more efficient as compared to Li^+ (Table 1, entries 7, 8), Na^+ (Table 1, entries 1, 2) and H^+ (Table 1, entries 3, 4).

Large lipophilic Cs^+ (Table 1, entries 9, 10) and Bu_4N^+ (Table 1, entry 11) ions were also inefficient. Seemingly, the stability and structure of the ion pairs formed in solution by the complexes were of paramount importance in the reaction. This concept was supported by the use of 18-crown-6 as an additive, which resulted in the complete disappearance of the asymmetric catalytic efficiency of Δ-**1c**.

Table 1 Asymmetric trimethylsilylcyanation of benzaldehyde.[a]

Entry	Catalyst	Conditions A		Conditions B	
		Yield (%)	ee[b] (%) (configuration)	Yield (%)	ee[b] (%) (configuration)
1	Δ-**1a**	80	0	80	6.5 (R)[c]
2	Λ-**1a**	85	0	80	0[c]
3	Δ-**1b**	70	0	70	0[c]
4	Λ-**1b**	72	0	76	0[c]
5	Δ-**1c**	90	19 (*R*)	80–95	77 (*R*),[c] 45 (*R*),[d] 74 (*R*),[e] 0[f]
6	Δ-**1c**	85	0	80	0[c]
7	Δ-**1d**	80	6.5 (*S*)	83	6.5 (*S*)[c]
8	Λ-**1d**	80	0	85	0[c]
9	Δ-**1e**	70	0	70	0[c]
10	Λ-**1e**	75	0	75	0[c]
11	Δ-**1f**	90	0	92	0[c]

[a]Conditions A: benzaldehyde (1 mmol), TMSCN (1.1 mmol), catalyst **1** (2 mol%), CH_2Cl_2 (1 ml), stirring under Ar at ambient temperature; Conditions B: the same as A with a co-catalyst (0.1 mmol) added. [b]Determined by chiral GLC. [c]Co-catalyst is triphenylphosphine. [d]Co-catalyst is DPPE [1,2-bis(diphenylphosphinoethane)]. [e]Co-catalyst is indole. [f]Co-catalysts are Bu^{t}OH, H_2O and (*R*)-tryptophane.

Table 2 Time dependence of the enantiomeric excess of mandelonitrile in the Δ-**1c** catalysed reaction.[a]

Entry	*t*/min	Yield (%)	ee[b] (%)†
1	3	35	34 (*R*)
2	7	70	62 (*R*)
3	20	85	77 (*R*)
4	60	85	75 (*R*)

[a]Conditions: benzaldehyde (1 mmol), TMSCN (1.1 mmol), catalyst Δ-**1c** (2 mol%), triphenylphosphine (0.1 mmol) added, CH_2Cl_2 (1 ml), stirring under Ar at ambient temperature. [b]Determined by chiral GLC.

The time dependence of the product ee in the asymmetric trimethylcyanation of benzaldehyde catalysed by Δ-**1c** (conditions B, *c*) is presented in Table 2. The steady increase of the ee of the product with time indicates the formation of a real catalytic species different from the original complex during the reaction.

In summary, we identified a new multimetallic catalyst for asymmetric C–C bond formation reactions. The results will serve as an interesting addition to the rapidly growing field of multimetallic catalysts in organic synthesis.[4]

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