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Dynamic kinetic resolution of an azlactone catalyzed by octahedral chiral-at-metal cobalt(III) complexes under phase-transfer alcoholysis

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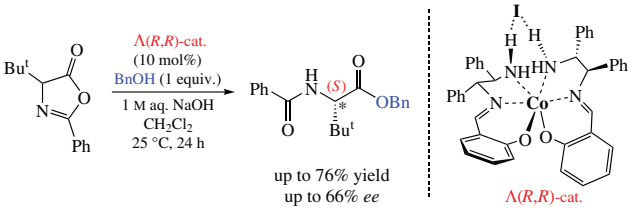
A family of well-defined octahedral cationic chiral-at-cobalt(III) catalysts based on (*R*,*R*)-1,2-cyclohexanediamine and (*R*,*R*)-1,2-diphenylethylenediamine has been examined in the dynamic kinetic resolution of an azlactone derived from *N*-benzoyl-*tert*-leucine. The reactions catalyzed by 10 mol% of Co^{III} complexes in the presence of 1 M aqueous NaOH solution under phase-transfer alcoholysis afforded the corresponding benzyl ester of *tert*-leucine with up to 76% yield and up to 66% enantioselectivity (*ee*).



Keywords: kinetic resolution, azlactone, amino acids, chiral-at-metal, cobalt(III) complexes.

Currently, chiral α-amino acids (α-AAs) play an important role in biochemistry, catalysis, drug design and the pharmaceutical industry.[1,2] Among the different strategies to generate enantioenriched α-AAs,[3–6] an asymmetric phase-transfer alkylation of readily available glycine derivatives with alkyl halides in the presence of chiral catalysts is one of the most accessible and convenient approaches.[7,8] Although this reaction allows one to obtain a diverse range of proteinogenic and unnatural α-AAs, mostly containing linear alkyl substituents,[7,8] the access to the enantioenriched congested α-AAs with branched or bulky groups at the α-carbon still remains a challenge.[9] For this purpose, the dynamic kinetic resolution of azlactones under phase-transfer alcoholysis is one of the straightforward protocols.[10–12]

We have previously introduced a new class of stereochemically inert cationic chiral-at-metal Co^{III} complexes **1**, **2** (Figure 1) as readily available and robust hydrogen bond donor phase-transfer 'organocatalysts in disguise'[13] for the asymmetric alkylation and Michael addition reaction of glycine derivatives with up to 96% enantioselectivity (*ee*).[14–17]

Given the importance of the enantiomerically pure bulky α-AAs (in particular, *tert*-leucine is a privileged chiral transient directing ligand in the asymmetric Pd-catalyzed C_{sp^3}-functionalization transformations[18]), we report here the preliminary results of the investigation of the well-defined chiral Co^{III} complexes **1**, **2** as phase-transfer catalysts for the dynamic kinetic resolution of an azlactone with benzyl alcohol (Scheme 1).

The studies started with an azlactone **A** derived from *N*-benzoyl-*tert*-leucine as a model substrate. The reaction conditions reported by Tokunaga *et al*. were used as a standard.[10] The resolution performed in $CHCl_3$ at 0 °C using a 1 M aqueous solution of NaOH as a base and one equivalent of benzyl alcohol in the presence of the Co^{III} complex Λ(*R*,*R*)-**1a** based on (*R*,*R*)-1,2-diphenylethylenediamine and salicylaldehyde gave the corresponding amino acid derivative **B** in 40% yield with *ee* of 58% (Table 1, entry 1). The *S*-configuration of the product was assigned by comparison of HPLC traces with literature data.[10] We then used the complex Λ(*R*,*R*)-**2b**, derived from (*R*,*R*)-1,2-cyclohexanediamine and 3,5-di-*tert*-butylsalicylaldehyde, which has previously shown high

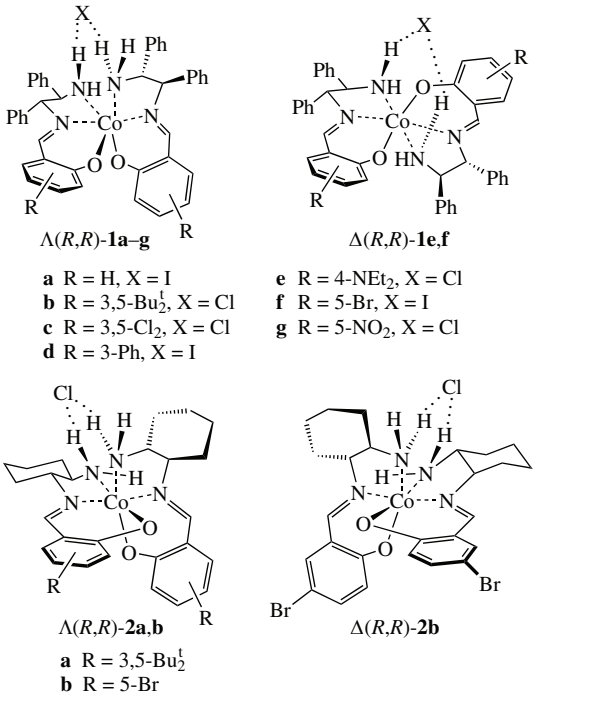
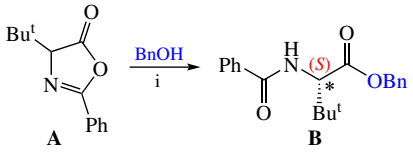


Figure 1 Structures of the octahedral chiral-at-metal Co^{III} complexes **1** and **2**.



Scheme 1 *Reagents and conditions*: i, BnOH (1 equiv.), catalyst (10 mol%), NaOH (1 M aq.), CH_2Cl_2, 25 °C, 24 h.

Table 1 Screening of chiral Co^{III} complexes **1**, **2** and conditions.[a]

Entry	Catalyst	Yield (%)[b]	*ee* (%)[c]
1[d,e]	Λ(*R*,*R*)-**1a**	40	58
2[d,e]	Λ(*R*,*R*)-**2a**	13	17
3[d]	Λ(*R*,*R*)-**1a**	40	58
4	Λ(*R*,*R*)-**1a**	60	60
5	Λ(*R*,*R*)-**1b**	11	50
6	Λ(*R*,*R*)-**1c**	18	60
7	Λ(*R*,*R*)-**1d**	26	60
8	Λ(*R*,*R*)-**1e**	47	43
9	Δ(*R*,*R*)-**1e**	30	0
10	Λ(*R*,*R*)-**1f**	31	58
11	Δ(*R*,*R*)-**1f**	28	30
12	Λ(*R*,*R*)-**1g**	15	63
13	Λ(*R*,*R*)-**2b**	40	10
14	Δ(*R*,*R*)-**2b**	22	10
15[f]	Λ(*R*,*R*)-**1a**	10	28
16[g]	Λ(*R*,*R*)-**1a**	–	–

[a]Reaction conditions: azlactone **A** (21.7 mg, 0.1 mmol), catalyst (10 mol%, 0.01 mmol), NaOH (1 M aq., 0.2 ml, 0.2 mmol, 2 equiv.), BnOH (10.3 μl, 0.1 mmol, 1 equiv.), CH_2Cl_2 (0.8 ml), room temperature, 24 h. [b]Yields were determined by ^{1}H NMR analysis using HMDSO as an internal standard. [c]Enantiomeric purity was determined by chiral HPLC analysis using the Chiralcel OD-H column. [d]$CHCl_3$ was used as a solvent. [e]Reaction was performed at 0 °C. [f]EtOH was used instead of BnOH. [g]Pr^{i}OH was used instead of BnOH.

enantiocontrol in asymmetric alkylation and Michael addition reactions.[14,15] However, this complex gave the desired product **B** with essentially lower *ee* (17%) and yield (13%) (entry 2). The reaction carried out at room temperature with the catalyst Λ(*R*,*R*)-**1a** provided similar results (entry 3). Changing the solvent to CH_2Cl_2 increased the yield and the enantiocontrol (60% *ee*) (entry 4).

Next, complexes **1** with electron-donor and acceptor substituents at the different positions in the salicylidene moiety were investigated (entries 5–12). Complexes **1** with Λ-configurations afforded the desired (*S*)-product **B** with similar *ee* values (43–64%), while the yields ranged between 11–47% (entries 5–8, 10 and 12).

On the other hand, the Δ-diastereomers of complexes **1e** and **1f** provided the corresponding ester **B** either with very low stereoselectivity (30% *ee*) or even in racemic form (entries 9 and 11). Notably, we have also observed differences in reaction enantioselectivity depending on the configuration at the metal center of the complexes in other reactions.[17] Interestingly, in the case of both the Λ- and Δ-complexes of **2b**, the formation of the same enantiomer of the product **B** was observed with 10% *ee* (entries 13 and 14). It is of note that the resolution of an azlactone **A** with ethanol gave the ethyl ester with low enantioselectivity (28%) and only 10% yield after 24 h (entry 15) while with Pr^{i}OH the reaction did not proceed (entry 16).

The effectiveness of different bases was then examined. Obviously, the aqueous solutions of Bu^{t}OK and KOH gave results comparable to those obtained with NaOH (Table 2, entries 1 and 2). The use of solid NaOH reduced the yield to 5%, although the *ee* was higher (66%) (entry 3). Cesium carbonate as the base produced the desired product **B** with 44% *ee* and 20%

Table 2 Screening of bases in the kinetic resolution of azlactone **A** catalyzed by chiral Co^{III} complex Λ(*R*,*R*)-**1a**.[a]

Entry	Base	Yield (%)[b]	*ee* (%)[c]
1[d]	Bu^{t}OK	42	60
2[d]	KOH	44	58
3	NaOH	5	66
4	Cs_2CO_3	20	44
5	K_3PO_4	55	5
6	Et_3N	traces	–
7	DIPEA	6	–
8	DBU	76	4

[a]Reaction conditions: see footnote to Table 1. [b]Yields were determined by ^{1}H NMR using HMDSO as an internal standard. [c]Enantiomeric purity was determined by chiral HPLC analysis using the Chiralcel OD-H column. [d]1 M aqueous solution (0.2 mmol, 2 equiv.) was used.

yield (entry 4). Somehow, K_3PO_4 proved to be less active in terms of enantioselectivity giving the ester **B** in moderate yield (55%) with only 5% *ee* (entry 5). Organic bases such as Et_3N and DIPEA were inactive in the reaction (entries 6 and 7); probably their basicity was not sufficient to deprotonate an azlactone. As expected, more basic DBU gave the amino acid derivative **B** in high yield (76%); however, the enantiocontrol was lost, suggesting a possible background reaction catalyzed by the base itself rather than by a Co^{III} catalyst **1a** (entry 8). It is noteworthy that in all cases the conversion was almost complete and the formation of the free amino acid due to the hydrolysis of azlactone **A** with water was observed.

In conclusion, we have herein presented preliminary results of the study of a family of well-defined octahedral cationic chiral-at-cobalt(III) complexes based on (*R*,*R*)-1,2-cyclohexanediamine and (*R*,*R*)-1,2-diphenylethylenediamine as phase-transfer catalysts for the dynamic kinetic resolution of an azlactone derived from *N*-benzoyl-*tert*-leucine with benzyl alcohol. Although the enantioselective control in the reaction was not high enough (*ee* up to 66%), yet the possibility of applying these Co^{III} complexes in new reaction was demonstrated. In this context, the implementation of the presented and modified Co^{III} complexes in other asymmetric transformations using azlactones as substrates is underway in our laboratory.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.015.

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