Bifunctional Catalysts

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Werner Complexes with ω-Dimethylaminoalkyl Substituted Ethylenediamine Ligands: Bifunctional Hydrogen-Bond-Donor Catalysts for Highly Enantioselective Michael Additions

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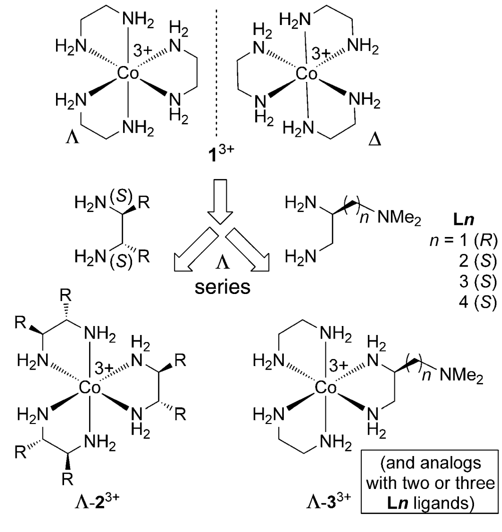
Abstract: *The racemic carbonate complex* $[Co(en)_2O_2CO]^+ Cl^-$ *(en = 1,2-ethylenediamine) and* (S)-$[H_3NCH((CH_2)_nNHMe_2)CH_2NH_3]^{3+}\,3\,Cl^-$ *($n = 1$–4) react (water, charcoal, 100°C) to give* $[Co(en)_2((S)\text{-}H_2NCH((CH_2)_nNHMe_2)CH_2NH_2)]^{4+}\,4\,Cl^-$ *(**3a–d**$H^{4+}\,4\,Cl^-$) as a mixture of Λ/Δ diastereomers that separate on chiral-phase Sephadex columns. These are treated with* $NaOH/Na^+\,BAr_f^-$ *($BAr_f = B(3,5\text{-}C_6H_3(CF_3)_2)_4$) to give lipophilic Λ- and Δ-**3a–d**$^{3+}\,3\,BAr_f^-$, which are screened as catalysts (10 mol%) for additions of dialkyl malonates to nitroalkenes. Optimal results are obtained with Λ-**3c**$^{3+}\,3\,BAr_f^-$ (CH_2Cl_2, −35°C; 98–82% yields and 99–93% ee for six β-arylnitroethenes). The monofunctional catalysts Λ- and Δ-$[Co(en)_3]^{3+}\,3\,BAr_f^-$ give enantioselectivities of <10% ee with equal loadings of Et_3N. The crystal structure of Δ-**3a**$H^{4+}\,4\,Cl^-$ provides a starting point for speculation regarding transition-state assemblies.*

During the past two decades, numerous types of small-molecule hydrogen-bond-donor catalysts have been developed, almost always under the umbrella of "organocatalysis".[1,2] These have included many chiral, enantiopure species, and applications to a variety of enantioselective organic reactions.[2] We have sought to broaden this field to include inorganic and organometallic hydrogen-bond donors that feature earth-abundant metals and chirality motifs not normally achievable in organic architectures.[3–5] Allied themes have been studied by Meggers and others.[6–8] Importantly, the performances of hydrogen-bond-donor catalysts are often markedly improved when they are rendered bifunctional.[5b,9–11] For example, thioureas constitute a widely applied class of twofold NH bond donors,[2,10,12] and the incorporation of tertiary amines can give catalysts that afford superior rates, yields, and enantioselectivities in addition reactions.[10]

In previous studies, our attention has been drawn to Werner complexes of cobalt(III) and 1,2-diamines.[3] These represent textbook examples of substitution inert low-spin d^6 complexes, and are therefore incapable of traditional-metal-based substrate activation. However, the coordinated NH groups are superb hydrogen-bond donors.[3] Furthermore, salts of the helically chiral ethylenediamine substituted cations $[Co(en)_2(A)(A')]^{n+}$ and $[Co(en)_3]^{3+}$ (**1**$^{3+}$) are the first inorganic molecules to be separated into enantiomers.[13] The mirror images of the trication **1**$^{3+}$ are depicted in Scheme 1, together with the Λ/Δ descriptors employed to distinguish the cobalt configurations. By using lipophilic anions such as BAr_f^- ($B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$), this species could be solubilized in nonpolar solvents that do not compete with substrates for the hydrogen bonding sites.[3a] However, while Λ- or Δ-**1**$^{3+}$ $3\,BAr_f^-$ proved to be competent catalysts, enantioselectivities have been modest in all reactions assayed to date (≤33% *ee*).



Scheme 1. Design of families of cobalt(III) hydrogen-bond-donor catalysts.

Hence, two related families of catalysts were targeted. As shown in Scheme 1, one involved analogues with 1,2-disubstituted diamines. As described elsewhere, those with aryl substituents have afforded greatly improved enantioselectivities.[3b] The other involved the exchange of one or more of the 1,2-ethylenediamine ligands by analogues with ω-dimethylaminoalkyl substituents, $H_2NCH((CH_2)_nNMe_2)CH_2NH_2$ (n = **a**, 1; **b**, 2; **c**, 3; **d**, 4; **L1–L4**).[14] Herein, we report that when a single ethylenediamine ligand in **1**$^{3+}$ is replaced by **L*n*** with a suitable methylene spacer length (n), exceptional catalysts are obtained that match or exceed the highest enantioselectivities realized with hydrogen-bond donors to date.

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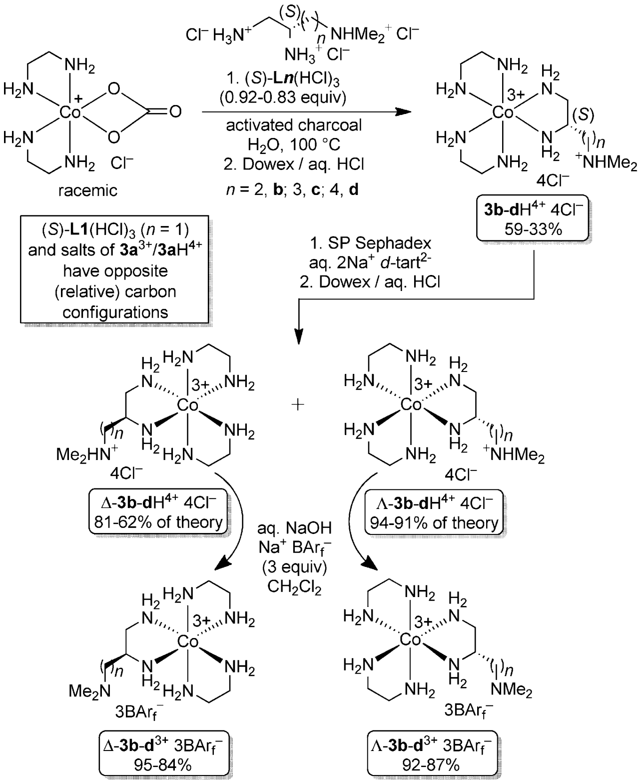


Scheme 2. Syntheses of bifunctional catalysts **3a–d**$^{3+}$ 3 BAr$_f^-$ from (*S*)-**L*n***(HCl)$_3$ ($n = 1$–4).

As depicted in Scheme 2, the triply protonated triamine ligands (*S*)-**L*n***(HCl)$_3$ ($n = 1$–4, 0.92–0.83 equiv)[14] and the racemic carbonate complex $[Co(en)_2O_2CO]^+$ Cl^-[15] were combined in water in the presence of activated charcoal and heated to 100°C. In this process, the charcoal labilizes the normally substitution inert cobalt(III) starting material,[16] and the carbonate ligand that is displaced acts as a dibase, deprotonating the two $-NH_3^+$ moieties of (*S*)-**L*n***(HCl)$_3$. The resulting tetracation salts $[Co(en)_2((S)\text{-}H_2NCH((CH_2)_nNMe_2H)CH_2NH_2)]^{4+}$ 4 Cl$^-$ (**3a-d** H^{4+} 4 Cl$^-$) were separated from redistribution products using a DOWEX 50WX2 ion exchange resin column (Scheme 2). This gave hydrates of **3a–d** H^{4+} 4 Cl$^-$ as orange powders in 59–33% yields (based upon the limiting triamine) as mixtures of Λ/Δ diastereomers (**a**, 30:70; **b–d**, 70–72:30–28), consistent with the use of a racemic cobalt carbonate precursor.

The reusable chiral support Sephadex has often been employed to separate enantiomeric and diastereomeric cobalt(III) diamine complexes.[17] When **3a-d** H^{4+} 4 Cl$^-$ were eluted from Sephadex columns with tartrate gradients, 2 Na$^+$ *d*-tart^{2-}, two well resolved bands were obtained. These were eluted through DOWEX columns to exchange the tartrate anions back to chloride anions. The resulting Λ- and Δ-**3a–d** H^{4+} 4 Cl$^-$ were characterized by NMR ($^1H/^{13}C\{^1H\}$, D$_2$O) and elemental analyses as summarized in the Supporting Information. The cobalt configurations were assigned by CD spectroscopy as illustrated in Figure 1 (inset) and the Supporting Information, and that of Δ-**3a** H^{4+} 4 Cl$^-$ was confirmed by the crystal structure shown in Figure 2.

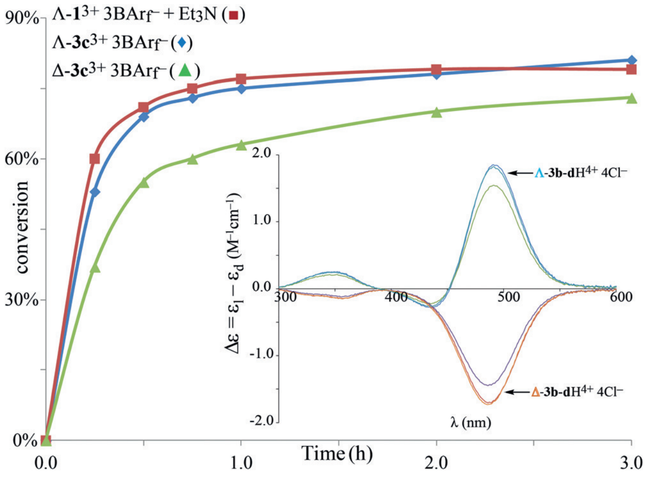


Figure 1. Rates of reaction of *trans*-β-nitrostyrene (**4a**) and dimethyl malonate (**5**-Me, 1.2 equiv) in CD$_2$Cl$_2$ in the presence of an internal standard and catalyst (2 mol%; all runs at equal concentrations, RT): (■) Λ-**1**$^{3+}$ 3 BAr$_f^-$/Et$_3$N, (◆) Λ-**3c**$^{3+}$ 3 BAr$_f^-$, (▲) Δ-**3c**$^{3+}$ 3 BAr$_f^-$, and (not depicted) Λ-**1**$^{3+}$ 3 BAr$_f^-$ (<3% conversion after 2 h); Inset: CD spectra of Λ-**3b-d** H^{4+} 4 Cl$^-$ and Δ-**3b–d** H^{4+} 4 Cl$^-$. For additional spectra, see the Supporting Information.

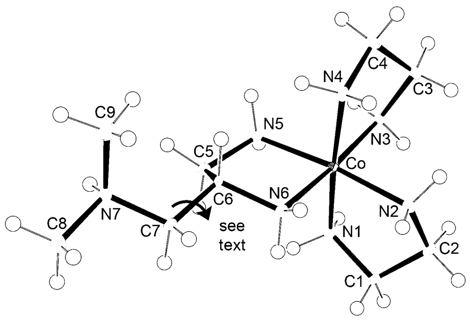
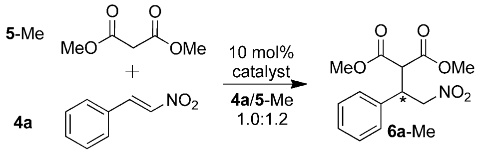


Figure 2. The crystal structure of the tetracation of Δ-**3a** H^{4+} 4 Cl$^-$·3 H$_2$O with ellipsoids set at 50% probability. For key bond lengths and angles, see the Supporting Information.[22]

It was next sought to solubilize deprotonated analogues of the diastereomerically pure cations in organic media. Thus, Λ- and Δ-**3a–d** H^{4+} 4 Cl$^-$ were treated with aqueous NaOH (1.0 equiv) and then CH$_2$Cl$_2$ solutions of Na$^+$ BAr$_f^-$. Workups gave Λ- and Δ-$[Co(en)_2((S)\text{-}H_2NCH((CH_2)_nNMe_2)CH_2NH_2)]^{3+}$ 3 BAr$_f^-$·xH$_2$O (**3a–d**$^{3+}$ 3 BAr$_f^-$·xH$_2$O; $x = 9$–12) as orange solids in 92–87% and 95–84% yields, respectively (51–25% overall from **L*n***). Attempts to completely remove the hydrate molecules, which are presumably hydrogen bonded to the NH moieties in a "second coordination sphere", resulted in decomposition (40–80°C, vacuum; see the Supporting Information).

The diastereomerically pure BAr$_f^-$ salts were screened as catalysts (10 mol%) for additions of dimethyl malonate (**5**-Me, 1.2 equiv) to *trans*-β-nitrostyrene (**4a**) at room temperature. This transformation has been effected by other hydrogen-bond-donor catalysts, always in conjunction with an external or internal base,[3b,5,18] as well as transition-metal catalysts.[19] In accord with the oxidative and hydrolytic stabilities of cobalt(III) diamine complexes, reactions were



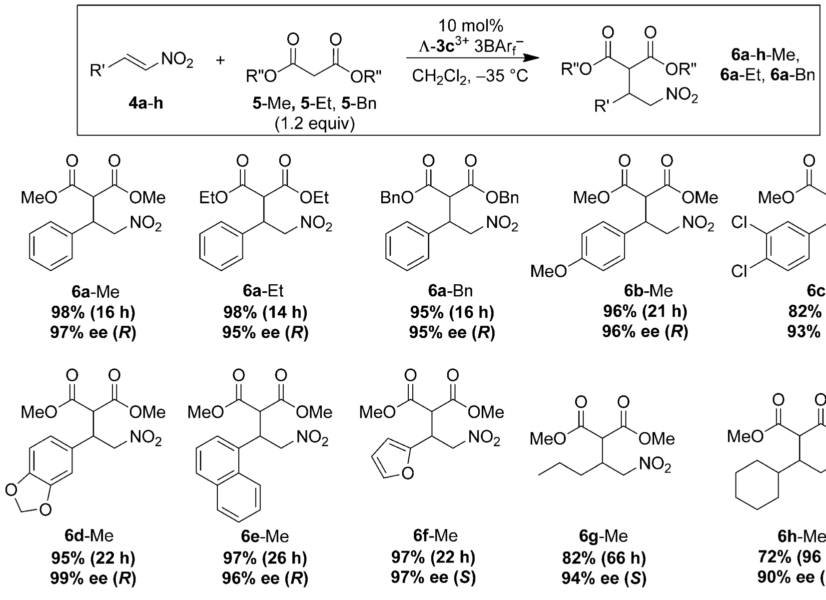
entry	solvent	catalyst	temp	conversion (%) (time)[a]	ee (%) (config)[a]
1	CD_2Cl_2	Λ-**3a**$^{3+}$ 3BAr$_f^-$	rt	20 (48 h)	21 (*S*)[b]
2	CD_2Cl_2	Δ-**3a**$^{3+}$ 3BAr$_f^-$	rt	33 (48 h)	11 (*S*)[b]
3	CD_2Cl_2	Λ-**3b**$^{3+}$ 3BAr$_f^-$	rt	85 (24 h)	75 (*R*)
4	CD_2Cl_2	Δ-**3b**$^{3+}$ 3BAr$_f^-$	rt	42 (45 h)	9 (*R*)
5	CD_2Cl_2	Λ-**3c**$^{3+}$ 3BAr$_f^-$	rt	99 (2 h)	86 (*R*)
6	CD_2Cl_2	Δ-**3c**$^{3+}$ 3BAr$_f^-$	rt	99 (4 h)	5 (*R*)
7	CD_2Cl_2	Λ-**3d**$^{3+}$ 3BAr$_f^-$	rt	85 (6 h)	48 (*R*)
8	CD_2Cl_2	Δ-**3d**$^{3+}$ 3BAr$_f^-$	rt	70 (3 h)	33 (*R*)
9	CD_3CN	Λ-**3c**$^{3+}$ 3BAr$_f^-$	rt	80 (24 h)	31 (*R*)
10	[D$_6$]acetone	Λ-**3c**$^{3+}$ 3BAr$_f^-$	rt	79 (4 h)	46 (*R*)
11	CD_2Cl_2	Λ-**3c**$^{3+}$ 3BAr$_f^-$	0 °C	99 (6 h)	86 (*R*)
12	CD_2Cl_2	Λ-**3b**$^{3+}$ 3BAr$_f^-$	−35 °C	35 (48 h)	73 (*R*)
13	CD_2Cl_2	Λ-**3c**$^{3+}$ 3BAr$_f^-$	−35 °C	97 (15 h)	97 (*R*)
14	CD_2Cl_2	Λ-**3d**$^{3+}$ 3BAr$_f^-$	−35 °C	75 (48 h)	62 (*R*)

[a] For experimental details see the supporting information. [b] The *relative* configuration of the carbon stereocenter in this catalyst is opposite to the others.

Scheme 3. Optimization of conditions for catalysis.

carried out in air. Conversions into the addition product **6a**-Me were assayed by ^{1}H NMR in the presence of an internal standard. Key data are summarized in Scheme 3.

When either diastereomer of **3a**$^{3+}$ 3BAr$_f^-$ was employed in CD_2Cl_2, reactions were sluggish at room temperature and **6a**-Me was obtained in only 21–11% *ee* (entries 1, 2). However, Λ-**3b**$^{3+}$ 3BAr$_f^-$ was a much more effective catalyst (entry 3), affording 85% conversion to **6a**-Me of 75% *ee* (*R* major) after 24 h. In contrast, the diastereomer Δ-**3b**$^{3+}$ 3BAr$_f^-$ was a sluggish catalyst (entry 4), and gave **6a**-Me of only 9% *ee* (*R* major). When the methylene tether was further lengthened to give Λ- and Δ-**3c**$^{3+}$ 3BAr$_f^-$, both diastereomers exhibited much faster rates (≥ 99% conversions, 2–4 h; entries 5–6). However, the Λ diastereomer again gave a much more enantioselective reaction (86% vs. 5% *ee*). Finally, Λ- and Δ-**3d**$^{3+}$ 3BAr$_f^-$ gave somewhat slower rates, with more comparable enantioselectivities (48% vs. 33% *ee*; entries 7, 8). Interestingly, in every case the dominant product configuration was controlled by the ligand-based carbon stereocenter.



Scheme 4. Scope of additions under optimum conditions.

The most enantioselective catalysts, Λ-**3b**-**d**$^{3+}$ 3BAr$_f^-$, were further studied. With Λ-**3c**$^{3+}$ 3BAr$_f^-$, the *ee* values decreased when reactions were conducted in acetonitrile or acetone (entries 9, 10 vs. 5). However, Λ-**3c**,**d**$^{3+}$ 3BAr$_f^-$ afforded much higher enantioselectivities when reactions were conducted at −35 °C (entries 13, 14), with the former giving 97% conversion to **6a**-Me of 97% *ee* after 15 h. Accordingly, these conditions were applied to a variety of other substrates according to Scheme 4. The yield data are for isolated products.

As shown in Scheme 4, enantioselectivities decreased only slightly when dimethyl malonate was replaced by the diethyl or dibenzyl esters (from 97% to 95% *ee*). When electron-donating or -withdrawing substituents were introduced on the phenyl ring of **4a**, the *ee* values remained high (99–93% *ee*). Similar values were obtained with other aryl moieties such as 1-naphthyl and 2-furyl (97–96% *ee*). However, particularly noteworthy were analogous additions to β-alkylnitroethenes. These afforded adducts of 94–90% *ee*, a rarely seen level of asymmetric induction, as further analyzed in the Supporting Information.

In view of these excellent results, the rates of several catalytic systems were monitored by ^{1}H NMR using 2% loadings in CD_2Cl_2 at ambient temperature. As shown in Figure 1, when the monofunctional complex Λ-**1**$^{3+}$ 3BAr$_f^-$ (Scheme 1), augmented by an equimolar quantity of Et_3N, was compared to bifunctional Λ-**3c**$^{3+}$ 3BAr$_f^-$, nearly equal rates were found. However, the former system gave only a 9% *ee*, as opposed to 81% for the latter. The less enantioselective diastereomeric catalyst Δ-**3c**$^{3+}$ 3BAr$_f^-$ gave a slower rate. Importantly, when Λ-**1**$^{3+}$ 3BAr$_f^-$ was employed in the absence of an external base, there was no detectable conversion after 2 h (< 3%).

The trends in Scheme 3 raise a number of issues. Efficacies in enantioselective catalysis are normally analyzed in the context of a ΔΔ$G^{\neq}$ value for two competing diastereomeric transition states. Given the lower symmetries of Λ-**3b**-**d**$^{3+}$ $3\,\mathrm{BAr_f}^-$ (C_1) compared to the trication **1**$^{3+}$ or substituted analogues **2**$^{3+}$ (Scheme 1; both D_3), a much wider range of ternary assemblies are possible. Since the carbon configurations of the catalysts set the dominant product configurations, we suggest that the malonate esters simultaneously interact with the dimethylamino groups and the proximal NH donor sites, and that this somehow fixes the nitroethene C=C enantioface that is predominantly attacked.[10a,20] For the system in Figure 2 (protonated form of a poor catalyst), this would correspond to N7 (after rotation about C6–C7) and the nearest hydrogen atoms on N1, N5, or N6. In any event, Scheme 3 establishes a "sweet spot" with respect to both rate and enantioselectivity with three methylene groups and Λ/S cobalt/carbon configurations.[21]

In conclusion, we have shown that the performance of hydrogen-bond-donor catalysts based upon the "second coordination sphere" of Werner cobalt(III) diamine complexes can be dramatically enhanced by incorporating additional functionality. Such cobalt systems are exciting new additions to the pool of chiral building blocks for enantioselective catalysts. Since many more NH bonds are available to simultaneously participate in transition-state assemblies than with thioureas or related NH bond donors, these species should also give rise to new chemistries not realizable with established catalysts. Finally, it is worth noting that few of the reviews on organocatalysis[1,2] attempt to treat related systems with "spectator" metal fragments that do not directly participate in bond-breaking or -making. This unfortunate emphasis on pedigree over functionality only serves to obscure logical mechanism-based connections and impede the discovery of new classes of catalysts. Indeed, given the countless numbers of classical coordination compounds featuring NH donor ligands, it is highly probable that many additional families of metal-containing hydrogen-bond-donor catalysts have been in existence for some time.

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[22] CCDC 1439942 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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