COBALT(III) WERNER COMPLEXES AS ASYMMETRIC CATALYSTS: A BIFUNCTIONAL APPROACH

A Dissertation

by

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DOCTOR OF PHILOSOPHY

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ABSTRACT

Alfred Werner's seminal work at the close of the 19th century was a stereochemical primer in the field of coordination chemistry. One limitation of these complexes, solubility, was modified more than 100 years later to usher in the *neo*complexes of Gladysz, et al. This chiral hydrogen bond-donor catalyst has demonstrated in many embodiments to be an effective and versatile agent to carry out asymmetric Michael-type reactions.

When coordinated with three diphenylethylene diamine (dpen) ligands, this homoleptic cobalt cation exists in two easily separable diastereomeric forms (Λ and Δ), and is most commonly paired with two chloride anions and a lipophilic, non-coordinating BAr_f^- anion ($B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$). Chloride anions can be easily metathesized in biphasic conditions with chiral anions. Though these anions give only modest benefit, the significance of the anion is observed in the data. In some cases, synergistic "matched" ion pairs compared to their diastereomeric "mismatched" pair give differences in enantioselectivities of greater than 20%.

The role of the anion was later exploited through the intentional incorporation of a Brønsted base. These anions give significant improvement in rates relative to external bases of equal pK_a and show comparable enantioselectivity to stronger external bases. These catalysts have also been shown to work effectively in solvent-free conditions with only minor detriment to stereoselectivity of the catalyzed reaction, but with reaction times rapidly accelerated.

Finally, libraries of novel ligands for bifunctional catalysis have been synthesized, where the synthesis of a small family of chiral secondary triamines is disclosed herein. These advances demonstrate a new bifunctional approach to catalysis with cobalt(III) Werner complexes.

DEDICATION

To Max, Reagan, and Jack, who taught me more than I could ever teach them.

ACKNOWLEDGEMENTS

I would like to acknowledge the support of my PI, John Gladysz, whose positive attitude and untiring drive were daily inspiration. His support and perseverance were a foundation through my PhD and the lessons learned have created a solid foundation for my future career.

I am thankful to the undergraduate students Max Selbst, Jack Gunn, and Reagan Lucas, who gave hours of their time working with me in the lab.

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CONTRIBUTORS AND FUNDING SOURCES

Contributors

Part 1. Faculty Committee Recognition

This work was supervised by a dissertation committee consisting of Dr. John A. Gladysz, Dr. David E. Bergbreiter, and Dr. Daniel A. Singleton of the Department of Chemistry, and Dr. Samuel Ma of the Department of Environmental Engineering.

Part 2. Student/Collaboration Contributions

The work in Chapter 2 was completed by the student in collaboration with William J. Maximuck, who contributed equally to this project, Subrata K. Ghosh, and Anil Kumar of the Department of Chemistry. All crystal structures were determined by crystallographers Dr. Kevin Gagnon of the Advanced Light Source, Lawrence Berkeley National Laboratory, 6 Cyclotron Road, Berkeley, CA 94720, and Nattamai Bhuvanesh of the Department of Chemistry.

The work in Chapter 3 was completed by the student in collaboration with undergraduate contributors Maximillian A. Selbst, Jack H. Gunn, and Reagan F. Lucas of the Department of Chemistry.

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1. INTRODUCTION[†]

1.1. Introduction

1911 was a good year for Alfred Werner, especially the second half. Between the 24th of July and the 18th of December, he submitted five papers detailing the resolution of racemic chiral cobalt(III) 1,2-ethylenediamine (en) complexes of the types shown in Figure 1.1 into their constituent enantiomers.[1] These were the first chiral inorganic compounds to be isolated in enantiopure form, a milestone in the history of stereochemistry. This work also circled back to Pasteur's landmark 1848 study in that the protocol for the trication $[Co(en)_3]^{3+}$ ($\mathbf{1}^{3+}$; Figure 1.1C) employed tartrate salts, the diastereomers of which could easily be crystallized apart. This procedure continues to be followed virtually unchanged to this day in the form of senior undergraduate inorganic laboratory experiments at many North American Universities.[2]

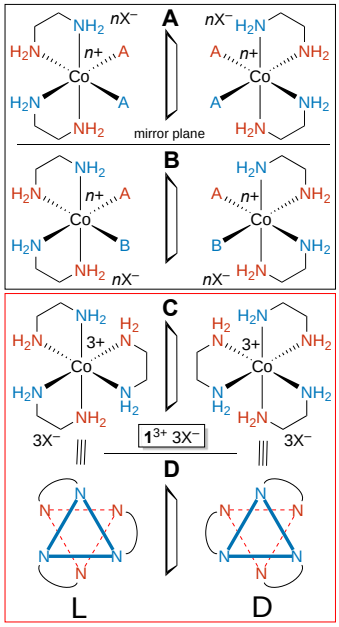


Figure 1.1. Racemic chiral 1,2-ethylenediamine cobalt(III) complexes resolved into enantiomers by Werner in 1911.

[†]Reprinted with permission from "Launching Werner Complexes into the Modern Era of Catalytic Enantioselective Organic Synthesis" by Wegener, A. R.; Kabes, C. Q.; Gladysz, J. A. *Acc. Chem. Res.* **2020**, *53*, 2299-2313. Copyright 2020 by the American Chemical Society

The complexes in Figure 1.1 can be considered "chiral at metal",[3] with configurations commonly denoted as Λ or Δ.[4,5] These correspond to left or right handed helical arrays of the chelating ligands, respectively, as depicted for $\mathbf{1}^{3+}$ $3X^{-}$ (Figure 1.1D). Numerous less obvious stereochemical features attend such complexes – one being the intrinsic chirality of the five membered chelate rings and implications for the positioning of any backbone substituents. A review has been published which provides an in-depth treatment.[5]

Importantly, the trication $\mathbf{1}^{3+}$ exhibits idealized D_3 symmetry. This means a principal C_3 axis, which runs perpendicular to the plane of the paper in Figure 1.1D, as well as three C_2 axes, contained in the plane of the paper. The former exchanges nitrogen atoms of the same color, and the latter nitrogen atoms of opposite colors. As shown in Figure 1.2E-F, the C_3 axis defines two "C_3 faces", each with three synperiplanar NH groups. Every C_2 axis defines one "C_2 face" with two roughly synperiplanar NH groups (Figure 1.2G-H). The protons associated with each NH_2 group are diastereotopic and normally give distinct ^{1}H NMR signals; one is directed at a C_3 face, and the other at a C_2 face.

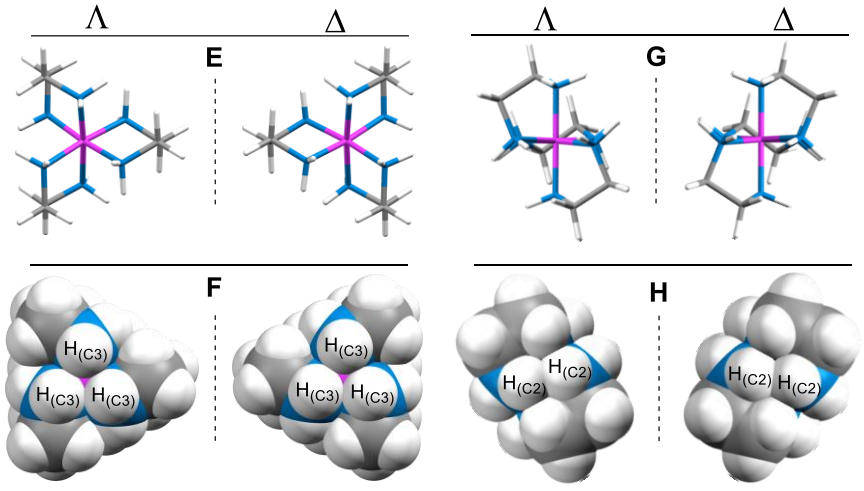


Figure 1.2. Idealized wireframe and space filling representations of the C_3 (E,F) and C_2 (G,H) faces of tris(ethylenediamine) cations $[M(en)_3]^{n+}$.

Werner later expanded his portfolio of enantiopure complexes to include other metals, e.g. $[M(en)_3]^{n+}$ nX^- with M/n = Cr/3, Rh/3, Ir/3, and Pt/4.[6] This body of work is still used today to illustrate textbook principles of inorganic chemistry in advanced courses. For example, the cobalt trication $\mathbf{1}^{3+}$ is notoriously substitution inert[7,8] owing to the high field nitrogen donor ligands and filled t_{2g} orbital set associated with low spin d^6 electronic configurations.[9] This precludes traditional modes of catalysis in which the metal directly binds and activates a substrate. Hence, there has been a conspicuous absence of applications in stoichiometric or catalytic organic synthesis.

The half-lives for the racemization or hydrolysis of $\mathbf{1}^{3+}$ $3Cl^-$ in 0.10 M aqueous NaOH at 25 °C have been estimated as $\geq$3.2 years.[7] Furthermore, no racemization occurs in aqueous solution during (a) 3 months at room temperature, (b) 75 minutes at 85 °C in the presence of 100 equiv of $NaNO_2$, or (c) 15 hours at reflux in the presence of HCl. However, when activated charcoal is added, racemization takes place within two minutes at 90 °C.[10,11] The charcoal (or trace impurities therein) is believed to function as a redox catalyst, generating small amounts of substitution labile cobalt(II).

Transition metal complexes can express a variety of chirality motifs, some of which have little or no counterpart in organic molecules.[12] Accordingly, there has been a long standing interest in bringing metal-containing structural units into the "chiral pool" for enantioselective organic synthesis.[13] With respect to cost, air- and water-stabilities, and ease of access, enantiopure salts of $\mathbf{1}^{3+}$ are very attractive building blocks. How might catalysis with such substitution inert species be effected?

In this regard, systems that operate in part by "outer" or "second" coordination sphere mechanisms have been receiving increasing attention.[14,15] For example, Noyori, Ikariya, and coworkers have developed a variety of chiral ruthenium complexes that feature chelates with Ru-NH linkages and serve as enantioselective catalysts for (transfer)

hydrogenations of ketones.[16] As excerpted in Figure 1.3, the mechanisms involve migration of an inner coordination sphere hydride ligand to the carbonyl carbon atom and outer sphere protonation of the oxygen atom by the NH moiety. Other types of catalysts that exploit outer sphere proton transfer steps are emerging.[15]

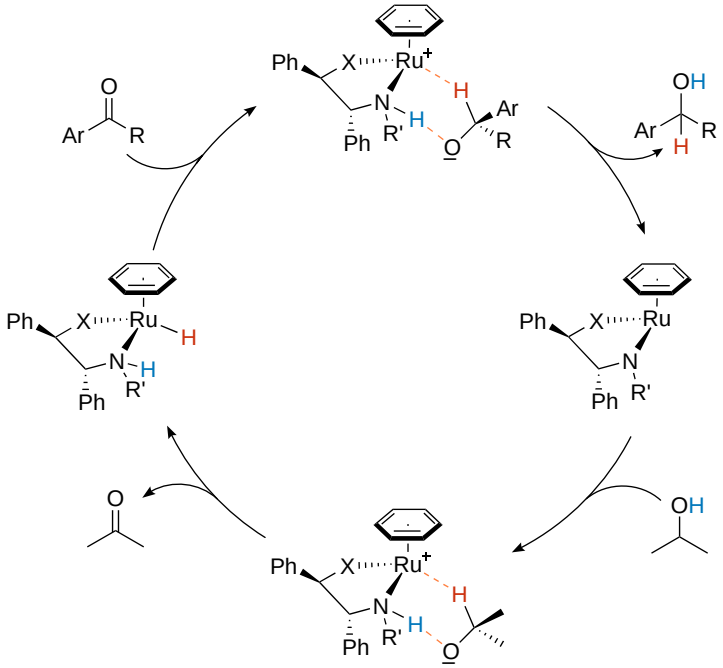


Figure 1.3. A family of enantioselective ruthenium catalysts for the transfer hydrogenations of ketones that involves migration of an inner coordination sphere hydride ligand and protonation by an outer sphere NH group.

Furthermore, over the last 20 years, many chiral "organocatalysts" have been developed that activate suitable substrates by serving as NH or OH hydrogen bond donors.[17] It seemed to us that the ligating NH groups of cationic 1,2-diamine complexes should be able to function analogously, prompted by two traits in particular. First, over 150 crystal structures of $[Co(en)_3]^{3+}$ ($\mathbf{1}^{3+}$) salts have been determined, and in every case hydrogen bonding is found between the NH groups and counter anions.[18] Often there is some water of crystallization, and these molecules also hydrogen bond to the NH groups. Second, the pK_a of $\mathbf{1}^{3+}$ $3Cl^-$, 14.9,[19] is typical of other NH hydrogen bond donor catalysts.[17]

The water of crystallization poses a concern, namely that for reactions carried out in protic media, the solvent could compete with substrates for the NH hydrogen bonding sites. This could retard or even shut down catalysis. Thus, lipophilic salts of $\mathbf{1}^{3+}$, which at the time were essentially unknown, were sought out.

1.2. First Generation Catalyst

Werner carried out his chemistry under aqueous aerobic conditions. Halide salts are the most common end products, and none exhibit any appreciable lipophilicity.[1] The racemic tetraphenylborate salt $\mathbf{1}^{3+}$ $3B(C_6H_5)_4^-$ was prepared some time later[20] and noted to be soluble in methanol and acetone. Related fluorinated tetraarylborate salts, particularly with the "barf" anion, $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$ (BAr_f^-), were sought out. This species is highly lipophilic, very poorly coordinating,[21] and a feeble hydrogen bond acceptor.[22]

Thus, as described by Ganzman in 2008, an aqueous solution of the iodide salt $\mathbf{1}^{3+}$ $3I^-$ was combined with a CH_2Cl_2 solution of Na^+ BAr_f^-.[23] As shown in Figure 1.4, the color associated with the trication $\mathbf{1}^{3+}$ was extracted into the CH_2Cl_2 phase. After taking the CH_2Cl_2 layer to dryness, analytically pure $\mathbf{1}^{3+}$ $3BAr_f^-$ was obtained. However, the trication "carries" some water into CH_2Cl_2, presumably hydrogen bonded to the NH groups in a second coordination sphere. This is found for all salts of the formula $[M(en)_3]^{n+}$ $nBAr_f^-$, which are similarly prepared (M/n = Cr/3, Rh/3, Ir/3, Pt/4).[24] TGA data indicate that the water molecules can be removed, but samples rapidly rehydrate in the often humid Texas atmosphere. Interestingly, the hydration levels drop when aryl substituents are added to the ethylenediamine ligand backbones.

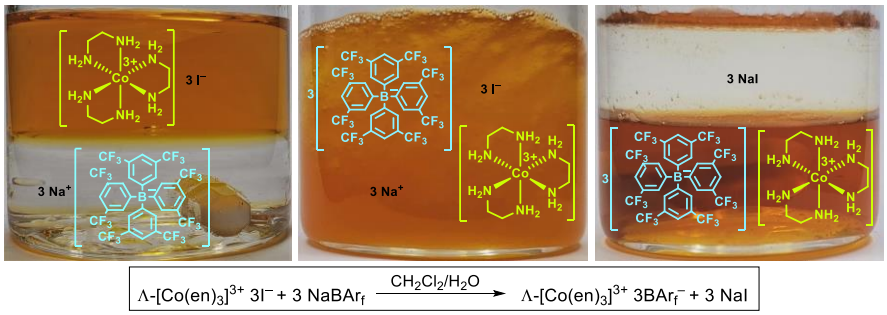


Figure 1.4. Synthesis of the lipophilic salt Λ-$[Co(en)_3]^{3+}$ $3BAr_f^-$ under biphasic conditions. Left: reactants in orthogonal liquid phases; middle: rapidly stirred mixture; right: products in orthogonal liquid phases.

Also reported in 2008, the enantiopure cobalt salts Λ- and Δ-$\mathbf{1}^{3+}$ $3BAr_f^-$ catalyzed a number of Michael type additions known to be effected by organic hydrogen bond donors in the presence of a Brønsted base.[23,24] These are summarized in Figure 1.5 and provided a welcome "proof of principle". Yields before workup were always ≥94%.

However, the enantioselectivities were modest. Those for the addition in Figure 1.5J topped out at 21-33% ee, whereas those in Figure 1.5K-L reached 31-52% ee. These are not bad starting points for new enantioselective catalysts, but optimization efforts involving the solvent or base were not productive. Salts of other metals were investigated,[24] and the chromium and rhodium analogs usually gave incrementally better results (Figure 1.5). The tetracationic platinum complex $[Pt(en)_3]^{4+}$ $4BAr_f^-$ always yielded poorer results, perhaps due in part to its much greater Brønsted acidity (pK_a 5.5),[25] inviting independent reaction with the base.

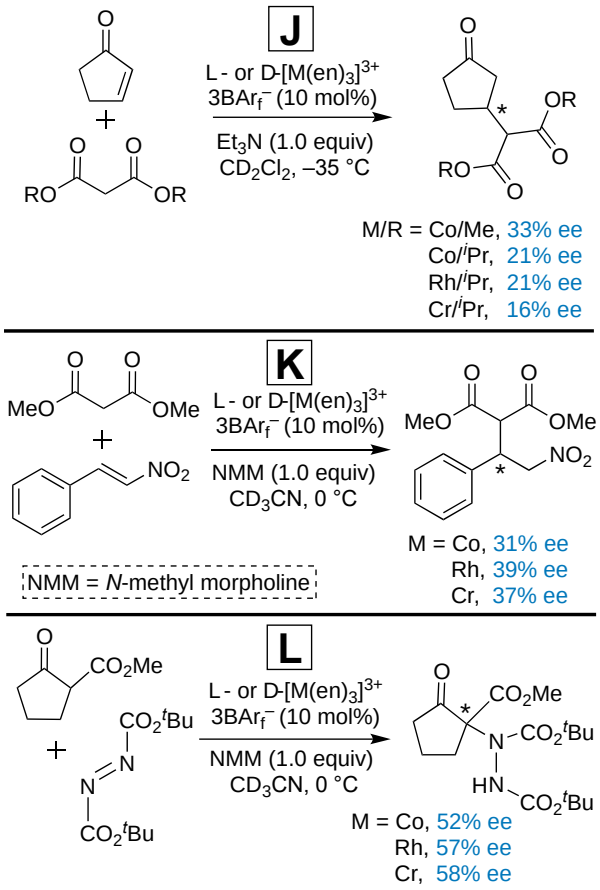


Figure 1.5. Test reactions for catalyst screening.

1.3. Second Generation Catalysts: Aryl Substituents

In 2008, it was alertly noted that the non-*meso* diastereomer of 1,2-diphenylethylenediamine (dpen) could be purchased in enantiomerically pure form at surprisingly low prices (now <$300/100 g, *S*,*S* or *R*,*R*). Further, the corresponding cobalt complexes $[Co(dpen)_3]^{3+}$ $3X^-$ ($\mathbf{2}^{3+}$ $3X^-$) had already been synthesized.[26,27]

However, due to the presence of both cobalt and carbon stereocenters, diastereomers become possible: $\Lambda/(S,S)_3$ and $\Delta/(S,S)_3$ and their enantiomers $\Delta/(R,R)_3$ and $\Lambda/(R,R)_3$, denoted Λ- or Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $3X^-$ and Δ- or Λ-(*R*,*R*)-$\mathbf{2}^{3+}$ $3X^-$. Fortunately, each can be accessed with high diastereoselectivities. As sketched in Figure 1.6, it is customary to begin with substitution labile cobalt(II) precursors, and introduce the dpen ligands under aerobic conditions. Normally oxidation to cobalt(III) "locks down" the coordination

sphere. However, a small amount of charcoal is added, which scrambles the cobalt configurations as in the racemizations described above.

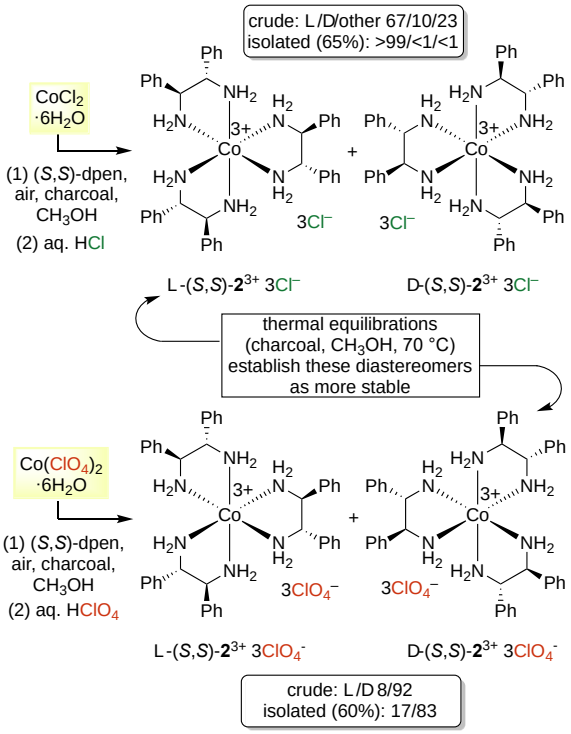


Figure 1.6. Diastereoselective syntheses of Λ- and Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 3X^{-}.

Reaction of the chloride complex $CoCl_2$ and (*S*,*S*)-dpen yields predominantly Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 3Cl^{-}.[27] The acetate complex $Co(OAc)_2$ gives parallel results. However, the perchlorate salt $Co(ClO_4)_2$ affords mainly the opposite diastereomer, Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 3ClO_4^{-}. In each case, the thermodynamically preferred diastereomer dominates, as established in separate thermal equilibrations with charcoal. When Cl^{-}/ClO_4^{-} or ClO_4^{-}/Cl^{-} exchange is carried out with the more stable diastereomer at room temperature, the less stable diastereomer of the new salt is obtained.

Thus, all possible diastereomers can be isolated in pure form and reasonable yields. The trication Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ is favored with counter anions that are good hydrogen bond acceptors. Although this trend is still being studied computationally, several crystallographic features suggest that this diastereomer should be an enthalpically stronger

hydrogen bond donor. For example, Figure 1.7 (left) illustrates the convergent nature of the synperiplanar C_3 NH groups, and the relatively unencumbered C_2 NH groups. The two C_3 sites are thought to form stronger hydrogen bonds, and are always occupied in crystal structures of halide salts.[27,28]

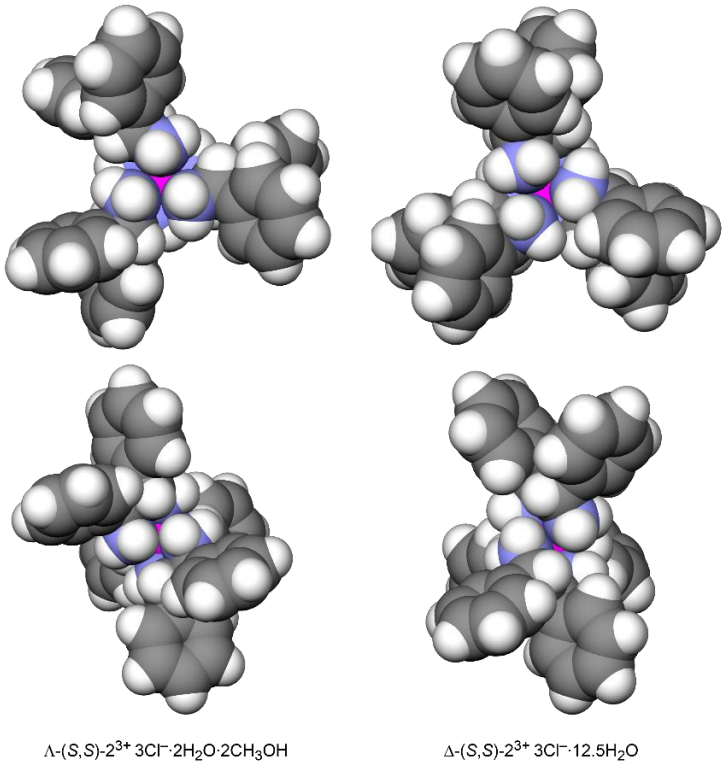


Figure 1.7. Views of the diastereomeric trications Λ- and Δ-(*S*,*S*)-**2**$^{3+}$ down the formal C_3 and C_2 axes, taken from the crystal structures of the trichloride salts.

Conversely, the trication Δ-(*S*,*S*)-**2**$^{3+}$ is favored with anions that are poor hydrogen bond acceptors. As can be seen in Figure 1.7 (right), the C_3 NH groups exhibit slightly divergent orientations (avg. NH···HN distance 2.63 Å vs. 2.39 Å in Λ-(*S*,*S*)-**2**$^{3+}$), and the C_2 NH groups are sterically less accessible. The greater stability of the perchlorate salt Δ-(*S*,*S*)-**2**$^{3+}$ 3ClO_4^- must therefore derive from other structural features. Intuitively, it would seem that Δ-(*S*,*S*)-**2**$^{3+}$ should represent the more stable form of the trication in the gas phase.

The next step was to render these salts lipophilic by exchanging the chloride or

perchlorate anions for BAr_f^-. The diastereomers Λ- and Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $3BAr_f^-$ were prepared, as exemplified for the former in Figure 1.8. However, it was also found that only one BAr_f^- anion was required to solubilize the trications in organic solvents, presumably due to additional lipophilicity imparted by the six phenyl groups. For example, the mixed salts Λ- and Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^-BAr_f^-$, which are easily isolated (and recycled after use) by silica gel column chromatography, were soluble in CH_2Cl_2. These mono(barf) catalysts bring two advantages. One is cost; chloride is among the least expensive anions. Second, molecular weights are greatly reduced. This becomes important for heavier catalysts that, when used at higher loadings, may outweigh many types of organic substrates.

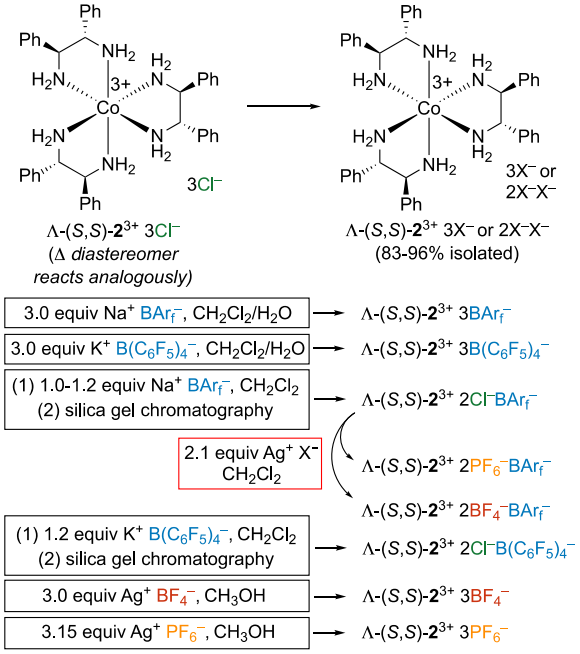
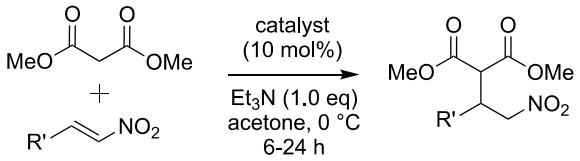


Figure 1.8. Representative anion metatheses.

It was a simple matter to synthesize other mixed or non-mixed salts, using standard protocols as outlined in Figure 1.8. The tris(tetrafluoroborate) salt Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $3BF_4^-$ was less lipophilic than the others, but still soluble in most organic solvents at typical catalyst loadings. Several catalysts were prepared with the poorly coordinating and hydrogen bond accepting tetra(pentafluorophenyl)borate anion, $B(C_6F_5)_4^-$, in place of BAr_f^-. These

exhibited comparable solubilities.

For all reactions studied, the catalysts in Figure 1.8 gave much higher enantioselectivities than the first-generation ethylenediamine analogs Λ- and Δ-**1**$^{3+}$ 3BAr$_f^-$.



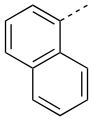
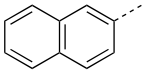
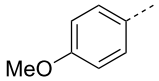
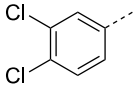
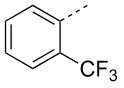
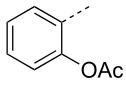
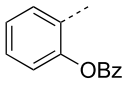
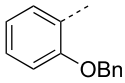
R'	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ yield / ee (% / %)	Λ-(*S*,*S*)-**2**$^{3+}$ 2BF$_4^-$BAr$_f^-$ yield / ee (% / %)	Λ-(*S*,*S*)-**2**$^{3+}$ 3BF$_4^-$ yield / ee (% / %)
	94 / 87 (***R***)	97 / 90 (***R***)	97 / 93 (***R***)
	>99 / 92 (***R***)	98 / 93 (***R***)	98 / 95 (***R***)
	95 / 88 (***R***)	92 / 83 (***R***)	96 / 93 (***R***)
	95 / 82 (***R***)	87 / 78 (***R***)	95 / 85 (***R***)
	>99 / 80 (***R***)	94 / 90 (***R***)	93 / 93 (***R***)
	98 / 81 (***R***)	86 / 86 (***R***)	-
	>99 / 90 (***R***)	98 / 93 (***R***)	97 / 95 (***R***)
	98 / 84 (***R***)	96 / 94 (***R***)	97 / 96 (***R***)
	94 / 92 (***R***)	86 / 93 (***R***)	95 / 96 (***R***)
	98 / 94 (***R***)	95 / 96 (***R***)	98 / 98 (***R***)
	-	91 / 91 (***S***)	96 / 92 (***S***)
	-	83 / 80 (***S***)	93 / 86 (***S***)

Figure 1.9. Optimized conditions for additions of dimethyl malonate to nitroalkenes with monofunctional cobalt catalysts.

For additions of malonate esters to nitroalkenes, Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2Cl^{-}BAr$_f^{-}$ afforded higher ee values than the diastereomer Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2Cl^{-}BAr$_f^{-}$, and both were superior to the corresponding non-mixed tris(barf) catalysts Λ- and Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 3BAr$_f^{-}$.[29] The Λ and Δ catalysts gave predominantly opposite enantiomers, establishing that the cobalt stereocenter is configuration determining. The counter anion set moderately affects the enantioselectivities, as shown with the substrates in Figure 1.9. For reasons not yet understood, the tris(tetrafluoroborate) salt Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 3BF$_4^{-}$ delivers the best results.

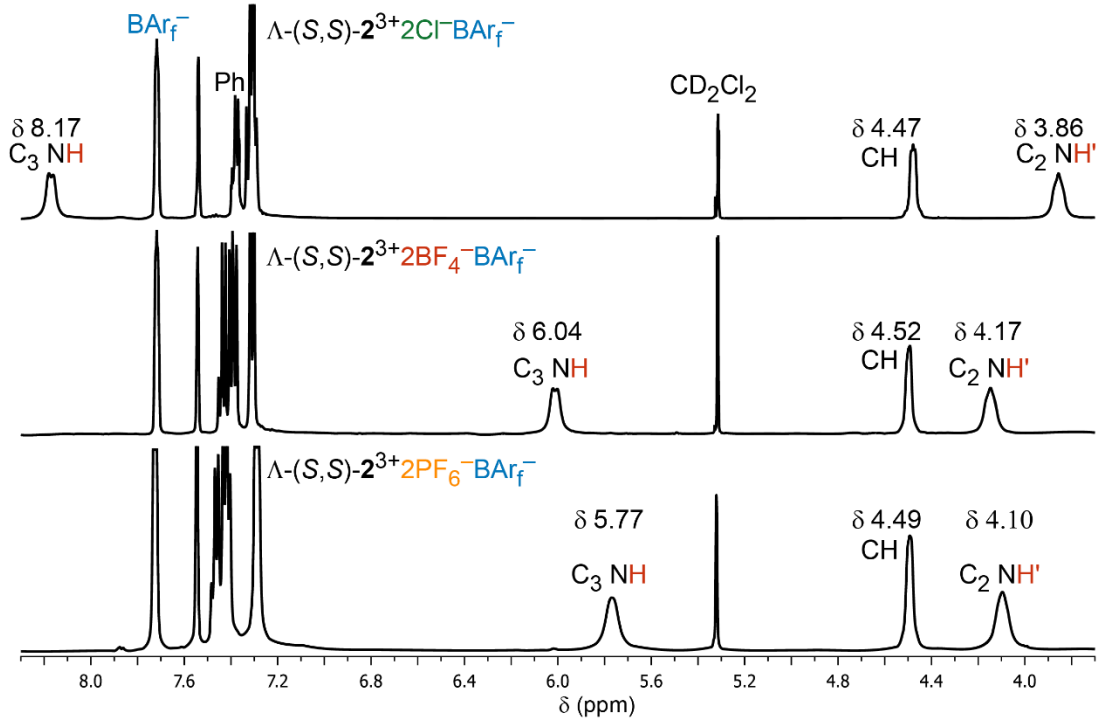


Figure 1.10. ^{1}H NMR spectra (CD_2Cl_2) of mixed salts Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2X^{-}BAr$_f^{-}$.

For the mixed salts $\mathbf{2}^{3+}$ 2X^{-}BAr$_f^{-}$, there is good evidence that the two non-tetraarylborate anions (2X^{-}) preferentially associate with the two *C*$_3$ faces of the trication, which are thought to be the enthalpically stronger hydrogen bonding sites. The ^{1}H NMR spectra of the catalysts in Figure 1.10 are easily interpreted in this context. First, separate signals for the diastereotopic NHH' protons are observed. The chemical shifts of the upfield signals vary over a modest range (δ 3.86-4.17), but the others spread over a wide

range, shifting downfield from δ 5.77 to δ 6.04 to δ 8.17 as the hydrogen bond acceptor strengths of X^- increase ($PF_6^- < BF_4^- < Cl^-$). Hence, the relatively constant upfield signals are assigned to the weaker hydrogen bonding C_2 NH groups, and the downfield signals to the stronger hydrogen bonding C_3 NH groups.

For the reactions in Figure 1.9 and catalysts in Figure 1.10, rates increase in the order $2Cl^- < 2BF_4^- < 2PF_6^-$. These and other data suggest that an anion must first disengage from a C_3 face so that substrates can bind. However, perhaps the other anion remains engaged with the other C_3 face. This might be a factor in the counter anion dependence of the enantioselectivities.

Additionally, enantiopure 1,2-diarylethylenediamines can be synthesized with impunity by the clever route in Figure 1.11.[30] The starting material (*R*,*R*)-**II**, a bis(*o*-hydroxylated) dpen, is commercially available. The aryl aldehyde corresponding to the new residue is added to generate the bis(Schiff base) (*R*,*R*)-**III**, which undergoes a diaza-Cope rearrangement to give (*S*,*S*)-**IV**. The equilibrium is driven by resonance interactions between the OH and C=N groups in (*S*,*S*)-**IV**, which afford "resonance assisted hydrogen bonds".[31] However, catalysts derived from the new 1,2-diarylethylenediamine ligands have seldom proved superior.

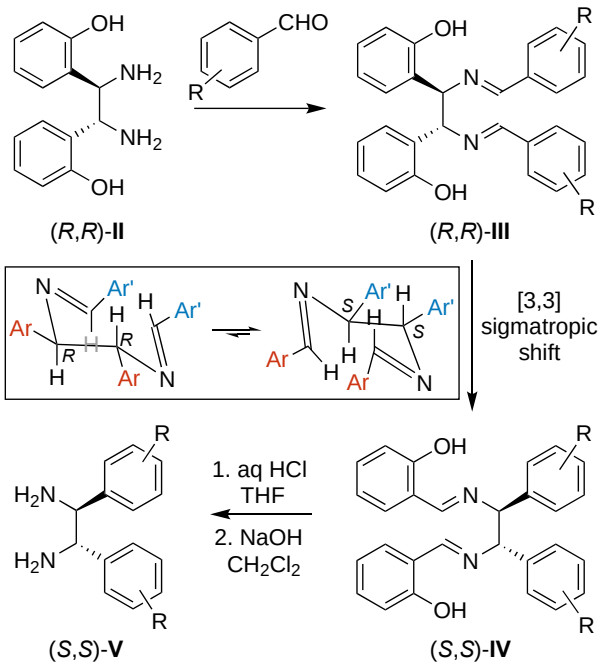


Figure 1.11. Syntheses of substituted dpen ligands.

1.4. Third Generation Catalysts: Bifunctional Systems with Brønsted Bases

Some of the "best in class" enantioselective organic hydrogen bond donor catalysts are bifunctional. A case in point would be Takemoto's catalyst (**VI**, Figure 1.12),[32] in which a dimethylamino group attached to a carbon stereocenter has been incorporated into a thiourea. It can be used in place of the cobalt catalysts and external bases for some of the reactions described in this chapter.

In a quest for still better catalysts, syntheses of ethylenediamine ligands were developed in which one CH group was replaced by a tethered tertiary amine, $(CH_2)_nNMe_2$.[33] These chiral species were accessed in 6-9 standard steps and 26% average overall yields from enantiopure building blocks costing \$13/mol (n = 1), \$178/mol (n = 2,3), or \$456/mol (n = 4). An analogous series of ligands with tethered secondary amines, $(CH_2)_nNHMe$ (n = 1-4), has also been economically synthesized (5-7 steps, 33% average yields from enantiopure building blocks costing \$7-17/mol).[34]

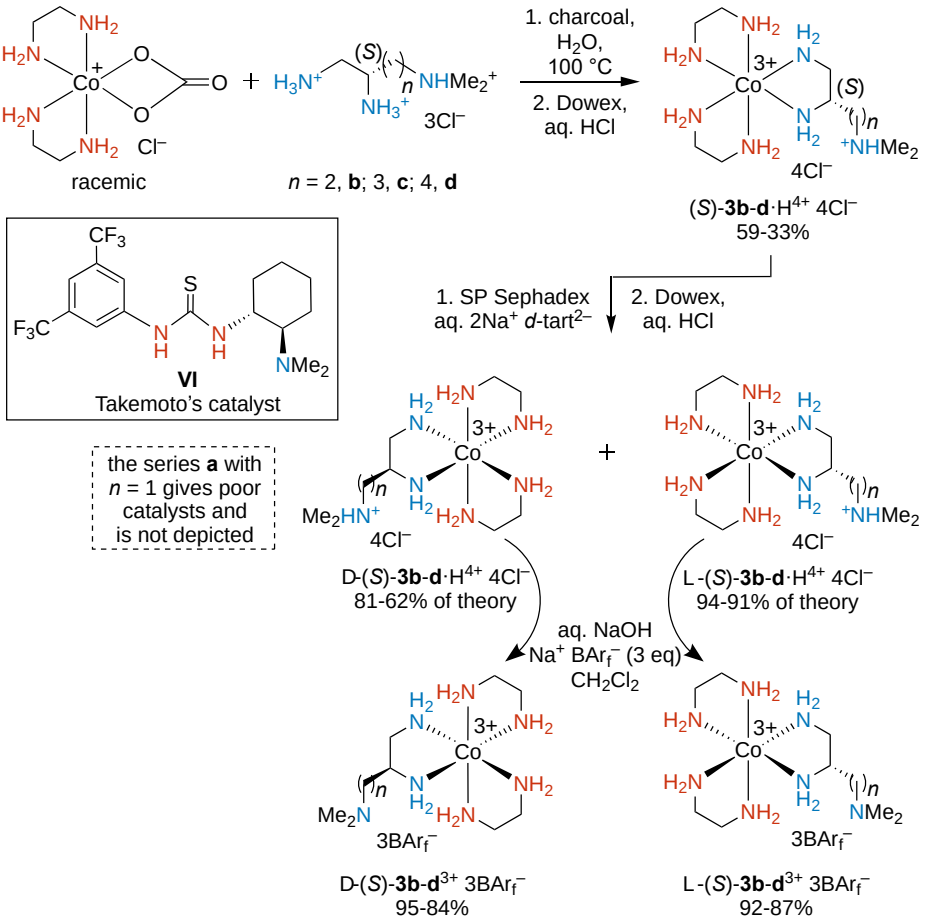


Figure 1.12. Syntheses of bifunctional (tertiary amine-containing) cobalt catalysts.

As shown in Figure 1.12, the readily available carbonate complex $[Co(en)_2(O_2C{=}O)]^+$ Cl^- was treated with tris(hydrochloride) salts of the tethered tertiary amines.[35] The racemate was utilized as the more effective Co/C diastereomer could not be predicted in advance. The carbonate leaving group serves (formally) as the base for deprotonating the two NH_3^+ moieties of the hydrochloride salt. The diastereomers of the adducts $[Co(en)_2((S)\text{-}H_2NCH((CH_2)_nNMe_2H)CH_2NH_2)]^{4+}$ $4Cl^-$ (**3b-d**·H^{4+} $4Cl^-$) could be easily separated on Sephadex (sulfonated dextrose), a chiral support that is one of the "tricks of the trade" for resolving isomeric cobalt(III) complexes.[36] Subsequent anion exchange afforded the lipophilic salts Λ- and Δ-(*S*)-**3b-d**$^{3+}$ $3BAr_f^-$.[3]

These catalysts were applied to the dimethyl malonate/β-nitrostyrene test reaction

frequently used above. Poor enantioselectivities were obtained with Δ-(*S*)-**3b-d**$^{3+}$ 3BAr$_f^-$ (9, 5, 33% ee). However, the diastereomers Λ-(*S*)-**3b-d**$^{3+}$ 3BAr$_f^-$ performed much better (75, 86, 48% ee). In all six cases, the *R* product dominated, showing that the carbon stereocenter is configuration determining.

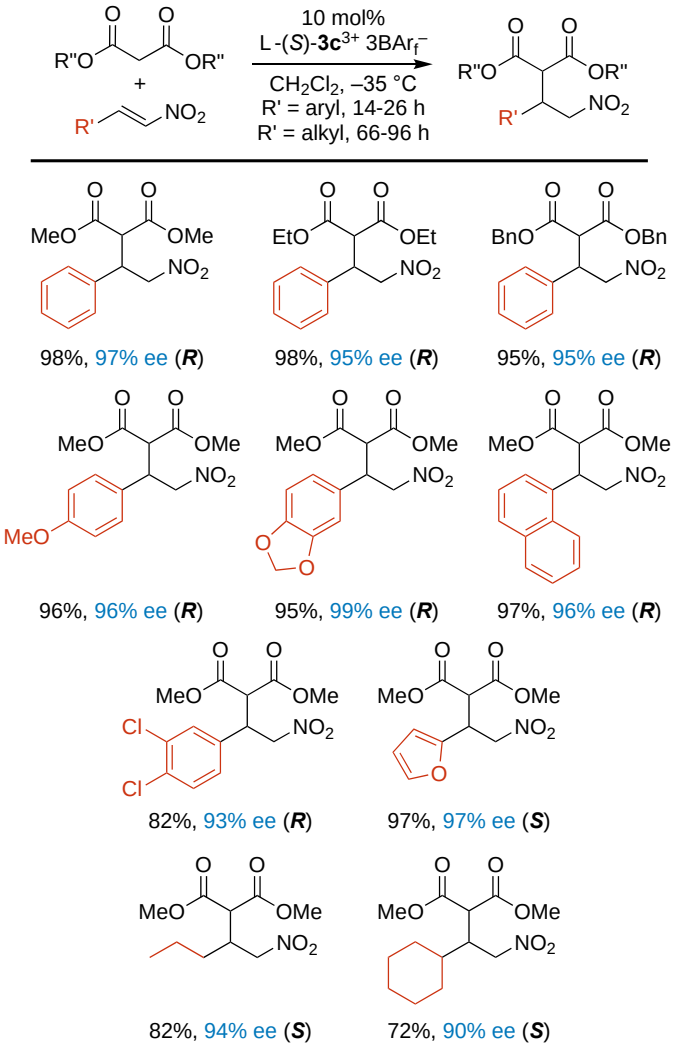


Figure 1.13. Optimized conditions for additions of malonate esters to nitroalkenes with a bifunctional cobalt catalyst.

It was then found that with Λ-**3c**$^{3+}$ 3BAr$_f^-$, still higher enantioselectivities could be obtained on reasonable time scales at –35 °C (97% ee, 98% conversion, 15 h). Accordingly, these conditions were applied to a variety of substrates, including nitroalkenes with aliphatic substituents, with the results depicted in Figure 1.13. The ee

values exceed the best obtained with the dpen catalysts in Figure 1.9. Although it can be challenging to compare enantioselective catalysts in an even-handed manner, the Gladysz group is unaware of systems with comparable overall effectiveness, as analyzed in depth elsewhere.[28]

1.5. Applications

The scope and limitations of new classes of catalysts must be defined. Thus, attention was turned to other transformations known to be catalyzed by hydrogen bond donors. In the many cases surveyed, scout reactions using the catalyst family Λ- and Δ-(*S*,*S*)-**2**$^{3+}$ 2X^{-}X'$^{-}$ commonly gave ee values of >50% with little effort. Attention was then focused upon the obvious variables (counter anions, catalyst stereochemistry, auxiliary reagents/cocatalysts, solvent, etc.). In nearly all cases, at least some ee values of >90% could be attained – and sometimes this regime was consistently realized. Two illustrative investigations follow.[37,38]

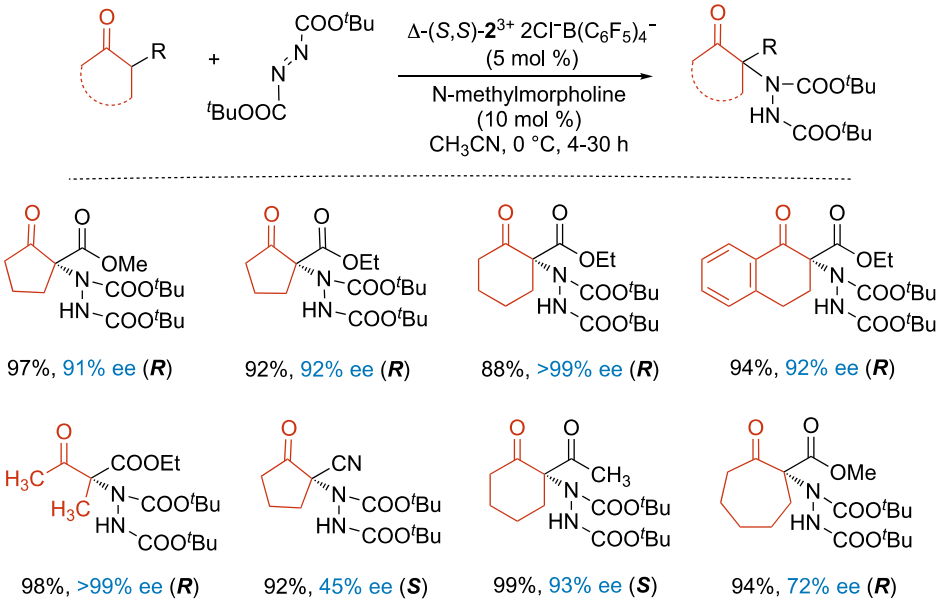


Figure 1.14. Optimized conditions for additions of 1,3-dicarbonyl compounds to di(*t*-butyl) azodicarboxylate.

The first, already introduced in Figure 1.5L, involves additions of 1,3-dicarbonyl compounds to di(*t*-butyl) azodicarboxylate, a process frequently termed (due to the ease

of nitrogen-nitrogen bond cleavage) an α-amination.[37] When catalyzed by the tetra(pentafluorophenyl)borate salt Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^{-}B(C_6F_5)_4^{-}$ as depicted in Figure 1.14, uniformly high yields were obtained, with ee values of >99-91% for educts with five- or six-membered ring ketoesters, 72-45% for other cyclic motifs, and >99% for an acyclic system. In contrast to the additions to nitroalkenes described above, the Λ-(*S*,*S*) diastereomers gave slightly lower ee values, as did the analogous $2Cl^{-}BAr_f^{-}$ salts. This suggests that these are not operationally invariant catalysts confined to "one mechanism" of enantioselection. Rather, they have a certain "phenotypic plasticity" that can be adapted to a variety of types of transformations.

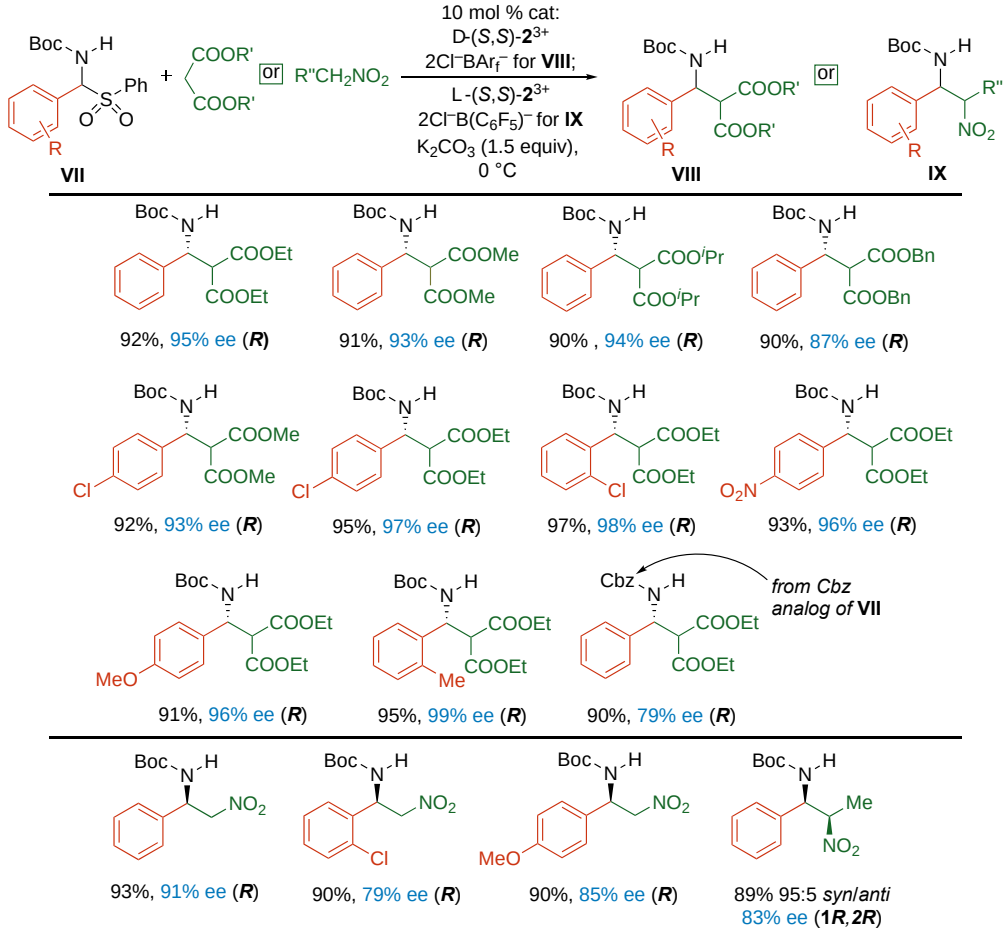


Figure 1.15. Optimized conditions for additions of malonate esters and nitroalkanes to functional equivalents of aryl imines.

At first glance, the transformations in Figure 1.15[38] seem to employ rather exotic (and chiral) α-amido sulfones **VII**. However, these are merely surrogates for imines, which are generated in situ in the presence of a base, and have much longer shelf lives. In one series, the conjugate base of a malonate ester adds to the C=N bond to afford **VIII**. Optimum ee values are obtained with Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^{-}BAr_f^{-}$, the diastereomer opposite to that employed in Figure 1.10. The averages match those of the best catalysts in the literature.

In the other series, the conjugate base of a nitroalkane adds to the C=N bond to yield **IX**. The best results are now obtained with Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^{-}B(C_6F_5)_4^{-}$, in which the cobalt configuration and tetraarylborate anion have been altered. Here, the ee values are slightly lower than the best literature catalysts.

1.6. Conclusion

In closing, the seminal work of Alfred Werner has found renewed significance in the modern chemical world through the modifications and applications of the complexes disclosed herein. This new class of hydrogen bond-donor catalysts continues to be utilized in reactions previously accessible with only conventional methods, and is a canvas for catalyst design through the addition of novel modes of bifunctionality, allowing for continued innovation in the field of asymmetric catalysis.

1.7. References

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2. CHIRAL TRICATIONIC TRIS(1,2-DIPHENYLETHYLENEDIAMINE) COBALT(III) HYDROGEN BOND DONOR CATALYSTS WITH DEFINED CARBON/METAL CONFIGURATIONS; MATCHED/MISMATCHED EFFECTS UPON ENANTIOSELECTIVITIES WITH ENANTIOMERIC CHIRAL COUNTER ANIONS[†]

2.1 Introduction

There has been a marked increase in interest in enantioselective catalysis using chiral organic hydrogen bond donors over the last 20 years.[1] This derives in part from widespread needs to direct the configurations of carbon stereocenters in pharmaceutical and agricultural chemicals. The Gladysz group has been interested in developing chiral transition metal containing hydrogen bond donors,[2-5] which can provide binding motifs and modes of action that greatly differ from their organic counterparts. Several other laboratories have had parallel interests.[6-8]

One major thrust has involved cobalt catalysts closely related to enantiopure $[Co(en)_3]^{3+}$ salts prepared by Werner over a century ago (en = ethylenediamine),[9,10] but have found little synthetic application in the interim. These feature 12 NH groups that can serve as hydrogen bond donors, although they would not be expected to be simultaneously engaged with the substrates at any point in the catalytic cycle. The enantiomers of the parent trication, the configurations of which are conventionally termed Λ and Δ, are depicted in Figure 2.1 (top). In idealized geometries, they exhibit D_3 symmetry, with a principal C_3 axis and three C_2 axes lying in a perpendicular plane. As illustrated by structures **I** and **II** (Figure 2.1, middle), each of the two C_3 faces feature three approximately synperiplanar N-H groups, and each of the three C_2 faces two. Other stereochemical properties of the cobalt complexes in this study have been reviewed.[11]

[†]Reprinted with permission from "Chiral Tricationic Tris(1,2-diphenylethylenediamine) Cobalt(III) Hydrogen Bond Donor Catalysts with Defined Carbon/Metal Configurations; Matched/Mismatched Effects upon Enantioselectivities with Enantiomeric Chiral Counter Anions" by Kabes, C. Q.; Maximuck, W. J.; Ghosh, S. K.; Kumar, A.; Bhuvanesh, N.; Gladysz, J. A. *ACS Catal.* **2020**, *10*, 3249-3263. Copyright 2020 by the American Chemical Society.

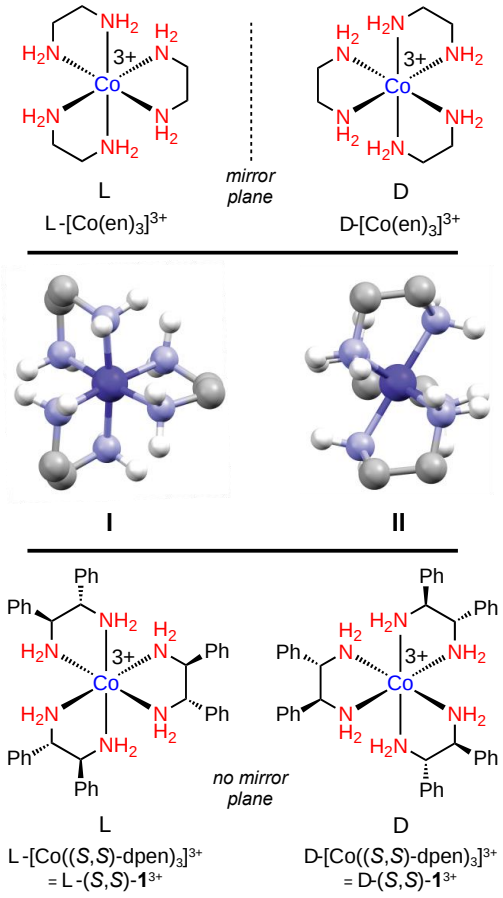


Figure 2.1. Relevant chiral cobalt tris(1,2-diamine) trications.

Werner developed his coordination chemistry in aqueous media. However, for catalysis it was first necessary to solubilize such cobalt salts in organic solvents, so that the NH donor groups would not be saturated by hydrogen bonded water molecules. This was accomplished using lipophilic anions such as tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAr_f^- or $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$), which is depicted in Figure 1.2.[12] All $[Co(en)_3]^{3+}$ salts investigated have been highly active catalysts, but the enantioselectivities have been modest.[4c,12] Importantly, replacing a single en ligand by one with an appended $(CH_2)_3NMe_2$ unit – affording a bifunctional catalyst that obviates the need for an external base – gives a highly enantioselective catalyst for additions of malonate esters to aromatic and aliphatic nitroalkenes.[3]

Highly enantioselective catalysts can also be obtained when all three en ligands are replaced by (*S*,*S*)- or (*R*,*R*)-1,2-diphenylethylenediamine, or dpen.[2,4a,b,13] Both enantiomers are commercially available at surprisingly low prices.[14] Given the greater lipophilicity of dpen versus en, salts with a single BAr_f^- anion generally have good solubilities in organic solvents.[15] An example, valid for any combination of cobalt and carbon configurations, would be $[Co(dpen)_3]^{3+}$ $2Cl^-BAr_f^-$. With this trication, it has been possible to prepare an extensive library of mixed (and non-mixed) anion salts,[15] all of which afford slightly different enantioselectivities.[2,4a] The mechanisms of these condensations are not yet well understood. However, it is speculated that when hydrogen bond accepting anions are present, one may remain associated with the trication during the enantiomer determining step.[2,4a]

Over the last decade, there have been increasing applications of chiral anions and Brønsted acids in enantioselective catalysis.[16,17] In view of the dependence of the ee values of catalysts derived from $[Co(dpen)_3]^{3+}$ upon the counter anions, it is anticipated that further optimization would be possible by incorporating chiral anions. It was thought that one enantiomer of an anion might be "matched" with respect to the cobalt/carbon configurations, leading to higher ee values, whereas the other enantiomer could be "mismatched", leading to lower ee values. Such phenomena are often observed in enantioselective transformations that involve diastereomeric combinations of two chiral reactants.[18]

Herein, the syntheses of a variety of diastereomeric salts of the trication $[Co(dpen)_3]^{3+}$ are detailed – all featuring the cobalt and carbon configurations depicted in Figure 2.1 (bottom) – with the representative chiral anions in Figure 2.2.[19,20] These are subsequently evaluated as enantioselective catalysts in two typical addition reactions. Indeed, the ee values often show significant matched/mismatched relationships derived

from the configurations of the anions (avg $\Delta_{\%ee} = 10$). Although these exceed those of the best catalysts with achiral anions in only a few cases, this study illustrates an underutilized approach to the optimization of "charged" enantioselective catalysts that, to my knowledge, has been rather infrequently investigated.[21-23]

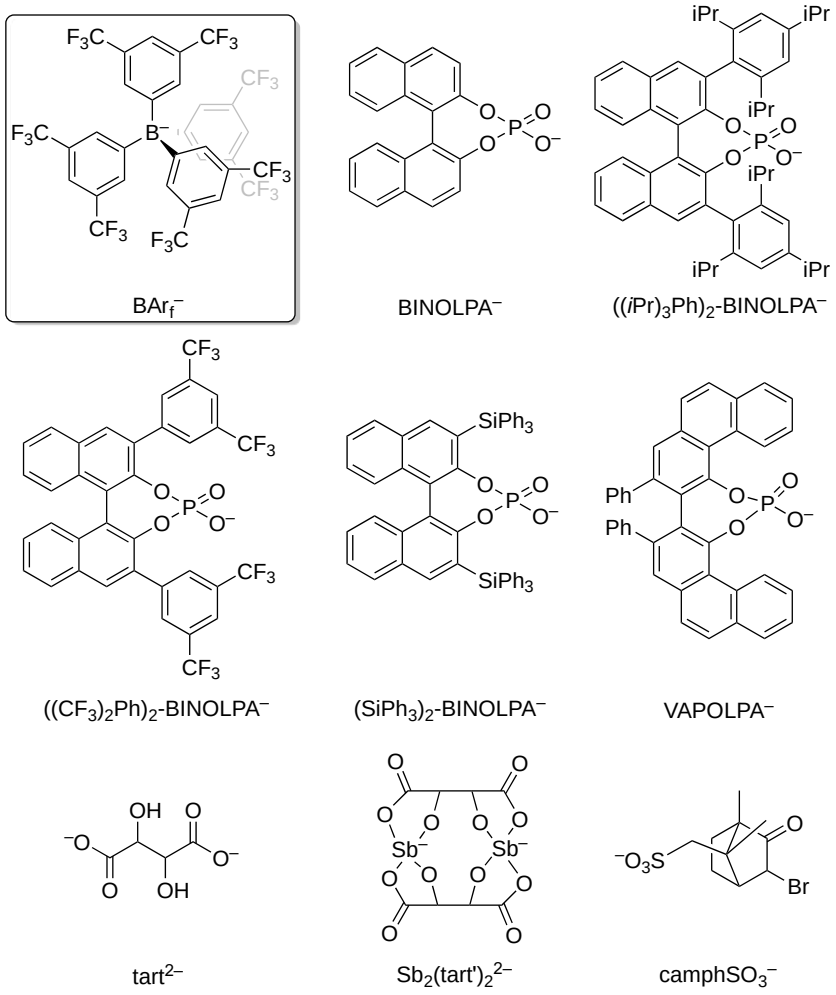


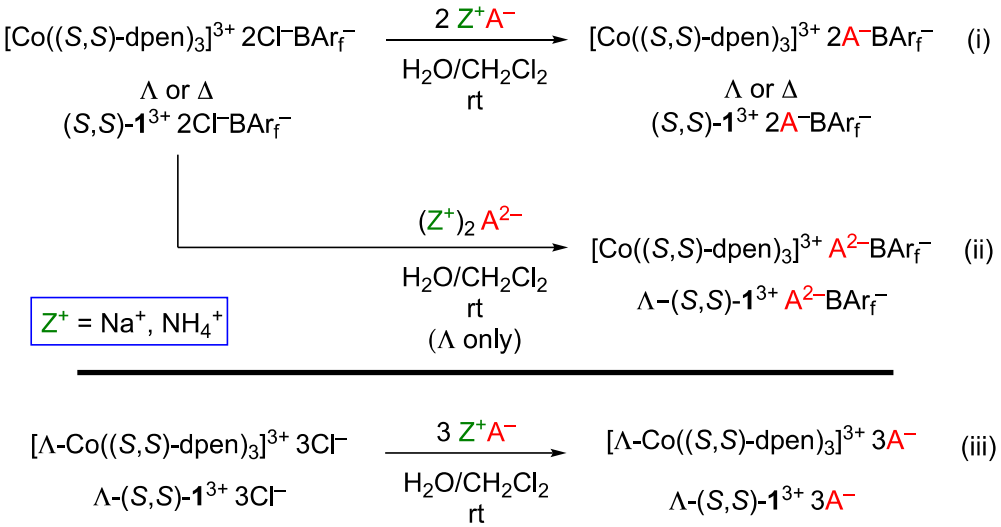
Figure 2.2. Structures of lipophilic or chiral anions used in this study and their dominant literature abbreviations. Specific configurations of the chiral anions are not depicted, as both enantiomers are generally used.

2.2. Results

2.2.1 Syntheses and Characterization of Catalysts

The diastereopure and enantiopure salts Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 3Cl$^-$ (Λ-(*S*,*S*)-**1**$^{3+}$ 3Cl$^-$), Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$ (Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$), and Δ-[Co((*S*,*S*)-

dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$ (Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$) were prepared according to previously reported procedures.[15] Note that the configurations of the dpen-based carbon stereocenters are kept constant (*S*,*S*), but those of the cobalt stereocenter are varied (Λ/Δ), such that both diastereomers are represented. The enantiomeric salts derived from (*R*,*R*)-dpen would be expected to give identical ee values.



Scheme 2.1. Syntheses of cobalt(III) catalysts with chiral anions (A$^-$) from Figure 2.1.

The new salts containing chiral anions were synthesized as summarized in Scheme 2.1. As with other manipulations in this study, the reactions were carried out in air. In one series (eq i), Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$ was treated with 2.0-4.3 equiv of a sodium or ammonium salt of a chiral *mono*anion from Figure 2.2 (A$^-$; both enantiomers) in biphasic aqueous dichloromethane. Workups gave the target complexes Λ-(*S*,*S*)-**1**$^{3+}$ 2A$^-$BAr$_f^-$ depicted in Chart 2.1 in 44-99% yields. In several cases, diastereomeric salts with opposite cobalt configurations, Δ-(*S*,*S*)-**1**$^{3+}$ 2A$^-$BAr$_f^-$, were analogously prepared. With the tartrate derived *di*anions, Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$ was similarly treated with 1.0-2.4 equiv of the respective salts to give Λ-(*S*,*S*)-**1**$^{3+}$ A^{2-}BAr$_f^-$ in 94-99% yields (eq ii). Finally, some salts with *three* chiral monoanions, Λ-(*S*,*S*)-**1**$^{3+}$ 3A$^-$, were analogously prepared from Λ-(*S*,*S*)-**1**$^{3+}$ 3Cl$^-$ in 72-78% yields as shown in eq iii.

The new cobalt(III) salts, which are summarized in Chart 2.1 (entries 3-25), were characterized by microanalyses and NMR spectroscopy (^{1}H, ^{13}C) as detailed in the experimental section. All were soluble in dichloromethane, acetone, and acetonitrile. The camphorsulfonate salts were somewhat more lipophilic and also dissolved in THF. As also seen with salts of achiral anions (including the starting materials in Scheme 2.1), the new species were isolated as hydrates. The ^{1}H NMR spectra exhibited broad OH signals, and the stoichiometry suggested by integration was usually close to that calculated from the microanalytical data. When these differed, microanalytical values were given precedence since NMR integrations can be enhanced by protic impurities. The water molecules are included in all stoichiometry and yield calculations, as given in the experimental section, but for simplicity are not represented in the graphics or main text.

As noted with salts of achiral anions earlier, the diastereotopic N**HH'** protons gave distinct NMR signals. As can be seen from **I** and **II** in Figure 2.1, one of these protons is associated with a C_3 face, and the other with a C_2 face. Earlier studies have shown that the Δδ values reflect, at least in part, the differential magnitudes of anion hydrogen bonding at the two sites (C_3 NH groups always favored as reflected by downfield chemical shifts, as shown in Figure 2.3).[2,15] Thus, one of the four diastereomers of the camphorsulfonate salts, Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camph$SO_3^-$$BAr_f^-$, exhibited a much greater Δδ value than the other three (4.02 vs. 1.09-1.89 ppm). Larger differences were also found with Λ-(*S*,*S*)-**1**$^{3+}$ (*R*,*R*)-tart^{2-}BAr_f^- and Λ-(*S*,*S*)-**1**$^{3+}$ (*S*,*S*)-tart^{2-}BAr_f^-, but here they were independent of the configuration of the dianion (both 3.03 ppm). The next largest differences were in the 2.54-2.42 ppm range (two of the four diastereomeric BINOLPA$^-$ salts, and one of the VAPOLPA$^-$ salts).

Also of interest is the degree to which the other ^{1}H NMR signals differ in salts that are identical except for the configuration of the anion. To a first approximation, greater

trication/anion association should yield greater differentiation. However, in most cases the Δδ values were less than 0.08 ppm (ignoring multiplets), even for the camphorsulfonate salts. Larger Δδ differences were found only with the downfield signals of the salts with enantiomeric $((CF_3)_2Ph)_2$-BINOLPA$^-$ anions (Δδ 0.17 ppm) and enantiomeric $(SiPh_3)_2$-BINOLPA$^-$ anions (Δδ 0.13 ppm).

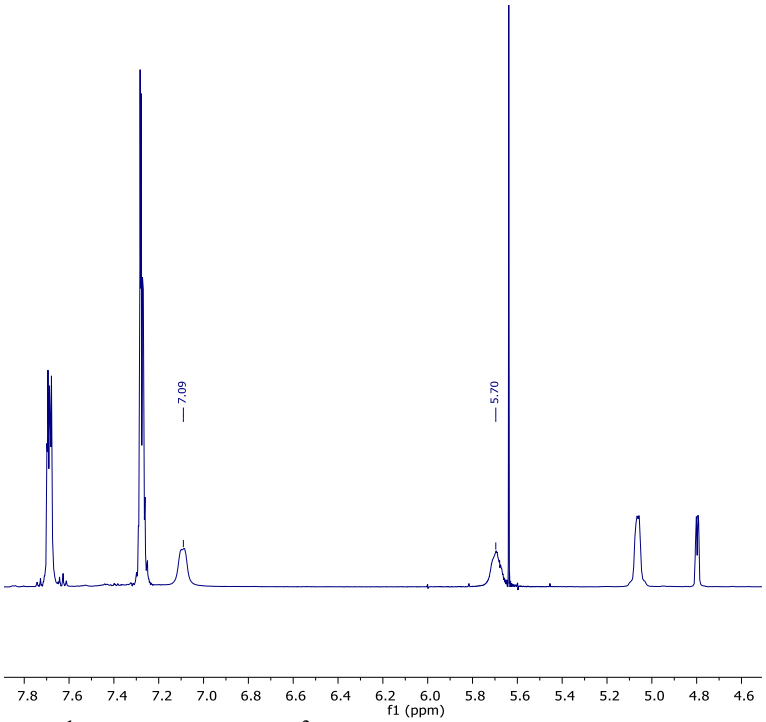


Figure 2.3. Representative ^{1}H-NMR of Λ-(*S*,*S*)-**1**$^{3+}$ 3(1*R*)-camphSO$_3^-$ showing diastereotopic N-H peaks at 7.09 and 5.70 ppm.

Single crystals of $[Co(dpen)_3]^{3+}$ salts are generally much more difficult to obtain than for other types of metal complexes under study in the Gladysz laboratory. Thus, it was a pleasant surprise when crystals of Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camphSO$_3^-$BAr$_f^-$ could be grown from dichloromethane. Data were collected using synchrotron radiation, and the structure was solved as outlined in Appendix A (Table 1) and the experimental section. An ORTEP representation and a partial structure that highlights hydrogen bonding

interactions are provided in Figure 2.4. The latter constitutes a view down one of the idealized C_2 axes.

In the >150 published crystal structures of $[Co(en)_3]^{3+}$ salts[24] and six of $[Co(dpen)_3]^{3+}$ salts,[2,13,25] trication/anion hydrogen bonding has been of particular interest. As can be seen in Figure 2.4, each RSO_3^- moiety hydrogen bonds to an opposite C_3 face, with each of the three oxygen atoms associated with a unique N-H bond. The N<u>H</u>···<u>O</u> distances range from 1.97 to 2.13 Å (average 2.03 Å). The corresponding <u>N</u>(H)···<u>O</u> distances range from 2.865 to 3.010 Å (average 2.920 Å), with N-H···O angles of 162.0° to 169.2°. These atomic separations compare closely with those found in the corresponding ammonium salt (averages 1.94 and 2.850 Å),[26] which however exhibits a different hydrogen bonding motif (each oxygen atom associating with a different ammonium cation).

2.2.2 Enantioselective Catalysis

As shown in Chart 2.1, the salts prepared in Scheme 2.1 were evaluated as catalysts for additions of dimethyl malonate to *trans*-β-nitrostyrene in the presence of Et_3N (1.0:1.1:1.0 mol ratio). Reactions were carried out in acetone-d_6 at 0 °C with 10 mol% of catalyst and an internal standard. After 24 h, the yield of the addition product (**2**) was determined by ^{1}H NMR versus the standard. After workup, the ee values were assayed by HPLC. As shown in entry 1, the principal starting cobalt(III) complex in Scheme 2.1, Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$, gave (*R*)-**2** in 87% ee. The diastereomer Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$, which usually affords somewhat lower enantioselectivities in additions to nitroalkenes, yielded the opposite enantiomer (*S*)-**2** in 77% ee (entry 2). However, this diastereomer sometimes gives superior results for other addition reactions.[4a] Two additional salts with achiral bromide and iodide counter anions were also tested (Λ-(*S*,*S*)-**1**$^{3+}$ 2X$^-$BAr$_f^-$; entries 30-31), but these data are only analyzed in the discussion section.

Interestingly, the diastereomeric camphorsulfonate salts Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$ and Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camphSO$_3^-$BAr$_f^-$ (entries 3 and 5), which differ in the anion configuration, gave (*R*)-**2** with comparably high ee values (87%, 88%; $\Delta_{\%ee}$ = 1). When the cobalt configurations were inverted (Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$ or Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camphSO$_3^-$BAr$_f^-$; entries 4 and 6), the ee values dropped (50%, 56%; $\Delta_{\%ee}$ = 6) and the yields diminished somewhat (69-82% versus 94-84%). Also the dominant enantiomer was now (*S*)-**2**, showing that the cobalt configuration of the catalyst controls the carbon configuration of the product.

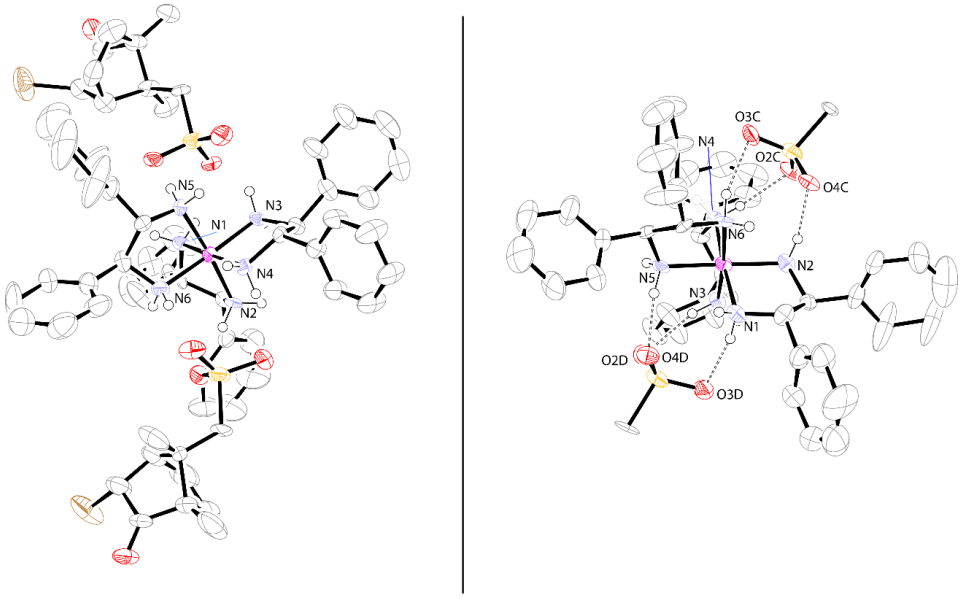


Figure 2.4. Left: Molecular structure of Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camphSO$_3^-$BAr$_f^-$ with the large BAr$_f^-$ anion omitted; the ellipsoids are depicted at the 50% probability level. Right: A view of hydrogen bonding between the NH and RSO$_3^-$ groups. Bond lengths (Å) and angles (°) about cobalt: Co(1)-N(1), 1.986(7); Co(1)-N(2), 1.985(5); Co(1)-N(3), 1.957(7); Co(1)-N(4), 1.976(7); Co(1)-N(5), 1.983(8); Co(1)-N(6), 1.986(8); N(1)-Co(1)-N(2), 83.0(3); N(1)-Co(1)-N(3), 92.2(3); N(1)-Co(1)-N(4), 174.2(3); N(1)-Co(1)-N(5), 93.9(3); N(1)-Co(1)-N(6), 90.8(3); N(2)-Co(1)-N(3), 92.2(3); N(2)-Co(1)-N(4), 92.9(3); N(2)-Co(1)-N(5), 174.5(3); N(3)-Co(1)-N(4), 83.7(3); N(3)-Co(1)-N(5), 92.5(3); N(3)-Co(1)-N(6), 175.1(3); N(4)-Co(1)-N(5), 90.5(3); N(4)-Co(1)-N(6), 93.6(3); N(5)-Co(1)-N(6), 83.5(3). Angles and distances relevant to hydrogen bonding: O(2C)···H(4B), 2.05; O(3C)···H(6B), 2.01; O(4C)···H(2B), 1.97; O(2D)···H(3B), 2.01; O(3D)···H(1B), 2.13; O(4D)···H(5B), 2.02; O(2C)···N(4), 2.936; O(3C)···N(6), 2.907; O(4C)···N(2), 2.865; O(2D)···N(3), 2.895; O(3D)···N(1), 3.010; O(4D)···N(5), 2.910; O(2C)···H(4B)-N(4), 162.8; O(3C)···H(6B)-N(6), 168.0; O(4C)···H(2B)-N(2), 169.2; O(2D)···H(3B)-N(3), 163.9; O(3D)···H(1B)-N(1), 162.0; O(4D)···H(5B)-N(5), 166.2.

Four diastereomeric BINOLPA$^-$ salts were analogously assayed as catalysts (entries 7-10). Again, the two Λ diastereomers gave similarly high ee values (88%, 85%). The two Δ diastereomers gave lower ee values (73%, 71%), but higher than those of thecorresponding camphorsulfonate salts. These differences (entries 4 and 6 versus 8 and 10) underscore the important but still ill-defined role that the counter anions play in determining enantioselectivities. Furthermore, it is clear that *all* of the salts of the Δ diastereomers with chiral anions give ee values lower than that of the parent salt with achiral anions, Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$ (entries 2, 77% ee, versus 4, 6, 8, 10, 50-73% ee). In other words, in the Δ-(*S*,*S*) series, all combinations of trication/anion configurations are "mismatched" relative to Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$.

Salts of three substituted BINOLPA$^-$ anions and VAPOLPA$^-$, a related biphenanthryl species (Figure 2.2), were also evaluated. However, in view of the data in entries 3-10, and the greater expense of these anions, efforts were restricted to Λ diastereomers. As shown in entries 13-14, the fluorinated BINOLPA$^-$ derivatives gave ee values very close to those of the parent BINOLPA$^-$ salts (88% and 84% versus 88% and 85% in entries 7, 9). However, the others were not as effective. With the VAPOLA$^-$ salts, there was a particularly large difference in enantioselectivities between diastereomers with opposite anion configurations (entries 11-12, 87% versus 65% ee; $\Delta_{\%ee}$ 22).

Studies of salts of dianions or three chiral monoanions were also limited to Λ diastereomers. As shown in entries 18-21, the two types of tartrate containing catalysts gave ee values that only slightly depended upon the configuration of the anions ($\Delta_{\%ee}$ 1-5). Somewhat greater but still modest differences were found with the tris(camphorsulfonate) and tris(BINOLPA$^-$) salts in entries 22-25. Nonetheless, entries 22 and 23 provide the second highest $\Delta_{\%ee}$ among pairs of salts with opposite anion configurations (67% versus 75% ee). Throughout Chart 2.1, the anion configuration has

no effect on the dominant configuration of **2** (i.e., the product configuration is controlled by that of the trication).

As shown in Chart 2.2, the same cobalt(III) salts were evaluated as catalysts for additions of methyl 2-oxocyclopentanecarboxylate to di-*tert*-butylazodicarboxylate in the presence of N-methylmorpholine (NMM; 1.0:1.0:1.0 mol ratio). Reactions were carried out in CD_3CN at 0 °C with 10 mol% of catalyst and an internal standard. Yields and enantioselectivities of the addition product (**3**) were determined as in Chart 2.1. As shown in entry 1, the principal starting cobalt(III) complex in Scheme 2.1, Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $2Cl^-BAr_f^-$, gave (*S*)-**3** in 76% ee. The diastereomer Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ $2Cl^-BAr_f^-$, which usually affords somewhat higher enantioselectivities in additions to di-*tert*-butylazodicarboxylate,[4a] gave the opposite enantiomer (*R*)-**3** in 92% ee (entry 2). Salts that feature the perfluorinated tetraarylborate $B(C_6F_5)_4^-$ in place of BAr_f^- can give slightly higher ee values.[4a] However, since the primary interest was in assaying the effects of counter anion configurations, BAr_f^- salts (as in Chart 2.1).

The diastereomeric camphorsulfonate salts Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*R*)-camph$SO_3^-BAr_f^-$ and Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*S*)-camph$SO_3^-BAr_f^-$ (entries 3, 5), which differ only in the anion configuration, gave (*S*)-**3** with comparable ee values (68%, 67%). When the cobalt configurations were inverted (Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*R*)-camph$SO_3^-BAr_f^-$ or Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*S*)-camph$SO_3^-BAr_f^-$; entries 4, 6), the ee values dropped slightly (66%, 62%; (*R*)-**3** dominant), per the pattern in Chart 2.1. However, the lower enantioselectivities for the Δ diastereomers are opposite to the trend in entries 1-2 of Chart 2.2.

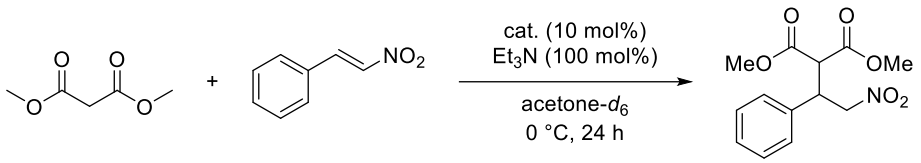
The four diastereomeric $BINOLPA^-$ salts were analogously assayed as catalysts (entries 7-10). The two Λ diastereomers gave ee values of 57% and 64%. Now, in line with entries 1-2, the two Δ diastereomers afforded higher ee values, 92% and 81%. Furthermore, in both diastereomer series there is a significant dependence upon the anion

configuration ($\Delta_{\%ee}$ 7-11).

The salts of the Λ diastereomers with substituted BINOLPA$^-$ anions and VAPOLPA$^-$ demonstrate the potential for matched and mismatched trication/anion chiralities. The difference between the ee values in entries 13-14 (69%, 77%; $\Delta_{\%ee}$ 8) is moderate, but that for entries 11-12 (73%, 54%; $\Delta_{\%ee}$ 19) is substantial and that for entries 15-16 (83%, 20%; $\Delta_{\%ee}$ 63) is huge. Also, in the last case the ee value significantly exceeds that of the benchmark catalyst with achiral chloride anions (83% versus 76% for entry 1).

As shown in entries 18-21, the two types of tartrate containing catalysts gave ee values that only moderately depended upon the configuration of the anions (73% versus 66% and 70% versus 67%; $\Delta_{\%ee}$ 7 and 3). However, the differences became large again for the tris(BINOLPA$^-$) salts (entries 24-25, 58% versus 25% ee; $\Delta_{\%ee}$ 33). In parallel to Chart 2.1, in no case did the anion configuration affect the dominant configuration of the addition product **3**.

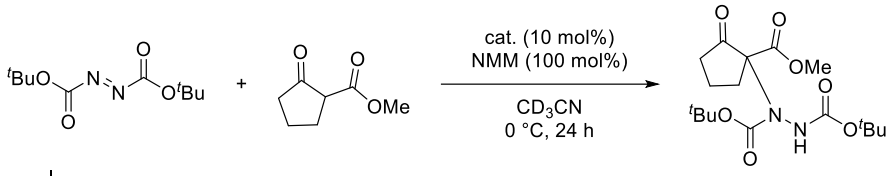
Several salts not published in the original report of these data were also synthesized and evaluated for catalytic activity. These include Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^-$BF$_4^-$, Λ-(*S*,*S*)-**1**$^{3+}$ (1*R*)-camphSO$_3^-$2BF$_4^-$, Λ-(*S*,*S*)-[Co(α-dnen)$_3$]$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$, and Λ-(*S*,*S*)-[Co(α-dnen)$_3$]$^{3+}$ 2(*R*)-BINOLPA$^-$BAr$_f^-$. These four catalysts give enantioselectivities generally on-par with similar analogs of the BAr$_f^-$ variety and excellent conversion (entries 26-27, Chart 2.1). Additionally, cations where the 1,2-diphenylethylene diamine (dpen) was changed to 1,2-di*napthyl*ethylene diamine (dnen) (entries 28-29, Chart 2.1) were used to explore the potential benefit of a more sterically hindered cation. A significantly decreased selectivity was observed though conversion remained high (entries 28-29, Chart 2.1).



entry	catalyst	ee (%) (config)	yield (%)[a]
1[b]	Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	87 (*R*)	93
2[c]	Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	77 (*S*)	95
3	Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^{-}$BAr$_f^{-}$	87 (*R*)	94
4	Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^{-}$BAr$_f^{-}$	50 (*S*)	69
5	Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camphSO$_3^{-}$BAr$_f^{-}$	88 (*R*)	84
6	Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camphSO$_3^{-}$BAr$_f^{-}$	56 (*S*)	82
7	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA^{-}BAr$_f^{-}$	88 (*R*)	73
8	Δ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA^{-}BAr$_f^{-}$	73 (*S*)	96
9	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-BINOLPA^{-}BAr$_f^{-}$	85 (*R*)	75
10	Δ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-BINOLPA^{-}BAr$_f^{-}$	71 (*S*)	>99
11	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-VAPOLPA^{-}BAr$_f^{-}$	87 (*R*)	>99
12	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-VAPOLPA^{-}BAr$_f^{-}$	65 (*R*)	99
13	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-((CF$_3$)$_2$Ph)$_2$-BINOLPA^{-}BAr$_f^{-}$	88 (*R*)	>99
14	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-((CF$_3$)$_2$Ph)$_2$-BINOLPA^{-}BAr$_f^{-}$	84 (*R*)	>99
15	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-(SiPh$_3$)$_2$-BINOLPA^{-}BAr$_f^{-}$	75 (*R*)	>99
16	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-(SiPh$_3$)$_2$-BINOLPA^{-}BAr$_f^{-}$	79 (*R*)	>99
17	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-((*i*Pr)$_3$Ph)$_2$-BINOLPA^{-}BAr$_f^{-}$	78 (*R*)	>99
18	Λ-(*S*,*S*)-**1**$^{3+}$ (*R*,*R*)-tart^{2-}BAr$_f^{-}$	85 (*R*)	81
19	Λ-(*S*,*S*)-**1**$^{3+}$ (*S*,*S*)-tart^{2-}BAr$_f^{-}$	80 (*R*)	88
20	Λ-(*S*,*S*)-**1**$^{3+}$ (Sb$_2$((*R*,*R*)-tart')$_2$)$^{2-}$BAr$_f^{-}$	87 (*R*)	98
21	Λ-(*S*,*S*)-**1**$^{3+}$ (Sb$_2$((*S*,*S*)-tart')$_2$)$^{2-}$BAr$_f^{-}$	88 (*R*)	93
22	Λ-(*S*,*S*)-**1**$^{3+}$ 3(1*R*)-camphSO$_3^{-}$	67 (*R*)	72
23	Λ-(*S*,*S*)-**1**$^{3+}$ 3(1*S*)-camphSO$_3^{-}$	75 (*R*)[d]	78
24	Λ-(*S*,*S*)-**1**$^{3+}$ 3(*S*)-BINOLPA^{-}	79 (*R*)	86
25	Λ -(*S*,*S*)-**1**$^{3+}$ 3(*R*)-BINOLPA^{-}	75 (*R*)	87
26	Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^{-}$BF$_4^{-}$	85 (*R*)	>99
27	Λ-(*S*,*S*)-**1**$^{3+}$ (1*R*)-camphSO$_3^{-}$2BF$_4^{-}$	84 (*R*)	>99
28	Λ-(*S*,*S*)-[Co(α-dnen)$_3$]$^{3+}$ 2(1*R*)-camphSO$_3^{-}$BAr$_f^{-}$	28 (*R*)	>99
29	Λ-(*S*,*S*)-[Co(α-dnen)$_3$]$^{3+}$ 2(*R*)-BINOLPA^{-}BAr$_f^{-}$	35 (*R*)	>99
30	Λ-(*S*,*S*)-**1**$^{3+}$ 2Br^{-}BAr$_f^{-}$	83 (*R*)	95
31	Λ-(*S*,*S*)-**1**$^{3+}$ 2I^{-}BAr$_f^{-}$	77 (*R*)	97

[a]Yields were determined by ^{1}H NMR relative to the internal standard Ph_2SiMe_2 per the experimental section. [b]These results agree with those reported earlier for an identical reaction (reference 2). [c]A 40% ee was found earlier for the corresponding reaction in CD_2Cl_2 (reference 2). [d]The ee values for analogous reactions in CD_2Cl_2 and CD_3CN were 70% and 73%, respectively.

Chart 2.1. Enantioselective additions of dimethyl malonate to *trans*-β-nitrostyrene.



entry	catalyst	ee (%)(config)	yield (%)[a]
1[b]	Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	76 (*S*)	98
2[c]	Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	92 (*R*)	99
3	Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^{-}$BAr$_f^{-}$	68 (*S*)	99
4	Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^{-}$BAr$_f^{-}$	66 (*R*)	86
5	Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camphSO$_3^{-}$BAr$_f^{-}$	67 (*S*)	86
6	Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camphSO$_3^{-}$BAr$_f^{-}$	62 (*R*)	89
7	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA^{-}BAr$_f^{-}$	57 (*S*)	89
8	Δ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA^{-}BAr$_f^{-}$	92 (*R*)	89
9	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-BINOLPA^{-}BAr$_f^{-}$	64 (*S*)	90
10	Δ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-BINOLPA^{-}BAr$_f^{-}$	81 (*R*)	91
11	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-VAPOLPA^{-}BAr$_f^{-}$	73 (*S*)	89
12	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-VAPOLPA^{-}BAr$_f^{-}$	54 (*S*)	80
13	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-((CF$_3$)$_2$Ph)$_2$-BINOLPA^{-}BAr$_f^{-}$	69 (*S*)	91
14	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-((CF$_3$)$_2$Ph)$_2$-BINOLPA^{-}BAr$_f^{-}$	77 (*S*)	88
15	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-(SiPh$_3$)$_2$-BINOLPA^{-}BAr$_f^{-}$	83 (*S*)	92
16	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-(SiPh$_3$)$_2$-BINOLPA^{-}BAr$_f^{-}$	20 (*S*)	87
17	Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-((*i*Pr)$_3$Ph)$_2$-BINOLPA^{-}BAr$_f^{-}$	63 (*S*)	23
18	Λ-(*S*,*S*)-**1**$^{3+}$ (*R*,*R*)-tart^{2-}BAr$_f^{-}$	73 (*S*)	98
19	Λ-(*S*,*S*)-**1**$^{3+}$ (*S*,*S*)-tart^{2-}BAr$_f^{-}$	66 (*S*)	>99
20	Λ-(*S*,*S*)-**1**$^{3+}$ (Sb$_2$((*R*,*R*)-tart')$_2$)$^{2-}$BAr$_f^{-}$	70 (*S*)	89
21	Λ-(*S*,*S*)-**1**$^{3+}$ (Sb$_2$((*S*,*S*)-tart')$_2$)$^{2-}$BAr$_f^{-}$	67 (*S*)	92
22	Λ-(*S*,*S*)-**1**$^{3+}$ 3(1*R*)-camphSO$_3^{-}$	40 (*S*)	94
23	Λ-(*S*,*S*)-**1**$^{3+}$ 3(1*S*)-camphSO$_3^{-}$	48 (*S*)	91
24	Λ-(*S*,*S*)-**1**$^{3+}$ 3(*S*)-BINOLPA^{-}	58 (*S*)	94
25	Λ -(*S*,*S*)-**1**$^{3+}$ 3(*R*)-BINOLPA^{-}	25 (*S*)	95
26	Λ-(*S*,*S*)-**1**$^{3+}$ 2Br^{-}BAr$_f^{-}$	71 (*S*)	99
27	Λ-(*S*,*S*)-**1**$^{3+}$ 2I^{-}BAr$_f^{-}$	71 (*S*)	99

[a]Yields were determined by ^{1}H NMR relative to the internal standard Ph_2SiMe_2 per the experimental section. [b]A 76% ee was found earlier for the corresponding reaction in CD_2Cl_2 at room temperature (reference 4b). [c]A 91% ee was found earlier for the corresponding reaction with Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$.

Chart 2.2. Enantioselective additions of methyl 2-oxocyclopentane-1-carboxylate to di-*tert*-butyl azodicarboxylate.

2.3 Discussion

The syntheses of the new $[Co(dpen)_3]^{3+}$ salts (Scheme 2.1) and their NMR properties generally parallel those of analogs with achiral anions reported earlier.[2,15] The complexes derived from tartrate or deprotonated tartrate[19a] (entries 18-21, Charts 2.1 and 2.2) represent the first $[Co(dpen)_3]^{3+}$ salts of dianions. However, Werner's original resolution of $[Co(en)_3]^{3+}$ also involved diastereomeric tartrate salts.[9e]

The crystal structure of Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*S*)-camph$SO_3^-$$BAr_f^-$ (Figure 2.4) represents the first for a "mixed salt" of $[Co(dpen)_3]^{3+}$. Trichloride,[2] triiodide,[13] and tris(nitrate) salts[25] have been crystallographically characterized previously. The new structure provides a welcome validation of many earlier claims made by the Gladysz group of mixed salts in this series of compounds.[2,15] Although the NMR and chromatographic evidence was compelling, there are cases where a species assigned as a mixed salt was later shown to be a mixture of two non-mixed salts.

The most striking feature of the crystal structure is the hydrogen bonding pattern. As noted above, the three roughly synperiplanar N-H units on each C_3 face hydrogen bond to separate oxygen atoms of the RSO_3^- moieties. According to a recent analysis, this can be classified as a $[C_3,C_3,C_3][3]$ trication/anion interaction.[24] In the arsenate salt $[Co(en)_3]^{3+}$ AsO_4^{3-}, three oxygen atoms of the tetrahedral trianion similarly bind a C_3 face.[27] The enhanced lipophilicities noted for all of the diastereomeric camphorsulfonate salts suggest that some RSO_3^-/H-N hydrogen bonding is maintained in solution. Although BAr_f^- is one of the feeblest hydrogen bond accepting anions,[28,29] there are a few F/HC and F/HN van der Waals contacts in the crystal (2.62, 2.65, 2.45 Å). However, the distances are much greater than those of the hydrogen bonds in Figure 2.4.

The trication also crystallizes in what is termed an *ob*$_3$ orientation.[11] When the structure is viewed down the C_3 axis, the three N**C**-**C**N bonds lie roughly in a

perpendicular plane (that of the paper). As detailed elsewhere, this follows from the relative cobalt and dpen configurations (Δ/*S*,*S*).[11] In the case of the opposite diastereomer (e.g., Δ/*R*,*R*), the N**C**-**C**N bonds preferentially align parallel to the C_3 axis, in what is termed a *lel*$_3$ orientation.

The diastereomeric tartrate salts of $[Co(en)_3]^{3+}$ originally prepared by Werner have been extensively studied, and not surprisingly, their association constants differ.[20a,30] Analyses of the crystal structures, and those of the diastereomeric tris(*trans*-1,2-cyclohexanediamine) analogs,[31] reveal a number of features that promote stronger hydrogen bonding and/or enhanced stabilities for certain chirality combinations. These phenomena can be viewed in the context of matched/mismatched trication/anion chiral recognition, and made us optimistic that there would be conceptually related rate driven effects on product enantioselectivities when similar species were used as asymmetric catalysts.

Indeed, the many pairs of diastereomeric catalysts in Charts 2.1 and 2.2 (entries 3-25) generally give different enantioselectivities. In a few cases, the differences are substantial (entries 11-12, Charts 2.1 and 2.2; entries 15-16, Chart 2.2), amounting to $\Delta_{\%ee}$ of 19-63, but most are moderate, in the range of $\Delta_{\%ee}$ of 3-8. From a statistical viewpoint, the average/high/median $\Delta_{\%ee}$ values in Charts 2.1 and 2.2 are 5/22/4 and 15/63/8, respectively, or in aggregate 10/63/6. Nonetheless, only in the case of Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-$(SiPh_3)_2$-BINOLPA$^-$BAr$_f^-$ (entry 15, Chart 2.2) is there an appreciable improvement over the enantioselectivity of the benchmark catalyst with achiral anions, Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$ BAr$_f^-$ (83% ee versus 76% ee).

In this context, it would be naive to expect or imply that the ee values for diastereomeric catalysts with different anion configurations should be symmetrically distributed about the ee value for any related catalyst with achiral anions. As shown in

entries 30 and 31 of Chart 2.1, the bromide and iodide salts Λ-(*S*,*S*)-**1**$^{3+}$ 2Br^{-}BAr$_f^{-}$ and Λ-(*S*,*S*)-**1**$^{3+}$ 2I^{-}BAr$_f^{-}$ give lower enantioselectivities than the chloride salt (83% and 77% ee versus 87% ee). Relative to these values, one diastereomer of most of the salts with opposite anion configurations shows an improvement. A reviewer (who critiqued the manuscript corresponding to this chapter) has also questioned whether (1) the chiral anions directly affect product formation, or (2) the differing levels of hydrogen bonding in the diastereomeric salts are largely responsible for the observed $\Delta_{\%ee}$ values. Computational studies along these lines are in progress.[32,33]

Another approach to catalyst optimization would be to replace the phenyl groups of [Co(dpen)$_3$]$^{3+}$ with other types of aryl groups. Indeed, dozens of such species have been prepared in the Gladysz laboratory and representative examples reported.[15] However, in a series of experiments conducted with 2Cl^{-}BAr$_f^{-}$ salts and the test reaction in Chart 2.1, none of these afforded the addition product **2** with significantly higher enantioselectivities. In many cases, the ee values diminished. A similar result was observed when the Cl^{-} is replaced with a chiral anion (entries 28-29, Chart 2.1). Thus, two independent approaches to catalyst optimization have not been very productive, although it remains possible that introducing chiral anions into catalysts with other types of aryl groups may still give substantial improvements.

In summary, this study has greatly expanded the range and numbers of chiral cobalt(III) hydrogen bond donor catalysts that can be applied in enantioselective synthesis, specifically by the incorporation of chiral anions. The motivating thesis regarding "matched" and "mismatched" pairings of trication and anion configurations could be successfully established, as reflected by the significant average/median $\Delta_{\%ee}$ values (10/6). However, the performance of the matched systems only occasionally exceeds those of a benchmark catalyst with achiral 2Cl^{-}BAr$_f^{-}$ anions. Nonetheless, this illustrates a

seldom employed approach to the optimization of enantioselective catalysts[21-23] – and one of a very few involving isolated salts[21] – that could be spectacularly successful in other cases. Additional strategies for optimizing and enhancing the efficacy of this catalyst family are under study and will be described in future reports.

2.4 Experimental

General Data. All operations were carried out under ambient (air) atmospheres. NMR spectra were recorded on standard FT spectrometers at ambient probe temperatures. Chemical shifts (δ/ppm) were referenced to solvent signals (^{1}H: acetone-d_5, 2.05; CHD_2CN, 1.94; ^{13}C: acetone-d_6, 29.8; CD_3CN, 1.32). Microanalyses were conducted by Atlantic Microlab. HPLC analyses employed a Shimadzu instrument package (pump/autosampler/detector LC-20AD/SIL-20A /SPD-M20A). Reaction, HPLC, and deuterated solvents as well as the educts and bases in Charts 2.1 and 2.2 were used as received from common commercial sources (generally given in previous reports).[2,4a] Chiral anions or their precursors were used as received from the following sources: (1*R*)- and (1*S*)-ammonium 3-bromocamphor-8-sulfonate, 2 × Alfa Aesar (98%); (*R*)- and (*S*)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, 2 × Chem-Impex International, Inc. (≥99%); (*R*)- and (*S*)-VAPOL hydrogenphosphate and (*R*)- and (*S*)-3,3'-bis(triphenylsilyl)-1,1'-binapthyl-2,2'-diyl hydrogenphosphate, 4 × Santa Cruz Biotechnology; (*S*)-3,3'-bis(triphenylsilyl)-1,1'-binapthyl-2,2'-diyl hydrogenphosphate, Sigma-Aldrich (96%); (*R*)- and (*S*)-3,3'-bis(3,5-trifluoromethyl)-1,1'-binapthyl-2,2'-diyl hydrogenphosphate and (*S*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binapthyl-2,2'-diyl hydrogenphosphate, 3 × Strem (98%); (*R*,*R*)-tart^{2-}·2H_2O, Alfa Aesar (99%); (*S*,*S*)-tartaric acid, Sigma-Aldrich (99%). The catalysts or catalyst precursors Λ-(*S*,*S*)-**1**$^{3+}$ 2$Cl^-BAr_f^-$·2H_2O,[15] Δ-(*S*,*S*)-**1**$^{3+}$ 2$Cl^-BAr_f^-$·H_2O,[15] Λ-(*S*,*S*)-**1**$^{3+}$ 3Cl^-·3H_2O,[15] and Λ-(*S*,*S*)-**1**$^{3+}$ 2$I^-BAr_f^-$·0.5H_2O[13] were prepared as described previously.

Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$ (Λ-(*S*,*S*)-1^{3+} 2(1*R*)-camphSO$_3^-$BAr$_f^-$). A round bottom flask was charged with a solution of Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H$_2$O (0.0520 g, 0.0312 mmol) in CH_2Cl_2 (5 mL). A solution of (1*R*)-ammonium 3-bromocamphor-8-sulfonate (0.0420 g, 0.128 mmol, 4.3 equiv) in distilled H_2O (5 mL) was added. The biphasic mixture was vigorously stirred. After 1 h, the aqueous phase was removed and the orange organic phase was washed with distilled H_2O (2 × 5 mL). The solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$·H_2O as a bright orange solid (0.0586 g, 0.0267 mmol, 87%), mp 151-155 °C (dec, open capillary). Anal. Calcd. for $C_{94}H_{88}BBr_2CoF_{24}N_6O_8S_2$·$H_2O$ (2197.40): C 51.38, H 4.13, N, 3.82; found C 51.10, H 4.25, N 3.75.

NMR (acetone-d_6, δ/ppm): ^{1}H (400 MHz) BAr$_f^-$ at 7.79 (s, 8H, *o*), 7.67 (s, 4H, *p*); dpen at 7.60-7.56 (m, 12H, *o*-Ph), 7.40-7.26 (m, 24H, *m-, p*-Ph, N**H**H'), 5.42 (br s, 6H, NH**H'**), 5.10 (s, 6H, C**H**NH$_2$); 2.83 (s, 3H, **H**$_2$O); camphSO$_3^-$ at 4.82 (d, J = 4.3 Hz, 2H), 3.23 (d, J = 15.1 Hz, 2H), 3.13 (t, J = 4.2 Hz, 2H), 2.81-2.77 (m, 2H), 2.28-2.16 (m, 2H), 2.12-2.07 (m, 2H), 1.87-1.77 (m, 2H), 1.37 (ddd, J = 14.5, 9.4, 5.5 Hz, 2H), 1.29 (s, 6H), 0.95 (s, 6H); ^{13}C{^{1}H} (100 MHz) BAr$_f^-$ at 162.6 (q, $^1J_{BC}$ = 49.8 Hz, *i*), 135.5 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 274.0 Hz, **C**F$_3$), 118.4 (s, *p*); dpen at 136.8 (s, *i*-Ph), 130.0, 129.7 (2 × s, *o-, m-*, *p*-Ph), 63.4 (s, **C**HNH$_2$); camphSO$_3^-$ at 211.3, 60.0, 54.9, 54.5, 48.3, 47.9, 30.7, 22.9, 18.0, 10.0 (10 × s).

Δ-(*S*,*S*)-1^{3+} 2(1*R*)-camphSO$_3^-$BAr$_f^-$. Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·H_2O (0.3295 g, 0.2002 mmol), CH_2Cl_2 (10 mL), (1*R*)-ammonium 3-bromocamphor-8-sulfonate (0.2624 g, 0.7987 mmol, 4.0 equiv), and distilled H_2O (10 mL) were combined in a procedure analogous to that for Λ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$. An identical workup gave Δ-(*S*,*S*)-**1**$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$·H_2O as a bright orange solid (0.383 g, 0.174 mmol,

87%), mp 176-182 °C (dec, open capillary). Anal. Calcd. for $C_{94}H_{88}BBr_2CoF_{24}N_6O_8S_2 \cdot H_2O$ (2197.40): C 51.38, H 4.13, N, 3.82; found C 51.25, H 4.24, N 3.91.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.79 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.55-7.42 (m, 12H, *o*-Ph), 7.34-7.17 (m, 18H, *m*-, *p*-Ph), 7.04 (s, 6H, N**H**H'), 5.95 (d, $^3J_{HH}$ = 11.0 Hz, 6H, NH**H'**), 5.19 (br s, 6H, C**H**NH_2); 2.95 (br s, 6H, $\mathbf{H}_2O$); camphSO_3^- at 4.68 (d, $^3J_{HH}$ = 4.0 Hz, 2H), 3.11 (d, $^2J_{HH}$ = 14.5 Hz, 2H), 3.00-2.97 (m, 2H), 2.67 (d, $^2J_{HH}$ = 14.5 Hz, 2H), 2.29-2.19 (m, 2H), 2.13-2.07 (m, 2H), 1.87-1.75 (m, 2H), 1.42-1.33 (m, 2H), 1.29 (s, 6H), 0.99-0.82 (m, 6H); $^{13}C\{^1H\}$ (100 MHz) BAr_f^- at 162.5 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 129.9 (m, *m*), 125.3 (q, $^1J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (m, *p*); dpen at 137.3 (s, *i*-Ph), 129.7 (s, *p*-Ph), 129.5, 129.4 (2 × s, *o*-, *m*-Ph), 66.1 (s, **C**HNH_2); camphSO_3^- at 211.3, 60.1, 54.8, 54.5, 48.3, 47.7, 30.6, 22.8, 17.9, 10.0 (10 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*S*)-camph$\mathbf{SO_3^-BAr_f^-}$. Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $2Cl^-BAr_f^- \cdot 2H_2O$ (0.108 g, 0.0648 mmol), CH_2Cl_2 (10 mL), (1*S*)-ammonium 3-bromocamphor-8-sulfonate (0.0892 g, 0.272 mmol, 4.2 equiv), and distilled H_2O (10 mL) were combined in a procedure analogous to that for Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*R*)-camph$SO_3^-BAr_f^-$. An identical workup gave Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*S*)-camph$SO_3^-BAr_f^- \cdot H_2O$ as a bright orange solid (0.122 g, 0.0555 mmol, 85%), mp 145-151 °C (dec, open capillary). Anal. Calcd. for $C_{94}H_{88}BBr_2CoF_{24}N_6O_8S_2 \cdot H_2O$ (2197.40): C 51.38, H 4.13, N, 3.82; found C 51.55, H 4.40, N 3.70.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.79 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.55 (s, 12H, *o*-Ph), 7.31 (br s, 24H, *m*-, *p*-Ph, N**H**H'), 5.42 (s, 6H, NH**H'**), 5.11 (s, 6H, C**H**NH_2); 2.90 (br s, 6H, $\mathbf{H}_2O$); camphSO_3^- at 4.82 (s, 2H), 3.22 (d, $^2J_{HH}$ = 15.0 Hz, 2H), 3.15 (s, 2H), 2.81 (d, $^2J_{HH}$ = 14.0 Hz, 2H), 2.29-2.18 (m, 2H), 2.13-2.07 (m, 2H),

1.87-1.75 (m, 2H), 1.42-1.33 (m, 2H), 1.29 (s, 6H), 0.99-0.82 (m, 6H); $^{13}C\{^{1}H\}$ (125 MHz) BAr_f^- at 162.5 (q, $^{1}J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 129.9 (m, *m*), 125.3 (q, $^{1}J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (m, *p*); dpen at 136.8 (s, *i*-Ph), 129.9 (s, *p*-Ph), 129.8, 129.7 (2 × s, *o*-, *m*-Ph), 63.4 (s, **C**HNH_2); camphSO_3^- at 211.2, 60.0, 54.8, 54.4, 48.3, 47.8, 30.7, 22.8, 18.0, 10.0 (10 × s).

Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*S*)-camph$\mathbf{SO_3^-BAr_f^-}$. Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ $2Cl^-BAr_f^-\cdot H_2O$ (0.0250 g, 0.0152 mmol), CH_2Cl_2 (5 mL), (1*S*)-ammonium 3-bromocamphor-8-sulfonate (0.0105 g, 0.0319 mmol, 2.1 equiv), and distilled H_2O (5 mL) were combined in a procedure analogous to that for Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*R*)-camph$SO_3^-BAr_f^-$ (3 h reaction time). An identical workup gave Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*S*)-camph$SO_3^-BAr_f^-$ as a bright orange solid (0.0322 g, 0.0148 mmol, 97%), mp 156-160 °C (dec, open capillary). Anal. Calcd. for $C_{94}H_{88}BBr_2CoF_{24}N_6O_8S_2$ (2179.41): C 51.80, H 4.07, N, 3.86; found C 51.95, H 4.27, N 3.92.

NMR (acetone-d_6, δ/ppm): ^{1}H (300 MHz) BAr_f^- at 7.80 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.51-7.45 (m, 12H, *o*-Ph), 7.28-7.22 (m, 18H, *m*-, *p*-Ph), 7.07 (s, 6H, N**H**H'), 5.91 (d, $^{3}J_{HH}$ = 11.1 Hz, 6H, NH**H'**), 5.17 (br s, 6H, C**H**NH_2); 2.90 (br s, 5H, $\mathbf{H}_2O$); camphSO_3^- at 4.74 (d, $^{3}J_{HH}$ = 3.8 Hz, 2H), 3.11 (d, $^{2}J_{HH}$ = 14.7 Hz, 2H), 3.04-2.98 (m, 2H), 2.70 (d, $^{2}J_{HH}$ = 14.4 Hz, 2H), 2.22-2.09 (m, 2H), 1.83-1.70 (m, 2H), 1.39-1.33 (m, 2H), 1.24 (s, 6H), 0.91 (s, 6H); ^{13}C $\{^{1}H\}$ (75 MHz) BAr_f^- at 162.5 (q, $^{1}J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 129.9 (m, *m*), 125.3 (q, $^{1}J_{CF}$ = 270 Hz, **C**F_3), 118.4 (m, *p*); dpen at 137.4 (s, *i*-Ph), 129.6 (s, *p*-Ph), 129.4, 129.3 (2 × s, *o*-, *m*-Ph), 66.2 (s, **C**HNH_2); camphSO_3^- at 211.2, 60.0, 54.8, 54.4, 48.2, 47.7, 30.6, 22.7, 18.0, 10.0 (10 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*R*)-BINOLPA$\mathbf{^-BAr_f^-}$. A round bottom flask was charged with a solution of Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $2Cl^-BAr_f^-\cdot 2H_2O$ (0.0250 g, 0.0152 mmol) in CH_2Cl_2 (5 mL), (*R*)-BINOLPAH (0.0111 g, 0.0319 mmol, 2.1 equiv), NaOH (0.0013 g, 0.033 mmol, 2.2

equiv), and distilled H_2O (5 mL). The biphasic mixture was vigorously stirred. After 1 h, the aqueous phase was removed. The solvent was removed from the orange organic phase by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA$^-$BAr$_f^-$·3H_2O as an orange solid (0.0307 g, 0.0133 mmol, 88%), mp 166-174 °C (dec, open capillary). Anal. Calcd. for $C_{114}H_{84}BCoF_{24}N_6O_8P_2$·3$H_2O$ (2307.66): C 59.34, H 3.93, N, 3.64; found C 59.26, H 3.99, N 3.65.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr$_f^-$ at 7.80 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.91 (br s, 6H, N**H**H'), 7.65-7.55 (m, 12H, *o*-Ph), 7.35-7.19 (m, 18H, *m*-, *p*-Ph), 5.37 (br s, 6H, NH**H'**), 5.19-5.09 (m, 6H, C**H**NH_2); 3.02 (br s, 9H, **H**$_2$O); BINOLPA$^-$ at 8.18 (d, $^3J_{HH}$ = 8.5 Hz, 4H), 8.08 (d, $^3J_{HH}$ = 8.0 Hz, 4H), 7.55-7.50 (m, 4H), 7.46 (d, $^3J_{HH}$ = 8.5 Hz, 4H), 7.43-7.35 (m, 8H); ^{13}C{^{1}H} (125 MHz) BAr$_f^-$ at 162.5 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 129.9 (m, *m*), 125.3 (q, $^1J_{CF}$ = 270 Hz, **C**F_3), 118.4 (m, *p*); dpen at 137.1 (s, *i*-Ph), 129.9 (s, *p*-Ph), 129.8, 129.7 (2 × s, *o*-, *m*-Ph), 63.6 (s, **C**HNH_2); BINOLPA$^-$ at 150.3 (d, $^2J_{CP}$ = 9.3 Hz), 133.4, 132.1, 131.2, 129.4, 127.4, 127.3, 125.9, 122.9, 122.6 (9 × s).

Δ-(*S*,*S*)-1^{3+} 2(*R*)-BINOLPA$^-$BAr$_f^-$. Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·H_2O (0.0250 g, 0.0152 mmol), CH_2Cl_2 (5 mL), (*R*)-BINOLPAH (0.0111 g, 0.0319 mmol, 2.1 equiv), NaOH (0.0013 g, 0.033 mmol, 2.2 equiv), and distilled H_2O (5 mL) were combined in a procedure analogous to that for Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA$^-$BAr$_f^-$. An identical workup gave Δ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA$^-$BAr$_f^-$·H_2O as an orange solid (0.0295 g, 0.0129 mmol, 85%), mp 178-182 °C (open capillary). Anal. Calcd. for $C_{114}H_{84}BCoF_{24}N_6O_8P_2$·$H_2O$ (2271.63): C 60.28, H 3.82, N, 3.70; found C 59.91, H 4.27, N 3.66.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr$_f^-$ at 7.81 (m, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 7.40-7.33 (m, 12H, *o*-Ph), 7.32-7.24 (m, 18H, *m*-, *p*-Ph), 7.20 (br s, 6H, N**H**H'),

6.04 (d, $^3J_{HH}$ = 11.0 Hz, 6H, NH**H'**), 5.17-5.08 (m, 6H, C**H**NH_2); 2.94 (br s, 8H, $\mathbf{H}_2O$); BINOLPA$^-$ at 8.11 (d, $^3J_{HH}$ = 9.0 Hz, 4H), 8.05 (d, $^3J_{HH}$ = 8.0 Hz, 4H), 7.58-7.52 (m, 12H), 7.52-7.47 (m, 4H); ^{13}C {^{1}H} (125 MHz) BAr_f^- at 162.5 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 129.9 (m, *m*), 125.3 (q, $^1J_{CF}$ = 270 Hz, **C**CF_3), 118.4 (m, *p*); dpen at 137.5 (s, *i*-Ph), 130.9 (s, *p*-Ph), 129.5, 129.2 (2 × s, *o*-, *m*-Ph), 66.1 (s, **C**HNH_2); BINOLPA$^-$ at 150.5 (d, $^2J_{CP}$ = 9.3 Hz), 133.3, 132.0, 129.7, 129.3, 127.4, 127.1, 125.8, 122.89, 122.87 (9 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*S*)-BINOLPA$^-$$BAr_f^-$. Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2Cl$^-$$BAr_f^-$·2$H_2O$ (0.0850 g, 0.051 mmol), CH_2Cl_2 (15 mL), (*S*)-BINOLPAH (0.0415 g, 0.112 mmol, 2.2 equiv), NaOH (0.0045 g, 0.11 mmol, 2.2 equiv) and distilled H_2O (15 mL) were combined in a procedure analogous to that for Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*R*)-BINOLPA$^-$$BAr_f^-$ (3 h reaction time). An identical workup gave Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*S*)-BINOLPA$^-$$BAr_f^-$·2$H_2O$ as an orange solid (0.0944 g, 0.0407 mmol, 80%), mp 166-174 °C (dec, open capillary). Anal. Calcd. for $C_{114}H_{84}BCoF_{24}N_6O_8P_2$·2$H_2O$ (2307.62): C 59.80, H 3.87, N, 3.67; found C 60.06, H 4.00, N 3.63.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.80 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.80 (br s, 6H, N**H**H') 7.61-7.54 (m, 12H, *o*-Ph), 7.33-7.27 (m, 18H, *m*-, *p*-Ph), 5.38 (br s, 6H, NH**H'**), 5.14 (s, 6H, C**H**NH_2); 2.96 (br s, 9H, $\mathbf{H}_2O$); BINOLPA$^-$ at 8.11-8.01 (m, 8H), 7.54-7.48 (m, 4H), 7.44-7.33 (m, 12H); ^{13}C{^{1}H} (125 MHz) BAr_f^- at 162.5 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 129.8 (m, *m*), 125.3 (q, $^1J_{CF}$ = 270 Hz, **C**CF_3), 118.4 (m, *p*); dpen at 137.2 (s, *i*-Ph), 129.8 (s, *p*-Ph), 129.7 (s, *o*-, *m*-Ph), 63.4 (s, **C**HNH_2); BINOLPA$^-$ at 150.3 (d, $^2J_{CP}$ = 9.3 Hz), 133.3, 132.0, 131.1, 129.4, 127.4, 127.2, 125.8, 122.9, 122.7 (9 × s).

Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*S*)-BINOLPA$^-$$BAr_f^-$. Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2Cl$^-$$BAr_f^-$·$H_2O$ (0.0250 g, 0.0152 mmol), CH_2Cl_2 (5 mL), (*S*)-BINOLPAH (0.0111 g, 0.0319 mmol, 2.1 equiv),

NaOH (0.0013 g, 0.033 mmol, 2.2 equiv), and distilled H_2O (5 mL) were combined in a procedure analogous to that for Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA$^-$BAr$_f^-$ (4 h reaction time). An identical workup gave Δ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-BINOLPA$^-$BAr$_f^-$·H_2O as an orange solid (0.0329 g, 0.0146 mmol, 96%), mp 178-182 °C (dec, open capillary). Anal. Calcd. for $C_{114}H_{84}BCoF_{24}N_6O_8P_2$·$H_2O$ (2271.63): C 60.28, H 3.82, N, 3.70; found C 60.83, H 4.37, N 3.67.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr$_f^-$ at 7.81 (m, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 7.40-7.33 (m, 12H, *o*-Ph), 7.32-7.24 (m, 18H, *m*-, *p*-Ph), 7.20 (br s, 6H, N**H**H'), 6.04 (d, $^3J_{HH}$ = 11.0 Hz, 6H, NH**H'**), 5.17-5.08 (m, 6H, C**H**NH_2); 2.94 (br s, 8H, **H**$_2$O); BINOLPA$^-$ at 8.11 (d, $^3J_{HH}$ = 9.0 Hz, 4H), 8.05 (d, $^3J_{HH}$ = 8.0 Hz, 4H), 7.58-7.52 (m, 12H), 7.52-7.47 (m, 4H); ^{13}C {^{1}H} (125 MHz) BAr$_f^-$ at 162.5 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 129.9 (m, *m*), 125.3 (q, $^1J_{CF}$ = 270 Hz, **C**F_3), 118.4 (m, *p*); dpen at 137.5 (s, *i*-Ph), 130.9 (s, *p*-Ph), 129.5, 129.2 (2 × s, *m*-Ph), 66.1 (s, **C**HNH_2); BINOLPA$^-$ at 150.5 (d, $^2J_{CP}$ = 9.3 Hz), 133.3, 132.0, 129.7, 129.3, 127.4, 127.1, 125.8, 122.97, 122.95 (9 × s).

Λ-(*S*,*S*)-1^{3+} 2(*R*)-VAPOLPA$^-$BAr$_f^-$. Crude Na^+ (*R*)-VAPOLPA$^-$ was prepared by charging a vial with (*R*)-VAPOLPAH (0.0850 g, 0.136 mmol), NaOH (0.0054 g, 0.14 mmol, 1.0 equiv), and MeOH/H_2O (10 mL, 1:1 v/v). The mixture was vigorously stirred (rt, overnight). The solvent was removed by rotary evaporation. To the white residue was added a solution of Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·$2H_2O$ (0.0532 g, 0.0319 mmol, 0.33 equiv) in CH_2Cl_2 (10 mL). The mixture was vigorously stirred (rt, overnight). The phases were allowed to separate and the orange organic phase washed with water (2 × 10 mL) and dried (Na_2SO_4). The solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ 2(*R*)-VAPOLPA$^-$BAr$_f^-$·$3H_2O$ as a bright orange solid (0.0879 g, 0.0313 mmol, 98%), mp 160-172 °C (dec, open capillary). Anal. Calcd. for $C_{154}H_{108}BCoF_{24}N_6O_8P_2$·$3H_2O$ (2812.29): C 65.77, H 4.09, N 2.99;

found C 65.70, H 4.14, N 2.79.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.79 (s, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 7.52 (m, 6H, N**H**H'), 7.31-7.19 (m, 18H), 6.96-6.86 (m, 12H), 5.58 (br s, 6H, NH**H'**), 4.83 (s, 6H, C**H**NH_2); 2.97 (br s, 9H, $\mathbf{H}_2O$); VAPOLPA$^-$ at 10.01 (d, $^3J_{HH}$ = 7.9 Hz, 4H), 8.03 (d, $^3J_{HH}$ = 7.5 Hz, 4H), 7.94 (d, $^3J_{HH}$ = 8.8 Hz, 4H), 7.90 (d, $^3J_{HH}$ = 8.8 Hz, 4H), 7.64 (s, 4H), 7.14 (m, 12H), 6.98 (t, $^3J_{HH}$ = 7.7 Hz, 8H), 6.52 (d, $^3J_{HH}$ = 7.5 Hz, 8H); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 49.7 Hz, *i*), 135.6 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 271.8 Hz, **C**F_3), 118.5 (m, *p*); dpen at 136.1 (s, *i*-Ph), 130.4 (s, *p*-Ph), 130.1, 129.8 (2 × s, *o*-, *m*-Ph), 64.2 (s, **C**HNH_2); VAPOLPA$^-$ at 151.2 (d, $^2J_{CP}$ = 9.4 Hz), 142.4, 140.9, 135.4, 134.4, 130.0, 129.6, 129.5, 129.2, 128.6, 128.5, 128.2, 127.6, 127.5, 127.4, 127.2, 127.0, 122.7 (17 × s).

Λ-(*S*,*S*)-1^{3+} 2(*S*)-VAPOLPA$^-$BAr$_f^-$. Crude Na^+ (*S*)-VAPOLPA$^-$ was prepared by charging a vial with (*S*)-VAPOLPAH (0.0545 g, 0.0907 mmol), NaOH (0.0036 g, 0.091 mmol, 1.0 equiv), and MeOH/H_2O (5 mL, 1:1 v/v). The mixture was vigorously stirred (rt, overnight). The solvent was removed by rotary evaporation and the white residue dried by oil pump vacuum (rt, overnight). A vial was charged with Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$$BAr_f^-$ ·2H_2O (0.0341 g, 0.0205 mmol), distilled H_2O (5 mL), CH_2Cl_2 (5 mL), and crude Na^+ (*S*)-VAPOLPA$^-$ (0.0255 g, 0.0410 mmol, 2.0 equiv). The biphasic mixture was vigorously stirred (rt, overnight). The orange organic phase was separated and the solvent removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-VAPOLPA$^-$$BAr_f^-$·4$H_2O$ as a bright orange solid (0.0572 g, 0.0202 mmol, 99%), mp 171-180 °C (dec, open capillary). Anal. Calcd. for $C_{154}H_{108}$-$BCoF_{24}N_6O_8P_2$·4H_2O (2830.31): C 65.35, H 4.13, N 2.97; found C 65.35, H 4.23, N 2.55.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.81 (s, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 7.49 (br s, 6H, N**H**H'), 7.30 (t, $^3J_{HH}$ = 7.3 Hz, 6H, *p*-Ph), 7.22 (t, $^3J_{HH}$ = 7.5 Hz,

12H, *m*-Ph), 7.16 (d, $^3J_{HH}$ = 6.9 Hz, 12H, *o*-Ph), 5.04 (br s, 6H, NH**H'**), 4.60 (s, 6H, C**H**NH_2); 2.97 (br s, 15H, $\mathbf{H}_2O$); VAPOLPA$^-$ at 9.74 (d, $^3J_{HH}$ = 8.0 Hz, 4H), 8.04 (d, $^3J_{HH}$ = 7.5 Hz, 4H), 7.95 (d, $^3J_{HH}$ = 8.3 Hz, 4H), 7.90 (d, $^3J_{HH}$ = 8.3 Hz, 4H), 7.78-7.67 (m, 8H), 7.58 (s, 4H), 7.17-7.12 (m, 4H), 6.99 (t, $^3J_{HH}$ = 7.3 Hz, 8H), 6.60 (d, $^3J_{HH}$ = 7.3 Hz, 8H); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 49.7 Hz, *i*), 135.6 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 271.8 Hz, **C**F_3), 118.5 (m, *p*); dpen at 136.1 (s, *i*-Ph), 130.4 (s, *p*-Ph), 130.1, 129.6 (2 × s, *o*-, *m*-Ph), 64.2 (s, **C**HNH_2); VAPOLPA$^-$ at 151.2 (d, $^2J_{CP}$ = 9.5 Hz), 142.4, 140.9, 135.4, 134.4, 130.8, 129.8, 129.5, 129.2, 128.6, 128.5, 128.2, 127.6, 127.5, 127.4, 127.2, 127.0, 122.7 (17 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*R*)-((CF$_3$)$_2$Ph)$_2$-BINOLPA$^-$BAr$_f^-$. Crude Na^+ (*R*)-((CF$_3$)$_2$Ph)$_2$-BINOLPA$^-$ was prepared by charging a vial with (*R*)-((CF$_3$)$_2$Ph)$_2$-BINOLPAH (0.0850 g, 0.107 mmol), NaOH (0.0043 g, 0.11 mmol, 1.5 equiv), and MeOH/H_2O (10 mL, 1:1 v/v). The mixture was vigorously stirred (rt, overnight). The solvent was removed by rotary evaporation and the white residue dried by oil pump vacuum (rt, overnight). A solution of Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2Cl$^-$BAr$_f^-$·2H_2O (0.0594 g, 0.0357 mmol, 0.33 equiv) in CH_2Cl_2 (10 mL) was added. The biphasic mixture was vigorously stirred. After 1 h, the phases were allowed to separate. The orange organic phase was washed with water (2 × 10 mL) and dried (Na_2SO_4). The solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*R*)-((CF$_3$)$_2$Ph)$_2$-BINOLPA$^-$BAr$_f^-$·3H_2O as a bright orange solid (0.0497 g, 0.0157 mmol, 44%), mp 165-171 °C (dec, open capillary). Anal. Calcd. for $C_{146}H_{92}BCoF_{48}N_6O_8P_2\cdot 3H_2O$ (3156.04): C 55.56, H 3.13, N 2.66; found C 55.75, H 3.32, N 2.47.

NMR (acetone-d_6, δ/ppm): ^1H (500 MHz) BAr_f^- at 7.79 (s, 8H, *o*), 7.67 (s, 4H, *p*); dpen at 7.24 (t, $^3J_{HH}$ = 7.4 Hz, 6H, *p*-Ph), 7.14 (t, $^3J_{HH}$ = 7.7 Hz, 12H, *m*-Ph), 6.94 (d, $^3J_{HH}$ = 7.3 Hz, 12H, *o*-Ph), 7.00 (br s, 6H, N**H**H'), 5.12 (br s, 6H, NH**H'**), 4.42 (s, 6H,

C**H**NH_2); 2.84 (br s, 8H, **H**$_2$O); $((CF_3)_2Ph)_2$-BINOLPA$^-$ at 8.80 (s, 8H), 8.40 (s, 4H), 8.21 (d, $^3J_{HH}$ = 8.1 Hz, 4H), 8.03 (s, 4H), 7.57 (t, $^3J_{HH}$ = 7.5 Hz, 4H), 7.38 (t, $^3J_{HH}$ = 8.1 Hz, 4H), 7.19 (d, $^3J_{HH}$ = 8.5 Hz, 4H); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 130.0 (m, *m*), 125.3 (q, $^1J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (m, *p*); dpen at 134.9 (s, *i*-Ph), 130.4 (s, *p*-Ph), 129.8, 128.9 (2 × s, *o*-, *m*-Ph), 63.5 (s, **C**HNH_2); $((CF_3)_2Ph)_2$-BINOLPA$^-$ at 147.1 (d, $^2J_{CP}$ = 9.3 Hz), 140.9, 134.9, 133.2, 132.6 (4 × s), 132.1 (q, $^2J_{CF}$ = 33.5 Hz), 131.8 (d, $^2J_{CP}$ = 3.0 Hz), 131.6 (s), 129.4 (q, $^1J_{CF}$ = 272.0 Hz, **C**F_3) 128.3, 127.6, 127.3, 126.8 (4 × s), 123.6 (d, $^2J_{CP}$ = 2.0 Hz), 121.8 (s).

Λ-(*S*,*S*)-1^{3+} 2(*S*)-((CF$_3$)$_2$Ph)$_2$-BINOLPA$^-$BAr$_f^-$. Crude Na^+ (*S*)-$((CF_3)_2Ph)_2$-BINOLPA$^-$ was prepared by charging a vial with (*S*)-$((CF_3)_2Ph)_2$-BINOLPAH (0.0515 g, 0.0667 mmol), NaOH (0.0040 g, 0.10 mmol, 1.5 equiv), and MeOH/H_2O (5 mL, 1:1 v/v). The mixture was vigorously stirred (rt, overnight). The solvent was removed by rotary evaporation and the white residue dried by oil pump vacuum (rt, overnight). A vial was charged with Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H_2O (0.0567 g, 0.0340 mmol), distilled H_2O (5 mL), CH_2Cl_2 (5 mL), and crude Na^+ (*S*)-$((CF_3)_2Ph)_2$-BINOLPA$^-$ (0.0541 g, 0.0681 mmol, 2.0 equiv). The biphasic mixture was vigorously stirred (rt, overnight). The orange organic phase was separated and the solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-$((CF_3)_2Ph)_2$-BINOLPA$^-$BAr$_f^-$·3H_2O as a bright orange solid (0.1013 g, 0.03210 mmol, 94%), mp 159-164 °C (dec, open capillary). Anal. Calcd. for $C_{146}H_{92}BCoF_{48}N_6O_8P_2$·3$H_2O$ (3156.04): C 55.56, H 3.13, N 2.66; found C 55.60, H 3.15, N 2.53.

NMR (acetone-d_6, δ/ppm): ^1H (500 MHz) BAr_f^- at 7.81 (s, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 7.29 (t, $^3J_{HH}$ = 7.4 Hz, 6H, *p*-Ph), 7.08 (t, $^3J_{HH}$ = 7.3 Hz, 12H, *m*-Ph), 6.98 (d, $^3J_{HH}$ = 6.5 Hz, 12H, *o*-Ph), 6.73 (br s, 6H, N**H**H'), 5.47 (br s, 6H, NH**H'**), 4.29 (s, 6H, C**H**NH_2); 3.04 (br s, 8H, **H**$_2$O); $((CF_3)_2Ph)_2$-BINOLPA$^-$ at 8.97 (s, 8H), 8.38 (s, 4H),

8.25-8.12 (m, 4H), 8.00 (s, 4H), 7.65-7.51 (m, 4H), 7.46-7.33 (m, 4H), 7.27-7.21 (m, 4H); $^{13}C\{^{1}H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^{1}J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 130.0 (m, *m*), 125.3 (q, $^{1}J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (m, *p*); dpen at 134.9 (s, *i*-Ph), 130.4 (s, *p*-Ph), 129.8, 128.9 (2 × s, *o*-, *m*-Ph), 63.5 (s, **C**HNH_2); $((CF_3)_2Ph)_2$-BINOLPA$^-$ at 147.1 (d, $^{2}J_{CP}$ = 9.3 Hz), 140.9, 134.9, 133.2, 132.6 (4 × s), 132.1 (q, $^{2}J_{CF}$ = 33.5 Hz), 131.8 (d, $^{2}J_{CP}$ = 3.0 Hz), 131.6 (s), 129.4 (q, $^{1}J_{CF}$ = 272.0 Hz, **C**F_3) 128.3, 127.6, 127.3, 126.8 (4 × s), 123.6 (d, $^{2}J_{CP}$ = 2.0 Hz), 121.8 (s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*R*)-$(SiPh_3)_2$-BINOLPA$^-$$BAr_f^-$. Crude Na^+ (*R*)-$(SiPh_3)_2$-BINOLPA$^-$ was prepared by the charging a vial with (*R*)-$(SiPh_3)_2$-BINOLPAH (0.0515 g, 0.0667 mmol), NaOH (0.0040 g, 1.0 mmol, 1.5 equiv), and MeOH/H_2O (5 mL, 1:1 v/v). The mixture was vigorously stirred (rt. overnight). The solvent was removed by rotary evaporation and the white residue dried by oil pump vacuum (rt, 17 h). A vial was charged with Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $2Cl^-BAr_f^-\cdot 2H_2O$ (0.0545 g, 0.0327 mmol), distilled H_2O (5 mL), CH_2Cl_2 (5 mL), and crude Na^+ (*R*)-$(SiPh_3)_2$-BINOLPA$^-$ (0.0580 g, 0.0654 mmol, 2.0 equiv). The biphasic mixture was vigorously stirred (rt, overnight). The orange organic phase was separated and the solvent removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*R*)-$(SiPh_3)_2$-BINOLPA$^-$$BAr_f^-$ $\cdot 6H_2O$ as a bright yellow solid (0.1040 g, 0.03063 mmol, 94%), mp 149-157 °C (dec, open capillary). Anal. Calcd. for $C_{186}H_{140}BCoF_{24}N_6O_8P_2Si_4\cdot 6H_2O$ (3395.28): C 65.80, H 4.51, N 2.48; found C 65.72, H 4.53, N 2.45.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.81 (s, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 7.29-7.23 (m, 18H, *m*-, *p*-Ph), 7.12-7.06 (m, 12H, *o*-Ph), 6.50 (br s, 6H, N**H**H'), 4.88 (br s, 6H, NH**H'**), 4.12 (s, 6H, C**H**NH_2); 3.12 (br s, 10H, $\mathbf{H}_2O$); $(SiPh_3)_2$-BINOLPA$^-$ at 8.17 (s, 4H), 7.90 (d, $^{3}J_{HH}$ = 8.1 Hz, 4H), 7.58-7.54 (m, 24H), 7.44 (t, $^{3}J_{HH}$ = 7.5 Hz, 4H), 7.34-7.27 (m, 20H), 7.20 (t, $^{3}J_{HH}$ = 7.5 Hz, 20H), 7.16 (d, $^{3}J_{HH}$ = 8.6 Hz, 4H);

$^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 49.8 Hz, *i*), 135.6 (s, *o*), 130.1 (m, *m*), 125.4 (q, $^1J_{CF}$ = 272.9 Hz, **C**F_3), 118.5 (m, *p*); dpen at 135.6 (s, *i*-Ph), 130.8 (s, *p*-Ph), 130.1, 129.6 (2 × s, *o*-, *m*-Ph), 63.9 (s, **C**HNH_2); $(SiPh_3)_2$-BINOLPA$^-$ at 155.6 (d, $^2J_{CP}$ = 9.3 Hz), 142.0, 137.8, 135.9, 135.1, 131.0, 130.2, 128.4, 128.1, 127.3, 127.2, 125.8, 122.6 (12 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*S*)-$(SiPh_3)_2$-BINOLPA$^-$$BAr_f^-$. (*S*)-$(SiPh_3)_2$-BINOLPAH (0.0538 g, 0.0714 mmol), NaOH (0.0057 g, 0.14 mmol, 2.0 equiv), MeOH/H_2O (5 mL, 1:1 v/v), Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $2Cl^-BAr_f^-\cdot 2H_2O$ (0.0512 g, 0.0307 mmol), distilled H_2O (5 mL), CH_2Cl_2 (5 mL), and crude Na^+ (*S*)-$(SiPh_3)_2$-BINOLPA$^-$ (0.0600 g, 0.0676 mmol, 2.2 equiv) were combined in a procedure analogous to that for Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*R*)-$(SiPh_3)_2$-BINOLPA$^-$ BAr_f^-. An identical workup gave Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*S*)-$(SiPh_3)_2$-BINOLPA$^-$$BAr_f^-\cdot 6H_2O$ as a bright orange solid (0.1028 g, 0.03028 mmol, 99%), mp 149-157 °C (dec, open capillary). Anal. Calcd. for $C_{186}H_{140}BCoF_{24}N_6O_8P_2Si_4\cdot 6H_2O$ (3395.28): C 65.80, H 4.51, N 2.48; found C 65.76, H 4.51, N 2.35.

NMR (acetone-d_6, δ/ppm): ^1H (500 MHz) BAr_f^- at 7.80 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.35-7.23 (m, 18H, Ph), 6.67 (br s, 6H, N**H**H'), 5.22 (br s, 6H, NH**H'**), 4.71 (s, 6H, C**H**NH_2); 3.18 (br s, 12H, $\mathbf{H}_2O$); $(SiPh_3)_2$-BINOLPA$^-$ at 8.04 (s, 4H), 7.80-7.77 (m, 4H), 7.65-7.59 (m, 24H), 7.39 (t, $^3J_{HH}$ = 7.6 Hz, 4H), 7.35-7.28 (m, 20H), 7.21 (t, $^3J_{HH}$ = 7.4 Hz, 20H), 7.21-7.18 (m, 4H); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 49.8 Hz, *i*), 135.6 (s, *o*), 130.1 (m, *m*), 125.4 (q, $^1J_{CF}$ = 271.4 Hz, **C**F_3), 118.5 (m, *p*); dpen at 135.6 (s, *i*-Ph), 130.8 (s, *p*-Ph), 129.9, 129.4 (2 × s, *o*-, *m*-Ph), 63.7 (s, **C**HNH_2); $(SiPh_3)_2$-BINOLPA$^-$ at 155.2 (d, $^2J_{CP}$ = 9.3 Hz), 142.0, 137.8, 135.9, 135.2, 131.0, 130.2, 128.4, 128.0, 127.11, 127.06, 125.6, 122.9 (12 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(*S*)-$((i\mathrm{Pr})_3Ph)_2$-BINOLPA$^-$$BAr_f^-$. Crude Na^+ (*S*)-$((i\mathrm{Pr})_3Ph)_2$-BINOLPA$^-$ was prepared by charging a vial with (*S*)-$((i\mathrm{Pr})_3Ph)_2$-BINOLPAH (0.0538 g,

0.0714 mmol), NaOH (0.0057 g, 0.14 mmol, 2.0 equiv), and MeOH/H_2O (5 mL, 1:1 v/v). The mixture was vigorously stirred (rt, overnight). The solvent was removed by rotary evaporation and the white residue dried by oil pump vacuum (rt, overnight). A vial was charged with Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H_2O (0.0640 g, 0.0384 mmol), distilled H_2O (5 mL), CH_2Cl_2 (5 mL), and crude Na^+ (*S*)-((*i*Pr)$_3$Ph)$_2$-BINOLPA$^-$ (0.0665 g, 0.0858 mmol, 2.2 equiv). The biphasic mixture was vigorously stirred (rt, overnight). The orange organic phase was separated and the solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ 2(*S*)-((*i*Pr)$_3$Ph)$_2$-BINOLPA$^-$ BAr$_f^-$·6H_2O as a bright orange solid (0.1123 g, 0.03541 mmol, 92%), mp 150-160 °C (dec, open capillary). Anal. Calcd. for $C_{174}H_{172}BCoF_{24}N_6O_8P_2$·6$H_2O$ (3171.07): C 65.91, H 5.85, N 2.65; found C 65.69, H 5.62, N 2.63.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr$_f^-$ at 7.81 (s, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 7.25-7.19 (m, 18H, Ph), 7.15-7.10 (m, 12H, Ph), 6.25 (br s, 6H, N**H**H'), 5.67 (br s, 6H, NH**H'**), 4.81 (s, 6H, C**H**NH_2); 3.31 (br s, 11H, **H**$_2$O); ((*i*Pr)$_3$Ph)$_2$-BINOLPA$^-$ at 8.01 (d, $^3J_{HH}$ = 8.1 Hz, 4H), 7.80 (s, 4H), 7.45 (t, $^3J_{HH}$ = 7.5 Hz, 4H), 7.27 (t, $^3J_{HH}$ = 7.6 Hz, 4H), 7.25-7.19 (m, 4H), 7.18 (s, 4H), 7.13 (s, 4H), 3.26-3.09 (m, 4H), 3.08-2.92 (m, 4H), 2.85-2.76 (m, 4H), 1.19-1.14 (m, 24H), 1.10 (t. $^3J_{HH}$ = 6.8 Hz, 24H), 1.08-1.03 (m, 12H), 0.93 (d, $^3J_{HH}$ = 6.8 Hz, 12H); ^{13}C {^{1}H} (125 MHz) BAr$_f^-$ at 162.2 (q, $^1J_{BC}$ = 51.9 Hz, *i*), 135.5 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 272.9 Hz, **C**F_3), 118.4 (m, *p*); dpen at 135.8 (s, *i*-Ph), 130.2 (s, *p*-Ph), 130.0, 128.9 (2 × s, *o*-, *m*-Ph), 63.6 (s, **C**HNH_2); ((*i*Pr)$_3$Ph)$_2$-BINOLPA$^-$ at 149.8 (d, $^2J_{CP}$ = 9.3 Hz), 148.6, 148.5, 147.8, 134.8, 133.9, 133.7, 132.6, 132.61, 132.55, 131.2, 128.9, 127.4, 126.5, 125.5, 123.8, 122.0, 120.8, 35.1, 31.7, 31.6, 26.3, 25.0, 24.9, 24.5, 24.4, 23.9 (25 × s).

Λ-(*S*,*S*)-1^{3+} (*R*,*R*)-tart^{2-}BAr$_f^-$. A vial was charged with Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$ ·2H_2O (0.0673 g, 0.0404 mmol), distilled H_2O (5 mL), CH_2Cl_2 (5 mL), and 2Na^+ (*R*,*R*)-

tart^{2-}·2H_2O (0.0093 g, 0.040 mmol, 1.0 equiv). The biphasic mixture was vigorously stirred (rt, overnight). The orange organic phase was separated and the solvent removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ (*R*,*R*)-tart^{2-}BAr_f^-·2H_2O as a bright orange solid (0.0693 g, 0.0398 mmol, 98%), mp 115-122 °C (dec, open capillary). Anal. Calcd. for $C_{78}H_{64}BCoF_{24}N_6O_6$·2$H_2O$ (1743.14): C 53.75, H 3.93, N 4.82; found C 53.86, H 4.17, N 4.47.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.80 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 8.27 (br s, 6H, N**H**H'), 7.58-7.52 (m, 12H, *o*-Ph), 7.35-7.27 (m, 18H, *m*-, *p*-Ph), 5.24 (br s, 6H, NH**H'**), 5.10 (s, 6H, C**H**NH_2); 2.95 (br s, 9H, $\mathbf{H}_2O$); tart^{2-} at 4.27 (s, 2H), 3.88 (s, 2H); ^{13}C{^{1}H} (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 271.7 Hz, **C**F_3), 118.4 (m, *p*); dpen at 137.4 (s, *i*-Ph), 130.1 (s, *p*-Ph), 129.8, 129.6 (2 × s, *o*-, *m*-Ph), 63.5 (s, **C**HNH_2); tart^{2-} at 176.5, 74.9 (2 × s).

Λ-(*S*,*S*)-1^{3+} (*S*,*S*)-tart^{2-}BAr_f^-. Crude 2Na^+ (*S*,*S*)-tart^{2-} was prepared by charging a vial with (*S*,*S*)-tartaric acid (1.0000 g, 6.6628 mmol), NaOH (0.5330 g, 13.33 mmol, 2.0 equiv), and distilled H_2O (4 mL). The mixture was vigorously stirred (30 min), and the solvent was removed by rotary evaporation. The white residue was dried by oil pump vacuum (rt, overnight). A vial was charged with Λ-(*S*,*S*)-**1**$^{3+}$ 2$Cl^-$$BAr_f^-$·2$H_2O$ (0.0605 g, 0.0363 mmol), distilled H_2O (5 mL), CH_2Cl_2 (5 mL), and crude 2Na^+ (*S*,*S*)-tart^{2-} (0.0167 g, 0.0861 mmol, 2.4 equiv). The biphasic mixture was vigorously stirred (rt, overnight). The orange organic phase was separated and the solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ (*S*,*S*)-tart^{2-}BAr_f^-·2H_2O as a bright orange solid (0.0611 g, 0.0351 mmol, 97%), mp 112-121 °C (dec, open capillary). Anal. Calcd. for $C_{78}H_{64}BCoF_{24}N_6O_6$·2$H_2O$ (1743.14): C 53.75, H 3.93, N 4.82; found C 53.53, H 3.93, N 4.57.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.80 (s, 8H, *o*), 7.68 (s, 4H, *p*);

dpen at 8.30 (br s, 6H, N**H**H'), 7.58-7.52 (m, 12H, *o*-Ph), 7.36-7.27 (m, 18H, *m*-, *p*-Ph), 5.27 (br s, 6H, NH**H'**), 5.09 (s, 6H, C**H**NH$_2$); 3.02 (br s, 7H, **H**$_2$O); tart^{2-} at 4.30 (s, 2H), 3.86 (s, 2H); ^{13}C{^{1}H} (125 MHz) BAr$_f^-$ at 162.6 (q, $^1J_{BC}$ = 49.9 Hz, *i*), 135.5 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 272.6 Hz, **C**F$_3$), 118.4 (m, *p*); dpen at 137.4 (s, *i*-Ph), 129.8 (s, *p*-Ph), 129.73, 129.66 (2 × s, *o*-, *m*-Ph), 63.4 (s, **C**HNH$_2$); tart^{2-} at 176.5, 74.9 (2 × s).

Λ-(*S*,*S*)-1^{3+} (Sb$_2$((*R*,*R*)-tart')$_2$)$^{2-}$BAr$_f^-$. A vial was charged with Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H$_2$O (0.0781 g, 0.0469 mmol), distilled H$_2$O (5 mL), CH$_2$Cl$_2$ (5 mL), and 2Na$^+$ (Sb$_2$((*R*,*R*)-tart')$_2$)$^{2-}$·5H$_2$O (0.0317 g, 0.0469 mmol, 1.0 equiv).[20b] The biphasic mixture was vigorously stirred (rt, overnight). The orange organic phase was separated and the solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ (Sb$_2$((*R*,*R*)-tart')$_2$)$^{2-}$BAr$_f^-$·0.5H$_2$O as a bright orange solid (0.0923 g, 0.0439 mmol, 94%), mp 170-185 °C (dec, open capillary). Anal. Calcd. for C$_{82}$H$_{64}$BCoF$_{24}$N$_6$O$_{12}$Sb$_2$·0.5H$_2$O (2103.68): C 46.82, H 3.11, N 4.00; found C 47.25, H 3.15, N 3.77.

NMR (acetone-*d*$_6$, δ/ppm): ^{1}H (500 MHz) BAr$_f^-$ at 7.80 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.64-7.56 (m, 12H, *o*-Ph), 7.31-7.24 (m, 18H, *m*-, *p*-Ph), 6.24 (br s, 6H, N**H**H'), 5.56 (br s, 6H, NH**H'**), 5.15 (s, 6H, C**H**NH$_2$); 3.45 (br s, 6H, **H**$_2$O); (Sb$_2$(tart')$_2$)$^{2-}$ at 3.92 (s, 4H); ^{13}C{^{1}H} (125 MHz) BAr$_f^-$ at 162.6 (q, $^1J_{BC}$ = 49.8 Hz, *i*), 135.5 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 271.9 Hz, **C**F$_3$), 118.4 (m, *p*); dpen at 136.8 (s, *i*-Ph), 130.0 (s, *p*-Ph), 129.9, 129.6 (2 × s, *o*-, *m*-Ph), 64.9 (s, **C**HNH$_2$); (Sb$_2$(tart')$_2$)$^{2-}$ at 181.8, 78.2 (2 × s).

Λ-(*S*,*S*)-1^{3+} (Sb$_2$((*S*,*S*)-tart')$_2$)$^{2-}$BAr$_f^-$. Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H$_2$O (0.0518 g, 0.0311 mmol), distilled H$_2$O (5 mL), CH$_2$Cl$_2$ (5 mL), and 2Na$^+$ (Sb$_2$((*S*,*S*)-tart')$_2$)$^{2-}$·5H$_2$O (0.0210 g, 0.0331 mmol, 1.1 equiv; prepared analogously to the enantiomer[20b]) were combined in a procedure analogous to that for Λ-(*S*,*S*)-**1**$^{3+}$ (Sb$_2$((*R*,*R*)-tart')$_2$)$^{2-}$BAr$_f^-$ ·0.5H$_2$O. An identical workup gave Λ-(*S*,*S*)-**1**$^{3+}$ (Sb$_2$((*S*,*S*)-tart')$_2$)$^{2-}$BAr$_f^-$·0.5H$_2$O as a

bright orange solid (0.0654 g, 0.0311 mmol, 99%), mp 174-185 °C (dec, open capillary). Anal. Calcd. for $C_{82}H_{64}BCoF_{24}N_6O_{12}Sb_2 \cdot 0.5H_2O$ (2103.68): C 46.82, H 3.11, N 4.00; found C 47.19, H 3.18, N 3.86.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.79 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.74-7.64 (m, 12H, *o*-Ph), 7.32-7.22 (m, 18H, *m*-, *p*-Ph), 6.45 (br s, 6H, N**H**H'), 5.74 (br s, 6H, NH**H'**), 4.98 (s, 6H, C**H**NH_2); 3.58 (br s, 6H, $\mathbf{H}_2O$); $(Sb_2(tart')_2)^{2-}$ at 4.64 (s, 4H); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 49.9 Hz, *i*), 135.5 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 271.9 Hz, **C**F_3), 118.5 (m, *p*); dpen at 136.6 (s, *i*-Ph), 130.5 (s, *p*-Ph), 129.7, 129.6 (2 × s, *o*-, *m*-Ph), 65.3 (s, **C**HNH_2); $(Sb_2(tart')_2)^{2-}$ at 181.8, 78.4 (2 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 3(1*R*)-camphSO$_3^-$. A suspension of Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $3Cl^- \cdot 3H_2O$ (0.0200 g, 0.0237 mmol) in CH_2Cl_2 (5 mL) and a solution of (1*R*)-ammonium 3-bromocamphor-8-sulfonate (0.0260 g, 0.0792 mmol, 3.3 equiv) in distilled H_2O (5 mL) were combined. The biphasic mixture was rapidly stirred. After 1 h, the phases were allowed to separate. The orange organic phase was washed with distilled H_2O (2 × 5 mL) and dried (Na_2SO_4). The solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 3(1*R*)-camphSO$_3^- \cdot 2H_2O$ as an orange solid (0.0304 g, 0.0183 mmol, 76%), mp 203-210 °C (dec, open capillary), Anal. Calcd. for $C_{72}H_{90}Br_3CoN_6O_{12}S_3 \cdot 2H_2O$ (1662.40): C 52.02, H 5.70, N, 5.06, found C 51.99, H, 5.75, N 4.84.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) dpen at 7.68 (m, 12H, *o*-Ph), 7.26 (m, 18H, *m*-, *p*-Ph), 7.07 (br s, 6H, N**H**H'), 5.67 (br s, 6H, NH**H'**), 5.05 (m, 6H, C**H**NH_2); 2.90 (br s, 6H, $\mathbf{H}_2O$); camphSO$_3^-$ at 4.78 (d, J = 3.8 Hz, 3H), 3.16 (t, J = 4.3 Hz, 3H), 3.02 (d, J = 14.2 Hz, 3H), 2.40 (d, J = 14.2 Hz, 3H), 2.29-2.15 (m, 3H), 2.01 (ddd, J = 13.2, 9.6, 3.8 Hz, 3H), 1.84-1.76 (m, 3H), 1.29 (ddd, J = 14.4, 9.4, 5.4 Hz, 3H), 1.18 (s, 9H), 0.86 (s, 9H); $^{13}C\{^1H\}$ (125 MHz) dpen at 136.2 (s, *i*-Ph), 129.6 (s, *p*-Ph), 128.7, 128.6 (2 × s,

o-, *m*-Ph), 62.6 (s, **C**$CHNH_2$); camphSO_3^- at 211.7, 60.0, 54.9, 54.7, 48.2, 47.9, 30.7, 22.8, 18.0, 10.2 (10 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 3(1*S*)-camph$\mathbf{SO_3^-}$. Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $3Cl^-\cdot 3H_2O$ (0.0200 g, 0.0234 mmol), CH_2Cl_2 (5 mL), (1*S*)-ammonium 3-bromocamphor-8-sulfonate (0.0260 g, 0.0792 mmol, 3.3 equiv), and distilled H_2O (5 mL) were combined in a procedure analogous to that for Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 3(1*R*)-camphSO_3^-. An identical workup gave Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 3(1*S*)-camph$SO_3^-\cdot 3H_2O$ as an orange solid (0.0286 g, 0.0170 mmol, 73%), mp 129 °C (dec, open capillary), Anal. Calcd. for $C_{72}H_{90}Br_3CoN_6O_{12}S_3\cdot 3H_2O$ (1680.41): C 51.46, H 5.76, N, 5.00; found C 51.54, H, 5.84, N 4.82.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) dpen at 7.68 (m, 12H, *o*-Ph), 7.26 (m, 18H, *m*-, *p*-Ph), 7.07 (br s, 6H, N**H**H'), 5.67 (br s, 6H, NH**H'**), 5.05 (m, 6H, C**H**NH_2); 2.92 (br s, 4H, $\mathbf{H}_2O$); camphSO_3^- at 4.78 (d, J = 3.8 Hz, 3H), 3.13 (t, J = 4.3 Hz, 3H), 2.94-2.88 (m, 3H), 2.56 (d, J = 14.2 Hz, 3H), 2.25-2.15 (m, 3H), 1.98 (ddd, J = 13.2, 9.6, 3.7 Hz, 3H), 1.69 (ddd, J = 15.0, 12.2, 3.8 Hz, 3H), 1.27 (ddd, J = 14.4, 9.4, 5.4 Hz, 3H), 1.22 (s, 9H), 0.88 (s, 9H); $^{13}C\{^1H\}$ (125 MHz) dpen at 137.1 (s, *i*-Ph), 130.4 (s, *p*-Ph), 129.5, 129.4 (2 × s, *o*-, *m*-Ph), 63.5 (s, **C**$CHNH_2$); camphSO_3^- at 211.7, 60.0, 54.9, 54.7, 48.2, 47.9, 30.7, 22.8, 18.0, 10.2 (10 × s).

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 3*(R)*-BINOLPA$^-$. A vial was charged with a suspension of Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $3Cl^-\cdot 3H_2O$ (0.0500 g, 0.0598 mmol) in CH_2Cl_2 (10 mL), (*R*)-BINOLPAH (0.0630 g, 0.181 mmol, 3.0 equiv), NaOH (0.0072 g, 0.18 mmol, 3.0 equiv) and distilled H_2O (10 mL). The biphasic mixture was vigorously stirred. After 4 h, the phases were allowed to separate. The orange organic phase was washed with distilled H_2O (2 × 10 mL) and dried (Na_2SO_4). The solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-$\mathbf{1}^+$ 3(*R*)-BINOLPA$^-\cdot 3H_2O$ as an orange solid (0.0855 g, 0.0468 mmol, 78%), mp 237-249 °C (dec, open capillary), Anal. Calcd. for

$C_{102}H_{84}CoN_6O_{12}P_3 \cdot 3H_2O$ (1827.76): C 67.03, H 5.18, N, 4.60, found C 66.84, H, 4.79, N 4.33.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) 8.09 (d, $^3J_{HH}$ = 8.8 Hz, 6H), 7.91 (d, $^3J_{HH}$ = 8.2 Hz, 6H), 7.71-7.59 (m, 6H, N**H**H'), 7.51-7.40 (m, 18H), 7.40-7.24 (m, 18H), 7.20-7.06 (m, 18H), 5.92 (br s, 6H, NH**H'**), 4.86 (br s, 6H, C**H**NH_2); 3.02 (br s, 6H, $\mathbf{H}_2O$); $^{13}C\{^1H\}$ (125 MHz) dpen at 137.1 (s, *i*-Ph), 130.0 (s, *p*-Ph), 129.4, 129.1 (2 × s, *o*-, *m*-Ph), 63.6 (s, **C**HNH_2); BINOLPA$^-$ at 150.5 (d, $^2J_{CP}$ = 9.2 Hz) 133.3, 132.0, 131.3, 129.4, 127.4, 126.9, 125.5, 123.0, 122.9 (9 × s).

Λ-(*S*,*S*)-1$^+$ 3(*S*)-BINOLPA$^-$. Λ-(*S*,*S*)-**1**$^{3+}$ 3Cl$^-\cdot 3H_2O$ (0.0500 g, 0.0598 mmol), CH_2Cl_2 (10 mL), (*S*)-BINOLPAH (0.0630 g, 0.181 mmol, 3.0 equiv), NaOH (0.0072 g, 0.18 mmol, 3.0 equiv), and distilled H_2O (10 mL) were combined in a procedure analogous to that for Λ-(*S*,*S*)-**1**$^{3+}$ 3*(R)*-BINOLPA$^-$. An identical workup gave Λ-(*S*,*S*)-**1**$^+$ 3(*S*)-BINOLPA$^-\cdot 4H_2O$ as an orange solid (0.0777 g, 0.0429 mmol, 72%), mp 234-240 °C (dec, open capillary), Anal. Calcd. for $C_{102}H_{84}CoN_6O_{12}P_3 \cdot 4H_2O$ (1809.74): C 67.70, H 5.12, N, 4.64, found C 67.84, H, 5.12, N 4.22.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) dpen at 7.65-7.53 (m, 12H, *o*-Ph), 7.44-7.32 (m, 18H, *m*-, *p*-Ph), 7.17 (br s, 6H, N**H**H'), 5.92 (s, 6H, NH**H'**), 5.19-5.09 (br s, 6H, C**H**NH_2); 3.02 (br s, 6H, $\mathbf{H}_2O$); BINOLPA$^-$ at 7.98 (d, $^3J_{HH}$ = 8.8 Hz, 6H), 7.91 (d, $^3J_{HH}$ = 8.2 Hz, 6H), 7.34-7.23 (m, 6H), 7.10-6.98 (m, 18H); $^{13}C\{^1H\}$ (125 MHz) dpen at 137.1 (s, *i*-Ph), 129.9 (s, *p*-Ph), 129.4, 129.3 (2 × s, *o*-, *m*-Ph), 64.1 (s, **C**HNH_2); BINOLPA$^-$ at 150.4 (d, $^2J_{CP}$ = 9.2 Hz), 133.3, 132.0, 131.3, 129.2, 127.4, 126.9, 125.5, 123.0, 122.9 (9 × s).

Λ-[Co((*S*,*S*)-α-dnen)$_3$]$^{3+}$ 2(*R*)-BINOLPA$^-$BAr$_f^-$. A small vial was charged with a solution of Λ-[Co((*S*,*S*)-α-dnen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-\cdot 2H_2O$ (0.0308 g, 0.0157 mmol) in CH_2Cl_2 (5 mL), (*R*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (0.0115 g, 0.0330

mmol, 2.10 equiv), H_2O (5 mL), and NaOH (0.0030 g). The biphasic mixture was vigorously stirred for 17 h. The aqueous layer was removed. The solvent was removed by rotary evaporation and the residue dried by oil pump vacuum (room temperature, 15 h) to give Λ-[Co((*S*,*S*)-α-dnen)$_3$]$^{3+}$ 2(*R*)-BINOLPA$^-$BAr$_f^-$ as a dark orange solid (0.0402 g, 0.0153 mmol, 98%), Mp: 160-169 °C (open capillary) (dec). Anal. Calcd. for $C_{138}H_{96}BCoF_{24}N_6O_8P_2 \cdot 4H_2O$ (2626.03): C 63.12, H 3.99, N, 3.20; found C 62.91, H 3.96, N 3.31.

NMR (acetone-d_6, δ in ppm): ^{1}H (400 MHz), BAr$_f^-$ at 7.81 (s, 8H, *o*), 7.68 (s, 4H, *p*); α-dnen at 9.72 (br s, 6H, N**H**H'), 8.51 (d, $^3J_{HH}$ = 8.0 Hz, 6H, $C_{10}H_7$), 8.02-7.95 (m, 24H, $C_{10}H_7$), 7.18 (s, 12H, $C_{10}H_7$), 5.61 (s, C**H**NH$_2$), 3.65 (br s, 6H, NH**H'**), 2.16 (br s, 9H, **H**$_2$O); (*R*)-BINOLPA$^-$ at 8.11-8.01 (m, 8H), 7.54-7.48 (m, 4H), 7.44-7.33 (m, 12H); 2.96 (br s, 9H, **H**$_2$O); ^{13}C{^{1}H} (100 MHz), BAr$_f^-$ at 162.5 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (s, *o*), 129.8 (m, *m*, the signal is overlapped by other peaks), 125.3 (q, $^1J_{CF}$ = 270 Hz, **C**F$_3$), 118.4 (m, *p*); α-dnen and (*S*)-BINOLPA$^-$ at 150.4, 150.3, 134.9, 133.4, 132.0, 131.9, 130.8, 130.6, 129.5, 129.4, 129.2, 128.4, 127.5, 127.4, 127.1, 125.8, 125.6, 125.6, 124.6, 124.1, 122.8, 122.7, 60.3 (**C**HNH$_2$) (24 × s).

Λ-[Co((*S*,*S*)-α-dnen)$_3$]$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$. A small vial was charged with a solution of Λ-[Co((*S*,*S*)-α-dnen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$·2H$_2$O (0.0338 g, 0.0172 mmol) in CH_2Cl_2 (5 mL). A solution of (1*R*)-3-bromocamphor-8-sulfonic acid ammonium salt (0.0118 g, 0.0360 mmol, 2.10 equiv) in H_2O (5 mL) was added and the biphasic mixture was vigorously stirred for 17 h. The aqueous layer was removed and the orange organic layer evaporated under vacuum. The residue was dried by oil pump vacuum at room temperature overnight to give Λ-[Co((*S*,*S*)-α-dnen)$_3$]$^{3+}$ 2(1*R*)-camphSO$_3^-$BAr$_f^-$·2H$_2$O as a dark orange solid (0.0370 g, 0.0147 mmol, 85%), Mp: 153-166 °C dec (open capillary). Anal. Calcd. for $C_{118}H_{102}BBr_2CoF_{24}N_6O_8S_2 \cdot 2H_2O$ (2517.81): C 56.29, H 4.24, N, 3.34;

found C 56.43, H 4.16, N 3.32.

NMR (acetone-d_6, δ in ppm): ^{1}H (500 MHz), BAr_f^- at 7.72 (s, 8H, *o*), 7.54 (s, 4H, *p*); α-dnen at 7.89 (s, 6H, N**H**H'), 7.43-7.30 (m, 30H, $C_6\mathbf{H}_5$), 4.53 (s, 6H, C**H**NH_2), 3.87 (s, 6H, NH**H'**); camphorSO_3^- at 4.32 (s, 2H), 3.34 (d, $^2J_{HH}$ = 15.0 Hz, 2H), 3.07 (s, 2H), 2.99 (d, $^2J_{HH}$ = 15.0 Hz, 2H), 2.21-2.14 (m, 4H), 1.79-1.69 (m, 2H), 1.45-1.41 (m, 2H), 1.26 (s, 6H), 0.91 (s, 6H); 2.37 (br s, 3H, $\mathbf{H}_2O$); $^{13}C\{^1H\}$ (126 MHz), BAr_f^- at 162.3 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.4 (s, *o*), 129.4 (q, $^2J_{CF}$ = 32.5 Hz, *m*), 125.1 (q, $^1J_{CF}$ = 271.3 Hz, **C**F_3), 118.0 (s, *p*); α-dnen at 135.1, 133.1, 132.5, 130.9, 129.7, 128.0, 127.3, 126.0, 124.1, 121.4, 60.1 (**C**HNH_2) (11 × s); camphSO_3^- at 213.8 (s, **C**=O), 60.5, 54.8, 48.1, 47.8, 30.8, 22.6, 18.4, 10.0 (8 × s), one carbon signal is obscured by the solvent peak.

Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*R*)-camph$SO_3^-$$BF_4^-$. A vial was charged with Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $3BF_4^-$ $\cdot 2H_2O$ (0.0464 g, 0.0468 mmol), Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 3(1*R*)-camph$SO_3^-\cdot 2H_2O$ (0.1555 g, 0.09354 mmol, 2.00 equiv), acetone (2.5 mL), and CH_2Cl_2 (5 mL). The mixture was sonicated (10 min) and the solvent removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*R*)-camph$SO_3^-BF_4^-\cdot 4H_2O$ as a bright orange solid (0.2005 g, 0.1359 mmol, 97%), mp 190-196 °C dec. (open capillary). Anal. Calcd. for $C_{62}H_{76}BBr_2CoF_4N_6O_8S_2\cdot 4H_2O$ (1475.05): C 50.49, H 5.74, N 5.70; found C 50.57, H 5.74, N 5.53.

NMR (acetone-d_6, δ in ppm): ^{1}H (400 MHz), dpen at 7.62-7.57 (m, 12H, *o*-Ph), 7.36 (br s, 6H, N**H**H'), 7.31-7.25 (m, 18H, *m*-, *p*-Ph), 5.49 (br s, 6H, NH**H'**), 5.12-5.04 (m, 6H, C**H**NH_2), 2.83 (br s, 16H, $\mathbf{H}_2O$); camphorSO_3^- at 4.80 (d, $^2J_{HH}$ = 3.9 Hz, 2H), 3.14 (t, $^2J_{HH}$ = 4.2 Hz, 2H), 3.07 (d, $^2J_{HH}$ = 14.2 Hz, 2H), 2.80 (m, 2H), 2.26-2.16 (m, 2H), 2.04-1.98 (m, 2H), 1.84-1.74 (m, 2H), 1.36-1.27 (m, 2H), 1.22 (s, 6H), 0.90 (s, 6H); $^{13}C\{^1H\}$ (100 MHz) dpen at 137.1 (s, *i*-Ph), 130.1 (s, *o*-Ph), 129.8 (s, *p*-Ph), 129.6 (s, *m*-Ph), 63.5 (s, **C**HNH_2); camphSO_3^- at 211.5 (s, **C**=O), 60.1, 54.8, 54.7, 48.3, 47.9, 30.7,

22.9, 18.0, 10.2 (9 × s).

Λ-(*S*,*S*)-1^{3+} (1*R*)-camphSO$_3^-$2BF$_4^-$. A vial was charged with Λ-(*S*,*S*)-**1**$^{3+}$ 3BF$_4^-$·2H$_2$O (0.0526 g, 0.0530 mmol), Λ-(*S*,*S*)-**1**$^{3+}$ 3(1*R*)-camphSO$_3^-$·2H$_2$O (0.0441 g, 0.0265 mmol, 0.500 equiv), acetone (2.5 mL), and CH$_2$Cl$_2$ (5 mL). The mixture was sonicated (10 min) and the solvent removed by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-**1**$^{3+}$ (1*R*)-camphSO$_3^-$2BF$_4^-$·3H$_2$O as a bright orange solid (0.0981 g, 0.0795 mmol, >99%), mp 183-192 °C dec. (open capillary). Anal. Calcd. for C$_{52}$H$_{62}$B$_2$BrCoF$_8$N$_6$O$_4$S·3H$_2$O (1233.66): C 50.63, H 5.56, N 6.81; found C 50.65, H 5.71, N 6.62.

NMR (acetone-d_6, δ in ppm): ^{1}H (400 MHz), dpen at 7.54 (s, 12H, *o*-Ph), 7.31 (br s, 24H, *m*-, *p*-Ph, N**H**H'), 5.40 (br s, 6H, NH**H'**), 5.10 (s, 6H, C**H**NH$_2$), 2.84 (br s, 12H, **H**$_2$O); camphorSO$_3^-$ at 4.82 (s, 1H), 3.21-3.09 (m, 2H), 2.76-2.70 (m, 1H), 2.26-2.14 (m, 1H), 2.04-1.98 (m, 1H), 1.86-1.76 (m, 1H), 1.38-1.32 (m, 1H), 1.26 (s, 3H), 0.93 (s, 3H); ^{13}C{^{1}H} (100 MHz) dpen at 137.0 (s, *i*-Ph), 130.0 (s, *p*-Ph), 129.8 (2 × s, *o*-, *m*-Ph), 63.5 (s, **C**HNH$_2$); camphSO$_3^-$ at 211.3 (s, **C**=O), 60.0, 54.9, 54.6, 48.3, 47.9, 30.7, 22.8, 18.0, 10.1 (9 × s).

Λ-(*S*,*S*)-1^{3+} 2Br$^-$BAr$_f^-$. A gas-circulating flask[15] was charged with Co(OAc)$_2$·4H$_2$O (0.1255 g, 0.5039 mmol), activated charcoal (0.1000 g), (*S*,*S*)-dpen (0.4250 g, 2.002 mmol, 4.0 equiv), and MeOH (50 mL). The mixture was vigorously stirred. After 30 h, the sample was filtered through Celite. Aqueous HBr (1.0 mL, 8.9 M) was added to the orange filtrate. The dark yellow solution was concentrated via rotary evaporation, and H$_2$O (50 mL) was added. The suspension was filtered. The filter cake was washed with H$_2$O (50 mL) and dried by oil pump vacuum (rt, overnight) to give crude Λ-(*S*,*S*)-**1**$^{3+}$ 3Br$^-$ as a dark yellow solid (0.4456 g, 0.4503 mmol if pure sample). A portion of this solid (0.1024 g, 0.1035 mmol if pure), Na$^+$ BAr$_f^-$ (0.0916 g, 0.103 mmol, 1.0

equiv), and CH_2Cl_2 (5 mL) were added to a round-bottom flask. The mixture was sonicated (5 min) and filtered. The filtrate was chromatographed (2.0 × 10 cm silica gel column), eluting with CH_2Cl_2/MeOH (100:0 to 97:3 (v/v)). The solvent was removed from the main yellow band by rotary evaporation. The residue was dried by oil pump vacuum (rt, overnight) to give Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $2Br^-BAr_f^-\cdot H_2O$ as a yellow solid (0.1356 g, 0.07807 mmol, 75% from Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $3Br^-$), mp 112-130 °C (dec, open capillary). Anal. Calcd. for $C_{74}H_{60}BBr_2CoF_{24}N_6\cdot H_2O$ (1736.86): C 51.17, H 3.60, N 4.84; found C 51.37, H 3.80, N 4.52.

NMR (acetone-d_6, δ/ppm): ^{1}H (500 MHz) BAr_f^- at 7.79 (s, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 8.04 (br s, 6H, N**H**H'), 7.53-7.48 (m, 12H, *o*-Ph), 7.34-7.30 (m, 18H, *m*-, *p*-Ph), 5.35 (br s, 6H, NH**H'**), 5.13 (s, 6H, C**H**NH_2); 2.88 (br s, 11H, $\mathbf{H}_2O$); $^{13}C\{^1H\}$ NMR (125 MHz): BAr_f^- at 162.6 (q, $^1J_{BC}$ = 50.3 Hz, *i*), 135.6 (s, *o*), 130.0 (m, *m*), 125.4 (q, $^1J_{CF}$ = 271.6 Hz, $\mathbf{C}F_3$), 118.5 (m, *p*); dpen at 137.1 (s, *i*-Ph), 130.1 (s, *p*-Ph), 130.0, 129.6 (2 × s, *o*-, *m*-Ph), 63.3 (s, **C**HNH_2).

Dimethyl 2-(2-nitro-1-phenylethyl)malonate (**2**; Chart 2.1)**.** An authentic sample of this known compound was obtained as a colorless oil by a literature procedure.[2] A 5 mm NMR tube was charged with a solution of *trans*-β-nitrostyrene (0.0054 g, 0.036 mmol, 1.0 equiv), catalyst (0.0036 mmol, 0.10 equiv), dimethyl malonate (0.0045 mL, 0.0052 g, 0.039 mmol, 1.1 equiv), and Ph_2SiMe_2 (0.0020 mL, internal standard) in acetone-d_6 (0.40 mL). A ^{1}H NMR spectrum was recorded to confirm the initial *trans*-β-nitrostyrene/standard ratio. A stir bar was added and the sample was cooled to 0 °C. Then Et_3N (0.0050 mL, 0.0036 g, 0.036 mmol, 1.0 equiv) was added and the mixture stirred. After 24 h, the stir bar was removed and the yield of **2** was assayed by ^{1}H NMR. The solvent was removed under reduced pressure to give an orange oil, which was added to a

plug of silica. The plug was eluted with hexanes/EtOAc (1:1 v/v). The solvent was removed from the fraction containing the product under reduced pressure. The enantiomeric excess was determined by HPLC (Chiralpak AD column, 98:2 v/v hexane/isopropanol, 1.0 mL/min, λ = 220 nm; for entry 20 t_R = 35.0 and 44.8 min (major and minor)).[34]

***N,N'*-bis(t-butoxycarbonyl)-1-hydrazino-2-oxocyclopentanecarboxylic acid methyl ester** (**3**; Chart 2.2)**.** This known compound was obtained as a colorless oil by a literature procedure.[4a] A 5 mm NMR tube was charged with a solution of di-*tert*-butylazodicarboxylate (0.0083 g, 0.036 mmol, 1.0 equiv), catalyst (0.0036 mmol, 0.10 equiv), methyl 2-oxocyclopentanecarboxylate (0.0046 mL, 0.0053 g, 0.037 mmol, 1.0 equiv), and Ph_2SiMe_2 (0.0020 mL, internal standard) in CD_3CN (0.40 mL). A ^1H NMR spectrum was recorded to confirm the initial di-*tert*-butylazodicarboxylate/standard ratio. A stir bar was added and the sample was cooled to 0 °C. Then NMM (0.0040 mL, 0.0037 g, 0.036 mmol, 1.0 equiv) was added and the mixture stirred. After 24 h, the stir bar was removed and the yield of **3** was assayed by ^1H NMR. The solvent was removed under reduced pressure to give an orange oil, which was added to a plug of silica. The plug was eluted with hexanes/EtOAc (7:3 v/v). The solvent was removed from the fraction containing the product under reduced pressure. The enantiomeric excess was determined by HPLC (Chiralpak AD column, 96:4 v/v hexane/isopropanol, 1.0 mL/min, λ = 210 nm; for entry 20 t_R = 14.0 and 20.2 min (minor and major).[35]

Crystallography. A solution of Δ-(*S*,*S*)-$\mathbf{1}^{3+}$ 2(1*S*)-camph$SO_3^-BAr_f^-$ (0.189 g, 0.0865 mmol) in CH_2Cl_2 (10 mL) was kept in a closed container at room temperature. After 2 d, brown block crystals were collected. Synchrotron radiation (see Acknowledgements) was employed for crystal screening, unit cell determination, and data collection on a D8 goniostat equipped with PHOTON detector at Beamline 11.3.1 (λ = 0.8857 Å). Integrated intensity information for each reflection was obtained by reduction

of the data frames with the program APEX2.[36] All data were corrected for Lorentz and polarization factors, as well as for crystal decay effects. The program SADABS[37] was employed to correct for absorption effects.

Systematic reflection conditions and statistical tests suggested the space group $P2_12_12_1$. A solution was readily obtained using SHELXTL (XS).[38] No reflections were observed above 1.0 Å resolution, possibly suggesting significant disorder. The absence of additional symmetry or voids was confirmed using PLATON (ADDSYM).[39] All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed in idealized positions and refined using a riding model. Elongated anisotropic displacement ellipsoids were noted for a phenyl group and several fluorine atoms. Efforts to model this disorder not only increased the number of restraints and/or constraints, but also did not improve the reliability factors. Consequently, RIGU and SIMU restraints were used to keep the ellipsoids reasonable. Also, difference Fourier maps indicated electron densities suggesting disordered and/or partially occupied solvent molecules; these could not be modeled and were eventually removed by MASK using OLEX2.[39] The structure was refined (weighted least squares on F^2) to convergence.[38,39] The Flack parameter (0.004(5)) confirmed the absolute configuration.[41]

2.5 References

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3. SYNTHESES OF ENANTIOPURE 1,2-ETHYLENEDIAMINES WITH TETHERED SECONDARY AMINES OF THE FORMULA H2NCH2CH((CH2)NNHME)NH2 (N = 1-4) FROM α-AMINO ACIDS: NEW AGENTS FOR ASYMMETRIC CATALYSIS[†]

3.1 Introduction

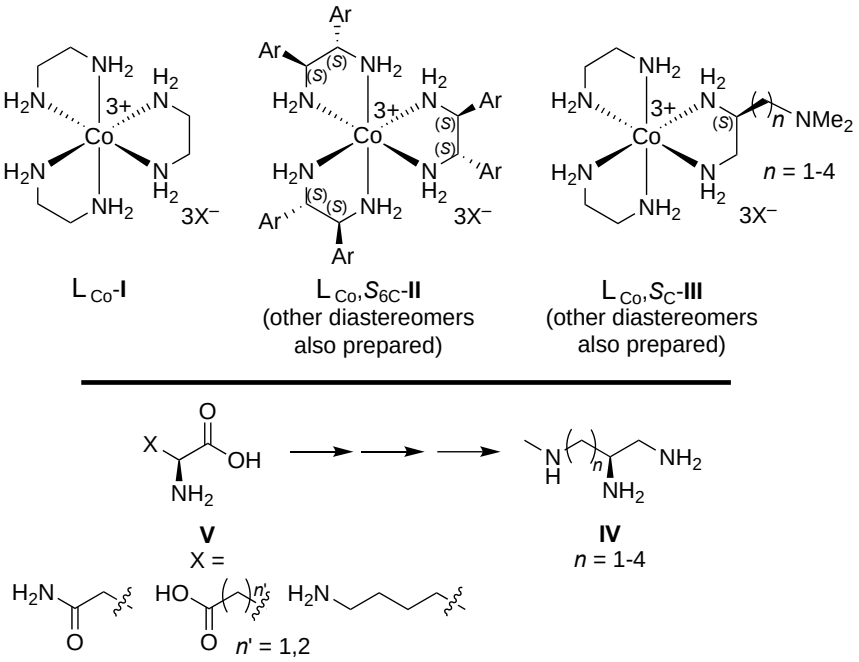
Transition metal complexes play a central role in enantioselective catalysis,[1] and in the absence of a metal based stereocenter, chiral ligands are normally required. Also, certain types of heteroatom donor ligands can themselves serve as Lewis base or nucleophilic catalysts, and these are frequently classified as "organocatalysts".[2] Despite the extensive history of chiral ligands,[3] there are many rather simple structures that remain to be synthesized.

The Gladysz group has been interested in exploiting cobalt(III) tris(1,2-diamine) complexes as hydrogen bond donor catalysts,[4-6] and other cobalt(III) systems have been analogously investigated by Belokon.[7] The unsubstituted tris(1,2-ethylenediamine) adduct $[Co(en)_3]^{3+}$ $3X^-$ (**I**; see Scheme 3.1), a "chiral at metal" species, was among the first inorganic complexes to be isolated in enantiomerically pure form, as reported by Werner some 108 years ago.[8] In these studies, one or more lipophilic tetraarylborate counteranions, BAr_4^-, have been exploited to solubilize these salts in organic solvents and remove water as a competitor for the substrate binding NH_2 groups.

All catalysts of the type **I** have given rather modest enantioselectivities.[4] However, excellent results have been obtained with the corresponding 1,2-diaryl substituted species **II** (Scheme 3.1),[5] as well as related bifunctional systems containing an appended tertiary amine, such as **III**.[6] The -NMe_2 moiety, which can be tethered with varying $(CH_2)_n$ spacer lengths (n = 1-4),[9] obviates the need for an external Brønsted base, as commonly required

[†]Reprinted with permission from "Syntheses of Enantiopure 1,2-Ethylenediamines with Tethered Secondary Amines of the Formula $H_2NCH_2CH[(CH_2)_n$ NHMe$]NH_2$ (n = 1–4) from α-Amino Acids: New Agents for Asymmetric Catalysis" by Kabes, C. Q.; Gunn, J. H.; Selbst, M. A.; Lucas, R. F.; Gladysz, J. A. *Synthesis* **2020**, *52*, 3277-3285. Copyright 2020 by Georg Thieme Verlag Stuttgart.

for many Michael-type addition reactions.



Scheme 3.1. Some enantioselective cobalt(III) hydrogen bond donor catalysts based upon chelating 1,2-diamines, and a new type of functionalized 1,2-diamine.

Chiral secondary amines – in particular a large family of proline derivatives – have played a key role in the development of organocatalysis.[10] This has evolved into a subfield termed "iminium catalysis" in reference to intermediates generated by the secondary amine and appropriate carbonyl compounds. I was curious whether this family of chiral cobalt(III) complexes, which could furthermore bring hydrogen bonding interactions into play, might provide a viable (or even superior) platform for such transformations.

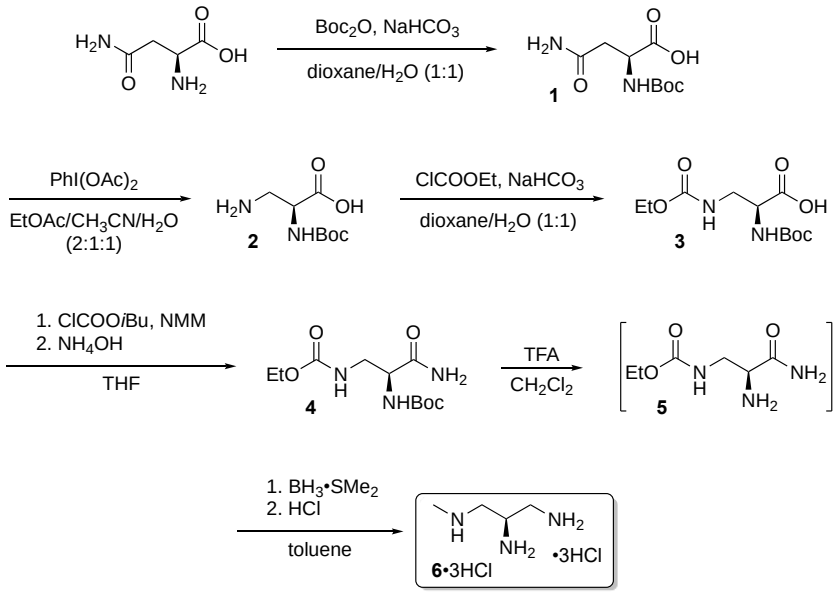
Surprisingly, the most obvious type of secondary amine containing ethylenediamine derivative, $H_2NCH_2CH((CH_2)_nNHMe)NH_2$ (**IV**; Scheme 3.1), has not been reported in the literature, either in racemic or enantiopure form, and for any value of *n*. Accordingly, I set out to develop practical syntheses from the inexpensive, commercially available α-amino acids **V**. As described below, tris(hydrochloride) adducts of the target molecules with *n* = 1-4 are easily prepared in 5-7 steps and 30-38% overall

yields. Apropos to the themed collection of articles in the edition this work was published in, in each case amide and carbamate functionalities are introduced that serve not merely as protecting groups, but rather as precursors to methylene or methyl units in the products.

3.2 Results

3.2.1 IV with $n = 1$

As shown in Scheme 3.2, commercial L-asparagine was converted to the known Boc derivative **1** in 79% yield.[11] The conditions were adapted from those for similar transformations in the literature.[12] As for all "new steps" in this study, the product was characterized by NMR (^{1}H, ^{13}C{^{1}H}) and microanalysis. Per an earlier report,[13] a modern version of the Hofmann rearrangement that uses an iodine(III) oxidant was employed to convert **1** to the primary amine **2** in 85% yield. The amine was subsequently treated with ethyl chloroformate to give the ethylcarbamate **3**, a new compound. Although it could be isolated in 96% yield, it (and similar species below) remained an oil and was used without exhaustive purification.



Scheme 3.2. Synthesis of **IV** with $n = 1$ (**6**).

In a standard sequence,[14] **3** and isobutyl chloroformate were combined to generate

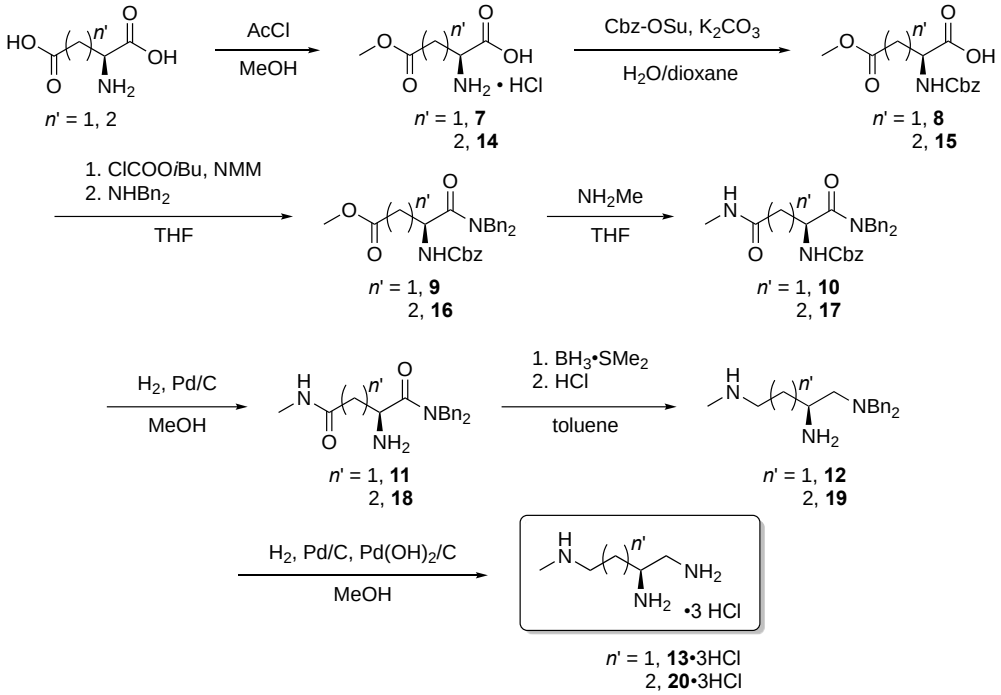
a mixed anhydride that upon treatment with NH_4OH gave the amide **4** in 55% yield. This completed the installation of the nitrogen atoms needed in the target molecule. Subsequent reaction with trifluoroacetic acid removed the Boc protecting group. However, the α-amino amide **5** was not isolated, but treated further with $BH_3 \cdot SMe_2$ in toluene. This reagent is also commercially available as a THF solution, but the higher boiling solvent was used as optimal rates and yields required elevated temperatures.[15] Reductions of both carbonyl functionalities to methyl or methylene groups were effected, and addition of HCl afforded the tris(hydrochloride) salt **6**·3HCl in 89% yield from **4**. This and the other hydrochloride adducts described below were hygroscopic and stored in desiccators. The overall yield for the five steps in Scheme 3.2 (or six if **5** is counted) is 32%.

3.2.2 IV with n = 2, 3

The availability of both L-aspartic and L-glutamic acid allowed these two syntheses to be developed in parallel, as summarized in Scheme 3.3. The methyl ester of the former, **7**, was prepared by a literature procedure (96%),[16] and the same recipe was applied to the higher homolog **14** (73%), which had previously been accessed by another route.[17] The amino groups were then protected with Cbz under standard conditions, but the products **8** and **15** were isolated as viscous oils that retained solvent (85%, 99%), and rigorous purifications were not attempted.

The carboxylic acid moieties in **8** and **15** were then converted to di(benzyl) amides by a route analogous to that used to access the amide **4** in Scheme 3.1. Workups gave **9** and **16** as waxy solids in 61% and 87% yields. Subsequent reactions with aqueous methylamine transformed the methyl ester moieties to methyl amides, completing the installation of nitrogen atoms and giving **10** and **17** (>99% each). When analogous sequences were attempted with simple amide ($CONH_2$) derivatives of **8** and **15**, products corresponding to **10** and **17** were not obtained, possibly due to intramolecular

condensations or alternative modes of methylamine attack.



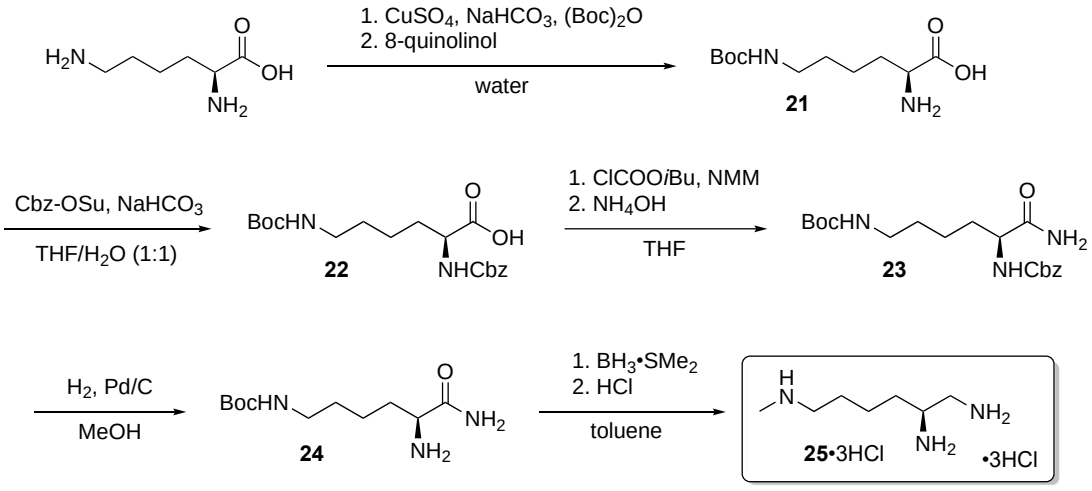
Scheme 3.3. Syntheses of **IV** with $n = 2$ and 3 (**13**, **20**).

The remaining steps required manipulation of the protecting groups and carbonyl functionalities. First, mild hydrogenolysis (Pd/C, 75 psig H_2) removed the Cbz groups to give the α-amino amides **11** and **18** (99-83%). Next, a BH_3 reduction analogous to that in Scheme 3.2 gave the triamines **12** and **19** (67%, 84%). Finally, a hydrogenolysis was carried out with the synergistically acting mixed heterogeneous catalyst[18] Pd/C and $Pd(OH)_2/C$ (75 psig H_2) in the presence of HCl. This removed the N-benzyl groups and gave the target tris(hydrochloride) salts **13**·3HCl and **20**·3HCl in 91 and 76% yields, respectively. The overall yields for the two sequences in Scheme 3.3 (7 steps) are 30% and 33%.

3.2.3 IV with $n = 4$.

As shown in Scheme 3.4, L-lysine was converted to its Boc protected form **21** by a literature procedure (74%).[19] The next step, protecting the remaining amino group with

Cbz to give **22** (79%), was taken from a recent patent.[20] The carboxylic acid was then converted to the amide **23** (86%) by the same protocol employed for a comparable step in Scheme 3.2. The Cbz group was removed using the same hydrogenolysis conditions as in Scheme 3.3 affording **24** in 91% yield. Reduction with BH_3 reduced the two carbonyl functionalities to methyl or methylene groups, and addition of HCl delivered the tris(hydrochloride) salt **25**·3HCl in 83% yield. The overall yield for the entire sequence in Scheme 3.4 (5 steps) is 38%.



Scheme 3.4. Synthesis of **IV** with $n = 4$ (**25**).

3.3 Discussion

The reactions used to access the title molecules in Schemes 3.2-3.4 are, for the most part, familiar to amino acid and peptide chemistry. As depicted in Scheme 3.1 (**V**), the starting materials for the sequences differ in the terminal functional group opposite to the α-amino acid moiety ($H_2N(C{=}O)$-, $HO(C{=}O)$-, H_2N-). That in Scheme 3.2 requires that a carbon atom be excised, and this is effected via a variant of a Hofmann rearrangement. In all cases, the primary amine that is most remote from the secondary amine is installed via a BH_3 reduction of an amide (-$(C{=}O)NR_2$) derived from the terminal carboxylic acid. The N-methyl or $MeHNCH_2$ units are introduced by BH_3 reductions of alkylcarbamate ($RO(C{=}O)NHCH_2$-; R = Et, *t*-Bu) or amide ($MeHN(C{=}O)$-) moieties.

The triamine tris(hydrochloride) end products **6**·3HCl, **13**·3HCl, **20**·3HCl, and **25**·3HCl have shelf lives of at least months. However, they are deliquescent and best kept in a desiccator. Nonetheless, the hydrated forms remain perfectly usable, although they have "goo"-like morphologies. There is no current data with the shelf lives of the corresponding free bases or triamines, but the series of triamines used to prepare **III** (Scheme 3.1) slowly degrade, presumably due to oxidation. Furthermore, tris(hydrochloride) adducts of such triamines can be directly used in recipes for preparing cobalt(III) complexes, as basic leaving groups (e.g., carbonate) can serve as "deprotecting" agents.[6]

The α-amino acid starting materials in Schemes 3.2-3.4 currently price at $12.80/mol, $7.10/mol, $10.06/mol, and $16.64/mol, respectively.[21] Since the overall yields of **6**·3HCl, **13**·3HCl, **20**·3HCl, and **25**·3HCl are 32%, 30%, 33%, and 38%, these ligands can be expected to be economically competitive with many others commonly used in enantioselective catalysis, despite the costs associated with the intervening steps. Surprisingly, I have been unable to locate any other derivatives of 1,2-ethylenediamine that incorporate a secondary amine on the carbon backbone, regardless of the tether or NHR (or NHAr) substituent. However, there are a number of related triamines or derivatives,[22] some of which have been employed as tris(hydrochloride) salts and served as precursors to tridentate ligands.[22a]

In summary, this work shown that a portfolio of enantiopure 1,2-ethyleneamines with tethered secondary amines ($(CH_2)_nNHCH_3$) are easily accessed from inexpensive commercially available α-amino acids via amide and carbamate intermediates.

3.4 Experimental

General Data. All operations were carried out under ambient (air) atmospheres unless noted. NMR spectra were recorded on standard FT spectrometers at ambient probe

temperatures (500 MHz) or 298 K (400 MHz). IR spectra were recorded on a Shimadzu IRAffinity-1 spectrometer (Pike MIRacle ATR system, diamond/ZnSe crystal). Capillary thermolyses were monitored with an Optimelt MPA 100 instrument. Chemical shifts (δ/ppm) were generally referenced to solvent signals (^{1}H: $CHCl_3$, 7.26; HDO, 4.79;[23] DMSO-d_5, 2.50; ^{13}C: $CDCl_3$, 77.16; D_2O, added dioxane at 67.2; DMSO-d_6, 39.5). Microanalyses were conducted by Atlantic Microlab.

Chemicals were treated as follows: *N*-methylmorpholine (Alfa Aesar, 99%) and trifluoroacetic acid (EMD, 99.5%), distilled before use; L-asparagine (Alfa Aesar, 98+), L-glutamic acid (multiple sources), dibenzylamine (Beantown, 98%), methylamine (Beantown, 40 wt% in H_2O), $BH_3{\cdot}SMe_2$ (Alfa Aesar, 2.0 M in toluene), di-*t*-butyl dicarbonate (Chem-Impex International Inc., 99.4 %), ethyl chloroformate (Alfa Aesar, 97%), isobutyl chloroformate (Alfa Aesar, 98%), *N*-(benzyloxycarbonyloxy)succinimide (Alfa Aesar, ≥95%), acetyl chloride (TCI, 98%), Pd/C (Sigma Aldrich, 10 wt% Pd, dry), and $Pd(OH)_2/C$ (Beantown, 20 wt% Pd, ca. 50% H_2O), used as received. Routine chemicals not noted above were used as received from common commercial sources.

***N*-Boc-L-Asparagine (1).**[24] L-asparagine (3.00 g, 22.7 mmol, 1.0 equiv) was suspended in a mixture of water (45 mL) and dioxane (45 mL), and K_2CO_3 (2.41 g, 22.7 mmol, 1.0 equiv) was added. Then di-*t*-butyl dicarbonate (5.95 g, 27.3 mmol, 1.2 equiv) was added in one portion with stirring. After 16 h, the solution was concentrated (to ca. 45 mL) by rotary evaporation and water (ca. 50 mL) was added. The solution was washed with petroleum ether (3 × 50 mL) and carefully acidified with 12.0 N HCl until no additional white precipitate formed. The precipitate was collected by filtration, washed with water, and dried by passive evaporation (fume hood) for several days to give **1** as a white solid (4.14 g, 17.8 mmol, 79%), mp 165.0-165.9 °C (open capillary).[25,26] Anal. Calcd. for $C_9H_{16}N_2O_5$ (232.24): C 46.55, H 6.94, N 12.06; found C 46.65, H 6.98, N

12.11.

NMR (DMSO-d_6, δ in ppm): ^{1}H (400 MHz) 12.52 (s, 1H), 7.32 (s, 1H), 6.92 (s, 1H), 6.88 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 4.32-4.15 (m, 1H), 2.49 (partially obscured dd, $^3J_{HH}$ = 5.4 Hz, 1H), 2.41 (dd, $^2J_{HH}$ = 15.37, $^3J_{HH}$ = 7.5 Hz, 1H,) 1.38 (s, 9H); ^{13}C{^{1}H} (100 MHz) 173.4, 171.4, 155.2, 78.1, 50.2, 36.7, 28.2 (7 × s).

3-Amino-*N*-Boc-L-alanine (2). This compound was prepared from **1** by a literature procedure.[13]

3-(Ethoxycarbonyl)amino-*N*-Boc-L-alanine (3). A suspension of **2** (1.00 g, 4.90 mmol, 1.0 equiv) and $NaHCO_3$ (0.905 g, 10.8 mmol, 2.2 equiv) in a mixture of dioxane (8 mL) and water (8 mL) was cooled to 0 °C. Ethyl chloroformate (0.56 mL, 5.9 mmol, 1.2 equiv) was added dropwise with stirring. After the mixture became clear, it was allowed to warm to room temperature. After 16 h total, water (20 mL) was added. The solution was washed with petroleum ether (2 × 30 mL), acidified with 12.0 N HCl (monitored by pH paper), and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was removed by rotary evaporation to give **3** as a viscous colorless oil that was used without further purification (1.294 g, 4.685 mmol, 96%). Anal. Calcd. for $C_{11}H_{20}N_2O_6$ (276.29): C 47.82, H 7.30, N 10.14; found C 47.93, H 7.61, N 9.57.

NMR ($CDCl_3$, δ in ppm): ^{1}H (500 MHz, 40 °C) 5.77 (br s, 1H), 5.38 (br s, 1H), 4.43-4.24 (m, 1H), 4.15-4.10 (m, 2H), 3.69-3.53 (m, 2H), 1.45 (s, 9H), 1.31-1.20 (m, 3H); ^{13}C{^{1}H} (125 MHz) 173.4, 157.9, 156.4, 80.8, 61.3, 54.6, 42.7, 28.4, 14.6 (9 × s).

3-(Ethoxycarbonyl)amino-*N*-Boc-L-alaninamide (4). A solution of **3** (0.730 g, 2.64 mmol, 1.0 equiv) in anhydrous THF (9 mL) was cooled to –15 °C in a flame dried flask. Then *N*-methylmorpholine (0.35 mL, 3.2 mmol, 1.2 equiv) added in one portion under an inert atmosphere with stirring, followed by isobutyl chloroformate (dropwise;

0.41 mL, 3.2 mmol, 1.2 equiv). After 30 min, NH_4OH (2 mL) was added and the solution allowed to warm to room temperature. After 16 h total, the solvent was removed by rotary evaporation and the white residue dissolved in EtOAc (50 mL). The solution was washed with water (30 mL), sat. $NaHCO_3$ (30 mL), and brine (30 mL), and then dried ($MgSO_4$). The solvent was removed by rotary evaporation. The residue was dry loaded onto a silica gel column that was packed and eluted with EtOAc (R_f = 0.3).[27] The solvent was removed from the product containing fractions by rotary evaporation to give **4** as a white solid (0.402 g, 1.46 mmol, 55%), mp 168.1-170.0 °C (open capillary). Anal. Calcd. for $C_{11}H_{21}N_3O_5$ (275.31): C 47.99, H 7.69, N 15.26; found C 48.25, H 7.71, N 15.02.

NMR (DMSO-d_6, δ in ppm): ^{1}H (500 MHz) 7.28 (s, 1H), 7.05 (s, 1H), 7.03-6.98 (m, 1H), 6.66 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 4.01-3.89 (m, 3H), 3.26-3.15 (m, 1H), 1.37 (s, 9H), 1.14 (t, $^3J_{HH}$ = 7.1 Hz, 3H); ^{13}C{^{1}H} (100 MHz) 172.1, 156.4, 155.1, 78.2, 59.8, 54.6, 42.2, 28.2, 14.6 (9 × s).

(*R*)-*N*^{1}-methyl-1,2,3-triaminopropane tris(hydrochloride) (6·3HCl**).** A flask was charged with **4** (0.299 g, 1.09 mmol, 1.0 equiv) and CH_2Cl_2 (2 mL) and cooled to 0 °C. Then trifluoroacetic acid (2 mL) was slowly added. The solution was stirred for 1 h, and the cold bath removed. After an additional 2 h, the solvent was removed by rotary evaporation. The residue was dried, first azeotropically with MeOH/toluene (1:1 v/v, 3 × 10 mL), and then by oil pump vacuum (overnight). The sticky white residue (**5**;[28] see Scheme 3.2) and BH_3·SMe_2 (3.8 mL; 2.0 M in toluene, 7.61 mmol, 7.0 equiv) were separately cooled to 0 °C, and slowly combined with stirring. The cold bath was removed, and after 1 h the solution was refluxed.[15] After 36 h, the mixture was cooled to 0 °C and MeOH (3 mL) added with stirring. After 1 h, the solvent was removed by rotary evaporation and 4.0 N HCl (6 mL) added. The solution was refluxed (14 h), cooled to room temperature, and taken to dryness by rotary evaporation. Then 12.0 N HCl (3 mL) was

added, and the solution cooled to 0 °C. The resulting precipitate was removed by filtration. The filtrate was taken to dryness by rotary evaporation. The oily residue was dissolved in water (10 mL), washed with diethyl ether (10 mL), and dried by rotary evaporation and oil pump vacuum (rt, 20 h) to give **6**·3HCl as a hygroscopic white solid (0.206 g, 0.967 mmol, 89%) that was stored in a desiccator to retard the formation of a goo.[29]

NMR (D_2O, δ in ppm): ^1H (500 MHz) 4.08-3.92 (m, 1H), 3.57-3.32 (m, 4H), 2.82 (s, 3H); $^{13}C\{^1H\}$ (125 MHz) 48.9, 47.2, 40.0, 34.5 (4 × s)

L-Aspartic acid 4-methyl ester hydrochloride (7). This compound was prepared from L-aspartic acid by a literature procedure.[16]

***N*-Cbz-L-aspartic acid 4-methyl ester (8).** A round bottom flask was charged with a suspension of **7** (10.00 g, 54.47 mmol, 1.0 equiv) and K_2CO_3 (18.82 g, 136.2 mmol, 2.5 equiv) in acetone (52 mL) and water (69 mL). Then *N*-(benzyloxycarbonyloxy)succinimide (14.93 g, 59.92 mmol, 1.1 equiv) was added in one portion with stirring. After 16 h, the solution was washed with diethyl ether (2 × 25 mL) and carefully acidified to pH 4 with 12.0 N HCl (monitored by pH paper). The milky sample was extracted with EtOAc (3 × 50 mL). The extract was washed with brine and dried ($MgSO_4$). The solvent was removed by rotary evaporation to give **8** as a viscous colorless oil (13.07 g, 46.47 mmol, 85%).

NMR ($CDCl_3$, δ in ppm): ^1H (500 MHz) 9.40 (br s, 1H), 7.45-7.30 (m, 5H), 5.85 (d, $^2J_{HH}$ = 8.5 Hz, 1H), 5.14 (s, 2H), 4.72-4.62 (m, 1H), 3.71 (s, 3H), 3.09 (dd, $^2J_{HH}$ = 17.4, $^3J_{HH}$ = 4.4 Hz, 1H), 2.89 (dd, $^2J_{HH}$ = 17.3, $^3J_{HH}$ = 4.6 Hz, 1H); $^{13}C\{^1H\}$ (100 MHz) 175.2, 171.6, 156.3, 136.0, 128.6, 128.3, 128.2, 67.4, 52.3, 50.2, 36.4 (11 × s).

***N*-Cbz-L-aspartic acid 1-dibenzyl amide 4-methyl ester (9).** A round bottom flask was charged with **8** (3.39 g, 12.0 mmol, 1.0 equiv; in a common embodiment, this represented the product flask from the previous synthesis) and anhydrous THF (27 mL).

The solution was transferred via cannula to a flame dried three neck flask under an inert atmosphere. Then *N*-methylmorpholine (1.6 mL, 14 mmol, 1.2 equiv) was added in one portion with stirring. The flask was placed in a –15 °C NaCl/ice bath. Isobutyl chloroformate (1.9 mL, 14 mmol, 1.2 equiv) was slowly added dropwise to give a white slurry. After 30 min, dibenzylamine (3.2 mL, 17 mmol, 1.4 equiv) was added in one portion and the cold bath removed. After 16 h, the mixture was filtered and the filter cake washed with THF. The solvent was removed from the combined filtrate/ washings by rotary evaporation. The oily residue was dissolved in EtOAc. The solution was washed with aqueous citric acid (10% w/v), saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and taken to dryness by rotary evaporation. The residue was column chromatographed on silica gel (30:70 v/v EtOAc/Hexanes, R_f = 0.4).[27] The solvent was removed from the product containing fractions by rotary evaporation and oil pump vacuum (rt) to give **9** as a colorless oil that slowly became a waxy colorless solid (3.4 g, 7.4 mmol, 61%), mp 60.1-76.8 °C (open capillary). Anal. Calcd. for $C_{27}H_{28}N_2O_5$ (460.53): C 70.42, H 6.13, N 6.08; found C 70.28, H 6.13, N 6.04.

NMR ($CDCl_3$, δ in ppm): ^{1}H (400 MHz) 7.35-7.02 (m, 15H), 5.76 (d, $^3J_{HH}$ = 9.3 Hz, 1H), 5.14-5.05 (m, 1H), 4.92 (q, $^2J_{HH}$ = 12.2 Hz, 2H), 4.70 (d, $^2J_{HH}$ = 14.8 Hz, 1H), 4.60 (d, $^2J_{HH}$ = 16.8 Hz, 1H), 4.42 (d, $^2J_{HH}$ = 16.7 Hz, 1H), 4.27 (d, $^2J_{HH}$ = 14.8 Hz, 1H), 3.58 (s, 3H), 2.76 (dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 6.8 Hz, 1H), 2.62 (dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ =5.7 Hz, 1H); ^{13}C{^{1}H} (100 MHz) 171.1 (double intensity), 155.5, 136.7, 136.2, 136.0, 129.0, 128.8, 128.6 (double intensity), 128.3, 128.1, 127.9, 127.6, 127.1, 67.2, 52.1, 50.0, 48.4, 48.3, 37.7 (19 × s).

(*S*)-2-(Benzyloxycarbonyl)amino-*N*^{1},*N*^{1}-dibenzyl-*N*^{4}-methylbutanediamide (10). A round bottom flask was charged with **9** (2.00 g, 4.34 mmol, 1.0 equiv) and THF (14.5 mL). The suspension was treated with aqueous methylamine (40 wt%; 3.8 mL, 43

mmol, 10 equiv) with stirring.[31] After 16 h, the mixture was taken to dryness by rotary evaporation to give **10** as a fluffy white solid (1.99 g, 4.34 mmol, 100%), mp 168-173 °C (open capillary), Anal. Calcd. for $C_{27}H_{29}N_3O_4$ (459.55): C 70.57, H 6.36, N 9.14; found C 70.36, H 6.36, N 9.10.

NMR ($CDCl_3$, δ in ppm): ^{1}H (500 MHz) 7.32 (m, 11H), 7.22-7.03 (m, 4H), 6.07 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 6.01 (s, 1H), 5.20-5.10 (m, 1H), 5.03 (q, J = 12.2 Hz, 2H), 4.87 (d, $^2J_{HH}$ = 16.4 Hz, 1H), 4.80 (d, $^2J_{HH}$ = 15.1 Hz, 1H), 4.53 (d, $^2J_{HH}$ = 16.4 Hz, 1H), 4.27 (d, $^2J_{HH}$ = 15.1 Hz, 1H), 2.71 (d, $^3J_{HH}$ = 3.6 Hz, 3H), 2.68-2.54 (m, 2H); ^{13}C{^{1}H} (100 MHz) 172.5, 170.0, 155.8, 136.5, 136.4, 135.9, 129.0, 128.8, 128.6, 128.2, 128.2, 127.9, 127.7, 127.6, 127.4, 67.1, 50.7, 48.7, 48.5, 39.6, 26.3 (21 × s).

(*S*)-2-Amino-*N*^{1},*N*^{1}-dibenzyl-*N*^{4}-methylbutanediamide (11). A Fischer-Porter bottle that had been purged with N_2 was charged with **10** (1.00 g, 2.18 mmol), CH_2Cl_2 (4 mL), and MeOH (4 mL). Then Pd/C (10 wt% Pd; 0.050 g, 5 wt% of **10**) was added to the solution. The bottle was pressurized with 50 psig of H_2 and after a few minutes vented. This step was repeated three times. The bottle was then pressurized with 75 psig of H_2, and the mixture stirred overnight. The sample was vented and filtered through Celite. The filter cake was washed with MeOH (ca. 50 mL). The solvent was removed from the filtrate/washings by rotary evaporation. The viscous colorless residue was passed through a silica gel column (8:92 v/v MeOH/CH_2Cl_2).[27] The solvent was removed from the product containing fractions by oil pump vacuum (r.t., 16 h) to give **11** as a viscous colorless oil (0.703 g, 2.16 mmol, 99%). Anal. Calcd. for $C_{19}H_{23}N_3O_2$ (325.41): C 70.13, H 7.12, N 12.91; found C 68.94, H 7.28, N 12.55.[30]

NMR ($CDCl_3$, δ in ppm): ^{1}H (400 MHz) 7.42-7.21 (m, 7H), 7.20-7.10 (m, 4H), 4.98 (d, $^2J_{HH}$ = 14.9 Hz, 1H), 4.68 (d, $^2J_{HH}$ = 17.0 Hz, 1H), 4.43-4.26 (m, 2H), 4.11 (d, $^2J_{HH}$ = 14.9 Hz, 1H), 3.69 (s, 2H), 2.71 (d, $^3J_{HH}$ = 4.8 Hz, 3H), 2.68-2.54 (m, 2H);

$^{13}C\{^{1}H\}$ (100 MHz) 173.4, 170.5, 136.5, 135.9, 129.2, 128.9, 128.1 128.0, 127.7, 126.8, 49.9, 49.0, 48.7, 40.4, 26.3 (15 × s).

(*S*)-1-(Dibenzyl)amino-2-amino-4-(methylamino)butane (12). A flame dried three neck flask was charged with **11** (1.20 g, 3.70 mmol, 1.0 equiv) and anhydrous toluene (3 mL) under an inert atmosphere, and was cooled to 0 °C. Then $BH_3 \cdot SMe_2$ (9.25 mL; 2.0 M in toluene, 18.5 mmol, 5.0 equiv) was added to the slurry with stirring, and the cold bath removed. After 30 min, the resulting solution was slowly heated to reflux.[15] After 20 h, the sample was cooled to room temperature, and 10% HCl slowly added dropwise with vigorous stirring until no further foaming occurred. The solution was neutralized with 2.0 N aqueous NaOH, and solid KOH (7.5 g) was added (caution, exothermic). The mixture was again refluxed (16 h), and after cooling the cloudy aqueous phase was separated. Water was added until it became clear (ca. 10 mL). It was then extracted with EtOAc (2 × 40 mL). The extracts were washed with water and brine (2 × 30 mL), dried (Na_2SO_4), and taken to dryness by rotary evaporation. The oil was dissolved in THF (5 mL) and 12.0 N HCl (1.0 mL) added. The milky sample was taken to dryness by rotary evaporation and the residue dissolved in water (25 mL). The water was washed with diethyl ether (2 × 30 mL) and made basic with 2.0 N aqueous NaOH. The oily white suspension was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and taken to dryness by rotary evaporation and oil pump vacuum (rt) to give **12** as a clear oil (0.738 g, 2.48 mmol, 67%). Anal. Calcd. for $C_{27}H_{29}N_3O_4$ (297.45): C 76.72, H 9.15, N 14.13; found C 72.78, H 8.93, N 13.01.[30]

NMR ($CDCl_3$, δ in ppm): ^{1}H (400 MHz) 7.38-7.28 (m, 8H), 7.27-7.20 (m, 2H) 3.74 (d, $^{2}J_{HH}$ = 13.5 Hz, 2H), 3.40 (d, $^{2}J_{HH}$ = 13.5 Hz, 2H), 3.01-2.93 (m, 1H), 2.62 (t, J = 7.0 Hz, 2H), 2.39 (s, 3H), 2.35 (dd, $^{2}J_{HH}$ = 12.5, $^{3}J_{HH}$ = 4.3 Hz, 1H), 2.29 (dd, $^{2}J_{HH}$ = 12.5, $^{3}J_{HH}$ = 9.2 Hz, 1H), 1.62-1.53 (m, 1H), 1.49 (br s, 1H), 1.34-1.22 (m, 1H). $^{13}C\{^{1}H\}$

(100 MHz) 139.4, 129.1, 128.4, 127.1, 61.7, 59.1, 49.5, 47.7, 36.4, 35.1 (10 × s).

(*S*)-1,2-Diamino-4-(methylamino)butane tris(hydrochloride) (13·3HCl**).** A Fischer-Porter bottle that had been purged with N_2 was sequentially charged with a solution of **12** (0.810 g, 2.72 mmol) in MeOH (9 mL), 12.0 N HCl (1.0 mL), Pd/C (10 wt%; 0.121 g), and $Pd(OH)_2/C$ (20 wt%; 0.121 g). The bottle was pressurized with 50 psig of H_2 and after a few minutes vented. This step was repeated three times. The bottle was then pressurized with 75 psig of H_2, and the bottom portion placed in a 55 °C bath. The mixture was stirred. After 48 h, the bath was removed and the bottle vented. The contents were filtered through Celite. The filter cake was washed with MeOH, and the solvent removed from the filtrate/washings by rotary evaporation. The yellow residue was dissolved in water (10 mL) and washed with diethyl ether (10 mL). The aqueous layer was taken to dryness by rotary evaporation and oil pump vacuum (rt) to give **13**·3HCl as a viscous yellow oil (0.540 g, 2.47 mmol, 91%) that was stored in a desiccator.[29]

NMR (D_2O, δ in ppm): ^1H (500 MHz) 3.78 (p, $^3J_{HH}$ = 6.6 Hz, 1H), 3.46-3.33 (m, 2H), 3.30-3.14 (m, 2H), 2.76 (s, 3H), 2.26-2.11 (m, 2H); $^{13}C\{^1H\}$ (100 MHz) 47.8, 45.3, 41.3, 33.6, 27.5 (5 × s).

L-Glutamic acid 5-methyl ester hydrochloride (14). A round bottom flask was charged with MeOH (25 mL) and cooled to 0 °C. Acetyl chloride (6.8 mL, 95 mmol, 1.4 equiv) was added dropwise and the solution stirred for 30 min. In a separate flask, a slurry of L-glutamic acid (10.00 g, 67.97 mmol, 1.0 equiv) in MeOH (25 mL) was cooled to 0 °C. The solution was added dropwise to the slurry at 0 °C. The mixture was stirred at 4 °C (20 h) and then concentrated to ca. 1/3 the original volume by rotary evaporation while maintaining a temperature below 10 °C. Diethyl ether was added until the product precipitated (ca. 125 mL). The precipitate was collected by filtration and dried by oil pump vacuum (rt) to give **14** as a white solid (9.800 g, 49.59 mmol, 73%), mp 143.4-148.1 °C

(open capillary), that was used without further purification.

NMR (D_2O, δ in ppm): ^1H (400 MHz) 4.11 (t, $^3J_{HH}$ = 6.7 Hz, 1H), 3.71 (s, 3H), 2.74-2.53 (m, 2H), 2.44-2.09 (m, 2H); $^{13}C\{^1H\}$ (100 MHz) 175.6, 172.4, 53.0, 52.9, 30.0, 25.5 (6 × s).

***N*-Cbz-glutamic acid 5-methyl ester (15).** A round bottom flask was charged with a suspension of **14** (5.00 g, 25.3 mmol, 1.0 equiv) and $NaHCO_3$ (4.46 g, 53.1 mmol, 2.1 equiv) in water (28 mL) and THF (56 mL). Then *N*-(benzyloxycarbonyloxy)succinimide (6.94 g, 27.8 mmol, 1.1 equiv) was added in one portion with stirring. After 15 h, the mixture was concentrated by rotary evaporation (removing THF), and water (20 mL) added. The solution was washed with petroleum ether (50 mL) and carefully acidified to pH 4 with 12.0 N HCl (ca. 7 mL, monitored by pH paper). The milky sample was extracted with EtOAc (3 × 50 mL). The extract was washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed by rotary evaporation to give **15** as a colorless oil (7.36 g, 24.9 mmol, 99%). Anal. Calcd. for $C_{14}H_{17}NO_6$ (295.29): C 56.95, H 5.80, N 4.74; found C 55.38, H 5.75, N 4.80.[30]

NMR ($CDCl_3$, δ in ppm): ^1H (400 MHz) 10.00 (s, 1H), 7.44-7.25 (m, 5H), 5.59 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 5.17-5.04 (m, 2H), 4.50-4.38 (m, 1H), 3.65 (s, 3H), 2.56-2.34 (m, 2H), 2.29-2.17 (m, 1H), 2.09-1.92 (m, 1H); $^{13}C\{^1H\}$ (100 MHz) 175.6, 173.8, 156.5, 136.1, 128.7, 128.4, 128.2, 67.4, 53.3, 52.1, 30.2, 27.3 (12 × s).

***N*-Cbz-glutamic acid 1-dibenzyl amide 5-methyl ester (16).** A flame dried flask was charged with a solution of **15** (5.16 g, 17.5 mmol, 1.0 equiv) in anhydrous THF (58 mL) under an inert atmosphere and cooled to –15 °C (NaCl/ice bath). Then *N*-methylmorpholine (2.3 mL, 21 mmol, 1.2 equiv) was added in one portion with stirring. Next isobutyl chloroformate (2.7 mL, 21 mmol, 1.2 equiv) was added dropwise to give a white slurry. After 45 min, dibenzylamine (4.7 mL, 24 mmol, 1.4 equiv) was added in one

portion and the cold bath removed. After 16 h, the mixture was filtered and the filter cake washed with THF. The solvent was removed from the combined filtrate/washings by rotary evaporation. The oily residue was dissolved in EtOAc. The solution was washed with aqueous citric acid (10% w/v), saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and taken to dryness by rotary evaporation. The residue was column chromatographed on silica gel (30:70 v/v EtOAc/Hexanes, R_f = 0.4).[27] The solvent was removed from the product containing fractions by oil pump vacuum to give **16** as a colorless oil that slowly became a waxy colorless solid (7.20 g, 15.2 mmol, 87%) mp 73.8-76.7 °C (open capillary). Anal. Calcd. for $C_{28}H_{30}N_2O_5$ (474.56): C 70.87, H 6.37, N 5.90; found C 70.81, H 6.44, N 5.89.

NMR ($CDCl_3$, δ in ppm): ^{1}H (500 MHz) 7.40-7.27 (m, 11H), 7.23-7.13 (m, 4H), 5.75 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 5.20-5.03 (m, 2H), 4.92 (d, $^2J_{HH}$ = 14.7 Hz, 1H), 4.88 (m, 1H), 4.79 (d, $^2J_{HH}$ = 16.5 Hz, 1H), 4.41 (d, $^2J_{HH}$ = 16.5 Hz, 1H), 4.20 (d, $^2J_{HH}$ = 14.8 Hz, 1H), 3.63 (s, 3H), 2.47 (dt, $^2J_{HH}$ = 15.6, $^3J_{HH}$ = 7.7 Hz, 1H), 2.39 (dt, $^2J_{HH}$ = 17.1, $^3J_{HH}$ = 6.2 Hz, 1H), 2.20-2.07 (m, 1H), 1.93-1.77 (m, 1H); ^{13}C{^{1}H} (100 MHz) 173.4, 172.3, 156.3, 136.8, 136.4, 135.9, 129.1, 128.9, 128.7, 128.28, 128.25, 128.1, 128.0, 127.7, 127.2, 67.1, 51.9, 50.6, 49.8, 48.0, 29.6, 28.9 (22 × s).

(*S*)-2-(benzyloxycarbonyl)amino-*N*^{1},*N*^{1}-dibenzyl-*N*^{5}-methylpentanediamide (17). A round bottom flask was charged with **16** (3.00 g, 6.32 mmol, 1.0 equiv) and THF (31 mL). The suspension was treated with aqueous methylamine (40 wt%; 5.5 mL, 63 mmol, 10 equiv) with stirring.[31] After 36 h, the sample was taken to dryness by rotary evaporation to give **17** as a fluffy white solid (2.97 g, 6.28 mmol, 99%), mp 135.2-138.5 °C (open capillary). Anal. Calcd. for $C_{28}H_{31}N_3O_4$ (473.57): C 71.02, H 6.60, N 8.87; found C 71.25, H 6.65, N 8.77.

NMR ($CDCl_3$, δ in ppm): ^{1}H (400 MHz) 7.45-7.23 (m, 11H), 7.16 (m, 4H), 6.17

(s, 1H), 6.01 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 5.17-5.03 (m, 3H), 4.74-4.62 (m, 2H), 4.29 (d, $^2J_{HH}$ = 16.8 Hz, 1H), 4.00 (d, $^2J_{HH}$ = 14.8 Hz, 1H), 2.66 (d, $^3J_{HH}$ = 4.8 Hz, 3H), 2.29-2.22 (m, 2H), 2.18 (m, 1H), 1.84 (m, 1H); $^{13}C\{^1H\}$ (100 MHz) 172.8, 172.1, 156.8, 136.6, 136.3, 135.8, 129.1, 128.9, 128.7, 128.3, 128.2, 128.1, 128.0, 127.8, 126.9, 67.1, 50.7, 49.7, 48.2, 32.4, 31.0, 26.4 (21 × s).

(*S*)-2-Amino-*N*^{1},*N*^{1}-dibenzyl-*N*^{5}-methylpentanediamide (18). A Fischer-Porter bottle that had been purged with N_2 was charged with **17** (4.00 g, 8.45 mmol), CH_2Cl_2 (12 mL), and MeOH (12 mL). Then Pd/C (10 wt% Pd; 0.200 g, 5 wt% of **17**) was added to the solution. The bottle was pressurized with 50 psi of H_2 and after a few minutes vented. This step was repeated three times. The bottle was then pressurized with 75 psig of H_2, and the mixture stirred overnight. The sample was vented and filtered through Celite. The filter cake washed with MeOH (ca. 50 mL). The solvent was removed from the filtrate/washings by rotary evaporation. The viscous colorless residue was passed through a short silica gel column (8:92 v/v MeOH/CH_2Cl_2).[27] The solvent was removed from the product containing fractions by oil pump vacuum (r.t., 16 h) to give **18** as an amorphous white solid (2.37 g, 6.97 mmol, 83%). Anal. Calcd. for $C_{20}H_{25}N_3O_2$ (339.44): C 70.77, H 7.42, N 12.38; found C 69.60, H 7.62, N 12.05.[30]

NMR ($CDCl_3$, δ in ppm): ^1H (400 MHz) 7.60-7.22 (m, 6H), 7.24-7.08 (m, 4H), 5.92 (s, 1H), 5.18 (d, $^2J_{HH}$ = 14.8 Hz, 1H), 4.81 (d, $^2J_{HH}$ = 17.2 Hz, 1H), 4.34 (d, $^2J_{HH}$ = 17.2 Hz, 1H), 4.08 (d, $^2J_{HH}$ = 14.8 Hz, 1H), 3.67 (dd, *J* = 9.6, 3.3 Hz, 1H), 2.72 (d, $^3J_{HH}$ = 4.8 Hz, 3H), 2.52-2.39 (m, 1H), 2.35-2.23 (m, 1H), 2.18-2.03 (m, 1H), 1.80 (s, 2H), 1.73-1.59 (m, 1H); $^{13}C\{^1H\}$ (100 MHz) 176.6, 173.1, 137.2, 136.9, 129.1, 128.8, 128.1, 127.7, 127.6, 126.5, 50.9, 49.5, 48.9, 32.2, 30.9, 26.3 (16 × s).

(*S*)-1-(Dibenzyl)amino-2-amino-5-(methylamino)pentane (19). A flame dried three neck flask was charged with **18** (1.05 g, 3.09 mmol, 1.0 equiv) and anhydrous toluene

(3 mL) under an inert atmosphere, and was cooled to 0 °C. Then $BH_3 \cdot SMe_2$ (7.7 mL; 2.0 M in toluene, 15 mmol, 5.0 equiv) was added to the slurry with stirring, and the cold bath removed. After 30 min, the resulting solution was slowly heated to reflux.[15] After 20 h, the sample was cooled to room temperature, and 10% HCl was slowly added dropwise with vigorous stirring until no further foaming occurred. The solution was neutralized with 2.0 N aqueous NaOH, and solid KOH (7.5 g) was added (caution! exothermic). The mixture was again refluxed (16 h) and cooled. The cloudy aqueous phase was separated. Water was added until it became clear (ca. 10 mL). It was then extracted with EtOAc (2 × 40 mL). The extracts were washed with water and brine (2 × 30 mL), dried (Na_2SO_4), and taken to dryness by rotary evaporation. The oil was dissolved with THF (5 mL) and 12.0 N HCl (1.0 mL) added. The milky sample was taken to dryness by rotary evaporation and the residue dissolved in water (25 mL). The water was washed with diethyl ether (2 × 30 mL) and made basic with 2.0 N aqueous NaOH. The oily white suspension was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and taken to dryness by rotary evaporation and oil pump vacuum (rt) to give **19** as a clear oil (0.805 g, 2.59 mmol, 84%). Anal. Calcd. for $C_{20}H_{29}N_3$ (311.47): C 77.12, H 9.39, N 13.49; found C 75.22, H 9.48, N 12.85.[30]

NMR ($CDCl_3$, δ in ppm): ^1H (500 MHz) 7.41-7.28 (m, 8H), 7.25-7.19 (m, 2H) 3.75 (d, $^2J_{HH}$ = 13.5 Hz, 2H), 3.36 (d, $^2J_{HH}$ = 13.5 Hz, 2H), 2.98-2.79 (m, 1H), 2.53 (m, 2H), 2.40 (s, 3H), 2.36 (dd, $^2J_{HH}$ = 12.6, $^3J_{HH}$ = 3.8 Hz, 1H), 2.27 (dd, $^2J_{HH}$ = 12.6, $^3J_{HH}$ = 9.6 Hz, 1H), 1.62-1.30 (m, 6H), 1.21-1.10 (m, 1H); $^{13}C\{^1H\}$ (125 MHz) 139.4, 129.0, 128.3, 127.1, 61.6, 59.1, 52.3, 48.6, 36.5, 33.4, 26.6 (11 × s).

(*S*)-1,2-Diamino-5-(methylamino)pentane tris(hydrochloride) (20·3HCl**).** A Fischer-Porter bottle that had been purged with N_2 was sequentially charged with a solution of **19** (0.735 g, 2.36 mmol) in MeOH (8 mL), 12.0 N HCl (1 mL), Pd/C (10 wt%;

0.075 g), and $Pd(OH)_2/C$ (20 wt%; 0.075 g). The bottle was pressurized with 50 psig of H_2 and after a few minutes vented. This step was repeated three times. The bottle was then pressurized with 75 psig of H_2 and the mixture was stirred. After 4 d, the bottom portion of the bottle was placed in a 55 °C bath. After 3 d, the bath was removed and the bottle vented. The contents were filtered through Celite. The filter cake was washed with MeOH, and the solvent removed from the filtrate/washings by rotary evaporation. The yellow residue was dissolved in water (10 mL) and washed with diethyl ether (10 mL). The aqueous layer was taken to dryness by rotary evaporation and oil pump vacuum (rt) to give **20**·3HCl as a viscous yellow oil (0.434 g, 1.80 mmol, 76%) that was stored in a desiccator.[29]

NMR (D_2O, δ in ppm): ^1H (500 MHz) 3.72-3.60 (m, 1H), 3.38-3.28 (m, 2H), 3.13-3.01 (m, 2H), 2.71 (s, 3H), 1.91-1.71 (m, 4H); $^{13}C\{^1H\}$ (100 MHz) 49.7, 48.7, 41.2, 33.4, 27.8, 22.0 (6 × s).

***N*^{6}-Boc-L-lysine (21).** This compound was prepared from L-lysine by a literature procedure.[19]

***N*^{2}-Cbz-*N*^{6}-Boc-L-lysine (22).** This compound was prepared from **21** according to a patent.[20]

***N*^{2}-Cbz-*N*^{6}-Boc-L-lysinamide (23).** A flame dried three neck flask was charged with **22** (2.44 g, 6.42 mmol, 1.0 equiv) and anhydrous THF (8 mL) under an inert atmosphere and placed in a –15 °C NaCl/ice bath. Then *N*-methylmorpholine 0.85 mL, 7.7 mmol, 1.2 equiv) was added in one portion with stirring, followed by isobutyl chloroformate (dropwise; 1.0 mL, 7.7 mmol, 1.2 equiv). A white solid formed. After 30 min, NH_4OH (5 mL) was added and the cold bath removed. After 3 h, the solvent was removed by rotary evaporation and the residue dissolved in EtOAc (100 mL). The solution was washed with sat. $NaHCO_3$ and brine (50 mL), and then dried ($MgSO_4$). The solvent

was removed by rotary evaporation. The residue was column chromatographed on silica gel (4:96 v/v MeOH/CH_2Cl_2, R_f = 0.3).[27] The solvent was removed from the product containing fractions by rotary evaporation to give **23** as a white solid (2.09 g, 5.50 mmol, 86%), mp 138.1-141.5 °C (open capillary). Anal. Calcd. for $C_{19}H_{29}N_3O_5$ (379.46): C 60.14, H 7.70, N 11.07; found C 60.25, H 7.86, N 11.00.

NMR (DMSO-d_6, δ in ppm): ^{1}H (500 MHz) 7.44-7.28 (m, 6H), 7.26 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.05-6.90 (m, 1H), 6.77 (t, $^3J_{HH}$ = 5.8 Hz, 1H), 5.01 (s, 2H), 3.91-3.84 (m, 1H), 2.96-2.77 (m, 2H), 1.65-1.54 (m, 1H), 1.54-1.43 (m, 1H), 1.41-1.16 (m, 13H); ^{13}C{^{1}H} (125 MHz) 174.0, 156.0, 155.6, 137.1, 128.3, 127.8, 127.7, 77.4, 65.4, 54.5, 31.6, 29.2, 28.3, 22.9 (14 × s).

***N*^{6}-Boc-L-lysinamide (24)** A Fischer-Porter bottle that had been purged with N_2 was charged with **23** (2.08 g, 5.48 mmol) and MeOH (18 mL). Then Pd/C (10 wt% Pd; 0.200 g, 10 wt% of **23**) was added to the solution. The bottle was pressurized with 50 psig of H_2 and after a few minutes vented. This step was repeated three times. The bottle was then pressurized with 75 psig of H_2, and the mixture stirred overnight. The sample was vented and filtered through Celite. The filter cake was washed with MeOH (ca. 50 mL). The solvent was removed from the filtrate/ washings by rotary evaporation. The residue was column chromatographed on silica gel (15:82:3 v/v/v MeOH:EtOAc:NH_4OH, R_f = 0.4).[27] The solvent was removed from the product containing fractions by rotary evaporation to give **24** as a white solid (1.22 g, 4.97 mmol, 91%), mp 102.2-104.0 °C (open capillary). Anal. Calcd. for $C_{11}H_{23}N_3O_3$ (245.32): C 53.86, H 9.45, N 17.13; found C 54.06, H 9.57, N 16.93.

NMR ($CDCl_3$, δ in ppm): ^{1}H (500 MHz) 7.10 (s, 1H), 5.85 (s, 1H), 4.66 (s, 1H), 3.34 (dd, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 4.5 Hz, 1H), 3.15-3.02 (m, 2H), 1.89-1.72 (m, 1H), 1.61-1.44 (m, 5H), 1.41 (m, 11H); ^{13}C{^{1}H} (125 MHz) 178.3, 156.2, 79.2, 55.1, 40.2, 34.7,

30.0, 28.5, 22.9 (9 × s).

(*S*)-1,2-Diamino-6-(methylamino)hexane tris(hydrochloride) (25·3HCl**).** A flame dried three neck flask was charged with **24** (0.440 g, 1.79 mmol, 1.0 equiv) and cooled to 0 °C. A sample of $BH_3 \cdot SMe_2$ (5.4 mL; 2.0 M in toluene, 10.76 mmol, 6.0 equiv) was cooled to 0 °C and added dropwise with stirring under an inert atmosphere. The cold bath was removed. After 1 h, the solution was refluxed.[15] After 36 h, the mixture worked up exactly as described for **6**·3HCl. This gave **25**·3HCl as a hygroscopic white solid (0.381 g, 1.50 mmol, 83%) that was stored in a desiccator to retard the formation of a goo.[29]

NMR (D_2O, δ in ppm): ^1H (500 MHz) 3.69-3.57 (m, 1H), 3.40-3.24 (m, 2H), 3.09-2.99 (m, 2H), 2.69 (s, 3H), 1.90-1.63 (m, 4H), 1.61-1.36 (m, 2H); $^{13}C\{^1H\}$ (125 MHz) 49.9, 49.2, 41.3, 33.4, 30.2, 25.7, 22.0 (7 × s).

3.5 References

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(28) In a separate experiment, **5** was further purified via silica gel column chromatography (15:82:3 v/v/v MeOH:EtOAc:NH_4OH)). NMR (DMSO-d_6, δ in ppm): ^{1}H (500 MHz), 7.55 (s, 1H), 7.27 (s, 1H), 7.09 (s, 1H), 3.98 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 3.13 (m, 1H), 1.16 (t, $^3J_{HH}$ = 7.1 Hz, 3H); $^{13}C\{^1H\}$ (125 MHz), 173.1, 156.5, 59.9, 54.1, 43.7, 14.7 (6 × s).

(29) Appropriate microanalyses could not be obtained for the tris(hydrochloride) salts of the title compounds, presumably due to their hygroscopic nature, as detailed in the text. The data were always a better but still imperfect fit to mono- or dihydrates (low C, low N).

(30) (a) This sample cannot be represented as analytically pure, but the microanalytical data are nonetheless presented to illustrate the best results obtained to date. (b) Gabbaï, F. P.; Chirik, P. J.; Fogg, D. E.; Meyer, K.; Mindiola, D. J.; Schafer, L. L.; You, S.-L. An Editorial About Elemental Analysis, *Organometallics* **2016**, *35*, 3255-3256.

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4. CHIRAL COBALT(III) TRIS(1,2-DIAMINE) CATALYSTS THAT INCORPORATE "SMART" OR "TASK SPECIFIC" ANIONS FOR THE BIFUNCTIONAL ACTIVATION OF NUCLEOPHILES AND ELECTROPHILES IN ENANTIOSELECTIVE ADDITION REACTIONSSOLVENT-FREE CATALYSIS WITH CO(III) WERNER COMPLEXES†

4.1 Introduction

There are large numbers of reactions that require (1) a catalyst and (2) a Brønsted base that is frequently nitrogenous.[1,2] The base is sometimes required in stoichiometric quantities,[1] whereas other times catalytic loadings suffice.[2] In certain instances, it has proved possible to covalently link these entities such that superior bifunctional catalysts are obtained.[3,4] One case in point would be Takemoto's catalyst (Figure 4.1),[3a] in which an achiral thiourea that is an effective hydrogen bond donor is joined with a chiral dimethylaminocyclohexyl fragment. However, applying this strategy to enantioselective catalysis can pose complications. Introducing functional groups will often require lengthier catalyst syntheses, and potentially generates additional stereocenters. This may lead to mixtures of diastereomers, which are sometimes difficult to separate.

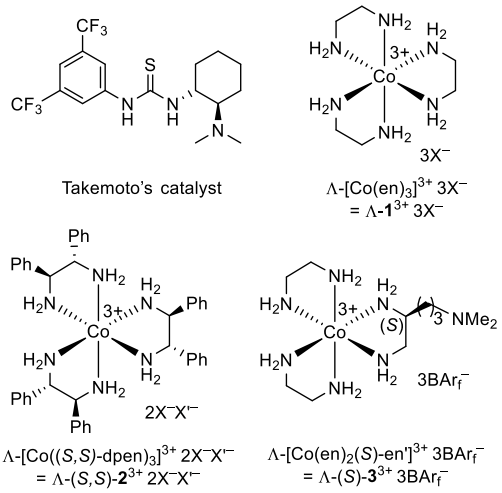


Figure 4.1. Relevant previously studied catalysts.

†Reprinted with permission from "Chiral Cobalt(III) Tris(1,2-diamine) Catalysts That Incorporate Nitrogenous Base Containing Anions for the Bifunctional Activation of Nucleophiles and Electrophiles in Enantioselective Addition Reactions" by Kabes, C. Q.; Lucas, R. F.; Gunn, J. H.; Gladysz, J. A. *ACS Catal.* **2021**, *10*, 7762-7771 Copyright 2021 by the American Chemical Society.

These issues arose in research with hydrogen bond donor catalysts based upon the substitution inert, chiral-at-cobalt Werner salts Λ- or Δ-$[Co(en)_3]^{3+}$ $3X^-$ ($\mathbf{1}^{3+}$ $3X^-$; Figure 4.1).[5-7] Here Λ or Δ denote the cobalt configurations, en denotes ethylenediamine, and X^- is most often the lipophilic and poorly hydrogen bond accepting[8] anion BAr_f^- (B(3,5-$C_6H_3(CF_3)_2)_4^-$). The latter allows this chemistry to be carried out in nonpolar solvents that lack functional groups that might compete for the NH hydrogen bonding sites. However, the D_3 symmetric parent trication, historically important as the first inorganic species resolved into enantiomers,[5] always gave mediocre enantioselectivities in addition reactions of carbon-hydrogen bonds commonly carried out with nitrogenous Brønsted bases.[7]

Happily, excellent enantioselectivities were obtained with two types of modified catalysts (Figure 4.1, bottom). The first featured three 1,2-diphenylethylenediamine (dpen) ligands.[9] Both enantiomers of the non-meso diastereomer are commercially available at surprisingly low prices.[10] Furthermore, both the Λ and Δ diastereomers of various lipophilic mixed salts $[Co((S,S)\text{-dpen})_3]^{3+}$ $2X^-X'^-$ ((S,S)-$\mathbf{2}^{3+}$ $2X^-X'^-$) can be synthesized with high diasteroselectivities.[9a,11] Due to the six phenyl groups in the trication, one BAr_f^- anion (X') is sufficient to provide good solubilities in nonpolar solvents. These have proved, when used with Et_3N or *N*-methylmorpholine, to be highly enantioselective catalysts for a variety of carbon-hydrogen bond addition reactions.[9]

The second featured two en ligands and a third in which one CH hydrogen atom had been replaced by a tertiary-amine-containing $CH_2CH_2CH_2NMe_2$ moiety, Λ-$[Co(en)_2((S)\text{-}H_2NCH((CH_2)_3NMe_2)CH_2NH_2)]^{3+}$ $3BAr_f^-$ (Λ-(S)-$\mathbf{3}^{3+}$ $3BAr_f^-$).[12] This catalyst provided even higher enantioselectivities, and now in the absence of an external base. However, the synthesis of the enantiopure substituted ethylenediamine ligand was not trivial,[13] and the catalyst was obtained as a ca. 50:50 mixture of diastereomers, one of

which gave poor enantioselectivities and required a chromatographic separation.[14]

For large numbers of metal based catalysts, including the cobalt complexes in Figure 4.1, the locus of reactivity is a cation. Thus, the possibility of incorporating nitrogenous Brønsted bases into the accompanying counter anions was considered, as represented by **I** in Figure 4.2. It is well known that counter anions can have significant influences upon rates, product distributions, and enantioselectivities,[15] but they are seldom if ever purposefully functionalized. In earlier efforts, the trications Λ- and Δ-(*S*,*S*)-**2**$^{3+}$ were combined with both enantiomers of various chiral anions, and observed "matched" and "mismatched" combinations that afforded enhanced or diminished enantioselectivities, respectively.[16] Some related studies have been reported by others.[17,18]

Accordingly, it is reported in this chapter the combination of Λ- and Δ-(*S*,*S*)-**2**$^{3+}$ with what can be termed "smart" or "task specific" anions – namely, achiral carboxylate and related oxyanions that contain nitrogenous Brønsted bases and are furthermore readily available. These catalysts distinctly outperform benchmark systems that employ catalytic or stoichiometric quantities of the oxyanion-free Brønsted bases. This simple strategy, which represents a new paradigm for bifunctional catalysts and has the potential for considerable generality, has not to my knowledge been previously utilized to enhance the performance of any type of catalyst, enantioselective or otherwise.

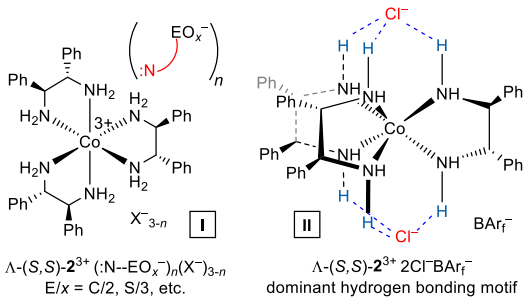


Figure 4.2. Left: design concept, catalysts with "smart" anions containing nitrogenous Brønsted bases (I); Right: dominant ion pairing motif in solution for Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ in solution (**II**; each chloride ion associated with one of the two C_3 symmetric NH faces).

4.2 Results

4.2.1. Catalyst design and synthesis.

The diastereomeric mixed salts Λ or Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$ were synthesized by a two step procedure from Co(OAc)$_2$ and (*S*,*S*)-dpen as previously described.[9a,11] Both are isolated as hydrates, as are nearly all new cobalt(III) salts below. For simplicity, the water molecules are ignored in the main text and graphics, but are fully represented in the experimental section. They are factored into all formula weights and yield calculations.

These salts can be chromatographed on silica gel (typical eluent: 98:2 v/v DCM/MeOH), and ^{1}H NMR spectra always show the same relative integration of CH protons in the cation and anion (the NH protons can exchange in some deuterated solvents[11]). Furthermore, the D_3 symmetric trication features two C_3 symmetric faces with three nearly synperiplanar NH bonds, each ideally positioned for hydrogen bonding to a chloride anion as shown in **II** in Figure 4.2. Accordingly, six NH protons exhibit ^{1}H NMR chemical shifts considerably downfield from the others. Thus, these systems can be confidently represented as mixed 2Cl^{-}BAr$_f^{-}$ salts, both in solution and the solid state. One with chiral sulfonate anions in place of the chloride anions has been crystallographically characterized.[16]

Given the effectiveness of the dimethylamino containing catalyst Λ-(*S*)-**3**$^{3+}$ 3BAr$_f^{-}$ in Figure 4.1, it would be logical to investigate salts of Λ- and Δ-(*S*,*S*)-**2**$^{3+}$ with carboxylate or other oxyanions that contain aliphatic tertiary amines. There are a number of obvious candidates, many of which would be available in enantiopure form. However, such salts gave disappointing results in initial screens, some of which are briefly described in the discussion section.

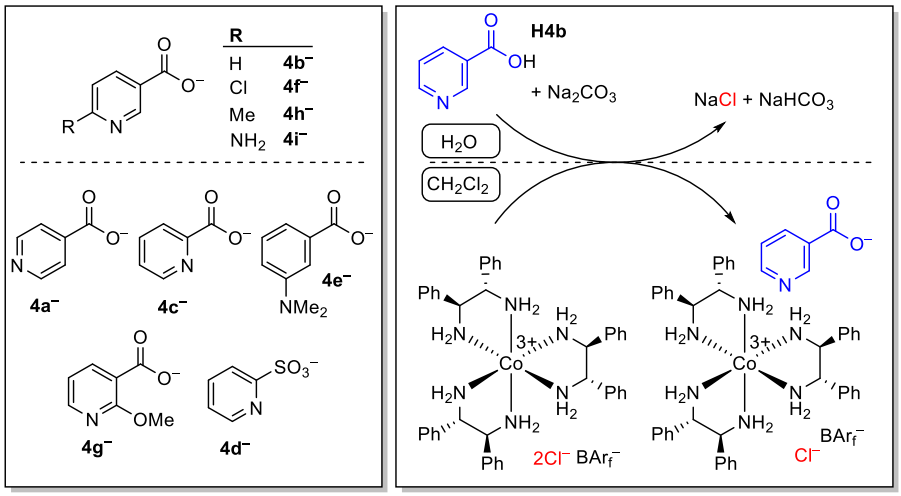


Figure 4.3. Biphasic synthesis the representative mixed salt Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $\mathbf{4b}^{-}Cl^{-}BAr_f^{-}$ ($\mathbf{4b}^{-}$ = nicotinate^{-}), and alternative Brønsted base containing anions examined in this study

Thus, attention was turned to carboxylic or sulfonic acids that contained more weakly basic pyridyl or *N*,*N*-dimethylanilinyl moieties. As shown in Figure 4.3, DCM solutions of Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^{-}BAr_f^{-}$ were treated with aqueous solutions of Na_2CO_3 and the inexpensive commercially available acids **H4** corresponding to the conjugate bases $\mathbf{4}^{-}$ in Figure 4.3 (3.0-3.3 equiv each). The organic phases were separated and taken to dryness to give the catalysts Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $\mathbf{4}^{-}Cl^{-}BAr_f^{-}$ as air stable hydrated orange solids in 88-99% yields. Even though the loadings of the acids **H4** were sufficient to displace both chloride anions, only one was exchanged, giving rather rare examples of trication salts that feature, at least in a formal sense, three different monoanions. Selected salts of the opposite diastereomer, Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $\mathbf{4}^{-}Cl^{-}BAr_f^{-}$ (epimeric at cobalt), were similarly prepared.

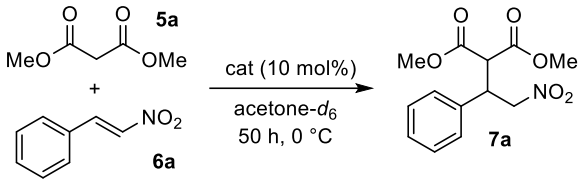
All catalysts were characterized by NMR (^{1}H, ^{13}C) and microanalyses, as summarized in supporting information (SI). The ^{1}H NMR spectra exhibited the correct relative integrations of CH protons in the trication and the $\mathbf{4}^{-}$ and BAr_f^{-} anions. The chemical shifts of six NH protons were considerably downfield of the other six (3.85-2.25 ppm for the Λ diastereomers). The microanalytical data also matched the proposed

formulations. However, in solution it would be easy to envision alternative ion pairings, as further treated in the discussion section.

4.2.2. Catalyst screening; first series.

Initial catalyst screening was carried out with salts of the anions **4a-e**$^-$, representing the conjugate bases of isonicotinic, nicotinic, picolinic, 2-pyridinesulfonic, and 3-(dimethylamino)benzoic acid – or expressed differently, all three possible pyridine carboxylates, one pyridine sulfonate, and *N*,*N*-dimethylaminobenzoate. Two test transformations, shown in Charts 4.1 and 4.2, were selected. The first, the reaction of dimethyl malonate (**5a**) and β-nitrostyrene (**6a**) to give the addition product **7a**, has been rather widely studied.[9a,19] The other, the addition of the 1,3-dicarbonyl compound **9a** to di-*t*-butyl azodicarboxylate (**8**) to give **10a**, has been less investigated.[9b,20] Both can be effected with various chiral hydrogen bond donor catalysts and stoichiometric or catalytic quantities of trialkylamine bases.

Chart 4.1 shows the initial results for the former reaction, carried out at 0 °C in acetone-d_6 with 10% catalyst loadings and an NMR standard to determine absolute yields. First, the parent catalyst Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$, which lacks Brønsted basic nitrogen atoms, did not effect catalysis alone. Further, as shown in entries 1a-b, yields of **7a** increased to only 3-7% when catalytic or stoichiometric amounts of pyridine were added. *N*,*N*-dimethylaniline, modeling the free base in 3-dimethylaminobenzoate (**4e**$^-$), gave even lower yields (entries 2a-b). However, the five salts Λ-(*S*,*S*)-**2**$^{3+}$ **4a-e**$^-$Cl$^-$BAr$_f^-$ afforded **7a** in 83-85% ee (as determined by HPLC) and 60-94% yields after 24 h. Aside from **7a**, only unreacted starting material was evident by NMR.



entry	catalyst	base	yield (%)[a]	% ee (config)[b]
1a	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	Py 10 mol%	3	-
1b	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	Py 100 mol%	7	-
2a	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	PhNMe$_2$[c] 10 mol%	1	-
2b	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	PhNMe$_2$[c] 100 mol%	1	-
3	Λ-(*S*,*S*)-**2**$^{3+}$ **4a**$^-$Cl$^-$BAr$_f^-$	-	90	84 (*R*)
4	Λ-(*S*,*S*)-**2**$^{3+}$ **4b**$^-$Cl$^-$BAr$_f^-$	-	70	85 (*R*)
5	Λ-(*S*,*S*)-**2**$^{3+}$ **4c**$^-$Cl$^-$BAr$_f^-$	-	70	85 (*R*)
6	Λ-(*S*,*S*)-**2**$^{3+}$ **4d**$^-$Cl$^-$BAr$_f^-$	-	60	83 (*R*)
7	Λ-(*S*,*S*)-**2**$^{3+}$ **4e**$^-$Cl$^-$BAr$_f^-$	-	60	84 (*R*)
8	Δ-(*S*,*S*)-**2**$^{3+}$ **4a**$^-$Cl$^-$BAr$_f^-$	-	69	31 (*S*)
9	Δ-(*S*,*S*)-**2**$^{3+}$ **4b**$^-$Cl$^-$BAr$_f^-$	-	92	54 (*S*)
10	Δ-(*S*,*S*)-**2**$^{3+}$ **4i**$^-$Cl BAr$_f^-$	-	85	65 (*S*)

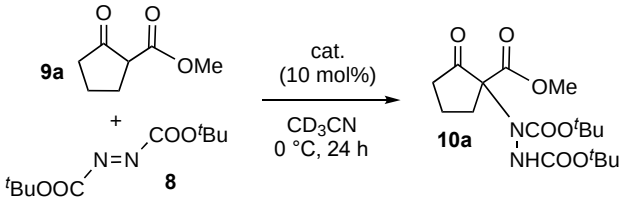
[a]Assayed by ^{1}H NMR relative to the internal standard Ph_2SiMe_2.
[b]Assayed by chiral HPLC. [c]24 h reaction time.

Chart 4.1. Catalyst screening: additions of dimethyl malonate (**5a**) to *trans*-β-nitrostyrene (**6a**).

As illustrated by entries 8 and 9, the opposite diastereomers Δ-(*S*,*S*)-**2**$^{3+}$ **4a**,**b**$^-$Cl$^-$ BAr$_f^-$ afforded lower ee values, with the opposite enantiomer of **7a** predominating. This paralleled earlier results with Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ and the external base Et_3N, and shows the cobalt configuration to be the primary determinant of the product configuration. Analogous behavior was found for all salts of Δ-(*S*,*S*)-**2**$^{3+}$ examined.

Chart 4.2 summarizes the data for the latter reaction, similarly carried out but in CD_3CN. Entries 1 and 2 show that the combination of Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ and external pyridine (10-100 mol%) affords the addition product **10a** in moderate yields (27-65%) and enantioselectivities (52-67% ee). However, entries 3-7 establish that significantly better results are achieved with the five bifunctional catalysts Λ-(*S*,*S*)-**2**$^{3+}$ **4a-e**$^-$Cl$^-$BAr$_f^-$ (83-

99% yields, 65-77% ee). Aside from **10a**, only unreacted starting material was evident by NMR.



entry	catalyst	base	yield (%)[a]	% ee (config)[b]
1	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	Py 10 mol%	27	52 (*S*)
2	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	Py 100 mol%	65	62 (*S*)
3	Λ-(*S*,*S*)-**2**$^{3+}$ **4a**$^{-}$Cl^{-}BAr$_f^{-}$	-	99	75 (*S*)
4	Λ-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$	-	99	77 (*S*)
5	Λ-(*S*,*S*)-**2**$^{3+}$ **4c**$^{-}$Cl^{-}BAr$_f^{-}$	-	99	70 (*S*)
6	Λ-(*S*,*S*)-**2**$^{3+}$ **4d**$^{-}$Cl^{-}BAr$_f^{-}$	-	83	65 (*S*)
7	Λ-(*S*,*S*)-**2**$^{3+}$ **4e**$^{-}$Cl^{-}BAr$_f^{-}$	-	91	73 (*S*)
8	D-(*S*,*S*)-**2**$^{3+}$ **4a**$^{-}$Cl^{-}BAr$_f^{-}$	-	99	67 (*R*)
9	D-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$	-	99	83 (*R*)
10	D-(*S*,*S*)-**2**$^{3+}$ **4i**$^{-}$Cl BAr$_f^{-}$	-	99	82 (*R*)

[a]Assayed after by ^{1}H NMR relative to the internal standard Ph_2SiMe_2. [b]Assayed by chiral HPLC.

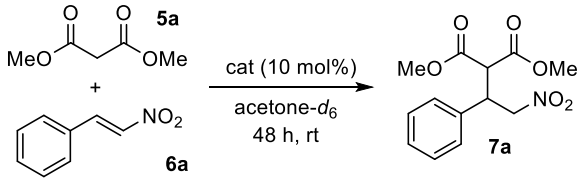
Chart 4.2. Catalyst screening: additions of methyl 2-oxocyclopentane-1-carboxylate (**9a**) to di-*t*-butyl azodicarboxylate (**8**).

As illustrated by entries 8 and 9, the opposite diastereomers Δ-(*S*,*S*)-**2**$^{3+}$ **4a**,**b**$^{-}$Cl^{-} BAr$_f^{-}$ give **10a** with comparable yields (99%) and enantioselectivities (67-83% ee) and opposite absolute configurations. By a modest margin, the highest ee value is now realized in the Δ diastereomer series (83% vs 77%), paralleling earlier results with Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$ and the external base *N*-methylmorpholine.[9b] Thus, the diastereomer that gives the best enantioselectivities depends upon the test reaction.

4.2.3. Catalyst screening; second series.

Overall, the top performer among (*S*,*S*)-**2**$^{3+}$ **4a-e**$^{-}$Cl^{-}BAr$_f^{-}$ was judged to be nicotinic acid derived (*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$, although other salts were not without

promise. In the interest of further optimization, analogs with the substituted nicotinates **4f-i**$^{-}$ (Figure 4.3) were investigated. These feature both electron donating and withdrawing groups. As summarized in Chart 4.3, Λ-(*S*,*S*)-**2**$^{3+}$ **4f-i**$^{-}$Cl^{-}BAr$_f^{-}$ were evaluated in the same malonate/nitroalkene addition reaction employed in Chart 4.1, but now carried out for 48 h at room temperature unless noted.



entry	catalyst	yield (%)[a]	% ee (config)[b]
1	Λ-(*S*,*S*)-**2**$^{3+}$ **4f**$^{-}$Cl^{-}BAr$_f^{-}$	33	79 (*R*)
2	Λ-(*S*,*S*)-**2**$^{3+}$ **4g**$^{-}$Cl^{-}BAr$_f^{-}$	69	84 (*R*)
3	Λ-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$	63	86 (*R*)
4	Λ-(*S*,*S*)-**2**$^{3+}$ **4h**$^{-}$Cl^{-}BAr$_f^{-}$	58	84 (*R*)
5	Λ-(*S*,*S*)-**2**$^{3+}$ **4i**$^{-}$Cl^{-}BAr$_f^{-}$	95[c]	87 (*R*)

[a]Assayed by ^{1}H NMR relative to the internal standard Ph_2SiMe_2. [b]Assayed by chiral HPLC. [c]This yield is after 22 h.

Chart 4.3. Catalyst optimization: effect of nicotinate anion substituents upon yields and enantioselectivities for the addition in Chart 4.1.

As shown in entry 1, the 6-chloronicotinate catalyst Λ-(*S*,*S*)-**2**$^{3+}$ **4f**$^{-}$Cl^{-}BAr$_f^{-}$ afforded the poorest results, with a distinctly lower yield of **7a** (33%) and slightly lower enantioselectivity (79% ee). The 2-methoxy and 6-methyl substituted catalysts Λ-(*S*,*S*)-**2**$^{3+}$ **4g**,**h**$^{-}$Cl^{-}BAr$_f^{-}$ (entries 2, 4) performed comparably to Λ-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$, giving yields of 69-58% and enantioselectivities of 84% ee. More importantly, 6-amino substituted Λ-(*S*,*S*)-**2**$^{3+}$ **4i**$^{-}$Cl^{-}BAr$_f^{-}$ (entry 5) afforded a distinctly higher yield and rate (95% after 22 h as compared to 68-33% after 48 h) and a slightly higher enantioselectivity (87% ee). This corresponds to the least acidic nicotinic acid, or the most basic and presumably most hydrogen bond accepting nicotinate.

In order to better define the trends in Chart 4.3, yields were monitored as a function of time. The results, shown in Figure 4.4, dramatically illustrate the superior qualities of

the 6-aminonicotinate catalyst Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $\mathbf{4i}^{-}Cl^{-}BAr_f^{-}$ and the deleterious effect of an electron withdrawing 6-chloro substituent. However, outside of the product **7a**, in all cases only starting material could be detected by NMR.

4.2.4. Catalyst scope.

The 6-aminonicotinate salt Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $\mathbf{4i}^{-}Cl^{-}BAr_f^{-}$ was then applied to the additions of dimethyl malonate to fourteen aryl substituted nitroolefins (**6a-n**) at 0 °C in acetone-d_6. As summarized in Chart 4.4, after 24 h the products **7a-n** were obtained in average/ median yields and ee values of 82%/90% and 85%/87%, respectively. The dominant absolute

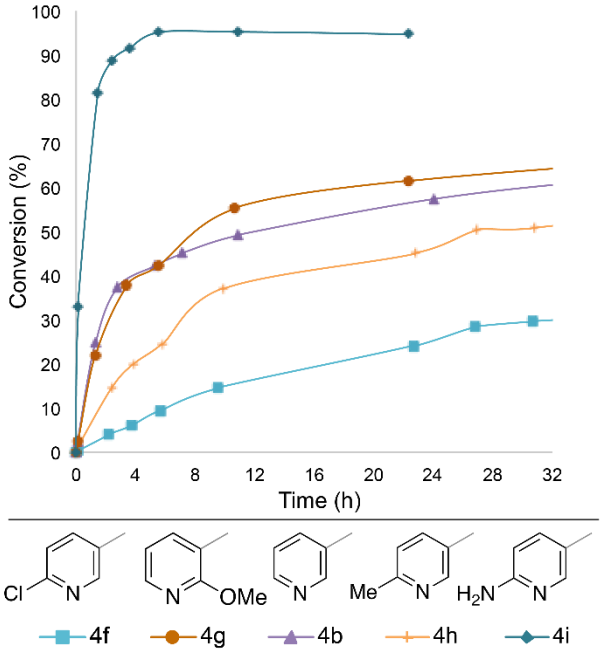
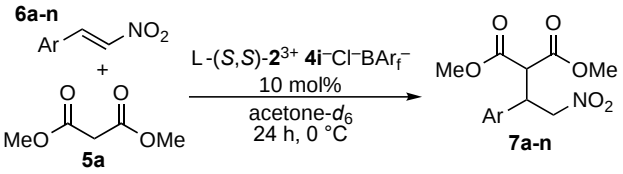


Figure 4.4. Effect of nicotinate anion substituents upon the rates of addition of dimethyl malonate (**5a**) to *trans*-β-nitrostyrene (**6a**) under the conditions of Chart 4.3.

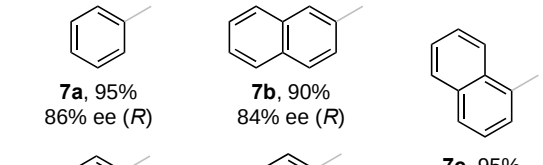
configurations of most adducts could be assigned by previously established chiral HPLC relationships, as documented in the SI. These always corresponded to the same relative configuration. Thus, for the three cases for which HPLC assignments have not yet been established (**7e**,**l**, **m**), identical relative configurations were presumed.

Under the default conditions for Chart 4.4, the two lowest yields were encountered with 2-(benzyloxy)phenyl and 2-furyl substituents (**7k**,**n**; 37%, 28%). However, NMR analyses showed substantial amounts of starting materials. Accordingly, after the standard 24 h reaction time, another 10 mol% charge of catalyst was added. After an additional 24 h, the yields had markedly increased (95%, 87%), raising the average/median yields to 90%/93%. To ensure that the NMR yields in the charts translate into comparable preparative yields, the reaction of **5a** and **6f** was repeated on a 0.1 g scale. A chromatographic workup gave **7f** in 88% yield and 96% ee.

When the aryl groups in **6a**-**n** were replaced by a *trans*-β-styryl (PhCH=CH) moiety, the yields and enantioselectivities dropped to 14% and 73% ee. Thus, extensions of these protocols to nitroalkenes that lack aryl substituents may be problematic. When dimethyl malonate (**5a**) was replaced by diethyl malonate (**5a**-**Et**) in the addition to **6a**, the yield and enantiomeric excess of the product (**7a**-**Et**) fell only slightly (90%, 80% ee). However, the decreases were dramatic for diisopropyl and di-*t*-butyl malonate.



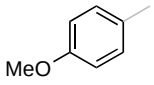
aryl groups[a]



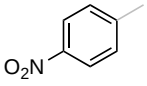
7a, 95%
86% ee (*R*)

7b, 90%
84% ee (*R*)

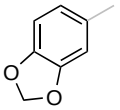
7c, 95%
90% ee (*R*)



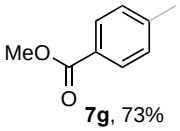
7d, 99%
71% ee (*R*)



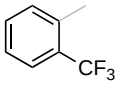
7e, 85%
76% ee (*R*)[b]



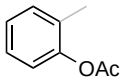
7f, 90%
97% ee (*R*)



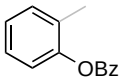
7g, 73%
67% ee (*R*)



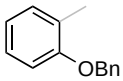
7h, 99%
91% ee (*R*)



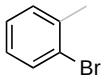
7i, 82%
91% ee (*R*)



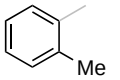
7j, 99%
91% ee (*R*)



7k, 95%
91% ee (*R*)[c]



7l, 99%
87% ee (*R*)[b]



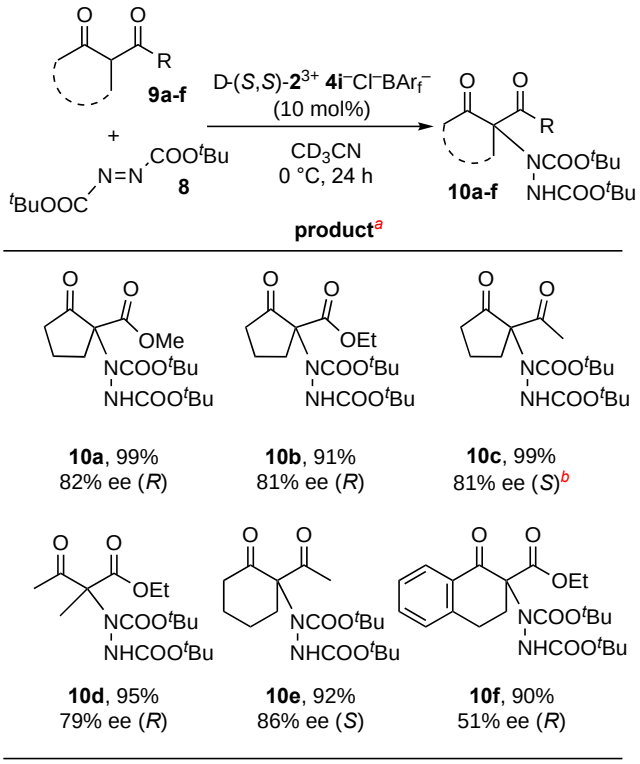
7m, 74%
82% ee (*R*)[b]

7n, 87%
84% ee (*S*)[c]

[a]Yields assayed by ^{1}H NMR relative to the internal standard Ph_2SiMe_2; ee values assayed by chiral HPLC. [b]This configuration is inferred as described in the text. [c]This yield is after 48 h; an additional 10 mol% of catalyst is added after 24 h.

Chart 4.4. Substrate scope: additions of dimethyl malonate (**5a**) to aryl-substituted nitroolefins (**6a-n**) with the optimized catalyst Λ-(*S,S*)-**2**$^{3+}$ **4i**$^–$Cl$^–$BAr$_f^–$.

The scope of 1,3-dicarbonyl compound additions to di-*t*-butyl azodicarboxylate (**8**) that can be catalyzed by the opposite diastereomer Δ-(*S,S*)-**2**$^{3+}$ **4i**$^–$Cl$^–$BAr$_f^–$ at 0 °C in CD_3CN was similarly explored. As sketched in Chart 4.5, six different substrates (**9a-f**) afforded products (**10a-f**) in yields ranging from 90 to 99% (average 94%) and enantioselectivities ranging from 86% to 51% ee (average 77%). The dominant absolute configurations were assigned as for Chart 4.4.



[a]Yields assayed by ^{1}H NMR relative to the internal standard Ph_2SiMe_2; ee values assayed by chiral HPLC. [b]This configuration is inferred as described in the text.

Chart 4.5. Substrate scope: additions of dicarbonyl compounds (**9a-f**) to di-*t*-butyl azodicarboxylate (**8**) with the optimized catalyst Δ-(*S,S*)-**2**$^{3+}$ **4i**$^–$Cl$^–$BAr$_f^–$.

4.3 Discussion

The most significant and seemingly unprecedented aspect of this report involves the extraordinary synergism that can be realized when nitrogenous Brønsted bases are incorporated into the counter anions of the tricationic cobalt(III) hydrogen bond donor catalyst (*S,S*)-**2**$^{3+}$. This synergism is enormous for the test reaction in Chart 4.1, and substantial for that in Chart 4.2. The catalysts can be said to have "smart" or "task specific" counter anions that feature "built in bases". Counter anions have been modified to achieve certain phase affinities,[21] and chiral counter anions have been used to optimize the performance of certain cationic chiral metal catalysts.[16-18] However, the Gladysz group is unaware of any purposeful attempts to introduce functional groups into counter anions that would take part in bond breaking and bond making.

In the neighboring field of ionic liquids, considerable attention has been given to "task specific" cations and anions for optimizing performances in diverse applications, including catalysis.[22] However, even in this voluminous literature, The Gladysz group is unable to find prior efforts to achieve function by incorporating sp^2- or sp^3-hybridized nitrogen donor atoms into the anions.[23] Searches involving "ionic liquids" and "nicotinate" or related combinations give no hits.

The overall constitution of the mixed salt catalysts (*S*,*S*)-**2**$^{3+}$ **4**$^{-}$Cl^{-}BAr$_f^{-}$ is secure from the NMR and microanalytical data. Nonetheless, it can be questioned whether they might be better represented by other formulations, as in solution it would be easy to envision ion pairing equilibria. It is possible that the dominant species feature two of the hydrogen bond accepting (or "non-BAr$_f^{-}$") anions per cobalt trication – i.e., (*S*,*S*)-**2**$^{3+}$ $\underline{\underline{\mathbf{4}^{-}}}$ $\underline{\underline{\text{Cl}^{-}}}BAr_f^{-}$, (*S*,*S*)-**2**$^{3+}$ $\underline{\underline{2\mathbf{4}^{-}}}BAr_f^{-}$, and (*S*,*S*)-**2**$^{3+}$ $\underline{\underline{2\text{Cl}^{-}}}BAr_f^{-}$ – so as to maximize the types of interactions in **II** (Figure 4.2). However, at this time one can only guess at the most productive assembly for catalysis.

Mechanistic analysis is also impeded by the many NH donor groups that might participate at any stage on the reaction coordinate. It would be easy to envision simultaneous interactions involving four or five – a much more complex situation than with Takemoto's catalyst (Figure 4.1), which can only offer two NH groups. Thus, it becomes pure speculation to propose a detailed mechanism. The nicotinate anion almost certainly deprotonates the 1,3-dicarbonyl reactants in Charts 4.1-4.5, but there are numerous possible motifs for this step, especially with respect to hydrogen bonding.[24] However, such issues sometimes prove computationally tractable, as for a bifunctional cationic chiral ruthenium hydrogen bond donor catalyst with a covalently linked nitrogenous Brønsted base.[4]

Despite these uncertainties, certain phenomenological observations may offer

insight. For example, the pK_a(BH) and pK_a(BH$^+$) values for the nicotinate anion **4b**$^-$ and nicotinic acid **H4b** are 4.75 and 2.07, respectively.[25,26] Thus, both species are weaker bases than Et_3N (pK_a(BH$^+$) 10.7) and *N*-methylmorpholine (pK_a(BH$^+$) 7.4),[25] the most effective external bases for the reactions in Charts 4.1-4.5. Both are also less basic than pyridine (pK_a(BH$^+$) 5.17) or *N*,*N*-dimethylaniline (pK_a(BH$^+$) 5.15),[25] the other external base that is ineffective (Chart 4.1, entries 2a-b) until incorporated into an oxyanion. However, any initial impression that a lower basicity may be of importance is dashed by the much poorer results with the 6-chloronicotinate anion **4f**$^-$ (pK_a (BH) 3.24)[28] and the superior results with the 6-aminonicotinate anion **4i**$^-$ (pK_a(BH) 6.30).[28]

Another issue is whether the nicotinate anions function as oxygen or nitrogen bases. The equilibrium between the *N*-protonated zwitterionic and *O*-protonated non-zwitterionic forms of nicotinic acid **H4b** is highly dependent upon solvent and temperature,[27] with the latter generally favored in organic solvents. Thus, the O-protonation of **4b**$^-$ would be thermodynamically preferred. However, with 6-aminonicotinic acid **H4i**, the equilibrium should shift in the *N*-protonated zwitterion direction, as supported by the much enhanced basicity of 2-aminopyridine (pK_a (BH$^+$) 6.71)[25] versus pyridine. Since 6-aminonicotinate gives the most effective catalyst, (*S*,*S*)-**2**$^{3+}$ **4i**$^-$Cl$^-$BAr$_f^-$, this argues for a key role of the nitrogenous basic site.

In Charts 4.1 and 4.2, the yield and ee data are benchmarked – appropriately – to the external bases pyridine and *N*,*N*-dimethylaniline, which are ineffective or only moderately effective. However, for a full picture it is also important to compare the new data to optimized results with Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ and the external bases Et_3N and *N*-methylmorpholine.[9a,b] While the yields are similar, the average ee values are slightly lower. In Chart 4.4, those for the eight substrates common to both studies are 87% ee (this work) versus 89% ee (Et_3N external base).[9a] With Chart 4.5, those for the five substrates

common to both studies are 76% ee (this work) versus 93% ee (*N*-methylmorpholine external base).[9b]

Charts 4.1-4.3 by no means exhaust the possible optimization strategies for this class of catalysts. For example, the overall efficacy of the isonicotinate catalyst Λ-(*S*,*S*)-**2**$^{3+}$ **4c**$^{-}$Cl^{-}BAr$_f^{-}$ is not so different from that of Λ-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$. Indeed, a variety of substituted isonicotinic acids are commercially available, and certain adducts might outperform the benchmark 6-aminonicontinate catalyst Λ-(*S*,*S*)-**2**$^{3+}$ **4i**$^{-}$Cl^{-}BAr$_f^{-}$. In the course of this work, a number of salts of Λ-(*S*,*S*)-**2**$^{3+}$ with various trialkylamine containing counter anions (e.g., $Me_2N(CH_2)_nCO_2^{-}$, n = 1-3; $Me_2N(CH_2)_2SO_3^{-}$) were prepared, partially characterized, and screened as catalysts. While some gave moderate enantioselectivies, they did not attain the levels in Chart 4.1.

Furthermore, there is seemingly an excellent opportunity to apply multivariate analysis or machine learning methods to guide future generations of catalyst optimization,[29] especially considering the "drop in" nature of the base-containing counter anions, and flexibility in the other counter anion. For example, $B(C_6F_5)_4^{-}$ salts are sometimes slightly superior to BAr$_f^{-}$ salts.[9b-d] Finally, the many enantiopure carboxylate anions that can be derived from chiral alkaloids, which often feature pyridine or related heteroarene units, clearly merit future investigation.

4.4 Conclusion

Bifunctional catalysis is an immense field with numerous contributors and much current activity. Despite this breadth, no case is known in which bond breaking and making for a reaction promoted by an ionic catalyst is distributed between the cation and functional groups built into the anion. This strategy, as implemented with the title catalysts (*S*,*S*)-**2**$^{3+}$ **4**$^{-}$Cl^{-}BAr$_f^{-}$, is clearly competitive with covalently tethered bifunctional catalysts. Furthermore, the generality is strongly supported by two types of test reactions

involving carbon-carbon and carbon-nitrogen bond formation (Charts 4.1-4.5), two types of otherwise poorly effective "built in" bases (pyridine, *N*,*N*-dimethylaniline), and two types of host oxyanions (carboxylate, sulfonate). It cannot be dismissed as a one-off curiosity.

This work also adds to the growing body of catalytic reactions that are promoted by non-covalent interactions between ligands and substrates.[30] Some of the more relevant earlier efforts involve cationic bifunctional chiral-at-metal containing hydrogen bond donor catalysts investigated by Meggers and Gong[31] and Belokon and Larianov.[14,32] However, the data herein establish a mold-breaking new paradigm for the design of bifunctional catalysts, which is furthermore not limited to species with metal-containing cations. Additional applications of "smart" or "task specific" functionality-containing anions in such systems will be described in future reports.

4.5 Experimental

General. All operations were carried out under air atmospheres. NMR spectra were recorded on standard FT spectrometers at ambient probe temperatures (500 MHz) or 298 K (400 MHz). Chemical shifts (δ/ppm) were generally referenced to solvent signals: ^{1}H, residual $CHCl_3$ (7.26), acetone-d_5, (2.05), or CHD_2CN (1.94); ^{13}C, $CDCl_3$ (77.16) or acetone-d_6 (29.84). IR spectra were recorded on a Shimadzu IRAffinity-1 spectrometer (Pike MIRacle ATR system, diamond/ZnSe crystal). Capillary thermolyses were monitored with an Optimelt MPA 100 instrument. Microanalyses were conducted by Atlantic Microlab. HPLC analyses were carried out with a Shimadzu instrument package (pump/autosampler/detector LC-20AD/SIL-20A/SPD-M20A). HPLC Traces are included in Appendix B.

The di-*t*-butyl azodicarboxylate (98%, Aldrich) was recrystallized from heptane (warm until dissolved) and petroleum ether (30-60 °C; added cold and sample kept at room

temperature until precipitation). The (*E*)-cinnamaldehyde, 4-formylbenzoic acid methyl ester, nicotinic acid, 2-methoxynicotinic acid, 6-aminonicotinic acid, 6-chloronicotinic acid, 6-methylnicotinic acid, isonicotinic acid, picolinic acid, 3-(dimethylamino)benzoic acid, 2-pyridinesulfonic acid, ammonium acetate, dimethyl malonate, diethyl malonate, di-*t*-butyl malonate, Ph_2SiMe_2, *trans*-β-nitrostyrene, and routine chemicals not specifically noted were used as received from common commercial sources.

Catalyst synthesis; general procedure. To a solution of (*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ ·*n*H_2O (Λ, *n* = 2 or Δ, *n* = 1) 0.050 g, 0.030 mmol, 1.0 equiv)[11] in DCM (5 mL) was added a solution of an aryl substituted carboxylic or sulfonic acid (**4a-i**, Figure 4.4.3; 0.089 mmol, 3.0 equiv.) and Na_2CO_3 (0.011 g, 0.099 mmol, 3.3 equiv.) in water (5 mL). The biphasic mixture was rapidly stirred for 30 min. The organic layer was separated, washed with water (5 mL), dried ($NaSO_4$), and taken to dryness by rotary evaporation.

Catalyst screening, nitrostyrene addition (Chart 4.1). A vial was charged with *trans*-β-nitrostyrene (**6a**; 0.009 g, 0.060 mmol, 1.0 equiv), dimethyl malonate (**5a**; 0.0076 mL, 0.066 mmol, 1.1 equiv), Ph_2SiMe_2 (0.0013 mL, internal standard), pyridine (1.0-0.0 equiv, delivered volumetrically), acetone-d_6 (0.600 mL), and a stir bar, and cooled to 0 °C. The catalyst (0.0060 mmol, 10 mol%) was added in one portion with stirring. After 50 h at 0 °C, the solution was transferred to an NMR tube and the yield of **7a** assayed by ^{1}H NMR. The solvent was removed by rotary evaporation, and the residue chromatographed on silica (glass pipet, 25:75 v/v EtOAc/ hexanes). The solvent was removed from the product containing fractions by rotary evaporation to give 7**a** as a colorless oil. Enantiomeric excesses were assayed by HPLC with a Chiralcel AD column (98:2 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 32.9 min (major), 43.6 min (minor).[9a.]

NMR ($CDCl_3$, δ/ppm): ^{1}H (400 MHz) 7.35-7.26 (m, 3H), 7.23-7.18 (m, 2H), 4.97-

4.80 (m, 2H), 4.23 (td, $^3J_{HH}$ = 8.9, 5.3 Hz, 1H), 3.85 (d, $^3J_{HH}$ = 9.0 Hz, 1H), 3.75 (s, 3H), 3.55 (s, 3H); $^{13}C\{^1H\}$ (100 MHz): 168.0, 167.4, 136.3, 129.2, 128.6, 128.0, 77.5, 54.9, 53.2, 53.0, 43.0 (11 × s).

Catalyst screening, azodicarboxylate addition (Chart 4.2). A vial was charged with methyl 2-oxocyclopentane-1-carboxylate (**9a**; 0.0076 mL, 0.061 mmol, 1.0 equiv), di-*t*-butyl azodicarboxylate (**8**; 0.014 g, 0.061 mmol, 1.0 equiv), Ph_2SiMe_2 (0.0013 mL, internal standard), pyridine (1.0-0.0 equiv, delivered volumetrically), CD_3CN (0.600 mL), and a stir bar, and cooled to 0 °C. The catalyst (0.0060 mmol, 10 mol%) was added in one portion with stirring. After 50 h at 0 °C, the solution was assayed and worked up per the preceding procedure to give **10a** as a colorless oil. Enantiomeric excesses were determined by HPLC with a Chiralcel AD column (96:4 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 13.7 min (min), 19.4 min (major).[9b]

NMR ($CDCl_3$, δ/ppm): ^1H (500 MHz) 6.70-6.03 (m, 1H), 3.76 (s, 3H), 2.97-2.03 (m, 5 H), 2.03-1.81 (s, 1H), 1.53-1.29 (m, 18H).

Catalyst screening, substituted nicotinate salts (Chart 4.3 and Figure 4.3). A vial was charged with **6a** (0.009 g, 0.060 mmol, 1.0 equiv), Ph_2SiMe_2 (0.0013 mL, internal standard), catalyst (0.0060 mmol, 10 mol%), and acetone-d_6 (0.600 mL). The solution was transferred to an NMR tube and an initial ^1H NMR spectrum recorded. Then **5a** (0.0076 mL, 0.066 mmol, 1.1 equiv) was added and a second ^1H NMR spectrum immediately acquired. A stir bar was added and the solution was stirred (48 h, rt). The yield of **7a** was periodically assayed by ^1H NMR (data: Figure 4.3). The solvent was removed by rotary evaporation and the residue chromatographed on silica (glass pipet, 25:75 v/v EtOAc/hexanes). The solvent was removed from the product containing fractions by rotary evaporation to give **7a** as a colorless oil, which was analyzed as described for Chart 4.1.

Substrate scope, nitroolefin additions (Chart 4.4). A vial was charged with nitroolefin (**6**; 0.060 mmol, 1.0 equiv), Ph_2SiMe_2 (0.0013 mL, internal standard), Λ-(*S*,*S*)-**2**$^{3+}$ **4i**$^{-}$$Cl^{-}BAr_f^{-}\cdot 2H_2O$ (0.0107 g, .0060 mmol, 10 mol%), and acetone-d_6 (0.600 mL). The solution was transferred to an NMR tube and an initial ^{1}H NMR spectrum recorded. The sample was cooled to 0 °C. A stir bar and **5a** (0.0076 mL, 0.066 mmol, 1.1 equiv) were added. The solution was stirred (24 h, 0 °C). The yield of product **7** was assayed by ^{1}H NMR, the solvent removed by rotary evaporation, and the residue chromatographed on silica (glass pipet, 25:75 v/v EtOAc/hexanes). The solvent was removed from the product containing fractions by rotary evaporation. Enantiomeric excesses were determined by HPLC as described below.

Substrate scope, azodicarboxylate additions (Chart 4.5). A vial was charged with a 1,3-dicarbonyl compound (**9**; 0.060 mmol, 1.0 equiv), Ph_2SiMe_2 (0.0013 mL, internal standard), di-*t*-butyl azodicarboxylate (0.0153 g, 0.066 mmol, 1.1 equiv) and CD_3CN (0.400 mL). The solution was transferred to an NMR tube and an initial ^{1}H NMR spectrum recorded. The sample was cooled to 0 °C. A stir bar and a solution of Λ-(*S*,*S*)-**2**$^{3+}$ **4i**$^{-}$$Cl^{-}BAr_f^{-}\cdot 2H_2O$ (0.0107 g, 0.0060 mmol, 10 mol%) in CD_3CN (0.200 mL) were added. The solution was stirred (24 h, 0 °C). The yield of product **10** was assayed by ^{1}H NMR, the solvent removed by rotary evaporation, and the residue chromatographed on silica (glass pipet, 25:75 v/v EtOAc/hexanes,) The solvent was removed from the product containing fractions by rotary evaporation. Enantiomeric excesses were determined by HPLC as described below.

Typical preparative reaction. A vial was charged with **6f** (see Chart 4.4; 0.100 g, 0.52 mmol, 1.0 eq), Λ-(*S*,*S*)-**2**$^{3+}$ **4i**$^{-}$$Cl^{-}BAr_f^{-}\cdot 2H_2O$ (0.092 g, 0.052 mmol, 10 mol%), and acetone (6 mL) and cooled to 0 °C. Then **5a** (0.082 g, 0.620 mmol, 1.2 eq) was added with stirring. After 48 h, the solvent was removed by rotary evaporation. The residue was

chromatographed on silica (glass column, 20:80 v/v EtOAc/hexanes). The solvent was removed from the product containing fractions by rotary evaporation to give **7f** as a white solid (0.148 g, 0.46 mmol, 88%, 96% ee), mp 86.0-88.6 °C (lit: 86.0-87.5 °C).[33] NMR ($CDCl_3$, δ/ppm, 500 MHz): ^{1}H (500 MHz) 6.70 (m, 3H), 5.94 (s, 2H), 4.87 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 4.9, 1H), 4.80 (dd, $^2J_{HH}$ = 13.1, $^3J_{HH}$ = 9.3 Hz, 1H), 4.15 (td, $^3J_{HH}$ = 9.2, 4.9 Hz, 1H), 3.80 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H); ^{13}C{^{1}H} (125 MHz) 167.9, 167.3, 148.2, 147.7, 129.7, 121.5, 108.8, 108.2, 101.4, 77.7, 55.0, 53.2, 53.0, 42.8, (14 × s). HPLC data are given below.

Syntheses of nitroolefin substrates

Nitroolefins **6a-d** and **6h-k** were used from a previous work, in which they were prepared by Henry reactions with nitromethane.[9a] Nitroolefins **6f**,**n** were available commercially, and **6e**,**l**, **m** were synthesized by literature procedures.[34]

***trans-p*-(methoxycarbonyl)-β-nitrostyrene (6g).**[35] A round-bottom flask was charged with 4-formylbenzoic acid methyl ester (0.250 g, 1.52 mmol, 1.0 equiv), nitromethane (1.5 mL), and ammonium acetate (0.035 g, 0.457 mmol, 30 mol%). The mixture was refluxed (2 h) and allowed to cool. The thick slurry was transferred to a sintered glass frit, and the solvent was pulled through by vacuum. The residue was triturated with a minimal amount of methanol, and the solid transferred to a vial and dried by oil pump vacuum (rt, 14 h) to give **6g** as a yellow-green solid (0.124 g, 0.598 mmol, 39%), mp 178.4-181.8 °C (open capillary). IR (powder film, cm^{-1}): 3103, 3051, 2959, 1710, 1635, 1517, 1497, 1281, 1105, 960, 770.

NMR ($CDCl_3$, δ/ppm): ^{1}H (400 MHz) 8.11 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 8.02 (d, $^3J_{HH}$ = 13.7 Hz, 1H), 7.62 (d, $^3J_{HH}$ = 13.7 Hz, 1H), 7.62 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 3.95 (s, 3H); ^{13}C{^{1}H} (100 MHz) 166.1, 138.8, 137.7, 134.3, 133.2, 130.6, 129.1, 52.7 (8 × s).

(1*E*,3*E*)-1-phenyl-4-nitro-1,3-butadiene (6o). A round-bottom flask was charged

with (*E*)-cinnamaldehyde (0.25 mL, 2.0 mmol, 1.0 equiv), nitromethane (1.5 mL), and ammonium acetate (0.046 g, 0.595 mmol, 30 mol%). The mixture was refluxed (2 h) and allowed to cool. The solvent was removed by rotary evaporation. The red oily residue was dissolved in a minimum of DCM, and loaded onto a silica column that was packed and eluted with EtOAc/hexanes (15:85 v/v). The solvent was removed from the combined product containing fractions by rotary evaporation and oil-pump vacuum (rt, 14 h) to give **6o** as an oily residue that slowly became a vermillion semi-solid (0.174 g, 1.00 mmol, 50%).[36]

NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.78 (ddd, $^3J_{HH}$ = 13.0, 11.6 Hz, $^4J_{HH}$ = 0.7 Hz, 1H), 7.55-7.47 (m, 2H), 7.44-7.37 (m, 3H), 7.24 (d, $^3J_{HH}$ = 13.1 Hz, 1H), 7.16 (d, $^3J_{HH}$ = 15.5 Hz, 1H), 6.87 (ddd, $^3J_{HH}$ = 15.5, 11.6 Hz, $^4J_{HH}$ = 0.6 Hz, 1H); ^{13}C{^{1}H} (100 MHz) 146.2, 139.3, 138.8, 135.3, 130.5, 129.2, 127.9, 120.7 (8 × s).

Syntheses of catalysts

Λ-(*S*,*S*)-2^{3+} 4a$^-$Cl$^-$BAr$_f^-$·2H$_2$O. Isolated according to the general procedure (main text) from Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H$_2$O and isonicotinic acid (0.011 g) as an orange solid (0.048 g, 0.027 mmol, 91%), mp 125.7-129.6 °C (open capillary, dec to green liquid). Anal. Calcd. for $C_{80}H_{64}BClCoF_{24}N_7O_2$·2H$_2$O (1752.62): C 54.83, H 3.91, N, 5.59; found C 54.98, H 3.91, N 5.36. IR (powder film, cm^{-1}): 3068, 1681, 1609, 1539, 1385, 1354, 1273, 1119, 679.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) isonicotinate at 8.69-8.63 (m, 1H), 7.92-7.86 (m, 1H); BAr$_f^-$ at 7.84-7.77 (m, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 8.54 (br s, 4H, N**H**H', overlapping isonicotinate), 7.63-7.46 (m, 12H), 7.36-7.16 (m, 18H), 5.26 (br s, 4H, NH**H'**), 5.17 (br s, 6H, C**H**NH$_2$); ^{13}C{^{1}H} (125 MHz) BAr$_f^-$ at 162.6 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.5 Hz, $^4J_{CF}$ = 2.9 Hz, *m*), 125.4 (q, $^1J_{CF}$ = 271.6 Hz, **C**F$_3$), 118.4 (sept, $^3J_{CF}$ = 4.0 Hz, *p*); dpen at 137.6 (s, *i*-Ph), 129.8, 129.7, 129.6 (3 ×

s, *o-, m-*, *p*-Ph), 63.5 (s, **C**HNH$_2$); isonicotinate at 172.8 (s, **C**OO$^-$), 150.7, 145.9, 124.2 (5 × s).

Λ-(*S*,*S*)-2^{3+} 4b$^-$Cl$^-$BAr$_f^-$·2H$_2$O. Isolated according to the general procedure from Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H$_2$O and nicotinic acid (0.011 g) as an orange solid (0.046 g, 0.026 mmol, 88%), mp 119.1-122.2 °C (open capillary, dec to green liquid). Anal. Calcd. for $C_{80}H_{64}BClCoF_{24}N_7O_2$·2H$_2$O (1752.62): C 54.83, H 3.91, N, 5.59, Cl, 2.00; found C 54.56, H 3.98, N 5.39. IR (powder film, cm^{-1}): 3063, 1609, 1539, 1387, 1354, 1275, 1119.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) nicotinate at 9.24 (dd, $^4J_{HH}$ = 2.1 Hz, $^5J_{HH}$ = 0.9 Hz, 1H), 8.65 (dd, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 8.34 (dt, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 2.0 Hz, 1H), 7.40 (ddd, $^3J_{HH}$ = 7.7 Hz, 4.8 Hz, $^5J_{HH}$ = 0.9, 1H); BAr$_f^-$ at 7.85-7.78 (m, 8H, *o*), 7.70 (s, 4H, *p*); dpen at 8.68 (br s, 5H, N**H**H', overlapping nicotinate), 7.62-7.46 (m, 12H), 7.35-7.22 (m, 18H), 5.25 (br s, 5H, NH**H'**), 5.18 (s, 6H, C**H**NH$_2$); ^{13}C{^{1}H} (125 MHz) BAr$_f^-$ at 162.6 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.5 Hz, $^4J_{CF}$ = 2.9 Hz, *m*), 125.4 (q, $^1J_{CF}$ = 271.9 Hz, **C**F$_3$), 118.4 (sept, $^3J_{CF}$ = 4.0 Hz, *p*); dpen at 137.6 (s, *i*-Ph), 129.72, 129.71, 129.6 (3 × s, *o-, m-*, *p*-Ph), 63.5 (s, **C**HNH$_2$); nicotinate at 173.1 (s, **C**OO$^-$), 152.1, 151.8, 137.4, 133.7, 123.6 (5 × s).

Δ-(*S*,*S*)-2^{3+} 4b$^-$Cl$^-$BAr$_f^-$·2H$_2$O. Isolated according to the general procedure from Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$·H$_2$O and nicotinic acid (0.011 g) as an orange solid (0.051 g, 0.029 mmol, 88%), mp 117.5 ºC (open capillary; dec to green liquid with gradual darkening at lower temperatures). Anal. Calcd. for $C_{80}H_{64}BClCoF_{24}N_7O_2$·2H$_2$O (1752.62): C 54.83, H 3.91, N, 5.59; found C 55.38, H 4.08, N 5.70. IR (powder film, cm^{-1}): 3067, 1684, 1596, 1457, 1382, 1354, 1275, 1120, 682.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) nicotinate at 9.14 (apparent s, 1H), 8.59 (dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 8.23 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 7.36-7.29 (m, 1H); BAr$_f^-$ at 7.82-7.74 (m, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 7.87 (br s, 1H, N**H**H',

overlapping nicotinate), 7.58-7.46 (m, 12H), 7.28-7.13 (m, 18H), 5.98 (br s, 1H, NH**H'**), 5.08 (s, 6H, C**H**NH_2); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 49.8 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.5 Hz, $^4J_{CF}$ = 2.9 Hz, *m*), 125.3 (q, $^1J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (sept, $^3J_{CF}$ = 4.0 Hz, *p*); dpen at 137.7 (s, *i*-Ph), 129.6, 129.4, 129.2 (3 × s, *o-, m-*, *p*-Ph), 66.0 (s, **C**HNH_2); nicotinate at[38] 152.0, 151.5, 137.2, 129.7, 123.6 (5 × s).

Λ-(*S*,*S*)-2^{3+} $4c^-Cl^-BAr_f^-$. Isolated according to the general procedure from Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^-BAr_f^-{\cdot}2H_2O$ and picolinic acid (0.011 g) as an orange solid (0.051 g, 0.029 mmol, 98%), mp 129.9 °C (open capillary; dec to green liquid with gradual darkening at lower temperatures). Anal. Calcd. for $C_{80}H_{64}BClCoF_{24}N_7O_2$ (1716.59): C 55.98, H 3.76, N, 5.71; found C 56.27, H 3.88, N 5.71. IR (powder film, cm^{-1}): 3029, 1609, 1579, 1549, 1387, 1354, 1274, 1118, 696.

NMR (acetone-d_6, δ/ppm):[37] ^1H (500 MHz) picolinate at 8.66 (br s, 1H), 8.15 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.85 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 7.43-7.35 (m, 1H); BAr_f^- at 7.83-7.79 (m, 8H, *o*), 7.69 (br s, 4H, *p*); dpen at 8.40 (br s, 4H, N**H**H'), 7.57-7.44 (m, 12H), 7.31-7.09 (m, 18H), 5.68 (br s, 4H, NH**H'**), 5.15 (s, 6H, C**H**NH_2); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.5 Hz, $^4J_{CF}$ = 2.9 Hz, *m*), 125.3 (q, $^1J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (sept, $^3J_{CF}$ = 4.0 Hz, *p*); dpen at 137.6 (s, *i*-Ph), 129.63 (double intensity), 129.58, (2 × s, *o-, m-*, *p*-Ph), 63.6 (s, **C**HNH_2); picolinate at 172.7 (s, **C**OO^-), 156.5, 149.7, 137.3, 125.4, 125.1 (5 × s).

Λ-(*S*,*S*)-2^{3+} $4d^-Cl^-BAr_f^-{\cdot}2H_2O$. Isolated according to the general procedure from Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^-BAr_f^-{\cdot}2H_2O$ and pyridine-2-sulfonic acid (0.014 g) as an orange solid (0.051 g, 0.029 mmol, 96%), mp 126.4-136.7 °C (open capillary; dec to green liquid). Anal. Calcd. for $C_{79}H_{64}BClCoF_{24}N_7O_3S{\cdot}2H_2O$ (1788.67): C 53.05, H 3.83, N, 5.48; found C 53.31, H 3.73, N 5.39. IR (powder film, cm^{-1}): 3216, 3079, 1610, 1457, 1354, 1274, 1118, 1024, 681.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) 2-pyridinesulfonate at 8.55 (d, $^3J_{HH}$ = 4.7 Hz, 1H), 8.10-7.99 (m, 2H), 7.56-7.48 (m, 1H); BAr_f^- at 7.81-7.78 (m, 8H, *o*), 7.67 (s, 4H, *p*); dpen at ca. 7.5 (N**H**H', overlapping Ar-C**H**, 2H), 7.49-7.39 (m, 12H), 7.31-7.12 (m, 18H), 5.25 (br s, 4H, NH**H'**), 5.05 (s, 6H, C**H**NH_2); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.5 Hz, $^4J_{CF}$ = 2.9 Hz, *m*), 125.4 (q, $^1J_{CF}$ = 274.5 Hz, **C**F_3), 118.4 (sept, $^3J_{CF}$ = 4.0 Hz, *p*); dpen at 136.9 (s, *i*-Ph), 129.8, 129.64, 129.62 (3 × s, *o-, m-*, *p*-Ph), 63.4 (s, **C**HNH_2); 2-pyridinesulfonate at 162.7, 150.2, 139.2, 126.1, 121.8 (6 × s).

Λ-(*S*,*S*)-2^{3+} 4e$^-$Cl$^-$$BAr_f^-$·2$H_2O$. Isolated according to the general procedure from Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2Cl$^-$$BAr_f^-$·2$H_2O$ and 3-(dimethylamino)benzoic acid (0.015 g) as an orange solid (0.053 g, 0.030 mmol, 99%), mp 99.8-106.9 °C (open capillary; dec to green liquid). Anal. Calcd. for $C_{83}H_{70}BClCoF_{24}N_7O_2$·2$H_2O$ (1793.45): C 55.55, H 4.16, N, 5.46; found C 56.39, H 4.39, N 5.42. IR (powder film, cm^{-1}): 1597, 1525, 1382, 1353, 1123, 696, 682.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) 3-(dimethylamino)benzoate at 7.51-7.39 (m, 3H), 6.9-6.82 (m, 1H), 2.98 (s, 6H, overlapping with H_2O); BAr_f^- at 7.83-7.78 (m, 8H, *o*), 7.69 (br s, 4H, *p*); dpen at 8.96 (br s, 4H, N**H**H'), 7.63-7.51 (m, 12H), 7.33-7.19 (m, 18H), 5.11 (br s, 9H, NH**H'** and C**H**NH_2); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.5 Hz, $^4J_{CF}$ = 2.9 Hz, *m*), 125.3 (q, $^1J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (sept, $^3J_{CF}$ = 4.0 Hz, *p*); dpen at 137.9 (s, *i*-Ph), 129.7, 129.67, 129.61, (3 × s, *o-, m-*, *p*-Ph), 63.5 (s, **C**HNH_2); 3-(dimethylamino)benzoate at 175.2 (s, **C**OO^-), 151.4, 139.4, 128.9, 128.2, 119.0, 115.0 (6 × s).

Λ-(*S*,*S*)-2^{3+} 4f$^-$Cl$^-$$BAr_f^-$·2$H_2O$. Isolated according to the general procedure from Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2Cl$^-$$BAr_f^-$·2$H_2O$ (0.100 g, 0.060 mmol), 6-chloronicotinic acid (0.028 g, 0.180 mmol), and Na_2CO_3 (0.021 g, 0.198 mmol) as an orange solid (0.103 g, 0.058 mmol, 96%), mp 129.4-133.3°C (open capillary; dec to green liquid). Anal. Calcd. for

$C_{83}H_{70}BClCoF_{24}N_7O_2 \cdot H_2O$ (1769.05): C 54.32, H 3.70, N, 5.54; found C 54.32, H 3.73, N 5.52. IR (powder film, cm^{-1}): 3040, 1609, 1585, 1537, 1393, 1354, 1275, 1119.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) 6-chloronicotinate at 8.99-8.94 (m, 1H), 8.37 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 2.3 Hz, 1H), 7.49 (dd, $^3J_{HH}$ = 8.2 Hz, $^5J_{HH}$ = 0.7 Hz, 1H); BAr_f^- at 7.89-7.77 (m, 8H, *o*), 7.70 (s, 4H, *p*); dpen at 8.55 (br s, 5H, N**H**H'), 7.60-7.52 (m, 12H), 7.39-7.23 (m, 18H), 5.29 (br s, 5H, NH**H'**), 5.20 (s, 6H, C**H**NH_2); 3.01 (br s, 4H, $\mathbf{H}_2O$); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 50.0 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.5 Hz, $^4J_{CF}$ = 2.9 Hz, *m*), 125.4 (q, $^1J_{CF}$ = 271.9 Hz, **C**F_3), 118.4 (sept, $^3J_{CF}$ = 4.0 Hz, *p*); dpen at 137.6 (s, *i*-Ph), 129.8, 129.7, 129.6 (3 × s, *o-, m-, p*-Ph), 63.5 (s, **C**HNH_2); 6-chloronicotinate at 171.9 (s, **C**OO^-), 153.3, 152.2, 140.8, 133.1, 124.1 (5 × s).

Λ-(*S*,*S*)-2^{3+} 4g$^-$Cl$^-$$BAr_f^-$·2$H_2O$. Isolated according to the general procedure from Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2Cl$^-$$BAr_f^-$·2$H_2O$ and 2-methoxynicotinic acid (0.014 g) as an orange solid (0.053 g, 0.030 mmol, 99%), mp 102.7-106.7 °C (open capillary; dec to green liquid). Anal. Calcd. for $C_{81}H_{66}BClCoF_{24}N_7O_3 \cdot 2H_2O$ (1782.65): C 54.58, H 3.96, N, 5.50; found C 55.14, H 3.90, N 5.46. IR (powder film, cm^{-1}): 3067, 1593, 1580, 1499, 1354, 1275, 1119.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) 2-methoxynicotinate at 8.22-8.13 (m, 1H), 8.07-7.97 (m, 1H), 7.01-6.90 (m, 1H), 3.96 (s, 3H); BAr_f^- at 7.85-7.79 (m, 8H, *o*), 7.70 (s, 4H, *p*); dpen at 8.69 (br s, 4H, N**H**H'), 7.64-7.46 (m, 12H), 7.36-7.17 (m, 18H), 5.21 (br s, 4H, NH**H'**), 5.14 (s, 6H, C**H**NH_2); $^{13}C\{^1H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^1J_{BC}$ = 49.8 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.0 Hz, $^4J_{CF}$ = 2.8 Hz, *m*), 125.4 (q, $^1J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (sept, $^3J_{CF}$ = 3.9 Hz, *p*); dpen at 137.7 (s, *i*-Ph), 129.7 (double intensity), 129.6 (2 × s, *o-, m-, p*-Ph), 63.5 (s, **C**HNH_2); 2-methoxynicotinate at 173.8 (s, **C**OO^-), 162.5, 147.8, 139.9, 123.9, 117.0 (5 × s), 53.5 (s, O**C**H_3).

Λ-(*S*,*S*)-2^{3+} 4h^{-}Cl^{-}BAr$_f^{-}$·H$_2$O. Isolated according to the general procedure from Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$·2H$_2$O (0.100 g, 0.060 mmol), 6-methylnicotinic acid (0.025 g, 0.180 mmol), and Na_2CO_3 (0.021 g, 0.20 mmol) as an orange solid (0.096 g, 0.055 mmol, 91%), mp 121.6-134.1 °C (open capillary; dec to green liquid). Anal. Calcd. for $C_{83}H_{70}BClCoF_{24}N_7O_2·H_2O$ (1748.64): C 55.64, H 3.92, N, 5.61; found C 55.56, H 3.96, N 5.61. IR (powder film, cm^{-1}): 3034, 1607, 1533, 1389, 1354, 1275, 1119.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) 2-methylnicotinate at 9.08 (apparent s, 1H), 8.21 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 2.1 Hz, 1H), 7.24, (m, 1H, overlapping with dpen), 2.54 (s, 3H); BAr$_f^{-}$ at 7.85-7.77 (m, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 8.72 (br s, 4H, N**H**H'), 7.62-7.46 (m, 12H), 7.36-7.19 (m, 18H), 5.16 (m, 10H, C**H**NH$_2$, NH**H'**); ^{13}C{^{1}H} (125 MHz) BAr$_f^{-}$ at 162.6 (q, $^1J_{BC}$ = 50.5 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^2J_{CF}$ = 31.5 Hz, $^4J_{CF}$ = 2.8 Hz, *m*), 125.3 (q, $^1J_{CF}$ = 271.8 Hz, **C**F$_3$), 118.4 (sept, $^3J_{CF}$ = 4.0 Hz, *p*); dpen at 137.7 (s, *i*-Ph), 130.9 (s, *o-, m-*, *p*-Ph), 63.5 (s, **C**HNH$_2$); 2-methylnicotinate at 173.4 (s, **C**OO^{-}), 160.7, 151.6, 137.8, 130.9, 122.8 (5 × s), 24.5 (s, **C**H$_3$).

Λ-(*S*,*S*)-2^{3+} 4i^{-}Cl^{-}BAr$_f^{-}$·2H$_2$O. Isolated according to the general procedure from Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$·2H$_2$O (0.100 g, 0.060 mmol), 6-aminonicotinic acid (0.025 g, 0.180 mmol), and Na_2CO_3 (0.021 g, 0.20 mmol) as an orange solid (0.095 g, 0.054 mmol, 90%), mp 118.4 °C (open capillary; dec to green liquid with gradual darkening at lower temperatures). Anal. Calcd. for $C_{83}H_{70}BClCoF_{24}N_7O_2·2H_2O$ (1767.64): C 54.36 H 3.93, N, 6.34; found C 54.34, H 3.87, N 6.11. IR (powder film, cm^{-1}): 3069, 1609, 1375, 1354, 1275, 1119.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) 6-aminonicotinate at 8.67 (d, $^4J_{HH}$ = 1.7 Hz, 1H), 8.00 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.2 Hz, 1H), 6.51, (dd, $^3J_{HH}$ = 8.5 Hz, $^5J_{HH}$ = 0.8 Hz, 1H), 5.70 (br s, 2H, N**H**$_2$); BAr$_f^{-}$ at 7.86-7.74 (m, 8H, *o*), 7.68 (s, 4H, *p*); dpen at 8.89 (br s, 2H, N**H**H'), 7.60-7.41 (m, 12H), 7.34-7.13 (m, 18H), 5.08 (br s, 8H, C**H**NH$_2$,

NH**H'**); $^{13}C\{^{1}H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^{1}J_{BC}$ = 49.7 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^{2}J_{CF}$ = 31.5 Hz, $^{4}J_{CF}$ = 2.8 Hz, *m*), 125.3 (q, $^{1}J_{CF}$ = 271.6 Hz, **C**F_3), 118.4 (sept, $^{3}J_{CF}$ = 4.0 Hz, *p*); dpen at 137.7 (s, *i*-Ph), 129.7 (double intensity), 129.6 (2 × s, *o-, m-*, *p*-Ph), 63.3 (s, **C**HNH_2); 6-aminonicotinate at 174.2 (s, **C**OO^-), 161.8, 151.8, 139.4, 123.2, 107.1 (5 × s).

Δ-(*S*,*S*)-2^{3+} 4i$^-$Cl$^-$$BAr_f^-$·2$H_2O$. Isolated according to the general procedure from Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2Cl$^-$$BAr_f^-$·$H_2O$ (0.200 g, 0.120 mmol), 6-aminonicotinic acid (0.050 g, 0.360 mmol), and Na_2CO_3 (0.042 g, 0.396 mmol) as an orange solid (0.202 g, 0.11 mmol, 95%), mp 110.5 °C (open capillary; dec to green liquid with gradual darkening at lower temperatures). Anal. Calcd. for C_{83}–$H_{70}BClCoF_{24}N_7O_2$·2H_2O (1767.64): C 54.36, H 3.93, N, 6.34; found C 54.02, H 3.97, N 6.37. IR (powder film, cm^{-1}): 3042, 1609, 1456, 1354, 1275, 1119.

NMR (acetone-d_6, δ/ppm):[37] ^{1}H (500 MHz) 6-aminonicotinate at 8.79 (apparent s, 1H), 7.94 (dd, $^{3}J_{HH}$ = 8.4 Hz, $^{4}J_{HH}$ = 2.2 Hz, 1H), 6.48, (d, $^{3}J_{HH}$ = 8.4 Hz, 1H), 5.85 (br s, 2H, N**H**$_2$); BAr_f^- at 7.84-7.79 (m, 8H, *o*), 7.69 (s, 4H, *p*); dpen at 7.75 (br s, 2H, N**H**H'), 7.57-7.42 (m, 12H), 7.32-7.09 (m, 18H), 6.18 (br s, 4H, NH**H'**) 5.07 (br s, 6H, C**H**NH_2); $^{13}C\{^{1}H\}$ (125 MHz) BAr_f^- at 162.6 (q, $^{1}J_{BC}$ = 50.0 Hz, *i*), 135.5 (br s, *o*), 130.0 (qq, $^{2}J_{CF}$ = 31.5 Hz, $^{4}J_{CF}$ = 2.8 Hz, *m*), 125.4 (q, $^{1}J_{CF}$ = 271.8 Hz, **C**F_3), 118.4 (sept, $^{3}J_{CF}$ = 4.0 Hz, *p*); dpen at 137.8 (s, *i*-Ph), 129.5, 129.4, 129.2 (3 × s, *o-, m-*, *p*-Ph), 66.1 (s, **C**HNH_2); 6-aminonicotinate at 173.5 (s, **C**OO^-), 161.7, 151.8, 139.4, 123.6, 107.2 (5 × s).

Nitroolefin addition products accessed by the general procedure for Chart 4.4

Dimethyl 2-(2-nitro-1-phenylethyl)malonate (7a). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (400 MHz) 7.35-7.26 (m, 3H), 7.23-7.18 (m, 2H), 4.97-4.80 (m, 2H), 4.23 (td, $^{3}J_{HH}$ = 8.9, 5.3 Hz, 1H), 3.85 (d, $^{3}J_{HH}$ = 9.0

Hz, 1H), 3.75 (s, 3H), 3.55 (s, 3H). $^{13}C\{^{1}H\}$ (100 MHz) 168.0, 167.4, 136.3, 129.2, 128.6, 128.0, 77.5, 54.9, 53.2, 53.0, 43.0 (11 × s). The enantiomeric excess was determined by HPLC with a Chiralcel AD column (98:2 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 32.9 min (major), 43.6 min (minor).[9a]

Diethyl 2-(2-nitro-1-phenylethyl)malonate (7a-Et). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.34-7.26 (m, 3H), 7.25-7.21 (m, 2H), 5.05-4.74 (m, 2H), 4.34-4.12 (m, 3H), 4.00 (q, $^{3}J_{HH}$ = 7.1 Hz, 2H), 3.82 (d, $^{3}J_{HH}$ = 9.4 Hz, 1H), 1.26 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H), 1.04 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 230 nm); t_R = 11.4 min (major), 24.4 min (minor).[39]

Diisopropyl 2-(2-nitro-1-phenylethyl)malonate (7a-*i*Pr). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz). 7.34-7.27 (m, 3H), 7.26-7.21 (m, 2H), 5.08 (sept, $^{3}J_{HH}$ = 6.3 Hz, 1H), 4.92 (dd, $^{2}J_{HH}$ = 12.9 Hz, $^{3}J_{HH}$ = 4.6 Hz, 1H), 4.87-4.79 (m, 2H), 4.20 (td, $^{3}J_{HH}$ = 9.5, 4.6 Hz, 1H), 3.76 (d, $^{3}J_{HH}$ = 9.6 Hz, 1H), 1.244 (d, $^{3}J_{HH}$ = 6.3 Hz, 3H), 1.242 (d, $^{3}J_{HH}$ = 6.3 Hz, 3H), 1.06 (d, $^{3}J_{HH}$ = 6.3 Hz, 3H), 1.01 (d, $^{3}J_{HH}$ = 6.3 Hz, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel OD column (95:5 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 10.5 min (major), 12.4 min (minor).[9a]

Dimethyl 2-(2-nitro-1-β-naphthylethyl)malonate (7b). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 8.18 (d, $^{3}J_{HH}$ = 8.6 Hz, 1H), 7.87 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H), 7.80 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H), 7.62 (ddd, $^{3}J_{HH}$ = 8.4, 6.8 Hz, $^{4}J_{HH}$ = 1.4 Hz, 1H), 7.53 (ddd, $^{3}J_{HH}$ = 8.0, 6.8 Hz, $^{4}J_{HH}$ = 1.1 Hz, 1H), 7.46-7.40 (m, 1H), 7.38 (d, $^{3}J_{HH}$ = 7.3 Hz, 1H), 5.27-5.20 (m, 1H), 5.18 (dd, $^{2}J_{HH}$ = 13.1 Hz, $^{3}J_{HH}$ = 8.2 Hz, 1H), 5.07 (dd, $^{2}J_{HH}$ = 13.1 Hz, $^{3}J_{HH}$ = 4.5 Hz, 1H), 4.11 (d, $^{3}J_{HH}$ = 7.6 Hz, 1H), 3.72 (s, 3H), 3.54 (s, 3H). The enantiomeric excess was determined by HPLC with a

Chiralcel OD column (70:30 v/v hexane/isopropanol, 1 mL/min, λ = 254 nm); t_R = 12.5 min (major), 35.5 min (minor).[9a]

Dimethyl 2-(2-nitro-1-α-naphthylethyl)malonate (7c). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 8.18 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 7.87 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.80 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.62 (ddd, $^3J_{HH}$ = 8.4, 6.9 Hz, $^4J_{HH}$ = 1.3 Hz, 1H), 7.58-7.48 (m, 1H), 7.47-7.35 (m, 2H), 5.27-5.24 (m, 1H), 5.18 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 8.2 Hz, 1H), 5.07 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 4.5 Hz, 1H), 4.11 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 3.72 (s, 3H), 3.54 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 254 nm); t_R = 14.4 min (major), 19.1 min (minor).[9a]

Dimethyl 2-(2-nitro-1-(4-methoxyphenyl)ethyl)malonate (7d). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.17-7.10 (m, 2H), 6.88-6.79 (m, 2H), 4.89 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.0 Hz, 1H), 4.82 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 9.2 Hz, 1H), 4.19 (td, $^3J_{HH}$ = 9.2, 5.0 Hz, 1H), 3.82 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.57 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AD column (80:20 v/v hexane/isopropanol, 1 mL/min, λ = 254 nm); t_R = 12.4 min (major), 18.0 min (minor).[9a]

Dimethyl 2-(2-nitro-1-(4-nitrophenyl)phenylethyl)malonate (7e). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 8.24-8.17 (m, 2H), 7.61-7.36 (m, 2H), 5.07-4.82 (m, 2H), 4.37 (td, $^3J_{HH}$ = 8.9, 5.2 Hz, 1H), 3.88 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 22.7 min (major), 35.1 min (minor).[40]

Dimethyl 2-(2-nitro-1-(3,4-dioxolophenyl)ethyl)malonate (7f). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 6.85-

6.59 (m, 3H), 5.95 (s, 2H), 5.01-4.58 (m, 2H), 4.15 (td, $^3J_{HH}$ = 9.3, 4.9 Hz, 1H), 3.80 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 44.8 min (major), 53.3 min (minor).[13]

Dimethyl 2-(2-nitro-1-(4-methoxycarbonyl)phenylethyl)malonate (7g). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 8.00 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.32 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 5.25-4.71 (m, 2H), 4.31 (td, $^3J_{HH}$ = 8.8, 5.3 Hz, 1H), 3.90 (s, 3H), 3.87 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 3.77 (s, 3H), 3.57 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 28.5 min (major), 42.8 min (minor).[41]

Dimethyl 2-(2-nitro-1-(2-(trifluoromethyl)phenylethyl)malonate (7h). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz). 7.72 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.53 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 7.43 (ddt, $^3J_{HH}$ = 7.7, 6.7 Hz, $^4J_{HH}$ = 1.0 Hz, 1H), 7.37 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 5.16 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 7.7 Hz, 1H), 4.94 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 4.5 Hz, 1H), 4.64 (td, $^3J_{HH}$ = 7.6, 4.5 Hz, 1H), 4.10 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel OD column (95:5 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 12.0 min (minor), 22.6 min (major).[9a]

Dimethyl 2-(2-nitro-1-(2-acetoxyphenyl)ethyl)malonate (7i). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.32 (ddd, $^3J_{HH}$ = 8.1, 7.2 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.26 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.23-7.18 (m, 1H), 7.14 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.2 Hz, 1H), 5.00-4.82 (m, 2H), 4.49 (td, $^3J_{HH}$ = 8.1, 5.3 Hz, 1H), 3.92 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 3.74 (s, 3H), 3.59 (s, 3H), 2.39 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel OD

column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 17.3 min (minor), 24.5 min (major).[9a]

Dimethyl 2-(2-nitro-1-(2-benzoyloxyphenyl)ethyl)malonate (7j). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 8.36-8.22 (m, 2H), 7.75-7.63 (m, 1H), 7.60-7.53 (m, 2H), 7.42-7.31 (m, 2H), 7.29-7.21 (m, 2H), 4.98 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 8.6 Hz, 1H), 4.91 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 4.9 Hz, 1H), 4.59 (td, $^3J_{HH}$ = 8.5, 4.9 Hz, 1H), 3.96 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 3.72 (s, 3H), 3.52 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 16.1 min (major), 25.7 min (minor).[9a]

Dimethyl 2-(2-nitro-1-(2-benzyloxyphenyl)ethyl)malonate (7k). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.53-7.46 (m, 2H), 7.45-7.40 (m, 2H), 7.39-7.34 (m, 1H), 7.24 (ddd, $^3J_{HH}$ = 8.3, 7.4 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.17 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 6.93 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.0 Hz, 1H), 6.90 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.1 Hz, 1H), 5.14 (d, $^2J_{HH}$ = 11.8 Hz, 1H), 5.11 (d, $^2J_{HH}$ = 11.8 Hz, 1H) 5.05 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 9.4 Hz, 1H), 4.84 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 4.44 (td, $^3J_{HH}$ = 9.6, 4.5 Hz, 1H), 4.17 (d, $^3J_{HH}$ = 9.9 Hz, 1H), 3.72 (s, 3H), 3.50 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel OD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 10.8 min (minor), 17.9 min (major).[9a]

Dimethyl 2-(2-nitro-1-(2-bromophenyl(ethyl)malonate (7l). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.61 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.0 Hz, 1H), 7.33-7.20 (m, 2H), 7.16 (td, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 5.13 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 8.5 Hz, 1H), 4.96 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 4.5 Hz, 1H), 4.77 (td, $^3J_{HH}$ = 8.2, 4.5 Hz, 1H), 4.11 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 3.73

(s, 3H), 3.66 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (70:30 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 8.3 min (minor), 14.1 min (minor).[42]

Dimethyl 2-(2-nitro-1-(2-methylphenyl)ethyl)malonate (7m). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.20-7.08 (m, 4H), 4.90 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 5.2 Hz, 1H), 4.85 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.8 Hz, 1H), 4.57 (td, $^3J_{HH}$ = 9.0, 5.2 Hz, 1H), 3.83 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 2.44 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (75:25 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 9.8 min (major), 19.1 min (minor).[43]

Dimethyl 2-(2-nitro-1-furylethyl)malonate (7n). This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.34 (dd, $^3J_{HH}$ = 1.9 Hz, $^4J_{HH}$ = 0.8 Hz, 1H), 6.29 (dd, $^3J_{HH}$ = 3.3, 1.9 Hz, 1H), 6.22 (dt, $^3J_{HH}$ = 3.3 Hz, $^4J_{HH}$ = 0.7 Hz, 1H), 4.98-4.84 (m, 2H), 4.38 (td, $^3J_{HH}$ = 8.2, 5.2 Hz, 1H), 3.94 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel OD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 10.7 min (minor), 21.4 min (major).[9a]

(*E*)-Dimethyl 2-(1-nitro-4-phenylbut-3-en-2-yl)malonate (7o). This known compound was obtained as a colorless oil. The ^{1}H NMR spectrum matches those reported earlier.[s10] NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.35-7.28 (m, 5H), 6.58 (d, $^3J_{HH}$ = 15.7 Hz, 1H), 6.10 (dd, $^3J_{HH}$ = 15.8, 9.0 Hz, 1H), 4.83-4.62 (m, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.73-3.71 (m, 2H). The nantiomeric excess was determined by HPLC with a Chiralcel IC column (99:1 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 46.2 min (minor), 55.4 min (major).[41]

Di-*t*-butyl azodicarboxylate addition products accessed by the general procedure for Chart 4.5

***N*,*N*'-Bis(t-butoxycarbonyl)-1-hydrazino-2-oxocyclopentanecarboxylic acid methyl ester (10a).** This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^1H (500 MHz) 6.70-6.03 (m, 1H), 3.76 (s, 3H), 2.97-2.03 (m, 5 H), 2.03-1.81 (s, 1H), 1.53-1.29 (m, 18H). The enantiomeric excess was determined by HPLC with a Chiralcel AD column (96:4 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 13.6 min (major), 20.0 min (minor).[9b]

***N*,*N*'-Bis(t-butoxycarbonyl)-1-hydrazino-2-oxocyclopentanecarboxylic acid ethyl ester (10b).** This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^1H (500 MHz) 6.69-6.02 (m, 1H), 4.34-4.11 (m, 2H), 2.92-2.04 (m, 5H), 2.05-1.82 (m, 1H), 1.54-1.35 (m, 18H), 1.34-1.22 (m, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AD column (96:4 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 10.6 min (major), 15.8 min (minor).[9b]

***N*,*N*'-Bis(t-butoxycarbonyl)-1-acetyl-1-hydrazino-2-oxocyclopentane (10c).** This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^1H (500 MHz) 6.55-5.99 (m, 1H), 2.93-1.58 (m, 9H), 1.52-1.36 (m, 18H). The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 5.8 min (major), 11.0 min (minor).[9b]

***N*,*N*'-Bis(t-butoxycarbonyl)-2-hydrazino-2-methyl-3-oxobutyric acid ethyl ester (10d).** This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^1H (500 MHz) 6.44-5.84 (m, 1H), 4.35-4.08 (m, 2H), 3.76 (s, 3H), 2.47-2.17 (m, 3 H), 1.65-1.56 (m, 3H), 1.55-1.36 (m, 18H), 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 14.0 min (minor), 19.4 min (major).[9b]

***N,N'*-Bis(t-butoxycarbonyl)-1-acetyl-1-hydrazino-2-oxocyclohexane (10e).** This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^1H (500 MHz) 6.30-5.66 (m, 1H), 3.19-1.7 (m, 2H), 1.53-1.31 (m, 18H). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 15.6 min (minor), 41.6 min (major).[44]

***N,N'*-Bis(t-butoxycarbonyl)-1-hydrazino-1,2,3,4-tetrahydro-1-oxonaphthalene-2-carboxylic acid ethyl ester (10f).** This known compound was obtained as a colorless oil. NMR ($CDCl_3$, δ/ppm): ^1H (500 MHz) 7.95-7.84 (m, 1H), 7.54-7.38 (m, 1H), 7.37-7.17 (m, 2H), 6.38-6.01 (m, 1H), 4.38-4.17 (m, 2H), 3.63-2.54 (m, 4H), 1.54-1.09 (m, 21H). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (80:20 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 9.3 min (minor), 11.6 min (major).[9b]

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5. SOLVENT FREE APPLICATION OF CHIRAL CO(III) WERNER COMPLEXES IN ENANTIOSELECTIVE CATALYSIS VIA BALL MILLING

5.1. Introduction

Over the last several decades there has been a persistent trend to reduce or eliminate the use of solvents in synthesis.[1] Among many strategies, the use of ball mills has received particular attention, typically for solid/solid reactions.[2] Several groups have successfully carried out asymmetric C–C, C–N, C–O, and C–X bond forming reactions in solvent free conditions.[3]

A family of catalysts has been developed derived from the chiral cobalt(III) trication $[Co(en)_3]^{3+}$ ($\mathbf{1}^{3+}$)[4] which Werner resolved into enantiomeric salts some 110 years ago.[5] Initial interest concerned the possible use of ball mills in the synthesis of Werner salts, where there are sometimes issues of diastereoselectivities. In some cases, the counter anions affect diastereoselectivites, and additives such as charcoal can promote epimerizations.[6] However, the use of the aforementioned catalysts in solvent-free conditions was regarded as having broader relevance for asymmetric synthesis.

Figure 5.1 depicts one example of an enantioselective Michael type addition that has previously been carried out with the hydrogen bond donor catalyst $[Co((S,S)\text{-dpen})_3]^{3+}$ $2Cl^{-}BAr_f^{-}$ ((*S*,*S*)-$\mathbf{2}^{3+}$), where BAr_f^{-} is the non-coordinating lipophilic anion ($B(3,5\text{-}C_6H_3(CF_3)_2)_4^{-}$), and the base Et_3N in solvent – usually acetone.[7] In this chapter, it is represented that such reactions can be carried out under solvent free conditions in ball mills, and realizing considerably faster rates, with only a slight decrease in enantioselectivities.

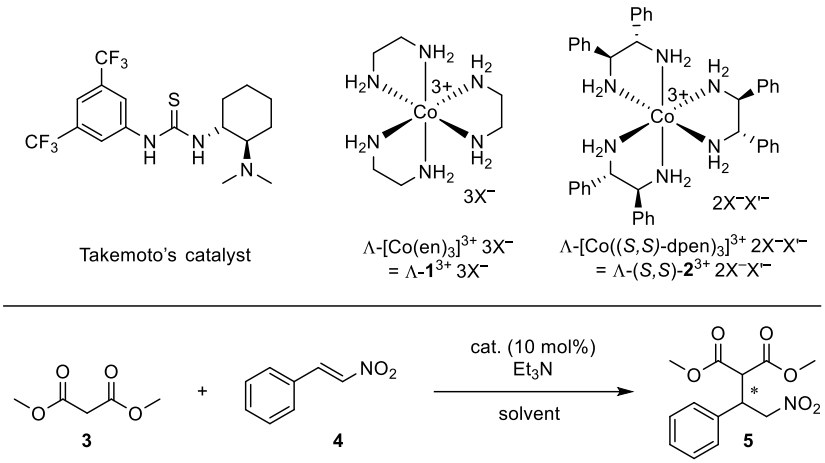


Figure 5.1. Examples of hydrogen bond-donor catalysts and the asymmetric Michael addition of dimethyl malonate (**3**) to *trans*-β-nitrostyrene (**4**).

5.2. Results

Having previously demonstrated the effectiveness of these catalysts in the asymmetric Michael addition of dimethyl malonate (**3**) to *trans*-β-nitrostyrene (**4**) shown in Figure 5.1, it was logical to use this as the test reaction. The reaction was first carried out using similar conditions to the most successful solution-phase reactions, where the catalyst is Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^{-}BAr_f^{-}$ and triethylamine is employed as the base in one stoichiometric equivalent. The reactants are combined in a disposable milling vial as shown in Figure 5.2. After 30 minutes of milling at room temperature, the entire reaction mixture was taken up in a deuterated solvent and analyzed by ^{1}H NMR. The reaction mixture showed complete conversion by comparison to internal standard. However, only a moderate ee of 44% was observed (entry 2, Table 5.1).

Next, pyridine was used under identical conditions as it was hypothesized the high pK_a of Et_3N may be too "aggressive". The lower pK_a of pyridine gave similar conversion (96%) but showed significantly improved ee (77%). Other bases are shown in Figure 5.1, though pyridine proved to be most effective; there was no benefit observed from chiral bases.

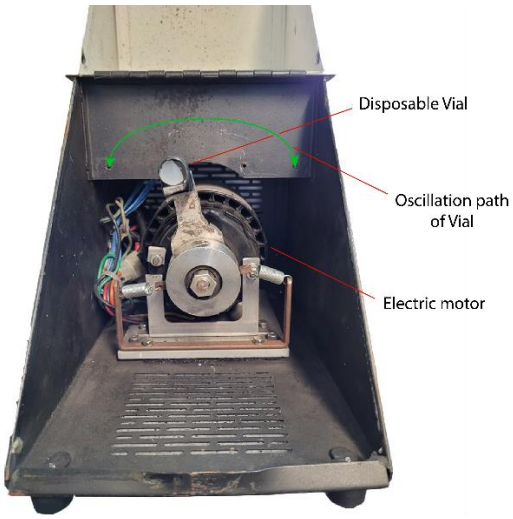


Figure 5.2. Ball mill features a polystyrene vial attached to an oscillating arm moved by an electric motor.

Table 5.1. Comparison of bases for the enantioselective addition of dimethyl malonate to *trans*-β-nitrostyrene.

entry	catalyst[a]	base	pK_a	ee (%) (config)[b]	yield (%)[c]
1	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	-	-	-	10
2	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	Et_3N	10.7	44 (*R*)	99
3	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	NMM	7.1	67 (*R*)	99[d]
4	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	Py	5.2	77 (*R*)	96
5	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	3-Br Py	2.9	53 (*R*)	15
6	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	*rac*-1-$PhCH_2NH_2CH_3$	9.5	55 (*R*)	99
7	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	(*S*)-1-$PhCH_2NH_2CH_3$	9.5	57 (*R*)	99
8	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	(*S*)-(4-Py)EtOH[e]	5.7[f]	76 (*R*)	90
9	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$	(*R*)-(2-Py)EtOH[g]	5.3[f]	71 (*S*)	59

[a]Reactions were conducted according to the general procedure with *trans*-β-nitrostyrene (0.060 mmol), Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ (10 mol%), base (0.060 mmol), and dimethyl malonate (0.066 mmol) for 30 min. [b]Determined by Chiral HPLC.[c]Yields were determined by ^{1}H NMR relative to the internal standard Ph_2SiMe_2. [d]20 minute reaction time. [e](*S*)-1-(4-pyridyl)ethanol.[f]Estimated, see ref. 8. [g] (*R*)-1-(2-pyridyl)ethanol.

Next, ten catalysts were analyzed differing predominantly in the anions using pyridine as the base, shown in Table 5.2. The anions are clearly significant on both the yield and the enantiomeric excess of the reaction. Simply changing chloride anions in Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ to bromide anions (entry 2) reduces the yield from 96% to 58% and

the ee from 77% to 71%. Changing to even weaker hydrogen bonding anions BF_4^- (entry 3) further diminishes the yield and ee to 36% and 56%, respectively.

Additionally, removal of the tightly binding halogens such as in entry 4 and 5 (Λ-(*S*,*S*)-**2**$^{3+}$ 3BAr_f^- and Λ-(*S*,*S*)-**2**$^{3+}$ 3BF_4^-) give equally low ee values of 46% and 48%, respectively. When one chloride anions is replaced with an anion containing a nitrogenous base,[8] yields remained excellent while ee values suffered only slightly (entries 6-8) in comparison to pyridine as an external base. Finally, the delta diastereomer Δ-(*S*,*S*)-**2**$^{3+}$ 2$Cl^-BAr_f^-$ gives excellent conversion but only moderate ee (50%), though this result was expected as this diastereomer is not as selective for this reactions.[7,10]

While the kinetic energy of the milling may generate some heat, the reaction vessel heats to ca. 50 °C in 30 minutes due to the radiant heat of the motor. A technique employed to mitigate this involves running the reaction in 10-15 minute intervals followed by equally timed periods of cooling; this gave no advantage in this reaction.

Table 5.2. Comparison of catalysts for the enantioselective addition of dimethyl malonate to *trans*-β-nitrostyrene.

entry	catalyst[a]	base	ee (%) (config)[b]	yield (%)[c]
1	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	Py	77 (*R*)	96
2	Λ-(*S*,*S*)-**2**$^{3+}$ 2Br^{-}BAr$_f^{-}$	Py	71 (*R*)	58
3	Λ-(*S*,*S*)-**2**$^{3+}$ 2BF$_4^{-}$BAr$_f^{-}$	Py	56 (*R*)	36
4	Λ-(*S*,*S*)-**2**$^{3+}$ 3BAr$_f^{-}$	Py	46 (*R*)	95
5	Λ-(*S*,*S*)-**2**$^{3+}$ 3BF$_4^{-}$	Py	48 (*R*)	31
6	Λ-(*S*,*S*)-**2**$^{3+}$ Cl^{-}BAr$_f^{-}$Nic^{-}	-	73 (*R*)	67
7	Λ-(*S*,*S*)-**2**$^{3+}$ Cl^{-}BAr$_f^{-}$Nic-NH$_2^{-}$	-	70 (*R*)	99
8	Λ-(*S*,*S*)-**2**$^{3+}$ Cl^{-}BAr$_f^{-}$Nic-OMe^{-}	-	68 (*R*)	99
9	Λ-(*S*,*S*)-**3**$^{3+}$ 3Cl^{-}	Et$_3$N	30 (*R*)	50
10	Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	Py	50 (*S*)	99

[a]Reactions were conducted according to the general procedure with *trans*-β-nitrostyrene (0.060 mmol), catalyst (10 mol%), pyridine (0.060 mmol), and dimethyl malonate (0.066 mmol) for 30 min. [b]Determined by Chiral HPLC.[c]Yields were determined by ^{1}H NMR relative to the internal standard Ph$_2$SiMe$_2$.

Additional reaction factors were explored such as catalyst loading (Table 5.3), reaction time (Table 5.4), the number of milling balls (Table 5.5), and the relative reaction scale (Table 5.6). Though variables at extreme low ends of the aforementioned criteria gave understandably poor results in some cases, virtually no influence of increased catalyst load or longer reaction time was observed. Surprisingly, there was little effect when the mass of material in the vial was increased by 50%, or when the reaction time was decreased by 30%.

After assessment of all the assayed variables, optimal conditions were determined for a substrate scope and 12 nitroolefins were evaluated. There seemed to be no recognizable trend in the influence of steric or electronic groups on yields or ee values. Average yields and ee values were 89% and 74%, while the median ee value was 80%. When diethyl malonate was used, the yield remained high (94%) while the ee suffered (54%). The diisopropyl malonate gave only a 28% yield.

Table 5.3. Comparison of catalyst loading for the enantioselective addition of dimethyl malonate to *trans*-β-nitrostyrene.

entry	catalyst[a]	loading (%)	ee (%) (config)[b]	yield (%)[c]
1	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	5	76 (*R*)	70
2	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	10	77 (*R*)	96
3	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	15	74 (*R*)	93
4	Λ-(*S*,*S*)-**2**$^{3+}$ Cl^{-}BAr$_f^{-}$Nic-NH$_2^{-}$	5	73 (*R*)	70
5	Λ-(*S*,*S*)-**2**$^{3+}$ Cl^{-}BAr$_f^{-}$Nic-NH$_2^{-}$	10	70 (*R*)	99

[a]Reactions were conducted according to the general procedure with *trans*-β-nitrostyrene (0.060 mmol), Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$ (10 mol%), pyridine (0.060 mmol), and dimethyl malonate (0.066 mmol) for 30 min. [b]Determined by Chiral HPLC. [c]Yields were determined by ^{1}H NMR relative to the internal standard Ph_2SiMe_2.

Table 5.4. Comparison of reaction time for the enantioselective addition of dimethyl malonate to *trans*-β-nitrostyrene.

entry	catalyst[a]	time	ee (%) (config)[b]	yield (%)[c]
1	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	10 min	76 (*R*)	62
2	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	20 min	72 (*R*)	97
3	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	30 min	77 (*R*)	96

[a]Reactions were conducted according to the general procedure with *trans*-β-nitrostyrene (0.060 mmol), Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$ (10 mol%), pyridine (0.060 mmol), and dimethyl malonate (0.066 mmol) for 30 min. [b]Determined by Chiral HPLC. [c]Yields were determined by ^{1}H NMR relative to the internal standard Ph_2SiMe_2.

Table 5.5. Comparison of milling conditions for the enantioselective addition of dimethyl malonate to *trans*-β-nitrostyrene.

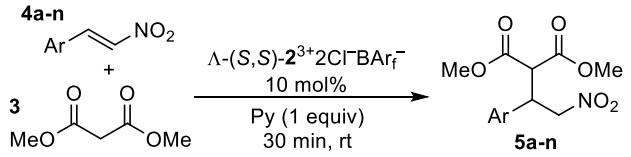
entry	catalyst[a]	milling balls	ee (%) (config)[b]	yield (%)[c]
1	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	2	76 (*R*)	98
2	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	3	77 (*R*)	96
3	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$	4	73 (*R*)	99

[a]Reactions were conducted according to the general procedure with *trans*-β-nitrostyrene (0.060 mmol), Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$ (10 mol%), pyridine (0.060 mmol), and dimethyl malonate (0.066 mmol) for 30 min. [b]Determined by Chiral HPLC. [c]Yields were determined by ^{1}H NMR relative to the internal standard Ph_2SiMe_2.

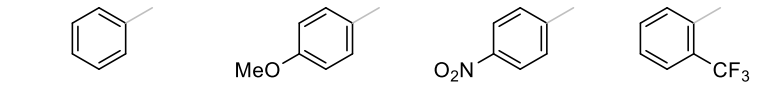
Table 5.6. Comparison of reaction scale for the enantioselective addition of dimethyl malonate to *trans*-β-nitrostyrene.

entry	catalyst[a]	relative scale	ee (%) (config)[b]	yield (%)[c]
1	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^-$	0.5	69 (*R*)	85
2	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^-$	1	77 (*R*)	96
3	Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^-$	1.5	73 (*R*)	95

[a]Reactions were conducted according to the experimental with *trans*-β-nitrostyrene, Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-} BAr$_f^-$ (10 mol%), pyridine (100 mol%), and dimethyl malonate for 30 min. [b]Determined by Chiral HPLC.[c]Yields were determined by ^{1}H NMR relative to the internal standard Ph_2SiMe_2.



aryl groups[a]

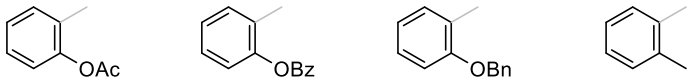


5a, 96%
77% ee (*R*)

5b, 92%
30% ee (*R*)

5c, 85%
76% ee (*R*)

5d, 99%
83% ee (*R*)

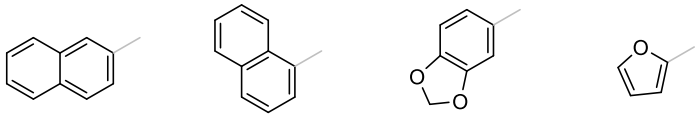


5e, 90%
89% ee (*R*)

5f, 80%
80% ee (*R*)

5g, 97%
84% ee (*R*)

5h, 86%
52% ee (*R*)



5i, 82%
74% ee (*R*)

5j, 81%[d]
84% ee (*R*)

5k, 88%
79% ee (*R*)

5l, 87%
84% ee (*R*)

[a]Reactions were conducted according to the general procedure with nitroolefin (0.060 mmol), Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^-$ (10 mol%), pyridine (0.060 mmol), and dimethyl malonate (0.066 mmol) for 30 min. [b]Determined by Chiral HPLC.[c]Yields were determined by 1H NMR relative to the internal standard Ph2SiMe2. [d]20 min reaction time.

Chart 5.1. Substrate scope for the enantioselective addition of dimethyl malonate to trans-β-nitrostyrene.

5.3. Discussion

Asymmetric catalysis under ball-milling conditions has been well explored over the last decade.[11] Chemistry with hydrogen bond-donors has been detailed in previous reports where thiourea catalysts similar to Takemoto's have been employed for asymmetric Baylis-Hillman reactions[12]. Similar Michael additions to nitroolefins have been carried out with the nucleophilic acetylacetone[13] or nitroketones[14], catalyzed with chiral squaramides or thioureas, respectively. The addition of dimethyl malonate to *trans*-β-nitrostyrene can be carried out with a cichona-derived catalyst in 30 minutes with 80% conversion and 91% ee by Xu, et al.[13]

I was pleasantly surprised to see that, under optimized conditions, Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-} BAr$_f^{-}$ gave similarly good conversion and high ee for a variety of substrates. This demonstrates the versatility of this complex, showing little deviation in conversion and enantioselectivity when applied to both electron rich and electron deficient nitroolefins. It is worth noting, however, that there is diminished enantioselectivity when di*ethyl* malonate is used in place of the standard dimethyl malonate, while the diisopropyl gave only 28% conversion – a trend observed in previous studies as well.[15] A key advantage of these conditions is the reduced reaction time. While solution phase reactions often require reaction times as long as 24 hours at reduced temperature (0 °C), ball mill reactions were complete in as little as 20 minutes at ambient temperature.

It was also observed that there was a fairly significant dependence upon the strength of the base with weaker bases giving significantly increased ee values, but only down to a certain pK_a; 3-bromopyridine gave poor conversion and enantioselectivity while the slightly stronger pyridine effected greater selectivity than *N*-methylmorpholine and triethylamine. In solution phase reactions, an opposite trend is generally observed, with

weaker bases giving poor results, and bases stronger than triethylamine leading to decomposition of the catalyst (NaOH, DABCO, etc.)[7,15]

While relative reaction scale, the number of milling balls, the catalyst loading, and the presence of enantiopure bases all seemed to have no effect on the reaction, the anions were a clear determinant of selectivity. In the first three entries of Table 5.2, a trend is observed where the halide (or BF_4^-) becomes increasingly weak in binding to the cation, correlating to a decrease in enantioselectivity. Based on this trend, one may postulate that the catalyst Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2F^-BAr_f^-$, with strongly bound F^- anions, would give even greater selectivity, though this catalyst has not yet be synthetically accessible.

Finally, the effect of temperature cannot be ignored. It is customary to conduct this reaction (when in solution phase) at decreased temperatures as this generally gives an advantage in stereoselectivity.[7,16] However, despite this solution-phase behavior, I have not found this to be analogous in the ball mill conditions. As described earlier, the reaction vessel heats gradually from the residual heat of the motor. If the reaction is instead conducted in increments of 10 minutes on/20 minutes off for the same total milling time, there is no advantage observed for the enantioselectivity. Though the research group does not does not currently have equipment to conduct the reaction at lower temperatures, the trend indicates there would be no significant advantage to milling at 0 °C or colder.

5.4. Conclusion

Co(III) complexes have been previously highly successful in solution phase catalysis, giving high conversions and enantioselectivities. Applications in mechanocatalysis showed surprisingly strong results, with mild basis giving superior ee values to stronger bases. Little effect from reaction conditions was also observed with the exception of catalyst composition, demonstrating the robustness of this catalyst and its versatility to conduct asymmetric Michael additions in significantly shorter reaction times

and without solvent with similar enantioselectivities and conversion to solution phase reactions.

5.5. Experimental

General: All reactions and workups were conducted in air. NMR spectra were recorded on standard FT spectrometers at ambient probe temperatures (500 MHz) or 298 K (400 MHz). Chemical shifts (δ/ppm) were generally referenced to solvent signals (^{1}H: $CHCl_3$, 7.26; acetone-d_5, 2.05; ^{13}C: $CDCl_3$, 77.16). HPLC analyses were carried out with a Shimadzu instrument package (pump/autosampler/detector LC-20AD/SIL-20A/SPD-M20A) Yields were calculated with ^{1}H NMR of the crude reaction mixture by relative integration of the internal standard (Ph_2SiMe_2, SiC**H**$_3$) to the benzylic C**H** of the product (generally found as a *td* at ca. 4.2 ppm).

The catalysts or catalyst precursors Λ-(*S*,*S*)-**1**$^{3+}$ 3Cl$^-$, Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H$_2$O, Δ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·H$_2$O, Λ-(*S*,*S*)-**1**$^{3+}$ 2BF$_4^-$BAr$_f^-$, Λ-(*S*,*S*)-**1**$^{3+}$ 2Br$^-$BAr$_f^-$, Λ-(*S*,*S*)-**1**$^{3+}$ 3BAr$_f^-$, and Λ-(*S*,*S*)-**1**$^{3+}$ 3BF$_4^-$ were prepared as previously described.[7,10,15] Nitroolefins **3d-g** were used from a previous work, in which they were prepared from a Henry reaction with nitromethane.[7] Nitroolefins **3a**, **3b**, **3k** and **3l** are available commercially and were used as received. The syntheses of **3c, 3i**, **3j**, and **3h** were adapted from literature procedures.[17] Ammonium acetate, dimethyl malonate, diethyl malonate, diisopropyl malonate, 2-methoxynicotinic acid, nicotinic acid, 6-aminonicotinic acid, Ph_2SiMe_2, and *trans*-β-nitrostyrene were used as received. Routine chemicals not noted above were used as received from common commercial sources.

General Procedure for Nitroolefin Addition: A polystyrene grinding vial was charged with *trans*-β-nitrostyrene (9.0 mg, 0.060 mmol, 1.0 equiv), dimethyl malonate (7.6 μL, 0.066 mmol, 1.1 equiv), Ph_2SiMe_2 (1.3 μL, internal standard), pyridine (4.9 μL, 0.060 mmol, 1.0 equiv), and Λ-(*S*,*S*)-**1**$^{3+}$ 2Cl$^-$BAr$_f^-$·2H$_2$O (10.2 mg, 0.0060 mmol, 10

mol%). Three milling balls were added and the vial capped and milled for 30 minutes. The residue was dissolved in acetone-d_6 and immediately assayed via ^{1}H NMR. The solution was then evaporated to dryness and the residue purified by silica column (glass pipette, EtOAc:Hexanes, 25:75 v/v). The product-containing fractions were combined and taken down by vacuum to give the desired product **5a** as a colorless oil. Enantiomeric excess was determined by HPLC with a Chiralcel AD column (98:2 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 32.9 min (major), 43.6 min (minor).[7]

NMR ($CDCl_3$, δ/ppm): ^{1}H (400 MHz): 7.36-7.27 (m, 3H), 7.25-7.19 (m, 2H), 4.93 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 5.4 Hz, 1H) 4.88 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 8.8 Hz, 1H), 4.24 (td, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 3.86 (d, $^3J_{HH}$ = 9.0 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H); ^{13}C{^{1}H} (100 MHz): 168.0, 167.4, 136.3, 129.2, 128.6, 128.0, 77.5, 54.9, 53.2, 53.0, 43.0 (11 × s).

Nitroolefin Substrate Scope

Diethyl 2-(2-nitro-1-phenylethyl)malonate (5a-Et). This known compound was obtained as a colorless oil according to the procedure for Scheme 1. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.44-7.12 (m, 5H), 4.92 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 4.8 Hz, 1H), 4.86 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 9.2 Hz, 1H), 4.31-4.16 (m, 3H), 4.01 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 3.82 (d, $^3J_{HH}$ = 9.4 Hz, 1H), 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 2H), 1.05 (t, $^3J_{HH}$ =7.1 Hz, 2H); ^{13}C{^{1}H} (125 MHz) 167.6, 167.0, 136.4, 129.1, 128.5, 128.2, 77.8, 62.3, 62.0, 55.1, 43.1, 14.1, 13.9 (13 x s). The enantiomer excess was determined by HPLC with a Chiralcel AD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 230 nm); t_R = 11.4 min (major), 24.4 min (minor).[18]

Diisopropyl 2-(2-nitro-1-phenylethyl)malonate (5a-*i*Pr). This known compound was not isolated as a pure product but identified by ^{1}H NMR as part of a crude reaction mixture.

Dimethyl 2-(2-nitro-1-(4-methoxyphenyl)ethyl)malonate (5b). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): 7.19-7.09 (m, 2H), 6.88-6.76 (m, 2H), 4.89 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.0 Hz, 1H), 4.83 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 9.2 Hz, 1H), 4.19 (td, $^3J_{HH}$ = 9.1, 5.0 Hz, 1H), 3.83 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.57 (s, 3H). $^{13}C\{^1H\}$ (100 MHz): 168.0, 167.4, 159.6, 129.1, 128.0, 114.5, 77.8, 55.4, 55.0, 53.1, 53.0, 42.5 (12 × s). The enantiomer excess was determined by HPLC with a Chiralcel AD column (80:20 v/v hexane/isopropanol, 1 mL/min, λ = 254 nm); t_R = 12.4 min (major), 18.0 min (minor).[7]

Dimethyl 2-(2-nitro-1-(4-nitrophenyl)phenylethyl)malonate (5c). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): 8.27-8.00 (m, 2H), 7.56-7.37 (m, 2H), 4.97 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 4.92 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 8.9 Hz, 1H), 4.37 (td, $^3J_{HH}$ = 8.9, 5.1 Hz, 1H), 3.88 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H); $^{13}C\{^1H\}$ (100 MHz): 167.3, 166.7, 143.5, 129.1, 124.2, 76.6, 54.1, 53.3, 53.2, 42.5 (10 × s)[19] The enantiomer excess was determined by HPLC with a Chiralcel OD-H column (80:20 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 22.7 min (major), 35.1 min (minor).[20]

Dimethyl 2-(2-nitro-1-(2-(trifluoromethyl)phenylethyl)malonate (5d). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): 7.75-7.66 (m, 1H), 7.60-7.48 (m, 1H), 7.47-7.39 (m, 1H), 7.37 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 5.16 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 4.94 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 4.5 Hz, 1H), 4.65 (td, $^3J_{HH}$ = 7.5, 4.5 Hz, 1H), 4.11 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H). The enantiomer excess was determined by HPLC with a Chiralcel OD column (95:5 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 12.0 min (minor), 22.6 min (major).[7]

Dimethyl 2-(2-nitro-1-(2-acetoxyphenyl)ethyl)malonate (5e). This known

compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): ^{1}H (400 MHz) 7.28-7.04 (m, 4H), 4.86 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 4.81 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 8.6 Hz, 1H), 4.43 (td, $^3J_{HH}$ = 8.2, 5.5 Hz, 1H), 3.85 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 3.69 (s, 3H), 3.47 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} (100 MHz) 169.2, 168.0, 167.4, 148.7, 129.4, 128.5, 128.2, 126.5, 123.5, 76.5, 53.8, 53.1 (double intensity), 36.7, 21.2 (14 x s). The enantiomer excess was determined by HPLC with a Chiralcel OD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 17.3 min (minor), 24.5 min (major).[7]

Dimethyl 2-(2-nitro-1-(2-benzoyloxyphenyl)ethyl)malonate (5f). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): 8.36-8.20 (m, 2H), 7.74-7.64 (m, 1H), 7.60-7.52 (m, 2H), 7.42-7.31 (m, 2H), 7.30-7.22 (m, 2H), 4.98 (dd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 8.5 Hz, 1H), 4.91 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 4.9 Hz, 1H), 4.59 (td, $^3J_{HH}$ = 8.6, 4.9 Hz, 1H), 3.96 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 3.72 (s, 3H), 3.53 (s, 3H); ^{13}C{^{1}H} (100 MHz): 168.0, 167.4, 164.9, 149.0, 134.1, 130.4, 129.5, 129.1, 129.0, 128.7, 128.3, 126.6, 123.6, 76.6, 53.9, 53. 1, 53.1, 36.7 (18 × s). The enantiomer excess was determined by HPLC with a Chiralcel AD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 16.1 min (major), 25.7 min (minor).[7]

Dimethyl 2-(2-nitro-1-(2-benzyloxyphenyl)ethyl)malonate (5g). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): ^{1}H (500 MHz) 7.51-7.45 (m, 2H), 7.45-7.40 (m, 2H), 7.39-7.33 (m, 1H), 7.24 (ddd, $^3J_{HH}$ = 8.3, 7.4 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.17 (dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.7 Hz, 1H), 6.93 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.1 Hz, 1H), 6.90 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.1 Hz, 1H), 5.14 (d, $^2J_{HH}$ = 11.7 Hz, 1H), 5.11 (d, $^2J_{HH}$ = 11.7 Hz, 1H), 5.05 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 9.4 Hz, 1H), 4.84 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 4.44 (td, $^3J_{HH}$ = 9.6, 4.6 Hz, 1H), 4.17 (d, $^3J_{HH}$ = 9.9 Hz, 1H), 3.72 (s, 3H), 3.50 (s, 3H); ^{13}C{^{1}H} (125

MHz): 168.4, 167.7, 156.7, 136.6, 130.9, 129.8, 128.9, 128.4, 127.7, 123.9, 121.3, 112.5, 76.1, 70.7, 53.0, 52.7, 52.6, 40.5 (18 × s). The enantiomer excess was determined by HPLC with a Chiralcel OD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 11.4 min (minor), 19.6 min (major).[7]

Dimethyl 2-(2-nitro-1-(2-methylphenyl)ethyl)malonate (5h). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): ^{1}H (400 MHz) 7.12-7.03 (m, 4H), 4.84 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 4.78 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 8.6 Hz, 1H), 4.51 (td, $^3J_{HH}$ = 8.9, 5.4 Hz, 1H), 3.76 (d, $^3J_{HH}$ = 9.3 Hz, 1H), 3.68 (s, 3H), 3.52 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} (100 MHz) 168.0, 167.3, 137.0, 134.5, 131.3, 128.1, 126.6, 125.8, 54.5, 53.0, 52.8, 52.6, 41.1, 37.7 (14 × s). The enantiomer excess was determined by HPLC with a Chiralcel AD-H column (75:25 v/v hexane/isopropanol, 1 mL/min, λ = 210 nm); t_R = 9.8 min (major), 19.1 min (minor).[21]

Dimethyl 2-(2-nitro-1-β-naphthylethyl)malonate (5i). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): 7.87-7.74 (m, 1H), 7.73-7.67 (m, 1H), 7.54-7.44 (m, 2H), 7.34 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ =1.9 Hz, 1H), 5.00 (d, $^3J_{HH}$ = 7.0 Hz, 2H), 4.43 (dt, $^3J_{HH}$ = 8.8, 7.0 Hz, 1H), 3.98 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 3.77 (s, 3H), 3.54 (s, 3H). The enantiomer excess was determined by HPLC with a Chiralcel OD column (70:30 v/v hexane/isopropanol, 1 mL/min, λ = 254 nm); t_R = 12.5 min (major), 35.5 min (minor).[7]

Dimethyl 2-(2-nitro-1-α-naphthylethyl)malonate (5j). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): 8.18 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 7.98-7.85 (m, 1H), 7.84-7.73 (m, 1H), 7.62 (ddd, $^3J_{HH}$ = 8.5, 6.8 Hz, $^4J_{HH}$ = 1.4 Hz, 1H), 7.53 (ddd, $^3J_{HH}$ = 8.0, 6.8 Hz, $^4J_{HH}$ = 1.1 Hz, 1H), 7.46-7.34 (m, 2H), 5.29-5.20 (m, 1H), 5.18 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.2 Hz, 1H), 5.07 (dd, $^2J_{HH}$

= 13.1 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 4.11 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 3.72 (s, 3H), 3.54 (s, 3H). The enantiomer excess was determined by HPLC with a Chiralcel AD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 254 nm); t_R = 14.4 min (major), 19.1 min (minor).[7]

Dimethyl 2-(2-nitro-1-(3,4-dioxolophenyl)ethyl)malonate (5k). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): 6.78-6.65 (m, 3H), 5.95 (s, 2H), 4.87 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 4.9 Hz, 1H), 4.80 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 9.3 Hz, 1H), 4.16 (td, $^3J_{HH}$ = 9.2, 4.9 Hz, 1H), 3.80 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H). $^{13}C\{^1H\}$ (100 MHz): 168.0, 167.3, 148.3, 147.8, 129.8, 121.5, 108.8, 208.3, 101.5, 77.7, 55.0, 53.2, 53.0, 42.9 (14 × s). The enantiomer excess was determined by HPLC with a Chiralcel AS-H column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 44.8 min (major), 53.3 min (minor).[22]

Dimethyl 2-(2-nitro-1-furylethyl)malonate (5l). This known compound was obtained as a colorless oil according to the general procedure. NMR ($CDCl_3$, δ/ppm): ^1H (400 MHz) 7.29 (d, 1H), 6.23 (t, 1H), 6.16 (d, 1H), 4.85 (dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 4.83 (dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 2.9 Hz, 1H), 4.33 (td, $^3J_{HH}$ = 8.0, 5.1 Hz, 1H), 3.88 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 3H); $^{13}C\{^1H\}$ (100 MHz) 167.5, 167.2, 149.4, 142.9, 110.6, 108.5, 75.3, 53.1, 53.0, 52.7, 52.6 (11 x s). The enantiomer excess was determined by HPLC with a Chiralcel OD column (90:10 v/v hexane/isopropanol, 1 mL/min, λ = 220 nm); t_R = 11.1 min (minor), 23.8 min (major).[7]

5.6. References

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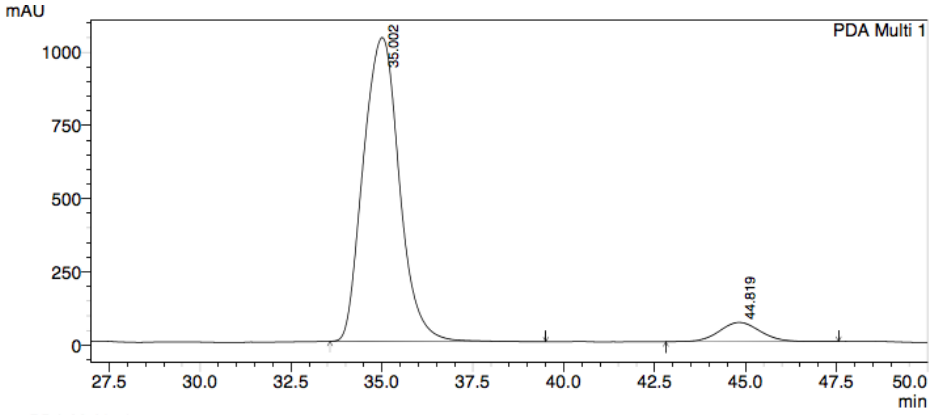
APPENDIX A: CHIRAL TRICATIONIC TRIS(1,2-DIPHENYLETHYLENEDIAMINE) COBALT(III) HYDROGEN BOND DONOR CATALYSTS WITH DEFINED CARBON/METAL CONFIGURATIONS; MATCHED/MISMATCHED EFFECTS UPON ENANTIOSELECTIVITIES WITH ENANTIOMERIC CHIRAL COUNTER ANIONS

Representative HPLC traces used for determination of ee values.



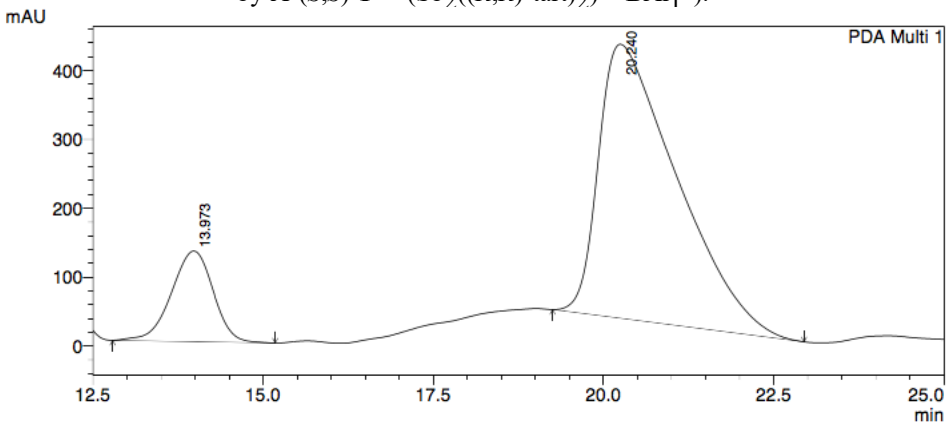
1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	35.002	71701778	1037932	93.391	94.071
2	44.819	5074494	65420	6.609	5.929
Total		76776271	1103352	100.000	100.000

Figure 1. HPLC trace for Chart 2.1, entry 20 (dimethyl 2-(2-nitro-1-phenylethyl)malonate (**2**), catalyzed by Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $(Sb_2((R,R)\text{-tart})_2)^{2-}BAr_f^-$).



1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.973	5635111	131564	15.006	24.854
2	20.240	31916174	397776	84.994	75.146
Total		37551285	529340	100.000	100.000

Figure 2. HPLC trace for Chart 2.2, entry 20 (*N,N'*-bis(*t*-butoxycarbonyl)-1-hydrazino-2-oxocyclopentanecarboxylic acid methyl ester (**3**), catalyzed by Λ-(*S*,*S*)-$\mathbf{1}^{3+}$ $(Sb_2((R,R)\text{-tart})_2)^{2-}BAr_f^-$).

Table 1. Summary of crystallographic data for Δ-(S,S)-$\mathbf{1}^{3+}$ 2(1S)-camph$SO_3^-$$BAr_f^-$.[a]

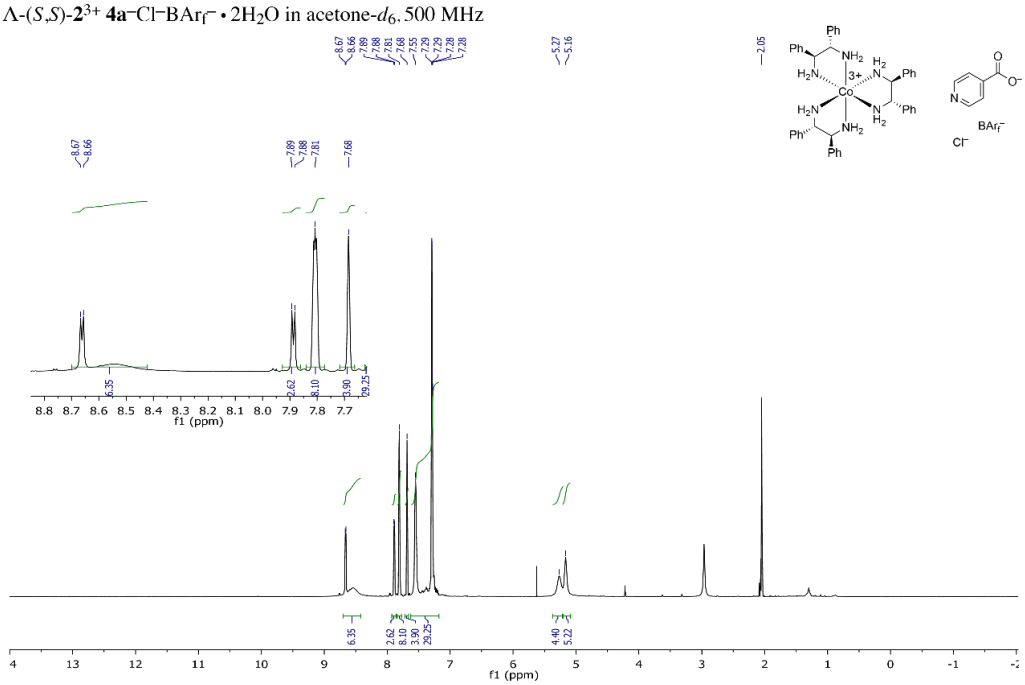
empirical formula	$C_{94}H_{88}BBr_2CoF_{24}N_6O_8S_2$
formula weight	2179.38
temperature of collection [K]	110.15
diffractometer	Bruker D8
wavelength [Å]	0.8857
crystal system	orthorhombic
space group	$P2_12_12_1$
unit cell dimensions:	
a [Å]	18.4403(12)
b [Å]	25.0680(17)
c [Å]	25.5947(17)
α [°]	90
β [°]	90
γ [°]	90
V [Å^3]	11831.4(14)
Z	4
ρ_{calc} [Mg/m^3]	1.224
absorption coefficient [mm^{-1}]	1.680
F(000)	4432
Crystal size [mm^3]	0.04 × 0.03 × 0.01
Θ [deg]	2.227 to 25.202
range / indices (*h*, *k*, *l*)	–17,17; 0,24; 0,24
reflections collected	10970
independent reflections	10970 [R(int) = 0.0898]
completeness to Θ = 25.202°	99.7%
absorption correction	semi-empirical from equivalents
max. and min. transmission	0.7454 and 0.6109
refinement method	full-matrix least-squares on F^2
data / restraints / parameters	10970 / 1388 / 1241
goodness-of-fit on F^2	1.016
final R indices [I>2σ(I)]	$R1$ = 0.0572, w$R2$ = 0.1477
R indices (all data)	$R1$ = 0.0777, w$R2$ = 0.1593
absolute structure (Flack) parameter	0.004(5)
largest diff. peak and hole [e.Å^{-3}]	0.489 / –0.374

[a] The solvent molecules associated with this structure were removed using MASK as detailed in the experimental section. Thus, the formula weight and density are underestimated.

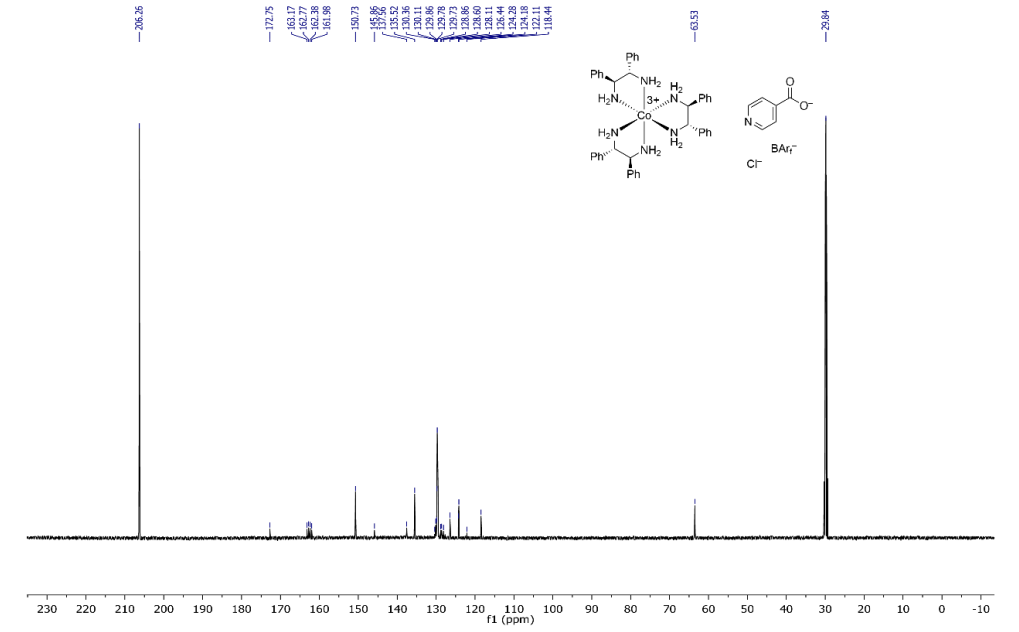
APPENDIX B: CHIRAL COBALT(III) TRIS(1,2-DIAMINE) CATALYSTS THAT INCORPORATE "SMART" OR "TASK SPECIFIC" ANIONS FOR THE BIFUNCTIONAL ACTIVATION OF NUCLEOPHILES AND ELECTROPHILES IN ENANTIOSELECTIVE ADDITION REACTIONSSOLVENT-FREE CATALYSIS WITH CO(III) WERNER COMPLEXES

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of catalysts

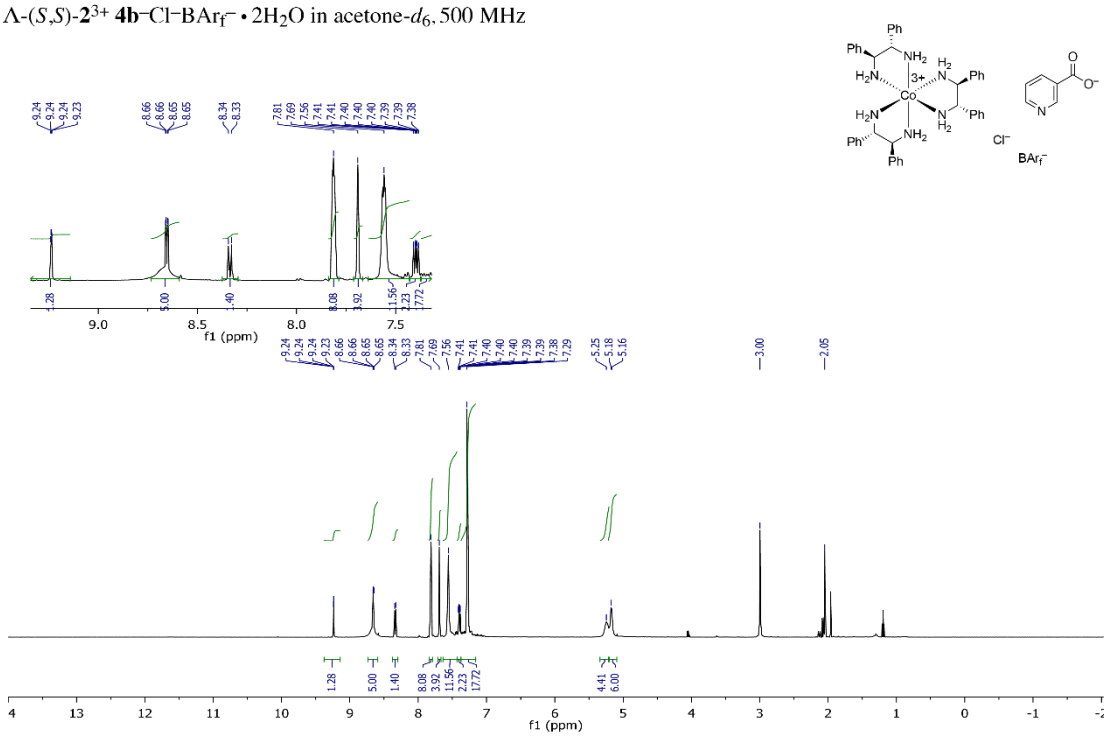
Λ-(*S*,*S*)-**2**$^{3+}$ **4a**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz



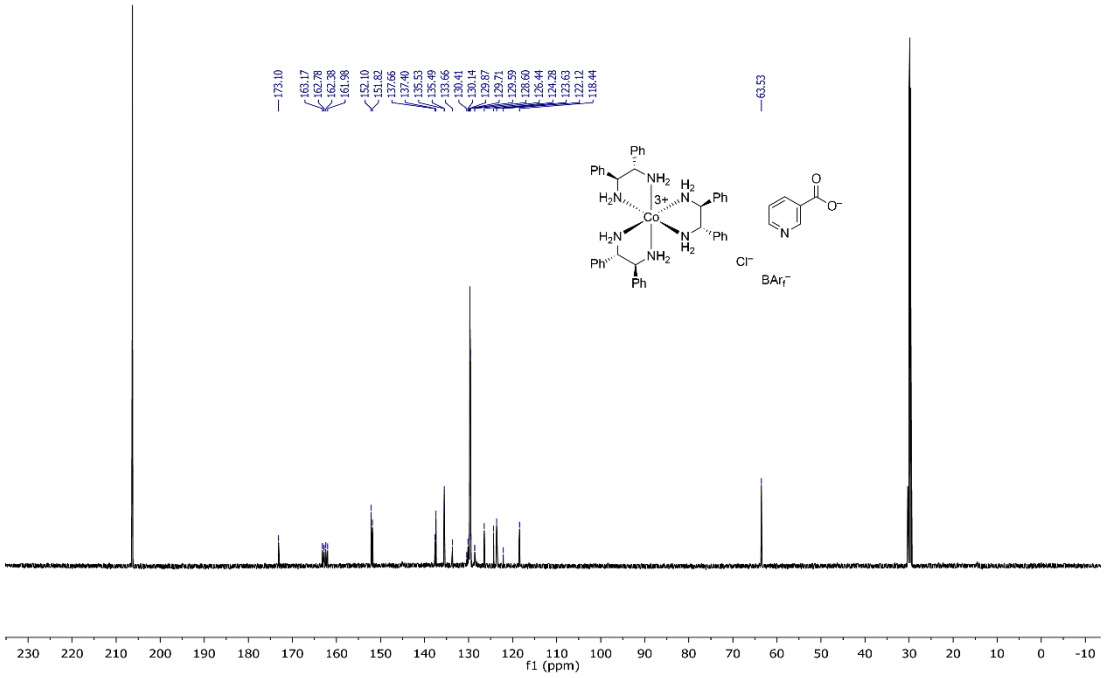
Λ-(*S*,*S*)-**2**$^{3+}$ **4a**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz



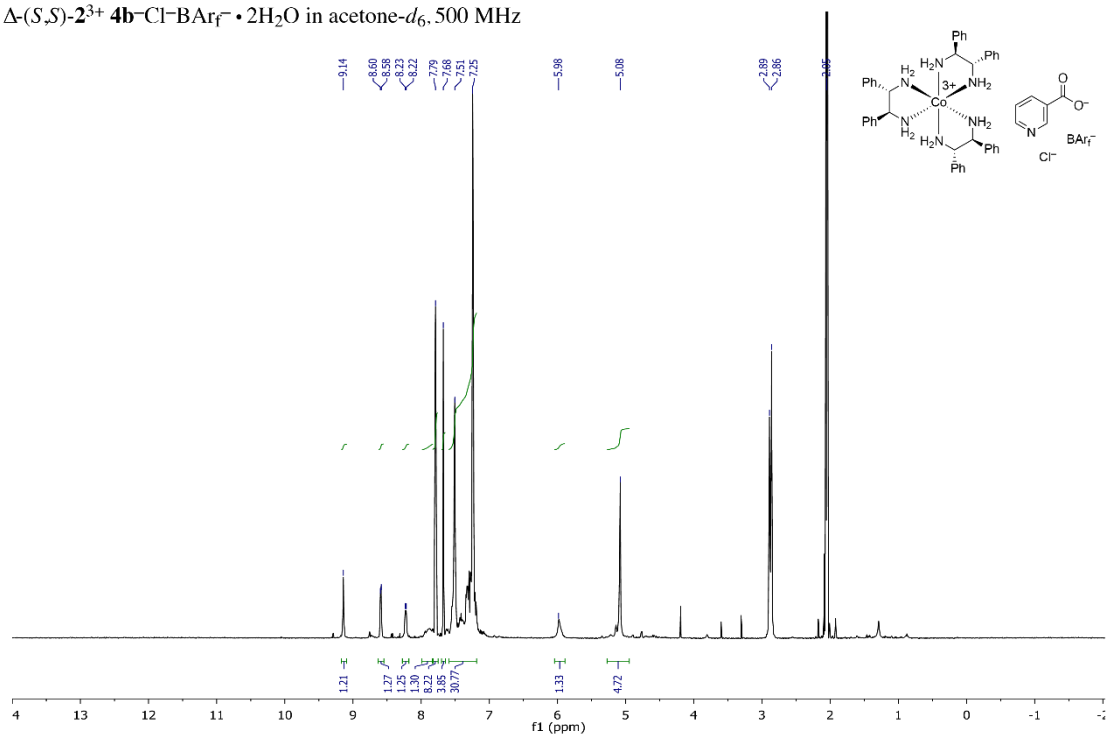
Λ-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz



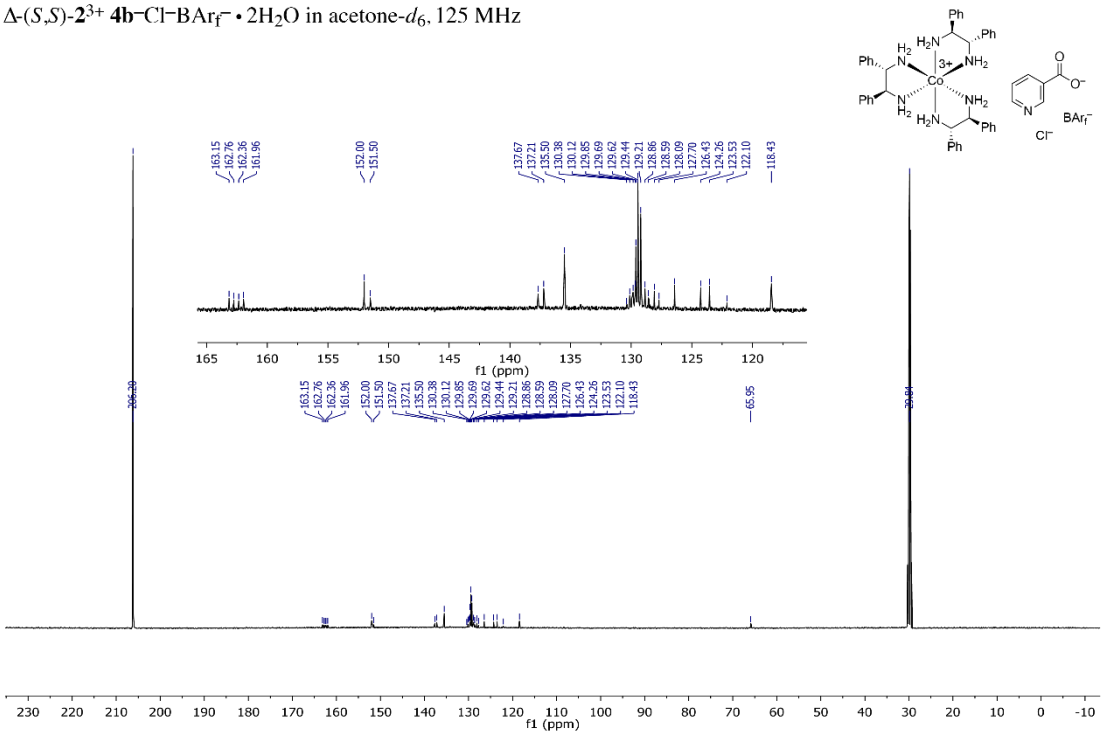
Λ-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz



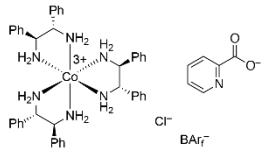
Δ-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz

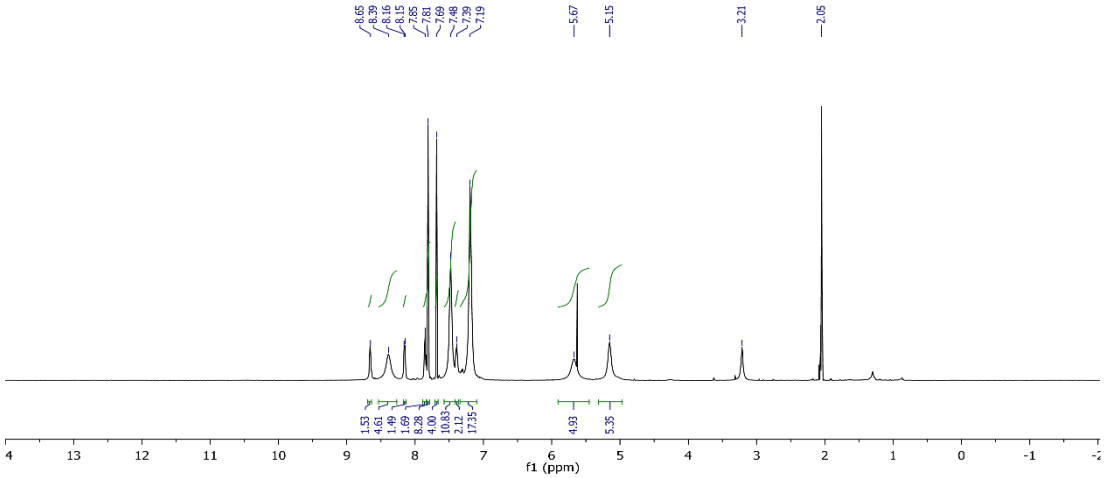


Δ-(*S*,*S*)-**2**$^{3+}$ **4b**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz

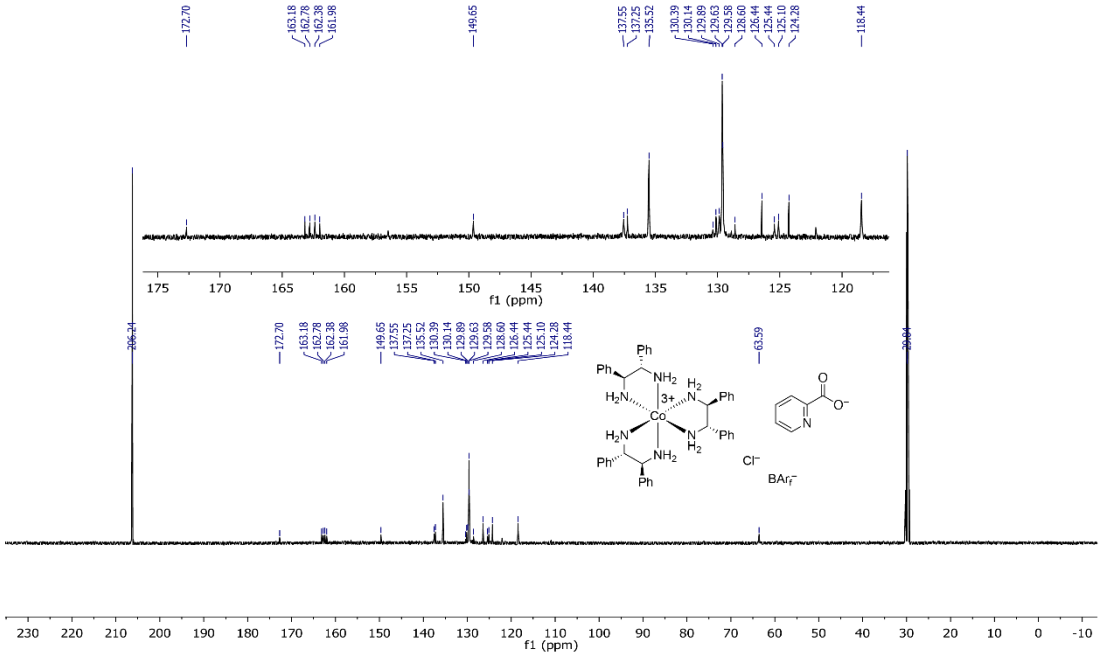


Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ **4c**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz

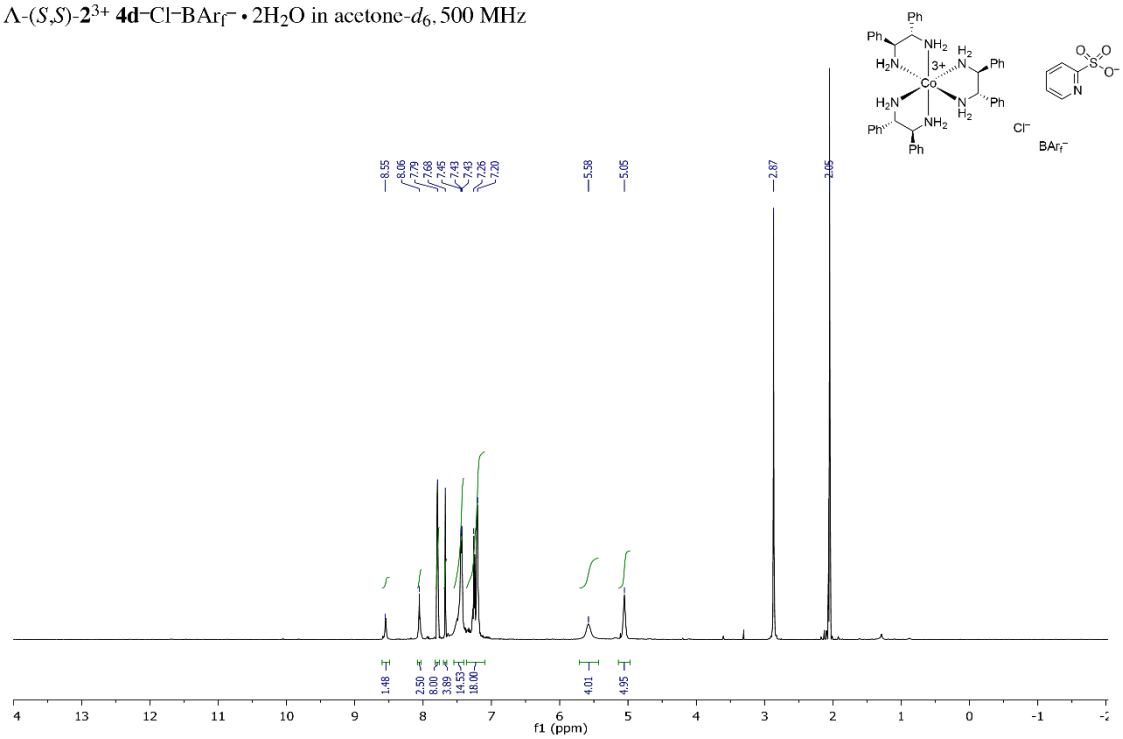




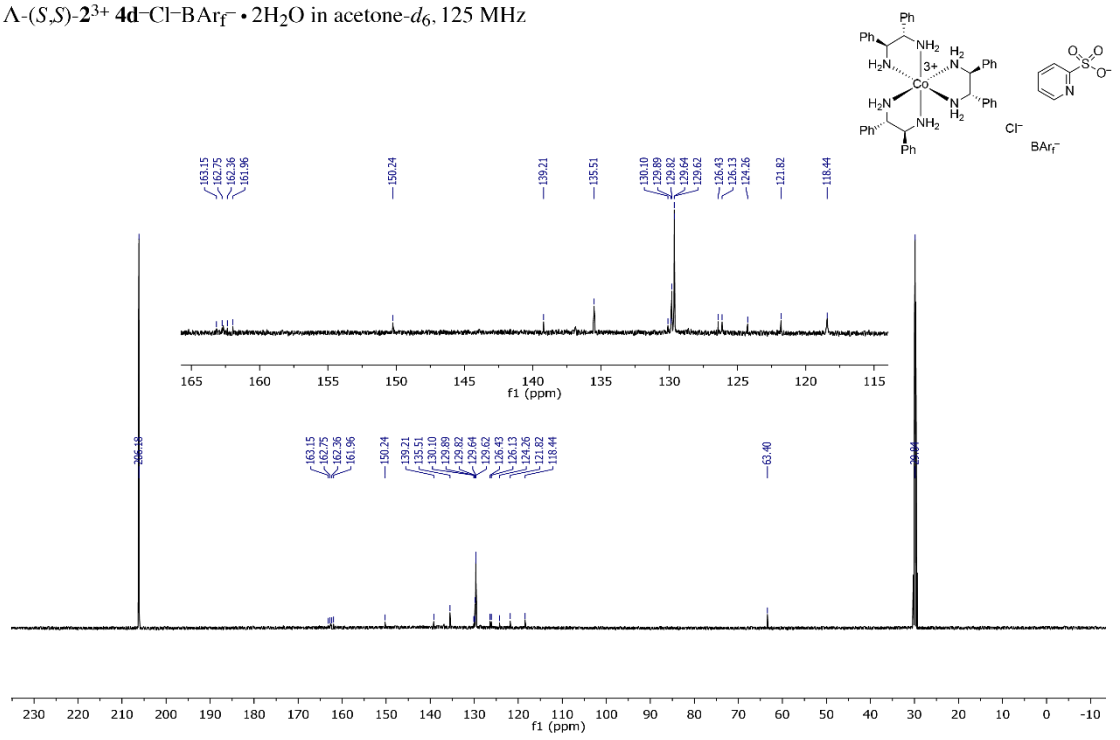
Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ **4c**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz



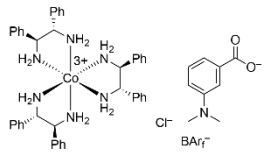
Λ-(*S*,*S*)-**2**$^{3+}$ **4d**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz

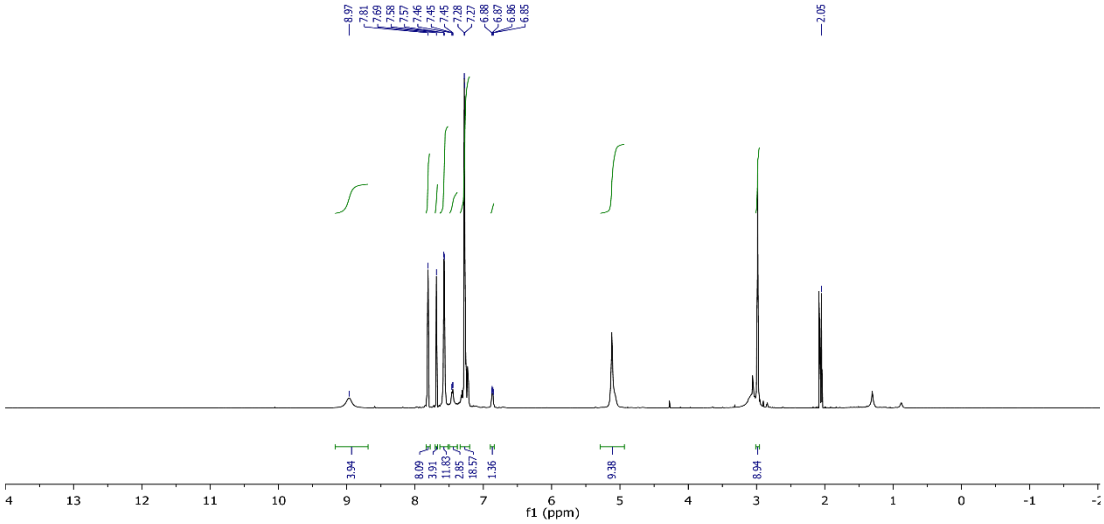


Λ-(*S*,*S*)-**2**$^{3+}$ **4d**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz

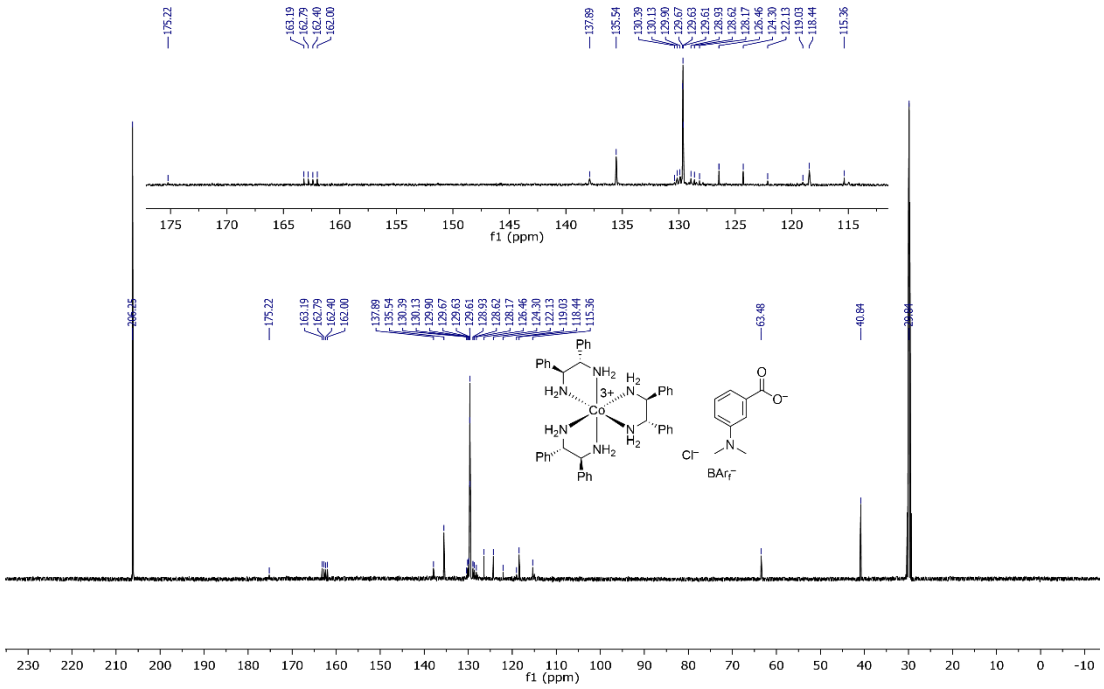


Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ **4e**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz

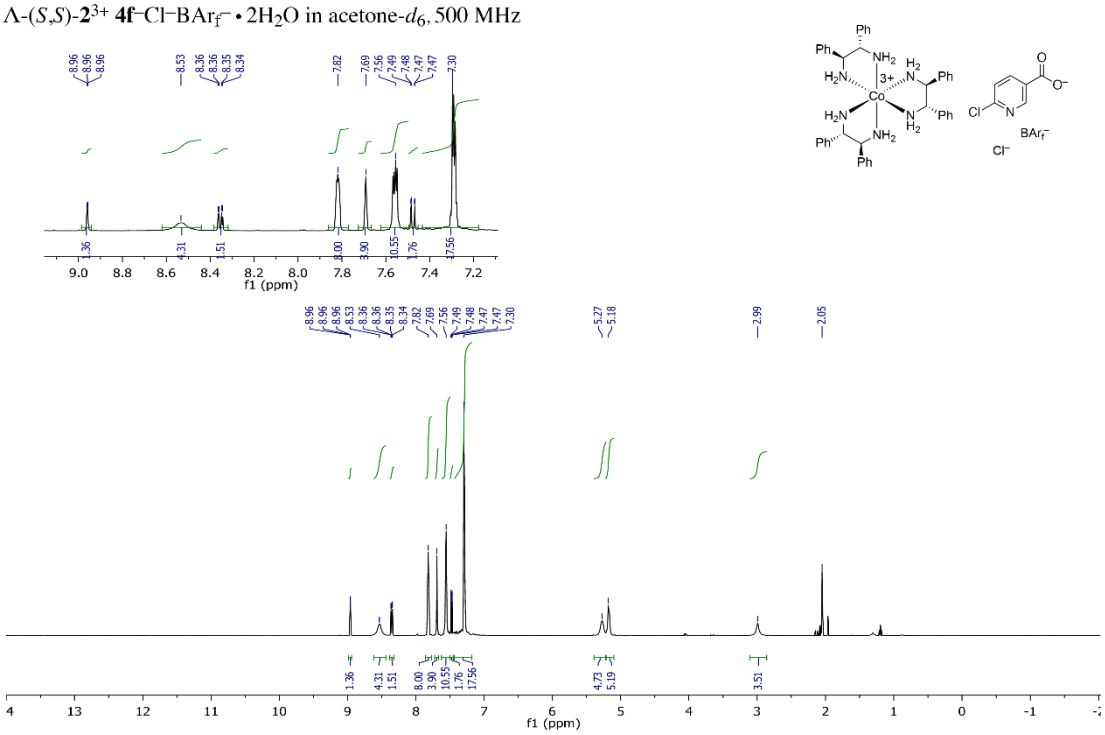




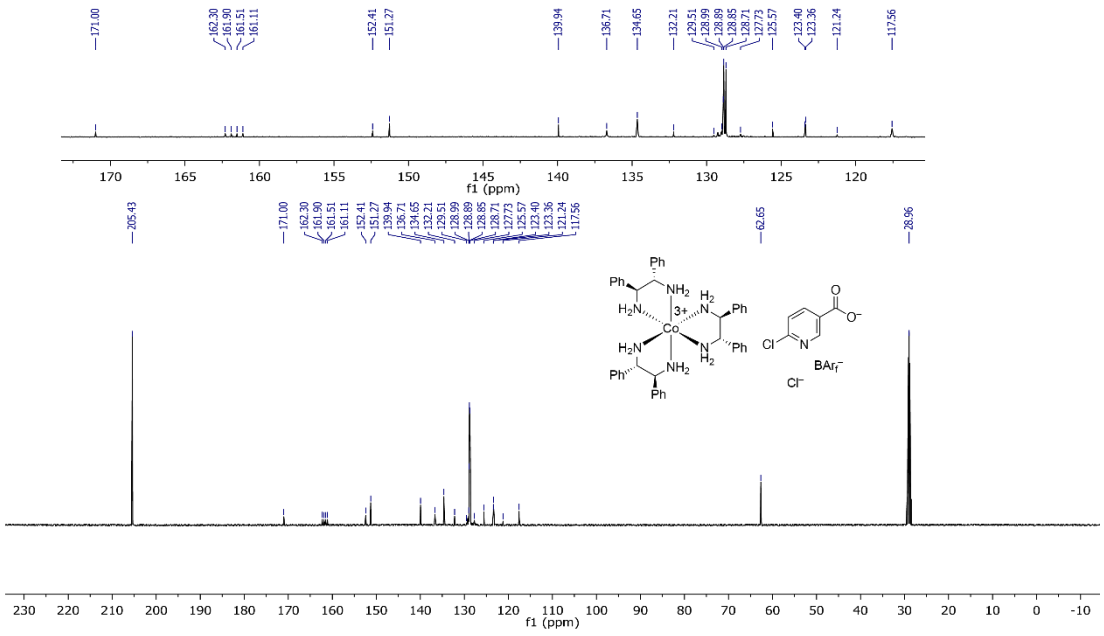
Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ **4e**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz



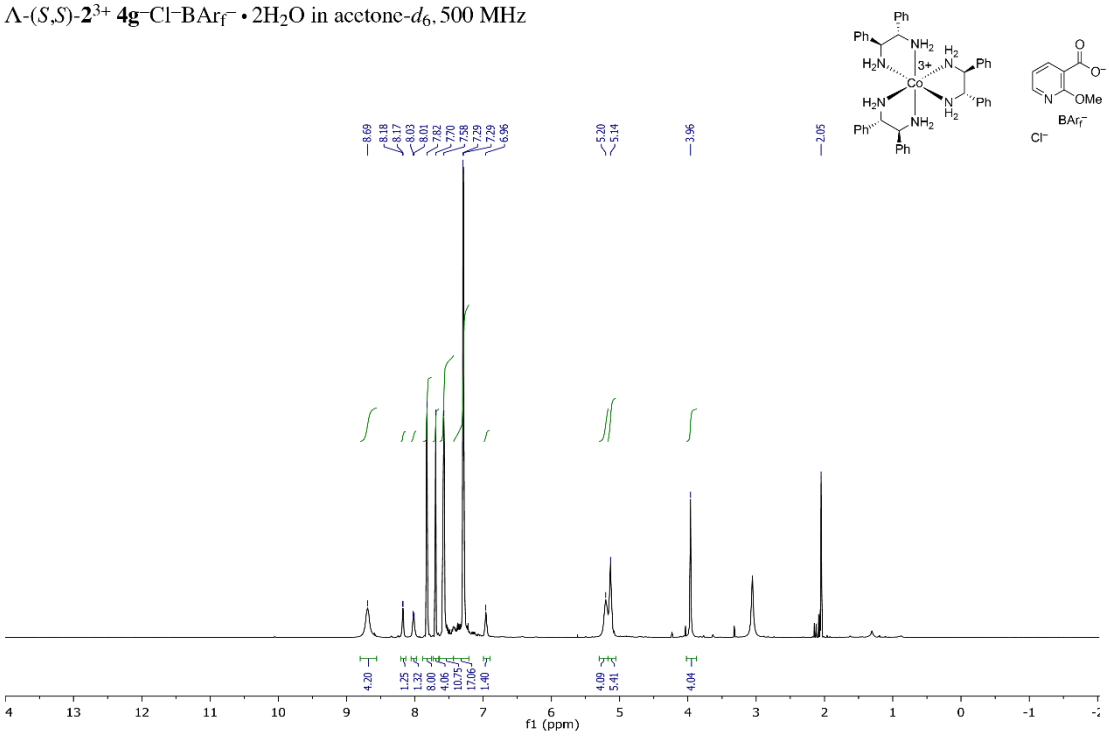
Λ-(*S*,*S*)-**2**$^{3+}$ **4f**$^{-}$–Cl^{-}–BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz



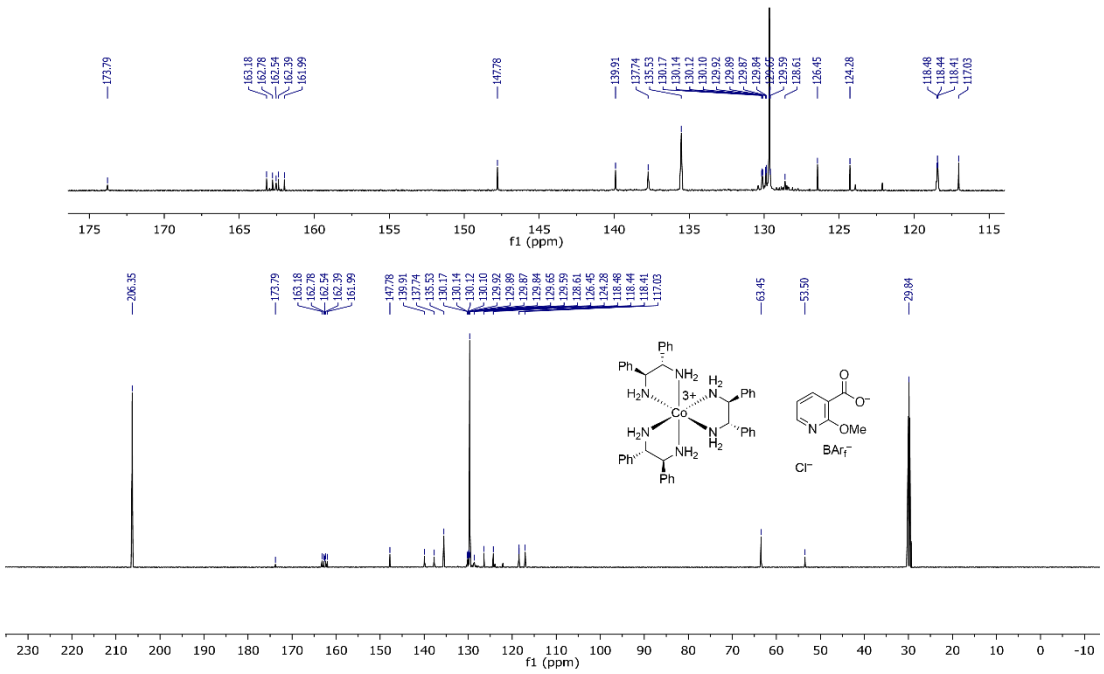
Λ-(*S*,*S*)-**2**$^{3+}$ **4f**$^{-}$–Cl^{-}–BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz



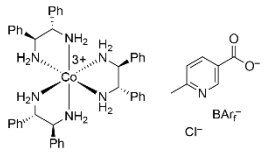
Λ-(*S*,*S*)-**2**$^{3+}$ **4g**–Cl^{-}–BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz

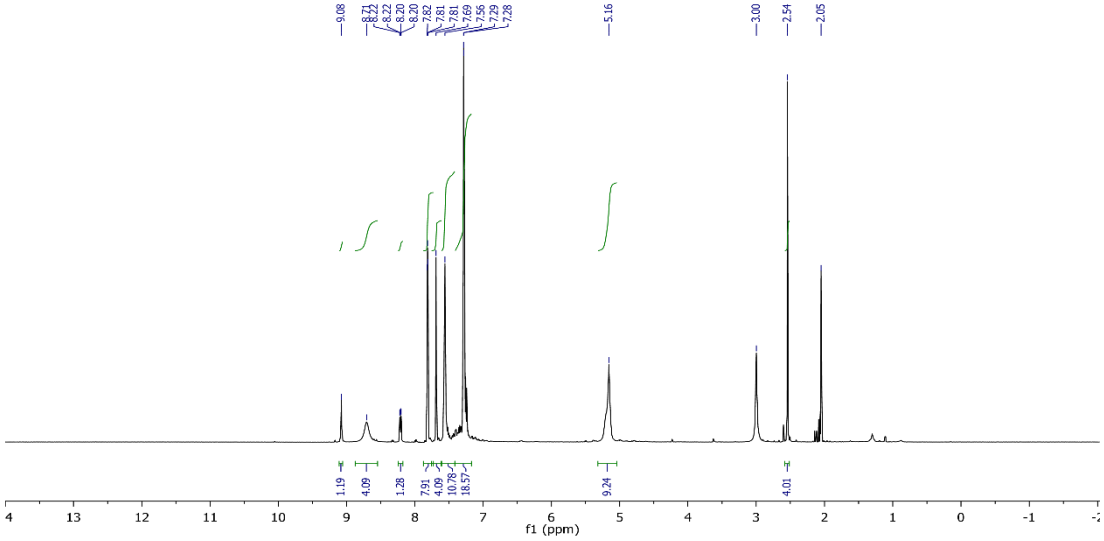


Λ-(*S*,*S*)-**2**$^{3+}$ **4g**–Cl^{-}–BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz

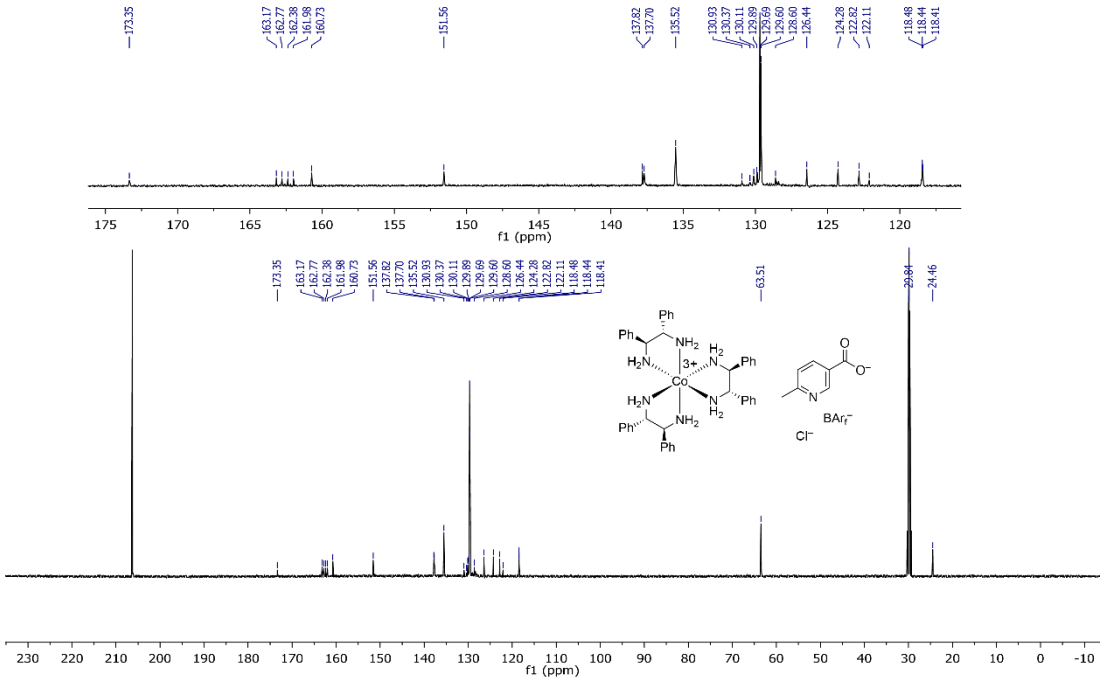


Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ **4h**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz

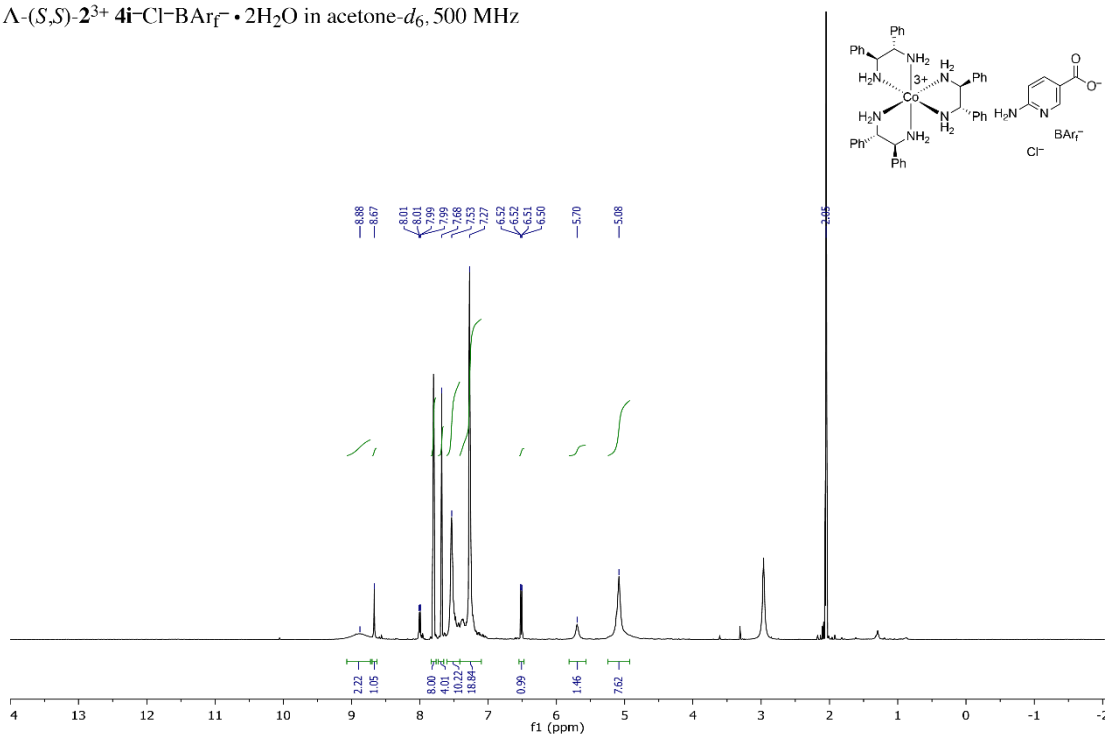




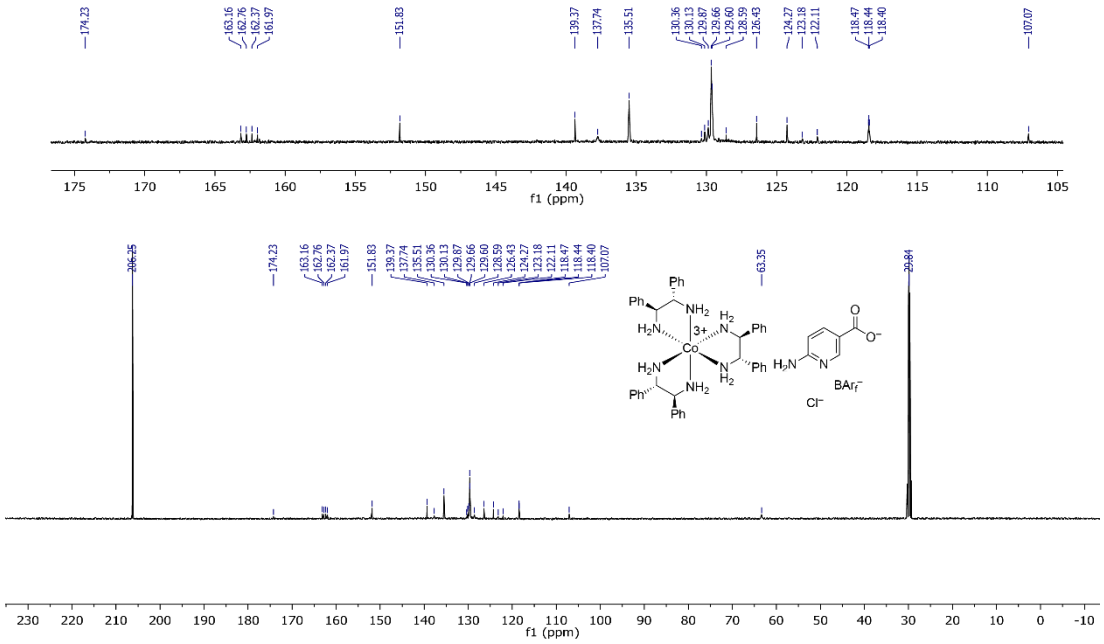
Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ **4h**$^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz



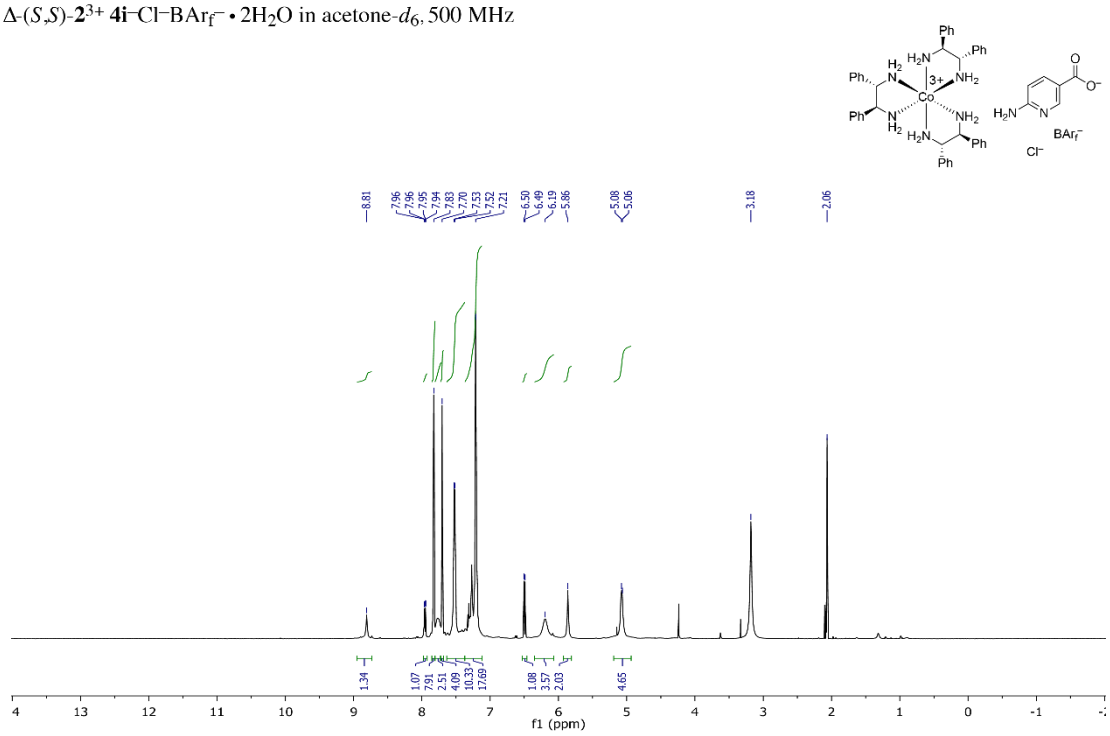
Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $\mathbf{4i}^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 500 MHz



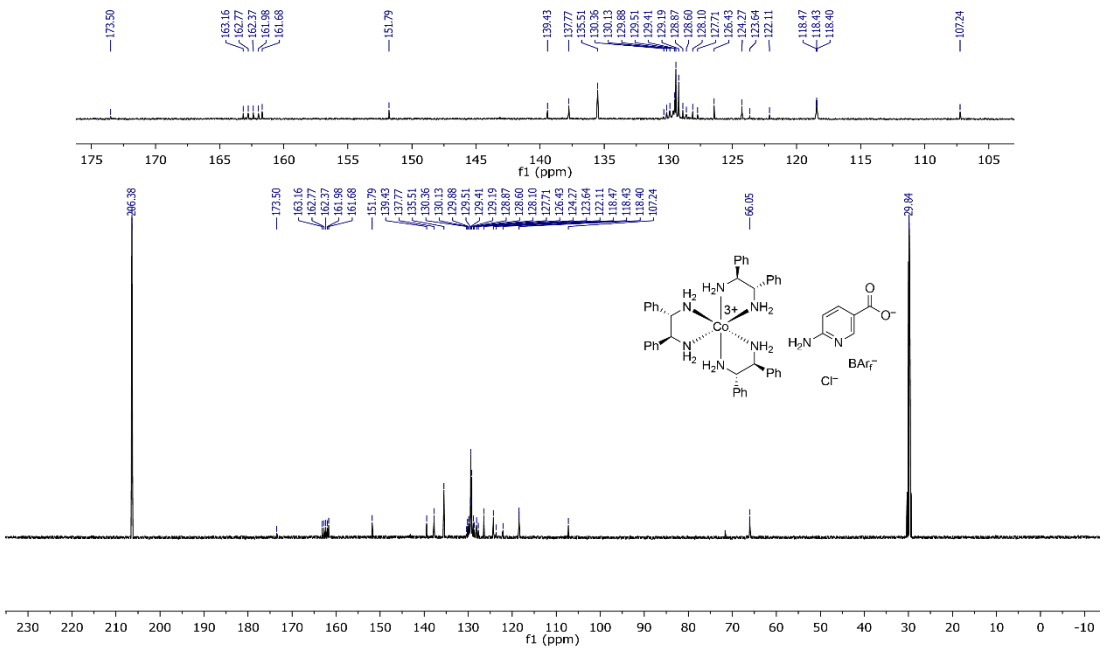
Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $\mathbf{4i}^{-}$Cl^{-}BAr$_f^{-}$ • 2H$_2$O in acetone-d_6, 125 MHz



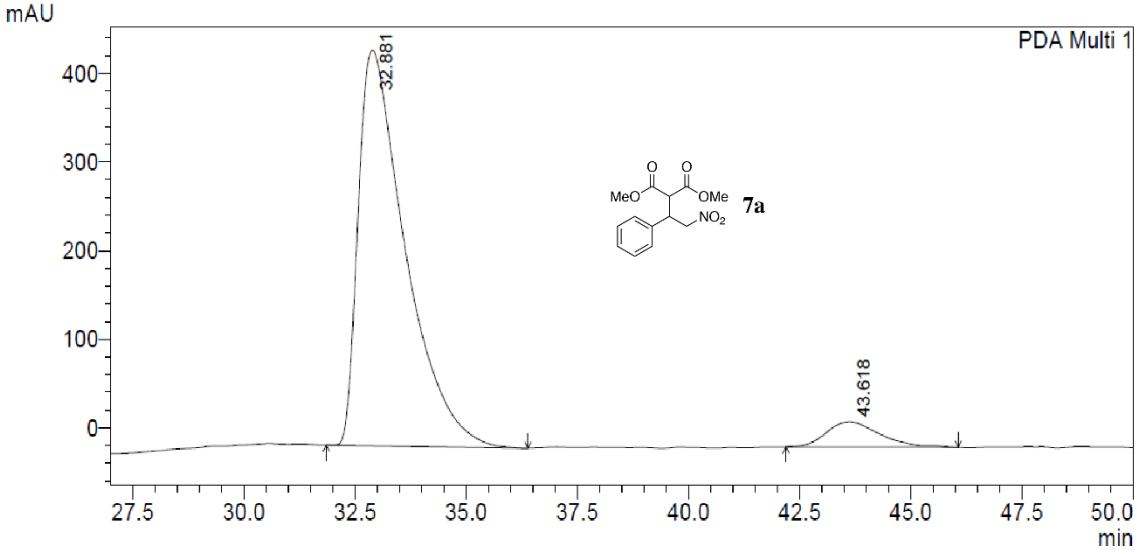
Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ **4i**–Cl–BAr_f^- • $2H_2O$ in acetone-d_6, 500 MHz



Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ **4i**–Cl–BAr_f^- • $2H_2O$ in acetone-d_6, 125 MHz



HPLC Traces

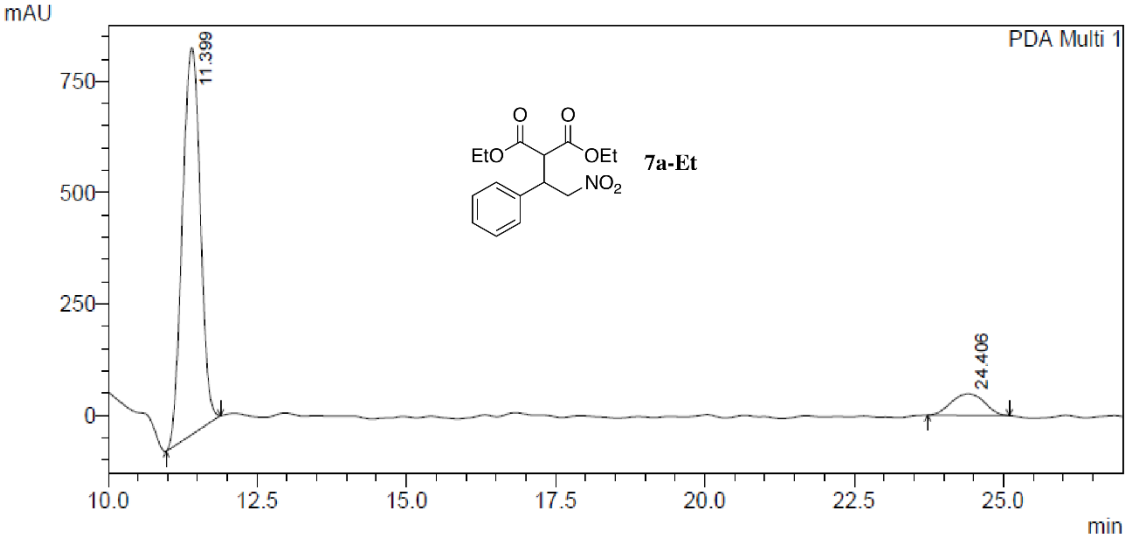


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	32.881	32859195	446548	93.222	94.002
2	43.618	2389229	28495	6.778	5.998
Total		35248424	475043	100.000	100.000

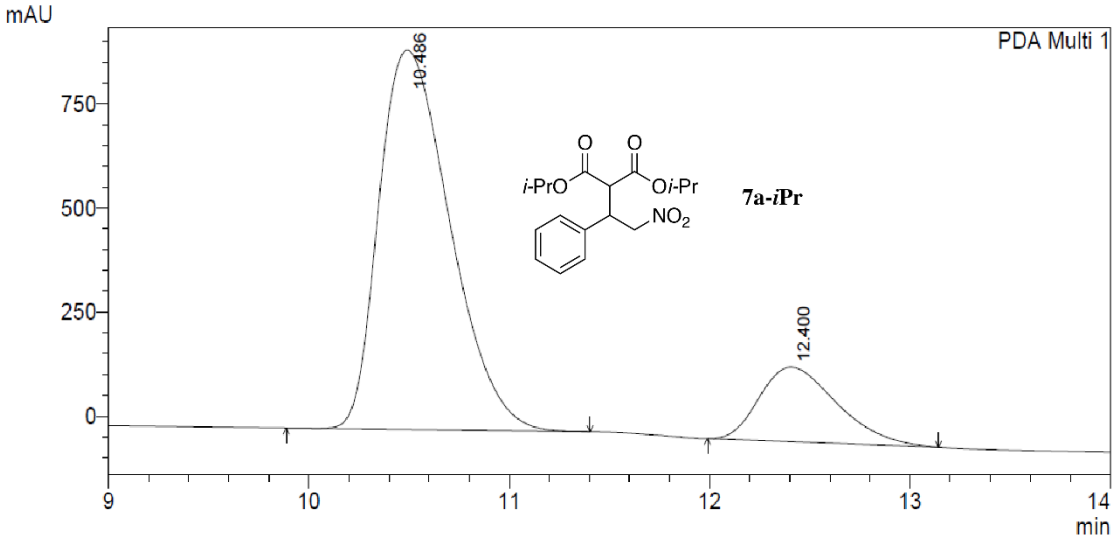


1 PDA Multi 1/230nm 4nm

PeakTable

PDA Ch1 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.399	18230992	867742	90.622	94.700
2	24.406	1886690	48561	9.378	5.300
Total		20117683	916303	100.000	100.000

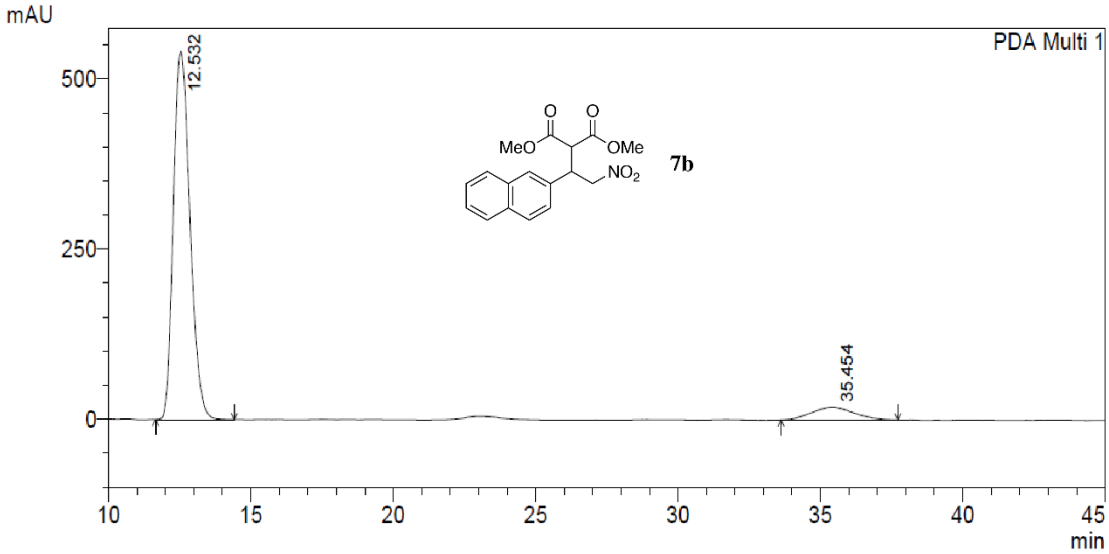


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.486	22512749	910958	82.386	83.565
2	12.400	4813147	179158	17.614	16.435
Total		27325896	1090115	100.000	100.000

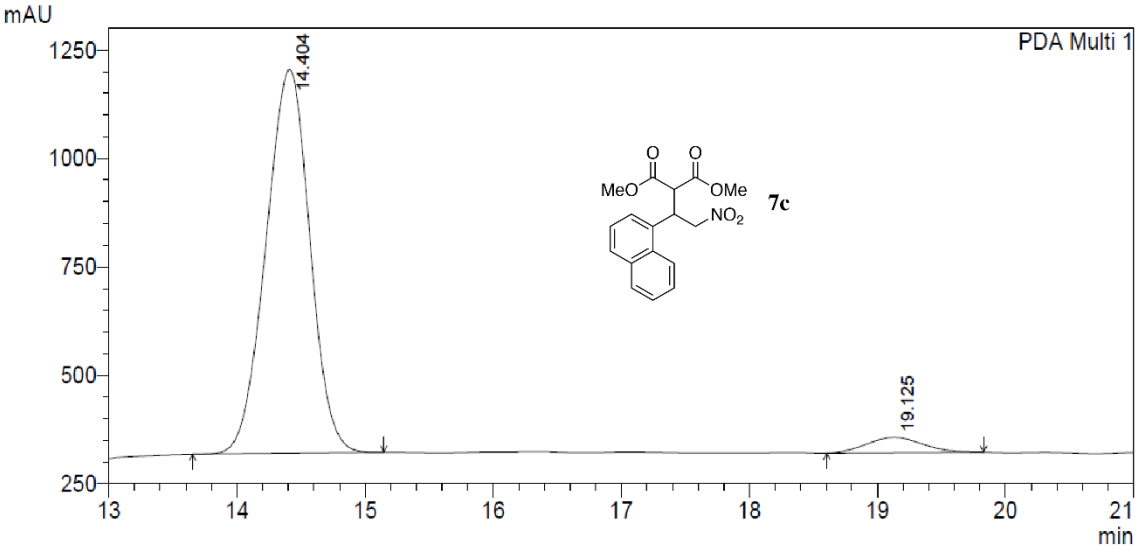


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.532	22001804	541358	91.843	96.668
2	35.454	1954107	18662	8.157	3.332
Total		23955910	560020	100.000	100.000

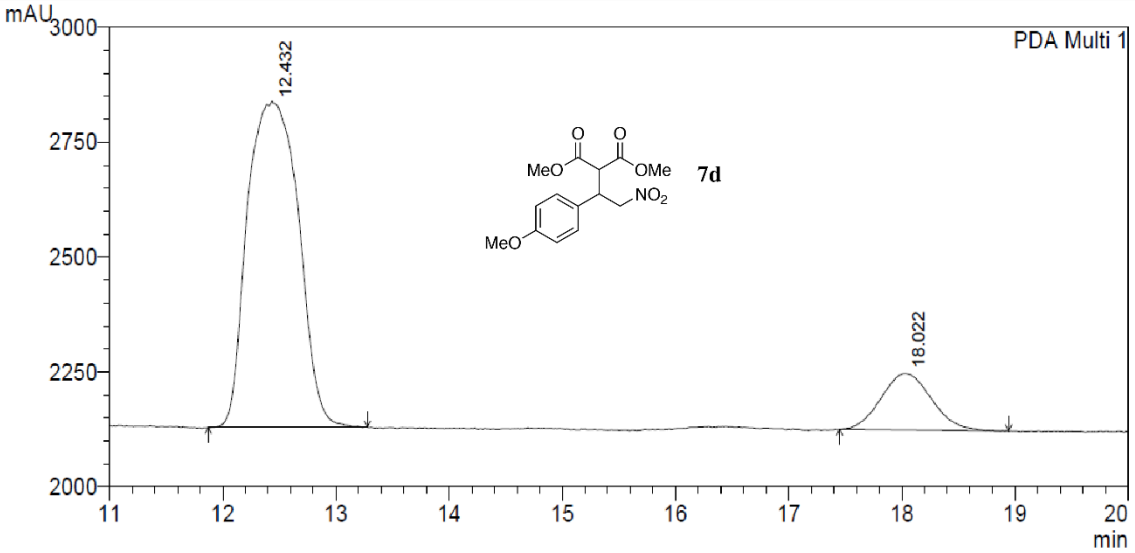


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.404	21101952	884579	95.177	96.158
2	19.125	1069249	35341	4.823	3.842
Total		22171200	919920	100.000	100.000

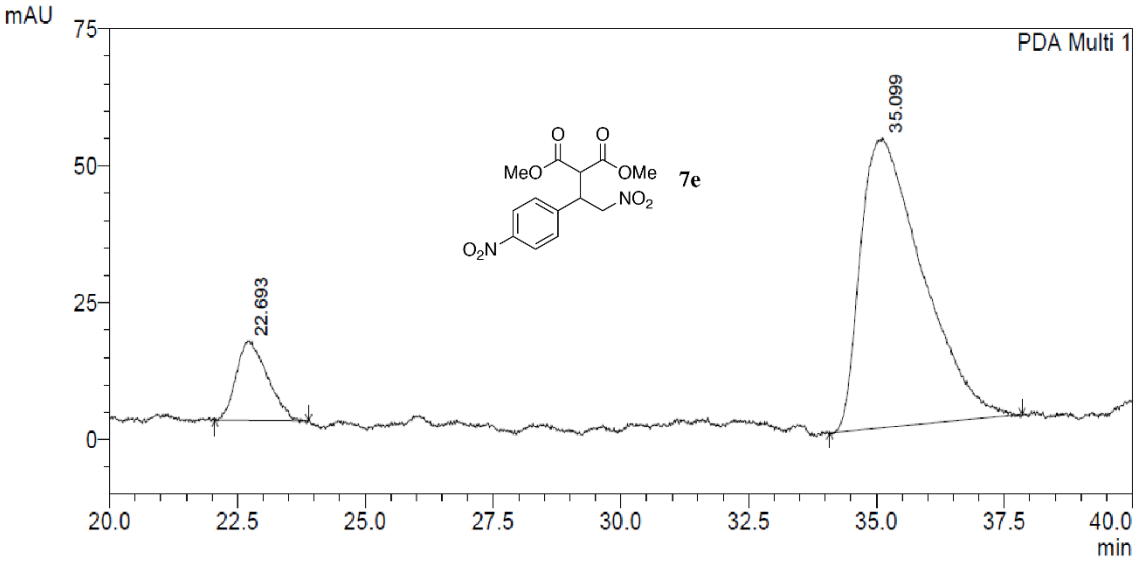


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.432	22262060	710105	85.509	85.321
2	18.022	3772708	122166	14.491	14.679
Total		26034767	832271	100.000	100.000

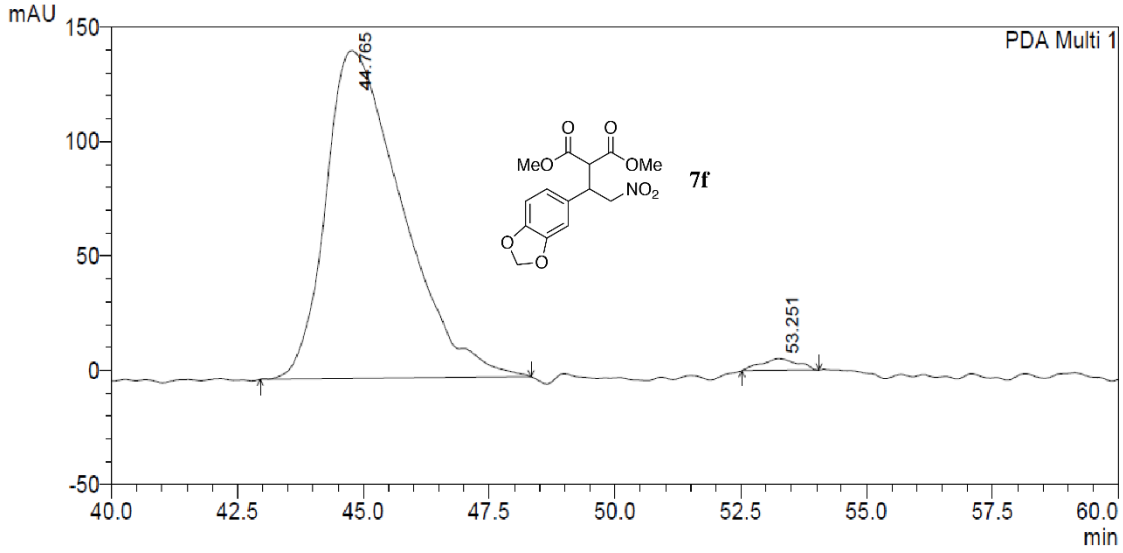


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.693	613772	14494	12.114	21.477
2	35.099	4453059	52992	87.886	78.523
Total		5066830	67486	100.000	100.000

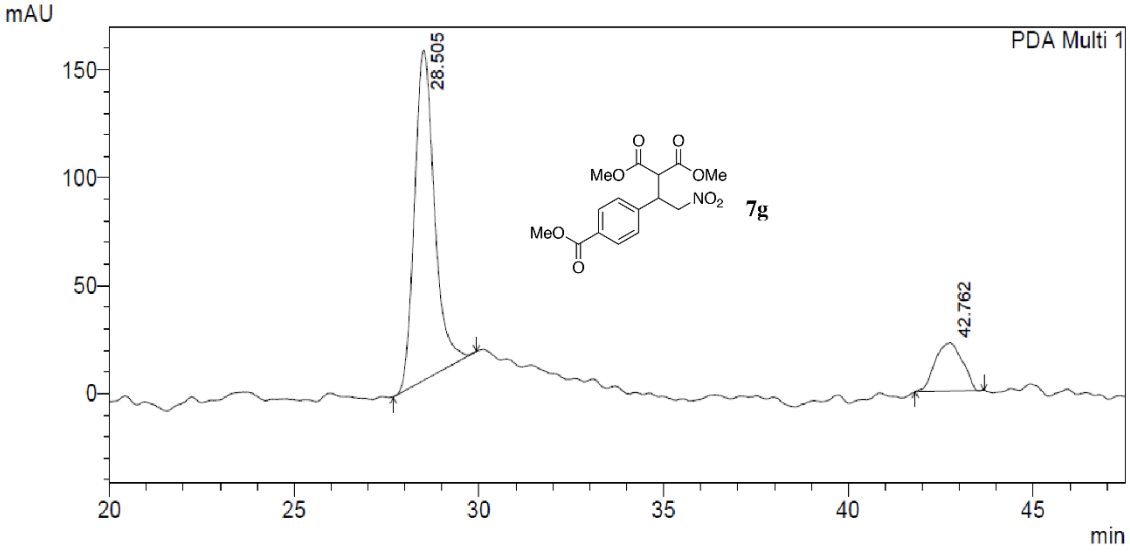


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	44.765	15100824	143230	98.312	96.516
2	53.251	259286	5171	1.688	3.484
Total		15360109	148401	100.000	100.000

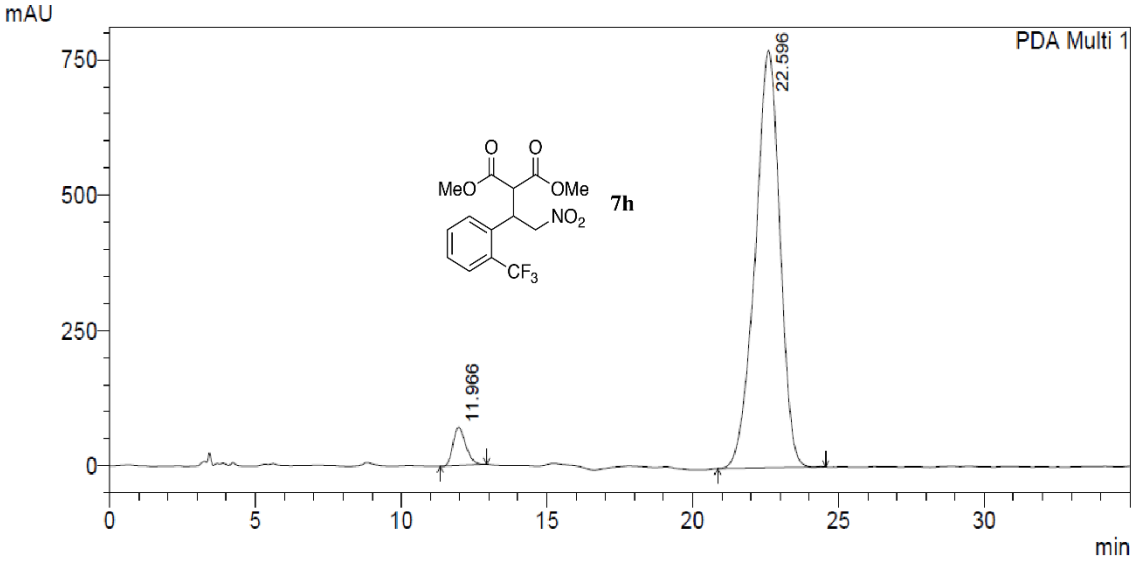


1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.505	5756305	153144	83.368	87.296
2	42.762	1148382	22286	16.632	12.704
Total		6904687	175430	100.000	100.000

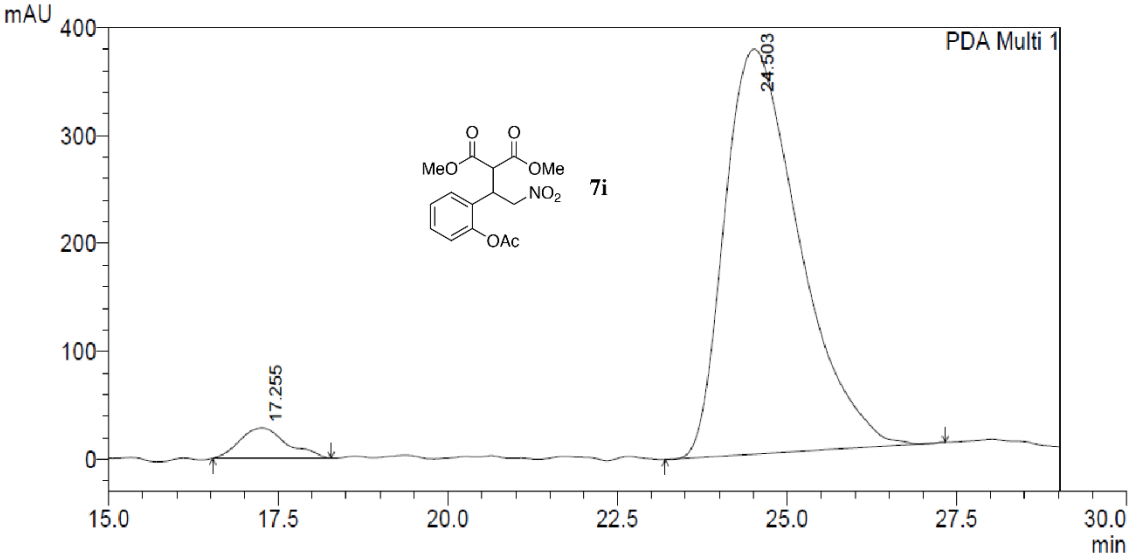


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.966	2141166	70585	4.490	8.393
2	22.596	45542705	770372	95.510	91.607
Total		47683871	840957	100.000	100.000

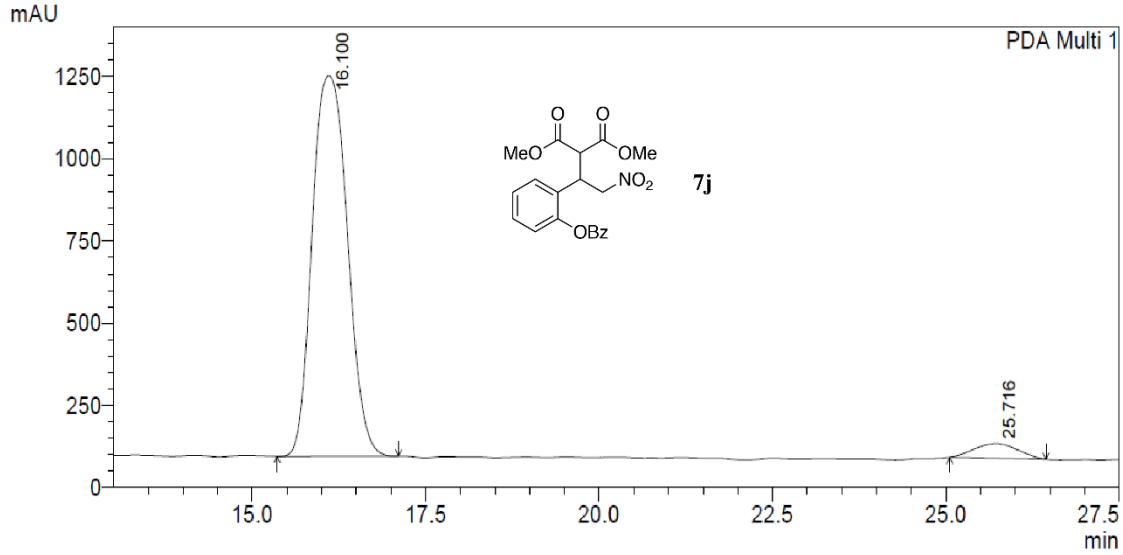


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.255	1375710	28163	4.560	6.975
2	24.503	28791723	375596	95.440	93.025
Total		30167433	403759	100.000	100.000

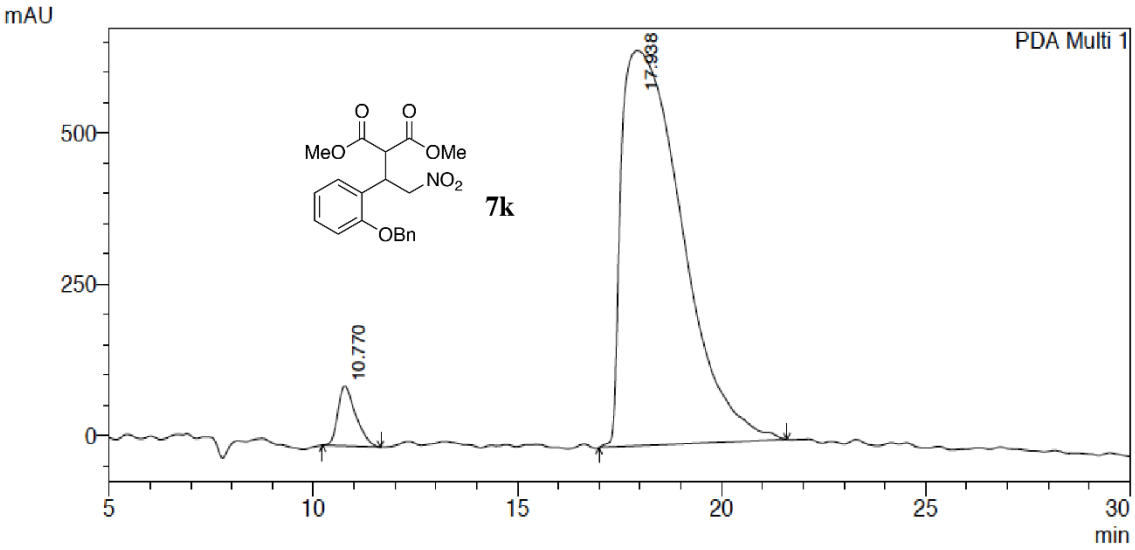


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.100	40843400	1156471	95.462	96.274
2	25.716	1941795	44760	4.538	3.726
Total		42785195	1201231	100.000	100.000

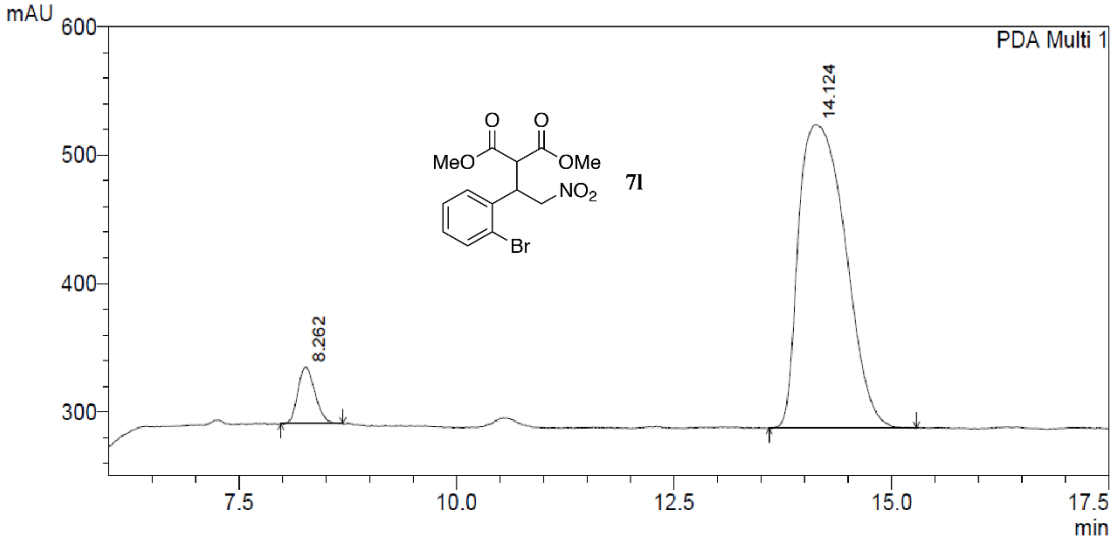


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.770	3007142	98777	4.264	13.143
2	17.938	67524994	652767	95.736	86.857
Total		70532135	751544	100.000	100.000

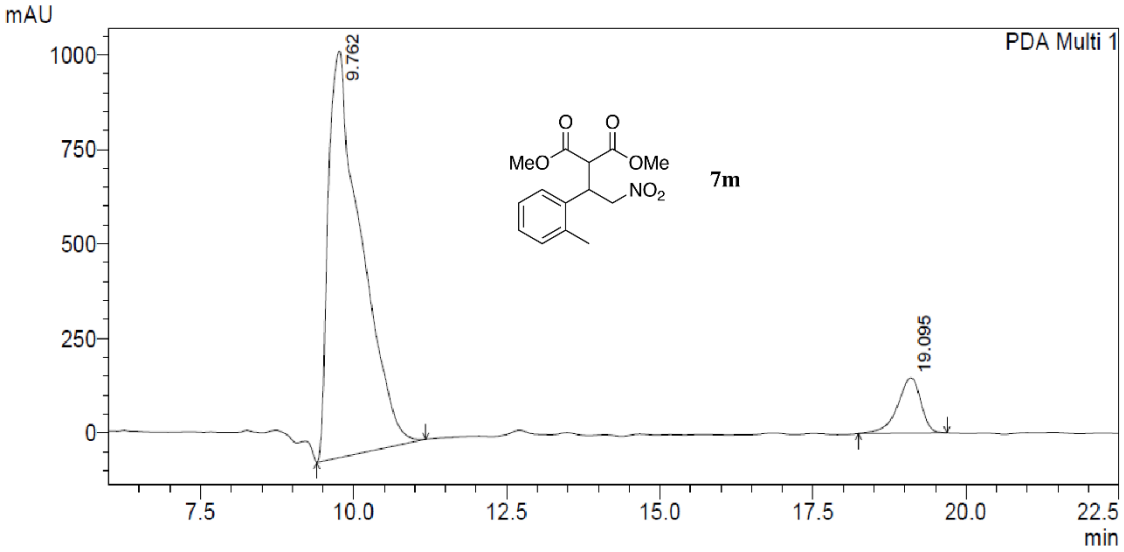


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.262	606589	44047	6.410	15.705
2	14.124	8855877	236412	93.590	84.295
Total		9462466	280459	100.000	100.000

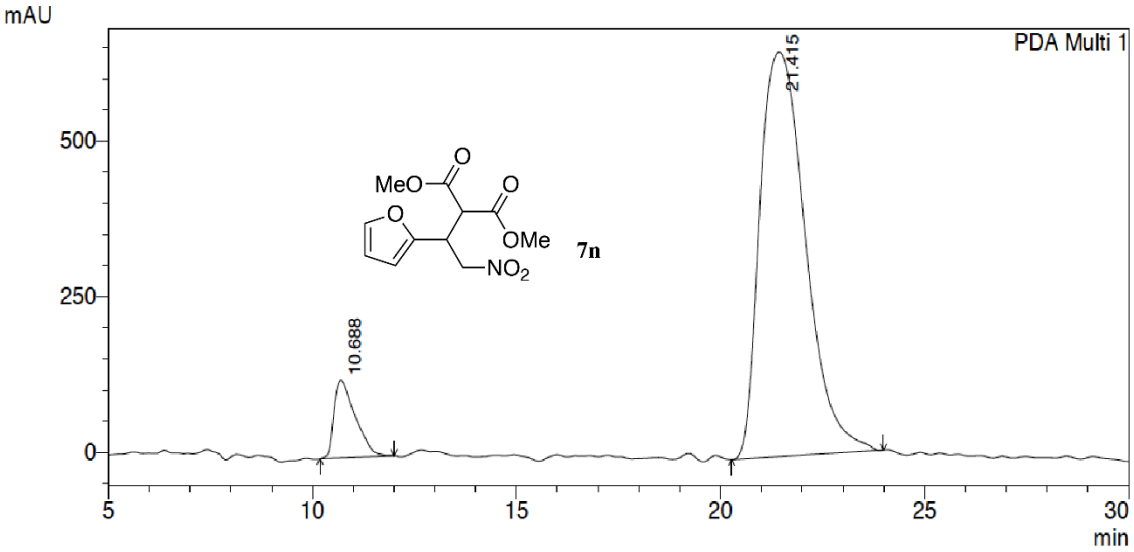


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.762	40142061	1075203	91.179	88.002
2	19.095	3883720	146590	8.821	11.998
Total		44025781	1221793	100.000	100.000

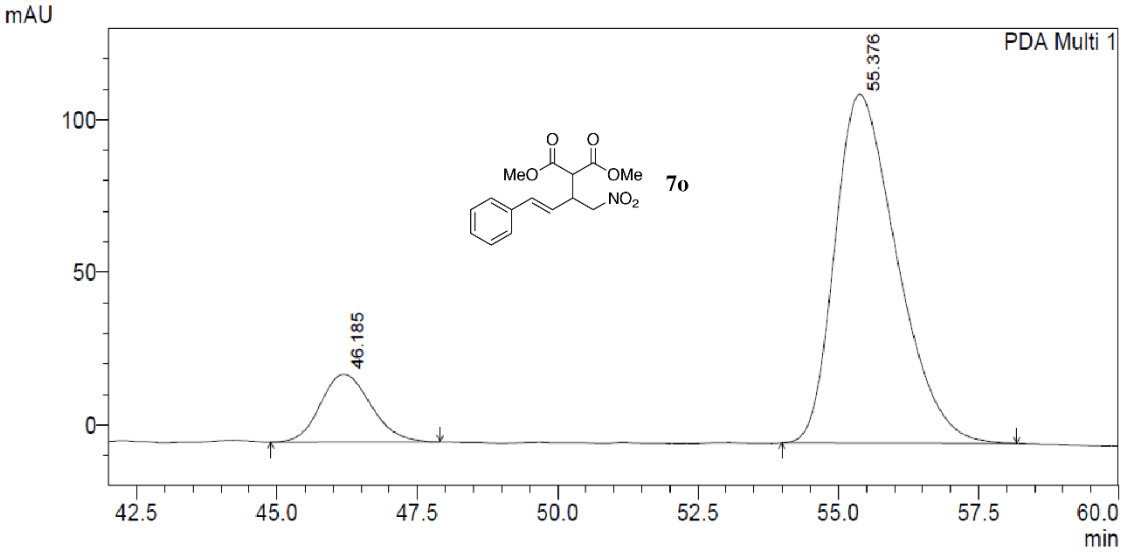


1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.688	4501488	124344	8.196	16.073
2	21.415	50423476	649299	91.804	83.927
Total		54924964	773643	100.000	100.000

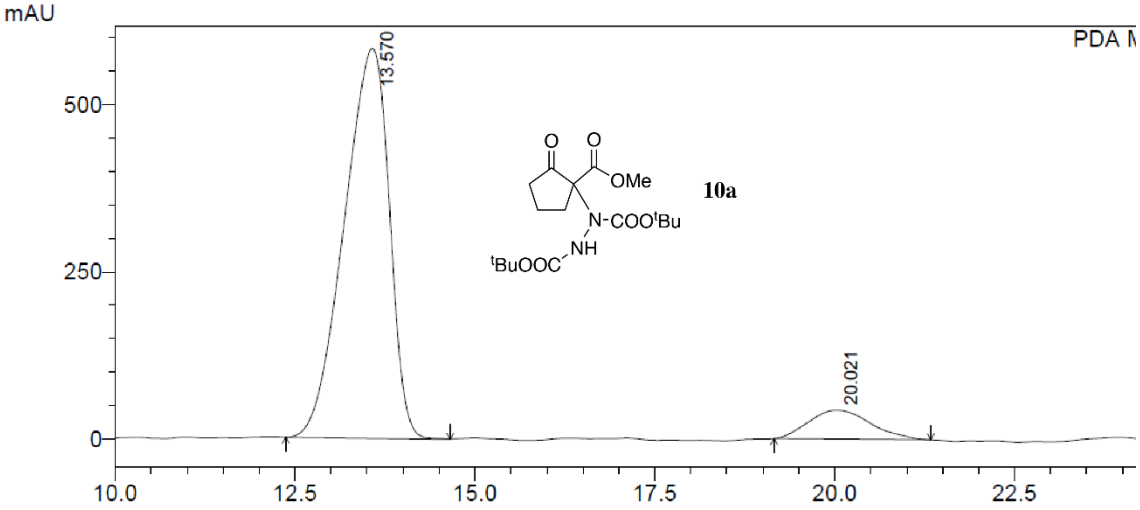


1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	46.185	1385094	22211	13.593	16.267
2	55.376	8804661	114324	86.407	83.733
Total		10189755	136534	100.000	100.000

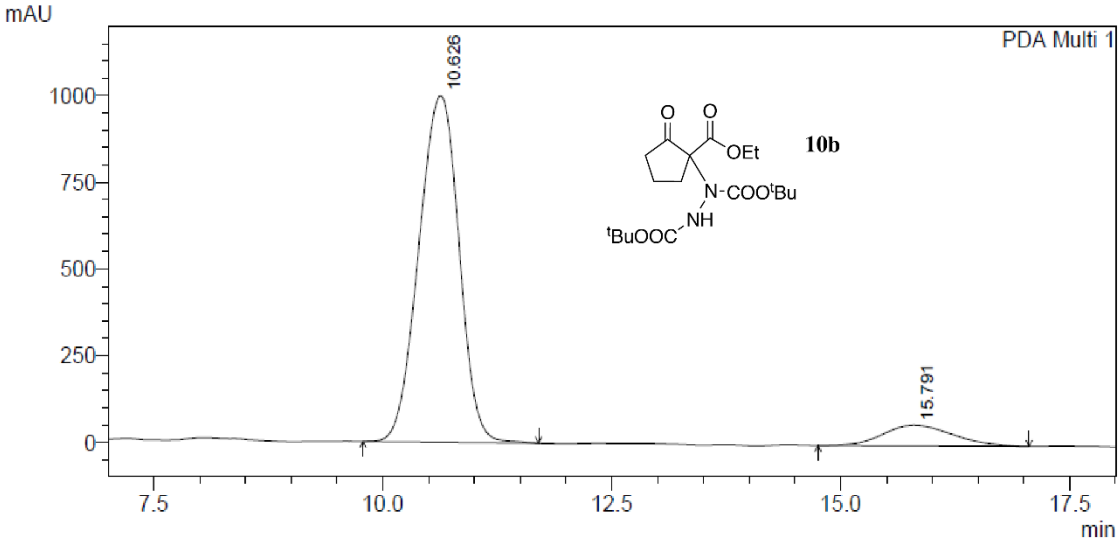


1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.570	25405995	583120	90.747	93.079
2	20.021	2590411	43358	9.253	6.921
Total		27996406	626478	100.000	100.000

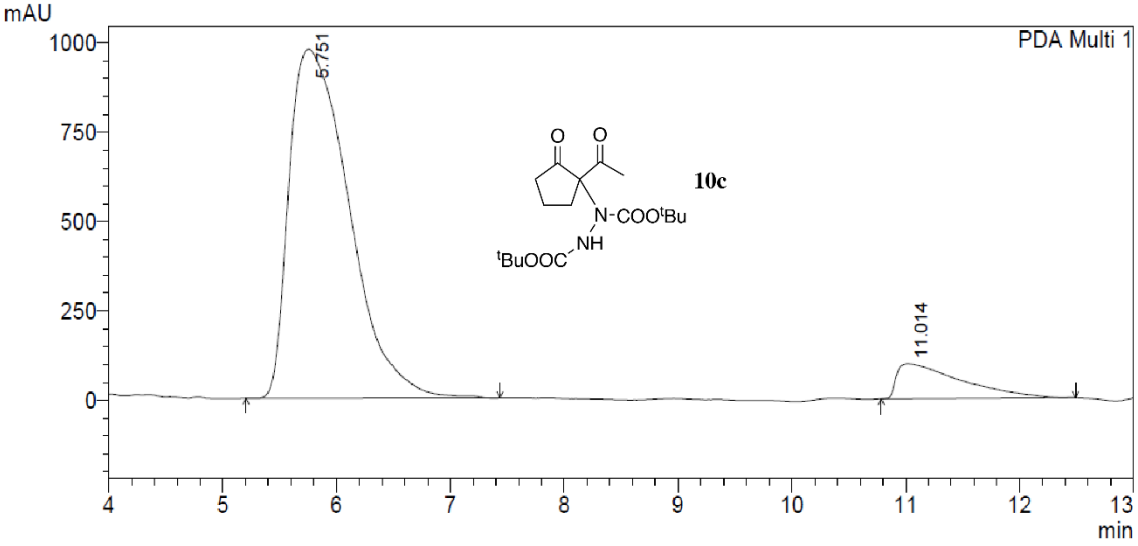


1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.626	30473749	998531	90.547	94.426
2	15.791	3181424	58947	9.453	5.574
Total		33655173	1057478	100.000	100.000

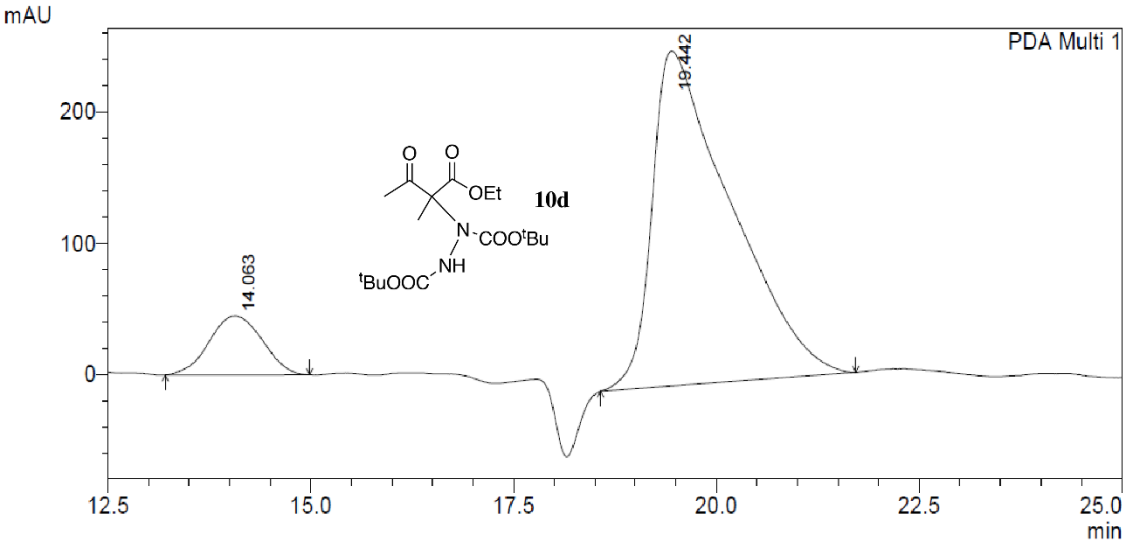


1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.751	35826029	976164	90.376	90.950
2	11.014	3815109	97136	9.624	9.050
Total		39641139	1073300	100.000	100.000

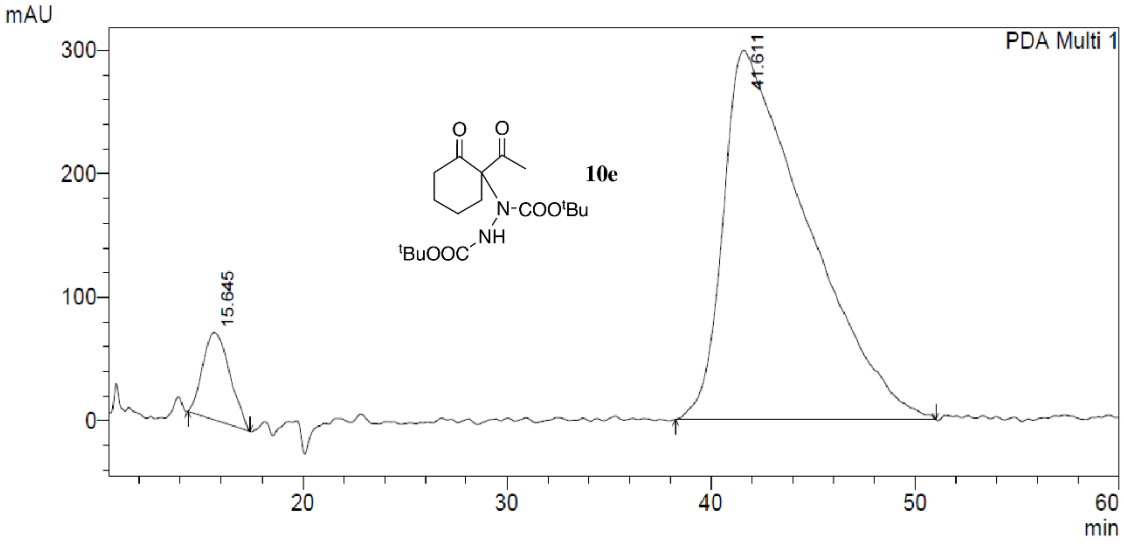


1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.063	2052636	44962	10.682	15.010
2	19.442	17162791	254582	89.318	84.990
Total		19215427	299544	100.000	100.000

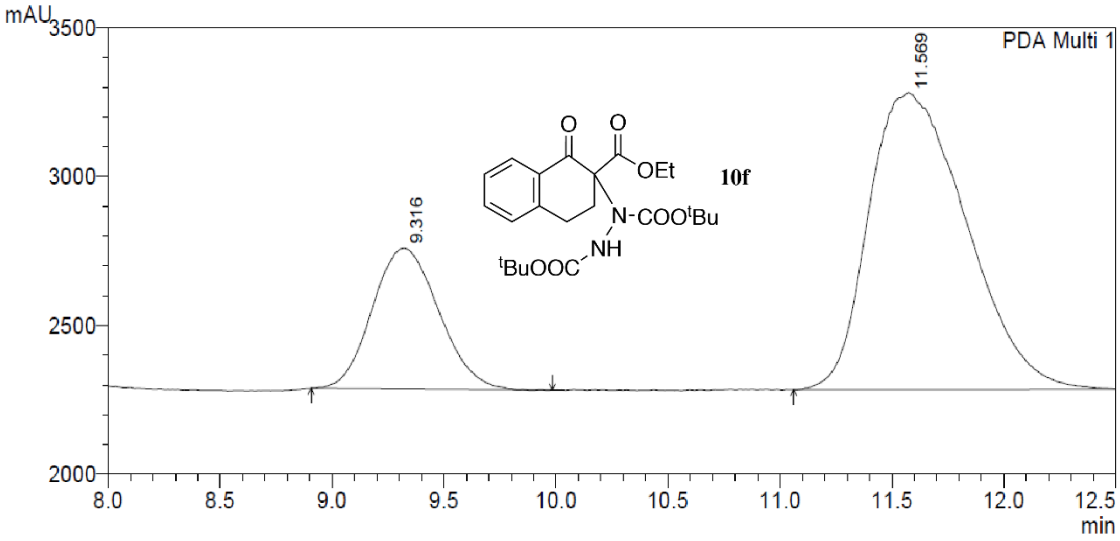


1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.645	6546369	70564	7.087	19.104
2	41.611	85825411	298801	92.913	80.896
Total		92371780	369365	100.000	100.000



1 PDA Multi 1/220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.316	9744256	472899	24.366	32.157
2	11.569	30246826	997711	75.634	67.843
Total		39991081	1470610	100.000	100.000