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An Air and Water Stable Hydrogen Bond Donor Catalyst for the Enantioselective Generation of Quarternary Carbon Stereocenters by Additions of Substituted Cyanoacetate Esters to Acetylenic Esters

Quang H. Luu and John A. Gladysz*[a]

Abstract: The chiral enantiopure cobalt(III) complex Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$B(C$_6$F$_5$)$_4^-$ (Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$B(C$_6$F$_5$)$_4^-$; dpen = 1,2-diphenylethylenediamine) is an effective catalyst, together with pyridine (10 mol% each), for enantioselective additions of substituted cyanoacetate esters NCCH(R)CO$_2$R' to acetylenic esters R"C≡CCO$_2$R"'. In the resulting adducts NC(R'O$_2$C)C-(R)CR"C=CHCO$_2$R"', C=C isomers in which the CO$_2$R"' moiety is *trans* to the new carbon-carbon bond dominate (avg. ratio 98:2). These are obtained in 70-98% ee (avg. 86%; data for optimum R' and R"'), as determined by ^{1}H NMR with the chiral solvating agent Λ-(*S*,*S*)-**2**$^{3+}$ 2I$^-$B-(3,5-C$_6$H$_3$(CF$_3$)$_2$)$_4^-$. NMR experiments show that the cyanoacetate and acetylenic esters and pyridine can hydrogen bond to certain NH groups of the catalyst. Rates are zero order in the cyanoacetate and acetylenic esters as well as the catalyst, and implications are discussed.

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Introduction

The efficient enantioselective synthesis of compounds with quaternary carbon stereocenters has been a subject of immense interest over the last 25 years, as reflected by an extensive review literature that emphasizes catalytic methods.[1] There has been a particular focus upon conjugate additions. In this context, racemic "active methylene compounds" with a single carbon-hydrogen bond and three unlike carbon substituents represent attractive building blocks. One obvious choice would be substituted cyanoacetate esters NCCH(R)CO_2R', large numbers of which are commercially available or easily prepared. However, many types of acceptors (e.g., conjugated cycloalkenones) would yield a second carbon stereocenter, such that diastereoselectivity also becomes an issue.

Given the new family of catalysts that we were interested in applying to this problem (*vide infra*), we sought to evaluate their efficacies one stereocenter at a time. One way to avoid generating a second stereocenter in additions of substituted cyanoacetate esters would be to employ an acetylenic acceptor, as generalized in Figure 1 (top). Of course, there would be the possibility of *cis*/*trans* or *Z*/*E* isomers about the resulting C=C linkage. However, this was seen as a more tractable complication.

Others have recognized the attractiveness of substituted cyanoacetate esters as building blocks.[2] Of particular value is the attendant installation of multiple functional groups that can be elaborated under different conditions.[3] However, there have only been scattered reports dealing with acetylenic acceptors, and the best literature methods are summarized in Figure 1. One of these, developed by Maruoka, used an enantiopure phase transfer catalyst (**I**).[2a] In this work, only cyanoacetate esters with aliphatic substituents gave high enantioselectivities. Another, developed by Ikariya, used an enantiopure ruthenium Lewis acid catalyst.[2b] However, only cyanoacetate esters with aryl substituents were reported. We saw these divergent strengths and weaknesses as opportunities that might be addressed with new types of catalysts.

In parallel with the review literature cited,[1] there has been extensive recent interest in chiral organic hydrogen bond donor catalysts.[4] Some of these are quite effective for the enanti-

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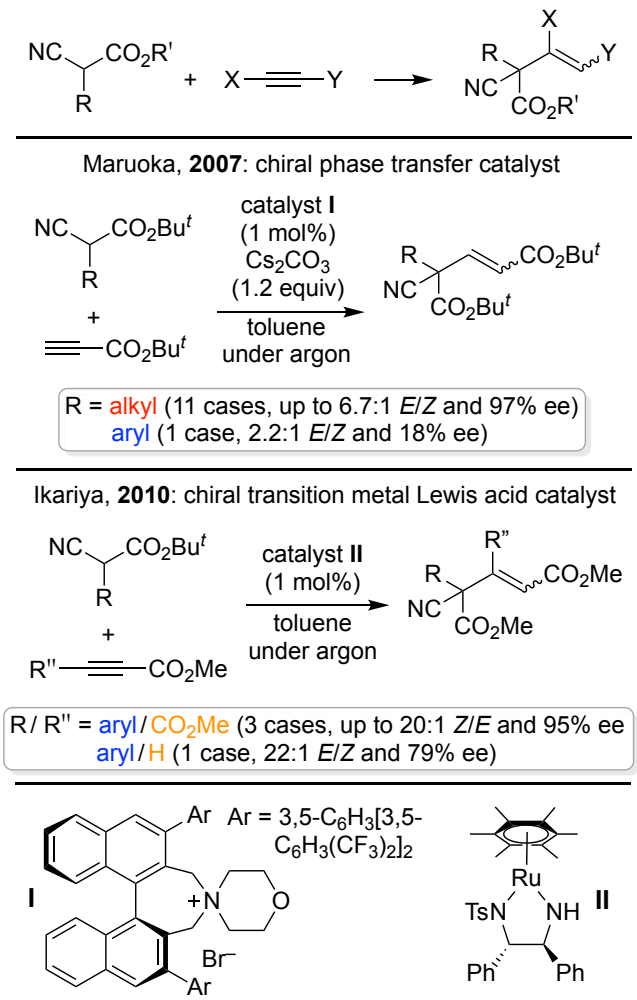

Figure 1. Enantioselective catalysts for additions of substituted cyanoacetate esters to acetylenic esters developed to date.

oselective construction of quaternary carbon centers from other combinations of reactants.[1f,5] Our research group,[6-9] together with several others,[10-12] has been interested in developing chiral transition metal containing hydrogen bond donors. One impetus has been the application of an untapped region of the chiral pool, believed to provide binding motifs and modes of action that significantly differ from organic counterparts.[13]

Our main catalyst family was inspired by Werner's reports of the first enantiopure chiral inorganic compounds over a century ago.[14,15] One of these, $[Co(en)_3]^{3+}$ $3Cl^-$ ($\mathbf{1}^{3+}$ $3Cl^-$; en = ethylenediamine),[14e] can be prepared by undergraduate students in an afternoon.[16] The configurations of such "chiral at metal" species are conventionally designated Λ and Δ,[17] as depicted in Figure 2 (top). The former exhibits a left handed helical array of chelate rings, and

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the latter a right handed array. However, tris(1,2-diamine) cobalt(III) complexes are substitution inert,[18,19] which precludes direct activation of substrates by the metal. But tellingly, crystal structures reveal extensive NH hydrogen bonding interactions with counter anions.[20]

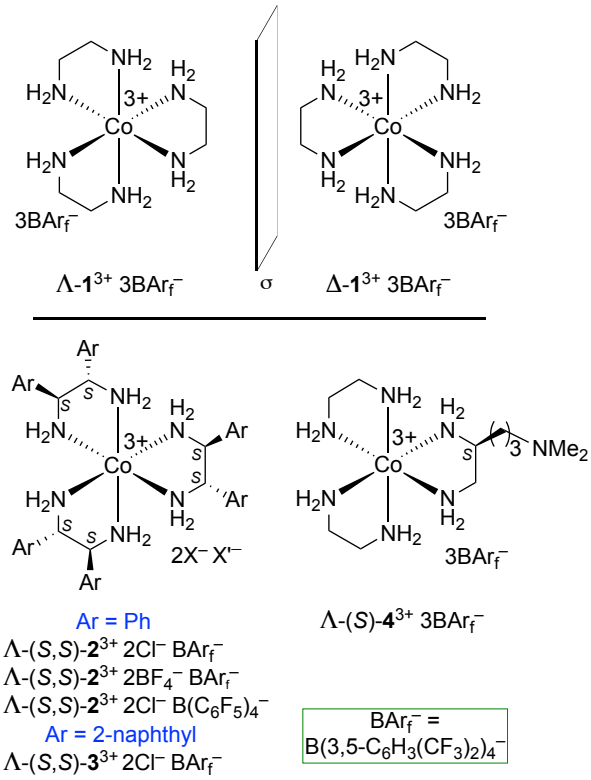

Figure 2. Catalysts screened in this study.

Accordingly, we prepared various tris(1,2-diamine) cobalt salts with one or more tetraarylborate anions of the formula $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$ (BAr_f^-) or $B(C_6F_5)_4^-$.[6-8,21] These anions are very poor hydrogen bond acceptors[22] and help to solubilize the trications in standard organic solvents. In aqueous solution, water would presumably compete for the substrate binding sites, and many educts would be insoluble. In any case, the complexes in Figure 2 have been applied to several types of carbon-carbon and carbon-nitrogen bond forming reactions known to be catalyzed by hydrogen bond donors.[6-8]

We have found that tris(adducts) of 1,2-diphenyl ethylenediamine (dpen), $[Co(dpen)_3]^{3+}$ $2X^-X'^-$ ($\mathbf{2}^{3+}$ $2X^-X'^-$), are often particularly enantioselective catalysts. The *S*,*S* and *R*,*R* enantiomers of this ligand are commercially available at surprisingly modest prices.[23] With the former, two sets of diastereomers are possible, the salts Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2X^-X'^-$ depicted in Figure 2, and the

cobalt epimers Δ-(*S*,*S*)-**2**$^{3+}$ 2X^{-}X'$^{-}$. The enantiomeric catalysts derived from (*R*,*R*)-dpen would be expected to give identical ee values (but opposite product configurations).

Analogous complexes have been prepared with a wide variety of aryl groups in place of the dpen phenyl groups.[21] Thus, a catalyst with 2-naphthyl substituents, Λ-(*S*,*S*)-**3**$^{3+}$ 2Cl^{-}BAr$_f^{-}$ (Figure 2), has been included in this study. In addition, a bifunctional catalyst with an internal tertiary amine, Λ-(*S*)-**4**$^{3+}$ 3BAr$_f^{-}$ (Figure 2), which obviates the need for an external base and has given highly enantioselective reactions,[8] has also been examined in screening reactions below.

Accordingly, in this paper we compare the efficacies of the complexes in Figure 2 and selected diasteromers as catalysts for enantioselective additions of substituted cyanoacetate esters to acetylenic esters (Figure 1, top). From the standpoints of isolated yields, ee values, and substrate generality, Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$ clearly emerges as the best of a limited number of other catalysts (Figure 1) that have previously been reported to effect this transformation.

Results

1. Catalyst Screening. In initial scout experiments, commercial dimethyl acetylenedicarboxylate (**4a**) and ethyl phenylcyanoacetate (**5a**) were combined in a 1.1:1.0 mol ratio in CH_2Cl_2 at a temperature specified in Table 1. Then the indicated catalyst (10 mol%) and base were added. The latter was applied in both stoichiometric (100 mol%) and catalytic (10 mol%) quantities. When TLC indicated that the reaction was complete, the solvent was removed and the residue taken up in $CDCl_3$. The *Z*/*E* ratio of the crude addition product **6aa** was then assayed by ^{1}H NMR (structure and data: Table 1; *Z*/*E* =CH 5.88-5.89/7.07-7.08 ppm, s). Chromatographic workups gave pure **6aa** in 99-95% yields. The ee values were determined by ^{1}H NMR using the chiral solvating agent Λ-(*S*,*S*)-**2**$^{3+}$ 2I^{-}BAr$_f^{-}$.[24] These and all other reactions and workups were carried out in air.

Table 1 shows that useful levels of enantioselectivities were found only with the catalyst Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$ and the base pyridine at –36 °C (entry 12). None of the other catalysts were effective (entries 2-6). Interestingly pyridine was best used in catalytic quantities (entry 12 vs. 13). Furthermore, these conditions gave close to the highest *Z*/*E* product ratio (91:9). As

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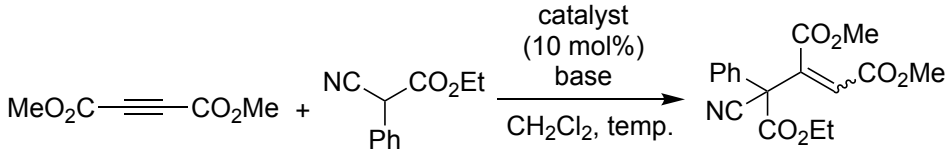
Table 1. Screening of catalysts for the addition of ethyl phenylcyanoacetate (**5a**) to dimethyl acetylenedicarboxylate (**4a**).[a]



4a **5a** **6aa**

Entry	Catalyst	Base (mol%)	Time (h)	Temp. (°C)	Yield (%)[b]	*Z*/*E*[c]	ee (%)[d]
1	-	Et_3N (100)	12	23	99	78/22	0/0
2	Λ-$\mathbf{1}^{3+}$ 3BAr_f^-	Et_3N (100)	0.20	23	99	61/39	0/0
3	Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$BF_4^-$$BAr_f^-$	Et_3N (100)	12	23	99	75/25	10/4
4	Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-$$BAr_f^-$	Et_3N (100)	12	23	99	78/22	0/0
5	Λ-(*S*,*S*)-$\mathbf{3}^{3+}$ 2$Cl^-$$BAr_f^-$	Et_3N (100)	12	23	99	83/17	16/0
6	Λ-(*S*)-$\mathbf{4}^{3+}$ 3BAr_f^-	-	12	23	99	69/31	18/40
7	Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-B(C_6F_5)_4^-$	Et_3N (100)	12	23	99	79/21	0/0
8	Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-B(C_6F_5)_4^-$	Et_3N (100)	11	23	99	85/15	36/2
9	Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-B(C_6F_5)_4^-$	Et_3N (10)	12	23	99	87/13	30/11
10	Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-B(C_6F_5)_4^-$	-	24	23	<1	-	-
11	Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-B(C_6F_5)_4^-$	Et_3N (10)	15	–36	99	88/12	54/13
12	Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-B(C_6F_5)_4^-$	pyridine (10)	17	–36	95	91/9	99[e]/10
13	Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-B(C_6F_5)_4^-$	pyridine (100)	17	–36	99	95/5	44/22
14	Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$Cl^-B(C_6F_5)_4^-$	pyridine (100)	12	23	99	95/5	14/13

[a]A vial was charged with stir bar, **4a** (0.0078 g, 0.055 mmol, 0.0068 mL), **5a** (0.0095 g, 0.050 mmol, 0.0087 mL), and CH_2Cl_2 (0.50 mL). The sample was bought to the indicated temperature, and a catalyst (0.0050 mmol, 10 mol%) and a base were added with stirring. The reaction was monitored by TLC and was worked up as described in the experimental section. [b]Isolated yields after chromatography. [c]Determined by ^{1}H NMR. [d]Determined by ^{1}H NMR using 10 mol% of the CSA Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ 2$I^-$$BAr_f^-$. [e]Lowering the catalyst loading to 5.0 or 2.0 mol% gave **6aa** in 59% or 38% ee.

with the other catalysts, the enantiomeric purity of the minor *E* isomer was poor (10% ee), but that of the major *Z* isomer was excellent (99% ee). However, the ee dropped to 58% when the ca-

talyst loading was decreased to 5%. Although Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}B(C_6F_5)$_4^{-}$ readily dissolves in CH_2Cl_2 solutions of the substrates, per the conditions employed in Table 1, it is only sparingly soluble in the absence of substrates. An expanded table with additional screening reactions is given in the supporting information (SI).

2. Reaction scope. The conditions in entry 12 of Table 1 were then applied to a variety of substrates as illustrated in Figure 3. When ethyl phenylacetate was replaced by ethyl benzylcyanoacetate (**5b**), the *Z*/*E* ratio of the product remained high (**6ab**; 99:1) but the enantiomeric purity fell to 44% ee. However, *t*-butyl benzylcyanoacetate (**5c**), which features a bulkier ester alkyl group, gave the corresponding adduct **6ac** as a >99:<1 *Z*/*E* mixture in 88% ee. Thus, *t*-butyl esters were used for the remaining reactions.

Next, the benzyl group in the preceding reaction was replaced by allyl, homoallyl, and related alkyl substituents. As shown for the adducts **6ad-g** in Figure 3, only *Z* isomers were obtained (88->99% yields), and with ee values of 70-98%. A series of four substrates with CH_2aryl substituents gave similar results (**6ah-k**, 70-99% yields, 85-91% ee). When di*ethyl* acetylenedicarboxylate (**4b**) and **5c** were similarly reacted, the enantiomeric purity of the product **6bc** was close to that obtained with **4a** (83% vs, 88% ee).

Other alkyne substrates were briefly investigated. When unsymmetrically substituted *t*-butyl propiolate (**4c**) and **5c** were analogously combined, a slower reaction took place. After 72 h at 23 °C, the addition product **6cc** (Figure 3) was isolated in 53% yield as a <1:>99 *Z*/*E* mixture with an enantiomeric purity of 94% ee. Note that despite the inverted *Z*/*E* ratio, the quarternary carbon atom remains *trans* to the carboalkoxy C=C substituent, exactly as in the other products. When di(*t*-butyl) acetylenedicarboxylate (**4d**) and **5c** were similarly combined, no reaction occurred, even after 72 h at 23 °C, presumably for steric reasons.

In view of evidence for catalyst/pyridine binding presented below, the reaction of **4a** and **5c** was also investigated with the more hindered Brønsted bases 2,6-dimethylpyridine (2,6-lutidine) and 2,6-di(*t*-butyl) pyridine (10 mol%). After 19 h, workups gave **6ac** in 99% and 22% yields, respectively. Much starting material remained in the second reaction. However, the enant-

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ioselectivities were essentially unaffected (89% and 86% ee), so these more costly bases offer no advantages.

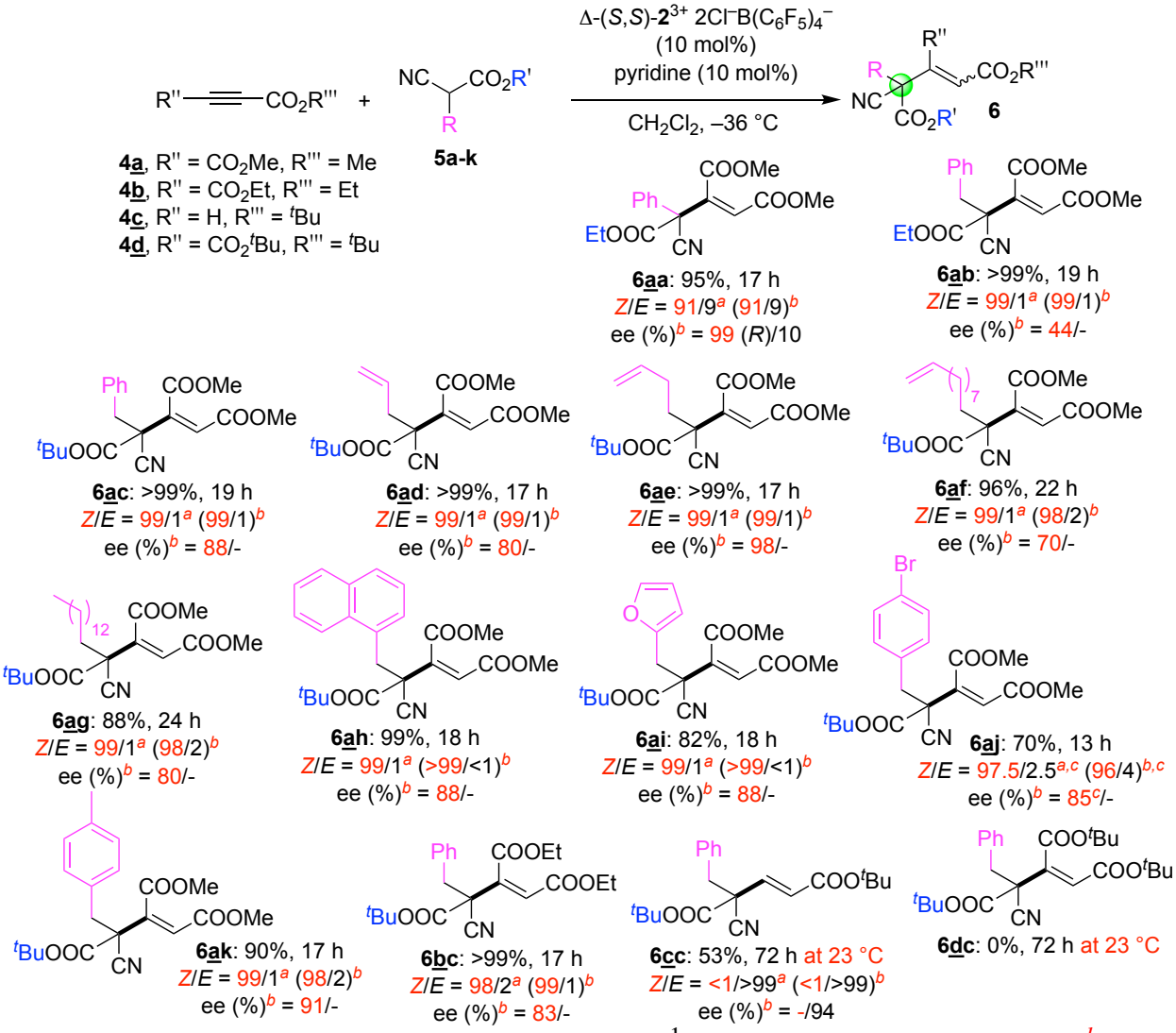

Figure 3. Substrate scope of the title reaction. [a]Determined by a ^{1}H NMR spectrum of the crude mixture. [b]Determined by ^{1}H NMR analysis of the purified product. [c]Average of six runs.

Of all the products in Figure 3, only **6aa** has been previously reported in the literature. The others were characterized by NMR (^{1}H, ^{13}C{^{1}H}) and C/H/N microanalyses, as summarized in the SI. For adducts with =CHCO$_2$R''' moieties, the ^{1}H NMR signal for the *E* C=C isomer was always downfield of the *Z*. Otherwise, all NMR features were routine. Four of the *t*-butyl cyanoacetate substrates were also new compounds (**5f**,**g**,**h**,**k**), and were prepared by standard procedures (usually alkylation) as described in the SI.

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3. Probes of mechanism. One fundamental question concerns the interaction of the reaction components with the catalyst Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$. The chiral cobalt trication has idealized D_3 symmetry, which means a principal C_3 axis that defines two "C_3 faces" and three C_2 axes in a perpendicular plane that define three "C_2 faces". These are illustrated in Figure 4,[7a] although it merits note that the idealized symmetry is never found crystallographically. For each NH$_2$ group, one proton is associated with a C_3 face, and the other (diastereotopic) with a C_2 face.

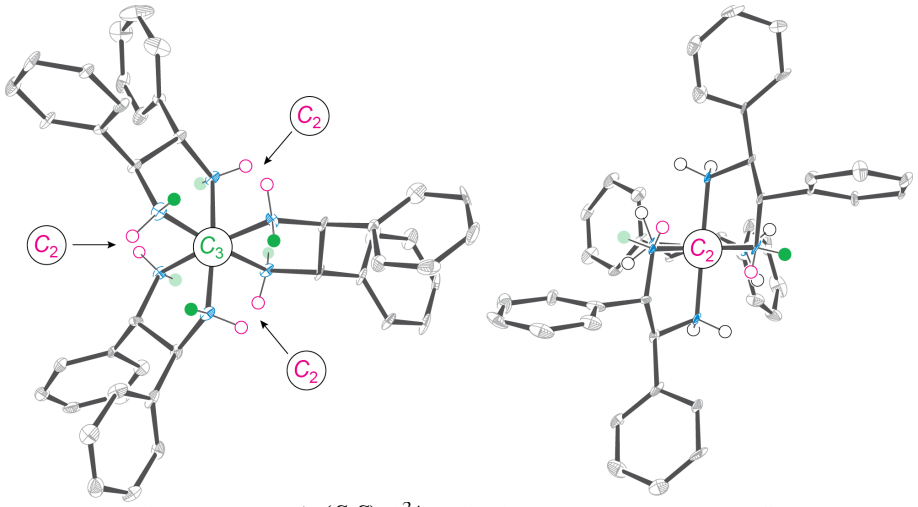

Figure 4. Representations of the trication Δ-(*S*,*S*)-**2**$^{3+}$; left, view down the idealized C_3 axis; right, view down one of three idealized C_2 axes.

Previous studies, especially with the diastereomeric BAr$_f^{-}$ salt Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}BAr$_f^{-}$, have established significant hydrogen bonding between the two chloride anions and the two C_3 faces.[7a,21] Each face offers three roughly synperiplanar NH protons, which are depicted in green in Figure 4. Hence, the ^{1}H NMR chemical shifts of these six NH protons are significantly downfield of the other six. Each C_2 face features two roughly synperiplanar NH protons, which are depicted in magenta.

Thus, 10.0 equiv of dimethyl acetylenedicarboxylate (**4a**), ethyl phenylcyanoacetate (**5a**), and pyridine were separately titrated into a sample of CD$_2$Cl$_2$ and the catalyst Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-} B(C$_6$F$_5$)$_4^{-}$. The amounts of the catalyst and solvent were identical to those used in Table 1, and therefore the catalyst was only partially soluble until ca. 4 equiv of the additive was present. This renders the spectra with 1.0-3.0 equiv of additive less rigorously comparable to the others. In any case, the initial chemical shift difference between the diastereotopic protons associated with the

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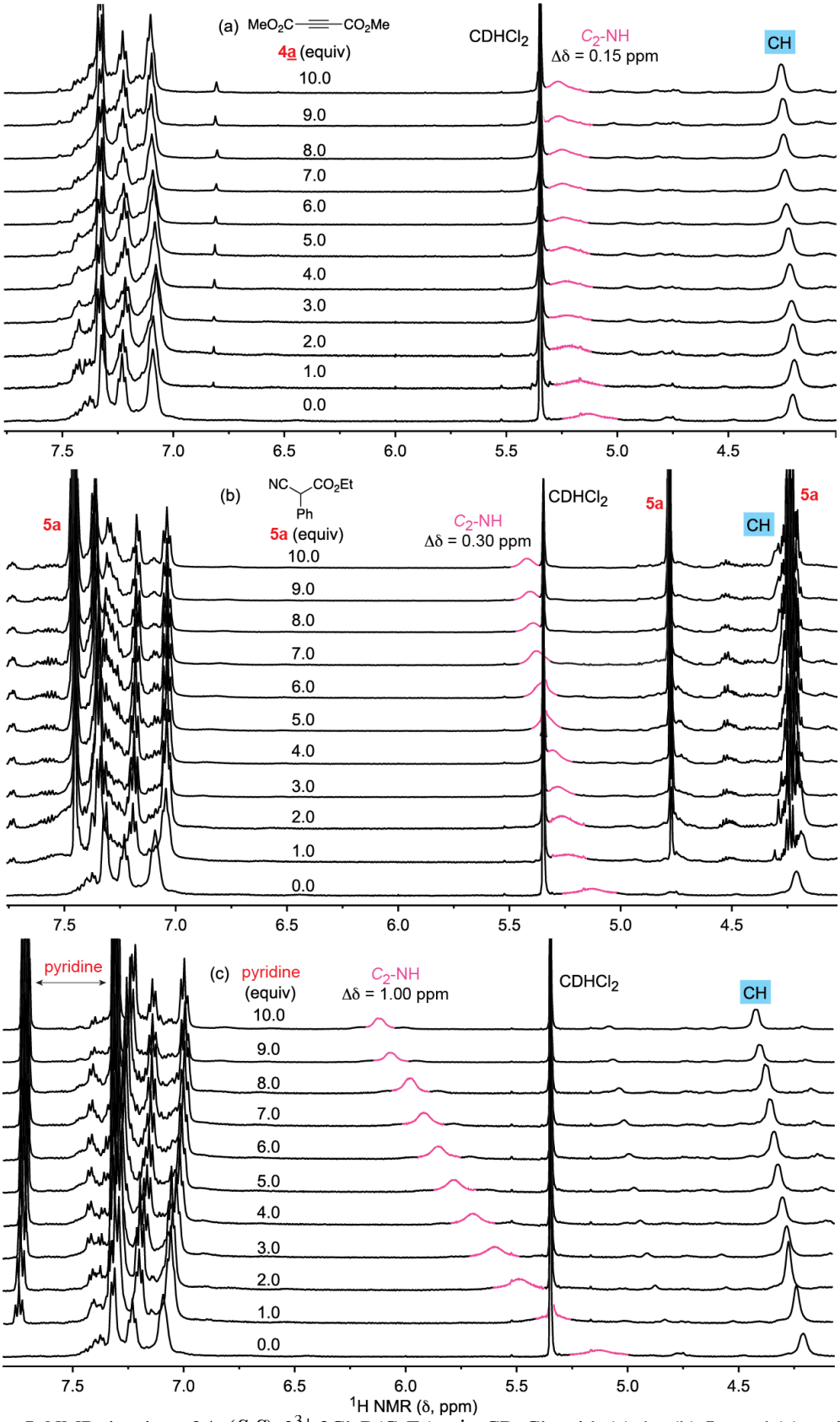

Figure 5. NMR titration of Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^{-}B(C_6F_5)_4^{-}$ in CD_2Cl_2 with (a) **4a**, (b) **5a**, and (c) pyridine.

C_3 and C_2 faces is ca. 2.1 ppm (the former signal is obscured by the phenyl protons of the catalyst).

As shown in Figure 5a (top), the successive addition of **4a** led to a slight downfield shift of the C_2 NH signal (δ 5.12 to 5.27 ppm; Δδ 0.15 ppm). Any shift of the obscured C_3 NH signal could be bounded as less than Δδ 0.01 ppm (upfield). For reference, the signal of the aliphatic CH groups, which always neighbor a NH_2 group, shifted less than the C_2 NH signal (δ 4.21 to 4.26 ppm; Δδ 0.05 ppm).

As shown in Figure 5b (middle), the successive addition of **5a** led to a more pronounced downfield shift of the C_2 NH signal (δ 5.12 to 5.42 ppm; Δδ 0.30 ppm). The C_3 NH signal was obscured by the phenyl protons of the catalyst and **5a**, and the aliphatic CH signal was obscured by the methylene protons of **5a**.

As shown in Figure 5c (bottom), the successive addition of pyridine led to a pronounced downfield shift of the C_2 NH signal (δ 5.12 to 6.12 ppm; Δδ 1.00 ppm). The C_3 NH signal was obscured by the aromatic protons of the catalyst and pyridine. The aliphatic CH signal shifted much less than the C_2 NH signal (δ 4.21 to 4.42 ppm; Δδ 0.21 ppm).

In a quest for further insight, reaction orders were sought. For this purpose, the recently popularized reaction progress kinetic analysis method was applied.[25] Accordingly, **4a**, **5a**, pyridine, Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^-B(C_6F_5)_4^-$, and CD_2Cl_2 were combined in a NMR tube in a manner similar to that in Table 1. but in the presence of the internal standard Ph_2SiMe_2. The reaction was monitored by ^1H NMR at –36 °C. The concentration of **5a** and the rate (Δ([**5a**])/Δt) were then plotted against the reaction time as shown in Figure 6 for three experiments with 2.0, 5.0, and 10 mol% catalyst loadings.

Concentration and rate data for **4a** were similarly treated (Figure s18, SI). Analyses established positive orders for **4a** and **5a** during the first hour after mixing. These then transitioned to zero order, which was maintained until the reaction was complete. The same data set was used for probing the order in catalyst. In an application of the time normalization method,[26] the concentration of **5a** was plotted against the normalized time (see experimental section) at different

orders *n* as shown in Figure s19 (SI). The best fit was obtained for $n = 0$, indicating a rate zero order in Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$. These data are further interpreted in the discussion section.

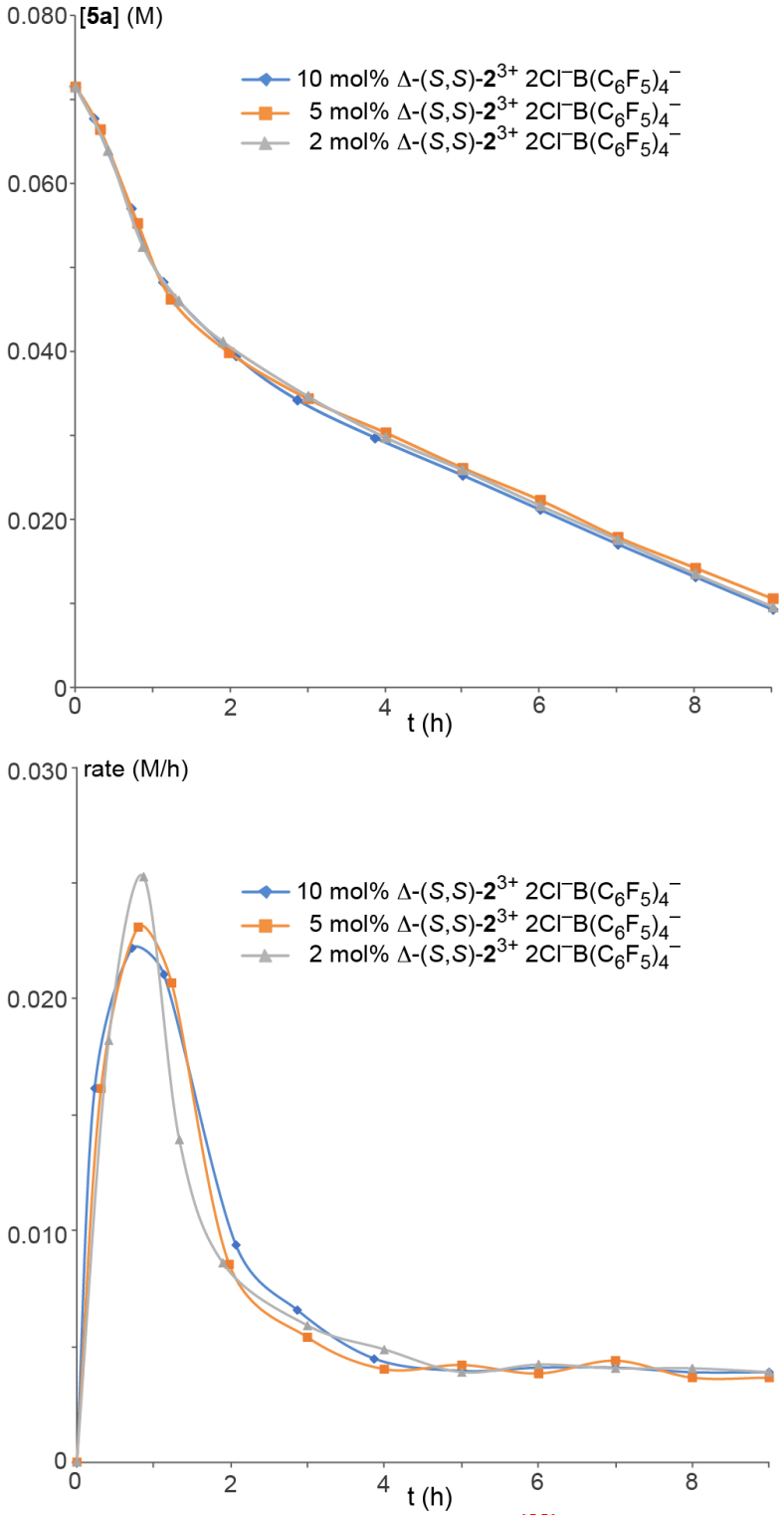

Figure 6. Application of the reaction progress kinetic analysis method[25] to a reaction similar to entry 12 of Table 1 (further details: see text). Top: plot of the concentration of **5a** versus time. Bottom: plot of Δ([**5a**])/Δt versus time.

Discussion

As summarized in Figure 3, the cobalt complex Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$ and the base pyridine represent the best available catalyst system for enantioselective additions of substituted cyanoacetate esters to acetylenic esters, a powerful route to quaternary carbon stereocenters. The products are amenable to a number of subsequent functionalization protocols,[3] rendering them versatile synthetic building blocks. Furthermore, the reactions may be conducted in air, and the cobalt catalyst is commercially available.[27]

The objective of Figure 3 is to present the substrate scope in its entirety, with full representation of strengths and weaknesses. In some of the products with lower ee values, it is a simple matter of introducing a bulkier ester alkyl group on the cyanoacetate to obtain much higher ee values (e.g., ethyl vs. *t*-butyl as in **6ab and 6ac**). However, replacing the methyl or ethyl groups of the acetylene dicarboxylate diester with *t*-butyl groups kills all reactivity (e.g., **6ac** or **6bc** vs. **6dc**). In any case, considering only the optimum ester alkyl groups (R', R"'), the ee values range from 70 to 98% with an average of 86%.

It would be premature to read too much significance into the poorer performing catalysts in Table 1. For example, bifunctional organocatalysts often give superior enantioselectivities.[4d,e] Indeed, Λ-(*S*)-**4**$^{3+}$ 3BAr$_f^{-}$, which features a tertiary amine tethered by a (CH$_2$)$_3$ spacer, has proven to be a highly enantioselective catalyst for certain addition reactions that require a Brønsted base,[8] and was therefore available in quantity for this study. However, catalysts with other tether lengths have also been prepared (e.g., (CH$_2$)$_n$ with n = 1-4), as have the corresponding Δ diastereomers, and these remain to be screened. In the same vein, the naphthyl substituted catalyst Λ-(*S*,*S*)-**3**$^{3+}$ 2Cl^{-}BAr$_f^{-}$ is not yet available as the Δ diasteromer or analogous 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$ salt, two attributes of the best catalyst in Table 1.

Our data also illustrate the versatility of the chiral solvating agent (CSA) Λ-(*S*,*S*)-**2**$^{3+}$ 2I^{-} BAr$_f^{-}$, which is easily prepared in one step from a commercial precursor, for determining the enantiomeric purities of analytes with Lewis basic functional groups.[24] For most of the products in Figure 3, only 10 mol% is required. It is not surprising that a class of complexes capable of

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highly sensitive chiral recognition also can effect highly enantioselective catalysis.

Finally, to round out the picture with respect to other chiral hydrogen bond donor catalysts, three protocols that give other types of addition products with quaternary carbon stereocenters are illustrated in Figure 8.[5,10e] All of these deliver excellent enantioselectivities. One, developed by Meggers, features an iridium containing catalyst with NH donor groups that effects additions of indoles to trisubstituted nitroalkenes.[10e]

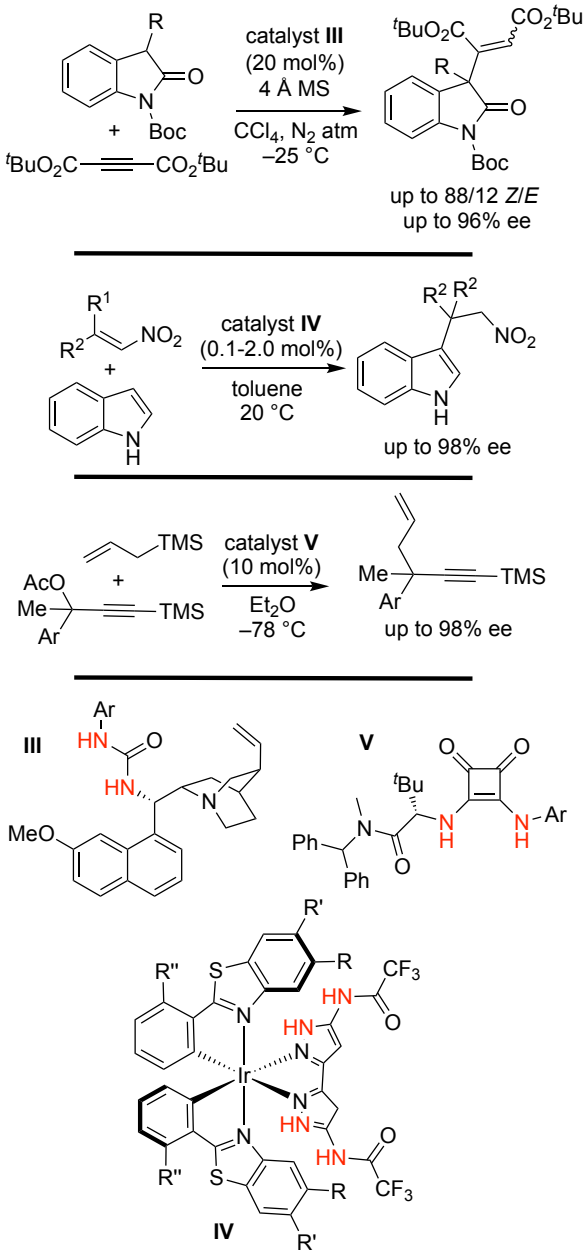

Figure 8. Enantioselective syntheses of compounds with quaternary sterecenters using other chiral hydrdogen bond donor catalysts.

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Some headway has been made in computationally determining the mechanisms of enantioselective addition reactions catalyzed by metal containing hydrogen bond donors.[9c] However, these have involved ruthenium catalysts where the NH groups are remote from the metal and only three can simultaneously participate in the transition state. The situations with cobalt(III) catalysts of the types in Figure 2 are potentially much more complex. For example, it is clear from Figure 4 that 4-5 NH groups could potentially participate in a transition state assembly.

In any case, NMR data (Figure 5) establish that the C_2 site is capable of binding both types of substrates as well as the base pyridine. The greater downfield shifts observed with pyridine suggest a stronger binding constant. This could be a factor in the lower enantioselectivities when pyridine is used in a ten fold molar excess of the catalyst as opposed to a 1:1 ratio (Table 1, entries 13 vs. 12). Similar NMR evidence has been obtained with related catalysts, such as the diastereomeric salt Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$, for substrate binding to the C_2 site.[7a,24]

However, there is also evidence that some level of access to the C_3 site can be required. Specifically, rates of additions of malonate esters to nitroalkenes become faster when the chloride ions of Λ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$BAr$_f^-$ are replaced by more weakly hydrogen bonding anions such as BF_4^- and PF_6^-.[7a] Our own view is that a multitude of mechanistic pathways is available to this family of cobalt(III) complexes for catalyzing various addition reactions. For example, with some reactions Λ diastereomers of (*S*,*S*)-**2**$^{3+}$ 2X$^-$X'$^-$ provide higher enantioselectivities,[7a,7c] and with other reactions Δ diastereomers are more effective.[7b]

The reaction orders supplied by the data in Figures 6, s18, and s19 generate more questions than answers. The zero order dependence upon the concentrations of the alkyne, cyanoacetate ester, and catalyst suggest a rest state and transition state of the same atomic compensation. A low energy ternary adduct is consistent with the enhanced solubility of Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl$^-$B(C$_6$F$_5$)$_4^-$ in CD_2Cl_2 in the presence of the alkyne and cyanoacetate substrates. However, efforts to further define the mechanism have been hampered by problems with parallel experiments involving pyridine. For some reason, the data do not give interpretable plots. Despite the incomplete picture, it was felt best to share all data at this time.

In terms of reactions that can be effected with organocatalysts, zero order behavior with respect to one or both substrates is not unusual.[25,28] Initial regimes with positive order, as observed in Figures 6 and s18, have been attributed to the interval required for accumulating both substrates on the catalyst to form the intermediate.[25,28b,c] Also, reactions of metal containing catalysts that are zero order in catalyst have ample precedent.[29]

In summary, this study has significantly expanded the scope of enantioselective reactions that can be catalyzed with chiral tris(1,2-diamine) cobalt(III) hydrogen bond donor catalysts of the types in Figure 2. Furthermore, it is the first that can be advertised as significantly improving upon existing literature catalysts, as opposed to being comparably effective. The synthesis and evaluation of new types of enantiopure cobalt(III) catalysts in additional organic reactions will be described in future reports.

Experimental Section

General. The complexes Λ-**1**$^{3+}$ 3BAr_f^-,[6] Λ-(*S*,*S*)-**2**$^{3+}$ 2$Cl^-BAr_f^-$,[21] Λ-(*S*,*S*)-**2**$^{3+}$ 2$BF_4^-BAr_f^-$,[21] Λ-(*S*,*S*)-**2**$^{3+}$ 2$Cl^-B(C_6F_5)_4^-$,[21] Δ-(*S*,*S*)-**2**$^{3+}$ 2$Cl^-B(C_6F_5)_4^-$,[21] Λ-(*S*,*S*)-**3**$^{3+}$ 2$Cl^-BAr_f^-$,[21] Λ-(*S*)-**4**$^{3+}$ 3BAr_f^-,[8] and Λ-(*S*,*S*)-**2**$^{3+}$ 2$I^-BAr_f^-$,[24] most of which are shown in Figure 2, were synthesized as reported earlier. Data on the starting materials, solvents, and instrumentation are provided in the supporting information (SI). All reactions and workups were conducted in air.

Catalyst screening (Tables 1 and s1). A vial was charged with a stir bar, **4a** (0.0078 g, 0.055 mmol, 0.0068 mL), **5a** (0.0095 g, 0.0050 mmol, 0.0087 mL), and CH_2Cl_2 (0.50 mL). The sample was bought to the indicated temperature, and the catalyst (0.0050 mmol, 10 mol%) and base were added with stirring (100 mol% base: neat Et_3N (0.0051 g, 0.050 mmol, 0.0070 mL) or pyridine (0.0040 g, 0.050 mmol, 0.0040 mL); 10 mol% base: 0.20 mL of a 0.025 M CH_2Cl_2 solution). The reaction was monitored by TLC (silica gel, 9:1 v/v hexanes/ethyl acetate). After the time indicated in Table 1, the vial was opened to air and (for low temperature runs) allowed to warm to room temperature. The solvent was removed by rotary evaporation, and $CDCl_3$ (0.70 mL) was added. The *Z*/*E* C=C ratio was assayed by ^{1}H NMR (*Z*/*E* =CH: 5.88-5.89/7.07-7.08

ppm, s/s). The sample was chromatographed (silica gel, 1 × 20 cm column, packed in and eluted with 9:1 v/v hexanes/ethyl acetate). The product containing fractions were combined and the solvents were removed by rotary evaporation to give **6aa**. See the SI for further data.

Additions of cyanoacetate esters 5 to acetylenic esters 4 (Figure 3). A vial was charged with a stir bar, an alkyne **4** (0.055 mmol), a cyanoacetate **5** (0.050 mmol), and CH_2Cl_2 (0.50 mL). Except for the last two systems in Figure 3, the sample was placed in a –36 °C freezer and stirred. After 10 min, Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^-B(C_6F_5)_4^-\cdot 3H_2O$ (0.010 g, 0.0050 mmol, 10 mol%) and a CH_2Cl_2 solution of pyridine (0.025 M, 0.20 mL, 0.0050 mmol) were added. The reaction was monitored by TLC (silica gel, 9:1 v/v hexanes/ethyl acetate). After the specified time, the samples of **6** were transferred to a hood, opened to air, and worked up analogously to those in Table 1. Additional data are supplied in the SI.

Determination of ee values.[24] An NMR tube was charged with $CDCl_3$ (0.30 mL), a product **6** (0.010 mmol), and a 0.0050 M $CDCl_3$ solution of the chiral solvating agent Λ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2I^-BAr_f^-\cdot 0.5H_2O$ (0.20 mL, (0.0010 mmol, 10 mol%) for **6aa**-**6ae**, **6ah**, **6ai**, **6ak**, **6bc**, and **6cc**; 0.40 mL (0.0020 mmol, 20 mol%) for **6af** and **6ag**; 0.80 mL (0.0045 mmol, 45 mol%) for **6aj**).[24] A ^1H NMR spectrum was acquired and selected signals of the enantiomers were integrated (see Figures s5-s17).

NMR titration experiments (Figure 5). An NMR tube was charged with Δ-(*S*,*S*)-$\mathbf{2}^{3+}$ $2Cl^-B(C_6F_5)_4^-\cdot 3H_2O$ (0.010 g, 0.0050 mmol) and CD_2Cl_2 (0.70 mL). The catalyst was only partially soluble. A ^1H NMR spectrum was recorded. A 1.0 M CD_2Cl_2 solution of pyridine was added in 0.0050 mL increments (0.0050 mmol). A ^1H NMR spectrum was recorded after each addition. The experiment was repeated with solutions of **4a** and **5a**.

Rate Experiments (Figure 6). A (determination of the order in **4a** and **5a**). An NMR tube was charged with a stir bar, **4a** (0.0078 g, 0.055 mmol, 0.0068 mL), **5a** (0.0095 g, 0.0050 mmol, 0.0087 mL), the internal standard Ph_2SiMe_2 (0.0021 g, 0.010 mmol, 0.0022 mL), and CD_2Cl_2 (0.50 mL). The sample was vigorously stirred. The resulting solution was cooled to –36 °C, the stir bar removed, and a ^1H NMR spectrum recorded. The stir bar was reintroduced, the

solution cooled to –36 °C, and Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$·3H$_2$O (0.010 g, 0.0050 mmol, 10 mol%), and a CD_2Cl_2 solution of pyridine (0.025 M, 0.20 mL, 0.0050 mmol) were added with stirring. ^{1}H NMR spectra were recorded at t (min) = 5, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420, 480, 540 (always temporarily removing the stir bar). The experiment was repeated with 5.0 and 2.0 mol% catalyst loadings. The reaction progress kinetic analysis method[25] was applied. The concentration of **5a** at each time point t was calculated from the relative integration of the standard and plotted versus t (Figure 6). The instantaneous rate (Δ([**5a**])/Δt) was similarly plotted and the same analysis was performed for **4a** (Figure s18). **B** (determination of the order in catalyst). The time normalization method[26] was used. The concentration of **5a** from **A** was plotted against the normalized time t' for each catalyst loading. The order in catalyst *n* was varied until the data points for all catalyst loadings overlaid (Figure s19).[26]

$$t' = t \times [\Delta\text{-}(S,S)\text{-}\mathbf{2}^{3+}\ 2Cl^{-}B(C_6F_5)_4^{-}]^n$$

where [Δ-(*S*,*S*)-**2**$^{3+}$ 2Cl^{-}B(C$_6$F$_5$)$_4^{-}$] represents total concentration of the catalyst in the reaction (M) and *n* is the order in catalyst.

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Conflict of interest

The authors have a financial interest in the cobalt(III) catalysts and chiral solvating agents described in this work, some of which are commercially available or easily accessed from commercial precursors.[27]

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TEXT for TABLE OF CONTENTS GRAPHIC

Thirteen examples of the title reaction are effected with a catalyst derived from the D_3 symmetric chiral trication Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ (dpen = 1,2-diphenylethylenediamine), which contains both cobalt and carbon stereocenters. The mechanism involves hydrogen bonding between the NH groups and the substrates.