Synthesis H. Joshi et al. Special Topic

Enantioselective Additions of Stabilized Carbanions to Imines Generated from α-Amido Sulfones By Using Lipophilic Salts of Chiral Tris(1,2-diphenylethylenediamine) Cobalt(III) Trications as Hydrogen Bond Donor Catalysts

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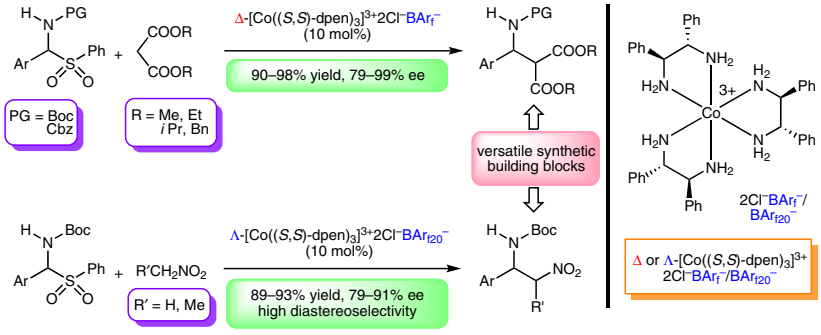
Published as part of the Special Topic *Cobalt in Organic Synthesis*



Received: 10.04.2017
Accepted after revision: 04.05.2017
Published online: 13.06.2017
DOI: 10.1055/s-0036-1590502; Art ID: ss-2017-c0236-st

Abstract The enantiopure salt Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$ [BAr$_f$ = B(3,5-C$_6$H$_3$(CF$_3$)$_2$)$_4$] is an effective hydrogen bond donor catalyst (10 mol%, r.t., CH_2Cl_2) for enantioselective additions of dialkyl malonates to Boc-derivatized aryl imines generated from sulfones [ArCH(SO$_2$Ph)NHBoc] in the presence of K_2CO_3 (ten examples, 91–97% isolated yields, 87–99% ee). The diastereomeric salt Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$ [BAr$_{f20}^-$ = B(C$_6$F$_5$)$_4^-$] is similarly applied to additions of nitroalkanes (four examples, 89–93% isolated yields, 79–91% ee). Precautions to exclude air or moisture are unnecessary.

Key words Werner complexes, cobalt, 1,2-diamine ligands, chiral-at-metal complexes, hydrogen bonding, enantioselective catalysis, chiral benzylic amines, lipophilic anions

There have been a variety of approaches to catalytic asymmetric syntheses of secondary benzylic amines of the formula ArCH(R)NHX,[1] which represent large families of pharmacologically active compounds or precursors thereof. Many of these have entailed nucleophilic additions to aryl imines (ArCH=NX), which are often termed Mannich reactions when malonate ester enolates are the nucleophiles, or aza-Henry reactions when conjugate bases of nitroalkanes are the nucleophiles. Electron-withdrawing nitrogen substituents (X) such as Boc [*tert*-butoxycarbonyl or O(C=O)*t*-Bu] or Cbz [carboxybenzyl or O(C=O)CH$_2$Ph] are often employed to facilitate additions and/or directly generate protected amines.[1–4]

Such Boc or Cbz derivatives are often synthesized as exemplified in Scheme 1 (top). First, a three-component condensation of an aromatic aldehyde, *tert*-butyl carbamate, and sodium phenyl sulfinate is carried out to give what is usually termed an α-amido sulfone (**1**).[5,6] These have an extended shelf life. Then the imine is prepared using a base such as K_2CO_3.[6] However, imines frequently undergo facile hydrolysis or are otherwise problematic to store.[5] Accordingly, there is an increasing trend toward utilization of the precursors **1** in enantioselective syntheses.[5,7] These protocols employ (1) a common base to generate the imine as well as the carbanion that adds to the imine, and (2) various catalysts, most often 'organocatalysts',[8] that act as hydrogen bond donors toward one or both reactants (Scheme 1, middle and bottom).[7]

We have been engaged in developing novel types of chiral metal-containing hydrogen bond donors for use in enantioselective catalysis.[9–16] This represents an overlooked type of catalyst, as many researchers approach this subject from the organocatalysis angle. All too frequently, this community erects a 'Maginot line' when it comes to transition metals, rather than thinking opportunistically about all classes of hydrogen bond donors. Only a few other investigators have sought to develop metal-containing hydrogen bond donor catalysts.[17,18]

Most, but not all of our efforts have involved substituted tris(ethylenediamine) complexes of cobalt(III).[9–12,14,15] This focus was inspired by the pioneering work of Werner, who first resolved the helically chiral enantiomers of the water-soluble trication [Co(en)$_3$]$^{3+}$ – the configurations of which are denoted Δ and Λ – via easily separated diastereomeric tartrate salts some 105 years ago.[19] Despite the promising beginning, this system has languished without applications in synthesis, as the cobalt center is 'substitution inert' (low spin d^6 with high field ligands) and therefore not accessible to organic substrates for activation via the usual modes of transition-metal-mediated catalysis. Our contributions were to (1) recognize that the coordinated NH groups are strong hydrogen bond donors,[9,12,15a,16b] and (2) apply lipo-

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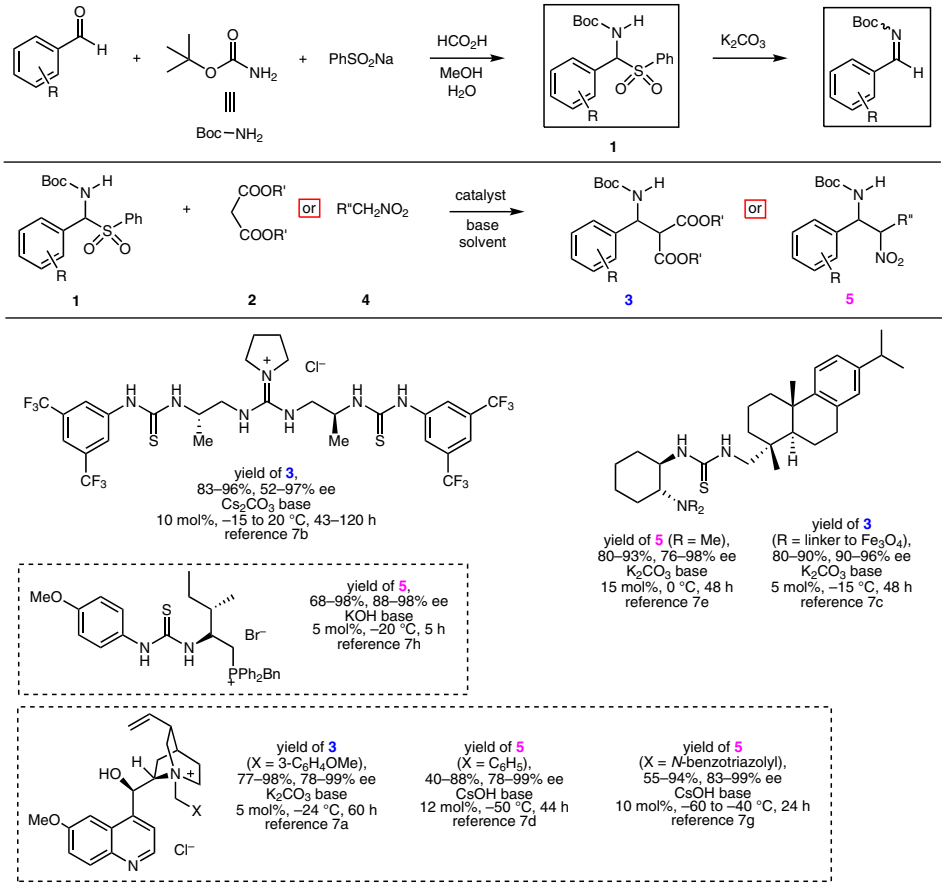

Scheme 1 Syntheses of α-amido sulfones and prior art regarding enantioselective reactions involving stabilized carbanions catalyzed by chiral hydrogen bond donors

philic anions to render these trications soluble in nonpolar organic solvents, thereby avoiding hydroxylic media that could compete with substrates for the hydrogen bonding sites.[9–11,15a]

Accordingly, in this paper we detail the successful application of two previously reported 'mixed salt' catalysts, Δ-$[Co((S,S)\text{-dpen})_3]^{3+}$ $2Cl^-BAr_f^-$ and Λ-$[Co((S,S)\text{-dpen})_3]^{3+}$ $2Cl^-BAr_{f20}^-$,[15a,20] to Mannich and aza-Henry reactions involving the imine precursor **1** (Scheme 1, middle). As shown in Figure 1, dpen refers to 1,2-diphenylethylenediamine, both enantiomers of which are commercially available at very inexpensive prices for enantiopure ligands (ca. $408–$420/100 g).[21] The abbreviations BAr_f^- and BAr_{f20}^- denote the well-known lipophilic anions $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$ and $B(C_6F_5)_4^-$. These catalysts, one of which is commercially available,[22] afford addition products **3** and **5** in yields and enantioselectivities that compare favorably with the highest achieved to date (Scheme 1, bottom).

As shown in Table 1, reactions of diethyl malonate (**2a**) (1.2 equiv) and the imine precursor **1a** (1.0 equiv) were carried out in the presence of a base (1.5 equiv) and 10 mol% of a catalyst derived from the trication $[Co((S,S)\text{-dpen})_3]^{3+}$ in CH_2Cl_2, MeCN, or toluene at room temperature or 0 °C. These and all other reactions below were conducted in air with 'off the shelf' solvents and reagents. Entries 1–5 (Table 1) pair the diastereomer Δ-$[Co((S,S)\text{-dpen})_3]^{3+}$ $2Cl^-BAr_f^-$ with five different bases in CH_2Cl_2. Of these, K_2CO_3 (Table 1, entry 5) gave the product **3aa** with the highest enantioselectivity (91% ee) and close to the highest isolated yield

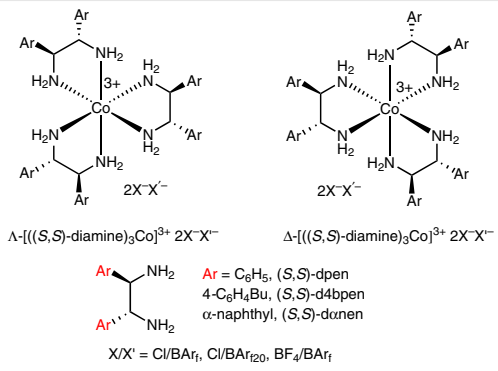

Figure 1 Catalysts used in this study

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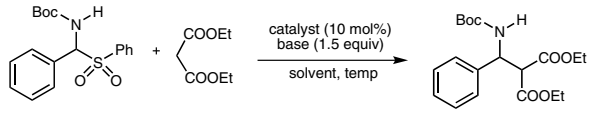
(95%). When lower loadings of K_2CO_3 were employed, the yield diminished, but higher loadings did not further help (Table 1, entries 6 and 7). Both MeCN and toluene were also evaluated as solvents (Table 1, entries 8 and 9). The former gave nearly racemic product; the latter gave a slightly higher enantioselectivity (94% ee), but the rate was much slower (28 vs 16 h).

As shown in Table 1, entry 10, the diastereomeric catalyst with the opposite configuration at cobalt, Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$, afforded a lower enantioselectivity (65% vs 91% ee). The dominant configuration of **3aa** switched from *R* to *S*, establishing the cobalt configuration as the principal determinant of the product configuration, as usually observed with other reactions.[10,11] Additional experiments with this catalyst, salts of each diastereomer with alternative counter anions, and analogues with other aryl groups in place of the phenyl moieties of dpen, are presented (entries 11–17). None of these offered any improvement, although switching the tetraarylborate anion of the Δ diastereomer from BAr$_f^-$ to BAr$_{f20}^-$ gave only a slight drop in ee (87%).

Next entry 5 was repeated, but at 0 °C (entry 18). The reaction was complete within 16 hours, and work-up gave **3aa** in 93% yield with a moderately higher ee value (95%). When the catalyst loading was reduced to 5.0 mol% (entry 19), the ee value dropped (89%), and the reaction slowed somewhat. Accordingly, the conditions in entry 18 were selected for the substrate scope studies summarized in Scheme 2.

Table 1 Optimization of the Catalyst and Conditions for the Addition of Diethyl Malonate (**2a**) to the Imine Derived from α-Amido Sulfone **1a**



1a **2a** **3aa**

Entry[a]	Catalyst	Solvent	Base	Temp	Yield (%)[b] (time)	ee (%)[c] (config)
1	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	Et_3N	r.t.	95 (12 h)	12 (*S*)
2	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	Cs_2CO_3	r.t.	98 (9 h)	41 (*R*)
3	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	Na_2CO_3	r.t.	93 (18 h)	79 (*R*)
4	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	KOH	r.t.	36 (22 h)	10 (*R*)
5	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	95 (16 h)	91 (*R*)
6[d]	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	72 (12 h)	90 (*R*)
7[e]	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	95 (12 h)	90 (*R*)
8	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	MeCN	K_2CO_3	r.t.	92 (18 h)	1 (*R*)
9	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	toluene	K_2CO_3	r.t.	96 (28 h)	94 (*R*)
10	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	96 (12 h)	65 (*S*)
11	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2[f]	K_2CO_3	r.t.	0 (72 h)	–
12	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	MeCN	K_2CO_3	r.t.	94 (18 h)	1 (*S*)
13	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	K_2CO_3	r.t.	97 (10 h)	63 (*S*)
14	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	K_2CO_3	r.t.	98 (12 h)	87 (*R*)
15	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2BF$_4^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	98 (8 h)	73 (*R*)
16	Δ-[Co((*S*,*S*)-dαnen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	94 (12 h)	30 (*R*)
17	Λ-[Co((*S*,*S*)-d4bpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	98 (12 h)	72 (*S*)
18	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	0 °C	93 (16 h)	95 (*R*)
19[g]	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	0 °C	91 (24 h)	89 (*R*)

[a] Reactions were carried out with 0.10 mmol of **1a** and 0.12 mmol of **2a** in 1.0 mL of solvent.
[b] Yield of isolated product.
[c] Enantioselectivities were determined by chiral HPLC analyses.
[d] 1.0 equiv of base.
[e] 2.0 equiv of base.
[f] 2 drops of H_2O were added.
[g] 5.0 mol% catalyst; with 2.0 mol%: 82% yield (37 h) and 88% ee (*R*).

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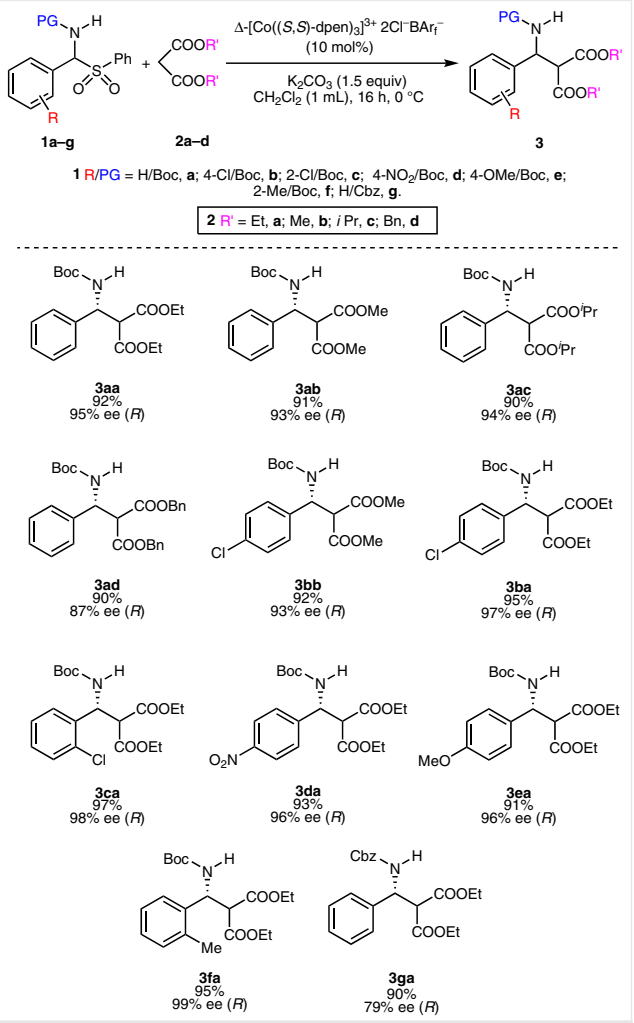


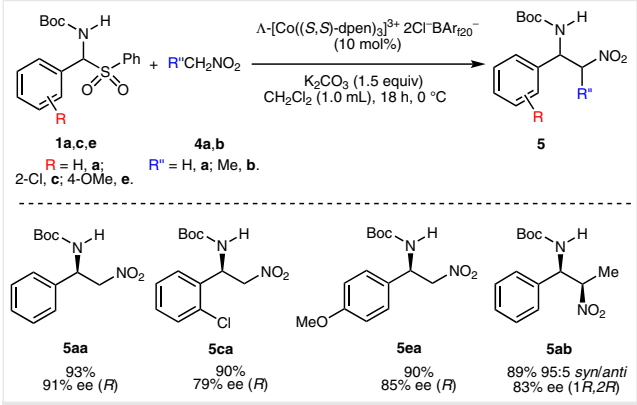
Scheme 2 Substrate scope for additions of dialkyl malonates **2a–d** to the imines derived from α-amido sulfones **1a–g** under the optimal conditions from Table 1

Scheme 2 shows that essentially identical results are obtained with aliphatic esters of malonic acid (**3aa**, **3ab**, **3ac**). The ee value dips to 87% for dibenzyl malonate (**3ad**). The excellent results with **3bb**, **3ba**, **3ca**, **3da**, **3ea**, and **3fa** (91–97% yields, 93–99% ee) show that both electron-withdrawing and electron-donating groups on the phenyl ring are accommodated, as well as *ortho* substituents. When the nitrogen functionality is switched from Boc to Cbz, the ee value drops to 79%. While this is acceptable for some applications, the Cbz analogues may benefit from a separate optimization protocol analogous to that in Table 1.

As summarized in Table 2, parallel efforts were made to optimize the reaction of nitromethane (**4a**) (2.0 equiv) and **1a** (1.0 equiv). In initial screens, a lead catalyst, Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$, emerged from the diastereomer series opposite of the lead catalyst in Table 1. As shown in entries 1–5 (Table 2), it was paired with five different bases (1.5 equiv) in CH_2Cl_2. As with Table 1, K_2CO_3 (entry 5) gave the product **5aa** with the highest enantioselectivity (87% ee) and isolated yield (96%). Lower or higher loadings of K_2CO_3 (entries 6 and 7), or MeCN or toluene solvents (entries 8 and 9), gave poorer results.

Several other catalysts were evaluated (entries 10–13). The diastereomer with the opposite configuration at cobalt, Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$, gave **5aa** in only 55% ee, and with the dominant carbon configuration *S* as opposed to *R*. The best catalyst in Table 1, Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$, gave a still lower ee value (41%, *S*). The opposite diastereomer, Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$, afforded a higher ee value (79%, *R*). The analogous catalyst in which the diamine phenyl groups had been replaced by 4-(butyl)phenyl groups (entry 13) gave poorer results (58% ee).

Finally, entry 5 was repeated, but at 0 °C (entry 14). The reaction was complete within a reasonable time frame (18 h), and afforded a 94% yield of **5aa** upon work-up. The ee value was moderately higher (91% vs 87%). Accordingly, these conditions were selected for the substrate scope studies summarized in Scheme 3. Although the enantioselectivities are quite good (79–91% ee), they lag behind those realized in Scheme 2. When nitroethane (**4b**) was employed, a second stereocenter was generated, and the diastereoselectivity was quite high (95:5). Note that the configurations of the benzylic stereocenters obtained using a Λ catalyst in Scheme 3 are, in a *relative* sense, opposite of those obtained using a Δ catalyst in Scheme 2.



Scheme 3 Substrate scope for additions of nitroalkanes **4a**,**b** to the imines derived from α-amido sulfones **1a**,**c**,**e** under the optimal conditions from Table 2

Several ancillary experiments were conducted. First, we wondered whether the cobalt(III) complexes might catalyze conversions of **1a–f** into the imines ArCH=NBoc. Thus, chloro-substituted **1b** (1.0 equiv), K_2CO_3 (1.5 equiv), CD_2Cl_2 (0.50 mL), and Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$ (10 mol%) were combined in an NMR tube in the *absence* of a malonate ester or nitroalkane. A second NMR tube was similarly charged, but without the cobalt(III) complex. Over the course of 11 hours, the second tube showed the clean con-

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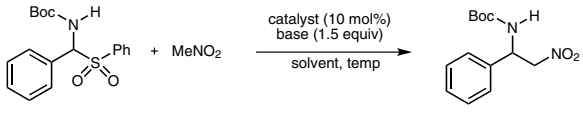
Table 2 Optimization of the Catalyst and Conditions for the Addition of Nitromethane (**4a**) to the Imine Derived from α-Amido Sulfone **1a**



1a **4a** **5aa**

Entry[a]	Catalyst	Solvent	Base	Temp	Yield (%)[b] (time)	ee (%)[c] (config)
1	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	Et_3N	r.t.	92 (14 h)	11 (*R*)
2	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	Cs_2CO_3	r.t.	98 (13 h)	13 (*R*)
3	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	Na_2CO_3	r.t.	93 (20 h)	64 (*R*)
4	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	KOH	r.t.	27 (24 h)	3 (*R*)
5	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	K_2CO_3	r.t.	96 (14 h)	87 (*R*)
6[d]	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	K_2CO_3	r.t.	67 (21 h)	76 (*R*)
7[e]	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	K_2CO_3	r.t.	96 (14 h)	77 (*R*)
8	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	MeCN	K_2CO_3	r.t.	94 (18 h)	14 (*R*)
9	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	toluene	K_2CO_3	r.t.	95 (29 h)	65 (*R*)
10	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	95 (14 h)	79 (*R*)
11	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	K_2CO_3	r.t.	95 (14 h)	55 (*S*)
12	Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	94 (18 h)	41 (*S*)
13	Λ-[Co((*S*,*S*)-dbpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$	CH_2Cl_2	K_2CO_3	r.t.	97 (14 h)	58 (*R*)
14	Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$	CH_2Cl_2	K_2CO_3	0 °C	94 (18 h)	91 (*R*)

[a] Reactions were carried out with 0.10 mmol of **1a** and 0.20 mmol of **4a** in 1.0 mL of solvent.
[b] Yield of isolated product.
[c] Enantioselectivities were determined by chiral HPLC analyses.
[d] 1.0 equiv of base.
[e] 2.0 equiv of base.

version of **1b** into the previously described imine (4-ClC_6H_4)CH=NBoc, consistent with literature reports (1.5 h, 68:32; 5.0 h, 33:67; 7.0 h, 24:76; 11 h, <1:>99).[3c,6a] Over the same time frame, **1b** was also consumed in the first tube, but concurrent hydrolysis of the imine to 4-chlorobenzaldehyde was evident (1.5 h, 33:34:33 **1b**/imine/aldehyde; 5.0 h, 16:22:62; 7.0 h, 14:19:67; 11 h, <1:<1:>99).

These data suggest two conclusions. First, the faster consumption of **1b** in the presence of Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$ (33% vs 68% remaining after 1.5 h) implies a catalyzed pathway. Second, the cobalt complex (a monohydrate)[20] appears to catalyze the hydrolysis of the imine (4-ClC_6H_4)CH=NBoc. This is not in itself surprising given the absence of any of the carbon nucleophiles in Schemes 1–3 and Tables 1 and 2. Accordingly, the conditions in Scheme 2 were applied to the isolated imine PhCH=NBoc[3c] and malonate ester **2a**. However, no addition product (**3aa**) could be detected. Rather, the hydrolysis products benzaldehyde and $BocNH_2$ formed in quantitative NMR yields. The same result was obtained when Et_3N was used in place of K_2CO_3. A scenario that reconciles these disparate observations is proposed below.

The preceding data dramatically illustrate the efficacy of the catalyst families in Figure 1 for enantioselective additions of stabilized carbanions to Boc derivatives of aryl imines that are generated in situ from the shelf-stable α-amido sulfone precursors **1**. Curiously, however, opposite cobalt/carbon diastereomers prove to be more effective for the two types of addends studied, dialkyl malonates **2** (Table 1 and Scheme 2) and nitroalkanes **4** (Table 2 and Scheme 3). This dichotomy has been encountered with other transformations,[10,11] and calls attention to how little is presently known about the mechanisms and the basis for enantioselection.

Many of the previously reported hydrogen bond donor catalysts applied to these transformations are based upon thioureas (Scheme 1, bottom). Since thioureas feature only two NH donor groups, there is a more restricted range of substrate binding possibilities. Accordingly, plausible transition-state models have been developed (usually with the aid of computations) for a number of enantioselective reactions catalyzed by chiral thioureas.[23] In contrast, the catalysts in Figure 1 feature *twelve* NH units. These are arrayed, in accord with the idealized D_3 symmetry, between two 'C_3 symmetric faces' and three 'C_2 symmetric faces', as shown in Figure 2. Transition-state assemblies that simultaneously

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access as many as 4–5 of these NH units are easily envisioned,[16b] making for a daunting number of possible geometries.

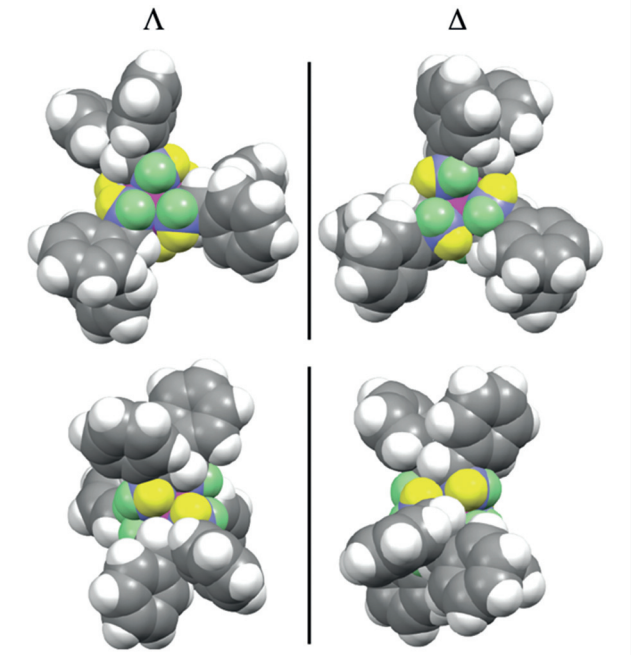

Figure 2 Hydrogen bonding sites of the trication $[Co((S,S)\text{-dpen})_3]^{3+}$ (left, Λ diastereomer; right, Δ diastereomer). The representations are taken from the crystal structures of the $3Cl^-$ salts, which lack idealized D_3 symmetry. What would correspond to the C_3 sites are shown at the top (green NH) and the C_2 sites at the bottom (yellow NH)

NMR experiments reported in connection with other synthetic studies have established that dialkyl malonates and β-nitrostyrene strongly interact with the C_2 faces of the catalyst Λ-$[Co((S,S)\text{-dpen})_3]^{3+}$ $2Cl^-BAr_f^-$.[10] However, the two C_3 faces of this catalyst are strongly hydrogen bonded to the two chloride counter anions, and there is good evidence that conjugate additions of malonates to β-nitrostyrene require a chloride ion to dissociate from at least one C_3 site (presumably to allow substrate binding).[10] It follows that both the α-amido sulfone precursors **1** and any imine intermediates ArCH=NBoc in Schemes 2 and 3 and Tables 1 and 2 should similarly hydrogen bond to these cobalt(III) systems, either via the Boc C=O or sulfone S=O moieties.

Given that basic solutions of Δ-$[Co((S,S)\text{-dpen})_3]^{3+}$ $2Cl^-BAr_f^-$ appear to catalyze both the disappearance of precursors **1** and the hydrolysis of imines ArCH=NBoc, we currently favor mechanisms in which **1** undergoes net phenyl sulfinic acid elimination and dialkyl malonate or nitroalkane addition *without* dissociating a free imine from the second coordination sphere of cobalt. To our knowledge, the possibility that the other hydrogen bond donor catalysts in Scheme 1 (bottom) might initially act upon **1** has not been previously considered. However, we presently lack any further insight.[24] The same goes as to why enantioselectivities are greater with one set of counter anions for a given reaction, but a different set of anions for another. We note in passing that it would be possible for one C_3 face to be engaged in hydrogen bonding with substrates, while the opposite C_3 face maintains hydrogen bonding with a counter anion or anions.

Regardless of the mechanisms by which these cobalt(III) catalysts function, one is usually able to achieve ee values of >50% for a transformation known to be catalyzed by chiral bond donors with a minimum of effort. In many cases, this can be optimized to the 90% ee range by varying the cobalt configuration, counter anions, solvent, and related parameters, or by introducing additional catalyst functionality.[12] In a separate effort, Meggers has applied a bifunctional chiral iridium(III) catalyst that can serve as both a hydrogen bond donor and Brønsted base to aza-Henry reactions of isolated aryl imines ArCH=NBoc.[17c]

It is always difficult to objectively compare the effectiveness of different classes of enantioselective catalysts. For example, the range of ee values (or average ee value) reported might be skewed by the inclusion of a single problematic substrate in one study, but not another. With this caveat, we note that **3ab**, **3ad**, and **3bb** in Scheme 2 have previously been similarly synthesized by others, but using different hydrogen bond donor catalysts, generally of the types depicted in Scheme 1. The best enantioselectivities reported earlier are 94% (vs our 93%),[7b] 95% (vs 87%),[7c] and 92% (vs 93%),[7b] respectively. Alternatively, **3bb**, **3ea**, and **3ga** have previously been prepared from the isolated imines ArCH=NBoc. The best results reported earlier are 90% (vs our 93%),[2d] 93% (vs 96%),[25] and 61% (vs 79%),[26] respectively. With regard to the nitroalkane additions in Scheme 3, our enantioselectivities are somewhat lower than the best literature results (**5aa**, 99%[7g] vs our 91%; **5ca**, 97%[7c] vs 79%; **5ea**, 97%[7h] vs 85%; **5ab**, 98%[7g] vs 83%).

Other types of comparisons are also relevant. For example, our catalyst system operates on more practical timescales than most of the others depicted in Scheme 1 (bottom). Naturally, longer timescales are often associated with lower temperatures applied to maximize ee values. Second, our catalyst loadings fall into the middle of the range, but could probably be optimized lower (with a trade off in temperature and time).

In summary, two principal conclusions derive from the preceding data. First, the scope of enantioselective reactions to which chiral hydrogen bond catalysts based upon the cobalt(III) trication $[Co((S,S)\text{-dpen})_3]^{3+}$ can be applied has been significantly extended. Second, practical new methodology for additions of conjugate bases derived from dialkyl malonates and nitroalkanes to Boc derivatives of aromatic imines – or their functional equivalents – has been developed. There is no need to exclude air or water, and one of the catalysts is commercially available. Additional applications of these and related systems in enantioselective catalysis will be reported in the near future.

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Reactions were conducted under air. $CDCl_3$ and CD_2Cl_2 were stored over molecular sieves. HPLC solvents (hexanes, Fischer; isopropanol, JT Baker, 2 × HPLC Grade) were degassed before use. Other solvents and materials: CH_2Cl_2 (EMD, ACS grade), hexanes, EtOAc (2 × Macron, ACS grade), toluene, MeCN (2 × BDH, ACS grade), diethyl malonate (**2a**) (Alfa Aesar, 99%), dimethyl malonate (**2b**) (Alfa Aesar, 98%), diisopropyl malonate (**2c**) (TCI, 99%), dibenzyl malonate (**2d**) (TCI, 99%), nitromethane (**4a**) (Sigma-Aldrich, 95+%), nitroethane (**4b**) (Alfa Aesar, 99%), Cs_2CO_3 (Alfa Aesar, 99%), K_2CO_3 (Fluka Analytical, 99%), Na_2CO_3 (Mallinckrodt Chemicals, ACS grade), KOH (Macron Fine Chemicals, ACS grade), Et_3N (Alfa Aesar, 98%), and silica gel (Silicycle SiliaFlash® F60) were used as received. The educts *N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)benzylamine (**1a**),[6a] *N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-4-chlorobenzylamine (**1b**),[6a] *N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-2-chlorobenzylamine (**1c**),[6a] *N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-4-nitrobenzylamine (**1d**),[6b] *N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-4-methoxybenzylamine (**1e**),[6b] *N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-2-methylbenzylamine (**1f**),[27] and benzyl phenyl(phenylsulfonyl)methylcarbamate (**1g**)[6b] and catalysts (see Figure 1 for abbreviations) Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$·H_2O, Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$·3H_2O, Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$·2H_2O, Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$·3H_2O, Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2BF$_4^-$BAr$_f^-$·3H_2O, Δ-[Co((*S*,*S*)-dαnen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$·4H_2O, and Λ-[Co((*S*,*S*)-d4bpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$·H_2O were prepared by literature procedures.[15a] Melting points were determined using an OptiMelt MPA 100 instrument. NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 on a Varian NMRS 500 MHz spectrometer at ambient probe temperature and referenced (δ in ppm) to solvent signals (^{1}H: residual $CHCl_3$, 7.26 or $CDHCl_2$, 5.32; ^{13}C{^{1}H}: $CDCl_3$, 77.2). HPLC analyses were carried out with a Shimadzu instrument package (pump/autosampler/detector LC-20AD/SIL-20A/SPD-M20A). Microanalyses were conducted by Atlantic Microlab.

Reactions, Table 1

A 5 mL vial was charged with **1a** (0.035 g, 0.10 mmol, 1.0 equiv), **2a** (0.019 g, 0.12 mmol, 1.2 equiv), catalyst (0.010 mmol, 10 mol%) and CH_2Cl_2 (1.0 mL). Then the base (0.15 mmol, 1.5 equiv) was added with stirring. The progress of the reaction was monitored by TLC. After the specified time, the mixture was chromatographed on a silica gel column (1.9 × 14 cm, 9:1 v/v hexanes/EtOAc). The solvent was removed from the product-containing fractions by rotary evaporation and oil pump vacuum (1 h) at r.t. The enantiomeric purities were assayed by chiral HPLC.[28]

Reactions, Scheme 2

A 5 mL vial was charged with **1a–g** (0.10 mmol, 1.0 equiv), **2a–d** (0.12 mmol, 1.2 equiv), Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_f^-$·H_2O (0.0170 g, 0.010 mmol, 10 mol%), and CH_2Cl_2 (1.0 mL). The mixture was cooled to 0 °C and K_2CO_3 (0.021 g, 0.15 mmol, 1.5 equiv) was added with stirring. Work-ups identical to those for Table 1 gave the data in Scheme 2. The enantiomeric purities were assayed by chiral HPLC (see Figures s1–s11 in the Supporting Information).[28]

Reactions, Table 2

A 5 mL vial was charged with **1a** (0.035 g, 0.10 mmol, 1.0 equiv), **4a** (0.012 g, 0.20 mmol, 2.0 equiv), catalyst (0.0010 mmol, 10 mol%), and CH_2Cl_2 (1.0 mL). Then the base (0.15 mmol, 1.5 equiv) was added with stirring. Work-ups similar to those for Table 1 (silica gel column: 1.9 × 14 cm, 8:2 v/v hexanes/EtOAc) gave the data in Table 2. The enantiomeric purities were assayed by chiral HPLC.[29]

Reactions, Scheme 3

A 5 mL vial was charged with **1a**,**c**,**e** (0.10 mmol, 1.0 equiv), **4a**,**b** (0.20 mmol, 2.0 equiv), Λ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ 2Cl$^-$BAr$_{f20}^-$·3H_2O (0.0150 g, 0.0010 mmol, 10 mol%), and CH_2Cl_2 (1.0 mL). The mixture was cooled to 0 °C and K_2CO_3 (0.021 g, 0.15 mmol, 1.5 equiv) was added with stirring. Work-ups identical to those for Table 2 gave the data in Scheme 3. The enantiomeric purities were assayed by chiral HPLC (see Figures s12–s15 in the Supporting Information).[29]

2-(*tert*-Butoxycarbonylaminophenylmethyl)malonic Acid Diethyl Ester (3aa)[2a]

This known compound was obtained as a white solid (0.0335 g, 0.092 mmol, 92%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.18 (m, 5 H, C_6H_5), 6.17 (br s, 1 H, NH), 5.46 (br s, 1 H, NHC*H*), 4.22–3.99 (m, 4 H, OCH_2, $OC'H_2$), 3.86 [br s, 1 H, C*H*C(O)OCH_2], 1.37 [s, 9 H, C(CH_3)$_3$], 1.21 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.08 (t, *J* = 7.0 Hz, 3 H, $C'H_2C'H_3$).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 168.0 [s, *C*(O)OCH_2], 166.7 [s, *C'*(O)$OC'H_2$], 154.7 [s, *C*(O)OC(CH_3)$_3$], 139.6, 128.4, 127.4, 126.1 (4 × s, C_6H_5), 79.5 [s, *C*(CH_3)$_3$], 61.8, 61.4, 56.8, 53.3 [4 × s, NHCH, *C*HC(O)OCH_2, *C*H_2CH_3, *C'*$H_2C'H_3$], 28.2 [s, C(*C*H_3)$_3$], 13.9 (s, CH_2*C*H_3), 13.7 (s, $C'H_2$*C'*H_3).

HPLC (Figure s1): Chiralpak AD column (90:10 v/v hexane/isopropanol, 0.8 mL/min, λ = 254 nm); t_R = 15.4 min (minor), 17.6 min (major).[2a,28]

2-(*tert*-Butoxycarbonylaminophenylmethyl)malonic Acid Dimethyl Ester (3ab)[2a]

This known compound was obtained as a white solid (0.0306 g, 0.091 mmol, 91%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H, C_6H_5), 6.14 (br s, 1 H, NH), 5.48 (br s, 1 H, NHC*H*), 3.92 [br s, 1 H, *C*HC(O)OCH_3], 3.73 (s, 3 H, OCH_3), 3.62 (s, 3 H, $OC'H_3$), 1.41 [s, 9 H, C(CH_3)$_3$].

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 168.2 [s, *C*(O)OCH_3], 167.5 [s, *C'*(O)OCH_3], 154.9 [s, *C*(O)OC(CH_3)$_3$], 139.2, 128.5, 127.5, 126.1 (4 × s, C_6H_5), 79.6 [s, C(CH_3)$_3$], 56.5, 53.3, 52.8, 52.4 [4 × s, NHCH, *C*HC(O)OCH_3, OCH_3, $OC'H_3$], 28.2 [s, C(*C*H_3)$_3$].

HPLC (Figure s2): Chiralpak AD column (90:10 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 15.9 min (minor), 20.5 min (major).[2a,28]

2-(*tert*-Butoxycarbonylaminophenylmethyl)malonic Acid Diisopropyl Ester (3ac)[2e]

This known compound was obtained as a white solid (0.0354 g, 0.090 mmol, 90%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.21 (m, 5 H, C_6H_5), 6.22 (br s, 1 H, NH), 5.47 (br s, 1 H, NHC*H*), 5.08–5.03 [m, 1 H, C*H*(CH_3)$_2$], 4.97–4.92 [m, 1 H, C'*H*($C'H_3$)$_2$], 3.82 [br s, 1 H, *C*HC(O)OCH(CH_3)$_2$], 1.40 [s, 9 H, C(CH_3)$_3$], 1.25, 1.23, 1.18, 1.03 [4 × d, *J* = 6.0/6.0/6.0/6.0 Hz, 3 H each, CH(C'*H*$_3$)(C*H*$_3$)/C'H(C'*H*$_3$)(C*H*$_3$)].

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 167.7 [s, *C*(O)OCH(CH_3)$_2$], 166.5 [s, *C'*(O)OCH(CH_3)$_2$], 155.0 [s, *C*(O)OC(CH_3)$_3$], 139.6, 128.5, 127.4, 126.2 (4 × s, C_6H_5), 79.5 [s, O*C*(CH_3)$_3$], 69.6, 69.2, 57.1, 53.4, [4 × s, NHCH, *C*HC(O)OCH(CH_3)$_2$, *C*H(CH_3)$_2$, *C'*H($C'H_3$)$_2$], 28.3 [s, C(CH_3)$_3$], 21.6, 21.4, 21.4, 21.3 [4 × s, CH(*C'*H_3)(CH_3), C'H(*C'*H_3)(CH_3)].

HPLC (Figure s3): Chiralpak AD column (95:5 v/v hexane/isopropanol, 0.8 mL/min, λ = 254 nm); t_R = 18.1 min (major), 22.1 min (minor).[28]

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2-(*tert*-Butoxycarbonylaminophenylmethyl)malonic Acid Dibenzyl Ester (3ad)[2d]

This known compound was obtained as a white solid (0.0441 g, 0.090 mmol, 90%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 13 H, C_6H_5, $CH_2C_6H_5$, $C'H_2C'_6H_5$), 7.13–7.11 (m, 2 H, $CH_2C_6H_5$), 6.23 (br s, 1 H, NH), 5.59 (br s, 1 H, NHC*H*), 5.16 (s, 2 H, $CH_2C_6H_5$), 5.07 (s, 2 H, $C'H_2C'_6H_5$), 4.04 [br s, 1 H, CHC(O)OCH$_2$C$_6$H$_5$], 1.44 [s, 9 H, C(CH$_3$)$_3$].

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 167.7 [s, *C*(O)OCH$_2$C$_6$H$_5$], 166.7 [s, *C'*(O)OC'H$_2$C'$_6$H$_5$], 154.9 [s, *C*(O)OC(CH$_3$)$_3$], 139.2, 134.9, 134.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.5, 126.1 (12 × s, C_6H_5, $CH_2C_6H_5$, $C'H_2C'_6H_5$), 79.7 [s, O*C*(CH$_3$)$_3$], 67.6, 67.2, 56.8, 53.3, [4 × s, NHCH, *C*HC(O)OCH$_2$C$_6$H$_5$, *C*H$_2$C$_6$H$_5$, *C'*H$_2$C'$_6$H$_5$], 28.1 [s, C(*C*H$_3$)$_3$].

HPLC (Figure s4): Chiralpak OD-H column (95:5 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 11.9 min (major), 14.4 min (minor).[2d,28]

2-[*tert*-Butoxycarbonylamino(4-chlorophenyl)methyl]malonic Acid Dimethyl Ester (3bb)[2d]

This known compound was obtained as a white solid (0.0343 g, 0.092 mmol, 92%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 4 H, C_6H_4), 6.14 (br s, 1 H, NH), 5.44 (br s, 1 H, NHC*H*), 3.87 [br s, 1 H, *CH*C(O)OCH$_3$], 3.74 (s, 3 H, OCH$_3$), 3.64 (s, 3 H, OC'H$_3$), 1.41 [s, 9 H, C(CH$_3$)$_3$].

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 168.2 [s, *C*(O)OCH$_3$], 167.3 [s, *C'*(O)OCH$_3$], 155.0 [s, *C*(O)OC(CH$_3$)$_3$], 137.9, 133.5, 128.7, 127.7 (4 × s, C_6H_4), 80.0 [s, *C*(CH$_3$)$_3$], 56.4, 52.9, 52.6 [3 × s, NHCH, *C*HC(O)OCH$_3$, OCH$_3$], 28.2 [s, C(*C*H$_3$)$_3$].

HPLC (Figure s5): Chiralpak OD-H column (95:5 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 7.6 min (major), 9.3 min (minor).[28]

2-[*tert*-Butoxycarbonylamino(4-chlorophenyl)methyl]malonic Acid Diethyl Ester (3ba)

This new compound was obtained as a white solid (0.0381 g, 0.095 mmol, 95%) per the procedure for Scheme 2.

Mp 73–75 °C (open capillary).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.22 (m, 4 H, C_6H_4), 6.19 (br s, 1 H, NH), 5.43 (br s, 1 H, NHC*H*), 4.23–4.02 (m, 4 H, OCH$_2$, OC'H$_2$), 3.82 [br s, 1 H, *CH*C(O)OCH$_2$], 1.39 [s, 9 H, C(CH$_3$)$_3$], 1.24 (t, *J* = 7.0 Hz, 3 H, CH$_2$*CH*$_3$), 1.13 (t, *J* = 7.3 Hz, 3 H, C'H$_2$*C'H*$_3$).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 167.9 [s, *C*(O)OCH$_2$], 166.9 [s, *C'*(O)OC'H$_2$], 154.9 [s, *C*(O)OC(CH$_3$)$_3$], 138.1, 133.3, 128.6, 127.6 (4 × s, C_6H_4), 79.7 [s, *C*(CH$_3$)$_3$], 61.9, 61.6, 56.6, 52.8 [4 × s, NHCH, *C*HC(O)OCH$_2$, *C*H$_2$CH$_3$, *C'*H$_2$C'H$_3$], 28.2 [s, C(*C*H$_3$)$_3$], 13.9 (s, CH$_2$*C*H$_3$), 13.8 (s, C'H$_2$*C'*H$_3$).

Anal. Calcd for $C_{19}H_{26}ClNO_6$ (399.87): C, 57.07; H, 6.55. Found: C, 57.11; H, 6.67.

HPLC (Figure s6): Chiralpak OD-H column (99:1 v/v, hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 11.6 min (major), 17.3 min (minor).[28]

2-[*tert*-Butoxycarbonylamino(2-chlorophenyl)methyl]malonic Acid Diethyl Ester (3ca)

This new compound was obtained as a colorless oil (0.0389 g, 0.097 mmol, 97%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.5 Hz, 1 H, C_6H_4), 7.31 (d, *J* = 7.5 Hz, 1 H, C_6H_4), 7.22–7.16 (m, 2 H, C_6H_4), 6.50 (br s, 1 H, NH), 5.77 (br s, 1 H, NHC*H*), 4.29–3.95 [m, 5 H, OCH$_2$, OC'H$_2$, *CH*C(O)OCH$_2$], 1.38 [s, 9 H, C(CH$_3$)$_3$], 1.26 (t, *J* = 7.0 Hz, 3 H, CH$_2$*CH*$_3$), 1.08 (t, *J* = 7.0 Hz, 3 H, C'H$_2$*C'H*$_3$).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 168.1 [s, *C*(O)OCH$_2$], 167.0 [s, *C'*(O)OC'H$_2$], 154.7 [s, *C*(O)OC(CH$_3$)$_3$], 136.7, 132.3, 129.6, 128.9, 128.1, 126.8 (6 × s, C_6H_4), 79.6 [s, *C*(CH$_3$)$_3$], 61.9, 61.4, 53.9, 51.1 [4 × s, NHCH, *C*HC(O)OCH$_2$, *C*H$_2$CH$_3$, *C'*H$_2$C'H$_3$], 28.2 [s, C(*C*H$_3$)$_3$], 13.9 (s, CH$_2$*C*H$_3$), 13.7 (s, C'H$_2$*C'*H$_3$).

Anal. Calcd for $C_{19}H_{26}ClNO_6$ (399.87): C, 57.07; H, 6.55. Found: C, 56.94; H, 6.56.

HPLC (Figure s7): Chiralpak AD column (98:2 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 21.4 min (minor), 23.6 min (major).[28]

2-[*tert*-Butoxycarbonylamino(4-nitrophenyl)methyl]malonic Acid Diethyl Ester (3da)[30]

This known compound was obtained as a yellow solid (0.0382 g, 0.093 mmol, 93%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.5 Hz, 2 H, C_6H_4), 7.50 (d, *J* = 9.0 Hz, 2 H, C_6H_4), 6.28 (br s, 1 H, NH), 5.54 (br s, 1 H, NHC*H*), 4.25–4.01 (m, 4 H, OCH$_2$, OC'H$_2$), 3.89 [br s, 1 H, *CH*C(O)OCH$_2$], 1.39 [s, 9 H, C(CH$_3$)$_3$], 1.25 (t, *J* = 7.0 Hz, 3 H, CH$_2$*CH*$_3$), 1.13 (t, *J* = 7.0 Hz, 3 H, C'H$_2$*C'H*$_3$).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 167.6 [s, *C*(O)OCH$_2$], 166.5 [s, *C'*(O)OC'H$_2$], 154.9 [s, *C*(O)OC(CH$_3$)$_3$], 147.3, 147.0, 127.4, 123.7 (4 × s, C_6H_4), 80.2 [s, *C*(CH$_3$)$_3$], 62.2, 61.7, 56.2, 53.0 [4 × s, NHCH, *C*HC(O)OCH$_2$, *C*H$_2$CH$_3$, *C'*H$_2$C'H$_3$], 28.2 [s, C(*C*H$_3$)$_3$], 13.9 (s, CH$_2$*C*H$_3$), 13.8 (s, C'H$_2$*C'*H$_3$).

HPLC (Figure s8): Chiralpak AS-H column (95:5 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 19.7 min (major), 25.1 min (minor).[28]

2-[*tert*-Butoxycarbonylamino(4-methoxyphenyl)methyl]malonic Acid Diethyl Ester (3ea)[25]

This known compound was obtained as a white solid (0.0361 g, 0.091 mmol, 91%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 9.0 Hz, 2 H, C_6H_4), 6.82 (d, *J* = 8.5 Hz, 2 H, C_6H_4), 6.12 (br s, 1 H, NH), 5.42 (br s, 1 H, NHC*H*), 4.23–4.02 (m, 4 H, OCH$_2$, OC'H$_2$), 3.83 [br s, 1 H, *CH*C(O)OCH$_2$], 3.75 (s, 3 H, OCH$_3$), 1.39 [s, 9 H, C(CH$_3$)$_3$], 1.23 (t, *J* = 7.3 Hz, 3 H, CH$_2$*CH*$_3$), 1.14 (t, *J* = 7.3 Hz, 3 H, C'H$_2$*C'H*$_3$).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 168.0 [s, *C*(O)OCH$_2$], 167.1 [s, *C'*(O)OC'H$_2$], 158.8 (s, C_6H_4), 154.9 [s, *C*(O)OC(CH$_3$)$_3$], 131.6, 127.3, 113.7 (3 × s, C_6H_4), 79.3 [s, *C*(CH$_3$)$_3$], 61.8, 61.4, 57.0, 55.1, 52.8 [5 × s, NHCH, *C*HC(O)OCH$_2$, OCH$_3$, *C*H$_2$CH$_3$, *C'*H$_2$C'H$_3$], 28.2 [s, C(*C*H$_3$)$_3$], 13.9 (s, CH$_2$*C*H$_3$), 13.8 (s, C'H$_2$*C'*H$_3$).

HPLC (Figure s9): Chiralpak AD column (95:5 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 33.8 min (major), 41.3 min (minor).[28]

2-[*tert*-Butoxycarbonylamino(2-methylphenyl)methyl]malonic Acid Diethyl Ester (3fa)[31]

This known compound was obtained as a white solid (0.0361 g, 0.095 mmol, 95%) per the procedure for Scheme 2.

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^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.24 (m, 1 H, C_6H_4), 7.15–7.11 (m, 3 H, C_6H_4), 6.26 (br s, 1 H, NH), 5.65 (br s, 1 H, NHC*H*), 4.22–4.01 (m, 4 H, OCH_2, $OC'H_2$), 3.73 [br s, 1 H, C*H*C(O)OCH_2], 2.44 (s, 3 H, CH_3), 1.37 [s, 9 H, $C(CH_3)_3$], 1.22 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.12 (t, *J* = 7.0 Hz, 3 H, $C'H_2C'H_3$).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 167.9 [s, *C*(O)OCH_2], 167.0 [s, *C'*(O)$OC'H_2$], 154.7 [s, *C*(O)$OC(CH_3)_3$], 137.8, 134.9, 130.5, 127.4, 126.0, 125.6 (6 × s, C_6H_4), 79.4 [s, $C(CH_3)_3$], 61.7, 61.4, 55.4, 50.2 [4 × s, NHCH, *C*HC(O)OCH_2, CH_2CH_3, $C'H_2C'H_3$], 28.1 [s, $C(CH_3)_3$], 18.9 (s, CH_3), 13.8 (s, CH_2CH_3), 13.7 (s, $C'H_2C'H_3$).

HPLC (Figure s10): Chiralpak AS-H column (95:5 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 5.8 min (major), 8.0 min (minor).[28]

2-(Benzyloxycarbonylaminophenylmethyl)malonic Acid Diethyl Ester (3ga)[26]

This known compound was obtained as a white solid (0.0360 g, 0.090 mmol, 90%) per the procedure for Scheme 2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 10 H, C_6H_5, $CH_2C_6H_5$), 6.54 (br s, 1 H, NH), 5.57 (br s, 1 H, NHC*H*), 5.14–5.06 (m, 2 H, $OCH_2C_6H_5$), 4.18–4.03 (m, 4 H, OCH_2, $OC'H_2$), 3.93 [br s, 1 H, C*H*C(O)OCH_2], 1.20 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.12 (t, *J* = 7.0 Hz, 3 H, $C'H_2C'H_3$).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 167.8 [s, *C*(O)OCH_2], 166.8 [s, *C'*(O)$OC'H_2$], 155.6 [s, *C*(O)$OCH_2C_6H_5$], 139.0, 136.3, 128.5, 128.3, 127.9, 127.6, 126.1 (7 × s, C_6H_5, $CH_2C_6H_5$), 66.8, 61.9, 61.5, 56.7, 53.8 [5 × s, NHCH, *C*HC(O)OCH_2, $CH_2C_6H_5$, *C*H_2CH_3, *C'*$H_2C'H_3$], 13.8 (s, CH_2CH_3), 13.7 (s, $C'H_2C'H_3$).

HPLC (Figure s11): Chiralpak AS-H column (98:2 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 45.2 min (major), 63.7 min (minor).[28]

tert-Butyl (2-Nitro-1-phenylethyl)carbamate (5aa)[6b]

This known compound was obtained as a white solid (0.0248 g, 0.093 mmol, 93%) per the procedure for Scheme 3.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5 H, C_6H_5), 5.38 (br s, 1 H, NH), 5.30 (br s, 1 H, NHC*H*), 4.86 (br s, 1 H, CH_2NO_2), 4.72–4.60 (m, 1 H, CH_2NO_2), 1.44 [s, 9 H, $C(CH_3)_3$].

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 154.9 [s, *C*(O)$OC(CH_3)_3$], 137.0, 129.2, 128.7, 126.4 (4 × s, C_6H_5), 80.7, 78.9 [2 × s, $C(CH_3)_3$, CH_2NO_2], 52.9 (s, NHCH), 28.3 [s, $C(CH_3)_3$].

HPLC (Figure s12): Chiralpak AD column (98:2 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 45.9 min (minor), 49.1 min (major).[3c,29]

tert-Butyl [1-(2-Chlorophenyl)-2-nitroethyl]carbamate (5ca)[3c]

This known compound was obtained as a white solid (0.0271 g, 0.090 mmol, 90%) per the procedure for Scheme 3.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 4 H, C_6H_4), 5.79 (br s, 1 H, NH), 5.74 (br s, 1 H, NHC*H*), 4.84 (br s, 1 H, CH_2NO_2), 4.79 (br s, 1 H, CH_2NO_2), 1.42 [s, 9 H, $C(CH_3)_3$].

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 154.5 [s, *C*(O)$OC(CH_3)_3$], 134.1, 132.5, 130.4, 129.8, 128.0, 127.6 (6 × s, C_6H_4), 80.6, 77.4 [2 × s, $C(CH_3)_3$, CH_2NO_2], 50.5 (s, NHCH), 28.2 [s, $C(CH_3)_3$].

HPLC (Figure s13): Chiralpak AD-H column (90:10 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 10.3 min (major), 14.4 min (minor).[7g,29]

tert-Butyl [1-(4-Methoxyphenyl)-2-nitroethyl]carbamate (5ea)[6a]

This known compound was obtained as a white solid (0.0268 g, 0.090 mmol, 90%) per the procedure for Scheme 3.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.5 Hz, 2 H, C_6H_4), 6.89 (d, *J* = 9.0 Hz, 2 H, C_6H_4), 5.32 (br s, 1 H, NH), 5.18 (br s, 1 H, NHC*H*), 4.83 (br s, 1 H, CH_2NO_2), 4.64–4.48 (m, 1 H, CH_2NO_2), 3.79 (s, 3 H, OCH_3), 1.44 [s, 9 H, $C(CH_3)_3$].

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 159.7 [s, *C*(O)$OC(CH_3)_3$], 154.8, 128.7, 127.6, 114.5 (4 × s, C_6H_4), 80.5, 78.8 [2 × s, $C(CH_3)_3$, CH_2NO_2], 55.3 (s, OCH_3), 52.3 (s, NHCH), 28.2 [s, $C(CH_3)_3$].

HPLC (Figure s14): Chiralpak OD column (90:10 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 26.6 min (major), 31.8 min (minor).[3c,29]

tert-Butyl (2-Nitro-1-phenylpropyl)carbamate (5ab)[4b]

This known compound was obtained as a white solid (0.0249 g, 0.089 mmol, 89%) and a 95:5 mixture of *syn*/*anti* diastereomers (determined by ^{1}H NMR) per the procedure for Scheme 3.

^{1}H NMR (500 MHz, $CDCl_3$; *syn*): δ = 7.38–7.30 (m, 3 H, C_6H_5), 7.26–7.24 (m, 2 H, C_6H_5), 5.59 (br s, 1 H, NHC*H*), 5.11 (br s, 1 H, $CHNO_2$), 4.95 (br s, 1 H, NH), 1.55 (d, *J* = 6.0 Hz, 3 H, $CHCH_3$), 1.42 [s, 9 H, $C(CH_3)_3$].

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$; *syn*): δ = 155.08 [s, *C*(O)$OC(CH_3)_3$], 137.4, 129.0, 128.4, 126.4 (4 × s, C_6H_5), 86.7 (s, $CHNO_2$), 80.4 [s, $C(CH_3)_3$], 57.0 (s, NHCH), 28.1 [s, $C(CH_3)_3$], 16.9 (s, $CHCH_3$).

HPLC (Figure s15): Chiralpak AD-H column (90:10 v/v hexane/isopropanol, 1.0 mL/min, λ = 254 nm); t_R = 13.0 min (syn_{major}), 15.6 min (syn_{minor}).[4b,29]

NMR Experiments

A

A 5 mm NMR tube was sequentially charged with **1b** (0.038 g, 0.10 mmol, 1.0 equiv), K_2CO_3 (0.210 g, 0.15 mmol, 1.5 equiv), Δ-[Co((*S*,*S*)-dpen)$_3$]$^{3+}$ $2Cl^-BAr_f^-·H_2O$ (0.017 g, 0.010 mmol, 10 mol%), and CD_2Cl_2 (0.50 mL). The relative amounts of **1b**, (4-ClC_6H_4)CH=NBoc, and 4-chlorobenzaldehyde were calculated using the integrals of the $OC(CH_3)_3$, *CH*=N, and *CH*=O signals, respectively. Data: see text.

B

A 5 mm NMR tube was sequentially charged with **1b** (0.038 g, 0.10 mmol, 1.0 equiv), K_2CO_3 (0.210 g, 0.15 mmol, 1.5 equiv), and CD_2Cl_2 (0.50 mL). Data were collected as in A.

Funding Information

We thank the Welch Foundation (Grant A-1656) for support.

Acknowledgment

We thank Mr. Sugam Kharel for help in purifying some starting materials.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590502.

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References

(1) Reviews: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; *Angew. Chem.* **1998**, *110*, 1096. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (e) Xiao-Hua, C.; Hui, G.; Bing, X. *Eur. J. Chem.* **2012**, *3*, 258. (f) Karimi, B.; Enders, D.; Jafari, E. *Synthesis* **2013**, *45*, 2769. (g) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887.

(2) For representative Mannich reactions involving Boc derivatives ArCH=NBoc and hydrogen bond donor catalysts, see: (a) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (b) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (c) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 3823; *Angew. Chem.* **2010**, *122*, 3911. (d) Sohtome, Y.; Tanaka, S.; Takada, K.; Yamaguchi, T.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 9254; *Angew. Chem.* **2010**, *122*, 9440. (e) Probst, N.; Madarász, Á.; Valkonen, A.; Pápai, I.; Rissanen, K.; Neuvonen, A.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8495; *Angew. Chem.* **2012**, *124*, 8623.

(3) For representative aza-Henry reactions involving Boc derivatives ArCH=NBoc and hydrogen bond donor catalysts, see: (a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466; *Angew. Chem.* **2005**, *117*, 470. (c) Pedrosa, R.; Andrés, J. M.; Ávila, D. P.; Ceballos, M.; Pindado, R. *Green Chem.* **2015**, *17*, 2217.

(4) For representative studies with metal-based catalysts, see: (a) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 117; *Angew. Chem.* **2006**, *118*, 123. (b) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925; and earlier work cited therein. (c) Tsubogo, T.; Shimizu, S.; Kobayashi, S. *Chem. Asian J.* **2013**, *8*, 872; and earlier work cited therein. (d) Karimi, B.; Jafari, E.; Enders, D. *Chem. Eur. J.* **2013**, *19*, 10142.

(5) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949.

(6) For general experimental conditions, see the supporting information of the following two references: (a) Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, *350*, 1785. (b) Mbofana, C. T.; Miller, S. J. *J. Am. Chem. Soc.* **2014**, *136*, 3285.

(7) (a) Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem. Eur. J.* **2007**, *13*, 8338. (b) Takada, K.; Tanaka, S.; Nagasawa, K. *Synlett* **2009**, *10*, 1643. (c) Zhu, H.; Jiang, X.; Li, X.; Hou, C.; Jiang, Y.; Hou, K.; Wang, R.; Li, Y. *ChemCatChem* **2013**, *5*, 2187. (d) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (e) Bengoa-Gomez, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955. (f) Jiang, X.; Zhang, Y.; Wu, L.; Zhang, G.; Liu, X.; Zhang, H.; Fu, D.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 2096. (g) Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* **2012**, *14*, 704. (h) Cao, D.; Chai, Z.; Zhang, J.; Ye, Z.; Xiao, H.; Wang, H.; Chen, J.; Wu, X.; Zhao, G. *Chem. Commun.* **2013**, *49*, 5972.

(8) (a) *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2013**. (b) Qin, Y.; Zhu, L.; Luo, S. *Chem. Rev.* **2017**, in press; DOI: 10.1021/acs.chemrev.6b00657.

(9) Ganzmann, C.; Gladysz, J. A. *Chem. Eur. J.* **2008**, *14*, 5397.

(10) Lewis, K. G.; Ghosh, S. K.; Bhuvanesh, N.; Gladysz, J. A. *ACS Cent. Sci.* **2015**, *1*, 50.

(11) Kumar, A.; Ghosh, S. K.; Gladysz, J. A. *Org. Lett.* **2016**, *18*, 760.

(12) Ghosh, S. K.; Ganzmann, C.; Bhuvanesh, N.; Gladysz, J. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 4356; *Angew. Chem.* **2016**, *128*, 4429.

(13) (a) Scherer, A.; Mukherjee, T.; Hampel, F.; Gladysz, J. A. *Organometallics* **2014**, *33*, 6709. (b) Mukherjee, T.; Ganzmann, C.; Bhuvanesh, N.; Gladysz, J. A. *Organometallics* **2014**, *33*, 6723.

(14) Thomas, C.; Gladysz, J. A. *ACS Catal.* **2014**, *4*, 1134.

(15) Full papers detailing catalyst syntheses: (a) Ghosh, S. K.; Lewis, K. G.; Kumar, A.; Gladysz, J. A. *Inorg. Chem.* **2017**, *56*, 2304. (b) Ghosh, S. K.; Ojeda, A. S.; Guerrero-Leal, J.; Bhuvanesh, N.; Gladysz, J. A. *Inorg. Chem.* **2013**, *52*, 9369.

(16) (a) Review of stereoisomerism in salts of the trication $[Co(en)_3]^{3+}$, and homologues with substituted 1,2-diamine ligands: Ehnbom, A.; Ghosh, S. K.; Lewis, K. G.; Gladysz, J. A. *Chem. Soc. Rev.* **2016**, *45*, 6799. (b) Review of hydrogen bonding in crystalline salts of the trication $[Co(en)_3]^{3+}$: Ghosh, S. K.; Ehnbom, A.; Lewis, K. G.; Gladysz, J. A. *Coord. Chem. Rev.* **2017**, in press; DOI: 10.1016/j.ccr.2017.04.002.

(17) (a) Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2013**, *135*, 10598. (b) Chen, L.-A.; Tang, X.; Xi, J.; Xu, W.; Gong, L.; Meggers, E. *Angew. Chem. Int. Ed.* **2013**, *52*, 14021; Angew. Chem. 2013, 125, 14271. (c) Ma, J.; Ding, X.; Hu, Y.; Huang, Y.; Gong, L.; Meggers, E. *Nat. Commun.* **2014**, *5*, 4531. (d) Huo, H.; Fu, C.; Wang, C.; Harms, K.; Meggers, E. *Chem. Commun.* **2014**, *50*, 10409. (e) Liu, J.; Gong, L.; Meggers, E. *Tetrahedron Lett.* **2015**, *56*, 4653. (f) Ding, X.; Lin, H.; Gong, L.; Meggers, E. *Asian J. Org. Chem.* **2015**, *4*, 434. (g) Xu, W.; Arieno, M.; Löw, H.; Huang, K.; Xie, X.; Cruchter, T.; Ma, Q.; Xi, J.; Huang, B.; Wiest, O.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2016**, *138*, 8774. (h) Huang, K.; Ma, Q.; Shen, X.; Gong, L.; Meggers, E. *Asian J. Org. Chem.* **2016**, *5*, 1198. (i) Ding, X.; Tian, C.; Hu, Y.; Gong, L.; Meggers, E. *Eur. J. Org. Chem.* **2016**, 887. (j) Xu, W.; Shen, X.; Ma, Q.; Gong, L.; Meggers, E. *ACS Catal.* **2016**, *6*, 7641. (k) Ma, Q.; Gong, L.; Meggers, E. *Org. Chem. Front.* **2016**, *3*, 1319.

(18) (a) Maleev, V. I.; North, M.; Larionov, V. A.; Fedyanin, I. V.; Savel'yeva, T. F.; Moscalenko, M. A.; Smolyakov, A. F.; Belokon, Y. N. *Adv. Synth. Catal.* **2014**, *356*, 1803. (b) Nickerson, D. M.; Mattson, A. E. *Chem. Eur. J.* **2012**, *18*, 8310. (c) Nickerson, D. M.; Angeles, V. V.; Auvil, T. J.; So, S. S.; Mattson, A. E. *Chem. Commun.* **2013**, *49*, 4289.

(19) Werner, A. *Chem. Ber.* **1912**, *45*, 121.

(20) All of the catalysts in Figure 1 are isolated as hydrates; see ref. 15. To aid readability, the associated water is not specified in the introduction, results, or discussion sections, as well as the graphics. However, the hydrates are specified in the experimental section (and the water included in calculating the catalyst loadings).

(21) These compounds are available from many vendors. The best prices in effect as of the submission date of this manuscript are from Ark Pharm (http://www.arkpharminc.com) for *R,R*-dpen ($420/100 g) and Aris Pharmaceuticals (http://www.arispharma.com) for *S,S*-dpen ($408/100 g).

(22) (a) https://secure.strem.com/catalog/v/27-4011/16/cobalt_1867120-15-7. (b) https://secure.strem.com/catalog/v/27-4010/16/cobalt_1542135-29-4.

(23) One representative computational investigation from several research groups: (a) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358. (b) Wang, X.-F.; Peng, L.; An, J.; Li, C.; Yang, Q.-Q.; Lu, L.-Q.; Gu, F.-L.; Xiao, W.-J. *Chem. Eur. J.* **2011**, *17*, 6484. (c) Sengupta, A.; Sunoj, R. B. *J. Org. Chem.* **2012**, *77*, 10525. (d) Roca-López, D.; Marqués-López, E.; Alcaine, A.; Merino, P.; Herrera, R. P. *Org. Biomol. Chem.* **2014**, *12*, 4503. (e) Breugst, M.; Houk, K. N. *J. Org. Chem.* **2014**, *79*, 6302. (f) Mittal, N.; Lippert, K. M.; De C, K.; Klauber, E. G.; Emge, T. J.; Schreiner, P. R.; Seidel, D. *J. Am. Chem. Soc.* **2015**, *137*, 5748. (g) Madarász, A.; Dósa, Z.;

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Varga, S.; Soós, T.; Csámpai, A.; Pápai, I. *ACS Catal.* **2016**, *6*, 4379. (h) Yan, C.-X.; Yang, F.; Yang, X.; Zhou, D.-G.; Zhou, P.-P. *J. Org. Chem.* **2017**, *82*, 3046.

(24) Additional scenarios have been raised by the reviewers, such as the direct displacement of the $PhSO_2$ moiety in **1** by nucleophiles. However, given that all substrates **1** are racemic, some type of dual pathway mechanism would be required. We have attempted to assay for a kinetic resolution in the consumption of **1**, but have been thwarted by experimental issues (data suggest little or no differentiation).

(25) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, 2571.

(26) Puglisi, A.; Benaglia, M.; Annunziata, R.; Rossi, D. *Tetrahedron: Asymmetry* **2008**, *19*, 2258.

(27) Wang, D.; Cao, P.; Wang, B.; Jia, T.; Lou, Y.; Wang, M.; Liao, J. *Org. Lett.* **2015**, *17*, 2420.

(28) The absolute configurations of **3aa**, **3ab**, and **3ad** were assigned by HPLC using conditions similar to those in the literature (see references 2a and 2d). The dominant enantiomers of the other products **3** were assumed to have analogous (relative) configurations.

(29) The absolute configurations of **5aa**, **5ca**, **5ea**, and **5ab** were assigned by HPLC using conditions similar to those in the literature (see references 3c, 4b, and 7g).

(30) Ananthanawat, C.; Banphavichit, V.; Vilaivan, T. *Synth. Commun.* **2006**, *36*, 1845.

(31) Kano, T.; Yurino, T.; Asakawa, D.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 5532; *Angew. Chem.* **2013**, *125*, 5642.

Downloaded by: Collections and Technical Services Department. Copyrighted material.