Chiral Anion Catalysis

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Sodium Salts of Anionic Chiral Cobalt(III) Complexes as Catalysts of the Enantioselective Povarov Reaction

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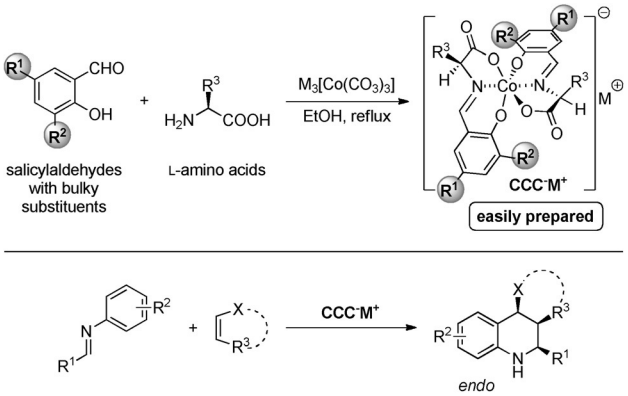
Abstract: *The sodium salts of anionic chiral cobalt(III) complexes (CCC^-Na^+) have been found to be efficient catalysts of the asymmetric Povarov reaction of easily accessible dienophiles, such as 2,3-dihydrofuran, ethyl vinyl ether, and an N-protected 2,3-dihydropyrrole, with 2-azadienes. Ring-fused tetrahydroquinolines with up to three contiguous stereogenic centers were thus obtained in high yields, excellent diastereoselectivities (endo/exo up to >20:1), and high enantioselectivities (up to 95:5 e.r.).*

The use of chiral anions as stereoinductors in the field of asymmetric catalysis has received increasing attention.[1] Whereas organic molecular anion catalysts have been widely employed, the potential of chiral metal complexes as counteranions in asymmetric catalysis has hardly been explored. Belokon et al. recently showed that salicylaldehyde-derived chiral Co^{III} complexes can be employed to accelerate a few C–C bond formation reactions by asymmetric counterion catalysis.[2b-d] However, these transformations proceeded with low to moderate enantioselectivities[2a–d] owing to the limitations of unsubstituted salicylaldehydes and the meridional stereoisomers of these complexes.[2e–f] We envisioned that easily prepared, structurally tunable, and stereochemically stable[2g] metal salts of anionic chiral Co^{III} complexes (CCC^-M^+) that are derived from salicylaldehydes with bulky substituents and L-amino acids would be more applicable to asymmetric catalysis than anticipated by common sense (Scheme 1). We hypothesized that the achiral cation can activate a substrate while the chiral counteranion might be applied to control the stereoselectivity of the transformation. Thus, we decided to test these catalysts in the challenging Povarov reaction[3] of simple 2-azadienes and dienophiles to generate structurally diverse 1,2,3,4-tetrahydroquinoline (THQ) derivatives with contiguous stereogenic centers, which are key structural motifs of numerous natural products and pharmacologically relevant molecules.[4]



Scheme 1. CCC^-M^+ catalysts used for the Povarov reaction.

The catalytic enantioselective Povarov reaction has been intensively investigated[5–7] since the pioneering work by Ishitani and Kobayashi, who employed a chiral ytterbium complex as the catalyst.[6a] In these cases, classical chiral Lewis acids[6] or chiral Brønsted acids[7] have generally been the catalysts of choice to promote asymmetric versions. Thus, the development of new chiral catalyst motifs that are principally distinct from traditional ones is still highly desirable. Herein, we show that the sodium salts of anionic chiral Co^{III} complexes (CCC^-Na^+) are able to act as promising chiral catalysts for the asymmetric Povarov reaction of a wide variety of simple 2-azadienes and dienophiles, such as 2,3-dihydrofuran, ethyl vinyl ether, and an N-protected 2,3-dihydropyrrole, giving rise to multiply substituted THQ derivatives in high yields and with excellent stereoselectivities (Scheme 1).

Our initial investigation started with the reaction of *N*-phenyl benzaldimine (**1a**) with 2,3-dihydrofuran (**2a**) in the presence of the Brønsted acids of various anionic chiral Co^{III} complexes (CCC^-H^+, **4a**–**4e**; 5 mol%), which are all derived from salicylaldehydes and L-amino acids (Table 1, entries 1–7).[2d] Among them, Λ-**4e**,[8] which bears a 3,5-di-*tert*-butyl-substituted (R^1, R^2) salicylaldehyde and a *tert*-butyl group (R^3) on the amino acid moiety, gave the highest enantiomeric ratio of 75:25 (entry 7). Interestingly, the use of sodium salt Λ-**4f** to replace its acidic form Λ-**4e** improved both the diastereo- and enantioselectivities (entry 8 vs. entry 7). The stereoselectivity could be enhanced by introducing a larger substituent, such as a trimethylsilyl, triethylsilyl, or triisopropylsilyl group, at the C3 position (R^2) of the salicylaldehyde moiety (entries 9–11). In particular, CCC^-Na^+ catalyst Λ-**4i**, which bears a triisopropylsilyl moiety at the C3 position, gave **3aa** in 91% yield, 20:1 d.r., and 87.5:12.5 e.r. (entry 11),

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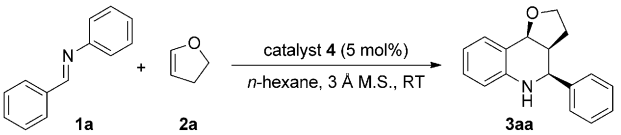
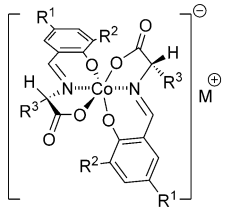
Table 1: Optimization of the reaction conditions.[a]



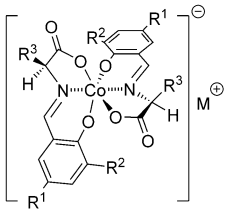
Entry	4	Yield[b] [%]	*endo*/*exo*[c]	e.r.[c]
1	Δ-**4a**	15	6:1	51.5:48.5
2	Λ-**4a**	39	4:1	52.5:47.5
3	Λ-**4b**	75	8:1	50:50
4	Λ-**4c**	42	8:1	52:48
5	Δ-**4d**	61	3:1	56:44
6	Λ-**4d**	12	3:2	55:45
7	Λ-**4e**	74	6.5:1	75:25
8	Λ-**4f**	73	10:1	80:20
9	Λ-**4g**	86	15:1	81.5:18.5
10	Λ-**4h**	88	15:1	82.5:17.5
11	Λ-**4i**	91	20:1	87.5:12.5
12	Λ-**4j**	69	10:1	58.5:41.5
13	Λ-**4k**	74	15:1	83.5:16.5
14	Λ-**4l**	N.R.	N.D.	N.D.
15[d]	Λ-**4i**	87	>20:1	88:12
16[e]	Λ-**4i**	92	>20:1	88.5:11.5
17[f]	Λ-**4i**	49	9:1	82.5:17.5
18[g]	Λ-**4i**	55	8:1	82.5:17.5
19[e,h]	Λ-**4i**	96	>20:1	89:11
20[e,i]	Λ-**4i**	93	>20:1	92:8
21[e,i,j]	Λ-**4i**	89	>20:1	93.5:6.5

[a] Unless otherwise noted, the reaction was performed with **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst **4** (0.01 mmol), and 3Å M.S. (20 mg) in *n*-hexane (2 mL) at room temperature for 6 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase; the relative configuration of the *endo* isomer was confirmed by ^{1}H NMR spectroscopy, and the e.r. values refer to the *endo* isomer. [d] 4Å M.S. were used. [e] 5Å M.S. were used. [f] Anhydrous Na_2SO_4 was used. [g] Anhydrous $MgSO_4$ was used. [h] The reaction was performed at −20 °C for 24 h. [i] The reaction was performed at −40 °C for 72 h. [j] Λ-**4i** (10 mol%). M.S. = molecular sieves, N.D. = not determined, N.R. = no reaction, TBDMS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl.



Δ-(*S*,*S*) configuration

Δ-**4a**: $R^1 = R^2 = H$, $R^3 = i$Pr, M = H;
Δ-**4d**: $R^1 = R^2 = t$Bu, $R^3 = i$Pr, M = H.



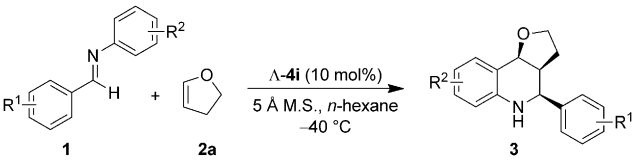
Λ-(*S*,*S*) configuration

Λ-**4a**: $R^1 = R^2 = H$, $R^3 = i$Pr, M = H;
Λ-**4b**: $R^1 = R^2 = H$, $R^3 = s$Bu, M = H;
Λ-**4c**: $R^1 = R^2 = H$, $R^3 = t$Bu, M = H;
Λ-**4d**: $R^1 = R^2 = t$Bu, $R^3 = i$Pr, M = H;
Λ-**4e**: $R^1 = R^2 = t$Bu, $R^3 = t$Bu, M = H;
Λ-**4f**: $R^1 = R^2 = t$Bu, $R^3 = t$Bu, M = Na;
Λ-**4g**: $R^1 = R^3 = t$Bu, R^2 = TMS, M = Na;
Λ-**4h**: $R^1 = R^3 = t$Bu, R^2 = TES, M = Na;
Λ-**4i**: $R^1 = R^3 = t$Bu, R^2 = TIPS, M = Na;
Λ-**4j**: $R^1 = R^3 = t$Bu, R^2 = TBDMS, M = Na;
Λ-**4k**: $R^1 = R^3 = t$Bu, R^2 = TIPS, M = K;
Λ-**4l**: $R^1 = R^3 = t$Bu, $R^2 = t$Bu, M = $(n$Bu$)_4$N.

whereas the use of a CCC$^-$Na$^+$ catalyst with *tert*-butyldimethylsilyl substituents (Λ-**4j**) resulted in much poorer results (entry 12). A comparison of potassium salt Λ-**4k** with Λ-**4i** suggested that the size of the cation has a subtle influence on the stereoselectivity (entry 13 vs. entry 11). Interestingly, the reaction did not work when the tetra-*n*-butylammonium salt Λ-**4l**, which is derived from chiral Co^{III} complex Λ-**4e** and tetra-*n*-butylammonium hydroxide, was used (entry 14). These results (entries 7–8, 11, 13, and 14) indicated that the alkali cations act as Lewis acids to accelerate the reaction while the coordinatively saturated anionic Co^{III} complexes only control the stereoselectivity.[2b,c] Various additives were then tested (entries 15–18), and 5Å molecular sieves turned out to be the optimal additive for this transformation; the THQ product **3aa** was thus obtained in 92% yield and 88.5:11.5 e.r. at ambient temperature (entry 16). Lowering the temperature resulted in enhanced enantioselectivity (entries 19 and 20), and the reaction proceeded well at −40 °C, providing product **3aa** in 92:8 e.r. (entry 20). Increasing the catalyst loading from 5 mol% to 10 mol% led to a further small enhancement of the enantioselectivity (entry 21).

With an optimized procedure established (Table 1, entry 20), we next explored the scope of the enantioselective Povarov reaction with respect to the 2-azadienes **1** (Table 2).

Table 2: Variation of the 2-azadiene.[a]



Entry	1	R^1	R^2	Yield[b] [%]	*endo*/*exo*[c]	e.r.[c]
1	**1a**	H	H	89 (**3aa**)	>20:1	93.5:6.5
2	**1b**	H	4-Me	85 (**3ba**)	>20:1	95:5
3	**1c**	H	4-Cl	84 (**3ca**)	>20:1	92:8
4	**1d**	H	4-Br	93 (**3da**)	>20:1	93:7
5	**1e**	H	4-CO_2Et	37 (**3ea**)	15:1	94:6
6[d]	**1f**	4-Me	4-Me	81 (**3fa**)	>20:1	88:12
7[d]	**1g**	4-NO_2	4-Me	89 (**3ga**)	>20:1	93.5:6.5
8[d]	**1h**	4-CN	4-Me	60 (**3ha**)	>20:1	92.5:7.5
9[d]	**1i**	4-Br	4-Me	86 (**3ia**)	>20:1	93.5:6.5
10[d]	**1j**	4-Cl	4-Me	88 (**3ja**)	>20:1	92.5:7.5
11[d]	**1k**	2,4-Cl_2	4-Me	40 (**3ka**)	>20:1	61.5:38.5

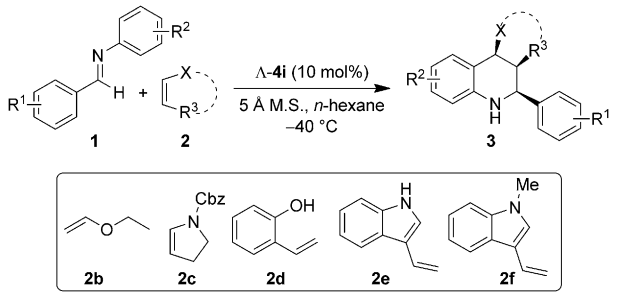
[a] Unless otherwise noted, the reaction was performed with **1** (0.2 mmol), **2a** (0.4 mmol), catalyst Λ-**4i** (0.02 mmol), and 5Å M.S. (20 mg) in *n*-hexane (2 mL) at −40 °C for 72 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase; the e.r. values refer to the *endo* isomer. [d] The reaction was performed at 0 °C for 72 h, and *n*-hexane/CH_2Cl_2 (20:1 v/v) was used as the solvent.

Various substituents on the aniline moiety of the *N*-aryl imine were nicely tolerated (**1a**–**1e**), and the corresponding *endo* tetrahydroquinolines were obtained in up to 93% yield, >20:1 d.r., and up to 95:5 e.r. (entries 1–5). The electronic nature of the substituent on the *para* position of the *N*-aryl ring did not exert an obvious influence on the stereoselectivity (entries 2–5), and the best enantiomeric ratio of 95:5 was obtained for product **3ba**, which features a 4-methyl substituent on the *N*-aryl ring (entry 2). However, the poor solubility of imines derived from substituted aldehydes in *n*-hexane at −40 °C always led to incomplete conversion. Therefore, a series of other solvents, such as CH_2Cl_2, $CHCl_3$,

and toluene, were then screened as co-solvents. Fortunately, when the reactions of these substrates were carried out in a CH_2Cl_2/*n*-hexane solvent mixture (1:20 v/v) at 0 °C, better results were obtained.[9] Thus, the *N*-aryl imines **1f**–**1j**, which bear either electron-donating, electron-withdrawing, or halogen substituents, furnished the corresponding products (**3fa**–**3ja**) with good stereoselectivities (entries 6–10). However, the introduction of a 2,4-disubstituted aryl ring (**1k**) led to a significantly diminished enantioselectivity (entry 11).

The scope of the Povarov reaction with regard to the dienophiles **2** was also evaluated (Table 3). Remarkably, the

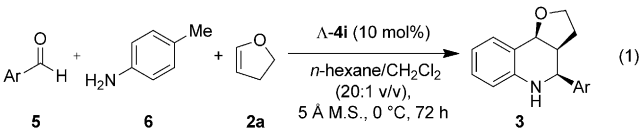
Table 3: Variation of the dienophile.[a]



Entry	1	2	Yield[b] [%]	*endo*/*exo*[c]	e.r.[c]
1[d]	**1a**	**2b**	64 (**3ab**)	>20:1	94:6
2[d]	**1b**	**2b**	44 (**3bb**)	>20:1	94.5:5.5
3	**1a**	**2c**	94 (**3ac**)	>20:1	93:7
4[e]	**1g**	**2c**	99 (**3gc**)	12:1	91:9
5	**1a**	**2d**	63 (**3ad**)	2:1	77.5:22.5
6	**1a**	**2e**	36 (**3ae**)	4:1	78:22
7	**1a**	**2f**	70 (**3af**)	>20:1	76:24

[a] Unless otherwise noted, the reaction was performed with **1** (0.2 mmol), **2** (0.4 mmol), catalyst Λ-**4i** (0.02 mmol), and 5Å M.S. (20 mg) in *n*-hexane (2 mL) at −40 °C for 72 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase; the e.r. values refer to the *endo* isomer. [d] The **1**/**2** ratio was 1:4, and the reaction was run for 5 days. [e] The reaction was performed at 0 °C, and *n*-hexane/CH_2Cl_2 (20:1 v/v) was used as the solvent.

with stereoselectivities similar to those observed for the corresponding reactions with preformed aldimines [Eq. (1)].



(1)

Ar = 4-$NO_2C_6H_4$ (**3ga**): 99% yield, >20:1 d.r., 91:9 e.r.
Ar = 4-BrC_6H_4 (**3ia**): 77% yield, >20:1 d.r., 92.5:7.5 e.r.
Ar = 4-ClC_6H_4 (**3ja**): 63% yield, >20:1 d.r., 90:10 e.r.

During our studies on the CCC^-Na^+ catalyzed Povarov reaction, we found a positive nonlinear effect for the reaction of benzaldimine **1a** with 2,3-dihydrofuran (**2a**) in the presence of 10 mol% of scalemic catalyst **4i** in *n*-hexane at −40 °C (Figure 1). Kinetic studies revealed that optically pure CCC^-Na^+ showed a higher catalytic activity than a racemic catalyst sample (Figure S2),[9] which might be the possible reason for the positive nonlinear effect.[10]

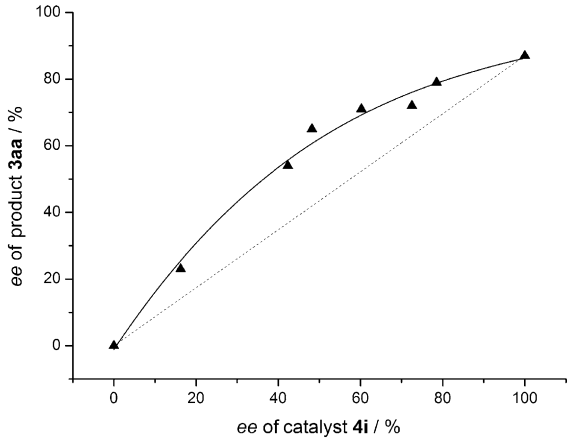


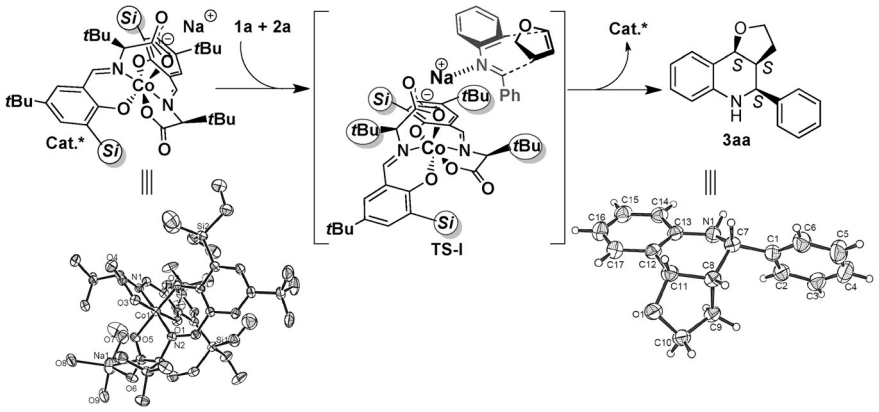
Figure 1. The CCC^-Na^+ catalyzed asymmetric Povarov reaction displays a nonlinear effect.

simple vinyl ether **2b** was able to undergo a Povarov reaction with the *N*-aryl imines **1a** and **1b** to smoothly generate THQ products with high levels of enantioselectivity (up to 94.5:5.5 e.r., entries 1 and 2). Furthermore, N-protected 2,3-dihydropyrrole **2c** was also a good substrate, generating the corresponding tetrahydroquinolines in excellent yields and with good stereoselectivities (entries 3 and 4). However, the use of either 2-hydroxystyrene (**2d**) or 3-vinylindole (**2e**), which contain acidic functional groups, as the dienophiles led to significantly reduced diastereo- and enantioselectivities (entries 5 and 6). *N*-Methyl-3-vinylindole (**2f**) gave the corresponding product in excellent diastereoselectivity and good yield, albeit with a moderate enantioselectivity (entry 7).

The one-pot three-component asymmetric Povarov reaction of 2,3-dihydrofuran (**2a**) and *para*-toluidine (**6**) with various aromatic aldehydes **5** catalyzed by Λ-**4i** (10 mol%) was also successful, furnishing the products **3** in good yields

According to these experimental data and the crystal structures of CCC^-Na^+ Λ-**4h**[11] and the products **3aa** and **3ia**,[12] we propose a transition state to explain the observed stereochemistry (Scheme 2). The sodium cation, in combination with the weakly coordinating chiral anion, is considered to act as a Lewis acid to activate 2-azadiene **1a**, leading to the possible transition state **TS-I**, as suggested by preliminary DFT calculations.[13] The [4+2] cycloaddition with 2,3-dihydrofuran (**2a**) should then preferentially occur on the *Si* face of 2-azadiene **1a**, because in the proposed **TS-I** structure, the *Re* face of the imine might be shielded by both the triisopropylsilyl and *tert*-butyl groups of the catalyst, which leads to the formation of (3a*S*,4*S*,9b*S*)-**3aa** as the major enantiomer.

In summary, we have demonstrated that the sodium salts of anionic chiral Co^{III} complexes are highly promising catalysts for the asymmetric Povarov reaction of 2-azadienes with various dienophiles, such as 2,3-dihydrofuran, ethyl vinyl ether, and an N-protected 2,3-dihydropyrrole, furnishing



Scheme 2. Proposed transition state.

structurally diverse *endo* tetrahydroquinolines with excellent diastereoselectivities (up to >20:1 d.r.) and high enantioselectivities (up to 95:5 e.r.). In this reaction, the *N*-aryl imines were probably activated by the sodium cation in combination with the weakly coordinating anionic chiral Co^{III} complex. More importantly, these findings might inspire the development of anionic Co^{III} complexes as alternative stereocontrol elements for enantioselective transformations. Further studies will focus on the elucidation of the exact reaction mechanism and the development of other asymmetric counteranion-directed reactions with chiral Co^{III} complexes.

Experimental Section

N-Aryl imine **1** (0.20 mmol), catalyst Λ-**4i** (19.5 mg, 0.02 mmol), activated 5Å M.S. (20 mg), and *n*-hexane (2 mL) were added to a 10 mL oven-dried vial at room temperature. The mixture was cooled down to −40 °C and stirred for 15 min. The dienophile **2** (0.40 mmol) was then added, and the resultant solution was stirred vigorously until the reaction was complete (monitored by TLC). The reaction was quenched with pre-cooled NEt_3 (−40 °C, 140 μL, 1.0 mmol); and the crude reaction mixture was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 10:1) to give the enantioenriched THQ derivative **3**.

Acknowledgements

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Keywords: asymmetric catalysis · 2-azadienes · cobalt complexes · Povarov reaction · tetrahydroquinolines

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Angew. Chem. **2015**, *127*, 11361–11365

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[12] CCDC 1021263 (**3aa**) and 1054919 (**3ia**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[13] To obtain insights into the role of the sodium salt of the anionic chiral Co^{III} complex in the asymmetric Povarov reaction, preliminary DFT calculations were carried out on the reactant complexes formed by catalyst Λ-**4i** with imine **1a** and 2,3-dihydrofuran (**2a**), respectively; see the Supporting Information for details.

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