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Brønsted Acids of Anionic Chiral Co(III) Complexes as Catalysts for the Stereoselective Synthesis of *cis*-4-Aminofuranobenzopyrans

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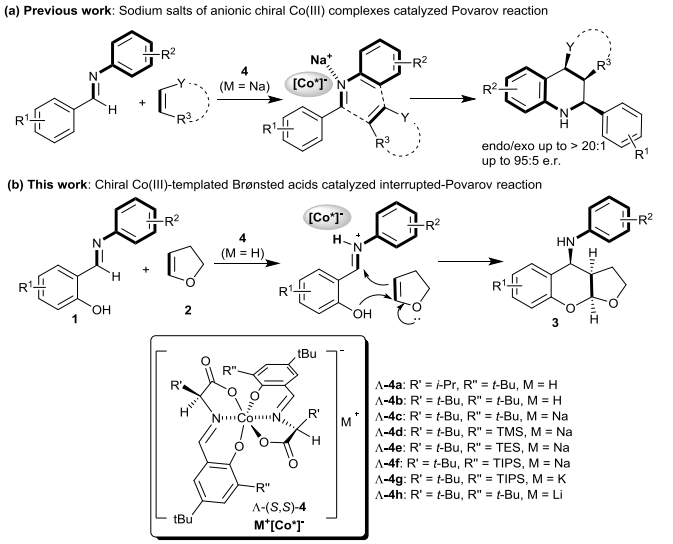
A highly enantioselective interrupted Povarov reaction of salicylaldimines and 2,3-dihydrofuran was developed, through the elegant Brønsted acid catalysis of anionic chiral Co(III) complexes. This reaction affords the *cis*-4-aminofuranobenzopyran derivatives with up to 95% yield, >20:1 dr and 96:4 er. Moreover, a one-pot three-component procedure of salicylaldehydes, anilines, and 2,3-dihydrofuran proves to be successful, with higher reaction efficiency.

Chiral anion catalysis has seen increasing application as a general strategy in the field of asymmetric catalysis.[1] Chiral anions (or anionic complexes) generated from organic small molecules, i.e. the conjugate bases of chiral phosphoric acids[2a-e] and anion-binding (thio)ureas,[2f,g] are common in this area. Metal-templated chiral anion catalysis is conceptually challenging, thus remains underdeveloped.[3] Our group have been focusing on the discovery of easy accesses to octahedral anionic chiral Co(III) complexes with tunable substituents and steric centers. A catalyst library is established through one-step assembly of commercially available amino acids, salicylaldehydes and earth-abundant cobalt salts, which facilitates rapid synthesis of optically pure heterocycles.[4] It is noteworthy that the counter cations of the anionic chiral Co(III) complexes are also crucial in terms of reactivity and the stereocontrol. In 2015, we reported a sodium salt of anionic chiral Co(III) complex (Λ-**4f**)-catalyzed Povarov reaction, wherein the alkali cation served as a Lewis acid to activate imines and the weakly coordinated chiral anion delivered excellent diastereoselectivity and enantioselectivity (Scheme 1a).[4a] Distinct from the traditional chiral metal complexes and organocatalysts, this feature should be able to make anionic chiral Co(III) complexes, in which the metal center does not activate substrates directly but just offers the environment of centrochirality, hold unique privilege in asymmetric catalysis.[5] Very recently, we demonstrated that Brønsted acids of anionic chiral Co(III) complexes, as bifunctional phase-transfer catalysts, enabled a highly enantioselective bromoamino-cyclization of olefins.[4b] Thus, we anticipated to expand this privileged concept to direct synthesis of valuable 4-aminobenzopyran derivatives, which are one of the common subunits of natural products with interesting biological activities,[6] including anti-hypertensive and anti-ischemic properties, and by that are of high synthetic importance.[7]



Scheme 1 Povarov reaction and interrupted Povarov reaction catalyzed by anionic chiral Co^{III} complexes

Catalytic Mannich-acetalization reaction of salicylaldimines and dienophiles, also referred as interrupted Povarov reaction,[8] was pioneered by Rueping and co-workers.[9a] Several variants using different dienophiles, such as vinyl ethers and enamides, were subsequently established, under the catalysis of chiral phosphoric acids[9b] or chiral N,N'-dioxide-Sc(OTf)$_3$ complexes[9c]. Thus, the development of new chiral catalytic systems that are capable of achieving the stereocontrol of

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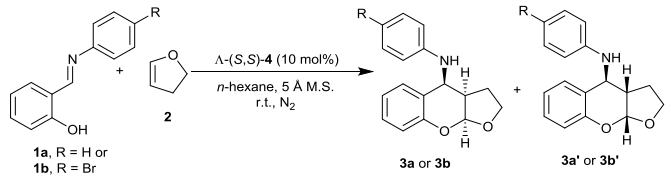
asymmetric versions is still highly desirable. Herein, we present a Brønsted acid of anionic chiral Co(III) complex-catalyzed enantioselective interrupted Povarov reaction of salicylaldimines (**1**) with 2,3-dihydrofuran (**2**), affording *cis*-4-aminofuranobenzopyrans derivatives with up to 96:4 er (Scheme 1b).

Table 1 Optimization of the reaction conditions.[a]



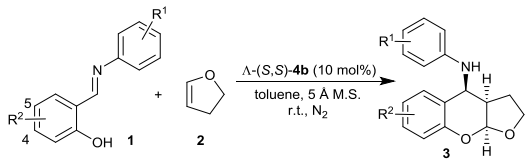
Entry	1	4	yield [%][b]	dr[c]	er[d]
1	**1a**	Λ-**4a**	16	5:1	49:51
2	**1a**	Λ-**4b**	89	10:1	84.5:15.5
3	**1a**	Λ-**4c**	43	8:1	64:26
4	**1a**	Λ-**4d**	9	9:1	45.5:54.5
5	**1a**	Λ-**4e**	16	4:1	58.5:41.5
6	**1a**	Λ-**4f**	44	5.5:1	57:43
7	**1a**	Λ-**4g**	9	4:1	56.5:43.5
8	**1a**	Λ-**4h**	34	5:1	61.5:48.5
9[e]	**1a**	Λ-**4b**	87	9:1	84:16
10[f]	**1a**	Λ-**4b**	80	8:1	84.5:15.5
11[g]	**1a**	Λ-**4b**	54	5:1	72.5:27.5
12[h]	**1a**	Λ-**4b**	57	7:1	76.5:23.5
13[i]	**1a**	Λ-**4b**	29	7:1	67:33
14[j]	**1a**	Λ-**4b**	53	4.5:1	77:23
15[k]	**1a**	Λ-**4b**	74	11:1	92:8
16[l]	**1a**	Λ-**4b**	50	18:1	94.5:5.5
17[l,m]	**1a**	Λ-**4b**	95	>20:1	96:4
18[l,m]	**1b**	Λ-**4b**	33	7:1	73.5:26.5
19[k,m]	**1b**	Λ-**4b**	64	7:1	73.5:26.5
20[n]	**1b**	Λ-**4b**	58	8:1	80.5:19.5
21[o]	**1b**	Λ-**4b**	67	9:1	80:20
22[p]	**1b**	Λ-**4b**	68	12:1	82:18

[a] Unless otherwise noted, the reaction was performed with **1a** or **1b** (0.2 mmol), **2** (0.4 mmol), catalyst Λ-**4** (0.02 mmol), and 5 Å M.S. (10.0 mg) in *n*-hexane (2 mL) under nitrogen at room temperature for 24 h. [b] Isolated yield of product. [c] Determined by ^{1}H NMR spectroscopy of the crude product, the relative configuration of the major product was confirmed by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis on a chiral stationary phase and the er values refer to the major product. [e] 3 Å M.S. were used. [f] 4 Å M.S. were used. [g] CCl_4 was used. [h] Toluene was used. [i] *t*-Butyl methyl ether was used. [j] The reaction was performed at 0 °C for 48 h. [k] The **1a/2** ratio was 1:1.2. [l] The **1a/2** ratio was 1.5:1. [m] *n*-hexane (1 mL) was used. [n] The **1b/2** ratio was 1:1.2 and toluene (1 mL) was used. [o] The **1b/2** ratio was 1:2 and toluene (1 mL) was used. [p] The **1b/2** ratio was 1:3 and toluene (1 mL) was used. M. S. = molecular sieves.

Initially, the reaction of salicylaldimine **1a** with 2,3-dihydrofuran **2** was performed by screening either Brønsted acids or alkali salts of various anionic chiral Co(III) complexes (Λ-**4a**-**4h**; 10 mol%), which are derived from 3,5-disubstitued salicylaldehydes and *L*-amino acids (Table 1, entries 1-8). Among them, Brønsted acid Λ-**4b**, which bears 3,5-di-*tert*-butyl-salicylaldehyde and *L*-*tert*-Leucine, delivered the highest yield of 89%, diastereomeric ratio of 10:1 and enantiomeric ratio of 84.5:15.5 (entry 2). The screening of the reaction parameters including additives and solvents suggested that the performance of the reaction in *n*-hexane gave higher stereoselectivity and 5 Å M.S. (10.0 mg) turned out to be the optimal additive for this transformation (entry 2 vs. entries 9-13). Lowering the temperature resulted in a diminished stereoselectivity (entry 14). To our delight, variation of the ratio of **1a/2** improved both the diastereo- and enantioselectivities (entries 15-16 vs. entry 2) and reducing the solvent volume led to a further enhancement of the yield (95%) and stereoselectivity (>20:1 dr and 96:4 er) (entry 17).

Under the optimized conditions, we next started to explore the scope of the asymmetric interrupted Povarov reaction with respect to the salicylaldimines **1**. Unfortunately, the poor solubility of imines derived from substituted aldehydes or anilines in *n*-hexane may lead to significantly reduced enantioselectivities. Thus, we turned back to examined the reaction of substrate **1b** with a 4-Br substituent on the N-aryl ring (Table 1, entry 18). The excess of 2,3-dihydrofuran **2** could slightly improve the yield of the product **3b** with maintained stereoselectivity (entry 19). Replacement of *n*-hexane with toluene and the use of a three times excess of **2** resulted in an enhancement of both the diastereo- and enantioselectivity (12:1 dr and 82:18 er) (entries 20-22). These conditions were therefore selected as optimal for further investigations on the substrate scope.

Table 2 Scope of the substrates.[a]



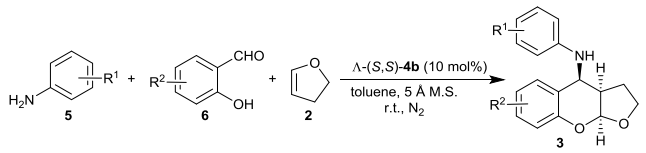
Entry	R^1	R^2	3	yield(%)[b]	dr[c]	er[d]
1	4-Br	H	**3b**	68	12:1	82:18
2	4-Cl	H	**3c**	75	11:1	81:19
3	4-F	H	**3d**	62	10:1	80.5:19.5
4	3-Cl	H	**3e**	51	10:1	75:25
5	H	4-NO_2	**3f**	46	7:1	74.5:25.5
6	H	5-Br	**3g**	56	7:1	82:18
7	H	5-Me	**3h**	51	14:1	82:18
8	H	5-Cl	**3i**	43	8:1	81:19
9	H	5-OMe	**3j**	44	12:1	76.5:23.5
10	4-Br	5-Br	**3k**	55	8:1	80.5:19.5
11	4-Br	5-Me	**3l**	44	10:1	75:25
12	4-Br	5-Cl	**3m**	52	11:1	81.5:18.5
13	4-Me	5-Cl	**3n**	31	15:1	81.5:18.5

[a] Unless otherwise noted, the reaction was performed with **1** (0.2 mmol), **2** (0.6 mmol), catalyst Λ-**4b** (0.02 mmol), and 5 Å M.S. (10.0 mg) in toluene (1 mL) under nitrogen at room temperature for 48 h. [b] Isolated yield of major product. [c] Determined by ^{1}H NMR spectroscopy of the crude product, the relative configuration of the major product was confirmed by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis on a chiral stationary phase and the er values refer to the major product.

As shown in Table 2, various salicylaldimines **1b**-**1e** with substituent on the N-aryl ring (R^1) were examined, giving *cis*-4-aminofuranobenzopyrans **3b**-**3e** in up to 75% yield with 12:1 dr and 82:18 er (Table 2, entries 1-4). Salicylaldimines with the

substituent (R^1) on the *para*-position of N-aryl ring afforded better results than that with the substituent on the *meta*-position (entries 1-3 vs. entry 4). However, the introduction of 4-nitro group on the salicylaldehyde moiety led to a diminished enantioselectivity (74.5:25.5 er, entry 5). The desired 4-aminofuranobenzopyran derivatives **3g**-**3j** with the substituent (R^2) on the aromatic ring of the salicylaldehyde moiety were obtained in good diastereoselectivities (up to 14:1 dr) and moderate enatioselectivities ranging from 76.5:23.5 er to 82:18 er (entries 6-9). Moreover, various salicylaldimines bearing either a 4-bromo or 4-methyl group on N-aryl ring, were subjected to the interrupted Povarov reaction, delivering the corresponding products **3k**-**3n** in up to 55% yield with 15:1 dr and 81.5:18.5 er (entries 10-13).

Table 3 Scope of three-component asymmetric interrupted Povarov reaction. [a]



Entry	R^1	R^2	3	yield(%)[b]	dr[c]	er[d]
1	4-Br	H	**3b**	72	>20:1	80:20
2	4-Cl	H	**3c**	85	>20:1	81:19
3	4-F	H	**3d**	64	>20:1	81.5:18.5
4	3-Cl	H	**3e**	74	>20:1	80:20
5	H	5-Br	**3g**	57	16:1	87.5:12.5
6	H	5-Me	**3h**	60	>20:1	84.5:15.5
7	H	5-Cl	**3i**	69	>20:1	90:10
8	4-Br	5-Br	**3k**	59	10:1	86:14
9	4-Br	5-Me	**3l**	64	>20:1	81.5:18.5
10	4-Br	5-Cl	**3m**	58	14:1	87:13
11	4-Me	5-Cl	**3n**	59	17:1	86:14

[a] Unless otherwise noted, the reaction was performed with **5** (0.2 mmol), **6** (0.2 mmol), **2** (0.6 mmol), catalyst Λ-**4b** (0.02 mmol), and 5 Å M.S. (10.0 mg) in toluene (1 mL) under nitrogen at room temperature for 48 h. [b] Isolated yield of major product. [c] Determined by ^{1}H NMR spectroscopy of the crude product, the relative configuration of the major product was confirmed by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis on a chiral stationary phase and the er values refer to the major product.

The one-pot three-component asymmetric interrupted Povarov reaction catalyzed by Brønsted acid Λ-**4b** was next investigated. To our delight, the reaction of various anilines **5** and salicylaldehydes **6** with 2,3-dihydrofuran **2** was successful, furnishing the *cis*-4-aminofuranobenzopyran **3** with higher reaction efficiency (up to >20:1 dr, 90:10 er) compared to those observed for the corresponding reactions with performed salicylaldimines (Table 3). The reactions between various 4-halo substituted anilines with salicylaldehyde provided the products **3b**-**3d** in excellent diastereoselectivities with maintained enantioseletivities (Table 3, entries 1-3 vs. Table 2 entries 1-3). Pleasingly, higher diastereo- and enantioselectivity (> 20:1 dr, 80:20 er) were observed for *m*-chloroaniline (Table 3, entry 4 vs. Table 2, entry 4). The salicylaldehydes bearing substituent at C5 were nicely tolerated, and the highest enantiomeric ratio of 90:10 were obtained for product **3i** (entries 5-7). A variety of substituted anilines and salicylaldehydes could undergo the three-component interrupted Povarov reaction smoothly to afford the desired heterocycles in good to excellent diastereoselectivities and with up to 87:13 er (entries 8-11). The absolute configuration of the major product **3k** was determined to be (3a*R*, 4*S*, 9a*S*) by a single crystal X-ray diffraction analysis (Figure 1),[10] which was identical with the known structure in the chiral phosphoric acids catalyzed reaction.[9b]

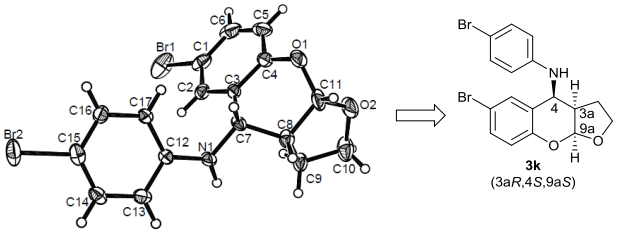


Figure 1 X-ray Structure of the Product **3k**.

In compared to the reported works,[9a,9c] the difference in stereoselectivity might be due to the activation model of the catalysts. Based on previous experimental data[4] and the crystal structure of **3k**, transition states to explain the stereochemistry were proposed (Figure 2). The imine could be protonated by the chiral Co(III)-templated Brønsted acid to form iminium ion and the nucleophilicity of the phenol group of the salicylaldimine would be enhanced via hydrogen bonding interaction with anion complex as shown in **TS-I** and **TS-II**, respectively. The Mannich reaction could favorably occur on the *Si*-face of the imine with 2,3-dihydrofuran in **TS-I**, followed by a fast ketalization to afford the (3a*R*, 4*S*, 9a*S*)-product, as the *Re*-face might be disfavored due to the steric repulsion between the *tert*-butyl substituent on the Schiff base and aryl of the salicylaldehyde (**TS-II**).

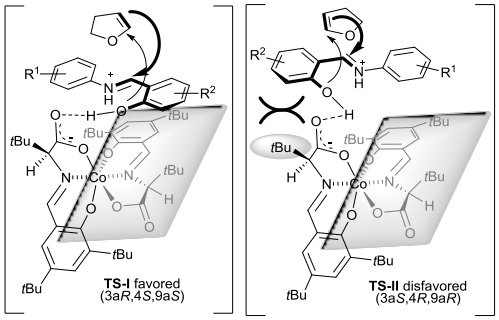


Figure 2 Proposed Transition States.

Conclusions

In summary, Brønsted acids of anionic chiral Co(III) complexes have been revealed to be able to catalyzed an enantioselective interrupted Povarov reaction of salicylaldimines and 2,3-dihydrofuran with up to 95% yield, >20:1 dr and 96:4 er. The three-component protocol also enables efficient access to a variety of chiral *cis*-4-

aminofuranobenzopyrans with higher outcomes. These findings not only showed the potential of the anionic chiral Co(III) complexes in asymmetric catalysis, but also will be able to inspire the future development of Brønsted acids of anionic chiral metal complexes. Further application of the catalyst in other reactions is currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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Notes and references

1 For selected reviews on chiral anions catalysis, see: (a) J. Lacour and V. Hebbe-Viton, *Chem. Soc. Rev.*, 2003, **32**, 373; (b) J. Lacour and D. Moraleda, *Chem. Commun.*, 2009, 7073; (c) Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.*, 2009, **38**, 1187; (d) M. Wenzel, J. R. Hiscock and P. A. Gale, *Chem. Soc. Rev.*, 2012, **41**, 480; (e) R. J. Phipps, G. L. Hamilton and F. D. Toste, *Nature Chem.*, 2012, **4**, 603; (f) M. Mahlau and B. List, *Angew. Chem., Int. Ed.*, 2013, **52**, 518; (g) K. Brak and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2013, **52**, 534.

2 For selected examples on chiral anions catalysis, see: (a) G. L. Hamilton, T. Kanai and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 14984; (b) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566; (c) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356; (d) S. Mayer and B. List, *Angew. Chem., Int. Ed.*, 2006, **45**, 4193; (e) G. L. Hamilton, E. J. Kang, M. Mba and F. D. Toste, *Science*, 2007, **317**, 496; (f) M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 4901; (g) M. S. Sigman, P. Vachal and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2000, **39**, 1279. (h) D. B. Llewellyn, D. Adamson and B. A. Arndtsen, *Org. Lett.*, 2000, **2**, 4165; (i) C. Carter, S. Fletcher and A. Nelson, *Tetrahedron: Asymmetry*, 2003, **14**, 1995.

3 For reviews on chiral-at-metal complexes in catalysis, see: (a) H. Brunner, *Angew. Chem., Int. Ed.*, 1999, **38**, 1194; (b) P. D. Knight and P. Scott, *Coord. Chem. Rev.*, 2003, **242**, 125; (c) M. Fontecave, O. Hamelin and S. Ménage, *Top. Organomet. Chem.*, 2005, **15**, 271; (d) E. B. Bauer, *Chem. Soc. Rev.*, 2012, **41**, 3153; (e) L. Gong, L.-A. Chen and E. Meggers, *Angew. Chem., Int. Ed.*, 2014, **53**, 10868; (f) Z.-Y. Cao, W. D. G. Brittain, J. S. Fossey and F. Zhou, *Catal. Sci. Technol.*, 2015, **5**, 3441.

4 (a) J. Yu, H.-J. Jiang, Y. Zhou, S.-W. Luo and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2015, **54**, 11209; b) H.-J. Jiang, K. Liu, J. Yu, L. Zhang and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2017, **56**, 11931.

5 For early reports of anionic chiral Co(III) complexes employing chiral ligands, see: (a) Y. N. Belokon, V. I. Maleev, D. A. Kataev, I. L. Mal'fanov, A. G. Bulychev, M. A. Moskalenko, T. F. Saveleva, T. V. Skrupskaya, K. A. Lyssenko, I. A. Godovikov and M. North, *Tetrahedron: Asymmetry*, 2008, **19**, 822; (b) Y. N. Belokon, V. I. Maleev, D. A. Kataev, T. F. Saveleva, T. V. Skrupskaya, Y. V. Nelyubina and M. North, *Tetrahedron: Asymmetry*, 2009, **20**, 1746; (c) V. I. Maleev, T. V. Skrupskaya, L. V. Yashkina, A. F. Mkrtchyan, A. S. Saghyan, M. M. Il'in and D. A. Chusov, *Tetrahedron: Asymmetry*, 2013, **24**, 178.

6 (a) E. E. Schweizer and D. Meeder-Nycz, *Chem. Heterocycl. Compd.*, 1977, **31**, 11; (b) J. D. Hepworth, *Comprehensive Heterocyclic Chemistry*, **Vol. 3** (Eds.: A. R. Katrizky and C.W. Rees), Pergamon, Oxford, 1984, p. 737.

7 (a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc.*, 2000, **122**, 9939; (b) R. Bergmann and R. Gericke, *J. Med. Chem.*, 1990, **33**, 492.

8 For a review on the interrupted Povarov reaction, see: M. Fochi, L. Caruana and L. Bernardi, *Synthesis*, 2014, **46**, 135.

9 (a) M. Rueping and M. Y. Lin, *Chem. Eur. J.*, 2010, **16**, 4169; (b) L. Bernardi, M. Comes-Franchini, M. Fochi, V. Leo, A. Mazzanti and A. Ricci, *Adv. Synth. Catal.*, 2010, **352**, 3399. (c) Y. Zhang, S. Dong, X. Liu, M. Xie, Y. Zhu, L. Lin and X. Feng, *Chem. Eur. J.*, 2011, **17**, 13684.

10 CCDC 1470802 (**3k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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A highly enantioselective interrupted Povarov reaction of salicylaldimines was developed, through the elegant Brønsted acid catalysis of anionic chiral Co(III) complexes.