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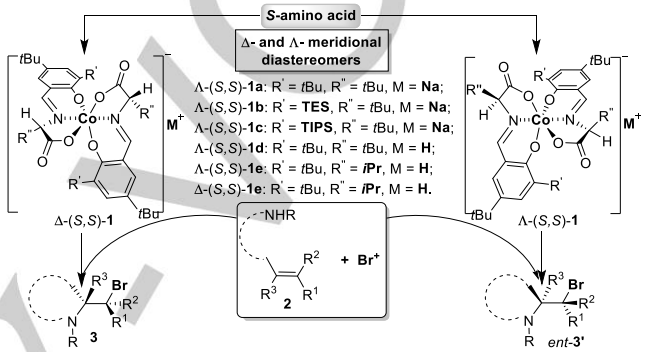
Switchable Stereoselectivity in Bromoaminocyclization of Olefins Catalyzed by Brønsted Acids of Anionic Chiral Co^{III} Complexes

Hua-Jie Jiang,[a] Kun Liu,[b] Jie Yu,*[b] Ling Zhang[a] and Liu-Zhu Gong*[a]

Abstract: Brønsted acids of anionic chiral Co^{III} complexes have been first found to act as bifunctional phase-transfer catalysts to shuttle the substrates across interface and control stereoselectivity. The diastereomeric chiral Co^{III}-templated Brønsted acids with the same chiral ligands enabled a switchably enantioselective bromoamino-cyclization of olefins to afford two opposite enantiomers of 2-substituted pyrrolidines with high enantioselectivities (up to 99:1 e.r.), respectively.

Chiral anions-mediated catalysis, including "asymmetric counteranion-directed catalysis" and "chiral anion phase-transfer catalysis", has steadily received increasing research interest,[1] while the conventional strategy for the establishment of their chirality mostly relies on the chiral organic molecular anion catalysts, such as borane anions,[2a-2b] phosphate anions[2c-2g] and anion-bonding (thio)ureas.[2h-2i] However, the potential of stereochemically stable octahedral chiral metal-complex counteranions, in which the metal center does not serve as a catalytic center to directly activate substrate by coordination but just offers a rigid framework and the environment of centrochirality, has much less been recognized in asymmetric catalysis.[3] Belokon and coworkers have introduced a series of salicylaldehyde derived chiral Co^{III}-complex counteranions, which are capable of affording a few C-C bond formation reactions, but with low to moderate enantioselectivities.[4] The most severe limitation of these Co^{III}-complexes turns out to be the stereocontrolled synthesis of defined meridional stereoisomers.[5] In addition, in the cases concerning chiral metal-complexes (Ru^{II}, Co^{III}) with chiral ligands,[4,6] the nature of asymmetric induction has not been identified for the moment.

We very recently demonstrated that sodium salts of anionic chiral Co^{III} complexes (Scheme 1, Λ-**1c**) were excellent catalysts of asymmetric Povarov reaction of simple 2-azadienes, wherein the weakly bonding nature of chiral ion-pair was considered to permit the alkali cation to work as a Lewis acid for the activation of imine functionality.[7] This feature is distinct from the traditional metal complexes wherein the positive charge on the metal is compensated by ligand coordination and thus would be able to make either acid or salt form of anionic chiral metal-complexes hold unique privilege in asymmetric catalysis. Therefore, the creation of structurally diverse range of new chiral metal-complexes and disinterment of their applications in asymmetric catalysis would be essentially important in synthetic organic chemistry. Herein, we will describe the Λ- and Δ-diastereomeric Co^{III}-complexes acting as "pseudo-enantiomers" to render the asymmetric reaction to give opposite enantiomers, and will demonstrate the versatility of the chiral Co^{III}-templated Brønsted acids as highly efficient catalysts for asymmetric bromoaminocyclization of olefins (Scheme 1).



Scheme 1. The Λ- and Δ-diastereomeric Co^{III}-complexes used for the inter-molecular bromoaminocyclization.

After the diastereoselective synthesis of sodium salts and Brønsted acids of anionic chiral Co^{III} complexes was achieved,[8] we chose bromoaminocyclization of olefins as a benchmark reaction,[9-10] which has received increasing interest as the corresponding products (e.g., pyrrolidines) are core structural element in biological pharmaceutical molecules, and organo-catalysts[11] and thereby are of high synthetic significance. The reaction of γ-amino-alkene **2a** with N-bromosuccinimide (NBS) was initially examined in the presence of 5 mol % of sodium salts of anionic chiral Co^{III} complexes, Λ-(*S*,*S*)-**1a**-**1c**. As anticipated, the desired reaction underwent smoothly to give 2-substituted pyrrolidine **3a** in good yields, but with low levels of enantioselectivity (Table 1, entries 1-3). Interestingly, the metal-templated Brønsted acids exhibited much higher catalytic activity and stereoselectivity than corresponding salts (entries 4-6). In particular, the Brønsted acid Λ-(*S*,*S*)-**1e** was able to provide **3a** with a 99% yield and 98:2 e.r. (entry 5). As anticipated, Δ-(*S*,*S*)-**1e**, the diastereomer of Λ-(*S*,*S*)-**1e**, indeed enabled the reaction to give the *ent*-**3a** in 94.5:5.5 e.r. (entry 6). The screening of other reaction parameters including additives, temperature and solvents suggested that the performance of the reaction in a nonpolar solvent gave higher enantioselectivity and 5 Å M.S. turned out to be the best additive while the reaction temperature exerted little effect on the stereoselectivity (entries 7-13).

Under the optimized conditions, the generality of the enantioselective bromoaminocyclization for the N-protecting group of alkene **2** was then explored. The alternation of sulfonyl-protected γ-amino-alkenes **2** was nicely tolerated, affording N-protected 2-substituted pyrrolidines **3** in up to 99% yield and 98:2 e.r. (Table 2, entries 1-9). The electronic feature and substitution pattern of the aryl group did not exert significant influence on the stereoselectivities, and the highest enantiomeric ratios were obtained for products **3a**, **3e**, **3f**, and **3h** (entries 1, 5, 6 and 8). However, the introduction of 2-nitro group to the N-

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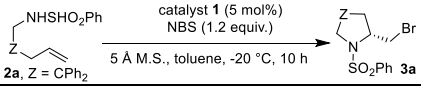
phenylsulfonyl led to a much diminished yield and enantioselectivity (entry 7).

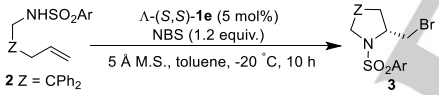
Table 1. Optimization of the enantioselective bromoaminocyclization of **2a**.[a]



entry	1	yield [%][b]	e.r.[c]
1	Λ-(*S*,*S*)-**1a**	53	67:33
2	Λ-(*S*,*S*)-**1b**	54	47.5:52.5
3	Λ-(*S*,*S*)-**1c**	43	53:47
4	Λ-(*S*,*S*)-**1d**	99	77.5:22.5
5	Λ-(*S*,*S*)-**1e**	99	98:2
6	Δ-(*S*,*S*)-**1e**	98	5.5:94.5
7[d]	Λ-(*S*,*S*)-**1e**	94	51:49
8[e]	Λ-(*S*,*S*)-**1e**	91	90:10
9[f]	Λ-(*S*,*S*)-**1e**	84	95:5
10[g]	Λ-(*S*,*S*)-**1e**	72	97.5:2.5
11[h]	Λ-(*S*,*S*)-**1e**	97	95:5
12[i]	Λ-(*S*,*S*)-**1e**	98	97.5:2.5
13[j]	Λ-(*S*,*S*)-**1e**	87	96:4

[a] Unless otherwise noted, the reaction was performed with **2a** (0.1 mmol), NBS (0.12 mmol), catalyst **1** (0.005 mmol) and 5 Å M. S. (100 mg) in toluene (2 mL) at -20 ˚C for 10 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] CH_2Cl_2 was used. [e] CCl_4 was used. [f] 3 Å M. S. was used. [g] 4 Å M. S. was used. [h] The reaction was carried out at 25 ˚C for 90 minutes. [i] The reaction was carried out at 0 ˚C. [j] The reaction was carried out at -40 °C. M. S. = molecular sieves.

Table 2. Variation of the N-protecting group.[a]

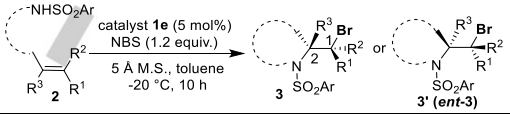


entry	3	Ar	yield (%)[b]	e.r.[c]
1	**3a**	Ph	99	98:2
2	**3b**	4-MeC_6H_4	99	96:4
3	**3c**	2,4,6-Me$_3C_6H_2$	99	93.5:6.5
4	**3d**	4-MeOC_6H_4	99	93.5:6.5
5	**3e**	4-$NO_2C_6H_4$	99	98:2
6	**3f**	3-$NO_2C_6H_4$	99	98:2
7	**3g**	2-$NO_2C_6H_4$	56	86:14
8	**3h**	1-naphthyl	99	98:2
9	**3i**	2-naphthyl	99	95.5:4.5

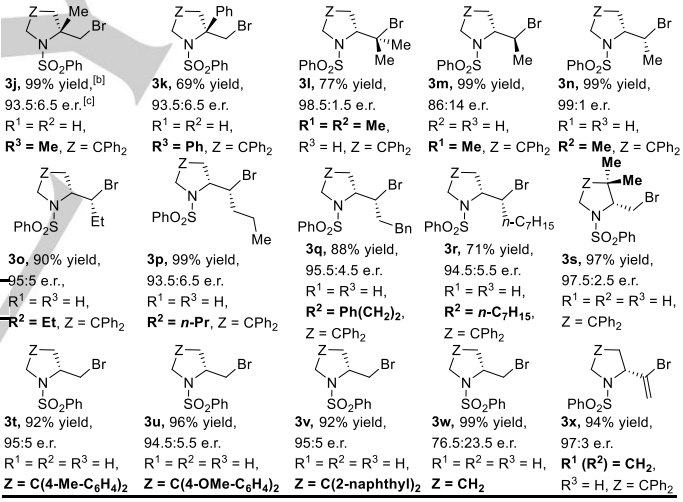
[a] Unless otherwise noted, the reaction was performed with **2** (0.1 mmol), NBS (0.12 mmol), catalyst Λ-(*S*,*S*)-**1e** (0.005 mmol) and 5 Å M. S. (100 mg) in toluene (2 mL) at -20 ˚C for 10 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

The capacity of the reaction catalyzed by Λ-(*S*,*S*)-**1e** to tolerate the substituent on the alkene moiety of **2** was next investigated (Table 3). The γ-amino-alkene bearing either a methyl or phenyl group at C2, delivered the corresponding 2-substituted pyrrolidine with a quaternary stereocenter in a high enantiomeric ratio of 93.5:6.5 (Table 3, **3j**-**3k**). Significantly, an excellent enantioselectivity (98.5:1.5 e.r.) was also obtained in the case of a trisubstituted olefin (**3l**). The geometry of carbon-carbon double bond greatly influences the stereoselectivity, as indicated by the fact that a tremendously higher enantioselectivity (99:1 e.r.) was observed for *cis*-γ-amino-alkene (**3n**) than *trans*-γ-amino-alkene (86:14 e.r.) (**3m**). A variety of *cis*-γ-amino-alkenes were proven to be excellent substrates in the bromoaminocyclization, to provide desired heterocycles in good yields and with up to 99:1 e.r. (**3n**-**3r**). α-Dialkyl-β-diphenyl-γ-amino-alkene and β-diaryl-γ-amino-alkenes could also undergo the asymmetric bromoaminocyclization smoothly to furnish the desired products in high enenatioselectivities (**3s**-**3v**). Although the α- and β-unsubstituted γ-amino-alkene underwent a clean reaction, a moderate enantioselectivity was offered (**3w**). To our delight, the halofunctionalization of allenes, which has relatively been unexplored,[12] could cleanly proceed catalyzed by the metal-templated Brønsted acid Λ-(*S*,*S*)-**1e**, providing the vinyl bromide intermediate in excellent yield and with 97:3 e.r. (**3x**). The absolute configurations of **3o** and **3x** were assigned by single-crystal X-ray diffraction analysis.[13]

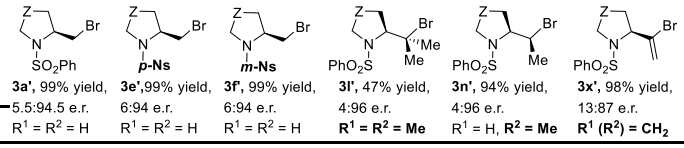
Table 3. Substrate scope of switchably enantioselective bromoaminocyclization.[a]



catalyzed by Λ-1e



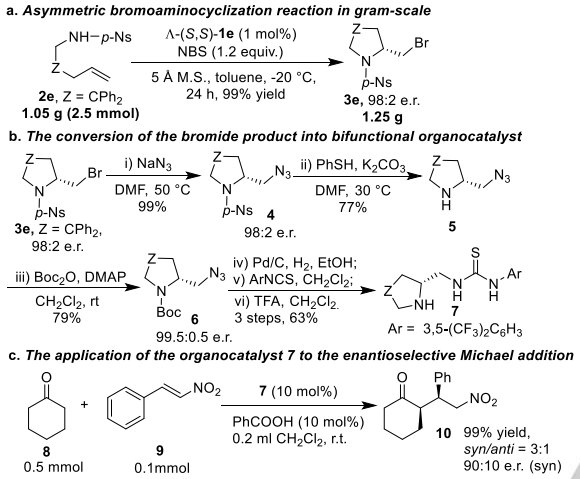
catalyzed by Δ-1e (R^3 = H, Z = CPh_2)



[a] Unless otherwise noted, the reaction was performed with **2** (0.1 mmol), NBS (0.12 mmol), catalyst **1e** (0.005 mmol) and 5 Å M. S. (100 mg) in toluene (2 mL) at -20 ˚C for 10 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. *p*-Ns = *p*-nitrophenyl sulfonyl; *m*-Ns = *m*-nitrophenyl sulfonyl.

The Δ-(*S*,*S*)-**1e** was also identified to be an alternative catalyst for the titled reaction, leading to the generation of desired products with opposite configurations in up to 96:4 e.r. (Table 3, **3a'**, **3e'**, **3f'**, **3l'**, **3n'**, **3x'**). In these cases, the metal-centered chirality in the Brønsted acids of anionic chiral Co^{III} complexes

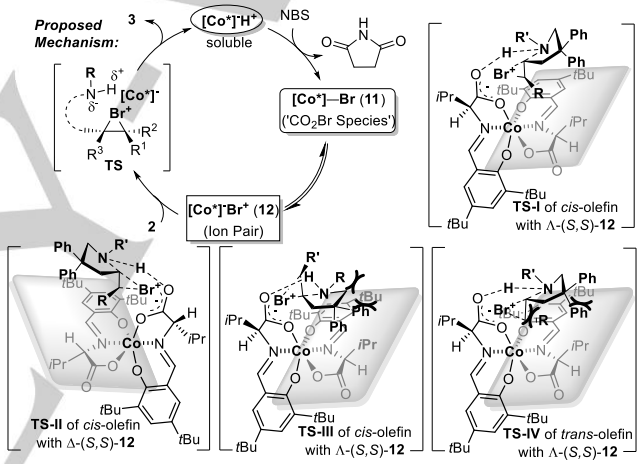
determined the stereochemistry and the chirality of *L*-amino acid moiety has little effect on the asymmetric induction. As such, both enantiomers of 2-substituted pyrrolidines could be accessed via the bromoaminocyclization, respectively catalyzed by the diastereomers of chiral Co^{III} complexes [Δ-(*S*,*S*)-**1e** and Λ-(*S*,*S*)-**1e**] without need to alter the chirality of *L*-valine, which is seemingly "one stone kills two birds". Such a unique feature makes chiral metal-templated Brønsted acids of this type superior to traditional chiral metal complex catalysts which basically rely on the alternation of the configuration of chiral ligands to switch the configuration of products.



Scheme 2. Synthetic versatility of the product.

Importantly, the asymmetric bromocyclization catalyzed by Brønsted acids of anionic chiral Co^{III} complexes could be scaled up. Even the presence of 1 mol% Λ-**1e** was sufficient to render a gram-scale reaction to give **3e** in 99% yield and with 98:2 e.r. (Scheme 2a). The resultant products can be easily converted into some other synthetically useful pyrrolidine derivatives.[14] For instance, a substitution reaction of bromide **3e** with NaN_3 afforded an azide **4** with maintained enantioselectivity of 98:2 e.r., which can be obtained in optically pure form after a single recrystallization (Scheme 2b).[15] The removal of the protecting group from the compound **6** with thiophenol generated an amine **5**, which was treated with Boc_2O to furnish **6**. The hydrogenation of the azide group of **6** over Pd/C, followed by a condensation reaction with 3,5-bis(trifluoromethyl)phenyl isothiocyanate and deprotection, provided 4,4-diphenyl pyrrolidine-thiourea **7** in an overall 63% yield over three steps. As a showcase, the bifunctional molecule **7** was applied to catalyze asymmetric Michael addition[16] of cyclohexanone **8** to nitroolefins **9**, giving the desired adduct **10** in 3:1 d.r. and 90:10 e.r. (Scheme 2c).[17]

Based on the kinetic data, ^{1}H-NMR analysis, NLE and MS experiment,[18] a plausible reaction mechanism was proposed (Scheme 3). The Brønsted acid might first undergo an exchange reaction with NBS to generate a covalent 'CO_2Br species' **11** and succinimide in nonpolar media. The resonant equilibrium of unstable **11** leads to the formation of the tight ion pair **12**. The chiral ion pair **12** is highly soluble in the nonpolar solvent and thereby undergoes the asymmetric bromoaminocyclization with the olefin substrate **2** to generate the product **3** and regenerate the Brønsted acid **1**. In this case, chiral Co^{III} complex-templated Brønsted acid functions like a bifunctional phase-transfer catalyst[1,19] to shuttle the less soluble brominating reagent to reaction solution and also control the stereochemistry. Moreover, based on the configuration of **3o**, transition states to explain the observed stereochemistry were proposed (Scheme 3).[10a-10b] The C-C double bond of alkene **2** attacks the bromiranium ion of the bifunctional chiral ion pair **12** and concertedly, the nucleophilicity of the sulfonamide group would be enhanced via hydrogen bonding interaction with anion complex as shown in transition states **TS-I** [with Λ-(*S*,*S*)-**12**] and **TS-II** [with Δ-(*S*,*S*)-**12**], respectively. The bromoaminocyclization could favorably occur on the *Re*-face of the *cis*-olefin in **TS-I**, as the *Si*-face might be disfavored due to the steric repulsion between the *tert*-butyl substituent of the Schiff base and the phenyl as well as the sulfonamide group (**R'**) of the substrate (**TS-III**). The lower e.r. for *trans*-olefins than *cis*-olefins (Table 3, **3m** vs **3n**) could be attributed to the slight interactions between the **R** group and the phenyl of the substrate and the two *tert*-butyl substituents of the Schiff base (**TS-IV**).



Scheme 3. Proposed mechanism and transition states.

In conclusion, Brønsted acids of anionic chiral Co^{III} complexes have been revealed to be able to catalyze a highly enantioselective bromoaminocyclization of γ-amino-alkenes with NBS. The employment of meridional diastereomers [Δ-(*S*,*S*)- and Λ-(*S*,*S*)-] of chiral Co^{III}-templated Brønsted acids accessed from easily available chiral source allows for the stereoselective formation of two enantiomers of 2-substituted pyrrolidines in high optical purity, respectively. The process could proceed with maintained stereoselectivity at gram scale even in the presence of 1 mol% catalyst. More importantly, it turned out that the chiral metal-complex acted as a phase-transfer catalyst to shuttle the substrates across interface and to control stereoselectivity. These findings not only showed the great potential of the anionic chiral Co^{III} complexes in asymmetric catalysis, but will be able to inspire the future development of anionic chiral Co^{III} complexes as either of Brønsted acid, Lewis acid, or alternative chiral phase-transfer catalysts for the creation of asymmetric transformations.

Experimental Section

A 10-mL oven-dried vial was charged with γ-amino-alkene **2** (0.10 mmol), catalyst **1e** (0.005 mmol), activated 5 Å molecular sieves (100 mg) and

distilled toluene (2 mL) at room temperature. The mixture was cooled to -20 ºC and stirred for 15 min. The NBS (0.12 mmol) was added and the resulting solution was stirred vigorously until the reaction was complete (monitored by TLC). The reaction was then quenched with pre-cooled NEt_3 (-20 ºC, 1.0 mmol) and saturated aqueous $Na_2S_2O_3$ (0.2 mL). The mixture was purified by flash column chromatography (silica gel, petrol ether/EtOAc = 10:1) to give the enantioenriched pyrrolidine derivatives **3**.

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Keywords: chiral Co^{III} complex • bromoaminocyclization • Brønsted acid • chiral anion phase-transfer catalysis

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[8] For the diastereoselective synthesis of the anionic chiral Co^{III} Complexes, see Supplementary Section 2 for details. The absolute configurations of the Λ-**1e** and Δ-**1e** were assigned by comparison of their CD spectra with it of Λ-**1d**. See Supplementary Section 9.2 for details.

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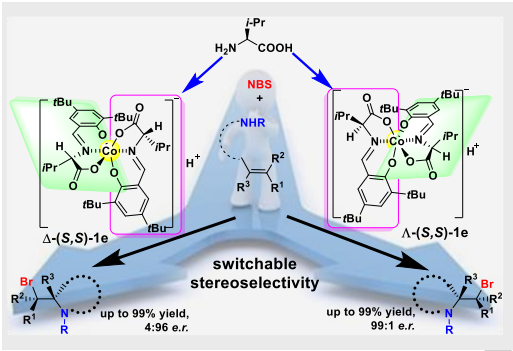
Brønsted acids of anionic chiral Co^{III} complexes have been found to act as bifunctional phase-transfer catalysts to shuttle the substrates across interface and control stereoselectivity. The diastereomeric chiral Co^{III}-templated Brønsted acids with the same chiral ligands enabled a switchably enantioselective bromoamino-cyclization of olefins to afford two opposite enantiomers of 2-substituted pyrrolidines with high stereoselectivities (up to 99:1 e.r.), respectively.



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Switchable Stereoselectivity in Bromoaminocyclization of Olefins Catalyzed by Brønsted Acids of Anionic Chiral Co^{III} Complexes