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Novel, Chiral, and Enantiopure C_2-Symmetric Thioureas Promote Asymmetric Protio-Pictet-Spengler Reactions by Anion-Binding Catalysis

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Dedicated to Professor Franco Cozzi, whose innovative studies on asymmetric organocatalytic reactions have enabled advances of profound fundamental and practical value, on the occasion of his 70th birthday.

Although anion-binding processes are well-known for their crucial role in molecular recognition, they have only recently been utilized for catalysis. Herein, a new class of chiral, enantiopure C_2-symmetrical thioureas that, in combination with 4-methoxybenzoic acid, promotes the enantioselective protio-Pictet-Spengler reaction to provide unprotected tetrahydro-β-carbolines in good yields (40–93%) and moderate-to-high enantioselectivities (34–95% ee) in one step from tryptamine and aldehyde derivatives is described. The formation of a chiral catalyst-anion complex was explored by ^{1}H NMR.

Chiral anion-binding catalysis has attracted the interest of the organic chemistry community as it is a powerful tool in the field of asymmetric organocatalysis.[1] The formation of an asymmetric catalytic system operating through close ion-pair interactions of a chiral catalyst-anion complex and a cationic intermediate enables discrimination of the enantiotopic faces of the charged prochiral intermediate.[2,3]

Specific noncovalent interactions, from hydrogen bonding to π-interactions, play a pivotal role in this context by organizing the contact ion pairs for the activation of ionic substrates.[4] Although it is difficult to define and translate novel catalyst structural features, the ability of small organic molecules containing urea, thiourea, and squaramide moieties to interact with anions and enhance the reactivity of an ion pair has been widely exploited in the last few years.[5] The structural diversity of these anion-binding catalysts is immense; therefore, the design of new chiral hydrogen-bond donor catalysts that are able to promote enantioselective bond formation remains a fascinating challenge. Additionally, most catalysts are C_1 symmetric and constitute a wide spectrum of structural flexibility (Figure 1A).

In the past two decades, anion-recognition chemistry has emerged as a frontier of research in the field of molecular recognition.[6] The greatest effort has focused on the development of neutral receptors capable of complexing anions able to detect the presence of poisonous substances in water or acting as a carrier for ions through a membrane *in vivo*. In this context, the synthesis and binding properties of some new symmetrical hydrogen-bonding donor anion receptors based on a tertiary amine base (tetraazacyclododecane scaffold), phenyl(thio)urea (binding site for the anions by hydrogen bonding), and glycine (linker) have been reported (Figure 1B).[7] These anion receptors (**1**, **2**) are able to adopt a conformation in which all binding sites are positioned to build up a high degree of structural organization in the presence of an anion such as carboxylate.

Given the strong interconnection between *anion-recognition chemistry* and *anion-binding catalysis*[8] and considering the high anion-binding properties of the previously reported nonchiral receptors (**1**, **2**), we aimed to synthesize and evaluate a possible new chiral ligand/catalyst strictly connected to **2** by substituting the glycine linker with an appropriate chiral amino acid. We hypothesized that the binding properties and the conformational preorganization of **2** could be preserved even after the introduction of chirality on the side chains of the tetraazacyclododecane scaffold. This class of catalysts would feature C_2 symmetry, rigidity imparted by the conformational constraints, and relatively simple diversification by changing the abundant natural L-amino-acid building blocks (Figure 1B, **3**).

Herein, we report a new class of chiral C_2-symmetrical anion-binding catalysts that, in combination with benzoic acid, promotes the enantioselective protio-Pictet-Spengler reaction to provide unprotected tetrahydro-β-carbolines[9] in good ee and yield in one step from tryptamine and aldehyde derivatives.

A small focused library of new C_2-symmetrical catalysts was synthesized starting from commercial, protected, and enantiopure amino acids, such as *N*-Cbz-L-valine and *N*-Cbz-L-*tert*-leucine, following the same synthetic approach described by our group for the preparation of achiral anion receptors (**2**).[7a] The choice to introduce isopropyl or *t*-butyl groups on the side arms of the catalyst was motivated by the fact that these two groups could have the appropriate characteristics to both preserve the binding properties for anions and favor the buildup of a well-organized structure due to their favorable intrinsic conformational biases and interstrand sidechain-side-

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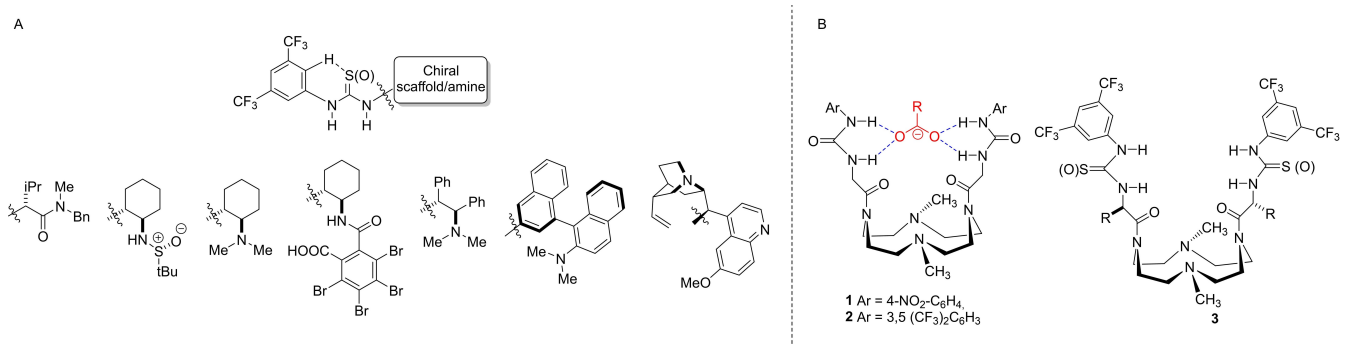
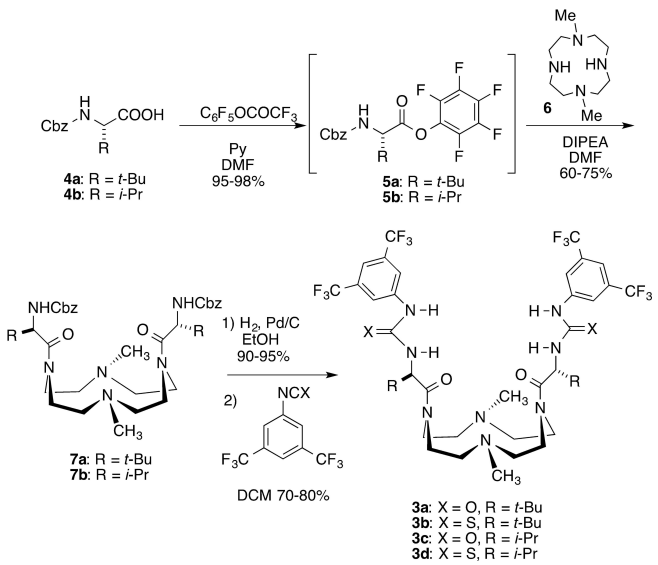


Figure 1. A) Some C_1-symmetrical (thio)urea organocatalysts. B) Structures of tetraazacyclododecane-derived anion receptors (**1**, **2**) and a new C_2-symmetrical (thio)urea organocatalyst (**3**) derived from **2**.

chain interactions,[10] which can be exploited for an asymmetric transformation. Scheme 1 outlines the synthetic approach for the easy and scalable preparation of catalysts **3a**–**d**.

Treatment of the *N*-Cbz amino acid with pentafluorophenyl trifluoroacetate and pyridine in DMF gave the corresponding activated ester **5a**–**b**, which was immediately reacted with 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (**6**) in dry DMF with *i*-Pr_2EtN at room temperature to furnish **7a**–**b**. Removal of the benzyloxycarbonyl protecting group by catalytic hydrogenolysis followed by treatment of the crude diamine (not isolated) with 2 equiv. of the corresponding isocyanate or isothiocynate in dry CH_2Cl_2 allowed the preparation of the desired bis-(thio)ureas (**3a**–**d**). The *N*-3,5-bis(trifluoro-methyl)phenyl group has been popularly used in the design of thiourea-based organocatalysts in the past.[11] The choice of two trifluoromethyl groups on the aromatic moieties of the (thio)ureas, widely employed in noncovalent organocatalysis,[3,4] was based on the ability of this fragment to increase NH polarization of the (thio)urea and prevent aggregation/self-association phenomena. The cumulative results reveal that the trifluoromethyl group not only increases N–H acidity but also contributes to the conformational rigidity of the catalyst by polarizing the adjacent H atoms, which in turn facilitates a hydrogen-bonding interaction with the sulfur or oxygen atom in the (thio)urea.[12]



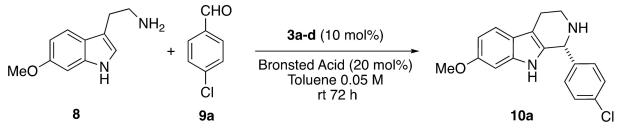
Scheme 1. Synthesis of new C_2-symmetrical anion-binding catalysts.

We selected the one-pot imine formation and asymmetric protio-Pictet – Spengler reaction between 6-methoxytryptamine and *p*-chloro benzaldehyde in the presence of a Brønsted acid, as a cocatalyst, as a model reaction (Table 1).

We were delighted to find that the Pictet-Spengler reaction, carried out at a relatively low concentration (0.05 M) in toluene and in the presence of the catalyst urea, L-*t*-leucine-based **3a**, and benzoic acid, gave the desired tetrahydro-β-carboline **10a**, albeit in a low yield and a modest stereoselectivity (Table 1, entry 1). Reactions performed in different solvents (see the supporting information) generally afforded worse results both in terms of the yield and stereoselectivity, compared to toluene, and revealed that the enantioselectivity is strongly dependent on the type of solvent used. For example, no stereoselectivity was achieved using a coordinating solvent such as THF, suggesting that the catalyst in this type of solvent was not able to bind to the carboxylate and activate the iminium ion, as expected from an anion-binding mechanism.

Using toluene as the solvent and catalyst **3a** (Table 1), several Brønsted acids were tested, with the aim to improve the enantioselectivity and to demonstrate that the stereochemical outcome depends on the nature of the counter anion. As expected, the Pictet-Spengler reaction did not proceed in the absence of a Brønsted acid as a co-catalyst (entry 2), while stronger acids, such as *p*-toluene sulfonic acid (PTSA) and diphenyl phosphate, were detrimental to the catalytic activity, providing the desired β-carboline without stereoselectivity (entries 4–5). The same effect was obtained using weaker acids like mandelic acid and a *para*-substituted phenol (entries 6–7). Based on these preliminary outcomes, it appears that benzoic acid has the optimal pKa (4.2) and structural features to promote the reaction with this catalytic system. Next, we envisioned that the introduction of a substituent, with the appropriate electronic and steric properties, in the aromatic ring of benzoic acid used as a co-catalyst could allow the formation of a highly organized transition state through addi-

Table 1. Selected optimization studies.[a]



8 9a 10a

Entry[a]	Catalyst **3**	Acid	Yield (%)[b]	*ee* (%)[c]
1	**a**	$C_6H_5CO_2H$	40	56
2	**a**	/	/	/
3	**a**	CH_3CO_2H	12	25
4	**a**	PTSA	16	0
5	**a**	Diphenyl phosphate	12	10
6	**a**	D-Mandelic acid	<10	16
7	**a**	4-MeO–C_6H_4OH	<10	40
8	**a**	2-F–$C_6H_4CO_2H$	31	40
9	**a**	4-F–$C_6H_4CO_2H$	67	65
10	**a**	4-Cl–$C_6H_4CO_2H$	25	35
11	**a**	4-MeO–$C_6H_4CO_2H$	50	70
12	**a**	4-NO_2–$C_6H_4CO_2H$	20	14
13	**a**	4-HO–$C_6H_4CO_2H$	45	12
14	**a**	4-$N(CH_3)_2$–$C_6H_4CO_2H$	49	48
15	**a**	4-CN–$C_6H_4CO_2H$	33	28
16	**a**	4-CF_3O–$C_6H_4CO_2H$	53	41
19	**a**	4-AcO–$C_6H_4CO_2H$	20	56
20	**a**	4-HO_2C–C6H4CO_2H	<10	7
21	**b**	4-MeO–$C_6H_4CO_2H$	58	50
22	**c**	4-MeO–$C_6H_4CO_2H$	51	50
23	**d**	4-MeO–$C_6H_4CO_2H$	93	92

[a] Reaction conditions: **8** (0.1 mmol), **9a** (0.11 mmol, 1.1 equiv), **3a–d** (0.01 mmol, 0.1 equiv), Brønsted acid (0.02 mmol, 0.2 equiv). [b] isolated yield. [c] determined by HPLC analysis of the *N*-Boc derivative on an AD–H column.

tional nonbonding interactions, resulting in a higher yield and stereoselectivity. Therefore, different substituted benzoic acids were tested and revealed that the presence of a substituent in the *para* position of benzoic acid provided higher yields and stereoselectivities (entries 8–20).

Among the *para*-substituted benzoic acids tested, the methoxy derivative was the best acidic cocatalyst for this transformation (entry 11), providing **10a** in 50% yield and 70% ee. Furthermore, the Brønsted acid screening demonstrated that the outcome of this reaction is strongly dependent on the nature of the counter anion; this fact supports the hypothesis that an anion-binding mechanism is involved in this transformation.

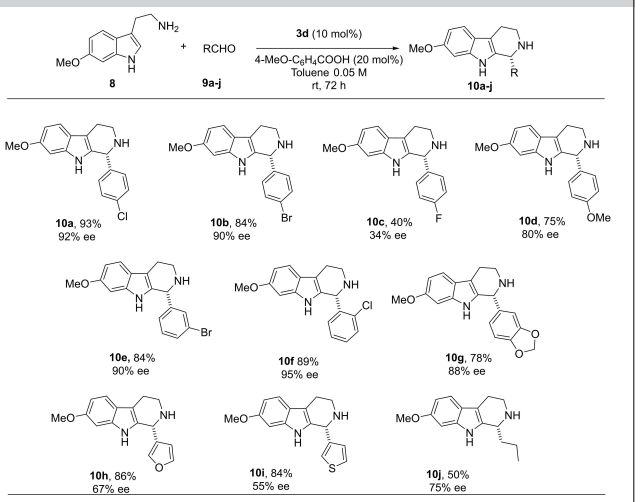
Further optimization studies, in terms of temperature, concentration, and stoichiometry of the reaction, did not lead to substantial improvements (see the supporting information). As expected, we found that the reaction concentration is a very important parameter. For example, using [**8**] = 0.1 M instead of 0.05 M resulted in a very impressive decrease in the yield and enantioselectivity (20% and 55%, respectively). This phenomenon is not uncommon for thiourea-based catalytic systems[13] and was rationalized by the self-aggregation of the catalyst, which may determine the formation of monomer and dimer (or higher) aggregates characterized by different catalytic and/or stereoselective profiles. Under the best conditions, we tested all of the newly synthesized C_2-symmetrical anion-binding catalysts (**3b–d**) (entries 21–23). Pleasingly, all the (thio)ureas tested were able to catalyze this process; in particular, thiourea **3d**, derived from L-valine, provided the tetrahydro-β-carboline derivative in a good yield (93%) and excellent enantioselectivity (92% ee) (entry 23). With optimized conditions in hand, various commercially available aldehydes were explored to evaluate the scope of the Pictet-Spengler reaction (Table 2). Generally, the reaction of different aldehydes (**9a–j**) with 6-methoxytryptamine (**8**) provided the desired product (**10a–j**) in good yield and good-to-moderate enantioselectivity.

Different substituents on the aromatic moiety of the aldehyde were well tolerated (**10a–g**), and the Pictet-Spengler adducts were obtained in good-to-high yields with very high control over the absolute stereochemistry (ee up to 95%), except with the 4-fluorobenzaldehyde (**10c**). In particular, replacing chlorine with bromine (**10b,e**) had no effect on the yield or the stereochemical outcome of the reaction, while introducing an electron-donating group on the aromatic ring caused a slight decrease in the enantioselectivity. However, the tetrahydro-β-carboline compounds (**10d,g**) were obtained in 75% and 78% yield, respectively. Using heteroaromatic aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde, the respective tetrahydro-β-carboline compounds (**10h,l**) were obtained in high yields but lower enantioselectivities, likely due to the coordination effect of the oxygen and sulfur of the aldehydes.

Of note, a moderate yield (50%) and enantioselectivity (75%) were detected when the reaction was conducted with an aliphatic aldehyde such as butyraldehyde (**10j**). Since enolizable aldehydes are very reactive as both nucleophiles and electrophiles, controlling the competing pathways to avoid self-aldol reactions and other potential side reactions associated with tautomerization of aldehydes and/or imines is still an intrinsically unsolved challenge for the chemoselectivity.

Moreover, less nucleophilic tryptamines, such as 5-methoxytryptamine and tryptophan methyl ester, were unreactive

Table 2. Scope of the Pictet-Spengler reaction.[a]



[a] Reaction conditions: **8** (0.2 mmol, 1 equiv), **9a–j** (0.11 mmol, 1.1 equiv), **3d** (0.02 mmol, 0.1 equiv), 4-MeO–C_6H_4COOH (0.04 mmol, 0.2 equiv). Isolated yield. Enantiomeric excess was determined by HPLC analysis of the *N*-Boc derivative on an AD–H column.

under these conditions. The basis for this intriguing difference in reactivity is not well understood. For a substrate such as 5-methoxytryptamine, the use of a more acidic additive was necessary, but the reaction proceeded in low ee and in modest yield.

The absolute configuration of the major enantiomer of **10a** (96:4 er) was determined to be *R* by comparison of polarimetry data reported for the same enantiopure compound.[9i] Assuming the same behavior of the catalytic system, the configuration of the other tetrahydro-β-carboline products **10b–j** was also assigned as *R*.

To obtain a better understanding of the activity and behavior of the catalysts, a ^{1}H NMR titration of **3a** in DMSO-d_6 at 298 K with sodium benzoate was carried out. As shown in Figure 2, the proton signals of the N–H bonds of the urea were clearly shifted downfield after the addition of at least 1 equiv. of the benzoate. Slight changes in the chemical shifts of other aromatic H atoms were also observed. In particular, the opposite shift was exhibited by Ho with respect to the Hp protons in the presence of the interacting anions. In contrast, by adding an excess of OH^-, i.e., deprotonating the urea units, both Ho and Hp exhibited upfield shifts, respectively (data not shown). The shift of both sets of hydrogens (ureido and aromatic) is in agreement with the statement that the host-guest interaction occurs at the ureido group. Interestingly, **3a** exhibited a complex number of signals in DMSO-d_6 and other deuterated solvents (i.e., the signals were very broad), suggesting the existence of two or more slowly interchanging conformers in solution on the NMR time scale. However, the resonances of the side arms collapsed in only one and sharp pattern of signals at 353 K, resulting from C_{2v} symmetry mediated on the NMR time scale. The ^{1}H NMR experiments carried out in the presence of benzoate showed similar behavior, although the spectra were sharper and shifted. These data suggest a cooperative H-bond to the carboxylate anion, which is accommodated inside the rigidified structure cavity of the catalyst.

In conclusion, a novel, chiral, and enantiopure hydrogen-bond donor C_2-symmetrical thioura-based compound has been developed as an anion-binding catalyst for the asymmetric protio-Pictet-Spengler reaction. These catalysts transfer the chirality effectively to the unprotected tetrahydro-β-carbolines in one step from 6-methoxy tryptamine and aldehyde derivatives to form a close chiral anion-pair complex with an iminium ionic substrate formed *in situ* between tryptamine and the aldehyde. Cooperative binding of the catalyst's hydrogen bond in its cavity to the benzoate anion and the reinforced catalyst structure upon this coordination were confirmed by ^{1}H-NMR. The unique features of the presented organocatalysts might also unveil further interesting applications in asymmetric anion-binding catalysis.

Conflict of Interest

The authors declare no conflict of interest.

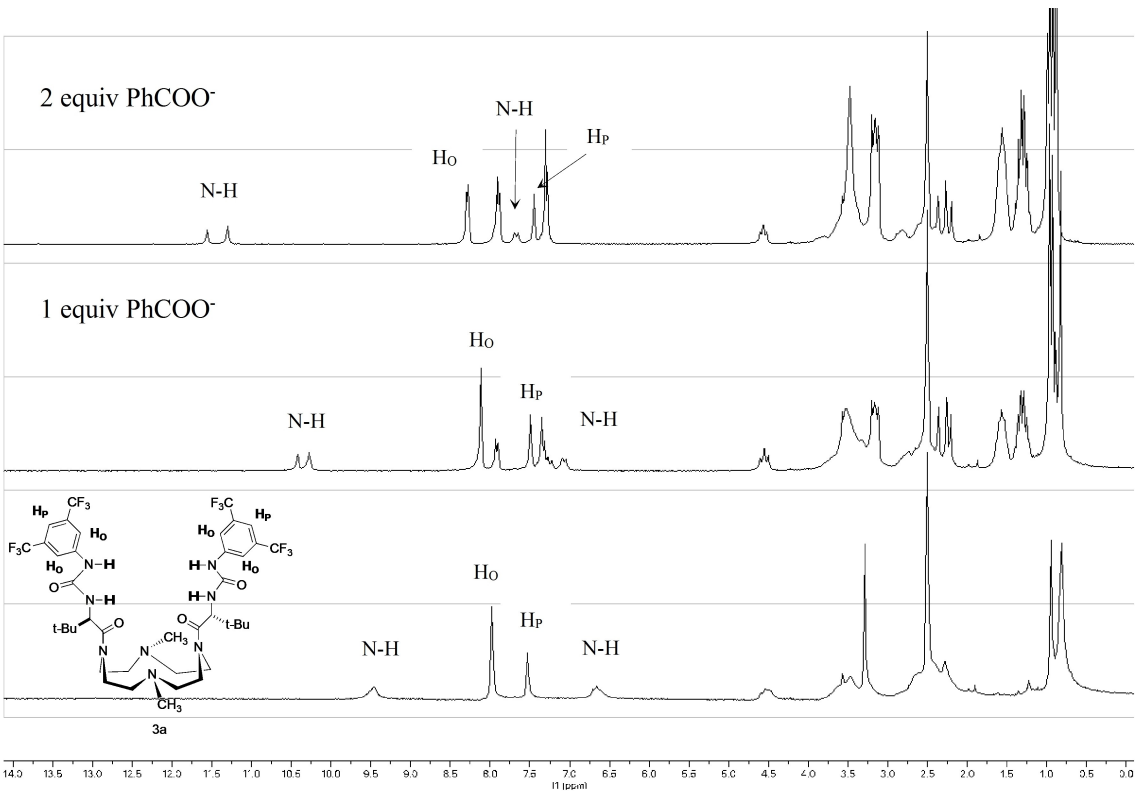


Figure 2. ^{1}H NMR spectra of **3a** in DMSO-d_6 at 298 K by adding 1 or 2 equiv. of sodium benzoate with respect to **3a**.

Keywords: Anion-binding · Organocatalysis · Ion-pairing · Pictet-Spengler reaction · Synthetic methods

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