Asymmetric Organocatalysis

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Exploiting the Multidentate Nature of Chiral Disulfonimides in a Multicomponent Reaction for the Asymmetric Synthesis of Pyrrolo-[1,2-*a*]indoles: A Remarkable Case of Enantioinversion

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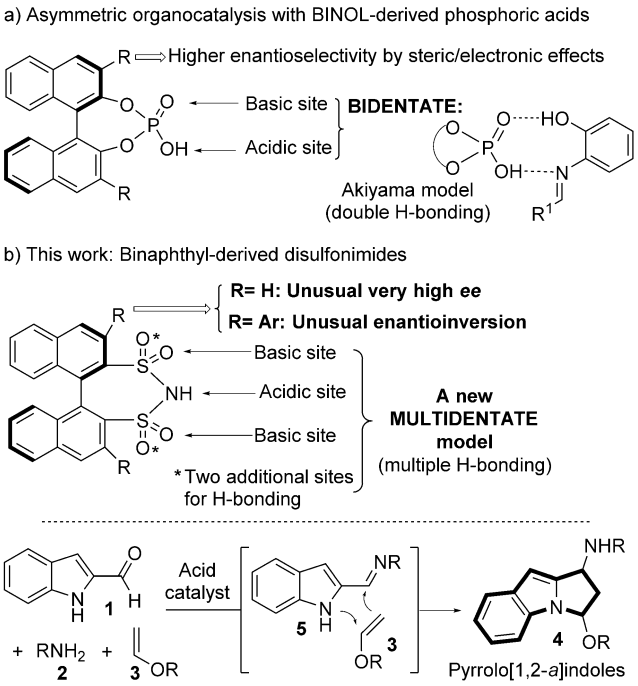
Abstract: *A new multicomponent coupling reaction for the enantioselective synthesis of pyrrolo[1,2-a]indoles under the catalysis of a chiral disulfonimide is described. The high specificity of the reaction is a consequence of the multidentate character of the Brønsted acid catalyst. Insights from DFT calculations helped explain the unexpected high enantioselectivity observed with the simplest 3,3′-unsubstituted binaphthyl catalyst as a result of transition-state stabilization by a network of cooperative noncovalent interactions. The remarkable enantioinversion resulting from the simple introduction of substituents at 3- and 3′-positions, the first reported example of this phenomenon in the context of binaphthalene-derived Brønsted acid catalysis, was instead attributed to destabilizing steric interactions.*

BINOL-derived phosphoric acids were introduced to the field of asymmetric organocatalysis independently by the research groups of Terada and Akiyama in 2004.[1] Since then, the use of catalysts of this type in organic synthesis has grown exponentially. The success of these BINOL-derived phosphoric acids is mainly due to their bifunctional character. Thus, the presence of an acidic site and a basic site allows double hydrogen-bond interactions with reagents such as imines (Scheme 1 a). Although the enantioselectivity observed with the simple BINOL phosphoric acid (R = H) is usually very low, an appropriate choice of substituents at the 3- and 3′-positions allows for extraordinary improvements. In 2009 and also independently, the research groups of List and Giernoth reported a new type of chiral organocatalyst based on a binaphthyl skeleton and containing a disulfonimide functionality.[2] These compounds were initially used as precatalysts in silicon-based Lewis acid catalysis,[3] and only very recently have they found utility as chiral Brønsted acid catalysts.[4] In this context, some remarkable features of these disulfonimides are presented herein.



Scheme 1. Chiral acid catalysts. Proposed multicomponent reaction.

We considered the possibility of synthesizing pyrrolo[1,2-*a*]indoles **4**,[5] which are targets of interest owing to their bioactivity, in a single synthetic operation from indole-2-carboxaldehydes **1**, amines **2**, and enol ethers **3** through an unprecedented acid-catalyzed formal [3+2] cyclization reaction between the imine **5** formed in situ and the enol ether **3** (Scheme 1 b).[6] In our initial experiments, 1*H*-indole-2-carboxaldehyde (**1a**) and 2,3-dihydrofuran (**3a**) were used as model substrates, and a wide range of anilines **2**, achiral and chiral acid catalysts, and reaction conditions were screened systematically (Scheme 2). Remarkably, a unique catalyst/aniline combination provided positive results. This combination included 3,5-bis(trifluoromethyl)aniline (**2a**) and the binaphthyl-based chiral disulfonimide (*R*)-**A** as the acid catalyst. The product of this highly specific reaction was the pyrrolo[1,2-*a*]indole derivative **4a**, which was formed with high enantioselectivity (e.r. 95:5) and isolated as a single diastereoisomer in high yield (90 %).[7]

The scope of this new enantioselective protocol for the synthesis of pyrrolo[1,2-*a*]indole derivatives is illustrated in

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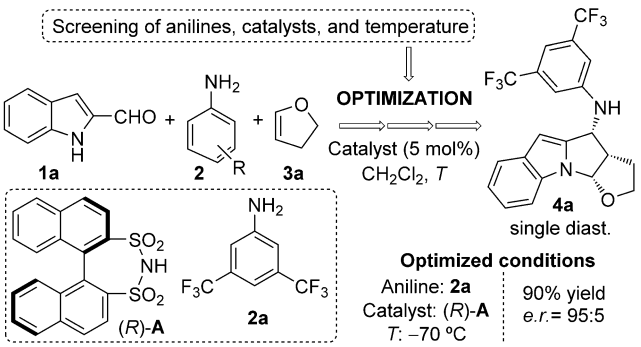
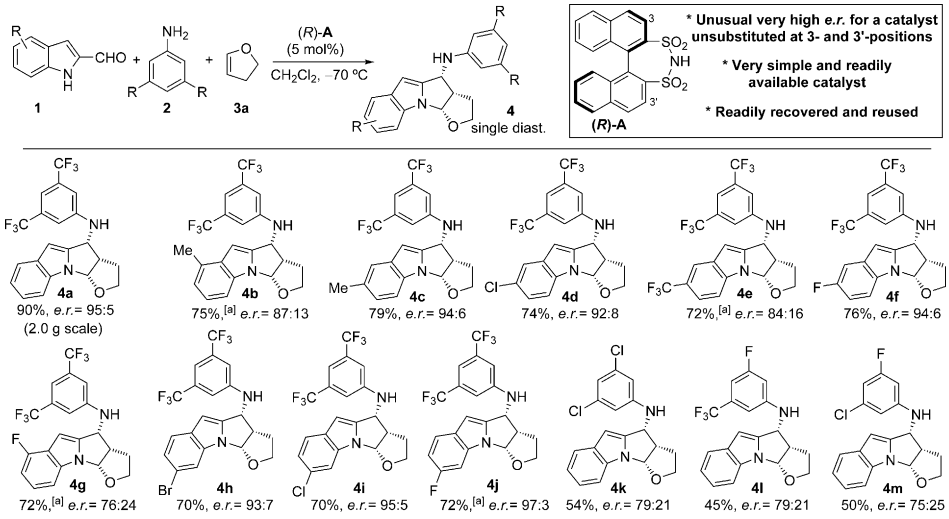


Scheme 2. Initial results and optimization.



Scheme 3. Scope of the reaction for the synthesis of pyrrolo[1,2-*a*]indoles **4**. [a] Fluorobenzene/dichloromethane (1:1) was used as the solvent.

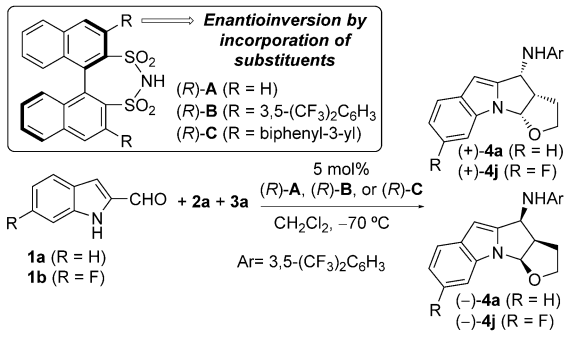
Scheme 3. The reactions proceeded cleanly in good yield, and high diastereo- and enantioselectivity were observed with differently substituted indole-2-carboxaldehyde derivatives **1**. Although anilines substituted at the 3- and 5-positions with halogen atoms and/or trifluoromethyl groups were converted into the desired pyrrolo[1,2-*a*]indole derivatives **4k**–**m**, the yields were lower than those observed with 3,5-bis(trifluoromethyl)aniline (**2a**). Other typical enol ethers, acyclic (butyl vinyl ether) or cyclic (3,4-dihydro-2*H*-pyran), were not appropriate substrates for our reaction.

Finally, this reaction could be performed on a gram scale with no erosion in yield, diastereoselectivity, or enantioselectivity (2.0 g of **4a**). Interestingly, the chiral catalyst (*R*)-**A** could be easily recovered and then reused without appreciable loss of activity. The high enantioselectivity observed with the 3,3′-unsubstituted disulfonimide (*R*)-**A** is notable, because whereas this simple disulfonimide (*R*)-**A** is readily available on a gram scale, the synthesis of derivatives with substituents at the 3,3′-positions is a tedious task. When we performed our reaction with the 3,3′-disubstituted disulfonimide (*R*)-**B** or (*R*)-**C**,[8] instead of the expected increase in enantioselectivity, we observed almost a complete switch of enantioselectivity (Table 1). This unusual phenomenon, access to each antipode of a product from a chiral source of the same absolute configuration, is known as enantioinversion, and, as far as we know, this example is the first in the context of binaphthyl-based catalysts.[9]

The pyrrolo[1,2-*a*]indole derivatives **4** are synthetically useful compounds that can be converted into other interesting molecules (Scheme 4). Thus, the treatment of **4a** with *N*-bromosuccinimide (NBS) led to selective bromination. Also, compound **4a** was transformed quantitatively into the diamine derivative **7**, which possesses the skeleton of the alkaloid gramine, by treatment with the Eschenmoser salt. Finally, a very simple protocol was developed to remove the aniline moiety in compound **4a**. Thus, oxidation with DDQ provided the imine **8**, which was converted into the ketone derivative **9** by hydrolysis.

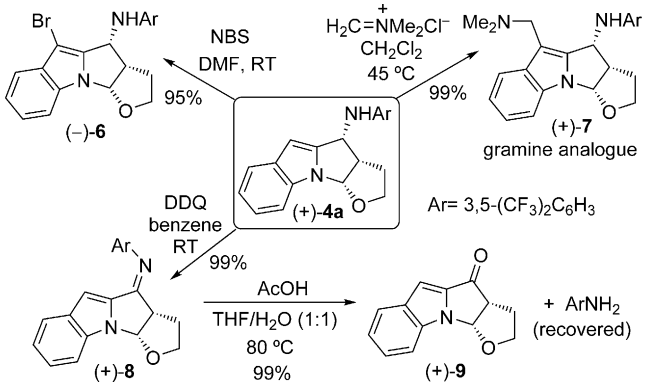
The formation of the pyrrolo[1,2-*a*]indole derivatives **4** can be rationalized by the mechanism depicted in Scheme 5. First, condensation of 1*H*-indole-2-carboxaldehyde (**1a**) and 3,5-bis(trifluoromethyl)aniline (**2a**) under the catalysis of acid (*R*)-**A** leads to the formation of the corresponding imine **5a**. The next step, the coordination of the chiral acid (*R*)-**A** to the imine **5a** to give a binary complex **5a**·(*R*)-**A**, was examined computationally at the wB97XD-PCM(CH_2Cl_2)/6-31G*//wB97XD/6-31G* level of theory. This study revealed *s-cis*-

Table 1: Enantioinversion by simple structural modification of the catalyst.

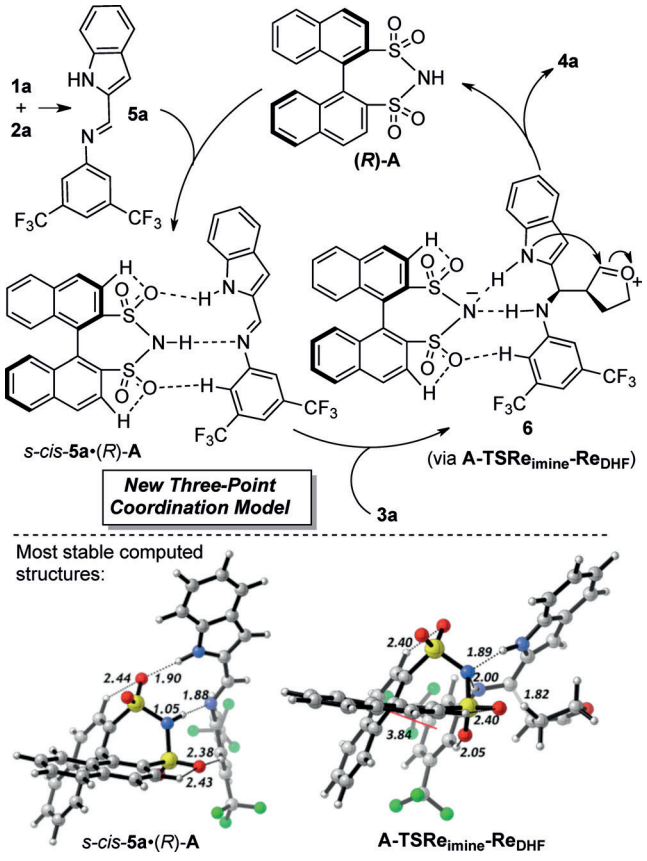


Entry	1	Catalyst	Products	Yield [%][a]	(+)-4/(−)-4[b]
1	**1a**	(*R*)-**A**	(+)-**4a**/(−)-**4a**	90	95:5
2	**1a**	(*R*)-**B**	(+)-**4a**/(−)-**4a**	86	22:78
3	**1a**	(*R*)-**C**	(+)-**4a**/(−)-**4a**	88	8:92
4	**1b**	(*R*)-**A**	(+)-**4j**/(−)-**4j**	75	97:3
5	**1b**	(*R*)-**C**	(+)-**4j**/(−)-**4j**	76	8:92

[a] Yield of the chromatographically purified material. [b] The (+)-**4**/(−)-**4** ratio was determined by high-performance liquid chromatography (HPLC) on a chiral stationary phase.



Scheme 4. Some simple and useful synthetic transformations of **4a**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF = *N*,*N*-dimethylformamide.



Scheme 5. Proposed mechanism for the formation of compounds **4**.

5a•(*R*)-**A** to be the most stable complex (Scheme 5; see also the Supporting Information). In this structure, an anticipated hydrogen bond between the nitrogen atom of the imine and the N–H group of the chiral disulfonimide was observed (1.88 Å). The N–H group of the indole is also engaged in hydrogen bonding with an oxygen atom of one of the SO_2 groups (ca. 1.90 Å).[10] Some remarkable CH–O hydrogen-bonding interactions were also recognized,[11] namely, between a hydrogen atom *ortho* to the N atom of the 3,5-bis(trifluoromethyl)phenyl moiety and a basic site of the disulfonimide (*R*)-**A** (SO_2–$HArCF_3$, ca. 2.38 Å),[12] and between the hydrogen atoms at the 3- and 3′-positions of the binaphthyl moiety and an oxygen atom of the neighboring SO_2 group (ca. 2.44 Å).

The mode of coordination of catalyst (*R*)-**A** to **5a** shown in *s-cis*-**5a**•(*R*)-**A** fully accounts for the extraordinary specificity of our reaction. Thus, the catalyst (*R*)-**A** behaves as a tridentate ligand to activate imine **5a** through a triple hydrogen-bonding interaction. Although disulfonimides have previously been proposed as bifunctional catalysts,[4a] as far as we know, their multidentate nature has not been considered before.[13] Strong experimental support for this three-point coordination model between imine **5a** and catalyst (*R*)-**A** was found in variations in the chemical shift of the NH group of the indole and the hydrogen atoms at the *ortho* positions of the 3,5-bis(trifluoromethyl)phenyl moiety in the ^{1}H NMR spectra of imine **5a** upon the addition of increasing amounts of (*R*)-**A** (see the Supporting Information).

The stereodetermining step of the reaction is the Mannich-type addition of the enol ether **3a** to the activated imine to give **6** (Scheme 5). Consequently, all possible approaches at the *Re* and *Si* faces of the imine in complex *s-cis*-**5a**•(*R*)-**A** and 2,3-dihydrofuran (**3a**; also referred to as DHF) to give the four possible stereoisomers of the initial adduct were computed (see the Supporting Information). Transition state **A-TSRe$_{imine}$-Re$_{DHF}$**, showing the precise stereochemistry of products **4**, was computed to be energetically favored (Scheme 5). Upon the interaction of 2,3-dihydrofuran (**3a**) with the complex *s-cis*-**5a**•(*R*)-**A**, several structural changes were noticed in the transition state **A-TSRe$_{imine}$-Re$_{DHF}$** with respect to the initial complex *s-cis*-**5a**•(*R*)-**A**. Most notably, the indole ring undergoes a slight displacement that weakens the initial stabilizing interaction between the indole N–H group and the oxygen atom of one of the SO_2 groups. In turn, the N–H group of the indole seeks stabilization by interacting with the nitrogen atom of the sulfonimide. Also, a strong stabilizing interaction between an *ortho* hydrogen atom of the bis(trifluoromethyl)phenyl group and an oxygen atom of one of the SO_2 groups (SO_2–$HArCF_3$) is observed in **A-TSRe$_{imine}$-Re$_{DHF}$** (2.05 Å). Interestingly, this transition structure shows a stabilizing π–π interaction between the 3,5-bis(trifluoromethyl)phenyl group and one of the naphthyl groups (parallel-displaced or PD arrangement).[14] To sum up, transition state **A-TSRe$_{imine}$-Re$_{DHF}$** is favored over the alternative transition states because it exhibits the strongest stabilizing noncovalent interactions (it has the strongest hydrogen bonding and is the only transition state with a stabilizing π–π interaction).

The last step of the process implies the interception of the oxonium species in **6** by the nitrogen atom of the indole (Scheme 5). This process is assisted by the basic sites of the catalyst (*R*)-**A**, which transform the acidic indole N–H group into a suitable nucleophile.

Finally, the computational study was extended to the analysis of the unusual enantioinversion phenomenon observed with 3,3′-substituted disulfonimide catalysts (*R*)-**B** and (*R*)-**C** (Figure 1; see also the Supporting Information).[9e] In contrast to the preferred *Re–Re* approach with the simpler unsubstituted catalyst (*R*)-**A**, with the substituted catalysts (*R*)-**B** and (*R*)-**C** the approaches involving the *Si* faces of the

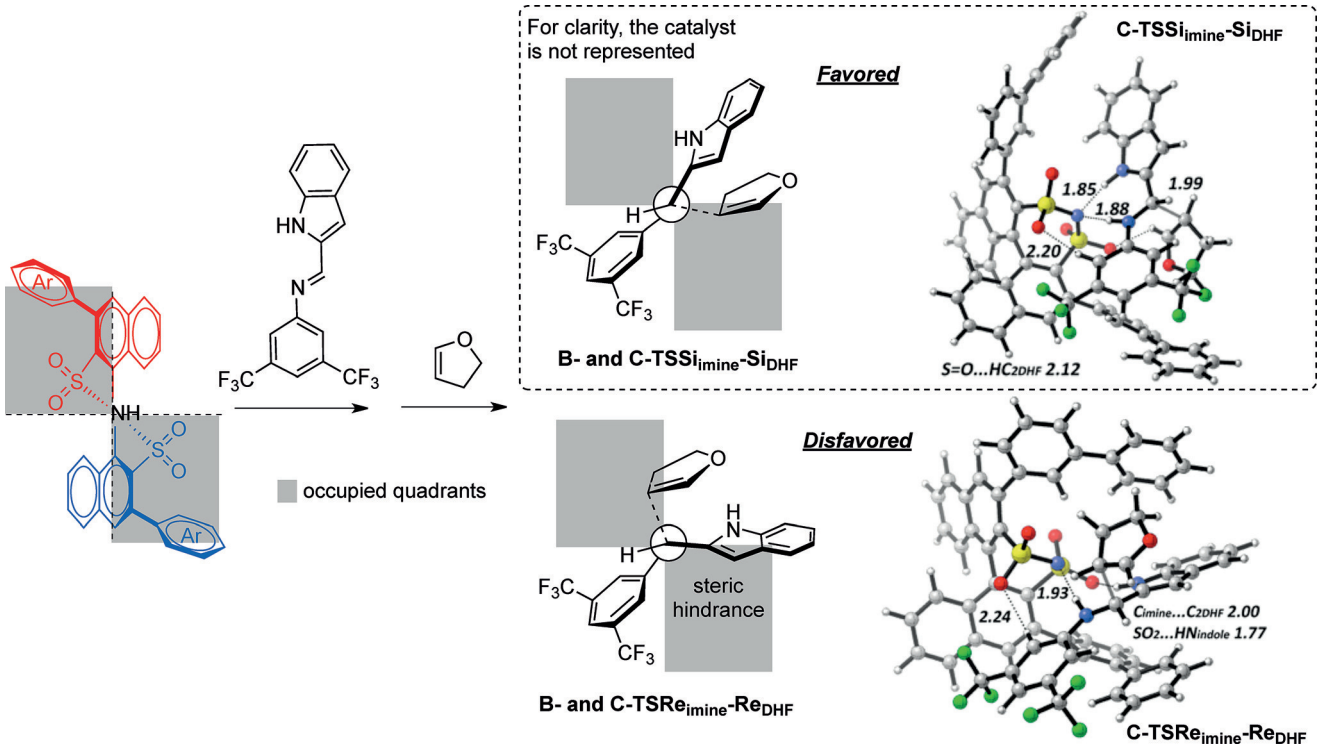


Figure 1. Four-quadrant model to explain the enantioselectivity observed with catalysts (*R*)-**B** and (*R*)-**C**.

imine and enol ether were computed to be energetically favored. The preferential formation of transition states involving the *Si* faces of the imine and enol ether (**B-** and **C-TSSi$_{imine}$-Si$_{DHF}$**) could be mainly attributed to steric effects, in sharp contrast to our observations for the unsubstituted catalyst (*R*)-**A**, in which case the preference for the *Re–Re* approach was mainly attributed to noncovalent interactions. In the case of substituted catalysts (*R*)-**B** and (*R*)-**C**, the approach of the enol ether to the activated imine forces the displacement of the indole moiety, which has several steric implications, as shown in the "four-quadrant model" depicted in Figure 1. For catalysts **B** and **C** with the *R* configuration, the upper-left and lower-right quadrants are occupied by the aryl substituents at the 3-and 3′-positions. Coordination of the imine occurs by placement of the indole and the 3,5-bis(trifluoromethyl)phenyl groups in the alternative empty quadrants. When the enol ether approaches through a *Re–Re* trajectory to reach transition state **B-TSRe$_{imine}$-Re$_{DHF}$** or **C-TSRe$_{imine}$-Re$_{DHF}$**, the indole group is displaced to the lower-right occupied quadrant (Figure 1, bottom; only **C-TSRe$_{imine}$-Re$_{DHF}$** is shown). However, when the reaction occurs via transition state **B-TSSi$_{imine}$-Si$_{DHF}$** or **C-TSSi$_{imine}$-Si$_{DHF}$**, the indole is displaced to the unoccupied upper-right quadrant in a less disfavored fashion (Figure 1, top; only **C-TSSi$_{imine}$-Si$_{DHF}$** is shown). This steric destabilization model depicted for catalysts (*R*)-**B** and (*R*)-**C** also reinforces our alternative transition-structure-stabilization model presented for the unsubstituted catalyst (*R*)-**A**, because for this catalyst the four quadrants in Figure 1 would be sterically equivalent. Under these circumstances, the steric effects do not play an important role, and so the stabilization effects in the transition states better justify the enantioselectivity observed. The extraordinary consequence of these two different models is that whereas the stabilizing noncovalent interactions with the unsubstituted catalyst (*R*)-**A** favor one enantiomer, the destabilizing steric effects related to catalysts (*R*)-**B** and (*R*)-**C** favor the formation of the opposite enantiomer. This analysis explains the experimentally observed enantioinversion phenomenon.

In summary, we have reported some exceptional features of chiral disulfonimides in the context of Brønsted acid catalysis. The multidentate character of this catalyst, which combines a hydrogen-bond donor and several basic functionalities within a very simple chiral small molecule, is the basis for the development of a new diastereo- and enantioselective multicomponent synthesis of pyrrolo[1,2-*a*]indole derivatives. Interestingly, very high enantioselectivity was observed with the simplest catalyst without substituents at the 3- and 3′-positions. We have also found that the incorporation of substituents at these positions leads to an unexpected switch of enantioselectivity: the first reported case of the enantioinversion phenomenon in the context of Brønsted acid organocatalysis. Finally, supported by computational studies, we propose some new models to explain our experimental observations: 1) an unprecedented three-point coordination mode of imine activation by the Brønsted acid organocatalyst; 2) a model based on stabilization effects in the transition states to account for the enantioselectivity observed with the parent 3,3′-unsubstituted catalyst; and 3) an alternative model based on steric destabilization to justify the enantioselectivity observed with the corresponding 3,3′-substituted catalysts and consequently the unusual enantioinversion phenomenon.

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