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Enantioselective Modular Synthesis of α-Aryl-α-Heteroaryl Aminonitriles with Parts per Million Organocatalyst Loading: Mechanistic Investigation for Stereochemical Origins

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ARTICLE

Enantioselective Modular Synthesis of α-Aryl-α-Heteroaryl Aminonitriles with Parts per Million Organocatalyst Loading: Mechanistic Investigation for Stereochemical Origins

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Heteroaromatic installation and peripheral modifications are the most common reactions in the pharmaceutical industry. However, the synthesis of biologically important aminonitrile-functionalized heteroaromatics remains unexplored. Although nucleophilic aminonitrile introduction and Strecker reaction under enantioselective catalytic conditions enable facile access to chiral aminonitriles, these approaches largely disfavor substrates with highly steric substituents on the imine carbon atom, thus affording limited products. Herein, we report an efficient and versatile method that combines the traditional methods to generate α-aryl-α-heteroaryl-aminonitriles. This methodology exhibits a broad scope and can form bonds even when using low-reactive Friedel-Crafts nucleophiles through a mild and practical protocol. It should be highlighted that the catalyst loading could be reduced to parts per billion, giving rise to phenomenal turn-over-number (TON) and turn-over-frequency (TOF) values. Interestingly, different stereochemistries between the pyrrole and indole adducts were obtained with the same (*R*)-derived chiral phosphoric acid catalysis. Computational studies have indicated that this unpredicted stereoreversal is due to the coordination system between iminonitriles and catalysts, helping us understand the origin of the stereochemical outcome of the traditional Friedel-Crafts reaction.

Introduction

An important aspect in the development of synthetic methodologies is the ability to access pharmacophores that occupy diverse regions of chemical space.[1] Heterocycles are one of the most important molecular motifs for chemical space due to their unique structural characteristics and properties.[2] Heteroaromatics are of particular interest because they are the primary constituent of alkaloids,[3] pharmaceuticals,[4] and are also versatile building blocks in organic synthesis.[5] Heteroatom installation into carbon ring systems often enhances biological activities and material functions (Figure 1a).[6] Thus, the replacement of the phenyl ring with a heteroarene has significant advantages and allows a wealth of enhanced bioactivities. Therefore, the discovery of new synthetic methods for highly functionalized heteroaromatics promotes the creation of new drug candidates. Our group has consistently been interested in developing and applying chiral nitriles.[7] Nitriles are increasingly found in pharmaceuticals and are recognized as active clinical candidates.[8] In addition, nitriles are one of the most versatile and essential synthetic handles due to their ability to participate in diverse transformations to functional groups such as ketones, acids, amides, amines, and heterocyclic compounds, rendering them valuable building blocks for the synthesis of biologically relevant molecules.[9] Furthermore, we became interested in the development of synthetic methods for the construction of heteroaryl-containing unknown chiral nitriles (Figure 1b).[10] Among the various classes of nitrile-containing organic frameworks, aminonitriles are most commonly found in pharmaceuticals and are key intermediates in the synthesis of natural products.[11] Aminonitriles are typically installed either by nucleophilic addition of the corresponding N-protected α-aminonitriles or by Strecker reaction from the corresponding aldehydes or ketones, amines, and cyanides (Figure 1c). However, the enantioselective variation of nucleophilic aminonitrile introduction has been reported independently by Nakamura,[12] Carretero,[13] Kobayashi,[14] Shibasaki,[15] and Fukazawa,[16] these early strategies suffered from expensive transition metal catalysts and limited applicability to substrates with low reactivity. These relatively poor advances are principally attributed to the difficulty in the control of stereoselectivity arising from the linear nature of the nitrile group and the relatively low acidity (pKa ~18 in DMSO).[17] Recently, Lee and coworkers developed an elegant strategy through the synergy of dual catalysis between a cyclopropenimine superbase and hydrogen-bonding donor.[18] However, since the N-protecting groups require deprotection after the key reaction for clinical applications, this reaction is still atom-economically inefficient. Furthermore, there are no reports on the enantioselective nucleophilic introduction of α-aryl substituted aminonitriles (Figure 1c, top left).

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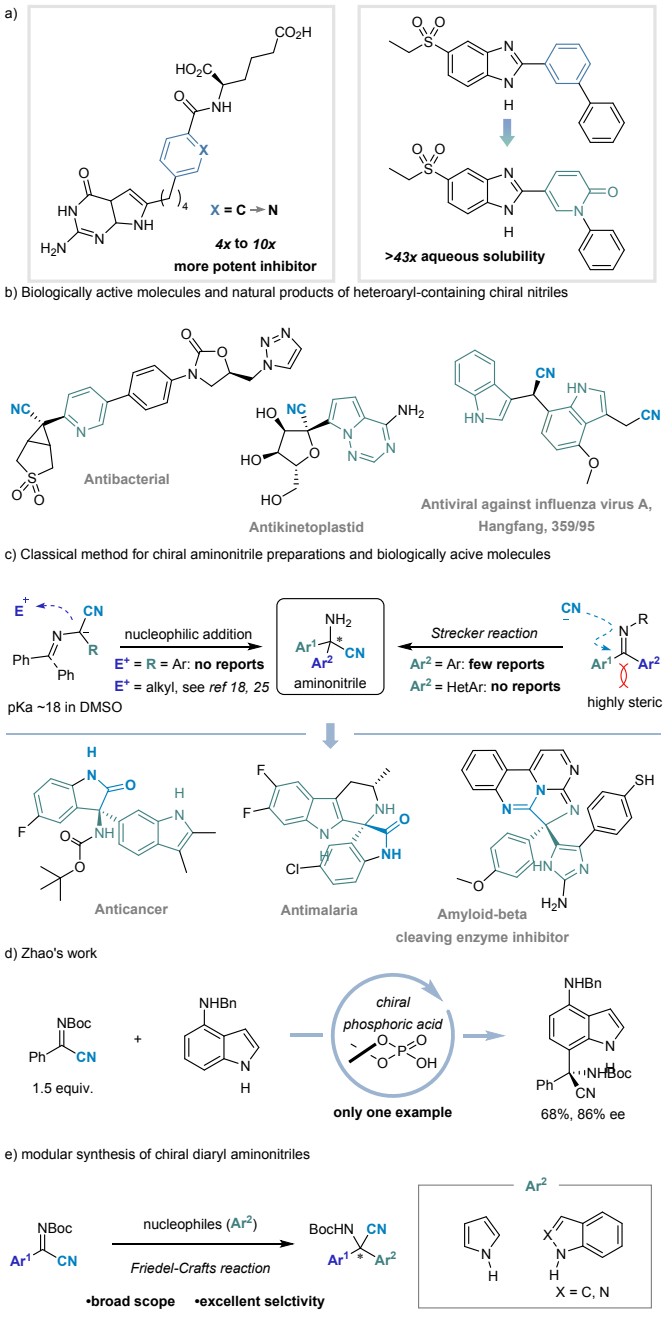


Fig. 1. Important molecules, past studies, and this work

In contrast, the asymmetric Strecker reaction is ideally atom-efficient and the most well known and powerful manifold for chiral aminonitrile preparation.[19] While remarkable progress has been achieved in this reaction in the last few decades by employing organocatalysts, most reported methods are simple variations of it. For instance, only a few reports have described the enantioselective Strecker reaction to produce imines with two aryl rings on the imine carbon atom. The first enantioselective reaction was reported by Shibasaki and coworkers, whose approach centered on using cyclized ketimines with plenty of reaction space, employing aluminum catalysis.[20] Although some analogous reactions have been reported,[21] their application has been limited in that both aryl rings have simple substituents such as halogen atoms or methyl groups on limited sites of the phenyl ring. This is probably due to the steric demands associated with forging fully substituted centers and poor stereodifferentiation between two similar aryl substituents. In addition, despite the remarkable significance of heteroaromatic rings, the stereoselective preparation of α-aryl-α-heteroaryl-aminonitriles via an asymmetric Strecker reaction has not been reported (Figure 1c, top right). To address these limitations, the discovery of direct, atom-economical, versatile, and fundamental alternative synthetic methods for constructing these structures would be beneficial. We recently reported the synthesis of α-thio- and seleno-substituted aminonitriles, which are difficult to access using Strecker reaction.[22] Considering these approaches, we sought to develop a complementary route that leveraged the advantages of nucleophilic reactions of iminonitriles to access these attractive aminonitrile structures. To the best of our knowledge, there are only three reports of asymmetric reactions of iminonitriles other than ours (acylation by Ye,[23] Friedel-Crafts reaction by Zhao,[24] and alkylation by Deng[25]). Although Zhao's report comprised notable outliers, only one scope of an iminonitrile with 4-aminoindole was demonstrated (Figure 1d). Therefore, general methods have proven elusive and the broader problem remains unresolved. In the field of nucleophilic heteroaromatic installation, the organocatalytic Friedel-Crafts reaction has emerged as a powerful method.[26] We herein describe an efficient method for the stereoselective modular synthesis of α-aryl-α-heteroaryl-aminonitriles (Figure 1e). This transformation represents a modular coupling that allows for the rapid diversification of diarylmethanes, which is well represented in pharmaceuticals.[27] In this study, a wide variety of heteroaromatics and other aromatic compounds were applied to give products in high yields and with excellent levels of enantioselectivity. Furthermore, despite the increasing importance of the development of asymmetric reactions with lower organocatalyst loadings over the past decade, parts-per-billion (ppb) loadings have not yet been reported.[28] We discovered that the products can be obtained with very high selectivities using only 50 ppb of the catalyst with extremely high catalyst efficiency (TON = 10,800,000, TOF = 64286). Notably, different stereochemistries between the pyrrole and indole adducts were obtained with the same (*R*)-derived chiral phosphoric acid catalysts, which agrees well with a series of theoretical studies. Using density functional theory (DFT) calculations, we clarified that the key to this unexpected stereoinversion was the coordinating system between the electrophile and the catalyst. Thus, this strategy is a robust, practical, and versatile approach for the construction of chiral aminonitriles that are difficult to access using other methods, enabling the identification of unknown chemical spaces.

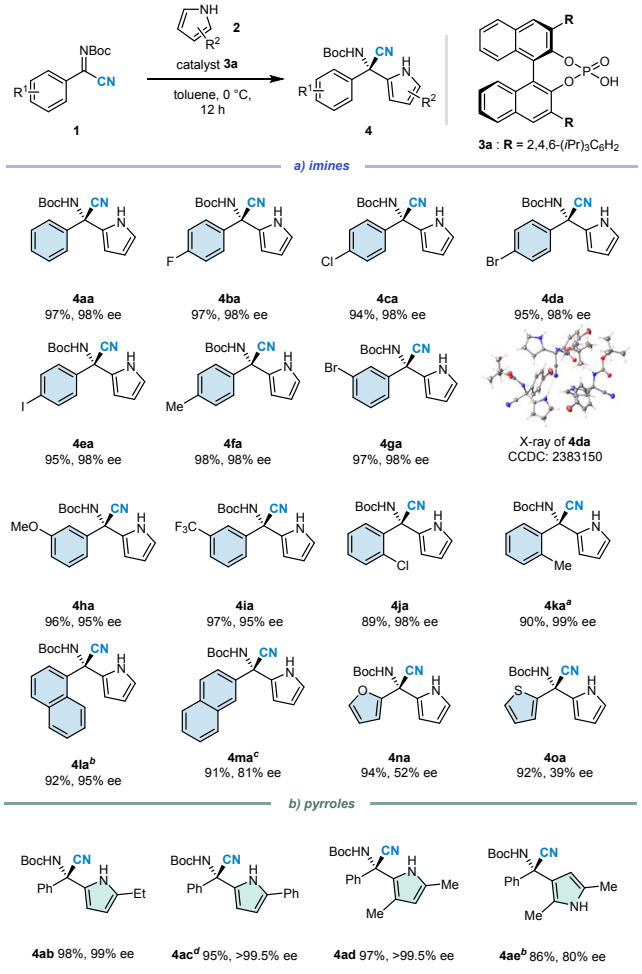
Results and discussion

According to previous studies on the preparation of diaryl aminonitriles, Ts-protected imines are used in most cases, which often require harsh deprotection conditions. Additionally, Boc protection/deprotection reactions are widely used in current pharmaceutical manufacturing.[29] Thus, the optimal conditions were determined for the asymmetric Friedel-Crafts reaction of N-Boc-protected iminonitrile **1a** with pyrrole **2a**. To our great delight, we found in the very first attempt that 3,3'-(2,4,6-(*i*Pr)$_3$C$_6$H$_2$)$_2$ (*R*)-BINOL-derived chiral phosphoric acid **3a** was the catalyst of choice,

delivering **4aa** in high yield with excellent enantioselectivity in toluene at 0 °C for 12 h (97%, 98% ee) and there was no need to further optimize parameters including catalyst structures, solvent, and temperature (see supporting information). From a practical perspective, it is worth noting that catalyst **3a** is commercially available and air-stable. We applied these general conditions to the reactions of various iminonitriles **1** with various pyrroles **2** to afford a broad array of enantioenriched α-aryl-α-heteroaryl-aminonitriles. The specific details of the reaction scope are presented in Table 1. The use of iminonitriles bearing a para-halogenated phenyl ring provided corresponding aminonitriles **4ba-4ea** in high yields and excellent enantiopurities (94-97% yield, 98% ee). The unique structure of the pyrrole-containing diaryl aminonitrile was ascertained via X-ray crystal analysis of **4da** to be (*S*) (CCDC: 2383150). Similarly, a substrate with a methyl group at the para-position underwent the reaction efficiently to produce **4fa** with high stereoselectivity (98% yield, 98% ee). As shown in the reactions of **1g-k** with pyrrole, regulation of the substitution patterns and steric hindrance at the meta- or ortho-positions of the aromatic had no adverse effect on the reaction efficiency and enantioselectivity, with the expected pyrrole adducts **4ga-4ka** being isolated in good yields and high enantioselectivities (90-97% yield, 95–>99.5% ee). The reactions using π-extended naphthalene substrates **1l-m** were also well incorporated in this manner (91-92% yield, 81-95% ee). Furthermore, heteroaryl iminonitriles were amenable to the protocol. For example, the reaction of 2-furyl iminonitrile **1n** and 2-thienyl iminonitrile **1o** worked well to provide two heteroaryl substituted aminonitriles **4na-4oa**, albeit with lower selectivities (92-94% yield, 39-52% ee). Subsequently, pyrroles with different substituents were tested. Interestingly, most cases exhibited extremely enhanced enantioselectivities. First, the reaction using 2-Et and 2-Ph pyrrole **2b-c** afforded chiral aminonitriles in excellent yields (**4ab**: 98% yield, 99% ee; **4ac**: 95% yield, >99.5% ee). 2,4-Me_2 pyrrole was also compatible with this reaction (**4ad**: 97% yield, >99.5% ee). In addition, 2,5-Me_2 pyrrole, which has limited applicability to the enantioselective reactions with ketimines, afforded product **4ae** in high yield with good stereoselectivity (86% yield, 80% ee), where the reaction takes place uniquely at the 3-position.[30]

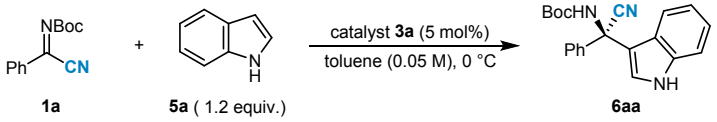
Based on these initial observations, we focused on the formation of indole-functionalized aminonitriles. However, the unsubstituted indole exhibited relatively poor selectivity under these standard conditions and afforded the product **6aa** with 72% ee (Table 2, run 1).

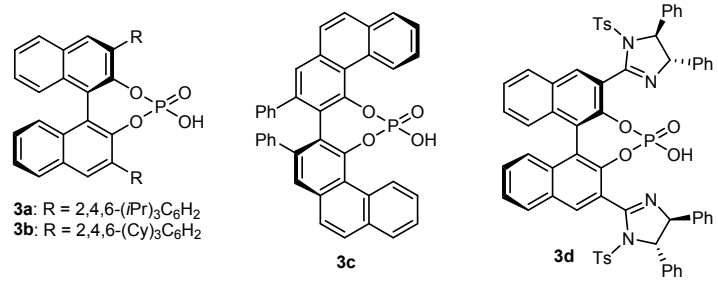
Table 1. Scope of the pyrrole-containing diaryl framework.



a) Scope of α-iminonitriles. b) Scope of pyrroles. Reactions were performed on a 0.05 mmol scale with **1** (0.05 mmol), 2 (0.06 mmol), and catalyst **3a** (5 mol%) in 1.0 mL of toluene (0.05 M) at 0 °C for 12 h. All the isolated yields of **4** are given. Ee was determined by chiral HPLC analysis. (a) 48 h. (b) 24 h. (c) 15 h. (d) 16 h.

Table 2. Optimization study of the asymmetric Friedel-Crafts reaction between iminonitrile **1a** and indole **5a** using chiral phosphoric catalysts **3**.[a]





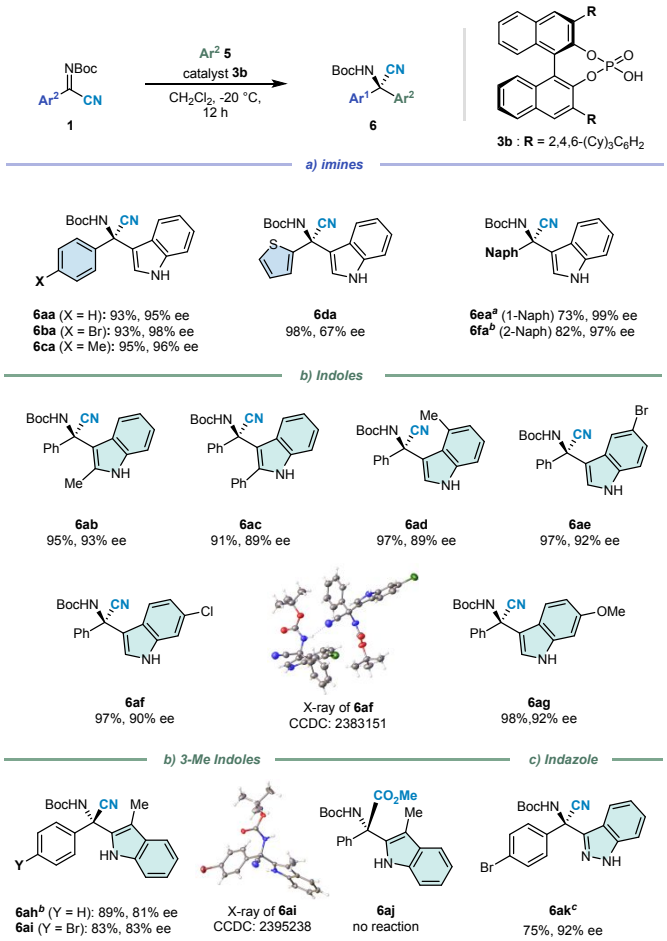
run	variations from standard condition	yield (%)[b]	ee (%)[c]
1	-	99	72
2	catalyst **3b**, 16 h	95	82
3	catalyst **3c**, 12 h	94	-73
4	catalyst **3d**, 24 h	19	9
5	catalyst **3b**, CH_2Cl_2 (0.1 M), 5 h	96	93
6	catalyst **3b**, $CHCl_3$ (0.1 M), 2 h	93	90
7	catalyst **3b**, $(CH_2Cl)_2$ (0.1 M), 2 h	94	87
8	catalyst **3b**, CH_2Cl_2 (0.1 M), -20 °C, 12 h	93	95

(a) The reaction was performed with 0.05 mmol of **1a**, 1.2 equiv. of **5a**, and catalyst **3** (5 mol%) for a given time. (b) The isolated yields of the products are given. (c) Ee was determined by chiral HPLC analysis.

Next, we explored the optimal conditions for the reaction between iminonitriles and indoles (Table 2). In accordance with our optimal pyrrole conditions, we first evaluated the catalyst structures. The more steric-hindered 3,3'-(2,4,6-$(Cy)_3C_6H_2$) substituted catalyst **3b** improved the enantioselectivity (run 2, 82% ee). Interestingly, a reversal of selectivity was observed in the reaction of VAPOL-derived catalyst **3c** (run 3, 73% ee), and the previously developed phosphoric acid catalyst was not effective for this reaction (run 4, 9% ee). Furthermore, a survey of solvents revealed that dichloromethane (CH_2Cl_2) was ideal while increasing the concentration provided improved enantioselectivity (run 5, 96% yield, 93% ee). Finally, excellent levels of enantiocontrol were achieved by lowering the reaction temperature (run 8, 93% yield, 95% ee), which was thus established as the optimal condition for preparing the indole-containing diaryl aminonitrile.

With a general set of conditions and optimized access to indole-containing diaryl aminonitrile **6**, the scope of this methodology was evaluated across a range of both iminonitrile and indoles, as shown in Table 3.

Table 3. Scope of the diaryl framework.



a) Scope of α-iminonitriles. b) Scope of indoles. c) Scope of other nucleophiles. Reactions were performed on a 0.05 mmol scale with **1** (0.05 mmol), **5** (0.06 mmol), and catalyst **3b** (5 mol%) in 0.5 mL of CH_2Cl_2 (0.1 M) at -20 °C for 12 h. All the isolated yields of **6** are given. Ee was determined by chiral HPLC analysis. (a) 168 h. (b) 36 h. (c) **3a** as catalyst in toluene for 96 h.

4-substituted iminonitriles showed that both electron-deficient and electron-rich phenyl rings underwent asymmetric Friedel-Crafts reactions in good yield with an excellent level of enantioselectivity (6aa-6ca, 93-95% yield, 95-98% ee). The use of the heteroarene iminonitrile gave rise to the desired product with good enantiopurity (**6da**, 75% ee). When using 1- or 2- naphthyl substituted iminonitrile, the reaction required a longer reaction time and still showed decreased yield (6ea-6fa, 75-82% yield, 97-99% ee), presumably because indole is more sterically hindered than pyrrole. After exploring the scope of the iminonitriles, we examined indoles with various substituents. As a result, an array of indoles 5 was successfully reacted and converted to the corresponding coupling products in high yields and enantioselectivities. 2-methylindole 5b and more sterically demanding 2-phenylindole 5c delivered each product in high yield with high stereoselectivity (6ab-6ac: 91-95% yield, 89-93% ee). Although 4-substituted indoles sometimes gave a lower yield owing to the steric effects, 4-methylindole afforded aminonitrile in 97% yield with 89% ee. Furthermore, as expected, indoles with various electronic and steric profiles (5-Br, 6-Cl, 6-OMe) also furnished the indole adducts **6ae-6ag** with high efficiency and enantiocontrol (97-98% yield, 90-92% ee). The absolute stereochemistry of the indole adduct was determined via single-crystal X-ray analysis to be (*R*) (CCDC: 2383151). It should be mentioned here that the opposite stereochemistry between the pyrrole and in-dole adducts was obtained with the same (*R*)-derived chiral phosphoric acid catalysts. However, 3-methylindole, which also has limited examples of enantioselective reactions with ketimines,[31] reacted with iminonitriles at the C2-position similarly to pyrrole, efficiently delivering the same stereochemical outcome with high selectivity (**6ah**: 89%, 81% ee; **6ai**: 83%, 83% ee). The reaction of 3-methylindole with the Boc-protected iminoester did not proceed under the standard conditions, presumably because of the more hindered reaction site. The reaction scope was surveyed for less reactive Friedel-Crafts nucleophiles. 1H-indazole also reacted and gave high selectivity (92% ee). Although sesamol and 1-naphthol, which have biologically significant aromatic cores also gave corresponding products, only low to modest selectivities were obtained in the results of several optimization process (see supporting information S7-8).

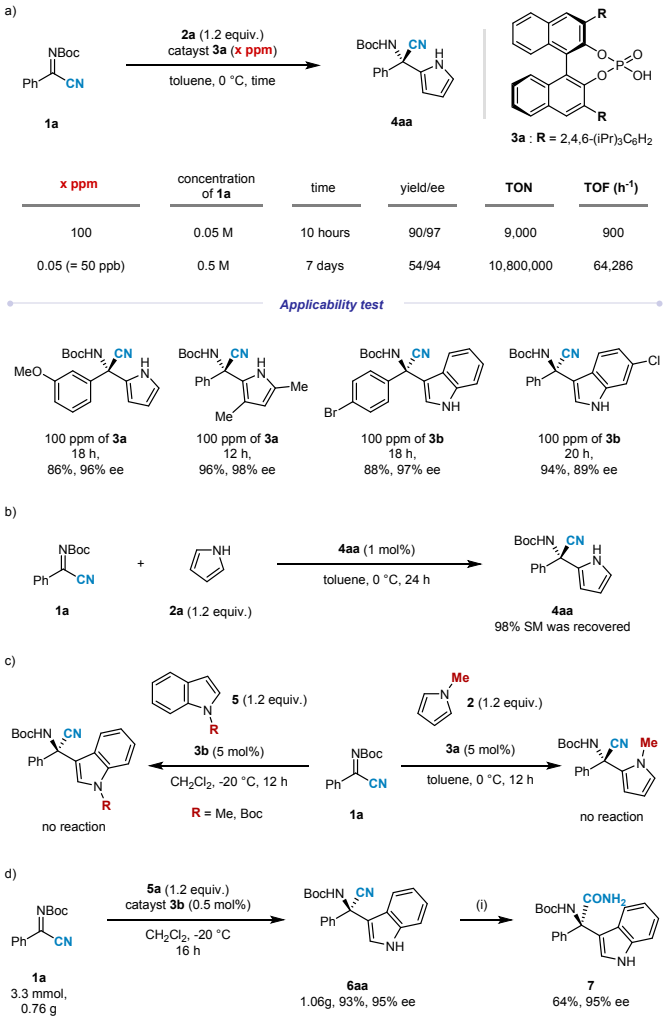


Fig. 2. Evaluation of the practicality and control experiments. a) Asymmetric reaction of iminonitrile **1a** with pyrrole **2a** with low catalyst loading. b) Evaluation of product as catalyst. c) Control experiments with *N*-protected pyrrole and indole. d) Gram-scale synthesis of indole adduct **6aa** and its transformation. (i) Acetaldoxime (3.0 equiv.) and $InCl_3$ (0.2 equiv.) in benzene at room temperature for 48 h.

Because the reaction proceeded smoothly in most cases, we next investigated the minimum amount of catalyst that could be used (Figure 2a). Although there are only a few highly enantioselective reactions catalyzed by extremely low catalyst loadings in the field of organocatalysis, some outstanding works were reported.[28] To the best of our knowledge, the minimum organocatalyst loading was described by List using multiple vessels (0.9 ppm, 80 days total, TON = 911,000, TOF ≈ 474).[28c] Based on this premise, we first investigated the reaction of iminonitrile **1a** and pyrrole **2a** using 100 ppm **3a** which successfully afforded the product (90% yield, 97% ee, TON = 9,000, TOF = 900). Moreover, the reaction with 50 ppb **3a** gave rise to highly enantioenriched **4aa** with extremely high TON and TOF (54% yield, 94% ee, TON = 10,800,000, TOF = 64,286). These results imply that the catalytic efficiency depends largely on the substrate concentration. Considering this, some examples were tested to demonstrate the applicability of low catalyst loading while maintaining efficiency (Figure 2a, bottom). Surprisingly, the reaction time did not need to be extended when using 100 ppm of the catalyst compared to 5 mol%. Hence, we hypothesized that one of the enantiomers of the product could catalyze the reaction. However, when iminonitrile **1a** and pyrrole were mixed with catalytic amount of product, only the starting materials were recovered, indicating that only chiral phosphoric acid could accelerate the reaction (Figure 2b). In addition, the use of *N*-protected pyrrole or indole did not give the products (Figure 2c). This result imply that the interaction between catalyst and each heteroaromatics (P=O---H-N) is crucial for this reaction. The robustness of this protocol was demonstrated by the gram-scale synthesis of **6aa** using 0.5 mol% of the catalyst, resulting in a yield and enantioselectivity comparable to those of the small-scale reaction (1.06 g, 93% yield, 95% ee). The obtained aminonitriles were smoothly transformed into corresponding aminoacetamides **7** without any loss of enantioselectivity (64% yield, 95% ee) (Figure 2c).

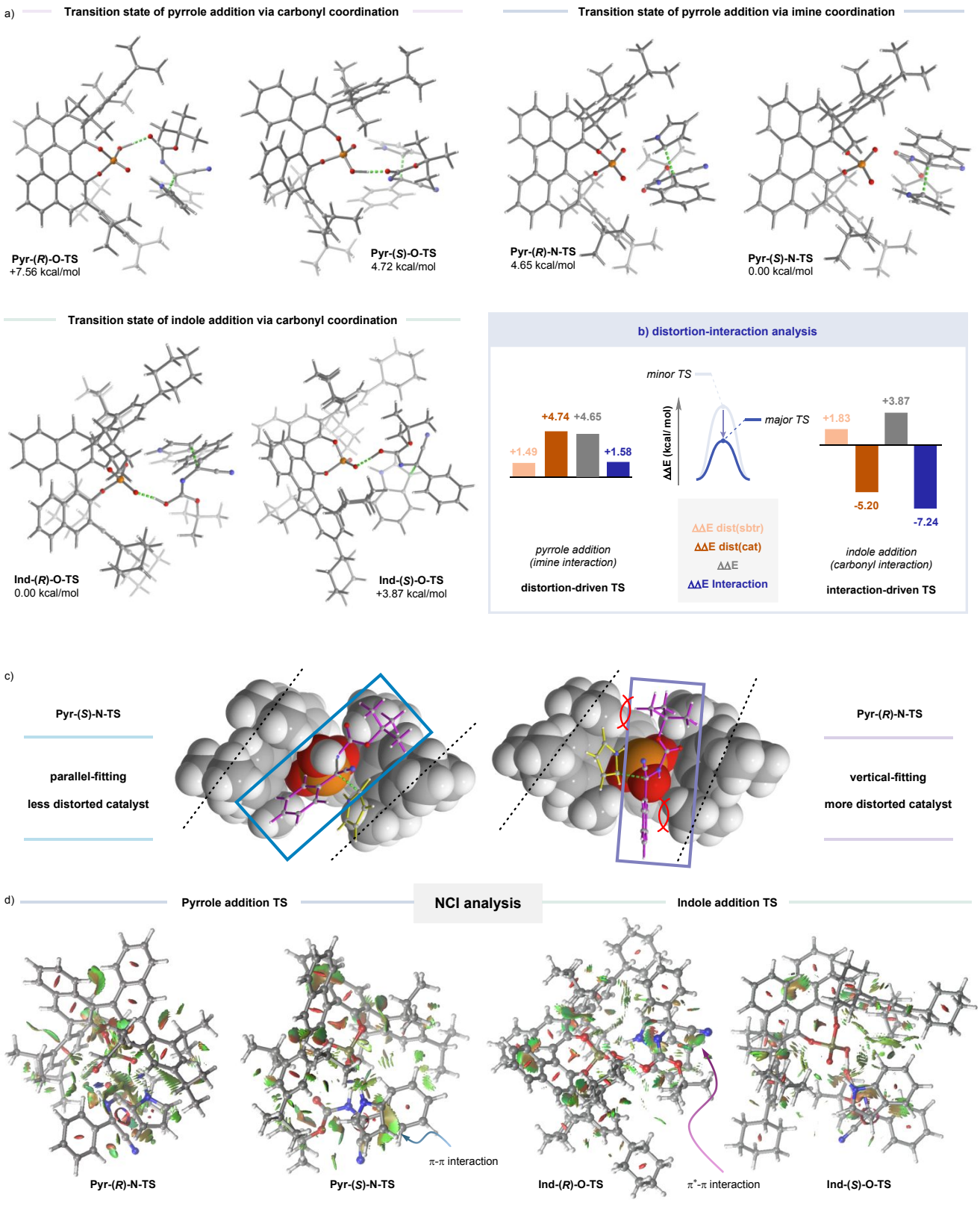


Fig. 3. Mechanistic Investigation. Computational study performed at the Gaussian 09 M06-2X/6-311+G(d,p)/CPCM(toluene or CH_2Cl_2)//B3LYP/6-31G(d) level.

Mechanistic investigations were conducted to understand the origin of the stereoinversion. It has been established that the activation mode of Friedel-Crafts reactions of pyrroles or indoles with imines typically involves two interactions: (1) interaction between the acidic hydrogen atom of the catalyst and the imines, (2) interaction between the phosphoryl oxygen and N-H bond or C-H bond of each

nucleophile,[32] which constitute Goodman's model.[33] Since the reaction did not proceed when the *N*-protected pyrroles or indoles were used (see supporting information for details), we conclude that the N-H bond, capable of forming an H-bonding network with the catalyst, is crucial to accelerate the reaction. Subsequently, we performed bench-marking computational studies to rationalize the obtained enantioselectivities. Based on a range of computational protocols, the most accurate energy differences to reproduce the empirical selectivity were obtained at the Gaussian 09 M06-2X/6-311+G(d,p)/CPCM(toluene or CH_2Cl_2)//B3LYP/6-31G(d) level of theory using iminonitrile **1a** and pyrrole or indole as model substrates. The comprehensive results of our theoretical studies on TSs for the reactions of iminonitriles and pyrroles or indoles are depicted in Figure 3a (top). We calculated four possible transition states (TSs) for the pyrrole addition reaction: carbonyl or imine coordination and (*R*) or (*S*) configuration. Following our expectations, TSs involving imine coordination TSs are energetically more stable than those involving carbonyl coordination. Each model indicated that the (S)-isomer can be generated as a major product (ΔΔE = +4.65 kcal/mol). By modelling the TSs of the reaction with indole, we discovered that the highly steric-hindered 2,4,6-Cy_3-BINOL-derived phosphoric acid catalyst could interact with only the carbonyl moiety to afford reasonable TSs and energy differences (ΔΔE = +3.87 kcal/mol), which suggested the (*R*)-isomer (Figure 3a, bottom). This is because the indole reacts at the remote C3 position, and when the catalyst interacts with the imine nitrogen atom, the complex becomes distorted. Overall, these computed scenarios indicate that product stereoreversal can be attributed to differences in the coordination systems. With some computational results in hand, we attempted to break down each interaction to clarify the factors that contributed to the stabilization of each TS. First, we performed a distortion-interaction analysis (Figure 3b). The greatest difference between the reactions of pyrroles and indoles was the degree of catalyst distortion. In the case of pyrrole addition, pyr-(*R*)-N-TS (minor TS) was more sterically distorted than pyr-(*S*)-N-TS (major TS) with stronger interaction energies, suggesting that pyrrole addition proceeds via a distortion-driven TS. Indeed, we found that the substrates fit better in the chiral pocket of pyr-(*S*)-N-TS as shown in Figure 3c. In contrast, ind-(*S*)-O-TS (minor TS) was less distorted than ind-(*R*)-O-TS (major TS) with weaker interaction energies, suggesting that indole addition proceeds via an interaction-driven TS. As the result of non-covalent-interaction (NCI) analysis, a relatively strong π-π interaction between pyrrole and the phenyl ring of iminonitrile was observed only in pyr-(*S*)-N-TS. The formation of an unexpected π-π* interaction between nitrile and indole was observed in ind-(*R*)-O-TS which we believe accounts for the favorability of the (*R*)-path. Both ind-(*S*)-O-TS and ind-(*R*)-O-TS exhibited an endo-orientation.

Conclusions

We report the rapid enantioselective construction of diversifiable α-aryl-α-heteroaryl-aminonitriles, which would otherwise be difficult to access through other aminonitrile synthesis strategies via heteroaryl introduction to iminonitriles. Our protocol is amenable to an extensive range of substrates, including 2,5-pyrrole, 3-Me indole, sesamol, naphthol, and indazole, which have been reported to undergo only a few asymmetric reactions with ketimines. The catalyst loading can be reduced to a ppb-scale minimum, which indicates unprecedented catalytic efficiency. DFT calculations for each transition state implied that the stereoreversal between the pyrrole and indole adduct could be attributed to the coordination system. A detailed computational analysis to investigate the effect of steric and non-covalent interactions revealed the factors affecting the energy differences. Collectively, these examples demonstrate the utility, modularity, practicality, and selectivity of iminonitriles in the construction of biologically important chiral aminonitriles containing a diaryl methane moiety.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included in the Supplementary Information. Crystallographic data for **4da**, **6af**, and **6ai** have been deposited at the CCDC under 2383150, 2395238, and 2383151.

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Data availability

The data supporting this article have been included in the Supplementary Information. Crystallographic data for **4da**, **6af**, and **6ai** have been deposited at the CCDC under 2383150, 2395238, and 2383151.