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Organocatalytic Asymmetric Mannich Reaction of Aromatic Imines

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Abstract: Various multifunctional enantiomerically pure organocatalysts were synthesized and screened in asymmetric Mannich reaction. Aromatic imines gave Mannich adducts with malonates in the presence of amino acid derived catalyst in very high enantiomeric purities (ee up to 98%). It is proposed that the network of hydrogen and halogen bonds with Lewis bases, together with the steric effect of the *tert*-butyl group of the catalyst, is responsible for the high stereoselectivity of the reaction.

Keywords: aromatic imine; asymmetric catalysis; Mannich reaction; non-covalent interactions; organocatalysis

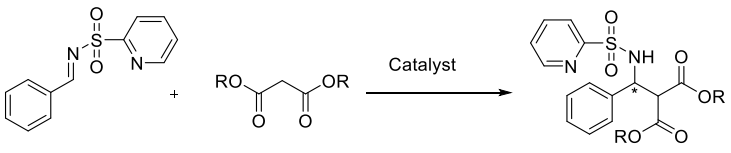
Introduction

Mannich reaction i.e. addition of enolized carbonyl compounds to an imine derived from an aldehyde or ketone and an amine, has been known for more than hundred years[1] and it has become an important method for creating C-C-bonds[2,3,4]. Obtained Mannich bases exhibit a broad spectrum of biological activities[5,6] and have also been used in the synthesis of numerous pharmaceuticals and natural products[7]. Application of asymmetric synthesis

enables access to enantiomerically pure targets. In recent years, methods of asymmetric organocatalysis have been widely used to achieve these valuable compounds[8,9,10]. Catalysts employing non-covalent interactions via hydrogen or halogen bonds and possessing also Lewis basic and $\pi-\pi$-interaction sites have been highly efficient in Mannich reactions, as demonstrated by our studies[11] and those of others[12,13,14]. Multifunctionality of the catalyst is essential to intensify weak non-covalent interactions.

Results and Discussion

As a continuation of our previous studies, we now report an asymmetric Mannich reaction between 2-sulfonylpyridine protected imine and malonate (Scheme 1). Pyridine containing protecting group was chosen considering our catalyst design. We envisioned that halogen bond (XB) will complement hydrogen bond to activate an imine towards the nucleophilic attack of the malonate. It is known that *N*-atoms are the strongest XB acceptors in electroneutral compounds[15]. It has also been shown that imines protected with heteroarylsulfonyl groups provide higher enantioselectivity than those protected with the more commonly used phenylsulfonyl or tosyl groups in addition reactions to imines[16].



Scheme 1: The catalytic Mannich reaction under study.

The model reaction was performed in the presence of various types of catalysts.

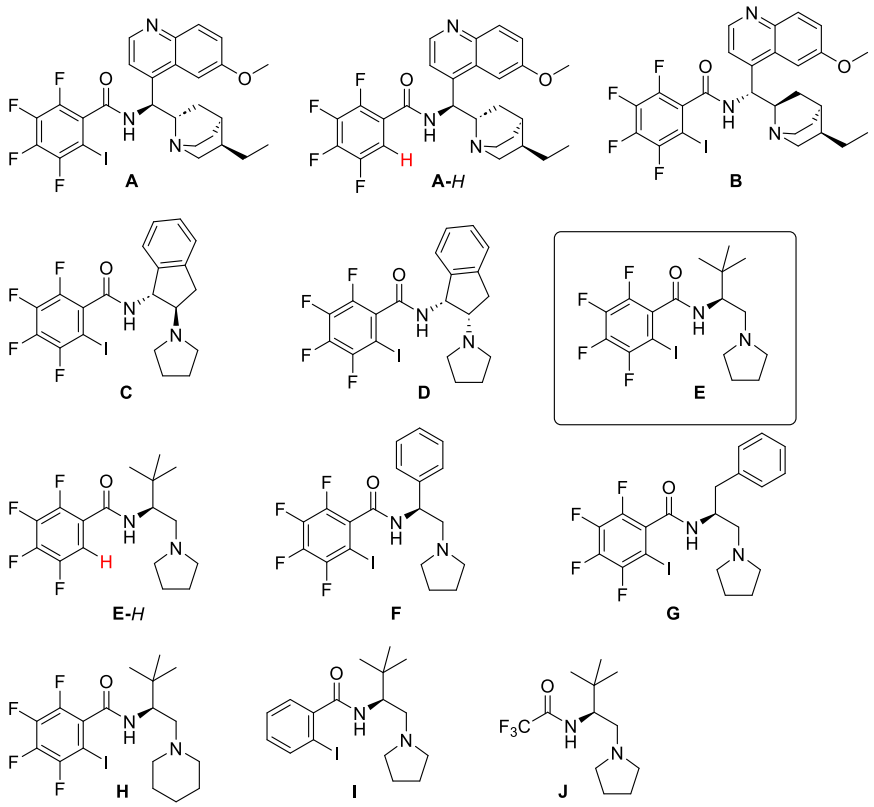


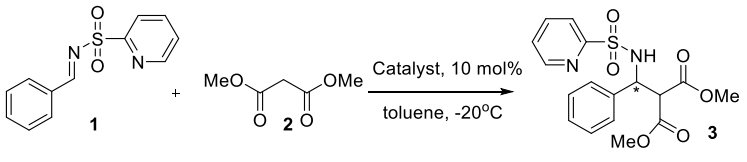
Figure 1: Screened catalysts.

The synthesis of catalysts is described in SI. All catalysts used are amides containing tertiary amines, which are needed for the activation of the malonate. We have previously shown the importance of an acidic amidic proton in the asymmetric Mannich reaction[11]. The majority of the catalysts are also potential halogen-bond donors containing tetrafluoro-iodophenyl or iodophenyl moieties, which enable the formation of additional non-covalent interactions between the catalyst and the reagents. The chirality of the catalysts is derived from either amino acid or amino alcohols (including cinchona alkaloid derivatives). There are three exceptional structures: catalysts **A**-*H* and **E**-*H*, which are the hydrogen analogues of the

corresponding iodine-containing compounds, and catalyst **J** as a trifluoroacetylated chiral tertiary amine, which lacks iodine.

The reaction of imine **1** with dimethyl malonate was selected for the investigation as a model reaction. Based on our previous experience the catalyst screening was carried out in toluene in the presence of 10 mol% of the catalyst and it was started with Arai type of catalyst **A**.[12] The features of the catalyst are the quinine moiety with reduced double bond and enhanced halogen-bonding ability due to highly electronegative substituents on phenyl ring. The reaction was relatively fast, achieving full conversion of the starting imine in 3 hours at rt and at -20°C in 5 hours. Decrease of the temperature increases the enantiomeric purity of the product (ee from 27% up to 52%) (Table 1, entries 1-3). The corresponding *H*-analogue of the catalyst **A** was less selective (ee 18%), (entries 4 and 5). This suggests that the halogen bond plays a role in determining the stereoselectivity of the reaction. The reaction with the similar quinidine derivative with reduced double bond (catalyst **B**) was slower and less selective affording the opposite enantiomer in low enantiomeric purity (ee 14%), (entry 6).

Table 1: Catalyst screening.



Entry	Catalyst	NMR conv % (time, h)	ee (%)
1.	**A**	100 (3)	27[a]
2.	**A**	100 (3)	38[b]

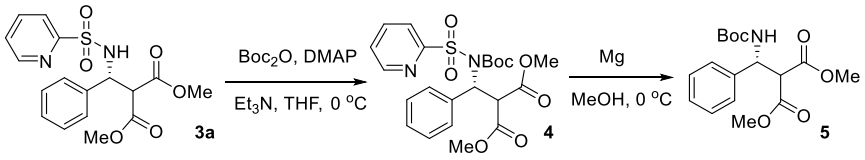
3.	**A**	100 (5)	52
4.	**A**-*H*	99 (3)	18[b]
5.	**A**-*H*	93 (5)	18[c]
6.	**B**	85 (5)	-14[d]
7.	**C**	24 (48)	ND
8.	**D**	10 (48)	ND
9.	**E**	89 (5)	83
10	**E**-*H*	93 (5)	71
11	**F**	93 (48)	28
12	**G**	99 (48)	38
13	**H**	98 (22)	78
14	**I**	100 (5)	78
15	**J**	100 (24)	74

[a] reaction at rt; [b] reaction at 0 ^{o}C; [c] reaction at -20 ^{o}C; [d] an opposite enantiomer was obtained

Aminoindanol based catalysts **C** and **D** were inefficient and stereomeric purity of the products were not determined (entries 7 and 8). The next group of catalysts consists of amino acid derivatives. The most selective was *tert*-leucine based catalyst **E** affording Mannich adduct in 83% of ee (entry 9). Replacing the five-membered pyrrolidine ring in the catalyst structure with the more flexible six-membered piperidine ring (catalyst **H**, entry 13) reduced its selectivity slightly (ee 78%). However, the catalyst derived from phenylglycine

(catalyst **F**) or phenylalanine (catalyst **G**) were much less selective (entries 11 and 12, respectively). To evaluate the role of potential halogen bond, the corresponding hydrogen analogue of catalyst **E** was synthesized and used in the model reaction (entry 10). The catalyst was still efficient but afforded the product in slightly less enantioselective way (ee 71%). When comparing the halogen bond donor properties of tetrafluoro iodophenyl and iodophenyl moieties, the latter is weaker as it is less electron-withdrawing. However, there is a very little difference between reactivity and selectivity for catalysts **E** and **I**. Catalyst **J** lacking iodophenyl core was much less reactive and 24 h were needed to reach the full conversion of the starting imine. However, the stereoselectivity remains high and is comparable to that in the previous examples. Our results demonstrate that with *tert*-leucine derived catalyst **E** the halogen bond is not essential for determining stereoselectivity, but halogen atom has a beneficial effect on both reactivity and stereoselectivity. The interaction between the catalyst **E** and imine was further elucidated by ^{19}F-NMR studies (see SI). However steric effect of the iodine can't be excluded in determining stereoselectivity.

To determine absolute configuration of product **3** the nitrogen atom was additionally protected with Boc_2O affording compound **4** followed by the removal of pyridinesulfonyl group with Mg in MeOH (Scheme 2)[17]. Although basic conditions caused partial racemization during the protection step, enantiomerically enriched Boc-protected amine **5** was obtained. Chiral HPLC analysis and comparison with an authentic sample revealed the *R*-configuration of the Mannich adduct[18]. Absolute configurations of other products were assigned by analogy.



Scheme 2: Determination of the absolute configuration.

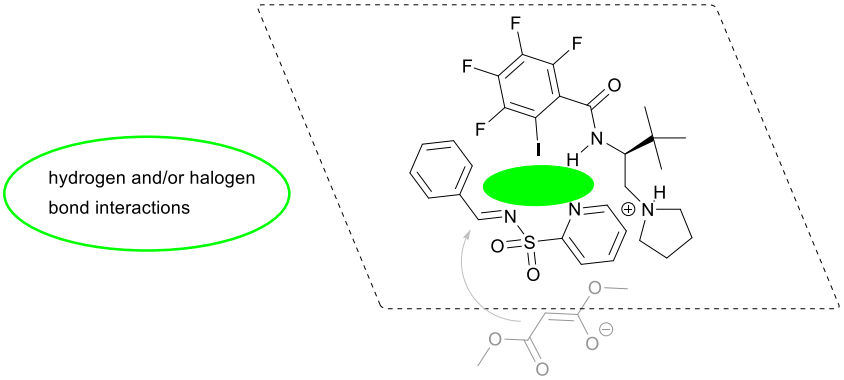


Figure 2: Model for the interaction of the catalyst with imine.

Based on the results obtained in catalyst screening, it is assumed that the catalyst and the imine are connected through a network of hydrogen or halogen bonds. Iodine may form halogen bonds with either of the nitrogen atoms of the imine. Halogen bond can be strengthened via hydrogen-bond-assisted halogen bonding[19,20]. Similarly, hydrogen bonds with the amidic proton are also possible. The direct effect of a specific interaction could not be determined. The network of non-covalent interactions formed stabilizes the complex between the catalyst and the imine. The sterically demanding *tert*-butyl group of the catalyst blocks the *si*-face of the imine and malonate attacks from *re*-face affording product in *R*-configuration (Figure 2).

To demonstrate the utility of elaborated catalytic system, the Mannich reaction between aromatic imines both with electron-withdrawing and electron-donating substituents in the phenyl ring, and malonate were carried out in the presence of 10 mol% of catalyst **E** in toluene at -20°C (Figure 3). The experimental procedure was simple, enantiomerically

enriched products **3a**-**i** were isolated by direct precipitation from the crude reaction mixture in good to high yields by adding a mixture of petroleum ether/Et_2O (see the Experimental Section).

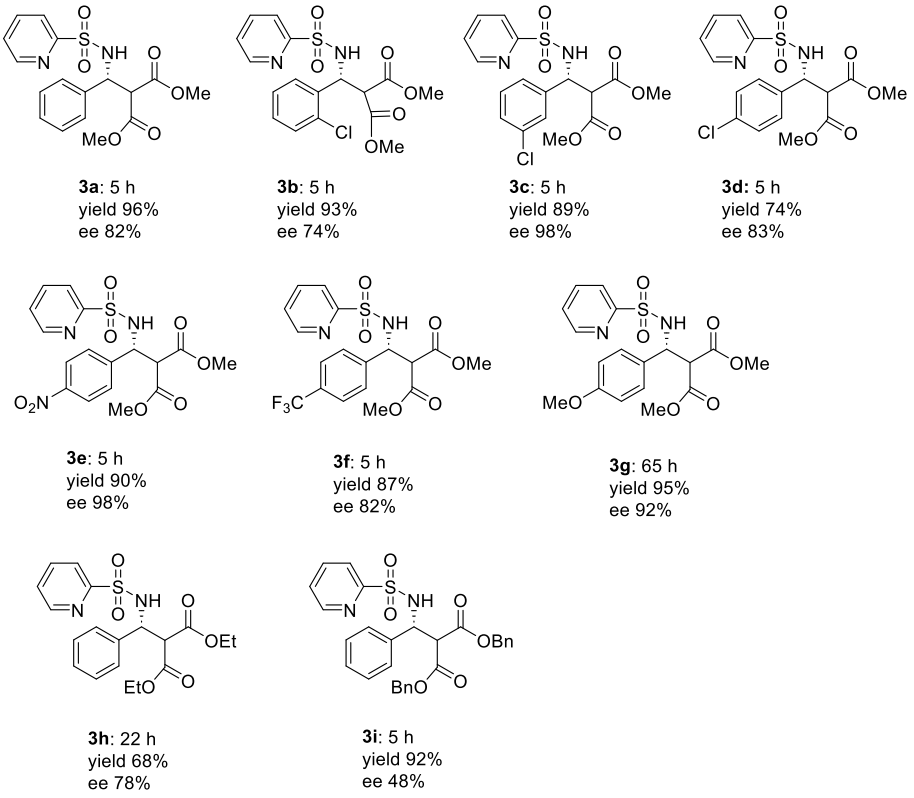


Figure 3: Substrate scope of an asymmetric Mannich reaction

Generally, the reactions are fast affording products in high to excellent enantiomeric purities. The substitution pattern in the phenyl ring has some influence on the results (compare compounds **3a**- **3d**). The *ortho*-Cl substituents in the aromatic ring of **1b** slightly decreases while the *meta*-position of Cl atom in **1c** increases enantioselectivity of reaction (compare **3b** and **3c**). Electron donating substituent decreases the rate substantially but stereoselectivity of the reaction remains still high (compound **3g**). Diethyl malonate proved to be less reactive

under standard conditions than dimethyl malonate and dibenzyl malonate gave product with high yield, but the selectivity dropped significantly (compound **3i**).

Conclusion

In conclusion, we have designed a new catalyst enabling highly enantioselective Mannich reaction of aromatic imines. Although the activation mechanism was not proved unambiguously, it is assumed that sterics of the chiral fragment together with a network of non-covalent interactions, including halogen and hydrogen bonds, are responsible for the high enantioselectivity of the reaction. Further development of the method and applications of obtained products are under the study.

Experimental

General Procedure for the Catalytic Asymmetric Mannich Reaction

Catalyst **E** (2.7 mg, 0.0057 mmol, 0.01 equiv.) was weighed into a reaction vessel, imine (0.057 mmol, 1.0 equiv.) and toluene (285 µL) were added. The mixture was stirred at room temperature until a suspension was formed (ca 5 min). After that, the reaction mixture was cooled to -20 °C. Malonic ester (0.171 mmol, 3.0 equiv.) was added to the reaction vessel via syringe. The reaction was stirred at -20 °C for an appropriate time. The progress of the reaction was monitored by ^{1}H NMR analysis. After completion of the reaction, the product was isolated by direct precipitation from the crude reaction mixture by adding a mixture of petroleum ether/Et_2O (4/1; 2 mL). Product was collected by filtration and washed with a mixture of petroleum ether/Et_2O (4/1; 4 × 2 mL).

Supporting Information File 1

Experimental procedures, synthetic details, NMR spectra, chiral HPLC chromatograms

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