Organocatalysis

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Cooperative Assistance in Bifunctional Organocatalysis: Enantioselective Mannich Reactions with Aliphatic and Aromatic Imines**

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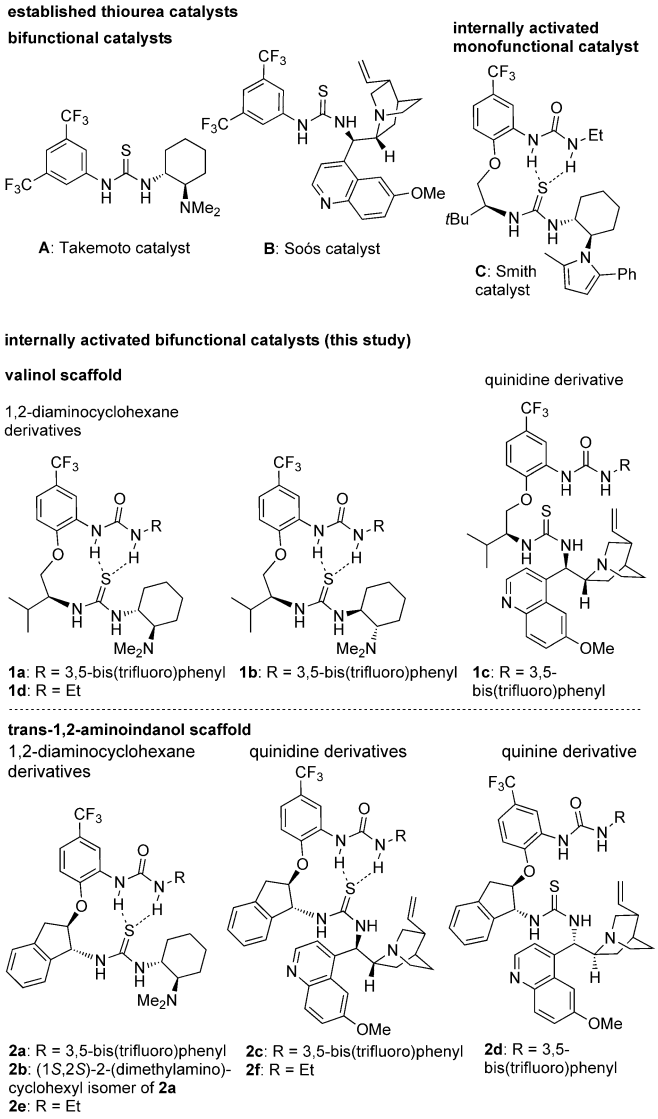
Bifunctional catalysts that contain a Brønsted-basic amine and a hydrogen-bond donor in the same molecule have been very successful catalysts for numerous enantioselective reactions.[1] Typical catalysts of this family include the diaminocyclohexane derivative **A** (Takemoto catalyst)[2] and the cinchona-alkaloid-derived catalysts such as **B** (Soós catalyst),[3] both of which contain a thiourea moiety (Scheme 1). The catalysts are capable of deprotonating suitable nucleophiles, such as activated carbonyl compounds. This proton-transfer reaction generates an ion pair, which is composed of the protonated catalyst and the anionic nucleophile interacting through hydrogen bonds. At least one of the NH moieties in the protonated catalyst is involved in activating the electrophilic reaction partner.[4]

The inherent problem associated with this activation mode is that the electrophilic partner and the anionic nucleophile must compete for the same hydrogen-bond-donor sites. As a result, only one of the hydrogen-bond donors in the catalyst may be used for the activation of the electrophile,[4a] thus reducing the level of activation of the electrophile. We reasoned that the presence of an intramolecular hydrogen bond[5] could provide significant improvement in the hydrogen-bond-donor capacity of the thiourea moiety through cooperative effects,[6] as already demonstrated by Smith and co-workers (catalyst **C**; Scheme 1).[5d]



Scheme 1. Structures of catalysts studied.

In the context of bifunctional catalysts, the success of such a design is contingent on the stability of the intramolecular hydrogen bonds of the catalysts when they are strongly bound to anionic substrates. The catalyst could refold, allowing the catalyst to wrap around the substrate. In other words, the catalyst could act as an anion receptor.[7] The thiourea moiety must also be accessible for the activation of both substrates simultaneously, while maintaining the conformation that

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allows the intramolecular hydrogen-bond interaction intact. As such, the design of a bifunctional catalyst that fulfils all of these criteria is highly challenging. Herein we describe the design of a new family of bifunctional catalysts based on a rigid urea–thiourea scaffold where the activating intramolecular hydrogen bonds are maintained in both the free catalyst as well as the catalyst–anion ion pair. These catalysts promote Mannich reactions between Boc-protected imines and malonates with a very wide scope: both aliphatic and aromatic substrates can be converted into product with excellent enantioselectivity.

In our initial design, we employed an amino-alcohol linker similar to that used by Smith and co-workers (Scheme 1, catalysts **1a**–**1d**). In our 2nd-generation version, we used the *trans*-1,2-aminoindanol linker (catalysts **2a**–**2f**; see below for the rationale of this design). Both the 1,2-diaminocyclohexane and 9-*epi*-aminoquinidine/quinine scaffolds were screened (Scheme 1).[8]

The X-ray structure of **1d**[9] (Figure 1) indicated that although the catalyst based on the L-valinol linker does fold in such a way that allows an intramolecular hydrogen-bonding interaction, there appeared to be a potential flaw in the initial design: the L-valinol (Smith-type) linker causes the arene–urea moiety to bend over the thiourea moiety, thus potentially

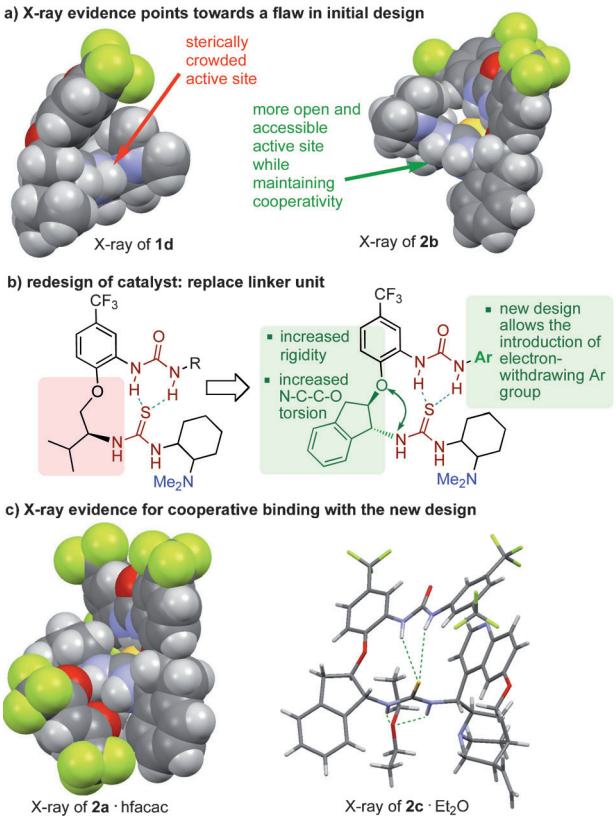


Figure 1. Selected X-ray structures to illustrate (a) accessibility to the active site, (b) redesign of the catalyst, and (c) demonstration of the stability of the catalyst conformation, which is enforced by an intramolecular hydrogen bond, when the catalyst is bound with neutral (**2c**, Et_2O solvate) or anionic (**2a**·hfacac) hydrogen-bond acceptors. For **2a**·hfacac, two slightly different binding modes were observed; only one of them is shown.[8,9]

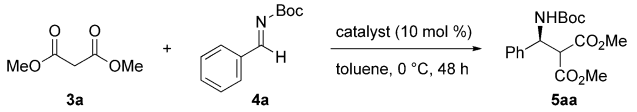
hindering the simultaneous binding of two substrates to the active site. We therefore replaced the linker with a more rigid *trans*-1,2-aminoindanol subunit, thus resulting in a more accessible active site (X-ray of **2b**, Figure 1). Importantly, the desired conformation was also observed in the hexafluoroacetylacetonate salt of **2a** (**2a**·hfacac; Figure 1c), and in the Et_2O solvate of quinidine-derived compound **2c**. The structure of **2a**·hfacac clearly shows that even after proton transfer and complex formation with the substrate mimic (hfacac), the intramolecular hydrogen-bonding interaction in **2a** is still present in the resulting cation–anion complex. One of the thiourea NH moieties is still accessible for binding of another substrate and the rigid linker moiety ensures sufficient open space near the thiourea moiety (compare the X-ray structures of **1d** and **2b**).

We selected the Mannich reaction between dialkyl malonates and both aromatic and aliphatic aldimines to evaluate the activity and the selectivity of the catalysts. This reaction is important because it provides a straightforward access to chiral β^3-amino acids. Although Mannich reactions with aromatic imines and malonates are promoted by bifunctional catalysts such as **B**,[10,11] aliphatic aldimines are typically unreactive with these catalysts, thus limiting the scope of the reaction. Aliphatic aldimines have been viable substrates in Mannich reactions only with the use of stoichiometric quantities of catalyst **B**[11] or stronger base.[12–14]

Consistent with the X-ray evidence (Figure 1), catalysts with the *trans*-aminoindanol linker were, typically, significantly more active and gave products with higher enantioselectivity (Table 1, entries 4–8) than those with the L-valinol linker (Table 1, entries 1–3). In the Mannich reaction with aromatic aldimine **4a,** catalyst **2c** displayed very high enantioselectivity, surpassing the selectivity observed with the benchmark catalysts **A** and **B** under similar reaction conditions.

In reactions of the aliphatic aldimine **6a** (Table 2), catalysts **2a** and **2b**, which contain the 1,2-diaminocyclohexane moiety, were catalytically active and afforded the product **7aa** in good yield and with good enantioselectivity (Table 2,

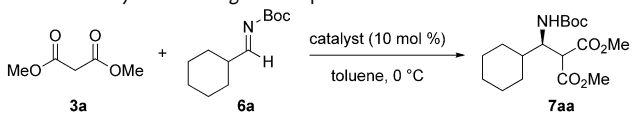
Table 1: Catalyst screening with aromatic aldimine **4a**.[a]



Entry	Catalyst	Yield [%][b]	e.r.[c]
1	**1a**	70	71.2:28.8
2	**1c**	29	16.8:83.2
3	**1d**	78	72.8:27.2
4	**2a**	81	96.9:3.1
5	**2c**	80	99.6:0.4
6	**2d**	44	35.0:65.0
7	**2e**	85	95.7:4.3
8	**2f**	73	96.4:3.6
9	**A**	82	95.0:5.0
10	**B**	88	95.8:4.2

[a] Reaction conditions: **3a** (0.15 mmol, 150 mol%), **4a** (0.10 mmol, 100 mol%), catalyst (0.01 mmol, 10 mol%), toluene (0.5 mL), 0°C, 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral column. Boc = *tert*-butoxycarbonyl.

Table 2: Catalyst screening with aliphatic aldimine **6a**.[a]



Entry	Catalyst	t [h][b]	Yield [%][c]	e.r.[d]
1	**1a**	48	22	91.2:8.8
2	**1b**	72	60	~20:80
3	**2a**	14	82	92.0:8.0
4	**2a**[e]	22	91	96.7:3.3
5	**2b**	14	99	3.8:96.2
6	**2c**	48	61	59.4:40.6
7	**2e**	48	63	91.8:8.2
8	**A**	48	n.r.	n.d.
9	**B**	48	n.r.	n.d.

[a] Reaction conditions: **3a** (0.10 mmol, 100 mol%), **6a** (0.30 mmol, 300 mol%), catalyst (0.01 mmol, 10 mol%), toluene (0.5 mL), 0°C. [b] Monitored by TLC. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral column. [e] Reaction conducted at −40°C. n.d. = not determined, n.r. = no reaction.

entries 3–5). In sharp contrast to catalysts **2a** and **2b**, the benchmark thiourea catalysts **A** and **B** failed to promote the desired Mannich reaction (Table 2, entries 8–9), underscoring the importance of the intramolecular hydrogen-bond activation in the catalyst.

The superior activity of the indanol scaffold is even more evident from in situ monitoring of the reaction of aliphatic imine **6a** by NMR spectroscopy (Figure 2). Catalysts **2a** and **2b** are significantly more active than **1a** and **1b**.

With these results, the scope of the Mannich reaction was investigated using various substituted aromatic and aliphatic aldimines (Table 3). When catalyst **2c** was used, aromatic aldimines bearing electron-donating as well as electron-withdrawing moieties afforded the corresponding products in excellent yield and enantioselectivity (Table 3, entries 3—5; for more examples see the Supporting Information). Furthermore, a range of malonate esters are tolerated (Table 3, entries 1, 2, 8, and 9).

Aliphatic aldimines of various steric demand were viable substrates (Table 3) in reactions catalyzed by **2a** and **2b**. Both cyclic and acyclic aliphatic imines afforded the corresponding Mannich products in excellent yield and enantioselectivity. The Mannich products can be readily decarboxylated to give the corresponding β-amino-acid derivatives[10,15] and, therefore, the present method allows the preparation of β^3-amino-acid[16] analogues of leucine (Table 3, entry 12) and valine (Table 3, entries 13 and 30). In reactions of aliphatic imines, various ester moieties on the malonates were tolerated, but the presence of sterically demanding moieties, as in diisopropyl malonate, resulted in slower reactions (Table 3, entry 29), and di-*tert*-butyl malonate was unreactive.[8] Finally, when 1 mol% of catalyst **2a** was used in a gram-scale reaction at a temperature amenable to large-scale reactions (−20°C) the product was obtained in excellent yield and enantioselectivity (Table 3, entry 30).

Further evidence for the proposed mode of action of catalyst **2a** was provided by computational studies. The Mannich reaction between malonic ester **3a** and aldimine **6d** (R′ = *i*Pr; Table 3) catalyzed by **2a** has been examined by density functional theory (DFT) calculations.[17] Conformational analysis of the catalyst indicates that the most stable form of **2a** in solution contains internal hydrogen bonds between the urea and thiourea moiety, allowing the cooperative action of the catalyst.[17]

An extensive conformational search for transition states for C–C bond formation that lead to the major and minor Mannich products, (*R*)-**7ad** and (*S*)-**7ad**, respectively, showed that imine activation occurs preferentially through a hydrogen-bond interaction between the imine nitrogen atom and the NH moiety proximal to the indane ring (Figure 3). The computational data reveal substantial differences between the relative Gibbs free energies of the **TS-*R*** and **TS-*S*** transition states (6.8 kcal mol^{-1}). This result is in line with the high enantioselectivities observed experimentally.

Structural analysis of these transition states suggest that the two reaction pathways have very different steric requirements. In **TS-*R***, the imine fits well into the cavity formed by the catalyst and the malonate, whereas in **TS-*S*** the Boc moiety of the imine has unfavorable steric interactions with the protonated amine and the indane ring units of the catalyst. The latter interaction results in significant charge separation because the malonate ion is displaced from its optimal position.

The imine nitrogen atom in **6d** is able to make only one hydrogen-bond contact with the catalyst in transition state **TS-*R*** (Figure 3). The high energetic cost in displacing the malonate from its optimal position means that only one hydrogen-bond-donor site is available for activation of the imine. However, even a single hydrogen-bond donor can provide significant substrate activation if its hydrogen-bond-donor capacity is enhanced by cooperative effects through an intramolecular hydrogen bond.[18]

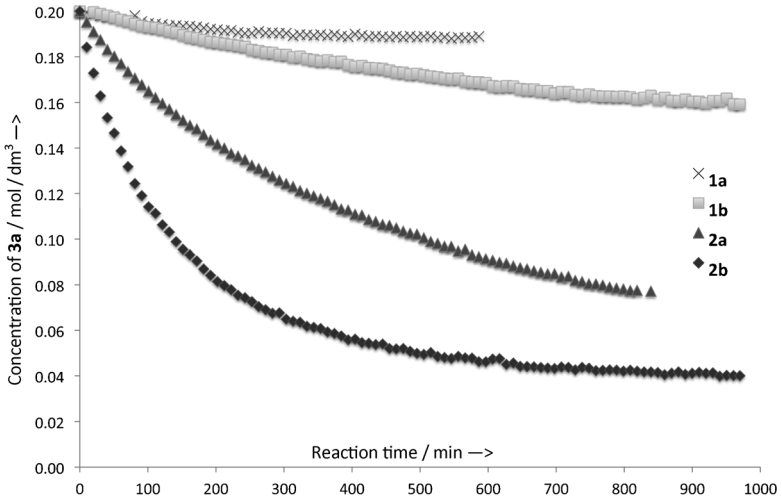
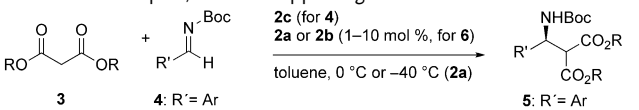


Figure 2. Comparison of the activity of the catalysts through in situ monitoring of the Mannich reaction of malonate **3a** with aliphatic imine **6a** through NMR spectroscopy (concentration of **3a** at t_0 is 0.2 M). Consumption of the malonate **3a** is monitored.

Table 3: Substrate scope with aliphatic and selected aromatic imines. For further examples, see the Supporting Information.[a]

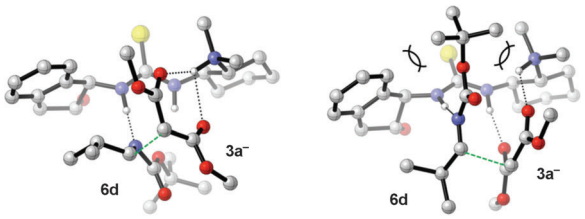


3 — **4**: R′= Ar, **6**: R′ = aliphatic — **5**: R′= Ar, **7**: R′ = aliphatic

Entry	Product	R	R′	*t* [h][b]	Yield [%][c]	e.r.[d]
1[e]	**5aa**	Me	Ph	48	80	99.6/0.4[f]
2[e]	**5ba**	Bn	Ph	16	95	99.3/0.7[f]
3	**5bc**	Bn	*p*-$CH_3C_6H_4$	24	93	98.3/1.7[f]
4	**5bd**	Bn	*p*-FC_6H_4	21	94	99.2/0.8[f]
5	**5bg**	Bn	*p*-$NO_2C_6H_4$	21	97	99.8/0.2
6	**5bh**	Bn	2-furyl	15	89	99.5/0.5[f]
7	**5bi**	Bn	2-naphthyl	24	87	98.0/2.0
8[e]	**5ca**	Et	Ph	45	95	99.4/0.6
9[e]	**5da**	*i*Pr	Ph	96	59	99.1/0.9
10	**7aa**	Me	cyclohexyl	22	91	96.7/3.3
11	**7ab**	Me	*n*Bu	14	99	98.4/1.6
12	**7ac**	Me	*i*Bu	24	96	99.3/0.7[f]
13	**7ad**	Me	*i*Pr	22	91	99.6/0.4
14	**7ae**	Me	Et	23	99	99.2/0.8
15	**7af**	Me	$PhCH_2CH_2$	20	99	98.2/1.8[f]
16	**7ag**	Me	$TBDPSO(CH_2)_2$	17	99	98.4/1.6
17	**7ah**	Me	cyclopentyl	24	99	99.2/0.8
18	**7ai**	Me	*n*-Hex	24	99	99.4/0.6
19	**7ba**	Bn	cyclohexyl	23	99	99.2/0.8[f]
20	**7ba**	Bn	cyclohexyl	14	99	0.3/99.7[g]
21	**7bb**	Bn	*n*Bu	22	99	1.3/98.7[g]
22	**7bc**	Bn	*i*Bu	22	98	0.6/99.4[g]
23	**7be**	Bn	Et	48	99	2.6/97.4[g]
24	**7bg**	Bn	$TBDPSO(CH_2)_2$	46	99	99.9/0.1
25	**7bh**	Bn	cyclopentyl	24	99	99.6/0.4
26[g]	**7bh**	Bn	cyclopentyl	22	99	3.3/96.7
27	**7bi**	Bn	*n*-Hex	24	96	98.2/1.2
28	**7ca**	Et	cyclohexyl	43	73	97.6/2.4
29	**7da**	*i*Pr	cyclohexyl	68	38	nd
30[h]	**7bd**	Bn	*i*Pr	24	98	98.1/1.9

[a] Reaction conditions: malonate **3** (0.15 mmol), imine **4** or **6** (0.45 mmol), catalyst **2c** (for imines **4**), **2a** or **2b** (for aliphatic imines **6**) (0.015 mmol, 10 mol%), toluene (0.75 mL), −40°C. [b] Reaction progress was monitored by TLC. [c] Yield of isolated product. [d] Determined by HPLC analysis. [e] **3** (0.15 mmol, 150 mol%), **4** (0.10 mmol, 100 mol%), catalyst **1b** (0.01 mmol, 10 mol%), toluene (0.5 mL) were used. [f] Absolute configuration determined by comparison of optical rotation with literature values. All other products have been assigned by analogy. [g] Reaction performed with catalyst **2b** at 0°C. [h] Reaction performed with 1.1 g of **3b** using 1 mol% of catalyst **2a** at −20°C. Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl.

In summary, we have identified bifunctional tertiary amine–thiourea catalysts, which contain a rigid *trans*-1,2-aminoindanol scaffold and a urea group that activates the thiourea group through intramolecular hydrogen bonds in a cooperative fashion. These catalysts promote the enantioselective Mannich reaction between malonates and both aliphatic and aromatic imines, thus providing a direct route to a wide variety of protected β^3-amino acids. Computational and X-ray data suggest that the intramolecular hydrogen bonds and the overall fold of the catalysts are maintained intact when the catalysts are unbound, when the catalysts are bound to the anionic substrate, and during C–C bond formation. Studies to expand the scope of these new catalysts as well as to understand the structural requirements for the stability of the catalyst conformation, and the anion binding properties of these catalysts, are in progress.



TS-*R* (0.0) **TS-*S*** (6.8)

Figure 3. Transition states located for organocatalytic Mannich reaction between **3a** and **6d** (R′ = *i*Pr). **3a**$^-$ denotes the malonate ion. The developing C–C bonds are illustrated by green dashed lines, whereas hydrogen bonds between the protonated catalyst and the substrates are illustrated as dotted lines. The urea moiety of the catalyst (linked to the indanol moiety) and the hydrogen atoms (except those of the NH moieties) are omitted for clarity. Computed relative Gibbs free energies (in kcal mol^{-1}) are shown in parenthesis.

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