Organocatalysis

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Conjugate-Base-Stabilized Brønsted Acids as Asymmetric Catalysts: Enantioselective Povarov Reactions with Secondary Aromatic Amines**

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Triggered largely by the seminal studies of Akiyama et al.[1] and Uraguchi and Terada[2] nearly a decade ago, the field of asymmetric Brønsted acid catalysis has experienced rapid growth.[3] Chiral phosphoric acids in particular have enabled an ever increasing number of asymmetric transformations.[3] In a continuing trend, catalysts that surpass the acidity of phosphoric acids are being prepared for the purpose of activating moderately basic substrates through asymmetric ion-pairing catalysis.[3,4] Cooperative approaches in which a Brønsted acid acts in concert with either another Brønsted acid[5] or with a (thio)urea catalyst[6] have emerged and hold exceptional promise.[7] Intriguing applications of asymmetric cooperative Brønsted acid catalysis have been reported by Jacobsen and co-workers who have demonstrated that a combination of achiral Brønsted acids and chiral (thio)urea catalysts can enable a range of enantioselective transformations.[8] The main role of the (thio)urea catalyst is to act as a chiral anion receptor for the Brønsted acid's conjugate base.[4,9,10] Herein we introduce a complementary concept for asymmetric Brønsted acid catalysis which merges certain features of previous approaches while perhaps offering some unique advantages.

As illustrated in Figure 1, we envisioned a new type of chiral Brønsted acid in which the acidic site of the catalyst is connected by an appropriate linker to an anion receptor moiety such as a thiourea.[11–13] Upon substrate protonation, the conjugate base associates with the anion recognition site,[14] thus resulting in the formation of a substrate/catalyst ion pair of type I. Alternatively, the catalyst could facilitate the condensation of two different substrates to result in an ion pair of type II. While the anion may still interact with the substrate through hydrogen bonding in the type I ion pair,[15] hydrogen bonding between the ions should be reduced markedly in the type II ion pair, thus resulting in strict ion pairing.[4j] Importantly, both types of ion pairs feature a rigid anion which should facilitate an efficient transfer of chirality.

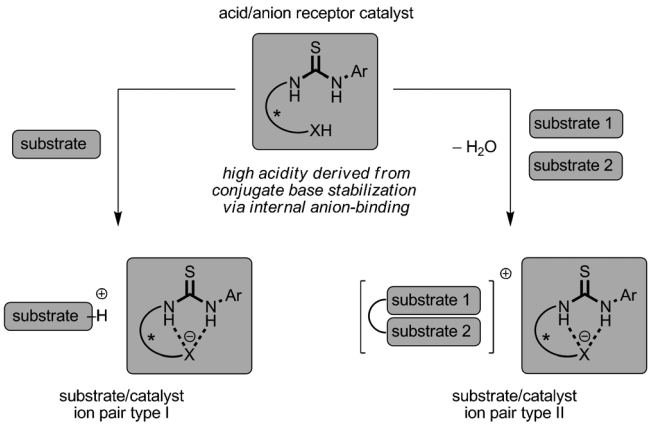

Figure 1. Internal anion-binding concept for asymmetric Brønsted acid/chiral anion catalysis.

While a range of acidic groups, XH, may be linked to an anion recognition site, we were particularly intrigued by the idea of using simple carboxylic acids. Although there are notable exceptions, in particular the prominent work of the Maruoka group, chiral carboxylic acids have not yet found widespread applications as asymmetric Brønsted acid catalysts.[16] This is likely because carboxylic acids are ultimately limited by their relatively weak acidities, thus restricting the number of substrates which can be activated. The propensity of carboxylate to engage in hydrogen bonding with a protonated substrate also reduces the potential level of substrate activation, as this interaction lowers the electrophilicity of the protonated species. Internal stabilization of the conjugate base (e.g., carboxylate) should circumvent both of these problems. Firstly, anion binding to the conjugate base is expected to lower the pK_a value of the acid, thus allowing an increase in acidity beyond what can typically be achieved for carboxylic acids. Secondly, internal anion binding reduces the ability of the carboxylate anion to participate in additional hydrogen-bonding interactions with the activated cationic substrate, thus increasing the electrophilicity of the latter. In addition, covalent attachment of the acidic site to the chiral acceptor as opposed to a dual catalysis approach addresses the potential issue of background reactivity caused by the achiral acid.

A number of chiral catalysts containing a carboxylic acid connected to an anion recognition site were readily assembled in as little as two steps (Figure 2).[17] We decided to test these catalysts in a challenging Povarov reaction[18] with indoline as

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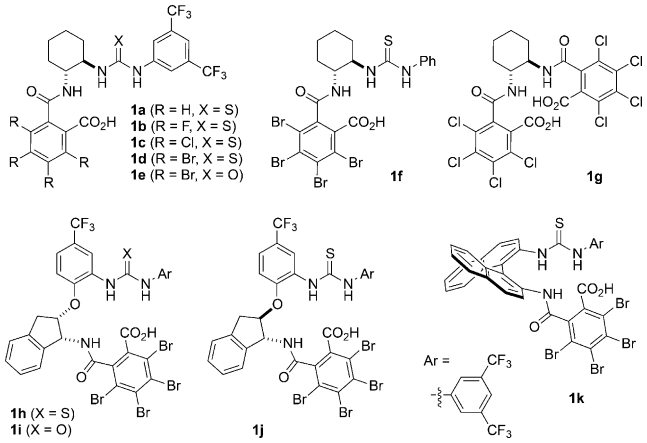
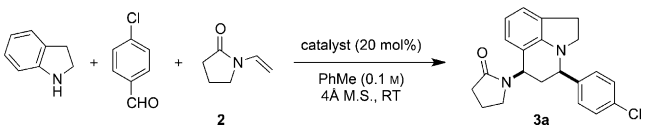


Figure 2. Catalysts evaluated in this study.

the amine to give the polycyclic products **3**, species which have previously been identified as potent tyrosine kinase inhibitors (see Table 1).[19] There has been significant recent interest in the development of asymmetric Povarov reactions.[20] Impressive results have been achieved with chiral Lewis acids,[21] although most studies have focused on asymmetric Brønsted acid catalysis.[22] Particularly noteworthy in this regard are the pioneering contributions by the groups of Akiyama,[22a] and Masson and Zhu.[22b] With the exception of Jacobsen's landmark contribution (combination of *ortho*-nitrobenzenesulfonic acid with a chiral urea catalyst),[8b] Brønsted acid catalysis of the Povarov reaction has been limited to chiral phosphoric acids.[20,22] Despite these advances, catalytic enantioselective Povarov reactions with secondary aromatic amines are all but unknown. This is probably at least in part due to the requirement of these reactions to involve strict ion pairs and the difficulty associated with controlling enantioselectivity in this context. In fact, in a number of previous reports on asymmetric Povarov reactions with imines derived from primary anilines, it was proposed that hydrogen-bond assisted ion pairs are a key element in controlling enantioselectivity.[20,22]

The three-component reaction of indoline, 4-chlorobenzaldehyde, and 1-vinylpyrrolidin-2-one (**2**) was selected as the model reaction to evaluate the potential of the new Brønsted acid catalysts (Table 1). Toluene was chosen as the solvent to facilitate the formation of tight ion pairs. The catalyst **1a**, prepared in one step from phthalic anhydride and the corresponding 1,2-cyclohexanediamine monothiourea,[17] was found to be capable of catalyzing this transformation. However, the reaction was sluggish and resulted in the recovery of racemic product (entry 1). A significant improvement with regard to both reactivity and selectivity was achieved with the tetrafluorophthalic-anhydride-derived catalyst **1b** (entry 2). The corresponding tetrachloro catalyst **1c** provided another marked increase in enantioselectivity (entry 3). While the tetrabromo catalyst **1d** displayed an almost identical level of selectivity, a dramatic increase in reactivity was observed (entry 4). The corresponding urea catalyst **1e** showed reduced activity and gave rise to product with lower *ee* value (entry 5). Replacement of the electron-withdrawing 3,5-bistrifluoromethyphenyl group[23] with

Table 1: Evaluation of chiral Brønsted acids in a three-component Povarov reaction with indoline.[a]



Entry	Catalyst	Solvent	*t* [h]	Yield [%]	*ee* [%]
1	**1a**	PhMe	96	24	0
2	**1b**	PhMe	96	51	28
3	**1c**	PhMe	96	57	58
4	**1d**	PhMe	72	75	59
5	**1e**	PhMe	96	77	36
6	**1f**	PhMe	96	48	28
7	**1g**	PhMe	48	0	–
8	**1h**	PhMe	60	71	11
9	**1i**	PhMe	72	72	3
10	**1j**	PhMe	96	64	0
11	**1k**	PhMe	72	68	23
12	**1d**	CH_3CN	12	77	0
13	**1d**	CH_2Cl_2	7	81	17
14	**1d**	Et_2O	30	79	34
15	**1d**	MTBE	15	85	31
16	**1d**	THF	48	74	0
17[b]	**1d**	PhMe	96	90	71
18[c,d,e]	**1d**	PhMe	110	94	92
19[d]	**1d**	PhMe	48	88	59
20[e]	**1d**	PhMe	96	74	61

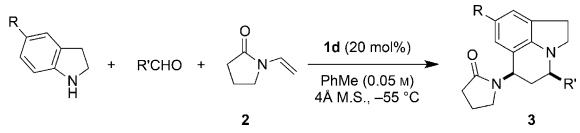
[a] Reactions were performed with 0.2 mmol of indoline and 1.02 equiv of each 4-Cl-benzaldehyde and **2**. Yields are those of chromatographically purified compounds. The *ee* values were determined by HPLC analysis; see the Supporting Information for details. [b] The reaction was conducted at 0 °C. [c] The reaction was conducted at −55 °C. [d] 2 equiv of each, 4-Cl-benzaldehyde and **2** were used. [e] The reaction was performed at a 0.05 M concentration. M.S. = molecular sieves, MTBE = methyl *tert*-butyl ether, THF = tetrahydrofuran.

a simple phenyl substituent (catalysts **1d** versus **1f**) also led to a drop in reactivity and selectivity (entry 6). The presence of a thiourea moiety was found to be crucial as the diacid **1g** failed to catalyze this transformation.[24] *Cis*- and *trans*-aminoindanol-derived urea and thiourea acid catalysts (**1h**–**j**) were all capable of promoting the title reaction but provided product with low *ee* values (entries 8–10). The 1,1′-binaphthyl-2,2′-diamine-based catalyst **1k** also showed a promising level of reactivity albeit poor selectivity (entry 11).

Continuing with the most promising catalyst, **1d**, various solvents were evaluated next. Perhaps not surprisingly, solvents with dielectric constants exceeding that of toluene resulted in product with reduced *ee* values (Table 1, entries 12–16). However, a reduction in temperature and solvent molarity resulted in improved *ee* values. The rate of the reaction could be increased by employing two equivalents of each 4-Cl-benzaldehyde and **2**. The best result was obtained in a reaction which was performed at −55 °C (entry 18). In the event, **3a** was isolated in 94% yield and with 92% *ee*.

The scope of the transformation was evaluated under the optimized conditions (Table 2). Indolines bearing different substituents at the 5-position readily underwent the three-

Table 2: Povarov reactions with selected indolines and aldehydes.[a]



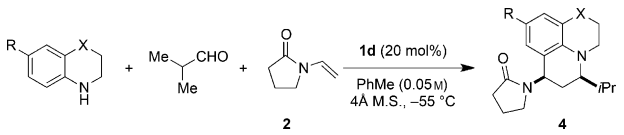
Entry	R	R′	*t* [h]	Product	Yield [%]	*ee* [%]
1	H	4-ClC_6H_4	110	**3a**	94	92
2	Cl	4-ClC_6H_4	120	**3b**	59	84
3	Br	4-ClC_6H_4	120	**3c**	76	86
4	Me	4-ClC_6H_4	96	**3d**	82	90
5	H	4-BrC_6H_4	96	**3e**	86	95
6	H	4-FC_6H_4	96	**3f**	76	93
7	H	4-CNC_6H_4	96	**3g**	92	91
8	H	3-$MeOC_6H_4$	96	**3h**	93	92
9	H	2-MeC_6H_4	120	**3i**	80	92
10	H	2-$MeOC_6H_4$	120	**3j**	59	93
11	H	C_6H_5	120	**3k**	71	79
12	H	3,4-$Cl_2C_6H_3$	96	**3l**	88	87
13	H	*i*Pr	24	**3m**	96	94
14	H	*i*Bu	26	**3n**	53	95
15	H	*t*Bu	96	**3o**	65	>99
16	H	neopentyl	96	**3p**	91	95
17	H	cyclohexyl	96	**3q**	51	90
18	H	cyclopentyl	12	**3r**	82	88

[a] Reactions were performed with 0.2 mmol of indoline and 0.4 mmol each of aldehyde and **2**. Yields are those of chromatographically purified compounds. The *ee* values were determined by HPLC analysis; see the Supporting Information for details.

component Povarov reaction with 4-chlorobenzaldehyde and **2** to produce products in good enantioselectivities (entries 1–4). Electronically diverse aromatic aldehydes with different substitution patterns provided the corresponding tetrahydroquinoline products in generally good yields and enantioselectivities (entries 5–12). Gratifyingly, aliphatic aldehydes were also viable substrates, affording products with excellent *ee* values (entries 13–18).

The scope of the Povarov reaction with regard to the amine was also explored (Table 3). High levels of enantioselectivity were observed with a number of tetrahydroquinolines (entries 1–3). Remarkably, while the dihydrobenzoxazine-derived product **4d** was obtained in 84% yield and near-perfect enantioselectivity (entry 4), the corresponding sulfur analogue was isolated in only 54% yield and 65% *ee* (entry 5). Finally, the tetrahydroquinoxaline-containing product **4f** was obtained with excellent selectivity (entry 6).

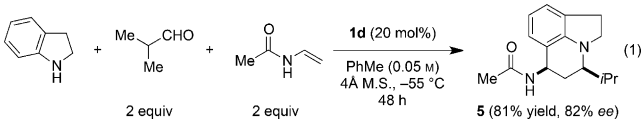
Table 3: Povarov reactions with selected secondary amines.[a]



Entry	R	X	*t* [h]	Product	Yield [%]	*ee* [%]
1	H	CH_2	48	**4a**	85	91
2	Me	CH_2	72	**4b**	74	93
3	MeO	CH_2	72	**4c**	82	97
4	H	O	72	**4d**	84	>99
5	H	S	96	**4e**	54	65
6	H	NCbz	72	**4f**[b]	65	97

[a] Reactions were performed with 0.2 mmol of amine and 0.4 mmol each of isobutyraldehyde and **2**. Yields are those of chromatographically purified compounds. The *ee* values were determined by HPLC analysis; see the Supporting Information for details. [b] Obtained as a 9:1 mixture of diastereomers. The *ee* value is given for the major diastereomer. Cbz = benzyloxycarbonyl.

Preliminary attempts to extend the scope to dienophiles other than **2** showed that substituted versions of **2** appear to be unreactive under the reaction conditions.[25] Simple vinyl ethers reacted relatively sluggishly.[26] However, *N*-vinylacetamide readily underwent the title reaction to provide product **5** in good yield, albeit with slightly diminished enantioselectivity [Eq. (1)].



While some of the catalysts (e.g., **1h–j**) might allow for the type of idealized bifurcated intramolecular hydrogen-bonding interaction as depicted in Figure 1, this scenario appeared less likely in the case of the most selective catalyst (**1d**). To obtain insights into the nature of conjugate base stabilization in the anionic form of **1d**, we prepared the corresponding tetrabutylammonium salt. The X-ray crystal structure of this salt is depicted in Figure 3. Interestingly, the anion was found to

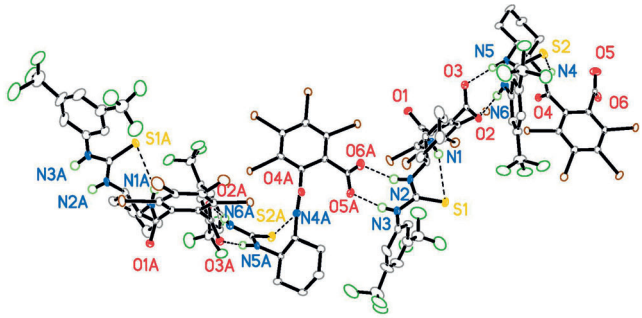


Figure 3. X-ray crystal structure of the tetrabutylammonium salt of catalyst **1d** (four repeating units).[28] For clarity, the tetrabutylammonium cations and solvent molecules are not shown. Only selected hydrogen atoms are depicted.

self-aggregate, thus resulting in a helical chain-type superstructure. Individual catalyst units interact through bifurcated binding of the carboxylate anion to the thiourea site of the neighboring molecule. In addition, the amide N–H proton is engaged in an internal hydrogen-bonding interaction with the thiourea sulfur atom of the same molecule, an interaction which likely increases the acidity of the thiourea site, thus contributing to better anion binding. It remains to be established whether or not this particular type of catalyst aggregation[27] is relevant to the catalytic process.

In summary, we have introduced conjugate-base-stabilized Brønsted acid catalysis as a new and highly generalizable

concept for asymmetric catalysis. The power of this design was demonstrated in the context of the first catalytic enantioselective Povarov reaction involving secondary aromatic amines such as indoline and tetrahydroquinoline. Further applications of this concept are currently being developed in our laboratory and will be reported in due course.

Experimental Section

General procedure: A flame dried vial was charged with 4-chlorobenzaldehyde (56 mg, 0.4 mmol, 2 equiv), **1d** (34 mg, 0.04 mmol, 0.2 equiv) and powdered 4 Å M.S. (100 mg). Freshly distilled toluene (4 mL) was added and the resulting mixture was cooled to −55 °C over 15 min. Indoline was then added (22.5 μL, 0.2 mmol, 1 equiv). After five minutes, 1-vinylpyrrolidin-2-one (**2**) (43 μL, 0.4 mmol, 2 equiv) was added and the reaction mixture was stirred at −55 °C. When indoline could no longer be detected by TLC analysis, triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was warmed to RT, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude reaction mixture purified by flash chromatography.

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