Asymmetric Catalysis

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A New Structural Motif for Bifunctional Brønsted Acid/Base Organocatalysis**

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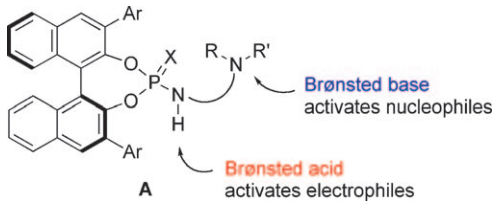
In recent years the concept of bifunctionality has enriched the field of asymmetric catalysis. Impressive progress has been made particularly in the area of enantioselective transition-metal catalysis,[1] but bifunctional organocatalysis is also being appreciated increasingly.[2] Indeed, various acids and bases have been combined to generate powerful organocatalysts that effectively orient substrates in an enzymelike manner. Remarkably though, the vast majority of these structures are based on natural products, such as proline and the cinchona alkaloids, whilst fully synthetic catalysts are rare.[3] Herein, we report the design and successful implementation of a new Brønsted acid/base motif for the highly enantioselective desymmetrization of *meso* anhydrides.

The alcoholytic catalytic asymmetric desymmetrization of *meso* anhydrides is a powerful strategy for the preparation of enantiomerically pure hemiesters, which are valuable building blocks for the synthesis of various natural products and biologically active substances.[4–6] Oda and Aitken pioneered a cinchona-alkaloid-catalyzed approach which furnished moderate enantioselectivities.[7,8] Bolm et al. developed a variant in which 110 mol% of either quinine or quinidine is utilized. This method generally provides excellent enantioselectivity (up to 99:1 e.r.) and is used frequently both in academic and industrial laboratories.[9] Later, Deng et al. introduced commercially available modified cinchona-alkaloid-derived Sharpless ligands $(DHQD)_2AQN$ and its pseudoenantiomer $(DHQ)_2AQN$ as catalysts (5–20 mol%), which also give high enantioselectivity.[10] More recently, Song et al. and Connon et al. observed highly enantioselective methanolyses of cyclic anhydrides catalyzed by cinchona-derived amine–thiourea bifunctional organocatalyst (10 mol%) at room temperature.[11,12] A remarkable breakthrough has been achieved very recently by Song et al.: they developed a robust cinchona-derived sulfonamide-based bifunctional organocatalyst, which shows unprecedented catalytic activity and excellent enantioselectivity in the methanolytic desymmetrization of *meso* cyclic anhydrides.[13]

Despite these important advances in bifunctional organocatalysis, modification of the cinchona alkaloids is limited, and access to both enatiomeric products with the same high enantioselectivity is not always ensured. Because of this and because new motifs for bifunctional organocatalysis are always needed, we became interested in exploring alternative fully synthetic structures. Our design is inspired by BINOL-derived phosphoric acids, recently introduced to asymmetric catalysis by Akiyama and Terada.[14] We were curious if it would be possible to incorporate a more basic site into such structures while retaining an acid functional group. We reasoned that this concept may be realized with structure **A** (Scheme 1), in which the base, which also has a Brønsted acidic site, is incorporated by means of a phosphoramide bond.[15]



Scheme 1. Design of a new bifunctional chiral Brønsted acid/base catalyst.

Indeed, several bifunctional chiral Brønsted acid/base catalysts (**3c–i**, Table 1, also see the Supporting Information) were synthesized from the corresponding optically active BINOL derivatives by phosphorylation or thiophosphorylation followed by amidation with aminopyridines or pyrimidines. Their catalytic activity and enantioselectivity were examined in the asymmetric methanolysis of *cis*-1,2-cyclohexanedicarboxylic anhydride (**1a**) in toluene in the presence of 10 equivalents of methanol. Remarkably, in comparison with phosphoric acid **3a** and phosphoramide **3b** (both of which are often considered bifunctional catalysts), the novel Brønsted acid/base catalyst **3c** was far more active and gave the corresponding hemiester product **2a** with a high enantioselectivity of 90:10 e.r. (Table 1, entries 1–3). We next studied the position of nitrogen in the pyridine ring; catalyst **3d**, which was prepared from 3-aminopyridine, was found to be less reactive and poorly enantioselective (Table 1, entry 4). Similarly, catalyst **3e** derived from 4-aminopyridine gave very low enantioselectivity and the opposite enantiomer of product **2a** (Table 1, entry 5). Also,when an additional basic site was introduced with the incorporation of 2-aminopyrimidine into catalyst **3f**, no improvement was observed (Table 1, entry 6). Furthermore, we investigated electronic effects with the electron-rich, DMAP-like catalyst **3g** and its electron-poor variant **3h**, which gave inferior results (Table 1, entries 7

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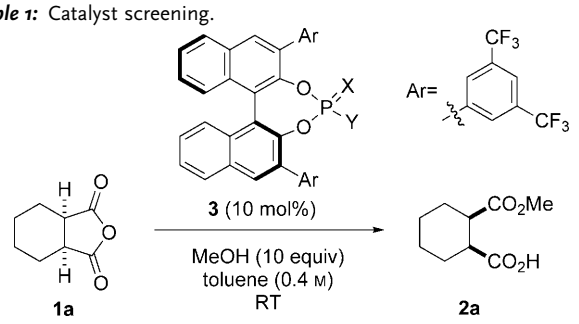
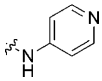
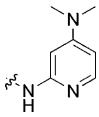
Table 1: Catalyst screening.



1a 2a

Entry	Cat.	X	Y	*t* [h]	Conv. [%][a]	e.r.[b]
1	**3a**	O	OH	24	80	61:39
2	**3b**	O	NHTf	24	80	0
3	**3c**	O		5	quant.	90:10
4	**3d**	O		8	quant.	60:40
5	**3e**	O		8	quant.	46:54
6	**3f**	O		8	quant.	74:26
7	**3g**	O		5	quant.	77:23
8	**3h**	O		23	95	77:23
9	**3i**	S		3	quant.	90:10
10[c]	**3i**	S		3	quant.	90:10
11[d]	**3i**	S		3	quant.	90:10
12[e]	**3i**	S		5	quant.	91:9
13[f]	**3i**	S		24	quant.	96:4

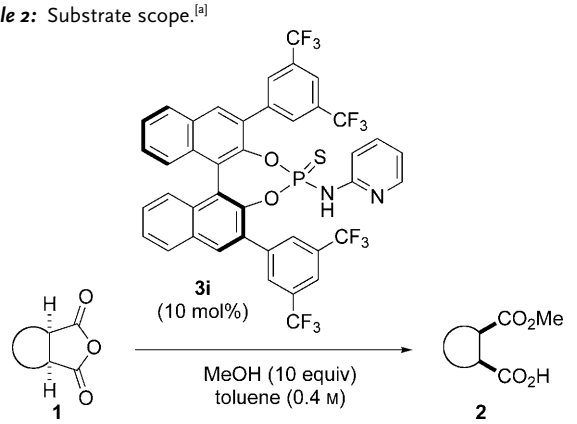
[a] From NMR analysis. [b] Determined by HPLC analysis on a chiral stationary phase (see the Supporting Information); quant. = quantitative. [c] The reaction was carried out in toluene (1.0 M). [d] The reaction was carried out in toluene (0.1 M). [e] The reaction was carried out at 0 °C. [f] The reaction was carried out at −35 °C.

and 8). Gratifyingly, we found that the sulfur analogue **3i** was more reactive than catalyst **3c** and just as enantioselective (Table 1, entry 9), and this catalyst was selected for further optimization. More interestingly, we found that the stereoselectivity of the Brønsted acid/base catalyst **3i** does not show significant concentration dependence (Table 1, entries 9–11).

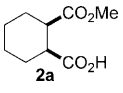
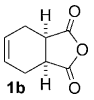
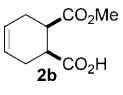
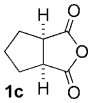
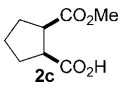
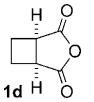
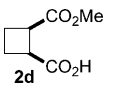
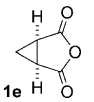
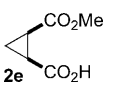
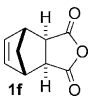
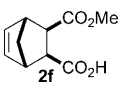
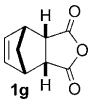
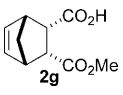
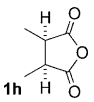
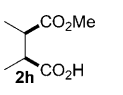
The bifunctional Brønsted acid/base catalyst **3i** proved to be a highly active catalyst and gave full conversion of **1a** to the desired product **2a** even at −35 °C. Moreover, at this temperature, the enantioselectivity increased to 96:4 e.r. (Table 1, entry 13).

With the promising bifunctional organocatalyst **3i** in hand, we next examined its scope and limitation in the desymmetrization of various *meso* cyclic anhydrides under optimized reaction conditions. As shown in Table 2, bicyclic (entries 1–5) and tricyclic anhydrides (entries 6 and 7) were readily converted into the corresponding hemiester products in high yields and enantioselectivities. Only in the case of cyclopropane derivative **1e** (entry 5 Table 2,) and the mono-

Table 2: Substrate scope.[a]



1 2

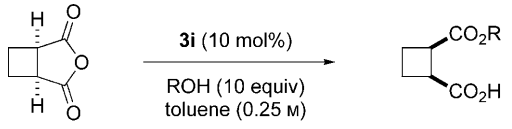
Entry	Anhydride	Product	*t* [d]	*T* [°C]	Yield [%][b]	e.r.[c]
1	 1a	 2a	1	−35	97	96:4
2	 1b	 2b	5	−30	92	95:5
3	 1c	 2c	5	−20	95	96:4
4[d]	 1d	 2d	1.5	−35	97	99:1
5[d,e]	 1e	 2e	4	−20	94	91:9
6[d]	 1f	 2f	6	−20	81	95:5
7[d,e]	 1g	 2g	6	−10	88	95:5
8[d]	 1h	 2h	4	−35	95	91:9

[a] Reaction scale: 0.5 mmol. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (see the Supporting Information). [d] The reaction was carried out in toluene (0.25 M). [e] The reaction was carried out with **3i** (15 mol%).

cyclic substrate **1h** (entry 8) were enantioselectivities below 95:5 e.r. observed.

The exceptionally high enantioselectivity in the methanolysis of cyclobutane anhydride **1d** (99:1 e.r.) to furnish hemiester product **2d** is particularly noteworthy when compared with the results obtained by employing the best known alternative methods (94:6/3:97 e.r. with Bolm's method using stoichiometric amounts of quinine or quinidine,[9b] 98:2 e.r. with Song's cinchona-derived sulfonamide catalyst, and 6:94 e.r. with Deng's method using $(DHQD)_2AQN$ as the catalyst (see the Supporting Information). In addition, using our methodology, the opposite enantiomer of **2d** can be prepared with the same enantioselectivity by using catalyst (*R*)-**3i** (Table 3, entry 2).

Table 3: Asymmetric alcoholysis of cyclic anhydride **1d** with different alcohols.[a]



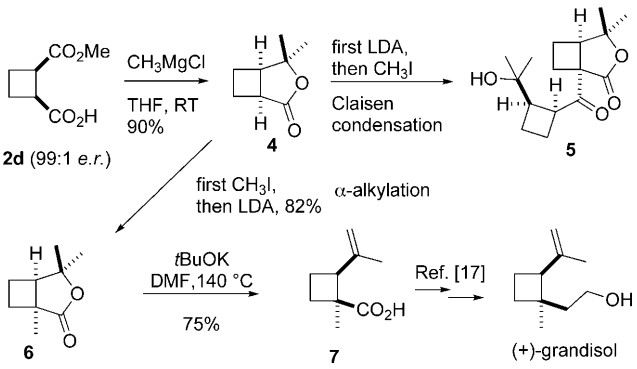
1d **2**

Entry	ROH	Hemiester	*T* [°C]	Yield [%][b]	e.r.[c]
1[d]	methanol	**2d**	−35	97	99:1
2[d,e]	methanol	*ent*-**2d**	−35	94	99:1
3[f]	ethanol	**2i**	−30	98	97:3
4[f]	1-propanol	**2j**	−30	93	98:2
5[f,g]	2-propanol	**2k**	10	91	97:3
6[f]	propargyl alcohol	**2l**	−30	91	97:3

[a] Reaction scale: 0.5 mmol. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (see the Supporting Information). [d] Reaction time: 36 h. [e] The reaction was carried out with (***R***)-**3i**. [f] Reaction time: 4 d. [g] The reaction was carried out in toluene (0.4 M).

The strength and scope of our methodology is further demonstrated in the alcoholysis of anhydride **1d** with different alcohols (Table 3). Rather independent of the steric demand of the alcohol, high enantioselectivity was also obtained in all cases including those with ethanol, 1-propanol, 2-propanol, and propargyl alcohol (Table 3, entries 3–6).

To illustrate the synthetic utility of our methodology, a short formal synthesis of (+)-grandisol, the main component of the sex pheromone of the cotton boll weevil, *Anthonomous grandis* Boheman, and other insects, was developed (Scheme 2).[16] As shown before (Table 3, entry 1), methanolysis of anhydride **1d** gave the corresponding hemiester **2d** in 97% yield and in 99:1 e.r. Upon treatment of ester **2d** with MeMgCl, lactone **4** was formed in 90% yield. Surprisingly, we found that when we tried to obtain the corresponding α-methylated lactone **6** by sequential addition of lithium diisopropylamide (LDA) to lactone **4** followed by MeI at −78°C only Claisen condensation product **5** was formed. Remarkably though, the intended α-alkylation could indeed be effected by adding LDA to a premixed solution of lactone **4** and MeI at −78°C. Under these conditions, lactone **6** was obtained in gratifying 82% yield. Finally, we found that



Scheme 2. Formal synthesis of (+)-grandisol.

subjecting lactone **6** to potassium tert-butoxide in DMF at higher temperature resulted in the clean elimination furnishing carboxylic acid **7** in 75% yield. The absolute configuration of intermediate **7** was determined by comparison of its optical rotation with the literature value.[17] Olefin **7** has already been transformed into (+)-grandisol, and our sequence therefore constitutes a formal synthesis.[17,18] In fact, of the catalytic asymmetric total syntheses of grandisol reported to date, our synthesis requires the fewest steps.

In conclusion, we have successfully developed a novel bifunctional chiral Brønsted acid/base organocatalyst **3i**, which shows good catalytic activity and good to excellent enantioselectivity in the methanolytic desymmetrization of a variety of *meso* cyclic anhydrides. Alcohols other than methanol were effective nucleophiles in the desymmetrization reaction and also provided excellent enantioselectivities. In addition, the synthetic utility of this methodology was demonstrated with the formal synthesis of (+)-grandisol. We are currently investigating the intriguing mode of action of our novel organocatalyst motif as well as its application in other transformations.

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