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Conjugate-Base-Stabilized Brønsted Acids: Catalytic Enantioselective Pictet–Spengler Reactions with Unmodified Tryptamine

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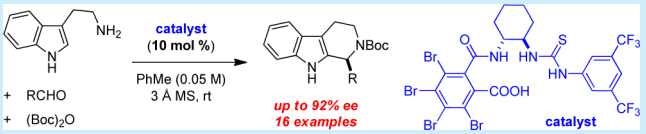
Supporting Information

ABSTRACT: A conjugate-base-stabilized Brønsted acid facilitates catalytic enantioselective Pictet–Spengler reactions with unmodified tryptamine. The chiral carboxylic acid catalyst is readily assembled in just two steps and enables the formation of β-carbolines with up to 92% ee. Achiral acid additives or in situ Boc-protection facilitate catalyst turnover.

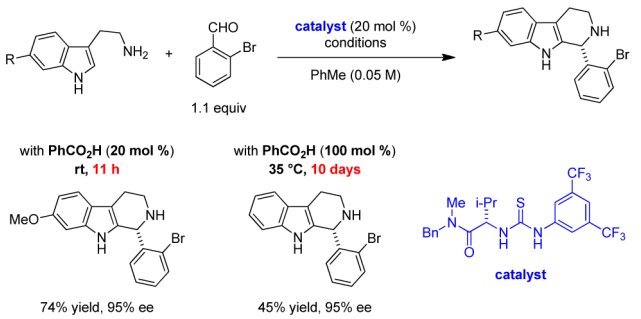


Over a century after its discovery, the Pictet–Spengler reaction[1] continues to pose challenges with regard to enantioselective catalysis.[2] Methods to access chiral tetrahydroisoquinolines via catalytic enantioselective Pictet–Spengler approaches remain elusive, and there is still no general solution to the prototypical Pictet–Spengler reaction of unmodified tryptamine with simple aldehydes.[2] The major difficulty in rendering these transformations catalytic enantioselective lies in the relatively low electrophilicity of β-phenylethylamine- or tryptamine-derived imines or iminium ions. A further challenge is posed by the enhanced basicity of the products over the starting materials, leading to problems of product inhibition and catalyst turnover. Here we report a strategy that addresses some of these limitations.

All challenges notwithstanding, impressive advances in asymmetric Pictet–Spengler methodology have been made in recent years.[2] While some issues have been addressed with stoichiometric[3] and enzymatic[4] approaches, the first small-molecule catalyzed enantioselective variant was reported by the Jacobsen group in 2004.[5] Their elegant strategy was based on in situ generated acyliminium ions, thus overcoming the inherently low reactivity of the corresponding imines.[6] Alternative approaches by List, Hiemstra, Jacobsen, and others have focused on modified tryptamines[7] and related but more reactive arylamines.[8] Catalytic enantioselective Pictet–Spengler reactions have also been reported with relatively electrophilic imines derived from isatin and tryptamine.[9] In addition, interesting catalytic enantioselective cascade approaches have been disclosed that involve a diastereoselective Pictet–Spengler step.[10]

An insightful study by Jacobsen et al. nicely illustrates the difficulty one faces when attempting to develop an enantioselective Pictet–Spengler reaction with unmodified tryptamine (Scheme 1).[7e] A reaction of 6-methoxytryptamine with 2-bromobenzaldehyde, performed at rt for 11 h and catalyzed by 20 mol % of each a thiourea catalyst and benzoic acid, readily provided the corresponding product in good yield and excellent ee. In stark contrast, the otherwise identical reaction with unmodified tryptamine required one equivalent of

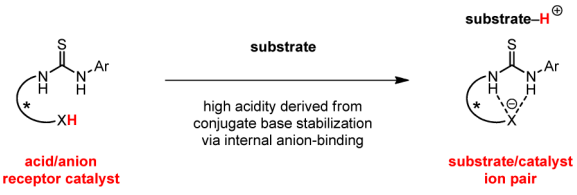
Scheme 1. Precedent by Jacobsen et al.



benzoic acid and elevated temperatures. Following an extended reaction time of 10 days, the expected product was isolated in moderate yield albeit with excellent ee.

We were hoping to overcome the low reactivity of tryptamine-derived iminium ions by applying our concept of internally conjugate-base-stabilized Brønsted acid catalysis (Scheme 2).[11,12] In essence, the cooperative action[13,14] of a catalyst with an acidic functional group and a covalently linked anion-recognition site[15−17] is thought, upon substrate protonation, to result in a rigid substrate/catalyst ion pair. Since hydrogen bonding between the ions is expected to be

Scheme 2. Internal Anion-Binding Concept for Asymmetric Brønsted Acid/Chiral Anion Catalysis



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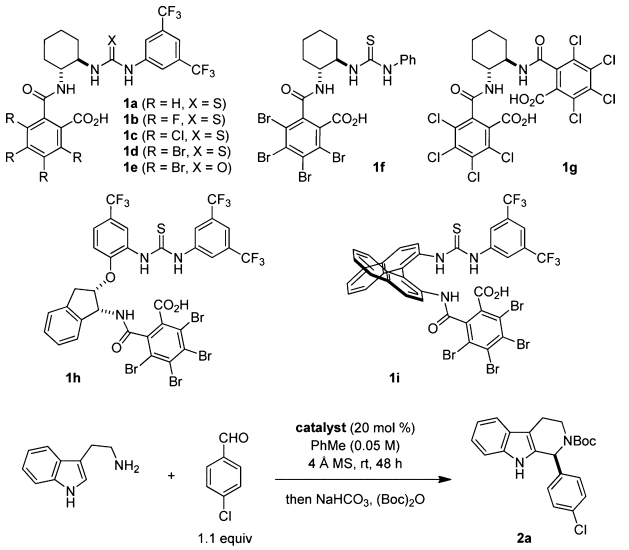
minimized in this scenario, the protonated substrate should display enhanced electrophilicity.

A number of carboxylic acids equipped with anion-recognition sites were evaluated for their ability to catalyze Pictet–Spengler reactions in enantioselective fashion.[18] The reaction of tryptamine with *p*-chlorobenzaldehyde was selected as the model reaction (Table 1). Due to the known sensitivity

Table 1. Evaluation of Catalysts[a]



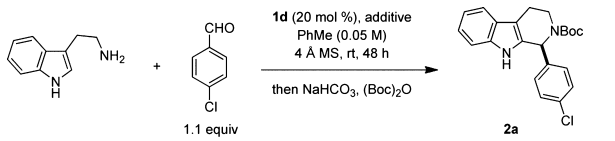
entry	catalyst	time (h)	yield (%)	ee (%)
1	**1a**	48	NR	
2	**1b**	48	10	20
3	**1c**	48	33	92
4	**1d**	48	37	94
5	**1e**	48	9	66
6	**1f**	48	NR	
7	**1g**	48	NR	
8	**1h**	48	NR	
9	**1i**	48	38	56
10	**1d**	72	36	94
11	**1d**	96	38	94

[a]Reactions were performed on a 0.2 mmol scale. Yields are isolated yields (over two steps) of chromatographically purified compounds. The ee's were determined by HPLC analysis.

of the products[7e] and to facilitate ee determination, the initially formed tetrahydro-*β*-carbolines were Boc-protected prior to purification. As summarized in entries 1–8, a number of catalysts were capable of promoting the title reaction while others proved to be unreactive. The best result was obtained with catalyst **1d** (entry 4), a carboxylic acid that is readily available in just two steps from (1*R*,2*R*)-cyclohexane-1,2-diamine.[11] Following a reaction time of 48 h, product **2a** was isolated in only 37% yield but with excellent enantioselectivity (94% ee). Unfortunately, extension of the reaction time to 72 or 96 h did not result in any noticeable increase in yield (entries 10 and 11). These results are indicative of product inhibition.

In order to improve catalyst turnover, we evaluated a number of achiral Brønsted acids as additives (Table 2).[19] The rationale for these experiments is based on the idea that an achiral acid that by itself is incapable of promoting the racemic background reaction may serve to protonate the product thus reducing the degree of product inhibition. A poorly soluble acidic additive

Table 2. Evaluation of Acid Additives[a]



entry	additive (mol %)	yield (%)	ee (%)
1	acetic acid (100)	37	85
2	benzoic acid (100)	16	80
3	4-trifluoromethylbenzoic acid (100)	41	79
4	Amberlyst 15 (200)	21	81
5	Amberlite CG-50 (200)	32	94
6	3,5-bis(trifluoromethyl) benzoic acid (100)	81	36
7	trifluoroacetic acid (100)	95	rac
8	terephthalic acid (100)	37	94
9	oxalic acid (100)	85	95
10	malonic acid (100)	>95	93
11	citric acid (100)	34	92
12[b]	malonic acid (100)	48	94

[a]See footnote a, Table 1. [b]with 10 mol % of catalyst **1d**.

may be ideal as it could cause the formation of relatively insoluble product salts, again facilitating catalyst turnover. Interestingly, addition of acetic acid (which is incapable of promoting the title reaction by itself) led to a slight but measurable drop in enantioselectivity without having an effect on the yield (entry 1). Benzoic acid led to a more pronounced drop in yield and ee (entry 2). A number of other acids including immobilized acids did not have a positive effect on the reaction outcome. Relatively strong acids such as 3,5-bis(trifluoromethyl)benzoic acid and trifluoroacetic acid improved substrate conversion (entries 6 and 7). However, the ee of the product dropped dramatically in these instances. Remarkable improvements in conversion without adverse effect on ee were observed with the relatively strong but poorly soluble oxalic acid (entry 9) and malonic acid (entry 10). Malonic acid as an additive provided the best result, resulting in near quantitative yield of product **2a** with 93% ee. Unfortunately, an attempt to lower the catalyst loading to 10 mol % without extending the reaction time led to incomplete conversion (entry 12). Furthermore, it proved difficult to extend the use of malonic acid as an additive to other aldehydes.

As an alternate strategy that could serve to circumvent or at least reduce product inhibition, we explored the in situ Boc protection of the tetrahydro-*β*-carboline product. To facilitate this pathway and to minimize the formation of *N*-Boc-tryptamine,[20] aldehyde and tryptamine were allowed to first undergo imine formation in situ by stirring for 12 h in the presence of molecular sieves prior to the addition of catalyst **1d** and $(Boc)_2O$. This proved to be a viable strategy that allowed for a reduction in catalyst loading to 10 mol %.[21] Furthermore, the replacement of 4 Å MS with 3 Å MS was found to have a beneficial effect on substrate conversion without affecting product ee's.

A range of electronically diverse benzaldehydes with different substitution patterns were tested under the optimized conditions (Scheme 3). Benzaldehydes bearing electron-withdrawing substituents in the *para* position formed the corresponding tetrahydro-*β*-carbolines in high yields and enantioselectivities (**2a–e**). While simple benzaldehyde also produced the corresponding product (**2h**) in good selectivity,

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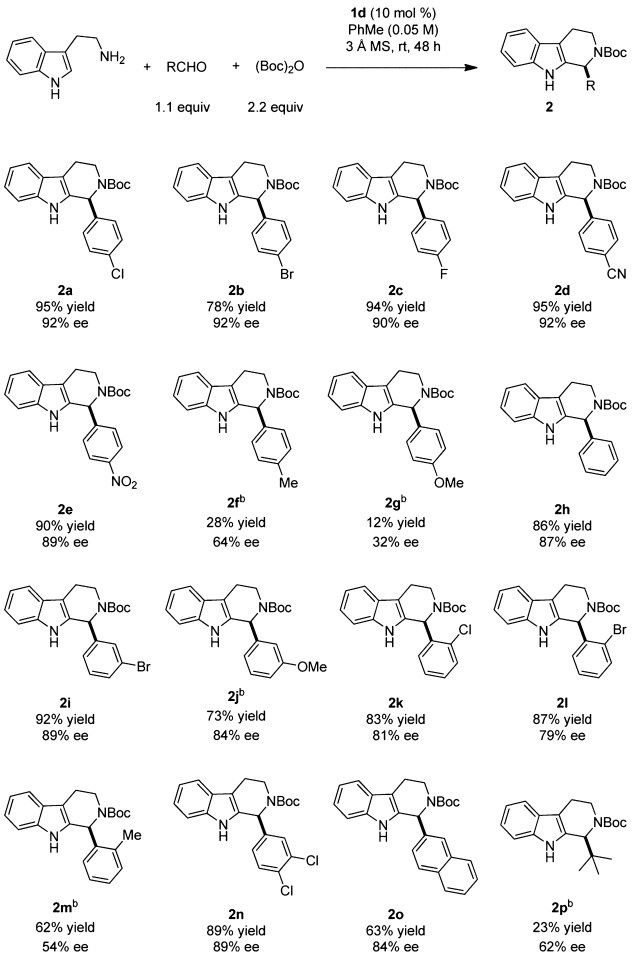
Scheme 3. Scope of the Pictet–Spengler Reaction[a]



[a]Reactions were performed on a 0.2 mmol scale. Aldehyde and tryptamine were allowed to stir in toluene in the presence of 3 Å MS for 12 h prior to addition of **1d** and $(Boc)_2O$. Yields are isolated yields of chromatographically purified compounds. The ee's were determined by HPLC analysis. See the Supporting Information for further details. [b]Reaction was run for 96 h.

p-methyl- and *p*-methoxybenzaldehyde were found to be poor substrates. The reaction was less sensitive to substitution on other positions of the phenyl ring. Products derived from aliphatic aldehydes were obtained in poor yields and modest enantioselectivities. Overall, the substrate scope complements that of Jacobsen's acyl-Pictet–Spengler reaction with tryptamine, which is ideally suited for aliphatic but not aromatic aldehydes.[5]

In summary, we have demonstrated the utility of conjugate-base-stabilized Brønsted acid catalysis in the context of challenging Pictet–Spengler reactions with unmodified tryptamine. Further applications of this concept are currently being developed in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, including an X-ray crystal structure of product **2i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

(2) Selected reviews on the Pictet–Spengler reaction and the biological relevance of tetrahydroisoquinolines and tetrahydro-*β*-carbolines: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (c) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (d) Youn, S. W. *Org. Prep. Proced. Int.* **2006**, *38*, 505. (e) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532. (f) Lorenz, M.; Van Linn, M. L.; Cook, J. M. *Curr. Org. Synth.* **2010**, *7*, 189. (g) Stockigt, J.; Antonchick, A. P.; Wu, F. R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538. (h) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.

(3) Selected Pictet–Spengler reactions with stoichiometric chiral promoters: (a) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348. (b) Bou-Hamdan, F. R.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2403.

(4) Selected reports on enzymatic Pictet–Spengler reactions: (a) Luk, L. Y. P.; Bunn, S.; Liscombe, D. K.; Facchini, P. J.; Tanner, M. E. *Biochemistry* **2007**, *46*, 10153. (b) Maresh, J. J.; Giddings, L. A.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stockigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 710.

(5) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

(6) Selected enantioselective acyl-Pictet–Spengler reactions: (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (b) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745. (c) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577. (d) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796. (e) Holloway, C. A.; Muratore, M. E.; Storer, R. l.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720. (f) Cai, Q.; Liang, X. W.; Wang, S. G.; Zhang, J. W.; Zhang, X.; You, S. L. *Org. Lett.* **2012**, *14*, 5022. (g) Aillaud, I.; Barber, D. M.; Thompson, A. L.; Dixon, D. J. *Org. Lett.* **2013**, *15*, 2946. (h) Toda, Y.; Terada, M. *Synlett* **2013**, *24*, 752.

(7) Catalytic enantioselective Pictet–Spengler reactions with modified tryptamines: (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (b) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485. (c) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405. (d) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; Gelder, R. d.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2009**, *11*, 2579. (e) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887. (f) Wanner, M. J.; Claveau, E.; van Maarseveen, J. H.; Hiemstra, H. *Chem.—Eur. J.* **2011**, *17*, 13680. (g) Rueping, M.; Volla, C. M. R. *RSC Adv.* **2011**, *1*, 79. (h) Huang, D.; Xu, F. X.; Lin, X. F.; Wang, Y. G. *Chem.—Eur. J.* **2012**, *18*, 3148. (i) Cai, Q.; Liang, X. W.; Wang, S. G.; You, S. L. *Org. Biomol. Chem.* **2013**, *11*, 1602.

(8) Catalytic enantioselective Pictet–Spengler reactions with other arylamines: (a) He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4490. (b) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564. (c) Cheng, D. J.; Wu, H. B.; Tian, S. K. *Org.*

dx.doi.org/10.1021/ol403773a | *Org. Lett.* XXXX, XXX, XXX–XXX

Lett. **2011**, *13*, 5636. (d) Li, Y.; Su, Y.-H.; Dong, D.-J.; Wu, Z.; Tian, S.-K. *RSC Adv.* **2013**, *3*, 18275.

(9) (a) Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. *Adv. Synth. Catal.* **2011**, *353*, 860. (b) Badillo, J. J.; Silva-Garcia, A.; Shupe, B. H.; Fettinger, J. C.; Franz, A. K. *Tetrahedron Lett.* **2011**, *52*, 5550. (c) MacDonald, J. P.; Badillo, J. J.; Arevalo, G. E.; Silva-García, A.; Franz, A. K. *ACS Comb. Sci.* **2012**, *14*, 285.

(10) Examples of catalytic enantioselective cascade reactions that involve a diastereoselective Pictet−Spengler step: (a) Franzén, J.; Fisher, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 787. (b) Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, *352*, 499. (c) Wu, X. Y.; Dai, X. Y.; Nie, L. L.; Fang, H. H.; Chen, J.; Ren, Z. J.; Cao, W. G.; Zhao, G. *Chem. Commun.* **2010**, *46*, 2733. (d) Fang, H.; Wu, X.; Nie, L.; Dai, X.; Chen, J.; Cao, W.; Zhao, G. *Org. Lett.* **2010**, *12*, 5366. (e) Rueping, M.; Volla, C. M. R.; Bolte, M.; Raabe, G. *Adv. Synth. Catal.* **2011**, *353*, 2853. (f) Wu, X.; Dai, X.; Fang, H.; Nie, L.; Chen, J.; Cao, W.; Zhao, G. *Chem.—Eur. J.* **2011**, *17*, 10510. (g) Hong, B.-C.; Liao, W.-K.; Dange, N. S.; Liao, J.-H. *Org. Lett.* **2013**, *15*, 468.

(11) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem.* **2013**, *52*, 14084.

(12) Selected reviews on asymmetric Brønsted acid catalysis: (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Terada, M. *Synthesis* **2010**, 1929. (d) Cheon, C. H.; Yamamoto, H. *Chem. Commun.* **2011**, *47*, 3043. (e) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (f) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 6706.

(13) Selected recent reviews on cooperative catalysis: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999. (c) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. (d) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6216. (e) Briere, J. F.; Oudeyer, S.; Dalla, V.; Levacher, V. *Chem. Soc. Rev.* **2012**, *41*, 1696. (f) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633.

(14) Examples of cooperative behavior involving (thio)urea and other acidic groups: (a) Shi, Y. L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129. (b) Weil, T.; Kotke, M.; Kleiner, C. M.; Schreiner, P. R. *Org. Lett.* **2008**, *10*, 1513. (c) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464. (d) Jones, C. R.; Pantos, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 7391. (e) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (f) Zhang, Z. G.; Lippert, K. M.; Hausmann, H.; Kotke, M.; Schreiner, P. R. *J. Org. Chem.* **2011**, *76*, 9764. (g) Marques-Lopez, E.; Alcaine, A.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2011**, 3700. (h) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578. (i) Probst, N.; Madarasz, A.; Valkonen, A.; Papai, I.; Rissanen, K.; Neuvonen, A.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8495. (j) Chen, X. J.; Zhu, W.; Qian, W. K.; Feng, E. G.; Zhou, Y.; Wang, J. F.; Jiang, H. L.; Yao, Z. J.; Liu, H. *Adv. Synth. Catal.* **2012**, *354*, 2151. (k) Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554. (l) Lin, S.; Jacobsen, E. N. *Nature Chem.* **2012**, *4*, 817. (m) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 1891. (n) Nickerson, D. M.; Angeles, V. V.; Auvil, T. J.; So, S. S.; Mattson, A. E. *Chem. Commun.* **2013**, *49*, 4289. (o) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 10089.

(15) Selected reviews on chiral-anion catalysis: (a) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373. (b) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073. (c) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (d) Beckendorf, S.; Asmus, S.; Mancheno, O. G. *ChemCatChem* **2012**, *4*, 926. (e) Avila, E. P.; Amarante, G. W. *ChemCatChem* **2012**, *4*, 1713. (f) Wenzel, M.; Hiscock, J. R.; Gale, P. A. *Chem. Soc. Rev.* **2012**, *41*, 480. (g) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nature Chem.* **2012**, *4*, 603. (h) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. (i) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534.

(16) Examples of anion-binding catalysis: (a) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434. (b) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779. (c) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (d) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358. (e) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (f) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286. (g) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558. (h) Kim, H. Y.; Oh, K. *Org. Lett.* **2011**, *13*, 1306. (i) Opalka, S. M.; Steinbacher, J. L.; Lambiris, B. A.; McQuade, D. T. *J. Org. Chem.* **2011**, *76*, 6503. (j) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872. (k) Wang, Y.; Yu, T. Y.; Zhang, H. B.; Luo, Y. C.; Xu, P. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12339. (l) Beckendorf, S.; Asmus, S.; Muck-Lichtenfeld, C.; Mancheno, O. G. *Chem.—Eur. J.* **2013**, *19*, 1581. (m) Schafer, A. G.; Wieting, J. M.; Fisher, T. J.; Mattson, A. E. *Angew. Chem., Int. Ed.* **2013**, 11321. (n) Borovika, A.; Tang, P.-I.; Klapman, S.; Nagorny, P. *Angew. Chem.* **2013**, *52*, 13424. See also ref 14.

(17) Our previous work on anion-binding catalysis: (a) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060. (b) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624. (c) Klauber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011**, *13*, 2464. (d) De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538. (e) De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 16802. (f) Mittal, N.; Sun, D. X.; Seidel, D. *Org. Lett.* **2012**, *14*, 3084. (g) Min, C.; Mittal, N.; De, C. K.; Seidel, D. *Chem. Commun.* **2012**, *48*, 10853.

(18) Examples of chiral carboxylic acids acting as Brønsted acid catalysts: (a) Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 3519. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080. (c) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (d) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556. (e) Ube, H.; Fukuchi, S.; Terada, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1203. (f) Hashimoto, T.; Kimura, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6844. (g) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nature Chem.* **2011**, *3*, 642. (h) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3489. (i) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 7279. (j) Hashimoto, T.; Gálvez, A. O.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 17667.

(19) Examples of cooperative catalysis of chiral and achiral Brønsted acids: (a) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141. (b) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832. (c) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2007**, 1441. (d) Li, G. L.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075. (e) Ren, H.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 5656.

(20) Control experiments have shown that *N*-Boc-tryptamine does not undergo the formation of products **2** under the reaction conditions.

(21) A potential acyl-iminium pathway was ruled out due to the relatively low electrophilicity of $(Boc)_2O$ and based on the fact that products were isolated with nearly identical ee's as in the case of the stepwise approach.