Organocatalysis

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Catalytic Enantioselective Synthesis of Lactams through Formal [4+2] Cycloaddition of Imines with Homophthalic Anhydride

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Abstract: *An amide-thiourea compound, operating through a novel ion pairing mechanism, is an efficient organocatalyst for the asymmetric reaction of homophthalic anhydride with imines. N-aryl and N-alkyl imines readily undergo formal [4+2] cycloaddition to provide lactams with high levels of enantio- and diastereoselectivity. The nature of the key chiral ion pair intermediate was elucidated by DFT calculations.*

Formal [4+2] cycloadditions of enolizable anhydrides and imines, first disclosed by Castagnoli, provide a powerful platform for the preparation of valuable lactams (Figure 1).[1]

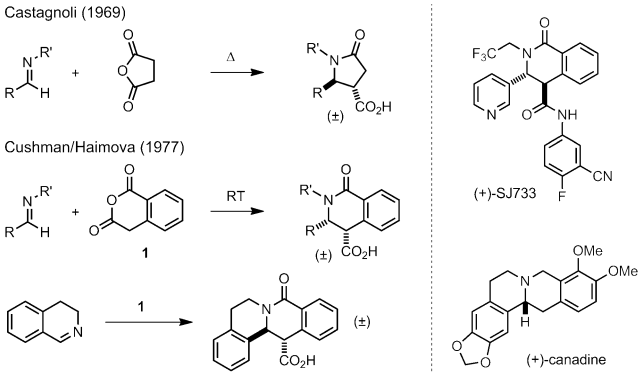

Figure 1. Access to pharmacophores through the reaction of enolizable anhydrides and imines.

While early reports focused on succinic anhydride and acyclic imines, this chemistry was later expanded by Cushman and Haimova to include homophthalic anhydrides (e.g., **1**) and dihydroisoquinolines,[2] thereby enabling the synthesis of a number of tetrahydroprotoberberine alkaloids such as (+)-canadine.[3] Small molecules with the same structural motif have been investigated as antimalarials (e.g., (+)-SJ733)[4] and as anti-cancer agents, among others.[5]

Owing to the utility of the lactam products, numerous combinations and variations of the imine and anhydride structures have been explored.[6] Significant efforts have been devoted to rendering these reactions asymmetric.[7] However, a catalytic enantioselective variant has remained elusive.[8,9] Here we present an asymmetric ion pairing approach that provides the first solution to this long-standing challenge.

Different mechanisms have been proposed for the title reaction, including an iminolysis pathway and a concerted [4+2] cycloaddition.[6,10] The perhaps most plausible mechanism for the reaction of homophthalic anhydride **1** with simple imines is shown in Figure 2. Imine and homophthalic

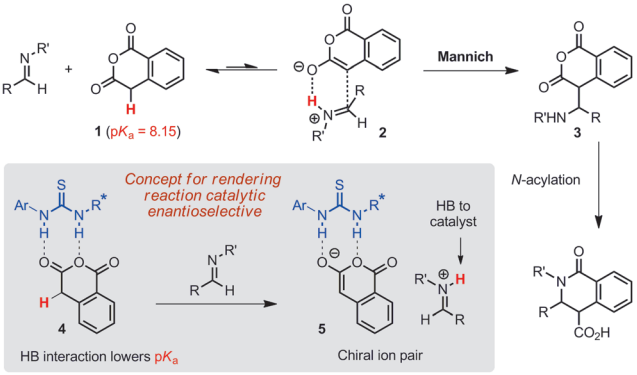

Figure 2. Proposed mechanism and ion pairing concept for enantioselective catalysis.

anhydride **1** are thought to form the hydrogen-bonded ion pair **2** in equilibrium. Ion pair **2**, which depending on the degree of proton transfer may also be considered as a complex of the imine with the enol form of the anhydride, undergoes a stereodetermining Mannich addition. The resulting intermediate **3** then engages in intramolecular aminolysis of the anhydride to form the lactam product. This scenario is supported by recent computational studies on closely related reactions of imines with α-cyanosuccinic anhydride,[11] and is consistent with the relatively high acidity of **1** ($pK_a = 8.15$).[12]

Since classic modes of substrate activation appeared unsuitable, we conceived of a new anion binding/ion pairing approach in order to render this reaction catalytic enantioselective (Figure 2).[13–15] Our concept is based on the notion that a hydrogen-bonding (HB)[16] catalyst, which itself remains neutral throughout the reaction, can confer enantioselectivity by simultaneously interacting with an anionic nucleophile and a cationic electrophile. Specifically, we envisioned that the interaction of a chiral thiourea catalyst

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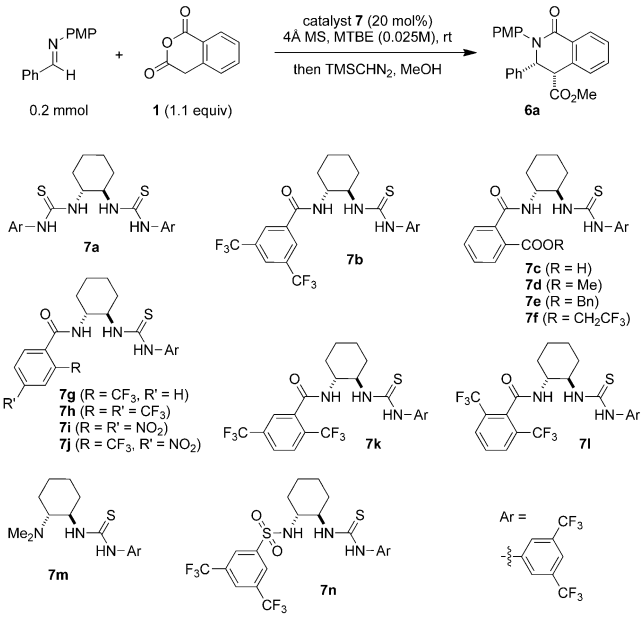
with homophthalic anhydride **1** would result in increased substrate acidity via complex **4**. This in turn would lower the barrier for ion pair formation, thereby enabling the generation of chiral ion pair **5**. Viewed from a different perspective, the presence of an anion receptor is expected to increase the equilibrium concentration of any ion pair intermediate. Interaction of the iminium ion in **5** with a secondary hydrogen-bonding acceptor site on the catalyst would contribute to the creation of a well-defined ion pair that is set up for an enantioselective Mannich addition step.

We initiated our survey with benzaldehyde-derived *N*-PMP imine and **1** (Table 1). In the absence of any catalyst, product **6a** was formed in 33% yield after 18 h (entry 1, reaction incomplete). The Nagasawa catalyst **7a**,[17] previously shown to be an efficient anion-binding catalyst,[14b] provided product **6a** in good yield, excellent d.r., and moderate *ee* (entry 2). Amide-thiourea catalyst **7b**[14c] provided significant improvements with regard to *ee* (entry 3). Unexpectedly, application of Brønsted acid catalyst **7c**[14g] resulted in further improvements (entry 4). However, the carboxylic acid functionality of **7c** apparently plays no role in the catalytic process, since the corresponding esters performed equally well or better (entries 5–7). The most electron-deficient ester catalyst **7f** gave the most favorable result (entry 7). This prompted us to evaluate other electron-withdrawing groups *ortho* to the amide group, in the absence or presence of other electron-withdrawing groups (entries 8–13). Amide-thiourea **7h** emerged as the superior catalyst with regard to selectivity and activity, providing product **6a** in excellent yield and d.r., and 88% *ee* following a reaction time of just one hour (entry 9). Interestingly, all three regioisomeric catalysts (**7b**, **7k** and **7l**) were significantly less active and selective. As anticipated, bifunctional catalysts containing basic sites capable of deprotonating **1**, as exemplified by the Takemoto catalyst (**7m**),[18] provided poor results (entry 14). Replacement of the catalyst amide moiety for sulfonamide proved unfruitful (compare catalysts **7b** and **7n**, entries 3 and 15). Finally, product **6a** was obtained with 90% *ee* in a reaction conducted at −40 °C (entry 16). A range of other solvents and parameters were evaluated but did not result in any further improvements.[19]

Table 1: Optimization of the reaction conditions.[a]

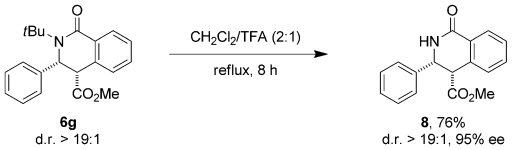


Entry	Catalyst	*t* [h]	Yield [%]	d.r.	*ee* [%]
1	–	18	33	>19:1	–
2	**7a**	15	72	>19:1	35
3	**7b**	21	87	>19:1	70
4	**7c**	22	70	>19:1	74
5	**7d**	29	73	>19:1	73
6	**7e**	42	78	>19:1	81
7	**7f**	20	87	>19:1	81
8	**7g**	3	69	10:1	80
9	**7h**	1	94	>19:1	88
10	**7i**	16	81	>19:1	70
11	**7j**	20	84	10:1	71
12	**7k**	20	84	>19:1	82
13	**7l**	18	58	>19:1	64
14	**7m**	120	46	6:1	17
15	**7n**	19	48	>19:1	59
16[b]	**7h**	41	85	>19:1	90

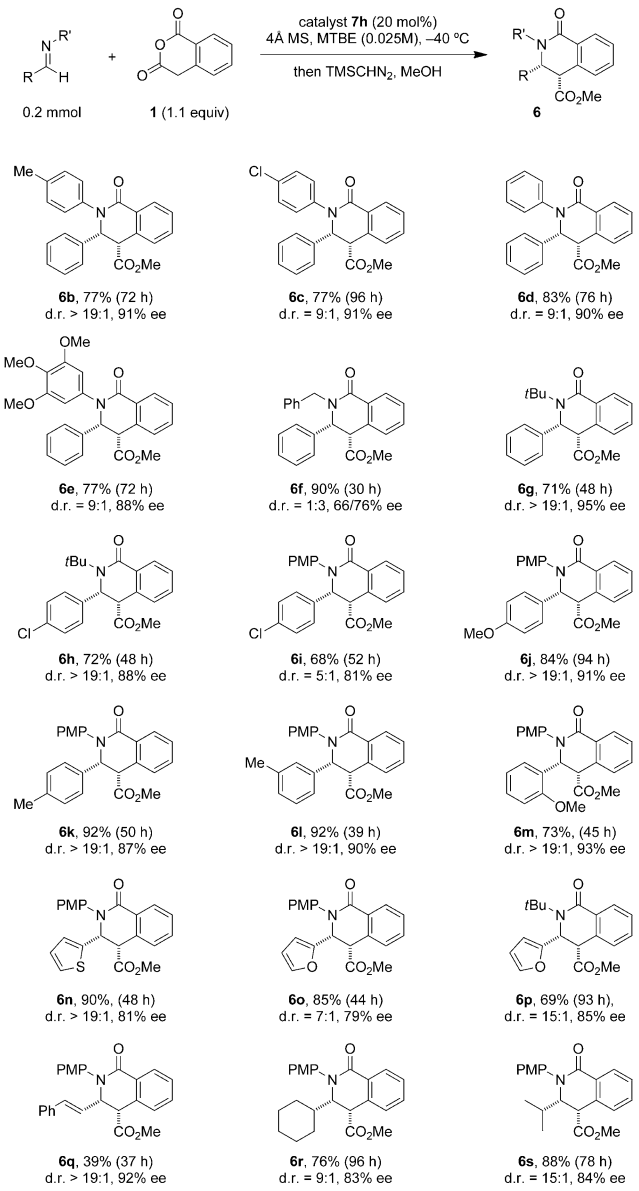
[a] Yields are given for chromatographically purified compounds. The *ee* values were determined by HPLC analysis; see the Supporting Information for details. [b] The reaction was performed at −40 °C.

The scope of the reaction was found to be relatively broad (Scheme 1). Different N-aryl groups on the imine were well-tolerated (products **6b**–**6e**). However, an N-benzylimine provided lower *ee* values and poor diastereoselectivity (**6f**). On the other hand, product **6g**, which has an N-*t*Bu group, was formed with excellent *ee*. Imines derived from a range of aromatic aldehydes, bearing electronically diverse substituents in different ring positions, were readily accommodated. Imines derived from heterocyclic aldehydes also performed well, although a slight reduction in *ee* was noted for furan-containing product **6o**. An improved result could be obtained upon switching the PMP group to *t*Bu (product **6p**). An α,β-unsaturated imine species was also tested under these reaction conditions to provide product **6q** in excellent *ee*. Product **6q** was formed in competition with the corresponding 3,4-cycloaddition product[20] (not shown), which was obtained in racemic form.[19] Imines derived from aliphatic aldehydes also participated in the title reaction. With the exception of N-benzyl product **6f**, all of the lactams were obtained predominantly as the kinetic *cis* products. While the diastereoselectivity was often found to be high, lower d.r. values may be due to epimerization of the initially formed products to their corresponding *trans* isomers, which is a well-known process.[6a]

The lactam products could be readily modified. Removal of the N-*t*Bu group in **6g** resulted in the formation of product **8** with excellent *ee* [Eq. (1)].[21] Importantly, no epimerization was noted under these conditions. Epimerization of **8** to **9** was

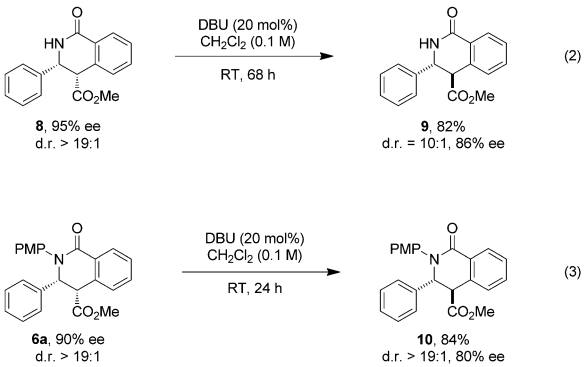


(1)



Scheme 1. Substrate scope.

achieved in good yield upon exposure to DBU, albeit with some loss in *ee* [Eq. (2), unoptimized]. Under similar conditions, epimerization of **6a** provided **10** [Eq. (3)].



To obtain insight into the mechanism of the reaction, we studied the dependence of product *ee* on catalyst *ee*. No nonlinear effects were noted, which is suggestive of a rate-limiting step that involves only one catalyst unit.[19] The organization of the proposed rate- and stereo-determining Mannich addition transition state (Figure 2) for the reaction of **1** and *N*-phenyl benzimine catalyzed by **7h** was investigated using B3LYP-GD3[22]/6-311 + G** PCM[23] (diethyl ether)// B3LYP/6-31G* calculations as implemented by Gaussian 09.[24] Consistent with our hypothesis, the reacting ion pair benefits from bifunctional stabilization through H-bonding interactions with the catalyst structure. Analysis of the lowest-energy transition structure leading to the major (*S*,*S*) enantiomer of product **6d** (***SS*-TS$_{\mathbf{Mannich}}$**, Figure 3)

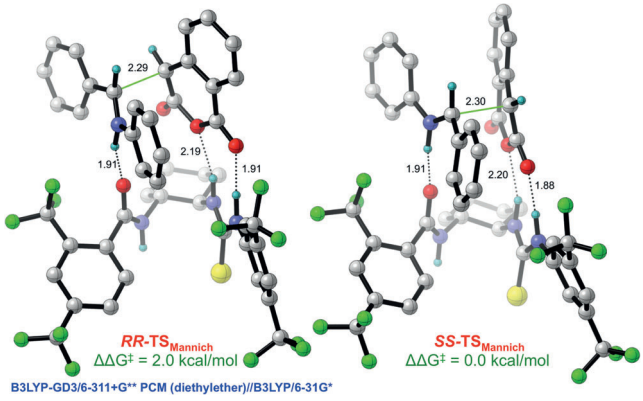


Figure 3. Lowest-energy transition structures leading to the major and minor enantiomers of product **6d**. All distances are in Å and some hydrogen atoms have been removed for clarity. C gray, O red, N blue, S yellow, F green, H cyan.

reveals the following key characteristics: 1) C–C bond formation is relatively early (2.30 Å); 2) the enolate of **1** is bound to the catalyst through two strong H-bonding interactions with the thiourea NH groups (1.88 Å and 2.20 Å); and 3) protonated imine is directed to the *re* face of this catalyst-bound enolate through a strong H-bonding interaction with the carbonyl oxygen of the amide moiety of the catalyst (1.91 Å). The corresponding transition structure leading to the minor (*R*,*R*) enantiomer (***RR*-TS$_{\mathbf{Mannich}}$**, Figure 3) benefits from very similar H-bonding interactions but is higher in energy ($\Delta\Delta G^{\ddagger} = 2.0$ kcal mol^{-1}) than ***SS*-TS$_{\mathbf{Mannich}}$**. This energy difference is consistent with the 90% experimental *ee* obtained for this reaction. We are currently investigating the complete free-energy profile and exact origin of the enantio- and diastereoselectivity of this reaction using experimental and computational approaches. The results of these investigations will be reported in due course.

In summary, we have developed the first catalytic enantioselective reactions of an enolizable anhydride with a range of simple imines. This formal [4+2] cycloaddition reaction represents a rare case of asymmetric ion pairing catalysis in which a neutral catalyst simultaneously interacts with an anionic nucleophile and a cationic electrophile that subsequently combine without generating byproducts.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anion binding · asymmetric catalysis · hydrogen bonding · ion pairing · organocatalysis

[1] a) N. Castagnoli, *J. Org. Chem.* **1969**, *34*, 3187; b) N. Castagnoli, M. Cushman, *J. Org. Chem.* **1971**, *36*, 3404.

[2] a) M. Cushman, J. Gentry, F. W. Dekow, *J. Org. Chem.* **1977**, *42*, 1111; b) M. A. Haimova, N. M. Mollov, S. C. Ivanova, A. I. Dimitrova, V. I. Ognyanov, *Tetrahedron* **1977**, *33*, 331.

[3] a) K. Iwasa, Y. P. Gupta, M. Cushman, *J. Org. Chem.* **1981**, *46*, 4744; b) K. Iwasa, Y. P. Gupta, M. Cushman, *Tetrahedron Lett.* **1981**, *22*, 2333.

[4] a) M. B. Jiménez-Díaz, D. Ebert, Y. Salinas, A. Pradhan, A. M. Lehane, M.-E. Myrand-Lapierre, K. G. O'Loughlin, D. M. Shackleford, M. Justino de Almeida, A. K. Carrillo et al., *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E5455; b) D. M. Floyd, P. Stein, Z. Wang, J. Liu, S. Castro, J. A. Clark, M. Connelly, F. Zhu, G. Holbrook, A. Matheny, M. S. Sigal, J. Min, R. Dhinakaran, S. Krishnan, S. Bashyum, S. Knapp, R. K. Guy, *J. Med. Chem.* **2016**, *59*, 7950.

[5] a) M. A. Cinelli, P. V. N. Reddy, P.-C. Lv, J.-H. Liang, L. Chen, K. Agama, Y. Pommier, R. B. van Breemen, M. Cushman, *J. Med. Chem.* **2012**, *55*, 10844; b) T. X. Nguyen, M. Abdelmalak, C. Marchand, K. Agama, Y. Pommier, M. Cushman, *J. Med. Chem.* **2015**, *58*, 3188; c) M. Chatterjee, A. Hartung, U. Holzgrabe, E. Mueller, U. Peinz, C. Sotriffer, D. Zilian (Julius-Maximilians-Universität Würzburg, Germany), WO2015185114A1, **2015**, p. 38.

[6] a) M. González-López, J. T. Shaw, *Chem. Rev.* **2009**, *109*, 164; b) M. Krasavin, D. Dar'in, *Tetrahedron Lett.* **2016**, *57*, 1635.

[7] Examples of asymmetric variants (through the use of enantioenriched starting materials, chiral auxiliaries, or resolutions): a) R. D. Clark, M. Souchet, *Tetrahedron Lett.* **1990**, *31*, 193; b) M. Cushman, J. K. Chen, *J. Org. Chem.* **1987**, *52*, 1517; c) Y. Vara, T. Bello, E. Aldaba, A. Arrieta, J. L. Pizarro, M. I. Arriortua, X. Lopez, F. P. Cossio, *Org. Lett.* **2008**, *10*, 4759; d) D. Q. Tan, A. Younai, O. Pattawong, J. C. Fettinger, P. H.-Y. Cheong, J. T. Shaw, *Org. Lett.* **2013**, *15*, 5126; e) J. Liu, Z. Wang, A. Levin, T. J. Emge, P. R. Rablen, D. M. Floyd, S. Knapp, *J. Org. Chem.* **2014**, *79*, 7593. See also reference [3].

[8] A moderately enantioselective and mechanistically distinct variant with *N*-sulfonylimines has recently been reported: S. A. Cronin, A. Gutierrez Collar, S. Gundala, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley, S. J. Connon, *Org. Biomol. Chem.* **2016**, *14*, 6955.

[9] Mechanistically distinct enantioselective catalytic reactions of aldehydes and ketones with enolizable anhydrides: a) C. Cornaggia, F. Manoni, E. Torrente, S. Tallon, S. J. Connon, *Org. Lett.* **2012**, *14*, 1850; b) F. Manoni, C. Cornaggia, J. Murray, S. Tallon, S. J. Connon, *Chem. Commun.* **2012**, *48*, 6502; c) C. Cornaggia, S. Gundala, F. Manoni, N. Gopalasetty, S. J. Connon, *Org. Biomol. Chem.* **2016**, *14*, 3040.

[10] a) M. Cushman, E. J. Madaj, *J. Org. Chem.* **1987**, *52*, 907; b) J. Kaneti, S. M. Bakalova, I. G. Pojarlieff, *J. Org. Chem.* **2003**, *68*, 6824.

[11] a) O. Pattawong, D. Q. Tan, J. C. Fettinger, J. T. Shaw, P. H.-Y. Cheong, *Org. Lett.* **2013**, *15*, 5130; b) M. J. Di Maso, K. M. Snyder, F. De Souza Fernandes, O. Pattawong, D. Q. Tan, J. C. Fettinger, P. H.-Y. Cheong, J. T. Shaw, *Chem. Eur. J.* **2016**, *22*, 4794.

[12] N. Mofaddel, N. Bar, D. Villemin, P. L. Desbène, *Anal. Bioanal. Chem.* **2004**, *380*, 664.

[13] Selected reviews on anion binding/ion pairing catalysis: a) J. Lacour, V. Hebbe-Viton, *Chem. Soc. Rev.* **2003**, *32*, 373; b) J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073; c) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; d) S. Beckendorf, S. Asmus, O. G. Mancheño, *ChemCatChem* **2012**, *4*, 926; e) E. P. Ávila, G. W. Amarante, *ChemCatChem* **2012**, *4*, 1713; f) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603; g) P. A. Woods, A. D. Smith, *Supramolecular Chemistry: From Molecules to Nanomaterials* **2012**, *4*, 1383; h) J.-F. Brière, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev.* **2012**, *41*, 1696; i) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518; *Angew. Chem.* **2013**, *125*, 540; j) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534; *Angew. Chem.* **2013**, *125*, 558; k) D. Seidel, *Synlett* **2014**, 783; l) N. H. Evans, P. D. Beer, *Angew. Chem. Int. Ed.* **2014**, *53*, 11716; *Angew. Chem.* **2014**, *126*, 11908; m) N. Busschaert, C. Caltagirone, W. Van Rossom, P. A. Gale, *Chem. Rev.* **2015**, *115*, 8038.

[14] Selected examples from our group: a) M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 16464; b) C. K. De, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 17060; c) E. G. Klauber, C. K. De, T. K. Shah, D. Seidel, *J. Am. Chem. Soc.* **2010**, *132*, 13624; d) C. K. De, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 14538; e) C. K. De, N. Mittal, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 16802; f) N. Mittal, D. X. Sun, D. Seidel, *Org. Lett.* **2012**, *14*, 3084; g) C. Min, N. Mittal, D. X. Sun, D. Seidel, *Angew. Chem. Int. Ed.* **2013**, *52*, 14084; *Angew. Chem.* **2013**, *125*, 14334; h) N. Mittal, D. X. Sun, D. Seidel, *Org. Lett.* **2014**, *16*, 1012; i) C. Min, C.-T. Lin, D. Seidel, *Angew. Chem. Int. Ed.* **2015**, *54*, 6608; *Angew. Chem.* **2015**, *127*, 6708; j) N. Mittal, K. M. Lippert, C. K. De, E. G. Klauber, T. J. Emge, P. R. Schreiner, D. Seidel, *J. Am. Chem. Soc.* **2015**, *137*, 5748; k) C. Zhao, S. B. Chen, D. Seidel, *J. Am. Chem. Soc.* **2016**, *138*, 9053.

[15] Examples of anion-binding catalysis: a) M. Kotke, P. R. Schreiner, *Tetrahedron* **2006**, *62*, 434; b) M. Kotke, P. R. Schreiner, *Synthesis* **2007**, 779; c) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404; d) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358; e) R. S. Klausen, E. N. Jacobsen, *Org. Lett.* **2009**, *11*, 887; f) R. R. Knowles, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 5030; g) A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286; h) R. P. Singh, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 9558; i) R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678; j) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986; k) J. A. Birrell, J.-N. Desrosiers, E. N. Jacobsen, *J. Am. Chem. Soc.* **2011**, *133*, 13872; l) Z. Zhang, K. M. Lippert, H. Hausmann, M. Kotke, P. R. Schreiner, *J. Org. Chem.* **2011**, *76*, 9764; m) S. Lin, E. N. Jacobsen, *Nat. Chem.* **2012**, *4*, 817; n) Y. Wang, T.-Y. Yu, H.-B. Zhang, Y.-C. Luo, P.-F. Xu, *Angew. Chem. Int. Ed.* **2012**, *51*, 12339; *Angew. Chem.* **2012**, *124*, 12505; o) A. G. Schafer, J. M. Wieting, T. J. Fisher, A. E. Mattson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11321; *Angew. Chem.* **2013**, *125*, 11531; p) A. Borovika, P.-I. Tang, S. Klapman, P. Nagorny, *Angew. Chem. Int. Ed.* **2013**, *52*, 13424; *Angew. Chem.* **2013**, *125*, 13666; q) V. Kumar, S. Mukherjee, *Chem. Commun.* **2013**, *49*, 11203; r) Q. Zhao, J. Wen, R. Tan, K. Huang, P. Metola, R. Wang, E. V. Anslyn, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 8467;

Angew. Chem. **2014**, *126*, 8607; s) Y. Gu, Y. Wang, T.-Y. Yu, Y.-M. Liang, P.-F. Xu, *Angew. Chem. Int. Ed.* **2014**, *53*, 14128; *Angew. Chem.* **2014**, *126*, 14352; t) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, O. G. Mancheño, *J. Am. Chem. Soc.* **2014**, *136*, 13999; u) O. García Mancheño, S. Asmus, M. Zurro, T. Fischer, *Angew. Chem. Int. Ed.* **2015**, *54*, 8823; *Angew. Chem.* **2015**, *127*, 8947; v) J. M. Wieting, T. J. Fisher, A. G. Schafer, M. D. Visco, J. C. Gallucci, A. E. Mattson, *Eur. J. Org. Chem.* **2015**, 525; w) J. Wen, R. Tan, S. Liu, Q. Zhao, X. Zhang, *Chem. Sci.* **2016**, *7*, 3047; x) D. D. Ford, D. Lehnherr, C. R. Kennedy, E. N. Jacobsen, *J. Am. Chem. Soc.* **2016**, *138*, 7860; y) D. D. Ford, D. Lehnherr, C. R. Kennedy, E. N. Jacobsen, *ACS Catal.* **2016**, *6*, 4616.

[16] Selected reviews on hydrogen-bonding catalysis: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; *Angew. Chem.* **2006**, *118*, 1550; d) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418; e) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; f) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; g) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516; h) P. M. Pihko, *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH, Weinheim, **2009**; i) S. Schenker, A. Zamfir, M. Freund, S. B. Tsogoeva, *Eur. J. Org. Chem.* **2011**, 2209; j) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047; k) T. J. Auvil, A. G. Schafer, A. E. Mattson, *Eur. J. Org. Chem.* **2014**, 2633.

[17] a) Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589; b) Y. Sohtome, N. Takemura, R. Takagi, Y. Hashimoto, K. Nagasawa, *Tetrahedron* **2008**, *64*, 9423.

[18] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[19] See the Supporting Information for details.

[20] A. Georgieva, E. Stanoeva, S. Spassov, M. Haimova, N. De Kimpe, M. Boelens, M. Keppens, A. Kemme, A. Mishnev, *Tetrahedron* **1995**, *51*, 6099.

[21] R. Fu, B. Zhao, Y. Shi, *J. Org. Chem.* **2009**, *74*, 7577.

[22] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.

[23] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999.

[24] M. J. Frisch et al. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, **2013**.

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Communications

Organocatalysis

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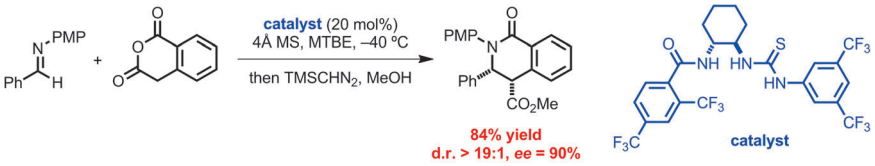
Catalytic Enantioselective Synthesis of Lactams through Formal [4+2] Cycloaddition of Imines with Homophthalic Anhydride



Get it together: An amide-thiourea compound, operating through a novel ion pairing mechanism, is an efficient organocatalyst for the asymmetric reaction of homophthalic anhydride with imines. *N*-aryl and *N*-alkyl imines readily undergo the formal [4+2] cycloaddition to provide lactams with high levels of enantio- and diastereoselectivity. The nature of the key chiral ion pair intermediate was elucidated by DFT calculations.

