

Catalytic Enantioselective Desymmetrization of *meso*-Diamines: A Dual Small-Molecule Catalysis Approach

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Supporting Information

ABSTRACT: The desymmetrization of *meso*-diamines was accomplished via enantioselective monobenzylation facilitated by the cooperative action of two small-molecule catalysts. A chiral acyl-transfer reagent is formed in situ through the interplay of benzoic anhydride, 4-(dimethylamino)-pyridine as a nucleophilic catalyst, and a chiral amide–thiourea cocatalyst.

Vicinal diamines are versatile building blocks, ubiquitous substructures of ligands for asymmetric catalysis,¹ and core components of many organocatalysts.² In addition, derivatives of vicinal diamines have been reported to possess a variety of biological activities (see the examples in Figure 1).³ Enantiopure trans or syn vicinal diamines are readily available by classical resolution of the corresponding racemic diamines.⁴ In addition, a number of catalytic enantioselective approaches to this structural motif have been reported.¹ In contrast, significantly fewer methods are available for the synthesis of enantioenriched cis or anti vicinal diamines.¹ One promising method is the aza-Henry (nitro-Mannich) reaction of nitroalkanes with imines. However, achieving high levels of diastereoselectivity has proved to be challenging, especially in the case of aryl nitromethanes.⁵ A notable recent advance is the catalytic enantioselective synthesis of *cis*-stilbenediamines by Johnston and co-workers, an innovation that was further applied to the synthesis of (–)-Nutlin-3.⁶

An attractive approach to enantioenriched cis vicinal diamines is the desymmetrization of *meso*-1,2-diamines by catalytic enantioselective acylation.⁷ Although several catalytic enantioselective approaches to the desymmetrization of *meso*-diols have been reported,⁸ the corresponding reaction with simple *meso*-1,2-diamines has remained elusive.^{9–13} Here we report the first example of such a process.

Although there are significant challenges associated with the high nucleophilicity of primary amines, a few elegant small-molecule-based approaches to the kinetic resolution of racemic amines and some of their less nucleophilic derivatives have been reported.¹⁴ However, this challenge has not been fully addressed, and no general solutions exist. For instance, the catalytic enantioselective monoacylation of *cis*-1,2-diamines has not been reported, perhaps because it offers some additional challenges. While the nucleophilicity of amines makes the intervention of chiral nucleophilic catalysts difficult,¹⁵ the monoacylation of diamines is challenging in itself because of facile diacylation, which often occurs even when a large excess of diamine is used.¹⁶

We recently developed a new concept for asymmetric nucleophilic catalysis in which a simple nucleophilic catalyst such as 4-(dimethylamino)pyridine (DMAP) is used in combination

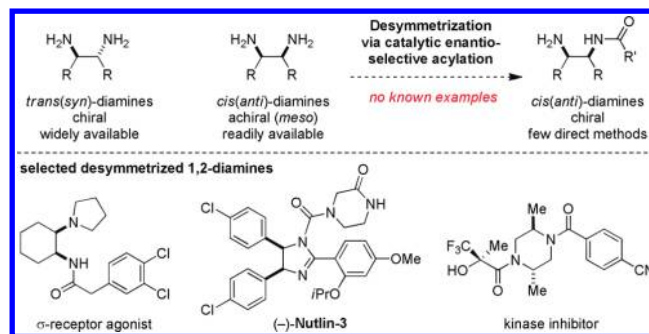


Figure 1. Proposed desymmetrization of *meso*-1,2-diamines and selected 1,2-diamine based drug candidates.

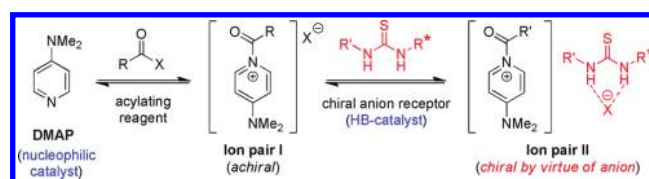


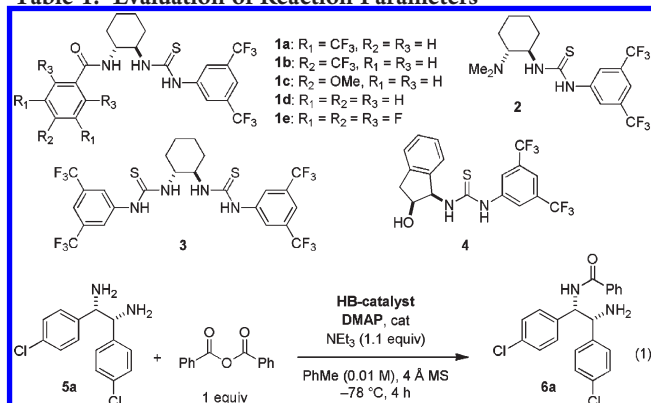
Figure 2. Concept for the in situ generation of chiral acylating reagents via a dual small-molecule catalysis approach.

with a chiral anion receptor (Figure 2).^{17,18} The achiral ion pair I is rendered chiral upon interaction with the chiral anion receptor.^{19–21} This concept was successfully applied to the kinetic resolution of benzylic,^{17a} propargylic,^{17b} and allylic amines.^{17c}

With the goal of applying the dual catalysis concept to the desymmetrization of *meso*-diamines, we initiated our studies by using *meso*-1,2-diamine **5a** as a model substrate (eq 1). The results of this survey are summarized in Table 1. Gratifyingly, reaction conditions similar to our previously optimized conditions^{17b} with catalyst **1a** (10 mol %) and DMAP (10 mol %) produced monobenzyolated product **6a** in good yield with excellent enantioselectivity (entry 1). The addition of triethylamine was necessary in order to achieve full conversion. Various amide–thiourea catalysts and other bifunctional thiourea catalysts were also evaluated under the same conditions but gave inferior results (entries 2–8). As expected on the basis of our earlier findings, the absence of both catalysts **1a** and DMAP led to very low conversion (entry 9). Interestingly, the use of DMAP (10 mol %) as the only catalyst led to substantial conversion

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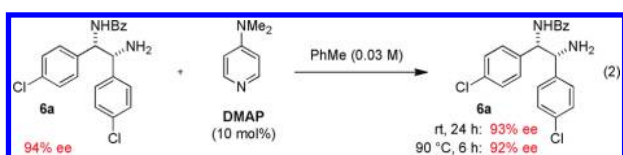
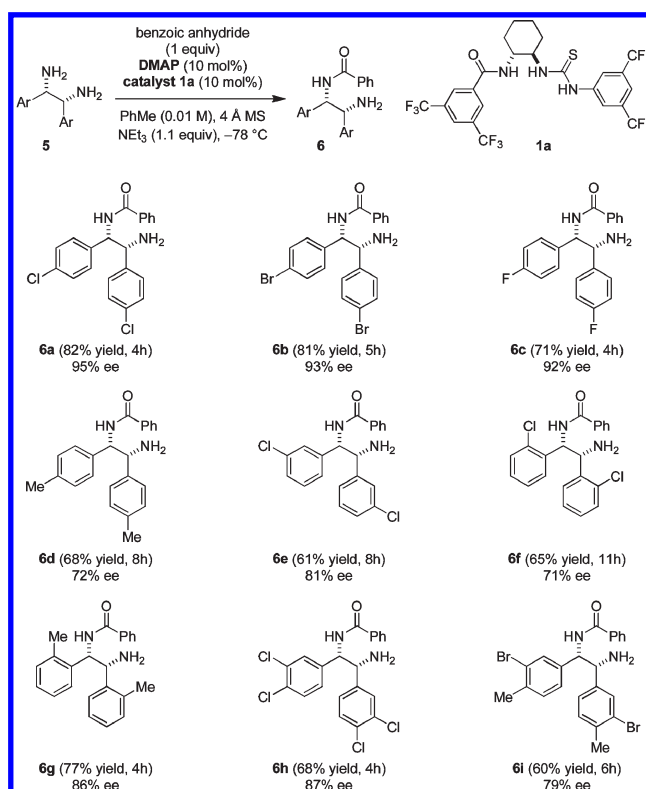
Table 1. Evaluation of Reaction Parameters^a

entry	HB-catalyst (mol %)	DMAP (mol %)	yield (%)	ee (%)
1	1a (10)	10	82	95
2	1b (10)	10	55	92
3	1c (10)	10	17	73
4	1d (10)	10	26	76
5	1e (10)	10	28	4
6	2 (10)	10	57	6
7	3 (10)	10	74	82
8	4 (10)	10	72	-26
9	none	none	<4	N/A
10	none	10	25	N/A
11	1a (10)	none	10	20
12 ^b	1a (5)	5	64	94
13 ^b	1a (2)	2	45	93
14 ^c	1a (10)	10	75	51

^aReactions were run on a 0.2 mmol scale. The ee's were determined by HPLC analysis (see the Supporting Information for details). ^bThe reaction was run for 7 h. ^cThe reaction was performed in the absence of molecular sieves.

(entry 10). The amide–thiourea catalyst **1a** alone gave rise to a small amount of enantioenriched product, but the efficiency of the process was poor. High enantioselectivity was maintained at lower catalyst loadings, albeit at the expense of conversion (entries 12 and 13). For reasons that are not yet clear, a reaction conducted in the absence of molecular sieves under otherwise optimal conditions led to a significant decrease in enantioselectivity (entry 14).²²

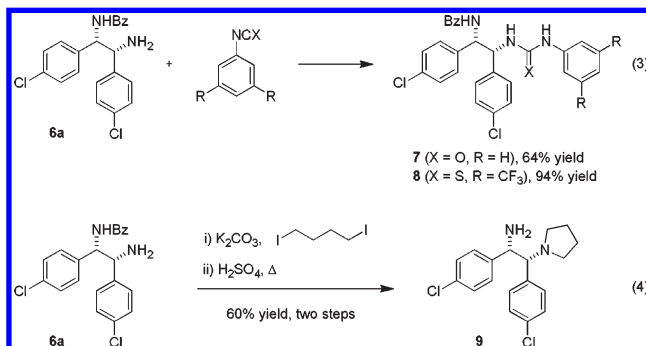
An initial concern was that the enantioenriched product **6a** might undergo racemization under the reaction conditions or during isolation by means of intra- or intermolecular acyl-transfer reactions. Control experiments were thus performed to test for this possibility (eq 2). A toluene solution of enantiomerically enriched product **6a** was stirred at room temperature in the presence of a catalytic amount of DMAP (10 mol %). Essentially no racemization could be detected within 24 h. Even exposure of this solution to a temperature of 90 °C for a period of 6 h led to only minor deterioration of the enantiomeric excess, indicating the considerable configurational stability of monoamide **6a**.

Chart 1. Scope of the Diamine Desymmetrization^a

^aSee footnote a of Table 1.

The scope of the desymmetrization was explored under the optimized reaction conditions (Chart 1). Substrates with electron-withdrawing groups at the para position of the aromatic rings gave rise to the desymmetrized diamine products in good yields with high levels of enantioselectivity. Substrates with various other substitution patterns also underwent monobenzylation to yield 1,2-diamine derivatives with good levels of enantioselectivity. Although their formation cannot be ruled out at this point, we did not observe any dibenzylated products under these conditions.²³

Davis and Johnston⁶ previously demonstrated that a mono-benzoyl diamine related to **6a** can be used as a direct precursor of Nutlin-3. Various other transformations of compounds **6** can be envisioned. For instance, as outlined in eq 3, **6a** was readily transformed into the corresponding urea- and thiourea derivatives **7** and **8**. In addition, dialkylation of **6a** followed by removal of the benzoyl group under acidic conditions resulted in the formation of diamine **9** (eq 4).



In summary, we have described the first catalytic enantioselective desymmetrization of *meso*-1,2-diaryl-1,2-diaminoethanes by monobenzylation. The cooperative action of two catalysts, DMAP as an achiral nucleophilic catalyst and amide–thiourea **1a** as a chiral anion receptor catalyst, afforded the monoacylated products in good yields with good to excellent enantioselectivities. Further applications of this dual catalyst approach are currently being investigated.

■ ASSOCIATED CONTENT

S Supporting Information. Complete ref 3c, experimental procedures, characterization data, and the X-ray crystal structure of compound **7** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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■ REFERENCES

- (1) For selected reviews of the synthesis and utility of diamines, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Savoia, D. *Top. Organomet. Chem.* **2005**, *15*, 1. (c) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140. (d) Faugeron, V.; Genisson, Y. *Curr. Org. Chem.* **2008**, *12*, 751. (e) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (f) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13.
- (2) For selected reviews of organocatalysis, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH, Weinheim, Germany, 2005. (c) Special issue on organocatalysis: List, B. *Chem. Rev.* **2007**, *107* (12), 5413 and subsequent articles. (d) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (e) Palomo, C.; Oiarbide, M.; Lopez, R. *Chem. Soc. Rev.* **2009**, *38*, 632.
- (3) For selected examples of biologically active diamine derivatives, see: (a) Radesca, L.; Bowen, W. D.; Dipaolo, L.; Decosta, B. R. *J. Med. Chem.* **1991**, *34*, 3058. (b) De Costa, B. R.; Dominguez, C.; He, X. S.; Williams, W.; Radesca, L.; Bowen, W. J. *Med. Chem.* **1992**, *35*, 4334. (c) Aicher, T. D.; et al. *J. Med. Chem.* **2000**, *43*, 236. (d) Lyubomir, V. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. *Science* **2004**, *303*, 844. (e) Govindaraju, T.; Kumar, V. A.; Ganesh, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 4144. (f) Kottli, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Design* **2006**, *67*, 101.
- (4) For examples, see: (a) Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 22. (b) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939.
- (5) For a review, see: (a) Marques-Lopez, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401. For selected examples, see: (b) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. (c) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.
- (6) Davis, A. T.; Johnston, N. J. *Chem. Sci.* **2011**, *2*, 1076.
- (7) For an excellent review of organocatalytic enantioselective acyl-transfer reactions, see: Mueller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012.
- (8) For examples of desymmetrization of *meso*-diols by small-molecule catalysts, see: (a) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (b) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410. (c) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 3383. (d) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67.
- (9) For the desymmetrization of *cis*-1,2-cyclohexanediamine with a stoichiometric amount of a chiral acylating reagent, see: Al-Sehemi, A. G. M. *J. King Abdulaziz Univ., Sci.* **2007**, *19*, 11.
- (10) For an enzymatic desymmetrization of *cis*-1,2-cyclohexanediamine, see: Berkessel, A.; Ong, M. C.; Nachi, M.; Neudorfl, J. M. *ChemCatChem* **2010**, *2*, 1215.
- (11) For the Pd-catalyzed desymmetrization of a *meso*-bis-sulfonamide via N-allylation, see: (a) Kitagawa, O.; Yotsumoto, K.; Kohriyama, M.; Dobashi, Y.; Taguchi, T. *Org. Lett.* **2004**, *6*, 3605. (b) Kitagawa, O.; Matsuo, S.; Yotsumoto, K.; Taguchi, T. *J. Org. Chem.* **2006**, *71*, 2524.
- (12) For examples of enzymatic resolution of racemic 1,2-diamines, see: (a) Luna, A.; Alfonso, I.; Gotor, V. *Org. Lett.* **2002**, *4*, 3627. (b) Quijada, F. J.; Gotor, V.; Rebollo, F. *Org. Lett.* **2010**, *12*, 3602.
- (13) For examples of enzymatic desymmetrization of *meso*-1,3-diamines, see: (a) Orsat, B.; Alper, P. B.; Moree, W.; Mak, C.-P.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 712. (b) Busto, E.; Gotor-Fernandez, V.; Montejo-Bernardo, J.; Garcia-Granda, S.; Gotor, V. *Org. Lett.* **2007**, *9*, 4203. (c) Rios-Lombardia, N.; Busto, E.; Gotor-Fernandez, V.; Gotor, V. *Eur. J. Org. Chem.* **2010**, 484.
- (14) For examples, see: (a) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234. (b) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (c) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264. (d) Anstiss, M.; Nelson, A. *Org. Biomol. Chem.* **2006**, *4*, 4135. (e) Arnold, K.; Davies, B.; Héroult, D.; Whiting, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2673. (f) Reznichenko, A. L.; Hampel, F.; Hultsch, K. C. *Chem.—Eur. J.* **2009**, *15*, 12819. (g) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870. For a recent review, see: (h) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613.
- (15) For selected reviews of nucleophilic and Lewis base catalysis, see: (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (c) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (d) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (e) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436. (f) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (g) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570. (h) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.
- (16) For selected strategies for monoacylation of diamines, see: (a) Kelly, T. R.; Caverio, M. *Org. Lett.* **2002**, *4*, 2653. (b) Zhang, Z.; Yin, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2003**, *5*, 3399. (c) Verma, S. K.; Acharya, B. N.; Kaushik, M. P. *Org. Lett.* **2010**, *12*, 4232.
- (17) (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.
- (18) During the revision of this manuscript, Jacobsen and co-workers reported a highly enantioselective acylation of silyl ketene acetals with acyl fluorides via a related dual catalyst approach. See: Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872.
- (19) For recent reviews of anion receptor chemistry, see: (a) Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7882. (b) Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, U.K., 2006; p 413. (c) Caltagirone, C.; Gale, P. A. *Chem. Soc. Rev.* **2009**, *38*, 520. (d) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (e) Gale, P. A. *Chem. Commun.* **2011**, 47, 82.
- (20) For examples of anion binding approaches to catalysis, see: (a) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434. (b) Kotke, M.;

Schreiner, P. R. *Synthesis* **2007**, 779. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (d) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (e) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887. (f) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358. (g) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968. (h) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (i) Schreiner, P. R. *Science* **2010**, *327*, 965. (j) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (k) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286. (l) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558. (m) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (n) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678.

(21) For other examples of chiral anion catalysis, see: (a) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803. (b) Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A. *Org. Lett.* **2000**, *2*, 4165. (c) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373. (d) Carter, C.; Fletcher, S.; Nelson, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1995. (e) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193. (f) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (g) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (h) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903. (i) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (j) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119. (k) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984. (l) Garcia-Garcia, P.; Lay, F.; Garcia-Garcia, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363. (m) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073. (n) Liao, S.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 628. (o) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275. (p) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. (q) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (r) Kim, H. Y.; Oh, K. *Org. Lett.* **2011**, *13*, 1306. (s) Rueping, M.; Uria, U.; Lin, M.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732.

(22) The reaction mixture was partially heterogeneous. This interesting feature could in fact be beneficial to the reaction outcome for reasons that remain to be explored further. Reactions conducted in other solvents (e.g., EtOAc, CH₂Cl₂) appeared to be more homogeneous but gave inferior results.

(23) Independently prepared samples of bisamides were found to be very poorly soluble in common organic solvents. This might have prevented the isolation of these products under the reaction conditions.