JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Nitrated Confined Imidodiphosphates Enable a Catalytic Asymmetric Oxa-Pictet–Spengler Reaction

Sayantani Das, Luping Liu, Yiying Zheng, M. Wasim Alachraf, Walter Thiel,* Chandra Kanta De,* and Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany

Supporting Information

ABSTRACT: The development of a highly enantioselective catalytic oxa-Pictet–Spengler reaction has proven a great challenge for chemical synthesis. We now report the first example of such a process, which was realized by utilizing a nitrated confined imidodiphosphoric acid catalyst. Our approach provides substituted isochroman derivatives from both aliphatic and aromatic aldehydes with high yields and excellent enantioselectivities. DFT calculations provide insight into the reaction mechanism.

The Pictet–Spengler reaction is an acid-catalyzed cyclocondensation of carbonyl compounds and aryl ethylamines forming aza-heterocycles.[1] It is a powerful and well-developed C–C bond forming approach to complex molecules, including natural products.[2] Jacobsen et al.[3] reported a chiral thiourea catalyzed asymmetric acyl-Pictet–Spengler reaction, and subsequently, our group developed a Brønsted acid catalyzed enantioselective Pictet–Spengler reaction.[4,5] In the analogous oxa-Pictet–Spengler reaction,[6] aryl ethanols react with carbonyl compounds to give 1-substituted isochromans.[7]

The isochroman motif constitutes the framework of many natural and synthetic bioactive products of interest (Figure 1).

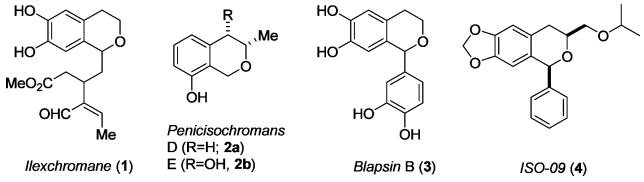


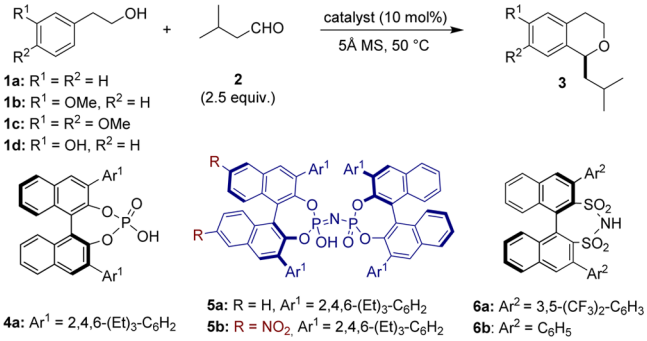
Figure 1. Structures of natural and synthetic isochromans.

Examples include ilexchromane (**1**) obtained from the dried roots of *Ilex pubescens* Hook et Arn,[8] penicisochromans D (**2a**) and E (**2b**) from *Penicillium* PSUF40,[9] Blapsin B (**3**) from *Blaps japanensis*,[10] and the synthetic apoptosis inhibitor of vascular endothelial cells ISO-09 (**4**).[11] In 2008, Jacobsen et al.[12] reported an enantioselective thiourea-catalyzed addition of silyl ketene acetals to oxocarbenium ions. Toward a potentially more general approach to isochromans, an asymmetric oxa-Pictet–Spengler reaction would clearly be of value. However, to the best of our knowledge, a highly enantioselective catalytic version is unprecedented.[13]

Herein, we report a catalytic asymmetric oxa-Pictet–Spengler reaction, which has been enabled through the design of nitrated confined imidodiphosphate catalysts.[14]

When we started our studies with phosphoric acid catalyst **4a**[16] and isovaleraldehyde, attempts to carry out the desired oxa-Pictet–Spengler reaction using phenylethanol (**1a**) only gave the symmetrical acetal intermediate[17] (Table 1, entry 1). Even the more electron-rich methoxy-substituted phenylethanols (**1b–1c**) were found to only give the acetal product (entries 2–3). We speculated that a solution to this problem might involve utilizing the bifunctional nature of these acid catalysts.[18] Specifically, a hydroxylated substrate may provide an

Table 1. Optimization of Reaction Conditions[a]



entry	substrate	catalyst	solvent	t (h)	yield (%)[b]	er
1	**1a**	**4a**	DCE	72	0	NA
2	**1b**	**4a**	DCE	72	0	NA
3	**1c**	**4a**	DCE	72	0	NA
4	**1d**	**4a**	DCE	72	97	60:40
5	**1d**	**5a**	DCE	72	46	80:20
6	**1d**	**6a**	DCE	8	99	49:51
7	**1d**	**6b**	DCE	8	99	51:49
8	**1d**	**5a**	PhMe	72	31	75:25
9	**1d**	**5a**	CyH	72	87	70:30
10	**1d**	**5a**	MTBE	72	32	94:6
11	**1d**	**5b**	MTBE	72	90	98:2
12	**1d**	-	MTBE	72	0	NA

[a]Reactions on a 0.02 mmol scale (0.2 M); er determined by HPLC (see Supporting Information).[15] [b]From ^{1}H NMR using an internal standard. DCE = 1,2-dichloroethane, CyH = cyclohexane, and MTBE = methyl *tert*-butyl ether.

Received: June 27, 2016
Published: July 26, 2016

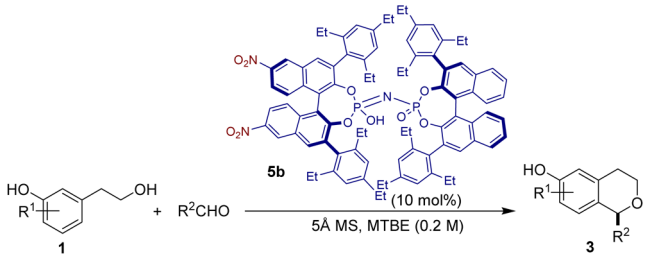
DOI: 10.1021/jacs.6b06626
J. Am. Chem. Soc. 2016, 138, 9429–9432

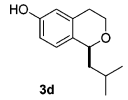
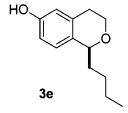
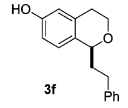
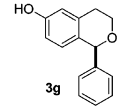
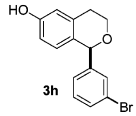
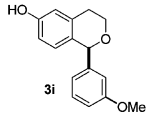
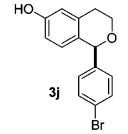
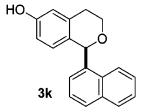
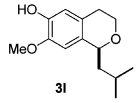
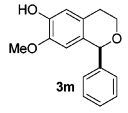
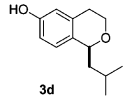
additional functional group for hydrogen bonding interactions with the catalyst. In previous studies, including enzymatic ones, a 3-hydroxyl has also proven to be beneficial.[19] Indeed, treating 3-(2-hydroxyethyl)phenol (**1d**) with isovaleraldehyde in the presence of catalyst **4a** gave the corresponding product (**3d**) in 97% yield and promising enantioselectivity (entry 4).[20] Encouraged by this result, we explored several other acids to identify a more selective catalyst. While imidodiphosphate (IDP) catalyst **5a** with its established ability in handling oxocarbenium ion intermediates significantly improved the enantioselectivity to 80:20 er,[21] it only gave moderate conversion (entry 5). To increase the yield of the reaction, more acidic Brønsted acid catalysts were considered and evaluated. Interestingly, disulfonimide (DSI)[22,23] catalysts **6a** and **6b** afforded product **3d** in quantitative yield in shorter reaction time but virtually racemic product. Thus, catalyst **5a** was used to optimize other reaction parameters. The evaluation of different solvents (entries 8−10) showed that MTBE gave the best enantioselectivity. However, the conversion still remained low. We envisioned that the introduction of nitro groups onto the IDP catalyst may increase its acidity thus providing higher yields.[24] Indeed, we synthesized nitro-IDP catalyst **5b**, which under optimized reaction conditions, afforded excellent results with 90% yield and 98:2 er (entry 11).

The scope of the reaction was explored under these optimized reaction conditions (Table 2). Remarkably, the reaction tolerates a variety of aliphatic and aromatic aldehydes (R^2CHO). Irrespective of the electronic and steric nature of the substituents, the isochroman products were obtained with good to excellent yields and enantioselectivities. We have also investigated other phenol derivatives (entries 9−10) and found them to be suitable substrates, delivering products **3l** and **3m** in excellent yields (92−98%) and er (up to >99:1). Reducing the catalyst loading to 5 mol % led to longer reaction times but still gave full conversion and excellent enantioselectivity (entry 11).

To understand the mechanism of our reaction, we initially employed density functional theory (DFT) to study the reaction between **1d** and **2** in the presence of a slightly simplified catalyst **5c** (**Cata**) (Ar_1 = 2,4,6-$(Me)_3$-C_6H_2).[15,25] The calculated free energy (enthalpy) profile is displayed in Figure 2a. A detailed discussion is given in the Supporting Information. Briefly, both **2** and **1d** initially coordinate to **5c** yielding hydrogen-bonded complexes (**Com1** and **Com2**). The reaction is initiated by protonation of aldehyde **2**, which is then attacked by the hydroxyl group of substrate **1d** that is concomitantly deprotonated by **5c** in an essentially barrierless process via transition state **TS1**. Thereafter, a proton transfer via **TS2** and the release of a water molecule generate mixed acetal intermediate **Int3**, featuring a weak covalent bond between the acetal carbon and an oxygen of catalyst **5c**. As expected for a hydroxylated substrate[19] (see above), **Int3** has a hydrogen bond between the phenolic hydroxyl group of **1d** and another oxygen atom of **5c**, which may direct the subsequent transformation. **Int3** undergoes a 6-endo-trig cyclization reaction with loss of aromaticity of the aryl ring, via regioisomeric transition states **TS3**/**TS3′**. This step is concerted but highly asynchronous, and it is also the rate-limiting step that determines the regioselectivity. The computed free energy (ΔG) of **TS3** (31.9 kcal/mol) is lower than that of **TS3′** (38.2 kcal/mol). The preference for para-substitution may be traced back to C−H···π interactions in **TS3** and **TS3′**. Figure 2b shows that the electrostatic potential

Table 2. Scope of the Asymmetric Oxa-Pictet−Spengler Reaction[a]



entry	product	t (d)/T (°C)	yield (%)	er
1	 3d	3/50	87	97:3
2	 3e	3/50	82	97.8:2.2
3	 3f	4/50	81	97.5:2.5
4	 3g	3/rt	91	98:2
5	 3h	3/rt	75	99:1
6	 3i	3/rt	93	98:2
7	 3j	3/rt	87	99.5:0.5
8	 3k	8/−10	73	95:5
9	 3l	3/50	92	99.6:0.4
10	 3m	3/rt	98	98.5:1.5
11[b]	 3d	5/50	97	97.6:2.4

[a]Reactions were performed at 0.1 mmol scale; er determined by HPLC analysis on chiral stationary phase.[15] [b]Reaction was run with 5 mol % catalyst loading; yield was determined by ^{1}H NMR using an internal standard.

DOI: 10.1021/jacs.6b06626
J. Am. Chem. Soc. 2016, 138, 9429−9432

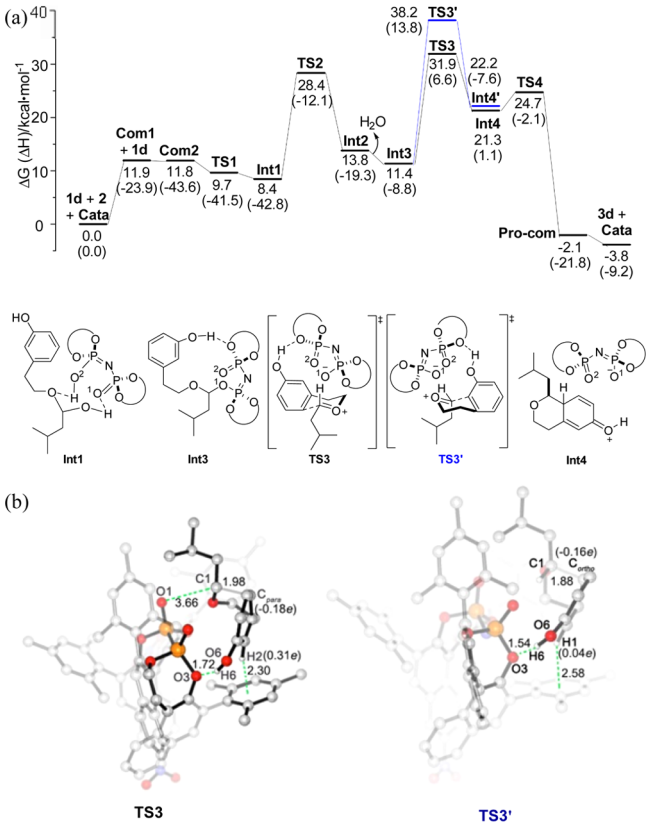


Figure 2. (a) Computed free energy (enthalpy) profile for the asymmetric oxa-Pictet–Spengler reaction in MTBE at the B3LYP-D3/TZVP//TPSS-D3/SVP level. Energy values are in kcal/mol. Black, full pathway with cyclization by para-nucleophilic attack; blue, cyclization by ortho-nucleophilic attack (not observed). Bottom, 2D representations of selected intermediates and transition states. (b) Selected electronic and structural parameters for **TS3** (left) and **TS3′** (right). Distances are in Å; ESP charges are in parentheses. A subsequent hydrogen transfer in **Int4** restores the aromaticity and leads to a complex containing the isochroman product **3d**, and catalyst release completes the reaction cycle.

(ESP) charge on H1 is much higher in **TS3** (0.31 e) than in **TS3′** (0.04 e), indicating a much stronger C–H···π interaction between **1d** and **Cata** in **TS3**. Moreover, C_{para} is slightly more negatively charged (−0.18 e) in **TS3** than is C_{ortho} (−0.16 e) in **TS3′**, which also should facilitate the cyclization. Consequently, **TS3** for para-substitution is earlier than **TS3′** for ortho-substitution, as indicated by the C1–C_{para} distance (1.98 Å) in **TS3** being larger than the C1–C_{ortho} distance (1.88 Å) in **TS3′**. Hence, the para-substitution is more favorable electronically and sterically in the 6-endo-trig cyclization (consistent with the observed experimental product). A subsequent hydrogen transfer in **Int4** restores the aromaticity and leads to a complex containing the isochroman product **3d**, and catalyst release completes the reaction cycle. The formation of the mixed acetal intermediate was corroborated by electrospray ionization mass spectrometry (ESI-MS) studies.[15]

We have developed the first highly enantioselective catalytic oxa-Pictet–Spengler reaction.[26] Our methodology furnishes isochromans in excellent yields and enantioselectivity from phenol ethanols and both aliphatic and aromatic aldehydes when treated with the nitrated chiral confined Brønsted acid catalyst **5b**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06626.

Detailed synthetic procedures, spectra and HPLC traces for all compounds; computational methods, and detailed computational results (PDF)

Crystallographic information file for **3l′** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*thiel@mpi-muelheim.mpg.de

*de@mpi-muelheim.mpg.de

*list@kofo.mpg.de

Author Contributions

S.D. and L.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous support by the Max-Planck-Society and the European Research Council (Advanced Grant "High Performance Lewis Acid Organocatalysis, HIPOCAT") is gratefully acknowledged. We thank Philip Kaib and Saihu Liao for early contributions and the members of our NMR, MS, HPLC, and X-ray crystallography departments for their excellent service.

■ REFERENCES

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

(2) (a) Bentley, K. W. *Nat. Prod. Rep.* **2004**, *21*, 395. (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (c) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

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

(4) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086.

(5) For subsequent studies by other groups, see (a) Cheng, D.-J.; Wu, H.-B.; Tian, S.-K. *Org. Lett.* **2011**, *13*, 5636. (b) Gobé, V.; Guinchard, X. *Chem. - Eur. J.* **2015**, *21*, 8511. (c) Huang, D.; Xu, F.; Lin, X.; Wang, Y. *Chem. - Eur. J.* **2012**, *18*, 3148. (d) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887. (e) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564. (f) Li, X.; Chen, D.; Gu, H.; Lin, X. *Chem. Commun.* **2014**, *50*, 7538. (g) MacDonald, J. P.; Badillo, J. J.; Arevalo, G. E.; Silva-García, A.; Franz, A. K. *ACS Comb. Sci.* **2012**, *14*, 285. (h) Mittal, N.; Sun, D. X.; Seidel, D. *Org. Lett.* **2014**, *16*, 1012. (i) Mons, E.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2014**, *79*, 7380. (j) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (k) Ruiz-Olalla, A.; Würdemann, M. A.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2015**, *80*, 5125.

(6) (a) Wünsch, B.; Zott, M. *Liebigs Ann. Chem.* **1992**, *1992*, 39. (b) For a review on the oxa-Pictet–Spengler reaction, see Larghi, E. L.; Kaufman, T. S. *Eur. J. Org. Chem.* **2011**, *2011*, 5195. (c) Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, *2*, 187.

(7) For examples of oxa-Pictet–Spengler reaction catalyzed by Lewis and Brønsted acid, see (a) Bianchi, D. o. A.; Rúa, F.; Kaufman, T. S. *Tetrahedron Lett.* **2004**, *45*, 411. (b) Chimirri, A.; De Sarro, G.; De Sarro, A.; Gitto, R.; Grasso, S.; Quartarone, S.; Giusti, P.; Libri, V.; Constanti, A.; Chapman, A. G. *J. Med. Chem.* **1997**, *40*, 1258. (c) Costa, P. R. R.; Cabral, L. M.; Alencar, K. G.; Schmidt, L. L.; Vasconcellos, M. L. A. A. *Tetrahedron Lett.* **1997**, *38*, 7021. (d) DeNinno, M. P.; Schoenleber, R.; Asin, K. E.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1990**, *33*, 2948. (e) Ennis, M. D.; Ghazal, N. B.; Hoffman, R. L.; Smith, M. W.; Schlachter, S. K.; Lawson, C. F.; Im, W. B.; Pregenzer, J. F.; Svensson, K. A.; Lewis, R.

DOI: 10.1021/jacs.6b06626
J. Am. Chem. Soc. 2016, 138, 9429–9432

A.; Hall, E. D.; Sutter, D. M.; Harris, L. T.; McCall, R. B. *J. Med. Chem.* **1998**, *41*, 2180. (f) Meyer, A. L.; Turner, R. B. *Tetrahedron* **1971**, *27*, 2609. (g) Steyn, P. S.; Holzapfel, C. W. *Tetrahedron* **1967**, *23*, 4449. (h) Wünsch, B.; Zott, M. *Tetrahedron: Asymmetry* **1993**, *4*, 2307.

(8) Zhou, Y. B.; Wang, J.-H.; Li, X. M.; Fu, X. C.; Yan, Z.; Zeng, Y. M.; Li, X. *J. Asian Nat. Prod. Res.* **2008**, *10*, 827.

(9) Trisuwan, K.; Rukachaisirikul, V.; Sukpondma, Y.; Phongpaichit, S.; Preedanon, S.; Sakayaroj, J. *Tetrahedron* **2010**, *66*, 4484.

(10) Yan, Y.-M.; Dai, H.-Q.; Du, Y.; Schneider, B.; Guo, H.; Li, D.-P.; Zhang, L.-X.; Fu, H.; Dong, X.-P.; Cheng, Y.-X. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4179.

(11) Zhang, L.; Zhu, X.; Zhao, B.; Zhao, J.; Zhang, Y.; Zhang, S.; Miao, J. *Vasc. Pharmacol.* **2008**, *48*, 63.

(12) For non-oxa-Pictet–Spengler asymmetric syntheses of chiral isochromans, see Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.

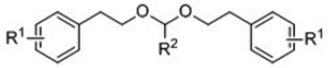
(13) For two singular examples of metal-mediated isomerization, oxa-Pictet–Spengler cascades with moderate enantioselectivity, see (a) Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 12910. (b) Ascic, E.; Ohm, R. G.; Petersen, R.; Hansen, M. R.; Hansen, C. L.; Madsen, D.; Tanner, D.; Nielsen, T. E. *Chem. - Eur. J.* **2014**, *20*, 3297.

(14) Introduction of nitro group in the catalyst backbone significantly increase the acidity of the catalyst; see refs 22c and 23.

(15) See Supporting Information for details.

(16) For selected examples of phosphoric acid catalysis, see (a) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Čorić, I.; Vellalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536. (d) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (e) Terada, M. *Synthesis* **2010**, *2010*, 1929.

(17) Symmetrical acetal intermediate:



(18) Monaco, M. R.; Pupo, G.; List, B. *Synlett* **2016**, *27*, 1027.

(19) (a) Ilari, A.; Franceschini, S.; Bonamore, A.; Arenghi, F.; Botta, B.; Macone, A.; Pasquo, A.; Bellucci, L.; Boffi, A. *J. Biol. Chem.* **2009**, *284*, 897. (b) Parra, R. D.; Maresh, J. *Comput. Theor. Chem.* **2016**, *1082*, 1.

(20) Early experiments using phosphoric acid **4a** with the corresponding 2-hydroxy substrate led to 7-membered cyclic acetal formation, whereas the 4-hydroxy substrate led to complex reaction mixtures.

(21) For selected examples of imidophosphoric acid catalysis, see (a) Coric, I.; List, B. *Nature* **2012**, *483*, 315. (b) Chen, Y.-Y.; Jiang, Y.-J.; Fan, Y.-S.; Sha, D.; Wang, Q.; Zhang, G.; Zheng, L.; Zhang, S. *Tetrahedron: Asymmetry* **2012**, *23*, 904. (c) Kim, J. H.; Čorić, I.; Vellalath, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 4474. (d) Liao, S.; Čorić, I.; Wang, Q.; List, B. *J. Am. Chem. Soc.* **2012**, *134*, 10765. (e) Liu, L.; Leutzsch, M.; Zheng, Y.; Alachraf, M. W.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2015**, *137*, 13268. (f) Tsui, G. C.; Liu, L.; List, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 7703. (g) Vellalath, S.; Čorić, I.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749. (h) Wu, K.; Jiang, Y.-J.; Fan, Y.-S.; Sha, D.; Zhang, S. *Chem. - Eur. J.* **2013**, *19*, 474. (i) Zhuo, M.-H.; Jiang, Y.-J.; Fan, Y.-S.; Gao, Y.; Liu, S.; Zhang, S. *Org. Lett.* **2014**, *16*, 1096.

(22) For selected examples of DSI as Lewis acid, see (a) Gandhi, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2573. (b) Guin, J.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 8859. (c) Guin, J.; Wang, Q.; van Gemmeren, M.; List, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 355. (d) Mahlau, M.; García-García, P.; List, B. *Chem. - Eur. J.* **2012**, *18*, 16283. (e) Ratjen, L.; García-García, P.; Lay, F.; Beck, M. E.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 754. (f) van Gemmeren, M.; Lay, F.; List, B. *Aldrichimica Acta* **2014**, *47*, 3. (g) Wang, Q.; Leutzsch, M.; van Gemmeren, M.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 15334. (h) Wang, Q.; List, B. *Synlett* **2015**, *26*, 807. (i) Wang, Q.; List, B. *Synlett* **2015**, *26*, 1525. (j) Wang, Q.; van Gemmeren, M.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 13592. For a review, see James, T.; van Gemmeren, M.; List, B. *Chem. Rev.* **2015**, *115*, 9388.

(23) For selected examples of DSI as Brønsted acid, see (a) Chen, L.-Y.; He, H.; Chan, W.-H.; Lee, A. W. M. *J. Org. Chem.* **2011**, *76*, 7141. (b) He, H.; Chen, L.-Y.; Wong, W.-Y.; Chan, W.-H.; Lee, A. W. M. *Eur. J. Org. Chem.* **2010**, *2010*, 4181. (c) Prévost, S.; Dupré, N.; Leutzsch, M.; Wang, Q.; Wakchaure, V.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 8770. (d) Treskow, M.; Neudörfl, J.; Giernoth, R. *Eur. J. Org. Chem.* **2009**, *2009*, 3693. (e) Wakchaure, V. N.; Kaib, P. S. J.; Leutzsch, M.; List, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 11852. (f) Galván, A.; González-Pérez, A. B.; Álvarez, R.; de Lera, A. R.; Fañanás, F. J.; Rodríguez, F. *Angew. Chem., Int. Ed.* **2016**, *55*, 3428.

(24) Harada, S.; Kuwano, S.; Yamaoka, Y.; Yamada, K.-i.; Takasu, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10227.

(25) Geometry optimizations for all species were performed at the TPSS-D3/SVP level, and single-point calculations at the gas-phase optimized geometries were then carried out at the B3LYP-D3/TZVP level with inclusion of continuum solvation.

(26) Note added in proof: An earlier version of this manuscript was submitted on May 3rd, 2016. During the revision of this manuscript an interesting paper describing related work appeared: Zhao, C.; Chen, B. S.; Seidel, D. *J. Am. Chem. Soc.* **2016**, *138*, 9053.

DOI: 10.1021/jacs.6b06626
J. Am. Chem. Soc. 2016, 138, 9429–9432