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Frustrated Lewis Pair (FLP)-Catalyzed Hydrogenation of Aza-Morita–Baylis–Hillman Adducts and Sequential Organo-FLP Catalysis

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ABSTRACT: Herein we report the metal-free diastereoselective frustrated Lewis pair (FLP)-catalyzed hydrogenation of aza-Morita–Baylis–Hillman (aza-MBH) adducts, accessing a diverse range of stereodefined β-amino acid derivatives in excellent isolated yields (28 examples, 89% average yield, up to 90:10 d.r.). Furthermore, sequential organo-FLP catalysis has been developed. An initial organocatalyzed aza-MBH reaction followed by in situ FLP formation and hydrogenation of the electron-deficient α,β-unsaturated carbonyl compounds can be performed in one-pot, using DABCO as the Lewis base in both catalytic steps.

KEYWORDS: frustrated Lewis pairs, metal-free hydrogenation, sequential catalysis, amino esters, stereoselective

Since the pioneering reports of Stephan1 and Erker,2 there has been an explosion of research into frustrated Lewis pair (FLP) chemistry.3 Of particular interest is the ability of FLPs to activate hydrogen for various metal-free catalytic reduction processes, presenting an attractive alternative to more traditional precious metal-catalyzed hydrogenation that has found ubiquitous application in industrial processes.4 FLP-catalyzed hydrogenation of various substrates including imines, silyl enol ethers, N-heterocycles, aldehydes, and ketones is now well-established, with B(C6F5)3 being the most commonly employed Lewis acid.5 In comparison, FLP-catalyzed hydrogenation of α,β-unsaturated carbonyl compounds has received considerably less attention.6 This can partly be attributed to the requirement for more specialized Lewis acids that are designed according to one or both of the following strategies: (1) increased steric shielding (size exclusion principle), e.g. B(C6F5)2(Mes);7 (2) attenuated Lewis acidity by replacing one or more of the C6F5 groups within B(C6F5)3.8 Such boranes exhibit increased functional group tolerance and can be used in combination with unhindered, highly nucleophilic Lewis bases, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), forming FLPs that, in the presence of hydrogen, catalytically reduce various α,β-unsaturated carbonyl compounds including acrylates, malonates, enones, and yrones (Scheme 1, eqs 1 and 2).7,8

Inspired by these reports, and cognizant that DABCO can serve as the Lewis base component of an FLP, we envisaged a new catalytic platform, namely sequential organo-FLP catalysis. In such processes, the same Lewis base would serve as both the organocatalyst (step 1) and the Lewis base component of the FLP (step 2) in sequential catalytic transformations in one-pot.10 This approach would expand the reactivity profile of FLP-catalyzed hydrogenation to include more complex and challenging substrates while demonstrating the wider applications of FLPs in organic synthesis and catalysis. Herein, we report the successful implementation of this strategy and...
Using the Childs–Lewis base, hydrogenation occurs in the absence of either Lewis acid or strength, B(2,4,6-F3C6H2)3, is optimal in this process, high-
ingesting the delicate balance that exists between borane Lewis acidity (and resulting hydridoborate anion nucleophilicity) and lighting the borane of intermediate Lewis acid enabled the hydrogenation of (±-1) to 100%, 70%, and 56%, respectively. It is

| entry | variation from “standard” conditions | yield (%) | d.r. |
|-------|------------------------------------|-----------|-----|
| 1     | none                               | >98 (96)  | 87:13 |
| 2     | no B(2,4,6-F3C6H2)3                 | <2        | -   |
| 3     | no DABCO                           | <2        | -   |
| 4     | B(2,6-F2C6H3)3 instead of B(2,4,6-F3C6H2)3 | 72       | 80:20 |
| 5     | B(C6F5)3, instead of B(2,4,6-F3C6H2)3 | 19        | -   |
| 6     | 2,6-lutidine instead of DABCO      | 85        | 88:12 |
| 7     | B(2,4,6-collidine instead of DABCO | 88        | 75:25 |
| 8     | benzene instead of toluene          | >98       | 83:17 |
| 9     | ([±]-1) = 0.32 M instead of 0.16 M  | >98       | 82:18 |
| 10    | 50 °C instead of 80 °C              | >98       | 87:13 |
| 11    | 25 °C instead of 80 °C              | <2        | -   |
| 12    | H2 (5 bar) instead of H2 (60 bar)   | >98       | 84:16 |
| 132   | 2.5 mol % catalyst instead of 10 mol % | >98     | 88:12 |

"Reactions performed using 0.1 mmol of aza-MBH adduct (±)-1 where ([±]-1) = 0.16 M in toluene. Yield after 24 h as determined by 1H NMR analysis of the crude reaction mixture. Isolated yield given in brackets as a mixture of diastereoisomers. Determined by 1H NMR analysis of the crude reaction mixture. Reaction performed using 0.5 mmol of aza-MBH adduct (±)-1."

In order to test our hypothesis, we initially focused on the FLP-catalyzed hydrogenation of aza-MBH adducts, selecting (±)-1 as a model substrate (Table 1). After extensive optimization,23 it was found that a FLP system composed of B(2,4,6-F3C6H2)3 (10 mol %) and DABCO (10 mol %) under H2 (60 bar) in toluene (([±]-1) = 0.16 M) at 80 °C for 24 h, enabled the hydrogenation of (±)-1, giving (±)-syn-2 as the major diastereoisomer (87:13 d.r.) in 96% combined isolated yield (entry 1). The observed diastereoselectivity compares favorably to reported heterogeneous Pd/C-catalyzed hydrogenation of N-sulfonyl aza-MBH adducts (1:1 d.r.).16,24 No hydrogenation occurs in the absence of either Lewis acid or Lewis base, forming FLP-type catalysis in operation (entries 2 and 3).18 Using the Childs method,19 Alcarazo and co-workers have determined the relative Lewis acidity of the three boranes tested, B(C6F5)3, B(2,4,6-F3C6H2)3, and B(2,6-F2C6H3)3, to be 100%, 70%, and 56%, respectively.22 It is interesting to note that the borane of intermediate Lewis acid strength, B(2,4,6-F3C6H2)3, is optimal in this process, highlighting the delicate balance that exists between borane Lewis acidity (and resulting hydridoborate anion nucleophilicity) and H2 activation within FLP-catalyzed hydrogenation of α,β-

described: (1) the first metal-free diastereoselective hydrogenation of aza-Morta–Baylis–Hillman (MBH) adducts;11 and (2) the sequential organocatalytic formation and in situ FLP-catalyzed hydrogenation of aza-MBH adducts,22 accessing a range of bespoke β-amino acid derivatives in one-pot (Scheme 1, eq 3).

For the purposes of assessing the scope of this protocol, the standard reaction conditions (Table 1, entry 1) were used to ensure full conversion across a range of substrates (Table 2).

Under these conditions, a variety of acrylate-derived aza-MBH adducts, including both alkyl and aryl esters undergo selective 1,4-reduction (R2 scope), giving the corresponding β-amino esters in excellent isolated yields and syn diastereoselectivity (products 3–8, 80–92% yield, up to 90:10 d.r.). Within the α,β-unsaturated carbonyl functionality, an enone was also regioselectively reduced, giving β-amino ketone 9 in 80% yield, albeit with negligible diastereoselectivity (55:45 d.r.).22 No competing carbonyl 1,2-reduction to the corresponding alcohol could be detected. A substrate limitation was identified upon testing an aza-MBH adduct bearing an enal functionality, which does not undergo hydrogenation, with starting materials returned. A variety of aryl substituted aza-MBH adducts (R2 scope) undergo hydrogenation to the corresponding β-amino esters in excellent yields (products 2 and 11–22, 88–96% yield, up to 89:11 d.r.). Within the aryl unit, 4-F, 3-F, 3-Me, and 2-F substitution is tolerated in addition to halogen (4-Cl and 4-Br), electron-donating (4-CF3 and 4-NO2) substituents. Extended aromatic systems (2-Np) and heteroaryls (2-thiophenyl and 2-furanyl) can also be present within the aza-MBH adduct, although heteroaryl substitution results in lower diastereoselectivities (products 21 and 22). An alkyl-substituted substrate required an extended reaction time of 48 h, giving 23 in 77% yield (67:33 d.r.). The reaction performs well upon scale up, using reduced catalyst loading (2.5 mol %), with the formation of (+)-syn-2 successfully carried out on a 10 mmol scale in 97% yield (88:12 d.r.) to provide 3.68 g of product. To the best of our knowledge, this is the lowest catalyst loading for a FLP-catalyzed hydrogenation of an α,β-unsaturated carbonyl compound reported to date. Various alkyl and aryl sulfonamide
Table 2. Scope of FLP-Catalyzed Hydrogenation of aza-MBH Adducts

| Reactions performed using 0.5 mmol of (±)-aza-MBH adduct. All yields are isolated yields after chromatographic purification as a mixture of diastereoisomers unless stated otherwise in brackets. Diastereomeric ratio (d.r.) as determined by 1H NMR analysis of the crude reaction mixture. B(2,4,6-F3C6H2)3 (2.5 mol %), DABCO (2.5 mol %). 48 h reaction time. |
|---|
| **R1 scope (7 examples)** |
| 1. R = OMe, 89%, 84:16 d.r. |
| 2. R = OPr, 92%, 84:16 d.r. |
| 3. R = O-tBu, 81%, 78:22 d.r. |
| 4. R = Om-Hex, 92% (78% syn, 14% anti), 81:19 d.r. |
| 5. R = OPh, 83%, 90:10 d.r. |
| 6. R = O-tBu, 80%, 82:18 d.r. |
| 7. R = Ph, 80%, (41% syn, 39% anti), 55:45 d.r. |
| **R2 scope (14 examples)** |
| 8. R = 4-F, 97%, 88:12 d.r. (10 mmol scale) |
| 9. R = 3-F, 93%, 84:16 d.r. |
| 10. R = 3-Me, 90%, 84:16 d.r. |
| 11. R = 2-F, 93%, 84:16 d.r. |
| 12. R = H, 95%, 83:17 d.r. |
| 13. R = 4-Cl, 92%, 85:15 d.r. |
| 14. R = 4-Br, 85%, 86:14 d.r. |
| 15. R = 4-OCH3, 88%, 85:15 d.r. |
| 16. R = 4-CF3, 92%, 87:13 d.r. |
| 17. R = 4-NO2, 95%, 84:16 d.r. |
| **R1 and R2 scope (7 examples)** |
| 18. R = 4-OMe, 96%, 98:2 d.r. |
| 19. R = NHPMP, 93%, 96:4 d.r. |
| 20. R = S, 96%, 79:22 d.r. |
| 21. R = O, 93%, 68:32 d.r. |
| 22. R = C6H4(OH)CH2, 89%, 78:22 d.r. |
| 23. R = C6H4(CH3)2, 89%, 78:22 d.r. |
| 24. R = Me, 86%, 89:11 d.r. |
| 25. R = Ph, 86%, 87:13 d.r. |
| 26. R = OMeC6H4, 89%, 86:12 d.r. |
| 27. R = OCF3C6H4, 90%, 87:13 d.r. |
| 28. R = NO2C6H4, 90%, 87:13 d.r. |
| 29. R = SO2R, 86% (56% syn, 30% anti), 67:33 d.r. |
| 30. < 2% conversion |
| 31. R = H, 80% (43% syn, 37% anti), 55:45 d.r. |

“Reactions performed using 0.5 mmol of (±)-aza-MBH adduct. All yields are isolated yields after chromatographic purification as a mixture of diastereoisomers unless stated otherwise in brackets. Diastereomeric ratio (d.r.) as determined by 1H NMR analysis of the crude reaction mixture. B(2,4,6-F3C6H2)3 (2.5 mol %), DABCO (2.5 mol %). 48 h reaction time.”

Table 3. Sequential Organo-FLP-Catalysis

| Reactions performed using 0.5 mmol of both aldimine and acrylate starting materials. All yields are isolated yields after chromatographic purification as a mixture of diastereoisomers unless stated otherwise in brackets. Diastereomeric ratio (d.r.) as determined by 1H NMR analysis of the crude reaction mixture. |
|---|
| **R1 and R2 scope (5 examples)** |
| 14. R = Me, 52%, 85:15 d.r. |
| 32. R = OEt, 65%, 81:19 d.r. |
| 33. R = OEt, 66%, (58% syn, 8% anti), 85:15 d.r. |
| 34. R = NHPMP, 51% (43% syn, 8% anti), 65:15 d.r. |
| 35. R = NHPMP, 65%, 80:20 d.r. |

“Reactions performed using 0.5 mmol of both aldimine and acrylate starting materials. All yields are isolated yields after chromatographic purification as a mixture of diastereoisomers unless stated otherwise in brackets. Diastereomeric ratio (d.r.) as determined by 1H NMR analysis of the crude reaction mixture.”

Having successfully developed the diastereoselective metal-free hydrogenation of aza-MBH adducts, we switched focus toward exploring sequential organo-FLP catalysis (Table 3). We envisaged an initial DABCO-catalyzed aza-MBH reaction, generating adducts that could be used directly without isolation in the previously optimized FLP-catalyzed hydrogenation, simply via addition of the borane Lewis acid (FLP formation) and placing the reaction mixture under a H2 atmosphere. The catalyst loading was increased to 15 mol % in order to achieve acceptable conversion within 24 h to the aza-MBH adduct during the organocatalytic step. To our delight, under these reaction conditions, a selection of β-amino esters can be accessed in synthetically useful yields directly from the corresponding acrylates and N-sulfonyl aldimines in one-pot.

Inhibited by ester, ketone, ether, heterocycle and (sulfon)amide functionalities within the aza-MBH adducts. In accordance with the mechanistic proposals made by Alcarazo and Paradies for FLP-catalyzed hydrogenation of electron-deficient olefins, we suggest that the mechanism of the FLP-catalyzed hydrogenation of aza-MBH adducts proceeds via initial activation of the substrate by [HDABCO] + through the formation of a hydrogen bond, followed by 1,4-addition of the borohydride [HB(2,4,6-F3C6H2)3]− (Scheme 2). A subsequent diastereodetermining DABCO-mediated 1,3-prototropic shift affords the observed β-amino acid derivatives.
be reported in due course.

In conclusion, we have developed the first metal-free diastereoselective hydrogenation of azo-MBH adducts using FLP catalysis, accessing a diverse array of stereodefined β-amino acid derivatives in excellent isolated yields. Furthermore, this protocol was used to introduce a new catalytic platform, sequential organo-FLP catalysis, where DABCO is used as both organocatalyst and the Lewis base component of the FLP in sequential catalytic steps. Ongoing studies are focused on further applications of FLPs in catalysis, and these results will be reported in due course.

■ ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b03077.

Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

Accession Codes

CCDC 1553097 and 1557916 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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■ REFERENCES

(1) For pioneering work, see: (a) Welch, G. C.; Juan, R. R. S.; Masuda, J. D.; Stephan, D. W. Science 2006, 314, 1124–1126. (b) Welch, G. C.; Stephan, D. W. J. Am. Chem. Soc. 2007, 129, 1880–1881.

(2) For pioneering work, see: Spies, P.; Erker, G.; Kehr, G.; Bergander, K.; Fröhlich, R.; Grimm, S.; Stephan, D. W. Chem. Commun. 2007, 5072–5074.

(3) For selected recent reviews, see: (a) Stephan, D. W.; Erker, G. Angew. Chem., Int. Ed. 2015, 54, 6400–6441. (b) Stephan, D. W.; J. Am. Chem. Soc. 2015, 137, 10018–10032. (c) Stephan, D. W. Acc. Chem. Res. 2015, 48, 306–316. (d) Stephan, D. W. Science 2016, 354, aaf7229. (e) Scott, D. J.; Fuchter, M. J.; Ashley, A. E. Chem. Soc. Rev. 2017, 46, 5689–5700.

(4) For selected reviews, see: (a) Stephan, D. W.; Greenberg, S.; Graham, T. W.; Chase, P.; Hastie, J. J.; Geier, S. J.; Farrell, J. M.; Brown, C. C.; Heiden, Z. M.; Welch, G. C.; Ullrich, M. Inorg. Chem. 2011, 50, 12338–12348. (b) Stephan, D. W. Org. Biomol. Chem. 2012, 10, 5740–5746. (c) Paradies, J. Synlett 2013, 24, 777–780. (d) Hounjet, L. J.; Stephan, D. W. Org. Process Res. Dev. 2014, 18, 385–391. (e) Shi, L.; Zhou, Y.-G. ChemCatChem 2015, 7, 54–66.

(5) Oestreich, M.; Hermeke, J.; Mohr, J. Chem. Soc. Rev. 2015, 44, 2202–2220.

(6) For selected overviews, see: (a) Paradies, J. Angew. Chem., Int. Ed. 2014, 53, 3552–3557. (b) Morozova, V.; Mayer, P.; Berzinni, G. Angew. Chem. Int. Ed. 2015, 54, 14508–14512.

(7) For examples utilizing the size exclusion approach to FLP design, see: (a) Erös, G.; Mehdi, H.; Pálai, I.; Rokob, T. A.; Kírly, P.; Tárkányi, G.; Soós, T. Angew. Chem., Int. Ed. 2010, 49, 6559–6563. (b) Erös, G.; Nagy, M.; Mehdi, H.; Pálai, I.; Nagy, P.; Kírly, P.; Tárkányi, G.; Soós, T. Chem. - Eur. J. 2012, 18, 574–585. (c) Győmöre, A.; Bakos, M.; Földes, T.; Pálai, I.; Domján, A.; Soós, T. ACS Catal. 2015, 5, S366–S372. (d) Dorkó, E.; Szabó, M.; Köti, B.; Pálai, I.; Domján, A.; Soós, T. Angew. Chem., Int. Ed. 2017, 56, 9512–9516.

(8) For examples utilizing the attenuated Lewis acidity approach to FLP design, see: (a) Xu, B.-H.; Kehr, G.; Fröhlich, R.; Wilbewling, B.; Schirmér, B.; Grimm, S.; Erker, G. Angew. Chem. Int. Ed. 2011, 50, 7183–7186. (b) Reddy, J. S.; Xu, B.-H.; Mahdi, T.; Fröhlich, R.; Kehr, G.; Stephan, D. W.; Erker, G. Organometallics 2012, 31, 5638–5649.

(9) For a comprehensive overview, see Bird, S. E.; Beutner, G. L. Angew. Chem., Int. Ed. 2008, 47, 1560–1638.

(10) For conceptually distinct approaches describing FLP tandem catalysis using B(C6F5)3, see: (a) Mahdi, T.; Stephan, D. W. Angew. Chem., Int. Ed. 2015, 54, 8511–8514. (b) Fu, M.-C.; Shang, R.; Cheng, W.-M.; Fu, Y. Angew. Chem., Int. Ed. 2015, 54, 9042–9046.

(11) For examples of diastereoselective FLP-catalyzed hydrogenation processes, see: (a) Heiden, Z. M.; Stephan, D. W. Chem. Commun. 2011, 47, 5729–5731. (b) Liu, Y.; Du, H. J. Am. Chem. Soc. 2013, 135, 12968–12971. (c) Zhu, X.; Du, H. Org. Lett. 2015, 17, 3106–3109. (d) Zhou, Q.; Zhang, L.; Meng, W.; Feng, X.; Yang, J.; Du, H. Org. Lett. 2016, 18, 5189–5191. (e) ref 7d.

(12) For selected reviews on the azo-Morita–Baylis–Hillman reaction, see: (a) Wei, Y.; Shi, M. Chem. Rev. 2013, 113, 6659–6690. (b) Hu, F.-L.; Shi, M. Org. Chem. Front. 2014, 1, 587–595.

(13) See the Supporting Information for full details of reaction optimization.

(14) The relative configurations of (±)-syn-2 (major diastereoisomer formed) and (±)-anti-6 (minor diastereoisomer formed) were confirmed by X-ray crystal structure analysis. The major (syn)
diastereoisomer of all other aza-MBH adducts except 9, 29, and 31 were assigned by analogy. Crystallographic data for (±)-syn-2 and (±)-anti-6 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 1553097 and 1557916, respectively.

(15) A control experiment revealed that diastereomerically pure (±)-syn-2 does not epimerize under the optimized reaction conditions.

(16) Campi, E. M.; Holmes, A.; Perlmutter, P.; Teo, C. C. Aust. J. Chem. 1995, 48, 1535−1540.

(17) For a single example of homogeneous Ir-catalyzed hydrogenation of N-sulfonyl aza-MBH adducts, providing primarily the syn diastereoisomer (89:11 d.r.) see: Raheem, I. T.; Jacobsen, E. N. Adv. Synth. Catal. 2005, 347, 1701−1708.

(18) ICP-AES analysis of crude reaction mixtures showed that no trace metals (Ru, Rh, Pd, Ir, Pt) were present above 4 ppb.

(19) Childs, R. F.; Mulholland, D. L.; Nixon, A. Can. J. Chem. 1982, 60, 801−808.

(20) No conversion to (±)-syn-2 is observed using a H2 balloon (1 atm).

(21) The relative configuration of the major diastereoisomer obtained for (±)-syn-9, (±)-syn-29 and (±)-syn-31 were confirmed by X-ray crystal structure analysis. Crystallographic data for the minor diastereoisomers formed (±)-anti-9, (±)-anti-29 and (±)-anti-31 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 1557918, 1557917, and 1557919, respectively.

(22) Alcohol functional groups can be tolerated in FLP-catalyzed hydrogenations in the absence of a strong Brønsted base. For examples of FLP-catalyzed aldehyde and ketone reduction, see: (a) Mahdi, T.; Stephan, D. W. J. Am. Chem. Soc. 2014, 136, 15809−15812. (b) Scott, D. J.; Fuchter, M. J.; Ashley, A. E. J. Am. Chem. Soc. 2014, 136, 15813−15816. (c) Scott, D. J.; Simmons, T. R.; Lawrence, E. J.; Wildgoose, G. G.; Fuchter, M. J.; Ashley, A. E. ACS Catal. 2015, 5, 5540−5544. (d) ref 7c. (e) ref 10a.

(23) An alternative strategy for FLP-catalyzed hydrogenation of aldehydes and ketones employs softer tin-based Lewis acids: Scott, D. J.; Phillips, N. A.; Sapsford, J. S.; Deacy, A. C.; Fuchter, M. J.; Ashley, A. E. Angew. Chem., Int. Ed. 2016, 55, 14738−14742.

(24) (a) Perlmutter, P.; Teo, C. C. Tetrahedron Lett. 1984, 25, 5951−5952. (b) Xu, Y.-M.; Shi, M. J. Org. Chem. 2004, 69, 417−425.

(25) The modest yields obtained for the one-pot sequential catalysis process is attributed to the formation of minor impurities during the organocatalytic step.

(26) A complex reaction mixture is produced when B(2,4,6-F3C6H2)3 is also present during the organocatalytic step.