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,9 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 ynones (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

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describe: (1) the first metal-free diastereoselective hydrogenation of aza-Morita–Baylis–Hillman (MBH) adducts;\(^\text{11}\) and (2) the sequential organocatalytic formation and in situ FLP-catalyzed hydrogenation of aza-MBH adducts,\(^\text{12}\) accessing a range of bespoke \(\beta\)-amino acid derivatives in one-pot (Scheme 1, eq 3).

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,\(^\text{13}\) it was found that a FLP system composed of B(2,4,6-F\(_3\)C\(_6\)H\(_2\))\(_3\) (10 mol %) and DABCO (10 mol %) under H\(_2\) (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.)\(^\text{14}\) in 96% combined isolated yield (entry 1).\(^\text{15}\) The observed diastereoselectivity compares favorably to reported heterogeneous Pd/C-catalyzed hydrogenation of N-sulfonyl aza-MBH adducts (1:1 d.r.).\(^\text{16,17}\) No hydrogenation occurs in the absence of either Lewis acid or Lewis base, confirming FLP-type catalysis is in operation (entries 2 and 3).\(^\text{18}\) Using the Childs’ method,\(^\text{19}\) Alcarazo and co-workers have determined the relative Lewis acidity of the three boranes tested, B(C\(_6\)F\(_5\))\(_3\), B(2,4,6-F\(_3\)C\(_6\)H\(_2\))\(_3\), and B(2,6-F\(_2\)C\(_6\)H\(_3\))\(_3\), to be 100%, 70%, and 56%, respectively.\(^\text{20}\) It is interesting to note that the borane of intermediate Lewis acid strength, B(2,4,6-F\(_3\)C\(_6\)H\(_2\))\(_3\), is optimal in this process, highlighting the delicate balance that exists between borane Lewis acidity (and resulting hydridoborate anion nucleophilicity) and H\(_2\) activation within FLP-catalyzed hydrogenation of \(\alpha\beta\)-unsaturated carbonyl compounds (entries 1, 4, and 5).\(^\text{21}\) Alternative Lewis bases, 2,6-lutidine and 2,4,6-collidine, which have been successfully employed by Paradies and co-workers in FLP-catalyzed hydrogenation of electron-deficient olefins,\(^\text{22}\) gave lower conversions to (±)-syn-2 (entries 6 and 7). A range of solvents were examined,\(^\text{15}\) including benzene (entry 8), but none were advantageous over toluene. To our delight, increasing the concentration [(±)-1] to 0.32 M (entry 9), reducing the temperature to 50 °C (entry 10), lowering the H\(_2\) pressure to 5 bar (entry 12),\(^\text{20}\) and reducing the catalyst loading to 2.5 mol % (entry 13) do not significantly detriment the conversion or diastereoselectivity of the reaction. Each of these factors improves the practicality and scalability of the metal-free hydrogenation procedure.

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 (R\(^1\) scope), giving the corresponding \(\beta\)-amino esters in excellent isolated yields and syn diastereoselectivity (products 3–8, 80–92% yield, up to 90:10 d.r.). Within the \(\alpha\beta\)-unsaturated carbonyl functionality, an enone was also regioselectively reduced, giving \(\beta\)-amino ketone 9 in 80% yield, albeit with negligible diastereoselectivity (55:45 d.r.).\(^\text{23}\) 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 (R\(^2\) scope) undergo hydrogenation to the corresponding \(\beta\)-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-CF\(_3\) and 4-NO\(_2\)) 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 \(\alpha\beta\)-unsaturated carbonyl compound reported to date. Various alkyl and aryl sulfonamide derivatives in one-pot (Scheme 1, eq 3).

### Table 1. Optimization of FLP-Catalyzed Hydrogenation

<table>
<thead>
<tr>
<th>entry</th>
<th>variation from “standard” conditions</th>
<th>yield(^a) (%)</th>
<th>d.r.(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>&gt;98 (96)</td>
<td>87:13</td>
</tr>
<tr>
<td>2</td>
<td>no B(2,4,6-F(_3)C(_6)H(_2))(_3)</td>
<td>&lt;2</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>no DABCO</td>
<td>&lt;2</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>B(2,6-F(_2)C(_6)H(_3))(_3) instead of B(2,4,6-F(_3)C(_6)H(_2))(_3)</td>
<td>72</td>
<td>80:20</td>
</tr>
<tr>
<td>5</td>
<td>B(C(_6)F(_5))(_3) instead of B(2,4,6-F(_3)C(_6)H(_2))(_3)</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>2,6-lutidine instead of DABCO</td>
<td>85</td>
<td>88:12</td>
</tr>
<tr>
<td>7</td>
<td>2,4,6-collidine instead of DABCO</td>
<td>88</td>
<td>75:25</td>
</tr>
<tr>
<td>8</td>
<td>benzene instead of toluene</td>
<td>&gt;98</td>
<td>83:17</td>
</tr>
<tr>
<td>9</td>
<td>[(±)-1] = 0.32 M instead of 0.16 M</td>
<td>&gt;98</td>
<td>82:18</td>
</tr>
<tr>
<td>10</td>
<td>50 °C instead of 80 °C</td>
<td>&gt;98</td>
<td>87:13</td>
</tr>
<tr>
<td>11</td>
<td>25 °C instead of 80 °C</td>
<td>&lt;2</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>H(_2) (5 bar) instead of H(_2) (60 bar)</td>
<td>&gt;98</td>
<td>84:16</td>
</tr>
<tr>
<td>13(^c)</td>
<td>2.5 mol % catalyst instead of 10 mol %</td>
<td>&gt;98</td>
<td>88:12</td>
</tr>
</tbody>
</table>

\(^{a}\)Reactions performed using 0.1 mmol of aza-MBH adduct (±)-1 where [(±)-1] = 0.16 M in toluene. \(^{b}\)Yield after 24 h as determined by \(^1\)H NMR analysis of the crude reaction mixture. Isolated yield given in brackets as a mixture of diastereoisomers. \(^{c}\)Determined by \(^1\)H NMR analysis of the crude reaction mixture. \(^{d}\)Reaction performed using 0.5 mmol of aza-MBH adduct (±)-1.
moieties are tolerated under optimized reaction conditions (R4 scope) including electron-rich (4-OMe) and electron-deficient (4-CF3 and 4-NO2) aromatic rings (products 24−28, 86−90% yield, up to 89:11 d.r.). Substituting the sulfonamide for a trichloroacetamide furnished β-amino ester 29 in 86% isolated yield (67:33 d.r.).21 Substrates containing nucleophilic amines (R4 = NHPMP) and hydroxyl groups (e.g., standard MBH adducts) do not undergo hydrogenation, presumably due to substrate inhibition via borane coordination and irreversible deprotonation in the presence of a strong Brønsted base (DABCO).22,23 Finally, a N-sulfonyl ketimine derived aza-MBH adduct bearing a quaternary stereogenic center undergoes FLP-catalyzed hydrogenation, giving 31 in 80% isolated yield, albeit with negligible diastereoselectivity (55:45 d.r.).21 In general, the FLP is tolerant of various functional groups and not irreversible inhibited by ester, ketone, ether, heterocycle and (sulfon)amide functionalities within the aza-MBH adducts. In accordance with the mechanistic proposals made by Alcarazo8c,d and Paradies8e 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.

**Scheme 2. Plausible Mechanism of the FLP-Catalyzed Hydrogenation**

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.24 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

| Table 2. Scope of FLP-Catalyzed Hydrogenation of aza-MBH Adducts
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>R1 scope (7 examples)</strong></td>
</tr>
<tr>
<td>1. R = OMe, 99%, 84:16 d.r.</td>
</tr>
<tr>
<td>2. R = Cl, 93%, 84:16 d.r.</td>
</tr>
<tr>
<td>3. R = OH, 90%, 84:16 d.r.</td>
</tr>
<tr>
<td>4. R = Or-Hex, 92% (78% syn, 14% anti), 81:19 d.r.</td>
</tr>
<tr>
<td>5. R = CO2Et, 95%, 63:17 d.r.</td>
</tr>
<tr>
<td>6. R = OH, 93%, 85:15 d.r.</td>
</tr>
<tr>
<td>7. R = NO2, 89%, 86:14 d.r.</td>
</tr>
<tr>
<td><strong>R2 scope (14 examples)</strong></td>
</tr>
<tr>
<td>2. R = 4-F, 97%, 88:12 d.r. (10 mmol scale)</td>
</tr>
<tr>
<td>4. R = 3-OH, 90%, 84:16 d.r.</td>
</tr>
<tr>
<td>5. R = 4-Cl, 92%, 85:15 d.r.</td>
</tr>
<tr>
<td>6. R = 4-Br, 98%, 86:14 d.r.</td>
</tr>
<tr>
<td><strong>R1 and R2 scope (7 examples)</strong></td>
</tr>
<tr>
<td>20. R = OMe, 99%, 84:16 d.r.</td>
</tr>
<tr>
<td>22. R = OEt, 93%, 68:32 d.r.</td>
</tr>
<tr>
<td>23. R = NO2, 95%, 84:16 d.r.</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Table 3. Sequential Organo-FLP-Catalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R1 and R2 scope (5 examples)</strong></td>
</tr>
<tr>
<td>14. R = OMe, 85:15 d.r.</td>
</tr>
<tr>
<td>15. R = Or-Bu, 85:15 d.r.</td>
</tr>
<tr>
<td>16. R = OAc, 85:15 d.r.</td>
</tr>
<tr>
<td>17. R = NO2, 90%, 87:13 d.r.</td>
</tr>
</tbody>
</table>

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.

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In conclusion, we have developed the first metal-free
diastereoselective hydrogenation ofaza-MBH adducts using
FLP catalysis, accessing a diverse array of stereodefined \(\beta\)-
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.

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optimization.

(14) The relative configurations of \(\alpha,\beta\)-syn-2 (major diastereoisomer
formed) and \(\alpha,\beta\)-anti-6 (minor diastereoisomer formed) were
confirmed by X-ray crystal structure analysis. The major \(\alpha,\beta\)-
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.


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


(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.


(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.