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Development of [3]ferrocenophane-derived N/B frustrated Lewis pairs for the metal-free catalytic hydrogenation of imines

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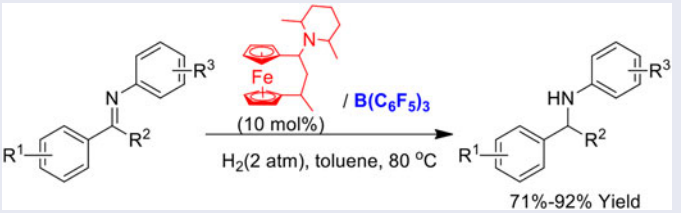
ABSTRACT

A series of novel [3]ferrocenophane-derived N/B frustrated Lewis pairs (FLPs) were synthesized and successfully applied to the catalytic hydrogenation of imines in 71–93% yields. This approach could be easily conducted on gram scale and provided versatile synthetic route for the key intermediate of sertraline hydrochloride without heavy metal residues.

GRAPHICAL ABSTRACT



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Ferrocenophane; frustrated Lewis pairs; hydrogenation; imine; metal-free

Introduction

Amines are key structural elements of many biologically active compounds, which were widely applied in pharmaceuticals, natural products, and agrochemicals.[1] Owing to their great importance, numerous methodologies have been developed for the access of amines. Among them, imine reduction represents one of the most powerful and efficient approaches for the obtaining of amines. Traditionally, the metal-catalyzed hydrogenation of imines was well established, exhibiting high efficiency in many transformations. Despite its unarguable efficiency, the use of metal catalysts limited its further application in pharmaceuticals.[2] As a consequence, there is a continued effort to develop practical strategies to access amines in a metal-free fashion.

FLP chemistry has attracted much attention in the past decade as a metal-free alternative to transition metal catalysis for the activation of dihydrogen and related transformations.[3] The FLP-catalyzed hydrogenation reaction,[4] has sparked scientific upheaval

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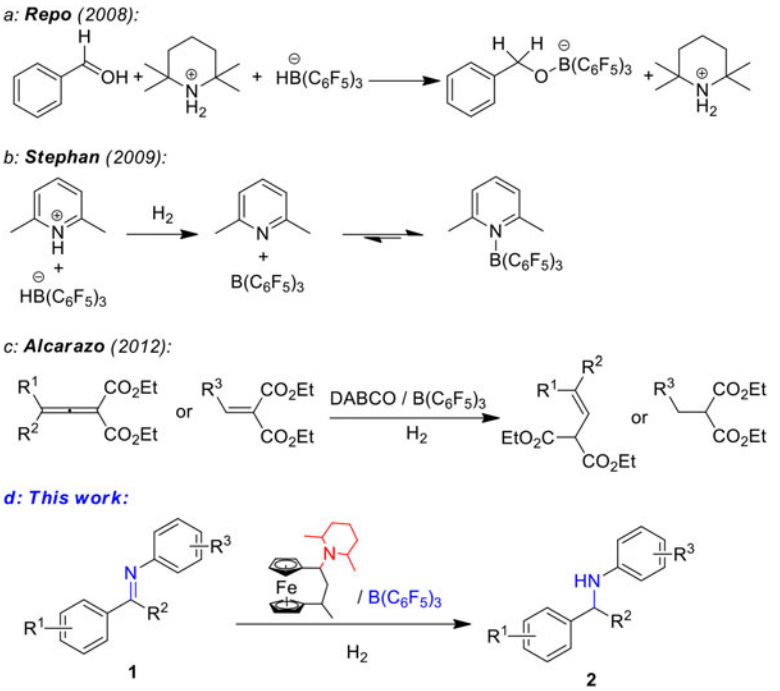
with a promise to develop metal-free hydrogenation technology. From the appearance of the FLP hydrogenation, the catalytic procedures were overwhelmingly accomplished with nitrogen, phosphorous or oxygen-centered LBs combined with $B(C_6F_5)_3$ as a sterically overcrowded LA. In contrast to the abundant phosphorous centered LBs that had been exploited as a component of FLPs,[5] N/B FLPs involving nitrogen-centered LBs are relatively rare. In 2008, Repo and coworkers described the FLP employing 2,2,6,6-tetramethylpiperidine (TMP) as a bulk LB and $B(C_6F_5)_3$ as an LA. This FLP successfully realized the stoichiometric reduction of benzaldehyde under hydrogenation (Scheme 1a).[6] In 2009, Stephan and coworkers discovered the combination of 2,6-lutidine and $B(C_6F_5)_3$ exhibit both classical Lewis acid-base and FLP reactivity. (Scheme 1b).[7] In 2012, Alcarazo and coworkers demonstrated the combination of triethylenediamine (DABCO) and $B(C_6F_5)_3$ could act as an FLP to realize the catalytic hydrogenation of electron-poor allenes and alkenes (Scheme 1c).[8]

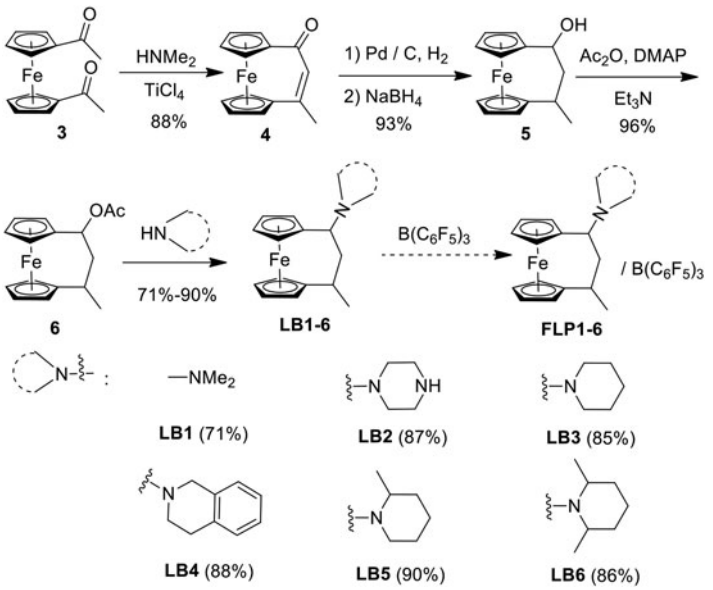
Inspirited by our previous work on P/B FLPs catalyzed hydrogenation of imines,[5c] we are interested in developing new types of N/B FLPs for the access of amines. Herein, we report a series of novel[3] ferrocenophane-derived N/B FLPs and their application in the catalytic hydrogenation of imines (Scheme 1d). Moreover, the current developed N/B FLP was capable of providing the key intermediate of sertraline hydrochloride on a gram scale.

Results and disscussion

The new [3]ferrocenophane-derived **FLP1-6** were successfully synthesized from commercially available 1,1'-diacetylferrocene **3** as the starting material (Scheme 2). Initially,



Scheme 1. Examples of N/B FLPs and their applications in hydrogenation.

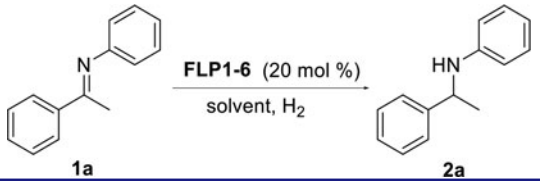


Scheme 2. Preparation of [3]Ferrocenophane-derived Lewis **LB1–6**.

the intramolecular aldol condensation of **3** promoted by $HNMe_2/TiCl_4$ system afforded 1,1'-(1-Methyl-3-oxo-1,3-allyl)ferrocene **4** in 88% yield. Compound **4** was subsequently reduced by Pd/C catalytic hydrogenation and $NaBH_4$ to form the corresponding 1,1'-(1-Methyl-3-hydroxy-1,3-propanediyl)ferrocene **5** in 93% yield. Then the key intermediate **6** was furnished from **5** by acetylation in 96% yield, followed by reacting with various secondary amines to provide the corresponding [3]ferrocenophane-derived bulk Lewis bases **LB1-6** in 71–90% yields. Notably, **FLP1-6** could be generated by mixing **LB1-6** with one equivalent of $B(C_6F_5)_3$.

In order to test the performance of the catalysts **FLP1-6** in the hydrogenation of imines, *N*-(1-phenylethylidene)aniline (**1a**) was chosen as a model substrate (Table 1). Employing 20 mol% of **FLP1** as the catalyst, the reduction of imine **1a** successfully took place and afforded the desired amine **2a** in 43% yield (Table 1, entry 1). Nevertheless, **FLP2** showed no catalytic activity in this hydrogenation reaction (Table 1, entry 2), which might be explained that $B(C_6F_5)_3$ was trapped by the secondary amine of **LB2**. Tertiary amine **LB3** instead of **LB2** could promote the reduction going on smoothly and resulted in a slightly higher yield of **2a** (52%) (Table 1, entry 3). These outcomes indicated that increasing the steric hindrance of Lewis base might be beneficial to the catalyst activity in hydrogenation. Therefore, more bulk Lewis bases were tested and **FLP6** showed the best activity among the screened catalysts **FLP1-6** (Table 1, entries 4-6). Next, optimization of reaction conditions was conducted. Decreasing the pressure of hydrogen from 5.0 MPa to 2.0 MPa extended the reaction time from 18 h to 24 h but did not affect the reaction yield (Table 1, entries 6 and 7). However, further reducing the pressure to 1.0 MPa led to a little drop in yield of **2a** to 72% (Table 1, entry 8). Moreover, the reaction temperature had an influence on the reaction outcomes and 80 °C turned out to be the optimal temperature (Table 1, entries 9 and 10). Notably, the catalyst loading could be reduced to 10 mol % at the price of longer

Table 1. Optimization of reaction conditions[a].



1a 2a

Entry	Cat	Press (MPa)	Solvent	Time (h)	Yield[b] (%)
1	**FLP1**	5.0	toluene	30	43
2	**FLP2**	5.0	toluene	30	Trace
3	**FLP3**	5.0	toluene	30	52
4	**FLP4**	5.0	toluene	30	65
5	**FLP5**	5.0	toluene	22	81
6	**FLP6**	5.0	toluene	18	84
7	**FLP6**	2.0	toluene	24	83
8	**FLP6**	1.0	toluene	48	72
9[c]	**FLP6**	2.0	toluene	30	84
10[d]	**FLP6**	2.0	toluene	48	79
11[c,e]	***FLP6***	***2.0***	***toluene***	***36***	***84***
12[c,f]	**FLP6**	2.0	toluene	48	73
13[c,e]	**FLP6**	2.0	$CHCl_3$	36	71
14[c,e]	**FLP6**	2.0	dioxane	48	26
15[c,e]	$B(C_6F_5)_3$	2.0	toluene	48	13

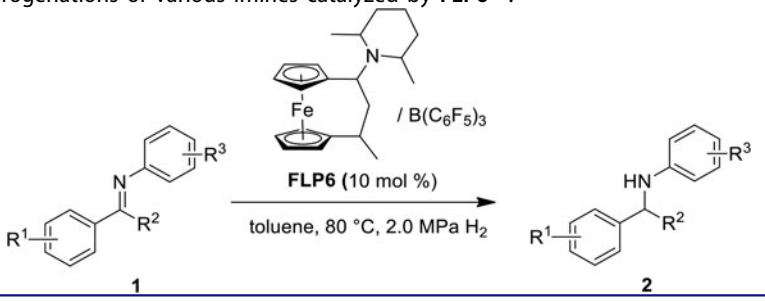
[a]Reactions were carried out with **1a** (1 mmol), **FLP** (0.2 mmol) in dry solvent under hydrogen at 100 °C.
[b]Isolated yield.
[c]Reaction was performed at 80 °C.
[d]Reaction was performed at 60 °C.
[e]0.1 mmol FLP was used.
[f]0.05 mmol FLP was used.

reaction time (Table 1, entries 11 and 12). Furthermore, the reaction solvents were also examined and toluene was chosen as the best medium for this transformation (Table 1, entries 13 and 14). In contrast, a dramatic drop in yield was observed in the absence of LB even after 48 h, which showed that [3]ferrocenophane-derived Lewis bases played a crucial role in this reduction process. Thus, the optimal reaction conditions are as follows: substrates (1.0 equiv.), hydrogen (2.0 MPa), **FLP6** (10 mol%) in toluene at 80 °C.

With the optimal reaction conditions in hand, the scope of substrates of this protocol was investigated and the results are shown in Table 2. The corresponding secondary amines **2a**–**r** were obtained in moderate to good yields. It was noteworthy that aldimines (**1b**–**d**) had better reactivity, affording the corresponding amines in shorter reaction time. Moreover, ketimines with electron-donating groups on the benzene rings (**1c**, **1e**, **1 g**, **1 h**, **1j**–**l**, **1n**, **1p,** and **1r**) gave the corresponding products in higher yields than those with electron-withdrawing groups (**1d** and **1f**). The reduction of imines with sterically hindered groups (**1q** and **1r**) was difficult and provided the corresponding products (**2q** and **2r**) with only moderate yields. To our delight, most of the substituted groups such as nitro (**1d**), chloro (**1f**), and bromo (**1l**–**o**) could be tolerated during the catalytic hydrogenation of imines.

Interestingly, current developed metal-free catalytic systems could be applied in the synthesis of a key intermediate of antidepressant drug sertraline hydrochloride on gram scale (Scheme 3). Initially, the condensation of 4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2H)-one **7** with methylamine in the presence of formic acid

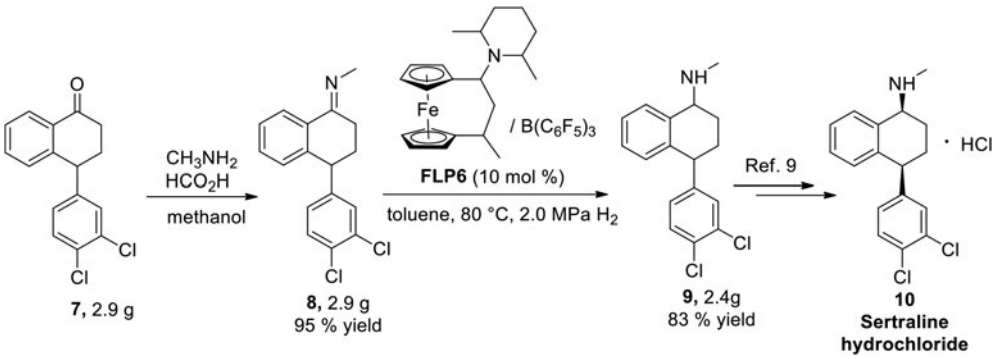
Table 2. Hydrogenations of various imines catalyzed by **FLP6**[a].



1 2

Entry	R^1	R^2	R^3	Time (h)	Yield[b] (%)
1	H	Me	H	36	**2a**, 84
2	H	H	H	18	**2b**, 82
3	4-OMe	H	H	16	**2c**, 86
4	4-NO_2	H	H	25	**2d**, 71
5	H	Me	2-Me	34	**2e**, 86
6	H	Me	4-Cl	36	**2f**, 82
7	H	Me	4-OMe	36	**2g**, 87
8	4-Me	Me	4-OMe	32	**2h**, 90
9	4-Me	Me	H	32	**2i**, 87
10	4-OMe	Me	H	28	**2j**, 92,
11	4-OMe	Me	4-OMe	27	**2k**, 93
12	4-OMe	Me	4-Br	28	**2l**, 91
13	4-Br	Me	H	36	**2m**, 83
14	4-Br	Me	2-OMe	34	**2n**, 79
15	4-Br	Me	4-Br	36	**2o**, 81
16	H	Et	2-OMe	36	**2p**, 80
17	H	Ph	H	42	**2q**, 75
18	H	Ph	2-OMe	48	**2r**, 71

[a]Reactions were carried out with **1a** (1 mmol), **FLP6** (0.1 mmol) in toluene under hydrogen (2.0 MPa) at 80 °C.
[b]Isolated yield.



Scheme 3. The preparation of the key intermediate for sertraline hydrochloride.

could obtain the imine **8** in 95% yield, followed by the **FLP6**-catalyzed hydrogenation of **8** to produce the key intermediate **9** in 83% yield. Finally, the key intermediate **9** could be converted to sertraline hydrochloride **10** according to the reference.[9]

Conclusion

In summary, a series of novel [3]ferrocenophane-derived N/B FLPs had been developed and were applied to the hydrogenation of imines under mild conditions to provide the

corresponding amines in good to excellent yield. Moreover, this protocol could be directly used for the preparation of the key intermediate for sertraline hydrochloride on gram–scale.

Experimental

General procedure for synthesis LB1-6

To a solution of **6** (5 mmol) in MeOH (10 mL) corresponding secondary amines (7.5 mmol) were added and the reaction mixture was stirred at 25 °C for 24 h. After the completion of the reaction, the solvent MeOH was evaporated in vacuo. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the organics were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel flash chromatography to afford the product **LB1-6**.

1,1′-(1-Methyl-3-dimethylamine-1,3-propanediyl)ferrocene (LB1)

Yellow solid; 71% yield; mp 93.0–94.5 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.24 (d, J = 5.6 Hz, 3H), 2.07–2.11 (m, 1H), 2.23 (s, 6H), 2.35–2.41 (m, 1H), 2.71–2.76 (m, 1H), 3.04–3.06 (dd, J = 7.2, 1.6 Hz, 1H), 3.96–3.95 (m, 1H), 3.99–4.00 (m, 1H), 4.03–4.06 (m, 2H), 4.09–4.11 (m, 2H), 4.15–4.16 (m, 1H), 4.21–4.22 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 17.7, 27.8, 29.9, 43.3, 47.1, 58.4, 67.3, 67.5, 68.1, 68.2, 68.6, 69.0, 69.3, 71.4, 81.8, 91.5 (in accordance with the literature).[10] MS (ESI): m/e (%) = 284.1 (100) $[M+H]^+$. HRMS (ESI): calcd for $C_{16}H_{22}FeN$ $[M+H]^+$: 284.1096. Found: 284.1109.

General procedure for synthesis 2a-r

FLP6 (8.6 mg, 0.01 mmol) was placed in a glass vial in the glovebox, then imine **1** (0.1 mmol) dissolved in dry toluene (2.0 ml) was added to the vial, and the vial was placed in a stainless steel autoclave. The reactions took place under 2.0 MPa H_2 pressure at 80 °C for 16–38 h. After the completion of the reaction, the solvent was evaporated in vacuo and the residue was purified by silica gel flash chromatography to afford the product **2a–r**.

N-(1-phenylethyl)-aniline (2a)

Colorless oil; 84% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.49 (d, J = 6.8 Hz, 3H), 3.99 (s, 1H), 4.43–4.48 (dd, J = 6.4 Hz, 6.8 Hz, 1H), 6.47–6.49 (t, 2H), 6.60–6.63 (m, 1H), 7.04–7.08 (m, 2H), 7.17–7.20 (m, 1H), 7.28–7.34 (m, 4H) (in accordance with the literature[5c]). MS (ESI): m/e (%) = 198.2 (100) $[M+H]^+$.

Funding

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