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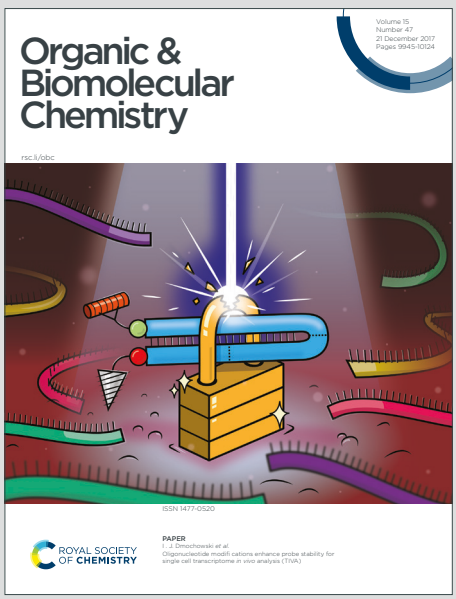

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ARTICLE

FLP-catalysis meets hydrogen-bond activation

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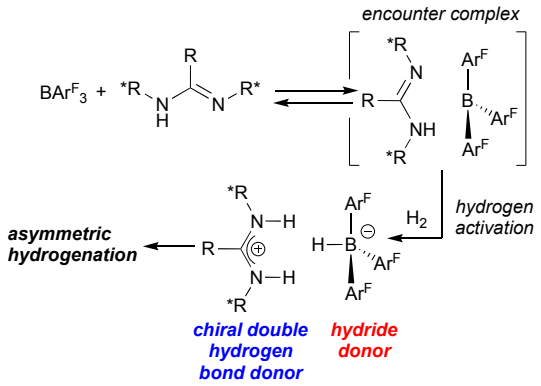
The potential of two chiral amidines and three non-chiral boranes in the metal-free hydrogen activation was explored. The resulting chiral amidiunium borohydride salts were investigated in asymmetric hydrogenation reactions of ketimines, activated double bonds and dehydro amioacid esters.

Introduction

The activation of organic molecules through hydrogen bonding has emerged to a widely applied mode in catalysis.[1] Asymmetric organocatalytic processes have been developed taking advantage of the interaction of chiral hydrogen bond donors.[2,3] In particular, the transfer hydrogenation[4] advanced to a useful tool for asymmetric metal-free reductions.[5–7] Among other hydrogen (H_2) surrogates,[8] Hantzsch's esters[9–13] proved to be most versatile. Although relay catalysis[14] may diminish the low atom economy of Hantzsch's ester transfer hydrogenations, the direct use of H_2 in metal-free processes is still underdeveloped, although highly desired.

The metal-free H_2-activation was realized in 2006 by the discovery of reversible heterolytic splitting of H_2 by a borane/phosphane Lewis pair,[15] later known as frustrated Lewis pair (FLP).[16] Subsequent transfer of the hydride and of the proton enables for catalytic metal-free hydrogenations.[17–24] Mostly, FLPs were modified by the interchange of the Lewis base, probably as a result of availability, whereas the Lewis acid part is usually represented by a triaryl borane.[23] Surprisingly, amidines have not yet been utilized as Lewis base in the H_2-activation but offer the potential to act as hydrogen bond donors for substrate activation.[25–30] (Scheme 1). Thereby, an asymmetric hydrogen bond donor for substrate activation and the hydride nucleophile are formed from molecular hydrogen, which may give rise to asymmetric FLP-catalysed hydrogenations using chiral Lewis bases.[22] The general feasibility of an asymmetric induction through hydrogen bonding was only recently reported by utilizing chiral oxazoles as Lewis bases for the hydrogenation of ketones and enones[31,32] and in the α-amination of carbonyl compounds.[33]



Scheme 1 Concept of hydrogen bond donor/FLP hybrid catalysis.

Results and Discussion

First, we investigated the interaction of the boranes **1a-c** with the two chiral amidines **2a** and **2b**[34–36] (Chart 1).

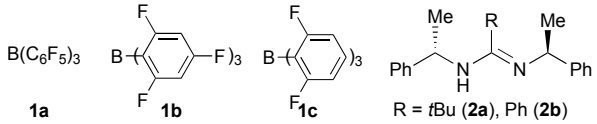


Chart 1 Utilised Lewis acids and Lewis bases as potential FLP-components.

The reaction of **1a** with **2a** produced the Lewis pair adducts **1a•2a** as judged by the ^{11}B NMR chemical shifts of $\delta(^{11}B)$ = –2.0, –7.5 ppm (compared to free **1a** $\delta(^{11}B)$ = 40 ppm). The ^{1}H NMR spectra did not provide further information of the solution structure due to severe line broadening caused by hindered conformational changes, which could not be resolved by variable temperature NMR experiments. Nonetheless, the reaction mixture was pressurised with H_2 (4 bar) and heated to 90 °C over night (Scheme 2).

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† Footnotes relating to the title and/or authors should appear here.
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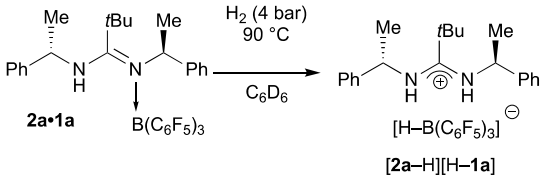
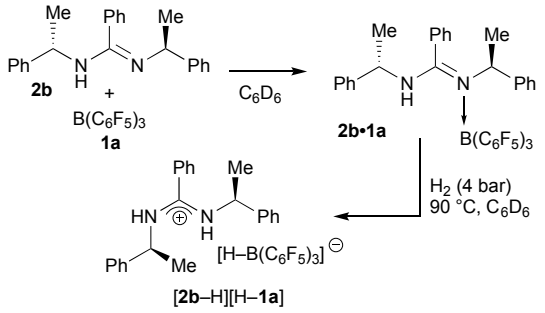


Scheme 2 H_2-Activation by the amidine/borane Lewis pair **2a•1a**.



Scheme 3 Reaction of $B(C_6F_5)_3$ (**1a**) with phenyl amidine **2b**.

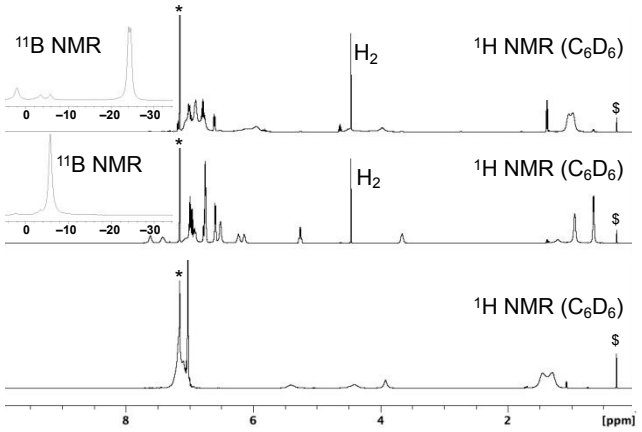


Fig. 1 bottom: ^{1}H NMR (500 MHz) spectrum of **2b** in C_6D_6 (0.16M); middle: ^{1}H NMR (500 MHz) spectrum of **2b•1a** and H_2 (4 bar) in C_6D_6 (inset: ^{11}B NMR (160 MHz, C_6D_6, 300 K) δ = –5.8 ppm; top: ^{1}H NMR spectrum of the reaction of **2b•1a** with H_2 (4 bar) at 90 °C in C_6D_6 (inset: ^{11}B NMR (160 MHz, C_6D_6, 300 K) δ = –24.3 (d, $^1J_{B\text{-}H}$ = 69 Hz) ppm; * solvent resonance; $ silicon grease impurity.

After 18 h, only small amounts of the H_2-activation product [**2a**–H][H–**1a**] were detected by ^{11}B NMR ($\delta(^{11}B) = -24$ ppm) with the characteristic $^1J_{B\text{-}H}$ coupling of 77 Hz. However, the majority of the Lewis pair **2a•1a** remained unreacted. The reactivity changed by the application of the phenyl derivative **2b** (Scheme 3). The reaction of **2b** with **1a** cleanly furnished the Lewis adduct **2b•1a** with separated and sharp resonances in the ^{1}H and ^{11}B NMR spectrum (Fig. 1 middle). The ^{1}H NMR spectrum revealed two sets of phenylethyl-groups in **2b** fragment with one set being significantly shifted to higher field. This presumably arises from the shielding effect of the electron-deficient pentaflurophenyl groups of **1a**. This observation and the ^{11}B NMR chemical shift of $\delta(^{11}B) = -5.8$ ppm strongly supports the formation of the Lewis adduct **2b•1a**. Subsequent reaction with 4 bar H_2 at 90 °C over night furnished the H_2-activation product [**2b**–H][H–**1a**] (Scheme 3) as evidenced by the intense ^{11}B NMR resonance at $\delta(^{11}B) = -24$ ($^1J_{B\text{-}H}$ = 69 Hz) ppm (see inset Fig.1 top). However, the ^{1}H NMR spectrum displayed significant line broadening, which complicates the interpretation. Therefore, we investigated the NMR pattern of the corresponding BF_4-salt, obtained by the reaction of **2b** with HBF_4. The ^{1}H NMR spectrum of [**2b**–H][BF_4] displays three sets for the phenylethyl groups (Fig. 2). One set for the C_2-symmetric *trans/trans* and two sets for the unsymmetrical *cis/trans* [**2b**–H] cation in solution in a ratio of 1:1.1 (Fig. 2).

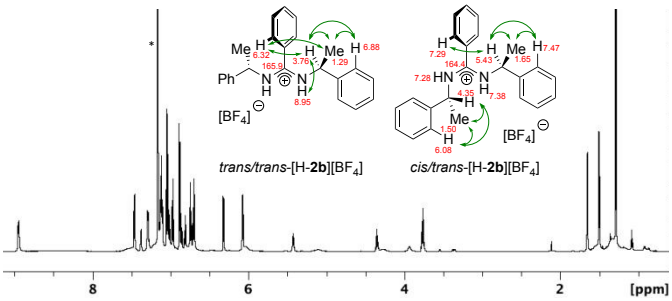
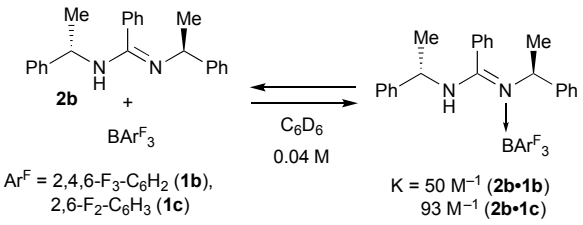


Fig. 2 ^{1}H NMR spectrum of [**2b**–H][BF_4] (0.04 M, C_6D_6, 500 MHz); red numbers denote ^{1}H and ^{13}C NMR chemical shifts; green arrows denote nOe contacts.

All resonances were assigned by 2D NMR experiments (HSQC, HMBC, COSY and NOESY). Particularly, the NOESY experiments were useful to match the resonances with the two conformers. Only one phenylethyl/phenyl n*O*e contact (5.43/7.29) was found for the *cis/trans* conformer. The two N–*H* protons in the symmetric *trans/trans* conformer generate a sharp resonance at $\delta(^1H) = 8.95$ ppm, whereas the unsymmetrical conformer exhibits two resonances at $\delta(^1H) = 7.38$ and 7.28 ppm. Comparison of the [**2b**–H][BF_4] ^{1}H NMR spectrum with the one obtained from the H_2-splitting by **1a•2b** supports the formation of the *cis/trans* isomer (compare Scheme 3) due to the absence of the low field resonance $\delta(^1H) = 8.95$ ppm. Furthermore, two resonances $\delta(^1H) = 1.05$ and 0.97 ppm (Fig. 1 top) are observed which indicate the presence of two magnetically inequivalent methyl groups.

Having the H_2-activation by the amidine/$B(C_6F_5)_3$ system established, we turned out attention to the application of the weaker Lewis acids. The two boranes **1b** and **1c** display a lower Lewis acidity of 87% and 82%, respectively, compared to $B(C_6F_5)_3$ (100%) according to the Gutmann-Beckett-method.[37–41] This reduced Lewis acidity is a key requirement for the tolerance of functionalized substrates, which will be used as hydrogen bond acceptors.[42,43] Again, the phenyl-substituted amidine **2b** was reacted with the boranes **1b** and **1c** in order to study the complexation properties (Scheme 4).



Scheme 4 Equilibrium of **2b** with the weaker Lewis acids **1b** and **1c**.

The reduced Lewis acidity resulted in the equilibration of the free components with the corresponding Lewis adducts **2b•1b**

and **2b•1c** in 3:2 ($K = 93\ M^{-1}$) and 1:1 ($K = 50\ M^{-1}$) ratio respectively. The ^{11}B NMR spectra clearly show the presence of free borane and B-N adduct (**1b**: $\delta(^{11}B) = 60.0, -5.4$ ppm); **1c**: $\delta(^{11}B) = 63.5, -4.7$ ppm). Encouraged by this result we attempted the H_2-activation and reacted the Lewis pairs with 4 bar H_2 at 90 °C for 18 h. Only small amounts of the corresponding H_2-activation products ([**2b**–H][H–**1b**]: $\delta(^{11}B) = -23.1$ ppm and [**2b**–H][H–**1c**] $\delta(^{11}B) = -22.4$ ppm) together with significant amounts of new B-N adducts were detected (**2b•1b**: $\delta(^{11}B) = -2.3, -4.7$ ppm; **2b•1c**: $\delta(^{11}B) = -1.5, -7.5$ ppm). The formation of new amidine/borane adducts after heating must be attributed to the kinetic barrier to other conformers leading to more stable adducts. Nonetheless, the formation of the Lewis adducts is not necessarily problematic for catalytic applications as long as they can be thermally cleaved (compare Scheme 2).

The thermodynamics of the hydrogen activation by the FLP **2b•1c** was investigated by density functional theory (DFT) as implemented in the ORCA package.[44,45] Structures were optimized using PBEh-3c/def2-mSVP[46–48] functional including dispersion correction D3BJ[49,50] and thermochemical properties at 90 °C were obtained from frequency calculations. Equilibrium geometries were confirmed by the absence of imaginary frequencies whereas transition states were characterized by one imaginary frequency along the reaction trajectory. Final energy evaluations were conducted with the double hybrid functional PWP95/def2-QZVPP[51–53,48] using RI-acceleration, D3BJ and solvation model based on density (SMD)[54] for benzene.

The *s-cis/trans* conformer of **2b** found to be 3.3 kcal/mol more stable than the *s-trans/trans* isomer (Fig.3).

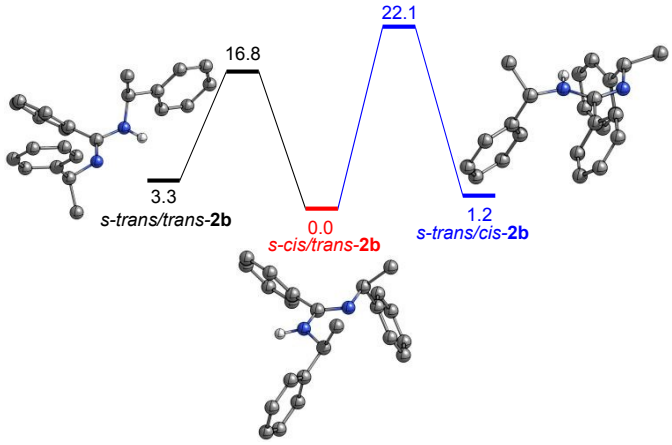


Fig. 3 Free energies for three conformers of **2b** and their transition state energies for interconversion and transition state energies in kcal/mol (selected hydrogen atoms were omitted for clarity).

The barrier for the interconversion of these to isomers by C–N bond rotation was calculated to 16.8 kcal/mol and can be readily achieved at 90 °C. The interconversion of *s-cis/trans*-**2b** to the 1.2 kcal/mol less stable *s-trans/cis* isomer requires substantially more energy (22.1 kcal/mol). Next we investigated the potential of these three conformers to act as Lewis bases in the H_2-splitting with **1c** (Fig.4).

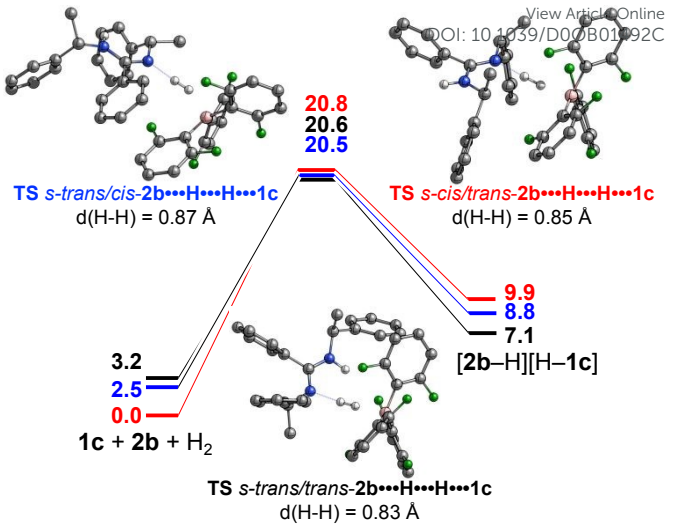
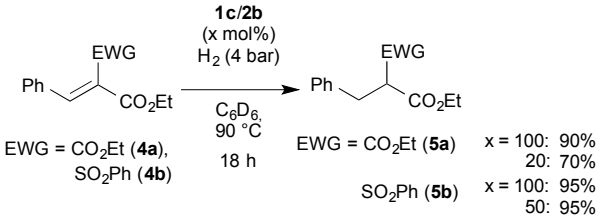


Fig. 4 Computed free reaction and transitions state energies for the H_2-activation by the three amidine conformers of **2b** with **1c** in kcal/mol (selected hydrogen atoms were omitted for clarity).

The energies for H_2-activation are in the same order of magnitude as the barriers for the conformer isomerisation, so that all three conformers were considered as active Lewis bases in the H_2-splitting. The activation of H_2 by the FLPs is endergonic by 3.9 kcal/mol to 9.9 kcal/mol, which is in agreement with the detection of traces of H_2-acivation products by NMR spectroscopy. The splitting of H_2 with the most stable conformer results in a barrier of 20.8 kcal/mol, whereas the energy for the H_2-activation with the other two conformers is by ca. 3 kcal/mol lower (17.4 kcal/mol and 18.0 kcal/mol). The subsequent deprotonation of the amidinium species may result in the equilibration of the amidine isomers of **2b**, offering an alternative pathway to isomerization. However, the computational study shows that the activation barriers are comparable for all three isomers.

Next, the FLP-system **1c**/**2b** was subjected to the hydrogenation of electron-deficient double bonds with suitable functional groups for hydrogen bond activation (Scheme 5).[55]



Scheme 5 Hydrogenation of electron-deficient double bonds (yields determined by NMR using silicon grease as internal standard).

The hydrogenation of **4a** and **4b** was successfully achieved in the presence of stoichiometric amounts of **1c**/**2b** after 18 h (4 bar H_2). In the presence of substoichiometric amounts of the catalyst, both reactions were efficiently promoted and the products **5a** and **5b** were obtained in 70% and 95% respectively.

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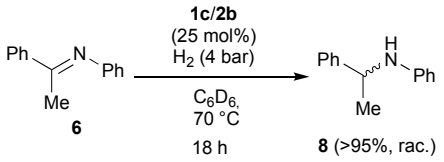
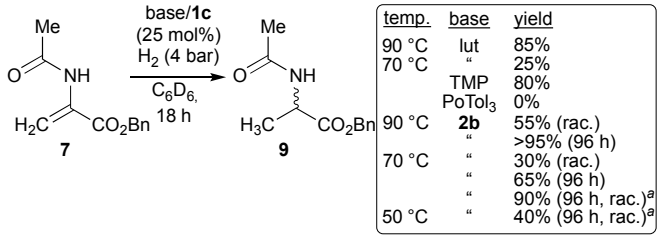
Finally, we investigated the asymmetric hydrogenation of the ketimine **6** and the dehydro amino acid **7** with the hydrogen bond donor/borane catalyst (Scheme 6 and 7).



Scheme 6 FLP-catalysed hydrogenation of **6**.



temp.	base	yield
90 °C	lut	85%
70 °C	"	25%
	TMP	80%
	$PoTol_3$	0%
90 °C	**2b**	55% (rac.)
	"	>95% (96 h)
70 °C	"	30% (rac.)
	"	65% (96 h)
	"	90% (96 h, rac.)[a]
50 °C	"	40% (96 h, rac.)[a]

Scheme 7 Lewis base influence on the FLP-catalysed hydrogenation of the dehydro amino acid **7** (yields determined by NMR using silicon grease as internal standard).

[a] performed with 80 bar H_2.

The ketimine **6** was reduced to the secondary amine **8** in excellent yield within 18 h, however the product was obtained in racemic form. The catalytic performance of **1c/2b** in the hydrogenation of **4a**, **4b** and **6** is comparable to earlier reports using **1c** as catalyst.[43,42,56]

Next, we investigated the FLP-catalyzed hydrogenation of the dehydro amino acid **7**. Since such substrates have not yet been reduced by FLP-catalysts, we first evaluated the **1c**/2,6-lutidine (lut) system at 90 °C. The hydrogenation of **7** to *N*-acetyl alaninylbenzoate **9** proceeded smoothly in 85% yield. The yield decreased to 25% when the reaction was performed at 70 °C. However, the yield was improved to 80% by using 2,2,6,6-tetramethylpiperidine (TMP) at the same temperature. When **2b** was employed as Lewis base, the reaction proceeded in comparable yields to the 2,6-lutidine system (55% and 30% after 18h and >95% and 65% after 96h at 90 °C and 70 °C respectively). The product **9** was isolated as racemic material. The pressure increase to 80 bar H_2 led only to slightly improved yields (90%, 80 bar H_2 *versus* 65%, 4bar H_2) but allowed us to perform the reaction at 50 °C. However, the products were obtained as racemic material.‡ The observed marginal change in the reaction speed suggests that not the H_2-activation is the rate determining step but the hydride/proton transfer.

Conclusions

In conclusion, we have shown for the first time that amidines are active Lewis bases in the heterolytic splitting of molecular hydrogen in the presence of electrophilic triaryl boranes. The FLPs are active hydrogenation catalysts for the reduction of electron-deficient double bonds. Prochiral substrates were reduced in high yields although in racemic form, which might be a result of the conformational flexibility of the double hydrogen bond donor.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

‡ Epimerization of the stereocentre in **2b** in the presence of 10 mol% **1c** at 90 °C does not occur.

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