Metal-free catalytic hydrogenation of imines with tris(perfluorophenyl)borane

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Metal-free homogeneous catalysed hydrogenation of various imines was accomplished with tris(perfluorophenyl)borane under moderate reaction conditions.

The use of homogeneous transition metal catalysis is one of the key technologies for carrying out organic transformations. In particular, the catalytic addition of molecular hydrogen to unsaturated organic compounds is of enormous interest in industry as well as in academia.[1,2] Especially in the last decades, the reduction of imines to generate secondary and primary amines has been the subject of interest in the pharmaceutical and chemical industries.[3] Recently, organocatalysts have been developed for hydrogenations of enones and imines with Hantzsch ester as the source of hydrogen.[4–6] In a continuation of this approach, the groups of G. Bertrand and D. W. Stephan demonstrated strikingly the possibility of metal-free hydrogen activation.[7–9] In particular, the work on 'frustrated Lewis pairs'—bulky Lewis acids and bases which are sterically precluded from forming simple Lewis adducts—for metal-free hydrogenations of imines has attracted considerable attention.[10–14] In this context the group of W. E. Piers has already demonstrated the $B(C_6F_5)$-catalysed hydrosilylation of imines.[15] We recently became interested in the extension of this concept to the possibility of using only simple boranes for catalytic hydrogenation reactions.

Herein, we report a new approach for catalytic imine hydrogenation, which relies on the exclusive use of tris(perfluorophenyl)borane **1** (Fig. 1) as the catalyst under moderate reaction conditions. *N*-benzylidene-4-methylbenzenesulfonamide **2**, *N*-(1-phenylethylidene)aniline **4** and 2,3,3-trimethyl-3*H*-indole **6** were chosen as benchmark substrates for the reactions in toluene solution (Scheme 1).

Table 1 summarises the main results.† The electron-poor imine **2** was reacted at 80 °C at a hydrogen pressure of 10 bar in the presence of 10 mol% of **1** in toluene for 15 h. At this low hydrogen partial pressure already a conversion of 7% with a selectivity of 43% towards **3** was monitored (Table 1, entry 1). Increasing the hydrogen pressure to 20 bar at 80 °C resulted in 89% conversion to the amine **3** with only the borane catalyst **1** present in the reaction mixture (entry 2). In addition, 8% hydrolysis by-products were obtained (entry 2). Even under rigorous exclusion of water, hydrolysis to benzaldehyde and tosylamine was observed under these reaction conditions. The ability of borane **1** to scavenge trace amounts of water is already well documented and could partially account for this effect.[16] The application of higher temperatures (100 °C) at 20 bar of hydrogen pressure affected the selectivity adversely and gave 21% hydrolysis by-product and 70% of the amine **3** (entry 3). The optimal selectivity for substrate **2** was obtained at 100 °C and 30 bar hydrogen pressure (99% conversion and 99% selectivity, entry 4). To further avoid hydrolysis problems, more stable imines were tested in the following reactions. The hydrogenation of compound **4** was accomplished

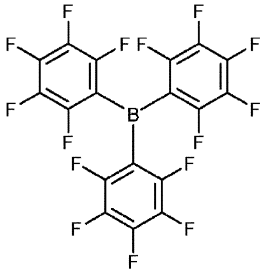

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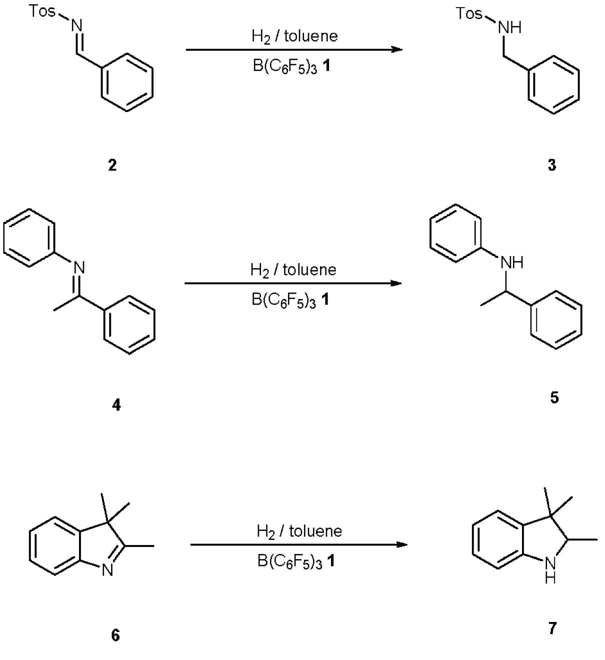
Fig. 1 Tris(perfluorophenyl)borane **1**.



Scheme 1 Metal-free hydrogenations of imines **2**, **4** and **6**.

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Table 1 Hydrogenations catalysed by **1** or **8**[a]

Entry	Substrate	Temp./ °C	Pressure/ bar	Catalyst/ mol%	Conversion (%)	Selectivity (%)
1	**2**	80	10	**1**/10.0	7	43
2	**2**	80	20	**1**/10.0	97	92
3	**2**	100	20	**1**/10.0	91	77
4	**2**	100	30	**1**/10.0	99	99
5	**4**	80	10	**1**/2.5	19	>99
6	**4**	80	10	**1**/5.0	68	>99
7	**4**	80	10	**1**/10.0	99	>99
8	**4**	50	10	**1**/10.0	29	>99
9	**4**	80	20	**1**/5.0	99	>99
10	**6**	100	40	**1**/10.0	0	—
11	**6**	140	20	**1**/10.0	21	>99
12[b]	**6**	140	40	**1**/10.0	53	>99
13[c]	**4**	65	20	**8**/10.0	>99	>99

[a] Conversion was determined by NMR; all parallel blank test reactions resulted in no conversion to the amines. [b] Reaction time: 22 h. [c] Enantiomeric excess of (**5**) was determined by GC analysis (Chirasil-Dex-CB).[17]

under much milder reaction conditions in comparison to **2**. Increasing the catalyst loading stepwise from 2.5 to 5.0 and 10.0 mol% ($T = 80$ °C, $p(H_2) = 10$ bar) resulted in 19, 68 and 99% conversion with a selectivity of 99% (entries 5–7). Lowering the reaction temperature to 50 °C at 10 bar hydrogen pressure reduced the conversion considerably to 29% (entry 8). In analogy to the substrate **2**, the application of a higher hydrogen pressure of 20 bar with 5 mol% catalyst resulted in full conversion to the product **5** (entry 9).

Changing the substrate to the sterically hindered imine **6** required more drastic reaction conditions. At 100 °C and 40 bar hydrogen pressure no product **7** could be detected (entry 10). However, at more elevated temperatures (140 °C) and 20 bar of hydrogen pressure, 21% of the product was obtained (entry 11). Increasing the hydrogen pressure to 40 bar at 140 °C gave **7** in a moderate yield of 53% (entry 12).

In order to evaluate the possibility of using this concept in asymmetric catalysis, the chiral borane **8**[18] (Fig. 2) was prepared and applied in the hydrogenation of substrate **4** at 65 °C and 20 bar hydrogen pressure. The reaction resulted in complete conversion to the product **5** with an enantiomeric excess of 13% *ee* (Table 1, entry 13). This finding corroborates the integral part of **8** in the catalytic active species and encourages further extension of this approach to other chiral boranes.

The mechanism of the hydrogen activation is still unclear, but in analogy to transition metal chemistry a side on interaction of H_2 on the Lewis acid **1** was discussed. Suggestions in this direction are supported by experimental data and computational studies which describe a weak $(\eta^2\text{-}H_2)BH_3$ adduct.[19–22] The intermediate Lewis acid–imine and –amine adducts generated have already been the subject of recent studies and imply the possibility of autocatalysis.[23–25]

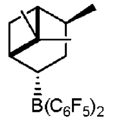

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Fig. 2 Chiral borane isomer derived from (+)-α-pinene.

In summary, metal-free imine hydrogenation has been accomplished using tris(perfluorophenyl)borane **1**[26] and chiral (+)-α-pinene derived borane **8** as the exclusive catalysts. The application of the reaction system in asymmetric catalysis and detailed mechanistic investigations are the subject of an ongoing study.

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Notes and references

† Procedure for a catalytic reaction: Substrate **4** (100 mg, 0.51 mmol) was dissolved in toluene (2.0 ml) in the presence of molecular sieves under argon and with rigorous exclusion of water and oxygen. Afterwards the solution was transferred to a stainless steel reactor with glass inlet (10 ml) containing the catalyst $B(C_6F_5)_3$ **1** (12.8 mg, 0.025 mmol). The reactor was flushed with hydrogen (3 × 10 bar) before being pressurised with hydrogen (20 bar) and stirred at 80 °C. After 15 h the reaction mixture was removed from the autoclave and the solvent was evaporated *in vacuo*. The conversion was determined by NMR spectroscopy. Isolated yield (93.1 mg, 0.47 mmol, 92%).

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