Asymmetric Hydrogenation

Enantioselective Hydrogenation with Chiral Frustrated Lewis Pairs**

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Dedicated to Professor Henri Brunner on the occasion of his 75th birthday

The development of transition-metal-catalyzed asymmetric hydrogenation could be stated as the cradle of modern enantioselective catalysis. Since the early asymmetric hydrogenation example from Knowles and Sabacky in 1968,[1] the method has rapidly advanced over the years into an important tool in academia and chemical industry.[2] In general, for these transformations the development of effective transition-metal complexes having chiral ligands was a basic prerequisite. However, since the pioneering work of Stephan and co-workers in 2006,[3] the field of homogenous hydrogenation has been extended to the possibility of metal-free hydrogenation based on the utilization of frustrated Lewis pairs (FLPs) for hydrogen activation.[4] Combinations of the strong Lewis acid tris(perfluorophenyl)borane ($B(C_6F_5)_3$) with a variety of sterically encumbered Lewis bases—phosphines,[5] nitrogen bases,[6] and carbon-derived bases[7]—can be used to activate hydrogen at ambient conditions. The concept was subsequently broadened from variations of the Lewis base to modifications of the Lewis acid structure, which resulted in intramolecular FLPs[8] and borane derivatives[9] with increased activity and stability. Furthermore, these chemical peculiarities rapidly found application in catalytic hydrogenation reactions. Some of the FLPs were found to serve as catalysts for the hydrogenation of imines, nitriles, and functionalized alkenes.[5b,6a,d,8c,9b,c,10] In the absence of bulky Lewis bases also imine substrates could adopt the function of the FLP partner, and $B(C_6F_5)_3$ was discovered to be sufficient as the catalyst for their hydrogenation.[6a,11] Additionally, recent mechanistic investigations and preparative experiments corroborated the assumption that for asymmetric transformations, the element of chirality has to be favorably incorporated into the Lewis acid structure. In early experiments employing α-pinene-derived chiral borane, asymmetric reduction of imines was achieved, albeit with low enantioselectivity (13% *ee*).[11] With these initial findings the synthesis

of effective chiral Lewis acids for application in asymmetric hydrogenation reactions was envisioned. On the basis of this concept, the first example of the highly enantioselective hydrogenation of imines with chiral FLPs is demonstrated herein.

The initial example with α-pinene-derived chiral borane confirmed the effectiveness of this catalyst structure. However, the stability of the Lewis acid emerged as a major drawback.[12] For the further investigations a chiral borane derived from camphor was considered to be a more suitable structural motif. Reaction of (1*R*)-(+)-camphor (**1**) with phenylmagnesium bromide (**2**) resulted in the tertiary alcohol **3** (Scheme 1). Subsequent dehydration with thionyl chloride/
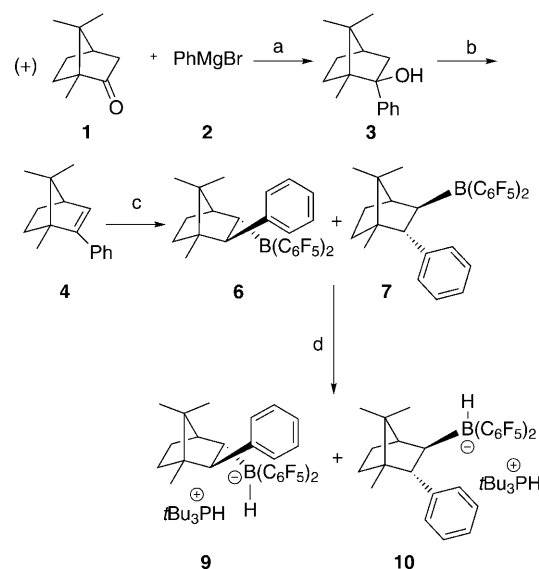
Scheme 1. Synthesis of chiral boranes and subsequent reaction of the FLPs with hydrogen. a) THF, 66°C, 12 h; b) pyridine, $SOCl_2$, −10°C, 1 h, 78%; c) $(C_6F_5)_2BH$ (**5**), *n*-pentane, RT, 1 h, 99%; d) *t*Bu$_3$P (**8**), H_2, *n*-pentane, RT, 30 h, 53%.

pyridine provided (1*R*,4*R*)-1,7,7-trimethyl-2-phenylbicyclo-[2.2.1]hept-2-ene (**4**) in 78% yield.[13] The hydroboration of **4** using bis(perfluorophenyl)borane (**5**)[12,14] in toluene or *n*-pentane gave the diastereomeric boranes **6** and **7** in a 1:4 ratio as confirmed by multinuclear NMR spectroscopy. The ^{11}B NMR spectra of the mixture exhibit only a broad resonance at $\delta = 81.8$ ppm. Moreover, the chemical shift difference between the *ortho* and *meta* F atoms of C_6F_5 fragments in the ^{19}F NMR spectra [**6**: $\delta = -161.1$ (*meta*), −149.8 (*para*), −132.1 (*ortho*), **7**: −161.3 (*meta*), −150.5

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(*para*), −130.8 ppm (*ortho*-C_6F_5)] suggest that neutral boron centers are present.[15]

As separation of the two diastereomers **6** and **7** was not possible at this point, partitioning of the salts formed from the FLPs after the hydrogen splitting was investigated. Treatment of an *n*-pentane solution of the borane mixture **6** and **7** with hydrogen at 25°C in the presence of tri-*tert*-butylphosphine (*t*Bu₃P; **8**) resulted in the precipitation of a colorless solid in 53% yield (Scheme 1). Multinuclear NMR spectroscopy corroborated the product as a mixture of the activated FLP salts **9** and **10** after the hydrogen splitting. Furthermore, recrystallization in dichloromethane and *n*-pentane produced single crystals consisting of **9** and **10** in a 1:1 ratio as confirmed by X-ray analysis (see the Supporting Information),[16] and precluded separation at this stage. However, a more detailed investigation revealed that the FLP **6/8** led to a faster hydrogen splitting reaction than the corresponding FLP **7/8**. This observation enabled isolation of the diastereomerically pure compounds **9** and **10** through kinetically controlled product formation. In the ³¹P NMR spectrum of compound **10** a doublet at $\delta = 59.8$ ppm with a J_{P-H} coupling of 431 Hz is consistent with the presence of the tri-*tert*-butylphosphonium [*t*Bu₃PH]⁺ cation. In the ¹H NMR spectrum a broad multiplet at $\delta = 2.87$ ppm and a doublet in the ¹¹B NMR spectrum at $\delta = -18.8$ ppm ($J_{B-H} = 88$ Hz) support the existence of a hydridoborate anion. The ¹⁹F NMR spectrum reveals two sets of typical C_6F_5 signals [$\delta = -132.3$ (*ortho*), −132.6 (*ortho*), −166.4 (*para*), −167.5 (*para*), −167.9 (*meta*), −168.5 ppm (*meta*-C_6F_5)], which can be attributed to the presence of two diastereotopic C_6F_5 rings. Comparable spectral data were observed for compound **9**. Single crystals of the salt **10**, suitable for X-ray structure determination, were grown from a dichloromethane/*n*-pentane solution, and one of two molecules in the asymmetric unit is shown in Figure 1.[16] The absolute configuration of the anion in the salt **10** was determined as bis(perfluorophenyl)-((1*R*,2*R*,3*R*,4*S*)-4,7,7-trimethyl-3-phenylbicyclo[2.2.1]heptan-2-yl)hydroborate. Interestingly, the phenyl ring in the chiral backbone is oriented parallel to one of the C_6F_5 rings and is separated by a distance of around 350 pm, thus providing the basis for a controlled conformation which should be important for subsequent effective catalytic applications.[17]
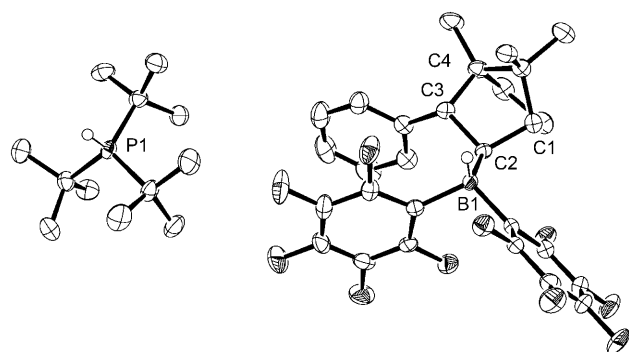

Figure 1. Crystal structure of **10**. Hydrogen atoms and solvent molecules were omitted for clarity—except for the hydrogen atoms bonded to boron and phosphorus. Thermal ellipsoids are set at 50% probability.

Accordingly, the absolute configuration of the anion in **9** was assigned by single-crystal X-ray analysis as (1*R*, 2*S*, 3*S*, 4*S*; Figure 2).[16] Again, a parallel orientation of the phenyl group and the C_6F_5 ring is observed, but there is a change in the orientation of the B–H bond, indicating the possibility of an altered chiral induction of the two isomers in an asymmetric hydrogenation reaction. In the solid state, **9** and **10** have multiple C−H⋯F hydrogen-bonding interactions that connect the phosphonium and hydridoborate moieties.[5b]
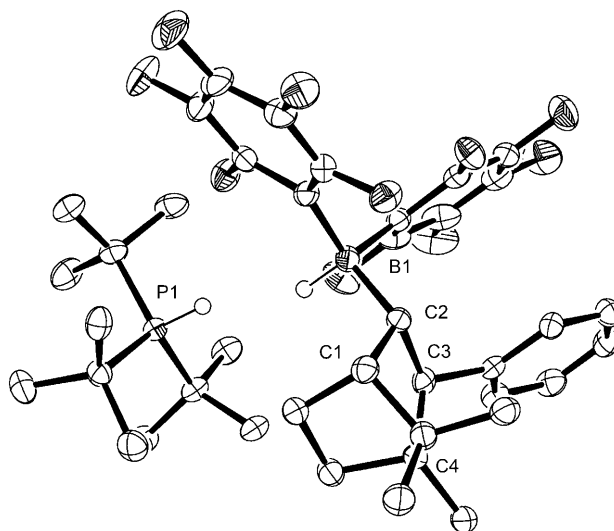

Figure 2. Crystal structure of **9**. Hydrogen atoms and solvent molecules were omitted for clarity—except for the hydrogen atoms bonded to boron and phosphorus. Thermal ellipsoids are set at 50% probability.

With the chiral compounds **9** and **10** in hand, the envisioned catalytic hydrogenation of prochiral imines was investigated (Table 1). In the presence of 5 mol% catalyst (1:1 mixture of **9** and **10**) at 65°C and 25 bar hydrogen, imine *N*-(1-*p*henylethylidene)aniline (**11a**) was transformed into the secondary amine **12a** with an enantioselectivity of 20% *ee* (*S* enantiomer; Table 1, entry 1). Using the diastereomerically pure salts (**9** and **10**) as catalysts for the hydrogenation of **11a** gave more encouraging results. In the case of hydrogenation using **9**, full conversion into the *S* product was achieved in 48% *ee* (Table 1, entry 2). Salt **10** led to the *R* enantiomer with an even higher enantioselectivity of 79% *ee* (Table 1, entry 3). In addition to this, a comparison of the measured enantioselectivities obtained with pure **9**, a 1:1 mixture of **9** and **10**, and pure **10** supported the assumption that catalyst **9** was more active in the catalytic hydrogenation than **10**. Correlating this observation to the fact that hydrogen splitting was also faster with the Lewis pair **6/8** (precursor of **9**) gives significant information with respect to the rate-determining step in the reactions using the two diastereomers.

To assess the substrate scope, a variety of substituted imine derivatives were hydrogenated using diastereomerically pure **10** as the catalyst. Upon increasing the steric hindrance of the substrate, the yield of the corresponding amine decreased significantly (Table 1, entries 4 and 5). For

Table 1: Hydrogenation catalyzed by chiral FLP salts.

11a: R¹ = Ph, R² = Ph
11b: R¹ = Ph, R² = 2-Me-C₆H₄
11c: R¹ = Ph, R² = 2,6(Me₂CH)C₆H₃
11d: R¹ = 4-MeO-C₆H₄, R² = Ph
11e: R¹ = Ph, R² = 4-MeO-C₆H₄
11f: R¹ = 2-Naphthyl, R² = Ph
11g: R¹ = 2-Naphthyl, R² = 4-MeO-C₆H₄

Entry[a]	Substrate	Catalyst	Yield [%][c]	ee [%][d]
1	11a	9/10 = 1:1	>99	20 (S)
2	11a	9	>99	48 (S)
3	11a	10	95	79 (R)
4[b]	11b	10	37	74 (−)
5[b]	11c	10	0	–
6	11d	10	96	81 (−)
7	11e	10	>99	81 (R)
8	11f	10	93	80 (−)
9	11g	10	96	83 (+)

[a] Reaction conditions: Catalyst (10 μmol), imine (0.2 mmol), H₂ (25 bar), $T = 65\,°C$, 15 h. [b] Reaction time: 20 h. [c] Yield was determined by ¹H NMR analysis. [d] Determined by HPLC or GC methods using a chiral column; absolute configurations assigned by comparison of retention times and optical rotations with literature values.

the imine 2-methyl-N-(1-phenylethylidene)aniline (**11b**), a slightly lower enantioselectivity of 74% ee was obtained at a conversion of only 37% (Table 1, entry 4). Upon applying the imine 2,6-diisopropyl-N-(1-phenylethylidene)aniline (**11c**), no catalyst activity could be observed. Notably, introducing a methoxy donor group to either of the phenyl rings in the imine gave enhanced conversion and selectivity. With either N-(1-(4-methoxyphenyl)ethylidene)aniline (**11d**) or 4-methoxy-N-(1-phenylethylidene)aniline (**11e**) an enantioselectivity of 81% ee was obtained (Table 1, entries 6 and 7). The hydrogenation of the 2-naphthyl imine derivative N-(1-(naphthalen-2-yl)ethylidene)aniline (**11f**) with catalyst **10** produced **12f** in 93% yield and in 80% ee (Table 1, entry 8). Moreover, the presence of a methoxy group in 4-methoxy-N-(1-(naphthalen-2-yl)ethylidene)aniline (**11g**) favored the catalytic hydrogenation with a higher conversion of 96% and a noticeable enantioselectivity of 83% ee.

In summary, stable chiral boranes that can be used in frustrated Lewis pairs have been synthesized and employed in hydrogen activation together with tBu₃P under mild reaction conditions. Moreover, significant enantioselectivity was obtained for the first time using the FLP concept with these chiral catalytic systems. The application of this system in other catalytic reactions and detailed mechanistic investigations are in progress and will be reported in due course.

Experimental Section

General procedure for the catalytic metal-free hydrogenation employing chiral FLPs: Under an argon atmosphere, imine (0.2 mmol), salt **10** (0.01 mmol), and dry toluene (1.0 mL) were transferred to a stainless steel autoclave. The autoclave was purged three times with hydrogen and finally pressurized to 25 bar. The reaction mixture was stirred at 65°C for the indicated period of time. The conversion of the substrate was determined by ¹H NMR spectroscopy of the crude reaction mixture, and the product was purified by flash chromatography on silica gel using n-pentane/ethyl acetate (10:1) as the eluent. The enantiomeric excess was determined

either by HPLC methods using a chiral stationary phase column (Chiralcel OD-H, AD-H and OJ-H) or by GC methods (Chirasil-Dex CB).

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