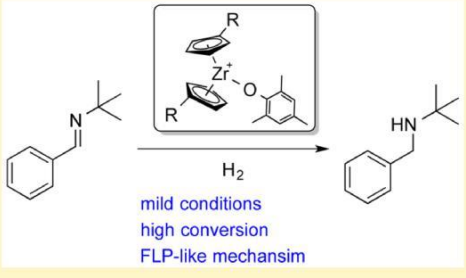
Zirconium-Catalyzed Imine Hydrogenation via a Frustrated Lewis Pair Mechanism

Stephanie R. Flynn, Owen J. Metters, Ian Manners, and Duncan F. Wass*

School of Chemistry, University of Bristol, Cantock's Close, Bristol, U.K.

* Supporting Information

ABSTRACT: Zirconium-based frustrated Lewis pairs (FLPs) are active imine hydrogenation catalysts under mild conditions. Complexes of the type $[Cp^R_2ZrOMes][B(C_6F_5)_4]$ utilize the imine substrate itself as the Lewis base component of the FLP. Catalyst performance is a function of ligand structure; in general more bulky, more electron rich cyclopentadienyl derivatives give the best results. However, Cp* derivatives are not catalytically active, being stable after initial heterolytic cleavage of H_2; this allows experimental verification of the competence of the zirconocene−imine pair in FLP-type heterolytic H_2 cleavage. Enamines and protected nitriles are also hydrogenated if an additional internal phosphine base is used.



INTRODUCTION

We have been exploring frustrated Lewis pairs (FLPs) in which the usual main group Lewis acid or base component is replaced with a transition metal complex.[1] Much of our work has focused on cationic zirconium phosphinoarlyoxide complexes that can be thought of as analogues of Stephan's and Erker's borane/phosphine FLPs with the borane replaced by an electrophilic zirconocene fragment.[2] These complexes demonstrate reactivity that mimics main group FLPs in reactions such as heterolytic H_2 cleavage and CO_2 binding and give distinctive reactivity in other examples, including catalytic amine−borane dehydrocoupling.[1] Other transition metal FLPs have subsequently been reported by us and others.[3,4]

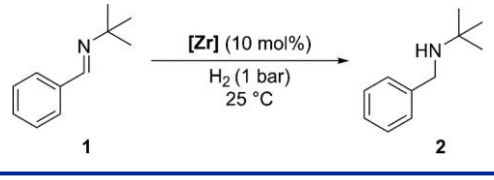
One of the most promising early results with main group FLPs was the catalytic hydrogenation of imines.[5] Initial results were modest in terms of activity and substrate scope, but these have subsequently been developed and extended to other substrates and catalytic systems that have much wider applicability.[6]

We were intrigued to investigate the potential of our zirconocene-based FLPs in catalytic hydrogenation reactions, particularly so since related metallocene complexes are well-known to facilitate hydrogenation reactions via more conventional insertion/elimination mechanisms.[7] Particularly relevant is the work of Buchwald and co-workers, who reported the highly successful asymmetric hydrogenation of imines with a chiral ansa-titanocene.[8] The active catalyst is proposed to be a titanium(III) hydride, with the first step of the mechanism thought to be 1,2-insertion to form a Ti-amide complex. Subsequent hydrogenolysis (via a σ-bond metathesis) leads to regeneration of the active species and liberation of amine.[9] The key point of these previous metallocene-catalyzed hydrogenation studies is that an active hydride complex must be formed, typically by addition of a hydride reagent (e.g., $RSiH_3$) to a transition metal precatalyst. The FLP-based mechanism proposed herein is quite different and needs only H_2 to form an active species via heterolytic cleavage, a potentially more simple and practical methodology.

RESULTS AND DISCUSSION

Initially, we screened a small selection of zirconocene phosphinoaryloxide complexes for the hydrogenation of the bulky imine ^{t}BuN CHPh with 1 bar of H_2 at room temperature (Scheme 1, Figure 1); the results are presented in Table 1.

Scheme 1. General Conditions Employed for Imine Hydrogenation Reactions



It is evident that there is a link between steric bulk and conversion. Indeed, a complex bearing indenyl ligands (6) was found to be extremely sluggish for this transformation, giving <1% conversion to 2 after 470 min. The less sterically congested, previously reported, complex 3 afforded 31% conversion to 2 after 410 min, with complete hydrogenation of the imine achieved within approximately 3 days.[1] It should be noted that FLP systems 3−6 are thought to be inactive toward the stoichiometric heterolytic cleavage of H_2, as evidenced by ^{31}P NMR spectroscopy (see Supporting Information). This may however be due to the presence of an equilibrium between the FLP and the resulting H_2 cleavage product, which due to the instability of the zirconium hydride lies in favor of the free FLP.

In the presence of a hydrogen acceptor such as an imine, H_2 cleavage may immediately precede H_2 transfer to the substrate.

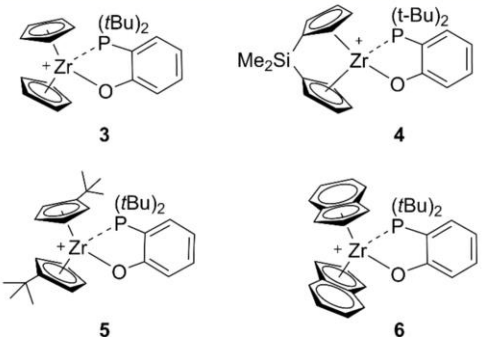


Figure 1. Zr−P complexes tested for hydrogenation of imine 1.

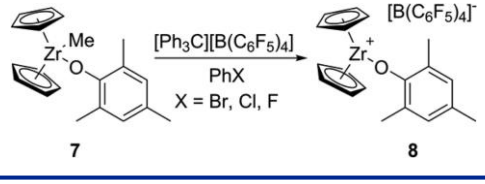
Table 1. Conversion Reaction Results[a]

complex	time (min)	conversion (%)
3	410	31
4	405	22
5	370	4
6	470	<1

[a]Reaction conditions: 10 mol % [Zr], PhCl (0.5 mL), 25 °C, 1 bar of H_2. All conversions as determined by ^{1}H NMR spectroscopy.

In experiments to confirm that complexes 3−6 are acting as an FLP, an analogous zirconocene aryloxide complex without the intramolecular Lewis basic phosphine moiety was screened. The synthesis of cation 8 was recently reported by our group (Scheme 2),[10] and to our initial surprise, when 10 mol % 8 was subjected to

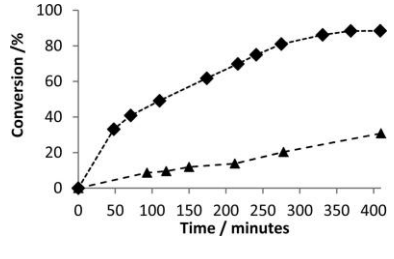
Scheme 2. Synthesis of Zr Cation 8[10]



conditions identical to those shown in Scheme 1, it led to a drastic increase in the rate of hydrogenation of imine, the reaction being complete in less than 7 h (Chart 1). With hindsight, we realized that this result is reminiscent of previous work by Stephan and co-workers using the Lewis acid $B(C_6F_5)_3$, where the imine substrate itself acts as the Lewis base in hydrogenation.[11]

Inspired by this result, a number of cationic zirconocene mesityloxide complexes were synthesized to explore the effect of

Chart 1. Comparison of Rates of Reaction for 3 (▲) and 8 ( )



sterics and electronics at the metal center (Figure 2). Complexes 9−11 were synthesized by the same route as 8 but were used in

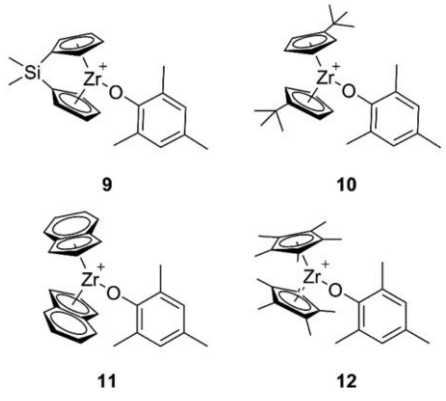
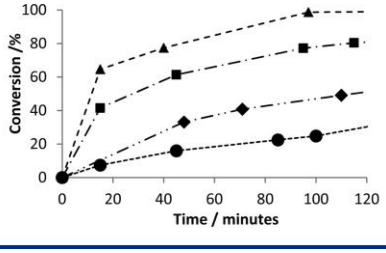


Figure 2. Cationic complexes synthesized (9−12). Counterion = $[B(C_6F_5)_4]^-$.

situ, as attempted isolation via hexane trituration yielded intractable oils. 12 was generated by an alternative method involving methyl abstraction from $Cp^*_2ZrMe_2$ using $[Ph_3C][B(C_6F_5)_4]$ prior to protolysis of the remaining methyl group using HO-Mes.[10]

Compounds 8−12 were tested for catalytic activity in the hydrogenation of ^{t}BuN CHPh in a series of NMR-scale reactions employing the conditions shown in Scheme 1. The in situ solutions of 8−12 were transferred to an NMR tube fitted with a Teflon needle valve and pressurized with 1 bar of dihydrogen (H_2). The reaction was followed by ^{1}H NMR spectroscopy, with the relative integrals of the peaks correspond-ing to the methylene protons (δ ~3.7 ppm) in the product and the CH NR (δ ~8.3 ppm) proton in the starting material used to generate quantitative data. The results of this study are shown in Chart 2. Note that 12 showed no conversion under these conditions.

Chart 2. Rates of Hydrogenation with Complexes 8 (⬥), 9 (●), 10 (■), and 11 (▲)



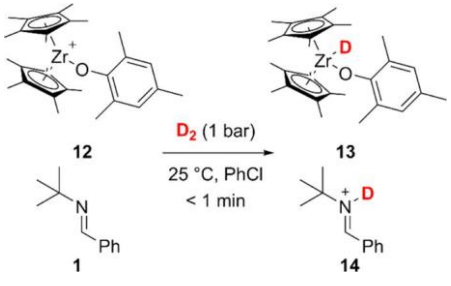
These data reveal a direct relationship between the ligand structure and rate of the hydrogenation. The least bulky ansa-zirconocene catalyst 9 gives 30% conversion after 120 min, with 8 showing an increased conversion of 50%. A sharp increase in conversion is observed with a monosubstituted tert-butyl group (10), with over 80% conversion to amine. The bis-indenyl complex 11 was found to be the most active, with the reaction proceeding to 97% completion after 90 min, while heating the reaction at 80 °C led to complete conversion to ^{t}BuNHCH$_2$Ph in under 60 min.

These observations reveal that the most sterically hindered, and most electron rich, catalysts perform more effectively for this transformation. However, there are limits to this trend since a

further increase of steric bulk at the zirconium center has a detrimental effect; 12 was found to be catalytically inactive under these conditions, leading to the formation of the stable zirconium hydride $Cp^*_2Zr(H)OMes$ and iminium species $[^tBuN(H)\text{-}CHPh][B(C_6F_5)_4]$.

Noting that this result could provide us with a mechanistic handle, the reaction was repeated, but with equimolar amounts of ^tBuN CHPh and $[Cp^*_2ZrOMes][B(C_6F_5)_4]$ and 1 bar of D_2. Formation of the hydrogen-activated FLP products Cp^* Zr(D)-(OMes) and $[^tBuN(D)$ CHPh$][B(C_6F_5)_4]$ (Scheme 3) was evidenced by ^2H NMR spectroscopy (Figure 3).

Scheme 3. Stoichiometric Reaction between 12 and Imine under a D_2 Atmosphere[a]



[a]Counterion = $[B(C_6F_5)_4]^-$.

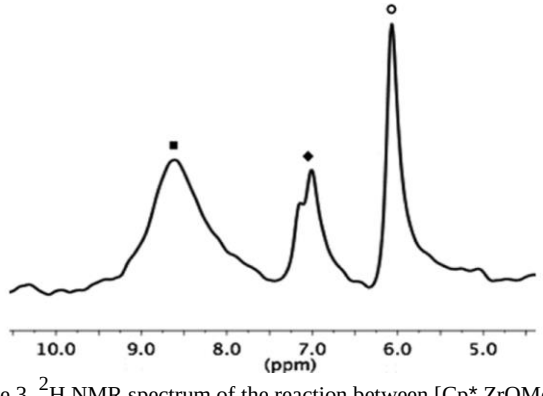


Figure 3. ^2H NMR spectrum of the reaction between $[Cp^*_2ZrOMes][B(C_6F_5)_4]$ (12), ^tBuN CHPh (1), and 1 bar of D_2 (PhCl). ▪ = 8.61 (br s, N-D), ◆ = 7.15−6.95 (m, deutero-PhCl), ○ = 6.07 (s, Zr-D).

In the ^2D NMR spectrum (Figure 3), the broad signal at δ 8.39 is indicative of ND and the sharp singlet at δ 5.85 of ZrD.[1,12] Generation of this intermediate suggests that steric bulk of the Cp* ligands prevents the hydride transfer to the carbon of the iminium, providing us with a proposed first step of a mechanistic cycle (Scheme 4).

This first step is heterolytic, FLP-type cleavage of dihydrogen between the Lewis acidic zirconium center and the imine nitrogen, to generate an activated iminium. The iminium carbon is now electrophilic and can be attacked by the zirconium hydride, leading to formation of a Zr-amine adduct. Release of the amine leads to regeneration of the active Zr species. This mechanism as shown in Scheme 4 is analogous to that proposed for the main group equivalent with Lewis acid the $B(C_6F_5)_3$.[11]

With our most efficient catalyst 11, we sought to test its catalytic activity toward a variety of imines. Our standard conditions were 10 mol % catalyst loading, 1 bar of H_2, and 25 °C in 0.5 mL of a PhX solvent (X = Br, Cl, F). Conversions based on ^1H NMR spectroscopy were calculated after 90 min (Table 2).

Scheme 4. Proposed Mechanistic Cycle for Imine Hydrogenation

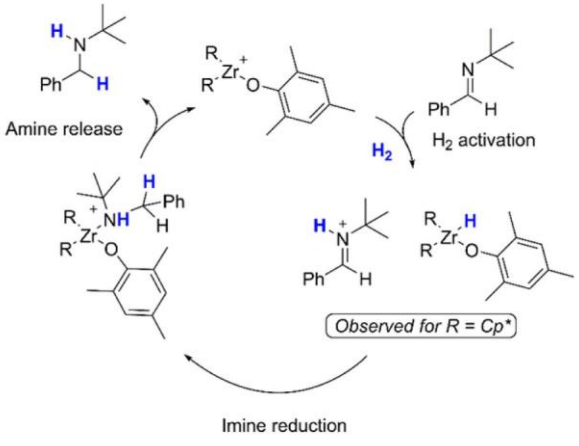
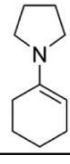


Table 2. Catalytic Hydrogenation of a Range of Imines by 11

Substrate —[Cat **11** (10 mol %); PhX, H_2 (1 bar), 25 °C, 90 min; X = Br, Cl, F]→ Product

Entry	Substrate	Conversion[a] (%)
1	*t*BuN=CHPh	97
2	*t*BuN=CH(*p*-BrC_6H_4)	88
3	*t*BuN=CH(*m*-BrC_6H_4)	89
4	*t*BuN=CH(*m*-$OMeC_6H_4$)	64
5	*t*BuN=CH(*p*-$NMe_2C_6H_4$)	35
6	MeN=CHPh	<2
7	(*p*-ClC_6H_4)N=CHPh	<2
8	BnN=CHPh	<2
9	(PhO_2S)N=CHPh	<2
10	(*p*-$OMeC_6H_4$)N=CHPh	<2
11	Ph-C≡N•$B(C_6F_5)_3$	0
12		0

[a]Conversion to the corresponding amine in all cases based on ^1H NMR spectroscopy.

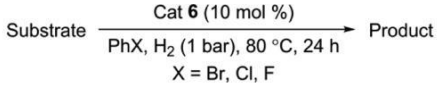
Imines bearing substituents on the phenyl ring (entries 1−5) were readily reduced in varying yields. Reducing the steric bulk on the nitrogen (entries 6−10) unsurprisingly decreases the hydrogenation significantly, as this is thought to preclude the initial heterolytic cleavage of H_2 through formation of a relatively stable Zr/N Lewis pair. Indeed, even addition of an electron-donating group (entry 10) on the nitrogen-bound aryl ring gives poor turnover, in line with this hypothesis. The introduction of the dimethylamino fragment (entry 5) reduces the rate, presumably due to the amine binding to the Zr center, inhibiting the reaction.

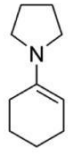
Preliminary attempts to reduce protected nitriles (entry 11) and enamines (entry 12) were unsuccessful. We hypothesized this may be due to the low Lewis basicity of these substrates, since the substrate itself must also be sufficiently Lewis basic to act as an integral part of the catalyst. With this in mind, we

reinvestigated our intramolecular Zr−P FLPs and specifically the indenyl complex 6.

Exposure of a solution of the substrate with 10 mol % catalyst 6 to dihydrogen led to hydrogenation and generation of the corresponding amines (Table 3), although these particular reactions are more sluggish and require higher temperatures to observe appreciable conversion.

Table 3. Catalytic Hydrogenation of Enamines and Protected Nitriles by 6



Entry	Substrate	Conversion[a] (%)
1		29
2	Ph-C≡N•B(C_6F_5)$_3$	40

[a]Conversion to the corresponding amine based on ^{1}H NMR spectroscopy.

The necessity of an internal phosphine base for these substrates suggests a different mechanism from that proposed for imine substrates in that heterolytic cleavage of H_2 across the Zr−P pair is followed by proton and hydride transfer to the substrate. It is noteworthy that heterolytic cleavage of H_2 by 6 is not observed by NMR spectroscopy in the absence of an external hydrogen acceptor, suggesting that the H_2 activation product is in rapid equilibrium with 6 at 25 °C and the transfer of the sequestered H_2 to the enamine is the rate-determining step in this case.

CONCLUSIONS

In conclusion, the combination of a Lewis acidic zirconium center with sterically hindered imines in the presence of dihydrogen results in heterolytic cleavage of H_2, generating a zirconium hydride and an iminium salt. With suitable ancillary ligands of Zr, the hydride can be delivered to the iminium, leading to the catalytic hydrogenation of tert-butyl-substituted imines under mild reaction conditions (1 bar dihydrogen, room temperature) via an FLP-type mechanism. These mild conditions compare favorably with similar chemistry using main group FLPs (for example 5 atm H_2, 120 °C reported by Stephan and co-workers[11]). For the hydrogenation of enamines and imines a further intramolecular phosphine Lewis basic fragment is required, with the mechanism involving heterolytic H_2 cleavage by the Zr/P FLP prior to transfer of the proton/ hydride to the substrate.

ASSOCIATED CONTENT

* Supporting Information

Experimental and spectroscopic details (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: duncan.wass@bristol.ac.uk; www.wassresearchgroup.com.

Author Contributions

The manuscript was written through contributions of all authors.

The authors declare no competing financial interests.

Notes

The authors declare no competing financial interest.

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