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Mechanistic Investigations of Reactions of the Frustrated Lewis Pairs (Triarylphosphines/$B(C_6F_5)_3$) with Michael Acceptors

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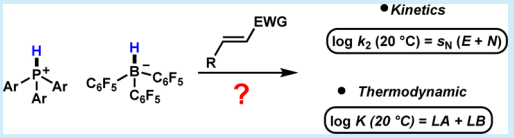
Supporting Information

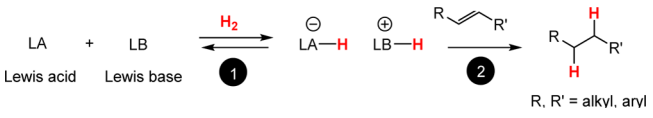
ABSTRACT: Frustrated Lewis pair (FLP)-catalyzed reduction of Michael acceptors is a challenging reaction that proceeds with specific FLP structures. Kinetics and equilibrium of the reactions of two phosphines (Ar_3P), namely tri(1-naphthyl)phosphine and tri(*o*-tolyl)phosphine, are reported with reference electrophiles. The reason for the failure of the FLPs ($Ar_3P/B(C_6F_5)_3$) to reduce activated alkenes under H_2 pressure is shown to be a hydrophosphination process that inhibits the reduction reaction. Kinetic and thermodynamic factors controlling both pathways are discussed in light of Mayr's free linear energy relationships.



Heterolytic bond splitting of inert molecules is undoubtedly one of the most challenging processes that continues to stimulate a large spectrum of research in modern organic chemistry.[1] While this type of activation has long been restricted to transition metals,[2] it has recently been demonstrated that pure organic molecules are effective in catalyzing such a reaction.[2] For instance, Stephan, Erker, and Paradies, to name a few, have shown that the combination of sterically hindered Lewis acids (typically $B(C_6F_5)_3$) with Lewis bases (phosphines, carbenes and amines) results in the formation of the so-called frustrated Lewis pairs (FLPs).[3] These complexes have proven to be efficient in cleaving H_2 heterolytically to form borohydrides that are nucleophilic enough to reduce a large variety of alkenes.[4]

From a simplified mechanistic point of view, the catalytic reduction of alkenes depends on the efficiency of FLPs to cleave H_2 (step 1, Scheme 1) and also on the ability of the formed borohydride salts to reduce alkenes (step 2). While the heterolytic splitting process of H_2 (step 1) has been extensively investigated, both computationally and experimentally,[5] mechanistic understanding of the reduction step remained scantily explored. To the best of our knowledge, only two reports dealing with this aspect have been reported. Berionni et al. quantified the hydricity of phosphonium and ammonium borohydrides by using the well-known Mayr's free energy relationship (vide infra). They demonstrated that the hydride-donating ability of these salts depends on the nature of the boron substituents.[6] On the other hand, Paradies et al. have isolated and characterized various FLPs, for instance, fluoroarylphosphines/$B(C_6F_5)_3$.[7] Importantly, it was shown that the acidity of the phosphonium ions plays a pivotal role in the hydrogenation of polarized C=C double bonds. Indeed, acidic phosphonium ions activate alkenes to the corresponding carbocations that can then be reduced by the borohydrides. For example, due to the high Brønsted acidity of its phosphonium salt, tri(1-naphthyl)phosphine ($(C_{10}H_7)_3P$) **1a** (pK_a ($C_2H_4Cl_2$) = 6.7)[7] has been shown to be a good Lewis base partner for $B(C_6F_5)_3$ to reduce a large variety of electron-rich olefins under H_2 pressure.[8]

Scheme 1. General Mechanistic Scheme of FLP Catalytic Reductions of Alkenes[a]



[a]LA and LB denote Lewis acid and Lewis base, respectively.

On the basis of these studies and especially on those of Berionni et al., who demonstrated that phosphonium and ammonium borohydrides react smoothly with quinone methides, α,β-unsaturated iminium ions, and benzylidene malononitriles under stoichiometric conditions, it is reasonable to assume that common Michael acceptors can be reduced under catalytic FLP conditions.[6] However, FLP reduction of Michael acceptors bearing oxygen atoms turned out to be problematic as only specific FLPs are effective in this reaction. In this context, Paradies stated "FLP-catalyzed hydrogenation of functionalized, especially oxygen containing, groups is highly challenging because of the strong Lewis basic character combined with insufficient steric shielding. Consequently, catalyst inhibition is one of the most problematic issues in FLP-mediated reductions of enones, malonates, or nitro-olefins".[1g]

In order to gain more mechanistic information about the reasons for the failure of $Ar_3P/B(C_6F_5)_3$ FLPs in the reduction of Michael acceptors, we decided to study kinetics and equilibrium of their reactions with phosphines **1a,b**. Because **1a,b** are known to be effective in cleaving H_2 in the presence of

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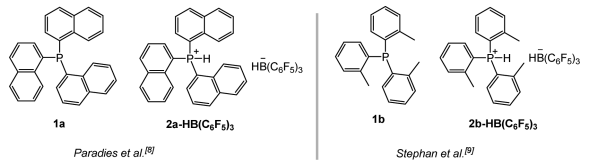
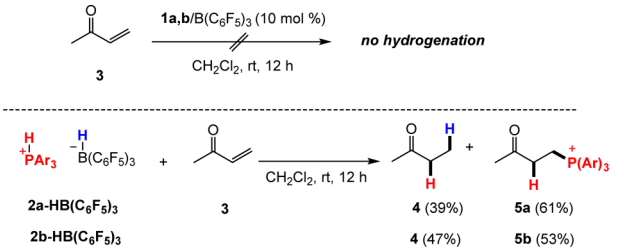
$B(C_6F_5)_3$ and the resulting phosphonium borohydrides **2a,b**–$HB(C_6F_5)_3$ salts have been isolated and characterized, we envisioned investigating their reactions with Michael acceptors (Scheme 2).[8,9]

Scheme 2. Structures of Phosphines 1a,b and the Corresponding Phosphonium Salts 2a,b–$HB(C_6F_5)_3$



To begin, the catalytic reduction of the methylvinylketone **3** with **1a,b**–$B(C_6F_5)_3$ (10 mol %) has been selected as a benchmark reaction. As shown in Scheme 3, both reactions did

Scheme 3. Catalytic Reduction of Methylvinyl Ketone 3 with 1a,b/$B(C_6F_5)_3$ (10 mol %) under H_2 Atmosphere (Top). Reaction of Phosphonium Ions 2a,b–$HB(C_6F_5)_3$ with Methylvinyl Ketone 3 in CH_2Cl_2 at Room Temperature (Bottom)



not proceed under atmospheric pressure of H_2 at room temperature, and only traces of the reduction adducts **4** can be detected within 12 h. However, ^{31}P NMR analysis of the crude mixtures showed the appearance of new peaks, which have been assigned to the phosphination adducts **5a,b**. The reaction outcomes have been found to be counterion independent as almost similar yields have been obtained when reactions have been performed when triflate phosphonium salts have been used instead of the trihydroborate salt(see the Supporting Information). In order to confirm the structures of **5a,b**, phosphonium borohydrides **2a,b**–$HB(C_6F_5)_3$ have been synthesized according to protocols previously described in the literature.[8,9] Interestingly, when **2a,b**–$HB(C_6F_5)_3$ were combined with 1 equiv of **3**, the expected reduced adducts **4** were observed along with the hydrophosphination adduct **5a,b** in 61:39 and 47:53 ratios, respectively (Scheme 3).

In order to gain mechanistic information into these insightful observations, we decided to quantify nucleophilicity and carbon Lewis basicity of phosphines **1a,b**. Indeed, Mayr et al. demonstrated, during the last two decades, the capability of the free linear energy relationship (eq 1) to describe kinetics of numerous nucleophile–electrophile combinations.[10]

$$\log k(20^{\circ}C) = s_N(E + N) \quad (1)$$

In this equation, while electrophiles are characterized by a single parameter E, nucleophiles are described by two parameters: nucleophilicity, N, and a nucleophile-specific susceptibility parameter, s_N. Based on this approach, we studied kinetics of the reactions of phosphines **1a,b** with benzydrylium ions **6a–c** (see Figure 2). When a large excess of phosphines **1a,b** is combined with benzhydrylium ions **6a–c**, mono-exponential decays of the absorbance of **6a–c** are observed (Figure 1). In line with previous studies by Mayr et al. on the

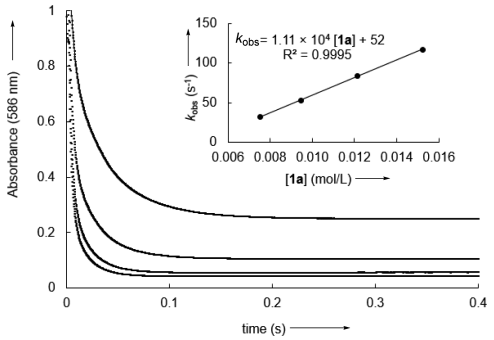


Figure 1. Plot of the absorbance at 586 nm versus time for the reactions of **6a** (1.35×10^{-4} mol/L) with **1a** at different initial concentrations.

reactivity of tertiary phosphines, reversible processes have also been observed when phosphines **1a,b** were combined with **6a–c**.[11]

Plotting rate constants k_{obs}, derived from monoexponential decays, against concentrations of nucleophiles **1a,b** gives linear correlations where the slopes yielded second-order rate constants for the reaction of **1a,b** with **6a–c**. Figure 2 shows

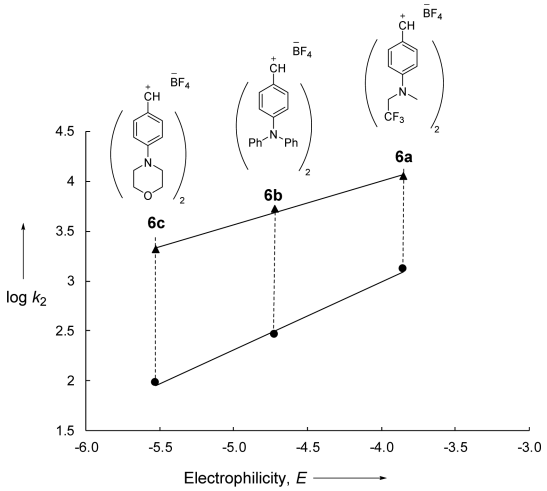


Figure 2. Plot of log k_2 vs E for reactions of phosphines **1a** (triangles) and **1b** (circles) with benzhydrylium ions **6a,c**.

linear correlations between the logarithms of the second order rate constants (log k_2) and the E parameters of the benzhydrylium ions **6a–c**, as required by the eq 1. The slopes of the correlation lines give the nucleophile-specific sensitivity parameters s_N, and the intercepts on the abscissa yield the nucleophilicity parameters N, which are gathered in Table 1.

Table 1 shows that **1a** is about 18 times more reactive than **1b**. This can presumably be due to the steric hindrance of the tolyl group due to its high Tolman angle (θ[**1b**] = 194°).[12]

As the reactions of phosphines **1a,b** with benzhydrylium ions proceeded incompletely, we also studied the corresponding equilibrium constants (K) by UV–vis spectroscopy. The Lewis basicity of **1a,b** has been quantified by using an approach recently introduced by Mayr, who found that the K values for

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Table 1. Second-Order Rate Constants, Nucleophilicity, and Lewis Basicity for Reactions of 1a,b with Benzhydrylium Ions 6a–c in MeCN or CH_2Cl_2 at 20 °C

phosphines	electrophiles	k_2 (M^{-1} s^{-1})	N, s_N	LB
1a[a]	**6a**	1.11×10^4	13.17, 0.44	8.62
	6b	5.23×10^3		
	6c	2.05×10^3		
1b[b]	**6a**	1.31×10^3	8.40, 0.68	7.77
	6b	2.87×10^2		
	6c	9.48×10^1		

[a]In acetonitrile. [b]In dichloromethane.

reaction of benzhydrylium ions with various Lewis bases can be expressed as the sum of a Lewis acidity parameter LA and a Lewis basicity parameter LB (eq 2).[13]

$$\log K(20°C) = \mathrm{LA} + \mathrm{LB} \quad (2)$$

By using the previously determined Lewis acidity (LA) of benzhydrylium ions and the measured equilibrium constants (K), the Lewis basicity of **1a** was determined to be 10 times higher than that of **1b** (Table 1).

Having the rate constants of the reactions of **1a,b** with benzhydrylium ions and the related equilibrium constants in hand, we then employed the Marcus equation (eq 3, working terms neglected) to calculate barriers $\Delta G_0^{\ddagger}$ for these reactions. First, we calculated the Gibbs energy of activation when the effect of the thermodynamic driving force is eliminated ($\Delta G_0 = 0$).[12]

Thus, by substituting $\Delta G^{\ddagger}$ and ΔG_0 into the Marcus eq 3, the intrinsic barriers $\Delta G_0^{\ddagger}$ for the reactions of **1a,b** with **6a–c** have been calculated (Table 2).

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + 0.5\Delta G_0 + ((\Delta G_0)^2/16\Delta G_0^{\ddagger}) \quad (3)$$

Table 2. Activation Energies $\Delta G^{\ddagger}$, Reaction Free Energies ΔG_0, and Intrinsic Barriers $\Delta G_0^{\ddagger}$ (in kJ/mol) for the Reactions of Benzhydrylium Ions 6a–c with Phosphines 1a,b

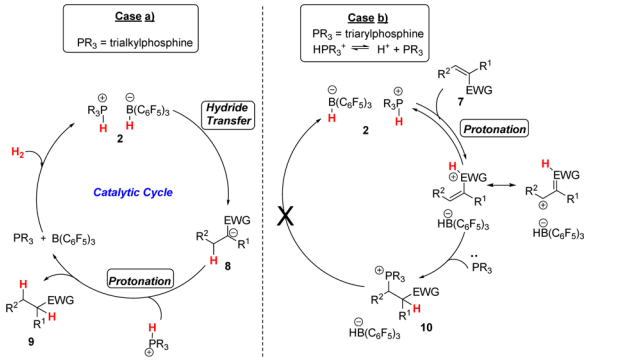
phosphines	Ar_2CH^+	$\Delta G^{\ddagger}$	ΔG^0	$\Delta G_0^{\ddagger}$
1a	**6a**	49.1	−18.4	57.9
	6b	50.9	−15.5	58.4
	6c	53.2	−10.7	58.4
1b	**6a**	54.3	−12.8	60.5
	6b	58.0	−10.9	63.3
	6c	60.7	−6.66	63.9

As shown in Table 2, the intrinsic barriers of the reactions of **1b** with **6a–c** are ~3–5 kJ/mol greater than those for **1a**. This indicates that more reorganizing energy is needed for the reaction of **1b** than for the reactions with **1a**, most probably due to the steric hindrance.

Based on the hydricity of phosphonium and ammonium borohydride determined by Berionni in one hand, and the nucleophilicity, carbon Lewis basicity, and intrinsic reactivity of phosphines, especially **1a,b**, on the other hand, the following reaction mechanism can be proposed (Scheme 4).

When the phosphonium borohydride **2**, formed upon heterolytic cleavage of H_2 by the FLPs, reacts with Michael acceptors **7**, two pathways are possible: (a) If the phosphonium ion is not acidic enough ($pK_a \geq 6$), typically in the case of trialkylphosphines, the borohydride is the only nucleophilic species present in the media and can react with the Michael

Scheme 4. Proposed Mechanisms for Phosphine–($B(C_6F_5)_3$) Hydrogenation of Michael Acceptors



acceptor to give the carbanion **8**, which is subsequently protonated to yield **9**. In this case, the nucleophilicity of the borohydrides is crucial for the feasibility of the reduction. This explanation holds also for ammonium borohydrides,[14] which have low Brønsted acidities and thus can efficiently reduce Michael acceptors.[1a] (b) If now the generated phosphonium borohydride is acidic, for instance, triarylphosphonium salts, then two nucleophiles are present in the media: the free phosphine and the borohydride.

On one hand, if the nucleophilicity of the borohydride is significantly greater than that of the phosphine, the hydrogenation pathway is predominant and only the saturated product **9** is formed. On the other hand, if the phosphine is more nucleophilic than the borohydride, such as in the case of tri(1-naphthyl)phosphine **1a** (N = 13.17 *vs* N = 10.01), the phosphorus addition at the terminal methylene group is kinetically favorable and the hydrophosphination adduct **10** can be formed. This may rationalize the failure of those phosphines in reducing activated alkenes in the presence of $B(C_6F_5)_3$ and under H_2 atmosphere. However, if the phosphine has a lower nucleophilicity than the borohydride, as in the case of **1b** (N = 10.01 vs 8.40), the hydride transfer step can take place faster than the addition of the phosphine, leading to the formation of **9**. The kinetic and thermodynamic data also rationalize the reaction outcomes for the addition of **2a,b**–$HB(C_6F_5)_3$ to **3**. The predominance of the hydrophsphination over the reduction adduct in the case of the reaction of **2a**–$HB(C_6F_5)_3$ with **3** (Scheme 3) is a consequence of the low Lewis basicity of **1b** and the high intrinsic reactivity $\Delta G_0^{\ddagger}$. To confirm our proposed mechanism, the reactions of **2a,b**–$HB(C_6F_5)_3$ with four Michael acceptors **3b–e** have been conducted in dichloromethane at room temperature. As depicted in Figure 3, while only reduction adducts **4b–e** have been observed when **2a,b**–$HB(C_6F_5)_3$ were combined with **3d,e**, a mixture of the hydrophosphination and reduction adducts has been detected for the reactions **2a,b**–$HB(C_6F_5)_3$ with the enones **3b,c**. Because the Mayr's rule of thumb

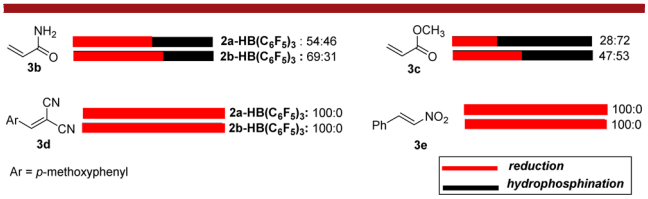


Figure 3. Product distributions of the reactions of **2a,b**–$HB(C_6F_5)_3$ with Michael acceptors **3b–e**.

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predicts that reactions of **3b** (E = −23.54)[15] and **3c** (E = −18.92)[15] with phosphines **1a,b** and borohydrides are not kinetically possible at room temperature, the observed reaction outcome given in Figure 3 is presumably the result of a proton induction at the carbonyl oxygen that enhances the electrophilicities of the enones **3b,c**. In the case of the reactions of **2a,b**−**HB**(C_6F_5)$_3$ with the Michael acceptors **3d,e**, phosphine and hydride transfer events are possible because of the high reactivity of both electrophiles. However, as proton activation is less favorable, the phosphine attacks are highly reversible and reduction pathway predominates.

In summary, we have performed kinetic and thermodynamic assessments of the nucleophilcity and carbon Lewis basicity of two hindered phosphines **1a,b**, commonly used in FLP chemistry. Though this work treats the reactivity of these two specific phosphines, it clearly demonstrates how one can use Mayr's kinetic and thermodynamic parameters to deeply understand reaction mechanisms of FLP−catalyzed reduction of Michael acceptors. Assessment of the nucleophilicity and Lewis basicity of other hindered phosphines are currently ongoing in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03868.

General procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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