Reaction Mechanisms

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Scope and Mechanisms of Frustrated Lewis Pair Catalyzed Hydrogenation Reactions of Electron-Deficient C=C Double Bonds

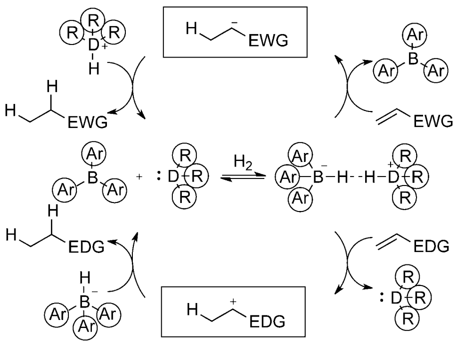
*Varvara Morozova, Peter Mayer, and Guillaume Berionni**

Dedicated to Professor Paul Knochel on the occasion of his 60th birthday

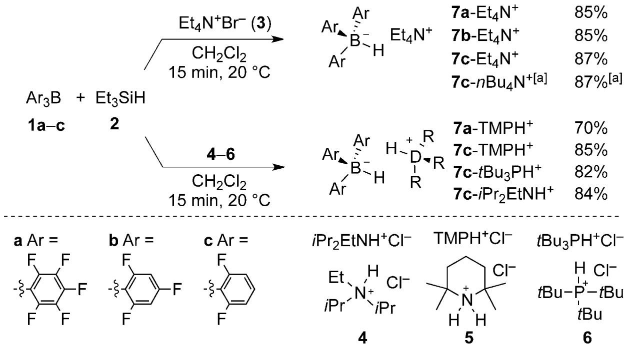
Abstract: *Several phosphonium and ammonium triarylborohydrides, which are intermediates in hydrogenation reactions catalyzed by frustrated Lewis pairs, were synthesized in high yield under mild conditions from triaryl boranes, ammonium or phosphonium halides, and triethylsilane. The kinetics and mechanisms of the reactions of these hydridoborate salts with benzhydrylium ions, iminium ions, quinone methides, and Michael acceptors were investigated, and their nucleophilicity was determined and compared with that of other hydride donors.*

Hydrogenation reactions catalyzed by frustrated Lewis pairs (FLPs) have attracted great attention in recent years, as these reactions avoid the use of metal catalysts and show unusual selectivity and functional-group tolerance.[1] The heterolytic cleavage of H_2 is only possible when the Lewis acidity of Ar_3B and the Lewis basicity of R_3D (D = P or N) exceed a certain strength, and when the formation of Lewis acid–base adducts is counteracted by steric shielding (Scheme 1).[2] Grimme, Paradies, and co-workers demonstrated that hydrogenation reactions of EDG-substituted C=C double bonds proceed through initial protonation, and that substrates with nucleophilicity parameters $1 < N < 5$ on the Mayr reactivity scale[3] can be hydrogenated by the use of a combination of tris(1-naphthyl)phosphane $(C_{10}H_7)_3P$ and $B(C_6F_5)_3$ as the catalyst.[4]

On the other hand, hydrogenation reactions of nitroalkenes and acrylates were not catalyzed by FLPs derived from $B(C_6F_5)_3$ (**1a**), but proceeded smoothly when a Lewis pair derived from the less acidic borane $B(2,6\text{-}F_2C_6H_3)_3$ (**1c**) was employed (Scheme 2).[5] Analogously, Alcarazo and co-workers explored the catalytic hydrogenation of electron-poor alkenes with FLPs derived from differently fluorinated triaryl boranes and 1,4-diazabicyclo[2.2.2]octane (DABCO) and found that only $B(2,4,6\text{-}F_3C_6H_2)_3$ (**1b**) and $B(2,6\text{-}F_2C_6H_3)_3$ (**1c**) showed catalytic activity.[6] In agreement with Paradies and co-workers, they observed that these less Lewis acidic boranes were more efficient in the hydrogenation of electron-deficient alkenes than $B(C_6F_5)_3$ (**1a**).[6] However, systematic mechanistic and kinetic studies to rationalize these observations have not yet been reported.



Scheme 1. Mechanism of the FLP-catalyzed hydrogenation of electron-poor (top) and electron-rich (bottom) C=C double bonds. EWG = electron-withdrawing group; EDG = electron-donating group.



Scheme 2. Synthesis of the ammonium and phosphonium hydridoborates **7a–c**, with the yields of the isolated products. [a] The salt **7c**-nBu_4N^+ was obtained by using $nBu_4N^+Cl^-$ instead of **3**. TMP = 2,2,6,6-tetramethylpiperidine.

To explore the scope and mechanism of hydrogenation reactions proceeding through initial hydride transfer (Scheme 1, top), we employed the benzhydrylium method[3] to quantify the nucleophilic reactivity of the hydride donors $HB(C_6F_5)_3^-$ (**7a**), $HB(2,4,6\text{-}F_3C_6H_2)_3^-$ (**7b**), and $HB(2,6\text{-}F_2C_6H_3)_3^-$ (**7c**), which are intermediates in FLP-catalyzed hydrogenation reactions. The tetraethylammonium triarylborohydrides (**7a–c**)-Et_4N^+ were synthesized by mixing equimolar amounts of a triaryl borane **1a–c**, triethylsilane (**2**), and $Et_4N^+Br^-$ (**3**) in CH_2Cl_2 (Scheme 2, top) according to a procedure reported by Piers and co-workers.[7] When **3** was

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[*] V. Morozova, Dr. P. Mayer, Dr. G. Berionni
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5-13, 81377 München (Germany)
E-mail: guillaume.berionni@cup.uni-muenchen.de
Homepage: http://www.cup.uni-muenchen.de/oc/mayr/

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replaced with a secondary or tertiary ammonium or phosphonium chloride **4–6** (Scheme 2, bottom), the corresponding triarylborohydrides **7**, which were previously synthesized by the cleavage of H_2 by FLPs,[5,6] were obtained in good yield in analytically pure form.

In the solid state, the triarylborohydride **7b**-Et_4N^+ featured short intramolecular interactions (about 2.55 Å) between the BH1 hydride and F1, F6, and F9 of the fluorinated aryl rings (Figure 1a), like in the pentafluorinated analogue nBu$_4$N$^+$HB(C$_6$F$_5$)$_3^-$.[8] X-ray diffraction analysis of **7c**-TMPH$^+$ (see the Supporting Information) agreed with that recently described by Paradies and co-workers, who obtained the same compound by heterolytic H_2 cleavage,[5] with the exception of the BH···HN distance, which we measured to be 1.97 Å at 173 K,[9] and which was 1.91 Å at 100 K.[5] A considerably shorter H···H distance (1.77 Å) was found for **7c**-iPr$_2$EtNH$^+$ (Figure 1b), which was recrystallized from CH_2Cl_2; this shorter H···H distance indicates a stronger proton···hydride interaction.[9]

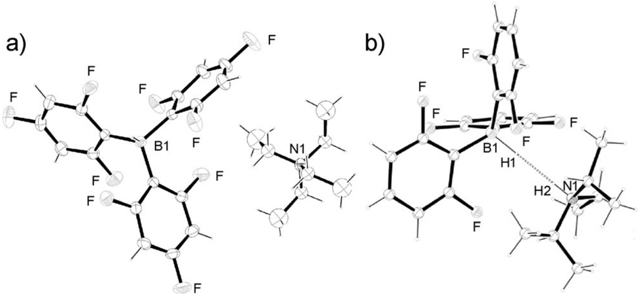
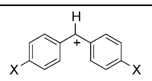
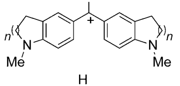
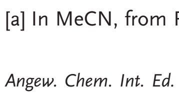


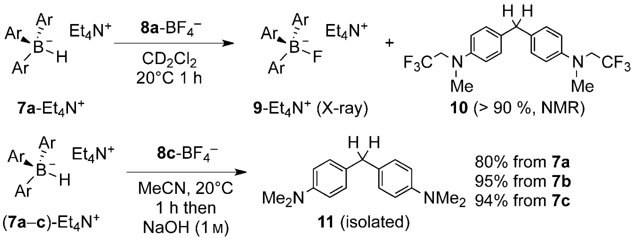
Figure 1. X-ray crystal structures of a) **7b**-Et_4N^+ (at 293 K) and b) **7c**-iPr$_2$EtNH$^+$ (at 100 K), with ellipsoids set at the 30% probability level.[9] For bond lengths and angles, see the Supporting Information.

To quantify the hydride-donating ability of **7a–c** and the effect of different counterions, we studied the kinetics of their reactions with the benzhydrylium ions **8a–h** (Table 1), which are employed as reference electrophiles of known electrophilicity.[3] The formation of the diaryl methanes **10** and **11** shows that the triarylborohydrides **7a–c** transferred their hydride quantitatively at 20 °C to the benzhydrylium center of **8a** and **8c** (Scheme 3).[9,10]

Table 1: Structures, absorption maxima λ_{max}, and electrophilicity parameters E for the benzhydrylium ions **8a–h** used as reference electrophiles in this study.[3]

		λ_{max} [nm][a]	E[b]
X = NMe(CH$_2$CF$_3$)	**8a**	586	−3.85
X = N(CH$_2$CH$_2$)$_2$O	**8b**	611	−5.53
X = NMe$_2$	**8c**	605	−7.02
X = N(CH$_2$)$_4$	**8d**	612	−7.69
	**8e** (n = 2)	620	−8.22
	8f (n = 1)	616	−8.76
	**8g** (n = 2)	642	−9.45
	8h (n = 1)	632	−10.04

[a] In MeCN, from Ref. [3a,b]. [b] From Ref. [3a].



Scheme 3. Reactions of **7a–c** with the benzhydrylium tetrafluoroborates **8a,c** and yields of the products. For the X-ray crystal structure of **9**-Et_4N^+, see the Supporting Information.[9,10]

Next, the kinetics of the reactions of the triarylborohydrides **7a–c** with the electrophiles **8b–h** were studied under pseudo-first-order conditions ([**7**] ≫ [**8**]). Monoexponential decay of the absorbance of **8b–h** was observed in all cases (Figure 2), and plots of k_{obs} versus the concentration of **7a–c** gave the second-order rate constants k_2 of these reactions (Table 2).

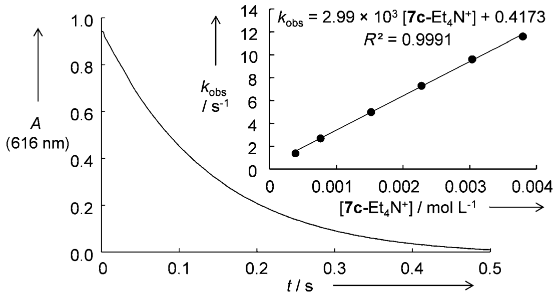


Figure 2. Exponential decay of the time-dependent absorbance of **8f** at λ = 616 nm during the reaction of **7c**-Et_4N^+ (2.28×10^{-3} M) with **8f** (6.5×10^{-6} M) in MeCN at 20 °C (k_{obs} = 7.3 s^{-1}). Inset: linear correlation between k_{obs} and the concentration of **7c**-Et_4N^+ ($k_2 = 2.99\times10^3$ M^{-1} s^{-1}).

Plots of the k_2 values of the reactions of triarylborohydrides **7** with the electrophiles **8** against their E parameters (Table 1) were linear (Figure 3), thus indicating the applicability of Equation (1) for determining the nucleophilicity parameters N and s_N of the triarylborohydrides **7a–c** (Table 2). The almost identical second-order rate constants k_2 of the reactions of **7c**-nBu$_4$N$^+$, **7c**-Et_4N^+, **7c**-tBu$_3$PH$^+$, **7c**-TMPH$^+$, and **7c**-iPr$_2$EtNH$^+$ with **8f**-BF_4^- (Table 2 and Scheme 4) show that the counterion has only a small effect on the reaction rate. According to Equation (1), the slopes of these correlation lines give the sensitivity parameters s_N of **7**. These values were similar to those of other B–H, Sn–H, and Si–H hydride donors ($0.6 < s_N < 0.8$).[11]

$$\log(k_2) = s_N(N + E) \qquad (1)$$

Whereas the triarylborohydrides **7b**-Et_4N^+ and **7c**-Et_4N^+ exhibit similar nucleophilicity ($N \approx 14$), thus showing that the *para* fluorine atom plays a negligible role, the pentafluorophenyl derivative **7a**-Et_4N^+ ($N = 10.04$) is considerably less

Table 2: Second-order rate constants k_2 of the reactions of triarylborohydrides (**7a–c**)-X$^+$ with **8b–h** in MeCN at 20°C, and nucleophilicity N and nucleophile-specific sensitivity parameters s_N for **7a–c**.

	Ar_2CH^+	k_2 [$M^{-1}s^{-1}$]	N, s_N[a]
7a-Et_4N^+	**8b**	1.98×10^3	10.04, 0.73
	8c	1.40×10^2	
	8d	5.50×10^1	
	8e	2.03×10^1	
7b-Et_4N^+	**8d**	8.48×10^3	14.13, 0.61
	8f	1.51×10^3	
	8h	3.02×10^2	
7c-Et_4N^+	**8e**	6.31×10^3	13.97, 0.66
	8f	2.99×10^3	
	8g	8.20×10^2	
	8h	4.34×10^2	
7c-nBu_4N^+	**8d**	9.85×10^3	13.90, 0.65
	8e	5.44×10^3	
	8f	2.35×10^3	
	8g	7.26×10^2	
7c-$TMPH^+$	**8e**	8.34×10^3	14.24, 0.65
	8f	3.60×10^3	
	8g	1.05×10^3	
	8h	5.95×10^2	
7c-tBu_3PH^+	**8d**	1.53×10^4	14.86, 0.58
	8f	3.26×10^3	
	8h	6.60×10^2	
7c-iPr_2EtNH^+	**8f**	3.59×10^3	14.94, 0.58
	8h	6.59×10^2	

[a] For the determination of N and s_N, see Figure 3 and the Supporting Information.

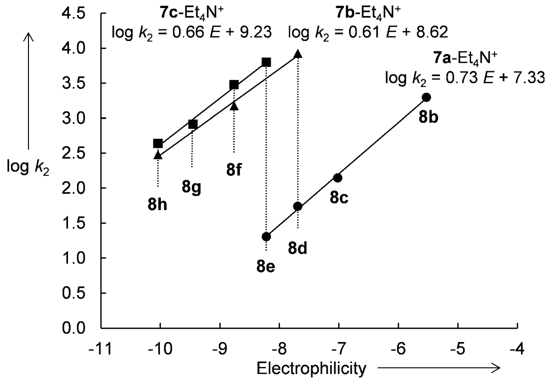
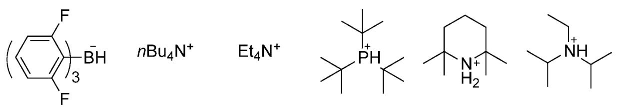


Figure 3. Correlation of the logarithm of the second-order rate constants k_2 for the reactions of triarylborohydrides **7c**-NEt_4^+ (■), **7b**-NEt_4^+ (▲), and **7a**-NEt_4^+ (●) with the benzhydrylium tetrafluoroborates **8b–h** in MeCN at 20°C with the electrophilicity parameters E of **8b–h** from Table 1.[3]

nucleophilic (Figure 4). The presence of two *meta* fluorine substituents thus reduces the hydride-donating ability of **7a** by a factor of approximately 10^4 and restricts the scope of hydrogenation with FLPs derived from tris(pentafluorophenyl)borane (**1a**) to the most electrophilic C=C double bonds.



7c	**7c**-nBu_4N^+	**7c**-Et_4N^+	**7c**-tBu_3PH^+	**7c**-TMPH$^+$	**7c**-iPr_2EtNH^+
k_2 / **8f** + **7c**	2.35×10^3	2.99×10^3	3.26×10^3	3.60×10^3	3.59×10^3
k_{rel}	1.0	1.3	1.4	1.5	1.5

Scheme 4. Second-order rate constants k_2 ($M^{-1}s^{-1}$) for the hydride-transfer reaction from hydridoborate **7c** with various counterions and the benzhydrylium ion **8f** in MeCN at 20°C.

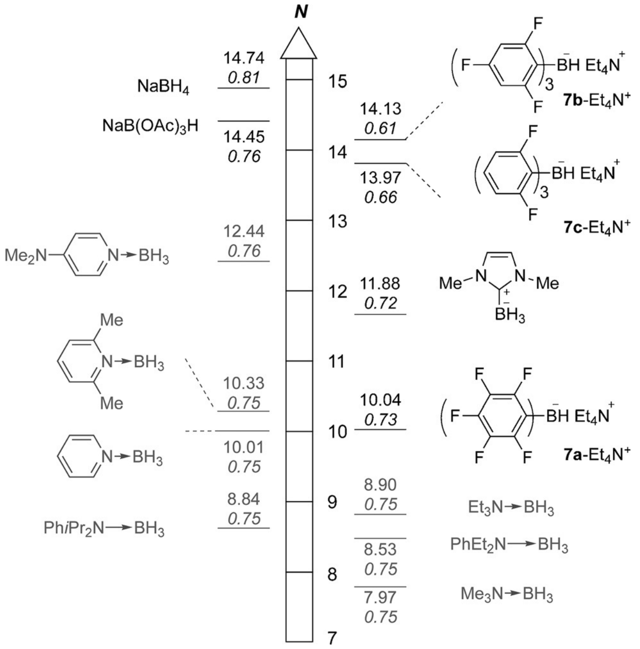
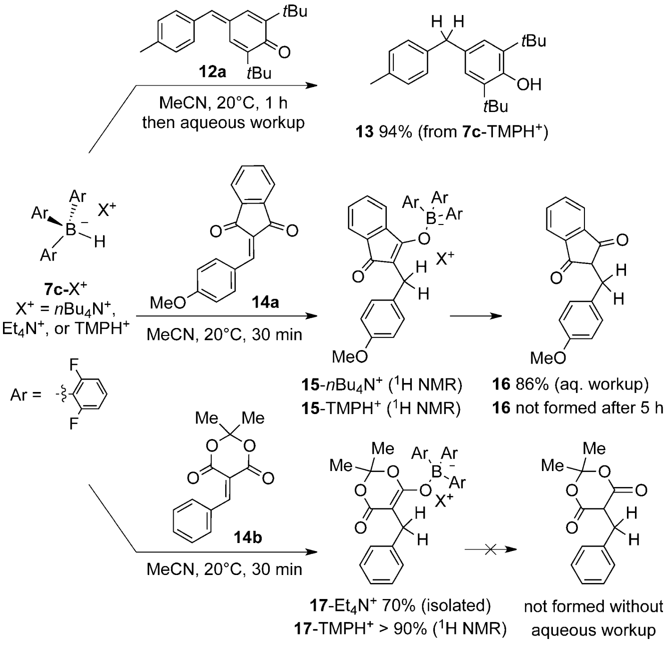


Figure 4. Comparison of nucleophilicity parameters N (sensitivity parameters s_N in italics) of the triarylborohydrides **7a–c** with those of amino and N-heterocyclic carbene boranes (CH_2Cl_2) and other borohydrides (DMSO).[11]

These nucleophilicity parameters can be used to rationalize the observations reported by the research groups of Paradies and Alcarazo, that hydrogenation reactions of alkylidene malonates, sulphones, and nitroolefins proceed slower with FLPs derived from the strong Lewis acid **1a** than with those derived from **1b** and **1c**.[5,6] The low nucleophilicity of **7a** ($N = 10.04$) also accounts for the failure of the stoichiometric reaction of $(C_6F_5)_3BH^-K^+$ with diethyl-2-benzylidenemalonate ($E = -20.55$),[12] as recently described by Alcarazo and co-workers.[6,12]

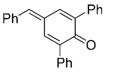
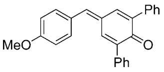
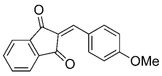
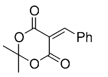
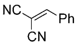
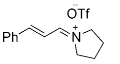
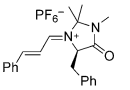
As the s_N values of **7a–c** are in a narrow range, thus indicating that their relative nucleophilicity depends little on the reactivity of the electrophile, the N values in Table 2 can be used for a direct comparison with other classes of hydrides. As shown in Figure 4, **7b**-Et_4N^+ and **7c**-Et_4N^+ are slightly less nucleophilic than sodium borohydride, $NaBH_4$ ($N = 14.74$),[11,13] and are among the most reactive hydride donors so far quantified by Equation (1). The hydridoborate **7a**-Et_4N^+ has the same nucleophilicity as the pyridine→BH_3 complex.[11]

^{1}H NMR spectroscopic monitoring of the stoichiometric reactions of **7c**-X$^+$ with the Michael acceptors **12** and **14** in CD_3CN showed that hydride transfer to the benzylidene



Scheme 5. Reactions of triarylborohydride **7c**-X^+ with electron-deficient C=C double bonds in MeCN (or CD_3CN) at 20°C, and characterization or isolation of the intermediate boron enolate. For details, see the Supporting Information.

Table 3: Second-order rate constants k_2 of the reactions of **7c**-$TMPH^+$ with quinone methides **12b**,**c**, Michael acceptors **14a–c,** and α,β-unsaturated iminium ions **18a**,**b** in MeCN at 20°C.[16]

Electrophile		λ_{max} [nm][a]	E[a]	k_2 [$M^{-1}\,s^{-1}$]	k_2^{calc}/ k_2^{exp}[b]
	**12b**	381	−11.87	15.2	2.28
	**12c**	415	−12.18	10.8 5.33[c]	2.02 2.85[c]
	**14a**	385	−11.32	0.347[d]	137[d]
	**14b**	317	−9.15	10.6	192
	**14c**	306	−9.42	23.1	58.8
	**18a**	348	−9.80	475 650[d]	1.62 1.18[d]
	**18b**	355	−7.37	42600	0.685

[a] From Ref. [16]. [b] The value k_2^{calc} was calculated from Equation (1). [c] Counterion: Et_4N^+. [d] Counterion: nBu_4N^+. Tf = trifluoromethanesulfonyl.

carbon atom was accompanied by the coordination of Ar_3B to the enolate oxygen atom (Scheme 5). Upon aqueous workup, the products **13** and **16** were obtained. As the protodeborylation of **15**-$TMPH^+$ or **17**-$TMPH^+$ with regeneration of the FLP catalyst TMP/**1c** is very slow (not observed after 5 h in CD_3CN at 20°C), we conclude that this step may be rate determining in many FLP-catalyzed hydrogenation reactions of acyl-substituted C=C double bonds.[14] In the reaction of **7c**-Et_4N^+ with **14b**, the resulting boron enolate **17**-Et_4N^+ ($\delta(^{11}B) = -3.0$ ppm) could even be isolated and fully characterized.[15]

To examine the potential of the N and s_N values of **7a–c** (Table 2) to predict the scope of reactions with electron-poor C=C double bonds, we measured the kinetics of their reactions with several Michael acceptors and iminium ions of known electrophilicity E.[16] As shown in Table 3, the k_2 values of the reactions of the triarylborohydride **7c** with the quinone methides **12b**,**c** and the iminium ions **18a**,**b** are in good agreement with the rate constants calculated from the tabulated electrophilicities E[16] and from the N and s_N values of **7a–c** (Table 2) obtained from Equation (1). In contrast, the measured k_2 values of the reactions with the Michael acceptors **14a–c** are 50–200 times lower than predicted, which is slightly outside the confidence range of Equation (1) (factor 10–100). Activation of the C=O or C≡N group of these electrophiles by coordination with $TMPH^+$ (pK_a(MeCN) ≈ 11) can be excluded, since, in this case, the experimental reaction rates would be higher than the calculated reaction rates.[6,14]

In conclusion, several FLP–H_2 salts were obtained by hydrogen-free synthesis and were used for kinetic and mechanistic studies. The reaction rates of hydride transfer to benzhydrylium ions and Michael acceptors have been shown to be almost independent of the counterion, but are strongly affected by the substitution pattern of the Ar_3B catalyst. The nucleophilicity parameters of the triarylborohydrides were compared with those of other hydride donors and used to analyze the synthetic potential of frustrated Lewis pair catalyzed hydrogenation reactions of electron-deficient C=C double bonds.

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[7] a) J. M. Blackwell, D. J. Morrison, W. E. Piers, *Tetrahedron* **2002**, *58*, 8247–8254; b) simultaneous to our investigations, a similar method was reported: W. L. Nie, C. Tian, M. Borzov, L. Maksim, Q. Liu, H. Hu, W. Hu, Y. Jiang, K. Li, H. Gong, G. Chen, CN 104262374A, **2015**.

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[9] CCDC 1413309 (**7b**-Et_4N^+), 1413310 (**7c**-$TMPH^+$), 1413311 (**7c**-$i Pr_2EtNH^+$), and 1413312 (**9**-Et_4N^+) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[10] The fluoroborate **9**–Et_4N^+ was formed by the abstraction of a fluoride atom from the BF_4^- counterion by the released $B(C_6F_5)_3$; see: a) K. S. Coleman, J. Fawcett, D. A. J. Harding, E. G. Hope, K. Singh, G. A. Solan, *Eur. J. Inorg. Chem.* **2010**, 4130–4138; b) M. Alcarazo, C. Gomez, S. Holle, R. Goddard, *Angew. Chem. Int. Ed.* **2010**, *49*, 5788–5791; *Angew. Chem.* **2010**, *122*, 5924–5927; for a higher-quality X-ray crystal structure of $[FB(C_6F_5)_3]^-$, see: c) S. Kronig, E. Theuergarten, D. Holschumacher, T. Bannenberg, C. G. Daniliuc, P. G. Jones, M. Tamm, *Inorg. Chem.* **2011**, *50*, 7344–7359.

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[12] For the electrophilicity parameters E of alkylidene malonates, see: O. Kaumanns, R. Lucius, H. Mayr, *Chem. Eur. J.* **2008**, *14*, 9675–9682. According to Equation (1), the calculated second-order rate constant of the stoichiometric reaction reported by Alcarazo and co-workers (Ref. [6]) is $2\times10^{-8}\,\text{M}^{-1}\,\text{s}^{-1}$, which corresponds to a half-life of more than 1.5 years at 20 °C with a 1 M concentration of the reagents.

[13] The reactivity difference of about 5 orders of magnitude between **7a** and BH_4^- corresponds to a $\Delta G^{\neq}$ value of approximately 8 kcal mol^{-1}, which is smaller than the recently calculated theoretical value of 15 kcal mol^{-1}: Z. M. Heiden, A. P. Lathem, *Organometallics* **2015**, *34*, 1818–1827.

[14] More Brønsted acidic counterions than $TMPH^+$, such as DABCO-H^+ and 2,6-lutidinium, may, however, activate Michael acceptors through a $R_3N^+H\cdots O/N$ H-bonding interaction and may protonate the intermediate boron enolate faster than $TMPH^+$ (see Ref. [5,6]).

[15] So far, only one boron enolate and an analogous nitronate formed during the FLP-catalyzed hydrogenation of an ynone and a nitrostyrene, respectively, have been characterized; see Ref. [5] and: B.-H. Xu, G. Kehr, R. Fröhlich, B. Wibbeling, B. Schirmer, S. Grimme, G. Erker, *Angew. Chem. Int. Ed.* **2011**, *50*, 7183–7186; *Angew. Chem.* **2011**, *123*, 7321–7324.

[16] For the electrophilicity parameters E of the electrophiles **12**, **14**, and **18**, see the reactivity database of E parameters: http://www.cup.lmu.de/oc/mayr/DBintro.html. Kinetics of the reactions of **7c**-$TMPH^+$ with nitrostyrenes were not measurable owing to UV/Vis overlap of their absorbances with those of the intermediate nitronates.

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