Hydrogenation |*Hot Paper*|

Structure–Reactivity Relationship in the Frustrated Lewis Pair (FLP)-Catalyzed Hydrogenation of Imines

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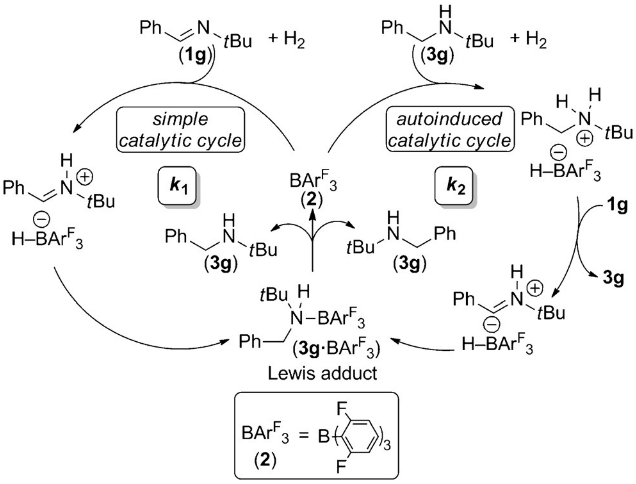
Abstract: The autoinduced, frustrated Lewis pair (FLP)-catalyzed hydrogenation of 16-benzene-ring substituted *N*-benzylidene-*tert*-butylamines with $B(2,6\text{-}F_2C_6H_3)_3$ and molecular hydrogen was investigated by kinetic analysis. The pK_a values for imines and for the corresponding amines were determined by quantum-mechanical methods and provided a direct proportional relationship. The correlation of the two rate constants k_1 (simple catalytic cycle) and k_2 (autoinduced catalytic cycle) with pK_a difference between imine and amine pairs (ΔpK_a) or Hammett's σ parameter served as useful parameters to establish a structure–reactivity relationship for the FLP-catalyzed hydrogenation of imines.

Introduction

The application of frustrated Lewis pairs (FLP) has grown immensely[1] since their first report to activate molecular hydrogen (H_2) in the absence of transition metals.[2] The development of new FLP-catalyzed reactions is in the focus of contemporary research resulting in spectacular transformations, for example, the activation of strong C–F bonds,[3] cross-couplings,[4] or cycloisomerizations.[5] However, the fundamental understanding of FLP reactivity with the aim to establish a structure–reactivity relationship is in its infancies. For example, kinetic and thermodynamic parameters of FLP-catalyzed hydrogenations were only recently experimentally determined,[6] although such reactions are the most widely investigated.[7] The interplay between the Lewis acid and the Lewis base in the H_2 activation is of utmost importance to achieve new challenging transformations, for example, the hydrogenation of olefins,[6b,7c,8] or to achieve functional-group tolerance.[9] Systematic investigations are still underrepresented, although they provide highly valuable information for the targeted design and rational choosing of FLPs for particular reactions. Such systematic studies placed the foundations for the great success of transition-metal catalysis establishing this chemistry as one of the most important and most diverse.[10] Key to this success story is the profound understanding of structure and reactivity. However, a direct measure to connect structure and thermodynamic parameters with kinetic features of FLP-catalyzed hydrogenations is not yet available.



Scheme 1. Proposed mechanism for the hydrogenation of *N*-benzylidene-*tert*-butylamine (**1g**).

In a recent study, we reported the mechanistic investigation of the FLP-catalyzed hydrogenation of imine **1g** by using boranes with reduced Lewis acidity.[6d] This first kinetic analysis provided evidence for the autoinduced mechanism as a result of the reduced free activation energy of the H_2 activation by the borane **2** and of the corresponding reaction product (**3g**) manifesting in an overall tenfold rate increase (Scheme 1). The gradual change of the responsible Lewis base for the H_2 activation from the less basic imine to the amine with pronounced basicity in the course of the reaction was found to be responsible for this unusual autoinduced mechanism, which is absent for the strong Lewis acid $B(C_6F_5)_3$.[6d] Consequently, the difference in acidity of the conjugate acids of the imine and the corresponding amine (ΔpK_a) is a significant and readily predictable thermodynamic parameter directly linked to the FLP reactivity. A broad range of pK_a values can be experimentally determined in various media[6b,11] or can be acquired through quantum-mechanical calculations with satisfactory precision.[12] A second readily available parameter is the Hammett's σ parame-

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ter,[13] which connects electronic properties of substrates with reactivity and allows the prediction of reaction rates and the support of reaction mechanisms.

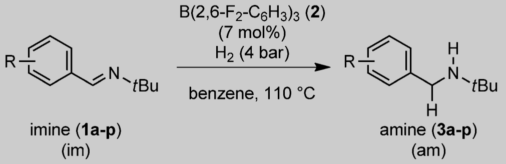
Herein, we present the elaboration of a structure–reactivity relationship for FLP-catalyzed hydrogenations of imines based on the correlation of acidity constants (pK_a) and rates with the Hammett's σ parameter. This was achieved by the kinetic investigation of *N*-benzylidene-*tert*-butylamine derivatives in the FLP-catalyzed hydrogenation deliberately utilizing the less Lewis acidic $B(2,6\text{-}F_2\text{-}C_6H_3)_3$ (**2**). Thereby, we probed the impact of the Lewis base basicity to the reaction rates of the simple and autoinduced catalytic cycle. Substituents on the phenyl ring influence the imine's and corresponding amine's basicity through electronic coupling, whereas the steric impact on the reaction rates can be disregarded. A series of suitable imine/amine pairs with fine-tuned ΔpK_a window of the conjugate acids is readily accessible, which enabled for the connection of Hammett's σ electronic parameters to kinetics of FLP-catalyzed hydrogenations. Because Hammett's electronic parameters are direct proportional to acid strengths, this approach connects a readily available thermodynamic parameter (pK_a) with FLP reactivity establishing a structure–reactivity relationship for FLP systems.

Results and Discussion

For the sake of easier discussion, we use the term "pK_a of imines and amines" for the pK_a of the corresponding conjugate acids.

The selection of appropriate imine/amine pairs is of paramount importance to provide a broad range of ΔpK_a values, which need to be correlated with kinetic data. Therefore, we initiated our investigation by the computational determination of pK_a values for a series of imines and amines, which are summarized in Table 1. For the calculation of the pK_a values, the geometries of the iminium and ammonium ions, as well as the corresponding neutral molecules, were optimized by using DFT method at BP-TZVP level of theory with the COSMO solvation model ($\varepsilon=\infty$) as implemented in TURBOMOLE 6.5 package.[14] Subsequently, the pK_a values were calculated for acetonitrile as a solvent by using the COSMO-RS standard method.[15,12a] The method was validated by the calculation of pK_a values of 2,6-lutidine (15.6) and 2,4,6-collidine (16.2), which were earlier employed in hydrogenation reactions.[9a] The experimental pK_a values[11a] for lutidine and collidine are 14.13 and 14.98, respectively, indicating the absolute precision of the COSMO-RS method. It must be noted that the precision of the relative difference between imine and amine, the ΔpK_a value, as well as the trends within substitution series, is expected to have higher precision due to the cancellation of errors. For our initial studied amine/imine pair (**1g**/**3g**), a ΔpK_a of 2.0 was determined providing further support of the quantum chemical approach. With the series of *N*-benzylidene-*tert*-butylamines summarized in Table 1, we were able to cover a broad ΔpK_a range from 0 to 3.3 units. Because the imine nitrogen atom is integrated into the π system of the molecule, the substitution on the benzene ring has greater impact on the basicity of imines. As a consequence, the calculated absolute pK_a window

Table 1. Hammett's σ electronic parameters, calculated pK_a values[a] of the conjugate acids of *N*-benzylidene-*tert*-butylamine (**1a**–**p**) and *N*-benzyl-*tert*-butyl-amine (**3a**–**p**) derivatives, difference of the corresponding pK_a values (ΔpK_a), and reaction rates of the simple catalytic cycle (k_1) and autoinduced catalytic cycle (k_2).



Entry	R	σ	pK_a[a] (im)	pK_a[a] (am)	ΔpK_a	k_1[b]	k_2[b]
1	4-O*t*Bu (**a**)	−0.45	17.4	18.0	0.6	7.78 ± 2.4	78.3 ± 16.3
2	4-OMe (**b**)	−0.27	17.0	17.9	0.9	13.2 ± 5.5	92.0 ± 27.4
3	4-OPh (**c**)	−0.32	16.3	17.3	1.0	7.96 ± 3.3	73.5 ± 22.3
4	4-Me (**d**)	−0.17	15.9	17.3	1.4	9.22 ± 5.7	88.6 ± 36.1
5	4-*t*Bu (**e**)	−0.20	15.7	17.2	1.5	9.41 ± 5.9	93.6 ± 41.9
6	3-Me (**f**)	−0.07	15.5	17.2	1.7	7.77 ± 4.7	81.6 ± 31.7
7	4-H (**g**)	0.00	15.3	17.3	2.0	5.62 ± 3.2	74.7 ± 25.4
8	3-OMe (**h**)	0.12	15.2	17.4	2.2	4.67 ± 2.5	71.3 ± 16.6
9	4-F (**i**)	0.06	15.1	16.9	1.8	6.47 ± 0.7	70.8 ± 21.1
10	4-Cl (**j**)	0.23	14.5	16.6	2.1	6.35 ± 3.5	80.8 ± 29.0
11	4-Br (**k**)	0.23	14.4	16.5	2.1	6.15 ± 3.3	74.5 ± 24.5
12	3-Cl (**l**)	0.37	13.8	16.4	2.7	3.67 ± 1.5	54.0 ± 10.5
13	4-CF_3 (**m**)	0.54	13.4	16.3	2.9	3.54 ± 2.0	54.0 ± 15.4
14	4-SO_2Me (**n**)	0.72	13.0	16.1	3.2	3.70 ± 1.9	39.5 ± 18.7
15	4-NO_2 (**o**)	0.78	12.3	15.6	3.3	2.51 ± 1.1	47.0 ± 8.6
16	2,2-Me-4-OMe (**p**)	n.a.	17.3	17.3	0.0	10.1 ± 0.1[c]	

[a] Calculated pK_a values for the corresponding conjugate acid in acetonitrile. [b] Data are given in [$L\,mol^{-1}\,h^{-1}$]. [c] Zero-order rate constant is given in $L\,mol^{-1}\,h^{-1}$. n.a. = not applicable.

for imines is twice as big (12.3 to 17.4 pK_a units) as for the amines (15.6 to 18.0 pK_a units). Substrates featuring electron-donating groups, such as 4-Oalkyl/aryl and 4-alkyl, showed high absolute pK_a values with relatively small ΔpK_a values (entries 1–6). Substrates with electron-withdrawing substituents, such as 4-NO_2 and 4-CF_3, gave comparably low absolute pK_a values and a large relative ΔpK_a value (entries 10–15). The plot of the imines' and amines' absolute pK_a, as well as the relative ΔpK_a value of the imine/amine pair versus the corresponding Hammett's σ parameter,[13b,16] resulted in direct proportional correlation (Figure 1 a and b) and can therefore be utilized to establish a structure–reactivity relationship. The negative slopes in the Hammett plots (ρ(im) = −3.77; ρ(am) = −1.67) indicate increasing positive charge in concert with the stabilization of protonated species. Stabilization of positive charge is more significant for the imine than for the amine, as was expressed by the more negative Hammett correlation for the imine (Figure 1 a). As can be seen from Figure 1 b, the difference of the pK_a (ΔpK_a) of imine/amine pairs increased with increasing −I effect of the substituent.[17]

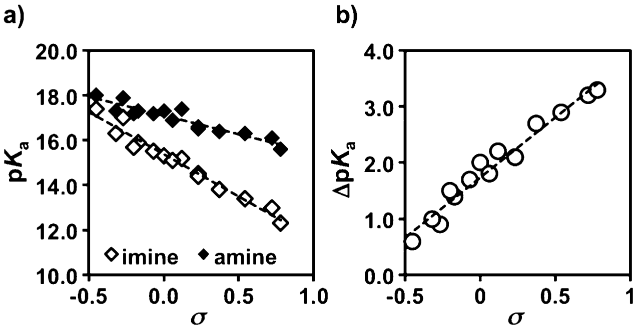


Figure 1. Plot of Hammett parameter σ versus a) calculated pK_a of imines and amines; b) versus ΔpK_a values of corresponding imine/amine pairs (**1 p**, entry 16, has not been included).

Next, we acquired the two rate constants for the standard (k_1) and autoinduced (k_2) cycle in the FLP-catalyzed hydrogenation of the 16 imines. The reactions were performed on 0.36 M scale, 7 mol% borane **2**, 4 bar hydrogen pressure, and 110 °C in [D_6]benzene by using hexamethylbenzene as internal standard. The reactions were monitored by ^{1}H NMR spectroscopy, and concentrations were determined by integration. The two different rate constants k_1 for the simple catalytic cycle and k_2 for the autoinduced catalytic cycle were determined by employing the rate law for autoinduced catalytic reactions (see the Supporting Information).[18] Qualitatively, all substrates (except of **1 p**, ΔpK_a = 0, see below) displayed autoinduced catalysis, as was evident from the significantly higher rate constants k_2 (Table 1). Hydrogenation reactions of electron-rich substrates exhibiting comparably high pK_a (and consequently a relative small ΔpK_a) displayed high rates for both cycles with k_2 being 8–10 times higher than k_1. In contrast, reactions of electron-poor substrates reacted comparably slower and resulted in smaller absolute rate constants, however, with significantly greater k_2 being up to 18 times higher than k_1. The subtle interplay between basicity and rate is more visual from the semi-logarithmic plot of rates versus ΔpK_a (Figure 2 a) and Hammett's σ parameters (Figure 2 b). The graphical analyses gave linear correlation for both the simple- and autoinduced catalytic cycle (Figure 2). However, k_1 displayed a stronger dependence on the ΔpK_a and σ expressed through a more negative slope of the linear fit than k_2 ($\rho(k_1)$ = −0.46; $\rho(k_2)$ = −0.25). This can be clearly understood by the significantly higher impact of electronic modification to the imine's nitrogen atom compared to the less electronically coupled amine's nitrogen. The absolute ρ values are small compared with those observed in other imine reactions,[19] denoting the cancellation of negative Hammett correlation of imine basicity by positive Hammett correlation of iminium ion electrophilicity. The correlation of the relative rate enhancement by the autoinduced catalytic cycles k_2/k_1 versus the corresponding ΔpK_a values revealed the highest rate enhancement for imine/amine pairs with largest differences in pK_a. However, this observation must not lead to the assumption that for these substrates, the highest yields will be obtained within the shortest reaction time, because the induction period is prolonged by the reluctant activation of H_2, which is the rate-determining step for the reaction.

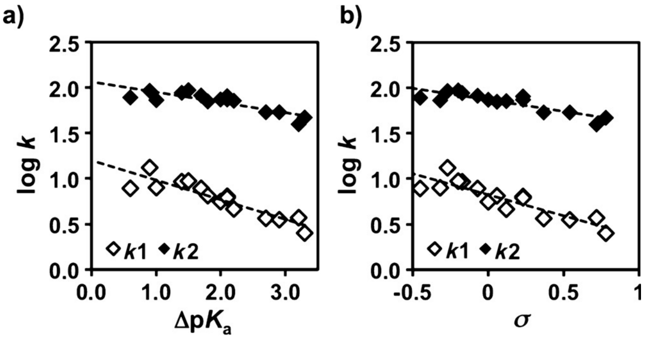


Figure 2. Semi-logarithmic plot of rate constants k_1 and k_2 versus a) ΔpK_a and b) Hammett σ parameters (**1 p**, entry 16, has not been included).

We put our theory to the test by the investigation of a imine/amine pair featuring a ΔpK_a of zero (entry 16, **1 p**/**3 p**). According to the small ΔpK_a value, the reaction should proceed through both cycles with comparable rates. Indeed, the plot of the concentration of **3 p** versus time gave a linear relationship suggesting a reaction of zero order (see Figure 3 a, k = 10.1 ± 0.1 L mol^{-1} h^{-1}). The apparent zero-reaction order for **1 p/3 p** arose from the constant concentration of Lewis base with identical pK_a making the H_2 activation independent from the nature of the Lewis base. For comparison, the sigmoidal curve for the formation of **3 a** (**1 a**: pK_a = 17.4, **3 a**: pK_a = 18.0; ΔpK_a = 0.6) is depicted in Figure 3. This imine has a comparable pK_a to **1 p**; however, as soon as small amounts of the amine **3 a** are formed, the autoinduced catalytic cycle takes over. Because the rate constant for the zero-reaction order is different form the autoinduced mechanism, the quantitative comparison is impossible. However, from a qualitative point of view, the autoinduced reaction with **1 a** provides 47 % yield of **3 a** within one hour. In contrast, **3 p** was produced in the same amount

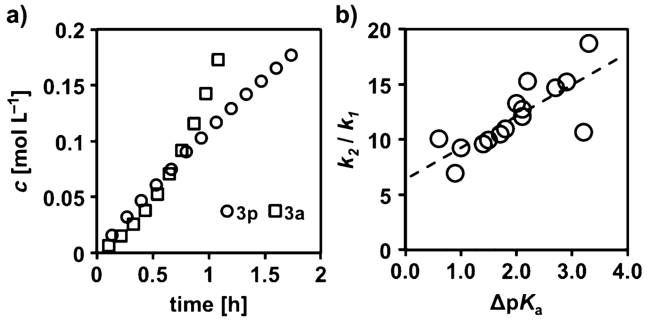


Figure 3. Concentration versus time plot for **3 p** and **a** for comparison (average of three independent experiments; zero-order rate constant for **1 p**: $k = 10.1 \pm 0.1\ \mathrm{L\,mol^{-1}\,h^{-1}}$).

of time in significantly lower yield (ca. 29% yield). As was demonstrated by these examples, the rational choice of the imine as Lewis base component of the FLP enables for the deliberate selection of the reaction mechanism through which and to which extent the catalytic hydrogenation proceeded.

Conclusion

In summary, we have presented kinetic data for the autoinduced FLP-catalyzed hydrogenation of 16 imines. First, the imines and amines were characterized by their quantum-mechanically acquired pK_a values. The pK_a and ΔpK_a of the corresponding imines and amines were correlated with the respective Hammett parameters providing a linear relationship. The rate constants k_1 and k_2 for the simple and autoinduced catalytic cycles were determined with k_2 being 8–18 times higher than k_1. Linear relationships were obtained by semi-logarithmic plot of the rate constants versus difference in the imine/amine pair (ΔpK_a) and Hammett σ parameters. The rate constant for the simple catalytic cycle k_1 was more susceptible to electronic changes than k_2. Significant differences in rates are annihilated when substrates with very small ΔpK_a of staring material and product are subjected to hydrogenation. The study clearly shows the connection of FLP reactivity with the electronic nature of the Lewis base establishing a structure–reactivity relationship for imine hydrogenations. Thereby, the FLP system and/or the substrates can now be specifically selected by the corresponding pK_a as an easy accessible thermodynamic parameter providing a key to the rational design of FLP-catalyzed reactions.

Experimental Section

General procedure for kinetic measurements

In a glovebox, the imine (**1 a–p**; 0.400 mmol, 1.00 equiv), $B(C_6F_2H_3)_3$ (**2**; 7 mol%, 0.070 equiv), and hexamethylbenzene (6.4 mg, 0.040 mmol, 0.10 equiv) were dissolved in C_6D_6 (1.10 mL), and the solution was divided in two equal parts and transferred into sealable NMR tubes equipped with JYoung Teflon tap. The substrate to catalyst ratio was determined by ^{1}H NMR spectroscopy (300 MHz) by using the resonance of C*H*=N (**1**, 1 H) and H_m (**2**, 6 H), respectively. The solution was freeze/pump/thawed twice and charged with H_2 at 77 K, when the NMR tube was immersed into liquid-N_2 container of a controlled depth (15 cm) and time (10 s) to create reproducible pressure. The sample was again checked by ^{1}H NMR spectroscopy and subjected to controlled motion (Heidolph Polymax 1040, 3 rpm) at the desired reaction temperature (Heidolph HeiTEC equipped with a heating block suitable for NMR tubes), marking the starting point (t_0) of the kinetic measurement. ^{1}H NMR spectra were recorded in suitable time intervals, including the measuring time (2 min) and the reaction time, the latter was used for further calculations. The conversion of the reaction was determined either by signal integration of the *tert*-butyl groups of the starting material (SM) and of the reaction product (Prod.) or the decay of the C*H*=N signal, using hexamethylbenzene (HMB) as an internal standard. All calculations and data analysis were performed with Microsoft Excel 2010, polynomial fitting, and linear regression with Originlab OriginPro 2015.[20] For details and exemplary analysis, see the Supporting Information.

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Keywords: autoinduced catalysis · frustrated Lewis pairs · Hammett correlation · hydrogenation · imines

[1] a) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46–76; *Angew. Chem.* **2010**, *122*, 50–81; b) G. Erker, D. W. Stephan, *Topics in Current Chemistry: Frustrated Lewis Pairs, Vols. I and II*, Springer, Berlin, Heidelberg, **2013**; c) D. W. Stephan, G. Erker, *Chem. Sci.* **2014**, *5*, 2625–2641; d) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2015**, *54*, 6400–6441; *Angew. Chem.* **2015**, *127*, 6498–6541; e) D. W. Stephan, *Acc. Chem. Res.* **2015**, *48*, 306–316; f) D. W. Stephan, *J. Am. Chem. Soc.* **2015**, *137*, 10018–10032.

[2] a) G. C. Welch, R. R. S. Juan, J. D. Masuda, D. W. Stephan, *Science* **2006**, *314*, 1124–1126; b) G. C. Welch, D. W. Stephan, *J. Am. Chem. Soc.* **2007**, *129*, 1880–1881; c) D. W. Stephan, *Org. Biomol. Chem.* **2008**, *6*, 1535–1539.

[3] a) C. B. Caputo, L. J. Hounjet, R. Dobrovetsky, D. W. Stephan, *Science* **2013**, *341*, 1374–1377; b) J. Zhu, M. Pérez, C. B. Caputo, D. W. Stephan, *Angew. Chem. Int. Ed.* **2016**, *55*, 1417–1421; *Angew. Chem.* **2016**, *128*, 1439–1443.

[4] a) M.-A. Legare, M.-A. Courtemanche, É. Rochette, F.-G. Fontaine, *Science* **2015**, *349*, 513–516; b) L. Greb, S. Tamke, J. Paradies, *Chem. Commun.* **2014**, *50*, 2318–2320.

[5] S. Tamke, Z.-W. Qu, N. A. Sitte, U. Flörke, S. Grimme, J. Paradies, *Angew. Chem.* **2016**, *128*, 4408–4411; *Angew. Chem. Int. Ed.* **2016**, *55*, 4336–4339.

[6] a) D. M. Camaioni, B. Ginovska-Pangovska, G. K. Schenter, S. M. Kathmann, T. Autrey, *J. Phys. Chem. A* **2012**, *116*, 7228–7237; b) L. Greb, S. Tussing, B. Schirmer, P. Ona-Burgos, K. Kaupmees, M. Lokov, I. Leito, S. Grimme, J. Paradies, *Chem. Sci.* **2013**, *4*, 2788–2796; c) A. Karkamkar, K. Parab, D. M. Camaioni, D. Neiner, H. Cho, T. K. Nielsen, T. Autrey, *Dalton Trans.* **2013**, *42*, 615–619; d) S. Tussing, L. Greb, S. Tamke, B. Schirmer, C. Muhle-Goll, B. Luy, J. Paradies, *Chem. Eur. J.* **2015**, *21*, 8056–8059; e) S. M. Whittemore, T. Autrey, *Isr. J. Chem.* **2015**, *55*, 196–201; f) S. M. Whittemore, G. Edvenson, D. M. Camaioni, A. Karkamkar, D. Neiner, K. Parab, T. Autrey, *Catal. Today* **2015**, *251*, 28–33; g) T. A. Rokob, A. Hamza, A. Stirling, I. Papai, *J. Am. Chem. Soc.* **2009**, *131*, 2029–2036; h) T. A. Rokob, A. Hamza, I. Papai, *J. Am. Chem. Soc.* **2009**, *131*, 10701–10710; i) T. Privalov, *Eur. J. Inorg. Chem.* **2009**, 2229–2237.

[7] a) D. W. Stephan, *Org. Biomol. Chem.* **2012**, *10*, 5740–5746; b) J. Paradies, *Synlett* **2013**, 777–780; c) J. Paradies, *Angew. Chem. Int. Ed.* **2014**,

53, 3552 – 3557; *Angew. Chem.* **2014**, *126*, 3624 – 3629; d) J. Paradies, *"Cooperative H2-Activation by Borane-Derived Frustrated Lewis Pairs" in Cooperative Catalysis: Designing Efficient Catalysts for Synthesis* (Ed.: R. Peters), Wiley-VCH, Weinheim, **2015**; e) S. Tussing, J. Paradies, *Dalton Trans.* **2016**, *45*, 6124 – 6128; f) D. J. Chen, J. Klankermayer, *Chem. Commun.* **2008**, 2130 – 2131; g) D. W. Stephan, S. Greenberg, T. W. Graham, P. Chase, J. J. Hastie, S. J. Geier, J. M. Farrell, C. C. Brown, Z. M. Heiden, G. C. Welch, M. Ullrich, *Inorg. Chem.* **2011**, *50*, 12338 – 12348; h) S. Tamke, C. G. Daniliuc, J. Paradies, *Org. Biomol. Chem.* **2014**, *12*, 9139 – 9144; i) D. J. Chen, Y. T. Wang, J. Klankermayer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9475 – 9478; *Angew. Chem.* **2010**, *122*, 9665 – 9668; j) G. Ghattas, D. J. Chen, F. F. Pan, J. Klankermayer, *Dalton Trans.* **2012**, *41*, 9026 – 9028; k) Y. B. Liu, H. F. Du, *J. Am. Chem. Soc.* **2013**, *135*, 6810 – 6813; l) M. Lindqvist, K. Axenov, M. Nieger, M. Raisanen, M. Leskela, T. Repo, *Chem. Eur. J.* **2013**, *19*, 10412 – 10418; m) M. Lindqvist, K. Borre, K. Axenov, B. Kótai, M. Nieger, M. Leskelä, I. Pápai, T. Repo, *J. Am. Chem. Soc.* **2015**, *137*, 4038 – 4041; n) S. Wei, H. Du, *J. Am. Chem. Soc.* **2014**, *136*, 12261 – 12264; o) Z. H. Zhang, H. F. Du, *Angew. Chem. Int. Ed.* **2015**, *54*, 623 – 626; *Angew. Chem.* **2015**, *127*, 633 – 636; p) Z. H. Zhang, H. F. Du, *Org. Lett.* **2015**, *17*, 6266 – 6269.

[8] a) L. Greb, P. Ona-Burgos, B. Schirmer, S. Grimme, D. W. Stephan, J. Paradies, *Angew. Chem. Int. Ed.* **2012**, *51*, 10164 – 10168; *Angew. Chem.* **2012**, *124*, 10311 – 10315; b) Y. Segawa, D. W. Stephan, *Chem. Commun.* **2012**, *48*, 11963 – 11965; c) L. J. Hounjet, C. Bannwarth, C. N. Garon, C. B. Caputo, S. Grimme, D. W. Stephan, *Angew. Chem. Int. Ed.* **2013**, *52*, 7492 – 7495; *Angew. Chem.* **2013**, *125*, 7640 – 7643; d) K. Chernichenko, A. Madarasz, I. Papai, M. Nieger, M. Leskela, T. Repo, *Nat. Chem.* **2013**, *5*, 718 – 723.

[9] a) L. Greb, C. G. Daniliuc, K. Bergander, J. Paradies, *Angew. Chem. Int. Ed.* **2013**, *52*, 5876 – 5879; *Angew. Chem.* **2013**, *125*, 5989 – 5992; b) J. A. Nicasio, S. Steinberg, B. Ines, M. Alcarazo, *Chem. Eur. J.* **2013**, *19*, 11016 – 11020.

[10] a) A. d. Meijere, S. Bräse, M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH, Weinheim, **2013**; b) J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Mill Valley, **2009**.

[11] a) I. Kaljurand, A. Kuett, L. Soovaeli, T. Rodima, V. Maeemets, I. Leito, I. A. Koppel, *J. Org. Chem.* **2005**, *70*, 1019 – 1028; b) G. Garrido, E. Koort, C. Rafols, E. Bosch, T. Rodima, I. Leito, M. Roses, *J. Org. Chem.* **2006**, *71*, 9062 – 9067; c) A. Kütt, I. Leito, I. Kaljurand, L. Soovaeli, V. M. Vlasov, L. M. Yagupolskii, I. A. Koppel, *J. Org. Chem.* **2006**, *71*, 2829 – 2838; d) E.-I. Rõõm, A. Kuett, I. Kaljurand, I. Koppel, I. Leito, I. A. Koppel, M. Mishima, K. Goto, Y. Miyahara, *Chem. Eur. J.* **2007**, *13*, 7631 – 7643; e) A. Kütt, T. Rodima, J. Saame, E. Raamat, V. Maemets, I. Kaljurand, I. A. Koppel, R. Y. Garlyauskayte, Y. L. Yagupolskii, L. M. Yagupolskii, E. Bernhardt, H. Willner, I. Leito, *J. Org. Chem.* **2011**, *76*, 391 – 395; f) K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping, I. Leito, *Angew. Chem. Int. Ed.* **2013**, *52*, 11569 – 11572; *Angew. Chem.* **2013**, *125*, 11783 – 11786; g) E. Raamat, K. Kaupmees, G. Ovsjannikov, A. Trummal, A. Kuett, J. Saame, I. Koppel, I. Kaljurand, L. Lipping, T. Rodima, V. Pihl, I. A. Koppel, I. Leito, *J. Phys. Org. Chem.* **2013**, *26*, 162 – 170; h) K. Vazdar, R. Kunetskiy, J. Saame, K. Kaupmees, I. Leito, U. Jahn, *Angew. Chem. Int. Ed.* **2014**, *53*, 1435 – 1438; *Angew. Chem.* **2014**, *126*, 1459 – 1462.

[12] a) A. Klamt, *COSMO-RS: From Quantum Chemistry to Fluid Phase Thermodynamics and Drug Design*, Elsevier Science, Amsterdam, **2005**; b) F. Eckert, I. Leito, I. Kaljurand, A. Kuett, A. Klamt, M. Diedenhofen, *J. Comput. Chem.* **2009**, *30*, 799 – 810; c) I. Leito, E. Raamat, A. Kutt, J. Saame, K. Kipper, I. A. Koppel, I. Koppel, M. Zhang, M. Mishima, L. M. Yagupolskii, R. Y. Garlyauskayte, A. A. Filatov, *J. Phys. Chem. A* **2009**, *113*, 8421 – 8424; d) J. M. Ho, M. L. Coote, *WIREs Comput. Mol. Sci.* **2011**, *1*, 649 – 660; e) G. C. Shields, P. G. Seybold, *Computational Approaches for the Prediction of pKa Values*, CRC Press, Boca Raton, London, New York, **2013**; f) F. Eckert, A. Klamt, *J. Comput. Chem.* **2006**, *27*, 11 – 19.

[13] a) *Physical Organic Chemistry*, 2nd ed. (Ed.: N. Isaacs), Prentice Hall, New Jersey, **1995**; b) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165 – 195; c) H. H. Jaffe, *Chem. Rev.* **1953**, *53*, 191 – 261; d) E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Sausalito, **2006**.

[14] TURBOMOLE V6.5 2013, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989 – 2007, TURBOMOLE GmbH, since **2007**; available from http://www.turbomole.com.

[15] F. Eckert and A. Klamt COSMOtherm, Version C3.0, Release 14.01; COSMOlogic GmbH&CoKG, Leverkusen, **2013**; Available at http://www.cosmologic.de/.

[16] a) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitan, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207 – 1216; b) C. Hansch, S. D. Rockwell, P. Y. C. Jow, A. Leo, E. E. Steller, *J. Med. Chem.* **1977**, *20*, 304 – 306; c) C. Hansch, A. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, **1979**.

[17] The correlation of pK_a, ΔpK_a, and rate constants k_1 and k_2 with sigma$+$ Hammett parameters gave comparable results. This supports the notion, that the pK_a is majorly influenced by inductive effects and resonance effects play a minor part.

[18] F. Mata-Perez, J. F. Perez-Benito, *J. Chem. Educ.* **1987**, *64*, 925.

[19] a) E. H. Cordes, W. P. Jencks, *J. Am. Chem. Soc.* **1963**, *85*, 2843; b) K. Koehler, W. Sandstrom, E. H. Cordes, *J. Am. Chem. Soc.* **1964**, *86*, 2413 – 2419; c) J. Archila, H. Bull, C. Lagenaur, E. H. Cordes, *J. Org. Chem.* **1971**, *36*, 1345; d) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358 – 15374.

[20] OriginLab Corporation 1991 – 2015, OriginPro, **2015**.

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