Nucleophilicity

From Carbanions to Organometallic Compounds: Quantification of Metal Ion Effects on Nucleophilic Reactivities**

Francisco Corral-Bautista, Lydia Klier, Paul Knochel, and Herbert Mayr*

Abstract: *The influence of the metal on the nucleophilic reactivities of indenyl metal compounds was quantitatively determined by kinetic investigations of their reactions with benzhydrylium ions (Ar$_2$CH$^+$) and structurally related quinone methides. With the correlation equation* $\log k_2 = s_N(N + E)$*, it can be derived that the ionic indenyl alkali compounds are 10^{18} to 10^{24} times more reactive (depending on the reference electrophile) than the corresponding indenyltrimethylsilane.*

Organometallic compounds are standard reagents in organic synthesis, which allow chemo- and stereoselective transformations.[1] Depending on the nature of the metal, the carbon–metal bond is more or less covalent and influences various properties, such as reactivity, selectivity, and tolerance towards functional groups. Organolithium compounds, for example, are highly reactive and poorly selective,[1] whereas organozinc[2] or organotin compounds[3] are much less reactive, but show higher selectivity.[4] While this trend is well-known, quantitative comparisons of the reactivities of free carbanions and different organometallics have to our knowledge so far not been described.
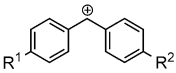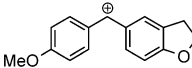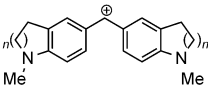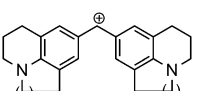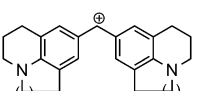
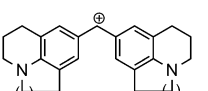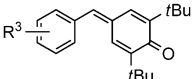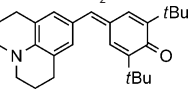In the linear free-energy relationship (1),[5] E is an

$$\log k_2(20\,°C) = s_N(N + E) \tag{1}$$

electrophile-specific parameter and N and s_N are nucleophile-specific parameters, which have been derived from the rates of the reactions of π-, n-, and σ-nucleophiles with benzhydrylium ions **1** and quinone methides **2** (reference electrophiles; Table 1).[6] Equation (1) has already been used to characterize the nucleophilic reactivities of a variety of organosilicon[6a,c,7] and organotin[6a,c] compounds, as well as of carbanions.[6b,8]

Herein we report on the kinetics of the reactions of various organometallic derivatives of indene (**3**-Met; Scheme 1) with reference electrophiles of widely differing reactivity (Table 1). In this way we will quantitatively

**Table 1:** Reference electrophiles used in this study.

Reference electrophile		$E^{[a]}$	λ_{max} [nm]
1a R^1 = Me, R^2 = Me		3.63	
1b R^1 = OPh, R^2 = Me		2.16	475
1c R^1 = OMe, R^2 = Me		1.48	488
1d R^1 = OMe, R^2 = OPh		0.61	517
1e R^1 = OMe, R^2 = OMe		0.00	513
1f		−0.81	520
1g R^1 = R^2 = N(Ph)(CH$_2$CF$_3$)		−3.14	601
1h R^1 = R^2 = N(Me)(CH$_2$CF$_3$)		−3.85	593
1i R^1 = R^2 = NPh$_2$		−4.72	672
1j R^1 = R^2 = morpholin-4-yl		−5.53	620
1k R^1 = R^2 = N(Me)(Ph)		−5.89	622
1l R^1 = R^2 = NMe$_2$		−7.02	613
1m R^1 = R^2 = pyrrolidin-1-yl		−7.69	620
1n	$n = 2$	−8.22	618
1o	$n = 1$	−8.76	627
1p	$n = 2$	−9.45	635
1q	$n = 1$	−10.04	630
2a R^3 = 4-Me		−15.83	371
2b R^3 = 4-OMe		−16.11	393
2c R^3 = 4-NMe$_2$		−17.29	486
2d		−17.90	521

[a] Electrophilicity parameters E from Ref. [6a–c,e].

[*] Dr. F. Corral-Bautista, Dr. L. Klier, Prof. Dr. P. Knochel,
Prof. Dr. H. Mayr
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13 (Haus F), 81377 München (Germany)
E-mail: Herbert.Mayr@cup.uni-muenchen.de

Met = K, Na, Li,
ZnCl·LiCl, ZnBr·LiBr,
SnMe$_3$, SiMe$_3$

3-Met
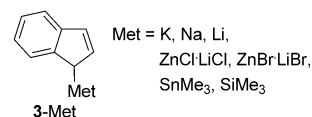
Scheme 1. Organometallic derivatives of indene.

determine the influence of the variable covalent character of the carbon–metal bond on its nucleophilic reactivity.

As the alkali and zinc derivatives of indene are highly reactive and have low stability, they were not isolated in

substance, but generated in DMSO solution by treating indene (3-H) with circa 1.05 equivalents of alkali *tert*-butoxide (KO*t*Bu, NaO*t*Bu, LiO*t*Bu) or TMP-ZnX·LiX (X = Cl, Br, TMP = 2,2,6,6-tetramethylpiperidyl).[9]

The potassium salt **3**-K was combined with the quinone methide **2b** in DMSO solution. Aqueous acidic work up and subsequent purification by column chromatography yielded 65% of **4** as a mixture of two diastereoisomers (Scheme 2).
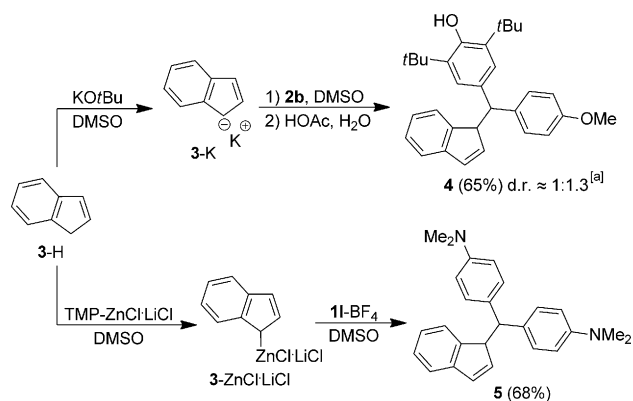

Scheme 2. Representative combinations of indenyl alkali and indenyl zinc derivatives **3**-Met with quinone methides and benzhydrylium salts. [a] Determined by ^{1}H NMR spectroscopy after chromatographic purification.

Treatment of a DMSO solution of **3**-H with a solution of TMP-ZnCl·LiCl (ca. 1.1 equiv) and subsequent combination with the benzhydrylium tetrafluoroborate **1l**-BF$_4$ gave crude **5** after aqueous work-up, which was recrystallized from dichloromethane/ethanol (Scheme 2).

(1*H*-Inden-1-yl)trimethylstannane (**3**-SnMe$_3$) was synthesized in 52% yield in analogy to the reported procedure for the corresponding tributylstannyl compound[10] by deprotonation of indene with *n*-butyllithium and subsequent addition of trimethyltin chloride. (1*H*-Inden-1-yl)trimethylsilane (**3**-SiMe$_3$) was prepared analogously by adding trimethylsilyl chloride to a solution of lithium indenide (**3**-Li) in THF.[11]

Combination of indenyltin **3**-SnMe$_3$ with **1e**-BF$_4$ in dichloromethane at ambient temperature yielded 97% of **6** after filtration over Al$_2$O$_3$ and chromatographic purification (Scheme 3).

As the reaction of **3**-SiMe$_3$ with the pregenerated benzhydrylium salts, which were used for the kinetic investigations (see below), led to complex product mixtures, **3**-SiMe$_3$ was combined with the covalent benzhydryl bromide **1a**-Br in acetonitrile (Scheme 4). GC/MS monitoring of the
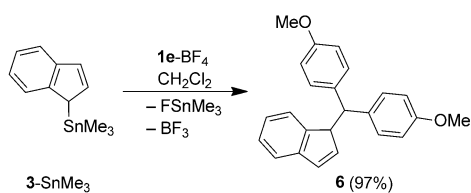
Scheme 3. Reaction of **3**-SnMe$_3$ with the benzhydrylium tetrafluoroborate **1e**-BF$_4$ in dichloromethane at ambient temperature.
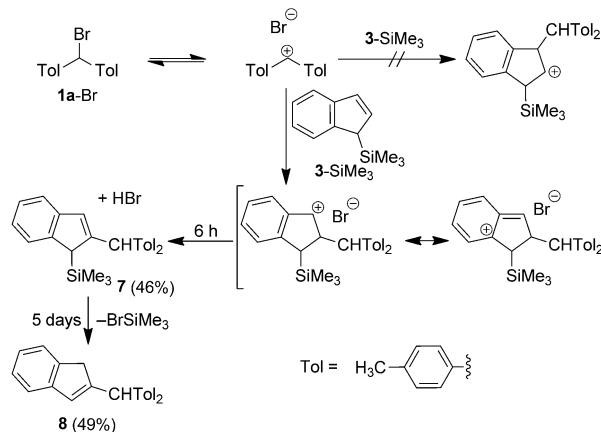
Scheme 4. Reaction of **3**-SiMe$_3$ with **1a**-Br in acetonitrile at ambient temperature.

reaction progress showed the formation of silylated product **7** within 4 to 6 h, which was isolated in 46% yield. The subsequent protodesilylation is much slower, and 49% of the 2-substituted indene **8** was isolated when the reaction mixture was worked up after 5 days. Evidence for electrophilic attack at 1- or 3-position of the indenyl moiety of **3**-SiMe$_3$ was not found. Obviously, the formation of a benzyl cation stabilized by a remote silyl group is preferred over the formation of a β-silyl stabilized alkyl cation.

The kinetic studies of the reactions of the metal derivatives of indene with benzhydrylium ions **1** and quinone methides **2** were performed in dichloromethane or DMSO solution at 20°C and monitored by UV/Vis spectroscopy at or close to the absorption maxima of the electrophiles. By using the indenyl derivatives **3**-Met in large excess (> 10 equiv), pseudo first-order kinetics were observed. The first-order rate constants k_{obs} were obtained by least-squares fitting of the exponential function $A_t = A_0 \exp(-k_{obs}t) + C$ to the time-dependent absorbances A_t of the electrophile (Figure 1). Second-order rate constants k_2 (Table 2) were obtained from linear correlations of k_{obs} with the concentrations of the organometallics as shown for the reaction of **3**-K with **2c** in Figure 1, and for other reactions in the Supporting Information.
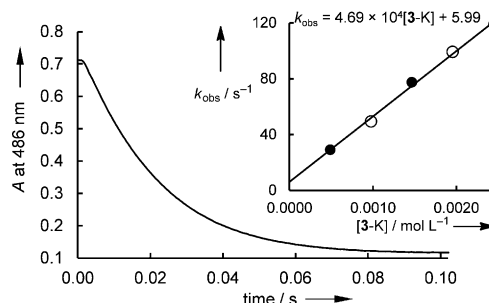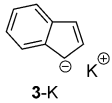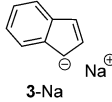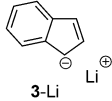
Figure 1. Plot of the absorbance *A* (at 486 nm) vs. time for the reaction of **3**-K (9.78×10^{-4} M) with **2c** (2.03×10^{-5} M) in DMSO at 20°C. Inset: Plot of pseudo-first-order rate constants k_{obs} versus nucleophile concentrations. ● in absence of 18-crown-6, ○ in presence of 1.2 equiv of 18-crown-6 with respect to **3**-K.

Table 2: Second-order rate constants k_2 for the reactions of the metalated indenes **3**-Met with reference electrophiles at 20°C in DMSO or CH_2Cl_2.[a]

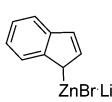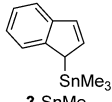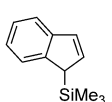| Nucleophile	N (s_N)	Electrophile	k_2 [L mol^{-1} s^{-1}]
3-K	24.16 (0.68) (DMSO)	**2a**	5.70×10^5
		2b	2.82×10^5
		2c	4.69×10^4
		2d	2.04×10^4
3-Na	23.74 (0.71) (DMSO)	**2a**	4.19×10^5
		2b	2.37×10^5
		2c	3.35×10^4
		2d	1.44×10^4
3-Li	23.66 (0.70) (DMSO)	**2a**	3.47×10^5
		2b	1.77×10^5
		2c	2.85×10^4
		2d	1.14×10^4
3-ZnCl·LiCl	18.1 (0.46) (DMSO)	**1l**-BF$_4$	1.4×10^5
		1m-BF$_4$	6.9×10^4
		1o-BF$_4$	1.9×10^4
		1p-BF$_4$	1.1×10^4
		1q-BF$_4$	5.5×10^3
3-ZnBr·LiBr	15.6 (0.51) (DMSO)	**1l**-BF$_4$	2.0×10^4
		1m-BF$_4$	1.2×10^4
		1n-BF$_4$	5.2×10^3
		1o-BF$_4$	2.8×10^3
3-SnMe$_3$	6.68 (0.81) (CH$_2$Cl$_2$)	**1g**-BF$_4$	7.36×10^2
		1h-BF$_4$	1.92×10^2
		1i-BF$_4$	3.74×10^1
		1j-BF$_4$	7.70
		1k-BF$_4$	4.79
3-SiMe$_3$	−0.10 (1.05) (CH$_2$Cl$_2$)	**1b**-BCl$_4$	1.15×10^2
		1c-BCl$_4$	3.77×10^1
		1d-BCl$_4$	3.40
		1e-GaCl$_4$	7.69×10^{-1}
		1f-GaCl$_4$	1.04×10^{-1}

[a] The rate constants for the reactions of **3**-ZnX·LiX are given with lower precision because only one to two half-lives were evaluated to determine k_{obs}.

As the first-order rate constants k_{obs}, which are measured in the presence and in the absence of 18-crown-6, are on the same plots of k_{obs} versus concentration [**3**-K] (Figure 1 and Supporting Information), we conclude that the reactivities of the potassium salt **3**-K determined in DMSO correspond to those of the free indenyl anion.

To be able to exclude that reactions of the chloride ions with the benzhydrylium ions affect the kinetic measurements, the benzhydrylium salt **1m**-BF$_4$ (ca. 1.4×10^{-5} M) was combined with excess LiCl (3.8×10^{-3} M) or Bu$_4$NCl (2.1×10^{-3} M) in DMSO. After mixing, the absorbance of the benzhydrylium ion decreased to 40–50% within 30 min, which is probably caused by a slow reaction of **1m**-BF$_4$ with DMSO. As the reactions of **1m**-BF$_4$ with the organozinc reagent **3**-ZnCl·LiCl proceed within less than 1 to 5 s under the conditions of the kinetic experiments, it can be excluded that the rate constants
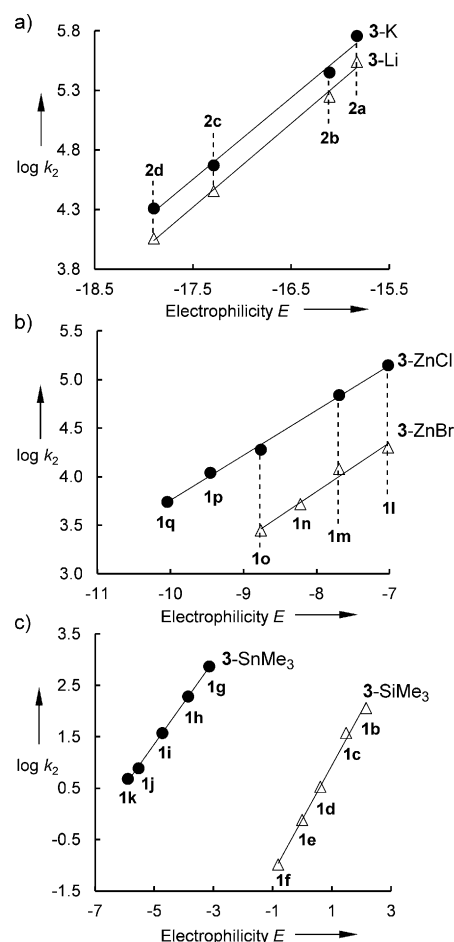

Figure 2. Correlation of $\log k_2$ for the reactions of the metalated indenes with reference electrophiles versus their electrophilicity parameters E: a) alkali metals: **3**-K and **3**-Li, b) zinc: **3**-ZnCl·LiCl and **3**-ZnBr·LiBr, c) tin and silicon: **3**-SnMe$_3$ and **3**-SiMe$_3$.

listed in Table 2 are affected by parallel reactions of **1m** with either DMSO or Cl$^-$. Analogous experiments showed that tetramethylpiperidine (TMPH), which was released by the reactions of indene with TMP-ZnX·LiX, did not affect the kinetics.

Plots of $\log k_2$ for the reactions of the indenyl derivatives **3**-Met with the reference electrophiles against their electrophilicity parameters E are linear, as shown in Figure 2 (the correlation for the sodium salt is shown in the Supporting Information). From the slopes of these correlations, the nucleophile-specific parameters s_N were derived, and the negative intercepts on the abscissa ($\log k_2 = 0$) correspond to the nucleophilicity parameters N (Table 2).

As discussed above, the common correlation line for the reactions of **3**-K in the presence and absence of 18-crown-6 implies that the rate constants measured for **3**-K in DMSO correspond to the reactivities of the free indenyl anions. Table 2 (and for **3**-Li also Figure 2a) shows that the sodium and lithium indenyls are roughly 1.2 to 1.4 (Na) and 1.6 (Li) times less reactive than the free indenyl anion. These small reactivity differences can be expected to disappear completely when electrophiles with $E > -10$ will be used (diffusion control).

Figure 2b illustrates that the relative reactivities of the indenylzinc halides **3**-ZnX·LiX are almost independent of the electrophilicity of their reactions partners. The indenylzinc chloride is 6 to 7 times more reactive than the indenylzinc bromide. Kinetics of the reactions of **3**-ZnI·LiI with **1l–o** could not be unequivocally evaluated and are therefore not reported herein. They indicated, however, that **3**-ZnI·LiI is approximately five times less nucleophilic than **3**-ZnBr·LiBr. Since the reactions of indenylzinc halides with **1m–q** follow complex kinetics in the absence of LiX, the influence of LiX on the nucleophilic reactivities of the indenylzinc halides cannot be described quantitatively.

The reactions of indenylmagnesium halides with quinone methides **2** in DMSO and THF did not follow second-order kinetics, even when Li salts were added. As a consequence, we failed to characterize indenyl Grignard compounds analogously.

Figure 3 illustrates that the nucleophilicity parameters of the metalated indenes cover a reactivity range of 24 units of N. Owing to the different sensitivities s_N, the resulting relative
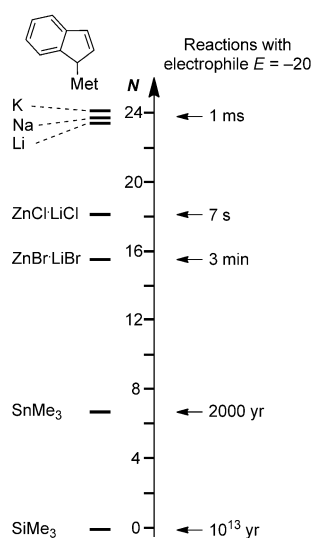

Figure 3. Nucleophilicity parameters of indenyl metal compounds **3**-Met and calculated half-reaction times (1 M solutions, $1/k_2$) for their reactions with a one-bond electrophile of $E = -20$ (20 °C).

reactivities of these compounds depend on the nature of the electrophiles. For reactions with a one-bond electrophile of $E = -20$ one can calculate relative reaction times from 1 ms to 10^{13} years. The effect of metal coordination on the reactivities of the indenyl moiety, as illustrated in Figure 3, can be considered typical for carbanions of related structures. However, the effect can be expected to be greater for less stabilized carbanions and to decrease for better stabilized carbanions.

The nucleophilic reactivities of main-group organometallics are often associated with the differences of the electronegativities of carbon and the corresponding metals. The nucleophilic reactivities of the indenyl derivatives **3**-Met do not correlate with the electronegativities of Allred–Rochow, Mulliken, Pauling, or Sanderson (Supporting Information,

Figures S1–S5).[12a–d] Though Allen's electronegativities[12e] indicate the trend of the observed nucleophilicities of **3**-Met correctly, if it is taken into account that all indenyl alkali compounds are almost ionic, Figure 3 provides to our knowledge the first quantitative comparison of nucleophilic reactivities of organometallics that differ that much in electronegativity.

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