Reactivity and Selectivity of Organotin Reagents in Allylation and Arylation: Nucleophilicity Parameter as a Guide

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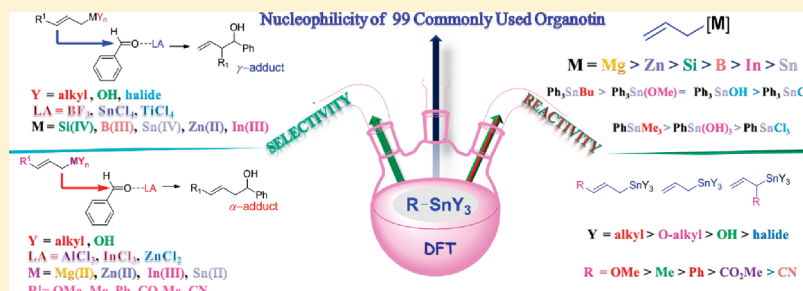
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S *Supporting Information*

ABSTRACT:

By using the inverse concept of electrophilicity and nucleophilicity and with two different available equations from the literature for electrodonating power, the global nucleophilicity index (N) of 99 organotin and 10 allylmetal reagents (metal = Mg, Zn, B, In, Si) have been calculated at the B3LYP/LAN2DZ, 6-31G(d) level of theory. The nucleophilicity scale is validated by the good linear fit between N-values of *para*-substituted arylstannanes and Hammett σ_p values of the substituents on the aryl ring. The global nucleophilicity index N has been utilized successfully to explain the reactivity of aryltin and allyltin reagents, to understand the effect of substituents directly attached to tin and those attached on the transferable group, and to rationalize the effect of solvents on reactivities of organotin reagents. The local nucleophilicity index value (N_k^-) proved to be a useful local descriptor. The N_k^- values at the α- and γ-position in various allylmetal reagents (metal = Mg, Sn, Zn, In, B, Si) have been calculated. Aided by local nucleophilicity values, the regioselectivity in carbonyl allylation (in the presence and in the absence of Lewis or Brønstead acid) has been analyzed.

1. INTRODUCTION

The nucleophilic reactivity of organotin reagents have been widely explored toward a multitude of carbon—carbon bond-forming reactions.[1] The repertoire of reactions mediated by organotin ranges from carbonyl addition to transmetalation-assisted coupling with organic halide and surrogates. Carbonyl addition reactions using *ex situ* or *in situ* generated organotin continue to attract attention due to challenging issues of selectivity (chemo-, regio-, stereo-, enantio-).[2] As for other main group metal reagents (chiefly Li, Mg, Zn, and In), the addition of organotin reagents to the carbonyl group has been studied with respect to the effects of a host of variables such as solvent and Lewis/Brønsted acid activators and even under oxide/polymeric support (Scheme 1).[3] Along with others, our group has been particularly interested in exploring the *in situ* generation of allyl-, propargyl-, and allenylstannanes under transition metal assistance in water or aqueous-organic medium and exploring their reactivity with various electrophiles.[4]

The cross-coupling of organic electrophiles with organometallic reagents serves as a straightforward route for the formation of carbon—carbon as well as carbon—heteroatom bonds

Scheme 1. Nucleophilic Addition of Organotin to Aldehyde
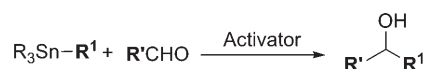
R^1 = Allyl, Aryl, Vinyl, Alkyl
Activator = Lewis acid, Bronstead acid, Metal salt, Metal Complex

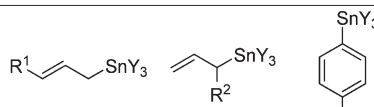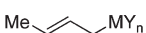**Scheme 2. Cross-Coupling Reaction between an Organometallic Reagent and Organic Electrophile**

(Scheme 2).[5,6] The nucleophilicity of the organometallic reagent is an important parameter in deciding the fate of the coupling reaction. For organotin-mediated Stille coupling, recent studies confirm an S_N2-type mechanism.[7]

Table 1. Organometallic Reagents Studied

Organotin reagents	Allylmetal reagents

Y = Cl, Br, OH, O-Alkyl, Alkyl
R¹, R², R³ = OMe, Me, H, Ph, CO₂Me, CN

M = Mg, Zn, B, Si, Sn, In
Y = Cl, Br, OH ; n = 1-3

A synthetic chemist is often faced with the challenge of tuning the reactivity of an organometallic compound in order to deliver the desired selectivity in a reaction. In view of this and the foregoing discussion, we became interested in classifying the organometallic reagents in general and organotin reagents in particular within empirical scales of nucleophilicity. We also sought to utilize nucleophilicity parameters in analyzing the reactivity and selectivity in carbonyl addition and coupling reactions.

The accessible quantitative scales of electrophilicity/nucleophilicity provide useful tools for the rationalization of chemical reactivity. One of the recent illustrations on the benefits of these scales is by Mayr et al.[8] In their method the rate constants have been correlated by the equation $\log k = s(N + E)$, in which electrophiles are characterized by one parameter (E) and nucleophiles by two parameters $(N$ and $s)$.[9] Using this approach an experimentally derived nucleophilicity scale has been evolved for π-nucleophiles, N-nucleophiles, σ-nucleophiles, and organometallic reagents including organosilicon and organotin by using reference electrophiles. Alongside these experimental scales of electrophilicity and nucleophilicity, theoretical[10] scales are highly desirable, as they can be used to further probe the reactivity and selectivity and their dependence on chemical substitution or stereochemical factors. In this work we have undertaken this task with respect to organotin reagents in general and allylmetal reagents in particular (Table 1)

2. THEORETICAL BACKGROUND

Global reactivity descriptors (GRDs) describe the reactivity of an atom, ion, or molecule as a whole. Indeed many global and local reactivity descriptors, based on density functional theory (DFT), are known.[11] One of the important GRDs is hardness, as was first introduced by Pearson in his famous hard−soft acid−base (HSAB) principle.[12] In general a chemical system is hard if it is less polarizable and magnetizable. The hardness (η) is defined as[11a]

$$\eta = (I - A) \approx (E_{HOMO} - E_{LUMO}) \tag{1}$$

Softness (S) is the reciprocal of hardness and is defined as

$$S = \frac{1}{\eta} = \frac{1}{(E_{HOMO} - E_{LUMO})} \tag{2}$$

Another important GRD is electrophilicity, which has been defined by Parr et al. as the energy of stabilization of a chemical species when it acquires an additional fraction of electronic charge from the environment.[13] The global electrophilicity index (ω) is defined as

$$\omega = \frac{\mu^2}{2\eta} \tag{3}$$

where μ is the electronic chemical potential,[14] defined as

$$\mu = \frac{(I + A)}{2} \approx \frac{(E_{HOMO} + E_{LUMO})}{2} \tag{4}$$

In an important contribution, Gazquez et al.[15] have defined *electrodonating power* (ω^-) as

$$\omega^- = \frac{I^2}{2(I - A)} \text{ and } \omega^- = \frac{(3I + A)^2}{16(I - A)} \tag{5}$$

Note that according to this definition, a low value of ω^- signifies a better electron donor. In order to equate with the general notion that "more is better", in the present work nucleophilicity is defined as the inverse of electrodonating power. By using the inverse relation between η and ω^- and employing eqs 6 and 7 (Scheme 3), we calculated the nucleophilicity of 99 commonly used organotin reagents.[16,17]

Scheme 3. Two Equations Used in This Work as Methods I and II

$$N = \frac{10}{\omega^-} \text{ where } \omega^- = \frac{I^2}{2(I - A)} \quad \rightarrow Method\ I \tag{6}$$

$$N = \frac{10}{\omega^-} \text{ where } \omega^- = \frac{(3I + A)^2}{16(I - A)} \quad \rightarrow Method\ II \tag{7}$$

As described later the global nucleophilicity index N has been utilized successfully to explain the nucleophilic reactivity of organotin and allylmetal reagents as well as understand the influence of substituent(s) and additives. Note that the global nucleophilicity index depends only on the electronic characteristics of the nucleophile and is independent of the electrophilic partner. Although GRD describes the overall behavior of a molecule, it does not represent the behavior of a specific atomic site or a given region of space in the molecule. Therefore to access the local behavior, local reactivity descriptors (LRDs) need to be introduced. Of course, the most fundamental LRD is the electron density, $\rho(r)$, itself. Another important LRD is the Fukui function indices (the naming arises due to its conceptual similarity to Fukui's frontier molecular orbital theory),[18] which can be expressed as

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)}\right)_{v(r)} \tag{8}$$

There are different types of Fukui functions, each for nucleophilic, electrophilic, and radical attacks. The application of finite difference and frozen core approximations to eq 8 results in the

corresponding Fukui functions, expressed as

$$f^+(r) = \left(\frac{\partial \rho}{\partial N}\right)^+_{v(r)} \approx \rho_{N+1}(r) - \rho_N(r); \text{ for nucleophilic attack}$$

$$(9)$$

$$f^-(r) = \left(\frac{\partial \rho}{\partial N}\right)^-_{v(r)} \approx \rho_N(r) - \rho_{N-1}(r); \text{ for electrophilic attack}$$

$$(10)$$

$$f^0(r) = \frac{1}{2}\left(f^+(r) + f^-(r)\right); \text{ for radical attack} \quad (11)$$

The nucleophilic character of a site within a molecule is expressed by a local nucleophilicity index $N^-(r)$ that is derived using the relationship $N^-(r) = N^* f^-(r)$. Conversely, the electrophilic character of a reactive site within a molecule is described by a local electrophilicity index expressed as $\omega^+(r) = \omega^* f^+(r)$. The $f^-(r)$ and $f^+(r)$ are the Fukui functions for electrophilic attack and nucleophilic attack at the specific site, respectively.[11d] The condensed-to-atom variants of the above quantities have been written as

$$f_k^+ = q_k(N+1) - q_k(N); \text{ for nucleophilic attack} \quad (12)$$

$$f_k^- = q_k(N) - q_k(N-1); \text{ for electrophilic attack} \quad (13)$$

$$f_k^0 = [q_k(N+1) - q_k(N-1)]/2; \text{ for radical attack} \quad (14)$$

where q_k is the electron population of the atom k in a molecule.

The nature of the density partitioning in any population analysis scheme states the relative magnitudes of f_k^α. In the present work, atomic populations were acquired via natural population analysis (NPA) method.[19] The corresponding condensed-to-atom forms of both the nucleophilicity index (N_k^-) and electrophilicity index (ω_k^+) for atom k are presented as

$$N_k^- = N^* f_k^- \quad (15)$$

$$\omega_k^+ = \omega^* f_k^+ \quad (16)$$

In this work, the local nucleophilicity descriptors (N_k^-)[20] have been used to explain the regioselectivity in carbonyl allylation (α- versus γ-attack) via allylmetal reagents (metal = Mg, Sn, Zn, In, B, Si).

3. CORRELATION OF CALCULATED GLOBAL NUCLEO-PHILICITY (*N*) OF ORGANOTIN REAGENTS WITH HAMMETT SUBSTITUENT CONSTANT (Σ_P)

The global and local nucleophilicity of organotin and allylmetal reagents were calculated at the B3LYP/LANL2DZ, 6-31G* level of theory[21] using eqs 6 (method I) and 7 (method II) in Scheme 3. Next we sought to validate the nucleophilicity scales obtained via methods I and II by judging the goodness of a linear fit between nucleophilicity (N) versus Hammett constant (σ_P) value. The *para*-substituted phenyl derivatives of trimethylstannane (4-R-C$_6$H$_4$-SnMe$_3$) were chosen as the test series, and the corresponding calculated N-values were plotted against the Hammett substituent constant (σ_P).[22] In each case we have obtained good linear correlation between N versus σ_P values (Figure 1). Note that the linear plots have negative slope. In other
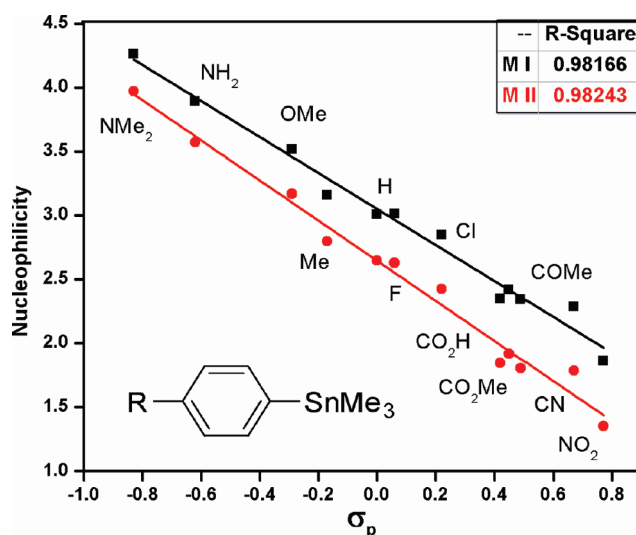

Figure 1. Plot of Hammett substituent constant (σ_P) versus calculated nucleophilicity in the two methods.
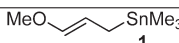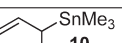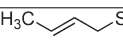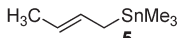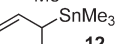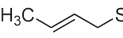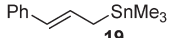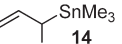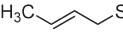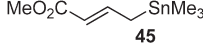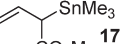
words, arylstannanes bearing an electron-releasing substituent ($-$ve σ_P value) at the phenyl ring are predicted to show better nucleophilic reactivity.

The reactivity of an organometallic reagent toward an electrophile depends majorly on the following factors: (i) the electronic nature of other functional group(s) bound to the metal; (ii) the steric and electronic demand of the transferable group; and (iii) the nature of the solvent and additives (if any). All these parameters play important roles in the design of a retrosynthetic plan by an organic chemist. For organotin reagents, there already exists an array of experimental results on the influence of the above parameters in carbonyl allylation and arylation, and in coupling reactions with organic electrophiles. We therefore analyzed all the probable internal (electronic and steric effect of substituent attached to tin) and external (effect of solvent and additive) factors responsible for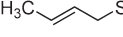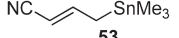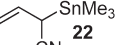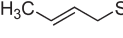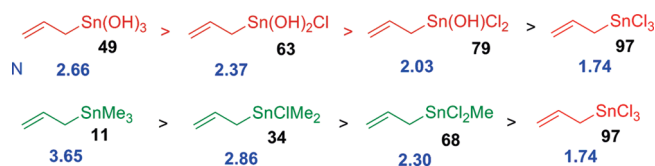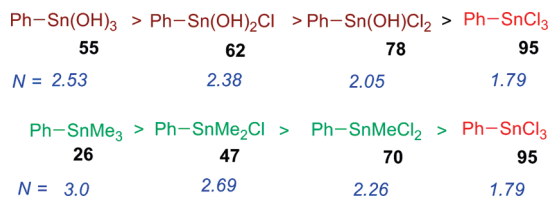 the reactivity of aryl- and allylstannanes by using the calculated global and local nucleophilicity values. The results are discussed in the next sections.

4. INFLUENCE OF SUBSTITUENT DIRECTLY ATTACHED TO TIN ON ORGANOTIN REACTIVITY

A number of studies have confirmed that Barbier allylation with organotin is facilitated by water.[23,24] However, the exact nature of the allyltin(IV) intermediates is often debated. Tagliavini and co-workers suggested the formation of either allylhydroxystannane or cationic hydrated allyltin intermediates.[25] Using NMR as a diagnostic tool, Masuyama and co-workers suggested the plausible formation of allylhydroxystannane as the reactive interactive.[26] We have observed that allylation is promoted by controlled addition of water in DMSO or by the addition of stoichiometric LiOH in anhydrous dichloromethane as solvent.[27] In hindsight, it appears that LiOH in DCM played a similar role as that of water in DMSO toward the possible generation of a reactive allylhydroxystannane. *Is the enhanced reactivity of this new species due to its enhanced nucleophilicity?* To analyze this proposal, we calculated both global and local nucleophilicity values of all probable allylchlorohydroxystannanes. Gratifyingly, the N-values obtained clearly showed that substitution of $-$Cl by $-$OH increases the nucleophilicity,

Table 2. Global Nucleophilicity (N) of Allyltin Reagents Obtained via Method I

Series I		Series II		Series III	
Compound	N	Compound	N	Compound	N
MeO⌁⌁SnMe$_3$ **1**	4.47	⌁SnMe$_3$ (Me) **10**	3.71	H$_3$C⌁⌁SnBu$_3$ **4**	3.98
H$_3$C⌁⌁SnMe$_3$ **5**	3.93	⌁SnMe$_3$ (OMe) **12**	3.65	H$_3$C⌁⌁SnMe$_3$ **5**	3.93
Ph⌁⌁SnMe$_3$ **19**	3.29	⌁SnMe$_3$ (Ph) **14**	3.53	H$_3$C⌁⌁Sn(Oi-Pr)$_3$ **21**	3.14
MeO$_2$C⌁⌁SnMe$_3$ **45**	2.71	⌁SnMe$_3$ (CO$_2$Me) **17**	3.41	H$_3$C⌁⌁Sn(OH)$_3$ **30**	2.89
NC⌁⌁SnMe$_3$ **53**	2.59	⌁SnMe$_3$ (CN) **22**	3.14	H$_3$C⌁⌁SnCl$_2$Br **90**	1.84

⌁Sn(OH)$_3$ **49** > ⌁Sn(OH)$_2$Cl **63** > ⌁Sn(OH)Cl$_2$ **79** > ⌁SnCl$_3$ **97**

N **2.66**   **2.37**   **2.03**   **1.74**

⌁SnMe$_3$ **11** > ⌁SnClMe$_2$ **34** > ⌁SnCl$_2$Me **68** > ⌁SnCl$_3$ **97**

3.65   **2.86**   **2.30**   **1.74**

Figure 2. Nucleophilicity (N) of allyltin obtained via method I.

Ph−Sn(OH)$_3$ > Ph−Sn(OH)$_2$Cl > Ph−Sn(OH)Cl$_2$ > Ph−SnCl$_3$
55   **62**   **78**   **95**

N = 2.53   2.38   2.05   1.79

Ph−SnMe$_3$ > Ph−SnMe$_2$Cl > Ph−SnMeCl$_2$ > Ph−SnCl$_3$
26   **47**   **70**   **95**

N = 3.0   2.69   2.26   1.79

Figure 3. Nucleophilicity (N) of phenyltin obtained via method I.

the N-values being in the order **49 > 63 > 79 > 97** (Figure 2). It is revealed that substitution of −Cl by −Me also increases the global nucleophilicity, the N-values being in the order **11 > 34 > 68 > 97** (Figure 2). The above reactivity order is in excellent agreement with the available experimental data.[28]

In an important contribution Chao-Jun Li and co-workers showed the remarkable effect of substituent (Y) on the reactivity of arylorganometallics Ar$_m$MY$_n$ (M = Sn, B, Bi) in carbonyl addition and in conjugate addition in water.[29] In the case of carbonyl addition, it was observed that in the absence of any other additive, PhSnMe$_3$ was reactive, while PhSnCl$_3$ was not. On the contrary, addition of alkali metal hydroxide to the latter made it reactive again. *Ex situ* generated Ph$_3$SnOH was also reactive in the absence of other additive. The similarity between the substituent effect on the reactivity of aryltin and allyltin derivatives prompted us to determine the global nucleophilicity value (N) of a series of phenylstannanes. Indeed the N-values of phenylstannanes also follow a trend similar to that in allylstannanes. As depicted in Figure 3, substitution of −Cl by −OH or −Me increases the nucleophilicity; the resulting order **55 > 62 > 78 > 95** and **26 > 47 > 70 > 95** is in good agreement with the experimental order of reactivity.[29] When we looked into other substituents, the N-value is found to decrease in the order alkyl > O-alkyl > OH > Br > Cl (see Table 2 later).

## 5. INFLUENCE OF SUBSTITUENT ON REACTIVITY AND SELECTIVITY IN ALLYLTIN-MEDIATED CARBONYL ALLYLATION

In carbonyl allylation reactions, the reactivity of an allylmetal reagent varies significantly depending on the metal, the substituents appended to the metal, and those appended to the allyl backbone. In carbonyl allylation via allyltin reagents, the reactivity is found to be dependent on the substituent on the allyl moiety and decreases in the order −OMe > −Me > −Ph > −CO$_2$Me > −CN.[30] We have found that the global nucleophilicity index N, which is a useful indicator of reactivity, also follows a similar order. For example, in a series of 3-substituted allyltrimethylstannanes, the N-value decreases in the order −OMe> −Me > −Ph > −CO$_2$Me > −CN (Table 2, Series I). Similar observations were made in the case of corresponding 1-substituted analogues (Series II). On the other hand, in 2-butenylstannanes C$_4$H$_7$SnY$_3$ (Series III), as we progress along Y = halide, OH, O-alkyl, and alkyl, global nucleophilicity increases along the series, indicating progressive enhancement of reactivity.

A major issue pertaining to carbonyl allylation of aldehydes by an allylmetal is how to direct the reaction to one of two possible regioisomers, α or γ. In the case of allyltin, it is generally believed that the γ-regioisomer arises via a six-member cyclic transition state, whereas the α-isomer is derived from an open transition state.[31] Typically a Lewis acid (LA, to activate the carbonyl center) or a second metal (to assist a trasmetalation) also assumes importance in guiding the selectivity (Scheme 4).[32]

In order to analyze the regioselectivity issue in carbonyl allylation, we have calculated the local nucleophilicity (N_k^-) index at the α- and γ-sites in three series of allyltin reagents R-SnY$_3$ (Y = Halo, Me, OH; R =substituted allyl). In a broad way, these three series reflect the reactivity of allyltrialkylstannanes (represented by Y = Me),[33] the reactivity of allylhalostannanes (represented by Y = Cl) generated *in situ* from Sn$^{0/II}$ and allyl halide in a Barbier fashion, and the reactivity of allylhydroxystannanes (represented by Y = OH) generated *in situ* from Sn^{II} and allyl halide in water.[34] We have also calculated ΔN_k^-, which is the differences between the local nucleophilicities at the two sites [$\Delta N_k^- = N_k^-(\gamma) - N_k^-(\alpha)$].[35] From the $N_k^-(\gamma)$, $N_k^-(\alpha)$, and ΔN_k^- values and the generalized experimental observation (please see Supporting Information, SI, Tables SI-6 to SI-9, Charts SI-1, SI-2) related to the three series defined as above, the following empirical relations are conjectured.[36]

(I) γ-attack becomes prevalent when $N_k^-(\alpha) < 0.07$

Scheme 4. Regioselectivity in Carbonyl Allylation
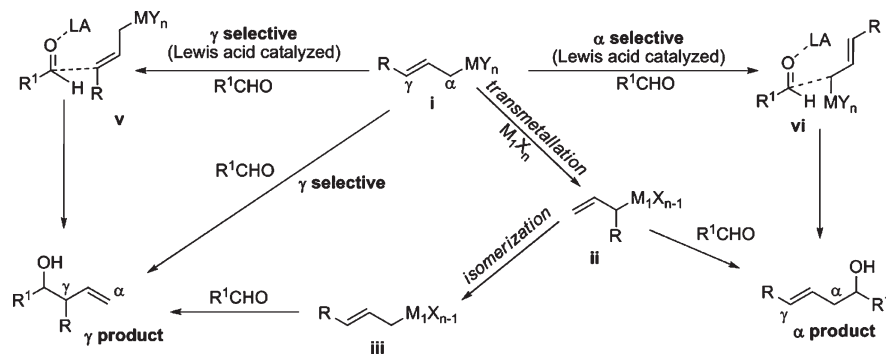
Table 3. Global Nucleophilicity (N), Local Nucleophilicity Index (N_k^-) Values at α- and γ-Positions, and ΔN_k^- Values of Allylmetal Reagents Obtained via Method I

Compound	N	N_k^- (γ)	N_k^- (α)	ΔN_k^-	Compound	N	N_k^- (γ)	N_k^- (α)	ΔN_k^-
86	1.88	0.39	-0.01	0.40	**90**	1.84	0.40	0.03	0.37
87	1.88	0.43	-0.02	0.45	**91**	1.82	0.47	0.07	0.40
88	1.87	0.09	-0.03	0.12	**94**	1.81	0.46	0.04	0.42
83	1.92	0.38	0.01	0.37	**98**	1.66	0.33	0.06	0.27
80	1.94	0.39	0.04	0.35	**99**	1.55	0.26	0.06	0.20
82	1.92	0.40	-0.04	0.44	**96**	1.78	0.42	0.11	0.31
81	1.92	0.40	0.03	0.37					

(II) γ-attack becomes prevalent when $N_k^-(\gamma) > 0.50$

(III) where $N_k^-(\alpha) < 0.07$ *and/or* $N_k^-(\gamma) > 0.50$, γ-attack becomes prevalent when $\Delta N_k^-(\gamma) > 0.25$

Within the scope of the above empirical relations, the following functional group dependence may be noted (see Tables 3 and 4).

1. In a series of substituted allylhalostannanes R-SnCl$_2$Br, carbonyl allylation shows γ-regioselectivity irrespective of the substituent on the allyl moiety (Table 3). This conforms to relations I and II.
2. In conformity to relations I and II, γ-regioselectivity is observed in allyltrihydroxystannanes **30**, **41**, **43**, **56**, **66**, and **67** (Table 4, Series I).
3. In conformity to relations I and II γ-regioselectivity is observed in allyltrimethylstannanes **1**, **5**, **12**, **17**, and **22** (Table 4, Series II).
4. Relation III could be applied to compounds **19**, **42**, **45**, **53**, and **71**, where a mixture of γ- *and* α-isomers is expected.

5. Compounds **10** and **14** are found to be exceptions to the relations I—III.
6. The local nucleophilicity also shows dependence on the oxidation state of the metal. For example, allyltin(II) compounds **110** and **111** promote α-selective carbonyl allylation, while the corresponding allyltin(IV) analogues **92** and **30** promote γ-selective carbonyl allylation (Tables 4 and 5). The observed selectivity can be easily explained by relation III.

6. INFLUENCE OF METAL ON REACTIVITY AND REGIOSELECTIVITY IN ALLYLMETAL REAGENTS

The chemistry of allyl-organometallics, in particular their reactivity and selectivity, is significantly affected by the metal center as well.[2−4,37] Much attention has been focused on the regioselectivity leading to the α- or γ-products from the reaction

Table 4. Global Nucleophilicity (N), Local Nucleophilicity Index (N_k^-) Values at α- and γ-Positions, and ΔN_k^- Values of Allyltin Reagents Obtained via Method I
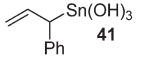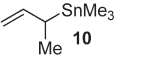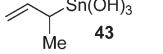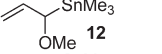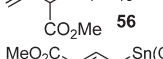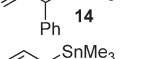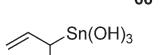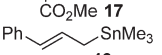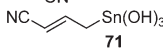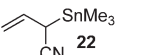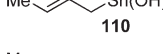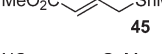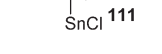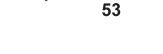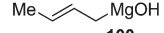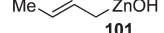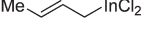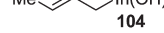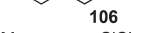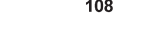
Series I					Series II				
Compounds	N	N_k^- (γ)	N_k^- (α)	ΔN_k^-	Compounds	N	N_k^- (γ)	N_k^- (α)	ΔN_k^-
H₃C⌒Sn(OH)₃ **30**	2.89	0.66	0.17	0.49	MeO⌒SnMe₃ **1**	4.47	0.40	0.03	0.37
Ph⌒Sn(OH)₃ **42**	2.75	0.24	0.08	0.16	H₃C⌒SnMe₃ **5**	3.93	0.94	0.43	0.51
Sn(OH)₃ / Ph **41**	2.75	0.36	0.17	0.19	SnMe₃ / Me **10**	3.71	0.26	0.15	0.11
Sn(OH)₃ / Me **43**	2.72	0.54	0.27	0.27	SnMe₃ / OMe **12**	3.65	0.85	0.49	0.36
Sn(OH)₃ / CO₂Me **56**	2.49	0.62	0.25	0.37	SnMe₃ / Ph **14**	3.53	0.53	0.43	0.10
MeO₂C⌒Sn(OH)₃ **66**	2.31	0.46	0.19	0.27	SnMe₃ / CO₂Me **17**	3.41	0.92	0.47	0.45
Sn(OH)₃ / CN **67**	2.30	0.57	0.25	0.32	Ph⌒SnMe₃ **19**	3.29	0.36	0.16	0.20
NC⌒Sn(OH)₃ **71**	2.20	0.39	0.15	0.24	SnMe₃ / CN **22**	3.14	0.72	0.45	0.27
Me⌒Sn(OH) **110**	2.87	0.72	0.60	0.12	MeO₂C⌒SnMe₃ **45**	2.71	0.41	0.41	0
Me⌒SnCl **111**	2.55	0.61	0.51	0.10	NC⌒SnMe₃ **53**	2.59	0.54	0.36	0.18

Table 5. Global Nucleophilicity (N), Local Nucleophilicity Index (N_k^-) Values at α- and γ-Positions, and ΔN_k^- Values of Allylmetal Reagents Obtained via Method I
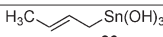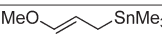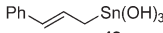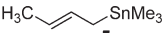
Series I					Series II				
Compound	N	N_k^- (γ)	N_k^- (α)	ΔN_k^-	Compound	N	N_k^- (γ)	N_k^- (α)	ΔN_k^-
Me⌒MgOH **100**	3.24	0.84	0.84	0	Me⌒MgCl **105**	2.71	0.70	0.51	0.19
Me⌒ZnOH **101**	3.03	0.73	0.33	0.40	Me⌒InCl₂	2.11	0.48	0.13	0.35
Me⌒In(OH)₂ **104**	2.97	0.74	0.30	0.44	Me⌒SnCl₃ **92**	1.82	0.42	0.02	0.40
Me⌒Sn(OH)₃ **30**	2.89	0.66	0.17	0.49	Me⌒ZnCl **106**	2.55	0.63	0.23	0.40
Me⌒Si(OH)₃ **102**	3.25	0.84	0.13	0.61	Me⌒SiCl₃ **107**	2.36	0.56	-0.02	0.58
Me⌒B(OH)₂ **103**	3.23	0.90	0.03	0.87	Me⌒BCl₂ **108**	2.28	0.59	0.02	0.57

of allylmetals with C═Z electrophiles such as carbonyl, imine, and acyclic systems. In most cases γ-adducts are obtained exclusively. In comparison, routes to α-selective allylations are limited.[38] Encouraged by the correlations of nucleophilicity indices with reactivity and selectivity in allylstannanes as described in the previous section, we aimed to probe the same for other allylmetals. Gratifyingly, the reactivity order and site selectivity (α- vs γ-) obtained from the global and local nucleophilicity indices are found to be in good agreement with experiment.[37−39] The results are highlighted in Table 5.

1. For chloro derivatives of allyl metals, the global nucleophilicity N decreases in the order Mg > Zn > Si > B> In > Sn.

2. For a series of hydroxy derivatives of allylmetals, N_k^- values showed an interesting trend. Thus N_k^- at the γ-position is found to be higher than at the α-position in the hydroxy derivatives of allylsilicon **102** and -boron **103**. However, for the corresponding derivatives of indium, **104**, and zinc, **101**, the local nucleophilicity value at the α-position becomes appreciable. However for the allylmagnesium derivative **100**, both α- and γ-positions show comparable local nucleophilicity.

3. The local nucleophilicity at the γ-position is found to be significantly higher than at the α-position in the chloro derivates of allylboron, **108**, silicon, **107**, and tin, **92**. However, for allylmagnesium **105**, both the α- and γ-position show comparable local nucleophilicity.

4. Solvent also influences the nucleophilic reactivity of an allylmetal reagent. For allyltrichlorostannane as a representative case, the global nucleophilicity values evaluated in
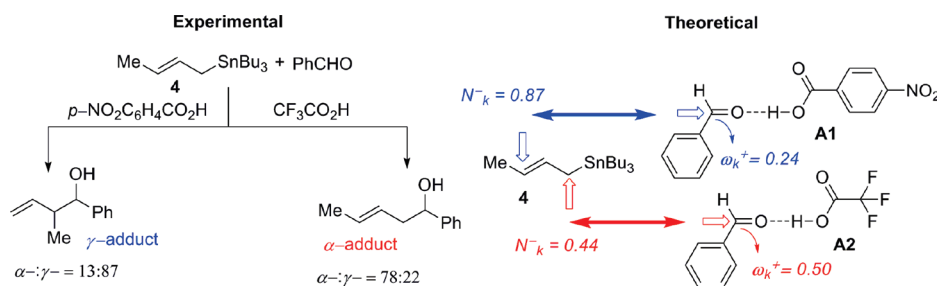
Figure 4. Experimental regioselectivity in Brønsted acid mediated allylation of aldehyde and a connection between local electrodonating power (N_k^-) and local electroaccepting power (ω_k^+).
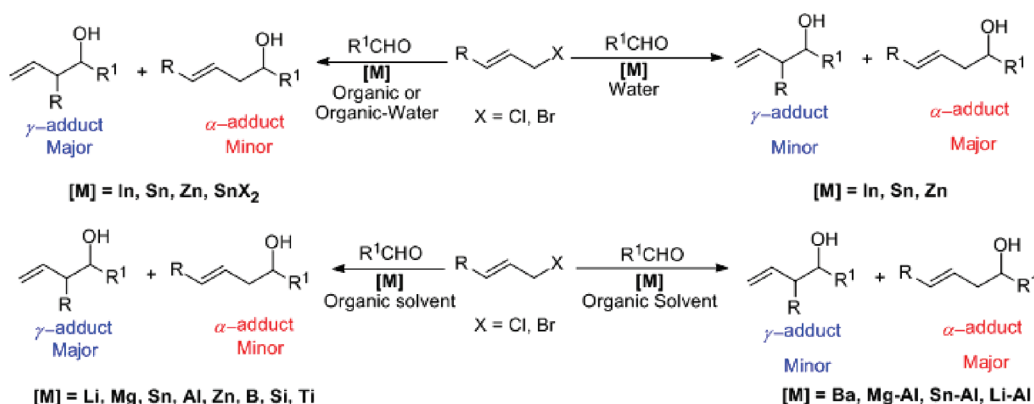
Figure 5. Experimental regioselectivity in Barbier-like aldehyde allylation (summarized from results in refs 34–36 and 46–48).

different solvents indicate that nucleophilicity increases with increasing polarity of the solvent.[40]

It is apparent from the above discussion that the electronic environment at or around the metal center in allyl metals controls the regioselectivity. Next, we wished to test those cases where an external reagent (Brønsted acid, Lewis acid) influences the regioselectivity in carbonyl allylation. Toward this, we looked into the local nucleophilicity (N_k^-)[41] at the reactive sites in allylmetals and the local electroaccepting power (ω_k^+)[42] at the carbonyl carbon.[43,44]

7. INFLUENCE OF BRØNSTED ACID ON REGIOSELECTIVITY IN ALLYLMETAL REAGENTS

Use of a Brønsted acid as a promoter in carbonyl allylation is of interest to synthetic chemists.[45] Yamamoto and co-workers reported the allylation of aldehydes with allytributyltin in acidic aqueous solution.[46] In a similar study, Loh et al. showed the influence of trifluoromethane sulfonic acid as a promoter in carbonyl allylation in water. Other studies on carbonyl allylation where carboxylic acids are used as promoters are also noteworthy.[47] Recently, Li et al. showed that in carbonyl allylation regioselectivity can be simply tuned by controlling the acidity of the carboxylic acids (Figure 4).[48] For example, under the aegis of 4-nitrobenzoic acid, the γ-adduct is the major product, but in the presence of trifluoroacetic acid, the α-adduct is the major product. We wished to derive an insight into the above from the point of view of local nucleophilicity.

It is well accepted that the hydrogen bond between benzaldehyde and trifluoroacetic acid is stronger than that

between benzaldehyde and 4-nitrobenzoic acid, the latter being a weaker acid. We calculated the local electroaccepting power (ω_k^+) at the carbonyl carbon in both the hydrogen-bonded structures **A1** and **A2** at the B3LYP/6-31G* level of theory. As shown in Figure 4, the ω_k^+ value at the carbonyl carbon in **A1** is significantly lower than the corresponding carbon in **A2**. One may also note that in 2-butenyltributyl-stannane **4** the local nucleophilicity (N_k^-) at the γ-position is significantly higher than at the α-position. When we compare the above data with the experimentally observed regioselectivity, it becomes apparent that in allylstannane **4** the α-position having a lower N_k^- value undergoes preferential interaction with the carbonyl site in **A2** having high ω_k^+ value. Conversely, the γ-position in **4** having a higher N_k^- value undergoes preferential interaction with the carbonyl site in **A1** having a lower ω_k^+ value. We will remain interested to see whether similar correlation is observed in other such regioselective reactions as well.

8. INFLUENCE OF LEWIS ACID ON REGIOSELECTIVITY IN BARBIER ALLYLATION

Lewis acid mediated allylation of aldehydes using externally generated allylmetal reagents is widely explored. The Barbier-like carbonyl allylation protocol generally involves the concurrent addition of allyl halide and carbonyl to elemental metal.[49] In such a case, the allylmetal reagent is generated and reacted *in situ*. Such a protocol leads to the *in situ* generation of metal salts as well, which themselves are Lewis acidic. It has been observed that in Barbier-like allylation the metal and the LA guide the regioselectivity[50] (Figure 5).

Table 6. Complex Formation Energy (ΔE_f in kJ mol^{-1}) and Local Electroaccepting Power (ω_k^+) at the Carbonyl Center in Benzaldehyde-LA Adducts

Aldehyde aduuct	Optimized structure	ΔE_f in KJ/mol	ω_k^+ (CHO)
		-132.8	1.86
		-110.7	1.74
		-72.8	1.71
		-52.8	1.54
		-36.4	1.11
		-28.1	0.60
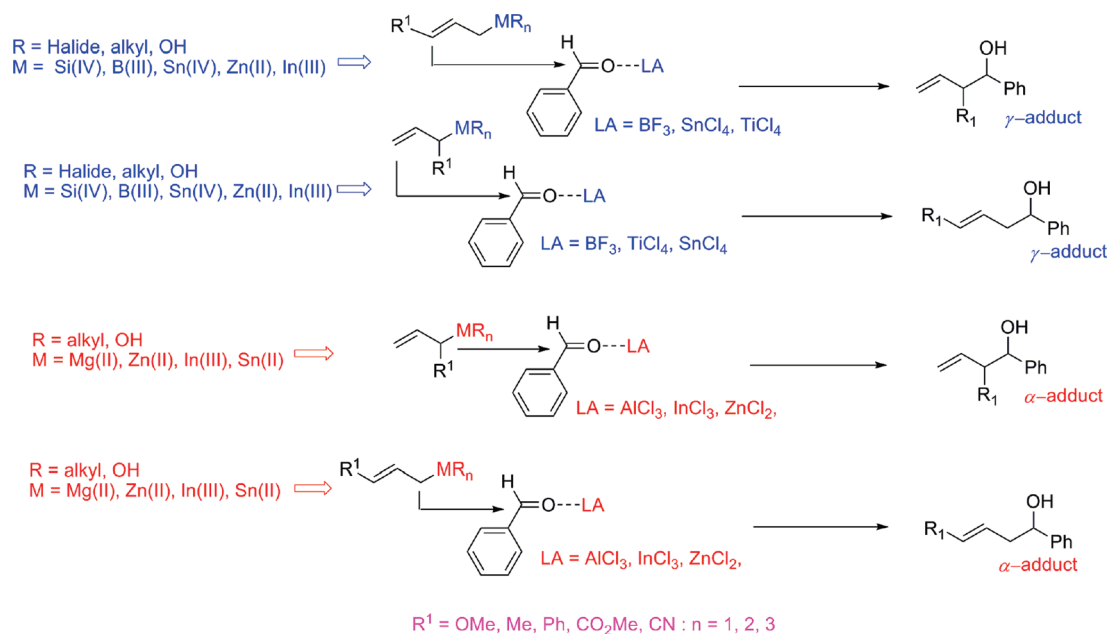
Figure 6. Relationship of Regioselectivity in Carbonyl Allylation with Local Electrodonating Power (N_k^-) and Local Electroaccepting Power (ω_k^+).

In most cases γ-regioselective allylation is observed. However, allyltin, allylmagnesium, and allyllithium are known to promote α-regioelectivity in the presence of LA such as AlCl$_3$. α-Regioselectivity is also observed for allylation of aldehydes under Barbier protocol using allyl halides and elemental indium(0), zinc(0), and tin(0).[51] In order to gain insight into the observed regioselectivity as above, we calculated the local electroaccepting power ω_k^+ at the carbonyl center in the aldehyde-LA adducts (Table 6).[52] The complex formation energy (ΔE_f) of the adducts was also evaluated.[53]

The ΔE_f values reveal that the affinity of the Lewis acids toward aldehyde coordination increases as TiCl$_4$ < SnCl$_4$ < BF$_3$ < ZnCl$_2$ < InCl$_3$ < AlCl$_3$. Interestingly, in these adducts, the ω_k^+ values at the carbonyl center also increase in the same order. By comparing the ω_k^+ values at the aldehyde-LA adducts (Table 6) and the N_k^- values at the α- and γ-carbon in each of the allyl metal reagents (Table 5) one could notice an apparent relationship that accommodates the experimentally observed regioselectivity: a carbonyl site having higher ω_k^+ value induces nucleophilic attack by the allylmetal site having lower N_k^- value

Table 7. Global Nucleophilicity (N) Values of 99 Commonly Used Organotin Reagents in Method I

#	Compound	N	#	Compound	N	#	Compound	N
1	MeO⌒⌒SnMe₃	4.47	34	⌒SnMe₂Cl	2.86	67	⌒Sn(OH)₃ / CN	2.30
2	Me₂N—⬡—SnMe₃	4.26	35	Ph⌒(Me)Sn(OH)₃	2.86	68	⌒SnMeCl₂	2.30
3	Me⌒⌒SnBu₃ / Me	4.15	36	Cl—⬡—SnMe₃	2.85	69	NC—⬡—SnMe₃	2.28
4	Me⌒⌒SnBu₃	3.97	37	⌒Sn(OPh)₃	2.84	70	Ph—SnCl₂Me	2.26
5	Me⌒⌒SnMe₃	3.93	38	⌒Sn(OMe)₃	2.83	71	NC⌒⌒Sn(OH)₃	2.20
6	H₂N—⬡—SnMe₃	3.89	39	Ph—Sn(OPh)₃	2.82	72	Ph—SnCl₂(O-i-pr)	2.10
7	Me⌒⌒SnBu₃	3.86	40	Ph⌒(Me)Sn(OH)₃	2.80	73	Ph—SnCl₂(OEt)	2.09
8	⌒SnBu₃ / OMe	3.81	41	⌒(Ph)Sn(OH)₃	2.75	74	⌒SnCl₂(O-i-pr)	2.09
9	⌒SnBu₃	3.72	42	Ph⌒⌒Sn(OH)₃	2.75	75	Ph—SnCl₂(O-n-pr)	2.09
10	⌒SnMe₃ / Me	3.71	43	⌒(Me)Sn(OH)₃	4.10	76	Ph—SnCl₂(OMe)	2.08
11	⌒SnMe₃	3.65	44	Ph₃SnOMe	2.72	77	⌒SnCl₂(OMe)	2.07
12	⌒SnMe₃ / OMe	3.65	45	MeO₂C⌒⌒SnMe₃	2.71	78	Ph—SnCl₂(OH)	2.05
13	H₃C⌒⌒SnMe₃	3.61	46	Ph₃SnOH	2.71	79	⌒SnCl₂(OH)	2.04
14	⌒SnMe₃ / Ph	3.53	47	Ph—SnClMe₂	2.69	80	Me₂C=C(Me)CH(Me)SnCl₂(Br)	1.94
15	MeO—⬡—SnMe₃	3.51	48	⌒Sn(OH)₃ / OMe	2.68	81	MeO⌒⌒SnCl₂(Br)	1.92
16	HO—⬡—SnMe₃	3.42	49	⌒Sn(OH)₃	2.66	82	Me₂C=CH⌒SnCl₂(Br)	1.92
17	⌒SnMe₃ / CO₂Me	3.41	50	Ph—Sn(O-i-pr)₃	2.62	83	Me⌒(Me)CH(Me)SnCl₂(Br)	1.91
18	⌒SnMe₂(OH)	3.35	51	Ph—Sn(O-n-pr)₃	2.61	84	Ph⌒(Me)CH(Me)SnCl₂(Br)	1.90
19	Ph⌒⌒SnMe₃	3.29	52	Ph—Sn(OEt)₃	2.61	85	Ph⌒(Me)SnCl₂(Br)	1.89
20	Me—⬡—SnMe₃	3.16	53	NC⌒⌒SnMe₃	2.59	86	Me⌒(Me)SnCl₂(Br)	1.88
21	Me⌒⌒Sn(O-i-pr)₃	3.14	54	Ph—Sn(OMe)₃	2.58	87	Me⌒(Me)SnCl₂(Br)	1.88
22	⌒SnMe₃ / CN	3.13	55	Ph—Sn(OH)₃	2.53	88	Ph⌒⌒SnCl₂(Br)	1.87
23	⌒SnBu₃	3.10	56	⌒Sn(OH)₃ / CO₂Me	2.49	89	O₂N—⬡—SnMe₃	1.85
24	Ph—SnBu₃	3.08	57	Ph₃SnCl	2.49	90	Me⌒⌒SnCl₂(Br)	1.84
25	F—⬡—SnMe₃	3.01	58	MeO₂C—⬡—SnMe₃	2.41	91	Me⌒⌒SnCl₂(Br)	1.84
26	⬡—SnMe₃	3.0	59	Ph—SnCl(O-n-pr)₂	2.41	92	⌒(Me)CH(Me)SnCl₂(Br)	1.82
27	Ph₃SnBu	2.94	60	Ph—SnCl(OEt)₂	2.41	93	⌒SnBr₃	1.81
28	⌒Sn(O-i-pr)₃	2.93	61	Ph—SnCl(OMe)₂	2.39	94	⌒(Me)SnCl₂(Br)	1.80
29	⌒Sn(O-n-pr)₃	2.93	62	Ph—SnCl(OH)₂	2.38	95	PhSnCl₃	1.79
30	Me⌒⌒Sn(OH)₃	2.89	63	⌒SnCl(OH)₂	2.37	96	⌒(Me)SnCl₂(Br)	1.78
31	⌒Sn(OEt)₃	2.89	64	HO₂C—⬡—SnMe₃	2.34	97	⌒SnCl₃	1.74
32	Ph₃SnPh	2.88	65	MeOC—⬡—SnMe₃	2.33	98	MeO₂C⌒⌒SnCl₂Br	1.66
33	Ph⌒(Me)CH(Me)Sn(OH)₃	2.87	66	MeO₂C⌒⌒Sn(OH)₃	2.31	99	NC⌒⌒SnCl₂Br	1.55

and *vice versa* (Figure 6). Thus soft/borderline halides of boron, tin, and titanium favor γ-selective allylation, while those of aluminum, indium, and zinc favor the α-selective allylation.

9. CONCLUSIONS

In this work, the global nucleophilicity indices (N) of 99 organotin and 10 allylmetal reagents (metal = Mg, Zn, B, In, Si)

have been calculated at the B3LYP/LANL2DZ, 6-31G* level of theory (Tables 7 and 5). The N-values offer an at-a-glance assessment of nucleophilic reactivity of the reagents and correlated well with the experimentally observed reactivity order.[1,54] In the case of allyltin and other allylmetal reagents, the regioselectivity in carbonyl allylation has been assessed from the local nucleophilicity index (N_k^-) at the α- or γ-carbon and from ΔN_k^- values and were found to be useful. In addition, the effect of Brønsted and Lewis acids on the reactivity and selectivity in carbonyl allylation was correlated with the local electroaccepting power (ω_k^+) at the carbonyl site in LA-aldehyde adducts and local nucleophilicity parameters (N_k^-) at the α- and γ-carbons.

■ COMPUTATIONS

All the geometries were optimized at the B3LYP/LANL2DZ, 6-31G* level of theory using the Gaussian 03 program.[55−57]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Computational methodology and all the results in detail are provided. Optimized structures of all the compounds with coordinates are given in Supporting Information SII and SIII. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

We dedicate this work to the fond memory of Prof. B. D. Gupta, IIT-Kanpur (Jan 20, 1949, to Mar 31, 2011).

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(36) The reader may note that the relationships are entirely empirical and pertain to around 200 experimental examples (see SI/8−11). It is not surprising that a larger experimental set may provide a marginal change to the empirical relations. Development of an elaborate theoretical basis to predict selectivity in organometallic reactions will be a pertinent challenge.

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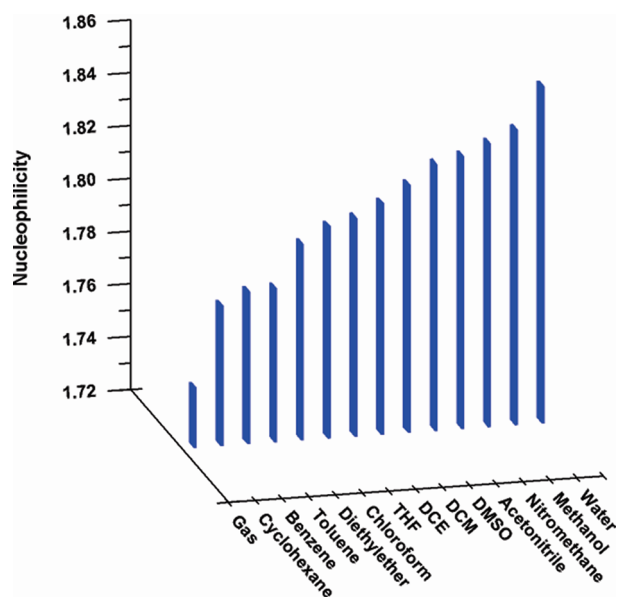
Plot of global nucleophilicity value (*N*) of allyltrichlorostannanes in different solvents. For selected examples of the solvent effect, see: (a) Cokley, T. M.; Harvey, P. J.; Marshall, R. L.; McCluskey, A.; Young, D. J. *J. Org. Chem.* **1997**, *62*, 1961. (b) Multzer, J.; Altenbach, H. J.; Braun, M.; Krohn, K.; Reissig, H. U. *Organic Synthesis Highlights*; VCH: Weinheim, Germany, 1991; p 71. (c) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59. (d) Ref 1c and references therein. (e) Marton, D.; Stivanello, D.; Tagliavini, G. *J. Org. Chem.* **1996**, *61*, 2731.

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(42) Local electrophilicity power (ω_k^+ is the corresponding local variants of the global electrophilicity (ω), and it is derived from the relation $\omega_k^+ = \omega^* f_k^+$ where f_k^+ is the corresponding Fukui function for nucleophilic attack at atom *k*. For details see the Supporting Information (SI).

(43) While attempting this exercise, we would like to recall advice from Torrent-Sucarrat et al: "The reactivity descriptors and principles rationalized within the framework of the conceptual DFT have allowed an easy understanding of many organic, inorganic, and biochemical reactions. However, one should always be careful not to use these indices and principles beyond their range of applicability; otherwise contradictory results are sometimes generated and skepticism about the utility of these concepts may arise." See: Torrent-Sucarrat, M.; Proft, F.; De.; Ayers, P. W.; Geerlings, P. *Phys. Chem. Chem. Phys.* **2010**, *12*, 1072, and reference therein.

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(53) For a better understanding of the electrophilicity generated at the benzaldehyde center after the coordination with the Lewis acidic metal center, local electrophilicity indices at the aldehyde center have

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