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Reactivities of allenic and olefinic Michael acceptors towards phosphines†

Feng An, [a] Harish Jangra, [a] Yin Wei, [b] Min Shi, *[bc] Hendrik Zipse *[a] and Armin R. Ofial *[a]

The kinetics of the reactions of tributylphosphine with allenic and olefinic Michael acceptors in dichloromethane at 20 °C was followed by photometric and NMR spectroscopic methods. Combination with DFT-calculated methyl anion affinities revealed the relevance of retroaddition barriers in phosphine-catalysed reactions when mixtures of allenic and olefinic substrates are used.

In 1995, the Lu group discovered (3+2)-cycloadditions, in which Bu_3P or Ph_3P are used as Lewis-basic catalysts to furnish cyclopentenes from mixtures of alkyl allenoates and electron-deficient alkenes (Fig. 1).[1] In recent years, the versatility of Lu cycloadditions was expanded by the development of several catalytic asymmetric versions, which were also applied to the synthesis of core units of natural products.[2] Computational and kinetic studies showed that phosphonium–dienolate formation can be considered to be the rate-determining step in the catalytic cycle.[2a,3]

The rates of adduct formations, in which only one new bond is formed between an electrophile and a nucleophile, can be discussed in a broader context and beyond the limitations of structurally analogous compound classes when the Mayr–Patz eqn (1) is used.[4–7] Thus, the nucleophilic reactivity of R_3P catalysts in a certain solvent is described by the two parameters N (nucleophilicity) and s_N (susceptibility) in eqn (1).[8] The reactivities of Michael acceptors are characterised by electrophilicity parameters E. It has been shown that once E, N and s_N of reaction partners in polar reactions are known the second-order rate constant k_2 for adduct formation can be predicted with an accuracy within two orders of magnitude.[5,6]

$$\log k_2(20\ ^\circ\mathrm{C}) = s_N(N + E) \quad (1)$$

Many of the R_3P-catalysed reactions are performed with mixtures of two competing electrophiles, which are often combined in a way that one of the electrophiles carries an sp- and the other one an sp^2-hybridised carbon as the electrophilic centre.[1,2,9] In this work, we set out to determine the kinetics of the adduct formation of R_3P with electron-deficient olefins and a set of alkyl and phenyl allenoates to gain a deeper understanding of the factors that influence the initial step of the related R_3P-catalysed organic reactions.[1,2,9]

First, we characterised the vinyl phosphonium triflates **3** obtained by Ph_3P reactions with **1a**, **1d**, **1f**, and **1i** (Fig. 2A) by spectroscopic methods (ESI†). It is reasonable to assume that the entire set of R_3P + **1a–1j** reactions that we followed kinetically also yield vinyl phosphonium triflates **3**. The kinetics of the carbon–phosphorus bond-formations between R_3P and **1a–1j** was followed by spectroscopic methods.

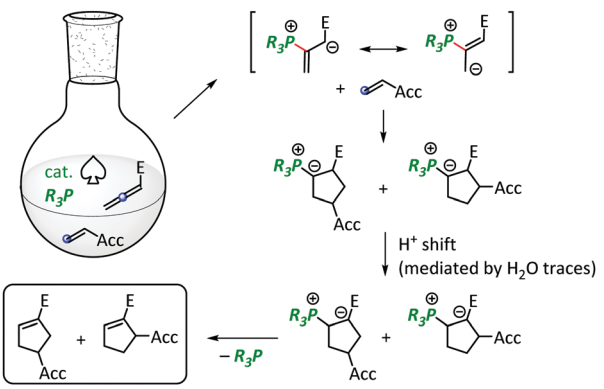

Fig. 1 Mechanism of the phosphine-catalysed Lu cycloaddition (E = ester group, Acc = electron-accepting group).

[a] *Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, München 81377, Germany. E-mail: zipse@cup.uni-muenchen.de, ofial@lmu.de*

[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China. E-mail: mshi@mail.sioc.ac.cn*

[c] *Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 MeiLong Road, Shanghai 200237, P. R. China*

† Electronic supplementary information (ESI) available: Additional tables and figures, procedures for the synthesis and spectroscopic characterisation of **1**, product studies, details of the kinetic experiments and DFT calculations. See DOI: 10.1039/d1cc06786a

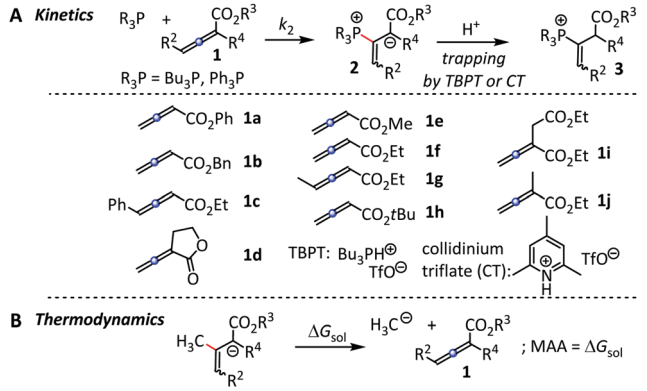

Fig. 2 (A) R_3P additions to **1** and (B) reference reaction for the determination of methyl anion affinities (MAA) by quantum-chemical methods.

Reactions of Bu_3P with alkyl allenoates **1a–1i** in CH_2Cl_2 at 20 °C were monitored photometrically by following the decrease of the UV absorptions of **1** at or close to their absorption maximum (λ_{max} = 242–262 nm). The Bu_3P addition reactions to **1** give rise to polymerisation, which can be avoided by trapping the zwitterionic adducts **2** with tributylphosphonium triflate (TBPT) as the proton source ($[TBPT]/[\mathbf{1}]_0$ = 2–3). TBPT is a weak Brønsted acid in CH_2Cl_2 and does not activate the electrophiles **1** by hydrogen-bonding to an oxygen of the ester group (as shown for the combination of **1f** + TBPT, ESI,† Fig. S7). To simplify the kinetic evaluation of the second-order reactions, we used the Bu_3P in at least 10-fold excess relative to the initial electrophile concentrations $[\mathbf{1}]_0$. Hence, the decrease of absorptions A of **1** could be fitted by the mono-exponential decay function $A = A_0 \exp(-k_{obs}t) + C$ to determine the (pseudo) first-order rate constants k_{obs} (s^{-1}).

For each Bu_3P + **1** pair, k_{obs} was determined at four or five different Bu_3P concentrations, which made it possible to calculate the second-order rate constants k_2 ($M^{-1}\ s^{-1}$) from the slope of the linear correlation of k_{obs} with $[Bu_3P]_0$. Fig. 3 visualises this procedure for the Bu_3P addition to **1f**.

Rate constants of the reactions of Ph_3P with **1a–1j** were determined by ^1H NMR spectroscopy using mesitylene as an internal integration standard and collidinium triflate (CT) as a proton source ($[CT]/[\mathbf{1}]_0$ = 2). Generally, Ph_3P additions to **1** are endergonic with retroadditions being faster than the addition reactions. Trapping of the zwitterionic intermediates **2** by CT is thus necessary to observe the kinetics of the addition (forward) reaction. By obeying the conditions for (pseudo)first-order kinetics, that is $[Ph_3P]_0/[\mathbf{1}]_0 > 9$, the time-dependent decrease of [**1**] could be fitted by the mono-exponential decay function to yield the rate constants k_{obs}. NMR experiments at four different $[Ph_3P]_0$ made it possible to determine the second-order rate constants k_2 for the Ph_3P additions to the electrophiles **1a–1j** from the slope of the linear correlation of k_{obs} with $[Ph_3P]_0$. Rate constants (k_2) for the reactions of Bu_3P with **1j** were determined analogously. Data of the individual kinetic measurements for the nucleophilic attack of Bu_3P and Ph_3P at the allenoates **1** are given in the ESI.† The experimentally determined second-order rate constants k_2 are compiled in Table 1.

Table 1 Second-order rate constants (k_2, in $M^{-1}\ s^{-1}$) for the additions of Bu_3P and Ph_3P to phenyl or alkyl allenoates **1** in dichloromethane at 20 °C

Electrophiles **1**	$k_2(Bu_3P)^a$	$k_2(Ph_3P)^b$	MAA[c]	PA[d]
1a	5.52	1.19×10^{-1}	182.5[e]	−15.0
1b	1.16	1.70×10^{-2}	163.1[e]	−22.6
1c	1.10	1.90×10^{-2}	165.5	−23.7
1d	9.55×10^{-1}	2.33×10^{-2}	171.2	−15.9
1e	8.40×10^{-1}	1.10×10^{-2}	167.6[e]	−26.5
1f	6.35×10^{-1}	7.67×10^{-3}	163.4[e]	−29.8
1g	5.00×10^{-1}	8.05×10^{-3}	152.7	−29.5
1h	2.47×10^{-1}	2.39×10^{-3}	153.9	−33.3
1i	2.01×10^{-1}	4.59×10^{-3}	142.5	−26.0
1j	1.96×10^{-2}[b]	3.49×10^{-4}	133.6	−38.3

[a] Photometry, CH_2Cl_2, 20 °C. [b] ^1H NMR spectroscopy, CD_2Cl_2, 20 °C. [c] MAA as defined in Fig. 2B [in kJ mol^{-1} at SMD(DMSO)/B3LYP/6-311++G(3df,2pd)//B3LYP/6-31G(d,p) level of theory, with Truhlar quasi-harmonic treatment]. [d] Phosphine affinities, PA, as defined in ESI, Table S42 [in kJ mol^{-1} at PCM(DCM,ua0)/B3LYP-D3/6-31+G(d,p) level of theory, with Truhlar quasi-harmonic treatment]. [e] MAA values from ref. 10.

The Bu_3P-based reactivity scale ($\log k_2$) for **1a–1j** is depicted in Fig. 4A. The phenyl ester **1a** is the strongest electrophile of the studied allenoates without further substituents at the cumulated π-system and reacts about 5 to 9 times faster with Bu_3P than the analogous benzyl (**1b**), methyl (**1e**), or ethyl esters (**1f**).[11] Replacement of the ethyl by a *t*-butyl group (**1f**→**1h**) attenuates reactivity by a factor of 3. An additional methyl

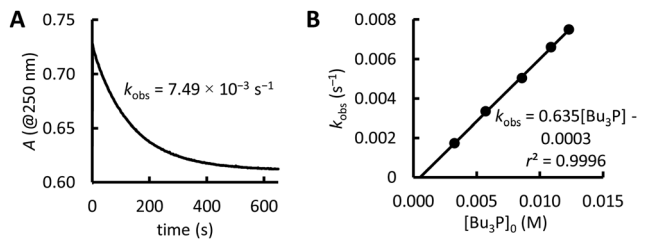

Fig. 3 (A) Kinetics of the reaction of Bu_3P with **1f**: mono-exponential decay of the absorbance A in the reaction of Bu_3P (12.3 mM) with **1f** (0.121 mM); (B) linear correlation of observed rate constants k_{obs} with $[Bu_3P]_0$.

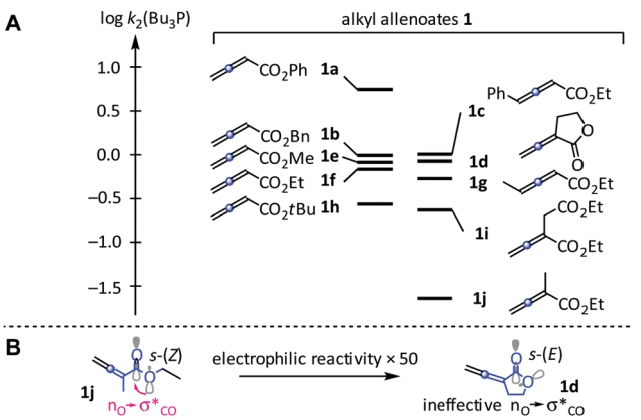

Fig. 4 (A) Relative reactivities of **1a–1j** in reactions with Bu_3P (in CH_2Cl_2, 20 °C). (B) Different stereoelectronic effects in **1d** and the open-chain analogue **1j**.

group (**1g**) at the 4-position of the alkyl allenoate has almost no influence on the reactivity of the electrophilic π-system, which remains at the level of the γ-unsubstituted **1f**. Extending the π-system by a terminal phenyl group enhances the reactivity of **1c** only slightly if compared to that of **1f**, probably because the phenylvinyl moiety in **1c** is perpendicular to the reactive π-system. In contrast, substituents in 2-position of **1** have a greater effect, and Bu_3P reacts slower by a factor of 32 with **1j** than with the parent **1f**. This reactivity gap can be reduced by attaching an electron-accepting group to the C-2 substituent. Thus, **1i** reacts 10-fold faster with Bu_3P than **1j** and is only 3 times less electrophilic (towards Bu_3P) than **1f**.

Consistent with previous work on the relative reactivity of open chain esters and lactones,[12] α-allenic γ-butyrolactone **1d** is a significantly more reactive electrophile than **1j**. The increase in electrophilic reactivity is explained by the different conformations of the CO–OR bonds, which is preferably in the *s*-(*Z*) conformation in **1j** but fixed in the unfavourable *s*-(*E*) conformation in **1d** (Fig. 4B).[12,13] Ineffective $n_O \rightarrow \sigma^*_{CO}$ interactions enhance the electron-deficiency of the reacting π-system, which enables the versatile use of allenic lactones in organic synthesis.[14]

Reactivity of **1** towards Bu_3P is transferrable to other R_3P as shown by the linear correlation ($r^2 = 0.9636$, $n = 10$) with a slope (1.02) close to unity for the Ph_3P *vs.* Bu_3P comparison (Fig. 5).

To gain a better understanding of R_3P-catalysed Lu reactions it is crucial to compare the R_3P reactivities of **1** with those of competing electrophiles, which are typically olefinic Michael acceptors. It was previously shown that MAAs of olefinic Michael acceptors correlate linearly with their Mayr *E* parameters.[15] MAA values have also been applied to rationalise R_3P-catalysed (3+2) annulations of **1a**, **1b**, **1e**, and **1f** with 2-aminoacrylates.[10] The data in Table 1 now show that the DFT-calculated MAA values for **1** (Table 1) are linearly related with their electrophilic reactivities towards the investigated R_3P nucleophiles, that is, Bu_3P and Ph_3P (ESI,† Fig. S1 and S2). A linear correlation of similar quality was obtained when $\log k_2$ for **1** + Ph_3P reactions were plotted against phosphine affinities, PA, which are defined analogously to MAA but use Ph_3P instead of the methyl anion as the Lewis base (Fig. S3, ESI†).

The nucleophilic reactivity of Bu_3P has previously been characterised by $N = 15.49$ ($s_N = 0.69$) on the basis of the kinetics of its additions to benzhydrylium ions ($E > -10.04$).[16] To avoid long range extrapolations for predicting reaction rates with Michael acceptors, we determined the kinetics of further reactions of Bu_3P with the structurally diverse neutral and positively charged electrophiles **4a–4r** of known Mayr *E*.[7] Second-order rate constants k_2 (CH_2Cl_2, 20 °C) were determined by applying the photometric methods described above for the **1** + Bu_3P reactions (see ESI† for individual rate constants). Fig. 6 shows that $\log k_2$ for the additions of Bu_3P to **4a–4r** follow a linear correlation ($r^2 = 0.9635$, $n = 18$) over a range of 16 units on the Mayr *E* scale, which gives $N(Bu_3P) = 19.11$ and $s_N = 0.48$. Applying the k_2 values for reactions of **1** (Table 1) in the correlation depicted in Fig. 6 indicates that **1a–1j** are located in the reactivity range $-22.7 < E < -17.5$.

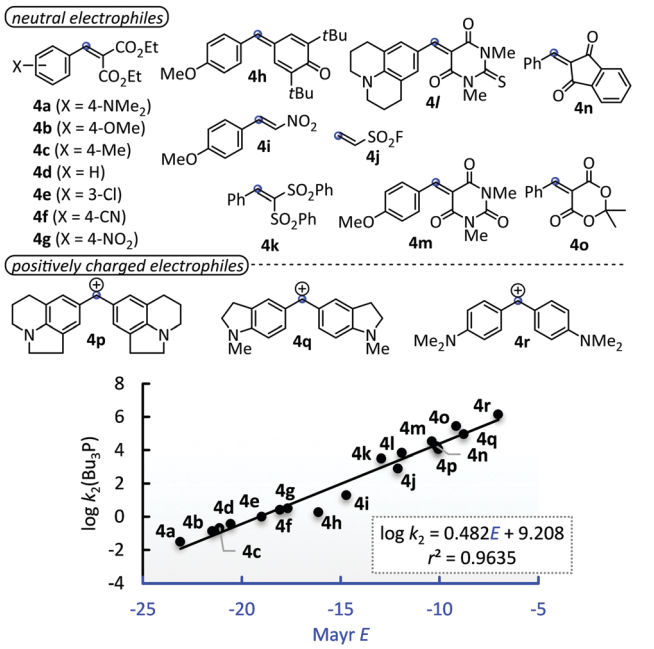

Fig. 6 Linear correlation of $\log k_2(Bu_3P)$ with the Mayr *E* parameters of structurally diverse Michael acceptors **4a–o** and benzhydrylium ions **4p–r** (k_2 in dichloromethane at 20 °C, see ESI† for details of the kinetic measurements, Table S1 (ESI†) gathers the data used to construct the correlation).

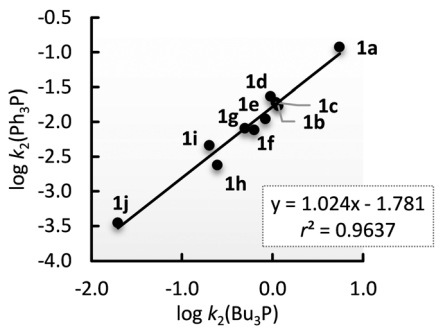

Fig. 5 Linear relation of $\log k_2(Bu_3P)$ and $\log k_2(Ph_3P)$ for reactions with **1**.

In classical Lu reactions, the R_3P catalyst first attacks the alkyl allenoate. The catalytic cycle continues with the reaction of a C-nucleophilic zwitterion with the second Michael acceptor in the reaction mixture. If the kinetics of the R_3P reactions with the two competing electrophiles would be the decisive factor, Lu reactions could be expected to occur only if **1** is more reactive towards the R_3P catalyst than the competing Michael acceptor (*e.g.*, **4**). This is not always the case, however. Already in the first publication on the R_3P-catalysed cycloaddition, the Lu group[1] used electrophiles with Mayr $E < -16.8$, that is, with comparable or even slightly higher electrophilicity than for **1**. This indicates that the thermodynamics for R_3P adduct formation is another crucial factor for the success of Lu reactions.

For reactions of vinyl cations with nucleophiles it has been observed that sp/sp^2 rehybridisation occurs *via* higher Marcus intrinsic barriers than for reactions that involve sp^2/sp^3

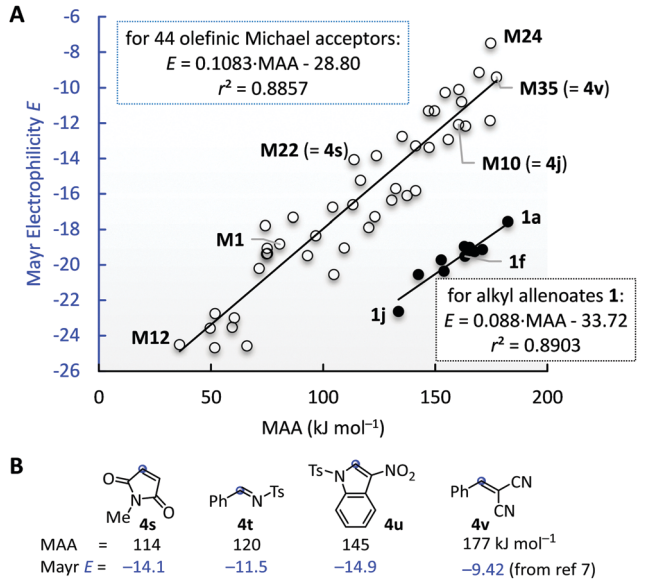

Fig. 7 (A) Separate linear relationships between the electrophilicities E of acceptor-substituted olefins **M1–M44** and allenes **1** with the calculated methyl anion affinities (MAA) (molecular structures of **M1–M44** and data used to construct the linear correlation are given in ESI,† Table S2; electrophilicities E for allenoates **1** estimated by applying the $k_2(Bu_3P)$ values from Table 1 in the correlation equation for Bu_3P additions to Michael acceptors in Fig. 6). (B) MAA values and electrophilicities E for Michael acceptors **4s–4v**.

rehybridisations.[17,18] Analogously, in this work the higher MAA for **1** than for equally reactive olefinic Michael acceptors[15a] (Fig. 7) along with the experimental kinetic data indicate that the main difference between **1** and Michael acceptors, such as **4**, are the Marcus intrinsic barriers for the R_3P addition at the differently hybridised electrophilic centres.

Even if the rate constants for the electrophile/R_3P additions are of the same order of magnitude, the MAA values show that allenoates **1** are considerably stronger Lewis acids than olefinic Michael acceptors or imines, such as **4t**. As a consequence, the differences in the barriers for the retroadditions differentiate the two competing classes of electrophiles. Owing to their higher energetic barrier for retroaddition, only the allenic electrophiles **1** generate sufficiently high concentrations of reactive zwitterions, which are the pivotal intermediates for the subsequent ring-forming reactions. Thus, allenoates **1** are capable to compete with much stronger electrophiles. For example, **1f** (MAA = 163 kJ mol^{-1}) can be used as a partner for the more electrophilic yet less Lewis acidic **4s**, **4t**, or **4u** in Lu cycloadditions.[19–21] Benzylidenemalononitrile (**4v**) seems to be an exception. However, despite of its high MAA, **4v** reacts reversibly with Bu_3P and does not form an adduct with Ph_3P (ESI†). Yet, free **4v** traps efficiently the zwitterion generated by Ph_3P and **1f** to yield cyclopentenes.[22,23]

The reactivities of allenic and olefinic Michael acceptors have been calibrated towards P-nucleophiles through determining the kinetics of their reactions with Bu_3P. Allenoates **1** are weaker electrofuges as well as weaker electrophiles than Michael acceptors **4** of similar Lewis acidity because of the higher intrinsic barriers for sp/sp^2 rehybridisation. The kinetic and thermodynamic data in this work will be instrumental for the design of novel R_3P-catalysed reactions with alkyl allenoates.

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Conflicts of interest

There are no conflicts to declare.

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