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# Systematic Evaluation of 1,2-Migratory Aptitude in Alkylidene Carbenes

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**ABSTRACT:** Alkylidene carbenes undergo rapid inter- and intra-molecular reactions and rearrangements, including 1,2-migrations of  $\beta$ -substituents to generate alkynes. Their propensity for substituent migration exerts profound influence over the broader utility of alkylidene carbene intermediates, yet prior efforts to categorize 1,2-migratory aptitude in these elusive species have been hampered by disparate modes of carbene generation, ultrashort carbene lifetimes, mechanistic ambiguities, and the need to individually prepare a series of  $^{13}\text{C}$ -labelled precursors. Herein we report on the rearrangement of  $^{13}\text{C}$ -alkylidene carbenes generated *in situ* by the homoligation of carbonyl compounds with  $[^{13}\text{C}]\text{-Li-TMS-diazomethane}$ , an approach that obviates the need for isotopically labelled substrates and has expedited a systematic investigation ( $^{13}\text{C}\{^1\text{H}\}$  NMR, DLPNO-CCSD(T)) of migratory aptitudes in an unprecedented range of more than 30 alkylidene carbenes. Hammett analyses of the reactions of 26 differentially substituted benzophenones reveal several counterintuitive features of 1,2-migration in alkylidene carbenes that may prove of utility in the study and synthetic application of unsaturated carbenes more generally.

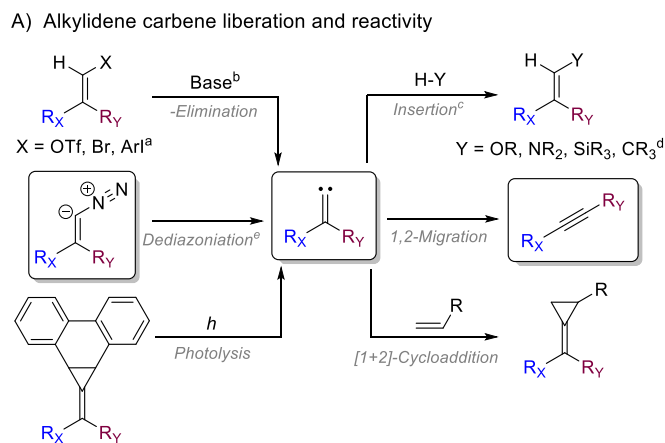
## INTRODUCTION

Alkylidene carbenes<sup>1-3</sup> can be liberated, *inter alia* by the deprotonation of terminal alkenyl (pseudo)halides,<sup>4,6</sup> thermolysis of diazoalkenes,<sup>7-12</sup> and photolysis of cyclopropanated phenanthrenes,<sup>13-15</sup> Scheme 1A. Alkylidene carbenes are extremely short-lived, readily undergoing 1,2-migration of a  $\beta$ -substituent to generate an alkyne.<sup>16</sup> This has been applied in well-established synthetic methodologies, such as the Corey-Fuchs reaction<sup>17</sup> and the Seyfirth-Gilbert,<sup>8-10</sup> Colvin,<sup>7, 12</sup> and Fritsch-Buttenberg-Wiechell (FBW) rearrangements.<sup>2</sup> However, this propensity for 1,2-migration can interfere with other desired modes of reactivity, such as H-Y insertion and [1+2]-cycloaddition,<sup>1, 18</sup> especially when these require intermolecular interception of the alkylidene carbene.

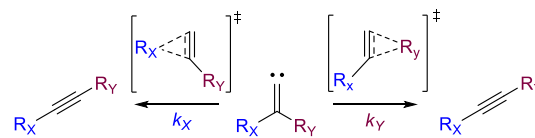
The identities of the alkylidene  $\beta$ -substituents ( $R_X$ ,  $R_Y$ ; Scheme 1B) influence the propensity for 1,2-migration, and both their relative and absolute migratory aptitudes should be considered. These factors not only dictate which group ( $R_X$ ,  $R_Y$ ) migrates, but also the intrinsic lifetime of the carbene during which it can be diverted. Furthermore, this lifetime is contingent on both substituents: the migrator and the stationary (or ‘bystander’)  $\beta$ -substituent, and thus one-dimensional trends for absolute migratory aptitude are inherently misleading.<sup>2</sup> Measurement of absolute rates of 1,2-migration requires direct detection of the alkylidene carbene, with Phillips, Hadad and Thamattoor reporting the first observation in solution ( $\text{PhMeC}=\text{C}:$ ) by femtosecond spectroscopy, just two years ago.<sup>15</sup>

It has long been recognized that some alkylidene  $\beta$ -substituents ( $R_X$ ,  $R_Y$ ) have a much greater propensity for 1,2-migration (e.g. H, Aryl, Alkynyl) than others (e.g., Alkyl),<sup>6-8</sup> yet only a few studies have sought to explicitly assess this, using isotopic  $^{13}\text{C}/^{14}\text{C}$  labelling. Milestones in this regard are studies by Stang (vinyl triflates; Ph vs Me),<sup>19</sup> Thamattoor (cyclopropanated phenanthrenes; H vs Ph,<sup>13</sup> Me vs Ph<sup>14</sup>), and Tykwinski<sup>20</sup> (Colvin rearrangement, and vinylidene dibromides;  $-\text{C}\equiv\text{CSiR}_3$  vs alkyl, Ar, alkenyl).

## Scheme 1 Alkylidene Carbene Liberation, Reactivity, Migratory Aptitudes and Bystander Effects



## B) Migratory aptitudes and bystander effects



$k_i$  = Absolute migratory aptitude of  $R_i$  ( $i = X, Y$ )

$k_X/k_Y$  = Relative migratory aptitude of  $R_X$

<sup>a</sup> Primary alkenyl triflates are likely the most reliable liberator of *bona fide* carbenes of all the alkenyl (pseudo)halides. <sup>b</sup> K<sup>+</sup>O<sup>-</sup>Bu is a common choice for generating ‘free’ carbenes. <sup>c</sup> Alkylidene carbenes can also undergo R-X insertion following ylide formation from Lewis bases (e.g., THF, THT, NEt<sub>3</sub>). <sup>d</sup> C-H insertions appear only to be feasible on an *intramolecular* basis. <sup>e</sup> Diazoalkenes are not readily isolable, and are postulated to be liberated from e.g., silylated  $\alpha$ -diazoalkoxides, *N*-nitrosocarbonamides, and *N*-(1-aziridinyl)aldimines.<sup>1-2</sup>

Whilst these studies confirmed several postulated trends of relative migratory aptitudes (e.g., H > alkyne > Ph > Me), the scope contrasts the extensive studies reported for saturated carbenes.<sup>21-23</sup> As such, systematic analysis of structure-reactivity relationships in alkylidene carbenes remains limited, and subject to a number of caveats.<sup>2</sup> For example, migratory aptitudes determined from different carbene precursors, under different rearrangement conditions, may or may not be directly comparable on a microscopic level. Moreover, whilst diazoalkenes and cyclopropanated phenanthrenes are considered reliable precursors to *bona fide* alkylidene carbenes, the possible intermediacy of carbenoids<sup>24-28</sup> must also be considered when e.g. alkenyl halides are employed.

Furthermore, although not previously discussed, the highly reactive nature of alkylidene carbenes poses additional questions about the microscopic basis for product selection, especially when both substituents are efficient, and thus competitive, migrators. In such cases, incomplete conformational equilibration in, and/or dynamic bypassing of, an incipient carbene cannot be excluded *a priori*. Thus, even when the formation of the free alkylidene carbene appears likely, a fundamental question remains as to whether the observed selectivity is established at the migration stage, or influenced by prior 'upstream' events.

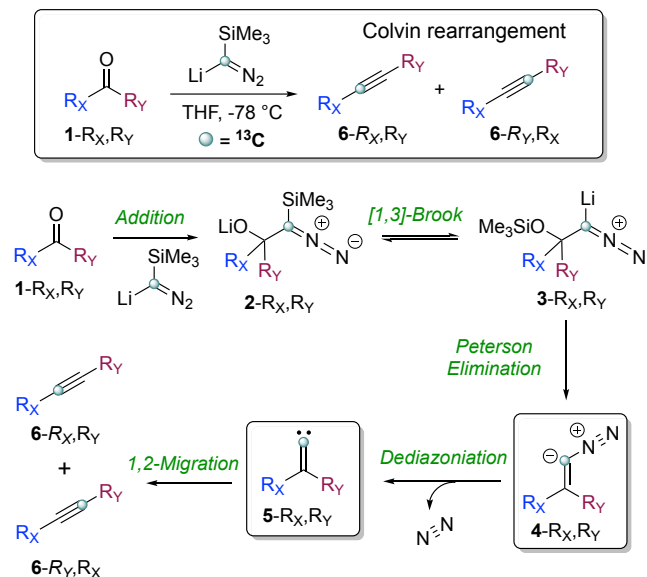
## RESULTS AND DISCUSSION

With all of the above issues in mind, we sought a systematic analysis of structure-reactivity relationships for 1,2-migration in alkylidene carbenes. As noted above, the measurement of relative migratory aptitude requires isotopic labelling (<sup>13</sup>C, <sup>14</sup>C), and if the label is installed in the precursor bearing the β-substituents, this becomes impractical and expensive if a large array of examples is to be surveyed. Herein we report on a) the use of the Colvin rearrangement<sup>7,12,20</sup> (Scheme 2) to expedite generation isotopically labelled, *bona fide* alkylidene carbenes from unlabelled carbonyls, and b) an extensive analysis of the 1,2-migratory aptitudes by quantum chemical calculations (KS-DFT; DLPNO-CCSD(T)).

**Preparation of [<sup>13</sup>C]-TMSDAM** Application of the Colvin rearrangement, Scheme 2, required *in situ* preparation of lithium [<sup>13</sup>C]-trimethylsilyldiazomethane ([<sup>13</sup>C]-Li-TMSDAM) by deprotonation (LDA) of [<sup>13</sup>C]-TMSDAM. The commercially-available unlabelled TMSDAM reagent is conventionally prepared from TMSCH<sub>2</sub>Cl via the corresponding Grignard.<sup>29</sup> However, after a range of preliminary experiments involving TMS<sup>13</sup>CH<sub>2</sub>X (X = Cl, Br, I) we pursued an alternative route based on amine diazotization.<sup>30</sup> The requisite <sup>13</sup>C-labelled amine (**11**) was prepared via a multistep chromatography-free sequence, starting from <sup>13</sup>CH<sub>3</sub>OH (**7**), Scheme 3. With the amine **11** in hand, we utilized Lebel's diazotization procedure, and after careful re-optimization for <sup>13</sup>C-labelled synthesis<sup>31</sup> prepared a large stock solution of [<sup>13</sup>C]-TMSDAM (**12**, 0.6M in 2-Me-THF; dried over molecular sieves).

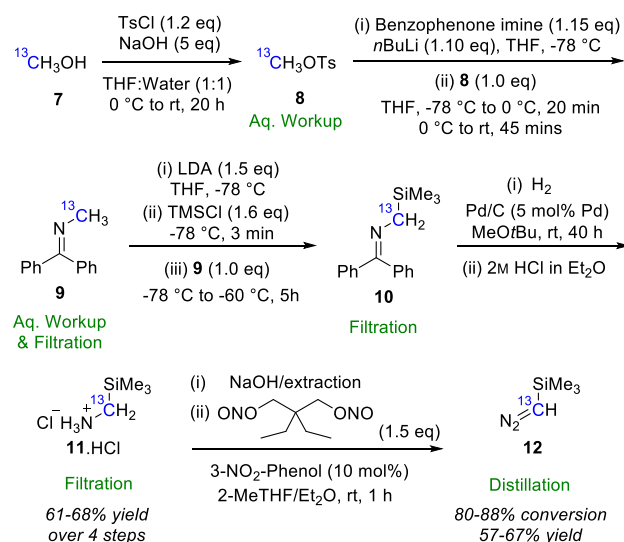
**Determination of Migratory Aptitudes** Using a single set of standardized conditions (Scheme 4) a broad range of aldehydes and ketones were converted to the corresponding [<sup>13</sup>C]-alkynes via Colvin rearrangement with [<sup>13</sup>C]-Li-TMSDAM. *In situ* low-temperature <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopic analysis of the reaction of [<sup>13</sup>C]-4-fluorobenzophenone with [<sup>13</sup>C]-Li-TMSDAM confirmed >85 % consumption of the ketone in under 20 min at -78 °C, to generate intermediates tentatively assigned (see below, and SI) as [<sup>13</sup>C<sub>2</sub>]-**2/3**, and substantial rearrangement to the alkyne ([<sup>13</sup>C<sub>2</sub>]-**6-Ph,Ar<sup>4,F</sup>**; <sup>1</sup>J<sub>CC</sub> = 183 Hz), as expected of an aryl

alkylidene carbene.<sup>32</sup> Controlled warming to -50 °C led to complete alkyne formation within minutes.



**Scheme 2 Expedient in situ Generation and Rearrangement of <sup>13</sup>C-labelled Alkylidene Carbenes (5).**

## Scheme 3 Preparation of [<sup>13</sup>C]-TMSDAM (12).

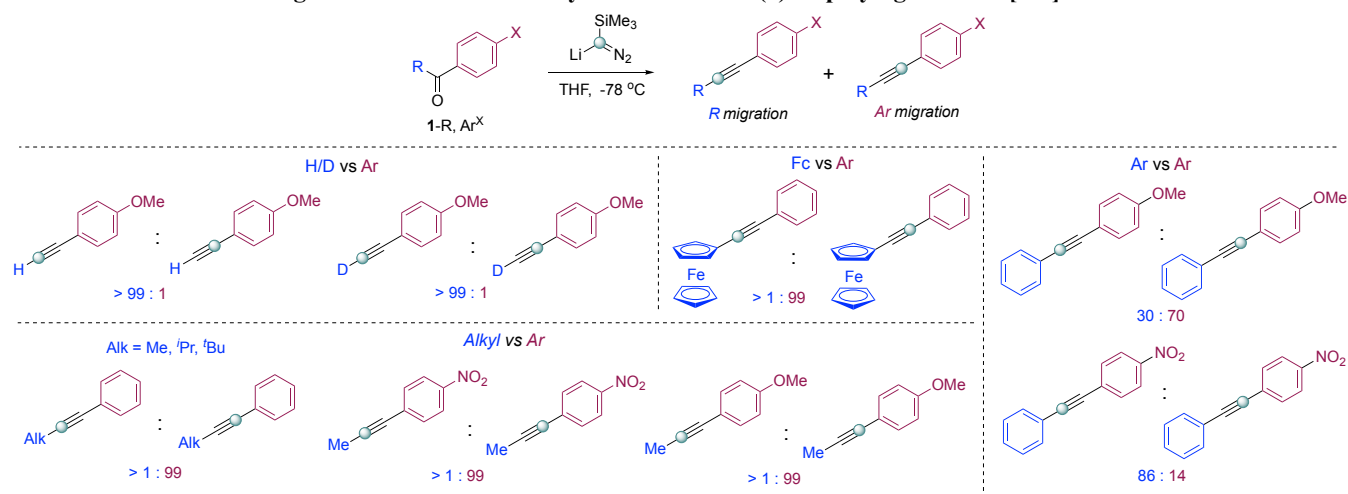


Prior studies on alkylidene carbenes liberated by photolysis of [<sup>13</sup>C<sub>1</sub>]-cyclopropanated phenanthrenes have shown 1,2-migration is highly-selective (exclusive) for H over Ph,<sup>13</sup> and for Ph over Me,<sup>14,19</sup> (i.e. H >> Ph >> Me). Exclusive H-migration was also observed herein, with no attenuation by electronic<sup>20</sup> (1-H,Ar<sup>4-OMe</sup>) and isotopic perturbation (1-D,Ar<sup>4-OMe</sup>), the latter indicative that the selectivity is not predicated on quantum tunneling. Analogously, exclusive aryl migration was observed for aryl/alkyl alkylidene carbenes generated from 1-Alk,Ph, where Alk = Me, <sup>i</sup>Pr, <sup>t</sup>Bu. However, benzophenones (1-Ar<sup>X</sup>,Ar<sup>Y</sup>) gave both alkyne <sup>13</sup>C-isotopomers in quantifiable ratios, with spectroscopic differentiation achieved by a combination of <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F NMR spectroscopy and, where necessary, <sup>1</sup>H-<sup>1</sup>H COSY and

$^1\text{H}$ - $^{13}\text{C}/^{19}\text{F}$ - $^{13}\text{C}$  HMBC analysis. The fractional migration of  $\text{Ar}^{\text{X}}$  ( $F_{\text{X}}$ ) in each case was quantified by  $^{13}\text{C}$  NMR (see SI), with values corroborated by integration of multiple distinct pairs of  $^{13}\text{C}$  signals. The relative migratory aptitude of  $\text{Ar}^{\text{X}}$ ,  $k_{\text{X}}/k_{\text{H}}$ , was then determined *via* equation 1.

$$\frac{k_{\text{X}}}{k_{\text{H}}} = \frac{F_{\text{X}}}{1 - F_{\text{X}}} \quad \text{Equation 1}$$

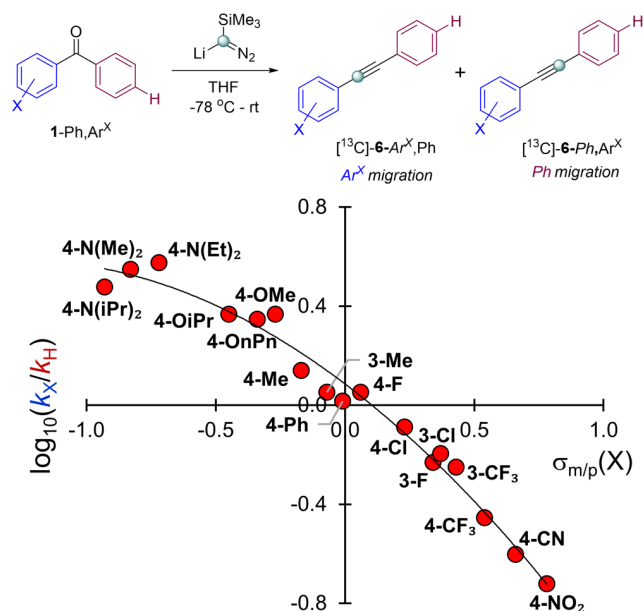
**Scheme 4 Colvin rearrangement of aromatic aldehydes and ketones (1) employing lithiated [ $^{13}\text{C}$ ]-TMSDAM.<sup>a</sup>**



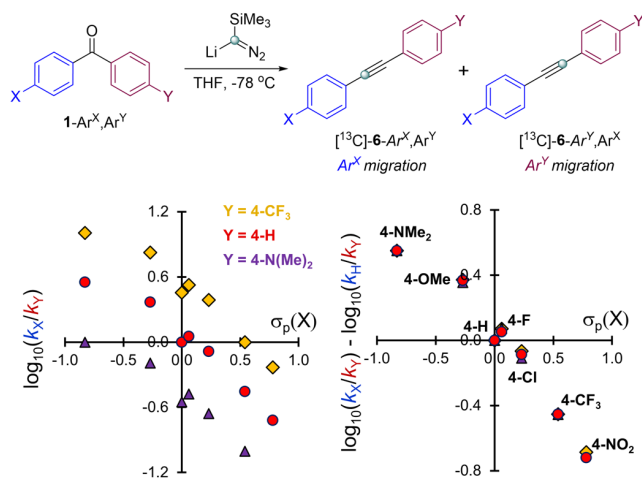
<sup>a</sup> [ $^{13}\text{C}$ ]-Li-TMSDAM generated *in situ* from LDA (1.0 – 1.2 equiv.) and [ $^{13}\text{C}$ ]-TMSDAM (**12**, 1.0 equiv.). Alkyne isotopomer ratios determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy after isolation by chromatography. Selectivities for diaryl alkynes were calculated by integration of the two alkyne  $^{13}\text{C}$  resonances; no significant effects from differential rates of longitudinal relaxation ( $T_1$ ) were observed, with selectivities corroborated by integration of parent/ $^{13}\text{C}$ - $^{13}\text{C}$  satellite signals for each *ipso* carbon; see SI.

Migratory aptitudes were initially determined for 17 mono-*m/p*-substituted benzophenones **1-Ph,Ar<sup>X</sup>**, with substituents spanning from very electron-deficient ( $\text{X} = 4\text{-NO}_2$ ;  $\sigma = 0.78$ ) to highly electron-rich ( $\text{X} = 4\text{-N}(\text{Pr})_2$ ;  $\sigma = -0.93$ ). Relative migratory aptitudes were found to be approximately proportional to the electron-richness of the migrating group. For example with 4-(*N,N*-diethylamino)benzophenone, migration of  $\text{Ar}^{\text{X}}$  dominated ( $F_{4\text{-N}(\text{Et})_2} = 79\%$ ;  $\Delta\Delta G_{195\text{K}}^\ddagger = -2.1 \text{ kJ mol}^{-1}$ ), whereas the converse was found with 4-nitrobenzophenone ( $F_{4\text{-NO}_2} = 16\%$ ;  $\Delta\Delta G_{195\text{K}}^\ddagger = +2.7 \text{ kJ mol}^{-1}$ ). Hammett analysis, Figure 1, revealed a modest sensitivity to electronic perturbation ( $\rho \approx -0.7$ ) and, interestingly, a small but significant deviation from linearity across the series, with selectivity tending towards a plateau for the most electron-donating substituents. No improvements in linearity were observed for with other substituent parameters, e.g.,  $\sigma_{\text{p}}^+$ .

Ultra-donating, anionic substituents (e.g.,  $\text{X} = 4\text{-S}^-$ ) unfortunately proved impractical, affording no alkyne products. However, exploration of other substituents led to ferrocenyl (Fc) as an interesting exception: although  $\text{C-sp}^2$  hybridized,  $\pi$ -conjugated and strongly electron-donating, phenyl migration dominated, giving  $> 99:1$  Ph:Fc, Scheme 4. To probe the influence of the ‘stationary’ substituent on migratory aptitudes, we next generated truncated Hammett correlations using an additional 13 benzophenones, in this case 4,4'-disubstituted **1-Ar<sup>X</sup>,Ar<sup>Y</sup>**;  $\text{Y} = p\text{-N}(\text{Me})_2, p\text{-CF}_3$ ; Figure 2.



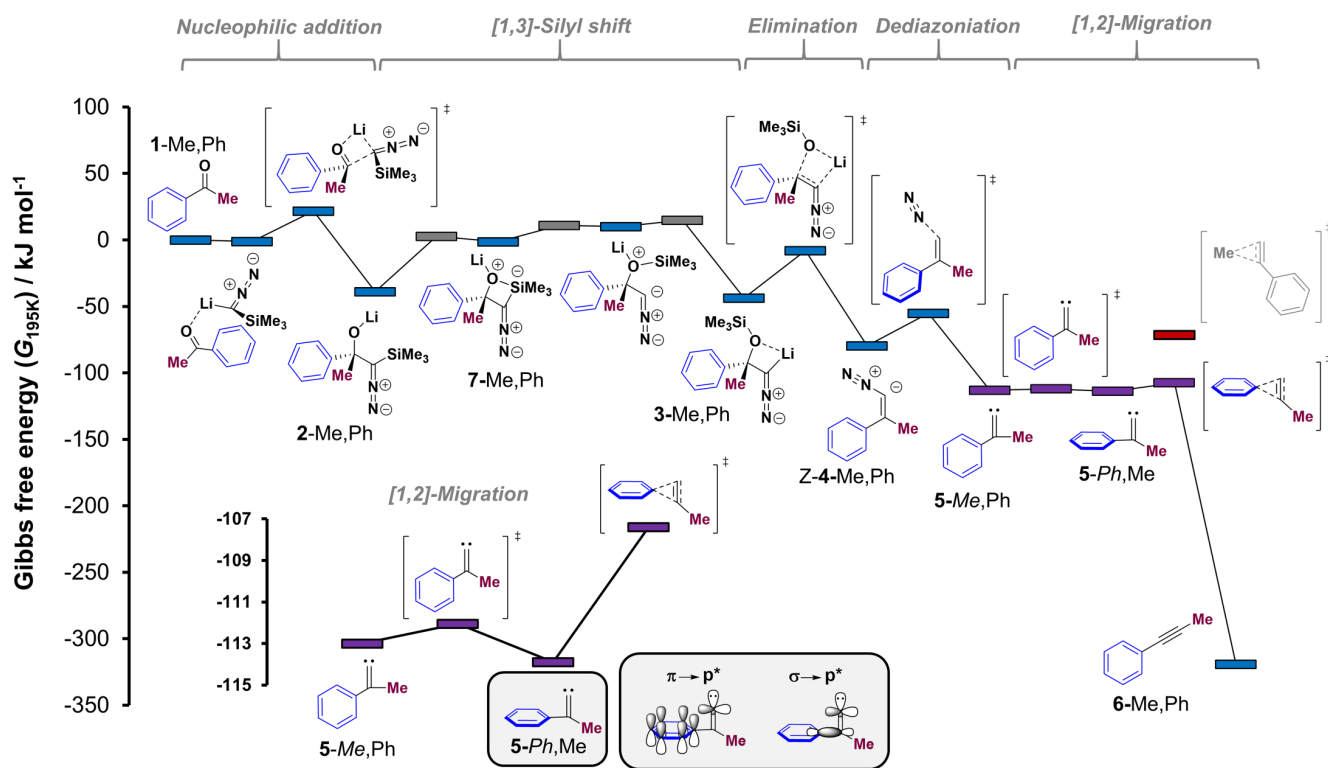
**Figure 1** Hammett analysis of the Colvin rearrangement of mono-substituted benzophenones [ $^{13}\text{C}$ ]-Li-TMSDAM generated *in situ* from LDA (1.2 equiv.) and [ $^{13}\text{C}$ ]-TMSDAM (1.0 equiv.) prior to the addition of ketone. Product isotopomer ratios determined by  $^{13}\text{C}\{^1\text{H}\}$  NMR, with selectivity corroborated by integration of multiple distinct pairs of  $^{13}\text{C}$  signals. Use of KHMDS in place of LDA, gave identical isotopomer ratios within experimental error for cases where the alkyne could be isolated in reasonable yield ( $\text{X} = 4\text{-N}(\text{Me})_2, 4\text{-OMe}, 4\text{-F}$ ).



**Figure 2.** Truncated Hammett correlations for Colvin rearrangement of 4,4'-disubstituted benzophenones. Left hand plot: Hammett correlations for the rearrangement of  $p,p'$ -disubstituted benzophenones **1**-Ar<sup>X</sup>,Ar<sup>Y</sup>. Right hand chart: overlaid correlations normalized according to the relative migratory aptitude of Ar<sup>Y</sup> in the *mono*-substituted benzophenone **1**-Ph,Ar<sup>Y</sup>. [<sup>13</sup>C]-Li-TMSDAM generated *in situ* from LDA (1.2 equiv.) and [<sup>13</sup>C]-TMSDAM (1.0 equiv.) prior to the addition of ketone. Isotopomer ratios in **6** determined by <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopy.

Strikingly, all three correlations were effectively indistinguishable in their gradient and curvature, as evident from overlay following  $y$ -axis normalization. Such behavior apparently precludes the involvement of any bystander effect on intramolecular selectivity, indicating that relative migratory aptitudes (but not absolute rates, *vide infra*) remain unaffected by the polar influence of the stationary substituent. These results also suggest that the nature of the migratory transition states remains fundamentally comparable across all of the substrates, irrespective of their polarity, i.e. discounting mechanistic discontinuities in limiting cases.

**Generation of Alkylidene Carbenes** Seeking to rationalize the observed selectivities (Scheme 4), in particular the curvature of the Hammett correlations (Figures 1 and 2), and to develop a general model for the 1,2-migration rates and aptitudes, we conducted extensive quantum chemical calculations using a combination of Kohn-Sham density functional theory (KS-DFT; Gaussian09) and local coupled cluster theory (DLPNO-CCSD(T); ORCA 4.0). In accordance with previous theoretical studies,<sup>13-14, 33-40</sup> independently computed T1 diagnostic values (DLPNO-CCSD(T), T1 < 0.02), exploratory unrestricted KS-DFT calculations, and wavefunction stability tests, all species were treated as closed-shell singlets in their ground states (see SI for details).



**Figure 3** Computed reaction pathway for the Colvin rearrangement of acetophenone (**1**-Me,Ph). Geometries and solvation free energies were obtained *via* restricted KS-DFT at the PBE0+GD3BJ/6-311+G(d,p)/IEFPCM(THF,UFF)/Ultrafine level of theory. Thermochemical corrections were computed at  $T = 195$  K using the rigid-rotor harmonic-oscillator approximation (*GoodVibes*) and linearly scaled harmonic frequencies ( $\nu_{\text{scale}} = 0.95$ ), with vibrational entropies corrected in accordance with Grimme's quasi-harmonic approach ( $f_{\text{cutoff}} = 100 \text{ cm}^{-1}$ ) and translational entropies adjusted to reflect a standard state of 1.0 M. Single-point, gas-phase potential energies were computed at the DLPNO-CCSD(T)/ma-def2-TZVPP/TightPNO level. A transition state for concerted elimination of LiOTMS from **2**-Me,Ph leading *directly* to **4**-Me,Ph could not be found. The transition states for loss of LiOTMS from **3**-Me,Ph leading to *E*-**4**-Me,Ph, and for loss of N<sub>2</sub> from *E*-**4**-Me,Ph leading to **5**-Me,Ph, are higher in energy and are not shown. See SI for full details.

To ensure the accuracy of optimized geometries for carbenic species, a range of KS-DFT functionals were carefully benchmarked against highly correlated DLPNO-CCSD(T)/CCSD(T)-F12 reference calculations, using several model alkylidene carbenes ( $\text{PhMeC}=\text{C}\cdot$ ,  $\text{Ph}_2\text{C}=\text{C}\cdot$ ; see SI). PBE0+GD3BJ,  $\omega\text{B97XD}$  and B3LYP+GD3BJ were considered sufficiently robust in this regard, affording disparate energies but, crucially, equilibrium geometries in close agreement with the coupled-cluster surfaces.

Initial DLPNO-CCSD(T) computations established a thermally-feasible pathway from acetophenone (**1-Me,Ph**) to 1-phenylpropyne (**6-Me,Ph**), Figure 3. Consistent with Colvin and Hamill's original proposal<sup>7</sup> and later work by Gilbert,<sup>9</sup> the diazoalkene  $\text{MePhC}=\text{CN}_2$  (**4-Me,Ph**) was identified as a key intermediate, formed *via* a nucleophilic addition,<sup>41-42</sup> [1,3]-silyl migration, and elimination sequence. Although the ionic nature of the intermediates mean that quantitative comparisons made in absence of explicit solvation should be interpreted with caution, lithiated silyl ether **3-Me,Ph** appears to be marginally favored over lithium alkoxide **2-Me,Ph** ( $\Delta G_{195\text{K}} = -5 \text{ kJ mol}^{-1}$ ), in a delicately balanced [1,3]-Brook equilibrium,<sup>43-46,32</sup> in which pre-equilibrium between lithium  $\alpha$ -diazoalkoxide **2-Me,Ph** and cyclic silicate **7-Me,Ph** is kinetically insignificant.

Elimination of LiOTMS from silyl ether **3-Me,Ph** generates diazoalkene **4-Me,Ph**, which contrary to most depictions, has a bent structure on the ground state surface, thus resembling a diazonium ylide rather than a heterocumulene.<sup>47-48</sup> Dediazonation of *Z*-**4-Me,Ph** affords singlet carbene **5-Me,Ph**. Analogously, *E*-**4-Me,Ph** (not shown) generates **5-Ph,Me**. The two conformational isomers (**5-Ph,Me** and **5-Me,Ph**, see Figure 3 inset) undergo rapid equilibration relative to ensuing 1,2-migration. Both carbenes have distorted structures, and in isomer **5-Ph,Me**<sup>14</sup> ( $C_{\text{ipso}}\text{-}C_{\beta}\text{-}C_{\alpha}$  bond angle,  $91^\circ$ ) the position of the aryl ring allows stabilizing  $\pi\text{-p}^*$  and  $\sigma\text{-p}^*$  donor-acceptor interactions (see inset to Figure 3). Exergonic 1,2-phenyl migration in **5-Ph,Me** ( $\Delta^\ddagger G_{195\text{K}} = 7 \text{ kJ mol}^{-1}$ ) generates alkyne **6-Me,Ph**. The analogous 1,2-methyl migration from **5-Me,Ph** is non-competitive ( $\Delta^\ddagger G_{195\text{K}} = 42 \text{ kJ mol}^{-1}$ ).

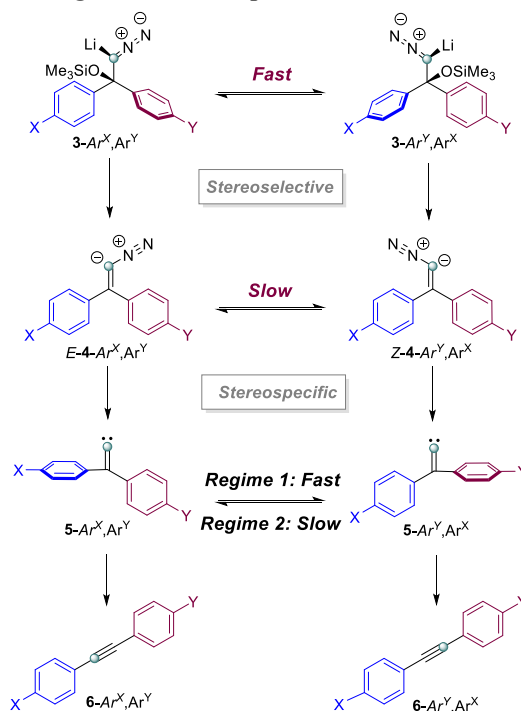
Based on the free energy profile in Figure 3, the dediazonation and migration steps (**4**  $\rightarrow$  **5**  $\rightarrow$  **6**) proceed rapidly, sequentially, and irreversibly after rate-limiting [1,3]-silyl migration / LiOSiMe elimination (**2/3**  $\rightarrow$  **4**). In situ <sup>13</sup>C NMR spectroscopic monitoring of the reaction of [<sup>13</sup>C]-**1-Ph**,  $\text{Ar}^{4\text{F}}$  with [<sup>13</sup>C]-Li-TMSDAM at  $-78^\circ\text{C}$  (see SI) revealed two intermediates with <sup>13</sup>C NMR shifts and couplings ( $^1J_{\text{CC}} = 39 \text{ Hz}$ ) consistent with a mixture of [<sup>13</sup>C<sub>2</sub>]-**2-Ph,Ar**<sup>4F</sup> and [<sup>13</sup>C<sub>2</sub>]-**3-Ph,Ar**<sup>4F</sup>, albeit likely present as higher-order lithium aggregates rather than monomers.

**Analysis of Relative Migratory Aptitudes** Having identified key intermediates *en route* to alkyne **6**, we set out to understand which processes are responsible for the phenomenological migratory aptitudes (Scheme 4, Figures 1, 2). The extremely low barrier predicted for aryl migration (Figure 3 inset) poses several subtleties for the reactions of benzophenones, which nominally lead to highly-reactive  $\beta,\beta$ -diaryl alkylidene carbenes ( $\text{Ar}^X\text{Ar}^Y\text{C}=\text{C}\cdot$ ; **5**). In such carbenes both substituents appear liable to undergo rapid migration, meaning that: (i) the rate of conformational equilibration in the incipient carbene **5** cannot necessarily be assumed to be rapid with respect to migration; and (ii) non-statistical dynamic effects on selectivity cannot be discounted *a priori*. DLPNO-CCSD(T)/ma-def2-QZVPP calculations indicate, for example, that after extrusion of N<sub>2</sub> from

$\text{Ph}_2\text{C}=\text{CN}_2$  ( $\Delta G_{195\text{K}} -28 \text{ kJ mol}^{-1}$ ), subsequent 1,2-phenyl migration in the nascent carbene **5** ( $\Delta^\ddagger G_{195\text{K}} 10 \text{ kJ mol}^{-1}$ ) is only marginally higher in barrier to its degenerate conformational interconversion ( $\Delta^\ddagger G_{195\text{K}} 7 \text{ kJ mol}^{-1}$ ).

With this in mind, we considered two limiting intramolecular regimes for product selection (Scheme 5). In regime 1, classical Curtin-Hammett conditions prevail: conformational equilibration of **5-Ar<sup>X</sup>Ar<sup>Y</sup>** is rapid and the observed product ratio depends only on the two competing 1,2-migration transition states. In regime 2, conformational equilibration is slow with respect to migration, and/or dynamic matching leads to significant bypassing of **5-Ar<sup>X</sup>Ar<sup>Y</sup>** as an intermediate. As a consequence, the observed product ratio depends on selectivity established in preceding steps of the mechanism.

**Scheme 5 Limiting regimes for product-selection in the Colvin rearrangement of benzophenones.<sup>a</sup>**



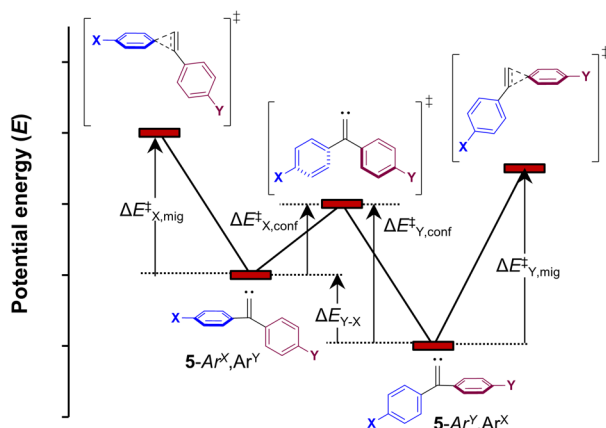
a) Italicization indicates that a substituent is either primed to migrate in a specific conformer/isomer, e.g., *5-Ar<sup>X</sup>*, *Ar<sup>Y</sup>*, or has undergone migration, e.g., *6-Ar<sup>X</sup>*, *Ar<sup>Y</sup>*.

Further analysis (DLPNO-CCSD(T)/ma-def2-QZVPP) indicates that *E/Z*-isomerization of the irreversibly generated diazoalkene **4** intermediate is expected to be slow ( $\Delta^\ddagger G_{195\text{K}} 51 \text{ kJ mol}^{-1}$  for **5-Ph,Ph**) compared to 1,2-aryl migration. Thus, under regime 2, the ratio reported by the <sup>13</sup>C-label would correspond to stereoselectivity at the stage of LiOTMS elimination from the lithiated silyl ether **3-Ar<sup>X</sup>,Ar<sup>Y</sup>**, not the migratory aptitude of the  $\square$ -substituents. Between the limits of regimes 1 and 2, where stereochemical / conformational interconversions in **4** / **5** are competitive with migration, the net selectivity arises from a number of factors.

To discern which, if either, of these regimes prevails for the benzophenone system, we first systematically probed, *via* computation, the potential energy surfaces of 28 distinct  $\beta,\beta$ -diaryl alkylidene carbenes ( $\text{Ar}^X\text{Ar}^Y\text{C}=\text{C}\cdot$ ), constructed from seven electronically-diverse *para*-substituted aryl groups ( $X, Y = 4\text{-NMe}_2, 4\text{-OMe}, 4\text{-Me}, 4\text{-H}, 4\text{-Cl}, 4\text{-CF}_3, 4\text{-NO}_2$ ). Key stationary points were located by restricted KS-DFT, following functional

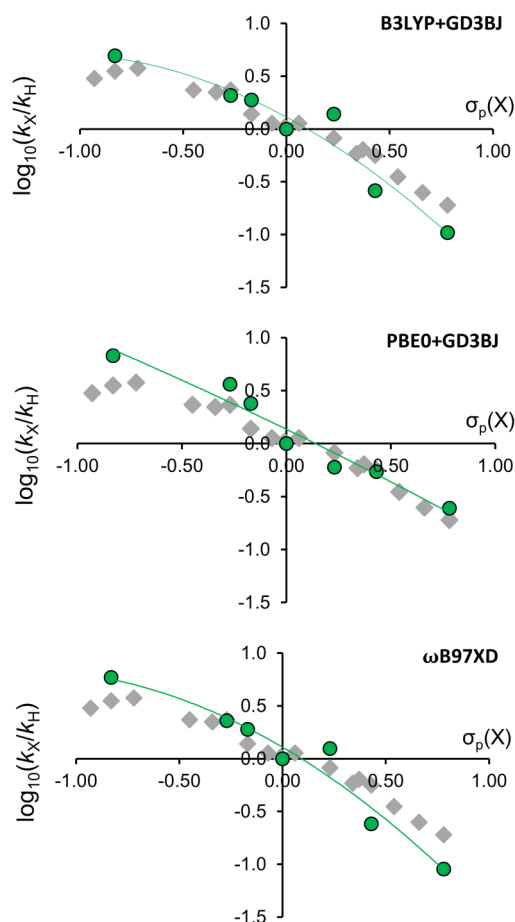
benchmarking against DLPNO-CCSD(T)/ma-def2-QZVPP calculations. For each of the seven symmetric ( $X = Y$ ) carbenes we located a single minimum energy structure, one migration transition state, and a  $C_{2v}$ -symmetric transition state leading to degenerate conformational interconversion.

For the 21 asymmetric carbenes ( $X \neq Y$ ), we identified two ground state conformers and two migratory transition states ( $\Delta^\ddagger E_{X,\text{mig}}$ ,  $\Delta^\ddagger E_{Y,\text{mig}}$ ), in addition to a *pseudo*  $C_{2v}$ -symmetric transition state for conformational interconversion ( $\Delta^\ddagger E_{X,\text{conf}}$ ,  $\Delta^\ddagger E_{Y,\text{conf}}$ ). Extensive  $\pi$ - $p^*$  and  $\sigma$ - $p^*$  interactions between the terminal  $\alpha$ -carbon and  $\beta$ -aryl substituents leads to significant geometrical distortions in both conformers of the  $\beta,\beta$ -diaryl alkylidene carbene system, with one aryl ring adopting a perpendicular orientation<sup>13,14</sup> with respect to the terminal  $C = C$  bond and the other remaining planar. In all 21 of the asymmetric carbenes, the ground state was found to be that in which the most electron rich substituent adopts the perpendicular orientation, with increasing electron-richness also leading to a progressive decrease in the ground state  $C_{\text{ipso}}-C_{\beta}-C_{\alpha}$  bond angle (e.g.,  $\text{Ph}_2\text{C}=\text{C}$ .,  $87^\circ$ ;  $\text{PhAr}^{4\text{-NMe}_2}\text{C}=\text{C}$ .,  $79^\circ$ ). The preference for the most electron rich aryl group being perpendicular to the terminal  $C = C$  bond is consistent with it being the better donor for non-classical  $\pi \rightarrow p^*$  conjugation and/or  $\sigma \rightarrow p^*$  hyperconjugation (see inset to Figure 3).



**Figure 4** Schematic potential energy surface of a  $\beta,\beta$ -diaryl alkylidene carbene

Having established the general PES topography of the  $\beta,\beta$ -diaryl alkylidene carbenes, Figure 4, we computed theoretical migratory aptitudes for seven carbenes derived from mono-*p*-substituted benzophenones **1-Ph,Ar<sup>X</sup>**. Selectivities were then computed for regime 1, where the product ratio depends solely on  $[\Delta^\ddagger E_{\text{H,mig}} + \Delta E_{\text{X-H}} - \Delta^\ddagger E_{\text{X,mig}}]$ . These calculations were then repeated using a range of computational methods, spanning different electronic structure theories (KS-DFT, DLPNO-CCSD(T)), select DFT functionals, basis sets and statistical mechanics approximations, in order to assess the method sensitivity of our analysis (see SI for full survey).



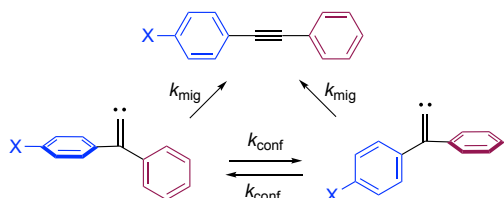
**Figure 5:** Computed Hammett correlations for *mono-p*-substituted benzophenones (**1-Ar<sup>X</sup>,Ph**;  $X = 4\text{-NMe}_2, 4\text{-OMe}, 4\text{-Me}, 4\text{-H}, 4\text{-Cl}, 4\text{-CF}_3, 4\text{-NO}_2$ ), obtained *via* three different computational methods. Relative rates calculated at  $T = 195$  K *via*  $k_X/k_H = \exp[(\Delta^\ddagger E_{\text{H}} - \Delta^\ddagger E_{\text{X}})/RT]$ , where  $\Delta^\ddagger E_i$  denotes the activation barrier for migration of  $\text{Ar}^i$  ( $i = X, \text{H}$ ), relative to the ground state, in  $\text{PhAr}^X\text{C}=\text{C}$ :. In each case, single-point gas-phase energies were computed with DLPNO-CCSD(T)/ma-def2-TZVPP/TightPNO, using geometries and solvation energies obtained with one of three different KS-DFT methods XCF/6-311+G(d,p)/IEFPCM(THF,UFF) (XCF = B3LYP+GD3BJ, PBE0+GD3BJ,  $\omega$ B97XD). Experimental correlations for all 17 benzophenones overlaid for comparison.

All of the methods led to the same conclusion: the more electron-rich aryl group in the  $\beta,\beta$ -diaryl alkylidene carbene migrates preferentially. Quantitative comparisons with experimental values proved more challenging since the transition states differ by at most a few  $\text{kJ mol}^{-1}$  ( $\log_{10} k_X/k_H = |0.8|$ ;  $\Delta\Delta^\ddagger G_{195\text{K}} = |3.7| \text{ kJ mol}^{-1}$ ). Nonetheless, the nominally highest-level results, obtained with DLPNO-CCSD(T), as summarized in Figure 5 (see SI for full discussion) reproduce both the gradient and subtle curvature of the parent Hammett correlation (Figure 1) with reasonable fidelity. This correspondence indicates that: (i) the alkylidene carbene **5** serves as a discrete, product-determining intermediate *en route* to alkyne **6**; (ii) the  $^{13}\text{C}$ -isotopomer ratios measured experimentally report the relative migratory aptitudes of the two competing aryl substituents in the free carbene **5**; (iii) regime 1, i.e. a classical Curtin-Hammett conditions, prevail; and (iv) the curvature of the Hammett cor-

relation is an intrinsic feature of the 1,2-migration in the alkylidene carbene, presumably reflecting the progressive stabilization of the ground-state by a non-classical  $\pi \rightarrow p^*$  interaction with more strongly electron-donating substituents.

Independent DLPNO-CCSD(T) calculations of the barriers to conformational interconversion in  $\beta$ -phenyl- $\beta$ -aryl alkylidene carbenes (Table 1) appear to confirm that other than for very electron-donating substituents (e.g. X = 4-NMe<sub>2</sub>) rearrangement proceeds under regime 1 ( $k_{\text{conf}} > 5 k_{\text{mig}}$ ).<sup>49</sup>

**Table 1 Computed relative rates of conformational interconversion versus migration in  $\beta$ -phenyl- $\beta$ -aryl alkylidene carbenes.<sup>a</sup>**



X	$k_{\text{conf}}/k_{\text{mig}}$	X	$k_{\text{conf}}/k_{\text{mig}}$
NMe <sub>2</sub>	1	NMe <sub>2</sub>	7
OMe	5	OMe	19
Me	6	Me	15
H	17	H	17
Cl	41	Cl	24
CF <sub>3</sub>	36	CF <sub>3</sub>	20
NO <sub>2</sub>	97	NO <sub>2</sub>	24

<sup>a</sup>Combined KS-DFT/DLPNO-CCSD(T) methodology, using geometries and solvation energies obtained at the PBE0+GD3BJ/6-311+G(d,p)/IEFPCM(THF,UFF) level of theory and single-point gas-phase energies obtained from DLPNO-CCSD(T)/ma-def2-TZVPP/TightPNO. Calculated at  $T = 195$  K in accordance with  $k_{\text{conf}}/k_{\text{mig}} = \exp[(\Delta^\ddagger E_{\text{mig}} - \Delta^\ddagger E_{\text{conf}})/RT]$ , Figure 4.

**Analysis of Absolute Migratory Rates** Alkylidene carbene intermediates are very short-lived, undergoing rapid partitioning between 1,2-migration to generate an alkyne versus carbene interception by insertion, cycloaddition, etc. Scheme 1. The 1,2-migration itself proceeds *via* two microscopically-distinct competing pathways, and both experiment and computation (Figures 1, 2, 5) show that more electron-donating  $\beta$ -substituents migrate preferentially, in agreement with prior observations.<sup>2,13,14,19,20</sup> It is tempting to generalize that alkylidene carbenes with electron-donating  $\beta$ -substituents rearrange faster than those with electron-withdrawing ones. However this would be incorrectly based on extrapolation from relative migratory aptitudes determined under a regime of intramolecular competition.

In fact the relative rates (migratory aptitudes) provide no direct insight to the practical aspects of employing alkylidene carbene intermediates because both 1,2-migrations converge, in the absence of isotopic desymmetrization, on the same alkyne. Of direct relevance however, are the absolute migratory aptitudes of both of the  $\beta$ -substituents, for these ultimately control the intrinsic lifetime of the alkylidene carbene and thus the propensity for carbene interception (Scheme 1). Indeed, ambiguities in the

literature concerning the apparent influence of the stationary ('bystander') substituent in Fritsch-Buttenberg-Wiechell rearrangements and related processes, may arise from misinterpretation or conflation of relative versus absolute migration rates.<sup>2</sup>

We explored this question theoretically, using a set of 28  $\beta$ , $\beta$ -diaryl alkylidene carbenes and computing the absolute activation barriers to 1,2-aryl migration, relative to the global minimum on each PES, for the full matrix of carbenes. As before, we reproduced these calculations using a range of methods (see SI). An example of these results, obtained from DLPNO-CCSD(T) calculations, are summarized Table 2 in the form of intrinsic lifetimes ( $\tau_{XY}$ , ns, at -78 °C). The data are also presented as a 2D contour plot (Figure 6) in the form of the absolute barrier to aryl migration as a function of both substituents. Whilst the barriers and lifetimes are necessarily highly-sensitive to the exact method of calculation, the underlying trends appear robust between different methods. Indeed, DLPNO-CCSD(T) calculations predict the lifetime of MePhC=C: to be 3 ps under ambient conditions, in reasonable agreement with the recent experimental measurements ( $\tau = 13.3$  ps) of Phillips, Hadad and Thamattoor.<sup>15</sup>

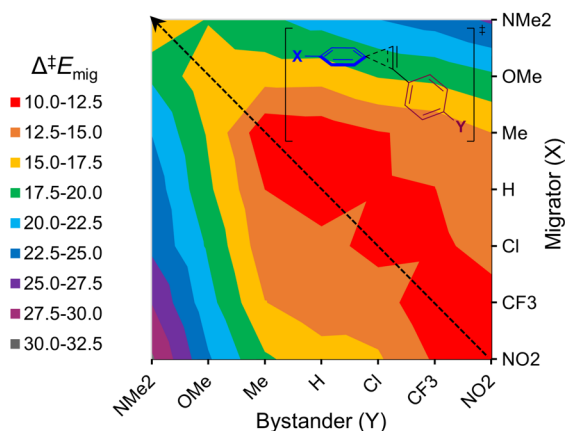
**Table 2 Computed lifetimes (ns) of 28  $\beta$ , $\beta$ -diaryl alkylidene carbenes Ar<sup>X</sup>Ar<sup>Y</sup>C=C: at -78 °C.<sup>a</sup>**

X or Y	NMe <sub>2</sub>	OMe	Me	H	Cl	CF <sub>3</sub>	NO <sub>2</sub>
NMe <sub>2</sub>	1	-	-	-	-	-	-
OMe	10	2	-	-	-	-	-
Me	36	8	0.1	-	-	-	-
H	89	4	0.2	0.1	-	-	-
Cl	203	10	0.3	0.3	0.2	-	-
CF <sub>3</sub>	482	15	0.6	0.4	0.3	0.1	-
NO <sub>2</sub>	1554	38	2.2	1.0	0.3	0.2	0.1

<sup>a</sup>Lifetimes  $\tau_{XY} = (k_{X,\text{mig}} + k_{Y,\text{mig}})^{-1}$  were calculated at  $T = 195$  K in accordance with  $k_{\text{mig}} = (k_B T/h) \exp[-(\Delta^\ddagger E_{\text{mig}})/RT]$ . Activation barriers were computed by a combined KS-DFT/DLPNO-CCSD(T) methodology, using geometries and solvation energies obtained at the PBE0+GD3BJ/6-311+G(d,p)/IEFPCM(THF,UFF)/Ultrafine level of theory and gas-phase, single-point energies from DLPNO-CCSD(T)/ma-def2-TZVPP/TightPNO. Values are computed and illustrative only.

The data in Table 2 and Figure 6 reveal two initially counter-intuitive trends: i) the intrinsic lifetimes are minimized by using electronically-matched substituents, i.e., the barriers to migration are lowest along the diagonal in Figure 6, and ii) the intrinsic lifetimes are maximized by strongly donating groups. Crucially, these lifetimes reflect the theoretical feasibility of intramolecular or inter-molecular interception of the nascent alkylidene carbenes following its release from a precursor (Scheme 1), and the effect of electronic matching on the lifetime is substantial, particularly for strongly-perturbing substituents. Thus whilst the intrinsic lifetimes of the symmetric carbenes, Ar<sub>2</sub>C=C:, are in the range 0.1 – 1 ns, some of the asymmetric carbenes are predicted to have lifetimes up to three to four orders of magnitude larger (0.1 – 1  $\mu$ s).





**Figure 6:** Contour map of activation barriers for 1,2-aryl migration in 28  $\beta,\beta$ -diaryl alkylidene carbenes computed using a combined KS-DFT/DLPNO—CCSD(T) methodology, with geometries and solvation energies obtained at the PBE0+GD3BJ/6-311+G(d,p)/IEFPCM(THF,UFF) level of theory and single-point gas-phase energies from DLPNO-CCSD(T)/ma-def2-TZVPP/TightPNO. Activation barriers are relative to the ground state, and reported in  $\text{kJ mol}^{-1}$ .

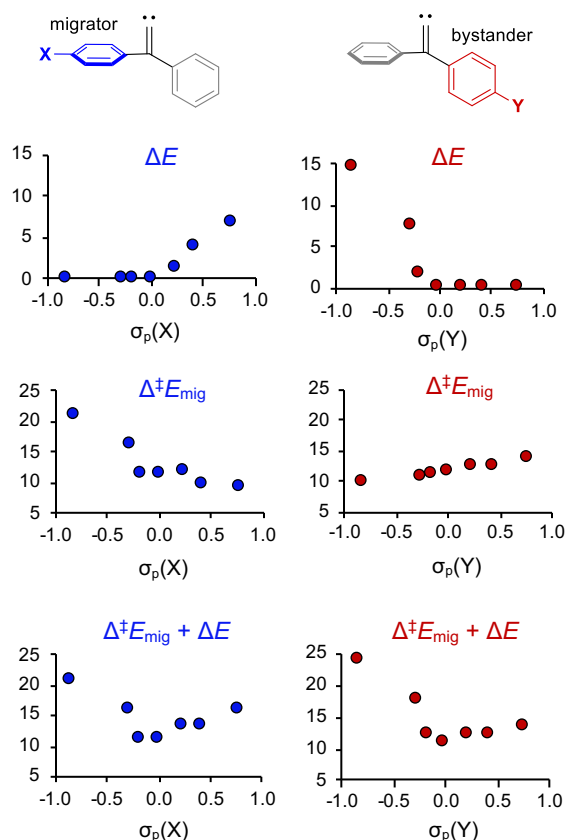
**Origins of the Electronic Matching Effect** The underlying basis for the effect is summarized in Figure 7, which is generated by analysis of various components taken from two cross-sections of the data in Figure 6. The left-hand series displays the effect of varying the substituent (X) on the migrating group when the bystander is phenyl, in the right-hand series the bystander substituent is varied (Y) when the migrating group is phenyl. Unsurprisingly both series show that electron-rich substituents provide thermodynamic stability to the ground state energy ( $\Delta E$ ) via enhanced  $\pi \rightarrow p^*$  and  $\sigma \rightarrow p^*$  donor-acceptor interactions (see inset to Figure 3) compared to Ph.

The second row displays the barrier to 1,2-migration ( $\Delta^\ddagger E_{\text{mig}}$ ) from the ground state of the specified conformer. For variation in migrator (X) the loss of  $\pi \rightarrow p^*$  stabilization during 1,2-migration results in larger barriers arising with electron-rich substituents. Conversely, for variation in bystander (Y) electron-rich substituents reduce the barrier via inductive transition state stabilization.

In the final row, the net effect of both sets of interactions shows how the overall barrier to alkyne formation, relative to the ground state, varies. In both cases the barrier is minimized by electronically matching the migrating substituent to the bystander. The minimum barrier is found at  $\sigma = 0$  in this case, because Ph has been selected as the reference group. As the  $\sigma$  value for the reference group is changed, the point of minimum barrier moves with it, as illustrated by the diagonal line in Figure 6.

## CONCLUSIONS

We have used the Colvin rearrangement of carbonyl compounds to systematically explore the rearrangement of alkylidene carbenes.<sup>20</sup> *In situ* labelling by use of [<sup>13</sup>C]-TMS-diazomethane, in conjunction with [<sup>13</sup>C]{<sup>1</sup>H} NMR spectroscopic analysis of the alkyne products, expedited the quantification of the intramolecular selectivity (migratory aptitude) in the 1,2-migration step. Preliminary experiments reproduced the migratory aptitudes  $\text{H} \gg \text{Ph} \gg \text{Alkyl}$  previously reported for alkylidene carbenes liberated by photolysis.<sup>13-14</sup>



**Figure 7:** Energetic rationale for substituent matching in  $\beta,\beta$ -diaryl alkylidene carbenes. First row: Difference in energy between the *specified conformer* and the ground state ( $\Delta E_i$ ;  $i = X, H$ ). Second row: activation barrier to migration, relative to the *specified conformer* ( $\Delta^\ddagger E_{\text{mig},i}$ ). Third row: activation barrier to migration, relative to the *ground state* ( $\Delta^\ddagger E_{\text{mig},i} + \Delta E_i$ ). Fourth row:  $(\Delta^\ddagger E_{\text{mig},X} - \Delta^\ddagger E_{\text{mig},H}) + (\Delta E_X - \Delta E_H)$ . All energies were obtained by a combined KS-DFT/DLPNO—CCSD(T) methodology, using geometries and solvation energies obtained at the PBE0+GD3BJ/6-311+G(d,p)/IEFPCM(THF,UFF) level of theory and single-point gas-phase energies from DLPNO-CCSD(T)/ma-def2-TZVPP/TightPNO. All energies reported in  $\text{kJ mol}^{-1}$ .

Changes to the electronics, sterics and isotopic identity (H/D) of the  $\square$ -substituents did not detectably perturb this trend. Thus, H-migration is not exclusively contingent on quantum-tunneling, and the hybridization of the migrating centre exerts substantial influence over the migratory aptitude of the  $\square$ -substituent.

High-level electronic structure calculations were conducted to explore both the mechanism and selectivity of the overall process. Calculations, together with *in situ* low temperature <sup>13</sup>C NMR spectroscopic studies, support the conclusion that the Colvin rearrangement proceeds via the sequence shown in Scheme 2, involving irreversible LiOSiMe<sub>3</sub> elimination, stereospecific dediazonation, then 1,2-migration in the free alkylidene carbene. Alternative routes (see SI) to the alkyne by 1,2-migration concerted with N<sub>2</sub> extrusion at the diazoalkene, or reaction via an oxonium ylide formed by THF coordination, could not be located on the ground state PES (KS-DFT).

Extensive experimental studies of differentially substituted benzophenones provided nuanced insights to the 1,2-migration step.

Hammett analysis of the intramolecular competitive rearrangement of alkylidene carbenes generated from mono-substituted benzophenones afforded a smooth but non-linear correlation, indicative that relative migratory aptitudes increase towards a plateau for the most electron-rich substituents in the series (Figure 1). The curvature and gradient of this correlation remained completely invariant to changes in the reference substituent, apparently discounting any mechanistic discontinuity in the limiting substrates (Figure 2).

Electronic structure calculations (Figure 5) reproduced both the gradient and curvature of the parent correlation. This is again indicative that product selection occurs under a Curtin-Hammett regime, with the *prima facie* implication that alkylidene carbenes generated from diazoalkenes are not subject to significant dynamic effects.<sup>50</sup> The non-linearity of the Hammett correlation reflects increasing ground-state stabilization by the  $\pi$ -substituents, *via* non-classical  $\pi \rightarrow p^*$  conjugation and/or  $\sigma \rightarrow p^*$  hyperconjugation (see inset to Figure 3).

A key aspect not fully deconvoluted in prior studies is that the relative migratory aptitudes do not necessarily reflect the overall propensity for 1,2-migration versus other competing processes (Scheme 1). Theoretical exploration of the absolute migratory aptitudes of a systematic matrix of 28  $\beta,\beta$ -diaryl alkylidene carbenes uncovered several effects not easily quantified by experimental interrogation. Calculations suggest, for example, that the intrinsic lifetimes are not primarily dependent upon the electron-donating/withdrawing abilities of the substituents *per se*, but upon the electronic disparity between the two substituents (Figure 6). Electron-donating groups, whilst more effective competitors under conditions of intramolecular competition, do not necessarily lead to faster migration. Indeed, highly polarized  $\beta,\beta$ -diaryl alkylidene carbenes appear to have lifetimes several orders of magnitude greater than symmetric analogues (Table 2). These systems may therefore provide new opportunities for direct spectroscopic detection, in solution in the nano- to micro-second regime.

The above findings on electronic matching add to a previous rather fragmentary body of evidence suggesting that the absolute migratory aptitude of a given substituent is not an intrinsic property, but mutually dependent on the stationary substituent, or bystander.<sup>51</sup> The synthetic ramifications of the matching effect, nevertheless, are not yet completely clear. For example, it is tempting to assume that longer intrinsic lifetimes established by mis-matching will increase the probability of interception of the carbene (Scheme 1). However, this is contingent on the extent to which the mis-matching also stabilizes the carbene ground-state to the competing processes. Highly-efficient bimolecular trapping processes that are kinetically competitive but limited by diffusion may benefit the most in this respect.

## ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Additional discussion, experimental procedures, characterization data, details of isotopomer assignments, NMR spectra of <sup>13</sup>C-labelled alkynes, computational methods and benchmarking calculations.

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Notes

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49. We initially considered this trend as possible contributing factor to the curvature in the Hammett plot (Figure 1) but have been unable to establish a firm conclusion in this respect.
50. Although this conclusion is also supported by theoretical barriers to conformational equilibration, it should be noted that alternative regimes, in which selectivity is governed further up-stream in the mechanism – by, e.g., stereoselective elimination – and the carbenes themselves are bypassed, cannot be ruled out definitively, if for example such upstream processes exhibit analogous selectivities
51. For a recent example, see Chen, F.J.; Lin, Y.; Xu, M.; Xia, Y.; Wink, D. J.; Lee, D. C–H Insertion by Alkylidene Carbenes To Form 1,2,3-Triazines and Anionic [3 + 2] Dipolar Cycloadditions To Form Tetrazoles: Crucial Roles of Stereoelectronic and Steric Effects. *Org. Lett.* **2020**, *22*, 718-723.

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