

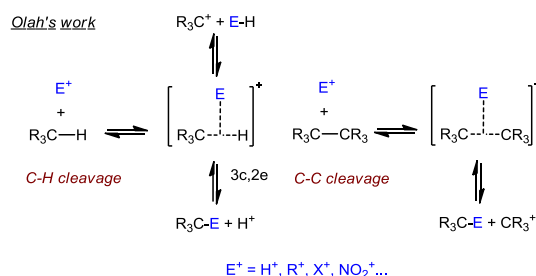
Measuring the relative reactivity of the carbon-hydrogen bonds of alkanes as nucleophiles

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Dedicated to Prof. Ernesto Carmona on the occasion of his 70th Birthday.

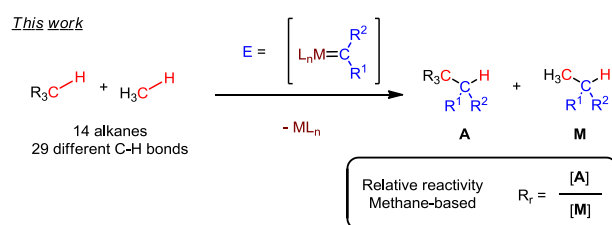
Abstract: We report the quantitative measurement of the relative reactivity of a series of C-H bonds of gaseous or liquid C_nH_{2n+2} alkanes ($n = 1-8$, 29 different C-H bonds), toward in situ generated electrophiles (copper-, silver- or rhodium-carbenes), with methane as the reference. This strategy surpasses the drawback of previous model reactions of alkanes with strong electrophiles suffering from C-C cleavage processes, which precluded direct comparison of relative reactivity of alkane C-H bonds.

Alkanes C_nH_{2n+2} are raw materials readily available but their conversion into value added compounds^[1,2,3] yet constitutes a challenge for modern chemistry due to the strength and the inertness of their carbon-hydrogen bonds, which display high bond dissociation energies, low polarity and low polarizability.^[4] Olah and co-workers^[5, 6] extensively studied the aliphatic electrophilic substitution (Scheme 1a), where a strong electrophile E^+ (H^+ , R^+ , NO_2^+ , X^+ ; R = organic group, X = halogen) is reacted with alkanes, including methane, leading to the substitution of E^+ for H^+ in the parent alkane. From these



methane < primary C-H < secondary C-H < C-C < tertiary C-H

sigma-basicity scale (mainly qualitative)



Scheme 1. Olah's work leading to the sigma bond reactivity scale, affecting both C-H and C-C bonds of alkanes. The scale of relative reactivity was mainly qualitative. Bottom: the quantitative reactivity relative to methane (R_r) has been measured for a number of alkanes using metallocarbene species as the electrophile, in a transformation lacking of C-C scission.

studies, the Olah σ -basicity scale or alkane σ -bond basicity scale^[7,8] describes, *in a qualitative manner* (derived from kinetic selectivities),^[9] the σ -donor ability of the C-C and C-H bonds in alkanes, that was found as methane < primary C-H < secondary C-H < C-C < tertiary C-H. This order finds enormous interest not only in the explanation of alkane reactivity trends but also to the so-called metal-alkane-sigma complexes.^[10,11] Alkanes indeed react with H^+ and other typical electrophiles at the C-H bonds but they also react at the C-C bonds, the latter precluding the quantitative evaluation of the relative reactivity between series of C-H bonds (Scheme 2a). As different reactants may afford the same products, it is not possible to perform significant competition experiments. On the other hand, Mayr and co-workers have propelled the huge development of quantitative nucleophilicity scales.^[12,13] For unactivated hydrocarbon C-H bonds, such scale reaches^[14] the tertiary C-H bond of tri-*p*-tolylmethane as the most nucleophilic site ($pK_a = 32-33$).^[15]

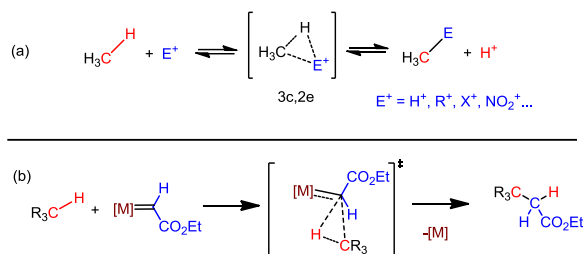
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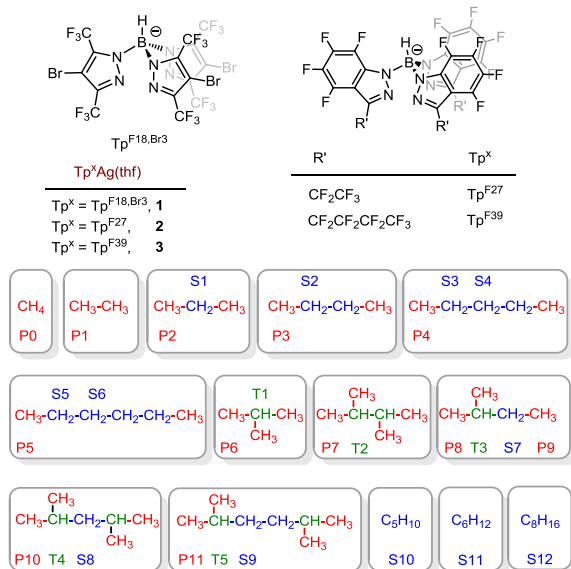
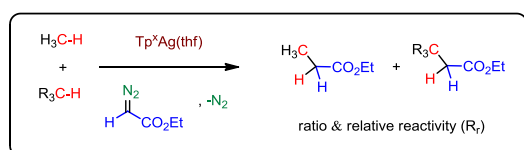
Therefore, there is a gap in the quantification of the C-H bond reactivity of alkanes with pK_a higher than 33^[16] since they require the use of very strong electrophiles.

During our continued research program toward alkane C-H bond catalytic functionalization by carbene insertion from diazo compounds (Scheme 2b),^[17,18,19,20] we have learnt that the metal-carbene intermediates involved are so reactive that allow the ultimate, challenging functionalization of methane. When this



Scheme 2. (a) Intermediacy of 3c,2e species in the electrophilic attack onto the sigma bonds of alkanes. (b) The metal-catalyzed carbene transfer from a diazo compound does not affect C-C bonds. (c) The transition state model for C-H functionalization proposed by Doyle and co-workers.

method is applied to the series of alkanes, each C-H bond leads to a distinct, isolable product in a direct manner, with no rearrangement nor cleavage processes of the hydrocarbon skeleton being observed. Since this transformation and Olah's system take place through similar transition states^[21] in which the electrophile attacks the sigma C-H bond (Scheme 2), we



Scheme 3. The competition experiments carried out with three silver catalysts and the 14 alkanes bearing the different 29 C-H bonds employed in this work.

have employed the former as a tool toward the quantitative measurement of the relative reactivity of the C-H bonds of a series of alkanes with the aforementioned very low pK_a values using methane as the reference.^{[22][23]} It is worth mentioning, however, that the proposal of 3c-2e geometries in Olah's

systems has been challenged, with alternative explanations involving single electron transfer reactions.^[24,25,26]

Competition experiments were carried out with mixtures of the fourteen alkanes shown in Scheme 3 and an electrophilic silver-carbene intermediate formed in situ upon reaction of ethyl diazoacetate (EDA), as the carbene source, with a silver complex $Tp^*Ag(thf)$ (**1-3**), where Tp^* stands for a hydrotrispyrazolylborate ligand (Scheme 3). The experiments were performed either in supercritical carbon dioxide or in liquid alkanes, since previous studies have shown that the site selectivity observed in this carbene insertion reaction does not depend on the reaction medium.^[27] In this manner, the relative reactivity (R_r) of each C-H bond referred to that of methane was accurately measured. The values for R_r obtained for the $Tp^{F18,Br3}Ag(thf)$ -catalyzed carbene insertion reactions for the twenty-nine C-H bonds existing in the studied alkanes are

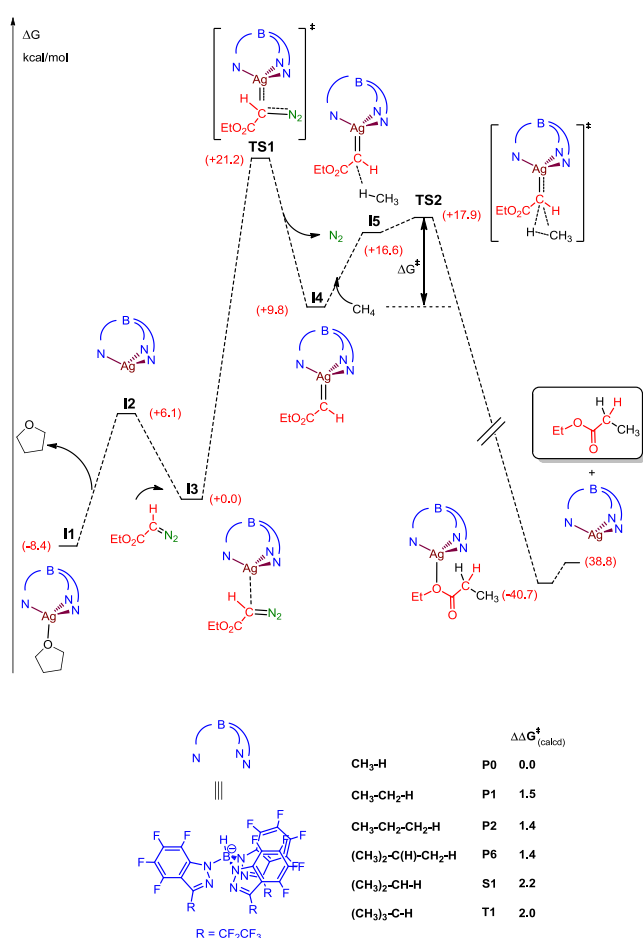
Table 1. The experimental values for the relative reactivity R_r and those of $\log(R_r)$ and $\Delta\Delta G^\ddagger$ (in kcal mol⁻¹) with **1** as the electrophile precursor (see Supporting Information for those with **2** and **3**)

Bond	R_r	$\log(R_r)$	$\Delta\Delta G^\ddagger$	Bond	R_r	$\log(R_r)$	$\Delta\Delta G^\ddagger$
P0	1	0	0,00	S1	70,8	1,85	2,65
P1	24,5	1,39	1,99	S2	55	1,74	2,49
P2	21,4	1,33	1,90	S3	79,4	1,9	2,72
P3	25,1	1,4	2,01	S4	44,7	1,65	2,36
P4	42,7	1,63	2,33	S5	95,5	1,98	2,84
P5	49	1,69	2,42	S6	40,7	1,61	2,31
P6	11,5	1,06	1,52	S7	40,7	1,61	2,31
P7	19,1	1,28	1,83	S8	1,9	0,28	0,40
P8	20,4	1,31	1,88	S9	16,6	1,22	1,75
P9	39,9	1,6	2,29	S10	100	2	2,86
P10	15,5	1,19	1,70	S11	61,7	1,79	2,56
P11	16,6	1,22	1,75	S12	85,1	1,93	2,76

Bond	R_r	$\log(R_r)$	$\Delta\Delta G^\ddagger$
T1	56,2	1,75	2,51
T2	29,5	1,47	2,11
T3	47,9	1,68	2,41
T4	5,5	0,74	1,06
T5	5	0,7	1,00

collected in Table 1 (see the Supplementary Information for the values of R_r for catalysts **2-3**). All values are normalized by the number of identical C-H bonds in each molecule, and range from $R_r = 1$ for methane to $R_r = 100$ for cyclopentane.

The reaction pathway for this type of transformation has been previously modeled with DFT.^{[21,23]28} We have carried out for this work a set of calculations with a B97D, a LANL2DZ, 6-31G(d) basis set, and full optimizations in solution (full computational details supplied in the Supporting Information). The reaction pathway considering catalyst **2**, species **11** in the calculations, is shown in Scheme 4. Nitrogen extrusion from the diazo compound (**13**) leading to the silver carbene intermediate (**14**) has a barrier of 21.2 kcal/mol, constituting the rate determining step. The barrier from the overall process from catalyst **2** is estimated in 29.6 kcal/mol, which matches reasonably well with experimental observations. In any case, this barrier plays no role on the discrimination between different C-H bonds, which takes place in the next step once the silver carbene is formed. Methane is the alkane showing the highest barrier with $\Delta G^\ddagger = 8.1$ kcal mol⁻¹. From **TS2**, the reaction proceeds in one irreversible step with a difference of 56.7 kcal mol⁻¹. Thus, once the C-H and C-C bonds are formed, reversibility is precluded, the functionalization of each C-H bond with this method taking place under kinetic control. Interestingly, the relative reactivity R_r also leads to a series of $\Delta\Delta G^\ddagger$ differences corresponding to the interaction between the electrophile (silver carbene) and the nucleophile (alkane C-H bond, Table 1). The plot of the computed and experimental



Scheme 4. The reaction pathway for the silver-catalyzed (using **2** as pre-catalyst) C-H bond functionalization by carbene insertion from ethyl diazoacetate. Values of calculated $\Delta\Delta G^\ddagger$ are given in kcal mol⁻¹.

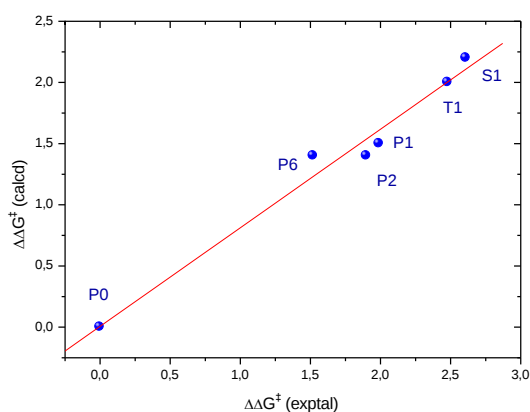


Figure 1. Plot of computed vs experimental $\Delta\Delta G^\ddagger$ values for **2** as the electrophile precursor (see Scheme 3 for the P, S and T bonds employed).

values or the C-H bonds of methane, ethane, propane and isobutane is shown in Figure 1, assessing a good correlation between calculations and the competition experiments outcome.

A data set collection of computational results is available in the ioChem-BD repository.²⁹

One concern that might arise at this point refers to the role of the alkane as nucleophile, which could be called into doubt, in the event that this transformation involves radical species, derived from homolytic scission of the C-H bond. However, we have collected some experimental evidence related to this issue. The competition experiments are carried out in pressure vessels that are not purged from initial air. In the event that radicals are formed, oxygen would avoid the formation of the desired products,^[30] at variance with the experimental observation. Additionally, the calculations show that the interaction of the C-H bond with the carbene carbon atom takes place in a sequential manner, the hydrogen interacting first.

For the first time, the quantitative measurement of the reactivity toward electrophiles (including activation free energies) of the C-H bonds of alkanes has been performed. A bar graph of log(*R_r*) for the three silver-based electrophiles is shown in Figure 2. A first look at the overall picture indicates the absence of a

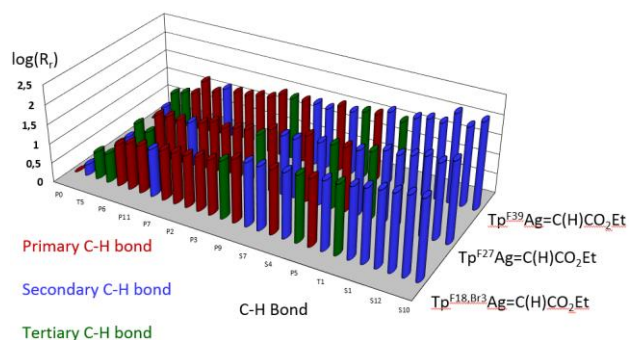
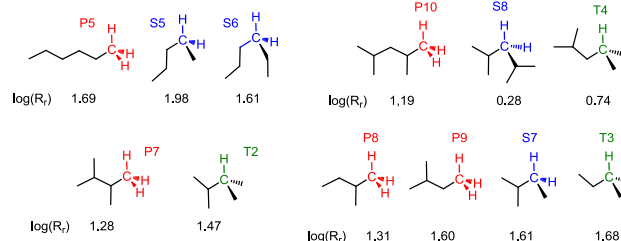


Figure 2. The values of *R_r* for the three silver-based electrophiles. Each type of bond is shown in a different color (primary, red; secondary, blue; tertiary, green).

general reactivity pattern associated with each type of C-H bond. Secondary sites (blue bars) are among the most reactive whereas some tertiary sites (green bars) are located among the less reactive C-H bonds. Primary sites also fall within the range for secondary and tertiary. We have compared the *R_r* values with those of the bond dissociation energies,^[31] but with no success: no trend is observed, albeit given the heterolytic nature of these transformations this is somewhat expected (see SI for a plot of

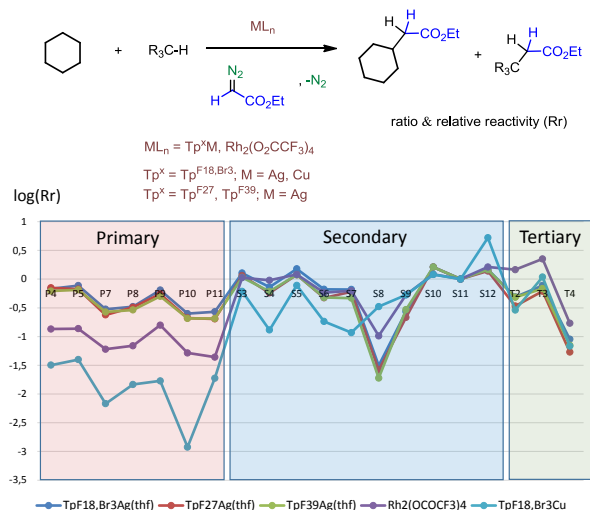


Scheme 5. Representative examples of the reactivity of C-H bonds of alkanes relative to methane, with complex **1** as electrophile precursor.

R_r vs. BDE, Fig. S33). These results do not accommodate well within the sigma-bond basicity scale, assessing the importance of the nature of the electrophile. It is worth mentioning that such qualitative scale was developed with electrophiles with low steric demand,^[32,33] at variance with those employed in this work. In addition, that scale was built mainly through *intramolecular* comparisons, due to the aforementioned drawback of C-C

scissions. Scheme 5 shows the results for several alkanes. Thus, with hexane as the substrate, secondary sites are more reactive than primary ones, and among the former, the less hindered C(2)-H bonds (S5) are more reactive than the other secondary C(3)-H bonds (S6). With 2,3-dimethylbutane, the tertiary C-H bond (T2) is also functionalized at a larger extend compared with the primary C-H bonds (P7), whereas with 2-methylbutane, the tertiary (T3) > secondary (S7) > primary (P8, P9) trend is also observed, both primary sites being different as the result of distinct steric hindrance. But when the steric pressure augments, such as in the case of 2,4-dimethylpentane, the observed values of 1.19, 0.28 and 0.74 for P10, S8 and T4, respectively, assessed Olah's concerns about the effect of size in the selectivity. Thus, our experimental data validate Olah's model at the intramolecular level but demonstrate that its application between C-H bonds of different substrates is, as best, in doubt.

Similar $\log(R_r)$ values cannot be determined for other metals due to the lack of significant reactivity of the corresponding *in situ* generated $L_nM=C(H)CO_2Et$ electrophiles towards methane and other gaseous alkanes.^[17,18,27] Thus, we have obtained the corresponding $\log(R_r)$ values using cyclohexane as the reference (Scheme 6) performing a series of competition experiments between such cycloalkane and the eight liquid alkanes (C_nH_{2n+2} , $n > 4$) shown in Scheme 3. The carbene insertion reaction (from ethyl diazoacetate) was catalyzed by complexes **1-3**, the dirhodium complex $[Rh_2(OCOCF_3)_4]$ (**4**) and the copper complex $Tp^{F18,Br3}Cu(thf)$ (**5**).^[20] Scheme 6 shows the values of $\log(R_r)$ for those five catalysts (see Supporting Information for details and full list of data). As expected, the three silver-based electrophiles behave similarly, and followed the same order previously established with methane as the reference. However, the use of rhodium or copper brings significant differences: primary sites are less reactive with the rhodium- and, more drastically, with the copper-based catalysts compared to the silver electrophiles. Since **1** and **5** only differ in the metal center, the Tp^x ligand being the same, it is the nature



Scheme 6. The effect of the metal in the relative reactivity of C-H bonds of alkanes, with cyclohexane as the reference.

of the metal that is influencing the reaction outcome. For secondary sites, the $\log(R_r)$ values are similar for **1-4**, but slightly lower for **5**. In the region of the tertiary sites, copper- and silver-based catalysts show similar behavior, the rhodium catalyst

providing the highest relative reactivity. Overall, the results are similar to those observed with methane as the reference.

In conclusion, we have measured the relative reactivity (R_r) with methane as the reference of twenty-nine carbon-hydrogen bonds of fourteen different alkanes acting as (weak) nucleophiles in their reaction with *in situ* generated silver-carbene complexes as the (strong) electrophile. Data collected with our model system using intermolecular competitions have shown the lack of a general pattern of reactivity for the reaction sites. Expansion to copper- and rhodium-based electrophiles, with cyclohexane as the reference, have shown the same behavior.

Acknowledgements

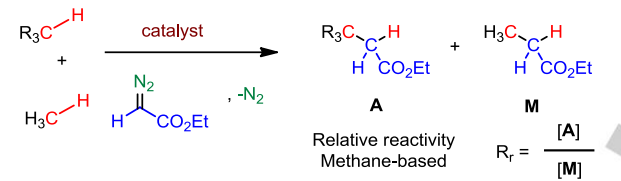
We thank MINECO for support with Grants CTQ2017-82893-C2-1-R, CTQ2014-62234-EXP, CTQ2015-73693-JIN, CTQ2017-87792-R, Severo Ochoa Excellence Accreditation 2014-2018 (SEV-2013-0319), Red Intecat (CTQ2016-81923-REDC). Junta de Andalucía is also acknowledged for Grant P12-FQM-1765. R. G. and A. O. thanks MINECO for FPI and Juan de la Cierva fellowships, respectively. The CNRS is thanked for support.

Keywords: C-H bond alkane reactivity C-H bond functionalization alkane nucleophilicity metal-carbene electrophiles alkane functionalization

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Alkane reactivity

The relative reactivity of the C-H bonds of alkanes C_nH_{2n+2} acting as nucleophiles is reported, ranging from $n = 1$ (methane as the reference) to $n = 8$, toward several silver- copper- or rhodium-carbene complexes acting as strong electrophiles. Data collected evidence the lack of a general trend for the reaction sites from an intermolecular point of view.	 Relative reactivity Methane-based $R_r = \frac{[A]}{[M]}$ 14 alkanes; 29 C-H bonds; Ag, Rh and Cu carbenes as electrophiles	Andrea Olmos, Riccardo Gava, Bárbara Noverges, Delia Bellezza, Kane Jacob, Maria Besora, W. M. C. Sameera, Michel Etienne, Feliu Maseras, Gregorio Asensio, Ana Caballero and Pedro J. Pérez Page No. – Page No. Measuring the relative reactivity of the carbon-hydrogen bonds of alkanes as nucleophiles
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