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Alkane Functionalization by Metal-Catalyzed Carbene Insertion from Diazo Reagents

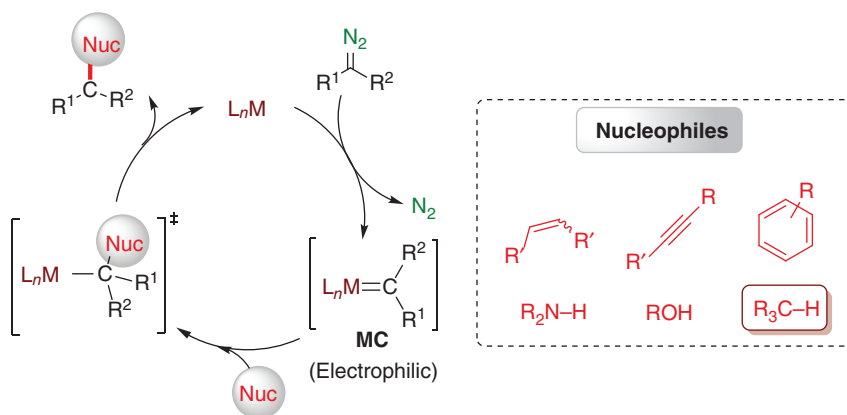
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1.1 Introduction

The metal-catalyzed decomposition of diazo compounds, known from the beginning of the twentieth century [1], occurs through the formation of metal-carbene intermediates which display electrophilic nature, mainly located at the carbenic carbon atom (MC, Scheme 1.1) [2]. Such feature is the origin of the reactivity toward nucleophiles triggering the transfer of the carbene group and subsequent functionalization of the latter. A variety of powerful nucleophiles have been employed along the years, such as unsaturated molecules (olefins, alkynes, or arenes) or amines and alcohols, for which carbene incorporation, either added to an unsaturated bond or inserted into a saturated one, was favored. At variance with that, the functionalization of the less nucleophilic carbon–hydrogen bonds by this methodology has developed at a lower rate [3]. Intramolecular transformations were described with a substantial degree of success, albeit many examples took advantage of the existence of carbon–hydrogen bonds vicinal to heteroatoms (N, O), of being located at benzylic positions, and/or of the formation of very stable five- or six-member rings. But when facing the modification of non-activated carbon–hydrogen bonds, and under intermolecular conditions, this reaction becomes a challenge that only in the last decade has been significantly achieved and with some goals yet to be reached.

In this chapter, an account of the state of the art on the functionalization of the carbon–hydrogen bonds of alkanes by carbene incorporation from diazo compounds is presented. In this sense, only saturated hydrocarbons C_nH_{2n+2} as well as their cyclic partners C_nH_{2n} are considered. Other C–H bonds in substrates containing activating groups (heteroatoms, aryl, or olefin) are not considered herein, unless a substantial degree of novelty is implicit. As shown in Figure 1.1, the strengths of the C–H bonds of the alkanes are considerably higher than those of substrates containing activating groups [4]. As a representative comparison, the C–H bond of cyclohexane displays a bond dissociation energy (BDE) of $99.5 \text{ kcal mol}^{-1}$, whereas the



Scheme 1.1 General catalytic cycle for several nucleophiles functionalization by carbene transfer from diazo compounds.

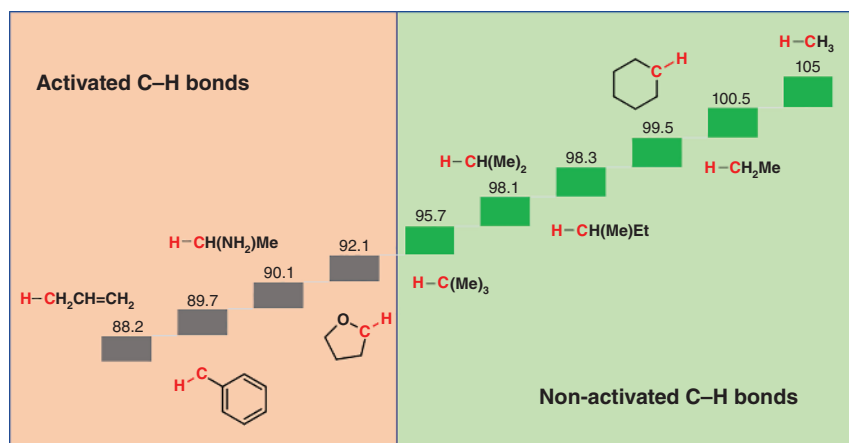
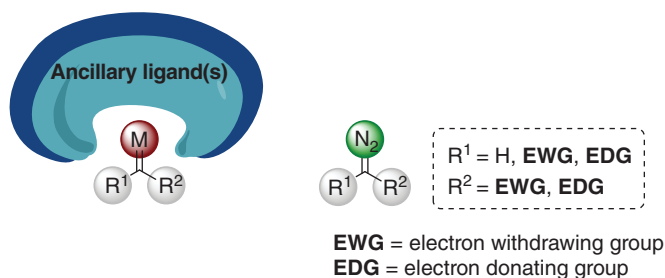


Figure 1.1 Bond dissociation energies of representative carbon-hydrogen bonds. Values in kcal mol⁻¹.

methyl C—H bonds of toluene are nearly 10 kcal mol⁻¹ below. Interestingly, some literature reports refer to the latter as “alkane functionalization,” although it is clearly far of being and behaving as an alkane.

Based on the low nucleophilicity of the targeted C—H bonds, the success of the carbene transfer depends on exerting a high electrophilicity in the metalcarbene intermediate (**MC**, Scheme 1.1) generated from the catalyst precursor and the diazo reagent. The carbenic carbon needs to be drained of electron density; therefore, reactivity toward the weak electrophile is increased. Several tactics can be employed to achieve such effect (Scheme 1.2). On one hand, electron donation from the ancillary ligand(s) bonded to the metal ion should be as low as possible while always ensuring that coordination is maintained. The use of a very poor coordinating ligand could be a problem if it is de-coordinated during catalysis. Additionally, the nature of the



Scheme 1.2 Factors affecting the electrophilicity of the carbenic carbon atom.

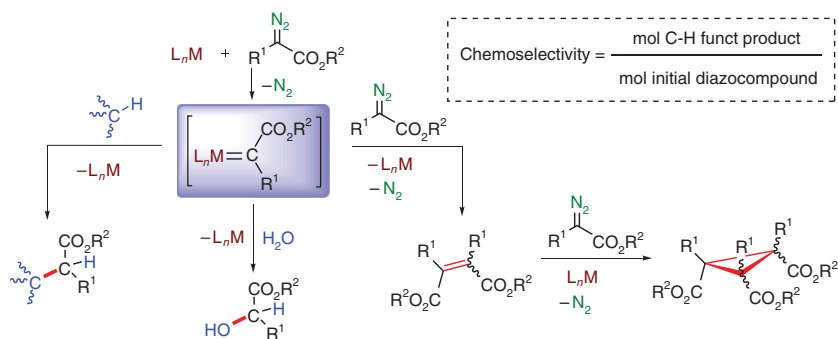
substituents at the diazo reagent may also help since electron withdrawing, electron donating, or the neutral H can be employed at those positions. It could be thought that using two electron-withdrawing groups could be the best option to enhance the reactivity. However, this is not the case since other side reactions can also occur (see Section 1.2), and very reactive metallocarbenes could enhance the formation of undesired products. A balance between the ancillary ligand, the metal center and the diazo substituent must be found to optimize the reaction outcome.

1.2 Chemo- and Regioselectivity

1.2.1 Definitions

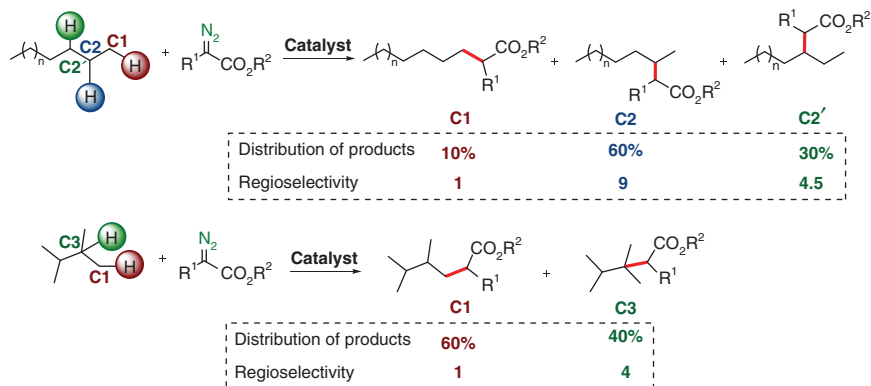
The metallocarbene intermediates are highly reactive and interact with available nucleophiles in the reaction mixture. In addition to the substrate employed, other side, non-desired reactions might occur, decreasing the selectivity of the process. Scheme 1.3 shows the most common byproducts derived from such behavior. Olefins derived from the catalytic coupling of two diazo molecules are the most frequent byproducts, in a process which usually is highly favored [5]. The use of slow addition techniques to maintain a low diazo concentration is a tactic to decrease their formation. Such olefins can also be transformed into cyclopropanes with a third diazo molecule, a reaction which may occur with highly active catalysts and high concentration of the olefins. When adventitious water is present, the O—H bond can also be modified upon incorporation of a carbene moiety. Because all these possible processes decrease the yields into the targeted alkane C—H bond functionalization product, the chemoselectivity is usually defined as the amount of the latter referred to the initial amount of the diazo reagent, which can also be transformed into the other byproducts. The formation of the olefins and cyclopropanes involve two and three, respectively, molecules of diazo reagent, a fact that needs to be accounted for the chemoselectivity value.

Regioselectivity in the context of alkane functionalization by this methodology refers to the distinct reactivity shown by the different C—H bonds available in the alkane molecule employed as substrate. Considering *n*-hexane as an example, three distinct potential sites are present, i.e. the primary C—H bonds at C1 and the secondary sites at C2 and C2' (Scheme 1.4). Once the reaction outcome is quantified, a



Scheme 1.3 Chemoselectivity in C–H bond functionalization by carbene insertion, with potential undesired side reactions.

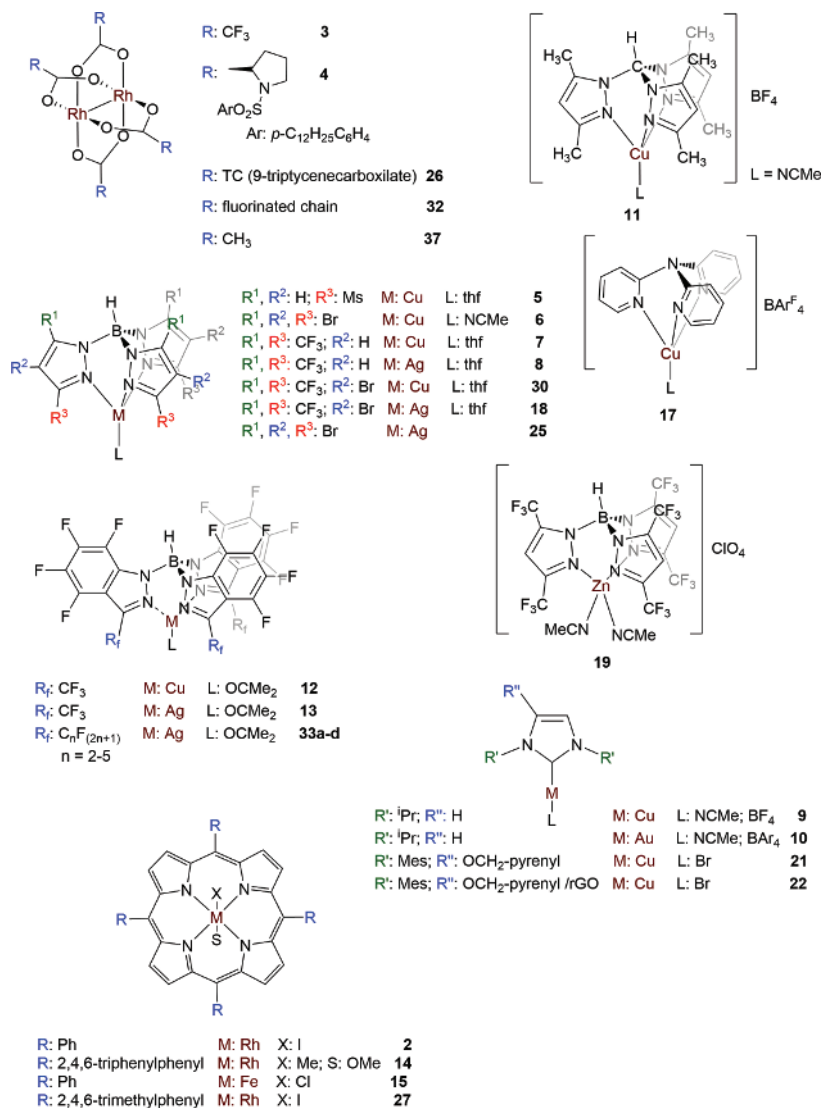
distribution of the three products derived from the carbene insertion in such those three sites is obtained. Albeit those numbers can be employed to define the selectivity of the catalyst, it is more convenient to correct them employing the number of C–H bonds existing at each site, therefore eliminating statistic effects. In this manner, six C–H bonds are available at C1 sites, whereas C2 and C2' contain four C–H bonds each. In the case of 2,3-dimethylbutane, there are 12 primary sites at C1 and 2 tertiary ones at C3. Scheme 1.4 shows a comparison with hypothetical values for the distributions of products and the regioselectivity defined as the latter corrected by the number of available C–H bonds. The selectivity toward C1 and C2 in hexane corresponds to a 1 : 9 ratio, which may be misinterpreted focusing only on the distribution of products (10 : 60). The case of 2,3-dimethylbutane is more pronounced: a 60 : 40 ratio for the distribution of products, which provides more of the primary site functionalized product, corresponds to a 1 : 4 regioselectivity favoring the tertiary site.



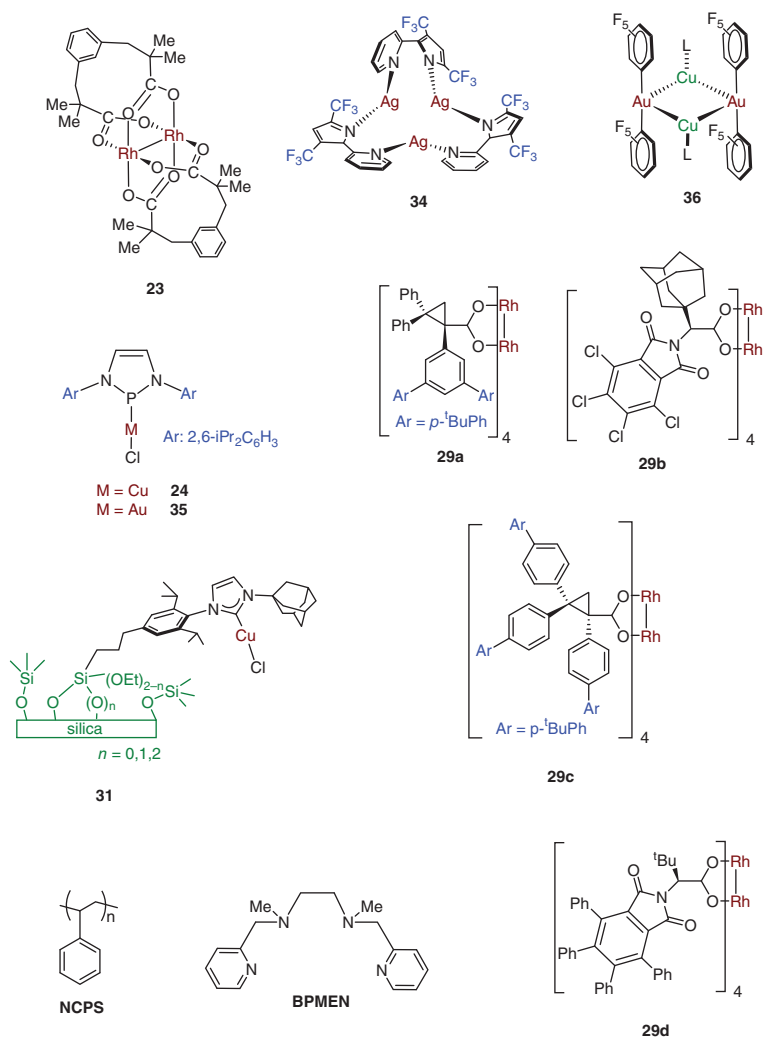
Scheme 1.4 Examples for the comparison of the distribution of products and the regioselectivity calculated employing the number of C–H bonds of each class in the substrate.

1.2.2 Catalysts

A number of catalysts have been described for the functionalization of the carbon–hydrogen bonds of alkanes and cycloalkanes through this methodology, many of them consisting of transition metal complexes bearing somewhat elaborated ligands. Scheme 1.5 displays all those commented along this chapter, either showing the structure of the catalyst or, in some cases, the ligand used as an additive



Scheme 1.5 Catalysts employed for the functionalization of alkanes or cycloalkanes by carbene insertion from diazo compounds.

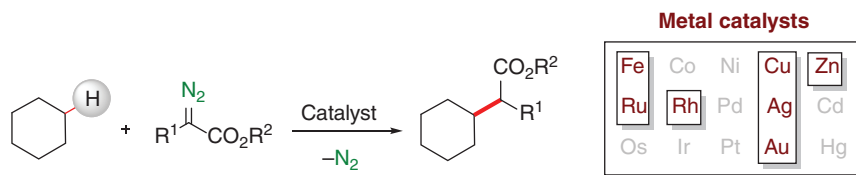


Scheme 1.5 (Continued)

along with a simple metal salt. Each catalyst is given a number which is later employed in the discussion of results.

1.2.3 Chemoselectivity

Cyclohexane is very often employed as the probe substrate to evaluate the potential of a catalyst toward the carbene transfer from a diazo compound and subsequent alkane C—H bond functionalization. With a substantial BDE value (99 kcal mol⁻¹), it is an appropriate reactant since only one product is formed, at variance with linear alkanes, and thus provides a measure of the chemoselectivity induced by

Table 1.1 Cyclohexane functionalization by metal-catalyzed carbene insertion.

Catalyst		R ¹	R ²	Yield (%)	Diazo addition ^a	Reference
CuSO ₄	1	H	CO ₂ Et	24	sa	[6]
CuSO ₄	1	H	CO ₂ Ph	17	sa	[6]
RhTPPI	2	H	CO ₂ Et	71	sa	[7]
Rh ₂ (OOCF ₃) ₄	3	H	CO ₂ Et	75	sa	[8]
Rh ₂ (S-DOSP) ₄	4	Ar	CO ₂ Et	80	sa	[9]
Tp ^{Me} Cu(thf)	5	H	CO ₂ Et	54	sa	[10]
Tp ^{Br³} Cu(NCMe)	6	H	CO ₂ Et	90	sa	[11]
Tp ^{(CF₃)₂} Cu(thf)	7	H	CO ₂ Et	58	sa	[12]
Tp ^{(CF₃)₂} Ag(thf)	8	H	CO ₂ Et	99	sa	[12]
[IPrCu(NCMe)]BF ₄	9	H	CO ₂ Et	80	sa	[13]
[IPrAu(NCMe)]BAR ^F ₄	10	H	CO ₂ Et	84	sa	[13]
[Tpm ⁺ Cu(NCMe)]BF ₄	11	H	CO ₂ Et	80	sa	[14]
Tp ^{F²1} Cu(OCMe ₂)	12	H	CO ₂ Et	99	sa	[15]
Tp ^{F²1} Ag(OCMe ₂)	13	H	CO ₂ Et	97	op	[15]
Rh(ttppp)(Me)(MeOH)	14	Ar	CO ₂ Et	80	op	[16]
Fe(TPP)Cl	15	Ar	CO ₂ Me	78	op	[17]
NCPS-Ru	16	Ph	CO ₂ Me	60	op	[18]
[(TPN)Cu(thf)]+BAR ^F ₄	17	H	CO ₂ Et	85	sa	[19]
Tp ^{(CF₃)₂B¹} Ag(thf)	18	H	CO ₂ Et	99	op	[20]
{LZn(NCMe) ₂ }ClO ₄	19	H	CO ₂ Et	91	sa	[21]
Fe(ClO ₄) ₂ /BPMEN	20	Ph	CO ₂ Me	84	op	[22]
L ^{Me} ₃ CuBr	21	H	CO ₂ Et	15	sa	[23]
L ^{Me} ₃ CuBr-rGO	22	H	CO ₂ Et	35	sa	[23]
[Rh ₂ (esp) ₂]	23	CONHPh	CO ₂ Me	89	sa	[24]
(ADAP)CuCl	24	H	CO ₂ Et	98	sa	[25]
[Tp ^{Br³} Ag] ₂	25	N-triftosylhydrazones		99	op	[26]

^[a] sa = slow addition; op = one portion.

the catalyst chosen. In this section, an overview of the catalytic systems described for the conversion of cyclohexane into the corresponding derivatives upon carbene insertion is given. Table 1.1 contains a list of such catalysts (see their structures in Scheme 1.5). The substituents at the diazo group are also detailed, as well as the temperature and the mode employed for the incorporation of the diazo reagent, either in one portion addition (op) or employing slow addition (sa) devices. Diazo-based yields are given as chemoselectivity values.

In spite of the interest of this transformation, only seven metals have been found as productive in terms of catalytic activity for this reaction: Fe, Ru, Rh, Cu, Ag, Au, and Zn. The first report from 1974 [6] employed simple copper(II) sulfate to generate ethyl 2-cyclohexylacetate in 24% yield. Since then, several metal

complexes have been described toward that end, most of them providing high yields into the functionalized product. Such degree of chemoselectivity has been frequently reached employing the slow addition technique which maintains the diazo concentration low enough to disfavor the formation of carbene-coupling products. Catalysts **6**, **8**, **12**, **19**, and **24** induce >90% yields into the functionalized product using such technique. Interestingly, some of the catalysts (**13**, **25**) induced very high yields adding the diazo reactant in one unique portion at the beginning of the experiment, demonstrating a very high chemoselectivity toward the C—H bond functionalization.

From the array of catalysts shown in Table 1.1, several trends can be extracted. First, the nature of the diazo reagent seems to be coupled with the metal of choice. Thus, the monosubstituted ethyl diazoacetate (EDA), with one acceptor substituent (CO_2Et), is largely employed with group 11 metal-based catalysts. EDA usually generates a highly reactive metalcarbene intermediate which therefore is disposed to verifying some of the non-desired reactions already commented in Scheme 1.3. In this sense, the observation of very high selectivities with some catalysts is of note, most of them with tridentate ligands surrounding the metal center (**6–8**, **11–13**, **17**, **18**, **25**). In other examples, monodentate ligands of type N-heterocyclic carbene (**9**, **10**, **21**, **22**) or alkoxydianaminophosphines (**24**) also give high yields into the functionalized product.

The other group of catalysts are rhodium-based, either mononuclear with porphyrin ligands or dinuclear derived from the parent dirhodium tetraacetate. These $\text{Rh}_2(\text{L-L})_4$ catalysts are the most relevant in the chemistry of carbene transfer reactions in view of their extensive use with outstanding performance in many reactions. Regarding alkanes as substrates, donor–acceptor diazo reagents are preferred, mainly with aryl (donor) and carboxylate (acceptor) groups. Their use will be developed in Sections 1.2.4 and 1.3.

Other metals such as iron, ruthenium, and zinc have been described for this transformation, with good to high yields. The iron catalyst **15** contains a porphyrin ligand, resembling the similar rhodium catalyst **2**. At variance with that, the ruthenium catalyst **16** is formed by nanoparticles of this metal supported onto a polystyrene material. In the case of zinc (**19**), albeit the complex is required for diazo decomposition, the authors could not rule out that carbene dissociation from the metal center could exist prior to attack to the C—H bond.

1.2.4 Regioselectivity

Except for methane and ethane, which will be discussed in a separate section, all acyclic alkanes display a number of distinct C—H bonds, providing several reaction sites. Because of this, catalysts exerting a certain control in the regioselectivity (see Scheme 1.4 for definition) are desired. In this sense, a tremendous advance in this area has taken place in the last decade. To discuss such development, three representative alkanes have been chosen: *n*-pentane, *n*-hexane, and 2,3-dimethyl butane, exemplifying the potential of a given catalyst to direct the carbene insertion to the different primary, secondary, or tertiary C—H bonds of these non-activated sites.

Table 1.2 contains the catalytic systems reported to date for effective *n*-pentane or *n*-hexane functionalization by carbene insertion from a diazo compound. A few are far of being considered regioselective, despite their good catalytic activity in terms of yields. Most are based on the coinage metals, which also employ EDA as the carbene source. Copper catalysts display very low or null capabilities for the functionalization of primary sites, whereas silver and gold provide mixtures of the three possible products at variable extent, with noticeable amounts of that derived from primary sites functionalization.

At variance with group 11 metals, rhodium-based catalysts have provided the best results to date for the selective functionalization to C1 or C2 positions in *n*-pentane or *n*-hexane. Catalyst Rh(tppp)(Me)(MeOH) (**14**) induced the highly selective incorporation of the C(Ph)CO₂Me carbene group into the primary C—H bonds of hexane, with a 10.5 : 1 regioselectivity for C1:C2 sites, respectively, and no incorporation into the C2' site. The dirhodium complex **4** promoted the preferential functionalization of the secondary C—H bond at C2 of pentane, with no activation of that at C1 and very minor at C2', the C2:C2' regioselectivity being 29 : 1.

The regioselectivity of this transformation seems to be governed by the steric hindrance of the catalytic pocket, defined by the geometry of the ancillary ligand(s). This is clearly observed when a series of Tp^FAg(L) catalyst with fluorinated ponytails variable in length, but similar electronic properties at the silver center were employed with several alkanes. Additionally, electronic effects are of note, particularly if the highly reactive EDA is employed, the control of the regioselectivity becoming more difficult. With less reactive, donor–acceptor diazo reagents, the regioselectivity is enhanced toward a site which is mainly defined by the steric pressure around the metalcarbene unit.

Carboxylate CO₂CH₂CCl₃ groups are the most effective substituents of the diazo group in this case. Extension of the latter system has led to more regioselective catalysts of composition Rh₂(L–L)₄. Due to their chiral nature and the enantioselectivity induced, they are discussed in Section 1.3.

2,3-Dimethylbutane constitutes the prototypical example to discern between tertiary and primary C—H bonds in terms of regioselectivity. Table 1.3 shows the most relevant catalysts employed with this substrate (see Scheme 1.5 for catalyst structures). Very high selectivity toward the tertiary C3 site can be achieved with Rh₂(OOCCH₃)₄ (**37**), Rh₂(OOCCH₃)₄ (**3**), or Tp^{Br3}Cu(NCMe) (**6**). On the other hand, such degree of regioselectivity has not yet been induced onto the primary sites of this substrate. Best results to date correspond to Rh(tppp)(Me)(MeOH) (**14**, 1 : 1.3 for C1:C3 regioselectivity), several silver catalysts of formulation Tp^xAgL (**8**, **13**, **28**; C1:C3 within the range 1 : 1.5–2), the gold catalyst [IPrAu(NCMe)]BAR^F₄ (**10**, with C1:C3 as 1 : 1.2), and the zinc catalyst (**19**, with C1:C3 as 1 : 1.9).

1.3 Enantioselectivity

In line with the continuously pursued great challenge of enantioinduction in catalytic reactions, the development of chiral complexes as catalysts for the

Table 1.2 Functionalization of *n*-pentane/*n*-hexane.

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Catalyst	R ¹	R ²	<i>n</i>	Yield (%)	Selectivity			References	
					C1	C2	C2'		
<i>Rh</i> ₂ (<i>OOCCF</i> ₃) ₄	H	CO ₂ Et	1	n.r.	1	14.1	11.6	[8, 27]	
<i>Rh</i> ₂ (<i>OOCTC</i>) ₄	H	CO ₂ Et	1	n.r.	1	3.1	0.9	[27]	
<i>RhTPPI</i>	H	CO ₂ Et	2	46.	1	13.4	4	[7]	
<i>RhTMPI</i>	H	CO ₂ Et	2	36	1	3.7	0.8	[7]	
<i>Rh</i> ₂ (<i>OOCR_F</i>) ₄	H	CO ₂ Me	2	92	1	14.4	6.9	[28]	
<i>Rh</i> (<i>tippp</i>)(<i>Me</i>)(<i>MeOH</i>)	Ph	CO ₂ Me	2	66	10.5	1		[16]	
<i>Rh</i> ₂ (<i>S-DOSP</i>) ₄	Ar	CO ₂ (CH ₂ CCl ₃)	1	98	n.d.	29	1	[9]	
<i>Dirhodium TPCP catalysts</i>	Ar	CO ₂ (CH ₂ CCl ₃)	1	99	1	30	n.d.	[29]	
<i>Tp^{Bn3} Cu</i> (<i>NCMe</i>)	H	CO ₂ Et	1	60	n.d.	3	1	[11]	

$Tp^{F21}Cu(OCMe_2)$	12	H	CO ₂ Et	1	47	1	18.5	7	[15]
$Tp^{(CF_3)_2Br}Cu(THF)$	30	H	CO ₂ Et	2	>99	1	15.8	4.1	[30]
$(TPN)Cu(THF)BAR^F_4$	17	H	CO ₂ Et	2	62	n.d.	1	1	[19]
$(ADAP)CuCl$	24	H	CO ₂ Et	1	34	1	35	27	[25]
$(NHC)Cu-SiO_2$	31	H	CO ₂ Et	2	45	1	31	17.5	[31]
$Tp^{Br_3}Ag(thf)$	25	H	CO ₂ Et	2	98	1	3.7	1.4	[32]
$Tp^{(CF_3)_2}Ag(thf)$	8	H	CO ₂ Et	1	81	1	1.7	0.9	[12]
$Tp^{Fn}Ag(THF)$	33	H	CO ₂ Et	2	>99	2.5–3	3.6–4.5	1	[33]
$Tp^{F21}Ag(OCMe_2)$	13	H	CO ₂ Et	2	>99	1.6	3.3	1	[15]
$Ag_3(3,5-(CF_3)_2PyrPy)_3$	34	H	CO ₂ Et	2	46	1	5	2	[34]
$[IPrAu(NCMe)]BAR^F_4$	10	H	CO ₂ Et	2	78	1	2.9	1.8	[13]
$(ADAP)AuCl$	35	H	CO ₂ Et	2	29	1	2	1	[35]
$[Au_2Cu_2(C_6F_5)_4(NCMe)_2]_n$	36	H	CO ₂ Et	1	90	n.d.	1.5	1	[36]
$Fe(CIO_4)_2/BPMEN$	20	Ph	CO ₂ Et	2	66	1.4	1	1.05	[22]
$NCPs-Ru$	16	Ph	CO ₂ Et	2	50	1	1 ^a		[18]

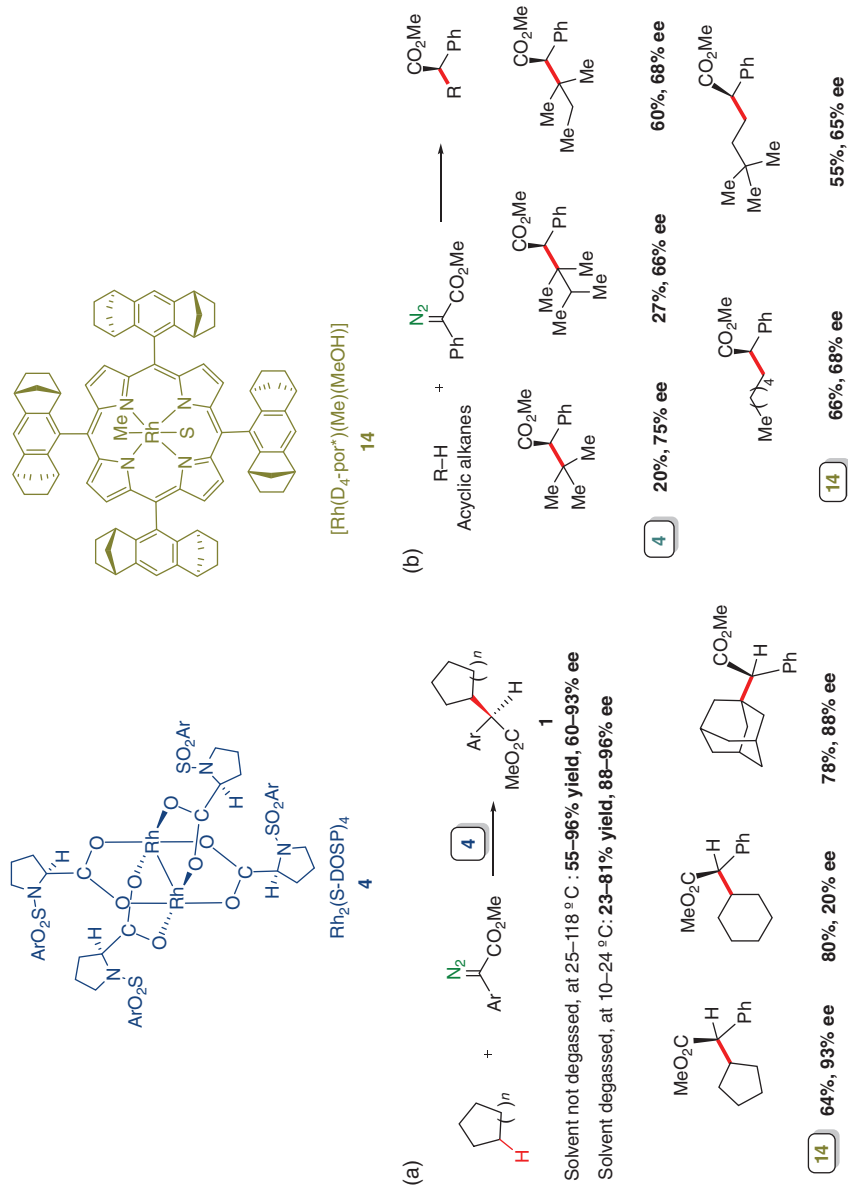
n.r., no reaction observed; n.d., not detected.

Table 1.3 Functionalization of 2,3-dimethylbutane.

Catalyst		R ¹	R ²	Yield (%)	Selectivity		References
					C1	C3	
<i>Rh</i> ₂ (<i>OOCCH</i> ₃) ₄	37	H	CO ₂ Et	n.r.	1	114	[8]
<i>Rh</i> ₂ (<i>OOCF</i> ₃) ₄	3	H	CO ₂ Et	n.r.	1	44	[8]
<i>Rh</i> ₂ (<i>OOC</i> <i>TC</i>) ₄	26	H	CO ₂ Et	n.r.	1	12	[8]
<i>Rh</i> ₂ (<i>S-DOSP</i>) ₄	4	Ar	CO ₂ Et	27	n.d.	1	[9]
<i>Rh</i> (<i>ttppp</i>)(<i>Me</i>)(<i>MeOH</i>)	14	Ph	CO ₂ Me	48	1	1.3	[16]
<i>Tp</i> ^{Br3} <i>Cu</i> (<i>NCMe</i>)	6	H	CO ₂ Et	56	n.d.	1	[11]
<i>Tp</i> ^{F21} <i>Cu</i> (<i>OCMe</i> ₂)	12	H	CO ₂ Et	16	1	15	[15]
[<i>IPrCu</i> (<i>NCMe</i>)] <i>BF</i> ₄	9	H	CO ₂ Et	48	1	40	[13]
(<i>TPN</i>) <i>Cu</i> (<i>THF</i>) <i>BAR'</i> ₄	17	H	CO ₂ Et	69	n.d.	1	[19]
<i>Tp</i> ^{(CF3)2Br} <i>Ag</i> (<i>thf</i>)	18	H	CO ₂ Et	66	1	1.5	[20]
<i>Tp</i> ^{F21} <i>Ag</i> (<i>OCMe</i> ₂)	13	H	CO ₂ Et	96	1	2	[15]
<i>Tp</i> ^{Br3} <i>Ag</i> (<i>thf</i>)	25	H	CO ₂ Et	98	1	2	[32]
<i>Tp</i> ^{(CF3)2} <i>Ag</i> (<i>thf</i>)	8	H	CO ₂ Et	85	1	1.5	[12]
<i>Ag</i> (3,5-(<i>CF</i> ₃) ₂ <i>PyrPy</i>)	34	H	CO ₂ Et	30	1	29	[34]
[<i>IPrAu</i> (<i>NCMe</i>)] <i>BAR'</i> ₄	10	H	CO ₂ Et	90	1	1.2	[13]
[<i>Au</i> ₂ <i>Cu</i> ₂ (<i>C</i> ₆ <i>F</i> ₅) ₄ (<i>NCMe</i>) ₂] _n	36	H	CO ₂ Et	88	1	94	[36]

functionalization of alkanes by carbene insertion has undergone an outstanding development in the last two decades. Seminal work [9] using *Rh*₂(*S-DOSP*)₄ (**4**) with cycloalkanes and a series of donor–acceptor aryldiazoacetates provided good yields and high levels of asymmetric induction (60–93% ee, Scheme 1.6a), which varied when the reaction conditions were modified using degassed cycloalkanes as solvents at lower temperatures (88–96% ee, Scheme 1.6a). Also, acyclic alkanes were used, such as isobutane, 2,3-dimethylbutane, and 2-methylbutane. In this case, insertion in tertiary sites was favored, forming the corresponding products with variable yields and good to high enantioselectivities (Scheme 1.6b).

The rhodium–porphyrin complex **14** was later reported for the same transformation employing *N*₂*C*(Ph)*CO*₂Me as the carbene source [8]. The use of cyclopentane, cyclohexane, and adamantane provided the corresponding products in good yields (64–80%) and with high enantioselectivities (88–93% ee) (Scheme 1.6a). This catalyst promoted a preferential selectivity toward the primary C—H bonds using *n*-hexane



Scheme 1.6 First examples of asymmetric functionalization of alkanes by carbene insertion.

and 2,2-dimethylbutane, with moderate enantioselection (65–68% ee, Scheme 1.6c). A significant feature of **14** is its ability to be recycled up to five times, without significant change in selectivity and enantioselectivity values.

Novel chiral dirhodium catalysts **29** with excellent regio-, diastereo-, and enantioselectivities have been disclosed in the last decade. Their capabilities are maximized with the use of trihaloethyl aryldiazoacetates as the carbene precursor, giving rise to much cleaner outcomes, due to the suppression of adverse reactions. It has been also proposed that this trihaloethyl group provides a slight increase in the electrophilicity of metallocarbene intermediate. In chronological order, the first member of the series was $\text{Rh}_2[\text{R}-3,5\text{-di}(\text{p-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$ (**29a**, Scheme 1.7) [37], which promoted the preferential functionalization of secondary C—H bonds, with high values of diastereo and enantiomeric ratios.

Turning this selectivity into tertiary C—H bonds of alkanes was achieved with the catalyst $\text{Rh}_2(\text{TCPTAD})_4$ (**29b**, Scheme 1.7) [38], with lower steric demand. The corresponding products were obtained with good yields and high stereoselectivity, in both the regio- and the enantio- cases. And the remaining and more challenging primary sites were reached using the complex $\text{Rh}_2[\text{R-tris}(\text{p-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$ (**29c**, Scheme 1.7) [39], which contains largely bulkier substituents to reduce the catalytic pocket and thus preventing the functionalization of both tertiary and secondary sites. The preferential functionalization of primary C—H bonds was thus reached with an excellent degree of asymmetric induction (Scheme 1.7).

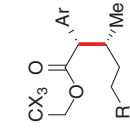
Further advancement for the controlled C—H bond functionalization was accomplished in the case of a variety of mono- and disubstituted cyclohexanes [40], using catalyst $\text{Rh}_2(\text{S-TPPTTL})_4$ (**29d**, Scheme 1.8). A collection of mono-substituted cyclohexanes were synthesized, predominantly functionalized in the equatorial position C3, with good yields (41–89%), as well as regio- (9.9 : 1–50 : 1 rr), diastereo- (3.3 : 1–26 : 1 dr), and enantioselectivities (47–98% ee) (Scheme 1.8).

1.4 Methane and Gaseous Alkanes as Substrates

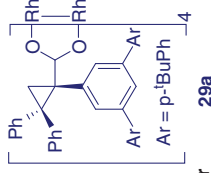
The previous sections 1.2 and 1.3 enumerate catalytic systems for the chemo-, regio-, diastereo-, and enantioselective functionalization of *liquid* alkanes $\text{C}_n\text{H}_{2n+2}$ ($n \geq 5$) upon metal-mediated carbene transfer from a diazo compound onto a carbon–hydrogen bond. The lighter members of the alkane series which are gaseous at room temperature, i.e. those with $n = 1\text{--}4$, were not satisfactorily modified with this methodology until a novel strategy was developed [41]. Such a tactic consists in the use of supercritical carbon dioxide as the reaction medium [42], where those gaseous hydrocarbons are soluble. In this manner, the only C—H bonds available in the reaction mixture are those of the hydrocarbons, which display the highest values of BDE of the series [4]. Because of this, any other solvent containing C—H bonds would be activated before the desired gaseous alkanes.

The mixtures scCO_2 -alkane form a fluid at 40 °C, using at least 80 bar of carbon dioxide, and provide a homogeneous medium where the catalyst and the diazo compound must dissolve. While EDA is completely soluble, only

Secondary C–H bonds

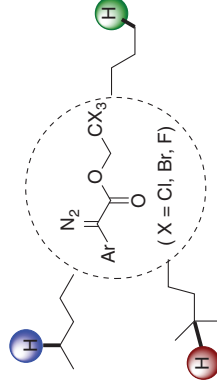


40–99% yield; 90–99% ee
9 : 1–34 : 1 rr; 7 : 1–55 : 1 dr



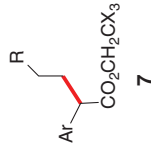
$\text{Rh}_2[\text{R-3,5-di}(\text{p-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$

Tertiary C–H bonds

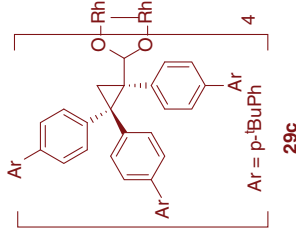


60–94% yields, 77–94% ee
87 : 13 rr

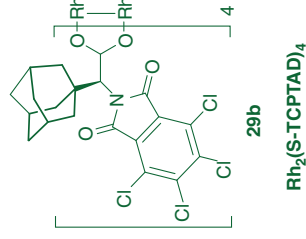
Primary C–H bonds



40–93% yields; 90–99% ee
84 : 16–98 : 2 rr

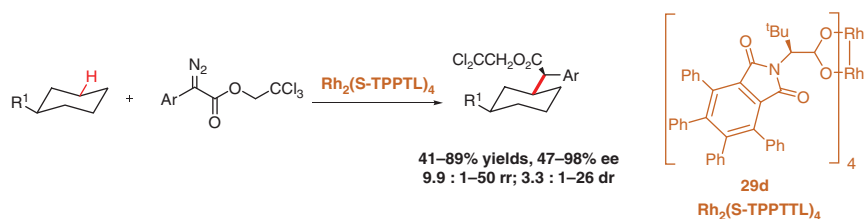


$\text{Rh}_2[\text{R-Tris}(\text{p-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$



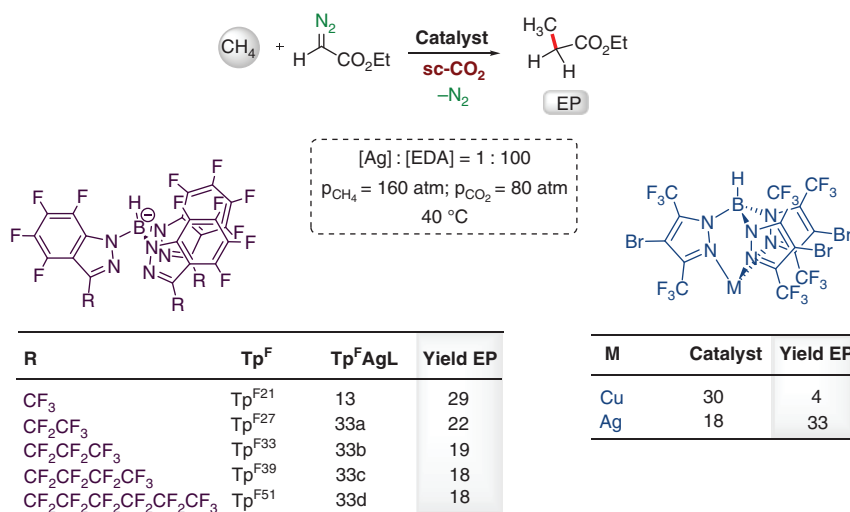
$\text{Rh}_2(\text{S-TCPTAD})_4$

Scheme 1.7 Dirhodium-based catalysts for the control of the reaction site: primary, secondary, and tertiary C–H bond preferential functionalization (regioisomeric ratio, rr; diastereoisomeric ratio, dr).



Scheme 1.8 Functionalization of mono- and disubstituted C–H bonds in cyclohexanes.

fluorine-containing catalysts are soluble in such mixture. Thus, a family of perfluorinated hydrotris(indazolyl)borate ligands (Scheme 1.9) was developed and the corresponding silver complexes synthesized [33], affording the first example of the functionalization of methane by incorporation of the CHCO₂Et unit from EDA: ethyl propionate was obtained in 29% yield, based on initial EDA, using catalyst **13** [41, 43]. Further development led to the synthesis of Tp^{(CF₃)₂,Br}ML (M = Cu, **30**; Ag, **18**) [44], which gave an improved yield of 33% with **18**. Additionally, catalyst **30** gave 4% of ethyl propionate, in the first example of copper for methane functionalization by carbene transfer.



Scheme 1.9 Methane functionalization by carbene insertion using silver-based catalysts.

Ethane, propane, and butane have also been employed as the substrates, with the above silver complexes bearing indazolyl- or pyrazolylborate ligands as well as the trinuclear silver complex **34** [34], containing pyrazolyl bridges between the metal ions. Scheme 1.10 displays the comparison between three catalysts, observing moderate to high yields (EDA-based) in most cases. The presence of two different C–H bonds in propane and butane leads to the formation of mixtures of two products, the values of regioselectivities being similar for **18** and **33a**, and significantly different for

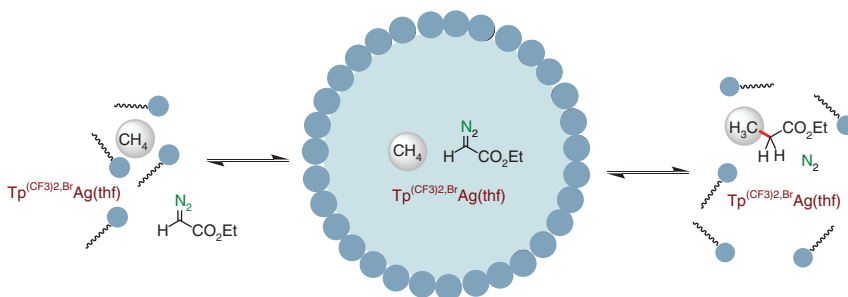
Alkane	Products	Yield (%)		
		33a	18	34
Ethane		84%	99%	17%
Propane		95% (1 : 3.6)	75% (1 : 3.8)	37.5% (1 : 14.5)
Butane		95% (1 : 2.1)	99% (1 : 1.9)	66% (1 : 10.1)

Regioselectivity (1^{ry} : 2^{ry})

Scheme 1.10 Alkane C2–C4 functionalization by carbene insertion using silver-based catalysts.

the trinuclear complex **34**. It is worth mentioning that the latter catalyst is employed under homogeneous conditions, using an organic solvent along with a high pressure of the alkane, whereas the former **18** and **33a** were tested under the abovementioned conditions employing scCO_2 as the reaction medium.

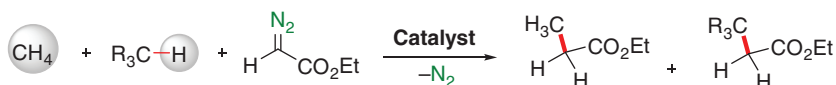
To complete this section, a unique example of the catalytic functionalization of methane and gaseous alkanes at room temperature in water deserves some comment. Catalyst **18** was employed in the reaction of EDA and methane using water as the solvent and in the presence of surfactants capable of generating micelles (Scheme 1.11) [45]. In the absence of such additives, no reaction took place, whereas when added above their critical micellar concentration, significant amounts of ethyl propionate were formed, reaching 14% yield when PFOS (perfluorooctane sulfonate) was employed. The formation of micelles constitutes the critical point in this tactic since methane accumulates in the inner volume of such aggregates, reaching 2 M values, nearly 4 orders of magnitude higher than the solubility of methane in water (c. 10^{-2} M). The other gaseous alkanes were also functionalized under the same conditions. Interestingly, the regioselectivity found in this micellar system was identical to that in the scCO_2 reaction medium. Such similarity is interpreted as due to a null effect of the micelle in the catalytic reaction, serving exclusively as a reaction vessel concentrating all the reactants.



Scheme 1.11 The room temperature functionalization of methane in water surfactant as reaction medium. Source: Based on Gava et al. [45].

1.5 Alkane Nucleophilicity Scale

The development of catalysts capable of transferring a carbene onto the C—H bond of methane provided an opportunity to carry out competition experiments between different alkanes and evaluate the relative reactivity of the distinct reaction sites. Thus, a complete study with 14 alkanes and cycloalkanes and 29 carbon–hydrogen bonds was performed [20], providing the first large set of intermolecular comparative reactivity using methane as the reference. The procedure consisted of experiments using exactly measured amounts of two alkanes and in a careful analysis of the final reaction mixture (Scheme 1.12).

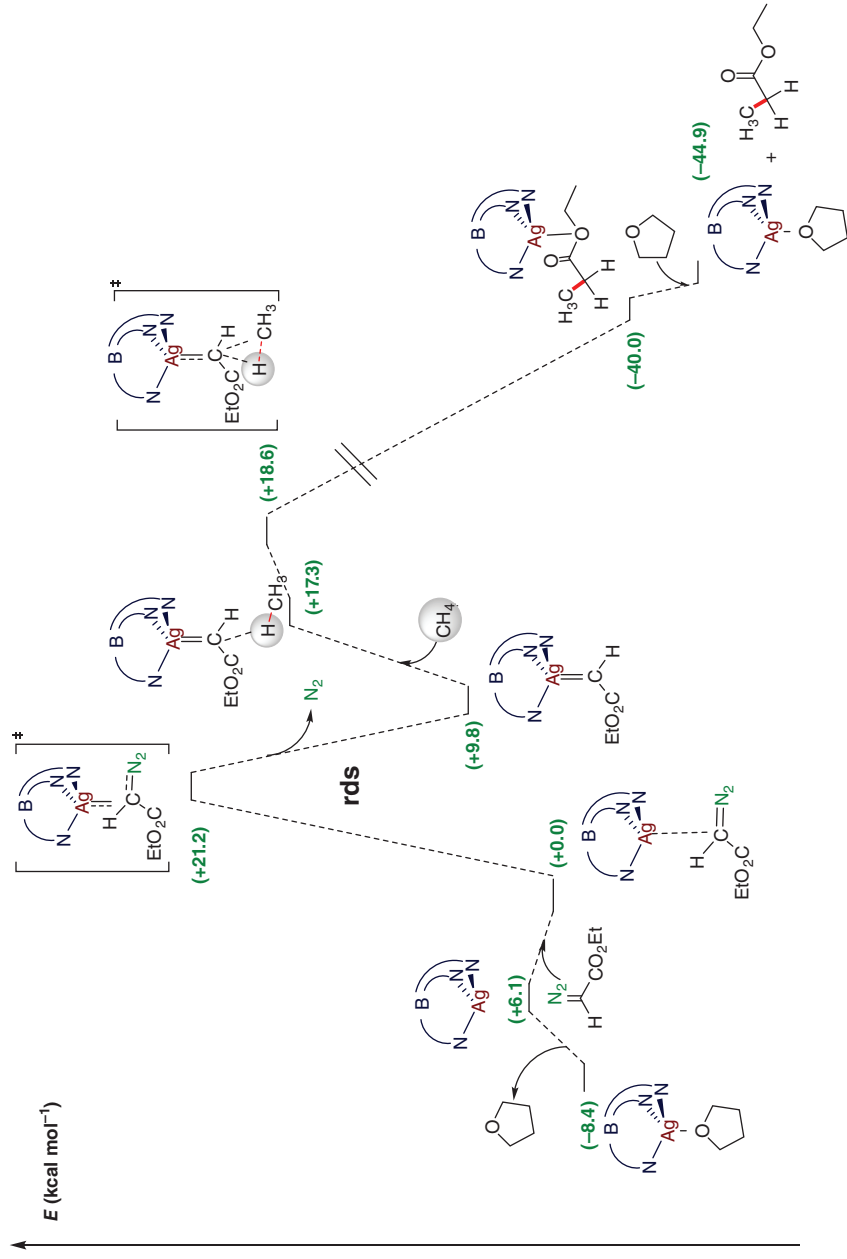


Scheme 1.12 Alkane competition experiments.

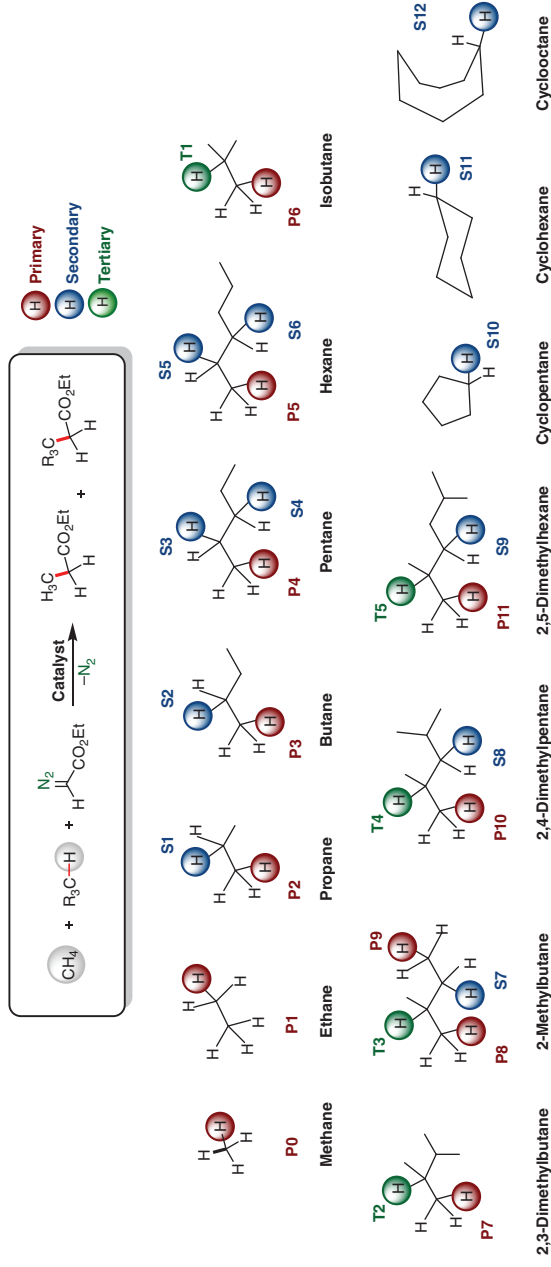
Scheme 1.13 displays the reaction profile. The rate determining step in this transformation is the formation of the metallocarbene, the barrier for the interaction of the latter with the C—H bond being lower in energy. Therefore, the rate determining step is not that where selectivity is decided. In addition, the product is formed in one final step which is irreversible. Because of this, the ratio of products derived from the functionalization of each bond can be connected to the difference in activation energies of such bonds.

The array of alkanes employed are displayed in Scheme 1.14, along with a plot of the values of the relative reactivity referred to methane, in log scale. It is noteworthy the observance that the usually claimed order of reactivity $1^\circ\text{r} < 2^\circ\text{r} < 3^\circ\text{r}$ C—H bonds is not followed in a general manner. This is a consequence of the origin of such trend, developed by Olah using small electrophiles (H^+ , NO_2^+ , etc.) [46], at variance with the bulkier organometallic metallocarbene complexes acting as electrophiles in this case.

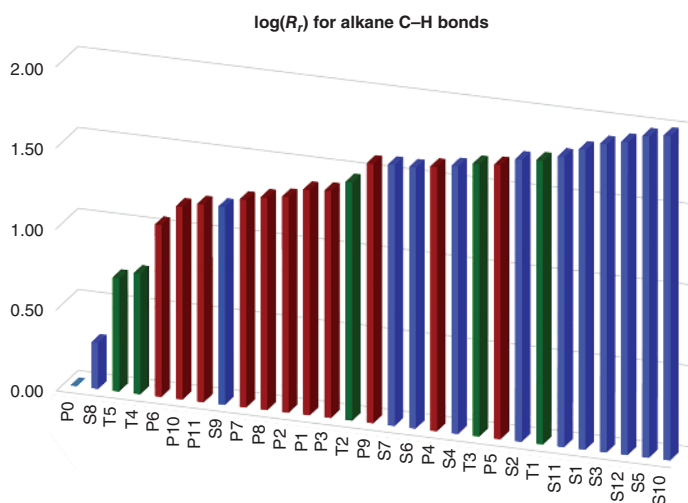
Further work with this experimental data allowed proposing a model for the quantitative prediction of such values employing a set of topological descriptors of the carbon–hydrogen bond being functionalized [47]. After a statistical treatment of experimental data, the new method, named as Q-DEAN (Quantitative DEscriptor-based Alkane Nucleophilicity), contains an equation with six descriptors, from which the observed experimental reactivity can be obtained. When the model is applied, a very good fitting between predicted and experimental data is found. Scheme 1.15 shows the general equation, the definition of the six descriptors, and a radial plot where the quality of the fitting is clearly visible.



Scheme 1.13 DFT calculations for the functionalization of methane with EDA using catalyst **33a**. Source: Based on Olmos et al. [20].

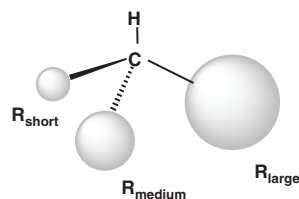


Scheme 1.14 Competition experiments carried out with the alkanes shown. The plot at the bottom shows the variation of $\log(R_i)$.

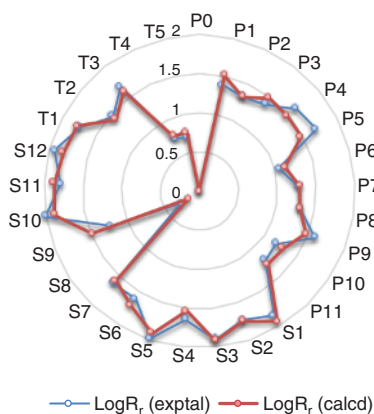


Scheme 1.14 (Continued)

$$\log(R_r) = A + c_{\text{type}} D_{\text{Ctype}} + \sum (c_{Ri} \times D_{Ri}) + c_{\beta} D_{\beta} + c_{st} D_{st}$$



Descriptors			
D_{Ctype}	Degree of substitution (1, 2 or 3)	D_{Rmedium}	Number of carbons in R_{medium}
D_{Rshort}	Number of carbons in R_{short}	D_{Rlarge}	Number of carbons in R_{large}
D_{st}	The steric factor (1 or 0)	D_{β}	Number of Me groups in C_{β}



Scheme 1.15 The Q-DEAN model, showing the good approach of the calculated data to the experimental values of relative reactivities (methane as reference; log values).

1.6 Conclusions and Outlook

In nearly two decades, the modification of unreactive alkanes upon carbene insertion into their carbon–hydrogen bonds has moved from nearly non-existent, far from utility examples to an array of catalytic systems exerting a high control in the selectivity. Very active catalysts induce very high yields, based on the diazo reagent, whereas a set of carefully designed metal complexes allows the selective functionalization of the distinct reaction sites, particularly in linear or branched alkanes. However, there are yet several drawbacks to surpass. Among them, the use of base metals, non-expensive and widely available, is not frequent, with the exception of copper. Expansion to other first row elements as well as improvement with copper-based catalysts should be developed. A second target would consist in the use of diazo reagents with a low degree of elaboration, therefore making the transformation of interest for a potential use. Finally, the development of strategies in which the catalyst is readily removed and, preferentially, reused, is nearly unknown in this particular area and should be also targeted in the next future.

Acknowledgments

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