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Review

Coinage Metal Catalyzed C#H Bond Functionalization of Hydrocarbons

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Coinage Metal Catalyzed C−H Bond Functionalization of Hydrocarbons

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Contents

1. Introduction

The usually employed term of Holy Grail in the search of efficient methods that convert readily available sources such as hydrocarbons into value added products is yet completely appropriate when we approach to the end of the first decade of this century.[1,2] In spite of decades of efforts of a plethora of research groups, only a reduced number of chemical systems have been described for the transformation of such substrates in a catalytic manner. This is in contrast with the large number of reports on the activation of carbon−hydrogen bonds through the intermediacy of transition metal complexes.[3–5] The term activation is usually applied in the sense defined by Shilov and Shul'pin:[4] "when we refer to the activation of a molecule, we mean that the reactivity of this molecule increases due to some action. (. . .) The main result of the activation of a C−H bond is the replacement of a strong C−H bond with a weaker, more readily functionalized bond." Given the large number of examples of the former relative to the already mentioned few examples of catalytic transformations, it seems that the latter is not always accessible.

There are several routes that could account for a metal-induced carbon−hydrogen bond activation process, under homogeneous conditions. Such mechanisms are shown in Figure 1.[1,6] The typical example of an organometallic activation is that
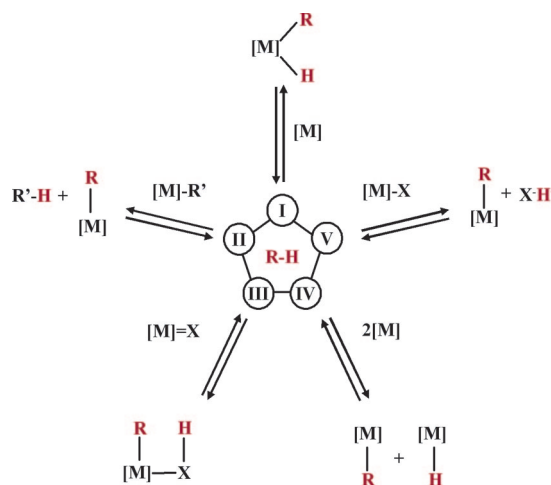

Figure 1. Mechanisms for the metal-mediated activation of carbon−hydrogen bonds: (I) Oxidative addition/reductive elimination; (II) sigma-bond metathesis; (III) 1,2-insertion−elimination; (IV) homolytic cleavage by two metals and (V) electrophilic activation.

based in the oxidative addition−reductive elimination of the C−H bond (I), in which the C−H bond is added to the metal center to generate two new metal−carbon and metal−hydride bonds. The sigma-bond metathesis route (II) would also provide the activation of the C−H bond, as well as the subsequent release of the functionalized product. The formal insertion of the C−H bond into unsaturated metal−ligand bonds (III) would afford the corresponding cleavage. Such cleavage, in a homolytic fashion (IV), can also be achieved with the intermediacy of two metal centers, leading to separate metal−alkyl and metal−hydride complexes. Finally, the electrophilic activation (V) supposes the displacement of the hydrogen atom by another group (X = halide, aquo), the R group usually being subsequently displaced from the metal center as a functionalized molecule. These pathways participate, to a different extent, in the few catalytic systems described to date for the activation and subsequent functionalization of C−H bonds of unreactive hydrocarbons. The alkane borylation[7] described by Hartwig and co-workers is mainly based in mechanism I. The alkane dehydrogenation process,[8] first reported by Kaska and Jensen,[8a] is also related to the same mechanism. Sigma-bond metathesis is usually employed with unsaturated reagents, from an efficient, catalytic point of view. The electrophilic activation, typical of late transition metals, was discovered by Shilov in the early 1970s, and is one of the most promising systems, yet to be improved.[2] This is in contrast with procedures described for the conversion of C−H bonds into several functionalities in complex, more elaborate molecules,[9] where the existence of activating groups, that weakens the targeted C−H bond and/or favors the reaction by assisted coordination, enhances the reactivity.

M. Mar Díaz-Requejo (1971) graduated in Chemistry at the Universidad de Sevilla (1994) and obtained her PhD from the Universidad de Huelva in 2000 with Prof. Pedro J. Pérez. She joined Prof. Brookhart's group at the University of North Carolina, Chapel Hill (USA) for a postdoctoral stay in 2001−2003. That year she was enrolled in the "Ramón y Cajal" Program in Spain, until 2006 when she was appointed for a junior lectureship in inorganic chemistry, a position currently effective at the Universidad de Huelva. Her current research work is related to the development of group 11 metal-based catalysts for the functionalization of C−H bonds by carbene and nitrene transfer reactions.

Pedro J. Pérez (1965) graduated in Chemistry in 1987 in Sevilla. He received his Ph.D. degree in Chemistry (1991) in the Universidad de Sevilla, under the direction of Prof. Ernesto Carmona. As a Fulbright Scholar, he then joined Prof. Brookhart's group at UNC−Chapel Hill where he started the research related to the use of copper-based catalysts for diazo decomposition. In 1993 he moved to a new University founded in Huelva, as an Assistant Professor (1993−1995), later becoming Lecturer (1995) and finally Professor of Inorganic Chemistry (2005). The general research interest of his group is related to the development of late transition metal complexes for their use as catalysts in transformations with low reactive substrates. He is also responsible of the Homogeneous Catalysis Laboratory, an Associate Unit to the Spanish National Council of Research (CSIC) (http://www.catalysisatuhu.com).

There are two main problems for the conversion of a low reactive C−H bond into a functionalized group. The first one is the usually high C−H bond dissociation energies (BDE), that strongly affect the reactivity. Figure 2 displays the BDE values for an array of carbon−hydrogen bonds.[10–12] The highest values correspond to methane and benzene, with 105 and 113 kcal/mol, respectively. The BDE for ethane also appears above the 100 kcal/mol barrier (101 kcal/mol). This is in contrast with other primary carbon−hydrogen bonds, such as those of toluene (benzylic C−H position) or propene (allylic C−H position), for which 90 and 88 kcal/mol bond energies have been reported, respectively. Secondary sites of plain alkanes are 3 kcal/mol lower than ethane (98 kcal/mol for propane and butane) whereas the tertiary C−H bond
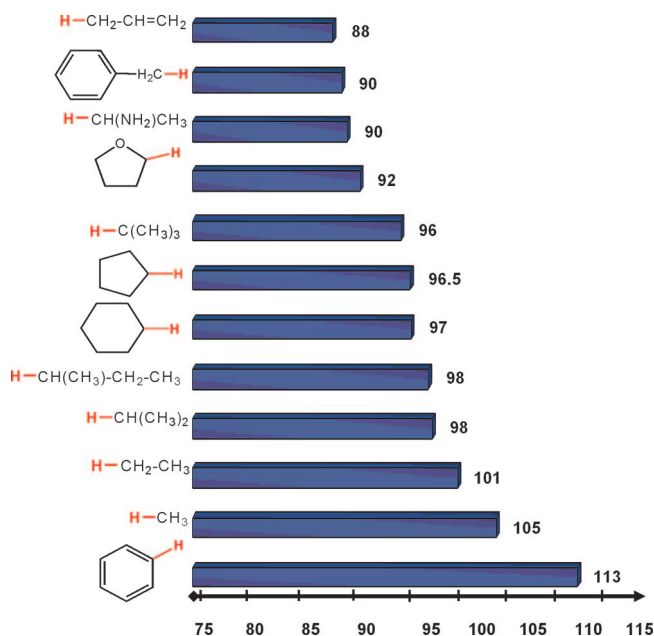

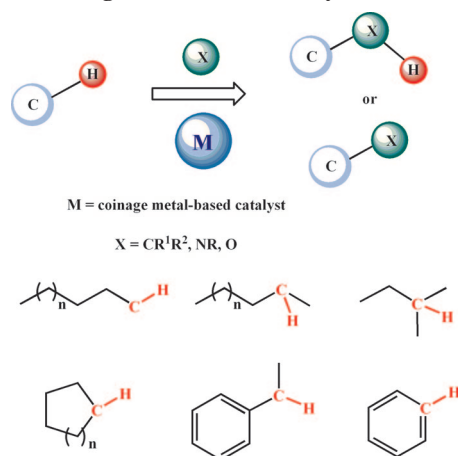**Figure 2.** Bond dissociation energies (BDE) of several types of carbon−hydrogen bonds.

of 2-methylpropane displays a BDE of 96 kcal/mol. Such a value is slightly lower than the dissociation energy for a C−H bond of cyclohexane (97 kcal/mol), and very similar to that of cyclopentane (96.5 kcal/mol). Finally, it is worth mentioning the BDE values for the α−C-H bond in ether or amines. As representative examples, such a bond in tetrahydrofuran displays a dissociation energy of 92 kcal/mol, whereas in the case of ethylamine, such energy is of 90 kcal/mol. It has been proposed that the presence of a vicinal O- or N-atom to a C−H bond diminishes its BDE in ca. 4 kcal/mol compared with their homologues in a saturated hydrocarbon.[12c]

As mentioned above, and in spite of those BDE values, a considerable number of metal-based systems have been reported to activate C−H bonds. However, a second problem may arise immediately after the activation takes place: the complex formed upon activation can be too stable to react further, and therefore the neat functionalization of the initial substrate is blocked. Alternatively, when the fragments derived from the C−H activation react with other reagent, the subsequent functionalized fragments may or may not be removed, only in the first case the desired functionalization being achieved. The explanation for the lack of a larger number effective catalytic systems based in the mechanisms shown in Figure 1 is that the M−R linkages are, very often, quite stable, and its removal of the coordination sphere is difficult to induce.[5]

2. Scope

In this contribution the current state of the art of the use of copper-, silver- and gold-based catalysts for the catalytic conversion of unreactive hydrocarbons into more elaborate, functionalized molecules is presented. We will focus exclusively on those reactions where a saturated carbon−hydrogen bond of the hydrocarbon is converted into another functionality in a process induced by the coinage metal catalyst. In most cases (Scheme 1), the overall transformation consists of the insertion of an X group into the C−H bond; a second, less frequent reaction supposes the loss of hydrogen in the final product, and the formation of an unsaturated bond C≡X. On the basis of their low reactivity as well as wide availability, we will refer only to C−H bonds of those hydrocarbons with sp³ (or sp²)

Scheme 1. Catalytic Functionalization of Carbon Hydrogen Bonds with Coinage Metal-Based Catalysts

M = coinage metal-based catalyst

X = CR^{1}R^2, NR, O

Scheme 2. Metal-Catalyzed Carbene Transfer from Diazo Compounds

Scheme 3. Metal-Catalyzed Functionalization of C—H Bonds by Carbene Insertion from Diazo Compounds

C—H bonds, excluding those with activating groups (heteroatoms or unsaturated bonds): alkanes (linear or branched, primary, secondary and tertiary sites), cycloalkanes and alkylaromatics (also primary, secondary and tertiary C—H bonds) will be considered herein (Scheme 1). The direct conversion of the sp^2 C—H bond of benzene or alkyl aromatics will also be included, given its high BDE.

An interesting common feature of the coinage metal-based catalytic systems included in the following sections is that the mechanisms shown in Figure 1 are not invoked to explain the conversion of the starting hydrocarbon into the functionalized molecule; no M—C and/or M—H bonds are formed by any activation process. This is probably the key of the relative success already obtained with these metals. Therefore, we avoid the use of the term activation to indicate that those classical mechanisms in Figure 1 are not involved in these coinage metal-mediated functionalization processes.
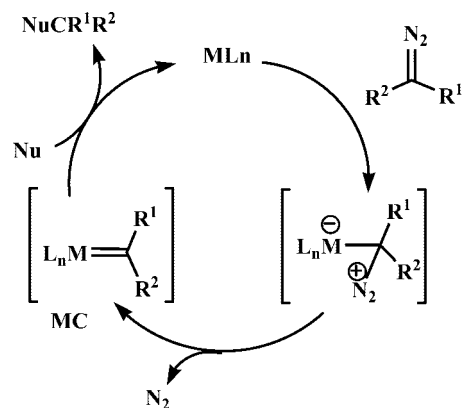
This contribution comprises those catalytic systems based on the coinage metals that suppose the functionalization of carbon—hydrogen bonds of nonactivated substrates or, at least, with no strong activating groups, of the type described above. Most of those catalytic systems can be classified into three types: functionalization by carbene insertion (from diazo compounds), functionalization by nitrene insertion (from iminoiodonanes or chloramine-T) and direct oxidation with a strong oxidant (hydrogen peroxide and others). These three groups are presented in the following sections in a similar manner: first, the functionalization reaction is described to continue with the nature of the different catalysts and reagents reported for such reaction. The achievements obtained, mechanistic information and some indications about the future goals complete each section.

3. C—H Bond Functionalization by Carbene Insertion from Diazo Compounds

3.1. The Reaction

The decomposition of diazo compounds by transition metal complexes and the subsequent transfer of the carbene moiety from the metal center to different saturated and unsaturated fragments have been known for decades.[13,14] The interaction of a diazo compound with a transition metal usually generates a transient metallocarbene, electrophilic in nature, that immediately reacts with surrounding nucleophiles in reaction mixture (Scheme 2). These metallocarbene species
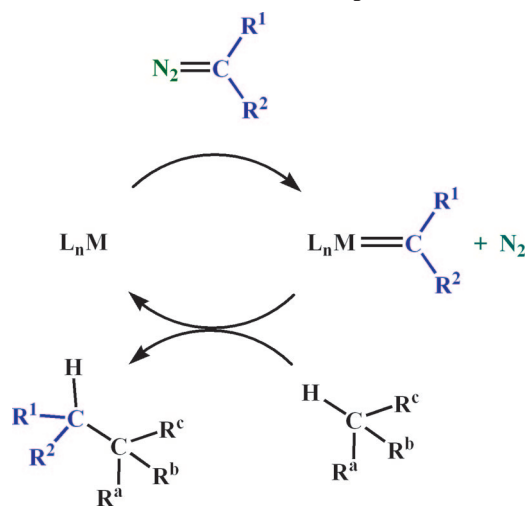
(**MC**) have scarcely been detected and/or isolated. In the case of the coinage metals, only with copper, and in two cases, it has been possible to detect such carbenoids.[15] The lack of a large number of these species detected is due to their high reactivity. Once formed, they react with available nucleophiles, to release the modified substrate as well as the active catalyst. The latter can readily react with another molecule of diazo compound, to reinitiate the catalytic cycle.

Many examples with different nucleophiles have been reported for this methodology.[13] Alkenes and alkynes can be converted into cyclopropanes and cyclopropenes, in an addition reaction. On the other hand, the insertion reaction has been reported for O—H and N—H bonds as well as for C—H bonds.[16] The latter corresponds to a homologation reaction, in which the functional groups in the starting diazo compounds are incorporated to the initial substrate, in a potentially useful transformation (Scheme 3).

3.2. The Catalysts and the Carbene Source

The first examples of a carbon—hydrogen bond modified by this methodology were based in copper sulfate and Cu(acac)$_2$ in the 1970s.[17,18] Shortly thereafter, the Belgian group of Theyssie, Noels, Demonceau and co-workers discovered the potential of rhodium acetate and related complexes of formulas Rh$_2$(L)$_4$ (L = bidentate ligand) as catalysts for diazo compound decomposition and subsequent transfer of the carbene group to an array of substrates.[19] After

Scheme 4. Reported Copper− and Silver−Trispyrazolylborate and Copper-Trispyrazolylmethane Complexes As Catalysts for the Functionalization of C−H Bonds by Carbene Insertion
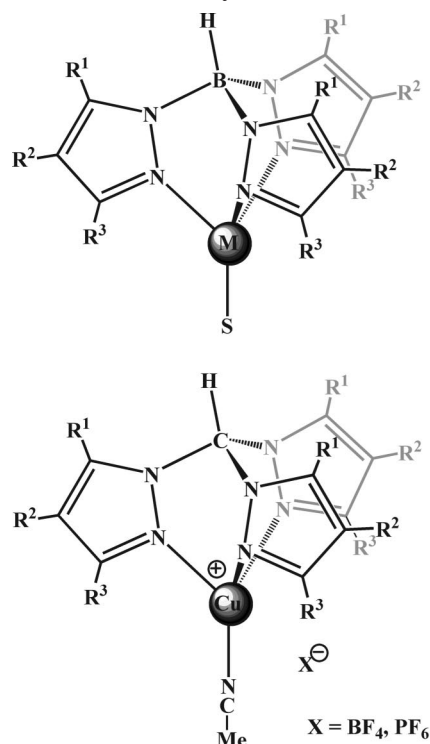
M	S	Tp^x	R^1	R^2	R^3	Ref[a]
Cu	---	Tp^{Ms}	H	H	Mes	23
Cu	CH_3CN	Tp^{Br3}	Br	Br	Br	24
Ag	Acetone/thf	Tp^{Br3}	Br	Br	Br	25
Cu	thf	$Tp^{(CF3)2}$	CF_3	H	CF_3	26
Ag	thf	$Tp^{(CF3)2}$	CF_3	H	CF_3	27

Tpm^x	R^1	R^2	R^3	Ref[a]
Tpm^*	Me	H	Me	28
Tpm^{Mes}	H	H	Mes	29

[a] Reporting the synthesis of the complexes

$X = BF_4, PF_6$

this seminal work, most of the advances in this field has been governed by the use of these rhodium-based catalysts, for a plethora of reactions and substrates, in both inter- and intramolecular fashions. The functionalization of C−H bonds has also been reported with those catalysts, including the asymmetric version.[13,14,20]

At the beginning of this decade, our group described the use of a copper-based catalyst,[21] containing a trispyrazolylborate ligand,[22] for the functionalization of cycloalkanes in moderate yield. This work served as a renaissance of this metal as catalyst for such transformation. Subsequent work from our laboratories and by Dias and Lovely have shown (see next section) that copper- and silver-containing trispyrazolylborate ligands display catalytic selectivity comparable, at least, with the above rhodium catalysts. Given the large number of trispyrazolylborate ligands reported, the number of potential Tp^xCu and Tp^xAg complexes as candidates for catalysts is obviously large. However, the best catalysts reported by those groups have a common feature: the metal center is bonded to a low-donating Tp^x ligand, therefore electron density at the metal center is decreased, i.e., its electrophilia is increased.[20] Scheme 4 shows the geometries of the complexes employed as catalysts with the ligands Tp^{Br3} (hydrotris(3,4,5-tribromo)pyrazolylborate) and $Tp^{(CF3)2}$ (hydrotris(3,5-bis(trifluoromethyl) pyrazolylborate)). Copper complexes containing the related trispyrazolylmethane ligands Tpm^x (Scheme 4) have also been found to promote the functionalization of C−H bonds by this methodology. These ligands are similar to the above Tp^x, but their neutral nature makes the copper complex cationic, a feature of importance in their catalytic activity, that will be discussed below.

After the results obtained with these complexes, another family of catalysts has been reported to induce the same transformation. In contrast with the above three donor Tp^x ligands, this new group of catalysts contains just one carbon donor from an N-heterocyclic carbene (NHC) ligand.[30] The

Scheme 5. N-Heterocyclic Carbene (NHC) Complexes of Copper and Gold Described for the Functionalization of C−H Bonds by Carbene Insertion

in situ generated catalysts   isolated, well-defined catalysts

$X = BAr'_4, PF_6, BF_4, OTf$

| NHC | IPr | IMes | IAd | I^tBu |
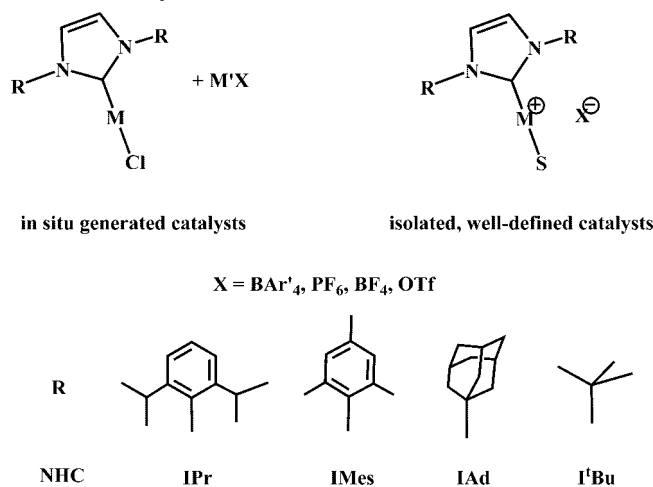
catalyst precursors were those of general formulas (NHC)-MCl,[31] with M = Cu or Au, although the presence of halide scavengers in the reaction mixture is required to promote the catalytic process. Several NHC ligands have been employed with different substituents at the N-atoms. Cationic complexes of formula [(NHC)M(S)]X derived from halide extrusion have also been used as well-defined catalysts (Scheme 5).[32,33]

Very recently, a copper(I) complex containing a β-diketiminate has been found to display catalytic capabilities similar to the previous coinage metal-based catalysts regarding the insertion of carbene groups into C−H bonds.[34] This complex was previously prepared[35] by the direct reaction of the protonated ligand with mesitylcopper(I), leading to an equilibrium between monomeric and dimeric structures (Scheme 6).

Although a number of diazo compounds are known,[13,14,20] in practice very few are employed in this type of transforma-

Scheme 6. Preparation of the Cu(β-diketiminate) Complex
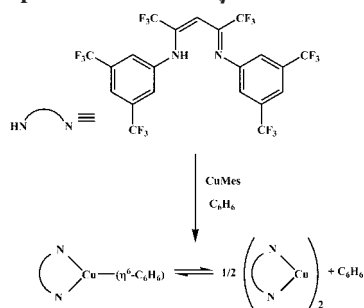
**Scheme 7. Different Diazo Compounds and Ethyl Diazoacetate (EDA)**[a]
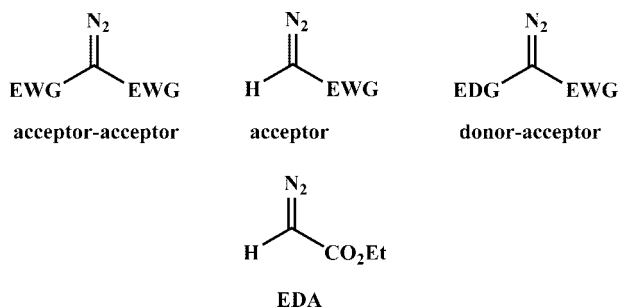
[a] EWG = electron withdrawing group; EDG = electron donating group.

tion, in spite of the importance of the nature of such a reactant. Substantial both steric and electronic effects may arise from the appropriate election of the diazo compound, since those features depend on the substituents in the diazo-containing carbon atom. From an electronic point of view, there are three types of diazo compounds, namely, acceptor, acceptor−acceptor and acceptor−donor (Scheme 7). The latter has been extensively employed by Davies and co-workers,[20] providing very interesting and leading results to the field, using rhodium-based catalysts. But in the case of the already described systems based on the coinage metals for C−H bond functionalization, only one diazo compound has been employed to date. It corresponds to ethyl diazoacetate (EDA, Scheme 7), a readily available, commercial diazo compound that also finds industrial applications, and that only contains a formally acceptor carboxylate group.
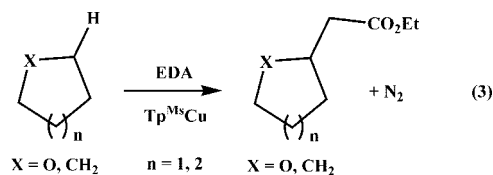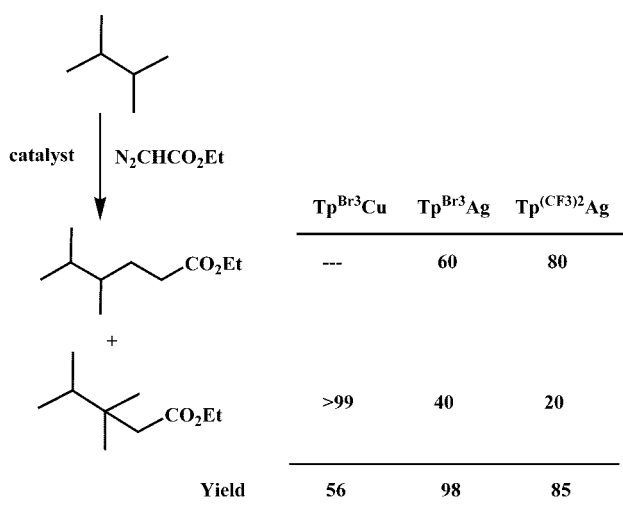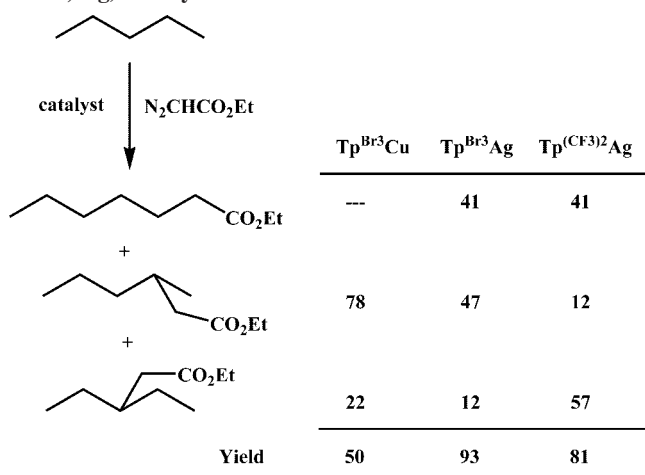
3.3. Achievements

As mentioned above, the first examples of the catalytic intermolecular functionalization by carbene insertion using diazo compounds as the carbene source were based on copper. In the mid-1970s, DeCicco and Scott[17] described the use of copper sulfate as catalyst for the decomposition of ethyl diazoacetate (EDA) and the subsequent insertion of the :CHCO₂Et group into the C−H bond of cyclohexane (eq 1). Further work by Wullfman and co-workers[18] showed that Cu(acac)₂ promoted the functionalization of the allylic C−H bond of cyclohexene, as a side reaction in the cyclopropa-nation of this cyclic olefin with diethyl diazomalonate (eq 2). Although the yields were low in both cases, these results supposed the opening of this area of research. Later Noels and co-workers[19] described the catalytic capabilities of complexes of formula Rh₂(O₂CR)₄ to induce carbene transfer reactions from diazo compounds, mainly EDA, to several saturated and unsaturated substrates. Among them, linear or branched alkanes could be functionalized by this methodology, with moderate yield. In spite of this rather effective

manner to modify unreactive C−H bonds of plain hydrocarbons, very few reports appeared in the literature since those results of the early 1980s, all them being based on rhodium catalysts.[20]
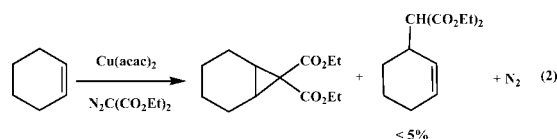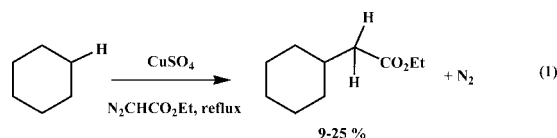
As a part of a research program based on the development of copper-based catalysts for diazo compound decomposition,[36] our group investigated the potential of complexes of the type Tp^{x}Cu (Tp^x = hydrotrispyrazolylborate ligand) to induce the insertion of carbene units into the C−H bonds of hydrocarbons. Such work led to the finding that the complex Tp^{Ms}Cu could promote[21] (eq 3) the functionalization of cycloalkanes (cyclopentane, cyclohexane) in moderate yield (50%) as well as that of cyclic ethers in high yield (>90%). Such differences can be explained in terms of the already mentioned (see Figure 1) values for the bond dissociation energies in both substrates. Interestingly, this catalyst was not as effective with other other alkanes with C−H bonds displaying higher BDEs. In order to improve the catalytic activity, previous work by Noels and co-workers[19] was of significance: they found that electron withdrawing groups in the ligands attached to the rhodium center provided the highest conversions of alkanes into functionalized products. Therefore, our group moved from Tp^{Ms}Cu to Tp^{Br3}Cu(NCMe), a complex in which the Tp^{Br3} ligand contains nine Br atoms. This complex provided[24,37] moderate to high yields into modified alkanes upon insertion of the :CHCO₂Et group, from EDA, into the carbon−hydrogen bonds of several linear or branched hydrocarbons (Scheme 8). After these results, Dias, Lovely and co-workers described[38,39] the use of the Tp$^{(CF3)2}$M(THF) complexes, with M = Cu or Ag, for the related transformation, the use of [Tp^{Br3}Ag]₂·(acetone) being shortly after reported from our laboratory.[25] It is noteworthy that the use of Cu derivatives with Tp^x ligands containing electron withdrawing substituents provided the functionalization of alkanes with BDEs higher than cyclic ethers, although only at secondary and tertiary sites. The silver-based catalysts induced, in addition, the insertion into the primary sites of hydrocarbons such as hexane, 2,3-dimethylbutane or 2-me-thylbutane, among others. The chemoselectivity is also quite high for the silver catalysts: it is worth mentioning that in these reactions EDA can also be converted into diethyl fumarate and maleate, as a side, nondesired reaction. Such transformation is nearly suppressed with [Tp^{Br3}Ag]₂·(acetone) as the catalyst.

Scheme 8. Functionalization of C−H Bonds with Tp^xM (M = Cu, Ag) Catalysts

	Tp^Br3Cu	Tp^Br3Ag	Tp^(CF3)2Ag
(product 1, CO₂Et)	---	41	41
(product 2, CO₂Et)	78	47	12
(product 3, CO₂Et)	22	12	57
Yield	50	93	81

	Tp^Br3Cu	Tp^Br3Ag	Tp^(CF3)2Ag
(product 1, CO₂Et)	---	60	80
(product 2, CO₂Et)	>99	40	20
Yield	56	98	85

The success of Tp^xCu and Tp^xAg complexes as catalysts for this transformation has not yet led to the use of the Tp^xAu analogues. Actually, gold remained undiscovered as a catalyst for diazo compound decomposition until very recently,[40] in contrast with all metals from groups 8 to 11. Also, a very active gold catalyst for the functionalization of C−H bonds has been developed with the aid of N-heterocyclic carbene ligands (NHC).[32] When the complexes (NHC)AuCl are reacted with EDA in the presence of cyclohexane, no reaction takes place, but the addition of 1 equiv (referred to Au) of a halide scavenger induces the conversion of cyclohexane into cyclohexylacetate in high yield. This is a consequence of the need of a coordination vacant around the metal center, a fact that was previously observed with the related (NHC)CuCl complex.[41] Thus, the use of equimolar mixtures of IPrAuCl (see Scheme 5 for IPr) and NaBAr′₄ provides high catalytic conversions in mixtures of different alkanes and ethyl diazoacetate, the preference for the primary sites being higher than in the previously commented Tp^xAg catalysts. But probably the most interesting feature is the ready tuning of this catalytic system, that allows a certain control of the reaction products. Scheme 9 displays the results obtained in the reaction of 2,3-dimethylbutane with EDA, in the presence of (NHC)MCl (M = Cu, Au) + M′X (halide scavenger) as the catalyst. The effect of the metal is outstanding: the primary:tertiary ratio reverses from Cu- to Au-based catalysts (13:87 vs 83:17). The use of different NHC ligands is also noteworthy: using gold complexes, four

different NHC ligands provided distinct regioselectivities just varying the group attached to the N-atoms (Scheme 9, entries 2−5). Finally, the counterion plays an important role in this transformation, particularly in the chemoselectivity. Under the same conditions, with copper catalysts (entries 1, 6−8), PF₆⁻ allows quantitative conversions whereas BAr′₄ only gave 48% yield into functionalization products (diethyl fumarate and maleate as byproduct). In good accord with this, a recent report by Gagosz and co-worker[42] has shown that the complex IPrAuNTf₂ (NTf = N(SO₂CF₃)₂) does not catalyze these transformations, probably as a result of a strong metal−anion interaction.

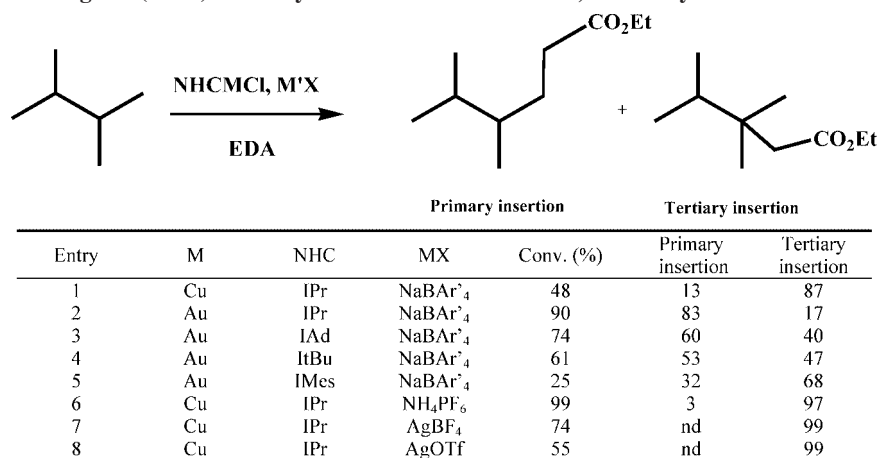The copper−(β-diketinimate) complex shown in Scheme 6 also shows catalytic activity toward this transformation.[34] n-Pentane and n-hexane can be functionalized with EDA in the presence of this complex to give mixtures of products derived of the insertion of the carbene moiety exclusively into secondary sites (eq 4):
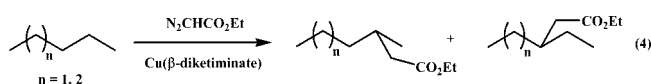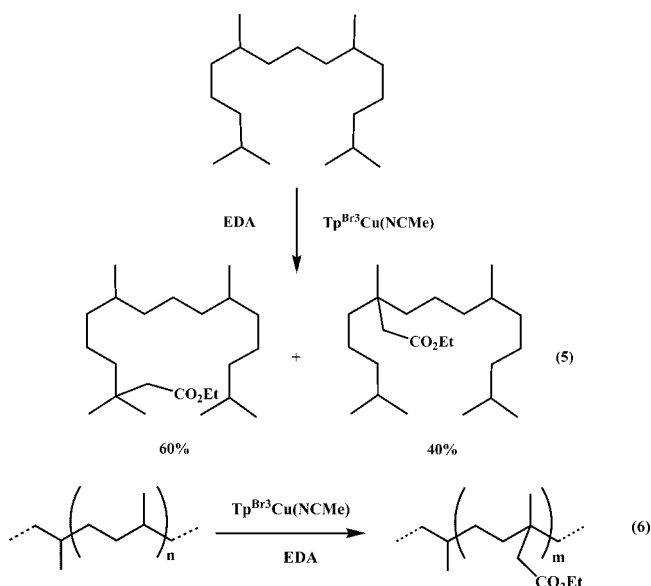

Those previous catalytic systems operate under homogeneous conditions, usually employing the alkane as the solvent. To facilitate catalyst and product separation, the cationic complexes [Tpm^xCu(NCMe)]⁺ (Tpm^x = trispyrazolylmethane ligand, see Scheme 4) have been tested as catalysts for EDA decomposition. First studies demonstrated[43] that the Tpm* derivative catalyzes several addition and insertion reactions of :CHCO₂Et into several substrates using the ionic liquid [bmim]PF₆ as reaction medium. The catalyst can be separated and recycled several times, maintaining a good degree of activity in each cycle. However, this catalyst is not efficient in the functionalization of C−H bonds. Further development of this system has led to the synthesis of new Tpm^x ligands containing mesityl substituents (see Scheme 4), that enhance the catalytic activity of the corresponding copper cationic complexes.[29] Cyclohexane is converted into cyclohexylacetate in 70% yield for five different cycles of recovery and recycling (Scheme 10). Other alkanes can also be functionalized although to a lesser extent.

On the other hand, the methodology of functionalization of unreactive C−H bonds has also been applied to higher hydrocarbons. Pristane (2,6,10,14-tetramethylpentadecane) reacts with EDA in the presence of Tp^Br3Cu(NCMe) as the catalyst,[37] to give a mixture of two products in high yield, that correspond to the insertion into the two distinct, available tertiary sites (eq 5). After these results, higher molecular weight hydrocarbons, i.e., polyolefins such as polybutene or polyethylene-co-octene, have been employed as the target,[44] with the idea of introducing polar groups into the polymers, once synthesized. The reaction of these materials with EDA in the presence of Tp^Br3Cu(NCMe) as catalyst affords modified polymers formed from the insertion of the :CHCO₂Et units into tertiary (polybutene, eq 6) and/or secondary C−H bonds (copolymer). Interestingly, the polymer analysis shows that the PDI (polydispersity, M_w/M_n) values of the starting materials and the functionalized polymers are similar, thus evidencing that chain scission is unlikely during the transformation. This methodology can therefore introduce polar groups into polyolefins in the absence of significant alterations of the polymer structure.

Scheme 9. Variables Affecting the (NHC)M-Catalyzed Functionalization of 2,3-Dimethylbutane

Entry	M	NHC	MX	Conv. (%)	Primary insertion	Tertiary insertion
1	Cu	IPr	NaBAr'$_4$	48	13	87
2	Au	IPr	NaBAr'$_4$	90	83	17
3	Au	IAd	NaBAr'$_4$	74	60	40
4	Au	ItBu	NaBAr'$_4$	61	53	47
5	Au	IMes	NaBAr'$_4$	25	32	68
6	Cu	IPr	NH$_4$PF$_6$	99	3	97
7	Cu	IPr	AgBF$_4$	74	nd	99
8	Cu	IPr	AgOTf	55	nd	99

The use of aromatic substrates has provided very interesting results with the three coinage metals as catalysts. It is well-

(5)

known[14] that the reaction of benzene with EDA in the presence of rhodium catalysts originates a cycloheptatriene derived from the Büchner reaction, in which a norcariene bicycle intermediate, formed by cyclopropanation of a ring double bond, undergoes a spontaneous ring expansion. The complexes Tp^{x}M (M = Cu,[45] Ag)[46] induce the same transformation, in high yield (Scheme 11a). When alkyl groups are attached to the aromatic ring, the silver Tp$^{(CF3)2}$Ag(THF) catalyst is quite selective[46] toward the Büchner reaction, the C−H bonds of the alkyl substituents remaining unreacted. Such behavior is in contrast with that of Tp^{x}Cu, where the election of the Tp^x ligand clearly influences the reaction product. The Tp^{Br3}-based catalyst favors the formation of cycloheptatrienes whereas that with Tp^{Ms} induces higher amounts of the products derived from the insertion of the :CHCO$_2$Et group into the C−H bond of the alkyl fragment (Scheme 11b).[45] A competition reaction between ethylbenzene and cyclohexane shows the former to be more prone to functionalization (in the benzylic position), in good accord with the relative values of the C−H bond energies (see Figure 2).

A third possible reaction in this type of substrates is the formal insertion of the carbene moiety into the aromatic C−H

Scheme 10. Recycling of the Catalysts in the Cyclohexane Functionalization Using [bmim]PF$_6$ as Reaction Medium
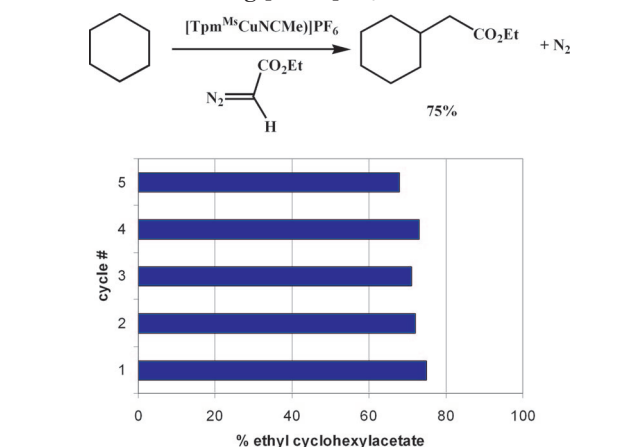
Scheme 11. Possible Transformations in the Metal-Catalyzed Reaction of Alkyl-Aromatic Substrates and EDA

bond (Scheme 11c). This is a reaction that can be readily promoted in an intramolecular manner,[14] but that has very few precedents in the intermolecular fashion,[47] using rhodium-based catalysts and elaborate diazo compounds. A significant advance comes from the use of the aforementioned IPrAuCl + NaBAr'$_4$ system, that promoted such insertion reaction in quite notable yields,[40] along with some amounts of the cycloheptatriene products. As shown in eqs 7 and 8, such insertion can be observed not only with benzene but also with toluene, where the product derived from the insertion into the sp^3 C−H bond of the methyl substituents is not

Table 1. Effect of the Catalysts in the Regioselectivity in the Functionalization of *n*-Pentane or *n*-Hexane with EDA

			selectivity		
catalyst	n	yield, %	primary C1	secondary C2	secondary C3
$Tp^{Br3}Cu(NCMe)$	1	50	nd[a]	1.7	1.0
$Tp^{Br3}Cu(NCMe)$	2	60	nd	3.0	1.0
$Tp^{Br3}Ag(thf)$	1	93	1.0	2.9	1.4
$Tp^{Br3}Ag(thf)$	2	98	1.0	3.7	1.4
$Tp^{(CF3)2}Ag(thf)$	1	81	1.0	1.7	0.9
$[IPrCu(NCMe)]BF_4$	1	75	nd	3.5	1.0
$[IPrAu(NCMe)]BAr'_4$	1	82	1.0	2.9	1.8
$Cu(\beta\text{-diket})$	2	90	nd	1.0	2.1

[a] Not detected.

Table 2. Effect of the Catalysts in the Regioselectivity in the Functionalization of 2,3-Dimethylbutane with EDA

		selectivity	
catalyst	yield, %	primary sites	tertiary sites
$Tp^{Br3}Cu(NCMe)$	56	nd[a]	11
$Tp^{Br3}Ag(thf)$	98	1	3.7
$Tp^{(CF3)2}Ag(thf)$	85	1	1.5
$[IPrCu(NCMe)]BF_4$	65	1	40
$[IPrAu(NCMe)]BAr'_4$	95	1	0.9

[a] Not detected.

observed. The use of the pyridine ligands as in [Au(tButPy)]$_2$(OTf) only gave the cycloheptatriene product, with no observation of that of the insertion into the C—H bond of the aromatic ring.[48]

(7)

25 %   75%

(8)

40 %   *o-,m-,p-*   60%
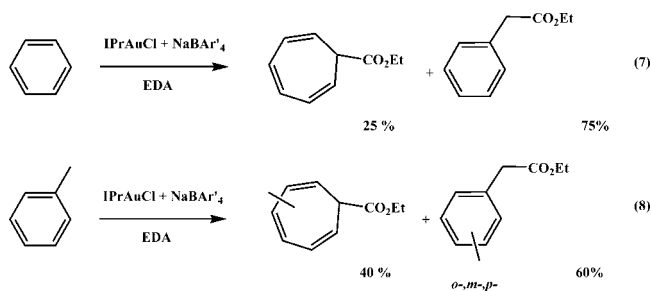
3.4. Selectivity and Mechanistic Considerations

The results obtained with hydrocarbons and coinage metals-based catalysts have shown that it is possible to convert C—H bonds of unreactive alkanes into a functional group. In terms of regioselectivity, the tertiary sites seem to be more reactive than secondary sites, the primary being, by large, the less reactive. This is observed for all the catalysts reported. Table 1 displays the values of the regioselectivities for *n*-pentane and *n*-hexane ($n = 1, 2$, in eq 4) with several catalysts. Primary activation is only observed with silver and gold. Secondary sites display the highest selectivities in all cases, the less hindered C2 site being more prone to functionalization. In the case of 2,3-dimethylbutane (Table 2), tertiary sites are readily functionalized, the trend tertiary > primary being observed in all cases with the exception of gold. The use of substrates with the three types of sites corroborates[24,25,32,39] the existence of the general trend tertiary > secondary > primary, that is parallel to the values of BDEs (see Figure 2), evidencing that electronic factors are crucial in the control of the selectivity. Only when electronics are similar, i.e., both secondary sites in linear alkanes, then the steric hindrance affects the regioselectivity.

As mentioned above, the reaction of a late transition metal complex and a diazo compound usually affords a metallo-carbene species, that has been detected in a few cases. With ethyl diazocatetate and group 11 metal complexes, such intermediates are quite reactive and have not been yet detected.[15a] In the case of trispyrazolylborate complexes, evidence for such electrophilic intermediates was collected using Tp*Cu and EDA in a study over styrene cyclopropanation, where the results of a Hammett's study where in good agreement with the existence of an electrophilic carbene.[49] In addition, the existence of free carbenes has been ruled out on the basis of (i) the observation of an effect of the catalyst in the regioselectivity of the C—H insertion reaction[24]
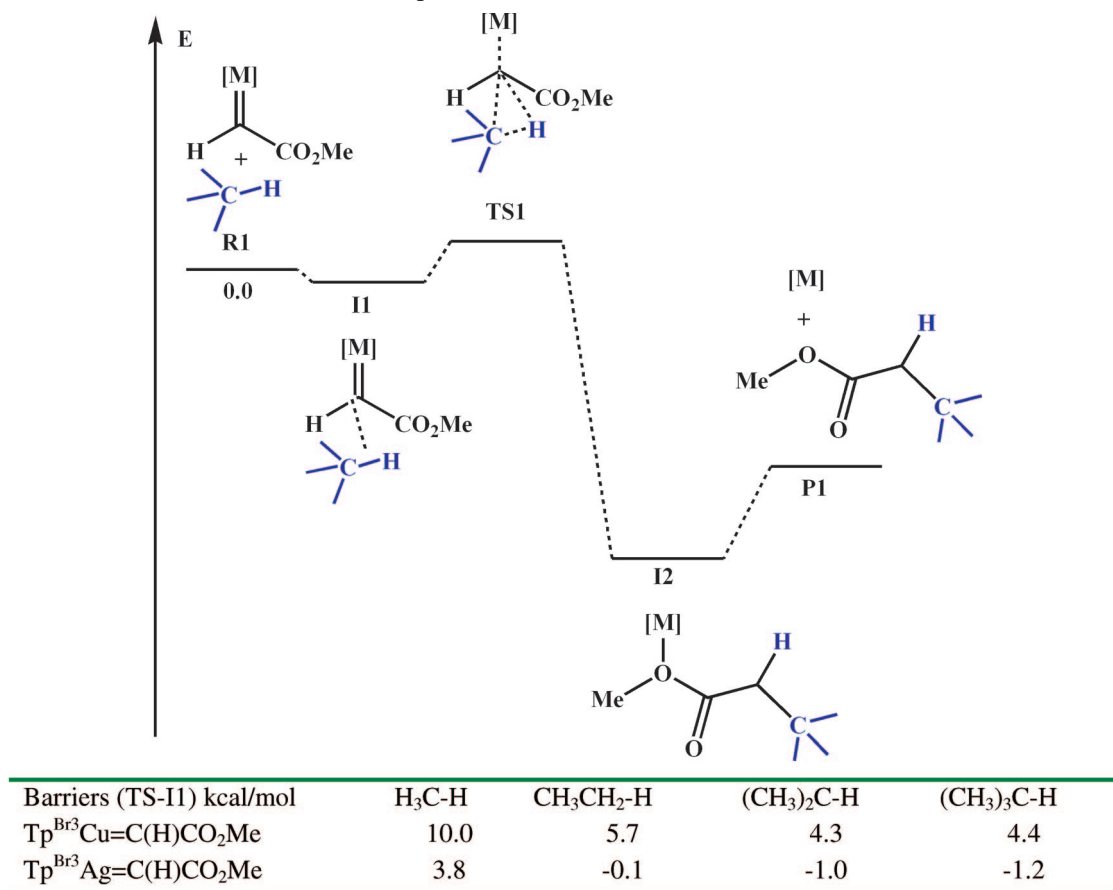
and (ii) competition experiments between benzene and cyclohexane,[25] that largely favored the conversion of the former into the cycloheptatriene products. But the interaction of such intermediates with the hydrocarbon is the key question to explain the functionalization reaction. Theoretical studies[50] based on the complexes $Tp^{Br3}M$ (M = Cu, Ag) have provided information about the energetics of the interaction of the metallocarbenes $Tp^{Br3}M$=C(H)CO$_2$Me (M = Cu, Ag) with alkanes. This study has shown that the reaction takes place under kinetic control. The metallocarbene and the alkane first form an intermediate I1 by a very weak interaction, from which a transition state TS1 is developed (Scheme 12). In the step in which this transition state is involved, the insertion of the carbene carbon atom into the C—H bond of the alkane occurs. Bond-breaking and bond-forming processes take place in a concerted way. A second intermediate I2 is formed from TS1, the former containing the product coordinated to the metal by an oxygen group. The final step consists of the dissociation of the product (P1) and release of the active catalyst. As shown in Scheme 12, the computed barriers for several hydrocarbons and both Cu- and Ag-based catalysts are in agreement with experimental data. The tertiary > secondary > primary trend for the regioselectivity fits with the order for the computed barriers, the regioselectivity being decided in the I1—S1 barrier). In addition, the barriers of the silver system are lower than those of copper, explaining the higher activity of the former and the lack of reactivity of the primary sites with the latter.

3.5. Future Development

The results shown in the previous section should be considered just as the beginning of a new area in the field of homogeneous catalysis toward effective functionalization reaction. Although coinage metals have been proven as potential catalysts for such transformations, further development of new catalysts is required to surpass the main drawbacks of this methodology. First, the activity of the catalysts must be increased in terms of TON and TOF values. Usually, catalyst loadings of 3−5% with respect to EDA are employed (TON = 20−35), and reaction times are usually long since the diazo compound is slowly added to avoid the formation of fumarate and maleate derivatives. Avoiding such slow addition devices is desirable, the diazo compound being then added in one portion. A second target should be the control of the selectivity, particularly toward primary sites, for which new catalysts with more elaborate ligands have yet to be designed. And finally, the asymmetric version of this transformation with the hydrocarbons discussed in this work is yet unknown for the coinage metals: only Rh-based catalysts have been reported in a few cases to induce a certain degree of asymmetry for a few substrates of this type.[20] A recent work using bisoxazoline−copper catalysts immobilized in laponite have induced moderate ee values in the reaction of tetrahydrofuran and PhC(N$_2$)-

Scheme 12. General Energy Profile of a Reaction Path for the Reaction of $Tp^{Br3}M=C(H)CO_2Me$ (M = Cu, Ag) and Alkanes and the Values for the TS1–I1 Barriers ([M] = $Tp^{Br3}M$)

| Barriers (TS-I1) kcal/mol	H_3C-H	CH_3CH_2-H	$(CH_3)_2C$-H	$(CH_3)_3C$-H
$Tp^{Br3}Cu=C(H)CO_2Me$	10.0	5.7	4.3	4.4
$Tp^{Br3}Ag=C(H)CO_2Me$	3.8	-0.1	-1.0	-1.2

CO_2Et,[51] but no data referred to less reactive C–H bonds have been described.

4. C–H Bond Functionalization by Nitrene Insertion

4.1. The Reaction

The formal insertion of a nitrene unit into a C–H bond constitutes a strategy for the functionalization of the former and the concomitant formation of an amine (eq 9).[52] This methodology has not been yet extensively explored, probably due to the success of other methods for the formation of carbon–hydrogen bonds, mainly based on the use of amines as substrates.[53] The conversion of a C–H bond into an amine functionality by nitrene insertion in an intermolecular fashion was discovered by Breslow and co-workers in the early 1980s,[54] and since then several catalytic systems based on iron, manganese, ruthenium and rhodium have been described.[52] Regarding the coinage metals, in the past decade an increasing number of contributions have been reported related to this transformation, with examples based on the three metals.
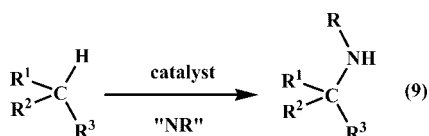
Most of the work described to date with this methodology has been carried out with substrates showing somewhat activated C–H bonds. As commented for Figure 2, benzylic or allylic positions display BDE values substantially lower than those of other low reactive hydrocarbons. Scheme 13 shows

Scheme 13. Substrates Commonly Employed in the C–H Bond Functionalization by Nitrene Insertion[a]
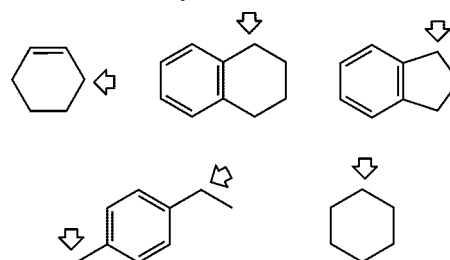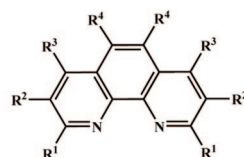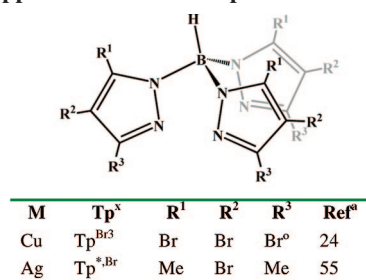

[a] Arrow indicates the position of the insertion.

the commonly employed substrates and the positions that have been aminated by metal-catalyzed nitrene insertion.[51] These or other substituted derivatives of such skeletons account for most of the examples. Few reports are related to plain, nonactivated hydrocarbons, as well as to the C–H bonds of aromatic rings. Similarly to the previous chapter, we will focus on the functionalization of C–H bonds of those hydrocarbons with sp^3 (or sp^2) C–H bonds, excluding those with activating groups (heteroatoms or unsaturated bonds).
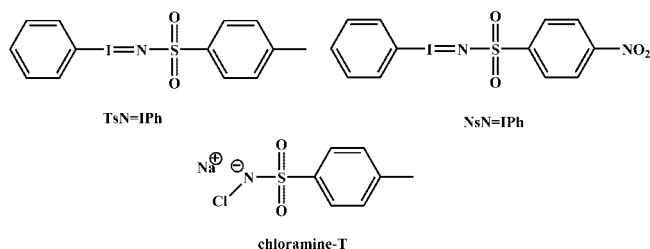
4.2. The Catalysts and the Nitrene Sources

Although reports on the use of coinage metal for nitrene insertion into C–H bonds are less frequent than those of carbene

Scheme 14. Reported Copper- and Silver Complexes as Catalysts for the Functionalization of C−H Bonds by Nitrene Insertion

M	Tp^x	R^1	R^2	R^3	Ref^a
Cu	Tp^{Br3}	Br	Br	Br^o	24
Ag	Tp^{*,Br}	Me	Br	Me	55

M	R^1	R^2	R^3	R^4	Ref^a
Cu	2,4,6-(CF$_3$)$_3$C$_6$H$_2$	H	H	H	56
Ag	H	H	Ph	H	57

Scheme 15. Nitrene Sources

TsN=IPh

NsN=IPh

chloramine-T

Scheme 16. Activation of Benzylic C−H Bonds with Cu-, Ag- and Au-Based Catalysts

	%	Reference
[Cu]	>95	61, 62
[Ag]	25	57
[Au]	90	63

|			Reference
[Cu]	30	20	61, 62
[Ag]	65	nd	57
[Au]	35	nd	63

from diazo compounds, the former reaction has been described with a higher variety of catalysts, ranging from simple salts to very elaborate ligands attached to the metal center. Thus, CuOTf, CuCl in acetonitrile, the [Cu(MeCN)$_4$]PF$_6$ complex or AuCl$_3$ have been employed as the catalytic precursor. When well-defined, isolated complexes were chosen, in all cases nitrogen donors were bonded to the metal center. Two different families of ligands have been used: trispyrazolylborates and phenanthroline derivatives, both with copper and silver (Scheme 14). The Tp^x-containing complexes are those of formula Tp^{Br3}Cu(NCMe)[24] and Tp^{*,Br}Ag,[55] whereas those with phenanthroline ligands correspond to the composition LCuSbF$_6$[56] and [(L)AgOTf]$_2$.[57]

Two different nitrene sources for the transformation depicted in eq 9 are usually employed: iminoiodonanes[52] or chloramine-T (Scheme 15). In both cases, the nitrene group corresponds to p-X-C$_6$H$_4$SO$_2$N (X = CH$_3$, NO$_2$) and the transfer of such unit also supposes the appearance of byproduct, iodobenzene or sodium chloride. Therefore, the use of chloramine-T is preferable since atomic economy is higher and byproduct is environmentally friendly. In addition, it is a readily affordable reagent whereas the iminoiodonanes have to be synthesized in the laboratory. However, chloramine-T is highly insoluble in most organic solvents, and the reaction rates are often governed by the slow dissolution rate.

4.3. Development and Mechanistic Considerations

Although an early report[58] showed that chloramine-T could be decomposed by copper powder in dioxane to give the corresponding insertion product, it was not until the past decade when Taylor and co-workers[59a] demonstrated the catalytic capabilities of CuOTf in combination with a bipy-like ligand (eq 10) to induce such insertion into the allylic C−H bonds of cyclohexene or in the benzylic C−H bonds of tetrahydronaphthalene, in low and moderate yields, respectively. The same group later reported[59b] the use of CuCl/MeCN for the same transformation, with some other hydrocarbons and cyclic ethers. In all cases the C−H bonds functionalized correspond either to benzylic positions and/ or to positions vicinal to O-atoms. The reactions are conducted at room temperature, and yields are moderate.
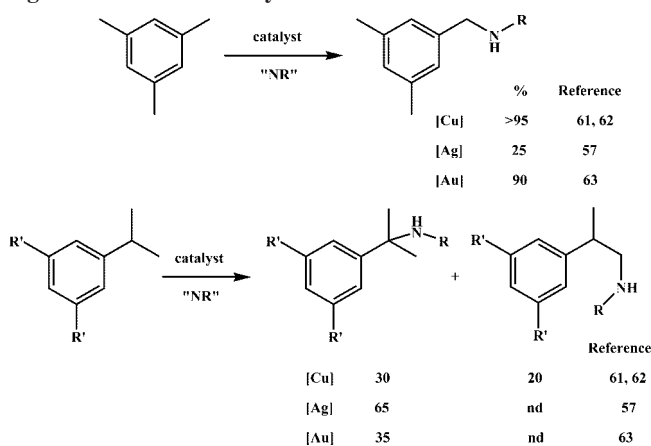
Very recently Nicholas and co-workers have reported the use of the related [Cu(MeCN)$_4$]PF$_6$ as a catalyst for benzylic amidation using chloramine-T.[60]
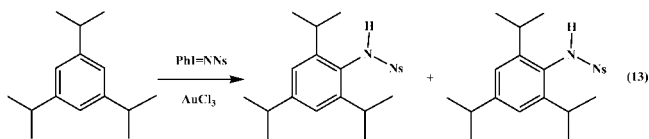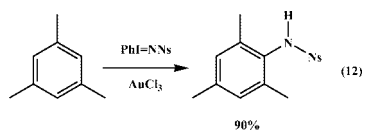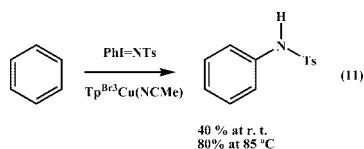

L =
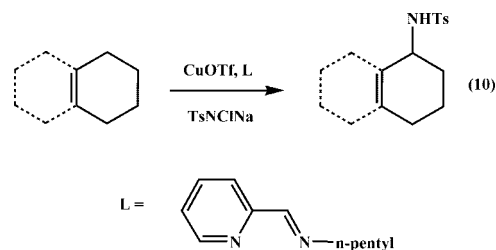
The complex Tp^{Br3}Cu(NCMe) has also been found to catalyze the transfer of the nitrene unit NTs (Ts = p-toluensulfonyl) from either NTs=IPh or chloramine-T to a series of aromatic substrates,[61,62] the benzylic positions being again the most favorable to undergo the insertion reaction. A dinuclear silver−phenanthroline complex[57] and AuCl$_3$[63] have been described by He and co-workers to induce the insertion of the NsN fragment into the C−H bonds of several alkyl-aromatic substrates, in what constitute the first examples of the use of both metals for this transformation. Scheme 16 shows the results obtained with those three coinage metal-based catalysts and several substrates where the benzylic position is the preferred site. The copper and gold catalysts display unique features, in addition to the expected functionalization of the benzylic C−H bonds. The former is capable of exerting the insertion of the nitrene group into other C−H bonds in the β-position related to the aromatic ring, such as the methyl groups of ^{i}Pr substituents. On the other hand, the use of AuCl$_3$ also gives a mixture of two products, the second one being derived of the direct functionalization of the aromatic C−H bond (vide infra).

The above copper and silver catalysts have also been employed in the amidation of cycloalkanes. Thus, cyclohex-

ane can be converted into the corresponding amide using TsN=IPh or NNs=IPh (Ns = p-nitrophenylsulfonyl) and the Cu- or Ag-based catalysts, respectively, in 65% and 40% yield, respectively. A major improvement in conversion is due to the use of the $Tp^{*,Br}Ag$ complex, that can convert cyclopentane and cyclohexane in 80% and 90% yield in 4 h at 80 °C (Scheme 17). The extension of this methodology to plain alkanes is reduced to a couple of reports. The above silver−phenanthroline complex has been reported[57] to induce the insertion of NNs into the tertiary sites of 2-methylbutane with a 22% yield. The use of $Tp^{*,Br}Ag$ by our group[55] with several linear or branched alkanes has allowed the general amidation of such substrates. Scheme 18 shows the compounds obtained with this catalyst and TsN=IPh as the nitrene source with n-hexane and 2,3-dimethylbutane. The overall yields observed with these substrates are 70% and 75%, respectively, the remaining NTs=IPh being converted into TsNH₂.

The direct amidation of aromatic C−H bonds has also been achieved, by nitrene insertion, with copper and gold. In the first case, the complex $Tp^{Br3}Cu(NCMe)$ induces the conversion of benzene into N-tosylaniline with 40% yield at room temperature and 80% yield at 85 °C (eq 11). However, as mentioned above, when C−H bonds at alkyl substituents are available, the insertion takes place into the latter sites, with no observation of any functionalization of the sp^2 C−H bonds. This is at variance with the use of $AuCl_3$ that promotes the sole insertion into the aromatic C−H bond of mesitylene, the methyl groups remaining unreacted (eq 12). Only when isopropyl groups were present, the tertiary sites were functionalized, along with the aromatics, in a 1.5:1, tertiary sp^3:sp^2 ratio (eq 13).

(11)

PhI=NTs / $Tp^{Br3}Cu(NCMe)$

40 % at r. t.
80% at 85 °C

(12)

PhI=NNs / $AuCl_3$

90%

(13)

PhI=NNs / $AuCl_3$

Available mechanistic information about this transformation is scarce. Previous work with other metal-based catalysts had evidenced differences with the carbene transfer reactions. While the rhodium-catalyzed nitrene transfer seemed to proceed throughout a concerted mechanism similar to that noted for the carbene insertion process,[64] other ruthenium-based catalysts were proposed to induce the nitrene insertion reaction with participation of radical species.[65] With coinage metals, both pathways (Scheme 19) have also been proposed for copper and silver. The concerted route supposes that the C−H bond interacts with the nitrene nitrogen, and the N−H and N−C bonds are formed simultaneously to the cleavage of the metal−nitrogen bond. On the other hand, the radical pathway would invoke the homolytic rupture of the C−H

Scheme 17. Amidation of Cyclopentane and Cyclohexane

catalyst	n	%
$Tp^{Br3}Cu$	2	65
LAgOTf	1	35
LAgOTf	2	40
$Tp^{*,Br}Ag$	1	80
$Tp^{*,Br}Ag$	2	90
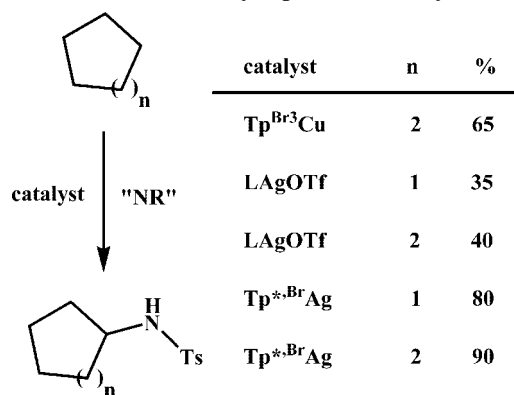
bond to give an alkyl radical and a nitrenoid species, where the metal oxidation state has been increased in one unit.

Taylor and co-workers[59] proposed that the CuCl/MeCN system operates through a concerted mechanism, on the basis of a series of Hammett's plots. However, the existence of a radical pathway has been proposed by Vedernikov and Caulton[66] as part of a cyclohexane dehydrogenation catalytic cycle based on copper. Moreover, the involvement of radical species in the related copper-catalyzed olefin aziridination reaction has been described both theoretically[67] and experimentally.[49,68] In the case of silver, some evidence for the presence of radicals in the case of $Tp^{*,Br}Ag$ as the catalyst has been presented.[55] Finally, the dinuclear structure of the catalyst precursor in He's system[57] has led to the proposal of a possible nitrene−disilver bridge as an intermediate, with no participation of radical species. Overall, it is clearly observable that, in the case of the insertion of nitrene groups into C−H bonds, the mechanism is strongly system-dependent.

The unique gold-catalyzed[63] system described for this transformation deserves a separate comment, since the mechanism proposed is not either the concerted or the radical route mentioned above. Instead, the catalytic cycle (Scheme 20) initiates by the aromatic C−H bond activation by the gold center, and the formation of a HCl molecule. The aryl−gold complex further reacts with the nitrene precursor with no formation of any metallonitrene species. The amine is finally formed upon reaction with HCl, that regenerates the starting $AuCl_3$.

4.4. Future Development

The degree of development of the nitrene insertion methodology is far from being as developed as that of the related carbene transfer reactions. Thus, basic goals such as alkane functionalization at higher yields are yet to be realized. In addition, no examples of the asymmetric version have been reported with the coinage metals. In fact, only very recently an effective, rhodium-based catalytic system has been described to induce high enantiomeric excesses in nitrene insertion reactions into activated positions such as benzylic or allylic C−H bonds.[69]

5. C−H Bond Oxidations

5.1. The Reaction and the Catalysts

The direct oxidation of an alkane C−H bond is of tremendous utility given both the availability of the starting materials and the importance of oxygenated derivatives.[4] Many efforts have been based on the use of most transition

Scheme 18. Amidation of Alkanes with Tp^{*,Br}Ag
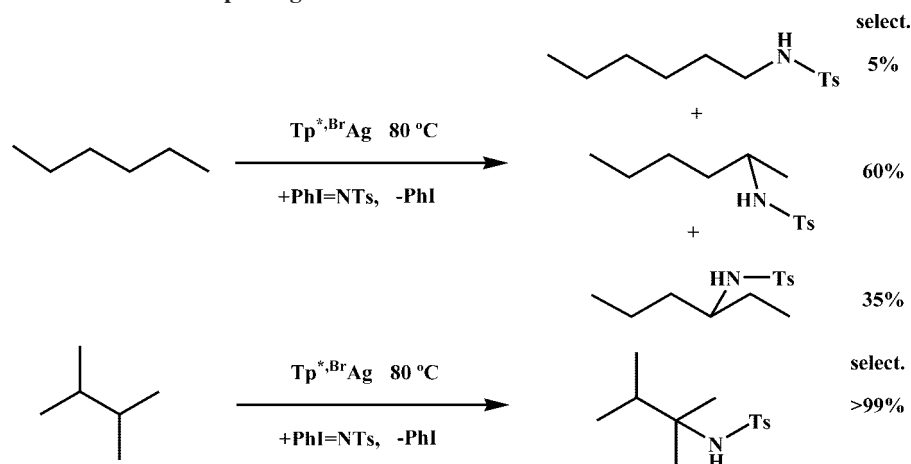
Scheme 19. Proposed Concerted (Left) and Radical (Right) Pathways for the Nitrene Insertion Reaction
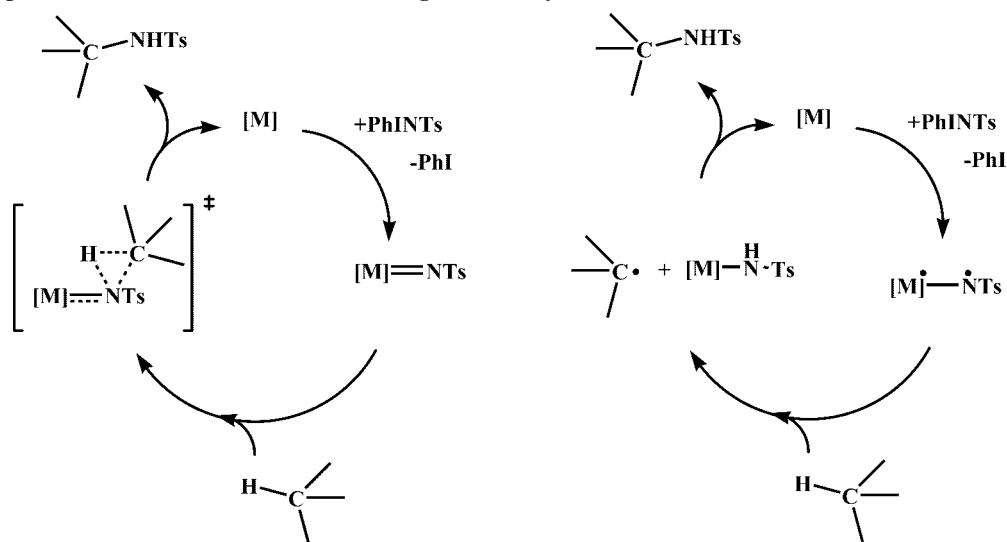
Scheme 20. Proposed Mechanism for the Au(III) Catalyzed Functionalization of sp^2 C–H Bonds
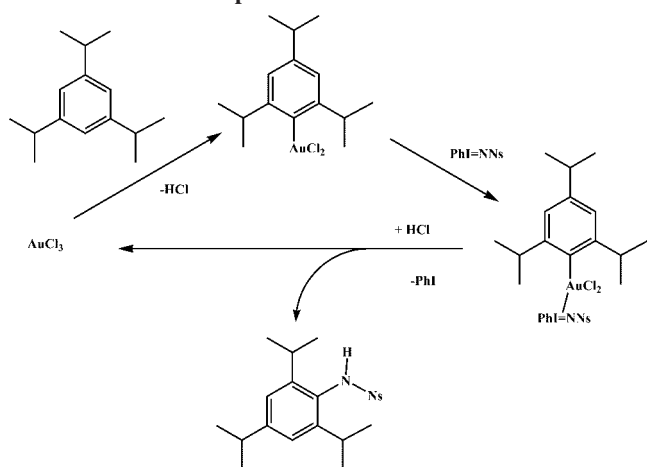
metals as catalysts for this process, under homogeneous or heterogeneous conditions. Regarding the coinage metals under homogeneous conditions, there are a number of contributions related to the use of copper to induce this transformation,[70–72] and just a few with gold (vide infra), whereas, to the best of our knowledge, silver still remains unreported to promote these reactions.

The oxidation of a nonactivated, aliphatic C–H bond usually consists of the use of a copper salt or complex and a strong oxidant, to convert the initial alkane into a mixture of ketones and alcohols. Cyclohexane has been frequently employed as the probe substrate, cyclohexanone and cyclohexanol being the products derived from the oxidation reaction (eq 14). The selectivity is very dependent on the catalytic system. The use of substrates with several potential reaction sites supposes the formation of mixtures derived from the oxidation, at different levels (ketones, aldehydes, alcohols) and sites.
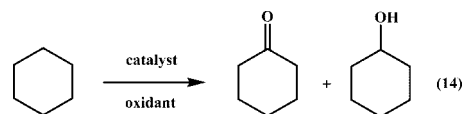
The catalyst precursors range from simple salts to more elaborate copper complexes, in most cases the oxidation state of the metal being +2. Scheme 21 displays the catalyst precursors described to date for this oxidation reaction. It is also worth mentioning that all the complexes employed contain N-donor ligands, a common feature in this catalytic system.

5.2. Development and Perspective

In the late 1980s, Geletii and co-workers introduced[73] the use of homogeneous copper catalysts for alkane C–H

Scheme 21. Copper-Based Catalysts Precursors for Alkane C—H Bond Oxidation Reactions

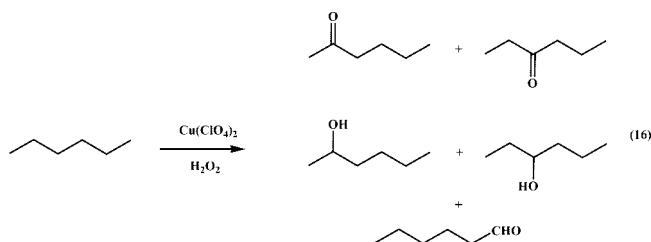| Catalyst precursor	Reference
Cu(ClO$_4$)$_4$/py	73,74
Cu(ClO$_4$)$_4$/py, AcOH	75
Cu(fod)$_2$	76
Cu(OH)$_2$	77
CuCl$_2$/18-crown-6	78,79
L^{1}CuOAc	80
[L^{2}CuCl]ClO$_4$	81
[Cu(en)$_2$](NO$_3$)$_2$	82
[Cu(bipy)$_4$]$^+$;[Tp^{x}Cu(py)]$^+$	83
[Cu$_2$(py$_2$SSpy$_2$)](ClO$_4$)$_2$	84
[Cu(MeCN)$_4$BF$_4$; [L^{3}Cu]	85
[L^{4}Cu]	86
[Cu(H$_2$tea)(N$_3$)]	87,88
{Cu$_3$(μ^3-OH)((μ-pz)$_3$}$^{2+}$	89
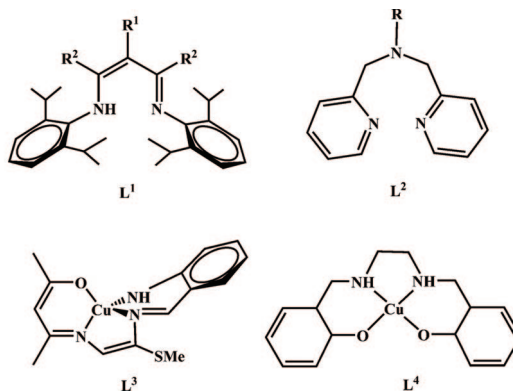
py = pyridine. AcOH = acetic acid. fod = 2,2-dimethyl-6,6,7,7,8,8,8,-heptafluoro-3,5-octadionate; en = ethylenediamine; tma: tetramethylacetate; bipy = bipyridine; Tp^x = trispyrazolylborate; tea = triethanolamine; pz = pyrazolyl; TBA: tetrabutylammonium

oxidation reactions, employing Cu(II) perchlorates in the presence of pyridine as the catalyst precursor, [Cu(py$_4$)]$^+$ being probably formed under the reaction conditions. 2-Methylbutane was employed as the substrate, and a mixture of 3-methyl-2-butanone and 2-methyl-2-propanol was obtained (eq 15):
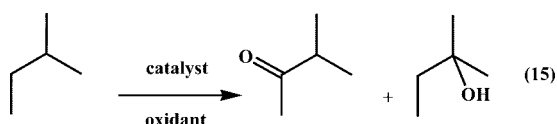
This can be considered as the seminal work for the use of coinage metals in this transformation. Shortly after, Geletii, Barton and co-workers incorporated the use of copper to the so-called Gif chemistry,[72] developed in Barton's group and mainly based, to that time, in iron catalysts. A series of contributions related to the use of copper(II), in a pyridine: acetic acid medium, as catalysts for the oxidation of hydrocarbons with hydrogen peroxide appeared in the early 1990s.[74,75] Conversions were always below 30% for an array of substrates, the selectivity being also quite low. For example, using Cu(ClO$_4$)$_2$ as the catalyst precursor, adamantane could be converted into a mixture of several compounds, including adamantone, adamantoles, as well as other compounds derived from the incorporation of pyridine into the hydrocarbon skeleton. No more regioselective was the oxidation of hexane with the same system: as shown in eq 16, hexanal, hexenones and hexanols were obtained in low yields. Hydrocarbon hydrocarboxylation[75b] was detected using elemental copper in the presence of CO and O$_2$, again in a pyridine/acetic acid, but with very low yields. Cyclopentane was converted into cyclopentylcarboxylic acid (<1%), whereas when cyclohexane was employed, a mixture of cyclohexylcarboxylic acid, cyclohexanone and cyclohexanol was observed, with an overall yield of <3%. Complexed copper as Cu(fod)$_2$ (fod = 2,2-dimethyl-6,6,7,7,8,8,8,-heptafluoro-3,5-octadionate) was later tested[76] for cyclooctane oxidation using *tert*-butylhydroperoxide as the oxidant, but the transformation was far from selective, a mixture of cyclooctene, cyclooctanone and cyclooctanol being obtained, albeit a ca. 13% of conversion was obtained under relatively mild conditions (60 °C, 1 atm of air or O$_2$).

A significant advance was introduced by Murahashi and co-workers that described the use of Cu(OH)$_2$ as the catalyst precursor for the room temperature oxidation of adamantane into adamantol in the presence of acetaldehyde, in 92% yield.[77] Further work from this group showed[78] that equimolar mixtures of CuCl$_2$ and 18-crown-6 catalyzed the oxidation of several hydrocarbons (cyclohexane, *n*-hexane, indane, tetraline, among others) into a mixture of ketones and alcohols (eq 17), the system being selective toward the formation of the ketones. A detailed study of an array of copper salts and crown ethers showed[79] that the hydroxide Cu(OH)$_2$ along with 18-crown-6 was the best combination. It is noteworthy that very high turnover numbers were observed, in the 10^4 range. Yields were based on acetaldehyde, the acetaldehyde:hydrocarbon molar ratio being 1:10. The highest conversions were observed for adamantane (30%) and indane (27%).
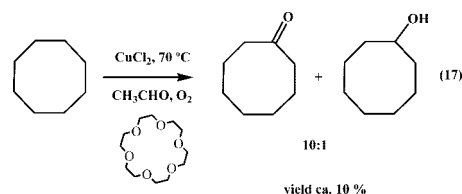
Copper(II) complexes with β-diketiminate ligands have been employed as models for particulate methane monooxygenase (pMMO) by Itoh and co-workers.[80] Both Cu(I) and Cu(II) sources can be employed, since they originate the same (bis)(μ-oxo)Cu$_2$ intermediate by reaction of the initial copper complexes and H$_2$O$_2$/O$_2$. Oxidation of cyclohexane or adamantane with those catalyst precursors gave mixtures of ketones and alcohols in ca. 20% overall yield (based in

H_2O_2). Nishida et al. also employed cyclohexane as the probe for the low yield copper-catalyzed oxygenation reaction with hydrogen peroxide.[81] Schuchard et al. described[82] the use of copper chelates with ethylene diamine or tetraacetate ligands for the same transformation, and t-BuOOH (tert-butylhydroperoxide, TBHP) as the oxidant, again yields remaining below the 10% value with a mixture of different products being obtained. A study of the ligand effect in the Cu(I)-induced dioxygen activation was reported by Costas and Llobet,[83] where several mono-, bi- and tridentate ligands were tested in the oxidation of several hydrocarbons with TBHP. The react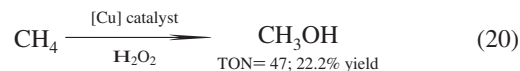ion of ethylbenzene with TBHP in the presence of those copper complexes (see Scheme 21) is quite selective, acetophenone being the major product detected in addition to minor amounts of 2-phenyl-2-ethanol (eq 18). The ketone:alcohol ratio found reached the value of 141.9: 1.4 (mmol) for an overall TON value of 28.

141.9 : 1.4

TON = 28

(18)
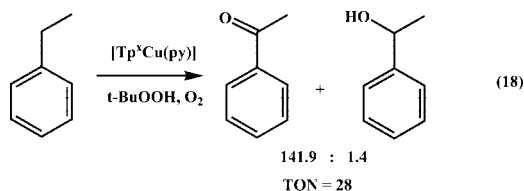
At variance with the above systems, which are based on the use of copper complexes with N-donor ligands, Kitakawa and co-workers described[84] a series of complexes with S-donors that display a certain, albeit low, activity for cyclohexane oxidation. Both H_2O_2 and TBHP could be employed as oxidant, with mixtures of cyclohexanone and cyclohexanol being detected at the end of the reaction. Shul'pin et al. later employed[85] ambidentate N−O ligands with several metals for alkane hydroperoxidation reaction, including copper. Maximum TON values of 1900 were reported for [Cu(MeCN)$_4$]BF$_4$ as the catalyst, cyclohexane as the substrate and peroxyacetic acid as the oxidant, although the reaction proceeded in low yield and a cyclohexyl hydroperoxide was also produced in addition to cyclohexanol and cyclohexanone. The strategy of N−O− ligands was further developed by Punniyamurthy and co-worker,[86] that employed the tetracoordinated Cu(II) complex [L^{4}Cu] (see Scheme 21) to oxidize several benzylic C−H bonds with H_2O_2. Thus, diphenylmethane was converted into a mixture of diphenylmethanol and benzoquinone upon using catalytic amounts of this complex in the presence of 10 equiv of 30% H_2O_2 at room temperature. If the reaction is carried out at 80 °C, benzophenone is obtained in 87% yield (eq 19). Other related Cu(II) complexes such as Cu(AcO)$_2$ or Cu-salen were also tested, although yields were lower than those observed with [L^{4}Cu]. Other alkylaromatics such as ethylbenzene, n-butylbenzene, ethylphenylacetate or tetraline were also oxidized in high yields (82−89%) to the corresponding ketones. However, the unreactive C−H bonds of cyclohexane led to an 18% conversion, in good accord with the different values of BDE for benzylic positions and cyclohexane (see Table 1).
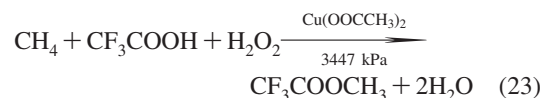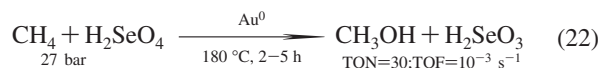

room temp   50:50 (34%)

80 °C   1>99   (87%)

(19)
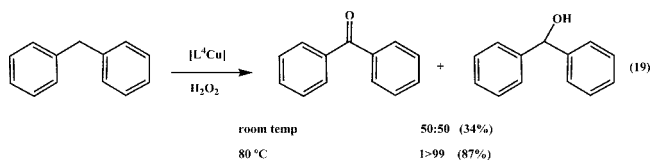
It has not been until very recently that Pombeiro and co-workers[87,88] have reported the most active to date copper catalytic system for hydrocarbon oxidation. Several multinuclear copper complexes containing the tetradentate triethanolamine ligands were prepared and tested as catalysts for the oxidation of cyclohexane in acetonitrile, using hydrogen peroxide as the oxidant. Such combination of reactants and solvents originate a biphasic reaction medium, acidic in nature by action of HNO_3. The study of several reaction conditions and catalysts showed that the complex Cu$_3$(H$_2$tea)$_2$(4-HOC$_6$H$_4$COO))$_2$(H$_2$O)] provided the best conversions in the oxidation of cyclohexane, up to 32%, using a 1:800 [catalyst]:[H_2O_2] ratio. Cyclohexanol and cyclohexanone were obtained in nearly 53:47 ratio, in a reaction where the catalyst accomplished a TON value of ca. 400. Interestingly, methane and ethane also underwent peroxidative oxidation with a tetranuclear copper catalyst at a pressure of 30 atm at 40 °C and with a [H_2O_2]:[catalyst] molar ratio of 1000. These reactions led to the formation of methanol and ethanol (eqs 20 and 21), respectively, from methane and ethane. Although TON and yields were low, the activation of this highly unreactive molecule by this procedure is quite remarkable in the sense that such figures are comparable to those of pMMO.

$$CH_4 \xrightarrow[H_2O_2]{[Cu]\ catalyst} CH_3OH \quad (20)$$
$$\text{TON= 47; 22.2\% yield}$$

$$CH_3CH_3 \xrightarrow[H_2O_2]{[Cu]\ catalyst} CH_3CH_2OH \quad (21)$$

Further work from Pombeiro's group[89] using multinuclear complexes containing copper ions has demonstrated the utility of such compounds as catalysts for the peroxidative oxidation of cycloalkanes. Thus, a trinuclear Cu$_3$ induces the conversion of cyclohexane or cyclopentane into the corresponding cycloketones and cycloalcohols with yield slightly below 32%. More interestingly, this system is quite selective toward the formation of the latter. The same feature has been observed with a heterotrimetallic[90] Fe/Cu/Co complex, again cyclohexane being converted into cyclohexanol as the main product, and with an overall conversion of 45%.

The direct oxidation of methane has been scarcely reported, in addition to Pombeiro's results, with coinage metals. Thus, Periana and co-workers described[91] the use of metallic gold as catalyst precursor in a 3 M solution of H_2SeO_4 in 96% H_2SO_4 for the conversion of methane into methanol. The reaction is carried out at 180 °C with TON = 30 and TOF = 10^{-3} s^{-1}. Se^{VI} is required as a stoichiometric oxidant (eq 22). The catalytic species seems to be cationic gold derived from the solution of the initial gold metal by action of selenic acid. A different approach has been reported by Lee and co-workers,[92] that employed copper salts for the methane oxidation by in situ generated hydrogen peroxide. The latter is formed by reacting H_2 and O_2 over Pd/C, and H_2O_2 is then used as the oxidant in the reaction of trifluoroacetic acid and methane, as shown in eq 23.

$$CH_4 + H_2SeO_4 \xrightarrow[180\ °C,\ 2-5\ h]{Au^0} CH_3OH + H_2SeO_3 \quad (22)$$
$$\text{27 bar} \qquad \text{TON=30;TOF=}10^{-3}\ s^{-1}$$

$$CH_4 + CF_3COOH + H_2O_2 \xrightarrow[3447\ kPa]{Cu(OOCCH_3)_2}$$
$$CF_3COOCH_3 + 2H_2O \quad (23)$$

From the results shown in this section, it is clear that copper-based catalysts have demonstrated a potential use in

hydrocarbon oxidation reactions, although development of more active catalysts is yet to be done. In addition, the use of hydrogen peroxide as the oxidant is desired not only because of its availability but also for its *green* nature. Further extension of the copper chemistry to the other coinage metals is also unknown to date.

6. Conclusions

Coinage metal complexes or salts have been described to catalyze a number of reactions where unreactive C−H bonds of hydrocarbons can be functionalized, in most cases, under mild conditions. The methodologies (carbene insertion, nitrene insertion, peroxidation reactions) display currently different degrees of development. Some of them (nitrene insertion, peroxidation) are yet to be improved in terms of catalyst activity. Control of the selectivity is also a major drawback in all these transformations with coinage metals. The induction of asymmetry with these catalysts is also of great interest, but no examples have been yet reported. Overall, this is a promising field in the homogeneous catalysis area, where simple catalysts can be of tremendous utility for the conversion of available raw materials such as hydrocarbons into value added products.

7. Acknowledgments

8. References

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CR078364Y