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Letter

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Water as reaction medium for intermolecular C-H alkane functionalization in micellar catalysis

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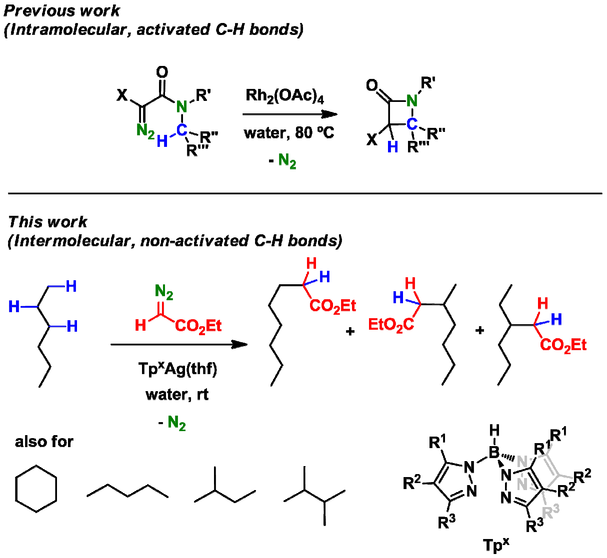
ABSTRACT: A series of alkanes C_nH_{2n+2} have been functionalized in water as the reaction medium, using a silver-based catalyst, upon insertion of carbene ($CHCO_2Et$ from N_2CHCO_2Et) groups into their carbon-hydrogen bonds of hexane, cyclohexane or 2-methylbutane, among others. The regioselectivity toward the distinct reaction sites is identical to that found in neat alkane, the water-based system allowing the use of a much shorter excess of the hydrocarbon. This is the first example of the intermolecular functionalization of alkanes with this strategy in water. The functionalized alkanes partially undergoes a incorporation of a second carbene unit to provide α-(acyloxy)acetates, in an unprecedented tandem reaction of this nature.

KEYWORDS. Alkane functionalization C-H activation catalysis in water carbene transfer copper and silver catalysts

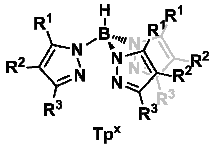
In spite of water being the solvent in Nature, modern chemistry have mostly relied in the use of organic, non-natural solvent for nearly all aspects: synthesis, catalysis, separation or purification procedures are mostly carried out in petrochemical-derived solvents.[1] Within catalytic applications, such use is probably the result of several drawbacks derived from low solubility and stability of many transition metal complexes employed as catalysts or the reactivity of water itself toward many transformations.[2] However, in the last decades several strategies have been employed toward that end,[3] since the use of water instead of an organic solvent contributes to a dramatic decrease of the so-called *Environmental Factor* or *E-factor*, introduced by Sheldon.[4] Thus, several strategies have been developed toward that end such as the design of water-soluble catalysts, the use of biphasic catalysis (with one solvent being water), or the addition of surfactants that provide hydrophobic vesicles where a large concentration of catalyst and reactants triggers the reaction. The latter methodology has been mainly developed, in recent years, by the group of Lipschutz,[5,6] showing that with the appropriate surfactant and water as the sole solvent, a number of interesting metal-catalyzed organic transformations take place under milder conditions with the same catalysts employed in organic solvents.

The transfer of a carbene group from a diazocompound catalyzed by a transition-metal complex is a well-known tool for the incorporation of such moiety to an array of substrates.[7] For decades those transformations were run in organic solvents, until in the last decade first Nishiyama[8]. and shortly after Charette[9] demonstrated the effectiveness of ruthenium-, rhodium-, and cobalt-based catalysts for the cyclopropanation of olefins in aqueous media, including the asymmetric version. Since then, a number of catalytic systems for the olefin cyclopropanation in water have been described.[10,11] Additionally, N-H bonds have also been functionalized with this methodology.[12]



Scheme 1. Top: Previous intramolecular functionalization of activated C-H bonds by carbene insertion in water. Bottom: the intermolecular, non-activated-alkane C-H bond functionalization in water.

In contrast, the functionalization of carbon-hydrogen bonds by metal-mediated carbene insertion remains undescribed in water as solvent. This methodology[13] has been resurrected in this century in such a way that even highly energetic C-H bonds such as those of methane and light alkanes have been modified.[14] However, in water as reaction medium only a few examples of the intramolecular functionalization have been described. Thus, the groups of Afonso[15] and Che[16] have reported (Scheme 1) the respective use of Rh- or Ru-based catalysts for the intramolecular insertion of a carbene group into a carbon-hydrogen bond, that in addition is somewhat activated by the presence of a neighboring heteroatom. To our knowledge, there is no report on the functionalization of alkanes C_nH_{2n+2} with diazo compounds, i. e., under intermolecular conditions and in the absence of activating groups. In this contribution we report on the catalytic capabilities of a Tp^x-containing (Scheme 2) silver catalyst capable of promoting the modification of several linear, branched and cyclic alkanes upon inserting $CHCO_2Et$ units from $N_2{=}CHCO_2Et$ (ethyl diazoacetate, EDA) in water as the solvent, in the first example of this transformation (Scheme 1).



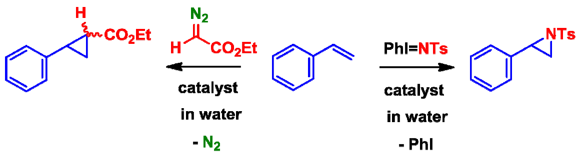
Tp^{Ms}: R^1 = R^2 = H; R^3 = Ms
Tp^{Br3}: R^1 = R^2 = R^3 = Br
Tp$^{(CF3)2,Br}$: R^1 = R^3 = CF$_3$; R^2 = Br

Scheme 2. Trispyrazolylborate ligands employed in this work.

We have been involved in a research program[13] focused in the use of group 11 metal-based catalysts for several transformations involving the functionalization of carbon-hydrogen bonds of unmodified alkanes and cycloalkanes upon the formal insertion of carbene, nitrene or oxo units, albeit organic solvents were employed in all cases. Actually, the solvent was, in most of the examples, the targeted substrate, and thus a large excess was employed relative to the other reactant. Thus, the use of water as the reaction medium could allow a decrease of such excess of the alkane and decrease the E-factor. Our first concern when facing the incorporation of water as the reaction medium was the stability of the catalysts. In a first approach, we chose two reactions as probes for the test of the catalytic capabilities in water of some of our already reported catalysts. They were the olefin cyclopropanation reaction with ethyl diazoacetate (EDA) and the styrene aziridination with PhI=NTs (Table 1).

The reactions were performed under two different conditions. The first set was carried out in water as the solvent whereas a second group of reactions was carried out in water with the so-called *Lipshutz surfactant*, TPGS-750-M as an additive.[5,6] The latter methodology has provided spectacular results in a number of metal-catalyzed transformations in water. The protocol was the same in both cases: the catalysts were suspended in deoxygenated (by intensive bubbling of a N_2 stream for a long period) water, or in water containing the surfactant, and the olefin was then added. Finally the carbene or nitrene precursor was incorporated ($N_2{=}CHCO_2Et$ or PhI=NTs, respectively) in one portion and the mixture stirred for 1-4 h at room temperature. At the end of the reaction, the products are extracted with several portions of ethyl acetate and the collected fractions dried with $MgSO_4$. Elimination of volatiles led to the crude products that were identified and quantified by NMR with internal standards (see Supporting Information for details).

Table 1. Screening of stability of copper-catalysts Tp^{x}Cu(L) in water toward carbene and nitrene transfer.[a,b]



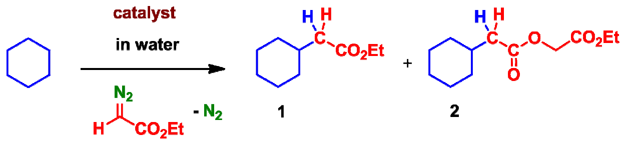
Catalyst	Reactant	Medium	Yield
Tp^{Ms}Cu(thf)	EDA	CH_2Cl_2[c]	>95 (98:2)[d]
Tp^{Ms}Cu(thf)	EDA	H_2O	>95 (98:2)[d]
Tp^{Ms}Cu(thf)	EDA	H_2O/ TPGS-750-M	>95 (98:2)[d]
Tp^{Br3}Cu(NCMe)	EDA	CH_2Cl_2[e]	82 (60:40)[d]
Tp^{Br3}Cu(NCMe)	EDA	H_2O	77 (60:40)[d]
Tp^{Br3}Cu(NCMe)	EDA	H_2O/ TPGS-750-M	79 (58:42)[d]
Tp^{Br3}Cu(NCMe)	PhI=NTs	CH_2Cl_2[f]	95
Tp^{Br3}Cu(NCMe)	PhI=NTs	H_2O	> 95
Tp^{Br3}Cu(NCMe)	PhI=NTs	H_2O/ TPGS-750-M	> 95

[a] General procedures: (a) cyclopropanation: 0,01 mmol of catalyst, 1 mmol EDA, 5 mmol styrene, 5 mL H_2O; (b) aziridination: 0,01 mmol of catalyst, 0,2 mmol PhINTs, 5 mL of water. A commercial solution (5%) of the surfactant from Aldrich was employed when needed (5 mL). [b] Yields quantified by NMR with internal standards upon extraction with ethyl acetate. See Supporting Information. [c] Reference 17. [d] *cis:trans* ratio of cyclopropanes. [e] Reference 18. [f] Reference 19.

The results are shown in Table 1, where the reaction outcome already reported[17,18,19] in dichloromethane as the solvent has also been incorporated for the sake of comparison. Clearly, the already described excellent catalytic behavior of the catalysts Tp^{Ms}Cu(thf) and Tp^{Br3}Cu(NCMe) in organic media can be extended to water as solvent with no difference neither in activities nor in diastereoselectivities, the latter referred to the relative ratio of *cis* and *trans* cyclopropanes obtained. Thus, these copper-based catalyst not only survive in water but also behave, from a catalytic point of view, as if they were in an organic solvent.

Such observation of identical behavior in the organic medium or in this water-containing system along with the lack of any effect of Lipshutz's surfactant has led us to the assumption that the reaction takes place inside a micelle formed by the olefin in water, with the catalyst dissolved therein. Regarding the carbene and nitrene precursors, EDA is soluble in water[9] whereas PhI=NTs poorly dissolves in the mixture of water and olefin, the reaction being thus quite slow, albeit productive. It is worth mentioning that the products derived from the activation of water in both processes, i.e. $HOCH_2CO_2Et$ (carbene insertion into OH) or $TsNH_2$ were not formed in significant amounts, reinforcing the proposal of micellar catalysis within the olefin phase.

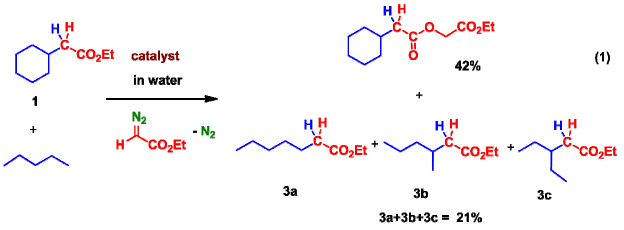
After the above results, we then focused in the functionalization of C-H bonds of unreactive hydrocarbons, i. e., lacking of any functional or activating group. Cyclohexane was chosen as the probe for the reaction with EDA in water as solvent, following the strategy developed with unsaturated substrates. An array of $Tp^{x}ML$ catalysts, with M being Cu or Ag, were tested, as detailed in Scheme 3. None of the copper complexes gave significant amounts of the expected product, ethyl 2-cyclohexylacetate (**1** in Scheme 3): EDA was essentially converted into a mixture of diethyl fumarate and maleate, as well as minor, but detectable amounts of $HOCH_2CO_2Et$ as the result of water activation. When moving to silver complexes, the situation was somewhat similar with $Tp^{*,Br}Ag$ as the catalyst: after 14 h at room temperature, only small amounts of the desired product were observed, and EDA was not fully consumed. But the use of $Tp^{(CF_3)_2,Br}Ag(thf)$ provided a significantly different reaction outcome, since under the same reaction conditions 45% yield (referred to EDA) of the functionalized product was obtained, all EDA being consumed (as inferred from GC studies). In addition, a second product identified as 2-ethoxy-2-oxoethyl 2-cyclohexylacetate was identified in the reaction mixture in 20% yield (also referred to EDA, each molecule formally derives from two molecules of the diazo compound and one of cyclohexane). We have previously described[20] the formation of such compounds when employing pure esters as the reactants in their reactions with EDA in the presence of related silver-based catalysts. According to the mechanistic interpretation already proposed,[20] the reaction requires a H_2O molecule and eliminates EtOH. However, this is the first time that we (or others) observe this tandem reaction in which the alkane is first converted into an ester and this is subsequently transformed into the α-(acyloxy)acetate. We believe that this is a consequence of the elevated concentration of the nascent product **1** in the micelle that favors its interaction with the catalyst and further EDA as well as the availability of H_2O (that was adventitious in the purely organic system). It is worth mentioning that in neat cyclohexane as the substrate, this silver catalyst $Tp^{(CF_3)_2,Br}Ag(thf)$ leads to >95% yield into **1**, with 10 mL of cyclohexane whereas in the H_2O-based system only 0.5 mL of the cycloalkane are added to 5 mL of water. The effect of the presence of the surfactant TPGS-750-M in the reaction mixture was also investigated, the yield into **1** being similar albeit that of **2** decreased from 20% to 6%. Reaction workup consisted of extraction of the products with diethyl ether and analysis of the organic solution by GC, using calibration curves previously developed with pure samples of the products (see Supporting Information for full description).



catalyst	Yield 1(%)	Yield 2 (%)
$Tp^{Ms}Cu(thf)$	nd	nd
$Tp^{Br3}Cu(NCMe)$	nd	nd
$Tp^{(CF3)2,Br}Cu(thf)$	3	nd
$Tp^{*,Br}Ag$	2	nd
$Tp^{(CF3)2,Br}Ag(thf)$	45	20
$Tp^{(CF3)2,Br}Ag(thf)^{a}$	41	6

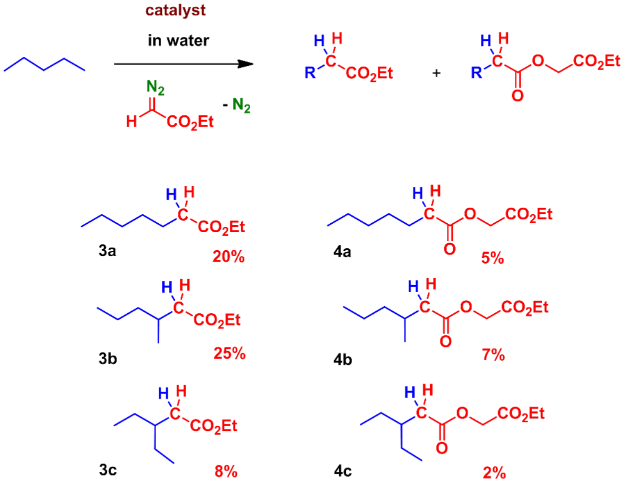
[a] Reaction performed in the presence of TPGS-750-M 2%

Scheme 3. Functionalization of cyclohexane in water



To demonstrate that the acyloxyacetate is formed from the ester, we have performed an experiment with pure **1** (commercial sample) and n-pentane. Under the same conditions than those shown in Scheme 3, a mixture of **2** and the esters derived from the insertion into the C-H bonds of pentane was obtained (eq 1). These result unambiguously demonstrate that the ester **1** is an intermediate in the formation of the acyloxyacetate **2**.

The observance of the catalytic properties of $Tp^{(CF_3)_2,Br}$Ag(thf) in water toward carbene insertion into the C-H bonds of cyclohexane led us to test a series of linear and branched alkanes. Scheme 4 shows the reaction of pentane with EDA using this silver complex as the catalyst (0,005 mmol of catalyst, 0,2 mmol of EDA, 0,5 mL -4,22 mmol- of pentane, 5 mL H_2O, rt, 14 h) a mixture of alkyl-acetates **3a-c** derived from the functionalization at C1, C2 and C-3 reaction sites was obtained with a respective 38:48:14 ratio of products. This selectivity is similar to that found when using pentane as the unique solvent,[14c] thus evidencing that the catalyst behavior is not influenced by the change of reaction medium. In addition to **3a-c**, three α-(acyloxy)-acetates **4a-c** were also formed as the result of the silver-catalyzed incorporation of a second carbene unit onto **3a-c**. Figure 1 contains the GC trace of the reaction mixture, from which an interesting feature has been extracted: the relative ratio of **3a-c** is maintained in **4a-c**, in what we interpret as the absence of any effect of the alkyl substituent in the reactivity of **3a-c** in the second transformation.



Scheme 4. Functionalization of pentane in water (yields based on EDA).

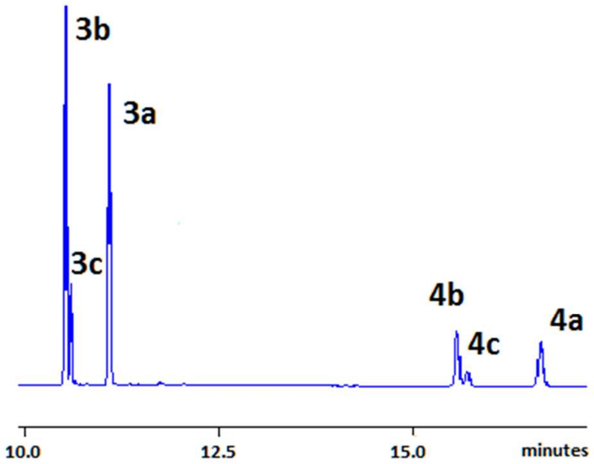
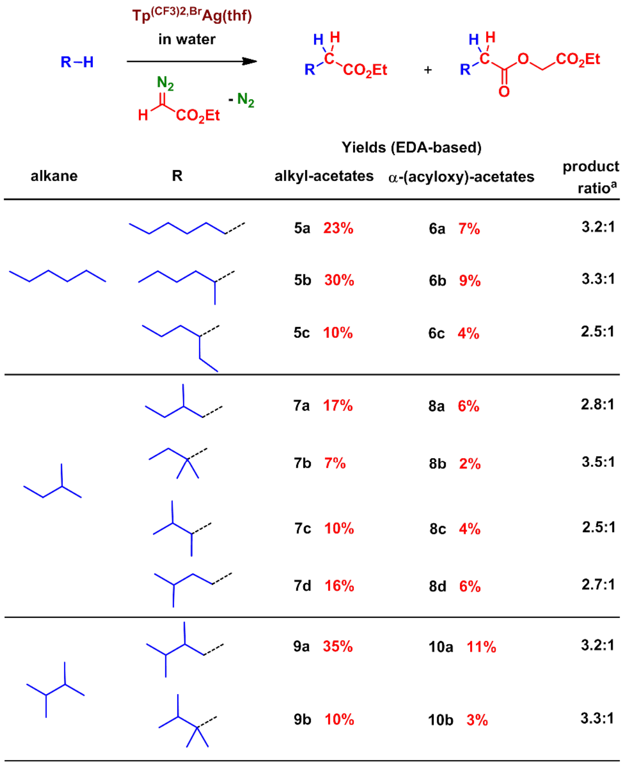


Figure 1. GC trace of the reaction mixture of the functionalization of pentane



[a] alkyl-acetates: α-(acyloxy)-acetates molar ratio

Scheme 5. Functionalization of linear and branches alkanes in water.

Three other alkanes have been studied, namely hexane, 2-methylbutane and 2,3-dimethyl-butane, with a similar behavior being observed: the products derived from the functionalization of the C-H bonds of the alkanes were obtained as well as some of the doubly activated derivatives. The overall conversion into functionalized products ranged within 59-83%, based in EDA. Scheme 5 displays the products and relative yields obtained. Similarly to the commented example of pentane, the regioselectivity of the alkane functionalization was nearly identical to those previously reported in neat alkane as the reaction media.[14c] Also, the relative ratio of alkyl-acetates was maintained in the α-(acyloxy)-acetates in all the experiments, again evidencing the lack of effect of the alkyl chain in the reactivity of the ester group toward the second incorporation of a carbene moiety.

Thus, we have found that the complex $Tp^{(CF_3)_2,Br}$Ag(thf) catalyzes the intermolecular functionalization of alkanes in water by carbene transfer from ethyl diazoacetate in the first example of this transformation in such medium. Interestingly, the regioselectivity observed, intended as the relative ratio of products derived from the insertion into the distinct sites, is nearly identical. Additionally, a concurrent reaction takes place by the silver-catalyzed incorporation of a second carbene unit onto the ester moiety of the alkane functionalized products. This consecutive transformation from alkanes is also unprecedented, and it is probably the result of the micellar nature of this catalytic system, that provide high concentrations of reactants and catalyst in a reduced volume. In our opinion, these findings open a new approach for the catalytic functionalization of hydrocarbons lacking of unsaturations or activating groups, which are desirable raw materials for future development.

ASSOCIATED CONTENT

General methods, synthetic procedures and catalytic experiments are provided in a pdf file. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

Authors declare no competing financial interests.

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Alkanes are functionalized with ethyl diazoacetate and a silver catalyst in water as the reaction medium leading to alkyl acetates and minor amounts of α-(acyloxy)-acetates, the latter deriving from a consecutive functionalization of the formers, in the first example of the intermolecular modification of alkanes by this methodology