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Make It Green: Copper-Catalyzed Olefin Aziridination in Water with an Iminoiodonane

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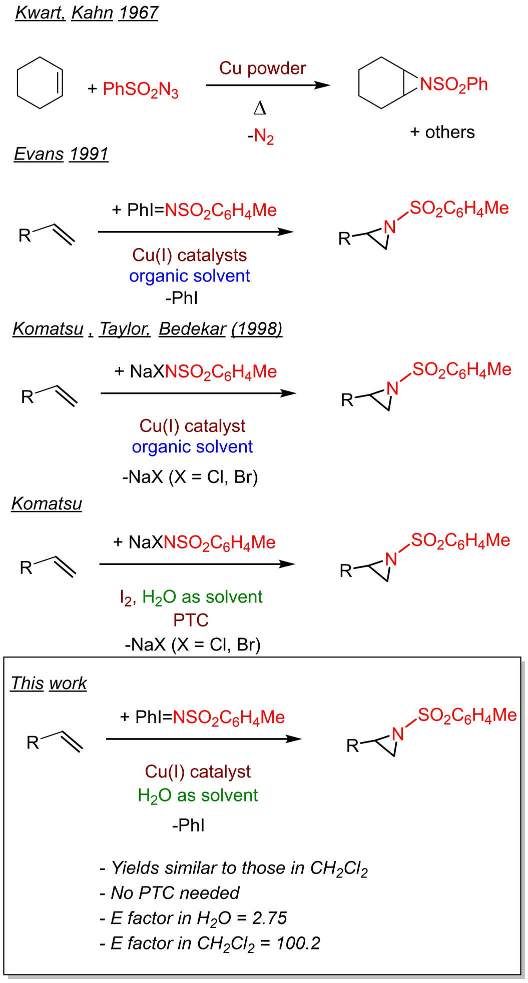
The copper complex $Tp^{(CF_3)_2,Br}Cu(NCMe)$ efficiently catalyses the aziridination of olefins in water using PhI=NTs as the nitrene source, with identical activity than that observed when using dichloromethane as the solvent, under the same experimental conditions. No specific modification of catalyst or substrates are required, nor the presence of additional phase transfer catalyst. Competition experiments and Hammett plots show that the behaviour of the metal centre is the same in both reaction media. This is the first example of a catalytic system employing PhI=NTs for olefin aziridination in water.

Introduction

In the context of modern chemistry, the development of sustainable processes verifying the Green Chemistry Principles proposed by Anastas and Warner is gaining interest among the scientific community.[1] One of these principles refers to the use of solvents and, more specifically, to the need of decreasing or eliminate solvents or to use innocuous ones. In this sense, replacing organic solvents by water as reaction medium would satisfy that postulate, also diminishing the E-factor, the waste/product ratio (mass-based) proposed by Sheldon.[2] However, in many cases the change of reaction medium to water requires the modification of one or more components of the catalytic system, either the catalyst or the reactant(s), introducing a certain degree of complexity.

The metal-catalysed olefin aziridination was discovered in 1967 by Kwart and Khan using copper powder as the catalyst for the nitrene transfer reaction from an organic azide (Scheme 1).[3] Since then, many catalytic systems have been disclosed for this reaction, with copper being the most common metal employed toward that end.[4] Following Evans' seminal work (Scheme 1),[5] copper-based catalysts for olefin aziridination are very frequently developed with iminoiodonane PhI=NTs[6] (Ts = *p*-toluenesulfonyl) or derivatives as the nitrene source. In 1998 significant advances in the use of haloamines-T (NaXNTs; X = Cl, chloramine-T; X = Br, bromamine-T, Scheme 1) were disclosed with copper catalysts. Komatsu employed anhydrous chloramine-T in acetonitrile for alkene aziridination using Cu(I),[7] whereas Taylor employed the trihydrated chloramine-T for the same transformation.[8] Bedekar provided the



Scheme 1. Copper-catalyzed olefin aziridination in organic solvent or in water.

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version using Bromamine-T reagent, also employing acetonitrile as solvent.[9] Further work, always in organic solvents, demonstrated a similarity between these haloamines-T and PhI=NTs as nitrene transfer agents with several metal-based catalysts.[10,11] Taking advantage of the solubility of those haloamines in water, several groups also described the olefin aziridination employing iodine as the catalytic species,[12] which required the presence of phase transfer catalysts (PTC, Scheme 1). Interestingly, we are not aware of any copper-based system for olefin aziridination that operates in water and employs PhI=NTs as the nitrene source.

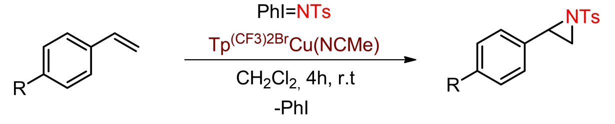
Our group has previously described a catalytic system for alkane C–H functionalization by carbene insertion in water,[13] where the reaction occurred inside the organic bubbles existing in the emulsion originated upon stirring the water-alkane mixture. Such organic phase dissolved the catalyst and the carbene source (a diazo compound), favouring the catalytic reaction due to the large concentration of reactants in small volumes, and avoiding the use of organic solvents. No PTCs were also needed. Following this idea, we have now expanded that study to the olefin aziridination reaction and found that the complex Tp$^{(CF3)2,Br}$Cu(NCMe)[14] (**1**) promotes the formation of aziridines in good to high yields with water as the reaction carrier, eliminating the use of the commonly employed dichloromethane solvent and without the need of any modification of catalyst and/or reactants to be employed in water. A considerable improvement of the E-factor[2] is achieved with this strategy (Scheme 1).

Results and Discussion

Dichloromethane as solvent for aziridination of styrenes

We first investigated the yet unreported catalytic capabilities of the complex Tp$^{(CF3)2,Br}$Cu(NCMe) toward the aziridination of styrenes, using PhI=NTs as the nitrene precursor, in dichloromethane as solvent. An array of styrenes was employed, with the results shown in Table 1. With a molar ratio of 1:20:100 for [**1**]:[PhI=NTs]:[olefin], referred to 0.0125 mmol of the catalyst, distinct reaction outcomes were observed upon 4 h of stirring at room temperature. Thus, styrene gave quantitative conversion into the aziridine, whereas styrenes bearing an electron-withdrawing group in the *para*-position (F, Cl, NO_2) led to slightly lower values, but always above 92%. Surprisingly, methyl- and methoxy-substituted styrenes provided lower yields, at variance with previous work in the literature with Tp^{x}Cu catalysts.[15,16] A closer look to the NMR of the reaction crudes revealed the presence of broad signals (see SI) which seems to correspond to polymeric material. It is very likely that the Lewis acidity of the copper centre, enhanced by this fluorinated trispyrazolylborate ligand, may induce a secondary transformation, which has not been investigated at this stage.

Table 1. Aziridination of styrenes using complex **1** as catalyst.[a]



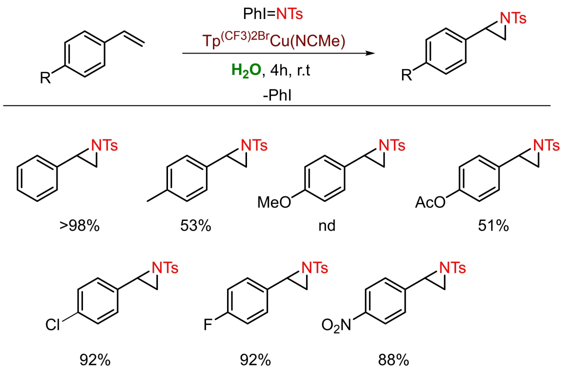
Entry	R	[%] Aziridine[b]
1	H	>98
2	OMe	55[c]
3	Me	84[c]
4	Cl	95
5	F	92
6	NO_2	94

[a] Reaction conditions: 0.0125 mmol catalyst, 1.25 mmol styrene, 0.25 mmol Ph=NTs, 5 mL of dichloromethane. [b] Determined by NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Polymeric material also detected.

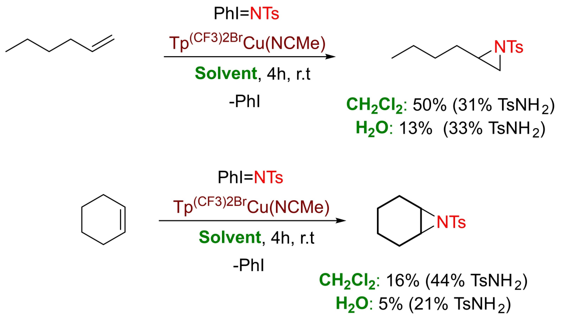
Olefin aziridination in water catalysed by 1

Once demonstrated the catalytic capabilities of complex **1** to promote the addition of the nitrene NTs group to the styrene C=C bond, a second array of experiments were performed in an identical manner to those of Table 1 but replacing dichloromethane with water as the solvent. In both cases an inert atmosphere of nitrogen was employed. The results (Scheme 2) were quite similar to those obtained with dichloromethane as solvent, just a minor decrease being observed. Thus, styrene provided the highest yield into aziridine and those with Cl, F or NO_2 substituents were aziridinated in 88–92% yield. Again, the Me-substituted styrene did not lead to high yields, a modest 53% of the aziridine was measured. Moreover, no aziridine was found in the experiment with the OMe group. In this case, an additional styrene with an AcO group was employed, which provided 51% yield of the aziridine. In the latter cases, NMR data also showed the broad resonances previously commented (see SI). It is worth mentioning that some greenish coloration is observed in the olefin phase.

We have also studied the aziridination reaction employing non-aromatic olefins, as it is the case of cyclohexene or 1-hexene. Scheme 3 shows the results of the experiments carried out in dichloromethane and in water. Maintaining the same reaction time than in the styrene experiments, lower yields were found, and mass balance was incomplete (Scheme 3),



Scheme 2. Aziridination of styrenes using complex **1** as catalyst. Experimental conditions as in Table 1, only solvent is changed from there.



Scheme 3. Aziridination of non-aromatic olefins using complex **1** as catalyst. Yields are based on initial PhI=NTs, which could not be completely accounted.

indicating that some initial PhI=NTs remained unreacted after 4 h. The lower conversions can be explained by (i) the less activated C=C bonds in these olefins (affecting both experiments solvents) and (b) their low polarity which decrease the potential to dissolve some of the nitrene source and/or the catalyst in the emulsion generated in water.

To assess the stability of the catalyst during the process, the final mixture was investigated by ^{19}F NMR, showing the same set of resonances than that of the starting material.

E-factor for the dichloromethane and water systems

In 1992, Sheldon proposed[2a] the use of the E-factor as a measurement on how "green" a given chemical process is. Its calculation is quite simple, just a fraction between the mass of waste generated in a reaction and the mass of the desired product. For the aziridination of styrene, catalysed by **1**, Table 2 contains the data employed for its calculation. It is worth noting that water is not considered in the calculation of the E-factor. For the reaction with styrene, which leads to quantitative conversion into the aziridine, 0.25 mmol (68 mg) of the latter are obtained in both cases, with PhI (0.25 mmol, 51 mg) being the by-product derived from PhI=NTs. However, the excess of olefin, as well as the catalyst and the solvent are also taken into the calculation for the E-factor. In this manner, a value of 100.2 is obtained for the reaction carried out in dichloromethane, a nearly 50-fold value of that obtained for the reaction carried out in water (E = 2.4). Therefore, the fact that the reaction takes place with the same extension in both solvents under identical conditions, without any modification of the catalyst or the addition of phase transfer catalysis, provides an outstanding advantage from the perspective of green chemistry in favour of the use of water as the reaction medium.

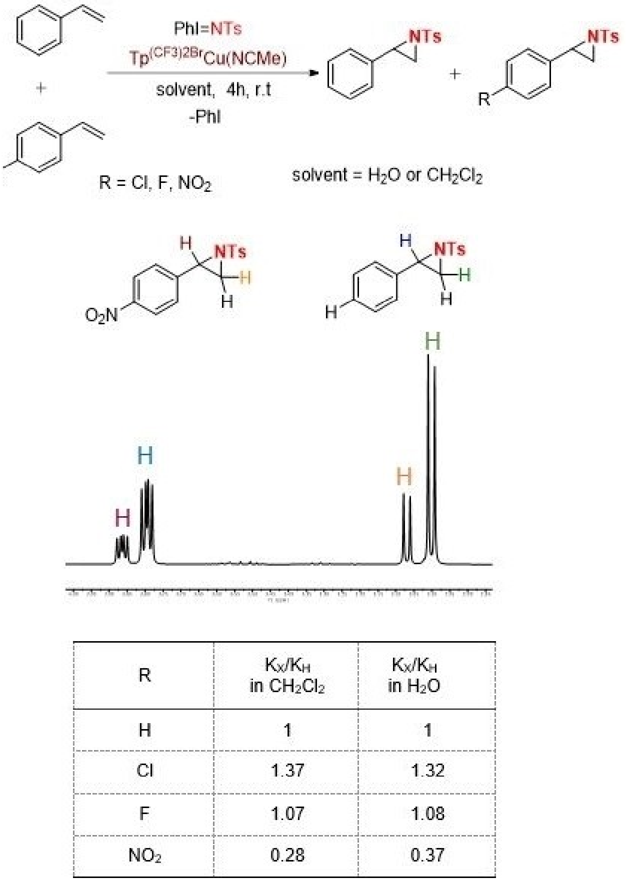
Table 2. The E-factors for the aziridination of styrene in dichloromethane and water.

	In CH_2Cl_2 (in mg)	In H_2O (in mg)
Product (aziridine)	68	68
Waste:		
PhI	51	51
Excess styrene	104	104
Catalyst	12	12
Solvent	6650	–
E-factor	**100.2**	**2.4**

Competition experiments with styrenes and Hammett correlations

Given the two different reaction media employed in this work, we wondered about the effect that such change could have in the reaction mechanism. Previous work from our laboratory has shown that the aziridination reaction catalysed with Tp^xCu cores is governed by a complex reaction mechanism in which triplet and singlet pathways are involved.[16] To shed light on a possible effect of the solvent on the reaction pathway, we have performed a series of competition experiments, the relative ratio of products being further correlated with Hammett's equation.

Scheme 4 shows the general competition reaction, as well as a representative example of the evaluation of the reaction outcome: the ^{1}H NMR spectrum of the reaction of an equimolar



R	K_X/K_H in CH_2Cl_2	K_X/K_H in H_2O
H	1	1
Cl	1.37	1.32
F	1.07	1.08
NO_2	0.28	0.37

Scheme 4. Top: Catalytic competition experiments with substituted styrenes, with conditions as in Table 1. Center: Selected region of the ^{1}H NMR spectrum of the reaction crude of the experiment using *p*-NO_2-styrene and styrene, in water as the solvent. Bottom: K_X/K_H values obtained.

mixture of *para*-nitrostyrene and styrene from which a 0.37:1 respective ratio of the aziridines is obtained. The OMe- and Me-substituted styrenes that gave polymeric material have not been included in this study since the competition data would have been masked by that side-reactivity. Experimental data for the full set of experiments is given in Scheme 4, and Figure 1 displays the plot derived from applying Hammett equation ($\log(K_X/K_H) = \rho\sigma$) the ratio of products, which for this transformation can be considered as K_X/K_H, employing the σ^+ scale. The degree of correlation in not very high, with R^2 values of 0.86–0.87. It is worth noting the high similarity between the two sets of data, which points toward a low effect of the media in the reaction pathway.

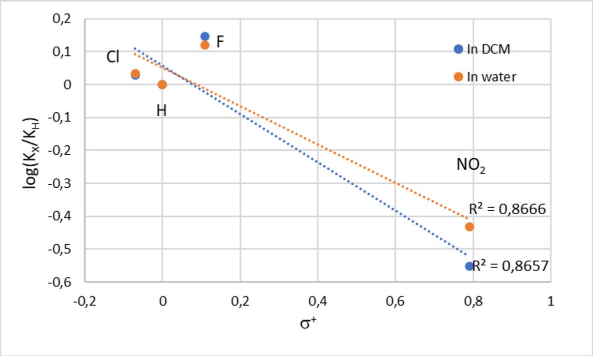


Figure 1. Plot of $\log(K_X/K_H)$ vs σ^+ for data obtained from competition experiments in dichloromethane or in water as reaction solvents.

Table 3. Fitting of competition experiment data in the dual Hammett equation $\log(K_X/K_H) = \rho^+\sigma^+ + \rho^\bullet\sigma^\bullet$ (deviations in bracketts, see SI).

$\sigma^\bullet$ scale	solvent	ρ^+	$\rho^\bullet$	R^2
Jackson	CH_2Cl_2	−0.60 (1.27)	−0.15 (1.49)	0.870
	H_2O	−0.52 (1.05)	−0.065 (1.23)	0.860
Ji	CH_2Cl_2	−1.28 (0.07)	1.33 (0.17)	0.998
	H_2O	−1.03 (0.04)	1.10 (0.09)	0.999
Fisher	CH_2Cl_2	−1.03 (0.40)	0.65 (0.73)	0.929
	H_2O	−0.81 (0.34)	0.50 (0.63)	0.919

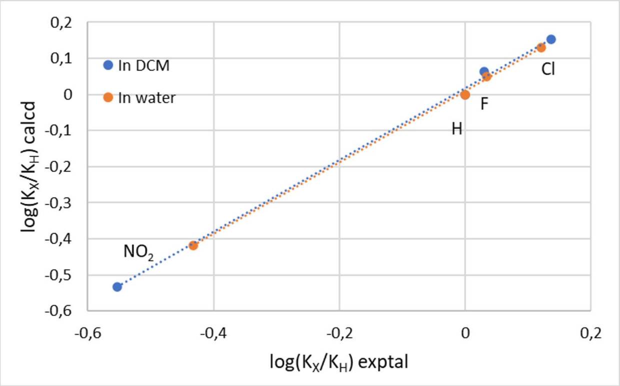


Figure 2. Correlations of the $\log(K_X/K_H)$ exptal vs the calculated value using the dual parameter Hammett equation with data in Table 3.

The lack of a good correlation of experimental data with Hammett equation, at variance with the olefin cyclopropanation reaction with this type of catalysts,[15] derives from the above mentioned complex pathway which involve polar and radical effects. Therefore, these experimental data must be fitted into a dual parameter Hammett equation of type $\log(K_X/K_H) = \rho^+\sigma^+ + \rho^\bullet\sigma^\bullet$, which accounts for both type of factors.[16] Several $\sigma^\bullet$ scales have been proposed in the literature, such as those by Jackson,[17] Ji[18] and Fisher.[19] We have employed these three scales to fit our experimental data in that dual parameter equation, and found that the best correlation was found employing Ji's scale, not only in terms of the R^2 values but also in the minima standard deviations of the ρ^+ and $\rho^\bullet$ values, and for both solvents studied (Table 3).

Once determined the optimal radical scale for our systems, the plot of the $\log(K_X/K_H)_{exptal}$ vs the corresponding values calculated from $\log(K_X/K_H) = \rho^+\sigma^+ + \rho^\bullet\sigma^\bullet$ (Figure 2) indicates an identical behaviour of this process in both reaction media employed, either dichloromethane or water. Therefore, the formation of the metallonitrene intermediates and its further interaction with the olefin substrate is not influenced by the reaction medium in terms of chemoselectivity.

It is worth noting that the already commented formation of polymeric materials with the Me- and MeO- derivatives has reduced the Hammett data to four examples, and therefore the regression and correlation must be taken with caution. In any case, previous work demonstrated that those electron-donating groups show the expected behavior of being more reactive than styrene.

Conclusion

We have found that a copper(I)-based complex catalyses the aziridination of styrenes in high yields using water as the reaction solvent and PhI=NTs as the nitrene source, without any additional modification of the catalyst, substrates, or the presence of a phase transfer catalyst. The use of a N_2 atmosphere ensures catalyst stability, with no effect of water on it. The comparison with the catalytic activity in dichloromethane indicates an identical behaviour, not only in terms of aziridine yields but also from a mechanistic point of view, as inferred from competition experiments and Hammett plots. This simple change of solvent involves a decrease of the E-factor calculated for this transformation by a factor or 50. This finding should aim at the use of water as the solvent for the general olefin aziridination from the perspective of the advancement of Green Chemistry.

Experimental Section

General Information: All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen atmosphere or in a glovebox (MBRAUN UNILAB). Solvents were purchased from commercial sources and deoxygenated immediately before their use. The water employed in the experiments was Milli-Q quality. Reagents were acquired from suppliers and used without any further purification. The complex **1**[14] and the nitrene precursor PhI=NTs[6] were synthesized according to literature procedures. NMR spectra were recorded on a Bruker 400 Hz spectrometer as solutions at 298 K and referenced to residual solvent peaks.

Catalytic experiments. Complex **1** (12.03 mg, 0.0125 mmol) was dissolved in deoxygenated water or DCM (5 mL). The olefin was then added in the desired excess (1.25 mmol), followed by the addition of PhI=NTs (93 mg, 0.25 mmol) in one portion. After 4 h of stirring at room temperature, the volatiles were removed under reduced pressure and the crude was analysed by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (the NMR sample was previously passed through a plug of silica gel). The aziridines were identified upon comparison with literature reports.[5,9]

Competition experiments

These experiments were carried out by following the above procedure, employing mixtures of styrene and the corresponding *p*-substituted styrene (1.25 mmol of each). When solid PhI=NTs was not observed, the volatiles were removed under vacuum and the relative ratio of aziridines was estimated by ^{1}H NMR spectroscopy of the reaction crude in $CDCl_3$ (the NMR sample was previously passed through a plug of silica gel).

Supporting Information

(see footnote on the first page of this article): NMR data of all catalytic experiments and fitting of competition experiments into Hammett equations.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Catalysis in Water · Copper Catalysis · E-Factor · Green Chemistry · Olefin Aziridination

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