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ORIGINAL ARTICLE

Functionalization of π-activated alcohols by trapping carbocations in pure water under smooth conditions☆

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KEYWORDS

π-Activated alcohols;
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Water

Abstract Acetic acid as catalyst in pure water was found to be an excellent reaction medium for the direct dehydrative functionalization of π-activated alcohols using a wide variety of interesting *C*-, *P*-, and *S*-centered nucleophiles, such as indoles, pyrrole, anilines, 1,3-dicarbonyl compounds, diphenyl phosphite and pyridine-2-thiol. The smooth reaction conditions, along with high yields, short reaction times, clean reaction crudes, an easy product isolation procedure, plus the reusability of the catalyst and the use of no excess of nucleophiles, make this approach an atom economical, green and appealing method to efficiently trap carbocations in pure water, leading to new Csp^3—X bonds (X = Csp^2, Csp^3, P and S).

1. Introduction

In the last decades, the role of alcohols as environmental friendly alkylation agents has gain increasing importance. The dehydrative functionalization of the C—OH bond is very convenient since only water is generated as by-product (Bandini and Tragni, 2009; Dryzhakov et al., 2016; Kumar and Van der Eycken, 2013). However, due to the poor capacity of the OH group as leaving group, the reaction generally requires its previous transformation into a good leaving group or its activation with an excess of a Brønsted acid or a stoichiometric amount of a Lewis acid.

Therefore, it is desirable the development of new direct catalytic C—X bond forming strategies, which avoid the need for wasteful pre-functionalization of the alcohol, allowing the use of mild reaction conditions.

It is accepted that π-activated alcohols with a Csp^3—OH bond (benzylic, allylic, propargylic alcohols) can proceed via conversion of the C—OH to a carbocation, followed by attack of the nucleophile (Dryzhakov et al., 2016; Emer et al., 2011). Hereof, the generation of stable carbocations from alcohols and their further S_N1 nucleophilic substitution has gain interest in the last decade (Baeza and Nájera, 2014; Biannic and Aponick, 2011; Cera et al., 2012; Gualandi et al., 2013;

☆ To Prof. Herbert Mayr for his contribution in the field of carbocations.

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Gualandi and Cozzi, 2013; Muzart, 2008; Ortiz and Herrera, 2017).

Herein, we describe a new direct dehydrative functionalization of Csp^3—OH bond of alcohols with various carbon nucleophiles such as, arenes/heteroarenes and active methylene compounds, *e.g.*, 1,3-dicarbonyl compounds; as well as non-carbon nucleophiles such as, phosphite and thiol.

In the case of arenes/heteroarenes, Friedel–Crafts (F–C) reaction represents one of the most powerful C—C bond forming tools in organic synthesis (Friedel and Crafts, 1877a, 1877b). Among the developed F–C reactions, together with the advantages that this strategy offers, the chemistry of indole has been widely explored to obtain valuable structural derivatives (Fu, 2010; Kochanowska-Karamyan and Hamann, 2010; Lancianesi et al., 2014). The importance of developing new 3-susbtituted indoles lies in the presence of this privileged motif in remarkable natural and unnatural compounds with pharmacological and agrochemical properties (Bronner et al., 2011; Kaushik et al., 2013; Wu, 2010; Zhang et al., 2015).

The use of water as solvent or as co-solvent has recently gained special attention as the most environmentally friendly medium (Jessop, 2011; Lindström, 2007). Moreover, the use of water would reduce the employment of harmful organic solvents and the consumption of drying agents, which is in agreement with some of the twelve principles in Green Chemistry (Anastas and Warner, 1998; Constable et al., 2007; Sheldon, 2012; Tundo et al., 2000). However, despite the number of processes that have been investigated and developed in water, this medium is still not commonly used as a sole solvent for organic reactions (Blackmond et al., 2007; Hayashi, 2006; Marqués-López et al., 2008). Therefore, the development of reactions in pure water is still an exciting research topic. Particularly, the dehydrative reaction in water is a most challenging task (Ortiz and Herrera, 2017).

Hence, in order to develop a more environmentally benign version of the reaction under study via a metal-free catalytic approach, we firstly focused on the secondary benzylic alcohol: 9*H*-xanthen-9-ol (**1a**) (Scheme 1), which has been centre of previous investigations using diverse conditions (Cozzi and Zoli, 2007, 2008; Cozzi et al., 2009; Funabiki et al., 2014; Liu et al., 2011, 2012; Petruzziello et al., 2012; Trillo et al., 2013; Vicennati and Cozzi, 2007; Wang and Ji, 2008; Xiao et al., 2011, 2012; Xiao, 2012; Zhang et al., 2010; Zhou et al., 2011; Zhu et al., 2011).

2. Materials and methods

2.1. General experimental methods

When necessary, purification of reaction products was carried out by flash chromatography using silical-gel (0.063–0.200 mm). Analytical thin layer chromatography was performed on 0.25 mm silical gel 60-F plates. ESI ionization method and mass analyzer type MicroTof-Q were used for the ESI measurements. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz, using $CDCl_3$ as the solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and to the central line of $CDCl_3$ (77.00 ppm) for ^{13}C APT-NMR (Attached Proton Test).

All commercially available solvents and reagents were used as received. The ^{1}H and ^{13}C NMR spectra for compounds **3aa** (Cozzi and Zoli, 2008), **3ab** (Wang and Ji, 2008), **3ac** (Wang and Ji, 2008), **3ad** (Liu et al., 2011), **3ae** (Liu et al., 2011), **3af** (Cozzi and Zoli, 2008), **3aaf** (Funabiki et al., 2014), **3ai** (Pintér and Klussmann, 2012), **3aj** (Pintér and Klussmann, 2012), **3ba** (Hikawa et al., 2013) and **3bc** (Hikawa et al., 2013) are consistent with values previously reported in the literature.

2.2. Representative procedure for the reaction of 9*H*-xanthen-9-ol (*1a*) with nucleophiles *2a-e*,*g-l*

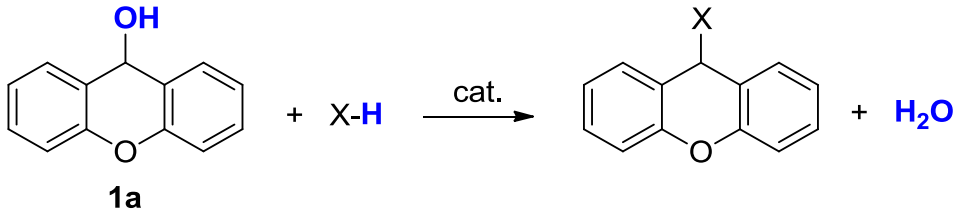
To a mixture of 9*H*-xanthen-9-ol (**1a**) (19.8 mg, 0.1 mmol) and AcOH (1.1 μL, 0.02 mmol) in distilled H_2O (0.5 mL), nucleophile **2a-e**,**g-l** (0.1 mmol) was added and the resulting mixture was stirred in a tube at room temperature until the disappearance of the starting material (checked by thin-layer chromatography, TLC). Then, the reaction mixture was extracted with Et_2O (4 × 1 mL). The combined organic layers were dried using Na_2SO_4, filtered and then concentrated under vacuum to afford the pure final product **3aa-ae**,**ag-al**. When necessary the crude was purified by column chromatography. Yields are reported in Table 2 and pure compounds were obtained as stable solids.

2.2.1. *N,N-Dimethyl-4-(9H-xanthen-9-yl)aniline (3ag)*

Following the general procedure, compound **3ag** was obtained after 6 h of reaction at room temperature as a grey solid in 88% yield. M.p. 149–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2H), 7.15–7.07 (m, 6H), 6.99 (ddd, J = 7.7 Hz, 7.0 Hz, 1.5 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 5.19 (s, 1H), 2.93 (s, 6H). ^{13}C APT-NMR (75 MHz, $CDCl_3$) δ 151.1 (2C), 129.7 (2C), 129.1 (2C), 127.1 (2C), 125.1 (2C), 123.1 (2C), 116.1 (2C), 112.9 (1C), 43.4 (2C), 40.7 (1C). IR (KBr film) (cm^{-1}) ν 3061, 3035, 2885, 2805, 1614, 1571, 1522, 1479, 1449, 1357, 1254, 1205, 1116, 1094, 937, 900, 843, 800, 749, 691, 618, 574, 555, 523, 462. HRMS (ESI+) calcd $C_{21}H_{20}NO$ 302.1539; found 302.1536 [M + H].

2.2.2. *3-Methoxy-N,N-dimethyl-4-(9H-xanthen-9-yl)aniline (3ah)*

Following the general procedure, compound **3ah** was obtained after 3 h of reaction at room temperature as a brown solid in



Scheme 1 Benchmark reaction for the catalytic direct dehydrative functionalization of 9*H*-xanthen-9-ol (**1a**).

89% yield. M.p. 163–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.08 (m, 6H), 6.96 (ddd, *J* = 7.8 Hz, 7.0 Hz, 1.5 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 6.22 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 5.69 (s, 1H), 3.86 (s, 3H), 2.93 (s, 6H). ^{13}C APT-NMR (75 MHz, $CDCl_3$) δ 157.2 (1C), 151.5 (2C), 150.5 (1C), 130.6 (1C), 129.5 (2C), 127.2 (2C), 125.5 (2C), 123.9 (1C), 122.9 (2C), 116.0 (2C), 105.3 (1C), 96.2 (1C), 55.5 (1C), 40.6 (2C), 36.3 (1C). IR (KBr film) (cm^{-1}) ν 2930, 1711, 1654, 1606, 1573, 1503, 1478, 1447, 1327, 1345, 1300, 1251, 1118, 1095, 1032, 892, 748. HRMS (ESI+) calcd $C_{22}H_{21}NO_2Na$ 354.1465; found 354.1476 [M + Na].

2.2.3. Diphenyl 9H-xanthen-9-ylphosphonate (*3ak*)

Following the general procedure, compound **3ak** was obtained after 3 h of reaction at room temperature as a purple solid in 60% yield. M.p. 158–161 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.51 (m, 2H), 7.37–7.31 (m, 2H), 7.22–7.05 (m, 10*H*), 6.83–6.79 (m, 4H), 4.92 (d, *J* = 23.9 Hz, 1H). ^{13}C APT-NMR (75 MHz, $CDCl_3$) δ 152.5 (d, *J* = 5.5 Hz, 2C), 150.5 (d, *J* = 10.5 Hz, 2C), 130.4 (d, *J* = 4.6 Hz, 2C), 129.5 (4C), 129.2 (d, *J* = 3.9 Hz, 2C), 124.9 (2C), 123.4 (d, *J* = 3.4 Hz, 2C), 120.2 (d, *J* = 4.3 Hz, 4C), 116.9 (d, *J* = 3.6 Hz, 2C), 116.0 (d, *J* = 8.5 Hz, 2C), 40.7 (d, *J* = 143.4 Hz, 1C). IR (KBr film) (cm^{-1}) ν 3074, 3060, 3037, 2914, 1586, 1574, 1486, 1476, 1458, 1451, 1263, 1253, 1205, 1183, 1159, 1117, 941, 925, 905, 825, 806, 769, 754, 688, 589, 507, 498, 485. HRMS (ESI+) calcd $C_{25}H_{19}O_4PNa$ 437.0913; found 437.0903 [M + Na].

2.2.4. 2-(9H-Xanthen-9-ylthio)pyridine (*3al*)

Following the general procedure, compound **3al** was obtained after 3 h of reaction at room temperature as a yellow solid in 84% yield. M.p. 77–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.9 Hz, 1.8 Hz, 0.9 Hz, 1H), 7.52–7.46 (m, 3H), 7.24–7.21 (m, 2H), 7.11–6.99 (m, 6H), 6.77 (s, 1H). ^{13}C APT-NMR (75 MHz, $CDCl_3$) δ 157.8 (1C), 152.1 (2C), 149.3 (1C), 136.4 (1C), 129.4 (2C), 128.6 (2C), 123.4 (2C), 123.2 (1C), 122.3 (2C), 120.5 (1C), 116.5 (2C), 41.2 (1C). IR (KBr film) (cm^{-1}) ν 3040, 2918, 2878, 2851, 1651, 1616, 1602, 1573, 1554, 1479, 1449, 1441, 1328, 1253, 1210, 1146, 1115, 1098, 1033, 984, 899, 830, 744, 717, 663, 470. HRMS (ESI+) calcd $C_{18}H_{13}NOSNa$ 314.0610; found 314.0614 [M + Na].

2.3. Procedure for the regioselective reaction of 9H-xanthen-9-ol (*1a*) with pyrrole (*2f*)

To a mixture of 9*H*-xanthen-9-ol (**1a**) (19.8 mg or 41.6 mg, 0.1 or 0.21 mmol) and AcOH (1.1 μL, 0.02 mmol) in H_2O (0.5 mL), pyrrole (**2f**) (13.8 μL or 6.9 μL, 0.2 or 0.1 mmol) was added and the resulting mixture was stirred in a tube at room temperature until the disappearance of the starting material (checked by thin-layer chromatography, TLC). After 3 h, the reaction mixture was extracted with Et_2O (4 × 1 mL). The combined organic layers were dried using Na_2SO_4, filtered and then concentrated under vacuum. The crudes were purified by column chromatography to afford the final products **3af** and **3aaf** with >95% yield.

2.4. Representative procedure for the reaction of 9H-xanthen-9-ol (*1a*) with indole (*2a*) in vinegar

To a mixture of 9*H*-xanthen-9-ol (**1a**) (19.8 mg, 0.1 mmol) and vinegar (0.5 mL), indole **2a** (11.7 mg, 0.1 mmol) was added and the resulting mixture was stirred in a tube at room temperature until the disappearance of the starting material (checked by thin-layer chromatography, TLC). After 1 h, the reaction mixture was extracted with Et_2O (4 × 1 mL). The combined organic layers were dried using Na_2SO_4, filtered and then concentrated under vacuum to afford the pure final product **3aa** with >95% yield without additional purification.

2.5. Representative procedure for the reaction of bis(4-methoxyphenyl)methanol (*1b*) with nucleophiles *2a,c*

To a mixture of bis(4-methoxyphenyl)methanol (**1b**) (24.7 mg, 0.1 mmol) and AcOH (1.1 μL, 0.02 mmol) in H_2O (0.5 mL), nucleophile **2a**,**c** (0.1 mmol) was added and the resulting mixture was stirred in a tube at 40 °C during 18 h. Then, the reaction mixture was extracted with Et_2O (4 × 1 mL). The combined organic layers were dried using Na_2SO_4, filtered and then concentrated under vacuum to afford the pure final product **3ba-3bc** with >99% yield without additional purification.

3. Results and discussion

To explore the viability of a catalytic version of the direct dehydrative functionalization of Csp^3—OH bond of alcohols, we chose acetic acid (AcOH) as commercially available, handy and cheap catalyst. To start with, we tested the aforesaid reaction with 1 equivalent of indole (**2a**) as nucleophile (Table 1). Using stoichiometric amounts of the substrates we minimized waste and facilitated the purification of the final product in completed reactions, where a simple extraction with ethyl ether (Et_2O) is sufficient.

We started our investigation using 30 mol% of AcOH as catalyst and different solvents (entries 1–7). To our delight, good results were obtained with all of them, even with pure water (entry 7), what encouraged us to continue with this green solvent, following our goal of developing a method as green as possible. It is interesting to highlight that in this case, the reaction has a heterogeneous appearance due to the low solubility of the reactants in water (Fig. 1, the solubility of indole in water is 16 μL/mL) (Pearlman et al., 1984). In the literature, hydrophobic effects are hypothesized to support the acceleration of the reactions using water as a solvent when the reactants are slightly soluble or insoluble in this medium (Breslow, 1991; Narayan et al., 2005; Pirrung et al., 2008; Rideout and Breslow, 1980), such as probably occurs in our case.

In F–C alkylations and mechanistically related reactions that are carried out in aqueous media, Brønsted acids are used to generate small equilibrium concentrations of carbocations (Hofmann et al., 2004). Thus, solvolytically generated carbocations can be trapped by π systems such as, donor-substituted arenes and alkenes. According to Mayr's nucleophilicity scales studies, these species are more nucleophilic than aqueous or

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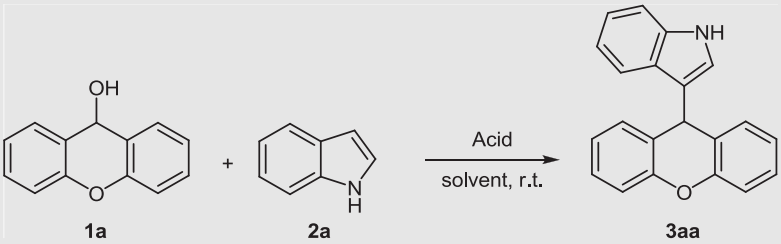
Table 1 Initial screening for the direct dehydrative alkylation of alcohol **1a**, using indole (**2a**) as nucleophile.[a]



Entry	Cat. (mol%)	Solvent (mL)	Time (h)	Conv.[b]
1	AcOH (30)	MeOH (0.5)	3	>99
2	AcOH (30)	CH_3CN (0.5)	3	>99
3	AcOH (30)	AcOEt (0.5)	3	>99
4	AcOH (30)	CH_2Cl_2 (0.5)	3	>99
5	AcOH (30)	$CHCl_3$ (0.5)	3	>99
6	AcOH (30)	Toluene (0.5)	3	>99
7	AcOH (30)	H_2O (0.5)	3	>99
8	AcOH (20)	H_2O (0.5)	3	>99 (95[c])
9	AcOH (10)	H_2O (0.5)	6	>99
10	AcOH (20)	H_2O (1)	7	95[c]
11	AcOH (20)	H_2O (2)	14	95[c]
12[d]	Vinegar (0.5)		1	>95[c]
13	–	H_2O (0.5)	18	n.r.[e]

[a] Otherwise indicated: To a solution of 9*H*-xanthen-9-ol (**1a**) (0.1 mmol) and AcOH (0.01–0.03 mmol) in the corresponding solvent (0.5, 1 or 2 mL) [0.2 M, 0.1 M or 0.05 M of **1a** in the solvent, respectively], indole (**2a**) (0.1 mmol) was added at room temperature. The reactions were monitored by thin-layer chromatography. After disappearance of the starting materials or a reasonable reaction time, product **3aa** was isolated by a simple extraction.
[b] Conversions determined by ^{1}H NMR spectroscopy.
[c] Isolated yield after extraction with ethyl ether (Et_2O, 4 × 1 mL).
[d] Reaction performed in 0.5 mL of vinegar of red wine as the reaction medium.
[e] No reaction observed.

Fig. 1 Appearance of the reaction using AcOH in pure water.

alcoholic solutions employed as solvents for S_N1 reactions (Hofmann et al., 2004). Moreover, although the carbocations have very short lifetimes in aqueous media as a consequence of their rapid reactions with molecules of water (Richard et al., 2001), those times can be significantly augmented by the introduction of electron-donating substituents on the aryl ring, as in 9*H*-xanthen-9-ol (**1a**). Additionally, the amount of catalyst was varied without remarkably impairing in the reactivity of the process (entries 7–9). With only 10 mol% of AcOH (entry 9), longer reaction time is required to complete the process. When no AcOH is used, no reaction is observed (entry 13). This lack of reactivity indicates that in our case the water by itself is not able to activate the reaction, in contrast to that previously proposed by Cozzi and Zoli, 2008. Remarkably, using vinegar as a cheap and accessible source of acidic protons, instead of the mixture AcOH/H_2O, the reaction is even faster (1 h *vs* 3 h) with very good yield (>95%) (entry 12). In order to facilitate the stirring, hindered by the high density of the reaction medium, we diluted the reaction using 1 and 2 mL of water, obtaining also good results but again, increasing the reaction time (entries 10 and 11, respectively). After exploring different parameters, the use of 20 mol% of AcOH and 0.5 mL of H_2O (entry 8) was considered as the conditions of choice, although good results were found as well in other cases.

In order to demonstrate the generality of the procedure and to establish the scope of this C—X bond formation protocol, we explored different nucleophiles that are able to trap the *in situ* generated carbocation (Table 2).

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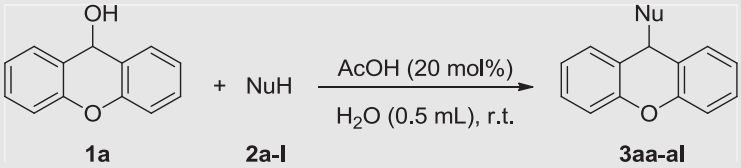
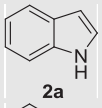
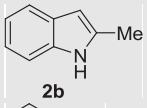
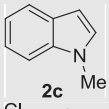
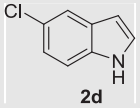
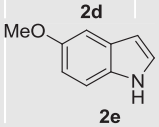
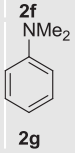
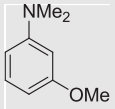
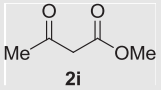
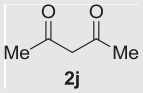
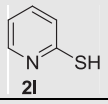
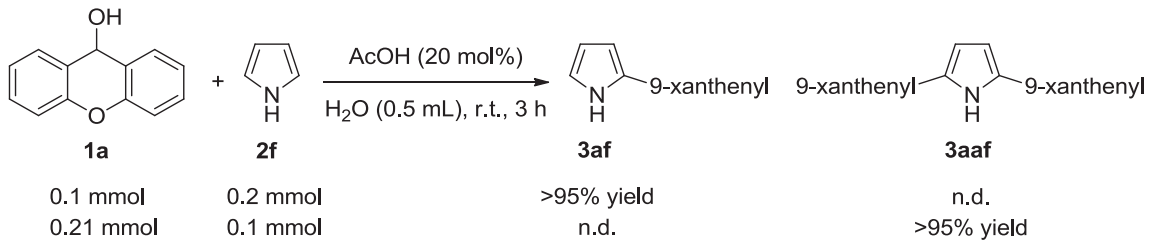
Table 2 Scope of the reaction.



Entry	Nucleophile	Product	Time (h)	Yield (%)[a]
1	 **2a**	**3aa**	3	95
2	 **2b**	**3ab**	3	91 (>99)[b]
3	 **2c**	**3ac**	3	93 (>99)[b]
4	 **2d**	**3ad**	3	76 (85)[b]
5	 **2e**	**3ae**	3	73 (86)[b]
6	 **2f**	**3af**/**3aaf**	3	(>99)[b]
7	 **2g**	**3ag**	6	88 (>95)[b]
8	 **2h**	**3ah**	3	89 (>99)[b]
9	 **2i**	**3ai**	10	81 (>99)[b]
10	 **2j**	**3aj**	3	83 (>99)[b]
11	$HP(O)(OPh)_2$ **2k**	**3ak**	3	60 (70)[b]
12	 **2l**	**3al**	3	84 (>99)[b]

[a] Isolated yields after simple extraction or column chromatography.
[b] Conversions determined by ^{1}H NMR spectroscopy.

Particularly, we were able to perform the reaction with different substituted indoles **2b-e** with very good to excellent yields (73–93%, entries 2–5). When the starting material is consumed, a further simple extraction with Et_2O from the reaction mixture would lead to the final product without a subsequent purification by column chromatography. Interestingly, when the reaction was performed using other heteroarene such as pyrrole (**2f**), a mixture of two compounds **3af**:**3aaf** (82:18) was initially observed in the reaction crude (entry 6). Since pyrrole derivatives are appealing compounds from a biological point of view, we further analyzed and explored in detail this reaction to improve the results (Scheme 2). We found that it



Scheme 2 Special case of pyrrole (**2f**) as nucleophile: Total control of the final product slightly varying the reaction conditions.

Table 3 Recycling the catalyst.

1 run	2 run	3 run	4 run	5 run
>99%[a]	95%[a]	93%[a]	89%[a]	89%[a]

[a] Conversions determined by ^{1}H NMR spectroscopy.

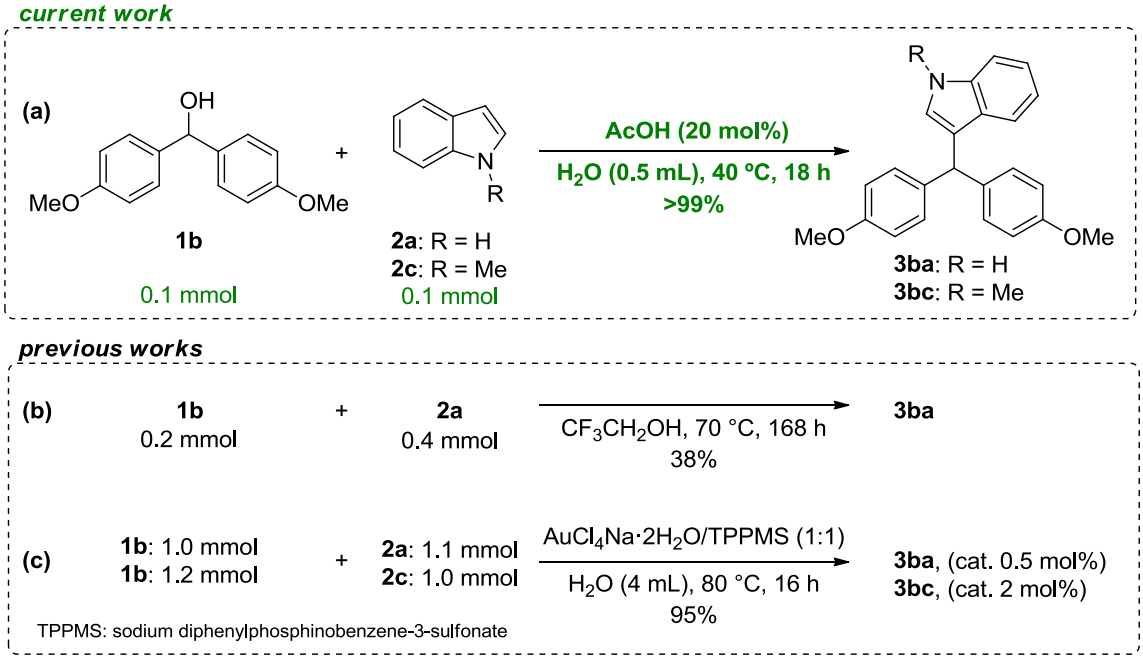
was possible to control the reaction regioselectivity, obtaining each single product just by varying the substrates initial ratio **1a**:**2f**. Thus, a full conversion into the product **3af** can be achieved using an excess of pyrrole (**2f**) (2 equiv.). Furthermore, compound **3aaf** was the unique reaction product when 2.1 equivalents of **1a** were added. This full control over the production of both compounds improves previous reported work, where a mixture of both products was always found (Funabiki et al., 2014).

We further checked the reactivity of other carbon nucleophiles, such as arenes (Csp^2—H, anilines **2 g-h**; entries 7 and 8) and active methylene compounds (Csp^3—H, 1,3-dicarbonyl compounds **2i-j**; entries 9 and 10), under the same reaction conditions. The final product containing the newly formed Csp^3—Csp^2 and Csp^3—Csp^3 bonds, were obtained also with high yields (88–89% and 81–83%, respectively).

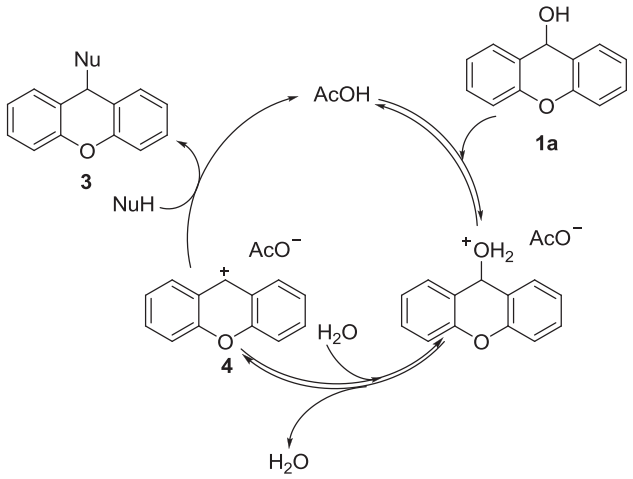
Finally, two more non-carbon nucleophiles, such as phosphite **2k** and thiol **2l**, also demonstrated to be suitable for this reaction. Thus, allowing an efficient formation of C—P and C—S bonds, respectively, in the final products (60–84%, entries 11 and 12).

We were also interested in determining whether the AcOH remained in the water after the extraction with Et_2O. In this case, we studied the possibility of reusing the catalyst several times. Hence, we performed a few cycles of the reaction of **1a** and **2a** reusing the resulting aqueous phase after each extraction (lower phase). Thus, after the first reaction was completed, the product was readily separated from the reaction vessel by a simple extraction with Et_2O (4 × 1 mL). Then, the resulting aqueous phase, with the remaining catalyst, was reused in the same vessel without any other treatment, adding again both reactants (**1a** and **2a**). As shown in Table 3, the process was carried out 5 times without considerable loss of reactivity (>99% → 89%). This result further demonstrates the simplicity and the green character of the developed procedure.

Remarkably, we were able to trap the carbocation generated from alcohol **1b** with the indoles **2a** and **2c**, following this simple procedure (*i.e.*, AcOH (20 mol%)/H_2O (0.5 mL) and 1 equivalent of the indole) (Scheme 3, a) (Bisaro et al., 2002; Coote et al., 1989; Gullickson and Lewis, 2003; Hofmann et al., 2004; Westermaier and Mayr, 2006). The reactions were



Scheme 3 Reaction of indoles **2a** and **2c** with pro-electrophilic alcohol **1b**, under current protocol conditions (a) and comparison with previous works: (b) (Cozzi and Zoli, 2007; Funabiki et al., 2014) and (c) (Hikawa et al., 2013).



Scheme 4 Proposed reaction mechanism.

heated at 40 °C during 18 h, obtaining clean reaction crudes and full conversions. In a previous work, this reaction failed on water and required a fluorinated solvent, higher temperature, an excess of substrates and longer reaction times, to provide a much lower yield of the final product **3ba** (38% *vs* > 99%) (Scheme 3, b) (Cozzi and Zoli, 2008; Funabiki et al., 2014). In a more recent publication the use of a gold catalyst is reported to achieve similar results, but requiring higher reaction temperature and the use of a slight excess of the substrates (Scheme 3, c) (Hikawa et al., 2013).

In the catalytic cycle illustrated in Scheme 4 the AcOH is responsible for the generation of the carbocation **4**. The final attack of the nucleophile (NuH) of the reaction will generate the products **3** observed.

Since water can also react as a nucleophile, the presence of water in an S_N1-type reaction could compete with the real nucleophile of the process, hindering the attack of the latter on the electrophile. For this reason our developed procedure is one of the scarce examples where carbocation can be trapped in pure water (Ortiz and Herrera, 2017), successfully demonstrating this challenging competitive process.

4. Conclusions

This study pioneers the use of easily accessible AcOH as suitable catalyst for the nucleophilic substitution of alcohols **1a-b** in pure water, affording final products with excellent yields after a simple extraction, in most of the cases. The mild and sustainable conditions and the operational simplicity of the procedure make this work an interesting example of trapping carbocations in pure water. The reusability of the catalytic medium has also been demonstrated to be possible without a significant efficiency loss after five times, following a very simple protocol. Finally, we were able to control by the first time the regioselectivity in the case of pyrrole as nucleophile, varying only the initial ratio of the substrates alcohol **1a**: pyrrole **2f**. As a result, this study signifies a pivotal precedent of a green and appealing process to efficiently trap carbocations in pure water allowing a variety of new C—X bonds formation.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.arabjc.2018.01.022.

References

Anastas, P., Warner, J.C., 1998. Green Chemistry: Theory and Practice. Oxford University Press, Oxford.
Baeza, A., Nájera, C., 2014. Recent advances in the direct nucleophilic substitution of allylic alcohols through S_N1-type reactions. Synthesis 46, 25–34.
Bandini, M., Tragni, M., 2009. π-Activated alcohols: an emerging class of alkylating agents for catalytic Friedel-Crafts reactions. Org. Biomol. Chem. 7, 1501–1507.
Biannic, B., Aponick, A., 2011. Gold-catalyzed dehydrative transformations of unsaturated alcohols. Eur. J. Org. Chem., 6605–6617
Bisaro, F., Prestat, G., Vitale, M., Poli, G., 2002. Alkylation of active methylenes via benzhydryl cations. Synlett, 1823–1826.
Blackmond, D.G., Armstrong, A., Coombe, V., Wells, A., 2007. Water in organocatalytic processes: debunking the myths. Angew. Chem. Int. Ed. 46, 3798–3800.
Breslow, R., 1991. Hydrophobic effects on simple organic reactions in water. Acc. Chem. Res. 24, 159–164.
Bronner, S.M., Im, G.-Y.J., Garg, N.K., 2011. Indoles and indolizidines. In: Majumdar, K.C., Chattopadhyay, S.K. (Eds.), Heterocycles in Natural Product Synthesis. Wiley-VCH Verlag, GmbH & Co. KGaA, pp. 221–265.
Cera, G., Chiarucci, M., Bandini, M., 2012. Accessing chemical diversity by stereoselective gold-catalyzed manipulation of allylic and propargylic alcohols. Pure Appl. Chem. 84, 1673–1684.
Constable, D.J.C., Dunn, P.J., Hayler, J.D., Humphrey, G.R., Leazer Jr., J.L., Linderman, R.J., Lorenz, K., Manley, J., Pearlman, B.A., Wells, A., Zaks, A., Zhang, T.Y., 2007. Key green chemistry research areas—a perspective from pharmaceutical manufacturers. Green Chem. 9, 411–420.
Coote, S.J., Davies, S.G., Middlemiss, D., Naylor, A., 1989. Enantiospecific synthesis of (+)-(*R*)-1-phenyl-3-methyl-1,2,4,5-tetrahydrobenz[*d*]azepine from (+)-(*S*)-*N*-methyl-1-phenyl ethanolamine (halostachine) via arene chromium tricarbonyl methodology. Tetrahedron Lett. 30, 3581–3584.
Cozzi, P.G., Benfatti, F., Zoli, L., 2009. Organocatalytic asymmetric alkylation of aldehydes by S_N1-type reaction of alcohols. Angew. Chem. Int. Ed. 48, 1313–1316.
Cozzi, P.G., Zoli, L., 2007. Nucleophilic substitution of ferrocenyl alcohols "on water". Green Chem. 9, 1292–1295.
Cozzi, P.G., Zoli, L., 2008. A rational approach towards the nucleophilic substitutions of alcohols "on water". Angew. Chem. Int. Ed. 47, 4162–4166.
Dryzhakov, M., Richmond, E., Moran, J., 2016. Recent advances in direct catalytic dehydrative substitution of alcohols. Synthesis 48, 935–959.
Emer, E., Sinisi, R., Capdevila, M.G., Petruzziello, D., de Vincentiis, F., Cozzi, P.G., 2011. Direct nucleophilic S_N1-type reactions of alcohols. Eur. J. Org. Chem., 647–666

Friedel, C., Crafts, J.M., 1877a. A new general synthetical method of producing hydrocarbons, etc. C. R. Hebd. Seances Acad. Sci. 84, 1392–1395.
Friedel, C., Crafts, J.M., 1877b. New general method for the synthesis of hydrocarbons, ketones, etc. C. R. Hebd. Seances Acad. Sci. 84, 1450–1454.
Fu, L., 2010. Advances in the total syntheses of complex indole natural products. Top. Heterocycl. Chem. 26, 433–480.
Funabiki, K., Komeda, T., Nishikawa, K., Yamada, K., Kubota, Y., Matsui, M., 2014. Commercially available simple ionic liquids-promoted dehydrative carbon-carbon bond-forming reaction of diarylmethanols and triarylmethanols with pyrroles, thiophene, furan and indoles. Tetrahedron 70, 9245–9252.
Gualandi, A., Cozzi, P.G., 2013. Stereoselective organocatalytic alkylations with carbenium ions. Synlett 24, 281–296.
Gualandi, A., Petruzziello, D., Emer, E., Cozzi, P.G., 2013. Alpha-alkylation by S_N1-type reactions. In: Dalko, P.I. (Ed.), Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications. Wiley-VCH, Weinheim, pp. 729–755.
Gullickson, G.C., Lewis, D.E., 2003. Reactions of active methylene compounds with benzhydrol during solvolysis in formic acid. Aust. J. Chem. 56, 385–388.
Hayashi, Y., 2006. In water or in the presence of water? Angew. Chem. Int. Ed. 45, 8103–8104.
Hikawa, H., Suzuki, H., Azumaya, I., 2013. Au(III)/TPPMS-catalyzed benzylation of indoles with benzylic alcohols in water. J. Org. Chem. 78, 12128–12135.
Hofmann, M., Hampel, N., Kanzian, T., Mayr, H., 2004. Electrophilic alkylations in neutral aqueous or alcoholic solutions. Angew. Chem. Int. Ed. 43, 5402–5405.
Jessop, P.G., 2011. Searching for green solvents. Green Chem. 13, 1391–1398.
Kaushik, N.K., Kaushik, N., Attri, P., Kumar, N., Kim, C.H., Verma, A.K., Choi, E.H., 2013. Biomedical importance of indoles. Molecules 18, 6620–6662.
Kochanowska-Karamyan, A.J., Hamann, M.T., 2010. Marine indole alkaloids: potential new drug leads for the control of depression and anxiety. Chem. Rev. 110, 4489–4497.
Kumar, R., Van der Eycken, E.V., 2013. Recent approaches for C-C bond formation via direct dehydrative coupling strategies. Chem. Soc. Rev. 42, 1121–1146.
Lancianesi, S., Palmieri, A., Petrini, M., 2014. Synthetic approaches to 3-(2-nitroalkyl) indoles and their use to access tryptamines and related bioactive compounds. Chem. Rev. 114, 7108–7149.
Lindström, U.M. (Ed.), 2007. Organic Reactions in Water: Principles, Strategies and Applications. Blackwell, Oxford.
Liu, L.-Y., Wang, B., Yang, H.-M., Chang, W.-X., Li, J., 2011. The direct substitutions of 9*H*-xanthen-9-ol with indoles in a room temperature ionic liquid medium $BmimBF_4$. Tetrahedron Lett. 52, 5636–5639.
Liu, L.-Y., Zhang, Y., Huang, K.-M., Chang, W.-X., Li, J., 2012. 1,3-Dichloro-tetra-*n*-butyl-distannoxane: a new application for catalyzing the direct substitution of 9*H*-xanthen-9-ol at room temperature. Appl. Organometal. Chem. 26, 9–15.
Marqués-López, E., Herrera, R.P., Fernández, R., Lassaletta, J.M., 2008. Uncatalyzed Strecker-type reaction of *N*,*N*-dialkylhydrazones in pure water. Eur. J. Org., 3457–3460
Muzart, J., 2008. Gold-catalysed reactions of alcohols: isomerisation, inter- and intramolecular reactions leading to C–C and C–heteroatom bonds. Tetrahedron 64, 5815–5849.
Narayan, S., Muldoon, J., Finn, M.G., Fokin, V.V., Kolb, H.C., Sharpless, K.B., 2005. "On water": unique reactivity of organic compounds in aqueous suspension. Angew. Chem. Int. Ed. 44, 3275–3279.
Ortiz, R., Herrera, R.P., 2017. Direct substitution of alcohols in pure water by Brønsted acid catalysis. Molecules 22, 574–585.
Pearlman, R.S., Yalkowski, S.H., Banerjee, S., 1984. Water solubilities of polynuclear aromatic and heteroaromatic compounds. J. Chem. Phys. Ref. Data 13, 555–562.
Petruzziello, D., Gualandi, A., Grilli, S., Cozzi, P.G., 2012. Direct and stereoselective alkylation of nitro derivatives with activated alcohols in trifluoroethanol. Eur. J. Org. Chem., 6697–6701
Pintér, A., Klussmann, M., 2012. Sulfonic acid catalyzed autoxidative carbon-carbon coupling reaction under elevated partial pressure of oxygen. Adv. Synth. Catal. 354, 701–711.
Pirrung, M.C., Sarma, K.D., Wang, J., 2008. Hydrophobicity and mixing effects on select heterogeneous, water-accelerated synthetic reactions. J. Org. Chem. 73, 8723–8730.
Richard, J.P., Amyes, T.L., Toteva, M.M., 2001. Formation and stability of carbocations and carbanions in water and intrinsic barriers to their reactions. Acc. Chem. Res. 34, 981–988.
Rideout, D.C., Breslow, R., 1980. Hydrophobic acceleration of Diels-Alder reactions. J. Am. Chem. Soc. 102, 7816–7817.
Sheldon, R.A., 2012. Fundamentals of green chemistry: efficiency in reaction design. Chem. Soc. Rev. 41, 1437–1451.
Trillo, P., Baeza, A., Nájera, C., 2013. Copper-catalyzed asymmetric alkylation of β-keto esters with xanthydrols. Adv. Synth. Catal. 355, 2815–2821.
Tundo, P., Anastas, P., Black, D.StC., Breen, J., Collins, T., Memoli, S., Miyamoto, J., Polyakoff, M., Tumas, W., 2000. Synthetic pathways and processes in green chemistry. Introductory overview. Pure Appl. Chem. 72, 1207–1228.
Vicennati, P., Cozzi, P.G., 2007. Facile access to optically active ferrocenyl derivatives with direct substitution of the hydroxy group catalyzed by indium tribromide. Eur. J. Org. Chem., 2248–2253
Wang, S.-Y., Ji, S.-J., 2008. Indium tris(dodecyl sulfonate) $[In(DS)_3]$–catalyzed formation of 3-(9*H*-xanthen-9-yl)-1*H*-indole derivatives in water at room temperature. Synth. Commun. 38, 465–472.
Westermaier, M., Mayr, H., 2006. Electrophilic allylations and benzylations of indoles in neutral aqueous or alcoholic solutions. Org. Lett. 8, 4791–4794.
Wu, Y.-J., 2010. New indole-containing medicinal compounds. Top. Heterocycl. Chem. 26, 1–29.
Xiao, J., 2012. Merging organocatalysis with transition metal catalysis: highly stereoselective α-alkylation of aldehydes. Org. Lett. 14, 1716–1719.
Xiao, J., Zhao, K., Loh, T.-P., 2011. Highly enantioselective intermolecular alkylation of aldehydes with alcohols by cooperative catalysis of diarylprolinol silyl ether with Brønsted acid. Chem. Asian J. 6, 2890–2894.
Xiao, J., Zhao, K., Loh, T.-P., 2012. The acid free asymmetric intermolecular α-alkylation of aldehydes in fluorinated alcohols. Chem. Commun. 48, 3548–3550.
Zhang, L., Cui, L., Li, X., Li, J., Luo, S., Cheng, J.-P., 2010. Asymmetric S_N1 α-alkylation of cyclic ketones catalyzed by functionalized chiral ionic liquid (FCIL) organocatalysts. Chem. Eur. J. 16, 2045–2049.
Zhang, M.-Z., Chen, Q., Yang, G.-F., 2015. A review on recent developments of indole-containing antiviral agents. Eur. J. Med. Chem. 89, 421–441.
Zhou, B., Yang, J., Li, M., Gu, Y., 2011. Gluconic acid aqueous solution as a sustainable and recyclable promoting medium for organic reactions. Green Chem. 13, 2204–2211.
Zhu, A., Li, L., Wang, J., Zhuo, K., 2011. Direct nucleophilic substitution reaction of alcohols mediated by a zinc-based ionic liquid. Green Chem. 13, 1244–1250.

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