Ruthenium/TFA-catalyzed regioselective C-3-alkylation of indoles with terminal alkynes in water: efficient and unprecedented access to 3-(1-methylalkyl)-1*H*-indoles†

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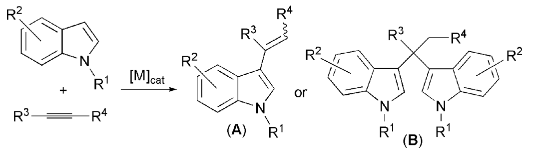
An unprecedented C-3-alkylation reaction of indoles with terminal alkynes in aqueous medium has been developed using catalytic amounts of ruthenium and trifluoroacetic acid.

The search for new efficient and selective synthetic methods to indoles continues to receive considerable attention since they are key structural units in a huge number of natural products and biologically active molecules.[1] In this context, the well-known nucleophilic nature of indolyl compounds, particularly at the C-3 position,[2] makes derivatization of the preformed heteroaromatic ring one of the most useful approaches to generate functionalized derivatives.[3] Among the different ways to perform the alkylation of indoles, the 1,2-addition to carbonyl compounds and imines, the Michael-type reactions with electron-deficient olefins, the ring-opening of epoxides and aziridines, and the well-known Pd-catalyzed allylic substitution processes (Tsuji–Trost reaction), are probably the most powerful and versatile ones.[4,5]

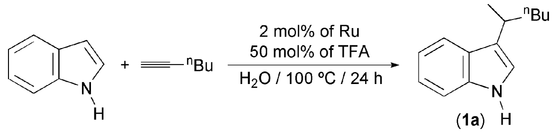
Recent studies have shown that indoles can also be alkylated using alkynes as electrophiles,[6] *via* metal-catalyzed hydroarylation of the C≡C bond,[7] the intermolecular version of this process giving an expeditious access to both 3-alkenyl-indoles (**A**) and bis(indolyl)alkanes (**B**) (Scheme 1).

However, despite its enormous synthetic potential, to date efficient catalysts available for these transformations are very scarce (mainly Ga(III), Pt(II), Au(I) and Au(III) derivatives).[6] This fact, along with our current interest in the application of ruthenium catalysts in heterocyclic chemistry,[8] encouraged us to study the suitability of ruthenium to promote alkylation reactions of indoles with alkynes.[9,10] In the context of these studies, a surprising and unprecedented result was encountered by performing the catalytic reactions in aqueous medium,[11] and in the presence of trifluoroacetic acid (TFA). Thus, as shown in Table 1, treatment of indole with excess of 1-hexyne (2.5 equiv.) in water at 100 °C led, in the presence of usual ruthenium complexes (2 mol% of Ru) and TFA (50 mol%), to the high yield formation of 3-(1-methylpentyl)-1*H*-indole (**1a**)[12] instead of the corresponding 3-alkenyl-indole **A** or bis(indolyl)alkane **B**.[13] No influence of the oxidation state of the metal on the reaction outcome was noted, both Ru(II) (entries 1–9), Ru(III) (entry 10) and Ru(IV) (entries 11–12) precatalysts being operative. Among them, the best result was obtained with the bis(allyl)-ruthenium(IV) dimer $[\{RuCl(\mu\text{-}Cl)(\eta^3:\eta^3\text{-}C_{10}H_{16})\}_2]$,[14] which afforded **1a** in 94% GC-yield after 24 h of heating (entry 12). Subsequent purification by column chromatography on silica gel provided an analytically pure sample of this alkylated indole in 84% isolated yield.



Scheme 1 Metal-catalyzed alkylations of indoles with alkynes.

Table 1 Ruthenium-catalyzed alkylation of indole with 1-hexyne[a]



Entry	Catalyst	Conversion[b]	Yield[b]
1	$[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$	57%	48%
2	$[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}1,3,5\text{-}C_6H_3Me_3)\}_2]$	93%	86%
3	$[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$	95%	91%
4	$[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6H_6)\}_2]$	87%	81%
5	$[RuCl_2(PPh_3)_3]$	91%	70%
6	$[Ru(\eta^3\text{-}2\text{-}C_3H_4Me)_2(COD)]$	85%	85%
7	$[RuCl_2(DMSO)_4]$	90%	82%
8	$[RuCl(\eta^5\text{-}C_5H_5)(PPh_3)_2]$	89%	81%
9	$[RuCl(\eta^5\text{-}C_9H_7)(PPh_3)_2]$	86%	73%
10	$RuCl_3\cdot nH_2O$	90%	82%
11	$[RuCl_2(\eta^3:\eta^2:\eta^3\text{-}C_{12}H_{18})]$	99%	77%
12	$[\{RuCl(\mu\text{-}Cl)(\eta^3:\eta^3\text{-}C_{10}H_{16})\}_2]$	99%	94%

[a] Reactions performed under an N_2 atmosphere at 100 °C using 1 mmol of indole (1 M solution in water) and 2.5 mmol of 1-hexyne. [Indole] : [alkyne] : [Ru] : [TFA] ratio = 100 : 250 : 2 : 50. [b] Determined by GC.

At this point, the following observations are of note: (*i*) the process is regioselective with respect to the indole, *N*- or *C*-2-substituted products not being observed in the crude reaction mixtures, (*ii*) the process is also regioselective with respect to the alkyne, *i.e.* the Markovnikov addition product is formed exclusively regardless of the catalyst employed, (*iii*) the use of water as solvent is imperative, **1a** being not formed in organic media (refluxing toluene, THF or CH_2Cl_2 solutions), (*iv*) the use of lower temperatures and/or TFA loadings reduces the yield of **1a** and slows down the reaction considerably,

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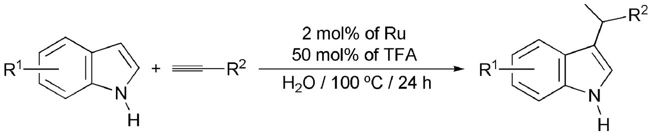
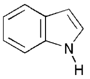
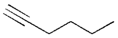
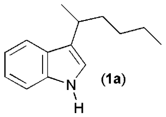
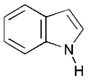
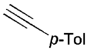
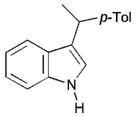
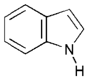
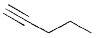
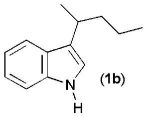
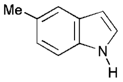
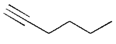
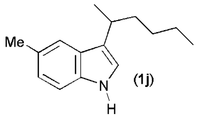
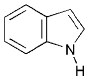
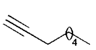
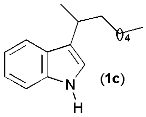
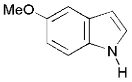
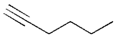
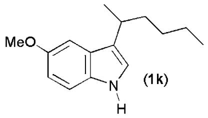
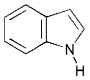
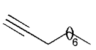
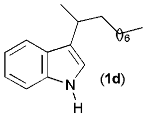
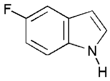
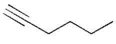
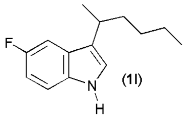
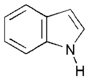
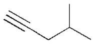
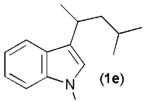
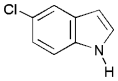
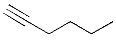
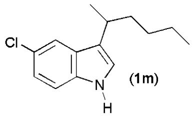
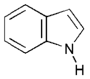
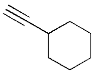
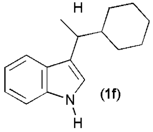
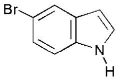
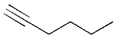
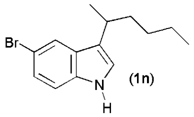
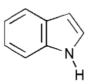
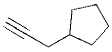
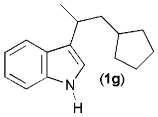
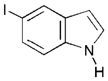
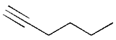
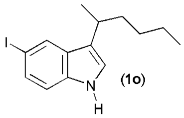
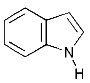
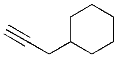
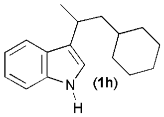
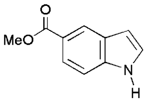
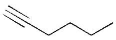
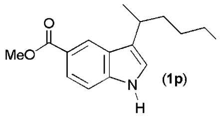
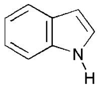
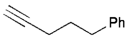
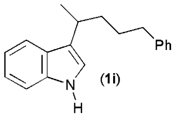
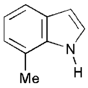
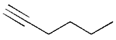
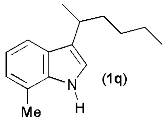
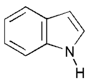
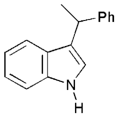
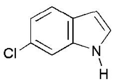
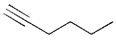
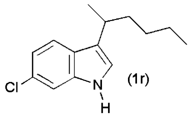
† Electronic supplementary information (ESI) available: Characterization data and copies of the NMR spectra of all compounds. See DOI: 10.1039/c002804e

Table 2 Scope of the alkylation reaction of indoles with terminal alkynes catalyzed by complex [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] in water[a]

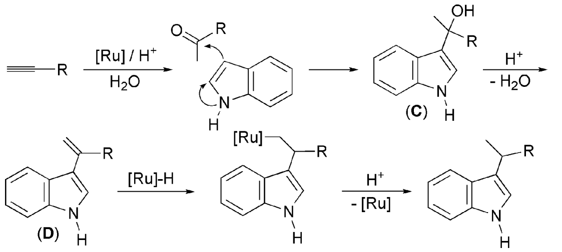


Entry	Indole	Alkyne	Product	Yield[b]	Entry	Indole	Alkyne	Product	Yield[b]
1			 (1a)	84%	11				0%
2			 (1b)	79%	12			 (1j)	82%
3			 (1c)	76%	13			 (1k)	79%
4			 (1d)	57%	14			 (1l)	69%
5			 (1e)	64%	15			 (1m)	67%
6			 (1f)	69%	16			 (1n)	57%
7			 (1g)	83%	17			 (1o)	82%
8			 (1h)	68%	18			 (1p)	87%
9			 (1i)	60%	19			 (1q)	60%
10				0%	20			 (1r)	65%

[a] Reactions performed under an N_2 atmosphere at 100 °C using 1 mmol of the corresponding indole (1 M solution in water) and 2.5 mmol of the appropriate terminal alkyne. [Indole] : [alkyne] : [Ru] : [TFA] ratio = 100 : 250 : 2 : 50. [b] Isolated yield after chromatographic work-up.

and (*v*) the excess of 1-hexyne present in the reaction medium is totally consumed during the catalytic reaction.[13] In addition, when a stoichiometric amount of 1-hexyne was used (indole : alkyne ratio = 1 : 1) the yield of **1a** also decreased, recovering part of the indole unchanged.

Using complex [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] the scope of this unusual alkylation reaction was explored (see Table 2).‡ The generality with respect to the terminal alkyne was firstly evaluated. Thus, as observed for 1-hexyne (entry 1), other aliphatic alkynes (entries 2–9) were able to couple with indole, the resulting 3-(1-methylalkyl)-1*H*-indoles **1b–i** being isolated in moderate to good yields (57–83%) after 24 h of heating. In contrast, starting from aromatic substrates, such as phenylacetylene or *p*-tolylacetylene, mixtures containing the expected



Scheme 2 Proposed mechanism.

alkylated indoles, albeit in very low yields (*ca.* 15%; GC-MS determined), were obtained. The major formation of several uncharacterized by-products prevented in these cases the isolation of the desired products (entries 10–11).

The compatibility of this C–C coupling reaction with other indolyl derivatives was also investigated. Thus, as shown in entries 12–20, several *NH*-indoles substituted at the benzenoid moiety could be effectively alkylated with 1-hexyne to afford the novel compounds **1j–r** in 57–87% yield. No remarkable influence of the position and electronic nature of the substituents was observed.

A tentative mechanistic proposal explaining the formation of **1a–r** is depicted in Scheme 2. Initially, a Ru-catalyzed Markovnikov hydration of the alkyne, a process favoured in acidic media,[15] takes place, generating a methyl ketone which readily undergoes 1,2-addition of the indolyl unit.[13b] Then, an acid-catalyzed dehydration of the resulting alcohol **C** probably occurs leading to the 3-alkenyl intermediate **D**.[16] Final reduction of the C=C bond of **D** by *in situ* formed Ru-hydride species delivers the observed products.[17]

In summary, an unprecedented and high-yielding procedure for the regioselective C-3 alkylation of indoles with alkynes in aqueous medium has been developed. Further studies aimed at clarifying the mechanism of this catalytic process and broadening its scope to the alkylation of other heteroaromatic substrates (pyrroles, furans, benzofurans, *etc.*) are currently in progress in our lab.

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Notes and references

‡ **General procedure for the catalytic reactions**: the corresponding indole (1 mmol), the appropriate terminal alkyne (2.5 mmol) and water (1 cm^3) were introduced into a sealed tube under a nitrogen atmosphere. $[\{RuCl(\mu\text{-}Cl)(\eta^3\text{:}\eta^3\text{-}C_{10}H_{16})\}_2]$ (0.006 g, 0.01 mmol; 2 mol% of Ru) and TFA (0.037 cm^3, 0.5 mmol) were then added at room temperature, and the resulting suspension heated at 100 °C for 24 h. After removal of the volatiles under vacuum, the residue was purified by column chromatography (silica gel) using a mixture of EtOAc/hexanes (1 : 50) as eluent.

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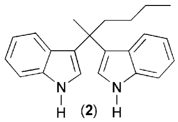
13 (*a*) Alkyne oligomers as well as minor amounts of a by-product, whose mass spectrum could correspond to the bis(indolyl) derivative **2** (MS (EI, 70 eV): *m*/*z* 316 (M$^+$, 10%), 301 (M$^+$ − Me, 5%), 259 (M$^+$ − Bu, 100%), 243 (M$^+$ − Me − Bu, 10%)), were detected in the crude reaction mixtures by ^{1}H NMR spectroscopy and GC/MSD. Formation of **2** is responsible for the difference observed between indole conversion and product yield; (*b*) Intermediate formation of hexan-2-one was observed by monitoring the reaction of indole with 1-hexyne by GC/MSD



(2)

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17 These hydride species, presumably generated from the excess of terminal alkyne present *via* oxidative addition to Ru(II) centres, could also be responsible for the alkyne oligomers observed. We note that Ru(IV)/Ru(II) reductions are well-known in the chemistry of $[\{RuCl(\mu\text{-}Cl)(\eta^3\text{:}\eta^3\text{-}C_{10}H_{16})\}_2]$. See ref. 14 and V. Cadierno, S. E. García-Garrido and J. Gimeno, *J. Am. Chem. Soc.*, 2006, **128**, 15094.