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Highly efficient click reaction on water catalyzed by a ruthenium complex†

Hai Xiao Siyang, Hui Ling Liu, Xin Yan Wu and Pei Nian Liu*

The highly efficient click reaction between terminal alkynes and azides has been achieved on water using ruthenium complex $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ as the catalyst, and the catalyst loading was decreased to 0.2 mol% on water from 5 mol% in organic solvent. The $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3/\text{H}_2\text{O}$ system also catalyzed the one-pot click reaction of bromides, sodium azide and alkynes; in this process, azides formed *in situ* and then underwent a click reaction with alkynes. In both aqueous processes, 1,4-disubstituted 1,2,3-triazoles were obtained in 50–89% yield with high regioselectivity.

Introduction

Water, which is unquestionably cheap, safe, non-toxic and readily available,¹ is becoming an increasingly popular medium for organic reactions.² Ever since Breslow adapted the Diels–Alder reaction to water,³ extraordinary advances have been made in performing organic chemistry in aqueous media.^{2,4} Chemists who make use of water as a solvent are often confronted with problems such as the antagonistic nature of water toward nucleophilic organic compounds⁵ and the limited solubility of the organic components. However, in some cases, using water as a solvent can accelerate reaction rates and enhance yield and selectivity compared to the same reaction in organic solvent,⁶ even when the reactants are only sparingly soluble or insoluble in water. Various factors have been proposed to explain how water can cause these enhancements. These factors include the hydrophobic effect,⁷ hydrogen bonding,^{8,9} and the method used to mix reactants in water.¹⁰ Another advantage of conducting reactions in aqueous solvent is that it facilitates the design of one-pot consecutive and multicomponent reactions (MCRs), which tend to be more environmentally friendly and atom-economical than conventional organic syntheses.¹¹

One of the most ingenious examples of “click chemistry”¹² is the copper-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and alkynes (CuAAC), discovered by Meldal¹³ and Sharpless.¹⁴ This click reaction is the most direct route to 1,4-disubstituted 1,2,3-triazoles,¹⁵ which are applied widely across

various fields, including biological science,¹⁶ synthetic organic chemistry,¹⁷ medicinal chemistry¹⁸ and material chemistry.¹⁹ Therefore, tremendous attention has been given to develop new protocols for the synthesis of various 1,2,3-triazoles.²⁰ The ruthenium-catalyzed azide–alkyne cycloaddition reaction (RuAAC) relying on pentamethylcyclopentadienyl ruthenium chloride catalysts has been reported to give 1,5-disubstituted-1,2,3-triazole with high regioselectivity.²¹

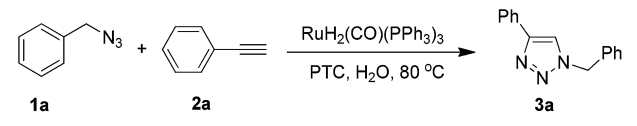
In an effort to adapt the RuAAC reaction to aqueous solvent, we took advantage of a ruthenium hydride complex, $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$, which we previously showed to catalyze the click reaction in organic solvent to afford 1,4-disubstituted-1,2,3-triazole with high regioselectivity.²² Here we report that the $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed click reaction on water led to much higher reactivity and proceeded efficiently at catalyst loadings as low as 0.2 mol%. The synthetic usefulness of this catalytic system was further demonstrated by achieving the one-pot multicomponent cycloaddition of bromides, sodium azide and alkynes.

Results and discussion

We began our investigation of ruthenium-catalyzed cycloaddition using benzyl azide (**1a**) and phenylacetylene (**2a**) as the model substrates, and the resulting reaction mixture was analyzed by ¹H NMR using PhSiMe_3 as the internal standard (Table 1). Initially, **1a** and **2a** were heated on water at 80 °C for 2 h in the presence of $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$; this led to 100% conversion and 86% yield of 1,4-disubstituted 1,2,3-triazole **3a** with 100% regioselectivity (entry 1). Encouraged by these results, we optimized the reaction by adding phase transformation catalyst (PTC), which can solubilize organic materials or form emulsions with them on water. In the presence of Bu_4NBr , catalyst loading could be reduced from 5 mol% to 0.2 mol% while maintaining a 100% conversion and generating the 1,4-disubstituted 1,2,3-triazole **3a** in >86% yield with 100%

Shanghai Key Laboratory of Functional Materials Chemistry, Key Lab for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Meilong Road 130, Shanghai 200237, China. E-mail: liupn@ecust.edu.cn; Fax: +86-21-64250552

† Electronic supplementary information (ESI) available: Analytical data for all known products (melting point, ¹H and ¹³C NMR, MS), copies of ¹H NMR spectra of all products, copies of ¹³C NMR spectra of **3i** and **3r**. See DOI: 10.1039/c4ra12960a

Table 1 RuH₂(CO)(PPh₃)₃-catalyzed click reaction of **1a** and **2a** on water under various conditions^a


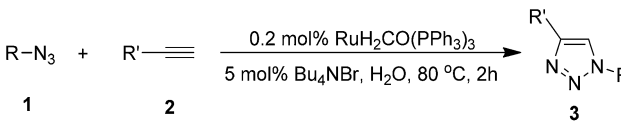
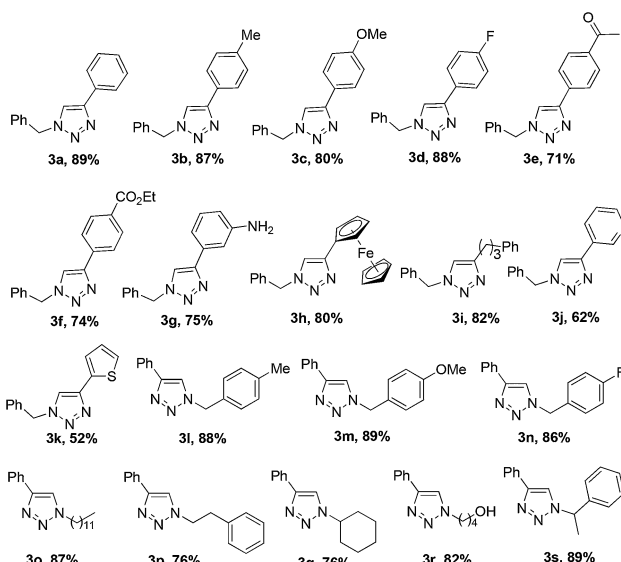
| Entry | S/C | PTC | Conv. ^b (%) | Yield ^c (%) |
|-----------------|------|---------------------|------------------------|------------------------|
| 1 | 20 | — | 100 | 86 |
| 2 | 20 | Bu ₄ NBr | 100 | 95 |
| 3 | 50 | Bu ₄ NBr | 100 | 95 |
| 4 | 100 | Bu ₄ NBr | 100 | 94 |
| 5 | 200 | Bu ₄ NBr | 100 | 86 |
| 6 | 500 | Bu ₄ NBr | 100 | 92 |
| 7 | 1000 | Bu ₄ NBr | 69 | 63 |
| 8 | 500 | CTAB | 100 | 95 |
| 9 | 500 | Bu ₄ NI | 99 | 87 |
| 10 | 500 | PEG2000 | 66 | 28 |
| 11 | 500 | Cyclodextrin | 64 | 47 |
| 12 | 500 | Tween-80 | 54 | 37 |
| 13 | 500 | — | 74 | 57 |
| 14 ^d | 500 | Bu ₄ NBr | 100 | 94 (89) ^e |

^a Reactions were performed in sealed tubes containing **1a** (0.5 mmol), **2a** (1.0 mmol), PTC (0.025 mmol) and water (0.5 mL) under N₂ for 2 hours, unless noted otherwise. ^b Conversions were estimated by integrating the area under the peaks for triazole and unreacted azide in ¹H NMR spectra. ^c Based on the integrated area of the peak for unreacted azide (**1a**) in ¹H NMR spectra, using PhSiMe₃ as the internal standard. ^d **1a** (0.5 mmol) and **2a** (0.6 mmol) were used. ^e Isolated yield is shown in parentheses.

regioselectivity (entries 2–6). Lowering catalyst loading below 0.1 mol% led to incomplete substrate conversion (entry 7).

Various other PTCs were then tested. Although CTAB gave 100% conversion and generated the desired 1,4-product in 95% yield, it also generated the 1,5-product as by-product in 3% yield (entry 8). Bu₄NI, PEG2000, cyclodextrin or Tween-80 were inferior to Bu₄NBr, giving either lower conversion or yields of products and selectivity (entries 9–12). Eliminating the PTC entirely led to poor conversion and yield (entry 13). Changing the reactant ratio (**1a** : **2a**) from 1 : 2 to 1 : 1.2 gave the desired 1,4-product in 89% isolated yield (entry 14).

Encouraged by the reaction efficiency, we examined its scope using the following optimized conditions: **1a** : **2a**, 1 : 1.2; RuH₂(CO)(PPh₃)₃, 0.2 mol%; Bu₄NBr, 5 mol%; H₂O, 0.5 mL; 80 °C; 2 h. These conditions worked well for a variety of terminal alkynes and azides (Table 2). All reactions of benzyl azide **1a** with aromatic alkynes containing electron-donating or electron-withdrawing groups proceeded smoothly to afford 1,4-substituted triazole products **3b–3g** in 71–88% yield. The results illustrate that the electronic properties of substituents on the benzene ring of alkynes does not appreciably affect the aqueous click reaction. Ferrocenylacetylene and alkyl alkyne were also effective in this ruthenium complex-catalyzed click reaction, producing the corresponding triazoles **3h** and **3i** in respective isolated yields of 80% and 82%. The reaction also proceeded

Table 2 RuH₂(CO)(PPh₃)₃-catalyzed cycloaddition of various alkynes and organic azides on water^{ab}



^a Reaction conditions: azide (0.5 mmol), alkyne (0.6 mmol), RuH₂(CO)(PPh₃)₃ (0.001 mmol), Bu₄NBr (0.025 mmol), 80 °C, 2 h, 0.5 mL of water. ^b Isolated yields are reported.

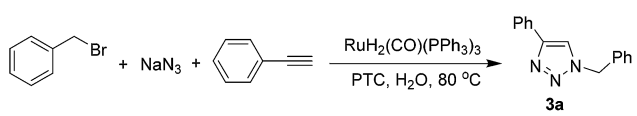
with 3-ethynylpyridine, giving **3j** in 62% yield, while using 2-ethynylthiophene gave **3k** in 52% yield.

Next we examined the substrate scope of organic azides. Benzyl azide bearing methyl, methoxy, or fluoride groups underwent this transformation efficiently, giving products **3l–3n** in 86–89% isolated yield. Alkyl organic azides also reacted efficiently, giving the desired products **3o–3q** with high isolated yields of 76–87%. The hydroxyl-functionalized azide was a good reaction partner, generating triazole **3r** with phenylacetylene in 82% yield. The reaction tolerated a substitution of the benzylic methylene of benzyl azide with a methyl group, leading to formation of **3s** in 89% yield. This suggests that the reaction is insensitive to steric hindrance of the azide.

Based on the above results, the RuH₂(CO)(PPh₃)₃-catalyzed click reactions on water gave yields similar to those of the corresponding reactions in organic solvent. At the same time, the use of aqueous solvent allowed us to reduce the catalyst loading from 5 mol% to 0.2 mol%.

Multicomponent reactions (MCRs) involve connecting three or more starting materials in a single synthetic operation with high atom economy and bond-forming efficiency.²³ This allows the construction of high molecular diversity and complexity in a relatively rapid and straightforward manner.²⁴ One-pot MCRs often involve shorter reaction times and higher overall yields than multi-step syntheses, thereby reducing energy and

Table 3 Optimization of conditions for the $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed, one-pot click reaction of benzyl bromide, sodium azide, and phenylacetylene on water^a



| Entry | S/C | PTC | Conv. ^b (%) | Yield ^c (%) |
|-------|------|-------------------------|------------------------|------------------------|
| 1 | 20 | Bu_4NI | 100 | 63 |
| 2 | 50 | Bu_4NI | 100 | 79 (84) ^d |
| 3 | 100 | Bu_4NI | 71 | 49 |
| 4 | 200 | Bu_4NI | 22 | 22 |
| 5 | 1000 | Bu_4NI | 21 | 22 |
| 6 | 50 | Bu_4NBr | 75 | 54 |
| 7 | 50 | — | 81 | 42 |

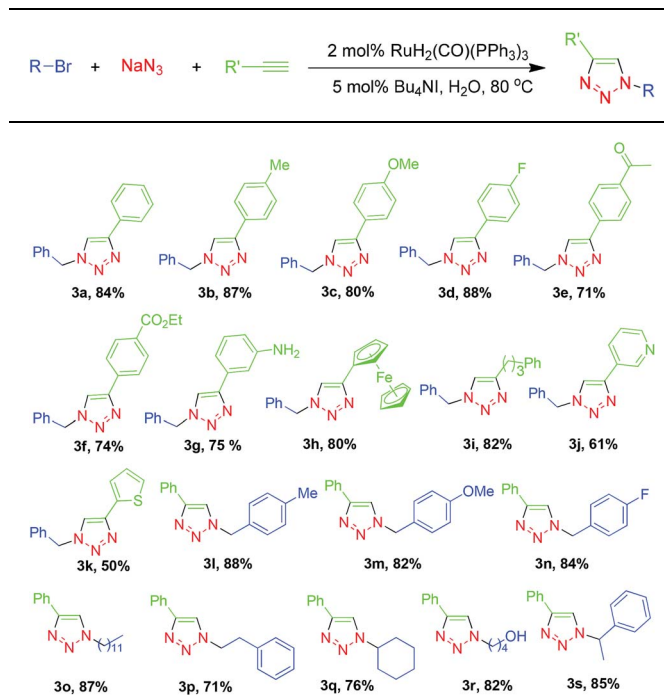
^a Reactions were performed in sealed tubes containing benzyl bromide (0.5 mmol), sodium azide (0.55 mmol), phenylacetylene (0.6 mmol), PTC (0.025 mmol) and water (0.5 mL) under N_2 for 2 hours. ^b Conversion rates were estimated by integrating the area under the peaks for triazole and unreacted benzyl bromide in ^1H NMR spectra. ^c Based on the integrated area of the peak for unreacted benzyl bromide in ^1H NMR spectra, using PhSiMe_3 as the internal standard. ^d Isolated yield is shown in parentheses.

manpower requirements.²⁵ Given the desirability of eliminating the need to store or manipulate organic azides, we envisaged a one-pot MCR involving an alkyne, sodium azide and bromide. Our plan was to generate organic azides *in situ* from suitable precursors, which would then undergo $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed azide-alkyne cycloaddition on water, thereby forming 1,2,3-triazoles. In this one-pot approach, we wished to avoid the need for interim purification of potentially unstable organic azide intermediates.

First, we screened various conditions for this one-pot MCR by taking as our model reaction the standard three-component click reaction of benzyl bromide and sodium azide with phenylacetylene. As we envisaged, the ruthenium complex $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ was amenable to this one-pot MCR on water, displaying high activity towards this multicomponent reaction to generate 1,4-disubstituted 1,2,3-triazoles from simple substrates. After screening various catalyst loadings and PTCs, we obtained **3a** in 84% isolated yield in the presence of 2 mol% catalyst after incubating the reaction for 2 h at 80 °C (Table 3).

Then we tested the scope of this one-pot RuAAC MCR (Table 4). A broad range of aromatic alkynes containing electron-donating or electron-withdrawing groups and heterocyclic alkynes were compatible with this reaction, affording the desired products **3a–3k** in 50–88% isolated yield. Various bromides including aromatic and alkyl substrates were also compatible with the reaction, providing 71–88% yields of the desired products **3l–3s**. These results demonstrate that the one-pot, three-component click reactions were comparable to the click reactions of alkynes and azides, although the one-pot format required increasing the catalyst loading of $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ to 2 mol%.

Table 4 $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed, one-pot click reaction of various bromides, sodium azide, and various alkynes^a



^a The reaction was carried out using bromide (0.5 mmol), sodium azide (0.55 mmol), alkyne (0.6 mmol) and Bu_4NI (0.025 mmol) in the presence of $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (0.01 mmol) on water (0.5 mL) at 80 °C for 2 h.

Conclusions

Using water as the reaction medium, we have developed a highly efficient $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed click reaction between terminal alkynes and organic azides to afford various 1,4-disubstituted triazoles in good to excellent yield. Catalyst loading (0.2 mol%) was much lower than that required in organic solvent (5 mol%). This catalytic system proved suitable for one-pot, three-component reactions of bromides, sodium azide, and alkynes, eliminating the need for interim purification of *in situ*-generated organic azides as well as significantly improving overall efficiency. We believe this protocol will offer a good option as an efficient click reaction and contribute substantially to the rapid growth in applications of click chemistry.

Experimental section

General information

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques, unless otherwise stated. $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ was prepared as described.²⁶ Freshly distilled water was used as solvent. Alkynes and other chemicals were purchased from Aldrich. Mass spectra were collected on an API QSTAR XLSystem (ESI) or GCT Premier™ Mass Spectrometer (CI). ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were collected on a

Bruker AV 400 MHz NMR spectrometer. ^1H and ^{13}C NMR chemical shifts were determined relative to TMS or residue of deuterium solvents.

Typical procedure for the $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed click reaction of various terminal alkynes and organic azides on water with low catalyst loading. To a mixture of azide (0.5 mmol), alkyne (0.6 mmol), and H_2O (0.5 mL) were added catalyst $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (0.001 mmol) and phase transformation catalyst (PTC) Bu_4NBr (0.025 mmol). The resulting solution was stirred at 80°C for 2 h. Then the reaction mixture was extracted three times with 1 mL CHCl_3 . The organic phases were combined, the solvent was evaporated under reduced pressure, and the residue was subjected to flash column chromatography on silica gel to afford the desired product. All the compounds reported here are known, except for **3i** and **3r** (see ESI †).

Typical procedure for $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed one-pot click reaction of benzyl bromide, sodium azide, and phenylacetylene on water. To a mixture of bromide (0.5 mmol), sodium azide (0.55 mmol), alkyne (0.6 mmol) and H_2O (0.5 mL) were added catalyst $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (0.01 mmol) and PTC Bu_4NI (0.025 mmol). The resulting solution was stirred at 80°C for 2 h. Then the reaction mixture was extracted three times with 1 mL CHCl_3 . The organic phases were combined, the solvent was evaporated under reduced pressure, and the residue was subjected to flash column chromatography on silica gel to afford the desired product. All the compounds reported here are known (see ESI †), except for **3i** and **3r**.

1-Benzyl-4-(3-phenyl-propyl)-1H-1,2,3-triazole (3i). Mp: $60\text{--}62.5^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3 , 25°C) δ 7.34–7.37 (m, 3H), 7.24–7.26 (m, 4H), 7.15–7.19 (m, 4H), 5.49 (s, 2H), 2.64–2.74 (dt, 4H), 1.94–2.02 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25°C) δ 148.4, 141.9, 135.0, 129.1, 128.6, 128.5, 128.4, 128.0, 125.9, 120.7, 54.0, 35.4, 31.3, 25.3; HRMS (ESI, TOF) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_3$ $[\text{M} + \text{H}]^+$ 278.1562, found 278.1567.

4-(4-Phenyl-1,2,3-triazol-1-yl)-butan-1-ol (3r). Mp: $88\text{--}90^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3 , 25°C) δ 7.82 (m, 2H), 7.78 (s, 1H), 7.43 (t, $J = 7.4$ Hz, 2H), 7.34 (t, $J = 7.4$ Hz, 1H), 4.47 (t, $J = 7.1$ Hz, 2H), 3.71 (t, $J = 6.1$ Hz, 2H), 2.04–2.12 (m, 2H), 1.60–1.66 (m, 3H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25°C) δ 147.8, 130.6, 128.9, 128.2, 125.7, 119.6, 61.9, 50.2, 29.3, 27.0; HRMS (ESI, TOF) calcd for $\text{C}_{12}\text{H}_{16}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 218.1288, found 218.1287.

Acknowledgements

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