Huisgen’s dipolar cycloaddition of organic azides and alkynes is the most direct route to 1,2,3-triazoles. However, because of the high activation energy (ca. 24–26 kcal/mol), these cycloadditions are often very slow even at elevated temperature (80–120 °C for 12–24 h) and produce mixtures of regioisomers. The discovery that Cu(I) efficiently and regiospecifically unites terminal alkynes and azides, providing 1,4-disubstituted 1,2,3-triazoles under mild conditions, was a welcome advance. Perhaps the most powerful click reaction to date, the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has quickly found many applications in chemistry, biology, and materials science.

The very success of the CuAAC highlights the need for selective access to the complementary regioisomers, the 1,5-disubstituted triazoles. Although they can be synthesized by the reaction of bromomagnesium acetylides with organic azides, this method lacks the scope and convenience of the CuAAC process. Herein we report that 1,5-disubstituted triazoles can be obtained by a ruthenium-catalyzed “fusion” of organic azides with alkynes.

Catalytic transformations of alkynes mediated by ruthenium complexes are well-known, and evidence for the intermediacy of ruthenium(I) acetylide, vinylidene, and ruthenametallicacyclic complexes has been provided. Therefore, ruthenium was a logical choice in our search for a new catalyst of azide–alkyne cycloaddition.

We have initially investigated the reaction of benzyl azide with phenylacetylene in the presence of various ruthenium complexes. In these screens, a mixture of benzyl azide and phenylacetylene (1:1.5 equiv, respectively) in benzene was heated at 80 °C for 4 h in the presence of 5% mol of a ruthenium complex. The resulting reaction mixture was then analyzed by 1H NMR. As revealed in Scheme 1, Ru(II) complexes do indeed catalyze the formation of 1,2,3-triazoles, with catalytic activity and regioselectivity being a sensitive function of the ligand environment around the ruthenium catalytic center.

Thus, in the presence of the acetate complex, Ru(OAc)2(PPh3)2, the azide was completely consumed, and the 1,4-disubstituted triazole product 1b, together with small amounts of dimers and oligomers of phenylacetylene, was formed.

Complexes such as RuCl2(PPh3)3 and RuHCl(CO)(PPh3)2 were rather ineffective; in their presence, less than 20% of benzyl azide reacted with phenylacetylene to give 1,4-disubstituted triazole 1b.

In contrast, CpRuCl(PPh3)2 catalyst resulted in 50% conversion of the reactants to a mixture of 1,5- and 1,4-disubstituted triazoles 1a and 1b in ca. 5:8:1 ratio. Then, a simple switch to the pentamethyl analogue, Cp*RuCl(PPh3)2, effected formation of only 1,5-regiosomer 1a, with complete conversion. Reactions with other [Cp*Ru] complexes, such as [Cp*RuCl]2, Cp*RuCl(NBD), and Cp*RuCl(COD), gave results similar to that with Cp*RuCl(PPh3)2.

This [Cp*RuCl]-based regiocontrol should prove to be useful, for to the best of our knowledge, no accounts reporting catalytic

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**Scheme 1. Ru-Catalyzed Cycloaddition of Benzyl Azide and Phenylacetylene**

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Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides

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Ruthenium-Catalyzed Cycloaddition of Benzyl Azide and Phenylacetylene

1a

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1b

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synthesis of 1,5-disubstituted triazoles from alkynes and azides has been published to date.

To evaluate the scope of this new ruthenium-catalyzed process with respect to the alkene component, reactions of benzyl azide with several terminal alkynes were carried out. Likewise, reactivity of representative azides with phenylacetylene was studied. Typically, the reactions were performed with 1 mol % of Cp*RuCl2(PPh3)2 catalyst at 0.07–0.15 M concentration of the components in refluxing benzene. Complete consumption of the benzyl azide at the end of the reaction was confirmed by 1H NMR or GC analysis of the final reaction mixture. A selection of examples is presented in Table 1. Thus, both aromatic and aliphatic alkynes reacted with benzyl azide to give the corresponding 1,5-disubstituted 1,2,3-triazoles. Alkynes with hydroxyl and aldehyde functional groups (entries 5–7) also readily participated in the reaction. Similarly, variations in the steric environment around the azide, at least to the extent represented by the cases herein, had no effect on the regioselectivity of the process.

In contrast, the nature of the azide component appears to have a considerable effect on the outcome of the reaction, both in terms of regioselectivity and catalytic efficiency. Although 1,5-triazole products were obtained in excellent yields from primary aliphatic azides, such as phenethyl azide (entry 8) and ω-azidopropanol (entry 9), tertiary azides, such as tert-butyl and adamantyl azide, produced triazoles in only low yields after 6 h. Higher catalyst loading (5 mol %) and extended reaction time resulted in somewhat improved yields. Finally, we note that reactions of aryl azides were plagued by low conversions and formation of noticeable amounts of byproducts, especially when more forcing conditions were attempted. Nevertheless, aromatic azides reacted smoothly with tertiary propargyl alcohols, resulting in 5-aryl 1,2,3-triazoles in good yields (entry 11).

A brief examination of the effect of the solvent revealed that benzene, toluene, THF, 1,2-dichloroethane, and dioxane perform equally well. Protic solvents had a detrimental effect on both yield and regioselectivity. Thus, benzyl azide reacted with phenylacetylene significantly slower in refluxing 2-propanol (5 h, 2 % mol of Cp*RuCl2(PPh3)2, 70% conversion), and a mixture of regioisomeric products 1a and 1b (7:1) was formed. In most cases, concentration of the azide and alkene can be varied from 0.01 to 1 M without a noticeable effect on conversion and regioselectivity.
Likewise, reactions can be carried out at temperatures ranging from ambient to 80 °C. For example, benzyl azide was almost quantitatively converted to the corresponding triazoles when it was allowed to react with a slight excess of Ph$_2$C(OH)CH¼CH or PhC¼CH in benzene at room temperature for 24 h in the presence of 5% mol of Cp*RuCl(PPh$_3$)$_2$.

The structures of new triazoles are fully consistent with their characterization data (PDF). X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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**Supporting Information Available:** Experimental procedures and characterization data (PDF). X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

**References**


(8) See Supporting Information for the details.


JA054114S

**Table 1.** Ru-Catalyzed Reactions of Azides with Terminal Alkynes

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>reaction time, h</th>
<th>yield, %</th>
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<tr>
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<td>1a</td>
<td>2</td>
<td>80</td>
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<td>3</td>
<td>82</td>
</tr>
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<td>4</td>
<td>4a</td>
<td>4</td>
<td>82</td>
</tr>
<tr>
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<td>5a</td>
<td>2</td>
<td>81</td>
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<tr>
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<td>8a</td>
<td>2</td>
<td>89$^b$</td>
</tr>
<tr>
<td>9</td>
<td>9a</td>
<td>2</td>
<td>82$^b$</td>
</tr>
<tr>
<td>10</td>
<td>10a</td>
<td>6</td>
<td>80$^c$</td>
</tr>
<tr>
<td>11</td>
<td>11a</td>
<td>12</td>
<td>94$^c$</td>
</tr>
</tbody>
</table>

$^a$ Benzene, 1–2 mmol scale, 80 °C, 1 mol % of Cp*RuCl(PPh$_3$)$_2$. $^b$ Dioxane, 60 °C. $^c$ Dioxane, 60 °C, 2 mol % of the catalyst.

**Table 3.** Proposed Intermediates in the Catalytic Cycle

![Scheme 3. Proposed Intermediates in the Catalytic Cycle](image-url)

[Supporting Information Available:](#) Experimental procedures and characterization data (PDF). X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.