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Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides

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Huisgen's dipolar cycloaddition of organic azides and alkynes is the most direct route to 1,2,3-triazoles.[1] 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.[2] Perhaps the most powerful click reaction[3] to date, the Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC) has quickly found many applications in chemistry, biology, and materials science.[4]

The very success of the CuAAC highlights the need for selective access to the complementary regioisomers, the 1,5-disubstituted triazoles.[5] Although they can be synthesized by the reaction of bromomagnesium acetylides with organic azides,[6] 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(II) acetylide, vinylidene, and ruthenametallacyclic complexes has been provided.[7] 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 ^{1}H 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.

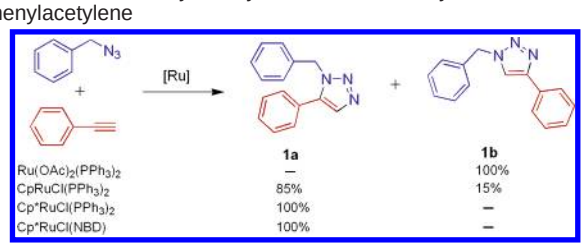
Thus, in the presence of the acetate complex, $Ru(OAc)_2(PPh_3)_2$, the azide was completely consumed, and the 1,4-disubstituted triazole product **1b**, together with small amounts of dimers and oligomers of phenylacetylene, was formed.

Complexes such as $RuCl_2(PPh_3)_3$ and $RuHCl(CO)(PPh_3)_3$ were rather ineffective; in their presence, less than 20% of benzyl azide reacted with phenylacetylene to give 1,4-disubstituted triazole **1b**.

In contrast, $CpRuCl(PPh_3)_2$ 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, $Cp^*RuCl(PPh_3)_2$, effected formation of only 1,5-regioisomer **1a**, with complete conversion. Reactions with other [Cp*Ru] complexes, such as $[Cp^*RuCl_2]_2$, Cp*RuCl(NBD), and Cp*RuCl(COD), gave results similar to that with $Cp^*RuCl(PPh_3)_2$.

This [Cp*RuCl]-based regiocontrol should prove to be useful, for to the best of our knowledge, no accounts reporting catalytic synthesis of 1,5-disubstituted triazoles from alkynes and azides have been published to date.

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



To evaluate the scope of this new ruthenium-catalyzed process with respect to the alkyne 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 $Cp^*RuCl(PPh_3)_2$ 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 ^{1}H 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 alkyne, 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 $Cp^*RuCl(PPh_3)_2$, 70% conversion), and a mixture of regioisomeric products **1a** and **1b** (7:1) was formed. In most cases, concentration of the azide and alkyne can be varied from 0.01 to 1 M without a noticeable effect on conversion and regioselectivity.

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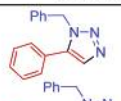
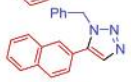
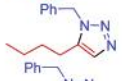
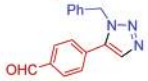
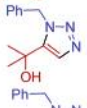
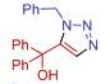
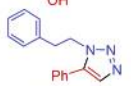
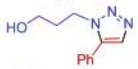
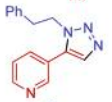
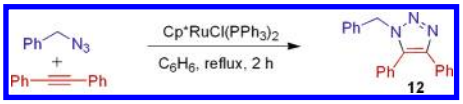
Table 1. Ru-Catalyzed Reactions of Azides with Terminal Alkynes[a]

entry	product		reaction time, h	yield, %
1		**1a**	2	80
2		**2a**	4	93
3		**3a**	3	82
4		**4a**	4	82
5		**5a**	2	81
6		**6a**	2.5	94
7		**7a**	4	87
8		**8a**	2	89[b]
9		**9a**	2	82[b]
10		**10a**	6	80[c]
11		**11a**	12	94[c]

[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.

Scheme 2. Ru-Catalyzed Synthesis of Triazoles from Internal Alkynes



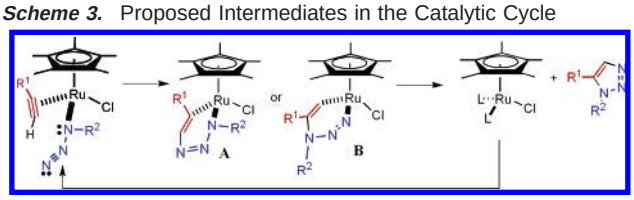
Likewise, reactions can be carried out at temperatures ranging from ambient to 80 °C. For example, benzyl azide was almost quantitatively converted to the corresponding triazoles when it was allowed to react with a slight excess of $Ph_2C(OH)C{\equiv}CH$ or $PhC{\equiv}CH$ in benzene at room temperature 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 ^{1}H, ^{13}C NMR, and MS data.[8] In addition, structures of **1a**, **6a**, and **7a** have also been confirmed by X-ray diffraction studies.

Since Cu(I) acetylides seem to be the bona fide intermediates in the CuAAC,[9] this transformation is limited to terminal alkynes. The [Cp*RuCl] system, in fortunate contrast, is active with internal alkynes as well. Thus, when a mixture of diphenylacetylene and benzyl azide (1.1:1 equiv, 0.15 M) was refluxed in benzene in the presence of ca. 1 % mol of Cp*RuCl(PPh$_3$)$_2$ for 2 h, the azide was completely converted to the triazole **12** (Scheme 2). The uncatalyzed reaction was very sluggish, and only a trace amount of triazole was detected even after 24 h at reflux.

The mechanistic underpinnings for this ruthenium(II)-catalyzed synthesis of triazoles need much more studies, but we offer the following tentative hypothesis. Since both terminal and internal alkynes participate in catalysis, the involvement of ruthenium

Scheme 3. Proposed Intermediates in the Catalytic Cycle



acetylides is unlikely (and not even possible for the latter). Of course, cyclotrimerization of alkynes is well-known and, for the specific case of the Cp*RuCl(COD) catalyst, has been shown to proceed via ruthenacyclopentadienes.[10] Therefore, we suggest that the newly discovered Ru-catalyzed triazole annulations represent a simple, and early, shunt off the usual alkyne oligomerization sequence. That is, oxidative coupling of an alkyne and an azide on ruthenium may initially give a six-membered ruthenacycle (Scheme 3; **A** is more likely than **B**), which then undergoes reductive elimination releasing the aromatic triazole product.

In summary, an experimentally convenient catalytic process for regioselective synthesis of 1,5-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles from organic azides and terminal and internal alkynes is now available. Together with the CuAAC, these transformations allow selective preparation of both regioisomers of 1,2,3-triazoles, heterocycles that have recently become popular as a means for establishing reliable and stable connections in organic synthesis, medicinal chemistry, and materials science.

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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.

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