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Ruthenium-Catalyzed Cycloaddition of Aryl Azides and Alkynes

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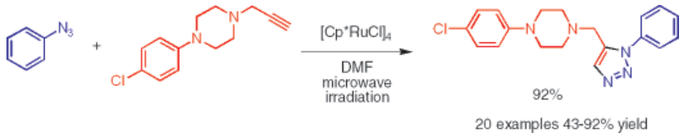
ABSTRACT



The formation of 1,5-disubstituted 1,2,3-triazoles from aryl azides and alkynes was readily accomplished using [Cp*RuCl]$_4$ catalyst in dimethylformamide. It was also demonstrated that the reaction provided higher yields, cleaner product, and shorter reaction times when carried out under microwave irradiation.

Since the discovery of the Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC),[1] the number of its applications in different fields of chemistry has exploded. The reaction has enabled discovery of novel bioactive compounds, ligands for transition metals, new materials, and bioconjugates, underscoring its exceptionally broad scope and fidelity.[2] Nevertheless, the CuAAC process works only with terminal alkynes and produces 1,4-disubstituted 1,2,3-triazoles. The recent addition to the family of catalytic azide−alkyne cycloadditions, the ruthenium-catalyzed process (RuAAC),[3] provides ready access to the complementary 1,5-regioisomers of 1,2,3-triazole. Furthermore, internal alkynes also participate in the RuAAC, thus significantly expanding the scope of this cycloaddition process. Bis(triphenylphosphine) pentamethylcyclopentadienyl ruthenium(II) chloride, Cp*RuCl(PPh$_3$)$_2$ (**1**),[4] was identified early on as an efficient catalyst in the original study.[3a]

Although RuAAC exhibits good scope with respect to both components, the reaction of alkynes with aryl azides is often plagued by low yields and formation of byproducts. Described herein are the results of our study aimed at the development of an improved catalytic system which engages aryl azides in the catalysis and allows facile access to 1-aryl-substituted 1,2,3-triazoles.

During our investigation of the catalytic activity of different ruthenium complexes in the reaction of aliphatic azides and alkynes, we found that pentamethylcyclopentadienyl ruthenium(II) chloride tetramer[5] [Cp*RuCl]$_4$ (**2**) in dimethylformamide performed significantly better than Cp*RuCl(PPh$_3$)$_2$ (**1**) in most other solvents. For example, the reaction of benzyl azide and phenylacetylene catalyzed by Cp*RuCl(PPh$_3$)$_2$ in tetrahydrofuran required 30 min at 65 °C to reach 90% conversion, whereas it proceeded to completion in only 15 min and at room temperature when catalyst **2** in dimethylformamide was used.

Catalyst **2** is easily prepared from [Cp*RuCl$_2$]$_n$ by treating the THF solution of the latter with LiBHEt$_3$, without

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(1) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3062.

(2) (a) Breinbauer, R.; Köhn, M. *ChemBioChem* **2003**, *4*, 1147−1149. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128−1137. (c) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2005**, 51−68. (d) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7−17. (e) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (f) Hawker, C. J.; Fokin, V. V.; Finn, M. G.; Sharpless, K. B. *Aust. J. Chem.* **2007**, *60*, 381.

(3) (a) Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999. (b) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680−8683. (c) Boren, B. C.; Narayan, S; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2007**, in press.

(4) Oshima, N.; Suzuki, H.; Morooka, Y. *Chem. Lett.* **1984**, 1161−1164.

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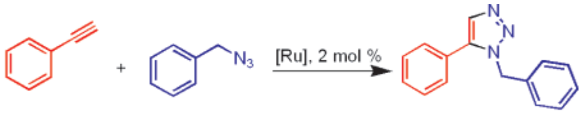
Scheme 1. RuAAC of Benzyl Azide and Phenylacetylene



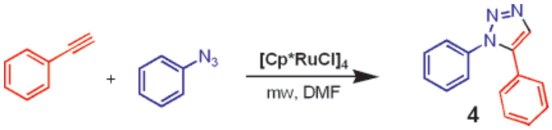
[Ru] = Cp*RuCl(PPh$_3$)$_2$, THF, 65 °C, 30 min, 93% yield
[Ru] = [Cp*RuCl]$_4$, DMF, rt, 15 min, 90% yield

rigorously excluding air and moisture (Scheme 1). Although it can be handled in air without a significant loss of activity, highest yields were obtained when freshly prepared (within 24 h) catalyst was used.

The finding of increased catalytic activity of **2** prompted us to investigate its performance in reactions that proved difficult when Cp*RuCl(PPh$_3$)$_2$ was used as a catalyst. To facilitate the optimization process, the reactions were performed under microwave irradiation.

Among different solvents tested in the reaction between 4-iodophenylazide and phenylacetylene (Table 1), dimethylformamide clearly stood out, producing the 1,5-disubstituted triazole product with highest conversion (ca. 70%), with acetonitrile in a distant second place (ca. 40% conversion). 1,4-Dioxane, tetrahydrofuran, toluene, and dimethylsulfoxide resulted in significantly lower efficiency of the reaction (Scheme 2).

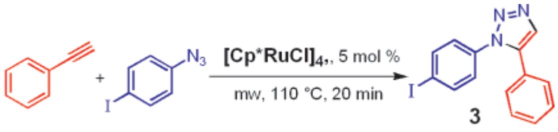
Table 1. Variation of Amount of Catalyst, Temperature, and Reaction Time



entry	[Ru], mol %	temp, °C	time, min	yield,[a] %
1	0	110	20	
2	5	110	20	69
3	10	110	10	66
4	10	100	40	73
5	10	110	20	73
6	10	90	20	69
7	2	110	20	33

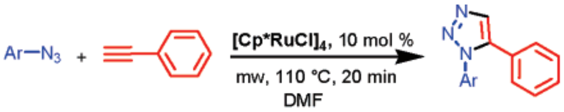
[a] Yield determined by quantitative GC analysis.

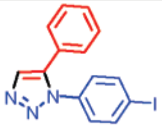
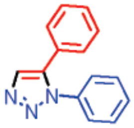
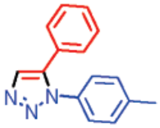
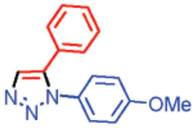
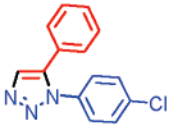
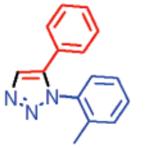
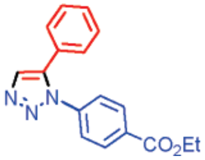
Scheme 2. Effect of Solvents on the Efficiency of the Reaction



PhCH$_3$	Dioxane	THF	CH$_3$CN	DMF	DMSO
<1.5%	~20%	~20%	~40%	~70%	<1%

Table 2. RuAAC: Azide Scope



entry	triazole product	yield, %[a]
1		72
2		87 58[b] 52[c]
3		63
4		71
5		71
6		43
7		49

[a] Isolated yield after flash chromatography. [b] Oil bath 65 °C. [c] Oil bath 110 °C.

Although catalyst **2** is a cluster compound, the labile Ru−Cl−Ru bonds are easily broken by donor ligands, and both organic azides and alkynes are evidently sufficiently potent to activate the tetramer. Furthermore, dimethylformamide is known to form complexes with ruthenium, thus acting as an activating and also stabilizing ligand in its own right.[6]

The efficiency of the reaction was improved when the amount of catalyst was increased to 10 mol % (entry 5, Table 1), while reducing the catalyst loading to 2 mol % was detrimental (entry 7). Slight variations of the reaction

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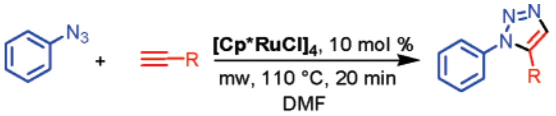
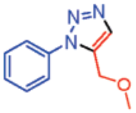
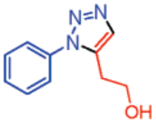
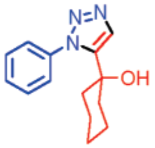
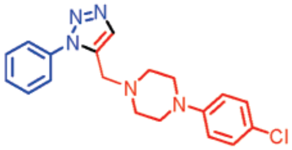
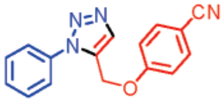
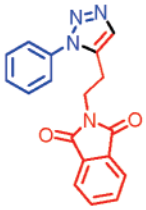
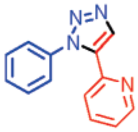
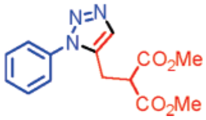
[6] Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630−6666.

Table 3. RuAAC: Alkyne Scope



entry	triazole product	yield, %[a]
1		87
2		75
3		72
4		92
5		56
6		55
7		56
8		49

[a] Isolated yield after flash chromatography.

temperature (90−110 °C) had little effect on the outcome (entries 4 and 6). Likewise, increasing the reaction time did not improve the conversion, suggesting that catalyst deactivation is a competing process.

With the optimized conditions in hand, we probed the scope of the reaction with respect to both the azide and the alkyne components. As evidenced by the results in Table 2, aryl azides with different substituents smoothly reacted with phenylacetylene, producing triazole products in generally good yield. Both electron-rich (entries 3 and 4) and moderately electron-poor (entry 7) aryl azides readily participated in the reaction. However, those containing sterically demanding substituents, diortho substituents, or strongly electron-withdrawing groups, such as (4-nitro)azidobenzene, failed to participate in the reaction, likely due to catalyst deactivation[3c] and/or decomposition of the azide at the elevated temperature. It is noteworthy that, although the reaction proceeded under conventional heating (oil bath) at 65 and 110 °C, the formation of byproducts was evident, and isolated yields were markedly lower.

The scope of the reaction with respect to alkyne was next investigated and found to be excellent. As Table 3 illustrates, a broad range of functional groups could be employed without significantly affecting the yield of the product triazole. Thus, alkynes containing an amine, alcohol, nitrile, and heterocyclic amine functionality readily participated in the reaction.

In summary, a highly active catalytic system for ruthenium-catalyzed cycloaddition of azides and alkynes is now available. Aryl azides, a troublesome class of substrates that failed to react cleanly using the original Cp*RuCl(PPh_3)$_2$ catalyst can now be readily and regioselectively converted to the corresponding triazoles upon a reaction with [Cp*RuCl]$_4$ catalyst in DMF at 90−110 °C under microwave irradiation.

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Supporting Information Available: Experimental procedures and full spectroscopic data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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