Exploiting Guanidine as a Ligand in Cobalt-Catalyzed Alkyne Cyclotrimerizations

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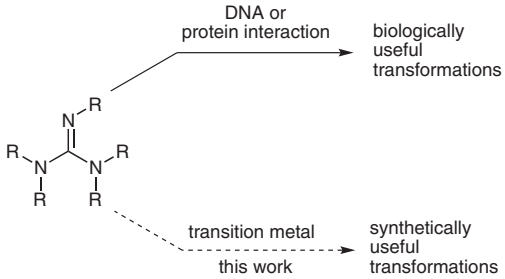
Abstract: The synthesis of polysubstituted arenes is accomplished via the regioselective cyclotrimerization of alkynes utilizing a guanidine-ligated cobalt catalyst.

Key words: alkynes, arenes, cycloaddition, regioselectivity, transition metals

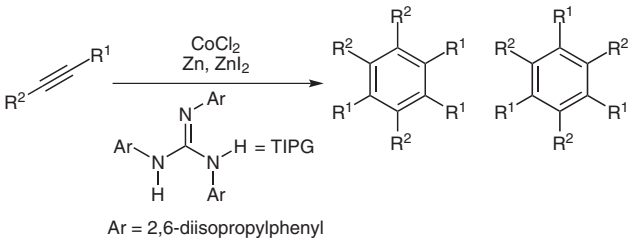
Guanine is one of nature's most important natural products as it is a major component of both DNA and RNA. The degradation of guanine produces various components, one of which is guanidine. Guanidine is generated by the oxidation of guanine and is found in the urine of mammals. Natural products containing a guanidine moiety exhibit a wide range of biological activity,[1] and the interaction of the guanidine motif with proteins leads to different modes of bioactivity. For example, guanidinium hydrochloride can act as a protein denaturation agent or it can stabilize folded proteins.[2] Another derivative, hydroxyguanidine, was discovered to inhibit the synthesis of DNA making it a potential antitumor drug.[3] Both natural and unnatural guanidine derivatives possess antiproliferative, antiviral, and antibacterial properties.[1,4] Consequently, many natural products bearing the guanidine functionality continue to be active targets of the synthetic organic community.[5]



Scheme 1 The diverse utility of guanidine derivatives

A major interest of our research group is the development of new catalysts for transition-metal-catalyzed reactions. The use of natural products in catalysis has been exploited in recent years. The most prominent examples are the NHC ligands, which were developed in large part because of the role of naturally occurring thiamine first proposed by Breslow.[6] Although guanidine is cheap and abundant, its use as a ligand in metal-catalyzed reactions has been limited. For example, only a few palladium-catalyzed processes have been developed utilizing guanidines as bases or ligands.[7] Guanidines are attractive in transition-metal catalysis because they are ambidentate, so binding to the metal center is possible through the sp^2 nitrogen or the two amino groups. Moreover, metal complexes ligated by guanidines may provide catalysts that can be employed in green chemical processes that occur in water instead of organic solvents. To explore the potential activity of guanidines as ligands in transition-metal-catalyzed reactions, we investigated the use of these catalyst systems in the cyclotrimerization of alkynes (Scheme 1).

The prevalence of highly substituted benzene derivatives in natural products prompts the investigations into efficient and reliable methods to generate these moieties. A useful tactic to create polysubstituted arenes is the [2+2+2] cyclotrimerization of alkynes.[8] Transition-metal catalysts such as Ti,[9] Pd,[10] Co,[11] Ru,[12] Ir,[13] and Rh[14] have been employed in this transformation to assist in overcoming the intrinsic entropic barrier associated with this reaction. Cobalt-catalyzed processes are particularly attractive due to their low cost and ease of handling. The ability to catalyze intermolecular cyclotrimerization reactions of unsymmetrical alkynes regioselectively remains a challenge. Hilt[11d] and Okamoto[11c] have shown these reactions proceed with good regioselectivity for the unsymmetrical arene product and obtained high yields using cobalt in combination with diimine or iminopyridine ligands. Typically, these reaction conditions required 5–10 mol% of cobalt and the corresponding ligand.



Scheme 2 Cobalt-catalyzed cyclotrimerization of alkynes

Because of the success of cobalt–imine complexes to catalyze the cyclotrimerization of alkynes, we investigated the use of guanidine ligands in this reaction (Scheme 2). As described earlier, guanidine can bind to cobalt as a

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neutral donor through the sp^2 nitrogen or as an anionic or dianionic donor via the amino groups.[15] Initially, it was expected that these ligands would coordinate to cobalt through the sp^2 nitrogen in the same fashion that imines bind to cobalt. Figure 1 shows the cobalt complex and the guanidine-based ligands that were employed for optimization studies.

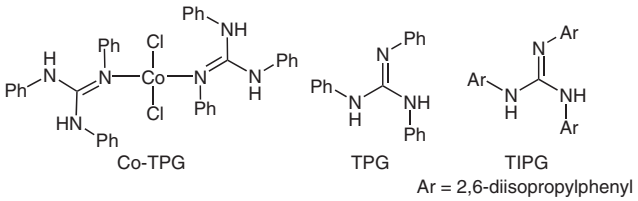
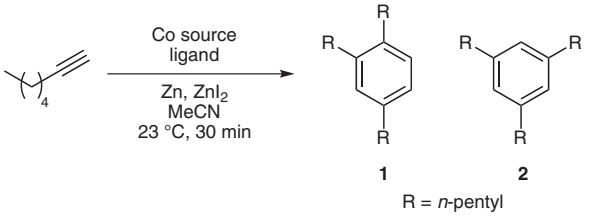


Figure 1 Cobalt complex and guanidine ligands

A guanidine-ligated cobalt complex[15d] (Co-TPG) and triphenylguanidine (TPG) with $CoCl_2$ were subjected to reaction conditions. To more greatly bias regioselectivity by crowding the metal center, we also employed the bulky tris(2,6-diisopropylphenyl) guanidine (TIPG) ligand, which was easily prepared according to a reported literature procedure.[16]

Table 1 Cyclotrimerization of 1-Heptyne Catalyzed by Guanidine-Ligated Cobalt Catalyst[a]



Entry	Co source (mol%)	Ligand (mol%)	Zn, ZnI_2 (mol%)	Ratio of **1**/**2**[b]
1	Co-TPG (10)	–	10	94:6
2	$CoCl_2$ (10)	TPG (20)	10	94:6
3	$CoCl_2$ (10)	TIPG (20)	10	95:5
4	$CoCl_2$ (5)	TIPG (10)	10	95:5[c]
5	$CoCl_2$ (10)	TIPG (10)	10	95:5
6	$CoCl_2$ (5)	TIPG (5)	10	95:5
7	$CoCl_2$ (2)	TIPG (2)	4	95:5

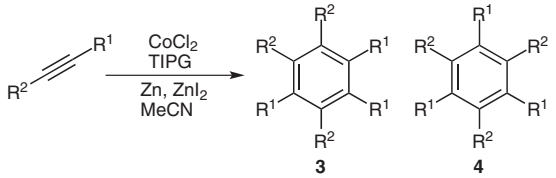
[a] The alkyne is added after all other reagents are heated at 50 °C for 5 min.
[b] Regioselectivity was determined by GC analysis.
[c] Reaction required 1 h to go to completion.

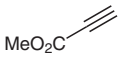
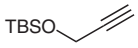
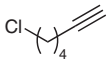
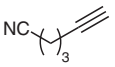
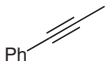
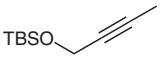
Upon exposure of 1-heptyne to an acetonitrile solution of 10 mol% Co-TPG and a catalytic amount of Zn/ZnI_2 the desired arene is obtained in complete conversion with high regioselectivity (Table 1, entry 1). Previously, Snyder has shown that the addition of zinc and zinc iodide increases reaction rates by effectively reducing the cobalt species to the active catalyst,[17] and the Zn/ZnI_2 system is commonplace in most Co-catalyzed cycloaddition reactions.[11,18] Comparison with the in situ generated catalyst with $CoCl_2$ and TPG provided identical results as the preformed catalyst. Employment of the more bulky TIPG ligand gave slightly better regioselectivity (Table 1, entry 3). Reducing the catalyst loading to 5 mol% $CoCl_2$ and 10 mol% TIPG slightly decreased the overall reaction rate as the reaction required 1 hour to reach completion, but the regioselectivity was conserved. The reaction also proceeded with 10 mol% $CoCl_2$ and 10 mol% TIPG in 30 minutes with 95:5 regioselectivity (Table 1, entry 3), suggesting that the active catalytic species only needs to be supported by a single TIPG ligand. This stoichiometry is intriguing as previous cobalt imine catalysts required a 1:1 ratio of metal to ligand when bidentate ligands were employed. Therefore, cobalt likely complexes in a bidentate fashion to the sp^2 nitrogen and one of the sp^3 amino groups of the guanidine. Using this 1:1 metal-to-ligand ratio we were able to lower the catalyst loading to 2 mol%. The addition of zinc and zinc iodide was also required for the reaction to proceed. The final optimized reaction conditions were 2 mol% $CoCl_2$, 2 mol% TIPG, 4 mol% Zn, and 4 mol% ZnI_2 in acetonitrile.

Various alkynes were exposed to the optimized reaction conditions in order to assess the scope of this new catalyst. Using only 2 mol% $CoCl_2$ and TIPG, high regioselectivities and yields were achieved for a variety of functionalized alkynes (Table 2). Triphenylbenzene was produced almost solely as the unsymmetrical product with a 99:1 regioselectivity.[19] Electron-deficient alkynes, such as methyl propiolate, underwent cyclotrimerization to give trimethyl benzene-1,2,4-tricarboxylate as the major product (Table 2, entry 3). This catalyst also tolerated silyl-protected alkynes as trimethylsilylacetylene gave the corresponding 1,2,4-trisubstituted arene in high yield (Table 2, entry 4). Other alkynes such as TBS-protected propargyl alcohol and 6-chloro-1-hexyne also proceeded smoothly to afford the corresponding arenes in excellent yields with good regioselectivities (Table 2, entries 5 and 6). Interestingly, an alkyne containing a pendant nitrile reacted to form the benzene product without interference from the nitrile (Table 2, entry 7). Cobalt-catalyzed cyclotrimerizations of alkynes that contain nitrile functionalities have been shown to form substituted pyridines.[20] However, we did not observe any pyridine side products during the reaction with this alkyne.

We then tested our reaction conditions on internal alkynes (Table 2, entries 8–10). Similar to the literature precedent, this reaction required elevated temperatures to proceed in high yield. The cyclotrimerization reaction of internal alkynes with this catalyst system required only two hours at 80 °C to reach completion. 3-Hexyne was converted to hexaethylbenzene, while phenyl propyne and *tert*-butyldimethylsilyloxy-2-butynol gave near quantitative yields and high regioselectivities (96:4 and 75:25, respectively) of the corresponding unsymmetrical arene products.

Table 2 Cyclotrimerization of Terminal and Internal Alkynes



Entry	Alkyne[a]	$CoCl_2$, TIPG (mol%)	Zn, ZnI_2	Ratio of **3**/**4**[b]	Yield (%)[c]
1		2	4	95:5	87
2		2	4	99:1	74
3		2	4	85:15	98
4		2	4	81:19	89
5		2	4	85:15	94
6		2	4	94:6	94
7		2	4	93:7	98
8		4	8	–	93
9		4	8	96:4	98
10		4	8	75:25	98

[a] The alkyne is added after all other reagents are heated at 50 °C for 5 min.
[b] Regioselectivity was determined by GC.
[c] Isolated yield is an average of two 1 mmol experiments.

In summary, we have reported a rare example of a guanidine-ligated transition-metal-catalyzed reaction. Our catalyst operates at lower loadings compared to typical cyclotrimerization reaction conditions, while still providing high yields and regioselectivities of the obtained arene products. This guanidine catalyst also allowed the cyclotrimerization of internal alkynes at enhanced rates with respect to the previous catalysts employed in this reaction. From a fundamental perspective, the success of this catalyst in cyclotrimerization reactions of alkynes further exposes guanidines as ligands in metal-catalyzed processes. Future work will explore the use of similar guanidine-ligated complexes in an aqueous medium. Unfortunately, the initial reactions to perform the guanidine-ligated cobalt-catalyzed cyclotrimerization in water or a water–THF mixture proved fruitless and ligand modification is under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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