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Rhodium-Catalyzed [(3+2)+1] Carbocyclization Reactions of Alkynylidenecyclopropanes with Carbon Monoxide: Regiospecific Construction of Polysubstituted Phenols

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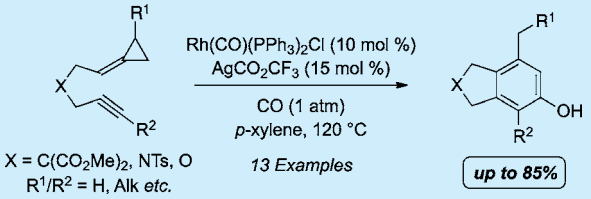
Supporting Information

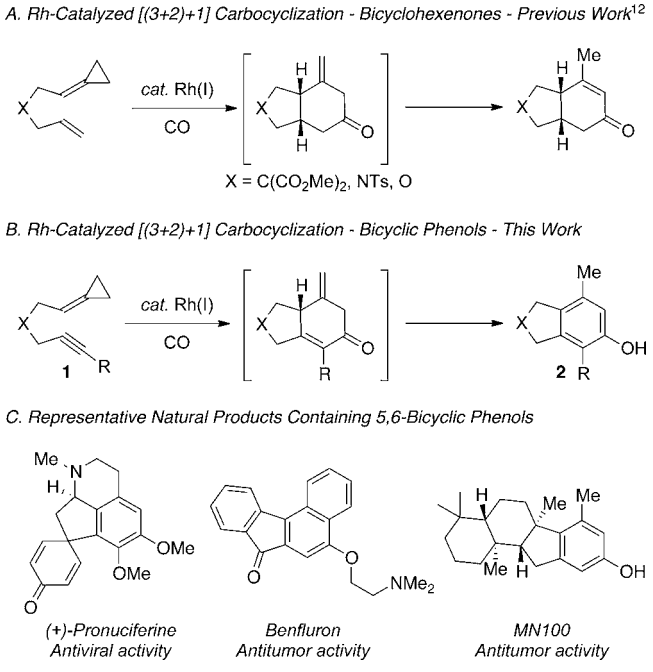
ABSTRACT: The development of the rhodium-catalyzed [(3+2)+1] carbocyclization reaction of alkynylidenecyclopropanes with carbon monoxide to construct polysubstituted phenols is described. This work offers a convenient method for the selective formation of tetra- and pentasubstituted phenols, which provide important intermediates for target directed synthesis. Finally, the ability to regiospecifically functionalize the phenols using conventional methods further illustrates the utility of this process.



Phenols represent extremely important motifs in organic chemistry, primarily due to their ubiquity in biologically interesting natural and unnatural products.[1] Nevertheless, the ability to directly construct a polysubstituted phenol is very challenging, particularly for the more classic synthetic approaches.[2] In contrast, metal-catalyzed cycloaddition reactions provide a versatile strategy for the construction of aryl rings, albeit relatively few carbocyclization reactions directly generate free phenols. This can be ascribed to the paucity of π-components containing a suitable C−O motif that can be effectively translated to the aryl product.[3,4] Notwithstanding this limitation, carbon monoxide has proven particularly effective as an exogenous π-component in a number of metal-mediated carbocyclizations, the most noteworthy of which is the venerable Pauson−Khand reaction.[5] Furthermore, this strategy offers a convenient approach to phenols by simply taking advantage of the tautomerization of dienones.[6] For example, the annulation of Fischer carbenes with alkynes and carbon monoxide provides an array of important phenols, albeit this method is limited by the use of stoichiometric quantities of toxic heavy metal complexes.[7] In contrast, Liebeskind and Wang have reported the rhodium-catalyzed [5+1] and [(3+2)+1] carbonylative carbocyclization reaction of cyclopropenes for the direct construction of phenols, although symmetrical cyclopropenes were employed to presumably circumvent the formation of constitutional isomers.[8] Hence, we envisioned that the ability to facilitate the construction of a polysubstituted phenol in a regiospecific manner would represent a significant and timely advance in this particularly important area of investigation.

In a program focused on the development of higher-order carbocyclization reactions with alkylidenecyclopropanes, we recently reported the rhodium-catalyzed [(3+2)+1] reaction with carbon monoxide to afford *cis*-fused bicyclohexenones in an efficient and stereoselective fashion (Scheme 1A).[9−13] Interestingly, this process initially provides the *exo*cyclic olefin,

Scheme 1. Rationale for the Development of the Rhodium-Catalyzed [(3+2)+1] Carbocyclization of ACPs with Carbon Monoxide



which is readily isomerized to the *endo*cyclic adduct.[12] We envisioned that simply replacing the alkene with an alkyne in the tether[14,15] would provide an opportunity to prepare tetra- and pentasubstituted bicyclic phenols (Scheme 1B), which are present in a number of important and challenging bioactive

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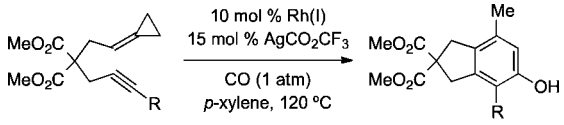
targets (Scheme 1C). For example, (+)-pronuciferine exhibits activity against hepatitis B, while benfluron and MN100 both display antitumor activity.[16] Herein, we now describe the rhodium-catalyzed [(3+2)+1] carbocyclization of carbon- and heteroatom-tethered alkynylidenecyclopropanes (ACPs) **1** with carbon monoxide to afford the bicyclic phenols **2** (Scheme 1B).

Table 1. Optimization of the Rhodium-Catalyzed [(3+2)+1] Carbocyclization Reaction with ACP 1a[a]



1a R = H
1b R = Me

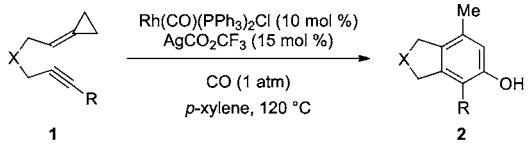
2a R = H
2b R = Me

entry	ACP **1**	Rh precomplex	ligand	concn (M)	yield (%)[b]
1	**a**	$Rh(PPh_3)_3Cl$	–	0.05	47
2	"	$[Rh(CO)_2Cl]_2$	–	"	0
3	"	"	PPh_3[c]	"	52
4	"	"	PPh_3[d]	"	53
5	"	"	dppp[c]	"	50
6	"	$Rh(CO)(PPh_3)_2Cl$	–	"	59
7	"	"	–	0.025	66
8	"	"	–	0.0125	52
9	***b***	***$Rh(CO)(PPh_3)_2Cl$***	–	***0.025***	***84***

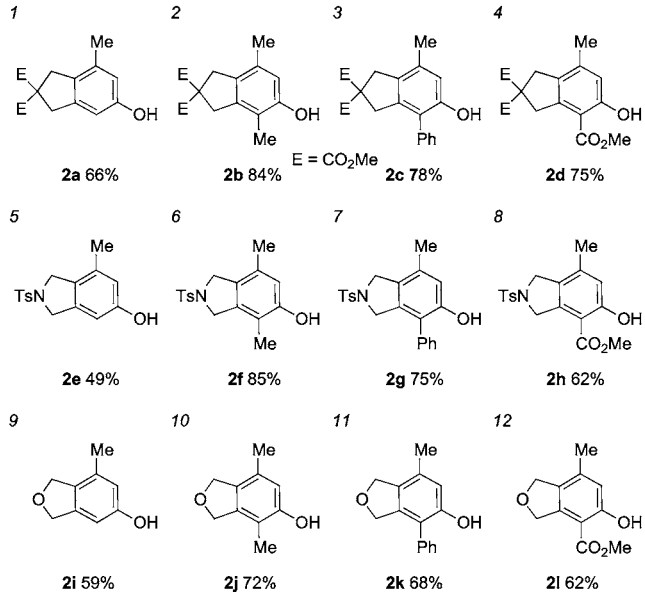
[a]All reactions were conducted on 0.25 mmol scale using 10 mol % rhodium precatalyst *modified* with $AgCO_2CF_3$ (15 mol %) in *p*-xylene at 120 °C in a sealed pressure tube. [b]Isolated yields. [c]10 mol %. [d]20 mol %.

Table 1 outlines the optimization and preliminary substrate scope for the development of an efficient [(3+2)+1] carbocyclization. Treatment of the ACP **1a** under similar conditions utilized for the related process,[12] namely Wilkinson's catalyst *modified* with $AgCO_2CF_3$, furnished the bicyclic phenol **2a** in modest yield (entry 1).[17] Additional optimization studies examined the effect of the silver salt, which demonstrated that silver trifluoroacetate is optimal for this process. Further efforts to improve the overall efficiency of this transformation focused on carbon monoxide-containing precatalysts. Interestingly, the complex devoid of a phosphine ligand was completely ineffective in the formation of **2a** (entry 2), whereas the addition of a phosphine ligand to the precatalyst provided modest improvement in the overall efficacy of this reaction relative to Wilkinson's catalyst (entry 3 vs 1). Nevertheless, further increasing the amount of phosphine rendered a similar yield, while a bidentate phosphine displayed comparable behavior (entries 4 and 5). Hence, given the impact of combining phosphine and carbon monoxide ligands, $Rh(CO)(PPh_3)_2Cl$ was employed as the precatalyst, which furnished the bicyclic phenol in an improved 59% yield (entry 6). Additional studies demonstrated that the efficiency could be further enhanced by simply lowering the concentration (entry 7) to afford **2a** in 66% overall yield, albeit any further reduction in concentration was not advantageous (entry 8). We hypothesized that the relatively modest yield for **2a** may be attributed to the C−H bond of the alkyne in **1a** interfering in the cycloaddition in a similar manner to the related rhodium-catalyzed [(2+2)+2] carbocyclization.[18] Gratifyingly, treatment of the substituted alkyne in ACP **1b** under the optimal reaction conditions furnished the bicyclic phenol **2b** in 84% overall yield (entry 9).

Scheme 2. Scope of the Rhodium-Catalyzed [(3+2)+1] Carbocyclization Reaction with ACPs 1[a,b]

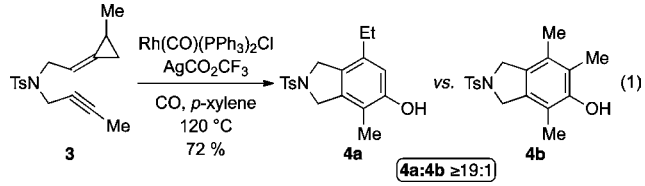


1 **2**



[a]All reactions were conducted on 0.25 mmol scale using $Rh(CO)(PPh_3)_2Cl$ (10 mol %) *modified* with $AgCO_2CF_3$ (15 mol %) in *p*-xylene at 120 °C in a sealed pressure tube. [b]Isolated yields.

Scheme 2 outlines the application of the optimized reaction conditions (Table 1, entry 9) to a range of carbon- and heteroatom-tethered ACPs. Interestingly, the nature of the tethering group did not impact the overall efficiency, albeit the oxygen-tethered substrates generally afforded slightly reduced yields in comparison to the other tethers. The reaction was also tolerant of a relatively diverse array of alkyne functionality, although the unsubstituted derivatives (entries 1, 5, and 9) were significantly lower yielding. Nevertheless, the introduction of a substituent at this position dramatically improved the overall efficiency of this process (entry 1 vs 2), which is in accord with the optimization studies outlined in Table 1. For instance, the methyl-substituted alkynes were slightly more efficient than the phenyl counterparts for each of the three tethers (entries 2, 6, and 10 vs 3, 7, and 11). Additionally, the ester substituents (entries 4, 8, and 12) facilitated the direct introduction of the carbonyl functionality, which provides an attractive group for the preparation of diversely functionalized aromatic systems. *Overall, this process provides a unique and direct approach to tetra- and pentasubstituted bicyclic phenols, which are present in important bioactive targets.*



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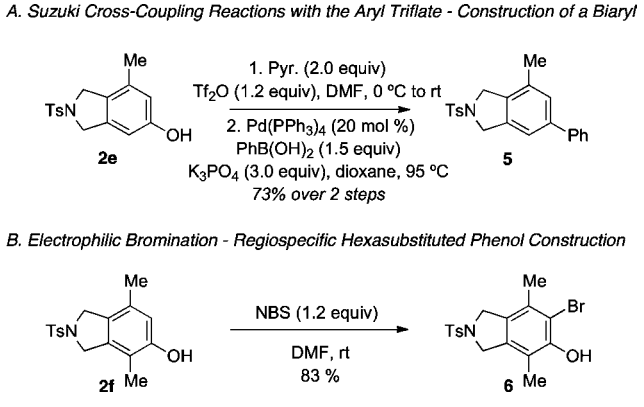
In an effort to further illustrate the scope of this process, we envisioned that substituted ACPs would extend the utility beyond the introduction of a simple methyl group in the *meta*-position, which would undoubtedly make this a more attractive strategy for synthetic applications. Gratifyingly, treatment of the ACP **3** under the standard reaction conditions furnished the bicyclic phenol **4a** in 72% yield as the exclusive constitutional isomer (eq 1). The regiochemical outcome for this process is similar to the analogous process with alkenylidenecyclopropanes.[12] Hence, the ability to selectively modify the *meta*-position of the bicyclic phenol in this manner brings important versatility to this transformation.

Additional studies focused on the direct functionalization of the bicyclic phenol. For example, Scheme 3A outlines the conversion of the phenol **2e** to the corresponding aryl triflate, which was then subjected to a Suzuki cross-coupling to afford the isoindoline derivative **5** in 73% yield over two steps.[19,20] This simple sequence illustrates the importance of the phenolic group, which can be used to access a large array of biaryl derivatives. Alternatively, halogenation of the bicyclic phenol **2f** with NBS afforded the *hexa*substituted aromatic ring **6**, which provides a handle for further cross-coupling reactions (Scheme 3B). Overall, these reactions nicely demonstrate the potential utility of this process.

Scheme 3. Functionalization Reactions of the Polysubstituted Phenols



In conclusion, we have developed a new rhodium-catalyzed [(3+2)+1] carbocyclization reaction of alkynylidenecyclopropanes with carbon monoxide to prepare tetra- and pentasubstituted bicyclic phenols. This transformation is extremely versatile in the context of the ACP tether. Moreover, we can readily functionalize the *ortho*-position of the phenol by installing substituents at the alkyne terminus of the alkynylidenecyclopropane. Furthermore, performing the carbocyclization with a substituted cyclopropylidene ring can also vary the substituent at the *meta*-position. In addition, activation of the phenol as the aryl triflate permits the Suzuki cross-coupling to provide a versatile route to substituted isoindoline fragments. Finally, we were able to access an unsymmetrical fully substituted aromatic ring in only two steps through the electrophilic halogenation of the phenol. Overall, the current rhodium(I)-catalyzed [(3+2)+1] carbocyclization reaction provides phenolic products, which have the propensity for being valuable synthetic intermediates for target directed synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds and CIF file for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) We propose that the reaction proceeds through an analogous mechanism to that of the previously described [(3+2)+1] carbocyclization with alkenylidenecyclopropanes, wherein the alkene present in the starting material is replaced with an alkyne. For further mechanistic studies with the alkenylidenecyclopropane derivative, see: Inglesby, P. A.; Bacsa, J.; Negru, D. E.; Evans, P. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 3952.

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