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Rhodium-Catalyzed Tandem Heterocyclization and Carbonylative [(3+2)+1] Cyclization of Diyne-enones

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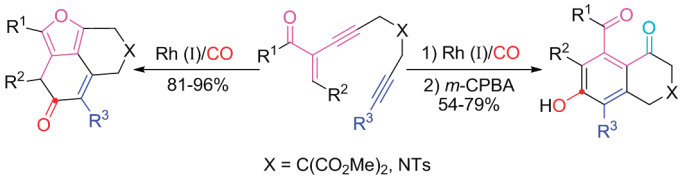
ABSTRACT



A simple and highly efficient rhodium-catalyzed tandem heterocyclization and carbonylative [(3+2)+1] cyclization reaction of readily available diyne-enone and carbon monoxide was developed, leading to a novel polycyclic furan scaffold. Synthetically useful highly substituted phenols can also be easily prepared via a straightforward one-pot synthetic strategy.

Transition-metal-catalyzed cyclization reactions have proven to be one of the most efficient and straightforward methods to construct complex polycyclic systems.[1] Among them, the construction of polycyclic compounds containing six-membered rings is actively pursued because of their significant role in many natural products and versatile applications as useful building blocks.[2] Thus, developing new strategies, such as three−component [$m + n + o$] cyclizations, has become increasingly important.[3] In the past decade, rhodium-catalyzed [2+2+2] and [4+2] cyclizations have been elegantly demonstrated to assemble various six-membered carbocycles.[1b,4,5] However, only limited examples of [3+2+1] cyclizations catalyzed by rhodium are reported where CO acts as a one-carbon synthon.[6] Recently, we have reported a rhodium-catalyzed domino heterocyclization and [(3+2)+2] carbocyclization of diyne-enone **1** and alkyne to afford fused tricycloheptadienes via a proposed metallacycle intermediate **4**,[7] where diyne-enone **1** could be easily prepared by the palladium-catalyzed Sonogashira

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cross-coupling reaction of α-bromo(iodo)-enones with 1,6-diynes. We envisaged that metallacycle intermediate **4** may be trapped by CO leading to a tricyclic scaffold **2**. Herein we describe a rhodium-catalyzed tandem heterocyclization and [(3+2)+1] cyclization of diyne-enones **1** and CO to afford polycyclic furan scaffold **2**, which could be easily converted to highly substituted bicyclic phenols **3** in the presence of an oxidant (Scheme 1).[8]

On the other hand, polycyclic furan structural units are unique architectures usually found in biologically active compounds.[9] The viridin family (Figure 1, viridin, virone, and wortmannolone) containing a fused tricyclic furan scaffold has been attracted attention because of the potent antiinflammatory and antibiotic properties and ability to selectively block certain intracellular signaling pathways associated with cell growth and development.[9] Moreover, phenols are commonly observed structural units in many natural products, polymers, and pharmaceuticals.[10] For example, ligudentatol and ligujapone (Figure 1) are isolated from Ligularia dentata roots that have been long used as a medicinal herb for easing breathing, stimulating blood flow, reducing inflammation, alleviating pain, stopping coughs, and getting rid of phlegm.[11] Furthermore, bicyclic phenol compound **5** potentiated TXA_2/PGH_2 receptor antagonistic activities.[12]

Scheme 1. Rhodium-Catalyzed Carbonylative [(3+2)+1] Cyclization

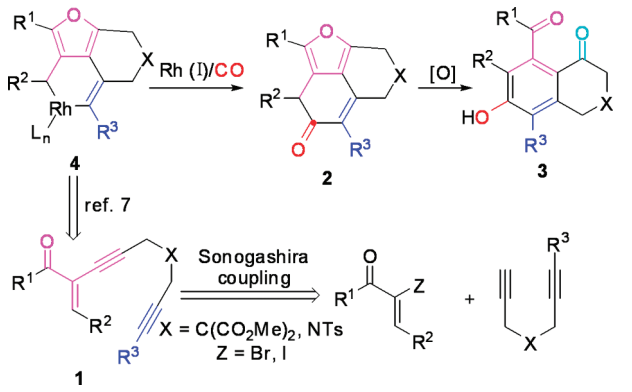

Figure 1. Some natural products containing polycyclic furan or phenol.

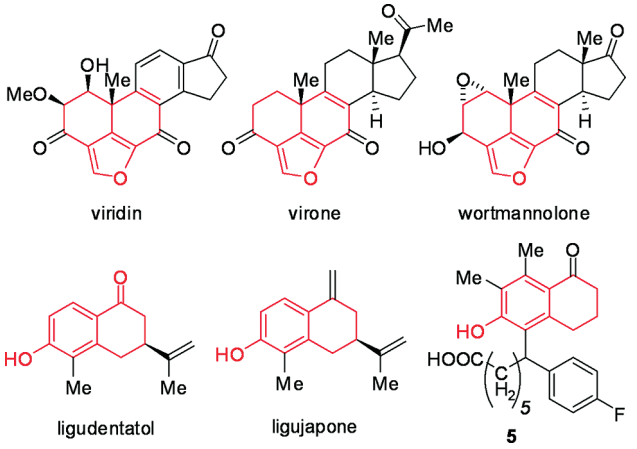

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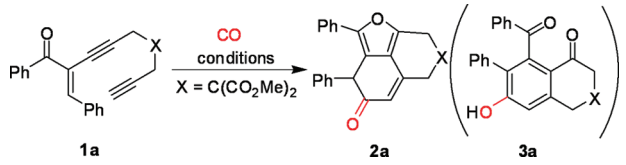
Table 1. Optimization of Reaction Conditions



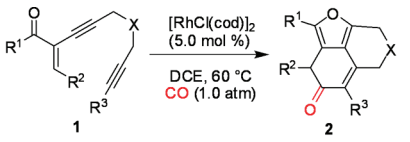
entry	conditions[a]	yield (%)[b]
1	$[RhCl(cod)]_2$, toluene, 1 h	21
2	$[RhCl(cod)]_2$, THF, 9 h	trace
3	$[RhCl(cod)]_2$, Dioxane, 5 h	41
4[c]	$[RhCl(cod)]_2$, DCE, 2 h	93
5	$[RhCl(CO)_2]_2$, DCE, 8 h	82
6[d]	$[RhCl(CO)(PPh_3)_2]$, DCE, 30 h	–
7	$[RhCl(cod)]_2/AgSbF_6$ (10 mol %), DCE, 1.5 h	trace
8[e]	$[RhCl(cod)]_2$, DCE, 4 h	90

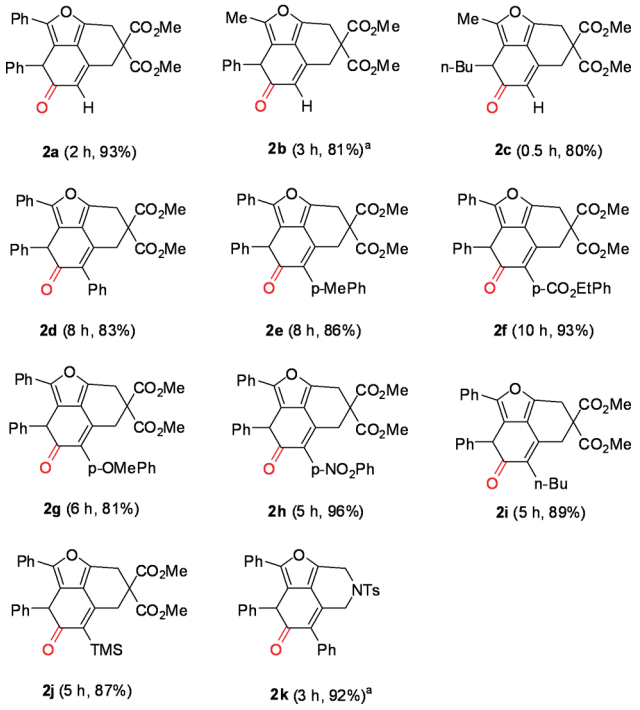
[a] Conditions (unless otherwise noted): Rhodium (5.0 mol %), **1a** (0.01 M), CO (1.0 atm), 60 °C. [b] Yield determined by ^1H NMR spectroscopy using dibromomethane as internal standard. [c] Yield of isolated product. [d] The compound **3a** was obtained in 48% isolated yield. [e] Reaction carried out under 0.2 atm of CO (1 atm of mixture gas CO/N_2 = 1:4).

To optimize the reaction conditions for this rhodium-catalyzed tandem heterocyclization and carbonylative [(3+2)+1] cyclization, the influences of solvent, catalysts, and the pressure of CO were investigated for the reaction of diyne-enone **1a** with CO (Table 1). We began this examination by treating **1a** with $[RhCl(cod)]_2$ (5.0 mol %) in toluene at 60 °C under carbon monoxide at atmospheric pressure. To our delight, the [(3+2)+1) cyclization indeed occurred, and the racemic tricyclic furan **2a** was formed in 21% yield after 1 h (Table 1, entry 1). To further identify optimal reaction conditions, THF, 1,4-dioxane, and 1,2-dichloroethane (DCE) were screened, and it proved that DCE is the best solvent for this transformation, affording **2a** in 93% isolated yield after 2 h (Table 1, entries 2−4). We then turned our attention to other rhodium complexes. $[RhCl(CO)_2]_2$ can also catalyze this reaction but is less efficient (Table 1, entry 5). Interestingly, when **1a** is treated with $[RhCl(CO)(PPh_3)_2]$, a bicyclic phenol **3a** can be isolated in 48% yield, which may be converted from **2a** in the presence of oxygen that acts as the oxidant and occasionally come into the reaction system from the air (Table 1, entry 6).[8g−j] Furthermore, $Rh(I)^+$ species (genernated from 1:1 ratio $[RhCl(cod)]_2 + AgSbF_6$ in situ) failed to catalyze this transformation (Table 1, entry 7). The reaction proceeds well under the lower pressure of CO albeit it requires reaction time (Table 1, entry 8).

The scope of this rhodium-catalyzed [(3+2)+1] cyclization reation was next investigated using various diyne-enone substrates (Scheme 2). The results indicate that this cyclization is tolerant of different substitutions (R^1−R^3) on the alkene, alkyne, and carbonyl moieties. The alkyne terminus R^3 can be the H, aryl, alkyl and trimethylsilyl group, which has a great impact on the reaction rate but has little effect on the yield (compounds **2a**−**j**). The structure

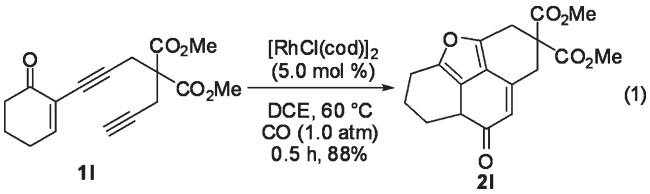
Scheme 2. Rhodium-Catalyzed [(3+2)+1] Cycloaddition Reaction





[a] Yield determined by ^1H NMR spectroscopy using dibromomethane as internal standard.

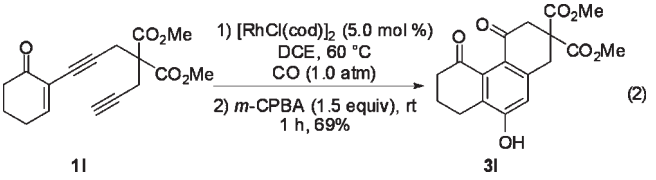
of **2h** was further confirmed by the X-ray crystallographic analysis.[14] This study also demonstrated that carbon and nitrogen tethers can be well tolerated (compounds **2a**−**k**);[13] however the oxygen-tethered substrate was decomposed under the reaction conditions. Gratifyingly, it is noteworthy that the diyne-enone **1l** with a cyclohexenone moiety can also undergo the [(3+2)+1) cyclization to afford the corresponding tetracyclic furan compound **2l** in 88% yield under the standard reaction conditions [eq 1] .



(13) Attempted isolation of the compounds **2b** and **2k** resulted in either decomposition or further oxidation.

(14) CCDC 795202 (**2h**) and 795203 (**3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

To show the synthetic application of polycyclic furan compounds, we investigated a one-pot synthetic strategy to construct highly substituted polycyclic phenols **3** which can be found in a wide range of compounds possessing diverse biological activities. Fortunately, after several attempts, we discovered that the polycyclic phenol structure **3a** could be synthesized in 61% yields (two steps) by a simple sequential one-pot operation, that is, Rh-catalyzed carbonylative [(3+2)+1] cycloaddition of diyne-enone in 1,2-dichloroethane (DCE) at 60 °C, followed by treatment with 1.5 equiv of 3-chlorobenzoperoxoic acid (*m*-CPBA) at room temperature (Scheme 3). The structure of **3a** was further confirmed by the X-ray crystallographic analysis.[14]

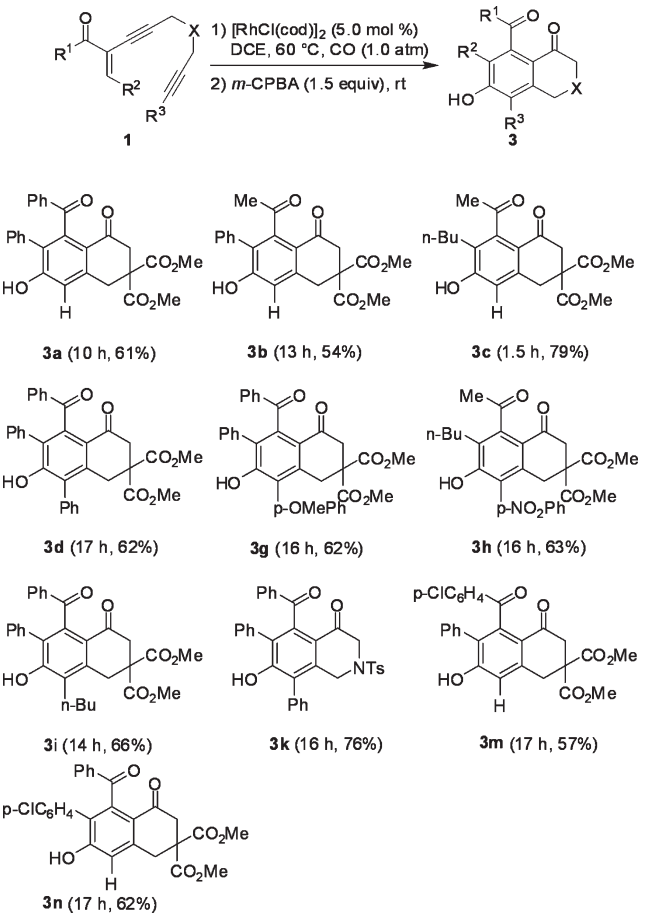


(2)

Studies on the scope of this one-pot sequential reaction indicate that it can be used to synthesize various multifunctional highly substituted phenol derivatives **3** in moderate to good yields, which are useful building blocks for further functional transformation (Scheme 3). Different R^1-substituted carbonyls and R^2-substituted alkenyls, including alkyls and aryls, were proven to be efficient to afford the desired products (compounds **3a**−**c**). It is noteworthy that the substrate containing both an alkyl substituted carbonyl and alkene moiety can give the corresponding bicyclic phenol **3c** in 79% yield. In addition, this one-pot operation strategy can be applied to various substrates with different substituents on the alkyne moiety (R^3) to furnish the corresponding products (compounds **3d**−**i**) in reasonable yields. The 1,2,3,4-tetrahydroisoquinolin-7-ol derivative **3k** can be afforded in 76% yield from the corresponding TsN-tethered substrate. The use of **1l** bearing a cyclohexenone moeity again led to tricyclic phenol compound **3l**. A halogen on the substitutent is aslo compatible (compounds **3m**−**n**).

In conclusion, we have developed a simple and highly efficient rhodium-catalyzed tandem heterocyclization and carbonylative [(3+2)+1] cyclization reaction of readily available diyne-enones and carbon monoxide for the synthesis of a novel polycyclic furan scaffold with product yields up to 96%, and a one-pot synthetic strategy to construct synthetically useful polycyclic phenols. Current efforts directed toward exploration of the full synthetic potential of this methodology, including catalytic asymmetric

Scheme 3. One-Pot Synthesis of Polycyclic Phenols



catalysis and its application in the synthesis of the natural products, are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, spectroscopic data for the substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.