

# Rhodium-Catalyzed Carbonylative [3 + 2 + 1] Cycloaddition of Alkyne-Tethered Alkylidenecyclopropanes to Phenols in the Presence of Carbon Monoxide

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**Supporting Information** 

**ABSTRACT:** A novel Rh-catalyzed carbonylative [3 + 2 + 1] cycloaddition of alkyne-tethered alkylidenecyclopropanes for the facile synthesis of bicyclic phenols in high yields has been developed. The reaction tolerated carbon and heteroatoms in the tether.



any useful reactions have been developed for the synthesis of cyclic compounds. Transition-metal-catalyzed cycloadditions have been extensively used in the synthesis of cyclic compounds.<sup>1</sup> Alkylidenecyclopropanes can undergo a number of interesting metal-assisted transformations. For example, alkylidenecyclopropanes have been used in nickelcatalyzed cycloadditions with activated alkenes.<sup>2</sup> Mascareñas et al. reported a palladium-catalyzed intramolecuar [3 + 2]cycloaddition with similar substrates.<sup>3</sup> However, the rhodiumcatalyzed intramolecular carbocyclization of alkylidenecyclopropanes is known to form a complex mixture of products.<sup>4</sup> Several years ago, Shi et al. developed the first intramolecular rhodium(I)-catalyzed [3 + 2] cycloaddition of alkylidenecyclopropanes<sup>4</sup> and the Evans group reported a rhodium-catalyzed [3 + 2 + 1] cycloaddtion.<sup>5</sup> During our catalyst screening process, we discovered a formal [3 + 2 + 1] cycloaddition of alkylidenecyclopropanes to afford phenol derivatives in the presence of a rhodium catalyst and carbon monoxide. In contrast to our expectation, the carbonylative [3 + 2 + 1]cycloaddition reaction has been rarely reported.<sup>6</sup> In addition, the formation of a six-membered ring by [3 + 2 + 1]carbonylative carbocyclization has not been well developed, because of the difficulty in introducing the required threecarbon component. Herein, we communicate the Rh(I)catalyzed [3 + 2 + 1] carbonylative carbocyclization of alkylidenecyclopropanes, for the synthesis of bicyclic phenols. A few years ago, Wang and co-workers<sup>7</sup> reported a carbocyclization of yne-cyclopropenes to afford phenol derivatives. Recently, Shi et al. reported<sup>8</sup> a Rh(I)-catalyzed tandem Pauson-Khand type reaction of 1,4-enynes, resulting in the formation of similar phenol derivatives.

The requisite alkylidenecyclopropane substrates were easily prepared by using known procedures.<sup>9</sup> Compound 1a (*N*-(but-2-yn-1-yl)-*N*-(2-cyclopropylideneethyl)-4-methylbenzene-sulfonamide) was chosen as a model substrate. A solution of 1a and  $[Rh(COD)Cl]_2$  (10 mol %) in toluene was heated at 100 °C under an atmosphere of CO (1 atm) for 11 h. Compounds

**2a** and **3a** were isolated in 21% and 15% yield, respectively (eq 1).Compound **2a** was the product of a formal [3 + 2 + 1]



cycloaddition, a phenol derivative. Compound 2a was synthesized by a rhodium-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes with vinylene carbonate.<sup>10</sup> Compound **3a** was the Pauson-Khand reaction product. Similar Pauson-Khand reaction products have been reported by de Meijere.<sup>11</sup> Encouraged by the formation of compound 2a, we endeavored to optimize the reaction conditions to obtain 2a as a major product. The reaction conditions used in our processes are shown in Table 1. The yield of desired product 2a was highly sensitive to the rhodium catalyst, the reaction solvent, and the reaction temperature used. When the same reaction was carried out using 1,4-dioxane as the solvent at 100 °C for 6 h, a mixture containing 2a and 3a in 61% and 11% yield, respectively, was isolated (entry 2). When  $[Rh(dppp)_2Cl]$  was used as the catalyst in 1,4-dioxane, the yields of 2a and 3a were decreased to 44% and 2%, respectively (entry 3). To our delight, the use of Rh(PPh<sub>3</sub>)<sub>3</sub>Cl as a catalyst in 1,4-dioxane at 100 °C for 13 h afforded 2a as the sole product in 64% yield (entry 4). Encouraged by this result, we studied the use of a cationic rhodium complex generated by the reaction of Rh(PPh<sub>3</sub>)<sub>3</sub>Cl with AgX as a catalyst in 1,4-dioxane at 100  $^{\circ}$ C (entries 5–13).

Interestingly, when  $AgSbF_6$  or  $AgClO_4$  was used as the source of a counteranion, no reaction was observed (entries 5 and 8). In the presence of  $AgBF_4$ ,  $AgPF_6$ , AgOTs, and  $AgSO_3CF_3$  as the source of a counteranion in 1,4-dioxane at 100 °C, a 39–59% yield of **2a** was isolated (entries 6, 7, 9, and

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Table 1. Optimization for Rh(I)-Catalyzed Carbonylative Cycloaddition<sup>*a*</sup>

TsN	10 ma 15 ma	l % Rh(l) bl % AgX		үон			
		(1 atm) Ivent		-		>	
	1a		2a		3	a	
entry	catalyst/AgX	solvent	temp (°C)	time (h)	<b>2a</b> <sup>c</sup> (%)	3a <sup>c</sup> (%)	
1	$[Rh(COD)Cl]_2$	toluene	100	11	21	15	
2	$[Rh(COD)Cl]_2$	dioxane	"	6	61	11	
3	Rh(dppp) <sub>2</sub> Cl	"	"	6	44	2	
4	Rh(PPh <sub>3</sub> ) <sub>3</sub> Cl	"	"	13	64		
5	″/AgSbF <sub>6</sub> <sup>b</sup>	"	"	6	NR		
6	″/AgBF4 <sup>b</sup>	"	"	6	55		
7	″/AgPF <sub>6</sub> <sup>b</sup>	"	"	6	56		
8	"/AgClO <sub>4</sub> <sup>b</sup>	"	"	6	NR		
9	″/AgOTs <sup>b</sup>	"	"	12	59		
10	″/AgSO <sub>3</sub> CF <sub>3</sub> <sup>b</sup>	"	"	7	39		
11	"/AgCO <sub>2</sub> CF <sub>3</sub> <sup>b</sup>	"	"	6	69		
12	"  "	"	"	6	77		
13	"  "	xylenes	120	2	91		
<sup>a</sup> Conditions: Substrate concentration 0.055 M. <sup>b</sup> Rh(PPh <sub>2</sub> ) <sub>2</sub> Cl (5 mo							

%) and AgX (7.5 mol %) were used. <sup>c</sup>Isolated yields.

10). When the reaction was carried out using  $AgCO_2CF_3$  in 1,4-dioxane at 100 °C for 6 h, the yield of **2a** increased to 69% (entry 11). Increasing the quantity of  $Rh(PPh_3)_3Cl$  (10 mol %) and  $AgCO_2CF_3$  (15 mol %) increased the yield of **2a** (77%) (entry 12). Furthermore, the reaction time was decreased to 2 h by using xylenes as the reaction solvent at 120 °C. The highest yield of **2a** (91%) was obtained in the presence of 10 mol %  $Rh(PPh_3)_3Cl$  and 15 mol %  $AgCO_2CF_3$  (entry 13). The structure of **2a** was confirmed by using X-ray diffraction crystallography (Figure 1).



Figure 1. X-ray structure of 2a.

To further expand the scope of the reaction, a variety of alkylidenecyclopropanes were investigated under the optimized reaction conditions (Table 2). A diverse range of substrates were tolerated under the optimized reaction conditions, resulting in the high yields (74%–91%) of compound 2. However, the nitrogen-tethered 1,6-enynes with a terminal alkyne or a vinyl group on the terminal alkyne afforded relatively lower yields (19% and 23% yields, respectively) (entries 2 and 7).<sup>12</sup> For nitrogen-tethered substrates, the introduction of an electron-donating group (-OMe) or electron-withdrawing group (-CI or  $-CF_3$ ) on the aryl ring did not improve the reaction (entries 4–6). Interestingly, for an enyne with a cyclopropyl group on the terminal alkyne, the

×	R	cat. Rh(I AgCO <sub>2</sub> CF <sub>3</sub>	) , co	X CH 2
entry	1	Х	R	yield (%) <sup>b</sup> $2$
1	1a	N-Ts	Me	<b>2</b> a, 91
2	1b	N-Ts	Н	<b>2b</b> , 19
3	1c	N-Ts	Ph	<b>2c</b> , 83
4	1d	N-Ts	C <sub>6</sub> H <sub>4</sub> -Cl-4	<b>2d</b> , 75
5	1e	N-Ts	C <sub>6</sub> H <sub>4</sub> -OMe-	4 <b>2e</b> , 79
6	1f	N-Ts	C <sub>6</sub> H <sub>4</sub> -CF <sub>3</sub> -4	<b>2f</b> , 74
7	1g	N-Ts	CH=CH <sub>2</sub>	<b>2g</b> , 23
8	1h	N-Ts	cyclopropyl	<b>2h</b> , 85
9	1i	0	Me	<b>2i</b> , 88
10	1j	0	Ph	<b>2</b> j, 84
11	1k	$C(CO_2Et)_2$	Me	<b>2k</b> , 74
12	11	$C(CO_2Et)_2$	Ph	<b>21</b> , 84
13	1m	TsN	~=- ~~	<b>2m</b> , 52
14	ln	TsN	Ph	<b>2n</b> , 14
15	10	TsN	Ph	NR

Table 2. Rh(I)-Catalyzed [3 + 2 + 1] Cycloaddition

Reactions<sup>a</sup>

<sup>*a*</sup>Reaction conditions: 10 mol % Rh(PPh<sub>3</sub>)<sub>3</sub>Cl, 15 mol % AgCO<sub>2</sub>CF<sub>3</sub>, 1 atm of CO in xylenes (0.055 M) at 120 °C for 3 h. <sup>*b*</sup>Isolated yields.

reaction proceeded smoothly to afford a cyclopropylbenzene derivative in 85% yield (entry 8). Both carbon- and oxygenlinked 1.6-envnes could be used in the reaction with similar results (entries 9-12). When 1,7-enynes were used in the reaction, the yield of a reaction was highly dependent upon the substituent on the alkyne. When a 1,7-enyne bearing a methyl group on the alkyne was used as the substrate, the corresponding product, tetrahydroisoquinolinol, was isolated in 52% yield (entry 13). This is the first report for the transformation of nitrogen-tethered 1,7-enynes to isoquinolinols.<sup>13</sup> Tetrahydroisoquinolines are present in various potent cytotoxic agents that display a range of antitumor, antimicrobial, and other interesting biological activities depending on their structures.<sup>14</sup> However, for a 1,7-enyne bearing a phenyl substituent on the alkyne, known to be inert in the goldcatalyzed cycloisomerization,<sup>15</sup> the reaction was sluggish under our optimized reaction conditions. The phenol derivative was isolated in a low yield (14%), whereas the 1-methylenehexahydro-1H-indene (4n) was isolated as the major product in 49% yield (entry 14 and eq 2). The presence of a gem-dimethyl group at the propargylic position does not result in any carbonylation and the 4-methylene-hexahydropentalene derivative was isolated in 33% yield (eq 3). The formation of compound 4 from alkylidenecyclopropanes has been reported



in the palladium-catalyzed cycloaddition reaction.<sup>16</sup> When the same reaction was conducted without CO, the reaction became slow and the yield of 4-methylene-hexahydropentalene did not improve. The presence of CO is beneficial for the reaction, even though the reaction to form **4** is not related to the carbonylation reaction.<sup>12,17</sup>

On the basis of the related previous studies,<sup>18,19</sup> a plausible reaction mechanism is outlined in Scheme 1. Alkylidenecyclo-

#### Scheme 1. Proposed Reaction Mechanism



propane (1) in the presence of a rhodium catalyst [Rh]undergoes a reaction to form a rhodium(I) intermediate (A), followed by ring opening of the cyclopropane moiety and the oxidative addition to the rhodium center to form **B**. In the formation of intermediate **B**, the rhodium center was inserted into the distal bond of the cyclopropane ring. A reductive cyclization followed by demetalation leads to compound 4. Coordination of CO to **B** leads to the formation of intermediate **C**. Insertion of CO, reductive elimination, and a 1,3-hydride shift lead to intermediate **D**. Subsequent isomerization of **D** affords the final product **2**.

In summary, we developed a novel rhodium-catalyzed carbonylative [3 + 2 + 1] cycloaddition of alkylidenecyclopropanes under mild reaction conditions, for the synthesis of phenols. A variety of tethers (nitrogen-, oxygen-, and *gem*-diester) could be employed to construct hetero- and carbobicyclic skeletons. The tether length allows the formation of 5,6- and 6,6-bicyclic systems. The products possess a phenol ring bearing a vinyl or a cyclopropyl substituent, which will provide access for further functionalization and operation.<sup>20</sup>

## ASSOCIATED CONTENT

### Supporting Information

General experimental procedure and characterization of all compounds are provided. 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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