Chemistry Letters

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Advance Publication on the web September 2, 2017
doi:10.1246/cl.170754

Formation of α-Monosubstituted Propargylamines from Terminal Alkynes and Secondary Amines Using a (PNO)Rh/Cu Tandem Catalyst System

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A novel (PNO)Rh/CuBr (PNO: phosphine-quinolinolate) tandem catalyst system was developed for facile synthesis of α-monosubstituted propargylamines from aliphatic terminal alkynes and secondary amines. Various terminal alkynes and amines were applicable to this reaction and the corresponding propargylamines were obtained in good yields.

Keywords: Rhodium catalysts | Terminal alkynes | Propargylamines |

Propargylamines are an important class of compounds that have been used as intermediates for various nitrogen-containing compounds.[1] Direct addition of terminal alkynes to imines or enamines can be regarded as one of the most facile methods for the preparation of propargylamines and has been extensively used in the synthesis of a variety of amines.[2-4] Since one of the most convenient, atom-efficient ways to prepare imines or enamines is hydroamination of alkynes, combinations of alkyne hydroamination and further alkyne addition to imines or enamines have also been studied to prepare propargylamines from alkynes and amines.[5-7] Copper catalysts, known to catalyze both the hydroamination and the alkyne addition, have mostly been employed for these reactions.[5,6] Most of the hydroamination/alkyne addition reactions reported so far produced α,α-disubstituted propargylamines because the hydroamination reactions generally proceeds in a Markovnikov fashion.[5] There have been a few reports on one-step propargylamine syntheses via anti-Markovnikov addition and alkyne addition using alkynes possessing aryl or electron-withdrawing substituents,[6,8] the corresponding high-yielding synthesis of propargylamines via anti-Markovnikov addition to aliphatic terminal alkynes has not been reported.

Our group has developed various transformations of terminal alkynes catalyzed by 8-quinolinolatorhodium complexes.[9] For example, we found the combination of an 8-quinolinolatorhodium complex bearing a cyclooctadiene ligand (Rh(Q)(cod)) with triarylphosohines are effective catalysts for the anti-Markovnikov hydroamination of arylacetylenes with secondary amines at room temperature.[9b] We recently synthesized novel rhodium(I) complexes bearing a PNO tridentate ligand containing an 8-quinolinolate and a phosphine moieties (Figure 1)[10] and found that the (PNO)Rh complexes can produce the anti-Markovnikov hydroamination product from an aliphatic terminal alkyne and piperidine at 110 ºC. It was also shown that vinylidene-bridged dirhodium complexes and (amino)carbene complexes can be prepared from (PNO)Rh complex **1a** with terminal alkynes and then with amines and are important intermediates in the anti-Markovnikov hydroamination of terminal alkynes. Therefore, we envisioned that the use of (PNO)Rh complex along with a copper catalyst would provide a novel tandem catalyst system which produce propargylamines via (PNO)Rh-catalyzed anti-Markovnikov hydroamination and copper-catalyzed alkyne addition.

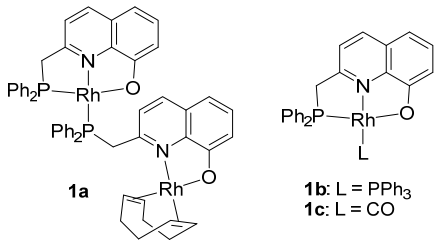
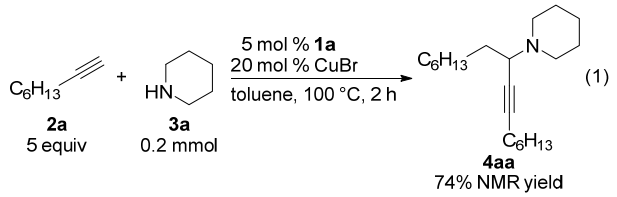


Figure 1. Rhodium complexes bearing a PNO tridentate ligand

Here we report the novel (PNO)Rh/Cu tandem catalyst system for facile synthesis of α-monosubstituted propargylamines from aliphatic terminal alkynes and secondary amines. The reaction is considered to proceed via the rhodium-catalyzed anti-Markovnikov hydroamination of terminal alkynes with secondary amines to form enamines, followed by copper-catalyzed alkyne addition to the enamines.

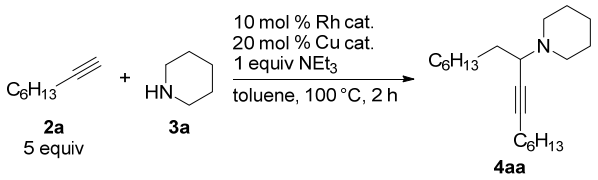
First, the reaction of 1-octyne (**2a**) with piperidine (**3a**) was performed in the presence of 5 mol % dinuclear (PNO)Rh complex **1a** and 20 mol % CuBr (eq. 1), and α-monosubstituted propargylamine **4aa**, possibly formed by the tandem anti-Markovnikov hydroamination/alkyne addition, was obtained in 74% NMR yield along with dimers of **2a**. In this reaction, no α,α-disubstituted propargylamine, which may be generated via the Markovnikov hydroamination, was observed.



The reaction conditions for the anti-Markovnikov hydroamination/alkyne addition was then examined (Table 1). Addition of 1 equiv of triethylamine slightly improved the yield to 77% (entry 1). In the absence of rhodium catalyst **1a**, the catalytic activity for the propargylamine formation was decreased, and the Markovnikov hydroamination/alkyne addition product became the major product (entry 2). When only **1a** was used as a catalyst, the propargylamine formation did not proceed and a trace amount of hydroamination

product was detected (entry 3). Then the copper catalysts were screened for the propargylamine formation. The use of other copper(I) catalysts such as CuCl, CuI, and CuCN gave product **4aa** in 40-74% yields (entries 4-6). Among the copper(II) catalysts examined, $CuCl_2$ and $CuBr_2$ showed similar catalytic activity to CuBr (entries 7 and 8), while the product yields of the reactions using other copper(II) salts such as $Cu(OAc)_2$ and $Cu(OTf)_2$ were significantly lower than that with CuBr (entries 9 and 10). The reactions using other (PNO)Rh catalysts were also conducted. The use of triphenylphosphine complex **1b** slightly improved the yield of product **4aa** to 83% (entry 11), while carbonyl complex **1c** showed lower catalytic activity (entry 12). The yield of **4aa** was further improved to 89% by reducing the amounts of the catalysts (entry 13).[11]

Table 1. Screening of Catalysts for the anti-Markovnikov Hydroamination/Alkyne Addition of **2a** with **3a**[a]



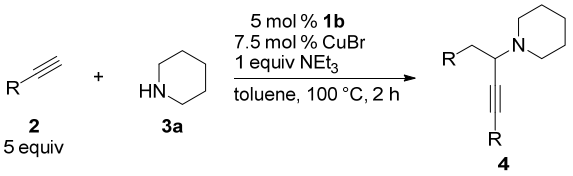
2a 5 equiv | **3a** | **4aa**

Entry	Rh catalyst	Cu catalyst	NMR yield (%)[b]
1	**1a** (5 mol %)	CuBr	77
2	none	CuBr	4[c]
3	**1a** (5 mol %)	none	nd[d]
4		CuCl	61
5		CuI	74
6		CuCN	40
7		$CuCl_2$	77
8		$CuBr_2$	75
9		$Cu(OAc)_2$	24
10		$Cu(OTf)_2$	trace
11	**1b**	CuBr	83
12	**1c**	CuBr	59
13[e]	**1b**	CuBr	89

[a]Reaction conditions: **2a** (1.0 mmol), **3a** (0.2 mmol), Rh catalyst (0.02 mmol), Cu catalyst (0.04 mmol), triethylamine (0.2 mmol), toluene 1.5 mL, 100 ºC, 2 h. [b]9*H*-Fuluorene was used as an internal standard. [c]The Markovnikov hydroamination/alkyne addition product was formed in 16% NMR yield. [d]Not detected. [e]Performed using 5 mol % of **1b** and 7.5 mol % of CuBr.

Various propargylamines were isolated by performing the anti-Markovnikov hydroamination/alkyne addition of several terminal alkynes using 0.4 mmol of amine **3a** (Table 2). Propargylamine **4aa** was isolated in 89% yield from the reaction of **2a** with **3a** (entry 1). The reactions of cyclohexylacetylene (**2b**) and 3-cyclohexyl-1-propyne (**2c**) also provided propargylamine products **4ba** and **4ca** in 89 and 92% yields, respectively (entries 2 and 3). Terminal alkynes containing a polar functional group such as **2d** and **2e** also gave the corresponding propargylamines (entries 4 and 5). The reaction of a substrate containing a THP-protected alcohol (**2f**) also proceeded efficiency (entry 6). In contrast, phenylacetylene (**2g**) was not a suitable substrate and gave only 10% NMR yield of the corresponding product **4ga** (entry 7). In this case, various byproducts such as the hydroamination product were observed.

Table 2. anti-Markovnikov Hydroamination/Alkyne Addition of Various Terminal Alkynes with **3a**[a]



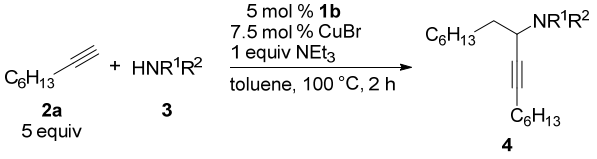
2 5 equiv | **3a** | **4**

Entry	**2**	R	**4**	isolated yield (%)
1	**2a**	C_6H_{13}	**4aa**	89
2	**2b**	Cy	**4ba**	89
3	**2c**	$CyCH_2$	**4ca**	92
4	**2d**	$NC(CH_2)_3$	**4da**	55
5	**2e**	$MeO_2C(CH_2)_3$	**4ea**	89
6	**2f**	$THPO(CH_2)_3$	**4fa**	91
7	**2g**	Ph	**4ga**	10[b]

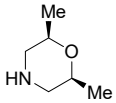
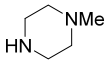
[a]Reaction conditions: terminal alkyne (2.0 mmol), **3a** (0.4 mmol), **1b** (0.02 mmol), CuBr (0.03 mmol), triethylamine (0.4 mmol), toluene 3.0 mL, 100 ºC, 2 h. [b]NMR yield determined by ^{1}H NMR using 9*H*-fluorene as an internal standard.

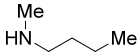
The scope of secondary amines were also investigated (Table 3). When cyclic secondary amines (**3b-3d**) were used as a substrate, the corresponding propargylamines (**4ab-4ad**) were obtained in 79-89% yields (entries 1-3). The reaction also proceeded using acyclic amines, *N*-benzylmethylamine (**3e**) and *N*-butylmethylamine (**3f**), to provide amines **4ae** and **4af** in 74 and 90% yields, respectively (entries 4 and 5).

Table 3. anti-Markovnikov Hydroamination/Alkyne Addition of **2a** with Various Secondary Amines[a]



2a 5 equiv | **3** | **4**

Entry	**3**	HNR^1R^2	**4**	isolated yield (%)
1	**3b**		**4ab**	89
2	**3c**		**4ac**	89
3	**3d**		**4ad**	79

4	**3e**		**4ae**	74
5	**3f**		**4af**	90

[a]Reaction condition: **2a** (2.0 mmol), secondary amine (0.4 mmol), **1b** (0.02 mmol), CuBr (0.03 mmol), triethylamine (0.4 mmol), toluene 3.0 mL, 100 ºC, 2 h.

A plausible mechanism of the anti-Markovnikov hydroamination/alkyne addition is shown in Figure 2. As we previously reported for the (PNO)Rh-catalyzed anti-Markovnikov hydroamination of terminal alkynes,[10] enamines were considered to be produced in this reaction as well via formation of a vinylidene intermediate and then conversion to an (amino)carbene complex, followed by 1,2-*β*-H shift. In the presence of a copper catalyst, a copper acetylide may be generated by the reaction with a terminal alkyne and a base. Addition of the acetylide to an iminium ion, formed by protonation of the enamine, would provide the propargylamine product. Reactions of enamines with copper acetylides to produce propargylamines have already been reported.[4]

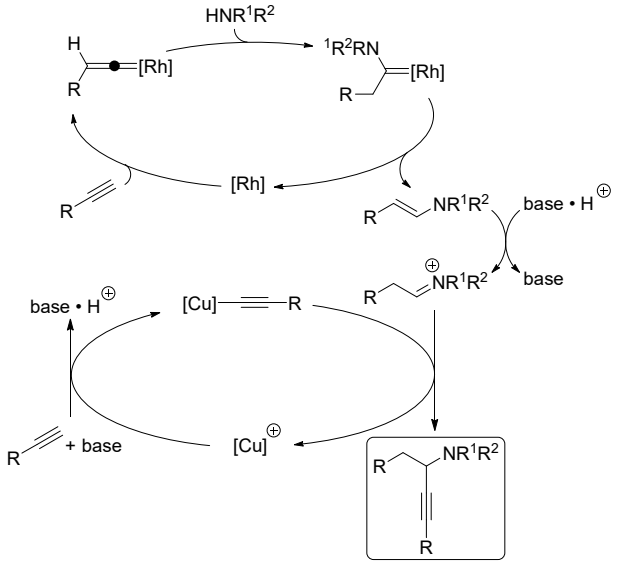
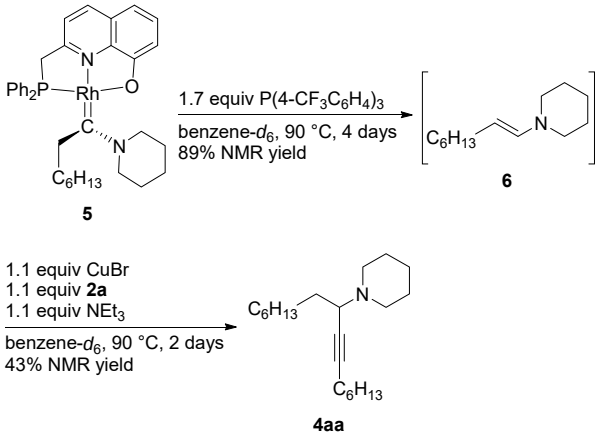


Figure 2. A proposed mechanism for tandem anti-Markovnikov hydroamination/alkyne addition catalyzed by (PNO)Rh complexes and copper co-catalyst

To examine the validity of the anti-Markovnikov hydroamination/alkyne addition mechanism, enamine **6** was generated in situ by the reaction of (amino)carbene complex **5** with tris(4-trifluoromethylphenyl)phosphine and then treated with terminal alkyne **2a**, CuBr, and triethylamine at 90 ºC (Scheme 1). The ^{1}H NMR spectra of the crude material showed that the corresponding propargylamine **4aa** was indeed formed in 43% NMR yield.[12]



Scheme 1. The generation of enamine **6** from (amino)carbene complex **5** and the reaction of **6** with terminal alkyne **2a**, CuBr and triethylamine

In conclusion, a facile method for the synthesis of α-monosubstituted propargylamines from aliphatic terminal alkynes and secondary amines was developed using the novel (PNO)Rh/Cu tandem catalyst system. Various terminal alkynes as well as secondary amines were applicable to this reaction. The reaction is considered to proceed via the (PNO)Rh-catalyzed anti-Markovnikov hydroamination to form enamines and copper-catalyzed alkyne addition to the enamines. Further developments of novel reactions via enamine intermediates are currently in progress by taking advantage of the excellent utility of the (PNO)Rh complexes in tandem catalysis.

This work was supported in part by JSPS KAKENHI Grant Numbers JP16H04150 and JP15H05839 (Middle Molecular Strategy). T.K. is also grateful for support by JSPS KAKENHI Grant Number JP16H01040 (Precisely Designed Catalysts with Customized Scaffolding).

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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11 See the Supporting Information for more details on the optimization of the reaction conditions.

12 See the Supporting Information for other experimental result that support the proposed mechanism.