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Anti-Markovnikov Addition of Both Primary and Secondary Amines to Terminal Alkynes Catalyzed by the $TpRh(C_2H_4)_2/PPh_3$ System

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The simple addition of a N−H bond to a C−C double or triple bond, known as hydroamination, offers an attractive route for synthesis of highly substituted nitrogen-containing organic molecules without formation of any side products.[1] Hydroamination of alkynes provides either enamines or imines, which undergo further synthetic transformations,[2] the exact nature of which depends on the type of amine. In general, a wide variety of metals, including early- and late-transition metals, lanthanides, and actinides, have been employed in catalytic intermolecular hydroamination of terminal alkynes to yield Markovnikov products.[3] In contrast, hydroamination of terminal alkynes in anti-Markovnikov fashion is rare (Scheme 1). The first anti-Markovnikov hydroamination of terminal alkynes with primary amines was realized using of the organouranium complex, $Cp^*_2UMe_2$, as a catalyst.[4] Subsequently, some titanocene derivatives have been applied to anti-Markovnikov alkyne hydroamination, although use of bulky primary amines, such as *tert*-butylamine and diphenylmethylamine, was required.[5] Recently, Schafer revealed the highly regioselective anti-Markovnikov hydroamination of terminal alkynes with a wide range of primary amines, catalyzed by bis(amidate)titanium complexes.[6] However, the complexes described above are not applicable to reactions with secondary amines because of the formation of imido−metal complexes (RN═M) as a crucial intermediate in the catalytic cycle.[7] The only previous report of anti-Markovnikov addition of secondary amines to terminal alkynes was limited to the Cs(OH)-catalyzed reaction of phenylacetylene with substituted anilines or N-heterocycles.[8,9] To the best of our knowledge, there is no catalytic system that allows *both primary and secondary amines to react with terminal alkynes* to give anti-Markovnikov products. We wish to disclose herein the anti-Markovnikov hydroamination of terminal alkynes not only with primary amines but also with secondary amines in the presence of a rhodium complex as a catalyst.

The initial hydroamination experiments of 1-octyne (0.5 mmol) with morpholine (1 mmol) at 100 °C for 24 h in a sealed-tube were performed to screen catalysts. Among the transition metal complexes examined, $TpRh(C_2H_4)_2$ (Tp = trispyrazolylborate) in combination with PPh_3 showed catalytic activity to furnish (*E*)-1-morpholino-1-octene (**2a**) in 61% yield, without the formation of the *Z*-isomer or the Markovnikov adduct.[10] Treatment of $RhCl(PPh_3)_3$ with commercially available KTp in situ also provided a catalyst with activity nearly comparable to that observed with the $TpRh(C_2H_4)_2/PPh_3$ system (56% yield). Both Tp and PPh_3 ligands were essential since the use of $TpRh(C_2H_4)_2$ or $RhCl(PPh_3)_3$ alone afforded dimerization products of 1-octyne[11] instead of the hydroamination product. Other rhodium complex systems, such as $[RhCl(cod)]_2/PPh_3$, $[Rh(cod)_2]BF_4/PPh_3$,[12] $CpRh(C_2H_4)_2/PPh_3$, and $Tp^*Rh(C_2H_4)_2/PPh_3$ (Tp* = tris(3,5-dimethylpyrazolyl)borate), were ineffective catalysts for the formation of **2a**. To further optimize the reaction conditions, the use of 1.5 mmol of morpholine at a higher dilution (2 mL of toluene) improved the yield of **2a** to 70% (Table 1, entry 1); **2a** was directly reduced with $NaB(OAc)_3H$ to isolate 4-octylmorpholine (**2a′**) in 66% yield. Similarly, several cyclic (entries 2 and 3) and acyclic amines (entries 4 and 5) also reacted with **1a** to give the corresponding *E*-isomers, **2b**−**2e**, while reactions of **1a** with dibenzylamine and *N*-methylaniline did not take place. When primary amines, such as benzylamine and octylamine were used, aldimines **2f** and **2g** were obtained, respectively, in moderate yields (entries 6 and 7). In contrast to the results of our previous study, which demonstrated that the $TpRuCl(PPh_3)_3$-catalyzed reaction of terminal alkynes with hydrazines yields nitriles,[13] the $TpRh(C_2H_4)_2/PPh_3$ system converted **1a** to hydrazone **2h** in 64% yield.

Scheme 1. Catalytic Addition of Amines to Terminal Alkynes

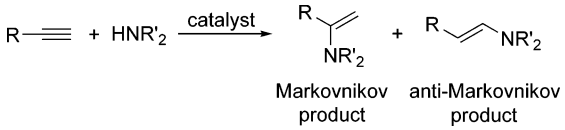
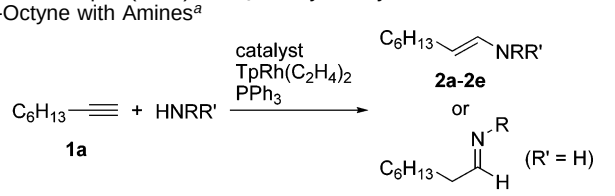
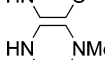
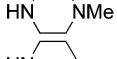
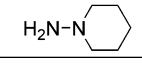


Table 1. $TpRh(C_2H_4)_2/PPh_3$-Catalyzed Hydroamination of 1-Octyne with Amines[a]



entry	amine	yield (%)[b]	entry	amine	yield (%)[b]
1		70 (**2a**)	4	HNBnMe	75 (**2d**)
2		71 (**2b**)	5	HNBuMe	70 (**2e**)
3		73 (**2c**)	6[c]	H_2NBn	52 (**2f**)
			7[c]	H_2NOct	46 (**2g**)
			8[c]		64 (**2h**)

[a] Reaction conditions: 1-octyne (0.5 mmol), amine (1.5 mmol), $TpRh(C_2H_4)_2$ (0.05 mmol), PPh_3 (0.1 mmol), in toluene (2 mL) at 100 °C for 24 h. [b] Yields determined by ^1H NMR spectroscopy with 1,3-dihydroisobenzofuran as an internal standard. [c] For 6 h.

Table 2 summarizes the results for the reaction of alkynes with benzylmethylamine (left column) and benzylamine (right column).[14] Both amines reacted with alkynes **1b**−**1d** to give the corresponding *E*-enamines **3b**−**3d** or imines **4b**−**4d**, respectively (entries 1−3). The reaction also occurred in the presence of functional groups, such as siloxy (**1e**), ester (**1f**), and nitrile (**1g**), on the terminal alkynes (entries 4−6). Alkynes **1h**−**1j** reacted with benzylmethylamine to yield **3h**−**3j**. In contrast, those of benzylamine gave no or little product with recovery of the starting alkynes, although the reasons for the lack of reaction remain unknown (entries 7−9). 2-Octyne, as an internal alkyne, did not react both with primary and secondary amines under the present reaction conditions at all.

Although details of the reaction mechanism are ambiguous, the formation of a vinylidene−rhodium complex[15] **I** seems likely to

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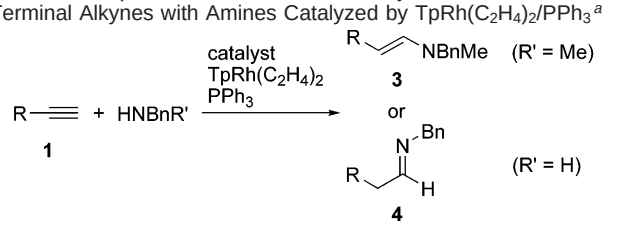
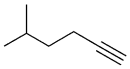
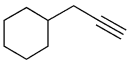
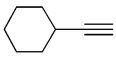
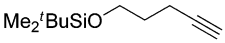
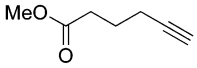
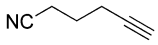
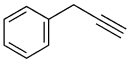
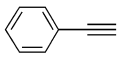
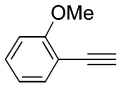
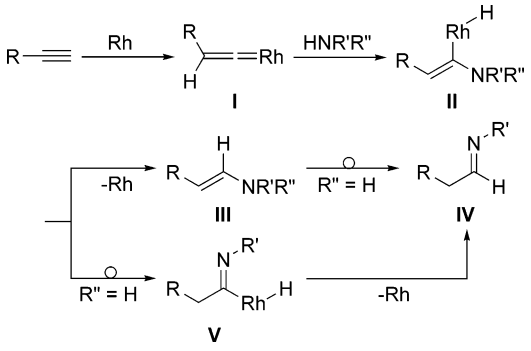
Table 2. Scope of the Anti-Markovnikov Hydroamination of Terminal Alkynes with Amines Catalyzed by $TpRh(C_2H_4)_2/PPh_3$ [a]



entry	alkyne		yields (%)[b] HNBnMe[c]	yields (%)[b] H_2NBn[d]
1		**1b**	85 (**3b**)	44 (**4b**)
2		**1c**	81 (**3c**)	62 (**4c**)
3		**1d**	73 (**3d**)	67 (**4d**)
4		**1e**	82 (**3e**)	48 (**4e**)
5		**1f**	73 (**3f**)	21 (**4f**)
6		**1g**	58 (**3g**)	36 (**4g**)
7		**1h**	53 (**3h**)	0
8		**1i**	64 (**3i**)	trace
9		**1j**	72 (**3j**)	trace

[a] Reaction conditions: alkyne (0.5 mmol), amine (1.5 mmol), $TpRh(C_2H_4)_2$ (0.05 mmol), PPh_3 (0.1 mmol), in toluene (2 mL) at 100 °C. [b] Yields determined by ^1H NMR spectroscopy with 1,3-dihydroisobenzofuran as an internal standard. [c] For 24 h. [d] For 6 h.

Scheme 2. Plausible Reaction Mechanism



be included in the reaction mechanism, as shown in Scheme 2, explaining that both primary and secondary amines add to the terminal carbon of alkynes. A terminal alkyne reacts with a rhodium complex to give **I**, which undergoes nucleophilic attack of an amine at the α-carbon atom of **I** to afford an α-aminovinylrhodium complex **II**.[9,16] Reductive elimination from **II** gives the enamine **III**. The aldimine **IV** forms either by tautomerization from **III** or via the iminorhodium complex **V**. The reaction of 1-deuterio-1-octyne with benzylamine to obtain information about the reaction mechanism was unsuccessful, as it resulted in rapid H/D scramble.

In summary, we have demonstrated herein the $TpRh(C_2H_4)_2/PPh_3$-catalyzed anti-Markovnikov hydroamination of terminal alkynes both with primary and secondary amines. Efforts are currently underway to investigate the scope and mechanism of the reaction.

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Supporting Information Available: Experimental procedures and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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