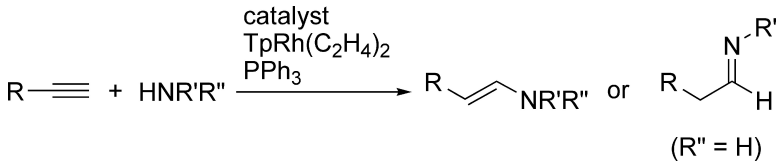
Communication

Anti-Markovnikov Addition of Both Primary and Secondary Amines to Terminal Alkynes Catalyzed by the TpRh(CH)/PPh System

Yoshiya Fukumoto, Harumi Asai, Masaki Shimizu, and Naoto Chatani

J. Am. Chem. Soc., **2007**, 129 (45), 13792-13793• DOI: 10.1021/ja075484e • Publication Date (Web): 20 October 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 10/20/2007

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

Yoshiya Fukumoto,* Harumi Asai, Masaki Shimizu, and Naoto Chatani

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

Received July 23, 2007; E-mail: fukumoto@chem.eng.osaka-u.ac.jp

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

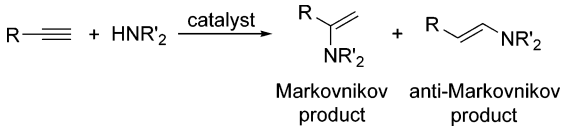
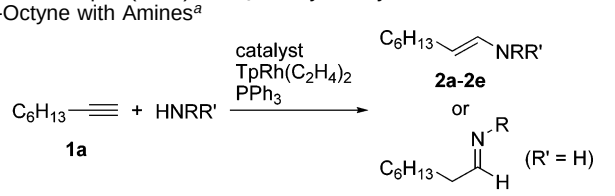
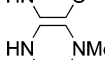
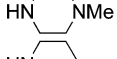
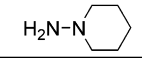


Table 1. $TpRh(C_2H_4)_2/PPh_3$-Catalyzed Hydroamination of 1-Octyne with Amines[a]



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**)

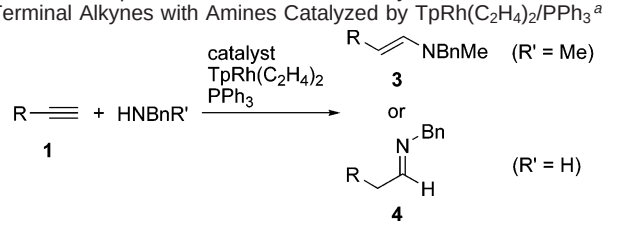
[a] Reaction conditions: 1-octyne (0.5 mmol), amine (1.5 mmol), $TpRh(C_2H_4)_2$ (0.05 mmol), PPh_3 (0.1 mmol), in toluene (2 mL) at 100 °C for 24 h. [b] Yields determined by ^1H NMR spectroscopy with 1,3-dihydroisobenzofuran as an internal standard. [c] For 6 h.

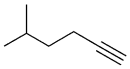
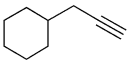
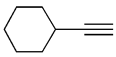
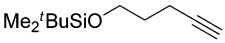
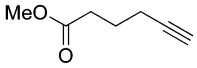
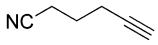
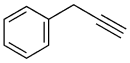
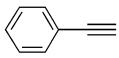
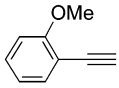
Table 2 summarizes the results for the reaction of alkynes with benzylmethylamine (left column) and benzylamine (right column).[14] Both amines reacted with alkynes **1b**−**1d** to give the corresponding *E*-enamines **3b**−**3d** or imines **4b**−**4d**, respectively (entries 1−3). The reaction also 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

10.1021/ja075484e CCC: $37.00

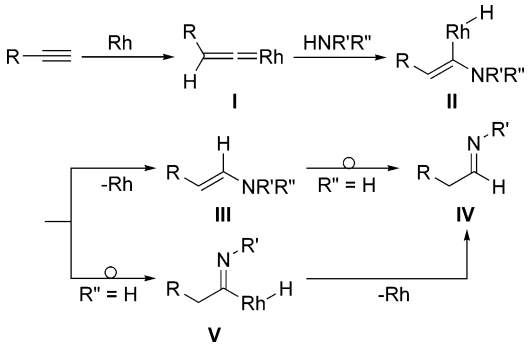
Table 2. Scope of the Anti-Markovnikov Hydroamination of Terminal Alkynes with Amines Catalyzed by $TpRh(C_2H_4)_2/PPh_3$ [a]



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.

Acknowledgment. We thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance with the HRMS and elemental analyses. Y.F. is grateful to Otsuka Pharmaceutical Co., Ltd., for financial support of this work.

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.

References

(1) For recent reviews on catalytic hydroamination, see: (a) Odom, A. L. *Dalton Trans.* **2005**, 225. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (c) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (d) Doye, S. *Synlett* **2004**, 1653. (e) Roesky, P. W.; Müller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708. (f) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935. (g) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104.

(2) For reviews on the chemistry of imines and enamines, see: (a) Sammakia T.; Abramite, J. A.; Sammons, M. F. Product Subclass of 6: Enamines. In *Science of Synthesis*; Molander, M., Ed.; Georg Thieme Verlag: Stuttgart, 2006; pp 405−411. (b) Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 125. (c) Kuckländer, U. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley-VCH: New York, 1994; pp 523−636.

(3) Recent reports on the intermolecular Markovnikov hydroamination of alkynes, see: (a) Lai, R.-Y.; Surekha, K.; Hayashi, A.; Ozawa, F.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Organometallics* **2007**, *26*, 1062. (b) Lingaiah, N.; Babu, N. S.; Reddy, K. M.; Prasad, P. S. S.; Suryanarayana, I. *Chem. Commun.* **2007**, 278.

(4) (a) Straub, T.; Haskel, A.; Neyroud, T. G.; Kapon, M.; Botoshansky, M.; Eisen, M. S. *Organometallics* **2001**, *20*, 5017. (b) Haskel, A.; Straub, T.; Eisen, M. S. *Organometallics* **1996**, *15*, 3773.

(5) (a) Tillack, A.; Jiao, H.; Castro, I. G.; Hartung, C. G.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2409. (b) Tillack, A.; Castro, I. G.; Hartung, C. G.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2541. (c) Haak, E.; Siebeneicher, H.; Doye, S. *Org. Lett.* **2000**, *2*, 1935.

(6) (a) Zhang, Z.; Leitch, D. C.; Lu, M.; Patrick, B. O.; Schafer, L. L. *Chem.—Eur. J.* **2007**, *13*, 2012. (b) Zhang, Z.; Schafer, L. L. *Org. Lett.* **2003**, *5*, 4733.

(7) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708.

(8) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193.

(9) The addition of 2-*N*-methylaminopyridine to 1-decyne in the presence of $RhCl(PPh_3)_3$ gave the corresponding anti-Markovnikov enamine in 40% yield. In this case, the pyridine ring was essential to obtain the product. Park, Y. J.; Kwon, B.-I.; Ahn, J.-A.; Jun, C.-H. *J. Am. Chem. Soc.* **2004**, *126*, 13892.

(10) ^1H NMR spectra of (*E*)- and (*Z*)-**2a**, see: Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *Tetrahedron Lett.* **1985**, *26*, 139.

(11) (a) Carlton, L.; Read, G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1631. (b) Yoshikawa, S.; Kiji, J.; Furukawa, J. *Makromol. Chem.* **1977**, *178*, 1077. (c) Singer, H.; Wilkinson, G. *J. Chem. Soc. (A)* **1968**, 849.

(12) $[Rh(cod)_2]BF_4/PPh_3$ catalyst system gave no hydroamination product in our reaction conditions, although Beller and co-workers reported that the system catalyzed the reaction of phenylacetylene with morpholine to give anti-Markovnikov adducts in 15% yield. See: Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339.

(13) Fukumoto, Y.; Dohi, T.; Masaoka, H.; Chatani, N.; Murai, S. *Organometallics* **2002**, *21*, 3845.

(14) All products except **2h** were reduced with $NaB(OAc)_3H$ (**2a**−**2e** and **3b**−**3j**), $LiAlH_4$ (**2f**,**2g** and **4b**−**4e**), or $NaBH_4$ (**4f**,**4g**) to isolate the corresponding amines. See Supporting Information.

(15) For recent reviews on catalytic reactions that proceeded via vinylidene-metal intermediate, see: (a) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. (b) Bruneau, C. In *Topics in Organometallic Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer: Berlin, 2004; Vol. 11 (Ruthenium Catalysts and Fine Chemistry), pp 125−153.

(16) (a) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074. (b) Fukumoto, Y.; Kinashi, F.; Kawahara, T.; Chatani, N. *Org. Lett.* **2006**, *8*, 4641.

JA075484E