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Rhodium-Catalyzed anti-Markovnikov Addition of Secondary Amines to Arylacetylenes at Room Temperature

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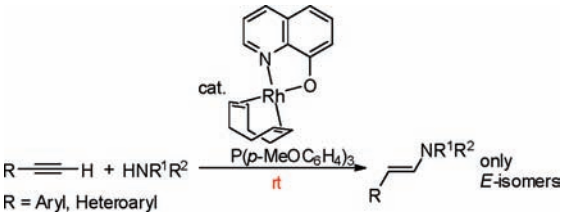
ABSTRACT



An efficient method for synthesis of *E*-enamines by the anti-Markovnikov addition of secondary amines to terminal alkynes is described. The reaction of a variety of aryl- and heteroarylacetylenes proceeded at room temperature using a combination of a 8-quinolinolato rhodium complex and P(*p*-MeOC$_6$H$_4$)$_3$ as a catalyst. The products were obtained as enamines by simple bulb-to-bulb distillation.

Hydroamination of alkynes provides an efficient way to construct carbon−nitrogen bonds and has been extensively studied over the past decade.[1−3] Particularly remarkable progress has been made for the addition of primary amines leading to imines with the aid of various transition metal catalysts. On the other hand, studies concerning catalytic addition of secondary amines to alkynes are still limited,[4−8] though they would offer straightforward and atom-economical methods to prepare enamines.[9] High temperatures were required for all of the previously reported methods, and most of these examples exhibited narrow substrate scopes. Recently, the reaction of substrates with several polar functional groups was reported with catalysts such as a TpRh catalyst[2c] and a Au catalyst with a P,N-ligand,[7b] but the reactions were performed at no less than 90 °C.

In search of the desired reaction, the hydroamination was first performed using 8-quinolinolato rhodium

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(2) Rhodium- or iridium-catalyzed intermolecular hydroamination of alkynes: (a) Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339. (b) Lai, R.-Y.; Surekha, K.; Hayashi, A.; Ozawa, F.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Organometallics* **2007**, *26*, 1062. (c) Fukumoto, N.; Asai, H.; Shimizu, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 13792. (d) Dabb, S. L.; Messerle, B. A. *Dalton Trans.* **2008**, 6368.

(3) Rhodium- or iridium-catalyzed intramolecular hydroamination of alkynes: (a) Müller, T. E. *Tetrahedron Lett.* **1998**, *39*, 5961. (b) Müller, T. E.; Pleier, A.-K. *J. Chem. Soc., Dalton Trans.* **1999**, 583. (c) Burling, S.; Field, L. D.; Messerle, B. A. *Organometallics* **2000**, *19*, 87. (d) Burling, S.; Field, L. D.; Li, H. L.; Messerle, B. A.; Turner, P. *Eur. J. Inorg. Chem.* **2003**, 3179. (e) Field, L. D.; Messerle, B. A.; Wren, S. L. *Organometallics* **2003**, *22*, 4393. (f) Burling, S.; Field, L. D.; Messerle, B. A.; Turner, P. *Organometallics* **2004**, *23*, 1714. (g) Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *Organometallics* **2005**, *24*, 4241. (h) Krogstad, D. A.; DeBoer, A. J.; Ortmeier, W. J.; Rudolf, J. W.; Halfen, J. A. *Inorg. Chem. Commun.* **2005**, *8*, 1141. (i) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (j) Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P.; Failes, T. *Organometallics* **2007**, *26*, 2058. (k) Burling, S.; Field, L. D.; Messerle, B. A.; Rumble, S. L. *Organometallics* **2007**, *26*, 4335. (l) Ebrahimi, D.; Kennedy, D. F.; Messerle, B. A.; Hibbert, D. B. *Analyst* **2008**, *133*, 817. (m) Dabb, S. L.; Ho, J. H. H.; Hodgson, R.; Messerle, B. A.; Wagler, J. *Dalton Trans.* **2009**, 634. (n) Kennedy, D. F.; Messerle, B. A.; Rumble, S. L. *New J. Chem.* **2009**, *33*, 818. (o) Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *Dalton Trans.* **2009**, 3599. (p) Clentsmith, G. K. B.; Field, L. D.; Messerle, B. A.; Shasha, A.; Turner, P. *Tetrahedron Lett.* **2009**, *50*, 1469. (q) Kennedy, D. F.; Nova, A.; Willis, A. C.; Eisenstein, O.; Messerle, B. A. *Dalton Trans.* **2009**, 10296. (r) Beeren, S. R.; Dabb, S. L.; Edwards, G.; Smith, M. K.; Willis, A. C.; Messerle, B. A. *New J. Chem.* **2010**, *34*, 1200. (s) Gainer, M. J.; Bennett, N. R.; Takahashi, Y.; Looper, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 684. See also ref 2b.

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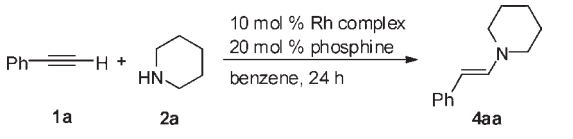
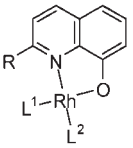
complexes which we found effective as catalysts for the addition of alcohols to terminal acetylenes to form enol ethers.[10,11] When the reaction of phenylacetylene (**1a**) with 3 equiv of piperidine (**2a**) was carried out with 10 mol % of dicarbonyl complex **3a** or cyclooctadiene (cod) complex **3b** at 80 °C for 24 h, only a small amount of the enamine product was detected (Table 1, entries 1 and 2). In contrast, when phosphine complex **3c** was used as a catalyst, anti-Markovnikov addition of **2a** to **1a** occurred to give enamine **4aa** in 7% yield with complete *E*-selectivity (entry 3). Use of phosphine with rhodium complexes **3a**,**b** was then examined (entries 4 and 5), and the reaction using 10 mol % of **3b** with 20 mol % of PPh_3 afforded **4aa** in 28% GC yield (entry 5). Replacement of the methyl group on the quinolinolate ligand to a hydrogen increased the yield to 58% (entry 6). To achieve milder reaction conditions, the reaction temperature was investigated. Remarkably, the reaction at room temperature led to only a slight decrease of the yield to 43% (entry 7). Phosphine additives were then screened to improve the yield. While less electron-donating $P(p\text{-}FC_6H_4)_3$ lowered the product yield (entry 8), higher yields were obtained with more electron-donating phosphines (entries 9−11).[12] Particularly, the reaction using $P(p\text{-}MeOC_6H_4)_3$ gave enamine **4aa** in 87% GC yield (entry 10). As a solvent, toluene can also be used, and the reaction provided **4aa** in comparable yield (entry 12). It should be noted that the reaction was not catalyzed by the phosphine itself, and without any rhodium complex, the reaction did not give any enamine product (entry 13). The use of other rhodium sources such as $[RhCl(cod)]_2$ in the presence of $P(p\text{-}MeOC_6H_4)_3$ also significantly decreased the yield (entry 14).

Table 1. Screening of Catalysts for anti-Markovnikov Addition of **2a** to **1a**[a]



1a **2a** **4aa**

entry	Rh complex	phosphine	temp	GC yield[b]
				
1	R = Me; $L^1 = L^2 = CO$ (**3a**)	–	80 °C	2%
2	R = Me; L^1-L^2 = cod (**3b**)	–	80 °C	trace
3	R = Me; $L^1 = CO$; $L^2 = PPh_3$ (**3c**)	–	80 °C	7%
4	**3a**	PPh_3	80 °C	nd[c]
5	**3b**	PPh_3	80 °C	28%
6	R = H; L^1-L^2 = cod (**3d**)	PPh_3	80 °C	58%
7	**3d**	PPh_3	rt	43%
8	**3d**	$P(p\text{-}FC_6H_4)_3$	rt	25%
9	**3d**	$P(p\text{-}CH_3C_6H_4)_3$	rt	77%
10	**3d**	$P(p\text{-}MeOC_6H_4)_3$	rt	87%
11	**3d**	$P(m\text{-}MeOC_6H_4)_3$	rt	63%
12[d]	**3d**	$P(p\text{-}MeOC_6H_4)_3$	rt	81%
13	–	$P(p\text{-}MeOC_6H_4)_3$	rt	nd[c]
14[e]	$[RhCl(cod)]_2$	$P(p\text{-}MeOC_6H_4)_3$	rt	4%

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Rh complex (0.02 mmol), phosphine (0.04 mmol) in benzene (0.6 mL), 24 h. [b] GC yield. [c] Not detected. [d] Toluene (0.6 mL) was used as a solvent. [e] With 0.01 mmol of $[RhCl(cod)]_2$.

Various secondary amines are applicable for the room temperature hydroamination, and the products can be isolated as enamines by bulb-to-bulb distillation[13] (Table 2). Enamine **4aa** formed by the reaction of **1a** with **2a** was isolated in 85% yield (entry 1). The addition of *N*-methylpiperazine (**2b**) and *cis*-2,6-dimethylmorpholine (**2c**) also provided enamines **4ab** and **4ac** in 82% and 76% yields, respectively (entries 2 and 3). Morpholine (**2d**) and acyclic amines **2e**,**f** were also added to **1a** in good yields when 10 equiv of these amines were used (entries 4−6).[14]

The anti-Markovnikov hydroamination is applicable to various terminal alkynes (Table 3). The addition of **2a** to

(4) Transition-metal-catalyzed anti-Markovnikov addition of secondary amines to terminal alkynes: (a) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246. (b) Leitch, D. C.; Turner, C. S.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 6382. (c) Cheung, H. W.; So, C. M.; Pun, K. H.; Zhou, Z.; Lau, C. P. *Adv. Synth. Catal.* **2011**, *353*, 411. See also ref 2a and 2c.

(5) Base-catalyzed anti-Markovnikov addition of secondary amines to phenylacetylene: Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193.

(6) Catalytic Markovnikov addition of secondary amines to terminal alkynes: (a) Barluenga, J.; Aznar, F.; Liz, R.; Rodes, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2732. (b) Uchimaru, Y. *Chem. Commun.* **1999**, 1133. (c) Zeng, X.; Frey, G. D.; Kousar, S.; Bertrand, G. *Chem.—Eur. J.* **2009**, *15*, 3056.

(7) Catalytic addition of secondary amines to internal alkynes: (a) Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2009**, *131*, 8690. (b) Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 18026. See also ref 4a.

(8) Related transformations: (a) Matsunaga, S. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 778. (b) Tsuchimoto, T.; Aoki, K.; Wagatsuma, T.; Suzuki, Y. *Eur. J. Org. Chem.* **2008**, 4035. (c) Zhou, L.; Bohle, D. S.; Jiang, H.-F.; Li, C.-J. *Synlett* **2009**, 937. (d) Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 942.

(9) Rhodium-catalyzed oxidative hydroamination of olefins to form enamines: (a) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2225. (b) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E.; Zapf, A. *J. Organomet. Chem.* **1998**, *566*, 277. (c) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E. *Eur. J. Inorg. Chem.* **1999**, 1121. (d) Tillack, A.; Trauthwein, H.; Hartung, C. G.; Eichberger, M.; Pitter, S.; Jansen, A.; Beller, M. *Monatsh. Chem.* **2000**, *131*, 1327.

(10) Kondo, M.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2011**, *133*, 32.

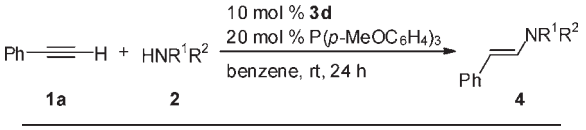
(11) Very recently, an interesting H/D exchange reaction at the β-position of aromatic α-olefins catalyzed by an 8-quinolinolato rhodium catalyst was reported: Giuseppe, A. D.; Castarlenas, R.; Pérez-Torrente, J. J.; Lahoz, F. J.; Polo, V.; Oro, L. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3938.

(12) Reduction of the catalyst loading under the reaction conditions was unsuccessful. Use of 5 mol % of **3d** with 10 mol % of $P(p\text{-}MeOC_6H_4)_3$ for the reaction of **1a** with **2a** resulted in formation of 39% GC yield of **4aa**.

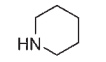
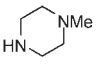
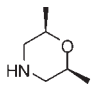
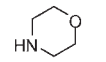
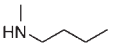
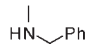
(13) In the previously reported hydroamination of alkynes with secondary amines, yields of the enamine products were mostly determined by ^1H NMR or GC analysis or by isolation after reduction to amines, except for ref 6a.

(14) The hydroamination of **1a** under the reaction conditions did not proceed with less basic secondary nitrogen nucleophiles including amides such as 2-oxazolidinone, 2-piperidinone, acetamide, and benzamide as well as aniline derivatives such as *N*-methylaniline and 1,2,3,4-tetrahydroquinoline.

Table 2. anti-Markovnikov Hydroamination of **1a** with Various Secondary Amines[a]

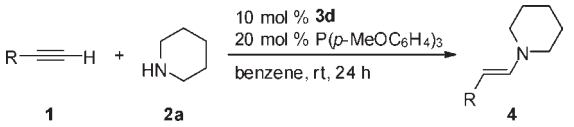


1a 2 4

Entry	2	HNR^1R^2	4	isolated yield (%)[b]
1	**2a**		**4aa**	85%
2	**2b**		**4ab**	82%
3	**2c**		**4ac**	76%
4[c]	**2d**		**4ad**	76%
5[c]	**2e**		**4ae**	80%
6[c]	**2f**		**4af**	73%

[a] Reaction conditions: **1a** (0.6 mmol), **2** (1.8 mmol), **3d** (0.06 mmol), P(*p*-$MeOC_6H_4$)$_3$ (0.12 mmol) in benzene (1.8 mL), rt, 24 h. [b] Enamine products **4** were isolated by bulb-to-bulb distillation. [c] Performed with 6.0 mmol of **2**.

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



1 2a 4

entry	1	R	4	isolated yield (%)[b]
1	**1b**	*p*-$F_3CC_6H_4$	**4ba**	90%
2	**1c**	*o*-$F_3CC_6H_4$	**4ca**	88%
3	**1d**	*p*-NCC_6H_4	**4da**	49%
4	**1e**	*p*-$MeO_2CC_6H_4$	**4ea**	70%
5	**1f**	*p*-AcC_6H_4	**4fa**	64%
6	**1g**	*p*-MeC_6H_4	**4ga**	82%
7	**1h**	*m*-MeC_6H_4	**4ha**	82%
8	**1i**	*p*-$MeOC_6H_4$	**4ia**	68%
9	**1j**	*o*-$MeOC_6H_4$	**4ja**	55%
10	**1k**	2-naphthyl	**4ka**	83%
11	**1l**	2-thienyl	**4la**	80%
12	**1m**	3-thienyl	**4ma**	65%
13	**1n**	*N*-methyl-2-indolyl	**4na**	67%
14	**1o**	3-pyridyl	**4oa**	22% (44%)[c]
15	**1p**	1-hexyl	**4pa**	3%[d] (50%)[c,d]

[a] Reaction conditions: **1** (0.6 mmol), **2a** (1.8 mmol), **3d** (0.06 mmol), P(*p*-$MeOC_6H_4$)$_3$ (0.12 mmol) in benzene (1.8 mL), rt, 24 h. [b] Isolated yields. [c] Isolated yields obtained at 80 °C are shown in parentheses. [d] Determined by ^{1}H NMR using 1,3-dihydroisobenzofuran as an internal standard.

arylacetylenes possessing electron-withdrawing groups such as CF_3, CN, CO_2Me, and Ac groups proceeded to afford the corresponding *E*-enamines (entries 1−5). Particularly, the reaction of substrates having a CF_3 group (**1b**,**c**) gave the product in excellent yields (entries 1 and 2). Arylacetylenes bearing electron-donating groups, Me and MeO groups, can also be used for the hydroamination, and the *E*-enamines were isolated in 55−82% yields (entries 6−9). 2-Ethynylnaphthalene (**1k**) was transformed into the corresponding enamine **4ka** in 83% yield (entry 10). Heteroarylacetylenes can be used as substrates for the hydroamination as well (entries 11−14). The reactions using 2- and 3-ethynylthiophenes (**1l**,**m**) afforded *β*-thienylenamines, which were isolated in 80% and 65% yields, respectively (entries 11 and 12). Indole derivative **1n** also gave the enamine in 67% yield (entry 13). When the reaction of 3-ethynylpyridine (**1o**) was conducted at room temperature, only 22% yield of the corresponding product was isolated (entry 14). In this case, heating was necessary to improve the yield, and the reaction at 80 °C afforded product **4oa** in 44% yield. Alkylacetylene **1p** showed poor reactivity at room temperature, but heating at 80 °C also increased the yield to 50% by NMR (entry 15).[15] Internal alkynes such as 1-phenyl-1-propyne were not applicable for this hydroamination, and no conversion of the alkynes was observed.

To gain insight into the in situ formed catalyst structure, a reaction of rhodium complex **3d** with 2 equiv of P(*p*-$MeOC_6H_4$)$_3$ was performed in benzene at rt. Recrystallization from benzene with hexane afforded an 8-quinolinolato rhodium complex possessing two phosphines (**5**) in 49% yield. The structure of complex **5** was confirmed by X-ray crystallographic analysis. When rhodium complex **3d** was mixed with 2 equiv of P(*p*-$MeOC_6H_4$)$_3$ in benzene-d_6, the ^{31}P NMR spectrum showed two doublets of doublets at 51.0 and 52.3 ppm, which are nearly identical to the signals observed for complex **5**. In addition, the use of 10 mol % of **5** as a catalyst for the hydroamination of **1a** with **2a** gave the corresponding product **4aa** in 62% GC yield (Scheme 1).[16] These results suggest that the COD ligand of **3d** is replaced by phosphine ligands during the catalytic reaction.

Although the reaction mechanism is yet unclear, based on the results that addition of amines occurred exclusively at the terminal carbon of alkynes and internal alkynes were not hydroaminated in this system, we speculate that the reaction proceeds via nucleophilic attack of amines at the α carbon of vinylidene-rhodium intermediates.[17]

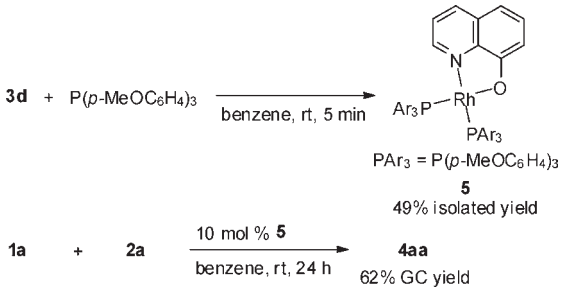
In summary, we developed an efficient method for synthesis of *E*-enamines by the anti-Markovnikov addition of secondary amines to terminal alkynes. The reaction

(15) *β*-Alkyl enamine product **4pa** could not be isolated by bulb-to-bulb distillation, while all aryl- and heteroarylenamines were isolable.

(16) The yield was lower than that obtained in the reaction using a mixture of **3d** with P(*p*-$MeOC_6H_4$)$_3$ (Table 1, entry 10) probably because complex **5** could not be completely dissolved in benzene during the reaction. Once it was crystallized, complex **5** is harder to dissolve in benzene without heating. Based on this fact, it is advantageous to use **3d** with P(*p*-$MeOC_6H_4$)$_3$ as a catalyst rather than complex **5**.

(17) (a) Wiedemann, S. H.; Lee, C. In *Metal Vinylidenes and Allenylidenes in Catalysis: From Reactivity to Applications in Synthesis*; Bruneau, C., Dixneuf, P. H., Eds.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2008; p 279. (b) Wakatsuki, Y. *J. Organomet. Chem.* **2004**, *699*, 4092. See also ref 2c.

Scheme 1. anti-Markovnikov Hydroamination Using Isolated Rhodium Complex **5**[a]



of a variety of aryl- and heteroarylacetylenes proceeded at room temperature. A combination of a 8-quinolinolato rhodium complex and $P(p\text{-}MeOC_6H_4)_3$ was found to be effective as a catalyst for the hydroamination. The products were obtained as enamines by simple bulb-to-bulb distillation. Extension of the scope of the nucleophiles and elucidation of the reaction mechanism are now underway.

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Supporting Information Available. Experimental procedures, spectroscopic data for new compounds, and a CIF file for complex **5**. This material is available free of charge via the Internet at http://pubs.acs.org.