ORGANIC LETTERS

2011
Vol. 13, No. 13
3388–3391

Ruthenium-Catalyzed Hydrovinylation of *N*-Acetylenamines Leading to Amines with a Quaternary Carbon Center

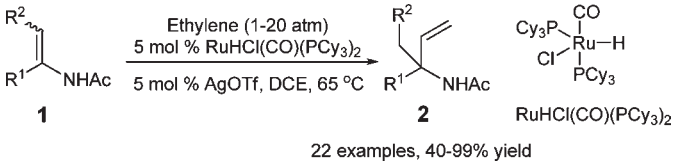
Qiu-Shi Wang, Jian-Hua Xie, Wei Li, Shou-Fei Zhu, Li-Xin Wang, and Qi-Lin Zhou*

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

qlzhou@nankai.edu.cn

Received April 29, 2011

ABSTRACT



A catalytic hydrovinylation of *N*-acetylenamines with ethylene is reported. This new hydrovinylation reaction is catalyzed by a ruthenium hydride complex, $RuHCl(CO)(PCy_3)_2$, providing a series of *N*-acetylamines with a quaternary carbon center with up to 99% yield.

Transition-metal-catalyzed carbon−carbon bond-forming reactions have become an essential tool for the efficient and environmentally benign synthesis of organic compounds.[1]

Among these reactions, catalytic hydrovinylation is attractive not only because it is one of the few practical processes that utilize feedstock carbon sources but also because the reaction products can be easily converted into pharmacologically important compounds such as 2-arylpropionic acids including ibuprofen and naproxen (which are nonsteroidal antiinflammatory drugs).[2]

Since its discovery,[3] catalytic hydrovinylation has been of perennial interest to chemists, and substantial progress has been made in this reaction. Olefin substrates such as vinylarenes, strained olefins, and 1,3-dienes have been successfully converted to more useful olefin products by means of various catalysts.[4] The hydrovinylation of functionalized olefins such as vinyl acetate, α-ketalsubstituted vinylarenes and α,β-unsaturated ketones and esters has also been reported.[5] However, the hydrovinylation of heteroatom-substituted olefins, which generates amines with a quaternary carbon center, remains a challenging task.[6]

Recently, we studied hydrovinylation of α-alkyl and α-ketal vinylarenes and obtained olefin products with an all-carbon quaternary center in high yields and high

(1) Beller, M. *Transition Metals for Organic Synthesis*, 2nd ed.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004.

(2) For recent reviews of hydrovinylation reaction, see: (a) Jolly, P. W.; Wilke, G. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: New York, 1996; Vol. 2, p 1024. (b) RajanBabu, T. V. *Chem. Rev.* **2003**, *103*, 2845. (c) RajanBabu, T. V. *Synlett* **2009**, *6*, 853. For synthesis of 2-arylpropionic acids via hydrovinylation, see: (d) Smith, C. R.; RajanBabu, T. V. *J. Org. Chem.* **2009**, *74*, 3066 and references therein.

(3) (a) Studiengesellschaft Kohle m.b.H. Neth. Appl. 6,409,179, 1963; *Chem. Abstr.* 1965, *63*, 5770h. (b) Alderson, T.; Jenner, E. L.; Lindsey, R. V., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 5638. (c) Bogdanović, B.; Henc, B.; Lösler, A.; Meister, B.; Pauling, H.; Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 954.

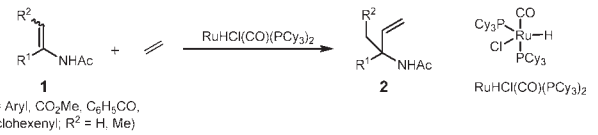
(4) For recent papers, see: (a) He, Z.; Yi, C. S.; Donaldson, W. A. *Org. Lett.* **2003**, *5*, 1567. (b) Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 1515. (c) Grabulosa, A.; Muller, G.; Ordinas, J. I.; Mezzetti, A.; Maestro, M. A.; Font-Bardia, M.; Solans, X. *Organometallics* **2005**, *24*, 4961. (d) Shi, W.-J.; Xie, J.-H.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2005**, *16*, 705. (e) Zhang, A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2006**, *128*, 54. (f) Shi, W.-J.; Zhang, Q.; Xie, J.-H.; Zhu, S.-F.; Hou, G.-H.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 2780. (g) Zhang, A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2006**, *128*, 5620. (h) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414. (i) Diez-Holz, C. J.; Böing, C.; Franciò, G.; Hölscher, M.; Leitner, W. *Eur. J. Org. Chem.* **2007**, 2995. (j) Sanchez, R. P., Jr.; Connell, B. T. *Organometallics* **2008**, *27*, 2902. (k) Moreau, B; Wu, J. Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337. (l) Lassauque, N; Franciò, G; Leitner, W. *Adv. Synth. Catal.* **2009**, *351*, 3133. (m) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295. (n) Gavenonis, J.; Arroyo, R. V.; Snapper, M. L. *Chem. Commun.* **2010**, *46*, 5692. (o) Liu, W.; RajanBabu, T. V. *J. Org. Chem.* **2010**, *75*, 7636.

(5) (a) Muller, G.; Ordinas, J. I. *J. Mol. Catal. A: Chem.* **1997**, *125*, 97. (b) Yi, C. S.; He, Z.; Lee, D. W. *Organometallics* **2001**, *20*, 802. (c) He, Z.; Yi, C. S.; Donaldson, W. A. *Synlett* **2004**, 1312. (d) Zhang, Q.; Zhu, S.-F.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. *Adv. Synth. Catal.* **2008**, *350*, 1507. (e) Ho, C.-Y.; Ohmiya, H.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1893. (f) Ogoshi, S.; Haba, T.; Ohasi, M. *J. Am. Chem. Soc.* **2009**, *131*, 10350.

10.1021/ol201142v
Published on Web 06/01/2011

chemo- and enantioselectivities.[4f,5d] These results encouraged us to investigate the hydrovinylation of heteroatom-substituted olefins. In this paper, we report the hydrovinylation of *N*-acetylenamines catalyzed by a ruthenium complex, $RuHCl(CO)(PCy_3)_2$, yielding amines with a quaternary carbon center in up to 99% yield (Scheme 1).

Scheme 1. Catalytic Hydrovinylation of *N*-Acetylenamines



1 (R^1 = Aryl, CO_2Me, C_6H_5CO, 1-cyclohexenyl; R^2 = H, Me)

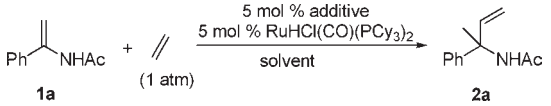
2

$RuHCl(CO)(PCy_3)_2$

In exploring the hydrovinylation of *N*-acetylenamines, we first investigated a wide range of catalysts in the reaction of *N*-acetyl-α-phenylenamine (**1a**) with ethylene. Ni and Pd complexes with various phosphorus ligands, which efficiently catalyze the hydrovinylation of vinylarenes,[4a−c] did not catalyze the hydrovinylation of **1a** either at room temperature or at elevated temperature. However, when the ruthenium hydride complex $RuHCl(CO)(PCy_3)_2$, which is an efficient catalyst for the hydrovinylation of vinylarenes, 1,3-dienes, and dienoates,[4a,n,5c] was used to catalyze the reaction, the desired hydrovinylation product **2a** was obtained in 75% yield. The side reactions were decomposition (to acetophenone, 16% yield) and dimerization of **1a** (< 5% yield).[7] We then examined the effect of reaction temperature and found 65 °C to be the optimal temperature in terms of substrate conversion and product yield. A solvent-screening experiment revealed that 1,2-dichloroethane (DCE) was the best reaction medium, and coordinating solvents such as *N*,*N*-dimethylformamide (DMF) and dioxane afforded no product. Addition of 4 Å molecular sieves (MS) prevented the decomposition of **1a** and consequently increased the yield of the hydrovinylation product. The counteranion of the catalyst was reported to strongly influence both the rate and the yield in the Ru- and Ni-catalyzed hydrovinylation reactions.[4j,8] We studied the effect of counteranion of the catalyst by adding different silver salts to exchange the chloride on the catalyst. The highest rate and yield were achieved with trifluoromethanesulfonic acid anion (OTf^-) as the counteranion, and the use of OTf^- also allowed us to reduce the catalyst load to 2 mol % (Table 1).

Under the optimal reaction conditions, a series of *N*-acetyl-α-arylenamines **1a**−**s** were allowed to react with ethylene, and the results are summarized in Table 2. The electronic properties of the substituent on the phenyl ring of the

Table 1. Catalytic Hydrovinylation. Optimization of the Reaction Conditions[a]



entry	additive	solvent	temp (°C)	conv[b] (%)	yield[c] (%)
1	NaBArF	DCE	65	92	75 (16)
2	NaBArF	DCE	45	64	19 (10)
3	NaBArF	DCE	85	79	52 (18)
4	NaBArF	toluene	65	94	42 (31)
5	NaBArF	DMF	65	10	0 (6)
6	NaBArF	dioxane	65	8	0 (5)
7	NaBArF/4 Å MS	DCE	65	92	80
8[d]	AgOTf/4 Å MS	DCE	65	100	95
9	$AgPF_6$/4 Å MS	DCE	65	89	81
10	$AgBF_4$/4 Å MS	DCE	65	52	33
11	$AgSbF_6$/4 Å MS	DCE	65	89	86
12[e]	AgOTf/4 Å MS	DCE	65	85	83

[a] Reaction conditions: 0.01 mmol of $RuHCl(CO)(PCy_3)_2$; 0.01 mmol of additive; 0.2 mmol of **1a**; 1 atm of ethylene; 3 mL of solvent, 20 h. [b] Determined by GC. [c] Isolated yield. The number in parentheses is the yield of acetophenone. [d] The reaction was completed in 2 h. [e] 2 mol % of catalyst was used.

substrate strongly influenced the reaction rate. Electron-withdrawing groups gave faster reactions. For example, the hydrovinylations of **1g** and **1l**, which have 4-CF_3 and 3,5-$(CF_3)_2$ groups, respectively, yielded the corresponding products (**2g** and **2l**) in nearly quantitative yields within 0.5 h (entries 7 and 12), whereas the substrate with a 4-MeO group (**1c**) provided the hydrovinylation product (**2c**) in 87% yield with 94% conversion in 10 h (entry 3). The reaction was also sensitive to the steric effect of the substituent, with ortho substitution leading to a slow reaction. For example, the hydrovinylation of *N*-[1-(2-methylphenyl)vinyl]acetamide (**1j**) afforded **2j** in only 40% yield after 20 h (entry 10). β-Methyl-substituted enamine **1q** (mixture of *Z* and *E* isomers), as well as cyclic enamines **1r** and **1s**, also underwent hydrovinylation and provided the corresponding products in moderate yields, although 10 mol % of catalyst was needed (entries 17−19). The heterocyclic *N*-acetylenamine, *N*-[1-(thiophene-2-yl)-vinyl]acetamide, was also a suitable substrate for this transformation, providing amine product **2p** in 100% conversion with 68% yield, although higher catalyst loading (10 mol %) and higher ethylene pressure (20 atm) were required (entry 16).

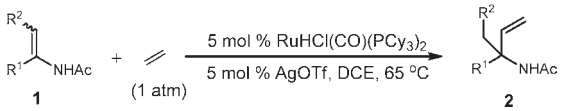
In the expansion of the scope of substrate of the reaction, we found that the *N*-acetylenamines containing an α-carbonyl group can also undergo hydrovinylation reaction to form a quaternary carbon center connecting three functional groups. Thus, the enamines methyl 2-acetamidoacrylate (**1t**) and *N*-(3-oxo-3-phenylprop-1-en-2-yl)acetamide (**1u**) reacted with ethylene in the presence of 10 mol % catalyst under 20 atm of ethylene pressure, producing α-amino acid derivative **2t** and α-amino ketone **2u** in 67 and 72% yield, respectively (entries 20 and 21). When enamine substrate

(6) For ruthenium-catalyzed codimerization and cooligomerization of *N*-vinylamides with alkenes or alkynes, see: (a) Tsujita, H.; Ura, Y.; Matsuki, S.; Wada, K.; Mitsudo, T.-a.; Kondo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5160. (b) Ura, Y.; Tsujita, H.; Mitsudo, T.-a.; Kondo, T. *Bull. Korean Chem. Soc.* **2007**, *28*, 2139. (c) Goossen, L. J.; Rodríguez, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 7544.

(7) Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. *Chem. Commun.* **2008**, 4637.

(8) RajanBabu, T. V.; Nomura, N.; Jin, J.; Nandi, M.; Park, H.; Sun, X. *J. Org. Chem.* **2003**, *68*, 8431.

Table 2. Hydrovinylation of *N*-Acetylenamines Catalyzed by $RuHCl(CO)(PCy_3)_2$[a]



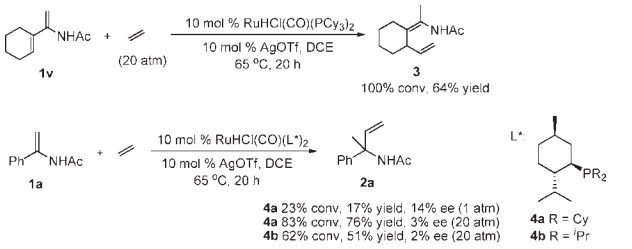
entry	R^1	R^2	product	time (h)	conv (%)[b]	yield (%)[c]
1	C_6H_5	H	**2a**	2	100	95
2	4-MeC_6H_4	H	**2b**	2.5	100	93
3	4-$MeOC_6H_4$	H	**2c**	10	94	87
4	4-FC_6H_4	H	**2d**	1	100	93
5	4-ClC_6H_4	H	**2e**	1.5	100	95
6	4-BrC_6H_4	H	**2f**	1	100	95
7	4-$CF_3C_6H_4$	H	**2g**	0.5	100	98
8	3-MeC_6H_4	H	**2h**	3	100	92
9	3-BrC_6H_4	H	**2i**	1	100	94
10	2-MeC_6H_4	H	**2j**	20	63	40
11	2-$MeOC_6H_4$	H	**2k**	20	93	91
12	3,5-$(CF_3)_2C_6H_3$	H	**2l**	0.5	100	99
13	3,4-$(OCH_2O)C_6H_3$	H	**2m**	3	100	89
14	2-naphthyl	H	**2n**	10	100	96
15	1-naphthyl	H	**2o**	20	78	74
16[d]	2-thiophenyl	H	**2p**	20	100	68
17[e]	C_6H_5	Me	**2q**	20	56	45
18[e]			**2r**	20	60	55
19[e]			**2s**	20	50	43
20[d]	CO_2Me	H	**2t**	20	80	67
21[d]	C_6H_5CO	H	**2u**	20	83	72

[a] The reaction conditions were the same as those in Table 1, entry 8. For details of operation and analysis, see the Supporting Information. [b] Determined by GC. [c] Isolated yield. [d] 10 mol % of $RuHCl(CO)(PCy_3)_2$ and 20 atm. [e] 10 mol % of $RuHCl(CO)(PCy_3)_2$.

has a vinyl group at the α-position such as *N*-(1-cyclohexenylvinyl)acetamide (**1v**), a conjugate hydrovinylation reaction occurred, giving product **3** in 64% yield (Scheme 2). However, no desired hydrovinylation product was isolated when the *N*-acetylenamine substrate has either a hydrogen (R^1 = H) or an alkyl group (R^1 = Me, *t*-Bu) at the α-position. These results disclosed that the *N*-acetylenamine substrate bearing an aromatic ring or an unsaturated group at the α-position is necessary to drive the reaction.

We then tried to realize the asymmetric version of the hydrovinylation of *N*-acetylenamines by introducing chiral phosphine ligands into the ruthenium catalyst. Among the many tested chiral phosphine ligands including diphosphines and monophosphines the phosphine **4a** with a (−)-menthyl moiety was the only one which afforded a low level of enantioselectivity. When the complex $RuHCl(CO)(\mathbf{4a})_2$ was subjected to catalyze the hydrovinylation of enamine **1a** the desired product **2a** was isolated in 17% yield with 14% ee (for the preparation of catalysts $RuHCl(CO)(\mathbf{4})_2$ and the crystal structure of $RuHCl(CO)(\mathbf{4b})_2$, see the Supporting Information). This result indicated a potential for achieving asymmetric induction in the ruthenium-catalyzed hydrovinylation of *N*-acetylenamines; however, a more efficient chiral ligand needs to be developed.

Scheme 2. Catalytic Hydrovinylation of **1v** and Enantioselective Hydrovinylation of **1a**



The *N*-acetyl α-arylenamines with an electron-withdrawing substituent on the phenyl ring exhibited higher reaction rates. This result is contrary to that observed in the hydrovinylation of vinylarenes, in which substrates with an electron-withdrawing group show lower or no reactivity.[2b] Figure 1 (left) is a comparison of the reaction rates of various substrates. Substrate **1f**, with a *p*-bromo group, showed the highest reaction rate, whereas **1c**, with a *p*-methoxy group, exhibited the lowest reaction rate. However, when a mixture of **1a**, **1c**, and **1f** was subjected to competitive hydrovinylation, the reaction rate of the three substrates decreased in the order **1c** > **1a** > **1f** (Figure 1, right); this order contrasted with the order observed in the respective individual reactions.

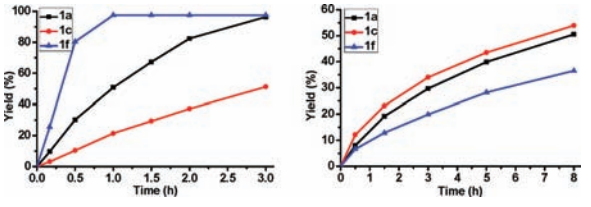


Figure 1. (Left) hydrovinylation **1a**, **1c**, and **1f**, separately. (Right) competitive hydrovinylation of **1a**, **1c**, and **1f** in one reaction.

To explain the electronic effect observed in the hydrovinylation of the *N*-acetylenamines and the substrate dependency of the reaction, we proposed a mechanism of hydrovinylation of *N*-acetylenamines.[9] As outlined in Figure 2, the formation of a benzylic, allylic, or *oxa*-allylic (X = O) ruthenium intermediate (**C**) is the key step to launch the reaction. Only the *N*-acetylenamines having an aryl, alkenyl, or carbonyl group at the α-position can form such intermediate, and no reaction took place for the substrate with an α-alkyl substituent or without substituent. In the reaction of *N*-acetyl α-arylenamines, the electron-rich substrates preferentially coordinated to the metal atom of the catalyst (step **A** to **B**), but the hydride transfer step (**B** to **C**), which is the rate-determining step, is faster for electron-deficient substrates. When the enamines **1a**,

(9) For the mechanism of Ru-catalyzed hydrovinylation of styrenes and 1,3-dienes, see ref 4a,4j.

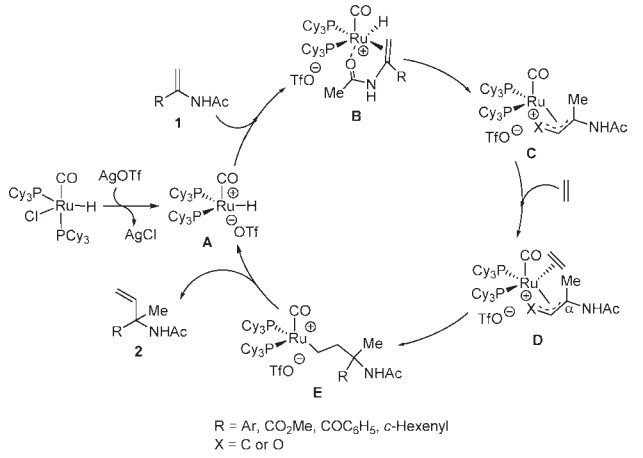
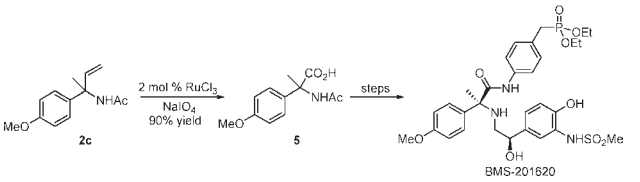


Figure 2. Proposed mechanism of hydrovinylation of enamines.

1c, and **1f** reacted separately, electron-deficient **1f** had a higher ability to accept hydride and reacted faster. However, in the competitive reaction of **1a**, **1c**, and **1f**, the electron-rich **1c** "occupied" the catalyst by preferentially coordinating to the metal and consequently showed a higher reaction rate.

This study provides a convenient approach to the synthesis of amines containing a quaternary carbon center, which are building blocks in the synthesis of various important compounds, such as α-amino acids and amino alcohols. As an example, **2c** was oxidized to α-amino acid **5** in high yield (90%) with $NaIO_4$ in the presence of catalytic $RuCl_3$. Amino acid **5** is the key intermediate in the synthesis of pharmaceuticals such as selective β_3 agonist BMS-201620 (Scheme 3).[10]

Scheme 3. Synthesis of α-Amino Acid **5**



In conclusion, a ruthenium-catalyzed hydrovinylation of *N*-acetylenamines with ethylene has been developed. This reaction provides a new method for the synthesis of amines and α-amino acids with a quaternary carbon center. Further studies on this reaction, especially on searching efficient chiral ligands to achieve asymmetric version of the reaction, are in progress in our laboratory.

Acknowledgment. We thank the National Natural Science Foundation of China and the National Basic Research Program of China (2010CB833300, 2011CB808600) for financial support.

Supporting Information Available. Experimental procedures and characterization of substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org

(10) Washburn, W. N.; Sun, C.-Q.; Bisacchi, G.; Wu, G.; Cheng, P. T.; Sher, P. M.; Ryono, D.; Gavai, A. V.; Poss, K.; Girotra, R. N.; McCann, P. J.; Mikkilineni, A. B.; Dejneka, T. C.; Wang, T. C.; Merchant, Z.; Morella, M.; Arbeeny, C. M.; Harper, T. W.; Slusarchyk, D. A.; Skwish, S.; Russell, A. D.; Allen, G. T.; Tesfamariam, B.; Frohlich, B. H.; Abboa-Offei, B. E.; Cap, M.; Waldron, T. L.; George, R. J.; Young, D.; Dickinson, K. E.; Seymour, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3525.