JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Rhenium-Catalyzed Regio- and Stereoselective Addition of Imines to Terminal Alkynes Leading to *N*-Alkylideneallylamines

Yoshiya Fukumoto,* Masato Daijo, and Naoto Chatani

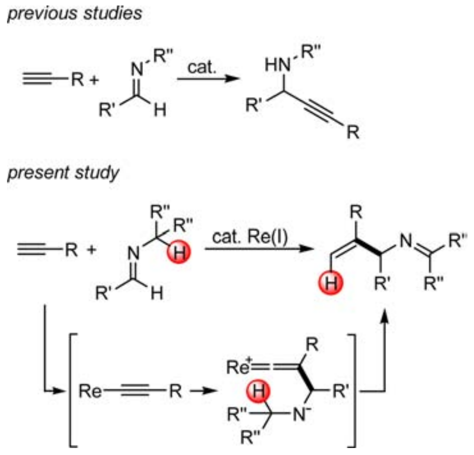
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

Supporting Information

ABSTRACT: The reaction of terminal alkynes with imines using $ReBr(CO)_5$ as a catalyst results in the production of *N*-alkylideneallylamines and not the conventional propargylamines. The substituent on the imine nitrogen is important, and a diphenylmethyl group gave the best result. The catalytic cycle of this regioselective C−C bond forming reaction appears to involve the formation of an alkynyl rhenium species and subsequent nucleophilic attack of the alkynyl β-carbon atom on the imine carbon to give a vinylidene rhenium species.

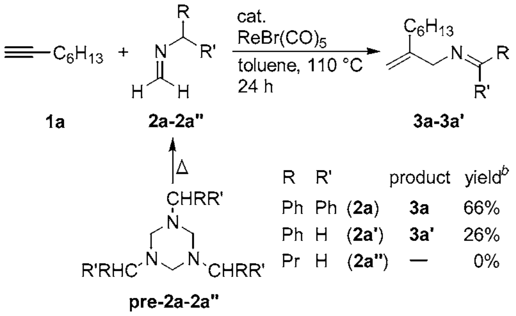
The reaction of terminal alkynes with electrophiles is one of the conventional methods for the synthesis of new acetylenic compounds that are amenable for further transformation into a wide range of structures.[1,2] The classical reaction involves the initial preparation of an alkynylmetal species by the reaction of terminal alkynes with a stoichiometric amount of strong bases such as organolithium reagents and the subsequent α-addition of electrophiles to the alkynylmetals. For example, imines have been widely studied as an electrophile in the synthesis of propargylamines, which was recently developed as a catalytic reaction.[3] The reaction proceeds through the nucleophilic addition of the alkynyl α-carbon to the imine carbon, leading to the formation of propargylaminometal species. On the other hand, electrophiles can also add to the alkynyl β-carbon to give vinylidene metal complexes.[4] Yorimitsu and Oshima et al. proposed that the reaction mechanism involved a β-addition step in the stoichiometric [2 + 2]cycloaddition/ring opening of the alkynyliron complexes to imines to give α,β-unsaturated iminoiron complexes mediated by $BF_3{\cdot}OEt_2$.[5,6] We disclose herein the rhenium-catalyzed reaction[7] of terminal alkynes with imines to give *N*-alkylideneallylamine derivatives. Allylamines are useful building blocks for the synthesis of a variety of nitrogen-containing organic molecules.[8] The present reaction permits the regioselective preparation of *N*-protected 1,2-disubstituted allylamines without the formation of any side products. In mechanistic aspects, to the best of our knowledge, this is the first catalytic reaction that appears to involve the nucleophilic attack of the alkynyl β-carbon atom on the imine carbon to produce a vinylidene rhenium complex in the catalytic cycle (Scheme 1).[9]

Scheme 1. Catalytic Addition of Imines to Terminal Alkynes



Treatment of 1-octyne (**1a**) with 1,3,5-tris(diphenylmethyl)-hexahydro-1,3,5-triazine (**pre-2a**), with the latter having undergone thermolysis to give *N*-diphenylmethyl imine **2a**,[10] in the presence of a catalytic amount of $ReBr(CO)_5$ in toluene at 110 °C for 24 h, afforded *N*-diphenylmethylidene-2-methylideneoctyl-1-amine (**3a**) in 66% yield (Scheme 2). No evidence of the presence of the corresponding propargylamine was observed, unlike the catalytic alkynylation of *N*-phenyl imines using $ReBr(CO)_2(THF)_3$, which was reported by Kuninobu and Takai et al.[11] The substituent on the imine nitrogen was important for the reaction to proceed efficiently.

Scheme 2. Rhenium-Catalyzed Addition of Imines to 1-Octyne (1a): Screening of Imines[a]



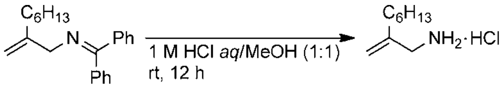
R	R'		product	yield[b]
Ph	Ph	(2a)	3a	66%
Ph	H	(2a')	3a'	26%
Pr	H	(2a'')	—	0%

[a]Reaction conditions: 1-octyne (**1a**, 1 mmol), 1,3,5-trialkylhexahydro-1,3,5-triazine (**pre-2a-2c**, 0.5 mmol), $ReBr(CO)_5$ (0.1 mmol), toluene (2 mL) at 110 °C for 24 h. [b]Product yields were determined by ^1H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

Received: March 7, 2012
Published: May 10, 2012

© 2012 American Chemical Society

In the case of the reaction with *N*-benzyl imine **2a′**, the yield of **3a′** was 26%, and when *N*-butyl imine **2a″** was used, no reaction was observed. The reaction of *N*-phenyl imine, which contains no α-hydrogen atom on the nitrogen substituent, resulted in the recovery of a large amount of **1a** with the formation of *N*-phenylpropargylamine in low yield. The diphenylmethylidene group in **3a** could be removed by treatment with a 1 M HCl *aq*/MeOH solution to give the corresponding allylamine hydrochloride (eq 1).



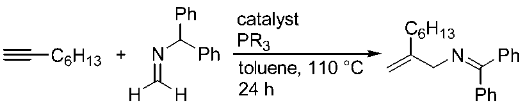
(1)

3a **3a**$_{NH2}$

85%

We next examined the use of various phosphines as an additive in the ReBr(CO)$_5$-catalyzed reaction of **1a** with **2a** (Table 1). When phosphines bearing electron-withdrawing groups on the phenyl ring such as P(4-CF$_3$C$_6$H$_4$)$_3$ and P(C$_6$F$_5$)$_3$ were used, the product yield was improved to 77% (entries 4 and 5). However, the addition of P(OPh)$_3$ retarded the reaction and a moderate amount of unreacted **1a** remained (entry 6). Table 1 shows some results obtained when some rhenium complexes were used with P(C$_6$F$_5$)$_3$ in place of ReBr(CO)$_5$. Whereas the other Re(I) complexes, including ReCl(CO)$_5$ and ReBr(CO)$_3$(THF)$_2$, resulted in catalytic activity comparable to that for ReBr(CO)$_5$ (entries 7 and 8), no reaction occurred when TpRe(CO)$_3$ (Tp = trispyrazolylborate) and Re$_2$(CO)$_{10}$ were used (entries 9 and 10). Complexes such as RhCl(PPh$_3$)$_3$, CpRuCl(PPh$_3$)$_2$, and AuCl(PPh$_3$), which are frequently used in catalytic reactions involving the vinylidene–metal complexes in the catalytic cycle,[12] were also ineffective in the present reaction.

Table 1. Rhenium-Catalyzed Addition of the Imine 2a to 1-Octyne (1a): Optimization of the Reaction Conditions[a]

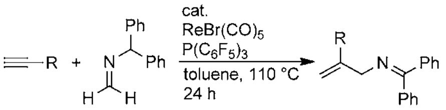


1a **2a** **3a**

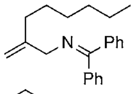
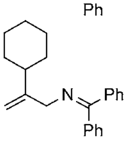
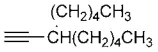
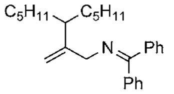
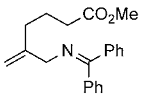
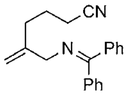
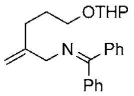
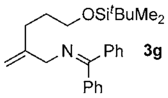
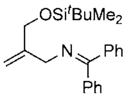
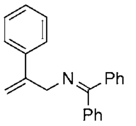
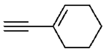
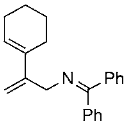
entry	catalyst	PR$_3$	yield (%)[b]
1	ReBr(CO)$_5$	none	66
2		PPh$_3$	70
3		P(4-MeOC$_6$H$_4$)$_3$	55
4		P(4-CF$_3$C$_6$H$_4$)$_3$	77
5		P(C$_6$F$_5$)$_3$	77 (73)[c]
6		P(OPh)$_3$	34
7	ReCl(CO)$_5$	P(C$_6$F$_5$)$_3$	70
8	ReBr(CO)$_3$(THF)$_2$		71
9	TpRe(CO)$_3$		0
10	Re$_2$(CO)$_{10}$		0

[a] Reaction conditions: **1a** (1 mmol), 1,3,5-tris(diphenylmethyl)-hexahydro-1,3,5-triazine (**pre-2a**, 0.5 mmol), catalyst (0.1 mmol), PR$_3$ (0.2 mmol), toluene (2 mL) at 110 °C for 24 h. [b] Product yields were determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield is in parentheses.

Table 2. Rhenium-Catalyzed Addition of the Imine 2a to Various Terminal Alkynes[a]



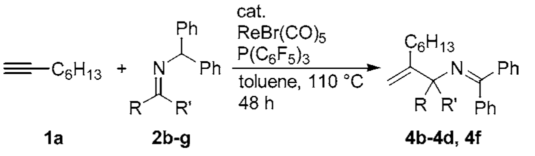
1a-j **2a** **3a-j**

entry	alkyne	product	yield (%)[b]
1	$\equiv$—(CH$_2$)$_5$CH$_3$ **1a**	 **3a**	73
2	$\equiv$—Cy **1b**	 **3b**	72
3	 $\equiv$—CH((CH$_2$)$_4$CH$_3$)(CH$_2$)$_4$CH$_3$ **1c**	 **3c**	66
4	$\equiv$—(CH$_2$)$_3$CO$_2$Me **1d**	 **3d**	70
5	$\equiv$—(CH$_2$)$_3$CN **1e**	 **3e**	74
6	$\equiv$—(CH$_2$)$_3$OTHP **1f**	 **3f**	76
7	$\equiv$—(CH$_2$)$_3$OSi^{t}BuMe$_2$ **1g**	 **3g**	73
8	$\equiv$—CH$_2$OSi^{t}BuMe$_2$ **1h**	 **3h**	41
9	$\equiv$—Ph **1i**	 **3i**	67[c]
10	 **1j**	 **3j**	54[c]

[a] Reaction conditions: **1** (1 mmol), 1,3,5-tris(diphenylmethyl)-hexahydro-1,3,5-triazine (**pre-2a**, 0.5 mmol), ReBr(CO)$_5$ (0.1 mmol), P(C$_6$F$_5$)$_3$ (0.2 mmol), toluene (2 mL) at 110 °C for 24 h. [b] Isolated yields. [c] The reaction was carried out at 80 °C for 48 h.

The scope of the present regioselective reaction of **2a** with regard to various terminal alkynes was investigated (Table 2). Cyclohexylacetylene (**1b**) and 3-pentyloct-1-yne (**1c**) reacted to give **3b** and **3c** in 72% and 66% isolated yields, respectively (entries 2 and 3). Functional groups including an ester (**1d**), a nitrile (**1e**), THP (**1f**), a siloxy group (**1g** and **1h**), and an alkene (**1j**) were tolerated in the reaction (entries 4–8 and 10). While the reaction of phenylacetylene (**1i**) under these reaction conditions gave **3i** in 58% yield, along with oligomerization products derived from **1i**, the yield was improved to 67% when the reaction temperature was lowered to 80 °C (entry 9). No evidence for the formation of propargylamines was found in any of the runs. However, when terminal alkynes bearing sterically demanding groups, such as *tert*-butyl and trimethylsilyl groups, were reacted under the standard reaction conditions, propargylamines were produced as the sole products in 70% and 87% yields, respectively.

Scheme 3. Rhenium-Catalyzed Addition of *N*-Diphenylmetyl Imines to 1-Octyne (1a)[a]



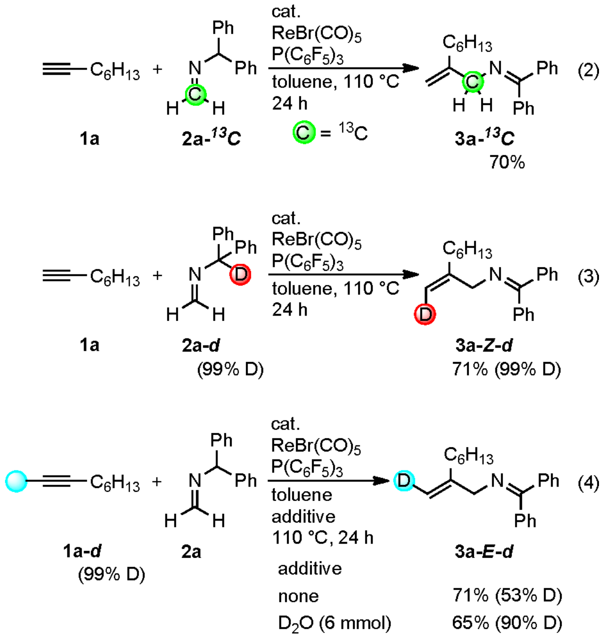
R	R'		product	yield[b]
Me	H	(2b)	4b	73%
C_5H_{11}	H	(2c)	4c	75%
Ph(CH$_2$)$_2$	H	(2d)	4d	61%
Cy	H	(2e)	—	0%
Ph	H	(2f)	4f	46%[c,d]
Me	Me	(2g)	—	0%

[a]Reaction conditions: **1a** (1 mmol), imine (1.5 mmol), ReBr(CO)$_5$ (0.15 mmol), P(C$_6$F$_5$)$_3$ (0.3 mmol), toluene (2 mL) at 110 °C for 48 h. [b]Isolated yields. [c]The reaction was run at 80 °C for 48 h. [d]Product yields were determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

The reaction was expanded to include some C-substituted imines other than **2a**, as shown in Scheme 3. The imine **2b** was treated under the aforementioned reaction conditions to give the 1-methyl-substituted allylamine **4b** in 62% yield, and in 66% yield when the reaction time was extended to 48 h with recovery of **1a** in *ca.* 10% yield. These results prompted us to change the reaction conditions by increasing the catalyst loading to 15 mol % and prolonging the reaction time to 48 h. As a result, the yield of **4b** was increased to 73% with complete consumption of **1a**. The altered reaction conditions were also used in the reactions of imines **2c**−**2g**. The reactivity of **2c** was similar to that of **2b**. However, the reaction of the cyclohexyl-substituted imine **2e** gave a complex mixture of unidentified products, none of which were the corresponding allylamine derivative, although the reason for this remains unclear. The reaction of the phenyl-substituted **2f** resulted in the formation of the desired product **4f** along with some unidentified byproducts. No conversion was observed when **2g** derived from acetone was used in the reaction.

To gain further insight into the reaction mechanism, some isotope labeling experiments were carried out (Scheme 4). As expected, when **1a** was reacted with ^{13}C-labeled imine **2a-^{13}C**, **3a-^{13}C** was formed, in which ^{13}C was incorporated into the allylic position (eq 2). Next, the reaction of **1a** with imine **2a-*d*** labeled with deuterium at the α-position of the diphenylmethyl group was examined. The deuterium shifted to the vinylic position in a *cis* configuration to the amino methyl group in the product **3a-*Z*-*d*** (eq 3). On the other hand, the reaction of **1a-*d*** with **2a** also gave the *trans* labeled product **3a-*E*-*d*** with good stereoselectivity. However, a moderate deuterium ratio of 53% D was observed, which would be attributed to the presence of trace H$_2$O in the reaction system. Therefore, the intentional addition of D$_2$O (6 mmol) to the reaction mixture improved the H/D ratio to 90%D (eq 4). These results demonstrated that the present reaction can be used to stereoselectively produce both *E*- and *Z*-monodeuterated allylamines.

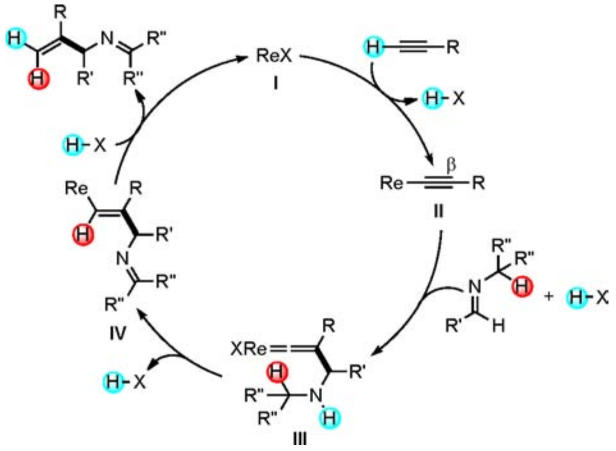
Scheme 4. Isotope Labeling Experiments[a]



additive	
none	71% (53% D)
D$_2$O (6 mmol)	65% (90% D)

[a]The reactions were run under the same reaction conditions described in Table 1. ^{13}C and deuterium contents were determined by ^{13}C and ^{1}H NMR spectroscopy.

Scheme 5. Proposed Reaction Mechanism



A plausible reaction mechanism for the reaction is depicted in Scheme 5. The reaction of a rhenium complex **I** with a terminal alkyne gives the alkynyl rhenium species **II** with the elimination of HX, which can rapidly undergo proton exchange with H$_2$O contained in the reaction system. The subsequent nucleophilic attack of the β-carbon of the rhenium alkynylide on an imine carbon then occurs to form the vinylidene rhenium species **III**.[13] The 1,5-shift of the hydrogen atom[14,15] adjacent to the nitrogen atom to the α-carbon atom of the vinylidene moiety gives the vinyl rhenium species **IV**. The final protonolysis of **IV** affords the product with the regeneration of **I**.[16] The α-phenyl group on the imine substituent would assist the intramolecular migration of hydrogen in **III** by stabilizing the partial cationic character of the carbon, to which the hydrogen is attached. Bulky *tert*-butyl and trimethylsilyl groups would inhibit the nucleophilic attack of the alkynyl β-carbon atom to the imine carbon; therefore, that of the α-carbon atom proceeds to afford propargylamines when *tert*-butylacetylene and trimethylsilylacetylene were used. In the case of the dimethylimine **2e**, neither β- nor α-addition was observed, presumably due to the steric hindrance.

In summary, the findings reported herein demonstrate the rhenium-catalyzed reaction of terminal alkynes with imines to afford allylamine derivatives. The diphenylmethyl group as the substituent on the imine nitrogen gave the best result. Deuterium labeling experiments revealed that the regioselective addition of hydrogen and the *N*-alkylideneaminoalkyl group to the terminal alkynes also proceeds stereoselectively. The C–C bond forming step via the nucleophilic attack of the alkynyl β-carbon on the imine carbon leading to the formation of a vinylidene rhenium species appears to be involved in the catalytic cycle.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

fukumoto@chem.eng.osaka-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 22550100). Thanks are given to the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for Assistance with HRMS and elemental analyses.

■ REFERENCES

(1) *Modern Acetylene Chemistry*, Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, Germany, 1995.

(2) For recent reviews, see: (a) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581–590. (b) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983.

(3) For reviews, see: (a) Yoo, W.-J.; Zhao, L.; Li, C.-J. *Aldrichimica Acta* **2011**, *44*, 43–52. (b) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263–4275. Catalytic additions of terminal alkynes to aldehydes and ketones have also been studied. For reviews, see: (c) Lu, G.; Li, Y.-M.; Li, X.-S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736–1744. (d) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095–4105. (e) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886. See also refs 2a and 2b.

(4) For reviews which contain the description of the addition of electrophiles to alkynyl β-carbons to give vinylidene metal complexes, see: (a) Davies, S. G.; McNally, J. P.; Smallridge, A. J. *Adv. Organomet. Chem.* **1990**, *30*, 1–76. (b) Cadierno, V.; Gamasa, M. P.; Gimeno, J. *Coord. Chem. Rev.* **2004**, *248*, 1627–1657.

(5) Nakaya, R.; Yasuda, S.; Yorimitsu, H.; Oshima, K. *Chem.—Eur. J.* **2011**, *17*, 8559–8561.

(6) For another recent example of β-addition of electrophiles to alkynyl metals, see: Boone, M. P.; Stephan, D. W. *Organometallics* **2011**, *30*, 5537–5542.

(7) For a review on the rhenium-catalyzed reactions, see: Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938–1953.

(8) For a review on the use of allylamines in the synthesis of *N*-heterocycles, see: Nag, S.; Batra, S. *Tetrahedron* **2011**, *67*, 8959–9061.

(9) For examples of the catalytic reactions involving the nucleophilic attack of an alkynyl β-carbon, see: (a) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644–661. (b) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31–34. (c) Joo, J. M.; Yuan, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 14818–14819.

(10) For a recent example of the use of **pre-2a** as the precursor of **2a**, see: Ma, T.; Fu, X.; Kee, C. W.; Zong, L.; Pan, Y.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 2828–2831.

(11) Kuninobu, Y.; Inoue, Y.; Takai, K. *Chem. Lett.* **2006**, *35*, 1376–1377.

(12) For recent reviews on the catalytic reactions involving vinylidene metal complxes, see: (a) *Metal Vinylidenes and Allenylidenes in Catalysis*; Bruneau, C., Dixneuf, P. H., Eds.; Wiley-VCH: Weinheim, Germany, 2008. (b) Trost, B. M.; McClory, A. *Chem.—Asian J.* **2008**, *3*, 164–194.

(13) For examples where the formation of a vinylidene rhenium complex is proposed as a key intermediate in catalytic reactions, see: (a) Xia, D.; Wang, Y.; Du, Z.; Zheng, Q.-Y.; Wang, C. *Org. Lett.* **2012**, *14*, 588–591. (b) Yudha, S. S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609–5611.

(14) For examples of the 1,5-hydrogen shift to the vinylidene β-carbon, see: (a) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471–5475. (b) Odedra, A.; Datta, S.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 3289–3292. (c) Bajracharya, G. B.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6204–6210. (d) Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 11606–11607.

(15) A similar retro-metallo-ene rearrangement of a β-aminoalkylvinyliene metal species was proposed previously; see: (a) Hyder, I.; Jiménez-Tenorio, M.; Puerta, M. C.; Valerga, P. *Organometallics* **2011**, *30*, 726–737. (b) Ipaktschi, J.; Mohsseni-Ala, J.; Dülmer, A.; Loschen, C.; Frenking, G. *Organometallics* **2005**, *24*, 977–989.

(16) The possibility of a mechanism involving the formation of a metallacycle by the oxidative coupling of terminal alkynes, imines, and rhenium species cannot be ruled out, although such a mechanism does not account for the regioselectivity of the products observed here, or the results shown in Scheme 2.