

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

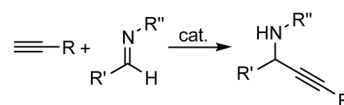
ABSTRACT: The reaction of terminal alkynes with imines using $\text{ReBr}(\text{CO})_5$ as a catalyst results in the production of *N*-alkylideneallylamines and not the conventional propargylamines. The substituent on the imine nitrogen is important, and a diphenylmethyl group gave the best result. The 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 $\text{BF}_3 \cdot \text{OEt}_2$.^{5,6} We disclose herein the rhenium-catalyzed reaction⁷ 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

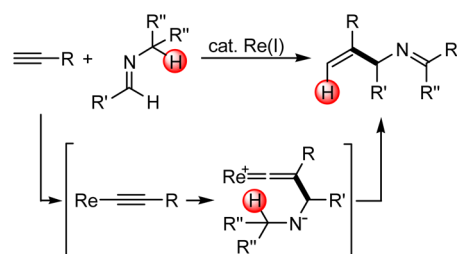
Treatment of 1-octyne (**1a**) with 1,3,5-tris(diphenylmethyl)-hexahydro-1,3,5-triazine (**pre-2a**), with the latter having undergone thermolysis to give *N*-diphenylmethyl imine **2a**,¹⁰ in the presence of a catalytic amount of $\text{ReBr}(\text{CO})_5$ in toluene

Scheme 1. Catalytic Addition of Imines to Terminal Alkynes

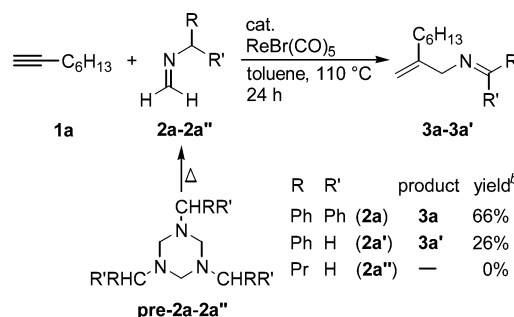
previous studies



present study



at 110 °C for 24 h, afforded *N*-diphenylmethylidene-2-methylideneoctyl-1-amine (**3a**) in 66% yield (Scheme 2). No

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

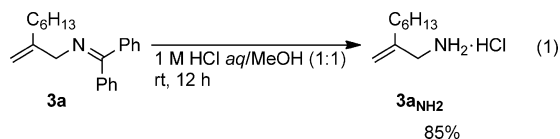
^aReaction conditions: 1-octyne (**1a**, 1 mmol), 1,3,5-trialkylhexahydro-1,3,5-triazine (**pre-2a-2c**, 0.5 mmol), $\text{ReBr}(\text{CO})_5$ (0.1 mmol), toluene (2 mL) at 110 °C for 24 h. ^bProduct yields were determined by ¹H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

evidence of the presence of the corresponding propargylamine was observed, unlike the catalytic alkynylation of *N*-phenyl imines using $\text{ReBr}(\text{CO})_2(\text{THF})_3$, which was reported by Kuninobu and Takai et al.¹¹ The substituent on the imine nitrogen was important for the reaction to proceed efficiently.

Received: March 7, 2012

Published: May 10, 2012

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).



We next examined the use of various phosphines as an additive in the $\text{ReBr}(\text{CO})_5$ -catalyzed reaction of **1a** with **2a** (Table 1). When phosphines bearing electron-withdrawing

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

entry	catalyst	PR ₃	yield (%) ^b
1	$\text{ReBr}(\text{CO})_5$	none	66
2		PPh_3	70
3		$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	55
4		$\text{P}(4\text{-CF}_3\text{C}_6\text{H}_4)_3$	77
5		$\text{P}(\text{C}_6\text{F}_5)_3$	77 (73) ^c
6		$\text{P}(\text{OPh})_3$	34
7	$\text{ReCl}(\text{CO})_5$	$\text{P}(\text{C}_6\text{F}_5)_3$	70
8	$\text{ReBr}(\text{CO})_3(\text{THF})_2$		71
9	$\text{TpRe}(\text{CO})_3$		0
10	$\text{Re}_2(\text{CO})_{10}$		0

^aReaction 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. ^bProduct yields were determined by ¹H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. ^cIsolated yield is in parentheses.

groups on the phenyl ring such as $\text{P}(4\text{-CF}_3\text{C}_6\text{H}_4)_3$ and $\text{P}(\text{C}_6\text{F}_5)_3$ were used, the product yield was improved to 77% (entries 4 and 5). However, the addition of $\text{P}(\text{OPh})_3$ 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 $\text{P}(\text{C}_6\text{F}_5)_3$ in place of $\text{ReBr}(\text{CO})_5$. Whereas the other $\text{Re}(\text{I})$ complexes, including $\text{ReCl}(\text{CO})_5$ and $\text{ReBr}(\text{CO})_3(\text{THF})_2$, resulted in catalytic activity comparable to that for $\text{ReBr}(\text{CO})_5$ (entries 7 and 8), no reaction occurred when $\text{TpRe}(\text{CO})_3$ (Tp = trispyrazolylborate) and $\text{Re}_2(\text{CO})_{10}$ were used (entries 9 and 10). Complexes such as $\text{RhCl}(\text{PPh}_3)_3$, $\text{CpRuCl}(\text{PPh}_3)_2$, and $\text{AuCl}(\text{PPh}_3)_3$, which are frequently used in catalytic reactions involving the vinylidene–metal complexes in the catalytic cycle,¹² were also ineffective in the present reaction.

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

Table 2. Rhenium-Catalyzed Addition of the Imine **2a to Various Terminal Alkynes^a**

entry	alkyne	product	yield (%) ^b
1	1a (C_8H_{13})	3a	73
2	1b (cyclohexyl)	3b	72
3	1c (C_8H_{13})	3c	66
4	1d (methyl ester)	3d	70
5	1e (nitrile)	3e	74
6	1f (THP)	3f	76
7	1g (siloxy)	3g	73
8	1h (siloxy)	3h	41
9	1i (phenyl)	3i	67 ^c
10	1j (cyclohexyl)	3j	54 ^c

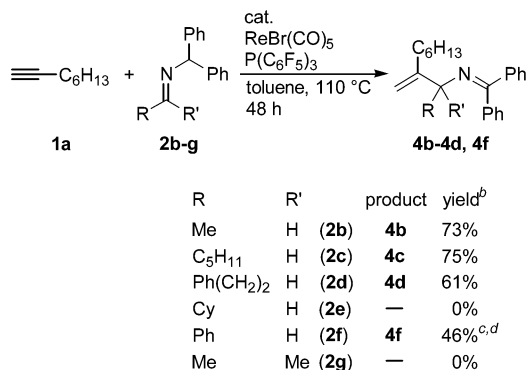
^aReaction conditions: **1** (1 mmol), 1,3,5-tris(diphenylmethyl)-hexahydro-1,3,5-triazine (**pre-2a**, 0.5 mmol), $\text{ReBr}(\text{CO})_5$ (0.1 mmol), $\text{P}(\text{C}_6\text{F}_5)_3$ (0.2 mmol), toluene (2 mL) at 110 °C for 24 h. ^bIsolated yields. ^cThe reaction was carried out at 80 °C for 48 h.

(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.

The reaction was expanded to include some C-substituted imines other than **2a**, as shown in Scheme 3. The imine **2b** was

Scheme 3. Rhenium-Catalyzed Addition of *N*-Diphenylmethyl Imines to 1-Octyne (1a**)^a**



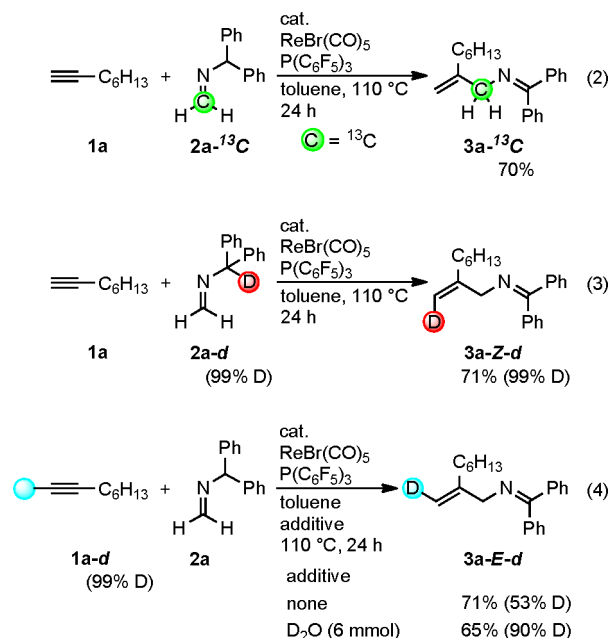
^aReaction conditions: **1a** (1 mmol), imine (1.5 mmol), ReBr(CO)₅ (0.15 mmol), P(C₆F₅)₃ (0.3 mmol), toluene (2 mL) at 110 °C for 48 h. ^bIsolated yields. ^cThe reaction was run at 80 °C for 48 h. ^dProduct yields were determined by ¹H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

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 ¹³C-labeled imine **2a-¹³C**, **3a-¹³C** was formed, in which ¹³C 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 H₂O in the reaction system. Therefore, the intentional addition of D₂O (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.

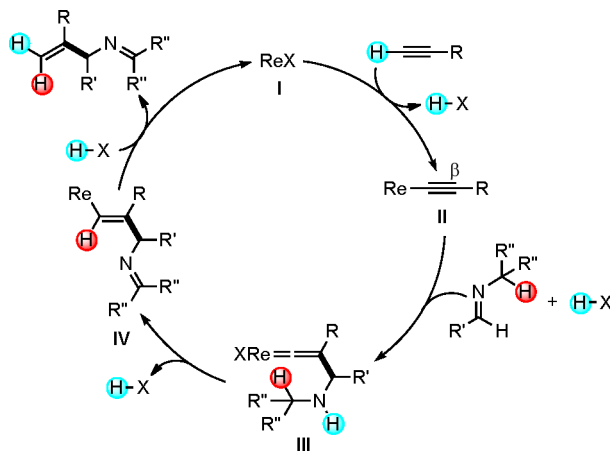
A plausible reaction mechanism for the reaction is depicted in Scheme 5. The reaction of a rhenium complex **I** with a terminal alkyne gives the alkynyl rhenium species **II** with the

Scheme 4. Isotope Labeling Experiments^a



^aThe reactions were run under the same reaction conditions described in Table 1. ¹³C and deuterium contents were determined by ¹³C and ¹H NMR spectroscopy.

Scheme 5. Proposed Reaction Mechanism



elimination of HX, which can rapidly undergo proton exchange with H₂O 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.

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(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.