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A New Class of Redox Isomerization of *N*-Alkylpropargylamines into *N*-Alkylideneallylamines Catalyzed by a $ReBr(CO)_5$/Amine *N*-oxide System

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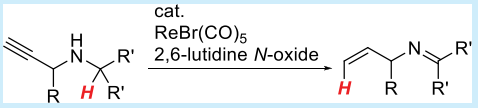
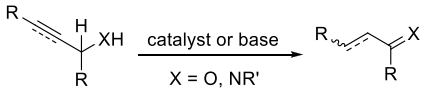
Supporting Information

ABSTRACT: Redox isomerization reaction wherein *N*-alkylpropargylamines are converted into *N*-alkylideneallylamines in the presence of rhenium(I) complexes as catalysts is described. Among the additives tested, certain pyridine *N*-oxides and tertiary amine *N*-oxides were effective for the reaction to proceed, and in particular, the use of 2,6-lutidine *N*-oxides gave the best results. The choice of a diphenylmethyl group as a substituent on the nitrogen atom was key to the success of the reaction, allowing it to reach completion.



Because of their utility in organic synthesis, the isomerization of allylic and propargylic alcohols has been an extensively investigated process.[1] Among various types of the isomerizations, redox isomerization is defined as a transformation involving the transfer of two hydrogen atoms from an allylic and propargylic CH−OH moiety to a C−C multiple bond, without the rearrangement or the reorganization of any other atoms in the molecule, to afford saturated and *α,β*-unsaturated carbonyl compounds, respectively (Scheme 1).

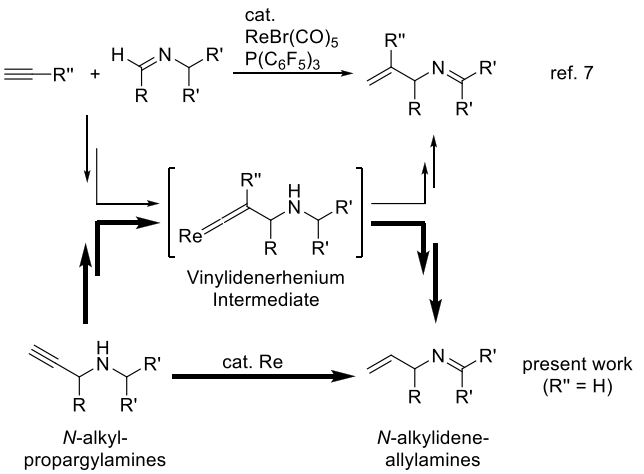
Scheme 1. Conventional Redox Isomerization of Allylic and Propargylic Alcohols and Amines



There are a number of examples of the use of transition-metal complexes as catalysts for these reactions.[2] Compared to the structurally related alcohols, however, the redox isomerization of *N*-monosubstituted allylic and propargylic amines has been explored far less. A few reports on reactions of propargylamines leading to the production of *α,β*-unsaturated imines mediated by ^{t}BuOK have appeared,[3] which probably proceeds via the formation of allenylamines.[4] The Meyer−Schuster-type rearrangement of *N*′-tosylpropargylhydrazines to *α,β*-unsaturated hydrazones catalyzed by $Y(OTf)_3$[5] or $FeCl_3$,[6] which involves a formal 1,3-nitrogen shift, has also been reported. On the other hand, to the best of our knowledge, the use of transition-metal complexes as catalysts for redox isomerization of propargylamines remains unexplored.

We report herein a new class of redox isomerization in which *N*-alkylpropargylamines are converted into *N*-alkylideneallylamines in the presence of rhenium complexes as catalysts. A working hypothesis that explains this isomerization is summarized in Scheme 2. We recently reported the development of a $ReBr(CO)_5/P(C_6F_5)_3$ catalyst system that promoted

Scheme 2. Working Hypothesis



the regio- and stereoselective hydroaminoalkylation of terminal alkynes with *N*-alkylimines, leading to the production of allylamine derivatives.[7] The reaction appears to proceed via the formation of a *β,β*-disubstituted vinylidenerhenium complex, one substituent of which is a 1-(monoalkylamino)alkyl group, as a key intermediate in the catalytic cycle.[8,9] We next assumed that the related 1-(monoalkylamino)alkyl vinylidenerhenium complex (R″ = H in Scheme 2) would be formed via a formal 1,2-hydrogen shift from an alkyne terminal carbon to the internal alkyne carbon when *N*-alkylpropargylamines were used as substrates, which is followed by the same reaction pathway to afford *N*-alkylideneallylamines. A related isomerization of *N*-propargyl-2,5-dihydro-1*H*-pyrroles into *N*-allylpyrroles catalyzed by CuBr was recently reported by Ma and co-workers.[10] Gong and co-workers reported that a gold complex could also

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Org. Lett. XXXX, XXX, XXX–XXX

be used to catalyze the isomerization of *N*-propargylisoindolines into *N*-allylisoindoles, which underwent a further transformation in situ to form *N*-allylisoindolinones under air, or a Diels–Alder reaction with alkenes or alkynes bearing electron-deficient substituents to form tricyclic compounds.[11] While it would be quite difficult to obtain substituent-free allylamine derivatives on the nitrogen atom from these products, the alkylidene group in the present product would be expected to be easily removed, e.g. by acidic hydrolysis, to give the corresponding free allylamines.

To test this hypothesis, we examined the $ReBr(CO)_5$-catalyzed reaction of *N*-(diphenylmethyl)oct-1-yn-3-amine (**1a**) in the absence and presence of $P(C_6F_5)_3$ (entries 1 and 2 in Table 1). Despite the fact that, in both cases, the reactions proceeded, along with complete consumption of **1a**, the product **2a** was produced in only moderate yields after 24 h. An *α,β*-unsaturated imine, which would be produced by the conventional redox isomerization, was not detected. In screening other transition metal complexes as catalysts, which are known to form vinylidenemetal complexes by reacting with terminal alkynes, some, such as $[ReBr(CO)_3(thf)_2]_2$, $ReCl(CO)_5$, $[IrCl(cod)]_2$, and CuBr, also showed catalytic activity that was comparable to $ReBr(CO)_5$ (Table S1 in the Supporting Information). When other aryl-substituted phosphines were added to the $ReBr(CO)_5$ catalyst system, the amount of **1a** that remained after the reaction increased with increasing electron-donating ability of the 4-substituents, although the product yields were comparable in all runs (entries 3–5). Among other phosphines examined, PCy_3 gave the best result of 63% (entry 6). However, these results encouraged us to further investigate additives with the goal of improving the yield of **2a**. After a number of unsuccessful attempts, a breakthrough came when pyridine *N*-oxide was used as an additive, to afford **2a** in 77% yield (entry 8). Various amine *N*-oxides, including substituted pyridine *N*-oxides (entries 9–12) and *N*-methylmorphorine *N*-oxide (entry 13), were also effective for the reaction. After further optimization of the reaction conditions, we were delighted to find that 2,6-lutidine *N*-oxide was the additive of choice for the reaction, which was completed in 2 h, even if the catalyst loading was reduced to 5 mol %, from the original concentration of 10 mol %, with **2a** being produced in 88% yield (entry 14). In this run, the product imine **2a** was isolated by NH_2-modified silica-gel column chromatography in 83% yield, with no evidence for the formation of a hydrolysis compound. On the other hand, 4-methoxypyridine *N*-oxide resulted in a decrease in product yield to a 32% yield under the optimized reaction conditions, with 58% of **1a** being recovered (entry 15). When 1,4-dioxane and DMF were used as solvents, a mixture of **1a** and **2a** was obtained in both cases (entries 16 and 17). Although $[IrCl(cod)]_2$ and CuBr were re-examined under the modified reaction conditions in order to compare their catalytic activities with the $ReBr(CO)_5$/2,6-lutidine *N*-oxide system, product yields were decreased in both cases (Table S2 in the Supporting Information).

The results shown in Scheme 3 illustrate the importance of the choice of substituent on the nitrogen atom, in terms of the reaction efficiency. Whereas, as has been described so far, diphenylmethyl-substituted propargylamine **1a** reacted smoothly to afford **2a** in 88% yield, other substituents, including benzyl (**1a′**), dicyclohexylmethyl (**1a′′**), and hexyl (**1a′′′**) groups, retarded the reaction markedly. These substituent effects were also reported in our previous study on the Re-catalyzed coupling of terminal alkynes with imines.

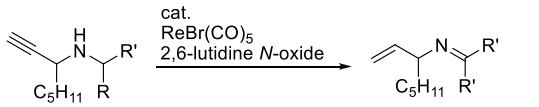
With the optimized reaction conditions in hand, the scope of the reaction with respect to substrate was examined (Scheme 4). Substrates **1a–1e** bearing some primary-alkyl substituted alkynes on the propargylic carbon reacted to provide the desired products **2a–2e**. In the case of the methyl-substituted compound **1c**, it was necessary to extend the reaction time to 4 h, because, after 2 h, a small amount of **1c** remained (Scheme S1 in the Supporting Information) and this complicated the separation of the desired product by column chromatography. Functional groups such as ester (**2f**), cyano (**2g**), benzyloxy (**2h**), and siloxy (**2i**) groups were tolerated. The reaction of isopropyl-substituted propargylamine **1j**, when carried out for 12 h, resulted in the isolation of the corresponding allylamine derivative **2j** in 84% yield (Scheme S2 in the Supporting Information). The cyclic ether (**2l**) and amide (**2m**) were also compatible with the reaction conditions. Although the

Table 1. Screening of Additives in the Rhenium-Catalyzed Redox Isomerization of 1a into 2a[a]

entry	additive	yield of **2a** (%)[b]	recovered **1a** (%)[b]
1	none	49	0
2	$P(C_6F_5)_3$	51	0
3	$P(4\text{-}CF_3C_6H_4)_3$	50	0
4	PPh_3	43	12
5	$P(4\text{-}MeOC_6H_4)_3$	44	36
6	PCy_3	63	3
7	PBu_3	30	38
8	pyridine *N*-oxide	77	0
9	4-MeOpyridine *N*-oxide	82	0
10	4-Clpyridine *N*-oxide	65	0
11	4-NO_2pyridine *N*-oxide	64	0
12	2,6-lutidine *N*-oxide	83	0
13	*N*-methylmorpholine *N*-oxide	70	0
14[c]	2,6-lutidine *N*-oxide	88 (83)[d]	0
15[c]	4-MeOpyridine *N*-oxide	32	58
16[c,e]	2,6-lutidine *N*-oxide	57	35
17[c,f]	2,6-lutidine *N*-oxide	66	23

[a]Reaction conditions: **1a** (1 mmol), $ReBr(CO)_5$ (0.1 mmol), and additive (0.2 mmol) in toluene (2 mL) at 110 °C for 24 h. [b]Yields of **1a** and **2a** were determined by ^1H NMR spectroscopy with 1,1,1,2-tetrachloroethane as the internal standard. [c]$ReBr(CO)_5$ (0.05 mmol) and 2,6-lutidine *N*-oxide (0.1 mmol) for 2 h. [d]The value in parentheses is the isolated yield. [e]In 1,4-dioxane. [f]In DMF.

Scheme 3. Effect of Substituents on the Amine Nitrogen[a]



	R	R'	
1a	Ph	Ph	**2a**, 88%[b]
1a'	Ph	H	**2a'**, 26% (46%)[b]
1a''	Cy	Cy	**2a''**, 0% (78%)[b]
1a'''	C_5H_{11}	H	**2a'''**, 11% (68%)[b]

[a]Reaction conditions: **1** (1 mmol), $ReBr(CO)_5$ (0.05 mmol), and 2,6-lutidine *N*-oxide (0.1 mmol) in toluene (2 mL) at 110 °C for 2 h. [b]The values in parentheses are the remaining amount of **1**. Yields of **1** and **2** were determined by ^1H NMR spectroscopy with 1,1,1,2-tetrachloroethane as the internal standard.

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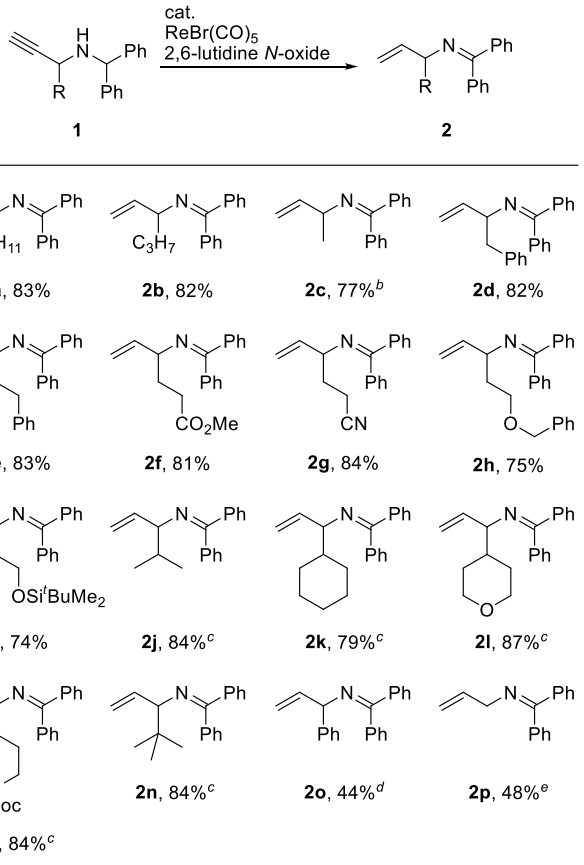
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 4. Scope of Substrates[a]

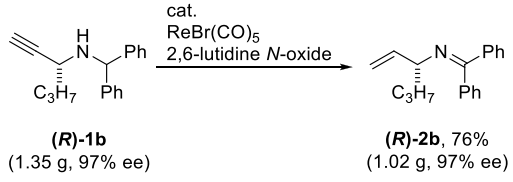


[a]Reaction conditions: **1** (1 mmol), $ReBr(CO)_5$ (0.05 mmol), and 2,6-lutidine *N*-oxide (0.1 mmol) in toluene (2 mL) at 110 °C for 2 h. The values refer to the isolated yield of products. [b]4 h. [c]12 h. [d]$ReBr(CO)_5$ (0.1 mmol), 2,6-lutidine *N*-oxide (0.2 mmol) at 80 °C for 48 h. [e]$ReBr(CO)_5$ (0.1 mmol), PCy_3 (0.2 mmol) at 110 °C for 24 h.

presence of a bulky *tert*-butyl group (**2n**) had no effect on product yield, the reaction of the phenyl-substituted substrate **1o** gave a complex reaction mixture, containing the desired product **2o** along with the starting **1o** in 23% and 32% yields, respectively. After modifying the reaction conditions, **2o** was obtained in 44% yield. Surprisingly, the $ReBr(CO)_5$/2,6-lutidine *N*-oxide catalytic system was not applicable to a simple propargylamine **1p**; the use of PCy_3 in place of 2,6-lutidine *N*-oxide improved the product yield of **2p** to 48%.

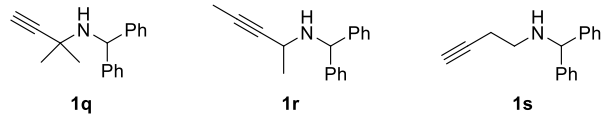
The $ReBr(CO)_5$/2,6-lutidine *N*-oxide catalyzed reaction of the chiral compound (*R*)-**1b** also proceeded well on a gram-scale, to produce (*R*)-**2b** in 76% yield, without any detectable loss of optical purity (Scheme 5). On the other hand, the reaction of dimethyl-substituted propargylamine **1q** resulted in the moderate recovery of **1q** in 59% yield with no formation of the desired product, and the use of the internal alkyne **1r** as a

Scheme 5. Gram Scale Experiment Using Optically Active Compound (*R*)-1b



substrate led to the complete recovery of the starting materials (Scheme 6). An application of the reaction to homopropargyl-

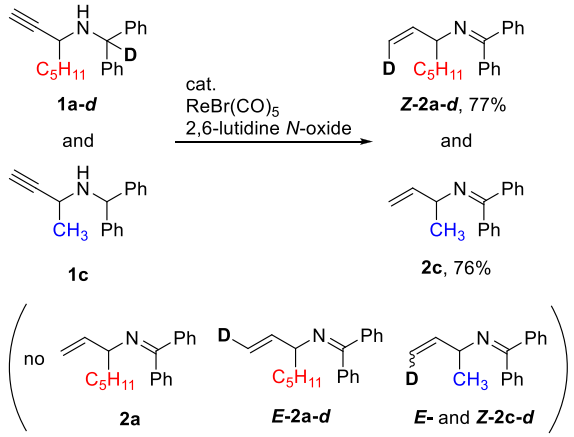
Scheme 6. Inapplicable Substrates



amine **1s** resulted in the formation of complex mixture of products, which did not include the corresponding homoallylamine derivative.

To gain further insights into the reaction mechanism, a crossover experiment was carried out using **1a**-*d*, in which the α-position of the diphenylmethyl group was labeled with deuterium, and **1c** (Scheme 7). After the reaction, the

Scheme 7. Crossover Experiment Using 1a-*d* and 1c[a]



[a]Reaction conditions: **1a**-*d* (0.5 mmol), **1c** (0.5 mmol), $ReBr(CO)_5$ (0.05 mmol), and 2,6-lutidine *N*-oxide (0.1 mmol) in toluene (2 mL) at 110 °C for 2 h. Yields were determined by ^1H NMR spectroscopy with 1,1,1,2-tetrachloroethane as the internal standard.

deuterium atom was incorporated into only the product *Z*-**2a**-*d* at the vinylic position in a *cis* configuration to the amino methyl group, and no crossover products such as **2a** and **2c**-*d* were observed. This result indicates that the 1,5-hydrogen shift from the α-position of the diphenylmethyl group to the alkyne terminal carbon occurs intramolecularly in a stereoselective manner.[12−14]

A plausible mechanism for the reaction is proposed in Scheme 8. The in situ generation of the coordinatively unsaturated complex **I** occurs via the oxidation of the CO ligand in the $ReBr(CO)_5$ precatalyst with the pyridine *N*-oxide and its subsequent release as CO_2 and pyridine.[15] Similar to the Re-catalyzed coupling reaction of terminal alkynes with imines, **I** then reacts with a propargylamine to give an alkynyl rhenium species **II** with the elimination of HBr. Protonation of **II** at the β-carbon of the alkyne next takes place to afford a vinylidenerhenium complex **III**.[16] A 1,5-shift of the hydrogen atom adjacent to the nitrogen atom to the α-carbon atom of the vinylidene moiety in **III** gives a vinyl rhenium species **IV**. This step determines the regio- and stereoselective introduction of the hydrogen atom in the final product. 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, which the hydrogen is attached to.

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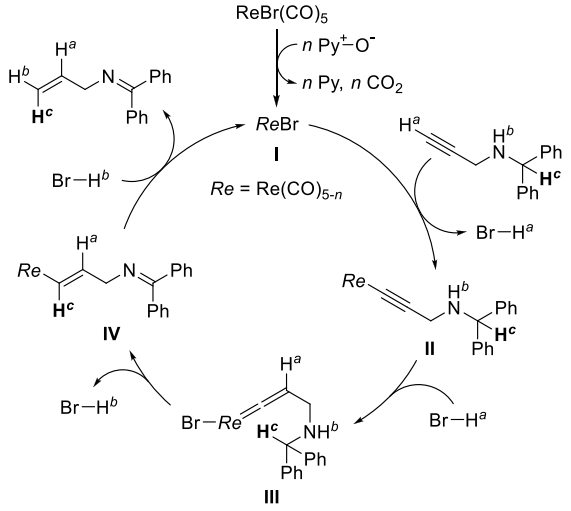
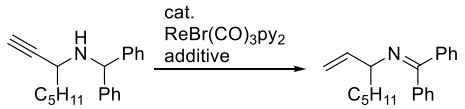
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 8. A Plausible Mechanism



The final protonolysis of **IV** affords the product with the regeneration of **I**. The superiority of 2,6-lutidine *N*-oxide as an additive compared to the other pyridine *N*-oxides examined can be attributed to steric hindrance by the two methyl groups in the byproduct 2,6-lutidine to coordinate with the pyridine nitrogen to the Re center in **I**. To confirm this assumption, $ReBr(CO)_3py_2$ was also examined as a catalyst in the reaction of **1a** under typical reaction conditions, and catalytic activity was very low (Scheme 9). Meanwhile, the reaction was also

Scheme 9. Reaction of 1a Catalyzed by $ReBr(CO)_3py_2$[a]



1a **2a**

additive	**2a**	recovered **1a**
none	23%	70%
2,6-lutidine *N*-oxide	69%	29%

[a]Reaction conditions: **1a** (1 mmol), $ReBr(CO)_3py_2$ (0.05 mmol) and additive (0.1 mmol) in toluene (2 mL) at 110 °C for 2 h. Yields of **1a** and **2a** were determined based on ^{1}H NMR spectral data with 1,1,1,2-tetrachloroethane as the internal standard.

accelerated in the presence of 2,6-lutidine *N*-oxide as the additive, indicating the importance of opening the coordination site around the Re center. In this sense, the result that **2p** was not formed in the $ReBr(CO)_5$/2,6-lutidine *N*-oxide catalytic system might be due to the deactivation of the catalyst **I** caused by the facile coordination of **1p**. On the other hand, it is also possible that the bulky PCy_3 ligand on **I** could inhibit the further coordination of the nitrogen atom in **1p** and/or **2p** to **I**; therefore, **1p** would react in the $ReBr(CO)_5$/PCy_3 catalytic system. The finding that the internal alkyne **1r** did not react at all is consistent with the formation of the vinylidenerhenium complex **III** in the proposed reaction mechanism. However, the possibility that the reaction proceeds via the formation of an alkyne-rhenium π-complex followed by the 1,5-hydrogen shift[17] cannot be completely ruled out at this present stage of our investigations.

In summary, we demonstrated a new class of redox isomerization in which *N*-alkylpropargylamines are converted into *N*-alkylideneallylamines using $ReBr(CO)_5$/2,6-lutidine *N*-oxide as the catalyst. A deuterium labeling experiment revealed that the α-hydrogen atom in the diphenylmethyl group was transferred regio- and stereoselectively to the vinylic position in a *cis* configuration to the amino methyl group in the product, indicating that the 1,5-hydrogen transfer occurred intramolecularly. More detailed studies regarding the reaction mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00325.

Detailed experimental procedures; characterization data of all of the new compounds; ^{1}H and ^{13}C NMR spectra of the products; copies of HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX