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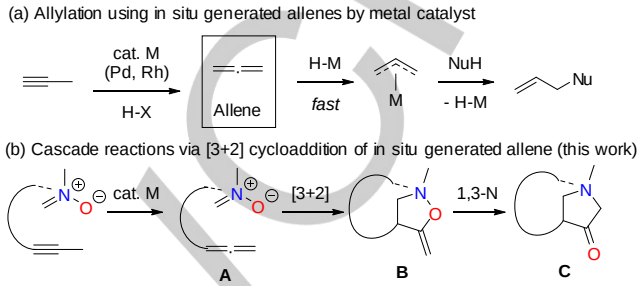
Rapid Access to Nitrogenous Heterobicycles via Rh(III)-catalyzed Isomerization from Alkynes to Allenes

Itaru Nakamura,*[a] Keisuke Takeda,[b] Yoshinori Sato,[b] and Masahiro Terada[a,b]

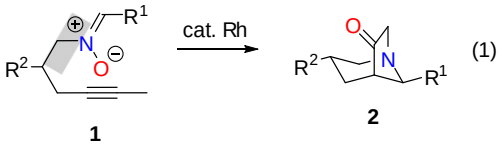
Abstract: We have disclosed that *N*-alkynylnitrones are efficiently converted to nitrogenous heterobicyclic compounds having a nitrogen atom at the bridgehead position by using a Rh(III)-catalyst. Our mechanistic studies suggest that the reaction proceeds via an allene intermediate, which is generated in situ through Rh(III)-catalyzed isomerization of the alkyne group.

Allenes have been frequently utilized in organic synthesis as three-carbon units owing to their high reactivity.[1] However, due to the inherent instability of this functional group, construction of highly functionalized organic molecules from functionalized allene species has been limited. In situ generation of allenes is one of the most effective solutions for this problem. Particularly, isomerization of alkynes by using transition metal catalysts, such as Pd^0,[2] Rh^I,[3,4] and Ru^{II},[5] has been widely utilized as an efficient and robust method to transiently generate allenes (Scheme 1a). These methodologies have been typically utilized as allylation reactions, because the generated allene rapidly undergoes addition of the metal hydride that is formed during the isomerization process, leading to the thermodynamically stable π-allylmetal intermediate.[1b] Accordingly, we envisioned that the generated allene **A** could be captured by a properly placed nitrone group in an intramolecular manner, and the expected cycloadduct **B** would rapidly rearrange via N-O bond cleavage, leading to nitrogenous heterobicycle **C**, which is beneficial for drug discovery (Scheme 1b).[6] Herein, we report that *N*-(4-hexynyl)nitrones **1** undergo cycloisomerization by the aid of rhodium catalysts, producing nitrogenous heterobicycles **2**, in good to acceptable yields [Eq(1)].

Initially, the previously reported reaction conditions using Pd and Rh catalysts were applied to the benzaldoxime **1a** and we found that the conditions using a rhodium catalyst reported by Breit afforded the 1-azabicyclo[3.2.1]octan-6-one **2a** having a nitrogen atom at the bridgehead with excellent diastereoselectivity, albeit in low chemical yields. Among Brønsted acids examined as a potential hydrogen source, only HBr showed improved catalytic activity (entry 3), while other protic acids, such as carboxylic acids and HCl, were ineffective (see SI). Thus, the reaction was conducted in the presence of several bromine sources in order to know if bromine atom affects on



Scheme 1. Transformations via metal-catalyzed in situ generation of allenes



efficiency of the present reaction, To our surprise, the use of Br_2 and LiBr as additive improved the chemical yield (entries 4 and 5), while the reaction in the absence of the Br additive did not afford the desired product at all (entry 6). The reaction with I_2 afforded the product in lower yield than that using Br_2 (entry 7). These results encouraged us to examine Rh^{III} as a catalyst, which is expected to be generated through oxidation of Rh^I by Br_2. To our delight, the reaction using $RhBr_3{\cdot}2H_2O$ in place of $[RhCl(cod)]_2$ afforded the desired product **2a** in good yield even in the absence of the additional bromine source (entries 8 and 9). In sharp contrast, the reaction using $RhCl_3$ was sluggish (entry 10). It should be noted that only dppp {1,3-bis(diphenylphosphino)propane} exhibited good catalytic activity and THF gave the best result among the solvents we tested (see SI).

Next, the optimal reaction conditions (Table 1, entry 9) were applied to various substrates, as summarized in Table 2. An electron-deficient aromatic group was efficient as a substituent at the nitrone carbon atom. The *p*-cyanophenyl group gave the desired product in good yield (entry 5). Bromo, chloro, and naphthyl groups were tolerated under the reaction conditions. While reaction of substrate **1i** having an electron-rich *p*-anisyl group at R^1 afforded **2i** in low yield (entry 8), **1j** having an alkyl substituent at R^1 did not afford the desired product under the present reaction conditions (entry 9). Both electron-rich and electron-poor aromatic substituents were applicable as substituents at R^2, affording the heterobicycles in good to acceptable yields (entries 12-14), while that having an alkyl group resulted in low chemical yield (entry 15). It should be noted that the substrate having an ethyl group, instead of a methyl group, at the alkyne terminus was not converted to the desired product at all.

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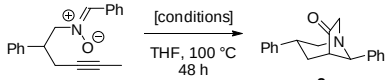
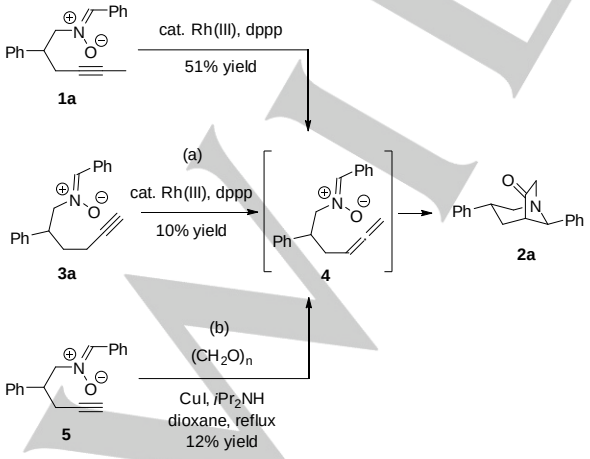
Table 1. Optimization of reaction conditions



Entry	Conditions (mol %)	Yield [%][a]
1	$Pd(PPh_3)_4$ (10), BzOH (10)	<1
2	$[RhCl(cod)]_2$ (5), dppp (11), BzOH (50)	16[d]
3	$[RhCl(cod)]_2$ (5), dppp (11), HBr (10)[b]	43 (37)
4	$[RhCl(cod)]_2$ (5), dppp (11), Br_2 (10)[c]	51
5	$[RhCl(cod)]_2$ (5), dppp (11), LiBr (10)	33
6	$[RhCl(cod)]_2$ (5), dppp (11)	<1
7	$[RhCl(cod)]_2$ (5), dppp (11), I_2 (10)	49 (29)
8	$RhBr_3 \cdot 2H_2O$ (10), dppp (20)	40
9	**$RhBr_3 \cdot 2H_2O$ (10), dppp (10)**[e]	**51 (49)**
10	$RhCl_3 \cdot 2H_2O$ (10), dppp (20)	7

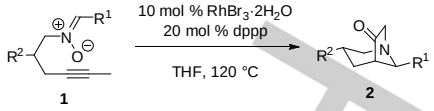
[a] Yields were determined by ^1H NMR using dibromomethane as an internal standard. Isolated yield is in parentheses. [b] 47% HBr aqueous solution was used. [c] Br_2-1,4-dioxane complex was used. [d] 15% of **1a** was recovered. [e] At 120 °C for 24 h.

The rhodium-catalyzed reaction of the *N*-(5-hexynyl)nitrone **3a**, in which the position of the alkynyl group was shifted by one carbon in comparison to **1a**, gave the identical product **2a** to that of the *N*-(4-hexynyl)nitrone **1a** (Scheme 2a). These results clearly support intermediacy of the same allene intermediate **4a**. Moreover, when the *N*-(4-pentynyl)nitrone **5** was treated with the standard conditions of Crabbe allene synthesis,[7] the heterobicycle **2a** was obtained, albeit in low chemical yield (Scheme 2b), supporting the in situ generation of the allene group. A mass spectrum corresponding to $[RhBr_2(dppp)]^+$ was detected in the reaction of **1a** under the optimal reaction conditions (Table 1, entry 9), suggesting that Rh^{III} coordinated by bromine atoms exists in the reaction media, presumably serving as a real catalytic species for the present reaction.



Scheme 2. Mechanistic studies

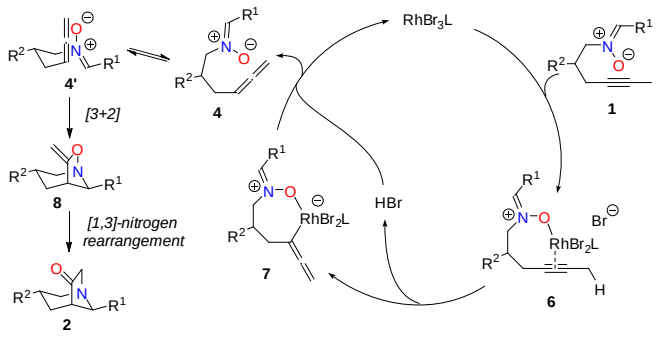
Table 2. Rh^{III}-catalyzed reaction of **1b-p**[a]



Entry	**1**	R^1	R^2	Time [h]	**2**	Yield [%][b]
1	**1b**	*p*-ClC_6H_4	Ph	30	**2b**	55
2	**1c**	*p*-BrC_6H_4	Ph	48	**2c**	37
3	**1d**	*p*-FC_6H_4	Ph	24	**2d**	48
4	**1e**	*p*-$F_3CC_6H_4$	Ph	20	**2e**	63
5	**1f**	*p*-NCC_6H_4	Ph	24	**2f**	65
6	**1g**	3,5-$(F_3C)_2C_6H_3$	Ph	24	**2g**	64
7	**1h**	2-naphthyl	Ph	24	**2h**	42
8	**1i**	*p*-$MeOC_6H_4$	Ph	24	**2i**	20
9	**1j**	Cy	Ph	24	-	<1
10	**1k**	Ph	*p*-$F_3CC_6H_4$	24	**2k**	33
11	**1l**	Ph	*p*-$MeOC_6H_4$	24	**2l**	51
12	**1m**	*p*-NCC_6H_4	*p*-ClC_6H_4	24	**2m**	49
13	**1n**	*p*-NCC_6H_4	*p*-$F_3CC_6H_4$	24	**2n**	46
14	**1o**	*p*-NCC_6H_4	*p*-$MeOC_6H_4$	24	**2o**	58
15	**1p**	Ph	*i*Bu	24	**2p**	25

[a] The reactions of **1b-p** (0.4 mmol) were carried out in the presence of 10 mol % of $RhBr_3 \cdot 2H_2O$ and 20 mol % of dppp in THF (2.0 mL) at 120 °C. [b] Isolated yields.

We propose a tentative reaction mechanism based on the reactivity of the rhodium catalyst as a π-acid, as illustrated in Scheme 3. First, the Rh^{III} catalyst is coordinated by the triple bond of substrate **1**, forming the σ,π-complex **6**. The π-coordination enhances acidity of the methyl group at the alkyne terminus, facilitating elimination of the proton.[8] The resulting allenylrhodium species **7** immediately undergoes protodemetallation leading to the allene intermediate **4**. Next, intramolecular [3+2] cycloaddition between the generated allene and the pendant nitrone leads to the bicyclic intermediate **8**, having a 5-methylenisoxazolidine ring.[10] Finally, [1,3]-nitrogen rearrangement involving N-O bond cleavage leads to the product **2**. The excellent diastereoselectivity is probably because both R^1 and R^2 are formally located at equatorial positions in the forming 6-membered ring in the [3+2] cycloaddition process as shown in intermediate **4'**. We consider that the in situ generated allene was effectively utilized for [3+2] cycloaddition not only because the nitrone is located at a suitable position in the key intermediate **4/4'** but also because the present catalyst system based on π-acid Rh^{III} is free from generation of metal hydride species, which cause the typical allylation reaction.



Scheme 3. A plausible mechanism

In conclusion, we have successfully developed a new method to generate allene intermediates by using a Rh^{III} catalyst. Since the reaction rapidly constructs nitrogenous heterobicyclic skeletons in a single operation under mild reaction conditions, the present method is potentially useful for the synthesis of new classes of heterocyclic compounds, which is beneficial for drug discovery.[11]

Experimental Section

To a mixture of **1f** (120.9 mg, 0.4 mmol), $RhBr_3 \cdot 2H_2O$ (15.1 mg, 0.04 mmol), and dppp (33.0 mg, 0.08 mmol) was added THF (2.0 mL) under argon atmosphere and the mixture was stirred at 120 °C for 24 hours. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using ethyl acetate. After removing solvents in vacuo, the crude product was purified by flash silica gel column chromatography using hexane/ethyl acetate (10/1), affording **2f** (78.1 mg, 0.26 mmol) in an analytically pure form.

Acknowledgements

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Keywords: rhodium • rearrangement • allene • heterocycles • cascade reaction

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[9] Typical π-acidic catalysts, such as $[(PPh_3)AuNTf_2]$ and $PtCl_4$, did not promote the present reaction.

[10] Attempts to observe the cycloaddition intermediate **8** was unsuccessful. Indeed, our preliminary calculations suggested that the product **2a** is 38.3 $kcalmol^{-1}$ more stable than the cycloaddition intermediate **8a**.

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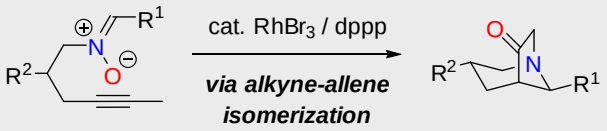

Rh^{III} catalyst rapidly constructs heterobicycles from *N*-alkynylnitrones. Mechanistic studies suggest that the present transformation proceeds via in situ generation of allene intermediate through Rh-catalyzed isomerization of alkyne.

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