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Rhenium-Catalyzed Insertion of Aldehyde into a C−H Bond: Synthesis of Isobenzofuran Derivatives

Yoichiro Kuninobu,* Yuta Nishina, Chie Nakagawa, and Kazuhiko Takai*

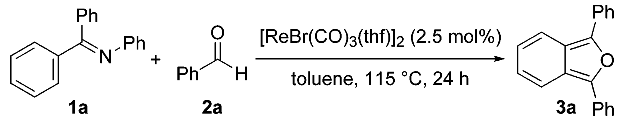
Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Okayama 700-8530, Japan

Received August 4, 2006; E-mail: kuninobu@cc.okayama-u.ac.jp; ktakai@cc.okayama-u.ac.jp

Chemical transformations via catalytic C−H bond activation are expected to become a powerful tool in organic synthetic chemistry.[1] Ruthenium and rhodium complexes have been commonly used for C−H bond activation, which is usually followed by the insertion of unsaturated molecules. However, the unsaturated molecules have been mainly limited to nonpolar ones, such as olefins and acetylenes.[1] Recently, the insertion reactions of α,β-unsaturated carbonyl compounds with $RhCl(PPh_3)_3$ have been reported as one example of the insertion of moderately polar molecules.[2] On the other hand, insertion of an aldehyde into the metal−carbon bonds derived from C−H bond activation has not been achieved.

We have recently reported on the rhenium-catalyzed insertion of unsaturated molecules, such as acetylenes,[3] α,β-unsaturated carbonyl compounds,[2c] and isocyanates.[4] Because rhenium has lower electronegativity than ruthenium and rhodium, the carbon−rhenium bond is more polarized than the carbon−ruthenium and −rhodium bonds, and so the organorhenium species will hopefully react with aldehydes such as Grignard reagents. We report herein the insertion of aldehydes into the C−H bond of aromatic ketimines, and the reactions provide isobenzofuran derivatives[5] via further intramolecular nucleophilic cyclization.

Treatment of ketimine **1a** (0.50 mmol) with benzaldehyde **2a** (0.50 mmol) in the presence of a rhenium catalyst, $[ReBr(CO)_3(thf)]_2$ (2.5 mol %), generated isobenzofuran derivative **3a** in 47% yield (Figure 1). In this reaction, benzophenone and an aldimine derived from **2a** and aniline were observed as side products. The result suggests that benzaldehyde was consumed by aniline and that ketimine **1a** was partially decomposed by water that was formed. Thus, we used 2 equiv of the aldehyde and added molecular sieves into the reaction mixture to remove the water. As a result, the yield of isobenzofuran derivative **3a** increased to 93% (Figure 1, Table 1, entry 1).[6]

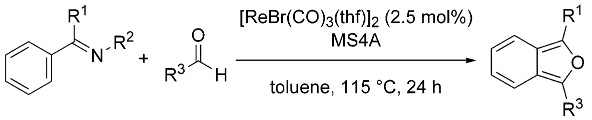


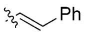
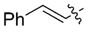
1a **2a** **3a**

2a (equiv)	molecular sieves (4A)	% yield
1.0	none	47%
2.0	none	67%
2.0	added	93%

Figure 1. Synthesis of isobenzofuran derivative **3a** by the reaction of aromatic ketimine **1a** with benzaldehyde **2a**.

Table 1. Reactions of Ketimines with Aldehydes[a]



entry	R^1	R^2	R^3	product	% yield[b]
1	Ph	Ph	Ph	**3a**	93 (95)
2	Ph	$PhCH_2$	Ph	**3a**	91 (95)
3		Ph	Ph	**3b**	79[c] (85)
4	Ph	Ph	p-$(MeO)C_6H_4$	**3c**	70 (76)
5	Ph	Ph	p-MeC_6H_4	**3d**	91 (94)
6	Ph	Ph	p-$CF_3C_6H_4$	**3e**	93 (98)
7	Ph	Ph	o-MeC_6H_4	**3f**	86 (90)
8	Ph	Ph		**3b**	78[c] (84)

[a] Ketimine (1.0 equiv) and aldehyde (2.0 equiv). [b] Isolated yield. The yield determined by ^1H NMR is reported in parentheses. [c] The product **3b** was isolated by recrystallization under an argon atmosphere.

The phenyl group on a nitrogen atom of ketimine **1a** could be replaced by a benzyl group without decreasing the yield of isobenzofuran **3a** (Table 1, entry 2). By using a ketimine, which was derived from *trans*-chalcone (benzylideneacetophenone) and aniline, the corresponding isobenzofuran derivative **3b** was obtained in 79% yield (Table 1, entry 3).

Next, we examined the substituents on the aromatic ring of aldehydes. The treatment of ketimine **1a** with aldehydes having electron-donating groups, such as a *para*-methoxy or a *para*-methyl group, provided the corresponding isobenzofurans **3c** and **3d** in 70% and 91% yields, respectively (Table 1, entries 4 and 5). By using an aldehyde bearing an electron-withdrawing group, the yield increased and the isobenzofuran derivative **3e** was obtained in 93% yield (Table 1, entry 6). Despite the bulkiness, *o*-tolualdehyde afforded the corresponding isobenzofuran **3f** in 86% yield (Table 1, entry 7). By using cinnamaldehyde instead of benzaldehyde, the reaction with **1a** also proceeded, and isobenzofuran derivative **3b** was obtained in 78% yield (Table 1, entry 8). However, a reaction of **1a** with nonanal gave a complex mixture in the absence of a trapping compound such as cyclooctene (vide infra). Another approach to obtain an isobenzofuran having 1-alkyl-3-phenyl substituents is a reaction between an imine derived from an alkyl phenyl ketone and benzaldehyde. Treatment of a ketimine of acetophenone ($R^1 = Me$) and benzaldehyde with a catalytic amount of $[ReBr(CO)_3(thf)]_2$ gave a mixture which contained ca. 10% of the desired isobenzofuran; however, isolation of the compound was difficult due to its instability.[7]

The proposed reaction mechanism is as follows (Scheme 1): (1) coordination of a nitrogen atom of an imine to a rhenium center; (2) C−H bond activation;[2c,3,4] (3) insertion of an aldehyde to the rhenium−carbon bond of the aryl−rhenium intermediate; (4) intramolecular nucleophilic attack of the alkoxy−rhenium moiety to a carbon atom of the imine; and (5) reductive elimination and

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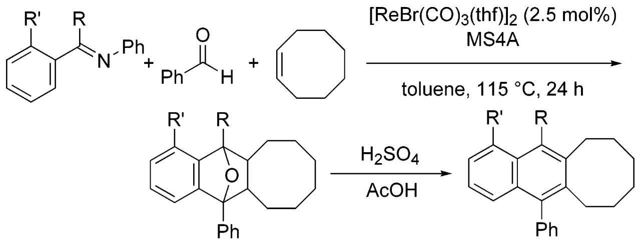
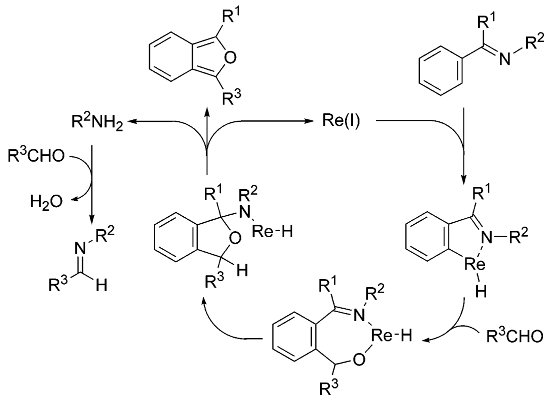


4a: R = Ph; R' = H 83% (*endo* / *exo* = 89 / 11) **5a**: 73%
4b: R = (*E*)-PhCH=CH-; R' = H 69% (*endo* / *exo* = 87 / 13) **5b**: 67%
4g: R, R' = $(CH_2)_3$ 79% (*endo* / *exo* = 93 / 7) **5g**: 79%

Figure 2. Three-component coupling of aromatic ketimine, aldehyde, and cyclooctene.

Scheme 1



elimination of aniline. Because the formed aniline reacts with the aldehyde, 2 equiv of the aldehyde is necessary to complete the reaction.

Isobenzofuran derivatives are useful compounds as building blocks of bioactive compounds[8] and functional materials.[5c,9] In addition, they have reactive diene moieties, and these can be used for Diels−Alder reactions.[10] In fact, when a reaction of ketimine **1a** and benzaldehyde (**2a**) was conducted in the presence of cyclooctene, a three-component coupling product **4a** derived from the Diels−Alder reaction of **3a** and cyclooctene was produced in 83% yield in one pot (Figure 2). Isobenzofuran derivatives having an alkenyl or an alkyl group which are readily oxidized by atmospheric oxygen could also be trapped with cyclooctene in one pot under an argon atmosphere. The corresponding adducts **4b** and **4g** were obtained in 69% and 79% yields, respectively, as stable forms (Figure 2). The formed Diels−Alder adducts **4a**, **4b**, and **4g** were aromatized[6d,8d,10] without isolation via the ring-opening reaction of cyclic ether and the elimination of water by treatment with acetic acid and sulfuric acid at 25 °C for 1.5 h.[11] The reaction produced the corresponding naphthalene derivatives **5a**, **5b**, and **5g** in 73%, 67%, and 79% yields, respectively (Figure 2).

An aliphatic aldehyde, 5-hexenal, could be used as the aldehyde component of the isobenzofuran formation (Figure 3, route A). In addition, a ketimine which can isomerize to an enamine could be employed (route B). Because the formed isobenzofuran was unstable, it was trapped in situ by an intramolecular Diels−Alder reaction. After acidic treatment, routes A and B produced a naphthalene derivative **5h** in 50% and 75% yields, respectively (Figure 3).

In summary, we have succeeded in the insertion of aldehydes into a C−H bond of aromatic ketimines by using a rhenium complex, $[ReBr(CO)_3(thf)]_2$, as a catalyst. The reactions provide isobenzofuran derivatives via C−H bond activation, insertion of the aldehyde, intramolecular nucleophilic cyclization, reductive elimination, and elimination of aniline. It is interesting to note that the carbon−rhenium bonds show nucleophilicity which is a characteristic property of early transition metals and that the rhenium complex can be used as a catalyst via reductive elimination which is usually observed for late transition metals.

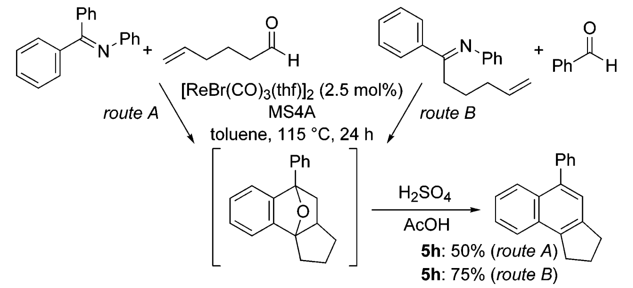


Figure 3. Intramolecular trapping of isobenzofurans.

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Supporting Information Available: General experimental procedure and characterization data for isobenzofuran derivatives and Diels−Alder adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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