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Rhenium-Catalyzed Synthesis of Indenones by Novel Dehydrative Trimerization of Aryl Aldehydes via C−H Bond Activation

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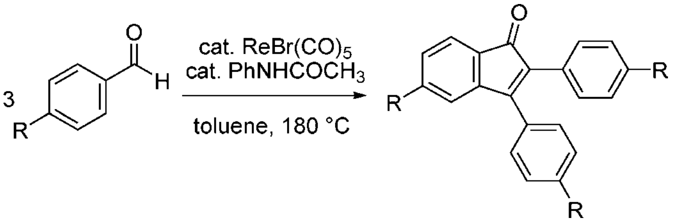
ABSTRACT



By heating aryl aldehydes with catalytic amounts of a rhenium complex, ReBr(CO)$_5$, and *N*-phenylacetamide in toluene, indenone derivatives are obtained in good to excellent yields. This reaction proceeds via (1) the formation of an isobenzofuran derivative by the insertion of an aldehyde into the C−H bond of another aldehyde (C−H bond activation) and successive intramolecular nucleophilic cyclization, (2) nucleophilic addition of the formed isobenzofuran derivative to the third aldehyde, (3) isomerization, and (4) intramolecular aldol condensation.

Cyclic compounds are useful and indispensable entries in organic chemistry. Transformation via C−H bond activation is one of the most efficient and powerful methods to construct cyclic skeletons, and the skeletons have been constructed by intramolecular cyclization[1,2] and annulation reactions. We previously reported the rhenium-catalyzed synthesis of cyclic compounds via C−H bond activation (two-component annulation).[3] These annulation reactions proceed via intermolecular insertion of an unsaturated molecule into a C−H bond, followed by intramolecular nucleophilic cyclization.[3] Three-component cycloadditions via C−H bond activation have also been reported (three-component annulation); however, these examples are rare.[3d,4] We report herein a rhenium-catalyzed three-component cycloaddition via C−H bond activation to produce indenone derivatives.[5−7]

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(1) (a) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692. (b) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581.

(2) Yang, S.; Li, Z.; Jian, X.; He, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3999.

(3) (a) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498. (b) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (c) Kuninobu, Y.; Nishina, Y.; Shouho, M.; Takai, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2766. (d) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376. (e) Kuninobu, Y.; Nishina, Y.; Matsuki, T.; Takai, K. *J. Am. Chem. Soc.* **2008**, *130*, 14062.

(4) (a) Tasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 12680. (b) Kuninobu, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2007**, *63*, 8463. (c) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019.

(5) There have been several reports on transition-metal-catalyzed syntheses of indenone derivatives. See: (a) Larock, R. C.; Doty, M. J. *J. Org. Chem.* **1993**, *58*, 4579. (b) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339. (c) Wender, P. A.; Paxton, T. J.; Williams, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 14814. (d) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766. (e) Liu, C.-C.; Korivi, R. P.; Cheng, C.-H. *Chem.−Eur. J.* **2008**, *14*, 9503.

(6) Indenones are used as starting materials for synthesizing indenes and indenyl−transition-metal complexes. See: (a) Anstead, G. M.; Ensign, J. L.; Peterson, C. S.; Katzenellenbogen, J. A. *J. Org. Chem.* **1989**, *54*, 1485. (b) Xi, Q.; Zhang, W.; Zhang, X. *Synlett* **2006**, 945.

(7) Indenones are key intermediates for the synthesis of bioactive products. See: Walspurger, S.; Vasilyev, A. V.; Sommer, J.; Pale, P. *Tetrahedron* **2005**, *61*, 3559.

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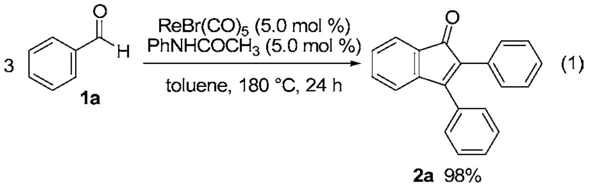
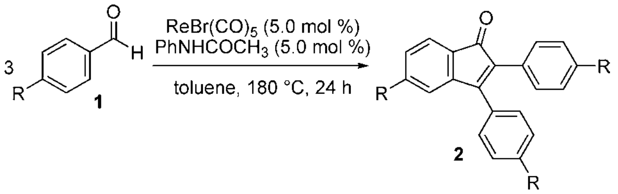
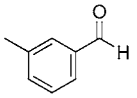
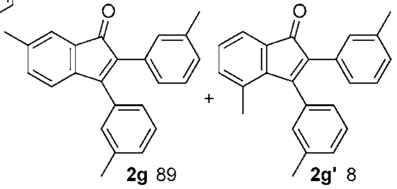
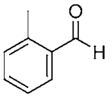
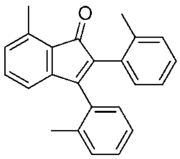
Treatment of benzaldehyde (**1a**) with catalytic amounts of a rhenium complex, $ReBr(CO)_5$, and *N*-phenylacetamide in toluene gave indenone derivative **2a** in 98% yield (eq 1).[8−11] Without the rhenium catalyst or amide, the reaction did not proceed, and starting material was recovered completely.



To examine the scope and limitations of the substrates, several aldehydes were investigated (Table 1). By the reaction of an aldehyde with a methoxy group at the para position, **1b**, the corresponding indenone derivative **2b** was obtained in 77% yield (entry 1). When an aldehyde bearing a methyl group, **1c**, was used, indenone **2c** was produced in almost quantitative yield (entry 2).

Table 1. Synthesis of Indenones from Several Aldehydes[a]

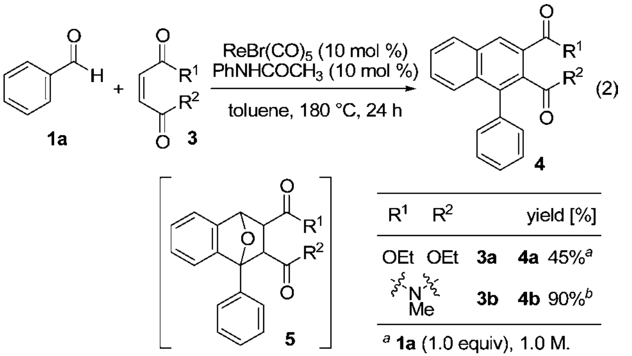


entry	R			yield [%][b]
1	MeO	**1b**	**2b**	77
2	Me	**1c**	**2c**	98
3	CF_3	**1d**	**2d**	90
4	MeO_2C	**1e**	**2e**	98
5	Br	**1f**	**2f**	98
6[c]		**1g**	 **2g** 89 + **2g′** 8	
7[c]		**1h**	 **2h**	98

[a] 1.0 M. [b] Isolated yield. [c] 2.0 M.

The corresponding indenone **2d** was generated by the reaction of an aldehyde with an electron-withdrawing group, **1d** (entry 3). These reactions were not affected by functional groups, such as a methoxycarbonyl group and bromine atom (entries 4 and 5). When 3-methylbenzaldehyde (**1g**) was used, indenones **2g** and **2g′** were generated in 89% and 8% yields, respectively (entry 6). In this reaction, although there are two possible products, **2g** was formed selectively. 2-Methylbenzaldehyde (**1h**), with only one ortho position available for reaction, also provided the corresponding indenone **2h** in 98% yield (entry 7). However, thiophene-2-carbaldehyde, pyridine-4-carbaldehyde, *trans*-2-decenal, and *trans*-cinnamaldehyde did not produce the corresponding indenone derivatives.

To elucidate the reaction mechanism, we attempted to capture a reaction intermediate. By heating benzaldehyde (**1a**) in the presence of an olefin with an electron-withdrawing group, **3a** or **3b**, naphthalene derivatives **4a** and **4b** were obtained in 45% and 90% yields, respectively (eq 2). This result indicates the formation of isobenzofuran intermediates[12,13] because the naphthalene derivatives **4** must be produced by the dehydration of **5**. The intermediate **5** is derived from a Diels−Alder reaction between isobenzofuran intermediates and dienophiles **3** by overcoming the nucleophilic addition of the isobenzofuran intermediate to the third aldehyde. The reactions in eq 2 are also three-component cycloaddition reactions via C−H bond activation.



R¹	R²		yield [%]
OEt	OEt	**3a**	**4a** 45%[a]
N Me		**3b**	**4b** 90%[b]

[a] **1a** (1.0 equiv), 1.0 M.
[b] **1a** (4.0 equiv), 0.10 M.

Next, we investigated the intermediate that formed after the generation of the isobenzofuran intermediate. It has already been reported that an acetal intermediate (in Scheme 1, between steps 8 and 9) was formed by the reaction

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(8) Investigation of several transition-metal complexes: $[ReBr(CO)_3(thf)]_2$, 98%; $Re_2(CO)_{10}$, 80%; $MnBr(CO)_5$, 0%; $Mn_2(CO)_{10}$, 0%; $Ru_3(CO)_{12}$, 0%; $RuH_2(CO)(PPh_3)_3$, 0%; $RhCl(PPh_3)_3$, 0%; $Ir_4(CO)_{12}$, 0%.

(9) Investigation of several additives: aniline, 80%; 4-methoxyaniline, 75%; 4-trifluoromethylaniline, 98%; *N*-methylaniline, 62%; *N*,*N*-dimethylaniline, 0%.

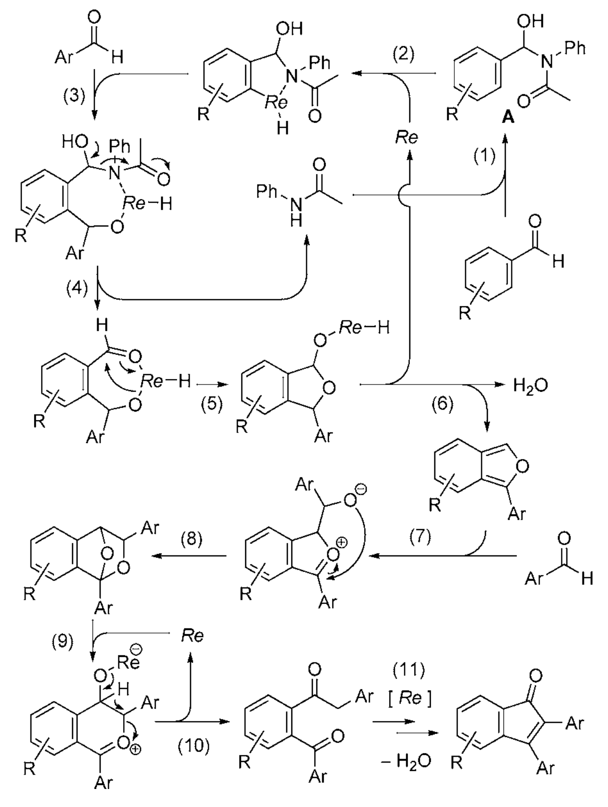
(10) The present reaction requires 180 °C, whereas the reaction reported in ref 3d proceeds at 115 °C. When the reaction was carried out at 115 °C in the presence of catalytic amounts of $ReBr(CO)_5$ and *N*-phenylacetamide, an intermediate, isobenzofuran, was not observed, and benzaldehyde was recovered completely. The result indicates that the formation of the isobenzofurans from 2 equiv of aldehydes requires heating at 180 °C.

(11) In the case of known cyclotrimerizations of aldehydes, 1,3,5-trioxane derivatives are formed. See: (a) Ishii, Y.; Nakano, T. (Daicel Chemical Industries, Ltd.), JP P2002-145877A, 2002. (b) Griesbeck, A. G.; El-Idreesy, T. T.; Fiege, M.; Brun, R. *Org. Lett.* **2002**, *4*, 4193.

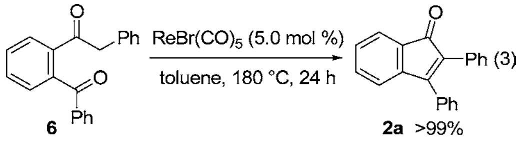
(12) We have already reported the rhenium-catalyzed synthesis of isobenzofuran derivatives via the insertion of aldehydes into a C−H bond of aromatic compounds followed by intramolecular nucleophilic cyclization and dehydration. See ref 3d.

(13) There has been a report on the reaction between 1-phenylisobenzofuran and a dienophile by Diels−Alder reaction. See: Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849.

Scheme 1. Proposed Mechanism for the Formaion of Indenones **2**



between an isobenzofuran derivative and an aldehyde.[14] After the formation of the acetal intermediate, a diketone (in Scheme 1, between steps 10 and 11) would be formed by rearrangement of the acetal. By heating diketone **6** in the presence of ReBr(CO)$_5$, indenone **2a** was obtained quantitatively (eq 3). This result shows that indenones are formed via diketone intermediates.



Based on the above experimental results, the mechanism for the formation of indenones is proposed as follows (Scheme 1): (1) formation of an α-hydroxy amide from an aldehyde and amide;[15] (2) oxidative addition of the C−H bond of the α-hydroxy amide to a rhenium center (C−H bond activation, α-hydroxy amide moiety works as a directing group);[16,17] (3) insertion of another aldehyde into the formed rhenium−carbon bond; (4) elimination of the amide; (5) intramolecular nucleophilic cyclization; (6) reductive elimination and the elimination of H_2O to give an isobenzofuran derivative[3d] and regeneration of the rhenium catalyst; (7) nucleophilic addition of the isobenzofuran derivative to the third aldehyde;[18] (8) intramolecular nucleophilic attack of the alkoxide to the carbon atom of the carbonyl group;[19] (9) ring-opening reaction of the acetal intermediate;[20] (10) formation of a diketone; (11) intramolecular aldol reaction and dehydration leading to an indenone derivative with the rhenium catalyst. This reaction is interesting because a single complex catalyzes the many reaction steps.

In summary, we have succeeded in the rhenium- and amide-catalyzed synthesis of indenone derivatives from 3 equiv of aldehydes. This reaction can be regarded as a new type of dehydrative trimerization of aldehydes. The rhenium complex functions both as a catalyst for C−H bond transformation and a Lewis acid. We hope that this reaction will become a useful method to synthesize indenone derivatives.

Acknowledgment. This work was partially supported by the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: General experimental procedure, characterization data for indenones **2** and naphthalenes **4**, and procedure for the synthesis of diketone **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Yick, C.-Y.; Chan, S.-H.; Wong, H. N. C. *Tetrahedron Lett.* **2000**, *41*, 5957.

(15) Another possibility is the formation of an aldimine from hydroxy amide intermediate **A** by the elimination of acetic acid from **A**, and the C−H activation of the aldimine occurs.

(16) The same reaction also proceeded by adding a catalytic amount of *N*-methylaniline instead of *N*-phenylacetamide. Therefore, we think that the amide might also react with an aldehyde with the nitrogen atom acting as a directing group. For examples of C−H bond transformations using a nitrogen (sp^3) atom as a directing group, see: (a) Diamond, S. E.; Szalkiewicz, A.; Mares, F. *J. Am. Chem. Soc.* **1979**, *101*, 490. (b) Uchimaru, Y. *Chem. Commun.* **1999**, 1133. (c) Kakiuchi, F.; Igi, K.; Matsumoto, M.; Hayamizu, T.; Chatani, N.; Murai, S. *Chem. Lett.* **2002**, 396. (d) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666.

(17) In this reaction, a nitrogen (sp^3) atom [not oxygen (sp^2) atom] is effective as a directing group.

(18) There have been several reports on nucleophilic addition of isobenzofurans to electrophiles. See: (a) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135. (b) Brown, S. N. *Inorg. Chem.* **2000**, *39*, 378.

(19) Instead of steps 7 and 8, the following step could also occur: hetero-Diels−Alder reaction between the formed isobenzofuran intermediate and the third aldehyde. In fact, there has been a report on a Diels−Alder reaction between an isobenzofuran derivative and aldehyde. See ref 13.

(20) A rhenium catalyst, ReBr(CO)$_5$, acted as a Lewis acid even in the presence of H_2O, which is formed by dehydration as shown in Scheme 1, steps 6 and 11.