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Highly Regio- and Stereoselective Ruthenium(II)-Catalyzed Direct *ortho*-Alkenylation of Aromatic and Heteroaromatic Aldehydes with Activated Alkenes under Open Atmosphere

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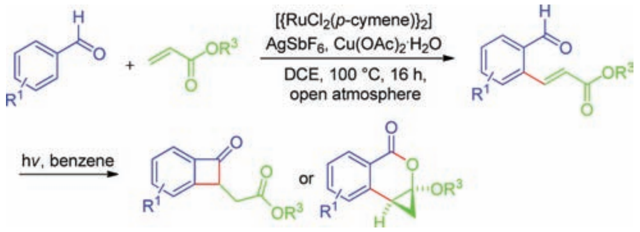
ABSTRACT



Various aromatic and heteroaromatic aldehydes reacted with activated alkenes in the presence of a catalytic amount of [{RuCl$_2$(*p*-cymene)}$_2$], AgSbF$_6$, and Cu(OAc)$_2$·H$_2$O to give substituted alkene derivatives in a highly regio- and stereoselective manner. The corresponding alkene derivatives were further converted into unusual four-membered cyclic ketones or a polycyclic isochromanone derivative via a photochemical rearrangement. Notably, the catalytic reaction was conducted under an open atmosphere.

The transition-metal-catalyzed chelation-assisted C–H bond activation and subsequent alkenylation at the *ortho* position of the aromatic ring with alkenes is a practical and highly atom-economical method to synthesize highly substituted olefins in organic synthesis.[1] This chemistry has been broadly applied to synthesize various natural products, drugs, and materials.[1] In this regard, an initial effort has been paid by Fujiwara's group for the development of alkenylation of electron-rich aromatic C–H bonds with alkenes in the presence of palladium complexes.[2] Later, several palladium-catalyzed directing group assisted couplings of aromatic C–H bonds with alkenes have been

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reported by the groups of Yu, Miura, and others.[3,4] In 2009, Yu's group reported nondirected *meta*-selective alkenylation of aromatics in the presence of palladium complexes.[5] Recently, rhodium(III)-catalyzed chelation-assisted oxidative alkenylation at the *ortho* position of aromatic C−H bonds with alkenes has been demonstrated.[6] And very recently, a few examples of ruthenium(II)-catalyzed chelation-assisted *ortho*-alkenylation of aromatic and heteroaromatic acids with alkenes have been described.[7] The directing groups frequently used in this Heck-type alkenylation reaction include amine, COOH, phenol, OH, oxime, imine, amide, pyridyl, ketone, and ester groups. Despite such significant diversity of directing groups, a weakly coordinating CHO-directed *ortho*-alkenylation of substituted aromatics with alkenes has not been explored in the literature.[8]

A number of competitive reactions such as decarbonylation and hydroacylation could be possible in the coupling of substituted aldehydes with alkenes in the presence of metal complexes.[9] Thus, the control of the competitive reactions is crucial to make this type of reaction beneficial to organic synthesis. Moreover, in most of the metal-catalyzed C−H bond activation reactions, a stoichiometric amount of oxidant is used to regenerate the active catalyst. These oxidants most likely oxidize aldehydes into acids subsequently in a facile manner. These types of competitive reactions seriously restrict the scope of aldehydes in C−H bond functionalization reactions. Recently, we demonstrated a ruthenium-catalyzed coupling of aromatic and heteroaromatic ketones with alkenes and cyclization of aromatic and heteroaromatic ketones and acids with alkynes in the presence of a catalytic amount of silver salt and $Cu(OAc)_2 \cdot H_2O$.[10] In these reactions, $Cu(OAc)_2 \cdot H_2O$ provided the acetate source to the ruthenium species in order to facilitate *ortho*-metalation by concerted deprotonation metalation pathway.[1c] These reactions were moisture-insensitive, and the remaining amount of active $Cu(OAc)_2$ source was regenerated by oxygen or atmosphere. These results prompted us to explore the possibility of using a catalytic amount of $Cu(OAc)_2 \cdot H_2O$ as a terminal oxidant in the Heck-type coupling of aromatic aldehydes with alkenes. Herein, we wish to report oxidative coupling of aromatic aldehydes with alkenes in the presence of a catalytic amount of $[\{RuCl_2(p\text{-cymene})\}_2]$, $AgSbF_6$, and $Cu(OAc)_2 \cdot H_2O$, giving alkene derivatives in good to moderate yields under open atmosphere in a highly regio- and stereoselective manner. The catalytic reaction was also compatible with heteroaromatic aldehydes. It is important to note that no decarbonylation of aldehydes, hydroacylation of aldehydes with alkenes, and oxidation of aldehydes to acids were observed in the reaction. The observed alkene derivatives were further converted into unusual four-membered cyclic ketones or polysubstituted isochromanone derivatives via a photochemical rearrangement.

When piperonal (**1a**) was treated with methyl acrylate (**2a**) in the presence of a catalytic amount of $[\{RuCl_2(p\text{-cymene})\}_2]$ (3 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (50 mol %) in 1,2-dichloroethane at 100 °C for 16 h under open atmosphere, a substituted alkene derivative **3a** was observed in 47% isolated yield with very high *E*-stereoselectivity. The catalytic reaction was also highly regioselective. In the substrate **1a**, there are two *ortho* aromatic C−H bonds for coupling. Very selectively, the alkenylation reaction takes place at the sterically hindered C−H bond of **1a** moiety predominately. In order to improve the yield, the catalytic reaction was carried out with longer reaction time (24 h), higher reaction temperature (130 °C), and more ruthenium catalytic loading (10 mol %). However, in these conditions, no improvement in the yield of **3a** was observed. Then, the reaction was carried out with an excess amount of methyl acrylate (**2a**) (6.0 equiv). The catalytic reaction proceeded well and gave **3a** in 84% isolated yield. The reaction did not proceed in the absence of either copper source or silver salt. Notably, the present

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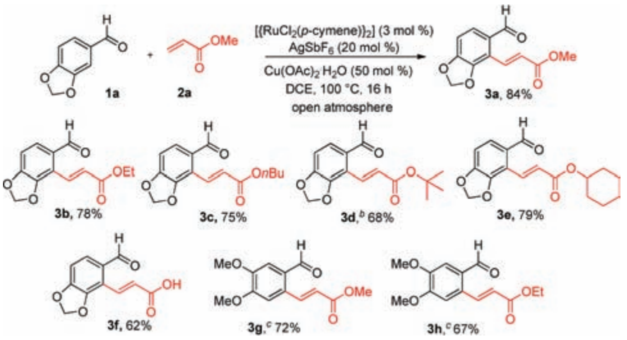
ruthenium-catalyzed open atmosphere reaction is inexpensive and environment-friendly for synthesizing 2-formyl phenylalkeno-derivatives **3** in a highly regio- and stereoselective manner.

Scheme 1. Alkenes Scope[a]

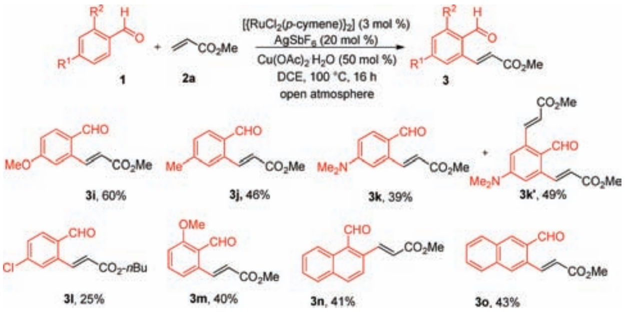


[a] All reactions were carried out using aldehydes **1a** and **1b** (1.0 mmol), alkenes **2** (**2a**–**b** in 6.0 mmol and **2c**–**f** in 5.0 mmol), [{RuCl$_2$(*p*-cymene)}$_2$] (3 mol %), AgSbF$_6$ (20 mol %), and Cu(OAc)$_2$·H$_2$O (50 mol %) in DCE at 100 °C for 16 h. Reported yields are for the isolated products. [b] The reaction was carried out in *tert*-BuOH. [c] Cu(OAc)$_2$·H$_2$O (2.0 mmol) was used for the reaction.

The scope of the present alkenylation reaction was further extended to various substituted activated alkenes (Scheme 1). Piperonal (**1a**) underwent alkenylation reaction with ethyl acrylate (**2b**) under similar reaction conditions to afford **3b** in 78% yield. Likewise, *n*-butyl acrylate (**2c**), *tert*-butyl acrylate (**2d**), and cyclohexyl acrylate (**2e**) afforded alkenylation products **3c**–**e** in 75, 68, and 79% yields, respectively. An acrylic acid was also a good coupling partner for this reaction. Thus, acrylic acid (**2f**) underwent coupling with piperonal (**1a**) to give an alkenylated product **3f** in 62% yield. These reactions were also highly regio- and stereoselective as like **3a**, whereas 3,4-dimethoxy benzaldehyde (**1b**) reacted with methyl acrylate (**2a**) to give an different type of regioselective product **3g** in 72% yield with very high *E*-stereoselectivity. In the substrate **1b** also, there are two *ortho* aromatic C–H bonds for coupling. Very selectively, the alkenylation reaction takes place predominately at the sterically less hindered C–H bond of **1b** moiety. Similarly, **1b** reacted with ethyl acrylate (**2b**) to provide an alkenylated product **3h** in 67% yield in a highly regio- and stereoselective manner.

This alkenylation reaction was successfully extended to various aromatic aldehydes **1** with methyl acrylate (**2a**) (Scheme 2). Thus, treatment of 4-methoxy benzaldehyde (**1c**), 4-methyl benzaldehyde (**1d**), and 4-dimethylamino benzaldehyde (**1e**) with methyl acrylate (**2a**) gave the corresponding alkenylated compounds **3i**–**k** in 60, 46, and 39% yields, respectively. In the reaction of 4-dimethylamino benzaldehyde (**1e**) with **2a**, in addition to mono alkenylation product **3k** in 39% yield, bis alkenylation product **3k′** was also observed in 49% yield. 4-Chloro benzaldehyde (**1f**) also reacted with *n*-butyl acrylate (**2c**) to provide a 2-formyl phenylalkeno-derivative **3l** in a low 25% yield. 2-Methoxy benzaldeyde (**1g**) also participated in the reaction, giving an alkenylated product **3m** in 40% yield. The reaction of 1-napthaldehyde (**1h**) with **2a** gave the corresponding coupling product, **3n**, in 41% yield. Under similar reaction conditions, 2-napthaldehyde (**1i**) reacted with **2a** to give an alkenylated product **3o** regioselectively in 43% yield, in which C3–H of 2-napthaldehyde was involved in the coupling reaction with **2a** selectively. The catalytic reaction was also tested with 4-cyano benzaldehyde and 4-methylester benzaldehyde. However, in these reactions, no expected coupling products were observed. It appears that the yield of this catalytic reaction is highly sensitive to the type of substituent used on the aromatic ring of aldehydes. Electron-rich substituents such as dioxole, OMe, Me, and NMe$_2$ on the aromatic ring gave the highest product yield, while the electron-withdrawing substituents such as Cl, CN, and CO$_2$Me afforded the lowest yield or no product.

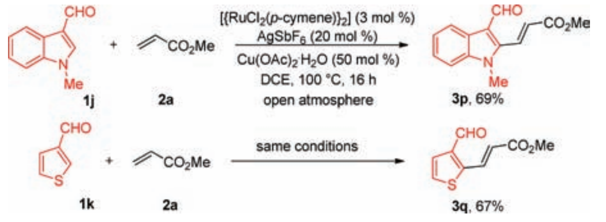
Scheme 2. Aldehydes Scope[a]



[a] All were carried out using aldehydes **1** (1.0 mmol), methyl acrylate (**2a**) (6.0 mmol), [{RuCl$_2$(*p*-cymene)}$_2$] (3 mol %), AgSbF$_6$ (20 mol %), and Cu(OAc)$_2$·H$_2$O (50 mol %) in 1,2-dichloroethane at 100 °C for 16 h under open atmosphere.

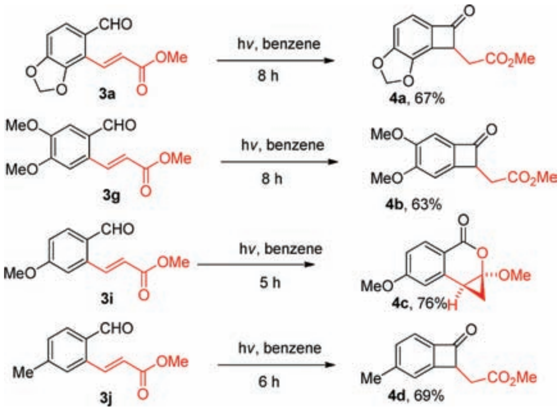
Heterocyclic aldehydes were also compatible for the present C–H bond activation reaction (Scheme 3). Thus, 1-methylindole-3-carboxaldehyde (**1j**) and 3-formylthiophene (**1k**) reacted with **2a** to give the corresponding coupling products **3p** and **3q** in 69 and 67% yields, respectively. The reaction tolerates a variety of functional groups such as Br, Cl, OMe, S, dioxole, and NMe$_2$ on the aromatic and heteroaromatic ring of aldehydes (Schemes 2 and 3).

Scheme 3. Heteroaromatic Aldehydes Scope



A synthetic application of product **3** in organic synthesis is shown in Scheme 4. The 2-formyl phenylalkeno-derivatives **3** were further converted into unusual four-membered cyclic

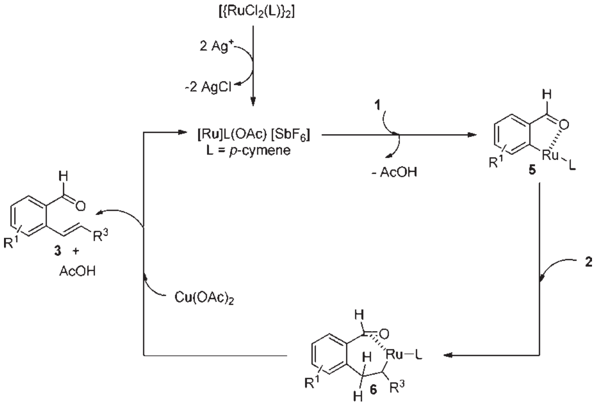
Scheme 4. Photochemical Rearrangement



ketones and a polysubstituted isochromanone derivative via a photochemical rearrangement.[11] Thus, when irradiation of **3a** in a benzene solution with a 450 W medium pressure mercury vapor lamp for 8.0 h was performed, a four-membered cyclic ketone **4a** was observed in 67% yield. Similarly, the irradiation of **3g** under similar reaction conditions for 8 h gave a four-membered cyclic ketone **4b** in 63% yield. Surprisingly, with the irradiation of **3i** in a benzene solution with a 450 W medium pressure mercury vapor lamp for 5.0 h, a polysubstituted isochromanone derivative **4c** was observed in 76% yield.[11] But, **3j** under similar reaction conditions gave a four-membered cyclic ketone **4d** in 69% yield. It is important to point out that isochromanone derivatives are widely occurring natural products that show various biological activities.[10c,11]

A plausible mechanistic rationale of coupling of aromatic and heteroaromatic aldehydes with alkenes is proposed in Scheme 5. The catalytic reaction is likely initiated by the removal of chloride ligand by Ag^+ salt from [{$RuCl_2$(*p*-cymene)}$_2$] complex. Coordination of the carbonyl oxygen of **1** to the ruthenium cationic species followed by *ortho*-metalation provides a five-membered ruthenacycle **5**.[1c] Coordinative insertion of alkene **2** into the Ru–carbon bond of ruthenacycle **5** affords an intermediate **6**. β-Hydride elimination from intermediate **6** in the presence of $Cu(OAc)_2 \cdot H_2O$ gives the final product **3** and regenerates the active ruthenium species for the next catalytic cycle. In the reaction, the remaining amount of active $Cu(OAc)_2$ source was regenerated under oxygen or atmosphere from the reduced copper source.

Scheme 5. Proposed Mechanism



In conclusion, we have demonstrated a ruthenium-catalyzed *ortho*-alkenylation of aromatic and heteroaromatic aldehydes with activated alkenes to afford substituted alkene derivatives in good to moderate yields. Further extension of the C–H bond activation of other chelating group substituted aromatics and functionalization with other π-components and detailed mechanistic investigations are in progress.

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Supporting Information Available. General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.

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