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Ruthenium-catalyzed regioselective oxidative coupling of aromatic and heteroaromatic esters with alkenes under an open atmosphere†

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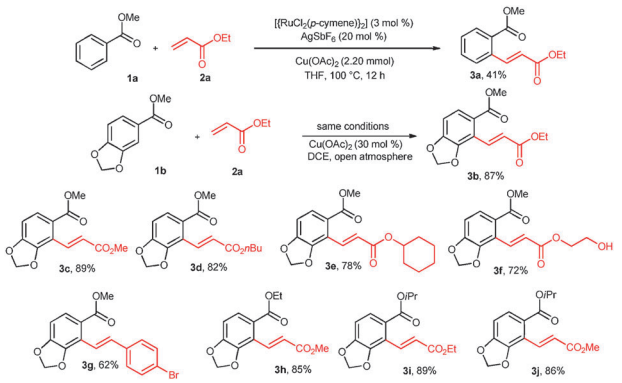
A ruthenium-catalyzed oxidative coupling of substituted aromatic and heteroaromatic esters with alkenes in the presence of catalytic amounts of $AgSbF_6$ and $Cu(OAc)_2$ to provide highly substituted alkene derivatives in good to excellent yields under an open atmosphere is described.

Chelation-assisted *ortho* C–H bond activation of directing group substituted aromatics and subsequent alkenylation with alkenes catalyzed by transition metal complexes is an efficient method for synthesizing substituted olefins in a highly regio- and stereoselective manner.[1] These reactions are environmentally friendly and highly atom-economical when compared with the other conventional methods such as carbon-halide functionalization.[2] In 1968, Fujiwara *et al.* demonstrated a palladium-catalyzed alkenylation of electron-rich aromatics with alkenes by C–H bond activation.[3] In 1986, Lewis's group showed a ruthenium-catalyzed *ortho* ethylation of phenol with ethylene.[4a] In 1993, Murai's group described a ruthenium-catalyzed heteroatom-directed *ortho* C–H bond activation of substituted aromatics and subsequent addition with alkenes leading to substituted alkane derivatives.[4b,c] Later, palladium-catalyzed heteroatom-directed *ortho*-alkenylation of substituted aromatics with alkenes *via* C–H bond activation has been demonstrated by the groups of Yu, Miura and others.[5,6] A *meta*-selective alkenylation of aromatics with alkenes catalyzed by a palladium pyridine complex has been illustrated by Yu and Sanford *et al.*[7] Subsequently, this type of heteroatom-directed *ortho*-alkenylation of substituted aromatics with alkenes in the presence of a rhodium catalyst has been successfully extended by the groups of Miura, Glorius and others.[8] Recently, a less expensive ruthenium complex has gained much attention in this type of reaction.[9,10] In this reaction, $Cu(OAc)_2$ has been used as an internal oxidant. This oxidant provides the acetate source to the ruthenium species which facilitates *ortho*-metalation by a concerted deprotonation metalation pathway.[1f]

Various directing groups such as amines, oximes, amides, pyridyl, COOH, phenol, OH and carbonyl can be used in the metal-catalyzed *ortho* alkenylation reactions. In the presence of strong directing groups, C–H bond activation reactions are facile. But, activation in the presence of weak directing groups such as aldehydes, esters, cyano and ketones are still a challenging task.[10] Herein, we would like to report *ortho*-alkenylation of aromatic esters with alkenes in the presence of catalytic amounts of $[\{RuCl_2(p\text{-cymene})\}_2]$, $AgSbF_6$ and $Cu(OAc)_2$, affording highly substituted alkene derivatives in a highly regio- and stereoselective manner. The catalytic reaction is also compatible with various heteroaromatic esters. Interestingly, the present ruthenium-catalyzed alkenylation reaction is carried out under an open atmosphere and only a catalytic amount of $Cu(OAc)_2$ has been used as a terminal oxidant, the reduced copper source being reoxidized by air.[9f,10]

Treatment of methyl benzoate (**1a**) with ethyl acrylate (**2a**) in the presence of catalytic amounts of $[\{RuCl_2(p\text{-cymene})\}_2]$ (3 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2$ (2.20 mmol) in THF at 100 °C for 12 h gave an alkene derivative **3a** in 41% isolated yield (Scheme 1). To improve the yield of the reaction, in addition to an ester directing group, a very weak directing group such as 1,3-dioxol (–O–CH_2–O–) was introduced at 3 and 4 positions of methyl benzoate **1a** in order to further activate the aromatic C–H bond efficiently. Interestingly, in the reaction of methyl piperonate (**1b**) with ethyl acrylate (**2a**) under similar reaction conditions, the corresponding alkenylated compound **3b** was obtained in excellent 85% isolated yield with a high *E*-stereoselectivity. The catalytic reaction is also regioselective and alkenylation takes place selectively at the sterically hindered C–H bond of **1b** whereby both ester and 1,3-dioxol substituents act as directing groups. Thus, C–H bond activation takes place selectively at the sterically hindered C–H bond. Next, the same



Scheme 1 Scope of alkenes **2a–f** with piperonates **1b–d**.

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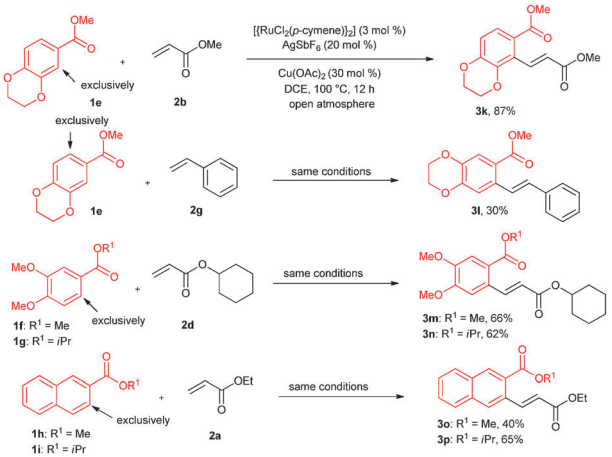
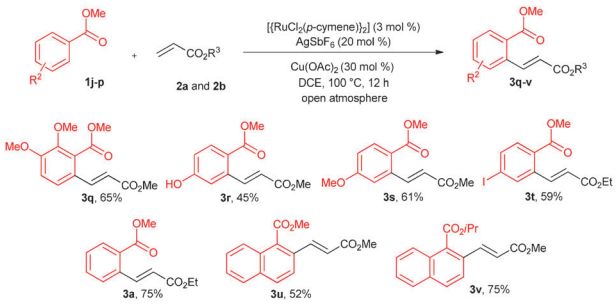
coupling reaction was carried out under an open atmosphere in the presence of $Cu(OAc)_2$ (0.30 mmol, 30 mol%) under similar reaction conditions. Interestingly, the corresponding alkene derivative **3b** was observed in 86% yield. The catalytic reaction was also tested with various solvents such as CH_3CN, toluene, MeOH, *tert*-BuOH, DMF, DME, DMA and DMSO. Among them, DCE (1,2-dichloroethane) solvent was equally effective for the reaction similar to that with THF, giving the coupling product **3b** in 87% yield under an open atmosphere in the presence of $Cu(OAc)_2$ (0.30 mmol, 30 mol%). Remaining solvents were totally ineffective for the reaction. However, the catalytic reaction did not proceed in the absence of either a copper source or silver salt.

Under similar reaction conditions, various acrylates **2b–e** were effectively coupled with substituted piperonates **1b–d** (Scheme 1). Thus, the reaction of methyl piperonate (**1b**) with methyl acrylate (**2b**), *n*-butyl acrylate (**2c**) and cyclohexyl acrylate (**2d**) afforded the corresponding alkenylated products **3c–e** in 89%, 82% and 78% yields, respectively. Very interestingly, 2-hydroxyethyl acrylate (**2e**) is also efficiently involved in the coupling reaction giving product **3f** in 72% yield. The catalytic reaction was also tested with styrenes. Thus, 4-bromostyrene (**2f**) reacted smoothly with **1b** yielding an alkenylated product **3g** in 62% yield. Next, the effect of replacing the methyl group in methyl piperonate (**1b**) by other substituents such as ethyl and isopropyl groups was investigated. Thus, ethyl piperonate (**1c**) reacted nicely with methyl acrylate (**2b**) affording compound **3h** in 85% yield. Similarly, isopropyl piperonate (**1d**) underwent coupling with ethyl and methyl acrylates **2a** and **2b** yielding coupling products **3i** and **3j** in 89% and 86% yields, respectively. These reactions were also highly regio- and stereoselective similar to that with **3b**.

In addition to **1b–d**, the regioselectivities of other unsymmetrical aromatic esters **1e–i** were also examined under the same reaction conditions (Scheme 2). The reaction of methyl 1,4-benzodioxane-6-carboxylate (**1e**) with methyl acrylate (**2b**) provided substituted alkene derivative **3k** in 87% yield in a highly regio- and stereoselective manner. Similar to that of **1b–d**, coupling reaction takes place at the sterically hindered C–H bond of **1e**. In contrast, **1e** reacted with styrene (**2g**) giving substituted *E*-stilbene derivative **3l**, albeit in only 30% yield in an opposite regiochemistry. In the reaction, the remaining amount of 70% of starting material **1e** was recovered. In the reaction, C–H bond activation takes place at the sterically less hindered C–H bond of **1e**. Similarly, methyl



Scheme 2 Regioselective studies of substituted aromatic esters.



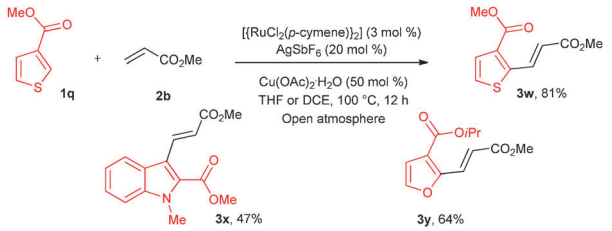
Scheme 3 Scope of aromatic esters.

3,4-dimethoxybenzoate (**1f**) and isopropyl 3,4-dimethoxybenzoate (**1g**) also regioselectively coupled with cyclohexyl acrylate (**2d**) providing coupling products **3m** and **3n** in 66% and 62% yields, respectively, in a highly regio- and stereoselective manner. In this case also, C–H bond activation takes place at the sterically less hindered C–H bond of **1f** and **1g**. A similar type of regioselective product **3o** in moderate 40% yield was observed in the reaction of methyl 2-naphthoate (**1h**) with ethyl acrylate (**2a**) under similar reaction conditions. Interestingly, isopropyl 2-naphthoate (**1i**) reacted efficiently with **2a** yielding the corresponding alkene derivative **3p** in good 65% yield.

The present alkenylation reaction was tested with various substituted aromatic esters **1** and ethyl or methyl acrylates (**2a** and **2b**) under the optimized reaction conditions (Scheme 3). The reaction of methyl 2,3-dimethoxybenzoate (**1j**) with methyl acrylate (**2b**) afforded coupling product **3q** in 65% yield. Methyl 4-hydroxybenzoate (**1k**) reacted with **2b** providing **3r** albeit in moderate 45% yield. Whereas, methyl 4-methoxybenzoate (**1l**) reacted with **2b** affording **3s** in 61% yield. Methyl 4-iodobenzoate (**1m**) also efficiently participated in the reaction giving the corresponding alkene derivative **3t** in 59% yield. Whereas, methyl 2-iodobenzoate (**1n**) reacted with **2a** providing coupling product **3a** in 75% yield, in which the *ortho* I group of **1n** participates in the coupling reaction *via* oxidative addition.[2] Methyl 1-napthoate (**1o**) reacted with **2b** affording the corresponding alkenylated derivative **3u** only in 52% yield. The yield of coupling product **3v** can be improved up to 75% by replacing the methyl group by an isopropyl group in 1-naphthoate (**1p**). The catalytic reaction was also tested with various electron-withdrawing group substituted aromatic esters such as methyl 4-nitrobenzoate and methyl 4-trifluorobenzoate under similar reaction conditions. However, in the reaction, no coupling product was observed and only starting material was recovered. It seems that electron-withdrawing group substituted aromatic ester was not a compatible substrate for the present coupling reaction.

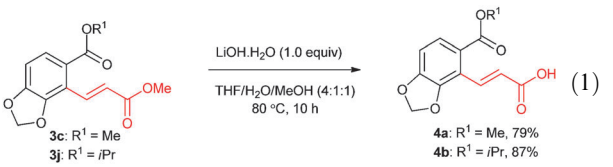
The present catalytic reaction was also examined with various heterocyclic esters (Scheme 4). Thus, methyl thiophene-3-carboxylate (**1q**) underwent coupling reaction with methyl acrylate (**2b**) providing an alkene derivative **3w** in 81% yield. Substituted indole (**1r**) and isopropyl furan-3-carboxylate (**1s**) also efficiently reacted with methyl acrylate (**2b**) giving the corresponding alkenylated products **3x** and **3y** in 47% and 64% yields, respectively. In the substrate **1r**, C–H bond activation takes place nicely at electron-rich C3–H carbon.

Next, the selective de-esterification of aromatic group substituted ester of compounds **3c** and **3j** was tried in the presence of $LiOH{\cdot}H_2O$ (1.0 equiv.) in $THF : H_2O : MeOH$



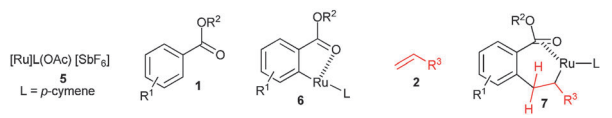
Scheme 4 Scope of heteroaromatic esters.

(4 : 1 : 1) at 80 °C for 12 h. Surprisingly, in the reaction, de-esterification takes place very selectively at unsaturated ester providing substituted carboxylic acids **4a** and **4b** in 79% and 87% yields, respectively (eqn (1)). An ester group connected with aromatic moieties of **3c** and **3j** remains intact. For selective de-esterification of aromatic group substituted ester, the reaction was tried with various bases such as NaOH and KOH under the same reaction conditions. In these reactions also, de-esterification selectively takes place at unsaturated ester. The coupling reaction of methyl piperonate (**1b**) with acrylic acid (**2h**) was tried under the optimized reaction conditions. However, in the reaction, coupling product **4a** was not observed and only acrylic acid dimerization was observed. By using the present de-esterification reaction, substituted acrylic acid derivatives can be synthesized in excellent yields.



(1)

The catalytic reaction proceeds *via* reaction of the [{$RuCl_2$(*p*-cymene)}$_2$] complex with $AgSbF_6$ giving cationic ruthenium complex **5** (eqn (2)). Coordination of the carbonyl oxygen of aromatic ester **1** to the ruthenium cationic species **5** followed by *ortho*-metalation affords ruthenacycle intermediate **6** (eqn (2)).[1f] Insertion of alkene **2** into the Ru–carbon bond of intermediate **6** provides a seven-membered ruthenacycle intermediate **7** (eqn (2)). β-Hydride elimination of intermediate **7** yields coupling product **3** and regenerates the active ruthenium species for the next catalytic cycle. The remaining amount of the active $Cu(OAc)_2$ source is regenerated under an atmosphere from the reduced copper source such as CuOAc.



(2)

In conclusion, we have developed a ruthenium-catalyzed highly regioselective *ortho*-alkenylation of aromatic and heteroaromatic esters with alkenes giving substituted alkene derivatives in a highly stereoselective manner. Further extension of the C–H bond activation of other directing group substituted aromatics and functionalization with other π-components and the detailed mechanistic investigation are in progress.

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