ORGANIC LETTERS
2011
Vol. 13, No. 9
2372–2375

Rhodium-Catalyzed Selective Olefination of Arene Esters via C–H Bond Activation

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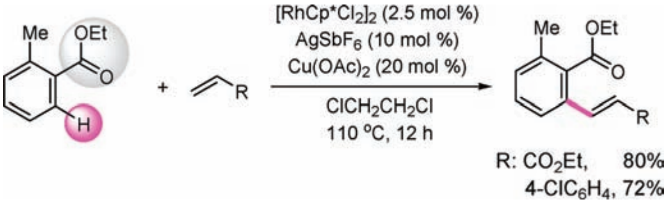
Received March 7, 2011

ABSTRACT

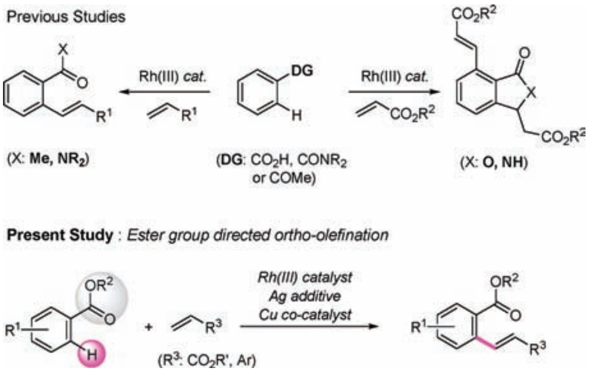


A new catalytic procedure of *ortho*-olefination of benzoates and benzaldehydes has been developed. Ester and carboxaldehyde units were revealed to be effective chelating groups in focusing the activation of aryl C–H bonds *ortho* to the directing moieties under the Rh-catalyzed oxidative conditions. The reaction is highly regioselective with a range of benzoates and benzaldehydes enabling the efficient olefination with acrylates, acrylic acid, and styrenes.

Transition-metal-catalyzed C–H bond activation has attracted much attention, and its synthetic applications have been elegantly demonstrated in organic synthesis, medicinal chemistry, and materials science.[1] Selectivity in the activation process can be controlled by suitably positioned directing groups. As a result, a wide range of coordinating moieties have been utilized for the efficient activation of C–H bonds. Among those, carbonyl groups are especially noteworthy because they are widely available and readily interconvertible with other functional groups. For this purpose, carboxylic acids, amides, or acetyls are frequently employed as chelating groups. In fact, there are elegant examples revealing that carboxylic acids are utilized as an effective controlling group in the C–H bond functionalization.[2]

Furthermore, arene or alkane amides can be arylated selectively under catalytic conditions.[3] Alkyl and aryl ketones are also used in the Ru- or Pd-catalyzed arylation to react with aryl boronates or halides, respectively.[4] Rhodium catalytic systems have been extensively investigated in the chelation-assisted C–H bond activation of carbonyl group containing compounds or their equivalents.[5] In particular, rhodium(III) catalysts bearing a cyclopentadienyl (Cp) ligand have been recently employed for the C–H bond functionalization.[6,7]

Scheme 1. Rh-Catalyzed Olefination of Carbonyl Compounds



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[1] For recent reviews on the C–H bond activation and its synthetic applications, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

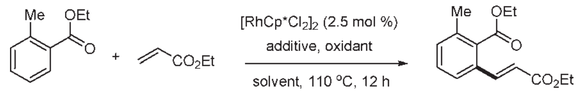
[2] Carboxylic acids as a directing group: (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (c) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (d) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

[3] Amides as a directing group: (a) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190.

10.1021/ol200600p

For instance, a range of substrates having carboxylic acid, carboxamide, or acetyl groups are readily olefinated under Rh-catalyzed oxidative conditions (Scheme 1).[8] It was demonstrated that acetophenones or benzamides are suitable substrates for the *ortho*-olefination using the Rh(III) catalytic system.[6g] In addition, oxime has been revealed as excellent directing group in the Rh-catalyzed oxidative aryl coupling with unactivated alkenes.[6h] Despite these significant contributions, there is still room for further improvement with regard to substrate scope and reaction conditions. For example, esters or carboxaldehydes are seldom used as directing groups in catalytic C−H bond functionalization.[9] This aspect is noteworthy since those functional groups are not only readily available but also easily converted to others such as alcohols, amides, or other carbonyl compounds.[10] During the course of our studies,[11] we found that *an ester or carboxaldehyde moiety works as an efficient directing group in the Rh(III)-catalyzed olefination of benzoates or benzaldehydes*.[12]

Table 1. Optimization of Reaction Conditions[a]



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

entry	additive (mol %)	oxidant (equiv)	solvent	yield (%)[b]
1[c]	None	$Cu(OAc)_2$ (1.5)	1,2-DCE	<1
2[c]	$AgSbF_6$(20)	None	1,2-DCE	15
3[c]	$AgSbF_6$(20)	$Cu(OAc)_2$ (1.5)	1,2-DCE	84
4	$AgSbF_6$(10)	$Cu(OAc)_2$ (1.5)	1,2-DCE	80
5[d]	$AgSbF_6$(4)	$Cu(OAc)_2$ (1.5)	1,2-DCE	60
6	$AgSbF_6$(10)	Cu(OAc) (1.5)	1,2-DCE	82
7	$AgSbF_6$(10)	Ag_2CO_3 (1.5)	1,2-DCE	12
8	$AgSbF_6$(10)	$Cu(OAc)_2$ (1.5)	^{t}AmylOH	44
9	$AgSbF_6$(10)	$Cu(OAc)_2$ (1.5)	DMF	<1
10	$AgSbF_6$(10)	$Cu(OAc)_2$ (1.5)	*o*-Xylene	<1
11	$AgBF_4$(10)	$Cu(OAc)_2$ (1.5)	1,2-DCE	10
12	$AgSbF_6$(10)	$Cu(OAc)_2$ (0.2)	1,2-DCE	80
13[e]	$AgSbF_6$(10)	O_2	1,2-DCE	<1
14[f]	None	$Cu(OAc)_2$ (0.2)	1,2-DCE	78

[a] Conditions: **1d** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive, and oxidant with solvent (0.7 mL) for 12 h at 110 °C in a screw-capped vial. [b] NMR yield. [c] 5 Mol % of $[RhCp^*Cl_2]_2$ was used. [d] 1 Mol % of $[RhCp^*Cl_2]_2$ was used. [e] Carried out in a pressure tube. [f] Carried out with $[RhCp^*(MeCN)_3][SbF_6]_2$ (5 mol %).

Ethyl 2-methylbenzoate was chosen as a test substrate to react with ethyl acrylate using a rhodium(III) catalyst under various conditions (Table 1). We were pleased to observe that the $[RhCp^*Cl_2]_2$ species (5 mol %) exhibited notable catalytic activity to afford the desired product in high NMR yield in the presence of $AgSbF_6$ (20 mol %) and 1.5 equiv of $Cu(OAc)_2$ (entry 3), whereas poor results were obtained in the absence of either additives (entries 1−2). The generated double bond was in an *E*-form almost exclusively. The olefination proceeded smoothly even with lower amounts of Rh catalyst (1 mol %, entry 5). While a similar catalytic activity of the rhodium catalyst was maintained with the use of a Cu(I) oxidant (entry 6), the same equivalent of silver carbonate resulted in a decreased yield (entry 7).

1,2-Dichloroethane was the solvent of choice; other media provided a sluggish olefination (entries 8−10).

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(8) For recent examples of the oxidative olefination or olefin hydroarylation of electron-deficient arenes, see: (a) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (b) Sun, Z.-M.; Zhang, J.; Manan, R. S.; Zhao, P. *J. Am. Chem. Soc.* **2010**, *132*, 6935. (c) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506.

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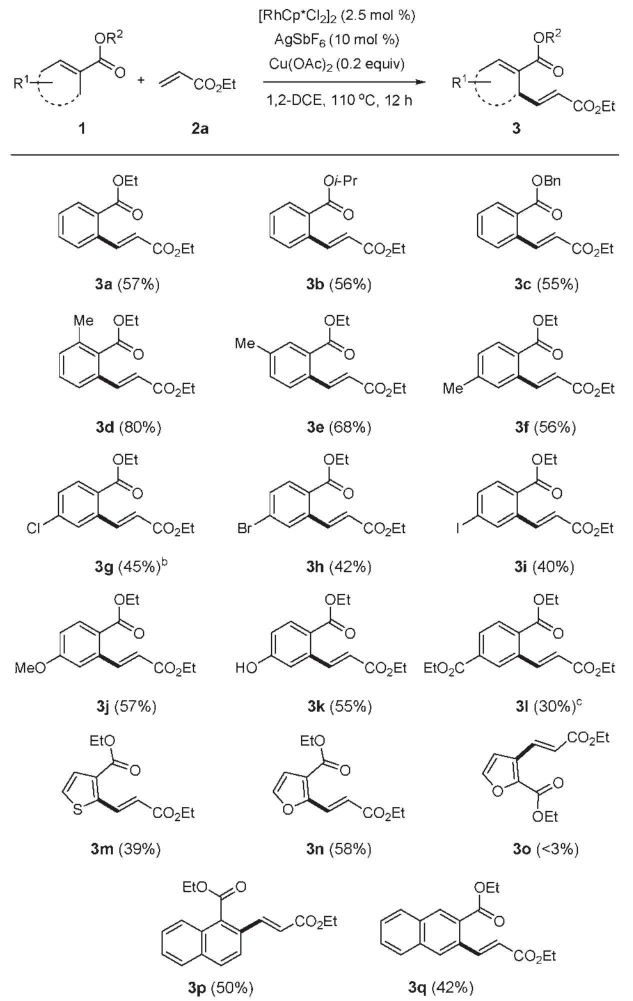
(12) During the preparation of this manuscript, Glorius et al. reported the Rh-catalyzed olefination of acetophenones (ref 6g). In this work, it was briefly shown as a footnote (ref 19) that an ester group directed olefination of ethyl benzoate with styrene took place using the same Rh catalyst (2.5 mol %, dioxane, 140 °C, 16 h) in 33% yield.

Silver additives other than $AgSbF_6$ were inferior (e.g., entry 11). The olefination proceeded smoothly even with a catalytic copper oxidant (entry 12).[6f,13] However, reaction under atmospheric oxygen did not give the desired product in the absence of a copper species (entry 13).[14] The use of a pregenerated cationic rhodium species as a catalyst afforded a similar product yield in the absence of a silver additive (entry 14),[15] thus indicating that the silver additive generates a cationic rhodium species *in situ*.

Scheme 2. *Ortho*-olefination of Arene Esters[a]



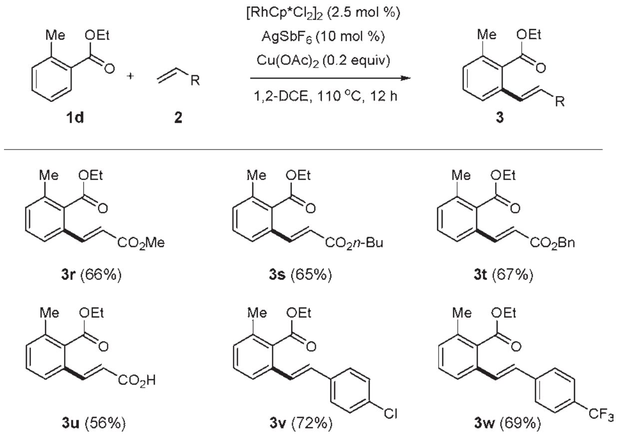
[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2$ (0.2 equiv) with 1,2-dichloroethane (0.7 mL) for 12 h at 110 °C in a screw-capped vial; yields of isolated products. [b] 1.5 equiv of $Cu(OAc)_2$ was used. [c] Double olefinated compounds were also produced in 9% yield as a mixture of 2,6- and 2, 5-isomeric bis-olefins.

To explore the substrate scope, we examined various types of arene esters in the reaction with ethyl acrylate as a counterpart (Scheme 2). It was observed that alteration of an alkoxy part of benzoates did not change the reaction efficiency, and a similar level of product yields was obtained in the olefination of ethyl, isopropyl, and benzyl benzoates (**3a**, **3b**, and **3c**, respectively).

It is noted that the moderate yields observed in the olefination of unsubstituted benzoates can be ascribed to the formation of bisolefinated compounds albeit as minor side products (< 5%).[16] The position of an additional substituent on substrates had little effect on the reaction efficiency as shown in the cases of ethyl benzoates bearing a methyl substituent at the 2-, 3-, or 4-position (**3d**, **3e**, and **3f**, respectively).

High regioselectivity was observed in the reaction of ethyl 3-methylbenzoate leading to olefination only at the C−H bond *para* to the methyl substituent presumably due to steric reasons (**3e**). Functional group tolerance was high as demonstrated in the reaction of ethyl benzoates bearing chloro, bromo, and iodo groups, albeit product yields were rather modest (**3g**−**3i**). While ethyl 4-methoxybenzoate underwent the olefination moderately (**3j**), reaction of an unprotected hydroxy-containing substrate provided the desired product (**3k**) with an acceptable yield, again showing high functional group tolerance. A substrate bearing two esteric moieties such as diethyl terephthalate underwent the olefination to give a mono-olefinic product (**3l**) as the major product in addition to a mixture of isomeric double olefinic compounds as minor products. A range of heterocyclic esters were next examined. For example, ethyl thiophene-3-carboxylate and ethyl furan-3-carboxylate underwent the olefination exclusively at the 2-position albeit in moderate yields (**3m** and **3n**).

Scheme 3. *Ortho*-olefination of Ethyl Benzoates[a]



[a] Conditions: **1d** (0.2 mmol), **2** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2$ (0.2 equiv) with 1,2-dichloroethane (0.7 mL) for 12 h at 110 °C in a screw-capped vial; yield of isolated products.

However, poor reactivity was observed in the reaction of heterocyclics bearing an ester moiety at the 2-position (e.g.,

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(13) (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (b) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326.

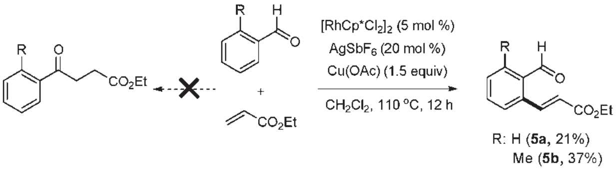
(14) Product yields were obtained from reactions under either O_2 or air atmosphere when catalytic amounts of copper additives were used.

(15) White, C.; Thompson, S. J.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1977**, 1654.

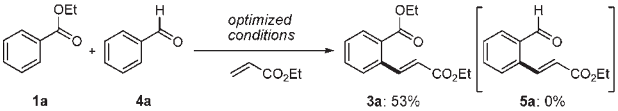
(16) When two reactants (**1a** and **2a**) were employed with the same ratio (1:1), **3a** was obtained in 26%.

3o). When ethyl 1-naphthoate was subjected to the optimal conditions, a single regioisomer (**3p**) was obtained. In addition, the regioselectivity still remained high in the case of ethyl 2-naphthoate leading to **3q** olefinated only at the 3-position of the naphthyl ring.

With the above promising results in hand, we next investigated the scope of alkene reactants in the olefination of ethyl 2-methylbenzoate (**1d**) under the optimized conditions (Scheme 3). As expected, acrylates of various alcohols were all smoothly reacted to afford the corresponding products in good yields (**3r**, **3s**, and **3t**). In addition, it was found that acrylic acid itself was olefinated with a similar efficiency to give an *E*-cinnamic acid derivative (**3u**) in moderate yield. Moreover, it was seen that styrenes readily underwent the olefination reaction. Indeed, a reaction of **1d** with a range of styrenes proceeded smoothly to furnish stilbene ester derivatives in synthetically useful yields (**3v** and **3w**).

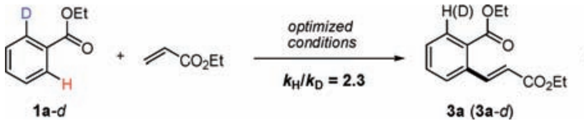


(1)



(2)

It was interesting to observe that a carboxaldehyde unit works as a directing group enabling selective olefination albeit in moderate yield (eq 1).[4b,17] This result is significant in that no hydroacylation adduct was observed under the conditions.[18] However, a significant amount of hydrodecarbonylation compounds were formed as the byproduct that is responsible for the low product yields in benzaldehydes. When a competition experiment was performed between ethyl benzoate and benzaldehyde, the olefination took place only at the former substrate, implying that the chelating ability of the formyl group is much weaker than that of an esteric moiety (eq 2).

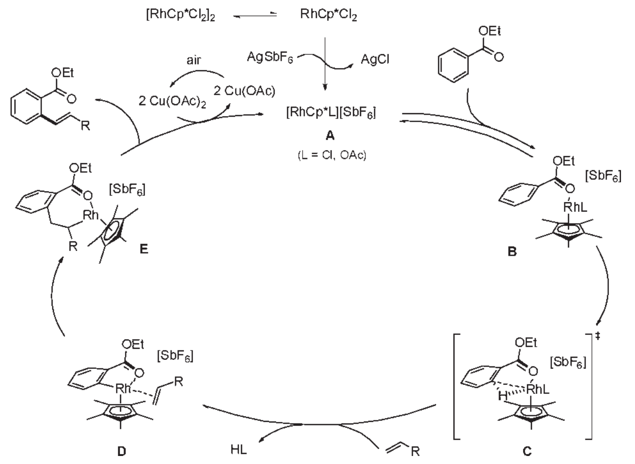


(3)

A significant kinetic isotope effect (KIE) was observed ($k_H/k_D = 2.3$),[19] implying that the C–H bond cleavage at the 2-position of ethyl benzoate is most likely involved in the rate-determining step (eq 3).

On the basis of the above data and precedent literature,[7a,13b,20] a plausible pathway is proposed in Scheme 4.

Scheme 4. Proposed Mechanism of Ester-Directed Olefination



It is postulated that $[RhCp^*Cl_2]_2$ dissociates initially into unsaturated monomeric complexes, with which $AgSbF_6$ reacts to generate a cationic Rh species **A**. Because of its highly electrophilic character, **A** is expected to readily coordinate to a carbonyl oxygen of ethyl benzoate to form **B**. Subsequent C–H bond activation at the *ortho*-position is assumed to take place leading to an arylrhodium species **D** presumably via a transition state **C**. Olefin insertion from **D** may generate a rhodacycle species **E** and β-hydride elimination of the intermediate provides an olefinated product, concomitantly releasing a Rh(I) species that is reoxidized to the +3 oxidation state by the action of a copper species. Reduced copper is assumed to be oxidized by oxygen or air.

In summary, we have found that an ester or carboxaldehyde unit can be utilized as an efficient chelating group to direct an olefination reaction via the regioselective C–H bond activation under the oxidative Rh(III) catalytic conditions. Although further improvements are desired with regard to the substrate scope and reaction efficiency, the present study demonstrates the directing ability of those readily available groups in the C–H bond functionalization.

Acknowledgment. This research was supported by the Korea Research Foundation (KRF-2008-C00024, Star Faculty Program) and MIRC (NRF-2010-0001957).

Supporting Information Available. Experimental details, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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