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Ruthenium-Catalyzed Oxidative Vinylation of Heteroarene Carboxylic Acids with Alkenes via Regioselective C−H Bond Cleavage

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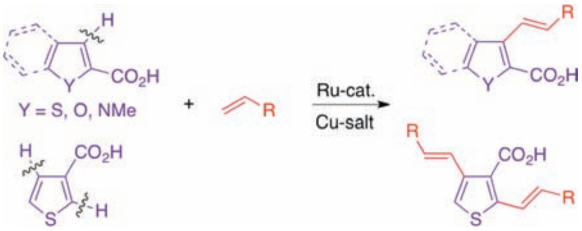
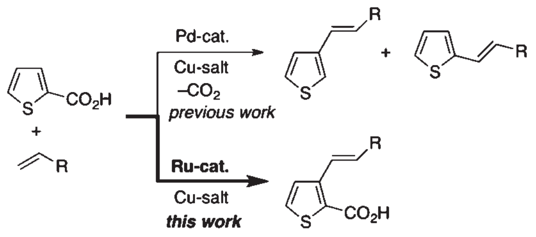
ABSTRACT



The ruthenium-catalyzed oxidative vinylation of thiophene-2-carboxylic acids with alkenes efficiently proceeds through directed C−H bond cleavage to give the corresponding 3-vinylated products. Similarly, benzothiophene-, benzofuran-, pyrrole-, and indolecarboxylic acids also undergo regioselective vinylation.

Transition-metal-catalyzed C−C bond formation reactions via C−H bond cleavage have attracted much attention from the atom- and step-economic points of view, and various catalytic processes involving different modes to activate the ubiquitously available bond have been developed.[1] Among the most promising strategies is the chelation-assisted version with the aid of directing groups, which allows regioselective functionalization. In particular, a carboxyl group is highly useful in organic synthesis because it can be readily removed and further transformed after its use as a directing group.[2] As such an example, we have demonstrated that heteroarene carboxylic acids undergo directed vinylation and decarboxylation upon treatment with alkenes and an oxidant under palladium catalysis.[2b] Thus, the reaction of indole-3-carboxylic acids gave 3-unsubstituted 2-vinylindole derivatives exclusively. Since the Pd-catalyzed oxidative direct vinylation (Fujiwara reaction) usually occurs at the electron-rich C3-position of parent indoles,[3] this reaction provides a rare vinylation method at the unusual C2-position. Its application to thiophene and benzothiophenecarboxylic acids was, however, problematic, in which mixtures of 2- and 3-vinylated products were formed (Scheme 1).[2b] These acids were found to undergo decarboxylation more readily under the Pd-catalyzed oxidative

Scheme 1



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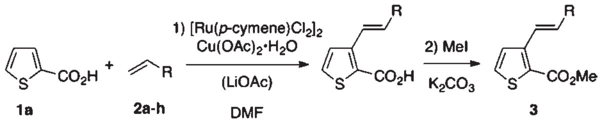
coupling conditions. Therefore, at least parts of the 2-vinylated products seem to arise from the sequence of the initial decarboxylation and subsequent nondirected vinylation of the resulting thiophene and benzothiophene. In the context of our study of catalytic coupling of carboxylic acids,[4] we have succeeded in finding that the regioselective vinylaition of a wide range of heteroarene carboxylic acids including thiophenecarboxylic acids can be realized by using Ru in place of Pd as the principal catalyst component.[5−7] Since decarboxylation is sluggish under Ru catalysis, the carboxyl function remains in the vinylated products and therefore, is utilizable for further catalytic transformations.[8,9] The results obtained for the coupling are described herein.

Table 1. Reaction of Thiophene-2-carboxylic Acid (**1a**) with Alkenes **2a**−**h**[a]



entry	2	R	LiOAc[b]	product, % yield[c]
1	**2a**	CO_2Bu	+	**3a**, 79 (74)
2	**2a**	CO_2Bu	−	**3a**, 72
3	**2b**	CO_2(*i*-Bu)	+	**3b**,(72)
4	**2c**	CO_2(*t*-Bu)	+	**3c**,(65)
5	**2c**	CO_2(*t*-Bu)	−	**3c**, 76 (72)
6	**2d**	CO_2Cy[d]	+	**3d**, 94 (79)
7	**2d**	CO_2Cy[d]	−	**3d**, 92
8	**2e**	CO_2Et	+	**3e**, 69
9	**2e**	CO_2Et	−	**3e**, 84 (75)
10	**2f**	CO_2Ph	+	**3f**, 78 (67)
11	**2f**	CO_2Ph	−	**3f**, 66
12	**2g**	CONH(*t*-Bu)	+	**3g**, 48 (36)
13	**2h**	CN	−	**3h**, 34 (26)[e]

[a] Reaction conditions: (1) [**1a**]/[**2**]/[$\{Ru(p\text{-cymene})Cl_2\}_2$]:[$Cu(OAc)_2\cdot H_2O$]/[LiOAc] = 0.25:1:0.005:0.5:0.75 (in mmol), in DMF (3 mL) at 80 °C for 6 h under N_2. (2) With the addition of MeI (1.25 mmol) and K_2CO_3 (1 mmol) at rt for 12 h. [b] Plus sign indicates that LiOAc was added. [c] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [d] Cy = cyclohexyl. [e] A minor amount of separable *Z*-isomer was also obtained (9%).

In an initial attempt, the reaction of thiophene-2-carboxylic acid (**1a**) with butyl acrylate (**2a**) (4 equiv) was conducted in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol %), $Cu(OAc)_2\cdot H_2O$ (2 equiv),[10,11] and LiOAc (3 equiv) as catalyst, oxidant, and additive, respectively, in DMF at 80 °C for 6 h under N_2. After the subsequent methyl esterification using iodomethane and K_2CO_3 for quantification, the 3-vinylated product **3a** was obtained in 79% yield (entry 1 in Table 1). The product yield slightly decreased under the conditions without LiOAc (entry 2). The reactions of **1a** with a variety of acrylates **2b**−**f** proceeded efficiently to produce the corresponding products **3b-f** in good yields (entries 2−11). In some cases, depending on the identities of alkenes employed, the product yields became somewhat higher in the absence of LiOAc (entries 5 versus 4 and 9 versus 8). *N*-(*tert*-Butyl)acrylamide (**2g**) also underwent the coupling with **1a** to afford product **3g** (entry 12). The reaction with acrylonitrile (**2h**) gave regioselectively vinylated product **3h** as a separable mixture of geometrical isomers (entry 13).

Next, the vinylation of other various heteroarene carboxylic acids was examined under similar reaction conditions in the presence of LiOAc. 5-Bromothiophene-2-carboxylic

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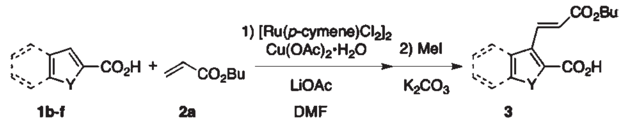
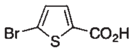
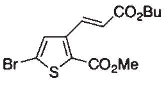
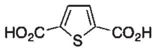
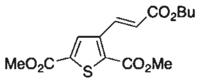
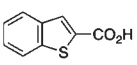
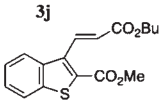
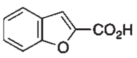
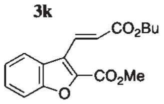
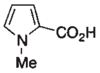
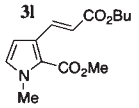
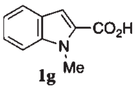
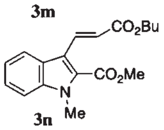
Table 2. Reaction of Heteroarenecarboxylic Acids **1b**−**g** with **2a**[a]



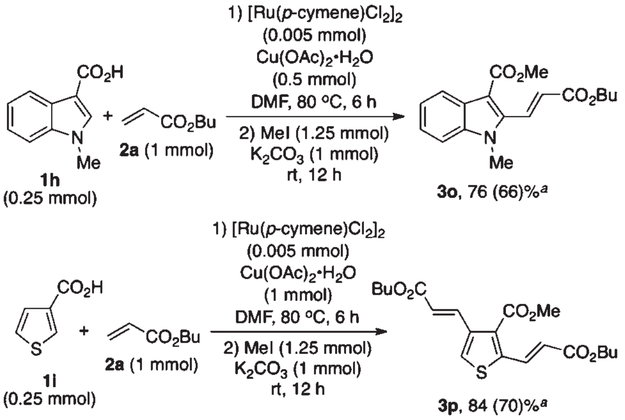
1b-f **2a** **3**

entry	1	product	% yield[b]
1	 **1b**	 **3i**	(51)
2[c]	 **1c**	 **3j**	47 (41)
3	 **1d**	 **3k**	95 (79)
4	 **1e**	 **3l**	66 (54)
5[d]	 **1f**	 **3m**	84 (69)
6	 **1g**	 **3n**	84 (72)

[a] Reaction conditions: (1) [**1**]/[**2a**]/[{Ru(*p*-cymene)Cl$_2$}$_2$]:[Cu(OAc)$_2$·H$_2$O]/[LiOAc] = 0.25:1:0.005:0.5:0.75 (in mmol), in DMF (3 mL) at 80 °C under N$_2$. (2) With the addition of MeI (1.25 mmol) and K$_2$CO$_3$ (1 mmol) at rt for 12 h. [b] GC yield based on the amount of **1** used. Value in parentheses indicates yield after purification. [c] [Cu(OAc)$_2$·H$_2$O] = 1 (in mmol). [d] At 70 °C.

acid (**1b**) and 2,5-thiophenedicarboxylic acid (**1c**) reacted with **2a** to form products **3i**[12] and **3j**, respectively (entries 1 and 2 in Table 2). In the latter case, no divinylated product could be detected in the reaction mixture. Similarly, 3-vinylated benzothiophene-2-carboxylate **3k** was obtained exclusively in 95% yield from benzothiophene-2-carboxylic acid (**1d**) (entry 3). The reactions of benzofuran- and pyrrole-2-carboxylic acids **1e** and **1f** with **2a** also gave the corresponding 3-vinylated products **3l** and **3m**, respectively, maintaining their carboxylic group (entries 4 and 5). Expectedly, 1-methylindole-2-carboxylic acid (**1g**) underwent the vinylation to afford 3-vinylated product **3n** in 84% yield (entry 6). It should be noted that such 3-vinylindole-2-carboxylic acid derivatives have attracted much attention due to their neuroprotective activities.[13] The present procedure provides a significant shortcut for the target.

Scheme 2[a]



[a] GC yield based on the amount of **1** used. Value in parentheses indicates yield after purification.

As shown in Scheme 2, 1-methylindole-3-carboxylic acid (**1h**) also underwent the regioselective vinylation at the C2-position to produce **3o**. Meanwhile, thiophene-3-carboxylic acid (**1i**) reacted with **2a** in a 1:2 manner to afford 2,4-divinylated product **3p** in 84% yield.

In summary, we have demonstrated that the ruthenium-catalyzed oxidative vinylation of heteroarene carboxylic acids with alkenes takes place efficiently through regioselective C−H bond cleavage without loss of the carboxyl function. Ru catalyst systems for oxidative C−C coupling reactions have been less explored than those with Pd or Rh. The present catalyst systems and related ones are expected to be applicable to other coupling reactions. Work is underway toward further development of the catalysis.

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

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(11) The yield of **3a** decreased to 20−40% by using Ag$_2$CO$_3$ or AgOAc in place of Cu(OAc)$_2$·H$_2$O as an oxidant.

(12) A small amount (8%) of debrominated product **3a** was also formed.

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