

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

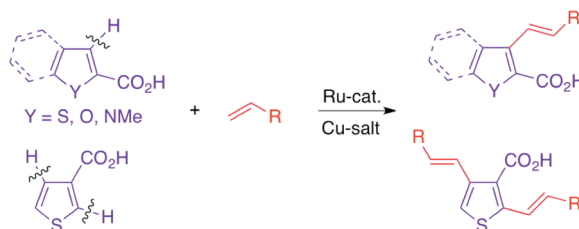
Takumi Ueyama, Satoshi Mochida, Tatsuya Fukutani, Koji Hirano, Tetsuya Satoh,* and Masahiro Miura*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

satoh@chem.eng.osaka-u.ac.jp; miura@chem.eng.osaka-u.ac.jp

Received December 6, 2010

ABSTRACT

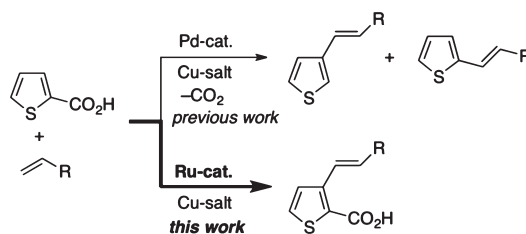


The ruthenium-catalyzed oxidative vinylation of thiophene-2-carboxylic acids with alkenes efficiently proceeds through directed C–H bond cleavage to give the corresponding 3-vinylated products. Similarly, benzothiophene-, benzofuran-, pyrrole-, and indolecarboxylic acids also undergo regioselective vinylation.

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 benzothiophene-carboxylic 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



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 vinylation 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.

(1) Selected recent reviews for C–H functionalization: (a) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (b) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395. (c) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K. *Synthesis* **2010**, 1399. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 46, 677. (f) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (h) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (i) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (j) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (k) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (l) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987. (m) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (n) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (o) Herrerias, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (p) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (q) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (r) Conley, B. L.; Tenn, W. J., III; Young, K. J. H.; Ganesh, S. K.; Meier, S. K.; Ziatdinov, V. R.; Mironov, O.; Oxgaard, J.; Gonzales, J.; Goddard, W. A., III; Periana, R. A. *J. Mol. Catal. A* **2006**, *251*, 8. (s) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (t) Rittling, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (u) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (v) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (w) Kakiuchi, F.; Murai, S. *Top. Organomet. Chem.* **1999**, *3*, 47. (x) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.

(2) Directed vinylation/decarboxylation: (a) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 5776. (b) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159. Directed arylation/decarboxylation: (c) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674. (d) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851. (e) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. For reviews, see ref 1b as well as the following: (f) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (g) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373.

(3) (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (c) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; John Wiley & Sons: Chichester, UK, 2004.

(4) (a) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 592. (b) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 68. (c) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7481. (d) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337. (e) Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3478. (f) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362. (g) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407.

(5) Nondirected oxidative vinylation on aromatic C–H bond under Ru catalysis has been reported: Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337.

(6) Ru-catalyzed directed vinylation using vinyl halides, vinyl boronates, and vinyl allyl acetates: (a) Ueno, S.; Kochi, T.; Chatani, N.; Kakiuchi, F. *Org. Lett.* **2009**, *11*, 855. (b) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858. (c) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Org. Chem.* **2007**, *72*, 3600. (d) Oi, S.; Tanaka, Y.; Inoue, Y. *Organometallics* **2006**, *25*, 4773. (e) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113. (f) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (g) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.

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 ₂ Bu	+	3a , 79 (74)
2	2a	CO ₂ Bu	–	3a , 72
3	2b	CO ₂ (<i>i</i> -Bu)	+	3b , 72
4	2c	CO ₂ (<i>t</i> -Bu)	+	3c , 65
5	2c	CO ₂ (<i>t</i> -Bu)	–	3c , 76 (72)
6	2d	CO ₂ Cy ^d	+	3d , 94 (79)
7	2d	CO ₂ Cy ^d	–	3d , 92
8	2e	CO ₂ Et	+	3e , 69
9	2e	CO ₂ Et	–	3e , 84 (75)
10	2f	CO ₂ Ph	+	3f , 78 (67)
11	2f	CO ₂ Ph	–	3f , 66
12	2g	CONH(<i>t</i> -Bu)	+	3g , 48 (36)
13	2h	CN	–	3h , 34 (26) ^e

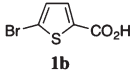
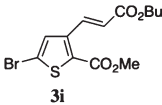
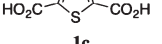
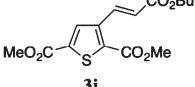
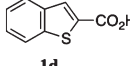
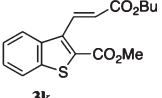
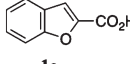
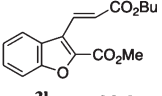
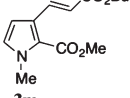
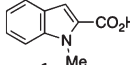
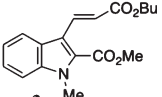
^a Reaction conditions: (1) [**1a**]/[**2**]/[Ru(*p*-cymene)Cl₂]₂:Cu(OAc)₂·H₂O]/[LiOAc] = 0.25:1:0.005:0.5:0.75 (in mmol), in DMF (3 mL) at 80 °C for 6 h under N₂. (2) With the addition of MeI (1.25 mmol) and K₂CO₃ (1 mmol) at rt for 12 h. ^b Plus sign indicates that LiOAc was added. ^c GC yield based 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*-cymene)Cl₂]₂ (2 mol %), Cu(OAc)₂·H₂O (2 equiv),^{10,11} and LiOAc (3 equiv) as catalyst, oxidant, and additive, respectively, in DMF at 80 °C for 6 h under N₂. After the subsequent methyl esterification using iodomethane and K₂CO₃ 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

(7) Ru-catalyzed directed oxidative arylation and alkylation: (a) Hiroshima, S.; Matsumura, D.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2010**, *12*, 5318. (b) Guo, X.; Deng, G.; Li, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 2071. (c) Kitazawa, K.; Kochi, T.; Sato, M.; Kakiuchi, F. *Org. Lett.* **2009**, *11*, 1951. (d) Oi, S.; Sato, H.; Sugawara, S.; Inoue, Y. *Org. Lett.* **2008**, *10*, 1823. (e) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (f) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (g) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (h) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.

Table 2. Reaction of Heteroarene-carboxylic Acids **1b–g** with **2a**^a

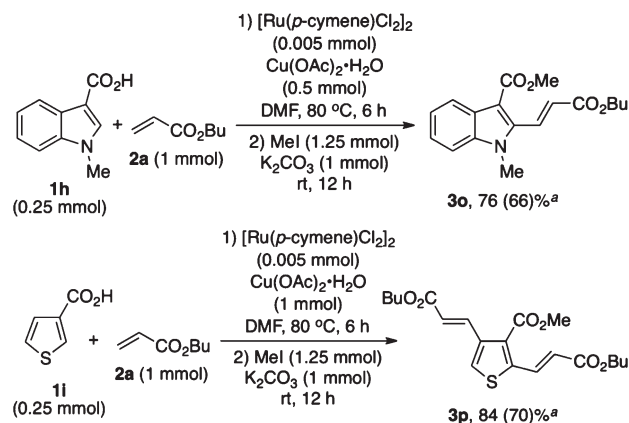
entry	1	product	% yield ^b
1			(51)
2 ^c			47 (41)
3			95 (79)
4			66 (54)
5 ^d			84 (69)
6			84 (72)

^a Reaction conditions: (1) [1]/[2a]/[1) [Ru(*p*-cymene)Cl₂]₂]/[Cu(OAc)₂·H₂O]/[LiOAc] = 0.25:1:0.005:0.5:0.75 (in mmol), in DMF (3 mL) at 80 °C under N₂. (2) With the addition of MeI (1.25 mmol) and K₂CO₃ (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·H₂O] = 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.

Acknowledgment. This work was partly supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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>.

(8) Selected examples of decarboxylative arylation: (a) Bilodeau, F.; Brochu, M.-C.; Guimond, N.; Thesen, K. H.; Forgiione, P. *J. Org. Chem.* **2010**, *75*, 1550. (b) Miyasaka, M.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2009**, *351*, 2683. (c) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (d) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (e) Forgiione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *126*, 11350. (f) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.

(9) Decarboxylative homocoupling: Cornella, J.; Lahlali, H.; Larrosa, I. *Chem. Commun.* **2010**, 46, 8276.

(10) A similar Ru/Cu catalyst system was employed in the oxidative coupling of areneboronic acids with alkenes: (a) Farrington, E. J.; Barnard, C. F. J.; Rowsell, E.; Brown, J. M. *Adv. Synth. Catal.* **2005**, *347*, 185. (b) Farrington, E. J.; Brown, J. M.; Barnard, C. F. J.; Rowsell, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 169.

(11) The yield of **3a** decreased to 20–40% by using Ag₂CO₃ or AgOAc in place of Cu(OAc)₂·H₂O as an oxidant.

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

(13) (a) Di Fabio, R.; Conti, N.; De Magistris, E.; Feriani, A.; Provera, S.; Sabbatini, F. M.; Reggiani, A.; Rovatti, L.; Barnaby, R. *J. Med. Chem.* **1999**, *42*, 3486 and references cited therein. (b) Di Fabio, R.; Capelli, A. M.; Conti, N.; Cugola, A.; Donati, D.; Feriani, A.; Gastaldi, P.; Gaviraghi, G.; Hewkin, C. T.; Micheli, F.; Missio, A.; Mugnaini, M.; Pecunioso, A.; Quaglia, A. M.; Ratti, E.; Rossi, L.; Tedesco, G.; Trist, D. G.; Reggiani, A. *J. Med. Chem.* **1997**, *40*, 841.