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Regioselective C–H Functionalization Directed by a Removable Carboxyl Group: Palladium-Catalyzed Vinylation at the Unusual Position of Indole and Related Heteroaromatic Rings

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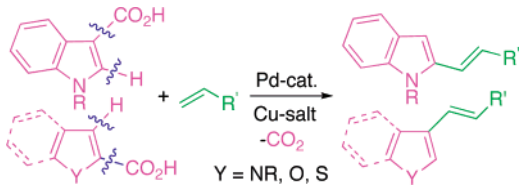
ABSTRACT



The palladium-catalyzed oxidative vinylation of indole-3-carboxylic acids with alkenes effectively proceeds via directed C–H functionalization and decarboxylation to produce the corresponding 2-vinylated indoles. Similarly, pyrrole-, furan-, and thiophenecarboxylic acids also undergo decarboxylative vinylation.

The indole nucleus is found in a great number of biologically active natural and unnatural compounds, and the synthesis of its derivatives is of considerable importance in organic synthesis. Recently, various methods for its derivatization by means of transition metal catalysis have been developed in addition to the traditional ones.[1] Among the effective, straightforward strategies for the introduction of a side chain into indoles is the palladium-catalyzed oxidative direct vinylation with alkenes via C−H bond cleavage (Fujiwara reaction).[2] The vinylation usually occurs at the electron-rich C3-position of indoles due to the electrophilic nature of the reaction. Gaunt and co-workers reported the solvent-controlled regioselective vinylation of indoles by palladium catalysis.[3] Thus, C3-vinylated products were produced almost exclusively in DMF/DMSO, whereas C2-vinylation products predominated in dioxane/acetic acid. However, the C2-vinylation was performed for only a few sets of substrate combinations with a relatively high palladium loading.

A general strategy for regioselective C−H functionalization is to utilize the coordination of a functional group in a given substrate to the metal center of a catalyst.[4] Various catalytic C−H alkylation and vinylation reactions of aromatic substrates bearing such a metal-directing group have been successfully developed. It was shown that an indole substrate bearing 2-pyridylmethyl group on the N1-position as the directing group undergoes C2-vinylation selectively.[5]

On the other hand, we demonstrated the oxidative coupling of benzoic acids with alkenes and alkynes involving ortho-vinylation under palladium-, rhodium-, and iridium catalyses.[6] Among them, the iridium-catalyzed reaction of carboxylic acids with alkynes is accompanied by decarboxylation

(1) For selected reviews, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.

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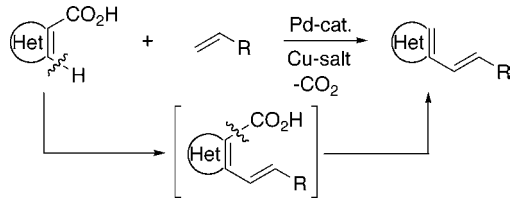
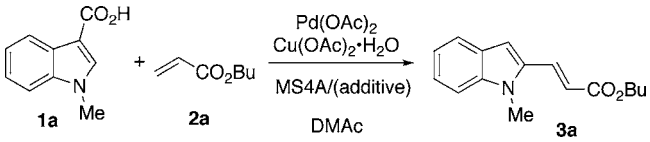
to form naphthalene derivatives as the 1:2 coupling products.[6a,7] This indicates that the carboxyl function may act as a unique, removable directing group. In the context of our further study of catalytic C−H functionalization,[6,8] it has been revealed that the selective synthesis of 2-vinylindoles can be achieved by the palladium-catalyzed oxidative coupling of indole-3-carboxylic acids with alkenes via regioselective vinylation directed by the carboxyl function and subsequent decarboxylation (Scheme 1, Het-CO_2H = indole-3-carboxylic acids). Furthermore, the protocol has been found to be applicable to the vinylation of other five-membered heteroaromatic systems. These new findings are described herein.

Scheme 1



When 1-methylindole-3-carboxylic acid (**1a**) (0.4 mmol) was treated with butyl acrylate (**2a**) (1.2 mmol) in the presence of $Pd(OAc)_2$ (0.02 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.8 mmol), and molecular sieves (MS4A, 400 mg) in DMAc at 120 °C for 2 h under N_2, butyl (*E*)-3-(1-methylindol-2-yl)-2-propenoate (**3a**) was formed in 42% yield (entry 1 in Table 1). No 3-vinylated products could be detected by GC-MS analysis. The yield of **3a** was somewhat enhanced at 140 °C (entry 2), while a further elevation of temperature showed no positive effect (entry 3). As an oxidant, AgOAc was less effective than the copper salt (entry 4). Fortunately, the yield of **3a** was almost doubled by addition of LiOAc (1.2 mmol) (entry 5). Other alkali metal salts examined were less effective than LiOAc (entries 6−8). It was confirmed that, under similar conditions, 1-methylindole (**4**) reacted with **2a** to give C3-vinylated product **5** selectively in 62% yield (Scheme 2).

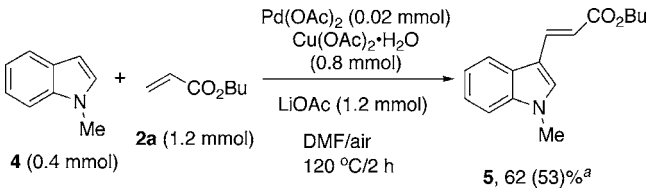
Table 1. Reaction of 1-Methylindole-3-carboxylic Acid (**1a**) with Butyl Acrylate (**2a**)[a]



entry	additive	temp (°C)	time (h)	% yield of **3a**[b]
1		120	2	42
2		140	2	48
3		160	1	42
4[c]		140	1	34
5	LiOAc	140	2	82 (71)
6	NaOAc	140	4	68
7	LiCl	140	4	46
8	Cs_2CO_3	140	4	52

[a] Reaction conditions: [**1a**]:[**2a**]:[$Pd(OAc)_2$]:[$Cu(OAc)_2 \cdot H_2O$]:[additive] = 0.4:1.2:0.02:0.8:1.2 (in mmol), MS4A (400 mg) in DMAc (10 mL) under N_2. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] AgOAc (0.8 mmol) was used in place of $Cu(OAc)_2 \cdot H_2O$.

Scheme 2



[a] GC yield. Value in parentheses indicates yield after purification.

Table 2 summarizes the results for the coupling reactions of a series of 1-substituted indole-3-carboxylic acids and alkenes using the catalyst system of $Pd(OAc)_2/Cu(OAc)_2 \cdot H_2O$/LiOAc. Acrylic acid derivatives **1b**−**d** and styrene (**1e**) underwent the coupling with **1a** to produce the corresponding

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(5) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854.

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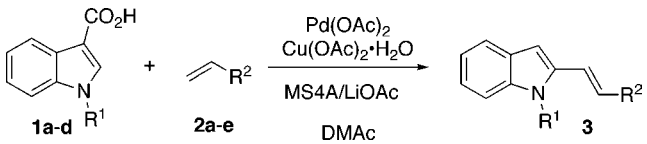
(7) The catalytic decarboxylation[7a,b,e,g] as well as decarboxylative arylation[7c−h,l] and vinylation reactions[7i−k] of carboxylic acids have recently been reported: (a) Goossen, L. J.; Thiel, W. R.; Rodríguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal.* **2007**, *349*, 2241. (b) Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Org. Lett.* **2007**, *9*, 2441. (c) Gribkov, D. V.; Pastine, S. J.; Schnürch, M.; Sames, D. *J. Am. Chem. Soc.* **2007**, *129*, 11750. (d) Goossen, L. J.; Melzer, B. *J. Org. Chem.* **2007**, *72*, 7473. (e) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (f) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781. (g) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (h) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (i) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (j) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433. (k) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (l) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.

(8) For example: (a) Uto, T.; Shimizu, M.; Ueura, K.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Org. Chem.* **2008**, *73*, 298. (b) Nakano, M.; Satoh, T.; Miura, M. *J. Org. Chem.* **2006**, *71*, 8309. (c) Terao, Y.; Wakui, H.; Nomoto, N.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236. (d) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407. (e) Nishinaka, Y.; Satoh, T.; Miura, M.; Nomura, M.; Matsui, H.; Yamaguchi, C. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1727. (f) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.

Table 2. Reaction of Indole-3-carboxylic Acids **1a**−**d** with Alkenes **2a**−**e**[a]



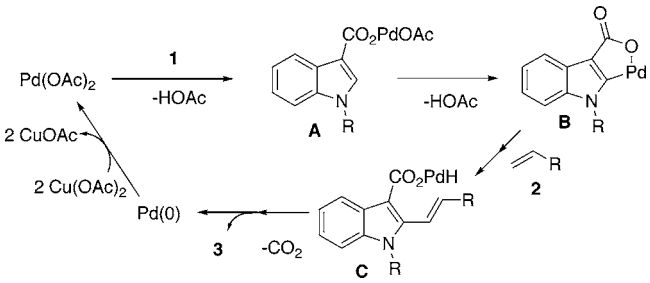
entry	1	R^1	2	R^2	time (h)	product, % yield[b]
1	**1a**	Me	**2b**	CO_2Et	8	**3b**, 71 (58)
2	**1a**	Me	**2c**	CO_2Cy[c]	4	**3c**, 68 (62)
3	**1a**	Me	**2d**	$CO_2(t\text{-Bu})$	8	**3d**, 61 (54)
4	**1a**	Me	**2e**	Ph	1	**3e**, 58 (47)
5	**1b**	$MeOCH_2$	**2a**	CO_2Bu	8	**3f**, 55 (50)
6	**1c**	Ph	**2a**	CO_2Bu	8	**3g**, 51 (43)
7	**1d**	4-MeC_6H_4	**2a**	CO_2Bu	4	**3h**, 48 (39)

[a] Reaction conditions: [**1**]:[**2**]:[$Pd(OAc)_2$]:[$Cu(OAc)_2$·H_2O]:[LiOAc] = 0.4:1.2:0.02:0.8:1.2 (in mmol), MS4A (400 mg), in DMAc (10 mL) at 140 °C under N_2. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] Cy = cyclohexyl.

2-vinylindoles **3b**−**e** selectively (entries 1−4). 1-(Methoxymethyl)- and 1-arylindole-3-carboxylic acids **1b**−**d** were also coupled with **2a** on their 2-position exclusively to give **3f**−**h** (entries 5−7). The reaction of 1-unprotected indole-3-carboxylic acid, however, did not proceed.

A plausible mechanism for the reaction of indole-3-carboxylic acids **1** with alkenes **2** is illustrated in Scheme 3.

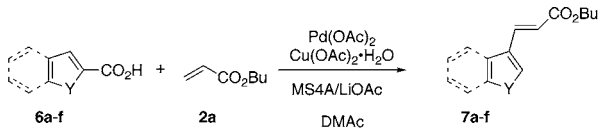
Scheme 3

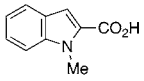
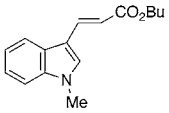
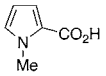
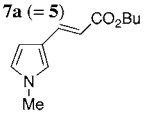
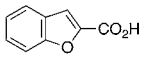
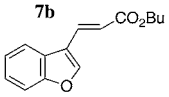
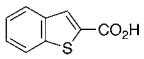
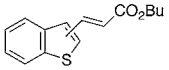
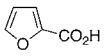
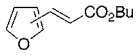
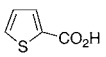
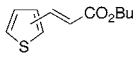


Coordination of the carboxyl oxygen to $Pd(OAc)_2$ with liberation of AcOH gives a palladium(II) carboxylate **A**. Then, directed palladation at the C2-position forming a palladacycle intermediate **B**, alkene insertion, and β-hydride elimination successively occur to produce a hydridopalladium carboxylate **C**. The subsequent steps involving decarboxylation and reductive elimination take place to form 2-vinylindole **3**. The resulting Pd(0) species may be oxidized in the presence of the copper(II) salt to regenerate $Pd(OAc)_2$. During palladium-catalyzed oxidative reactions, in general, the regeneration of Pd(II) from Pd(0) is considered to be the crucial step to determine catalyst efficiency.[9] One of the possible roles of added LiOAc is to provide acetate anions as ligand to prevent the deactivation of Pd(0) to metallic species.[10]

Next, the vinylation of other various heteroarene carboxylic acids was examined under similar reaction conditions. Expectedly, 1-methylindole-2-carboxylic acid (**6a**) reacted with **2a** via C3-vinylation and decarboxylation to form compound **7a** (= **5**) selectively in 85% yield (entry 1 in Table 3). Similarly, 3-vinylated pyrrole **7b** could be obtained

Table 3. Reaction of Heteroarenecarboxylic Acids **6a**−**f** with **2a**[a]



entry	6	time (h)	product	% yield[b]	C3:C2[c]
1	 **6a**	1	 **7a** (= **5**)	85 (70)	100:0
2	 **6b**	1	 **7b**	74 (62)	100:0
3	 **6c**	4	 **7c**	51 (37)	>95:5
4[d]	 **6d**	4	 **7d**	48 (34)[e]	7:1
5	 **6e**	5	 **7e**	39 (30)	~1:1
6[d,f]	 **6f**	8	 **7f**	65 (46)	5:1

[a] Reaction conditions: [**6**]:[**2a**]:[$Pd(OAc)_2$]:[$Cu(OAc)_2$·H_2O]:[LiOAc] = 0.4:1.2:0.02:0.8:1.2 (in mmol), MS4A (400 mg), in DMAc (10 mL) at 140 °C under N_2. [b] GC yield based on the amount of **6** used. Value in parentheses indicates yield after purification. [c] C3 = 3-vinylated products; C2 = 2-vinylated products. [d] At 120 °C. [e] Benzothiophene was also formed (16%). [f] Without LiOAc.

exclusively in 74% yield from 1-methylpyrrole-2-carboxylic acid (**6b**) (entry 2). This is one of the rare examples of the selective C3-vinylation of pyrroles. Usual electrophilic substitution reactions are known to take place at the C2-position predominantly. There is, to our knowledge, only one example of C3-vinylation in which the reaction is sterically controlled by the bulky 1-TIPS group on pyrrole.[11] The C3-

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(10) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254 and references therein.

(11) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528.

vinylation of benzofurans is also rare, because it is electrically and sterically unfavorable. The present directed decarboxylative vinylation method was found to be applicable to it. Thus, the reaction of benzofuran-2-carboxylic acid (**6c**) with **2a** gave C3-vinylated product **7c** predominantly, while a trace amount (less than 2% yield) of the C2-vinylated isomer was formed (entry 3). On the other hand, in the reaction of benzothiophene-2-carboxylic acid (**6d**) with **2a** under similar conditions, C3- and C2-vinylated products were obtained in a ratio of 7:1, along with a considerable amount (16%) of unsubstituted benzothiophene (entry 4). As with 1-methylindole (Scheme 2), benzothiophene itself underwent C2-vinylation predominantly under similar conditions (31%, C3:C2 = 1:9). Therefore, at least part of the C2-vinylated product formed in the reaction of **6d** seems to arise from the sequence of the initial decarboxylation and subsequent non-directed vinylation of the resulting benzothiophene. From furan- and thiophene-2-carboxylic acids, **6e** and **6f**, mixtures of the corresponding C3- and C2-vinylated products were formed (entries 5 and 6).

In summary, we have demonstrated that the palladium-catalyzed oxidative coupling of indole-3-carboxylic acids with alkenes proceeds efficiently via directed C−H vinylation and decarboxylation to exclusively give the corresponding 2-vinylindoles. Other related heteroarenecarboxylic acids also undergo the vinylation. The selective C3-vinylation of *N*-methylpyrrole-2- and benzofuran-2-carboxylic acids is notable. In these reactions, the carboxyl function effectively acts as a unique, removable directing group. Work is underway toward further development of relevant reactions around the key functional group.

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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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