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Oxidative Palladium(II)-Catalyzed C-7 Alkenylation of Indolines

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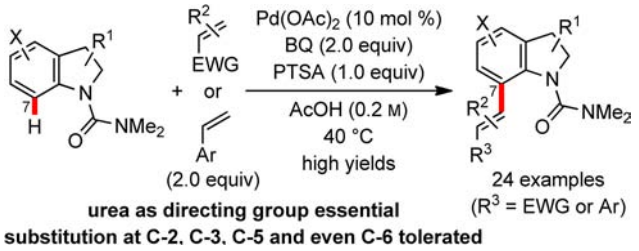
ABSTRACT



A mild procedure for C-7-selective C−H alkenylation of various indolines under oxidative palladium(II) catalysis is reported. A fully substituted urea, formed by carbamoylation of the indoline nitrogen atom, functions as a directing group. Both α,β-unsaturated acceptors and styrenes participate in this direct C−H functionalization. With a free NH group at the urea terminus, the nitrogen atom subsequently cyclizes in a 1,4-fashion to yield a six-membered ring.

The indoline nucleus is a ubiquitous motif in nature, and direct C−C bond formation at the arene C−H bonds with control of site selectivity is an attractive goal. Addressing the C-7 position by C−H arylation, alkenylation, or alkylation is particularly attractive but rare. A few groups disclosed oxidative palladium(II) catalyses that allow for the C-7-selective C−H arylation of indolines using pre-functionalized coupling partners,[1] and we recently reported the related dehydrogenative C−H/C−H coupling for the direct installation of an aryl group at C-7 (**I**→**II**, Scheme 1, left).[2] To achieve this challenging cross-coupling, we had to use the strong oxidant $Na_2S_2O_8$, and that required substitution at C-2 and C-3 of the indoline to prevent its oxidation to the corresponding indole. There are even less reports of the related C−H alkenylation. An early attempt involved the C-7-selective thallation of acetylated indoline with stoichiometric $Tl(TFA)_3$ in TFA followed by the addition of catalytic amounts of $Pd(OAc)_2$ and an electron-deficient alkene; the yield was low though.[3] The sole example of an oxidative C−H alkenylation of an indoline was just recently reported by the Carretero group.[4] Their method relies on the *N*-(2-pyridyl)-sulfonyl directing group and employs $Pd(OAc)_2$ (10 mol %) as the catalyst and *N*-fluoro-2,4,6-trimethylpyridinium triflate as the terminal oxidant in $ClCH_2CH_2Cl$ at 100 °C. Just recently, Sanford and co-workers accomplished the C-7 methylation of acetylated indoline under palladium(II) catalysis using MnF_3 as the stoichiometric oxidant.[5] We disclose here a broadly applicable, low-temperature C−H alkenylation of the indoline C-7 position where a urea unit acts as a directing group (**I**→**III**, Scheme 1, right).

There are many Lewis basic groups known today that function as the regiochemical control element in palladium(II)-catalyzed C−H bond activation.[6] The urea

(1) (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331 (using $[Ph_2I]BF_4$). (b) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554–5558 (using $PhB(OH)_2$). (c) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978–4979 (using $PhB(OH)_2$).

(2) Jiao, L.-Y.; Oestreich, M. *Chem.—Eur. J.* **2013**, *19*, 10845–10848.

(3) Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146–3154.

(4) Urones, B.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2013**, *15*, 1120–1123.

(5) Neufeldt, S. R.; Seigerman, C. K.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 2302–2305.

(6) For selected reviews, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (b) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. In *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009; pp 345–382. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (e) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (g) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780–1824. (h) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802. (i) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886–896.

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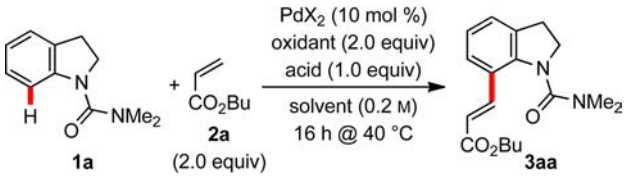
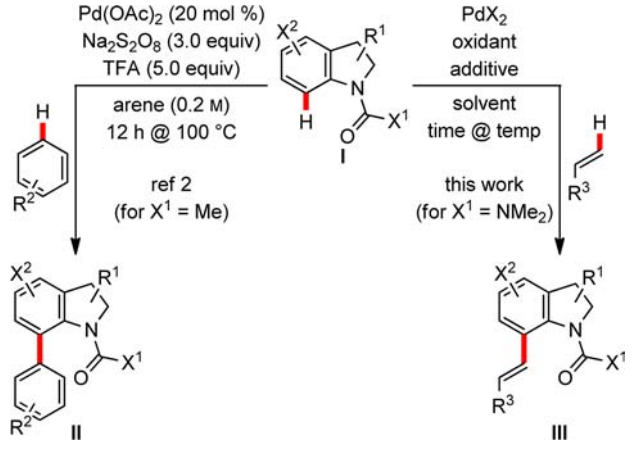
Table 1. Identification of the Catalyst System



entry	PdX_2	oxidant	acid	solvent	conversion (%)[a]	yield (%)[b]
1	**$Pd(OAc)_2$**	**BQ**	**PTSA**	**AcOH**	**100**	**89**
2	$Pd(TFA)_2$	BQ	PTSA	AcOH	94	80
3	$PdCl_2$	BQ	PTSA	AcOH	70	49
4	$(MeCN)_2PdCl_2$	BQ	PTSA	AcOH	78	52
5	$Pd(OAc)_2$	BQ	PTSA	toluene	95	36
6	$Pd(OAc)_2$	BQ	PTSA	DMF	62	55
7	$Pd(OAc)_2$	BQ	PTSA	NMP	43	32
8	**$Pd(OAc)_2$**	**BQ**	**PTSA**	**dioxane**	**93**	**71**
9	$Pd(OAc)_2$	BQ	TFA	AcOH	79	55
10	**$Pd(OAc)_2$**	**O_2 (1 atm)**	**PTSA**	**AcOH**	**90**	**66**
11	**$Pd(OAc)_2$**	**$Na_2S_2O_8$**	**PTSA**	**AcOH**	**92**	**63**
12	$Pd(OAc)_2$	$Cu(OAc)_2$	PTSA	AcOH	32	25
13	$Pd(OAc)_2$	Ag_2O	PTSA	AcOH	0	—
14	$Pd(OAc)_2$	Ag_2CO_3	PTSA	AcOH	0	—
15	$Pd(OAc)_2$	$PhI(OAc)_2$	PTSA	AcOH	95	—[c]

[a] Determined by GLC analysis with tetracosane as internal standard. [b] Isolated yield after purification by flash column chromatography. [c] Decomposition. BQ = 1,4-benzoquinone, PTSA = *p*-toluenesulfonic acid (as monohydrate), TFA = trifluoroacetic acid.

Scheme 1. Oxidative Palladium(II)-Catalyzed C-7-Selective C−H Bond Activation of Indolines: C-7 Arylation by Dehydrogenative C−H/C−H Cross-Coupling (left)[2] and Planned C-7 Alkenylation (right)



donor is, however, infrequently used, and we are aware of just two applications in the C−H alkenylation of anilines.[7−9] It was introduced by the Lloyd-Jones and Booker-Milburn team[10] and successfully utilized by the Lipshutz group[1c,11] in the C−H arylation of anilines. These couplings proceed at slightly elevated or even ambient temperature, and we reasoned that the assumed beneficial effect of the urea group would also apply to the C-7-selective C−H alkenylation of indolines.

Consequently, our investigation began with the alkenylation of the carbamoylated parent indoline **1a** with acrylate **2a** (**1a**→**3aa**, Table 1). Adopting the reaction setup elaborated by Yu and co-workers,[7b] we were delighted to find that, at 40 °C, C−C bond formation occurred selectively at C-7 at full conversion in excellent isolated yield (entry 1). No indoline-to-indole oxidation was observed. Decent results were also obtained at a lower catalyst loading (5.0 mol %) or with less alkene (1.2 equiv): 73% conversion and 63% yield and 92% conversion and 78% yield, respectively. Changing the palladium(II) source was detrimental (entries 2−4), and solvents other than acetic acid resulted in poor conversion and/or decomposition (entries 5−7), except for dioxane (entry 8). The nature and acidity of the

(7) (a) Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, 3874–3876. (b) Wang, L.; Liu, S.; Li, Z.; Yu, Y. *Org. Lett.* **2011**, *13*, 6137–6139.

(8) For rhodium(III)-catalyzed C−H bond alkenylation, see: (a) Willwacher, J.; Rakshit, S.; Glorius, F. *Org. Biomol. Chem.* **2011**, *9*, 4736–4740 (*N*-methoxy urea as oxidizing directing group attached to anilines). (b) Li, B.; Ma, J.; Xie, W.; Song, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2013**, *19*, 11863–11868 (C-2-selective alkenylation of indoles).

(9) For a urea-directed C-2-selective hydroarylation of a C−C triple bond with indoles as an indirect C−H alkenylation of indoles, see: Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910–6911.

(10) (a) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066–10067 (1,2-carboamination of 1,3-dienes). (b) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830–1833.

(11) (a) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781–784. (b) Jiang, Z.; Zhang, L.; Dong, C.; Su, X.; Li, H.; Tang, W.; Xu, L.; Fan, Q. *RSC Adv.* **2013**, *3*, 1025–1028.

acid added to the acid solvent appeared to be crucial as well: PTSA was superior to TFA (entry 1 vs 9). Benzoquinone as the oxidant was clearly optimal (entry 1 vs entries 10–15) but there were a few remarkable alternatives. Isolated yields were acceptable under aerobic conditions (entry 10) and using the strong oxidant $Na_2S_2O_8$ (entry 11) that would eventually oxidize the indoline at higher temperature.

A related fully substituted urea with an NEt_2 instead of an NMe_2 unit made no difference (**1b**→**3ba**, Figure 1, left). However, a urea with a free NH group at the terminus still promoted the C–H bond alkenylation, but its nitrogen atom subsequently cyclized onto the α,β-unsaturated acceptor to form a six-membered ring (**1c**→**4ca**, Scheme 2). Such domino processes are not unprecedented[12] but had not been observed by Yu and co-workers in the aforementioned C–H alkenylation of anilines.[7b] It is worthy of note that directing groups other than ureas either yielded little or no conversion or resulted in complete decomposition (**1d**–**1f**, Figure 1, right).

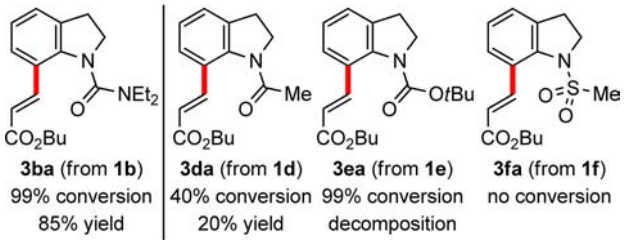
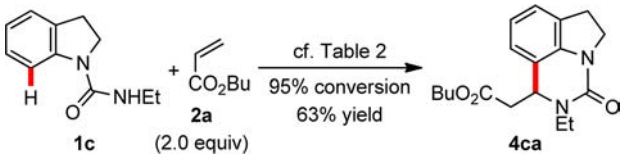


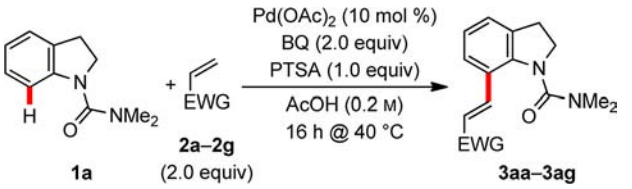
Figure 1. Variation of the directing group (for reaction conditions; see Table 1, entry 1).

Scheme 2. Free NH Group at the Urea Terminus: Domino Intermolecular C–H Alkenylation/Intramolecular Conjugate C–N Bond Formation



We then tested different acrylates **2a**–**2d**, MVK (**2e**), acrylonitrile (**2f**), and vinyl phosphonate **2g** under the previously established protocol (Table 2). Yields were consistently high with **2a**–**2d** (entries 1–4), and more reactive MVK (**2e**) cross-coupled in moderate yield (entry 5). Conversely, nitrile **2f** afforded the target compound in low yield (entry 6). The phosphonate **2g** reacted in excellent yield though (entry 7). Even substituted α,β-unsaturated acceptors participated, but yields were somewhat lower (Scheme 3). Methacrylate **2h** afforded a single diastereomer (**1a**→**3ah**) and crotonate **2i** both double bond isomers (**1a**→**3ai**).

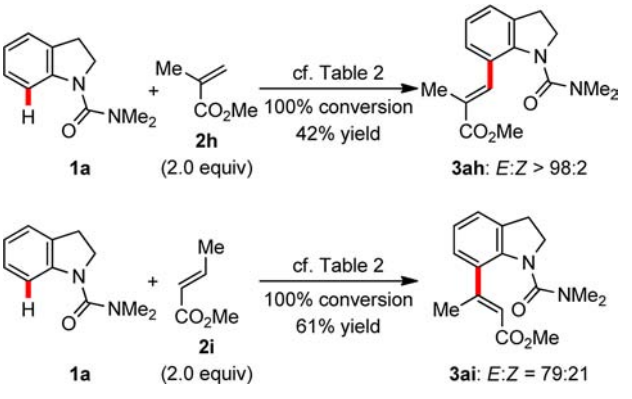
Table 2. Variation of the Alkene: α,β-Unsaturated Acceptors



entry	alkene	EWG	indoline	conversion (%)[a]	yield (%)[b]
1	**2a**	CO_2Bu	**3aa**	100	89
2	**2b**	CO_2Et	**3ab**	97	82
3	**2c**	CO_2Me	**3ac**	97	80
4	**2d**	CO_2Bn	**3ad**	99	87
5	**2e**	C(O)Me[c]	**3ae**	92	60
6	**2f**	CN	**3af**	99	21
7	**2g**	$P(O)(OEt)_2$	**3ag**	100	86

[a] Determined by GLC analysis with tetracosane as internal standard. [b] Isolated yield after purification by flash column chromatography. [c] Methyl vinyl ketone (MVK). EWG = electron-withdrawing group.

Scheme 3. Oxidative Palladium(II)-Catalyzed C-7-Selective C–H Alkenylation with Substituted α,β-Unsaturated Acceptors

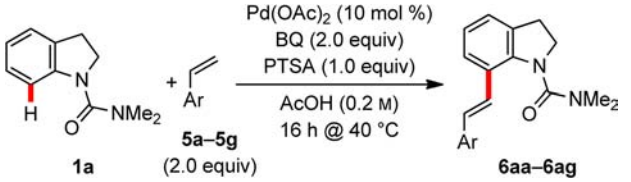


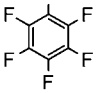
The work of Yu and co-workers included a single alkene as a coupling partner, *n*-butyl acrylate (**2a**).[7b] Gratifyingly, a whole range of styrenes **5a**–**5f** were compatible with our C-7 alkenylation, and that greatly enhances the scope of the method (Table 3). Electron-deficient styrenes **5a**–**5e** generally reacted in high yields (entries 1–5), and the lower yield for **5f** with an *ortho* bromo substituent might be due to sterics (entry 6). Electron-rich **5g** failed to react though (entry 7). No reaction was seen with α-olefins (not shown).

We finally tested various indoline substitution patterns in the C-7 alkenylation with acrylate **2a** (**7a**–**15a**, Scheme 4). Alkylation at C-2 or C-3 or even both had no consequences; isolated yields of **16aa**–**19aa** were high. Not surprisingly, methylation at C-5 had no effect (88% yield for **20aa**), but we expected a methyl group at C-6 flanking

(12) (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211–5215. (b) Kim, B. S.; Lee, S. Y.; Youn, S. W. *Chem.—Asian J.* **2011**, *6*, 1952–1957.

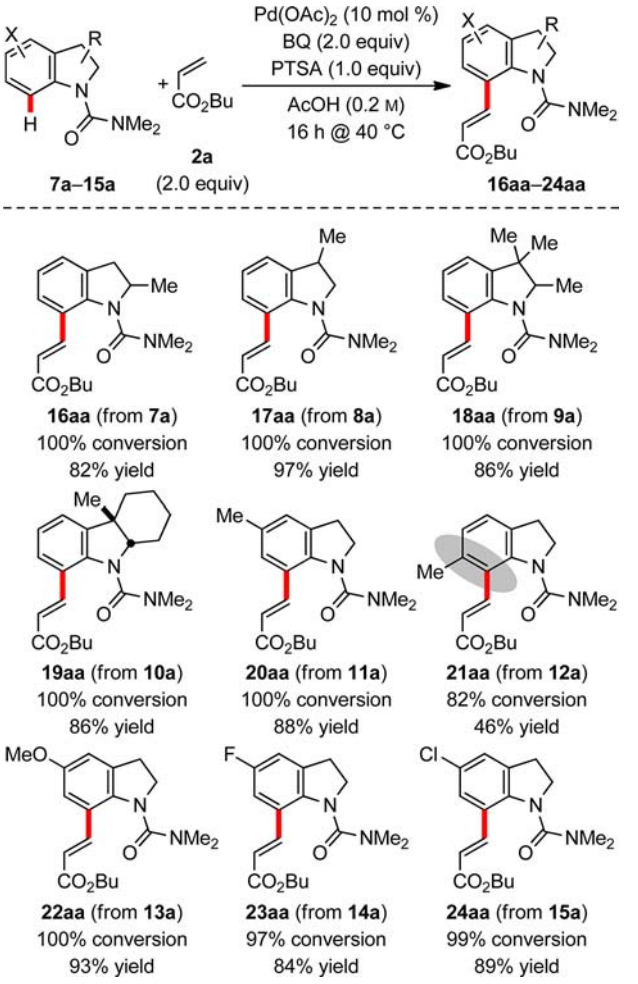
Table 3. Variation of the Alkene: Styrenes



entry	alkene	Ar	indoline	conversion (%)[a]	yield (%)[b]
1	**5a**		**6aa**	82	73
2	**5b**		**6ab**	100	88
3	**5c**		**6ac**	82	63
4	**5d**		**6ad**	96	82
5	**5e**		**6ae**	100	85
6	**5f**		**6af**	63	40
7	**5g**		**6ag**	13	—

[a] Determined by GLC analysis with tetracosane as internal standard. [b] Isolated yield after purification by flash column chromatography.

Scheme 4. Variation of the Indoline Motif[a,b]



[a] Conversion determined by GLC analysis with tetracosane as internal standard. [b] Isolated yield determined after purification by flash column chromatography.

the C−H bond to thwart the cross-coupling. However, the alkenylation still occurred in remarkable 46% isolated yield of **21aa**. For substitution at C-5, there was no electronic effect as electron-donating and -withdrawing groups invariably furnished high yields of **22aa**−**24aa**.

In summary, we reported herein a general method for the palladium(II)-catalyzed C-7-selective C−H bond alkenylation of indolines. BQ was optimal as the terminal oxidant, but it was also possible to perform the cross-coupling under aerobic conditions. Both α,β-unsaturated acceptors and styrenes reacted equally well, and substitution at various positions of the indoline was tolerated. The C-7-alkenylation of a C-6-methylated indoline showcased the strength of the new methodology.

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Supporting Information Available. General procedures, experimental details, characterization data, and ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.