

Synthesis of 3,3-Disubstituted Oxindoles by Palladium-Catalyzed Tandem Reaction of 2-(Alkynyl)aryl Isocyanates with Benzylic Alcohols

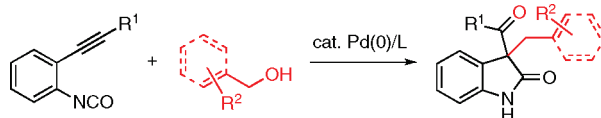
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ABSTRACT



A palladium complex sequentially promoted two mechanistically distinct reactions, the first, cyclization of 2-(alkynyl)aryl isocyanates with benzylic alcohols, and the second, [1,3] rearrangement of a benzyl group from oxygen to carbon, furnishing 3,3-disubstituted oxindoles in one pot.

Tandem reactions involving multistep transformations in sequence reduce synthetic steps and incidental wastes to greatly improve synthetic efficiency.^{1,2} There has been a growing interest in the development of multifunctional catalytic processes, wherein a single catalyst promotes two or more transformations in a single flask. Such catalytic systems have been named as “auto-tandem catalysts (ATCs)”.³ Palladium catalysts are most promising for this purpose because they are so versatile to promote a large number of reactions of different patterns.⁴ Elegant examples of palladium ATCs have appeared over the past several years.^{5,6} 2-Iodophenol reacted with methyl bromomethylacrylate and phenylboronic acid in the presence of a

palladium catalyst to give a dihydrobenzofuran derivative through a sequence of *O*-allylation/Heck/Suzuki coupling processes.^{5a} A tandem Buchwald–Hartwig coupling/cyclization reaction afforded indole derivatives starting from 2-alkynylhaloarenes and amines.^{5c} Fagnou developed a tandem Heck/C–H arylation reaction, and employed this strategy for the construction of cytotoxic carbazoles.^{5d} We describe herein a new palladium-catalyzed tandem reaction of 2-(alky-

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(2) For recent reviews, see: (a) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem.—Eur. J.* **2009**, *15*, 12168. (d) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (e) Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092.

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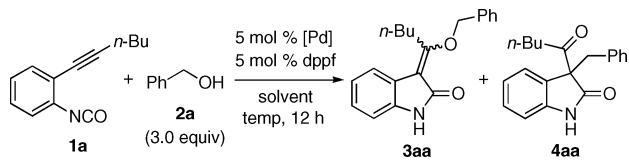
(5) (a) Szlosek-Pinaud, M.; Diaz, P.; Martinez, J.; Lamaty, F. *Tetrahedron Lett.* **2003**, *44*, 8657. (b) Gruber, M.; Chouzier, S.; Koehler, K.; Djakovitch, L. *Appl. Catal., A* **2004**, *265*, 161. (c) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (d) Leclerc, J.-P.; André, M.; Fagnou, K. *J. Org. Chem.* **2006**, *71*, 1711. (e) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319. (f) Meyers, C.; Rombouts, G.; Loones, K. T. J.; Coelho, A.; Maes, B. U. W. *Adv. Synth. Catal.* **2008**, *350*, 465. (g) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916.

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nyl)aryl isocyanates with benzylic (or allylic) alcohols.⁷ 3,3-Disubstituted oxindoles are synthesized in one pot through a sequence of cyclization and [1,3] rearrangement of a benzyl (or allyl) group from oxygen to carbon.⁸

We have previously reported a stereoselective synthesis of 3-(alkoxyalkylidene)oxindoles by the palladium-catalyzed cyclization of 2-(alkynyl)aryl isocyanates with alcohols.⁹ The scope of this reaction was examined in more detail, leading to the use of benzyl alcohol. Thus, 2-(1-hexynyl)phenyl isocyanate (**1a**, 1.0 equiv) was treated with benzyl alcohol (**2a**, 3.0 equiv) in the presence of Pd₂(dba)₃·CHCl₃/dppf (5.0 mol % of Pd; dppf = 1,1'-bis(diphenylphosphino)ferrocene) in THF at 40 °C for 12 h. After an extractive workup followed by chromatographic isolation, 3-(1-(benzyloxy)-pentylidene)oxindole (**3aa**) was obtained as the sole product in 81% isolated yield (Z:E = >20:1), being in accordance with the results we reported⁹ (Table 1, entry 1). When the

Table 1. Optimization of Reaction Conditions^a

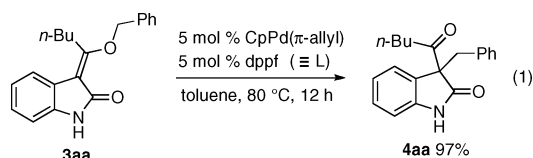


entry	[Pd]	t (°C)	solvent	yield of 3aa (%) ^b	yield of 4aa (%)
1	Pd ₂ (dba) ₃ ·CHCl ₃	40	THF	81 (>20:1)	0
2	Pd ₂ (dba) ₃ ·CHCl ₃	80	THF	56 (9:1)	13
3	Pd ₂ (dba) ₃ ·CHCl ₃	80	DME	57 (13:1)	13
4	Pd ₂ (dba) ₃ ·CHCl ₃	80	dioxane	54 (7:1)	16
5	Pd ₂ (dba) ₃ ·CHCl ₃	80	toluene	41 (1:2)	31
6	CpPd(π-allyl)	80	toluene	0	69

^a Reactions conducted on a 0.2 mmol scale. ^b Isomer ratios (Z/E) given in parentheses.

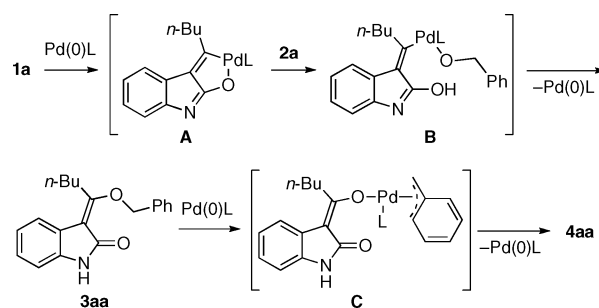
reaction was carried out at an elevated temperature of 80 °C, however, another minor product was formed in addition to **3aa** (entry 2). The structure of the new product was determined to be 3-benzyl-3-pentanoyloxindole (**4aa**) by ¹H and ¹³C NMR spectrometry. Careful examination of the reaction conditions revealed that **4aa** was selectively formed when toluene was used as the solvent and CpPd(π-allyl) as the catalyst (entry 6).

The isolated oxindole **3aa** was subjected to the same reaction conditions. Conversion of **3aa** took place smoothly to afford **4aa** in 97% yield in 12 h (eq 1).^{10,11}

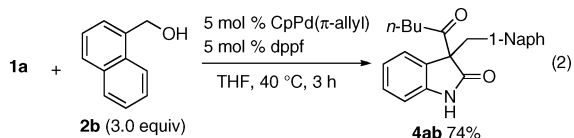


On the other hand, no [1,3] rearrangement of **3aa** was observed in the absence of the palladium catalyst even at 100 °C. These results indicated that **3aa** is initially formed by the palladium-catalyzed cyclization reaction of **1a** with **2a**, as we previously reported,⁹ and that the benzyl group bound to an enol oxygen subsequently undergoes 1,3-rearrangement onto an enol carbon, probably via a (η³-benzyl)palladium(II) complex **C**, to furnish **4aa** (Scheme 1).^{12,13} The involvement of a (η³-benzyl)palladium(II)

Scheme 1. Proposed Mechanism for the Pd(0)-Catalyzed Tandem Reaction from **1a** and **2a** to **4aa**



complex was supported by the result of an analogous reaction with 1-naphthylmethanol (**2b**). The reaction of **1a** with **2b** proceeded more rapidly than that with **2a** to afford the product **4ab** in 74% yield (eq 2). It has been reported that the formation of (η³-benzyl)palladium(II) intermediate from a benzyl ester through oxidative addition onto palladium(0) is slower than the formation of (η³-naphthylmethyl)palladium(II) intermediate from a



naphthylmethyl ester because the former process suffers from disruption of aromaticity.^{13a,f} Therefore, the slower reaction rate observed with **2a** accords with the involvement of (η³-benzyl)palladium(II) intermediate. Thus, the palladium catalyst mediates two distinct transformations in sequence, the first, alkyne/isocyanate cyclization, and the second, 1,3-

(7) For examples of tandem reactions including a rearrangement step, see: (a) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138. (b) Tanaka, K.; Okazaki, E.; Shibata, Y. *J. Am. Chem. Soc.* **2009**, *131*, 10822.

(8) For reviews of 3,3-disubstituted oxindole synthesis, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.

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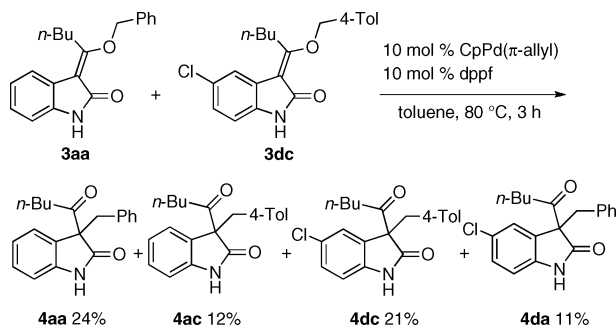
(10) For reviews of [1,3] rearrangement from oxygen to carbon, see: (a) Meek, S. J.; Harriy, J. P. A. *Tetrahedron* **2007**, *63*, 3081. (b) Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240.

(11) For examples of palladium-catalyzed [1,3] rearrangement, see: (a) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840. (b) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475. (c) Evans, P. A.; Brandt, T. A.; Robinson, J. E. *Tetrahedron Lett.* **1999**, *40*, 3105. (d) Langer, P.; Holtz, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 3086. (e) Ghobsi, A.; Hacini, S.; Wavrin, L.; Gaudel-Siri, A.; Corbères, A.; Nicolas, C.; Bonne, D.; Viala, J.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 4446.

(12) For reviews on palladium-catalyzed transformations of benzylic derivatives, see: (a) Liégault, B.; Renaud, J.-L.; Bruneau, C. *Chem. Soc. Rev.* **2008**, *37*, 290. (b) Kuwano, R. *Synthesis* **2009**, 1049.

rearrangement of a benzyl group. We also carried out a crossover experiment using the isolated 3-(alkoxyalkylidene)oxindoles **3aa** and **3dc**, which was prepared from 4-chloro-2-(1-hexynyl)phenyl isocyanate (**1d**) and 4-methylbenzyl alcohol (**2c**) (Scheme 2). Thus, a mixture of **3aa** and

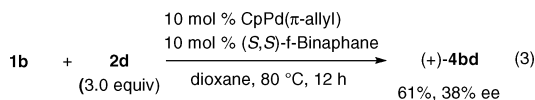
Scheme 2. Crossover Experiment with **3aa** and **3dc**



3dc was subjected to the same reaction conditions, and the formation of the crossover products **4ac** and **4da** was observed in addition to **4aa** and **4dc**.¹⁴ This result indicates that facile dissociation and/or exchange of the stabilized enolate anion occur with the intermediary (η^3 -benzyl)palladium(II) complex **C**.

The results obtained with various combinations of 2-(alkynyl)aryl isocyanates **1** and benzylic alcohols **2** are listed in Table 2. All three isomeric methylbenzyl alcohols (**2c–e**) gave the corresponding products **4ac–ae** in good yield (entries 1–3). Benzylic alcohols **2f** and **2g** having electron-donating and -withdrawing substituents as well as 3-pyridylmethanol (**2h**) were competent substrates for the tandem reaction (entries 4–6). Aryl groups were also tolerated as the R^1 substituent at the alkyne terminus of **1** (entries 7–9).

The asymmetric version was attempted by using **1b** and **2d** as the substrates. Although various chiral ligands were examined, only moderate chiral induction was attained. For example, (+)-**4bd** was obtained in 61% isolated yield with 38% ee when the ferrocene-type ligand (*S,S*)-f-Binaphane¹⁵ was used (eq 3).



We next used allylic alcohols instead of benzylic alcohols (Table 3). When allyl alcohol (**5a**, 10 equiv) was subjected

(13) For examples of benzylation reactions through (η^1 -benzyl or η^3 -benzyl)palladium(II) intermediates, see: (a) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, 33, 2509. (b) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, 125, 12104. (c) Narahashi, H.; Shimizu, I.; Yamamoto, A. *J. Organomet. Chem.* **2007**, 693, 283. (d) Fields, W. H.; Chruma, J. *J. Org. Lett.* **2010**, 12, 316. (e) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, 12, 1360. (f) Torregrosa, R. R. P.; Ariyaratna, Y.; Chattopadhyay, K.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, 132, 9280.

(14) See the Supporting Information for details.

(15) (*S,S*)-f-Binaphane = 1,1'-bis[(*S*)-4,5-dihydro-3H-bi[naphtho][2,1-c:1',2'-e]phosphepino]ferrocene, see: Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, 40, 3425.

Table 2. Pd(0)-Catalyzed Cyclization/[1,3] Rearrangement Reaction of **1** with Benzylic Alcohols **2**^a

entry	1	R^1	2	Ar	4	yield (%) ^b
1	1a	<i>n</i> -Bu	2c	4-Tol	4ac	75
2	1a	<i>n</i> -Bu	2d	3-Tol	4ad	73
3	1a	<i>n</i> -Bu	2e	2-Tol	4ae	73
4	1a	<i>n</i> -Bu	2f	4-MeO-C ₆ H ₄	4af	76
5	1a	<i>n</i> -Bu	2g	4-NO ₂ -C ₆ H ₄	4ag	63 ^c
6	1a	<i>n</i> -Bu	2h	3-pyridyl	4ah	67 ^d
7	1b	Ph	2d	3-Tol	4bd	68
8	1b	Ph	2f	4-MeO-C ₆ H ₄	4bf	74
9	1c	3-thienyl	2a	Ph	4ca	76

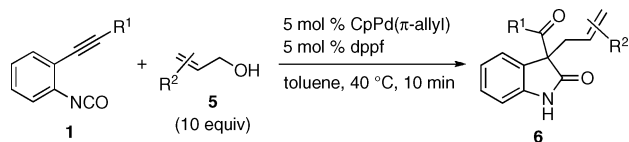
^a Reactions conducted on a 0.2 mmol scale. ^b Isolated yield. ^c With 7.5 mol % of CpPd(π -allyl)/dppe. ^d With 2 equiv of **2h** at 65 °C.

to the reaction with **1a** in the presence of CpPd(π -allyl)/dppe (toluene, 40 °C, 10 min), only the tandem product **6aa** was obtained in 59% yield (entry 1). The expected 3-(1-(allyloxy)pentylidene)oxindole was not detected at all, suggesting that the [1,3] rearrangement step of an allyl group was considerably faster than the cyclization step. This is probably because the formation of (η^3 -allyl)palladium(II) intermediate through oxidative addition onto palladium(0) is much faster than the formation of (η^3 -benzyl)palladium(II) intermediate. Various substituted allylic alcohols **5b–d** were suitable for the reaction with **1a** and **1b**, and the corresponding products were produced in yields ranging from 71% to 79% (entries 2–5). It was noteworthy that the reactions with **5c** and **5d** proceeded regioselectively and the formation of [3,3] rearrangement products (Claisen rearrangement products) was not observed. (*E*)- and (*Z*)-isomers of 2-hexen-1-ol (**5e**) gave the same product **6ae** having (*E*) configuration, being supportive of a common (η^3 -allyl)palladium(II) intermediate (entries 6 and 7). In the case of secondary alcohol **5f**, allylation took place regioselectively at the less substituted position to produce the product **6af** (entry 8).

Interestingly, when the reaction of **1a** with allyl alcohol (**5a**, 20 equiv) was carried out for a longer period of time (12 h), *N*-allylated oxindole **7aa** was formed as the major product (Table 4). The isolated oxindole **6aa** was subjected to a reaction with allyl alcohol (**5a**) in the presence of the same palladium catalyst, and **7aa** was obtained in 94% yield.¹⁶ This reaction involved three mechanistically distinct transformations (cyclization/[1,3] rearrangement/*N*-allylation), all catalyzed by a single palladium complex. The reaction of **1a** with allylic alcohols **5b** and **5c** for 12 h gave

(16) For catalytic substitution reactions of allylic alcohols, see: (a) Qü, J.; Ishimura, Y.; Nagato, N. *Nippon Kagaku Kaishi* **1996**, 256. (b) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, 124, 10968. (c) Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. *J. Am. Chem. Soc.* **2009**, 131, 14317, and references cited therein.

Table 3. Pd(0)-Catalyzed Cyclization/[1,3] Rearrangement Reaction of **1** with Allylic Alcohols **5**^a

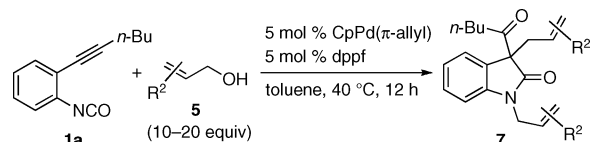


entry	1	5	6	yield (%) ^b
1	1a	5a	6aa	59
2	1a	5b	6ab	71
3	1a	5c	6ac	73
4	1a	5d	6ad	79
5	1b	5d	6bd	77
6	1a	(E)-5e^c	6ae	75
7	1a	(Z)-5e^d	6ae	63
8	1a	5f	6af	56 ^e

^a Reactions conducted on a 0.2 mmol scale. ^b Isolated yield. ^c E:Z = >20:1. ^d E:Z = 1:17. ^e With 20 equiv of **5f** for 3 h.

the corresponding *N*-allylated products **7ab** and **7ac** in 71% and 70% yield, respectively.

Table 4. Pd(0)-Catalyzed Cyclization/[1,3] Rearrangement/Allylation Reaction of **1a** with Allylic Alcohols **5**^a



entry	5	7	yield (%) ^b
1	5a	7aa	71 ^c
2	5b	7ab	71 ^d
3	5c	7ac	70 ^d

^a Reactions conducted on a 0.2 mmol scale. ^b Isolated yield. ^c With 20 equiv of **5a**. ^d With 10 equiv of **5b** and **5c**.

In summary, a new tandem process integrating a cyclization step and a [1,3] rearrangement step has been developed. The produced 3,3-disubstituted oxindoles are an important class of heterocycles often found in naturally occurring and biologically active molecules. Furthermore, three steps of cyclization/[1,3] rearrangement/*N*-allylation are sequentially catalyzed by a single catalyst system.

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Supporting Information Available: Experimental details and spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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