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

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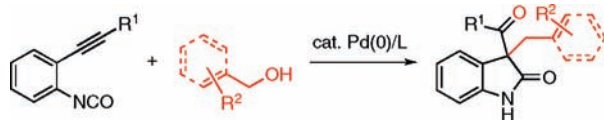
ABSTRACT



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-

(1) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.

(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.

(3) For taxonomy of auto-tandem catalyst, see ref 2c. For alternative classifications/terms, see: Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404.

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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.

(6) For recent examples catalyzed by transition metal complexes except palladium, see: (a) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489. (b) Kelly, B. D.; Allen, J. M.; Tundel, R. E.; Lambert, T. H. *Org. Lett.* **2009**, *11*, 1381. (c) He, H.; Liu, W.-B.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2010**, *49*, 1496. (d) Fructos, M. R.; Álvarez, E.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 4600. (e) Wender, P. A.; Stemmler, R. T.; Sirois, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 2532. (f) Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* **2010**, *12*, 1636.

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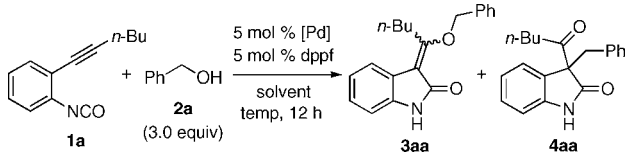
nyl)aryl isocyanates with benzylic (or allylic) alcohols.[7] 3,3-Disubstituted oxindoles are synthesized in one pot through a sequence of cyclization and [1,3] rearrangement of a benzyl (or allyl) group from oxygen to carbon.[8]

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 $Pd_2(dba)_3$•$CHCl_3$/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 reported[9] (Table 1, entry 1). When the

Table 1. Optimization of Reaction Conditions[a]

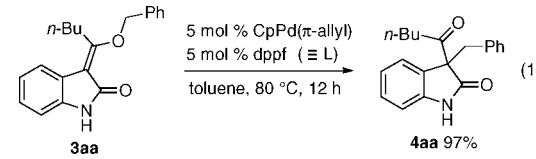


entry	[Pd]	*t* (°C)	solvent	yield of **3aa** (%)[b]	yield of **4aa** (%)
1	$Pd_2(dba)_3$•$CHCl_3$	40	THF	81 (>20:1)	0
2	$Pd_2(dba)_3$•$CHCl_3$	80	THF	56 (9:1)	13
3	$Pd_2(dba)_3$•$CHCl_3$	80	DME	57 (13:1)	13
4	$Pd_2(dba)_3$•$CHCl_3$	80	dioxane	54 (7:1)	16
5	$Pd_2(dba)_3$•$CHCl_3$	80	toluene	41 (1:2)	31
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.

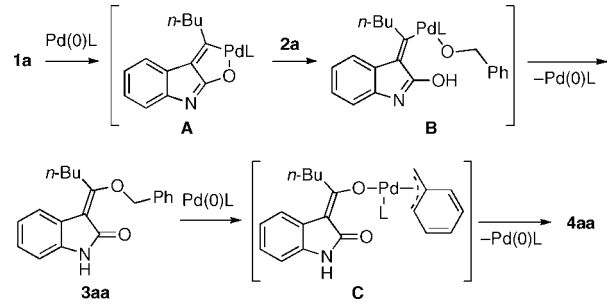
reaction was carried out at an elevated temperature of 80 °C, however, another minor product was formed in addition to **3aa** (entry 2). The structure of the new product was determined to be 3-benzyl-3-pentanoyloxindole (**4aa**) by ^{1}H and ^{13}C NMR spectrometry. Careful examination of the reaction 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]

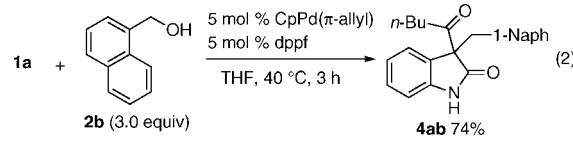


On the other hand, no [1,3] rearrangement of **3aa** was observed in the absence of the palladium catalyst even at 100 °C. These results indicated that **3aa** is initially formed by the palladium-catalyzed cyclization reaction of **1a** with **2a**, as we previously reported,[9] and that the benzyl group bound to an enol oxygen subsequently undergoes 1,3-rearrangement onto an enol carbon, probably via a (η^3-benzyl)palladium(II) complex **C**, to furnish **4aa** (Scheme 1).[12,13] The involvement of a (η^3-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 (η^3-benzyl)palladium(II) intermediate from a benzyl ester through oxidative addition onto palladium(0) is slower than the formation of (η^3-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 (η^3-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.

(9) Miura, T.; Toyoshima, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2009**, *38*, 1174.

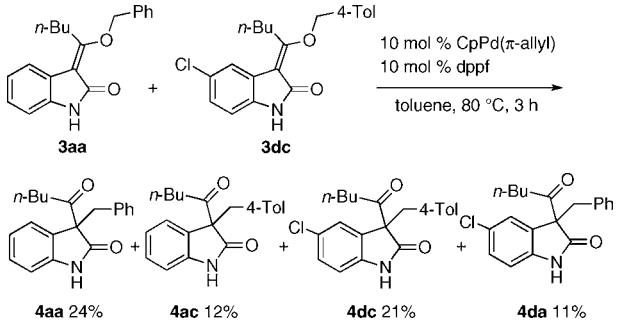
(10) For reviews of [1,3] rearrangement from oxygen to carbon, see: (a) Meek, S. J.; Harrity, J. P. A. *Tetrahedron* **2007**, *63*, 3081. (b) Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240.

(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

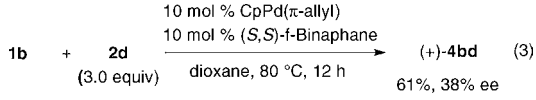
Scheme 2. Crossover Experiment with **3aa** and **3dc**



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**.

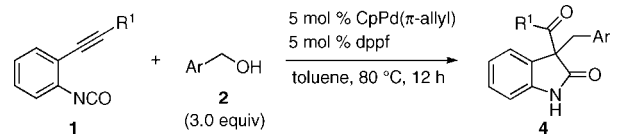
The results obtained with various combinations of 2-(alkynyl)aryl isocyanates **1** and benzylic alcohols **2** are listed in Table 2. All three isomeric methylbenzyl alcohols (**2c**−**e**) gave the corresponding products **4ac**−**ae** in good yield (entries 1−3). Benzylic alcohols **2f** and **2g** having electron-donating and -withdrawing substituents as well as 3-pyridinylmethanol (**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-Binaphane[15] was used (eq 3).



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

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**	*n*-Bu	**2c**	4-Tol	**4ac**	75
2	**1a**	*n*-Bu	**2d**	3-Tol	**4ad**	73
3	**1a**	*n*-Bu	**2e**	2-Tol	**4ae**	73
4	**1a**	*n*-Bu	**2f**	4-MeO-C_6H_4	**4af**	76
5	**1a**	*n*-Bu	**2g**	4-NO_2-C_6H_4	**4ag**	63[c]
6	**1a**	*n*-Bu	**2h**	3-pyridyl	**4ah**	67[d]
7	**1b**	Ph	**2d**	3-Tol	**4bd**	68
8	**1b**	Ph	**2f**	4-MeO-C_6H_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)/dppf. [d] With 2 equiv of **2h** at 65 °C.

to the reaction with **1a** in the presence of CpPd(π-allyl)/dppf (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

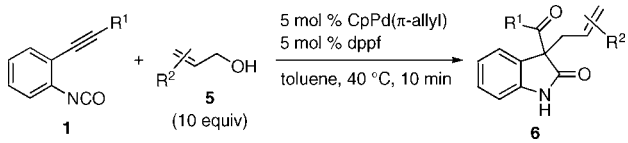
(13) For examples of benzylation reactions through (η^1-benzyl or η^3-benzyl)palladium(II) intermediates, see: (a) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2509. (b) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104. (c) Narahashi, H.; Shimizu, I.; 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.; Ariyarathna, 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-3*H*-binaphtho[2,1-*c*:1′,2′-*e*]phosphepino]ferrocene, see: Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425.

(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]

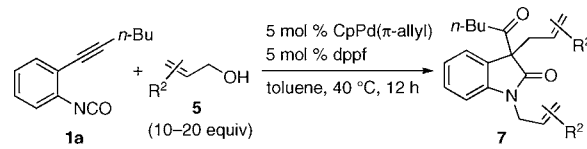


entry	1	5	6	yield (%)[b]
1	**1a**	**5a**	**6aa**	59
2	**1a**	**5b**	**6ab**	71
3	**1a**	**5c**	**6ac**	73
4	**1a**	**5d**	**6ad**	79
5	**1b**	**5d**	**6bd**	77
6	**1a**	(*E*)-**5e**[c]	**6ae**	75
7	**1a**	(*Z*)-**5e**[d]	**6ae**	63
8	**1a**	**5f**	**6af**	56[e]

[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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