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Stereoselective Oxindole Synthesis by Palladium-Catalyzed Cyclization Reaction of 2-(Alkynyl)aryl Isocyanates with Amides

Tomoya Miura, Takeharu Toyoshima, Yusuke Takahashi, and Masahiro Murakami*

Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510, Japan

murakami@sbchem.kyoto-u.ac.jp

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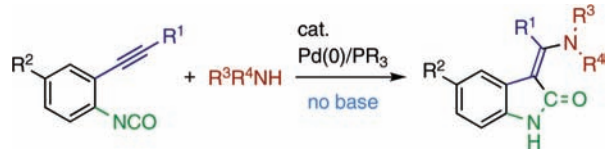
ABSTRACT



A new cyclization reaction occurred on treatment of 2-(alkynyl)aryl isocyanates with amides in the presence of a palladium(0)/diphosphine catalyst to stereoselectively form 3-(amidoalkylidene)oxindoles. A carbon−nitrogen bond as well as a carbon−carbon bond were simultaneously introduced onto the alkyne moiety to construct an oxindole skeleton with stereoselective placement of the amino substituent *cis* to the carbonyl group.

Transition metal-catalyzed C−N bond-forming reactions have been the subject of intense research[1] because of the importance of nitrogen-containing compounds. Oxindoles are often found in bioactive molecules as the key substructure,[2] which has driven increased interest in exploring new methods for their preparation. In particular, 3-(aminoalkylidene)oxindoles are of significant pharmaceutical value,[3] and therefore, methods to prepare them in a stereodefined way are in high demand. We report herein a palladium-catalyzed cyclization reaction of 2-(alkynyl)aryl isocyanates[4] with primary and secondary amides, which produces 3-(amidoalkylidene)oxindoles.[5] The reaction allows for the intermolecular C−N bond introduction onto the alkyne moiety *cis* to the developing carbonyl group in a stereoselective fashion.

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(5) For recent example of the synthesis of 3-alkylideneoxindoles with transition-metal catalysis other than reference,[4] see: (a) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972. (b) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (c) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799. (d) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291. (e) Tang, S.; Yu, Q.-F.; Peng, P.; Li, J.-H.; Zhong, P.; Tang, R.-Y. *Org. Lett.* **2007**, *9*, 3413. (f) Tang, S.; Peng, P.; Pi, S.-F.; Liang, Y.; Wang, N.-X.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1179. (g) Tang, S.; Peng, P.; Wang, Z.-Q.; Tang, B.-X.; Deng, C.-L.; Li, J.-H.; Zhong, P.; Wang, N.-X. *Org. Lett.* **2008**, *10*, 1875. (h) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058.

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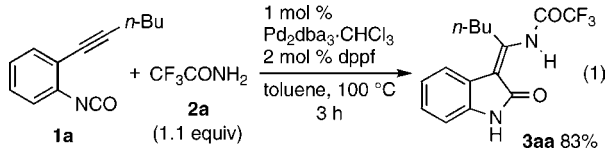
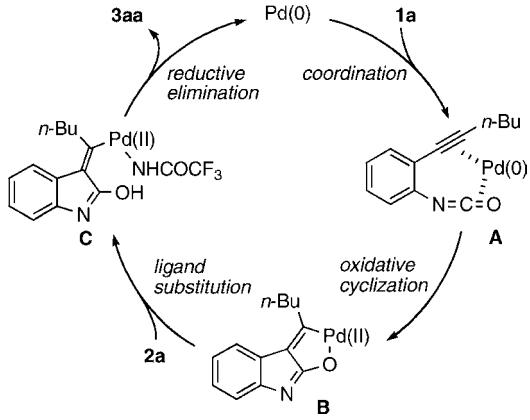
We previously described the palladium-catalyzed cyclization of 2-(alkynyl)aryl isocyanates with organoboron reagents.[6] In this reaction, an oxapalladacyclic intermediate formed by oxidative cyclization undergoes transmetalation with an organoboron species, converting a palladium−oxygen bond into a palladium−carbon bond. It was then envisaged that the use of protic nitrogen nucleophiles in place of organoborons would result in the generation of a palladium−nitrogen bond through ligand substitution, leading to the introduction of a carbon−nitrogen linkage. Thus, 2-(1-hexynyl)phenyl isocyanate (**1a**, 1.0 equiv) was treated with trifluoroacetamide (**2a**, 1.1 equiv) in the presence of $Pd_2(dba)_3$·$CHCl_3$/dppf (1 mol %; dppf = 1,1′-bis(diphenylphosphino)ferrocene) in toluene (0.05 M) at 100 °C. The reaction reached completion in 3 h, and an extractive workup followed by precipitation from CH_2Cl_2/hexane afforded the 3-(amidoalkylidene)oxindole **3aa** in 83% yield as a single stereoisomer (Z/E = >20:1,[7] eq 1).



We propose that the reaction proceeds through the pathway outlined in Scheme 1. Initially, both alkynyl and isocyanato

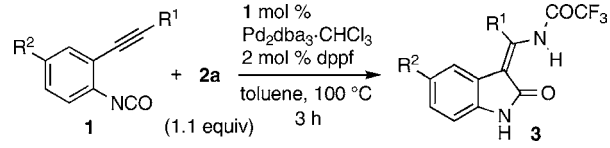
Scheme 1. Proposed Reaction Pathway

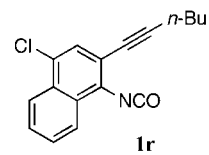
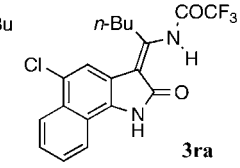


groups of **1a** coordinate to a palladium(0) center prompting oxidative cyclization to form oxapalladacyclic intermediate **B**.[8] The palladium(II) oxide moiety then acts as a base to promote ligand substitution by amide **2a** and thus, the additional usage of an external base is dispensed with for generation of the palladium(II) amide species **C**.[9] Finally, reductive elimination from **C** affords the product **3aa**, regenerating the palladium(0) catalyst.

As shown in Table 1, primary and secondary alkyl groups were suitable for the substituent at the alkyne terminus (entries 1−3). Even the bulky *tert*-butyl group permitted the reaction, albeit under more forcing conditions, to give the product **3ea** in 56% yield (entry 4). Substrates possessing a wide range of aryl and heteroaryl groups successfully participated in the cyclization reaction (entries 5−10). Vinyl-substituted substrate **1l** was also converted to the product **3la** in good yield (entry 11).[10] Functional groups including halide, ether, ester, and nitrile were tolerated on the aryl group of **1** (entries 12−17). Interestingly, even the bromo group of **1m** remained intact.

Table 1. Pd(0)-Catalyzed Cyclization Reaction of **1** with Trifluoroacetamide (**2a**)[a]



entry	**1**	R^1	R^2	**3**	yield (%)[b]
1	**1b**	*n*-Pr	H	**3ba**	86
2	**1c**	*i*-Pr	H	**3ca**	88
3	**1d**	cyclopropyl	H	**3da**	79
4	**1e**	*t*-Bu	H	**3ea**	56[c]
5	**1f**	Ph	H	**3fa**	99
6	**1g**	4-MeO–C_6H_4	H	**3ga**	93
7	**1h**	4-CF_3–C_6H_4	H	**3ha**	86
8	**1i**	4-CH_3–C_6H_4	H	**3ia**	93
9	**1j**	2-CH_3–C_6H_4	H	**3ja**	99
10	**1k**	3-thienyl	H	**3ka**	95
11	**1l**	vinyl	H	**3la**	72
12	**1m**	Ph	Br	**3ma**	99
13	**1n**	*n*-Bu	Cl	**3na**	74
14	**1o**	*n*-Bu	OMe	**3oa**	84
15	**1p**	*n*-Bu	CO_2Et	**3pa**	80
16	**1q**	*n*-Bu	CN	**3qa**	82
17					96

[a] Conditions: **1** (0.2 mmol), **2a** (0.22 mmol), $Pd_2(dba)_3$·$CHCl_3$ (2 μmol, 1 mol %), and dppf (4 μmol, 2 mol %) in toluene (4 mL) at 100 °C for 3 h under Ar. [b] Isolated yield (stereoisomer ratio = >20:1). [c] **2a** (0.6 mmol, 3 equiv) was used for 13 h.

(6) (a) Miura, T.; Toyoshima, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, *10*, 4887. See also: (b) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2007**, *9*, 5075. (c) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, *10*, 1743.

(7) The stereochemistry of the exocyclic double bond was assigned by a difference NOE study.

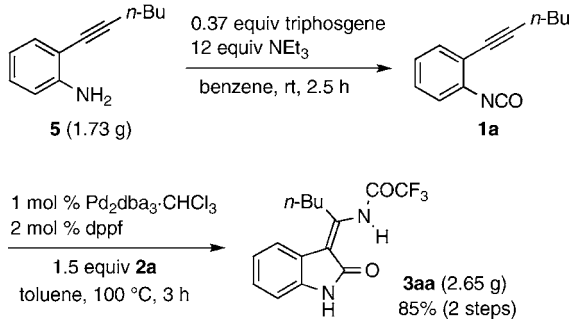
(8) A result supportive for the presumed oxapalladacycle was obtained by a ^1H NMR study; when **1a** was treated with a stoichiometric amount of Pd_2dba_3·$CHCl_3$ and dppf in THF-d_8 at 80 °C for 2 h, the signal ($-CH_2C_3H_7$) shifted downfield from 2.45 to 2.76 ppm. However, an attempt to isolate it as solids has been unsuccessful so far.

(9) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4206.

(10) The substrates with R1 = H and $SiMe_3$ gave a complex mixture.

A straightforward synthesis of **3aa** on a gram scale was also carried out to demonstrate the practicality of the present method (Scheme 2). Product **3aa** (2.65 g, 8.5 mmol) was

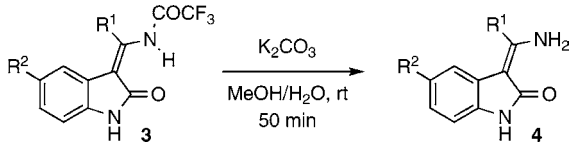
Scheme 2. Synthesis of **3aa** on Gram Scale



obtained starting from 2-(1-hexynyl)aniline (**5**, 1.73 g, 10 mmol) via the corresponding isocyanate **1a** without intervention of any chromatographic purification (85% yield over two steps).

Next, hydrolysis of the trifluoroacetylamide group was examined since 3-(free aminoalkylidene)oxindoles **4** have been identified as potent kinase inhibitors.[11] In fact, this group could be easily removed by treatment with the mild base K_2CO_3,[12] as exemplified in Table 2.

Table 2. Deprotection Reaction of Trifluoroacetyl Group[a]

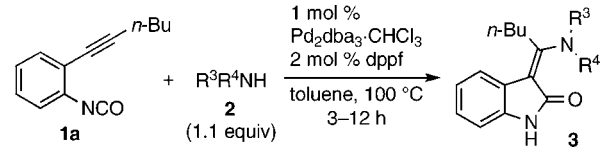


entry	**3**	R^1	R^2	**4**	yield[b] (%)
1	**3aa**	*n*-Bu	H	**4a**	89
2	**3fa**	Ph	H	**4f**	85
3	**3ka**	3-thienyl	H	**4k**	89
4	**3na**	*n*-Bu	Cl	**4n**	90

[a] Conditions: **3** (0.15 mmol), K_2CO_3 (0.77 mmol) in MeOH/H_2O (4.5/0.1 mL) at rt for 50 min under Ar. [b] Isolated yield (stereoisomer ratio = >20:1).

We studied the scope of nitrogen nucleophiles **2** for the reaction of **1a**; the results are listed in Table 3. A variety of primary amides **2b**−**e** including *N*-benzylurea worked well to give the corresponding 3-(amidoalkylidene)oxindoles

Table 3. Pd(0)-Catalyzed Cyclization Reaction of **1a** with **2**[a]



entry	**2**	R^3R^4NH	**3**	yield[b] (%)
1	**2b**	4-$CH_3C_6H_4SO_2NH_2$ ($TsNH_2$)	**3ab**	94
2	**2c**	$C_6H_5CONH_2$ ($BzNH_2$)	**3ac**	68
3	**2d**	$C_6H_5CH_2OCONH_2$ ($CbzNH_2$)	**3ad**	69[c]
4	**2e**	$C_6H_5CH_2NHCONH_2$	**3ae**	83
5	**2f**	phthalimide	**3af**	98[d]
6	**2g**	indolin-2-one	**3ag**	90
7	**2h**	oxazolidin-2-one	**3ah**	64
8	**2i**	aniline	**3ai**	44

[a] The reaction conditions are the same as those in Table 1 unless otherwise noted. [b] Isolated yield (stereoisomer ratio = >20:1). [c] **2d** (0.6 mmol, 3 equiv) and BINAP (4 μmol, 2 mol %) as the ligand were used. [d] **2f** (0.6 mmol, 3 equiv) was used.

3ab−**ae** in yields ranging from 68% to 94% (entries 1−4). The cyclization also occurred with secondary amides such as phthalimide (**2f**), indolin-2-one (**2g**), and oxazolidin-2-one (**2h**) to afford the corresponding products in good yield (entries 5−7). The reaction with aniline (**2i**) gave the product **3ai** in 44% yield, together with a side product arising from the direct addition of **2i** to the isocyanato group (entry 8).

In summary, we have developed a palladium-catalyzed amidative cyclization reaction to synthesize 3-(amidoalkylidene)oxindoles in a highly atom economical manner. The overall reaction accomplishes both intramolecular C−C bond formation and intermolecular C−N bond formation across a carbon−carbon triple bond in a stereoselective fashion. This unique example of cyclization will inspire the development of transition metal-catalyzed reactions producing valuable nitrogen-containing compounds via metallacyclic intermediates.

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

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(12) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1988**, *53*, 3108.