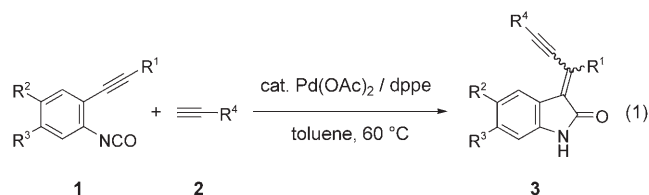


DOI: 10.1002/ange.200502252

Oxindole Synthesis through Intramolecular Nucleophilic Addition of Vinylpalladiums to Aryl Isocyanates**

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One of the main targets in the field of synthetic organic chemistry these days is the development of reactions promoted by a catalyst. Not only metal catalysts but also organo-derived catalysts have been studied and applied in various kinds of transformation.^[1] Among the transition metals applied in catalytic reactions so far, palladium complexes have found wide utility in various types of transformation.^[2] In most cases, organopalladium species containing a Pd–C bond generated during the course of the reaction act either as electrophiles or as neutral species, and it is rare for these species to behave as nucleophiles.^[3] Several methods have been reported to transform the electrophilic reactivity to a nucleophilic one, although these methods are generally based on the transmetalation of a C–Pd bond to a nucleophilic C–M bond in situ.^[4] Recently, direct nucleophilic reactions of organopalladiums to carbon–heteroatom unsaturated bonds were discovered by us and by other groups in the allylpalladation of imines and aldehydes,^[5] vinylpalladation of ketones, aldehydes, imines, and cyanides,^[6] and the arylpalladation of ketones and cyanides.^[7] We report herein the first example of intramolecular nucleophilic vinylpalladation of isocyanates to produce oxindoles **3**^[8] from 2-(alkynyl)phenylisocyanates **1** and terminal alkynes **2** [Eq. (1)].



During the course of our investigation into the dual-role catalysis of palladium and platinum in the reaction between 2-(alkynyl)phenylisocyanates and alcohols that leads to the formation of indoles,^[9] we found that a coupling reaction between 2-(alkynyl)phenylisocyanates **1** and terminal alkynes **2** took place to afford oxindoles **3**. We chose 2-(1-pentynyl)-phenylisocyanate **1a** and 1-pentyne **2a** as a standard set of starting materials for the optimization of the reaction conditions to yield the corresponding oxindole **3a** (Table 1).

Table 1: Optimization of reaction conditions for the formation of the oxindole **3a** from **1a** and **2a** [cf. Eq. (1)].^[a]

Entry	Pd catalyst (mol %)	Phosphine (mol %)	t [h]	Yield of 3a [%] ^[b]
1	Pd(OAc) ₂ (5)	tdmpp (10)	2	45 ^[c]
2	Pd(OCOCF ₃) ₂ (5)	tdmpp (10)	> 20	23 ^[c]
3	[(η ³ -C ₃ H ₅)PdCl] ₂ (2.5)	tdmpp (10)	> 20	0 ^[d]
4	Pd ₂ (dba) ₃ ·CHCl ₃ (2.5)	tdmpp (10)	> 20	7 ^[c,d]
5	Pd(OAc) ₂ (5)	ttmpp (10)	2	51 ^[c]
6	Pd(OAc) ₂ (5)	PPh ₃ (10)	2	17 ^[c]
7	Pd(OAc) ₂ (5)	dppe (5)	2	62 ^[c]
8	Pd(OAc) ₂ (5)	dppp (5)	2	50 ^[c,e]
9	Pd(OAc) ₂ (5)	dppb (5)	2	26 ^[c,e]
10	Pd(OAc) ₂ (3)	dppe (3)	2	80 ^[c]
11	Pd(OAc) ₂ (3)	dppe (3)	1	80 ^[f]
12 ^[g]	Pd(OAc) ₂ (3)	dppe (3)	1.5	76 ^[e,h]

[a] dba = *trans,trans*-dibenzylideneacetone, tdmpp = tris(2,6-dimethoxyphenyl)phosphine, ttmpp = tris(2,4,6-trimethoxyphenyl)phosphine, dppe = 1,2-bis(diphenylphosphanyl)ethane, dppp = 1,3-bis(diphenylphosphanyl)propane, dppb = 1,4-bis(diphenylphosphanyl)butane. [b] Yield of isolated product unless otherwise noted. [c] *E* isomer, (*E*)-**3a**, was obtained almost exclusively. [d] Substrate **1a** was recovered. [e] Yield measured by NMR spectroscopy with CH₂Br₂ as an internal standard. [f] Combined yield of the *E* and *Z* isomers (*E*)-**3a** and (*Z*)-**3a**. *E/Z* = 85:15. [g] The reaction was conducted at 40 °C. [h] (*E*)-**3a**/*Z*-**3a** = 33:67.

The reaction under a catalytic amount of Pd(OAc)₂ and TDMPP produced **3a** in 45 % yield in 2 h (entry 1). The *E* isomer of the oxindole, (*E*)-**3a**, was obtained almost exclusively (cf. Eq. (2) for structures of (*E*)- and (*Z*)-**3a**). The combination of Pd(OCOCF₃)₂ and TDMPP catalyzed the formation of **3a** in 23 % yield, but the [(η³-C₃H₅)PdCl]₂/TDMPP catalyst did not give the corresponding oxindole **3a** at all (entries 2 and 3). The desired oxindole **3a** was also obtained from the reaction with [Pd₂(dba)₃·CHCl₃] and TDMPP, although the yield was rather low (entry 4). We then investigated the effects of phosphine ligands combined with Pd(OAc)₂. The reactivity of ttmpp was comparable to

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[**] We thank members of the Research and Analytical Center for Giant Molecules at the Graduate School of Science, Tohoku University, for measurement of mass spectra, elemental analyses, and X-ray crystallographic analyses. This work was supported in part by a Grant-in-Aid for Encouragement of Young Scientists (B) from JSPS. T.S. also acknowledges JSPS for a fellowship in the Summer Program (2002).

that of TDMPP, whereas the reactivity of PPh_3 was inferior (entries 5 and 6). The bidentate phosphine ligands in dppe, dppp, and dppb also produced the corresponding oxindole **3a** (entries 7–9). Among these catalysts, the combination of $\text{Pd}(\text{OAc})_2$ and dppe showed the highest catalytic activity: **3a** was formed in 62 % yield. When the amounts of the catalysts were reduced to 3 mol % each for $\text{Pd}(\text{OAc})_2$ and dppe, the yield of the oxindole **3a** was increased to 80 % yield with almost exclusive formation of the *E* isomer, (*E*)-**3a** (entry 10). When the reaction was quenched right after the consumption of the starting isocyanate **1a** (1 h), a mixture of the *E* and *Z* isomers of the oxindole, (*E*)-**3a** and (*Z*)-**3a**, was obtained in 80 % combined yield with a ratio of 85:15 (entry 11). The reaction could proceed even at 40 °C to give the oxindole in 76 % combined yield with a 33:67 ratio of the *E* and *Z* isomers (entry 12).

With the optimized reaction conditions in hand, we examined the scope and limitations of the present palladium-catalyzed oxindole-forming reaction (Table 2). As men-

Table 2: Reaction between various isocyanates **1** and **2a**.^[a]

Entry	R ¹	R ²	R ³	1	t [h]	3	Yield [%] ^[b] (<i>E/Z</i>)
1	Pr	H	H	1a	2	3a	80 (>99:1)
2	cyclohexyl	H	H	1b	4	3b	58 (>99:1)
3	<i>t</i> Bu	H	H	1c	24	3c	26 (>99:1) ^[c]
4	Ph	H	H	1d	24	3d	— ^[d]
5	Pr	OMe	H	1e	1	3e	73 (>99:1)
6	Pr	SMe	H	1f	1	3f	52 (>99:1)
7	Pr	Cl	H	1g	1.5	3g	44 (>99:1)
8	Pr	H	OMe	1h	2	3h	48 (33:67)
9	Pr	H	CF ₃	1i	24	3i	33 (>99:1) ^[e]

[a] The reaction of **1** and **2a** (2 equiv) was conducted in the presence of $\text{Pd}(\text{OAc})_2$ (3 mol %) and dppe (3 mol %) in toluene (0.5 M) at 60 °C for the time shown in the table. [b] Yield of isolated product unless otherwise noted. [c] Substrate **1c** was recovered. [d] Complex mixture. [e] Substrate **1i** was recovered.

tioned above, treatment of **1a** with **2a** in the presence of a catalytic amount of $\text{Pd}(\text{OAc})_2$ (3 mol %) and dppe (3 mol %) in toluene (0.5 M) at 60 °C for 2 h afforded the *E* isomer of **3a** almost exclusively in 80 % yield after isolation (entry 1). The isocyanate **1b** bearing a cyclohexyl group at the end of the acetylenic group gave the corresponding oxindole **3b** in 58 % yield as the *E* isomer (entry 2). In the case of the isocyanate **1c** with a bulky *tert*-butyl substituent, the reaction did not reach completion even after 24 h, and the desired product **3c** was obtained in only 26 % yield (entry 3). The phenyl-substituted isocyanate **1d** gave a complex mixture of unidentified products (entry 4). The substrates **1e** and **1f**, having electron-donating methoxy and methylthio groups, respectively, *para* to the isocyanato group, produced the corresponding oxindoles **3e** and **3f** in moderate to good yields (entries 5 and 6). The isocyanate **1g** with an electron-withdrawing chloride substituent on the benzene ring gave the desired product **3g** in 44 % yield (entry 7). The reactions of isocyanates **1h** and **1i**, each bearing a substituent *para* to the alkynyl group, furnished the corresponding oxindoles **3h** and

3i, respectively, in moderate yields (entries 8 and 9). A mixture of *E* and *Z* isomers of the corresponding oxindole, (*E*)-**3h** and (*Z*)-**3h**, was obtained in the case of **1h**, which bears an electron-donating group *para* to the alkynyl group.

We next investigated the reactions between the isocyanate **1a** and a variety of terminal alkynes **2** (Table 3). With

Table 3: Reaction between **1a** and various terminal alkynes **2**.^[a]

Entry	R ⁴	2	t [h]	3	Yield [%] ^[b] (<i>E/Z</i>)
1	Pr	2a	2	3a	80 (>99:1)
2	cyclohexyl	2b	2	3j	53 (>99:1)
3	<i>t</i> Bu	2c	20	3k	16 (1:>99)
4	Ph	2d	0.5	3l	67 (22:78)
5	TMS ^[c]	2e	2.5	3m	61 (35:65)

[a] The reaction of **1a** and **2** (2 equiv) was conducted in the presence of $\text{Pd}(\text{OAc})_2$ (3 mol %) and dppe (3 mol %) in toluene (0.5 M) at 60 °C for the time shown in the table. [b] Yield of isolated product. [c] TMS = trimethylsilyl.

increases in the bulkiness of the terminal alkynes **2a–c**, the yields of the desired products **3a**, **3j**, and **3k** decreased (entries 1–3). It is worth mentioning that the *Z* isomer of **3k** was obtained almost exclusively when bulky *tert*-butylacetylene **2c** was used as the starting material. Phenylacetylene **2d** and (trimethylsilyl)acetylene **2e** reacted to produce the corresponding oxindoles **3l** and **3m**, respectively, in moderate yields as a mixture of the *E* and *Z* isomers (entries 4 and 5). The structures of oxindoles were determined by detailed analyses of the spectroscopic data. Furthermore, the structure of the oxindoles (*E*)-**3l** and (*Z*)-**3l** were unambiguously confirmed by X-ray crystallographic analyses (Figure 1).

The following mechanism is proposed for the unprecedented intramolecular vinylpalladation of isocyanates to form

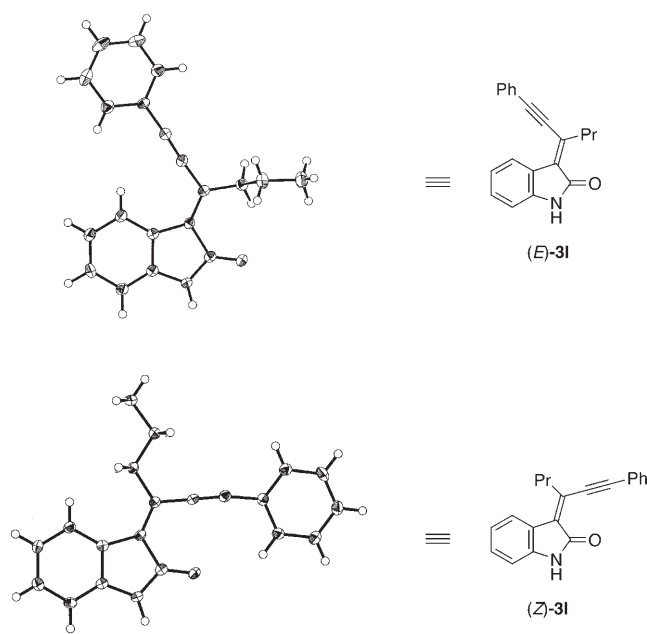
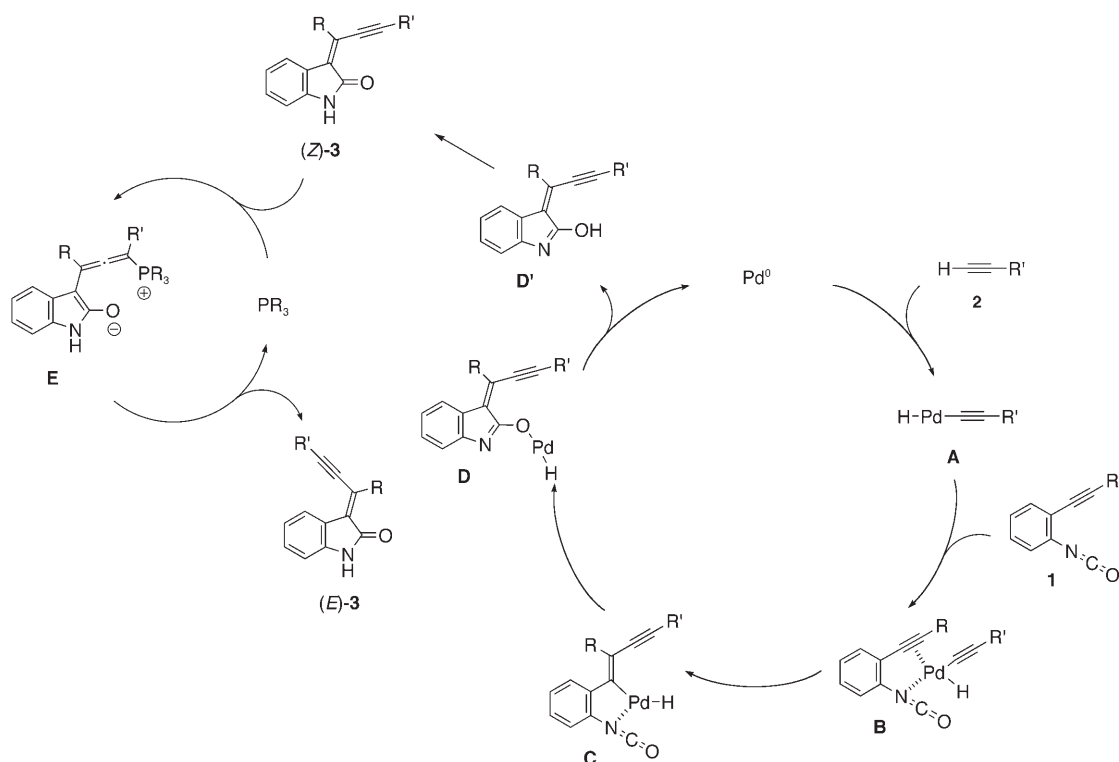


Figure 1. X-ray crystal structures of (*E*)-**3l** and (*Z*)-**3l**.

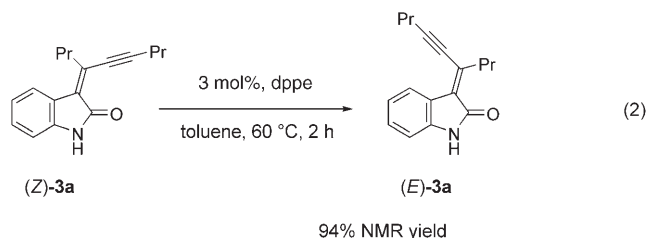


Scheme 1. Proposed mechanism for the formation of oxindoles through intramolecular vinylpalladation of isocyanates.

oxindoles (Scheme 1). A Pd^0 species is generated in situ^[10] and oxidatively adds to the C–H bond of terminal alkyne **2** to give intermediate **A**. The derived species **A** would coordinate to both the alkynyl and the isocyanato moieties in **1** to form intermediate **B**, in which the palladium metal behaves as a dual-role catalyst.^[9,11] Carbopalladation of the C–C triple bond in **1** yields the vinylpalladium intermediate **C**.^[12] Intramolecular nucleophilic attack of the vinylpalladium species on the isocyanato group would produce the cyclized oxy-palladium intermediate **D**, which would be transformed into **D'** after reductive elimination of the Pd^0 . The intermediate **D'** would isomerize to the corresponding oxindole (*Z*)-**3**.

Conversion of the *Z* isomer of oxindole **3** into its *E* isomer, (*E*)-**3**, is catalyzed by the phosphine, dppe, existing in the reaction mixture. Nucleophilic addition of the phosphine to the electrophilic carbon center in the alkynyl moiety of (*Z*)-**3** would produce the zwitterionic intermediate **E**.^[13] Rotation of the newly formed σ bond between the indole core and the allenyl moiety and subsequent elimination of the phosphine furnishes the corresponding *E* oxindole (*E*)-**3**. This explains well that the exclusive or predominant formations of *Z* oxindoles were observed when the reaction was conducted with the methoxy-substituted isocyanate **1h** and the bulky terminal alkynes **2c–e** as substrates. The electron flow from the properly substituted methoxy group to the enyne moiety in (*Z*)-**3i** or the steric congestion around the enyne moiety in (*Z*)-**3k–m** would hinder the nucleophilic approach of the phosphine toward the electrophilic carbon center in the alkynyl moiety in the corresponding *Z* oxindoles (entry 8 in Table 2 and entries 3–5 in Table 3). Indeed, the reaction of

(*Z*)-**3a** in the presence of a catalytic amount of dppe resulted in a clean formation of (*E*)-**3a** in 2 h [Eq. (2)].



We have achieved the synthesis of oxindoles **3** from aryl isocyanates **1** and terminal alkynes **2** in the presence of a catalytic amount of $\text{Pd}(\text{OAc})_2$ and dppe. This oxindole-forming reaction most probably proceeds through the intramolecular nucleophilic attack of a vinylpalladium species on the isocyanato group. Further studies on synthetic applications and a mechanistic investigation are in progress in our laboratory.

Experimental Section

1-Pentyne (60 μL , 0.6 mmol) was added to a toluene solution (0.6 mL) of **1a** (55.6 mg, 0.3 mmol), $\text{Pd}(\text{OAc})_2$ (2.0 mg, 0.009 mmol), and dppe (3.6 mg, 0.009 mmol) under an argon atmosphere. The solution was stirred at 60 °C for 2 h. The reaction mixture was cooled to RT, filtered through a short Florisil pad with AcOEt as

the eluent, and concentrated. The residue was purified by silica gel column chromatography to afford (*E*)-**3a** in 68% yield (51.7 mg).

Received: June 27, 2005

Published online: November 8, 2005

Keywords: alkynes · isocyanates · nucleophilic addition · oxindoles · palladium

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