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Editor's Choice

Stereoselective Synthesis of 3-(1-Cyanoalkylidene)oxindoles by Palladium-catalyzed Cyclization Reaction of 2-(Alkynyl)aryl Isocyanates with Copper(I) Cyanide

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A palladium-catalyzed cyclization reaction of 2-(alkynyl)-aryl isocyanates with copper(I) cyanide provides an efficient method for the stereoselective synthesis of (*Z*)-configured 3-(1-cyanoalkylidene)oxindoles.

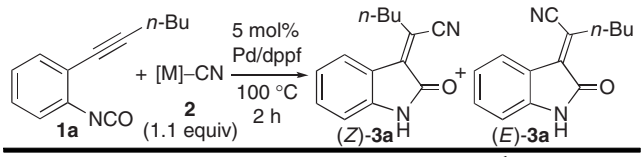
The 3-alkylideneoxindole (3-alkylideneindolin-2-one) skeleton is a prevalent structural motif found in a number of biologically active compounds in therapeutic use such as Semaxanib,[1] Sunitinib,[2] Tenidap,[3] and Soulieotine.[4] In addition, 3-alkylideneoxindoles have been widely employed as valuable intermediates in the synthesis of indole alkaloids and drug candidates.[5,6] Thus, considerable efforts have been made on the development of efficient methods for the construction of this skeleton. Transition-metal-catalyzed cyclization reactions present useful methods for the stereoselective synthesis of unsymmetrically substituted 3-alkylideneoxindoles.[7] For example, *N*-methyl-*N*,3-diphenylpropiolamide reacted with aryl halides in the presence of a palladium catalyst to give stereochemically defined 3-(1-aryl-1-phenylmethylidene)oxindoles through a sequence of carbopalladation/C–H activation/intramolecular C–C bond formation processes.[7a] Heteroatom-substituted 3-alkylideneoxindoles were synthesized by palladium-catalyzed cyclization reactions of *N*-methyl-*N*,3-diphenylpropiolamide with phthalimide[7c] or acetic acid.[7d] On the other hand, we have recently reported the palladium-catalyzed cyclization reactions of 2-(alkynyl)aryl isocyanates[8] with external nucleophiles such as organoboronic acids,[9a] amides,[9b] alcohols, and thiols.[9c] These reactions permit the stereoselective incorporation of various kinds of substituents on the exocyclic double bond of the resulting 3-alkylideneoxindoles. We next examined the possibility to incorporate a cyano nucleophile with good stereoselectivity analogous to that observed with other nucleophiles. In this paper are described the results of the palladium-catalyzed cyclization reaction of 2-(alkynyl)aryl isocyanates with copper(I) cyanide.[10]

When 2-(1-hexynyl)phenyl isocyanate (**1a**, 1.0 equiv) was treated with potassium cyanide (**2a**) (1.1 equiv) in the presence of $Pd_2(dba)_3 \cdot CHCl_3$/dppf (5.0 mol % of Pd; dppf = 1,1′-bis(diphenylphosphino)ferrocene) in DMF at 100 °C for 2 h, 3-(1-cyanopentylidene)oxindole (**3a**) was produced in 11% NMR yield (*Z*/*E* = 5:>95, Table 1, Entry 1). Although a cyano nucleophile was introduced on the exocyclic double bond, the observed stereochemistry was opposite to our expectation. The screening of metal cyanides revealed that the use of copper(I) cyanide considerably improved the yield and, in particular, selectively produced the (*Z*)-isomer (*Z*/*E* = 94:6, Entry 5). Furthermore, changing the solvent to 1,4-dioxane led to the best result in terms of both yield and selectivity (84% yield, *Z*/*E* = >95:5, Entry 6).[11,12]

We propose the following mechanism shown in Scheme 1, which is analogous to that we previously postulated for the cyclization reaction of 2-(alkynyl)aryl isocyanates with organoboronic acids.[9a] Initially, substrate **1a** binds to a palladium(0) catalyst to generate the chelate complex **A**, which undergoes oxidative cyclization to form the oxapalladacycle **B**. Subsequent transmetalation of **B** with copper(I) cyanide produces the palladium(II) cyanide **C**. Finally, reductive elimination affords the intermediary copper alkoxide **D** and regenerates the starting palladium(0) catalyst. Protonolysis of **D** occurs during aqueous workup to give the (*Z*)-configured **3a** in a stereoselective manner.

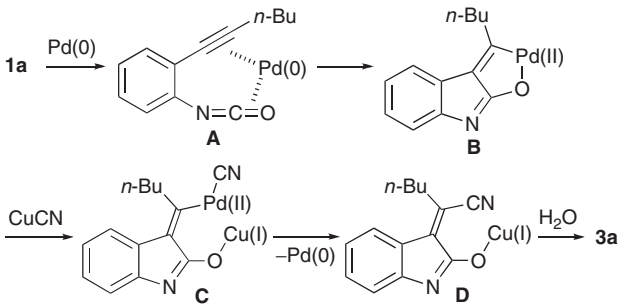
A variety of 2-(alkynyl)aryl isocyanates are subjected to the palladium-catalyzed reaction with copper(I) cyanide (**2e**) (Table 2). The substrates **1b**–**1d** possessing primary and secondary alkyl groups at the alkyne terminus reacted well to afford the corresponding 3-(1-cyanoalkylidene)oxindoles **3b**–**3d** in good yields with excellent selectivities (*Z*/*E* = >95:5, Entries 1–3). Even a bulky *tert*-butyl group permitted the reaction and

Table 1. Optimization of reaction conditions[a]



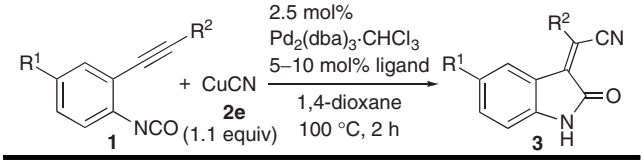
Entry	[M]–CN (**2**)	Solvent	Yield/%[b]	*Z*/*E*[c]
1	KCN (**2a**)	DMF	11	5:>95
2	$K_4Fe(CN)_6$ (**2b**)	DMF	0	—
3	*n*-Bu_3SnCN (**2c**)	DMF	44	89:11
4	$Zn(CN)_2$ (**2d**)	DMF	64	33:67
5	CuCN (**2e**)	DMF	99	94:6
6	CuCN (**2e**)	1,4-dioxane	99 (84)	>95:5

[a]Reaction conditions: **1a** (0.20 mmol), [M]–CN (0.22 mmol), $Pd_2(dba)_3 \cdot CHCl_3$/dppf (5.0 mol % of Pd) in solvent (2 mL) at 100 °C for 2 h. [b]^{1}H NMR yield using $CHCl_2CHCl_2$ as an internal standard, isolated yield in parenthesis. [c]The ratio determined by ^{1}H NMR.



Scheme 1. A proposed mechanism.

Table 2. Pd(0)-catalyzed cyclization of **1** with CuCN (**2e**)[a]

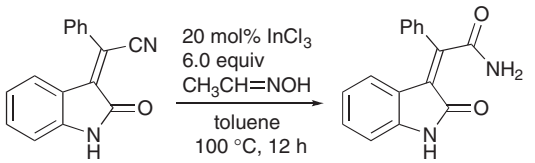


Entry	1	R^1	R^2	Ligand	3	Yield/%[b]	Z/E[c]
1	**1b**	H	*n*-Pr	dppf	**3b**	83	>95:5
2	**1c**	H	*c*-Pr	dppf	**3c**	89	>95:5
3	**1d**	H	*i*-Pr	dppf	**3d**	84	>95:5
4	**1e**	H	*t*-Bu	dppf	**3e**	58	93:7
5	**1f**	H	Ph	tfp[d]	**3f**	90	>95:5
6	**1g**	H	4-$MeOC_6H_4$	dppf	**3g**	90	92:8
7	**1h**	H	4-$CF_3C_6H_4$	tfp[d]	**3h**	84	95:5
8	**1i**	H	4-$CH_3C_6H_4$	dppf	**3i**	81	92:8
9	**1j**	H	2-$CH_3C_6H_4$	dppf	**3j**	87	>95:5
10	**1k**	H	3-Thienyl	tfp[d]	**3k**	77	93:7
11	**1l**	Br	Ph	tfp[d]	**3l**	66	>95:5
12	**1m**	Cl	*n*-Bu	dppf	**3m**	59	95:5
13	**1n**	OMe	*n*-Bu	dppf	**3n**	60	83:17
14	**1o**	CO_2Et	*n*-Bu	dppf	**3o**	74	>95:5

[a]Reactions conducted on a 0.20 mmol scale. [b]Isolated yield. [c]The ratio determined by ^{1}H NMR. [d]tfp = tris(2-furyl)phosphine.

the product **3e** was isolated in 58% yield (Entry 4). The substrates **1f**–**1k** possessing a wide range of aryl and heteroaryl groups successfully participated in the cyclization reaction (Entries 5–10). Tris(2-furyl)phosphine was used as the ligand in place of dppf in the reaction of **1f**, **1h**, **1k**, and **1l** in order to obtain the corresponding products in good yields. Functional groups including halide, ether, and ester were tolerated on the aryl group of **1** (Entries 11–14). Noteworthy was that even the bromo group of **1l** remained intact in the presence of a palladium catalyst.

The synthetic utility of 3-(1-cyanoalkylidene)oxindoles was exemplified by further transformation shown in eq 1. Treatment of **3f** (Z/E = >95:5) with acetaldehyde oxime (6.0 equiv) in the presence of $InCl_3$ (20 mol %)[13] resulted in the formation of 3-(1-carbamoylalkylidene)oxindole **4f** in 77% yield with retention of stereochemistry (Z/E = >95:5).



3f (Z/E = >95:5) **4f** 77% (Z/E = >95:5) (1)

In summary, we have demonstrated that copper(I) cyanide acts as a good coupling partner of 2-(alkynyl)aryl isocyanates in the presence of a palladium catalyst.[14] The present reaction provides a convenient and stereoseletive method for the synthesis of (*Z*)-configured 3-(1-cyanoalkylidene)oxindoles that are otherwise difficult to access due to the facile isomerization of the exocyclic double bond.[10]

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11 No cyclization of **1a** was observed in the absence of the palladium catalyst.

12 It was reported that Z/E isomerization of 3-alkylideneoxindoles occurred in the presence of a nucleophile and proceeded more rapidly in polar solvents than in nonpolar solvents.[8a,10b] When the isolated (*Z*)-**3a** (Z/E = >95:5) was subjected to the reaction conditions (1.1 equiv CuCN, 5.0 mol % $Pd_2(dba)_3$·$CHCl_3$/dppf, DMF, 100 °C, 2 h), isomerization from (*Z*)-**3a** to (*E*)-**3a** was observed (Z/E = 90:10). In contrast, treatment of (*Z*)-**3a** (Z/E = >95:5) in 1,4-dioxane under otherwise identical conditions gave a Z/E = 94:6 mixture.

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