doi:10.1246/cl.2012.798
Published on the web July 28, 2012

Synthesis of (1*H*)-Isochromen-1-imines by Nickel-catalyzed Reaction of 2-Iodobenzamides with Alkynes

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2-Iodobenzamides reacted with alkynes in the presence of a nickel(0)/P(4-ClC_6H_4)$_3$ catalyst to produce substituted (1*H*)-isochromen-1-imines. The reaction proceeded through the formation of an oxanickelacycle, alkyne insertion, and reductive elimination.

Transition-metal-catalyzed annulation reactions have expanded the repertoire of synthetic methods of heterocyclic compounds.[1] 2-Halobenzamides comprising a carbon–halogen bond and two nucleophilic sites at nitrogen and oxygen atoms in the molecule present a versatile platform for such reactions.[2] For example, 2-halobenzamides react with terminal alkynes in the presence of a copper catalyst to give 3-methyleneisoindolin-1-ones through the Sonogashira reaction and the following cyclization in a 5-*exo* mode at the nitrogen atom.[2d] The use of benzylamine in place of terminal alkynes leads to the formation of quinazolin-4(3*H*)-ones through cyclization in a 6-*endo* mode.[2i] Recently, Cheng and co-workers have reported that a nickel-catalyzed reaction of 2-halobenzamides with alkynes builds a six-membered ring by cyclization at the nitrogen atom to give 1(2*H*)-isoquinolones (Figure 1, top).[2f] Herein, we report that cyclization at the oxygen atom[3–5] becomes possible for the same substrate combination depending on the ligand used for nickel (Figure 1, bottom). The use of monodentate ligands such as P(4-ClC_6H_4)$_3$ directs the site of ring-closure to the oxygen atom of the amide group producing (1*H*)-isochromen-1-imines,[3,6] which are important structural motif for pharmacophores[7] as well as synthetic intermediates.[8]

Initially, a variety of phosphine ligands were examined using [Ni(cod)$_2$] as the catalyst precursor in a reaction of 2-iodo-*N*-(4-tolyl)benzamide (**1a**) with diphenylethyne (**2a**) (Table 1). A mixture of **1a** (1.0 equiv) and **2a** (1.5 equiv) in toluene was heated at 80 °C for 17 h in the presence of [Ni(cod)$_2$] (10 mol %), a phosphine ligand (Ni:P = 1:2), and K_2CO_3 (1.5 equiv). When dppe [1,2-bis(diphenylphosphino)ethane] was employed, *N*-cyclization product **3aa** (74%) was obtained in preference to *O*-cyclization product **4aa** (18%) in accordance with results reported by Cheng et al. (Entry 1).[2f] Other bidentate bisphosphine ligands such as dppm and dppp gave a considerable mixture of *N*-cyclization product **3aa** and *O*-cyclization product **4aa** (Entries 2 and 3). Much to our surprise, the use of monodentate triarylphosphine ligands switched the product selectivity in favor of the *O*-cyclization (Entries 4–6).[9] In particular, **4aa** was obtained in 77% isolated yield when P(4-ClC_6H_4)$_3$ was employed. Thus, it became possible to obtain either *N*-cyclization or *O*-cyclization by an appropriate choice of the ligand for nickel.

The results obtained with various combinations of 2-iodobenzamides **1a**–**1d** and alkynes **2a**–**2k** using a nickel(0)/P(4-ClC_6H_4)$_3$ catalyst are listed in Table 2. 2-Iodobenzamides **1b**–**1d** possessing aryl and alkyl groups on the nitrogen atom reacted with **2a** to exclusively afford the corresponding *O*-cyclization products **4ba**–**4da** in isolated yields ranging from 59% to 76% (Entries 1–3).[10] On the other hand, the reaction failed to occur with *N*-unprotected 2-iodobenzamide, which remained intact after heating even at 120 °C. In addition to diphenylethyne (**2a**), aliphatic internal alkynes such as oct-4-yne (**2b**) and 1,4-dibenzyloxybut-2-yne (**2c**) successfully participated in the annulation reaction (Entries 4 and 5). The regioselectivities observed with unsymmetrical internal alkynes varied with significant similarities to those observed in the case of *N*-cyclization reaction.[2f] Whereas 1-arylprop-1-ynes **2d**–**2f** showed moderate to good regioselectivities (83:17–95:5, Entries 6–8), little selectivity was observed with 4-methylpent-2-yne (**2g**) and 1-(trimethylsilyl)prop-1-yne (**2h**) (Entries 9 and 10). In contrast, the electron-deficient alkyne **2i** gave the single regioisomer **4ai**

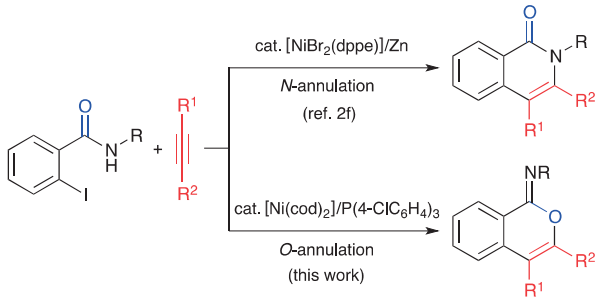
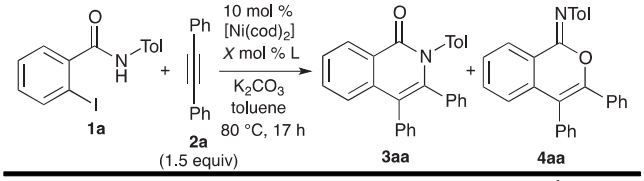


Figure 1. Two annulation pathways for the reaction of *N*-substituted 2-iodobenzamides with alkynes.

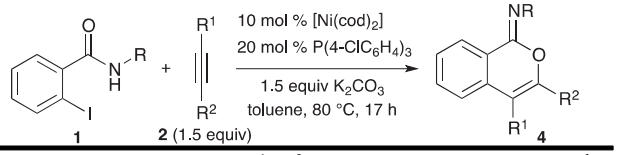
Table 1. Ni(0)-catalyzed annulation reaction: screening of phosphine ligands[a]



Entry	Ligand (L)	*X*	Yield/%[b]	
			3aa	**4aa**
1	dppe	10	73 (74)	18
2	dppm	10	9	17
3	dppp	10	26	49
4	PPh_3	20	0	82
5	P(4-$MeOC_6H_4$)$_3$	20	0	53
6	P(4-ClC_6H_4)$_3$	20	0	95 (77)

[a]All reactions were carried out on a 0.2 mmol scale. [b]NMR yield using mesitylene as an internal standard. Isolated yield in parenthesis.

Table 2. Ni(0)-catalyzed annulation reaction of *N*-substituted 2-iodobenzamides **1a**–**1d** with alkynes **2a**–**2k**[a]

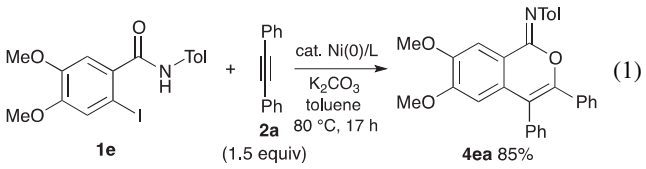


Entry	**1** (R)	**2** (R^1, R^2)	**4**	Yield/%[b,c]
1	**1b** (4-$CF_3C_6H_4$)	**2a** (Ph, Ph)	**4ba**	59
2	**1c** (4-$MeOC_6H_4$)	**2a** (Ph, Ph)	**4ca**	76
3	**1d** (Bn)	**2a** (Ph, Ph)	**4da**	66
4	**1a** (Tol)	**2b** (Pr, Pr)	**4ab**	84
5	**1a** (Tol)	**2c** (CH_2OBn, CH_2OBn)	**4ac**	84
6	**1a** (Tol)	**2d** (Me, Ph)	**4ad**	73 (84:16)[d]
7	**1a** (Tol)	**2e** (Me, 4-$CF_3C_6H_4$)	**4ae**	69 (83:17)[d]
8	**1a** (Tol)	**2f** (Me, 4-$MeOC_6H_4$)	**4af**	83 (95:5)[d]
9	**1a** (Tol)	**2g** (Me, *i*-Pr)	**4ag**	81 (52:48)
10	**1a** (Tol)	**2h** ($SiMe_3$, Me)	**4ah**	68 (68:32)[d]
11	**1a** (Tol)	**2i** (CO_2Et, Pr)	**4ai**	76 (>95:5)
12	**1a** (Tol)	**2j** (Bpin, Ph)	**4aj**	81 (>95:5)
13	**1a** (Tol)	**2k** (H, Ph)	**4ak**	38 (>95:5)[e]

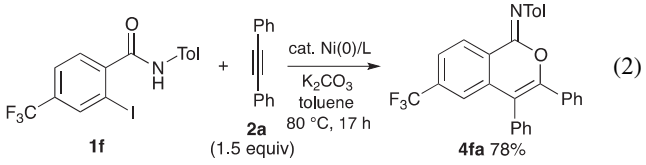
[a]Conditions: **1** (0.2 mmol), **2** (0.3 mmol), [Ni(cod)$_2$] (10 mol %), P(4-ClC_6H_4)$_3$ (20 mol %), and K_2CO_3 (0.3 mmol) in toluene (2 mL) at 80 °C for 17 h. [b]Isolated yield unless otherwise noted. [c]Combined yield of regioisomers. Numbers in parenthesis describe the regioselectivity. [d]Using **2** (0.6 mmol). [e]Using **2k** (1.0 mmol).

(Entry 11). High regioselectivity was observed also with boryl-substituted alkyne **2j** (Entry 12). The reaction of **1a** with phenylethyne (**2k**) gave the product **4ak** in only 38% yield because of self-oligomerization of **2k** (Entry 13).

(1*H*)-Isochromen-1-imines **4ea** and **4fa** having electron-donating and -withdrawing substituents on the benzene ring were synthesized in 85% and 78% yields, respectively (eqs 1 and 2).

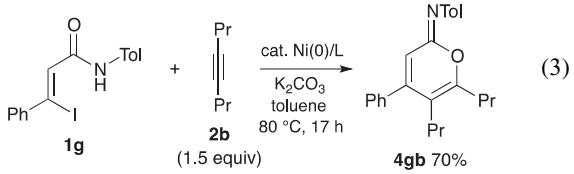


(1)



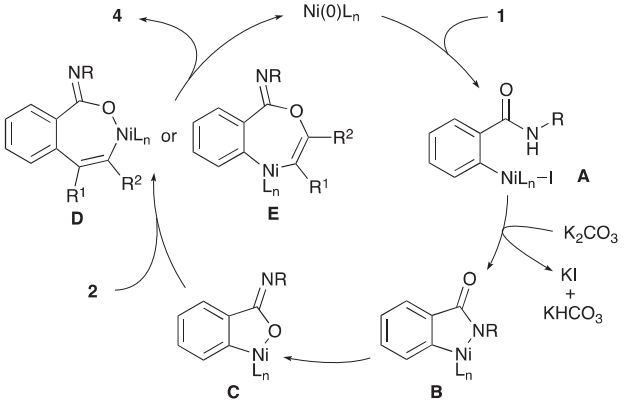
(2)

In addition, (2*H*)-pyran-2-imine derivative **4gb** was produced in 70% yield from 3-iodoacrylamide derivative **1g** and oct-4-yne (**2b**) (eq 3).



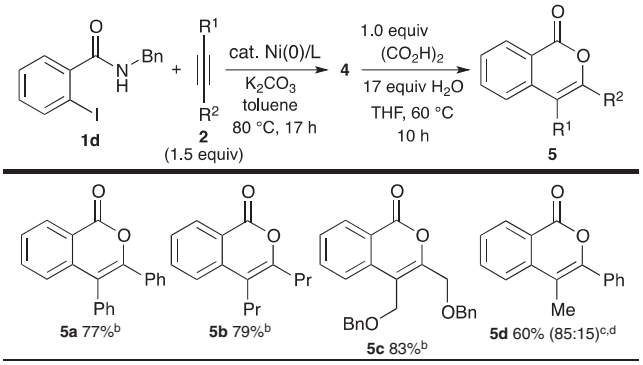
(3)

We assume the mechanism depicted in Scheme 1 for the production of **4** from **1** and **2**, which is closely related to that



Scheme 1. Proposed mechanism for the formation of **4** from **1** and **2**.

Table 3. Sequential reaction for the synthesis of (1*H*)-isochromen-1-ones[a]



[a]Conditions: **1d** (0.2 mmol), **2** (0.3 mmol), [Ni(cod)$_2$] (10 mol %), P(4-ClC_6H_4)$_3$ (20 mol %), and K_2CO_3 (0.3 mmol) in toluene (2 mL) at 80 °C for 17 h, and then $(CO_2H)_2$ (0.2 mmol) and H_2O (3.4 mmol) in THF (5 mL) was stirred at 60 °C for 10 h. [b]Isolated yield. [c]Combined yield of regioisomers. Numbers in parenthesis describe the regioselectivity. [d]Using **2d** (0.6 mmol).

proposed by Cheng et al. Initially, oxidative addition of the carbon–iodine bond of **1** onto nickel(0) affords the aryl–nickel species **A**. Subsequent deprotonation of the amide hydrogen by K_2CO_3 forms the five-membered ring azanickelacycle **B**.[5c] Allylic isomerization of **B** generates the five-membered ring oxanickelacycle **C**. We presume that the less coordinating character of P(4-ClC_6H_4)$_3$ compared with bidentate bisphosphine ligands offers a vacant site more facilely to promote the allylic isomerization. Then, insertion of alkynes **2** affords the seven-membered ring oxanickelacyclic intermediate **D** or **E**, depending on the nature of alkynes, as Cheng et al. explained for their *N*-cyclization reaction.[2f,11] Finally, reductive elimination follows to give *O*-cyclization products **4**, regenerating the nickel(0) complex for the next catalytic cycles.

When a crude mixture of **4** with an *N*-benzyl group was subjected to aqueous acidic conditions [oxalic acid (1.0 equiv) in THF/H_2O],[12] hydrolysis of the imine moiety readily took place to form the corresponding (1*H*)-isochromen-1-ones **5a**–**5d** in good yield (Table 3).

In conclusion, an efficient synthetic route of (1*H*)-isochromen-1-imines starting from 2-iodobenzamides and alkynes has been established.[13] Of note is that, unlike the case with the analogous reaction using dppe, *O*-cyclization products are exclusively formed when $P(4\text{-}ClC_6H_4)_3$ is employed as the ligand, presenting a complementary cyclization mode.

This work was supported in part by MEXT (Grant-in-Aid for Scientific Research on Innovative Areas Nos. 22105005 and 22106520, Young Scientists (A) No. 23685019), Takeda Science Foundation, and Asahi Glass Foundation.

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