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Nickel-catalyzed Heteroannulation of *o*-Haloanilines with Alkynes

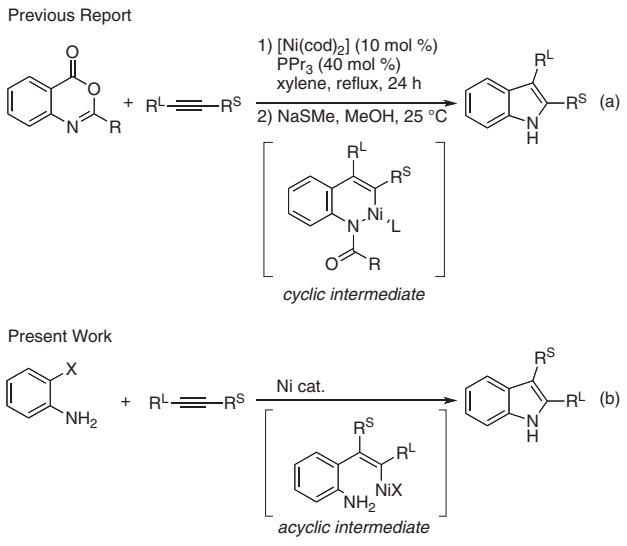
Yuji Yoshida, Takuya Kurahashi,* and Seijiro Matsubara*
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510

(Received June 9, 2011; CL-110482; E-mail: tkuraha@orgrxn.mbox.media.kyoto-u.ac.jp)

A nickel-catalyzed heteroannulation has been developed where *o*-haloanilines react with alkynes to afford 2,3-disubstituted indoles. IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) was found to be an effective ligand for the reaction.

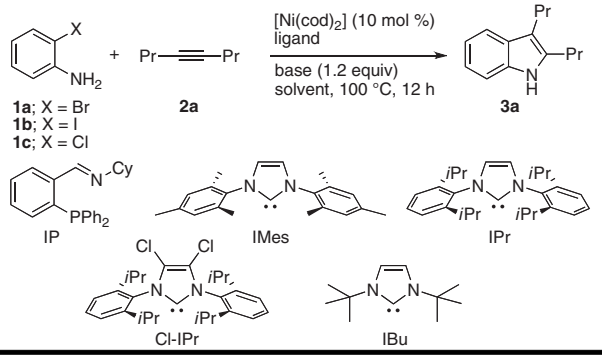
Among various heterocyclic compounds, indoles are especially important because they are found in both natural products and in pharmaceuticals.[1,2] Therefore the development of new synthetic methods to provide indoles is continuously in demand.[1b,2a,2b,3–5] Recently, we have developed cycloaddition of readily available anthranilic acid derivatives with alkynes to afford 2,3-disubstituted indoles.[6] We found that the nickel-catalyzed cycloaddition provides an opposite regioisomer to that of palladium-catalyzed Larock heteroannulations: the nickel-catalyzed reaction of anthranilic acid derivatives with unsymmetrical substituted alkynes affords 2,3-disubstituted indoles with bulky substituents on the 3 position (Scheme 1a), whereas palladium-catalyzed reaction of *o*-haloaniline with the same alkynes affords 2,3-disubstituted indoles with bulky substituents on the 2 position.[3] We assumed that such difference is ascribed to differences in the intermediate for alkyne carbometallation (i.e., cyclic or acyclic).[3,6] To test our hypothesis, we became intrigued by the development of nickel-catalyzed heteroannulation of *o*-haloaniline with alkynes to afford 2,3-disubstituted indoles and the observation of regioselectivity (Scheme 1b). Herein, we wish to report the results.[7]

The results of optimization of reaction conditions for the nickel-catalyzed heteroannulation of *o*-haloaniline **1** with **2a** are summarized in Table 1. It was found that the reaction with phosphine ligands, such as PPh_3, PCy_3, and PMe_3, proceeded



Scheme 1. Cycloaddition and heteroannulation.

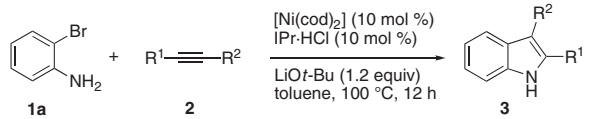
Table 1. Nickel-catalyzed heteroannulation of **1a** with **2a**[a]



Entry	1	Ligand	Base	Solvent	Yield/%[b]
1	**1a**	PPh_3 (40 mol %)	LiO*t*-Bu	toluene	14
2	**1a**	PCy_3 (40 mol %)	LiO*t*-Bu	toluene	8
3	**1a**	$PMePh_2$ (40 mol %)	LiO*t*-Bu	toluene	21
4	**1a**	PMe_2Ph (40 mol %)	LiO*t*-Bu	toluene	12
5	**1a**	PMe_3 (40 mol %)	LiO*t*-Bu	toluene	3
6	**1a**	PPr_3 (40 mol %)	LiO*t*-Bu	toluene	24
7	**1a**	dppf[c] (20 mol %)	LiO*t*-Bu	toluene	4
8	**1a**	dppe[d] (20 mol %)	LiO*t*-Bu	toluene	1
9	**1a**	IPr (10 mol %)	LiO*t*-Bu	toluene	72
10	**1a**	IMes·HCl (10 mol %)	LiO*t*-Bu	toluene	72
11	**1a**	IPr·HCl (10 mol %)	LiO*t*-Bu	toluene	79 (76)
12	**1a**	Cl-IPr·HCl (10 mol %)	LiO*t*-Bu	toluene	25
13	**1a**	IBu·HCl (10 mol %)	LiO*t*-Bu	toluene	18
14	**1a**	IPr·HCl (20 mol %)	LiO*t*-Bu	toluene	67
15	**1a**	IPr·HCl (10 mol %)	NaO*t*-Bu	toluene	5
16	**1a**	IPr·HCl (10 mol %)	KO*t*-Bu	toluene	6
17	**1a**	IPr·HCl (10 mol %)	NEt_3	toluene	6
18	**1a**	IPr·HCl (10 mol %)	DBU	toluene	5
19	**1a**	IPr·HCl (10 mol %)	DABCO	toluene	4
20	**1a**	IPr·HCl (10 mol %)	LiO*t*-Bu	benzene	74
21	**1a**	IPr·HCl (10 mol %)	LiO*t*-Bu	xylene	67
22	**1a**	IPr·HCl (10 mol %)	LiO*t*-Bu	dioxane	55
23	**1b**	IPr·HCl (10 mol %)	LiO*t*-Bu	toluene	28
24	**1c**	IPr·HCl (10 mol %)	LiO*t*-Bu	toluene	38
25	**1a**	IPr·HCl (10 mol %)	LiO*t*-Bu	toluene	73[e]
26	**1a**	IPr·HCl (10 mol %)	LiO*t*-Bu	toluene	74[f]
27	**1a**	IPr·HCl (5 mol %)	LiO*t*-Bu	toluene	70[g]
28	**1a**	IPr·HCl (10 mol %)	LiO*t*-Bu	toluene	<1[h]

[a]Reactions were carried out using $[Ni(cod)_2]$ (10 mol %), ligand, **1** (0.3 mmol), and **2a** (0.45 mmol, 1.5 equiv) in 2 mL of toluene at 100 °C for 12 h otherwise noted. [b]NMR yields based on **1**. Isolated yield is given in parenthesis. [c]dppf: 1,1′-bis(diphenylphosphino)ferrocene. [d]dppe: 1,2-bis(diphenylphosphino)ethane. [e]**2a** (1.0 mmol, 2 equiv). [f]**2a** (1.5 mmol, 3 equiv). [g]$[Ni(cod)_2]$ (5 mol %). [h]$AgSbF_6$ (100 mol %).

Table 2. Nickel-catalyzed heteroannulation of **1a** with **2**[a]



1a 2 3

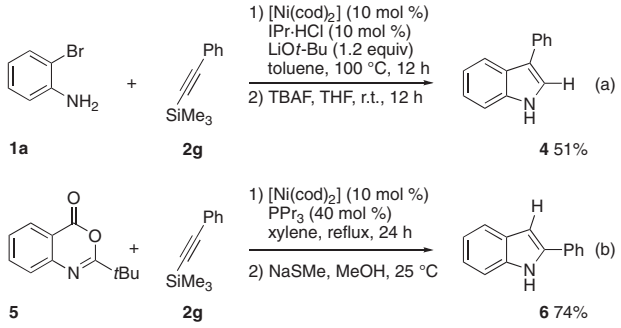
Entry	2	R^1	R^2	Major product	Yield/%
1	**2a**	Pr	Pr	**3a**	76
2	**2b**	Ph	Ph	**3b**	43
3	**2c**	*i*-Pr	Me	**3c**	85 (1/1)[b]
4	**2d**	*t*-Bu	Me	**3d**	28 (10/1)[b]
5	**2e**	Ph	Pr	**3e**	51[c,d]
6	**2f**	$SiMe_3$	C_6H_{13}	**3f**	56[c]
7	**2g**	$SiMe_3$	Ph	**3g**	59[c,d,e]
8	**2h**	$SiMe_3$	Me	**3h**	67[c]
9	**2i**	$SiMe_3$	$CH_2CH(OSi$*t*$-BuMe_2)Me$	**3i**	49[d] (3/1)

[a]Reactions were carried out using $[Ni(cod)_2]$ (10 mol %), IPr (10 mol %), **1a** (0.3 mmol), **2** (0.45 mmol, 1.5 equiv), and LiO*t*-Bu (0.36 mmol, 1.2 equiv) in 2 mL of toluene at 100 °C for 12 h otherwise noted. [b]Ratio of regioisomers (**3**/**3′**). [c]Single regioisomer. [d]Reaction time; 24 h. [e]Protodesilylated cycloadduct was obtained in 14% yield.

sluggishly to afforded indole **3a** in low yields (Entries 1–6). The use of bidentate phosphine ligands, such as dppf and dppe, gave even lower yield of desired **3a** (Entries 7 and 8). However, to our delight, it was found that the use of carbene ligands improved the yield of indole **3a** drastically. That is, the reaction of **1a** and **2a** in the presence of $[Ni(cod)_2]$ (10 mol %), IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) (10 mol %), and lithium *tert*-butoxide (1.2 equiv) in toluene (100 °C) afforded **3a** in 79% yield (Entry 11). Among various carbene ligands examined, IPr gave the best yield of **3a** (Entries 9–13). The reaction is sensitive toward base employed. The use of sodium *tert*-butoxide or potassium *tert*-butoxide in place of lithium *tert*-butoxide resulted in decreasing the yields of indole **3a** to 5% and 6% respectively (Entries 15 and 16). It was also found that the use of organic base, such as triethylamine, DBU, and DABCO, afforded trace amounts of **3a** (Entries 17–19). In other reaction solvents, such as benzene, xylene, and 1,4-dioxane, yields of **3a** were slightly lower (Entries 20–22).

With the optimized reaction conditions, the scope of the reaction was briefly examined and the results are summarized in Table 2. The heteroannulation is also compatible with aryl-substituted alkyne **2b** and afforded **3b** in 43% yield (Entry 2). The reaction of **1a** with unsymmetrical alkynes such as **2c** and **2d** also gave the indoles consisting of regioisomers in a range of 1/1 to 10/1 ratio (Entries 3 and 4). It was found that monoaryl-substituted alkyne **2e** reacted with **1a** to provide **3e** regioselectively.[3] The reaction of **1a** with unsymmetrical alkynes, containing sterically hindered substituents $SiMe_3$, gave correspondingly 2,3-disubstituted indoles regioselectivity (Entries 6–8). However, unsymmetrical alkynes **2i**, containing sterically hindered substituents on both ends, afforded 2,3-disubstituted indole **3i** with lower regioselectivity (Entry 9).[8,9]

In conclusion, we have developed nickel-catalyzed heteroannulation of *o*-haloaniline with alkynes to afford substituted indoles. It was found that IPr is an effective ligand for the reaction. The nickel-catalyzed heteroannulation of *o*-haloaniline with alkynes provides the same regioisomer as that of the palladium-catalyzed Larock heteroannulations. Thus, as shown in Scheme 2, the use of either nickel-catalyzed cycloaddition or heteroannulation may allow one to prepare different regioisomer of cycloadducts. Further efforts to elucidate an origin of regioselectivity are underway with the aid of theoretical calculations.[10]



Scheme 2. Cycloaddition and heteroannulation.

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References and Notes

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6 N. Maizuru, T. Inami, T. Kurahashi, S. Matsubara, *Org. Lett.* **2011**, *13*, 1206.
7 To the best of our knowledge, this is the first example of nickel-catalyzed heteroannulation of haloanilines with alkynes to form indoles.
8 Trace or lower amounts of indoles were obtained in the case using *o*-bromoanilides, such as *N*-acyl-*o*-bromoaniline and *N*-benzoyl-*o*-bromoaniline, in place of *o*-bromoaniline.
9 Terminal alkynes, such as triisopropylacetylene, 1-octyne, and phenylacetylene, failed to participate in the reaction, presumably due to rapid oligomerization of alkynes.
10 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

