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Pybox ligand-promoted copper(I)-catalyzed three-component tandem coupling-annulation of terminal alkynes, amines and *ortho*-alkynylaryl aldehydes

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ABSTRACT

Pybox ligand was utilized to promote a highly efficient, one-pot, copper(I)-catalyzed three-component tandem addition and cyclization of *ortho*-alkynylaryl aldehydes, primary amines, and terminal alkynes. Dihydroisoquinoline derivatives **2** were achieved with excellent to moderate yields. In some examples, water was found as an additive to activate the reaction with or without Pybox ligand. Compared with the reported methods, in which imine had to be pre-prepared and purified, the novel process provides a greener choice.

Dihydroisoquinolines are common structural units of natural products and exhibit interesting biological activities such as antibiotic properties.[1] Among the methods to construct such structures, the nucleophilic addition to acetylenic imines, which were prepared from *ortho*-alkynylaryl aldehydes and primary amines, followed by amine–alkyne cyclization is the most useful.[2] However, in most of the cases, the key starting material, acetylenic imines had to be pre-prepared from *ortho*-alkynylaryl aldehyde (**1**) and amine (**4**), and then were utilized as pure compounds. To the best of our knowledge, there are only a few examples utilizing acetylenic imines in situ prepared.[3] Since the imines are easily decomposed in the presence of water, the following reactions were usually carried out in an anhydrous solvent. Recently, Wu and co-workers reported an ultrasound-assisted, copper-surfactant co-catalyzed, three-component reaction of *ortho*-alkynylaryl aldehydes, primary amines, and terminal alkynes.[3c] As an alternative choice, herein, we hope to report a copper(I)–Pybox complex-catalyzed, three-component tandem coupling-annulation of terminal alkynes, amines, and *ortho*-alkynylaryl aldehydes, in which 1-(arylethynyl)-1,2-dihydroisoquinolines (**2**) were achieved with excellent to moderate yields.[4]

Metal-mediated Grignard-type reactions represent some of the most common methodologies in C–C bond formations. The methods based on the catalytic reaction of C–H bonds provide a highly atom-economic alternative, which avoids the utilization of stoichiometric amounts of metal and halides when compared to the classical methods.[5] During our earlier studies on the metal acetylides of group IB, such as Cu(I), Ag(I), and Au(I), we realized that the reactivities of the C–M bonds in metal acetylides could be adjusted by the introduction of N-donor and P-donor ligands, and in most cases, water was found to be helpful to cleave the C–M bonds.[6] Following this method, in current reaction, Pybox ligand was used with/without water to promote a copper(I)-catalyzed three-component tandem coupling-annulation.

2-(Phenylethynyl)benzaldehyde, aniline, and phenyl acetylene were selected as the prototype reaction. Referring to the reported method, in which the imine substrate had to be prepared previously, AgOTf was detected as the first attempt.[2b] It can be seen that under the literature conditions, no desired product **2a** was observed, while 2-phenylnaphthalene (**3**) was isolated as the major product with 50% of yield (Table 1, entry 1). While the loading of catalyst was increased to 10 mol %, **3** was still the only product. Considering the mechanism of copper-catalyzed formation of **3**, which resulted from a hetero-Diels–Alder reaction of **1a** and **5a,** and followed by rearrangement at higher temperature,[7] the reaction temperature was then decreased to 40 °C for 2 days, and 47% of **2a** was obtained without **3**. We tried to introduce water into the system. It was shown obviously that the yield of **2a** was decreased from 47% to 5%, and **3** became the major product (entry 4 vs entry 3). The above-mentioned results suggest that AgOTf was not an effective catalyst in the three-component tandem coupling-annulation reaction.

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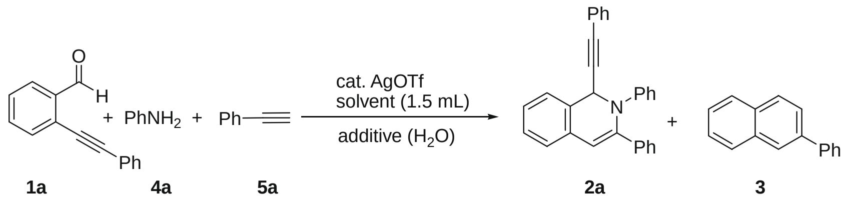
Table 1
Ag(I), Cu(I) and Cu(II)-catalyzed three-component tandem coupling-annulation of **1a**, **4a**, and **5a**[a]



Entry	Conditions	Yield[b] (%)	
		2a	**3**
1	AgOTf (5 mol %), DCE, 80 °C/6 h	0	50
2	AgOTf (10 mol %), DCE, 80 °C/9 h	0	48
3	AgOTf (10 mol %), DCE, 40 °C/2d	47	0
4	AgOTf (10 mol %), DCE/H_2O(15:1), 40 °C/9 h	<5	32
5	CuOTf (10 mol %), DCE, 40 °C/9 h	61	0
6	CuOTf (10 mol %), CH_2Cl_2, 40 °C/9 h	53	0
7	CuOTf (10 mol %), CH_2Cl_2/H_2O(15:1), 40 °C/9 h	68	0
8	CuOTf (5 mol %), CH_2Cl_2/H_2O(15:1), 40 °C/2d	76	0
9	CuOTf (10 mol %), H_2O, 40 °C/9 h	52	0
10	CuOTf (10 mol %), toluene, 40 °C/9 h	17	0
11	CuOTf (10 mol %), toluene/H_2O(15:1), 40 °C/9 h	60	0
12	CuOTf (10 mol %), THF, 40 °C/9 h	33	0
13	CuOTf (10 mol %), THF/H_2O(15:1), 40 °C/9 h	15	0
14	$Cu(OTf)_2$ (5 mol %), CH_2Cl_2/H_2O(20:1), 40 °C/2d	82	0

[a] 2-(Phenylethynyl)benzaldehyde (0.2 mmol), aniline (0.24 mmol, 1.2 equiv), and phenylacetylene (0.3 mmol, 1.5 equiv) in 1.5 mL of selected solvent.
[b] Isolated yield.

Copper(I) and copper(II) salts were then detected in the reaction (entries 5–14). It can be seen from Table 1 that the two catalysts can catalyze the reaction effectively with the promotion of water (entries 7, 8, and 14). However, compared with the reported method, with imine as a starting material,[2b] the yield is far from ideal. Considering the reported methods about copper, silver, and gold-catalyzed C–C bond formation reactions involved in the metal acetylides as key intermediates, in which ligands and/or water were believed to play the key role in adjusting the reactivities of M–C bond in metal acetylides,[6] a series of N-donor ligands in Figure 1 were detected for the reaction, and the results are listed in Table 2.

Several kinds of sp^2 N-donor ligands were scanned. Pybox **8** proved to be the best of choices, and up to 97% of **2a** was achieved at 40 °C overnight in CH_2Cl_2 (Table 2, entry 3). When desiccant, anhydrous $MgSO_4$, was added in the reaction to remove the 1 equiv of water produced in situ, the yield decreased (entry 4 vs entry 3). However, with the introduction of additional water, the reaction became worse (entry 6). It seems that a proper amount of water might be of benefit to the reaction. Some other solvents were also tested, and with Pybox–CuOTf as catalyst, 94% and 92% of yields were observed in toluene and THF solutions, respectively. It should be mentioned that in the reaction with THF as a solvent, the addition of water improved the reaction significantly, while only 72% of **2a** was obtained in dried THF (entry 12 vs entry 11).

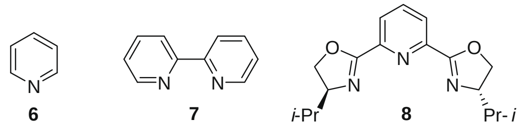


Figure 1. The ligands utilized in the reaction.

Table 2
Ligand-promoted, copper-catalyzed three-component tandem coupling-annulation of **1a**, **4a,** and **5a**[a]

Entry	Conditions	Yield[b] (%)	
		2a	**3**
1[c]	CuOTf/**6**, CH_2Cl_2, 40 °C/9 h	60	25
2[d]	CuOTf/**7**, CH_2Cl_2, 40 °C/9 h	56	19
3	CuOTf/**8**, CH_2Cl_2, 40 °C/9 h	97	0
4[e]	CuOTf/**8**, CH_2Cl_2, 40 °C/9 h	89	0
5	CuOTf/**8**, CH_2Cl_2, rt/2d	12	0
6	CuOTf/**8**, CH_2Cl_2/H_2O(15:1), 40 °C/9 h	60	0
7	CuOTf/**8**, DCE, 40 °C/9 h	13	54
8	CuOTf/**8**, DCE/H_2O(15:1), 40 °C/9 h	20	30
9	CuOTf/**8**, DCE/H_2O(1:1), 40 °C/9 h	36	9
10	CuOTf/**8**, toluene, 40 °C/9 h	94	0
11	CuOTf/**8**, THF, 40 °C/9 h	72	0
12	CuOTf/**8**, THF/H_2O(15:1), 40 °C/9 h	92	0
13	CuOTf/**8**, THF/H_2O(1:1), 40 °C/9 h	35	0
14	$Cu(OTf)_2$/**8**, CH_2Cl_2, 40 °C/9 h	84	4

[a] CuOTf (10 mol %), ligand (12 mol %), 2-(phenylethynyl)benzaldehyde (0.2 mmol), aniline (0.24 mmol, 1.2 equiv), and phenylacetylene (0.3 mmol, 1.5 equiv) in 1.5 mL of selected solvent.
[b] Isolated yield.
[c] CuOTf (10 mol %), ligand **6** (30 mol %).
[d] CuOTf (10 mol %), ligand **7** (12 mol %).
[e] Anhydrous $MgSO_4$ (100 mg) was added.

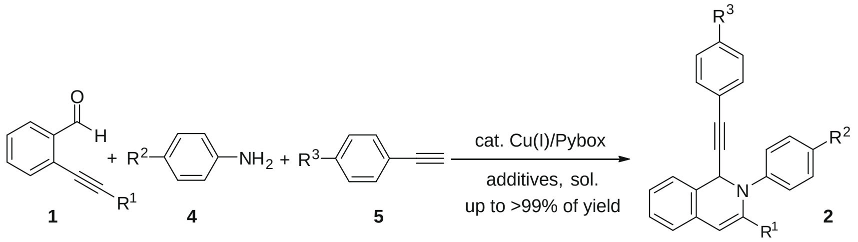
Subsequently, various acetylenic aldehydes were reacted with terminal alkynes and anilines under the standard reaction conditions (Table 3).[8] Obviously, the *ortho*-alkynylaryl aldehydes with the conjugated group on R^1 provide much better reactivities than the substrates with non-conjugated alkyl group (Table 3, entries 1–12 vs entries 13–15).

With (2-phenylethynyl)aldehyde (**1a**) as substrate, both electron-donating and electron-deficient arylacetylenes provide good to excellent yields for the desired products (entries 1–4), and a >99% of yield was achieved with 1-bromo-4-ethynylbenzene (**5b**) as the terminal alkyne (entry 2). On the other hand, aniline provides the best reactivity in comparison with other substituted aromatic amines (entry 1 vs entries 5–7). When cyclohexenyl group was introduced on R^1, ~80% of yields were observed for different substituted arylacetylenes and anilines (entries 8–12).

However, when alkyl group was introduced on R^1, the reactivities were decreased obviously, only moderate yields were obtained with *n*-butyl-substituted **1c** as a substrate (entries 13–15).

In order to further understand the effect of ligand and water on the reaction, copper phenylacetylide **9**, which was suggested as the

Table 3
Pybox–CuOTf catalyzed three-component tandem coupling-annulation of **1**, **4**, and **5**[a]



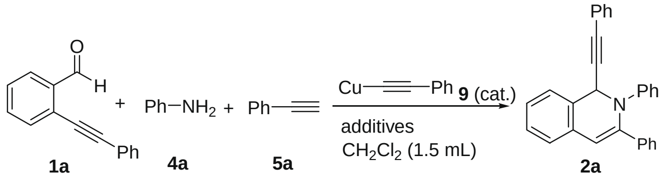
Entry	**1**:R^1	**4**:R^2	**5**:R^3	Product **2**	Yield[b] (%)
1	Ph– (**1a**)	H (**2a**)	H (**5a**)	**2a**	97
2	Ph–	H	Br (**5b**)	**2b**	>99
3	Ph–	H	Cl (**5c**)	**2c**	87
4	Ph–	H	CH_3 (**5d**)	**2d**	85
5	Ph–	CH_3 (**2b**)	H	**2e**	77
6	Ph–	Br (**2c**)	H	**2f**	93
7	Ph–	Br	Br	**2g**	86
8	Cyclohexenyl– (**1b**)	H	H	**2h**	83
9	Cyclohexenyl–	H	CH_3	**2i**	77
10	Cyclohexenyl–	H	Br	**2j**	76
11	Cyclohexenyl–	Br	H	**2k**	85
12	Cyclohexenyl–	CH_3	H	**2l**	84
13	*n*-Bu– (**1c**)	H	H	**2m**	40
14	*n*-Bu–	H	CH_3	**2n**	49
15	*n*-Bu–	Br	H	**2o**	42

[a] Conditions: CuOTf (10 mol %) and **8** (12 mol %) were mixed in 1.5 mL of CH_2Cl_2, stirred at room temperature for 20 min, and then *ortho*-alkynylaryl aldehyde (0.2 mmol), aniline (0.24 mmol, 1.2 equiv), and arylacetylene (0.3 mmol, 1.5 equiv) were added. The mixture was then stirred at 40 °C overnight.
[b] Isolated yield.

key intermediate in the reaction, was prepared and utilized as a catalyst (or a catalyst precursor). It can be seen from Table 4 that both water and Pybox ligand improved the reactions significantly. Furthermore, the results in entries 2 and 5 also suggested that a proper amount of water is helpful to the reaction, while worse results were observed with pure water (Table 4, entry 2 vs entry 3, entry 5 vs entry 6). Therefore, we reasoned that the Pybox ligand might be weakening and activating the copper–carbon bond in the copper acetylide. Coordination of the electron-donating Pybox ligand increases the electron density on copper, resulting in the weakening of the copper–carbon bond, which was then cleaved with the promotion of water produced in situ from the aldehydes and anilines.

Thus, a tentative mechanism for the Pybox–Cu(I) complex-catalyzed tandem addition/cyclization is proposed: The reaction of terminal alkynes with Pybox–Cu(I) complex generates the copper(I) acetylide species in the presence of anilines. The acetylide then reacts with imine formed in situ from aldehyde and aniline to give propargylic amine, followed by the amine–alkyne cyclization to give the vinylcopper intermediate; the carbon–copper bond is then quenched to give the final product **2** by protonolysis and regenerates the catalyst.[9]

Table 4
Copper phenylacetylide **9** catalyzed three-component tandem coupling-annulation of **1a**, **4a**, and **5a**[a]



Entry	Conditions	Yield[b] (%)
1	**9** 10 mol %, CH_2Cl_2, 40 °C	32
2	**9** 10 mol %, H_2O 1 equiv, CH_2Cl_2, 40 °C	56
3	**9** 10 mol %, H_2O, 40 °C	26
4	**9** 10 mol %, **8** 12 mol %, CH_2Cl_2, 40 °C	54
5	**9** 10 mol %, **8** 12 mol %, H_2O 1 equiv, CH_2Cl_2, 40 °C	81
6	**9** 10 mol %, **8** 12 mol %, H_2O, 40 °C	15

[a] 2-(Phenylethynyl)benzaldehyde (0.2 mmol), aniline (0.24 mmol, 1.2 equiv), and phenylacetylene (0.3 mmol, 1.5 equiv) in 1.5 mL of selected solvent.
[b] Isolated yield.

In conclusion, with the help of Pybox ligand, dihydroisoquinoline derivatives **2** were achieved successfully via a highly efficient, one-pot, copper(I)-catalyzed three-component tandem addition and cyclization of *ortho*-alkynylaryl aldehydes, anilines, and terminal alkynes. Compared with the reported methods, in which the imine intermediate had to be pre-prepared and purified, the novel process provides a greener choice. The three-component tandem addition and cyclization with other nucleophiles based on this catalytic system are currently under investigation.

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8. *General procedure:* Copper(I) trifluoromethanesulfonate benzene complex (0.0050 g, 10 mol % to copper(I)) and **8** (0.0072 g, 12 mol %) were mixed in 1.5 mL of CH_2Cl_2, stirred at room temperature for 20 min, and then, *ortho*-alkynylaryl aldehyde **1** (0.2 mmol), aniline **4** (0.24 mmol, 1.2 equiv), and arylacetylene **5** (0.3 mmol, 1.5 equiv) were added. The mixture was then stirred at 40 °C overnight. The reaction mixture was purified by flash column chromatography to give dihydroisoquinoline derivatives **2**.
9. See Refs. 6a–c and e,f.