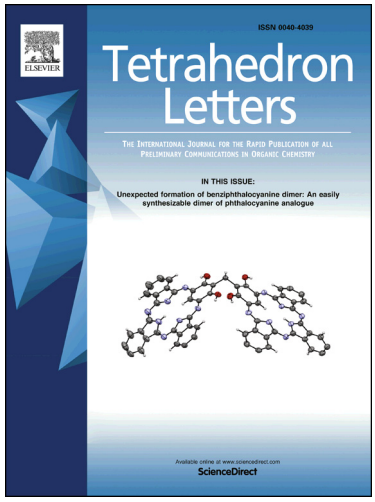

Copper-catalyzed tandem reaction directed toward synthesis of 2,2-disubstituted quinazolinones from vinyl halides and 2-aminobenzamides

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Copper-catalyzed tandem reaction directed toward synthesis of 2,2-disubstituted quinazolinones from vinyl halides and 2-aminobenzamides

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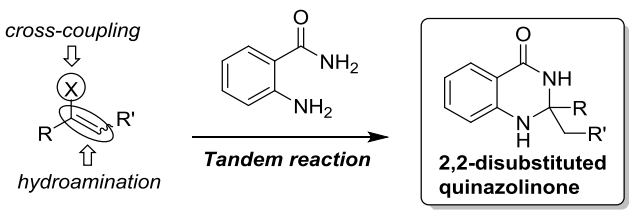
ABSTRACT

A copper-catalyzed tandem reaction with vinyl halides and 2-aminobenzamides has been developed. In this synthetic route, cross-coupling reaction of the amide moiety with vinyl halides initially progresses, followed by hydroamination, to provide 2,2-disubstituted quinazolinone derivatives. Moreover, the tandem reaction is used in a one-pot synthesis beginning with alkyne hydroiodination by PPh_3, I_2, and H_2O.

Quinazolinone, an *N*-heterocyclic compound, is an important scaffold included in a great number of pharmacologically active compounds.[1] Therefore, development of convenient methods for the construction of quinazolinone structures is of great importance.[2] However, there are very few methods for the synthesis of 2,2-disubstituted quinazolinones as compared to those for other substituted quinazolinones.[3] Condensation of 2-aminobenzamides with carbonyl compounds in the presence of acid catalysts is a simple and direct method to construct 2,2-disubstituted quinazolinones.[4] Unfortunately, the substrate scope of this reaction is limited because the bulkiness of the substituents on the amino and ketone groups reduces the rate of the condensation reaction.[5]

We became interested in expanding methods for the synthesis of 2,2-disubstituted quinazolinones by developing tandem reactions. Tandem reactions have been a focus of great interest in this decade because they can streamline synthetic processes by reducing time, solvent, and waste.[6] Our group has recently developed a convenient method to prepare vinyl halides by hydroiodination of alkynes with PPh_3, I_2, and H_2O.[7] Vinyl halides are considered to be one of the most versatile building blocks for tandem reactions[8] because they contain two reactive sites: the halogen group and the alkenyl group. Importantly, vinyl iodides are the most reactive among vinyl halides. Vinyl halides can be used for coupling reactions while the remaining vinyl groups can be used for addition reactions.

To exploit these features of vinyl halides, we designed a tandem reaction including cross-coupling and hydroamination: reaction of vinyl halides with 2-aminobenzamide to provide 2,2-disubstituted quinazolinone (Scheme 1). We assumed that the initial cross-coupling reaction of the amide moiety with the vinyl halide[9] would trigger the subsequent hydroamination of the aromatic amine[10] with intramolecular cyclization to afford 2,2-disubstituted quinazolinone. Herein, we wish to report a copper-catalyzed tandem reaction directed toward synthesis of 2,2-disubstituted quinazolinones from vinyl halides and 2-aminobenzamide.



Scheme 1. Tandem reaction of 2-aminobenzamide with vinyl halides to provide 2,2-disubstituted quinazolinone

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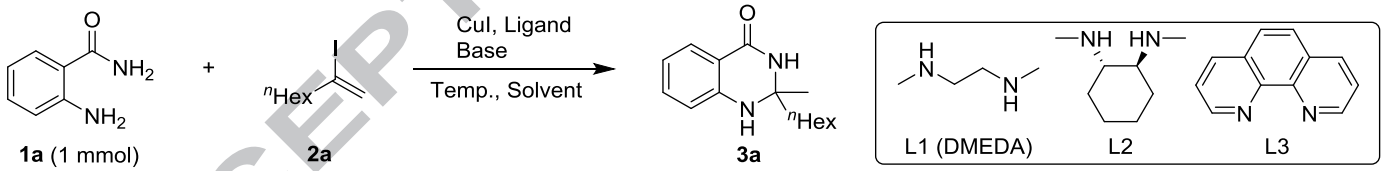
In preliminary experiments, we selected 2-aminobenzamide **1a** and 2-iodooct-1-ene **2a** as model substrates (Table 1). The initial reactions were carried out in dioxane using CuI (20 mol%) as the catalyst, DMEDA (40 mol%) as a ligand, and Cs_2CO_3 (2 equiv) as a base at 110 °C. When 1 equiv of vinyl iodide **2a** was employed, the expected product **3a** was obtained in 51% yield (entry 1). The vinyl iodide was completely consumed, and no other by-product derived from 2-aminobenzamide was observed. When 2 equiv of vinyl iodide **2a** was used, the yield was dramatically increased to 85% (entry 2). Decreased yields of **3a** were observed at lower temperatures (entries 3 and 4). When the amounts of CuI and DMEDA were decreased to 10 mol% and 20 mol%, respectively, similar reactivity was observed, although the reaction was prolonged from 21 h to 28 h (92%, entry 5). Increasing the amount of Cs_2CO_3 from 2 equiv to 3 equiv was also effective (93%, entry 6). When other bases such as K_2CO_3 and KO(*t*-Bu), which are often used with the copper catalyzed cross-coupling reaction of vinyl halides and aniline derivatives,[9a, 9c] were employed, the yields were lowered (entries 7 and 8). The use of DMF and NMP resulted in lower yield of **3a** because of the instability of the vinyl iodide in these solvents (entries 9 and 10). Other *N*,*N*-bidentate ligands that are often used for copper-catalyzed reactions, such as *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine (L2) and phenanthroline (L3), also resulted in good yields (entries 11 and 12). On the other hand, a lower yield of **3a** was observed in the absence of ligand (entry 13) and the desired product was not obtained in the absence of Cu catalyst (entry 14).

We next examined the substrate scope of the tandem reaction under the established reaction conditions (Table 2). To begin with, **1a** was treated with several aliphatic or aromatic vinyl iodides such as **2a**–**2d**. The desired reactions proceeded to give the corresponding 2,2-disubstituted quinazolinones (**3a**–**3d**) in high yields (entries 1-4). Substrates having methyl or benzyl substituent on the nitrogen atom of the amide group or amino groups (**1b**–**1e**) were also tolerated under the reaction conditions, providing the corresponding quinazolinone derivatives (**3e**–**3h**) in moderate to good yields (45–89%, entries 5-8). Increased amounts of catalyst and ligand, as well as long reaction times, were required in some cases (entries 7, 8). In addition, the reaction of α-bromostyrene (**2e**) with **1a**, **1d** or **1e** afforded the corresponding products in moderate to good yields (64–76%, entries 9-10). Some precedent quinazolinone synthesis using ketones with 2-aminobenzamides substituted at the *N*-position of the amino group resulted in low yields or no product formation.[5] Remarkably, this tandem reaction could afford 1-alkylated quinazolinone products, such as **3g**, **3h**, **3i**, and **3j**, in good yields.

To understand the reaction pathway, we conducted the copper-catalyzed reaction of vinyl iodides with aniline or benzamide independently (Scheme 2). Although the coupling product with aniline was not obtained (Eq. 1), the coupling product with benzamide was detected in 34% yield by HPLC (Eq. 2). The low yield of the reaction with benzamide is plausibly attributed to the instability of the product containing a terminal enamine. On the basis of the above results, we propose a plausible pathway, as shown in Scheme 3. Initially, the amide group reacts with the vinyl halide to produce an enamide intermediate. Then, intramolecular hydroamination of the intermediate or its tautomer with the amino group proceeds to afford 2,2-disubstituted quinazolinones. It is not clear that Cu catalyst participates in the hydroamination step because the latter hydroamination reaction proceeded promptly from the fact that only small amount of the enamide intermediate or its tautomer (imine) was detected in the course of the tandem reaction by LC/MS analysis.[11] In addition, hydroamination reactions of enamide with aromatic amine without Cu catalyst have reported.[10]

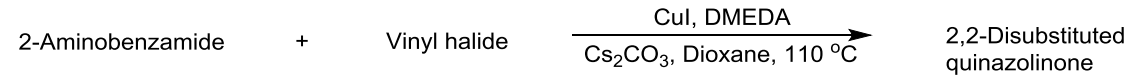
Table 1. Optimization of reaction conditions for the tandem reaction

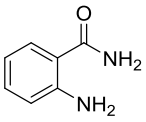
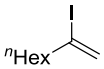
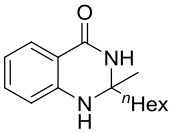
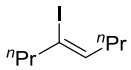
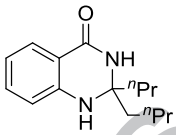
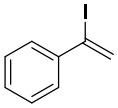
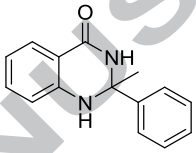
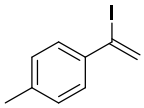
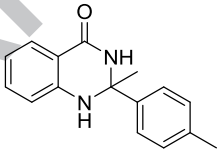
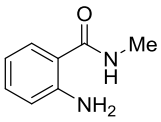
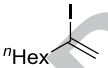
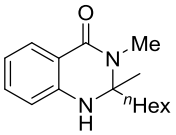
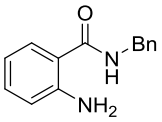
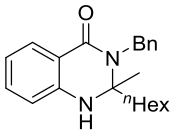
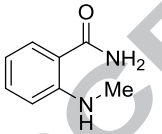
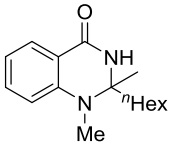
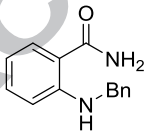
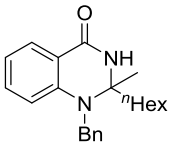
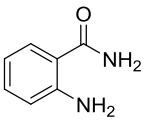
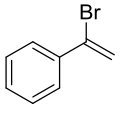
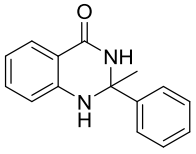
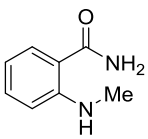
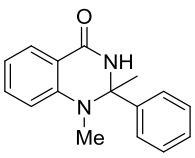


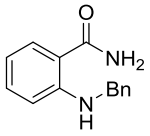
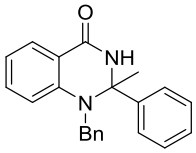
Entry	CuI (mol%)	Ligand (mol%)	Base (equiv)	Solvent	**2a** (equiv)	Temperature [a]	Time	Yield [b]
1	20	L1 (40)	Cs_2CO_3 (2)	Dioxane	1	110 °C	21 h	51%
2	20	L1 (40)	Cs_2CO_3 (2)	Dioxane	2	110 °C	21 h	85%
3	20	L1 (40)	Cs_2CO_3 (2)	Dioxane	2	25 °C	19 h	trace
4	20	L1 (40)	Cs_2CO_3 (2)	Dioxane	2	60 °C	19 h	43%
5	10	L1 (20)	Cs_2CO_3 (2)	Dioxane	2	110 °C	28 h	92%
6	10	L1 (20)	Cs_2CO_3 (3)	Dioxane	2	110 °C	18 h	93%
7	10	L1 (20)	K_2CO_3 (3)	Dioxane	2	110 °C	25 h	84%
8	10	L1 (20)	KOtBu (3)	Dioxane	2	110 °C	15 h	16%
9	10	L1 (20)	Cs_2CO_3 (3)	DMF	2	110 °C	12 h	73%
10	10	L1 (20)	Cs_2CO_3 (3)	NMP	2	110 °C	12 h	59%
11	10	L2 (20)	Cs_2CO_3 (3)	Dioxane	2	110 °C	13 h	93%
12	10	L3 (20)	Cs_2CO_3 (3)	Dioxane	2	110 °C	22 h	81%
13	10	none	Cs_2CO_3 (3)	Dioxane	2	110 °C	24 h	59%
14	none	none	Cs_2CO_3 (3)	Dioxane	2	110 °C	22 h	0%

[a] Bath temperature. [b] Determined by HPLC.

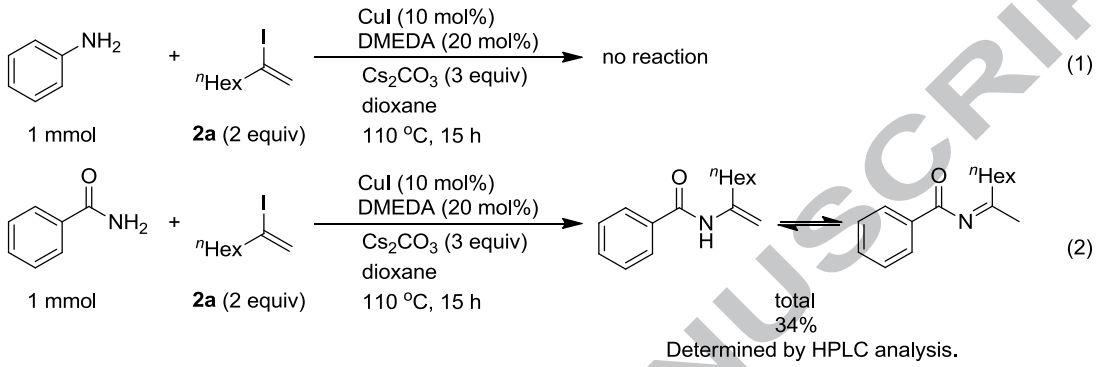
Table 2. Substrate scope of copper-catalyzed tandem reaction of 2-aminobenzamide with vinyl halides



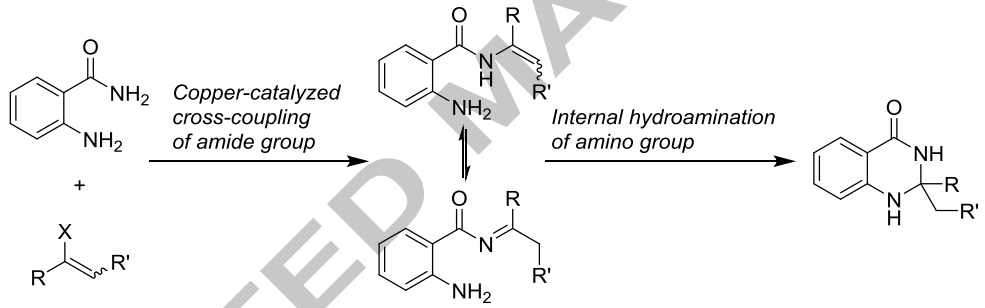
Entry	2-Aminobenzamide	Vinyl halide	Time	Product	Yield [a]
1 [b]	 **1a**	 **2a**	18 h	 **3a**	92% (83%)
2 [b]	**1a**	 **2b**	24 h	 **3b**	89% (81%)
3 [b]	**1a**	 **2c**	22 h	 **3c**	92% (89%)
4 [b]	**1a**	 **2d**	16 h	 **3d**	95% (93%)
5 [b]	 **1b**	 **2a**	32 h	 **3e**	72% (69%)
6 [b]	 **1c**	**2a**	36 h	 **3f**	94% (89%)
7 [c]	 **1d**	**2a**	24 h	 **3g**	89% (79%)
8 [c]	 **1e**	**2a**	43 h	 **3h**	58% (45%)
9 [b]	 **1a**	 **2e**	42 h	 **3c**	82% (76%)
10 [c]	 **1d**	**2e**	30 h	 **3i**	79% (71%)

11 [c]		**1e**	**2e**	60 h		**3j**	71% (64%)

[a] Determined by HPLC. Isolated yields are given in parentheses. [b] 2-Aminobenzamide (1 mmol,1 equiv), vinyl halide (2 equiv), CuI (10 mol%), DMEDA (20 mol%), Cs_2CO_3 (3 equiv). [c] 2-Aminobenzamide (1 mmol,1 equiv), vinyl halide (2.5 equiv), CuI (20 mol%), DMEDA (40 mol%), Cs_2CO_3 (3 equiv).



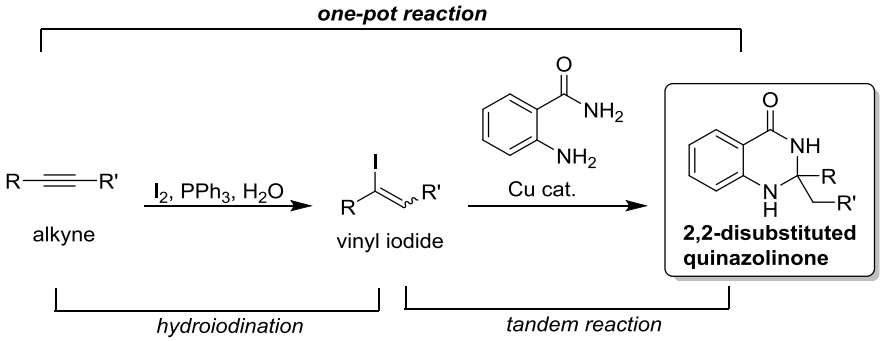
Scheme 2. Copper-catalyzed reaction of aniline or benzamide with vinyl iodide **2a**



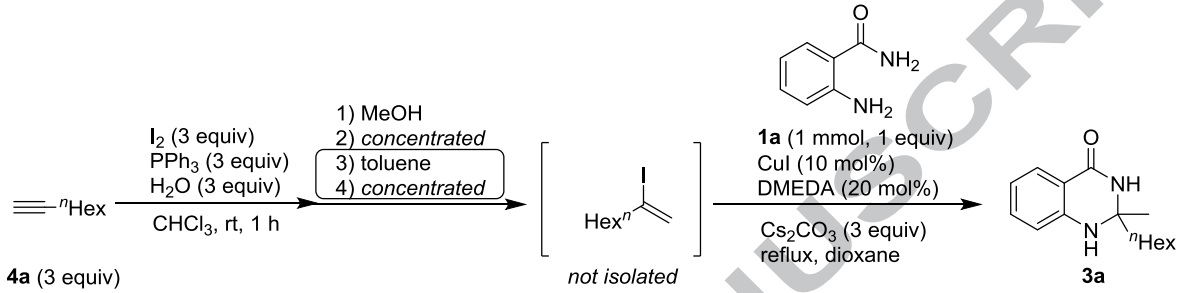
Scheme 3. A plausible pathway for the tandem reaction

Moreover, we considered that the tandem reaction can be applied to a one-pot synthesis including the generation of a vinyl iodide from an alkyne by hydroiodination (Scheme 4). As mentioned above, we have recently developed the hydroiodination of alkynes using PPh_3, I_2, and H_2O[7]. We predicted that the residue from this reaction system would not inhibit a subsequent tandem reaction. The one-pot synthesis of quinazolinone (Scheme 5) was performed as follows: the hydroiodination of 1-octyne in $CHCl_3$ was conducted using PPh_3, I_2, and H_2O as the hydroiodination reagents. The resulting mixture was treated with MeOH to give MeI and $Ph_3P{=}O$ in the same pot; then, MeOH, $CHCl_3$, MeI, and H_2O were removed in vacuo. Toluene was added to the residue and the volatiles were evaporated again; finally, copper-catalyzed tandem reaction of **1a** was conducted in the same pot to afford the expected product **3a** in 90% yield. Without the addition of toluene or upon incomplete evaporation of volatiles, only trace amounts of **3a** could be obtained. Therefore, removing the volatiles is necessary between reaction steps in this one-pot sequence. The scope of the one-pot reaction with several alkynes was examined (Table 3). The use of terminal aliphatic alkyne **4a**, internal aliphatic alkyne **4b**, and terminal aromatic alkynes **4c** and **4d** successfully afforded the corresponding products (**3a**-**3d**) in good isolated yields (entries 1-4).

In conclusion, we have developed a copper-catalyzed tandem reaction of vinyl halides and 2-aminobenzamides composed of cross-coupling and hydroamination to give 2,2-disubstituted quinazolinones. This tandem reaction can be utilized in a one-pot synthesis comprising hydroiodination, cross-coupling, and hydroamination steps. We believe that this method will reduce the reaction time while minimizing solvent usage and waste generation in the synthesis of 2,2-disubstituted quinazolinones.

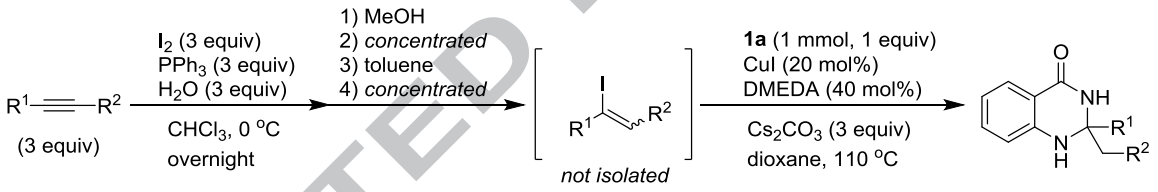


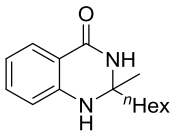
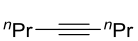
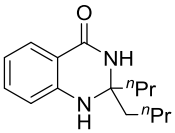
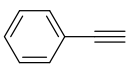
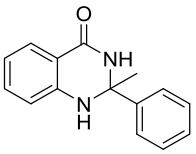
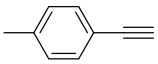
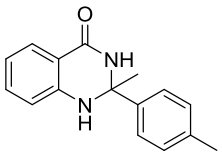
Scheme 4. One-pot synthesis of quinazolinones from alkynes



Scheme 5. One-pot synthesis of quinazolinone via hydroiodination of alkynes, and tandem reaction with 2-aminobenzamide

Table 3 Alkyne substrate scope for one-pot synthesis of quinazolinones



Entry	Alkyne		Time [a]	Product		Yield [b]
1		**4a**	31 h		**3a**	90% (82%)
2		**4b**	12 h		**3b**	79% (70%)
3		**4c**	37 h		**3c**	83% (75%)
4		**4d**	16 h		**3d**	83% (80%)

[a] Reaction time for copper-catalyzed tandem reaction. [b] HPLC yields. Isolated yields are given in parentheses.

Acknowledgments

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11. In the case of the tandem reaction of **1a** with **2a** under the optimized reaction condition, a ratio of **1a** / enamide intermediate or its tautomer / **3a**, based on HPLC peak areas, was 87 / 3 / 10 after 5 h and 3 / 0.1 / 97 after 18 h by using LC/MS spectrometer. These results implied that the latter hydroamination proceeded considerably faster than the initial Cu-catalyzed coupling reaction.

Highlights

· The tandem reaction affords quinazolinones from vinyl halides and 2-aminobenzamides.
· A cross-coupling reaction is followed by a hydroamination.
· The tandem reaction is used in a one-pot synthesis beginning with an alkyne.

Graphical Abstract

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Copper-catalyzed tandem reaction directed toward synthesis of 2,2-disubstituted quinazolinones from vinyl halides and 2-aminobenzamides

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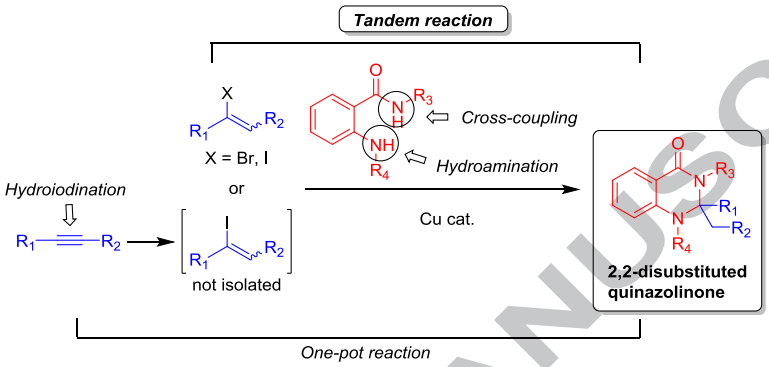
Kotaro Yamaguchi, Shin-ichi Kawaguchi*, Motohiro Sonoda*, Shinji Tanimori, Akiya Ogawa*



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