

# Synthesis of aryl azides and vinyl azides *via* proline-promoted CuI-catalyzed coupling reactions†

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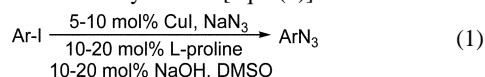
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The coupling reaction of aryl halides or vinyl iodide with sodium azide under catalysis of CuI/L-proline works at relatively low temperature to provide aryl azides or vinyl azides in good to excellent yields.

Aryl azides and vinyl azides have found growing applications in organic transformations, especially for the assembly of various heterocycles and metal complexes.<sup>1–3</sup> More interestingly, aryl azides are well known for their ability as photoaffinity labelling agents. This function relies on the fact that, upon irradiation an aryl azide expels molecular nitrogen to produce an electron-deficient nitrene species that is capable of inserting into a C–H bond thereby forming a covalent bond between a labelling agent and a protein.<sup>4</sup> Although aryl azides and vinyl azides have shown increasing importance in many aspects, synthetic studies toward these compounds are rare.<sup>5</sup>

The preparation methods for aryl azides are based mainly on the replacement of diazonium salts or some activated aryl halide with sodium azide.<sup>1,5</sup> Direct coupling of inactivated aryl halides with sodium azide catalyzed by CuI was reported to be possible but gave low yields, mainly because completion of the reaction needed a higher reaction temperature, which caused decomposition of the aryl azides.<sup>1,6</sup>

Recently, we have demonstrated that amino acids, as the additives, could promote Ullmann-type couplings thereby decreasing the reaction temperature.<sup>7,8</sup> As an extension of this work, we report here a proline-promoted, CuI-catalyzed coupling reaction of aryl halides or vinyl halides with sodium azide, which provides a variety of aryl azides and vinyl azides [eqn. (1)].



Initially, we used reaction of 4-iodoanisole with sodium azide as a model to explore the suitable reaction conditions. It was found that under the action of 10 mol% CuI, 20 mol% L-proline, and 20% NaOH in DMSO this reaction gave 4-methoxyphenyl azide in 92% yield at 60 °C [eqn. (1), entry 1 in Table 1]. Without the addition of NaOH the reaction gave only 64% yield for the same reaction time (entry 2). The action of NaOH seemed to convert L-proline to its sodium salt because if L-proline and NaOH were replaced with the L-proline sodium salt the reaction gave an identical yield (entry 3). Furthermore, in the absence of L-proline or its sodium salt, the reaction gave only 9% yield (entry 4), which indicated that L-proline plays an essential role in this reaction. In addition, we noticed that other amino acids such as *N*-methylglycine and *N,N*-dimethylglycine also worked as the additive for this reaction but gave slightly lower yields.

In order to explore the reaction scope, other aryl iodides with different substituents were tested and the results were summarized in Table 1. It was found that either electron-rich or electron-deficient aryl iodides were suitable for this reaction, giving desired coupling products in good to excellent yields. For sterically hindered substrates, a higher reaction temperature was required to

consume the starting material, and slightly lower yields were observed (entries 12 and 13). When 2-iodobenzoic acid was employed, the reaction could be completed at 40 °C but it gave a considerably lower yield because the product was not stable even under these conditions (entry 15). Note that a variety of functional groups of aryl iodides tolerated these reaction conditions, which include alkoxy, amino, bromo, fluoro, hydroxy, and carboxylate (entries 8–15). This feature would allow the present method to prepare a wide range of aryl azides. A further example is outlined in Scheme 1: from L-phenylalanine-derived iodide **1**, we obtained the aryl azide **2** in 91% yield.

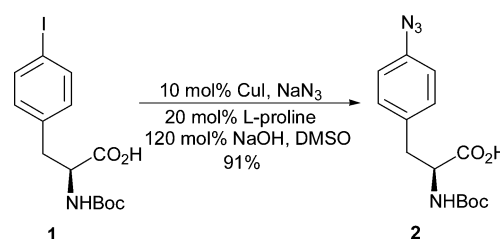
Further investigations indicated that aryl bromides did not work for the above reaction conditions because only a trace of coupling products was isolated, even when the reaction temperature was raised. However, after some attempts we were pleased to notice that if a mixed solvent (7:3 EtOH/H<sub>2</sub>O) was used, the coupling reaction of 4-bromoanisole with sodium azide provided 4-azidoanisole in 93% yield under the catalysis of 10 mol% CuI and 30 mol% L-proline at 95 °C [eqn. (2), and entry 1 in Table 2].

**Table 1** CuI/L-proline-catalyzed coupling reaction of aryl iodides with sodium azide<sup>a</sup>

Entry	Ar	T/°C	T/h	Yield <sup>b</sup> (%)
1	4-MeOC <sub>6</sub> H <sub>4</sub>	60	5	92
2	4-MeOC <sub>6</sub> H <sub>4</sub>	60	5	64 <sup>c</sup>
3	4-MeOC <sub>6</sub> H <sub>4</sub>	60	5	92 <sup>d</sup>
4	4-MeOC <sub>6</sub> H <sub>4</sub>	60	5	9 <sup>e</sup>
5	C <sub>6</sub> H <sub>5</sub>	60	5	91
6	4-MeC <sub>6</sub> H <sub>4</sub>	60	5	90
7	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	60	5	93
8	4-BrC <sub>6</sub> H <sub>4</sub>	60	10	82
9	4-HOC <sub>6</sub> H <sub>4</sub>	60	10	87
10	4-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	60	10	77
11	3-FC <sub>6</sub> H <sub>4</sub>	60	10	85
12	2-MeOC <sub>6</sub> H <sub>4</sub>	70	24	67
13	2-FC <sub>6</sub> H <sub>4</sub>	70	24	75
14	4-(HOCH <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	60	24	81
15	2-HOCC <sub>6</sub> H <sub>4</sub>	40	7	58 <sup>f</sup>

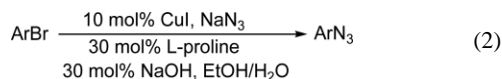
<sup>a</sup> Reaction conditions: aryl iodide (2 mmol), sodium azide (2.4 mmol), CuI (0.2 mmol), L-proline (0.4 mmol), NaOH (0.4 mmol) in 4 mL of DMSO.

<sup>b</sup> Isolated yield. <sup>c</sup> NaOH was not used. <sup>d</sup> L-Proline and NaOH were replaced with L-proline sodium salt. <sup>e</sup> Either L-proline or L-proline sodium salt was absent. <sup>f</sup> 2.4 mmol of NaOH was used.



**Scheme 1** Coupling of L-phenylalanine-derived iodide **1** with sodium azide.

† Electronic supplementary information (ESI) available: experimental procedures. See <http://www.rsc.org/suppdata/cc/b4/b400878b/>



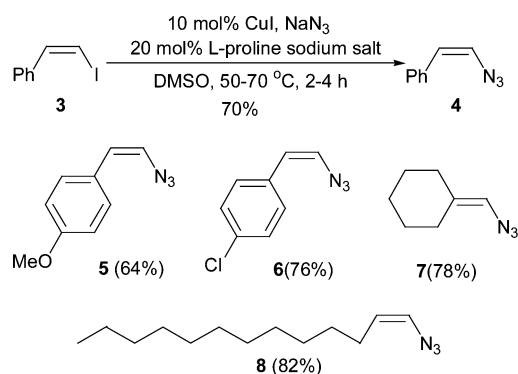
As illustrated in Table 2, a variety of aryl bromides, including those with amino, methoxy, chloro and carboxylate substituents, and *ortho*-substituted groups, showed great ability to react with sodium azide under these conditions, providing the corresponding coupling products in 66–93% yield.

For vinyl azides, a commonly used preparation method is the elimination of  $\beta$ -iodo azides, which come from the addition of iodine azide to olefins.<sup>3,9</sup> This procedure suffered from violent decomposition of iodine azide in some cases.<sup>9</sup> Thus, developing a relatively safe procedure is required. We reasoned that the coupling reaction of vinyl halides with sodium azide catalyzed by CuI/L-proline might meet this standard.<sup>10</sup> Attempts towards this goal were therefore undertaken. To our delight, heating a mixture of *cis*-2-phenyl-1-iodoethene **3** (2 mmol), sodium azide (2.4 mmol), CuI (0.1 mmol) and the L-proline sodium salt (0.2 mmol) in 4 mL of DMSO at 70 °C for 2 h afforded *cis*-2-phenyl-1-azidoethene **4** in 70% isolated yield (Scheme 2). In a similar manner, other vinyl azides bearing substituted phenyl groups (**5** and **6**), long aliphatic chains (**8**) or aliphatic rings (**7**) were obtained in good yields. These vinyl iodides were prepared according to Stock's method in a stereospecific manner (*Z/E* > 97:3).<sup>11</sup> During the reaction the

**Table 2** CuI/L-proline-catalyzed coupling of aryl bromides with sodium azide<sup>a</sup>

Entry	Ar	T/°C	T/h	Yield <sup>b</sup> (%)
1	4-MeOC <sub>6</sub> H <sub>4</sub>	95	10	93
2	C <sub>6</sub> H <sub>5</sub>	95	10	93
3	4-MeC <sub>6</sub> H <sub>4</sub>	95	10	91
4	2,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	95	30	70
5	4-ClC <sub>6</sub> H <sub>4</sub>	95	24	90
6	3-MeOC <sub>6</sub> H <sub>4</sub>	95	24	92
7	3-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	95	24	77
8	2-MeC <sub>6</sub> H <sub>4</sub>	95	24	90
9	3-HOOC <sub>6</sub> H <sub>4</sub>	95	24	66 <sup>c</sup>

<sup>a</sup> Reaction conditions: aryl bromide (2 mmol), sodium azide (4 mmol), CuI (0.2 mmol), L-proline (0.6 mmol), NaOH (0.6 mmol) in 4 mL of EtOH/H<sub>2</sub>O (7:3). <sup>b</sup> Isolated yield. <sup>c</sup> 2.6 mmol of NaOH was used.



**Scheme 2** CuI/L-proline sodium salt-catalyzed coupling reaction of vinyl iodide with sodium azide.

stereochemistry of C–C double bond of products was retained in all cases (*Z/E* > 97:3 determined by <sup>1</sup>H NMR). It is noteworthy that vinyl bromides were found not to work for these conditions.

As a summary, we have found that the CuI/L-proline-catalyzed coupling reaction of aryl halides or vinyl iodides with sodium azide could be carried out at relatively low temperatures, which allows the production of aryl azides or vinyl azides that possess a variety of functional groups in good to excellent yields. The present method opens a new avenue to the assembly of aryl azides or vinyl azides, and should be helpful for exploring further usages of these unusual compounds.

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