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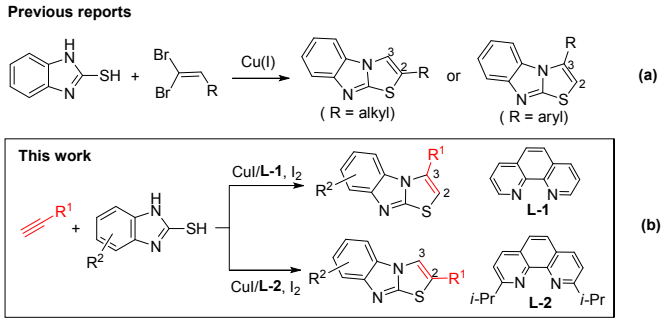
A simple, mild, and efficient catalytic aminothiolation of terminal alkynes for the synthesis of both 2- and 3-substituted thiazolo[3,2-a]benzimidazoles is established under the catalysis of copper (I), in which complementary regioselectivities could be achieved by using sterically different phenanthroline-based ligands.

Transition metal-catalyzed functionalization of alkynes into the corresponding alkenes with diverse functional groups has emerged as a powerful synthetic tool.[1] Due to the significant potential from atom- and step-economic standpoints, developing novel protocols for this direct functionalization strategy has gained much attention in recent years.[2,3] Imidazol[2,1-b]thiazole derivatives are heterocyclic compounds displaying diverse pharmacological, such as antitumor,[4] antifungal,[5] antidiabetic,[6] anthelmintic,[7] cardiodepressant,[8] and antitubercular[9] activities. Although compounds possessing the imidazol[2,1-b]thiazole structure show such appealing properties, efficient and selective method for the preparation of these compounds is still much in demand.[10-12] In 2010, Chen and coworkers reported an elegant Cu-catalyzed approach to 2-alkyl and 3-aryl imidazol[2,1-b]thiazole derivatives through regioselective 1,2-aminothiolation of 1,1-dibromoalkenes, wherein the regioselectivity was dependent on the substrate structure (Scheme 1, Eq. a).[11] To the best of our knowledge, a catalytic aminothiolation of easily available terminal alkynes to yield both 2- and 3-substituted thiazolo[3,2-a]benzimidazoles with controllable selectivity has not been reported in literature.

Herein we report a copper-catalyzed protocol for regioselective synthesis of both 2- and 3-substituted thiazolo[3,2-a]benzimidazoles from terminal alkynes, wherein a phenanthroline-based ligand and iodine play together crucial roles for the tunable regioselectivity (Scheme 1, Eq. b).

Scheme 1. Tunable Synthesis of 2- or 3-substituted thiazolo[3,2-a]benzimidazoles



Initially, we examined the reaction of 4-chlorophenylacetylene (**1a**) and 2-mercaptobenzimidazole (**2a**). The reaction proceeded smoothly in the presence of CuI (10 mol%), 1,10-phenanthroline (20 mol%), I_2 (1 equiv), and K_2CO_3 (2 equiv) at 80 °C, affording **3aa** selectively in 63% yield (Table 1, entry 1). Other copper salts, such as CuBr, CuCl, CuCN, $CuBr_2$, and $Cu(OTf)_2$, catalyzed the aminothiolation reaction as well, albeit with inferior yields (see Table S1 in Supporting Information). 1,10-Phenanthroline was found to be the most effective ligand for obtaining **3aa** compared to other ligands examined (Table 1, entry 1 *vs* entries 2−5). To our delight, when a slight excess (1.3 equiv) of **2a** was employed, yield of product **3aa** was improved to 83% (Table 1, entry 6). Screening of other solvents showed that ethanol and methanol were also suitable for the transformation, producing **3aa** in 79 and 75% yield, respectively (see Table S1 in Supporting Information). Reaction in ethereal solvents such as THF, 1,4-dioxane, and 1,2-dimethoxyethane resulted in dramatically decreased yields (Table S1). To be noted, when neocuproine was applied as ligand, regioselectivity was turned towards the production of 2-aryl substituted product **4aa**, which was seldom reported in literature (Entries 5 and 7). Pleasingly, reaction involving ligand **L-2**, a 1,10-phenanthroline derivative containing isopropyl group at C2 and C9, provided **4aa** as the major product in 71% yield along with **3aa** in 14% yield at 40 °C (Entry 8).

With the optimized conditions for both regioisomers in hand, we firstly explored the scope for the synthesis of isomer **3** with regard to

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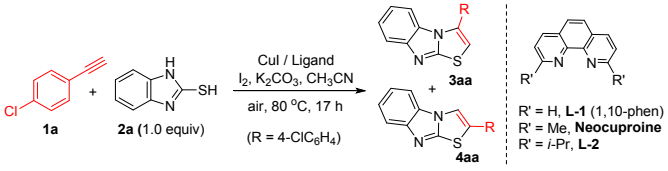
various terminal alkynes (Table 2). Aryl alkynes bearing either electron-withdrawing or electron-donating substituents on the aromatic ring, including fluoro, chloro, bromo, cyano, nitro, formyl, trifluoromethyl, and methoxy groups were all compatible, affording the corresponding products **3aa**–**3ka** in good to excellent yields. Notably, aryl alkynes with a heteroaromatic ring proved to be good substrates, leading to products **3la**–**3oa** containing multiple heterocycle rings, which are of great pharmaceutical importance. To our delight, even alkynes with a silyl group could be tolerated in this transformation, furnishing **3qa** and **3ra** in modest yields. Alkyl alkynes were also found to be suitable for the reaction (**3sa**–**3ua**). Furthermore, alkynes bearing amino, indolyl, ether, thioether, and even a free hydroxyl group could be converted to the corresponding aminothiolation products in modest to excellent yields (**3va**–**3Da**).

Table 1. Optimization of reaction conditions for the synthesis of thiazolo[3,2-a]benzimidazoles.[a]



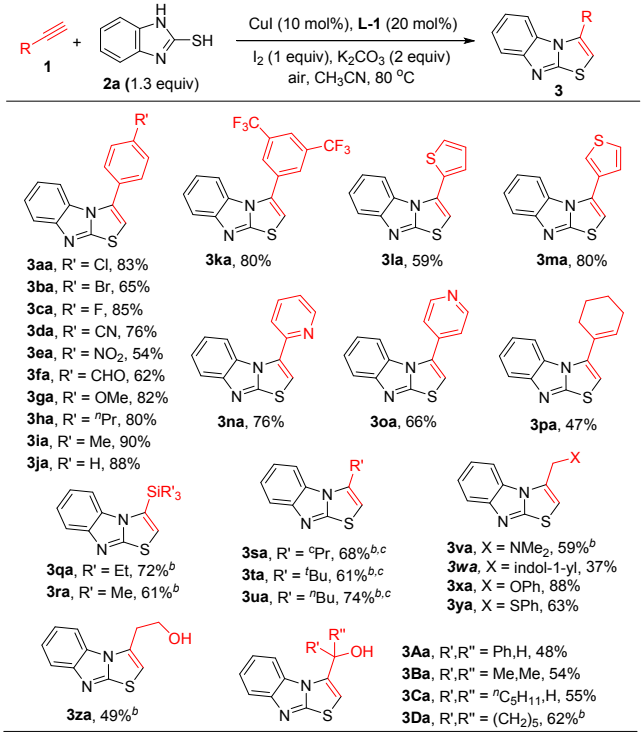
Entry	Ligand	**3aa** (%)[b]	**4aa** (%)[b]
1	1,10-Phen (**L-1**)	63	n.d.
2	2,2'-Bipyridine	15	n.d.
3	TMEDA	43	n.d.
4	PPh_3 (40%)	14	n.d.
5	Neocuproine	22	16
6[c]	**L-1**	**83**	n.d.
7[c,d]	Neocuproine	26	38
8[c,d,e]	**L-2**	**14**	**71**

[a]Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (0.02 mmol), ligand (0.04 mmol), I_2 (0.2 mmol), K_2CO_3 (0.4 mmol), CH_3CN (1 mL) at 80 °C for 17 h. [b]Isolated yield. [c]2a (0.26 mmol). [d]DMSO (1 mL) was used as solvent. [e]CuI (25 mol%) and **L-2** (30 mol%) at 40 °C. 1,10-Phen = 1,10-phenanthroline, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

The effect of substituent on 2-mercaptobenzimidazole was also investigated (Table 3). 2-Mercaptobenzimidazole with either an electron-withdrawing (nitro) or electron-donating (methoxyl and methyl) substituent afforded the corresponding products as a mixture of two isomers in modest yields.

Next, the scope of reaction affording 2-substituted thiazolo[3,2-a]benzimidazoles **4** as major product was investigated (Table 4). When aryl alkynes bearing an electron-withdrawing substituent such as chloro, bromo, cyano, and trifluoromethyl group were employed, regioselectivities of the reaction were generally good, affording isomers **4aa**–**4ka** as major products (Table 4, entries 1–4). However, aryl alkynes bearing an electron-donating substituent provided products with low regioselectivities (Table 4, entries 5 and 6). Similarly, alkyne bearing an electron-deficient aromatic system provided much higher regioselectivity than that with a relatively electron-rich heteroaromatic system (Table 4, entries 8 and 9 *vs* entry 7). The reaction of triethylsilylacetylene generated **4qa** as a sole isomer in good yield (Table 4, entry 10). Alkyl alkyne such as 1-hexyne **1u** was a suitable substrate, furnishing **4ua** in modest yield and selectivity (Table 4, entry 11). Gratifyingly, alkynes bearing ether and thioether moieties were also tolerated in the reaction, affording the desired products in modest yields yet good regioselectivities (Table 4, entries 12 and 13).

Table 2. Synthesis of 3-substituted thiazolo[3,2-a]benzimidazoles from structurally diverse alkynes.[a]

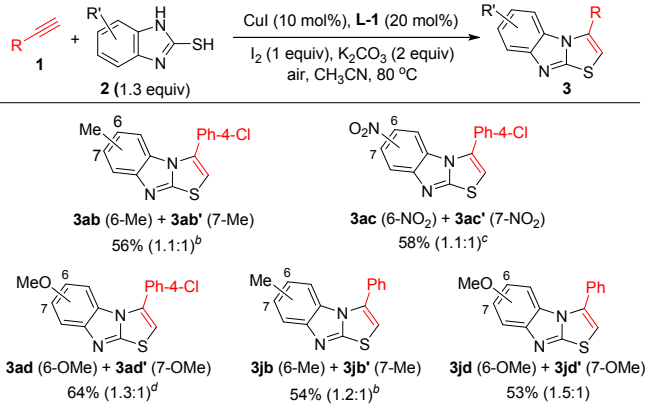


[a]Conditions: **1** (0.2 mmol), **2a** (0.2 mmol), CuI (0.02 mmol), **L-1** (0.04 mmol), I_2 (0.2 mmol), K_2CO_3 (0.4 mmol), CH_3CN (1 mL) at 80 °C for 17 h. [b]**1** (0.8 mmol) and **2a** (0.2 mmol) were used. [c]Reaction at 100 °C for 64 h using CuI (25 mol%) and **L-1** (50 mol%).

It was found that the protocol could be readily scaled up. When gram-scale (5 mmol) reactions were carried out, the desired products were obtained with good yields and excellent selectivities (Scheme 2). The structure of regioisomer **4** has been further confirmed by X-ray single-crystal diffraction analysis of **4na** (see supporting information).

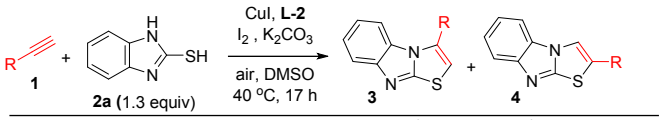
To gain insight into the mechanism of CuI-catalyzed aminothiolation, several control experiments were carried out. When the reaction was carried out without I_2 under O_2 atmosphere **3aa** was produced in 23% yield, whereas **3aa** was not obtained under N_2 (Scheme 3, Eq. a and b *vs* Entry 6, Table 1). These results suggest I_2 is essential for the efficiency of the transformation and might behave as more than an oxidant in the reaction. To evaluate whether a 1,2-diiodoalkene might be the intermediate of the transformation,[12c] we examined the reaction of independently prepared 1,2-diiodoalkene **1n'** with 2-mercaptobenzimidazole, which furnished a mixture of **3na** (17%) and **4na** (13%) (Scheme 3, Eq. c). In contrast, the reaction of pyridylacetylene **1n** provided a significantly different yield and ratio of **3na** (13%) and **4na** (71%) (Scheme 3, Eq. d), which indicates the latter reaction with **1n** does not proceed through 1,2-diiodoalkene intermediate **1n'**,[13] even though the possibility of its involvement in a minor pathway cannot be excluded.

Table 3. Substituent effect on 2-mercaptobenzimidazole.[a]



[a]Conditions: **1** (0.2 mmol), **2** (0.26 mmol), CuI (0.02 mmol), Ligand **L-1** (0.04 mmol), I_2 (0.2 mmol), K_2CO_3 (0.4 mmol), CH_3CN (1 mL) under air at 80 °C for 17 h. Isolated yield. [b]Two isomers were obtained as an inseparable mixture (ratio determined by ^1H NMR). [c]Reaction was run at 100 °C for 46 h. [d]Reaction with CuI (20 mol%) and 1,10-phen (40 mol%) at 80 °C for 26 h.

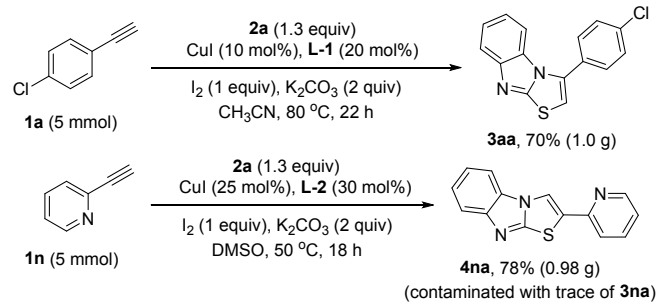
Table 4. Substrate scope for the reversal of regioselectivity affording 2-substituted thiazolo[3,2-a]benzimidazoles.[a]



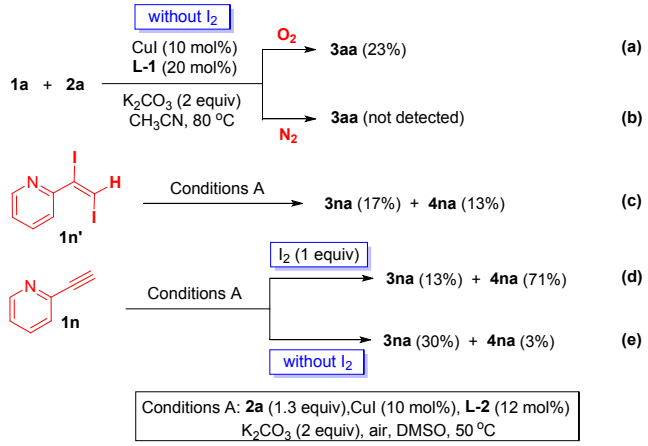
Entry	R (1)	3 (%)[b]	4 (%)[b]	4 : 3
1	4-ClC_6H_4 (**1a**)	14 (**3aa**)	71 (**4aa**)	5.1: 1
2	4-BrC_6H_4 (**1b**)	20 (**3ba**)	59 (**4ba**)	3.0: 1
3	4-CNC_6H_4 (**1d**)	6 (**3da**)	71 (**4da**)	11.8: 1
4	3,5-di-$CF_3C_6H_4$ (**1k**)	11 (**3ka**)	74 (**4ka**)	6.7: 1
5	4-$MeOC_6H_4$ (**1g**)	52 (**3ga**)	24 (**4ga**)	1: 2.2
6	4-*n*-PrC_6H_4 (**1h**)	38 (**3ha**)	44 (**4ha**)	1.2: 1
7	2-thienyl (**1l**)	22 (**3la**)	48 (**4la**)	2.2: 1
8	2-pyridyl (**1n**)	5 (**3na**)	80 (**4na**)	16.0: 1
9	4-pyridyl (**1o**)	<8 (**3oa**)	84 (**4oa**)	>10.5: 1
10	$SiEt_3$ (**1q**)	– [c]	71 (**4qa**)	–
11	*n*-Bu (**1u**)	11 (**3ua**)	42 (**4ua**)	3.8: 1
12	$PhOCH_2$ (**1x**)	5 (**3xa**)	57 (**4xa**)	11.4: 1
13	$PhSCH_2$ (**1y**)	7 (**3ya**)	68 (**4ya**)	9.7: 1

[a]Conditions: **1** (0.2 mmol), **2a** (0.26 mmol), CuI (0.05 mmol), ligand **L-2** (0.06 mmol), I_2 (0.2 mmol), K_2CO_3 (0.4 mmol), DMSO (1 mL) under air at 40 °C for 17 h. [b]Isolated yield. [c] **3qa** was not observed.

Scheme 2. Gram-scale regioselective aminothiolations.



Scheme 3. Control experiments



It is worthwhile to note that when the reaction was carried out with ligand **L-2** in the absence of I_2, regioselectivity of the transformation was reversed again (**3na**/**4na** = 10/1) and significantly lower yields were obtained (Scheme 3, Eq. e), which indicates I_2 is crucial in controlling the regioselectivity as well as improving efficiency of the reaction.

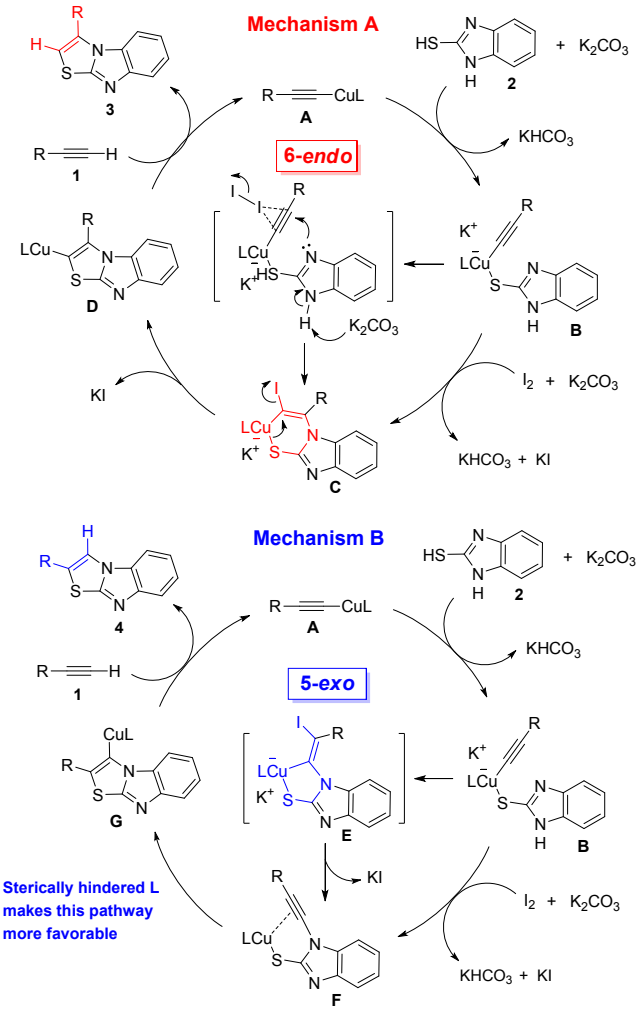
Based on these experiments, we propose plausible mechanisms for the I_2-assisted Cu-catalyzed aminothiolation of terminal alkynes to afford product **3** and **4** (Scheme 4).[11-14] In **Mechanism A**, the reaction proceeds with the formation of 1-alkynyl copper species **A**, which then react with **2** to yield intermediate **B**. Upon activation of the C–C triple bond with I_2, a thermodynamically favored *6-endo-dig* cyclization would convert **B** to the next intermediate **C**. Subsequently, **C** undergoes intramolecular substitution reaction to afford the penultimate intermediate **D**,[14] which upon proton transfer yields product **3** and regeneration of 1-alkynyl copper species **A**. In **Mechanism B** leading to regioisomer **4**, the common intermediate **B**, due to a strong repulsive interaction between iodine that activates the C–C triple bond and the sterically bulky ligand **L-2**, proceeds through a kinetically favored *5-exo-dig* cyclization over a *6-endo-dig* cyclization to generate an intermediate **F** via the cyclized precursor **E**. The intermediate **F** undergoes a thiocupration to afford **G**, which leads to regioisomer **4** upon proton transfer.

The regioselectivity in the reaction affording **4** with alkynes containing an electron-withdrawing substituent is relatively higher than that with an electron-donating one. This tendency of regioselectivity corroborates the proposed mechanisms, where the electron-withdrawing substituent on R on **B** renders the distal carbon of the I_2-activated triple bond more prone to nucleophile attack via *5-exo* mode, resulting in the formation of intermediate **E** over **C**, which will lead to final product **4**.

In summary, we have developed a novel Cu(I)-catalyzed methodology for tunable aminothiolation of terminal alkynes to afford 2- and 3-substituted thiazolo[3,2-a]benzimidazoles selectively under mild conditions. With the assistance of sterically different ligands, *5-exo-dig* and *6-endo-dig* cyclization occurred to afford 2- and 3-substituted thiazolo[3,2-a]benzimidazoles selectively. This protocol features broad substrate scope, mild conditions, good and tunable regioselectivity, excellent functional group tolerance, and scalability. Further insight into the detailed mechanism and application of the transformations to the preparation of heterocyclic

compounds of pharmaceutical interests are currently being pursued.

Scheme 4. Proposed mechanism for I_2-assisted Cu-catalyzed regioselective aminothiolation



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Conflicts of interest

There are no conflicts to declare.

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13 For more information, see control experiment in Supporting Information.

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