

Ligand-Free Copper-Catalyzed Regioselective C-2 Arylation of Imidazo[2,1-*b*]thiazoles

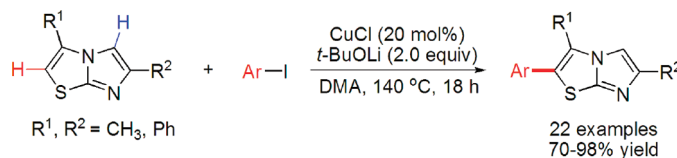
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ABSTRACT



An effective, regioselective C-2 arylation of imidazo[2,1-*b*]thiazoles catalyzed by Cu(I) has been developed. This arylation proceeded smoothly without promotion of the ligands, and various functional (22 samples) groups were well tolerated. Preliminary mechanistic studies of this arylation are also reported.

Many natural products and biologically active compounds containing imidazo[2,1-*b*]thiazole moieties have been discovered and synthesized so far.¹ As some typical examples, anthelmintics tetramisole (**i**),² thieno[3,2-*d*]pyrimidinone (**ii**),³ 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles (**iii**),⁴ C-2 aryl-substituted pilicides (**iv**),⁵ and ¹¹C-labeled imidazo[2,1-*b*]benzothiazoles (**v**)⁶ all showed effective

biological and medicinal activity (Figure 1). Milne et al.⁷ described the identification and characterization of a molecule (**vi**) bearing imidazo[2,1-*b*]thiazole as an activator of SIRT1, which was structurally unrelated to, and 1000-fold more potent, than resveratrol. And it can bind to the SIRT1 enzyme–peptide substrate complex at an allosteric site amino terminal to the catalytic domain and lower the Michaelis constant for acetylated substrates.

Imidazo[2,1-*b*]thiazoles designed with the desired substituents in appropriate positions were often specific (Figure 1). Current strategies for preparing imidazo[2,1-*b*]thiazole derivatives are focused on the construction of the fused ring with the desired aryl substituents or hopeful heterocycles at oriented position in advance.⁸ To the best of our knowledge, there has been no reported example of direct arylation of the imidazo[2,1-*b*]thiazole core.

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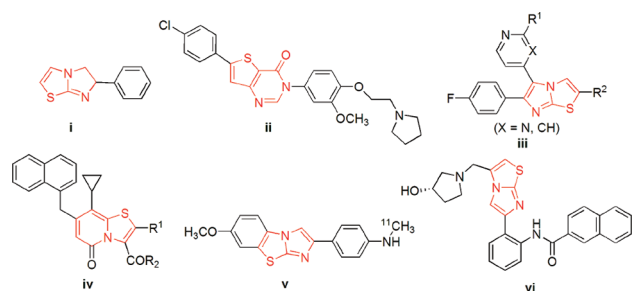


Figure 1. Imidazo[2,1-*b*]thiazoles with biological and medicinal activity.

The concept of direct arylation via C–H bond cleavage has received substantial attention over the past few years.⁹ Expensive metal-catalyzed sp² C–H bond arylations such as palladium,¹⁰ rhodium,¹¹ or ruthenium¹² have

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Table 1. Pd-Catalyzed Arylation of Imidazo[2,1-*b*]thiazole^a

entry	conditions	solvent	yields of 3a / 3a' (%)
1	Pd(OAc) ₂ /K ₃ PO ₄ /t-BuCO ₂ H ^d	DMF	5/6
2	Pd(PPh ₃) ₂ Cl ₂ /KOAc/H ₂ O ^e	NMP	22/13 (15) ^f
3	Pd(OAc) ₂ /PPh ₃ /K ₂ CO ₃ ^f	dioxane	19/3

^a Reaction was performed with **1a** (0.5 mmol) and **2a** (1.5 mmol) in 1 mL of solvent. ^b Unless specified, the yield was estimated by ¹H NMR. ^c Isolated yield of **3a**. ^d See ref 10i. ^e See ref 16. ^f See ref 21.

undergone explosive growth in the past few years. Less-expensive copper,¹³ iron,¹⁴ and nickel¹⁵ compounds have also shown to be highly active in catalytic direct arylations in recent years and have great potential for future development.^{9c,d} Although metal-catalyzed arylations on various heterocyclic systems such as indolizines,¹⁶ imidazo[1,5-*a*]pyrazines,¹⁷ xanthenes,¹⁸ and thiazoles¹⁹ exist, no direct, regioselective arylation of the imidazo[2,1-*b*]thiazole core have been developed so far.

3-Methyl-6-phenylimidazo[2,1-*b*]thiazole (**1a**) was selected as a substrate to investigate the possibility of arylation. In this substrate (**1a**), the activity of the C₂–H bond was clearly different from that of the C₅–H bond, deduced from their different chemical shifts (6.39 ppm for C₂–H and 7.61 ppm for C₅–H).²⁰ We initially tested direct arylation of **1a** using typical Pd-catalyzed conditions optimized in the literature.^{10i,16,21} As shown in Table 1, these approaches were largely unsuccessful. Both **3a**, C-2 arylated product, and **3a'**, C-5 arylated product, were obtained in poor yields,²² and byproduct biphenyl was also found in the reaction (< 5% yield).

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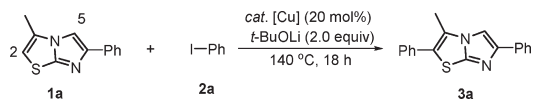
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(22) The arylation product (**3a** for C-2 position and **3a'** for C-5 position) was established by ¹H NMR; see the Supporting Information for details.

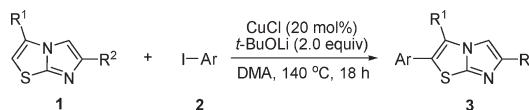
Table 2. Cu-Catalyzed C-2 Arylation of Imidazo[2,1-*b*]thiazole^a

entry	[Cu]	solvent ^b	yield of 3a ^c (%)
1	CuI	DMF/xylene (1:1)	87
2	CuCl	DMF/xylene (1:1)	89
3	CuBr	DMF/xylene (1:1)	87
4	CuCN	DMF/xylene (1:1)	80
5	CuCl ₂	DMF/xylene (1:1)	76
6	CuCl ₂ ·2H ₂ O	DMF/xylene (1:1)	51
7	Cu(OAc) ₂ ·2H ₂ O	DMF/xylene (1:1)	68 ^d
8	Cu(OTf) ₂	DMF/xylene (1:1)	54 ^d
9	Cu(acac) ₂	DMF/xylene (1:1)	62 ^d
10	CuCl	DMF	81
11	CuCl	DMA	94 (89) ^d
12	CuCl	DMA/xylene (1:1)	82

^a The reaction was performed with **1a** (0.5 mmol) and **2a** (1.5 mmol) in 1 mL of solvent at 140 °C for 18 h. ^b Substrate concentration = 0.5 M. ^c Unless specified, the yield was estimated by ¹H NMR. ^d Isolated yield.

Copper, as the first transition metal used to promote C–H bond functionalization, appeared to be underutilized as a catalyst for C–H bond arylation.²³ The successful Cu-catalyzed arylation by Daugulis^{13a,b} inspired us to attempt the possible direct arylation of imidazo[2,1-*b*]thiazole by Cu catalyst. The initial reaction was performed with **1a** and iodobenzene **2a** as reactants, *t*-BuOLi as a base, and DMF–xylene mixture as a solvent (Table 2). To our surprise, four Cu(I) salts showed good yields uniformly (entries 1–4). More promisingly, only regioselectively C-2-arylated imidazo[2,1-*b*]thiazole product was obtained, and no side product biphenyl was found. Unambiguous confirmation of the structure of a representative C-2-arylated product was obtained in the form of the X-ray structure of compound **3a**²⁰.

As shown in Table 2, Cu(II) salts, CuCl₂, CuCl₂·2H₂O, Cu(OAc)₂·2H₂O, Cu(OTf)₂, and Cu(acac)₂, were also tested in our studies and found to be effective but a little less active than Cu(I) (entries 5–9). Subsequently, we explored the effects of the solvent, base, and Cu-catalyst loading in the arylation. Equally good results were obtained in DMF or DMA–xylene mixtures, and DMA afforded the highest yields (94%, entry 11). Reducing the catalyst loading from 20 to 10 and 5 mol % lowered the yields of product from 94% to 86% and 73%, respectively. In the absence of the Cu catalyst, no arylated product was found. With these partially optimized arylation conditions, the bases were investigated, and a variety of weak inorganic bases (K₃PO₄, Cs₂CO₃, and K₂CO₃) were all

Table 3. Scope of Cu-Catalyzed Arylation of Imidazo[2,1-*b*]thiazole^a

entry	Ar	R ¹	R ²	product (% yield) ^b
1	Ph	CH ₃	Ph	3a (89) (94) ^c
2	4-CH ₃ C ₆ H ₄	CH ₃	Ph	3b (91) (97) ^c
3	4-OCH ₃ C ₆ H ₄	CH ₃	Ph	3c (91)
4	4-FC ₆ H ₄	CH ₃	Ph	3d (87)
5	4-CF ₃ C ₆ H ₄	CH ₃	Ph	3e (70)
6	3-OCH ₃ C ₆ H ₄	CH ₃	Ph	3f (87)
7	2-C ₂ H ₅ C ₆ H ₄	CH ₃	Ph	3g (94)
8	1-naphthyl	CH ₃	Ph	3h (97)
9	Ph	CH ₃	CH ₃	3i (80)
10	4-CH ₃ C ₆ H ₄	CH ₃	CH ₃	3j (84)
11	4-OCH ₃ C ₆ H ₄	CH ₃	CH ₃	3k (87)
12	4-FC ₆ H ₄	CH ₃	CH ₃	3l (72)
13	2-C ₂ H ₅ C ₆ H ₄	CH ₃	CH ₃	3m (92)
14	3-OCH ₃ C ₆ H ₄	CH ₃	CH ₃	3n (81)
15	1-naphthyl	CH ₃	CH ₃	3o (95)
16	Ph	Ph	Ph	3p (98)
17	4-CH ₃ C ₆ H ₄	Ph	Ph	3q (91)
18	4-OCH ₃ C ₆ H ₄	Ph	Ph	3r (92)
19	2-C ₂ H ₅ C ₆ H ₄	Ph	Ph	3s (86)
20	4-FC ₆ H ₄	Ph	Ph	3t (74)
21	4-CF ₃ C ₆ H ₄	Ph	Ph	3u (84)
22	1-naphthyl	Ph	Ph	3v (98)

^a The reaction was performed with **1** (0.5 mmol), **2** (1.5 mmol), *t*-BuOLi (2.0 equiv), and CuCl (20 mol %) in 1 mL of DMA at 140 °C for 18 h. ^b Isolated yield after column chromatography of the crude. ^c Determination from ¹H NMR.

unsuccessful. We then tested other alkoxide bases, *t*-BuOK and *t*-BuONa, and yields of 24% and 59% were obtained, respectively. No arylated product was found without bases. Furthermore, PhBr or PhCl, instead of PhI, only gave traces of product under optimized conditions. Optimization experiments indicated that the best result for C-2 arylation of imidazo[2,1-*b*]thiazoles was obtained in the presence of CuCl (20 mol %), aryl iodides (3.0 equiv), and *t*-BuOLi (2.0 equiv) in DMA at 140 °C.

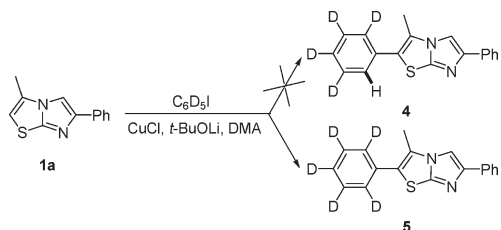
With optimized conditions in hand, the scope with respect to aryl iodides and imidazo[2,1-*b*]thiazoles was investigated (Table 3). A variety of functional groups on the substituents of the aryl iodides were well-tolerated. The electron-deficient and electron-rich aryl iodides were reactive in moderate to excellent yields (entries 1–8). Electron-rich aryl iodides gave a slightly higher yield than electron-deficient ones under the optimized conditions (entries 2, 3 vs entries 4, 5). Substantial steric hindrance was tolerated on the aryl iodides at the para-, meta-, and ortho-positions (entries 3 vs 6 vs 7) and afforded good results. Most

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Scheme 1. Mechanistic Considerations

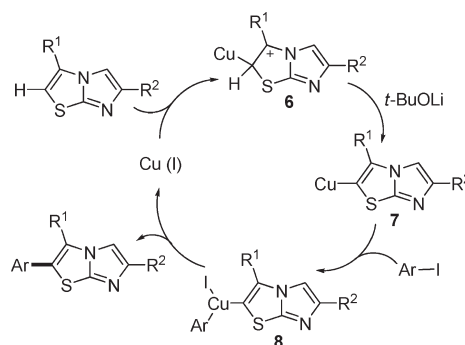


remarkably, the sterically hindered 1-naphthyl iodide also gave the desired regioselective C-2 arylation product in excellent yield (>95%, entries 8, 15, and 22). It should be noted that the substrates with aromatic groups at C-5 and C-3 gave better yields than the aliphatic groups (entries 1 vs 9 vs 16). Presumably, electronic effects rather than steric effects played a more important role in this reaction.

Naturally, we were interested in elucidating the mechanism for this arylation reaction and carried out preliminary mechanistic investigations of the coupling process. (i) Cu-assisted benzyne-type mechanisms,²⁴ (ii) deprotonation–metalation mechanisms, and (iii) typical F–C alkylations were considered. C₆D₅I was applied to the optimized conditions for mechanistic consideration (Scheme 1). Only compound **5**, instead of **4**, was found in the reaction, and no H–D exchange was observed. This result could not support the assumption that the reaction proceeded via a copper-assisted benzyne-type mechanism. And, according to the result that no desired arylated product was found without bases, the possibility of typical F–C alkylation was excluded because in typical F–C alkylation a Lewis acid is always necessary as catalyst.

Detailed mechanistic insight into this catalytic system led to the proposition that the addition between Cu(I) and heterocycle gave the unstable cationic intermediates **6**, then C₂–H proton was removed by *t*-BuOLi (Scheme 2) to give the organocopper species (**7**).²⁵ Reaction of **7** with aryl iodide gave a possible cu(III)–aryl species (**8**), and the desired arylation product was obtained by a reductive elimination from **8**. **8** was proposed to be involved as a key intermediate. Imidazo[2,1-*b*]thiazole contains both a π -deficient ring and a π -excessive ring. **8** formed at C-2 of the π -excessive thiazole ring should be more stable than the copper(III)–aryl species formed at C-5 of the π -deficient imidazole ring. Moreover, the possibility of neighbored-S atom strong concerted coordination made **8** more stable. Furthermore, cu(III)–aryl species from electron-rich aryl iodides were more stable than electron-deficient ones, and as a result, electron-rich aryl iodides gave higher yields than electron-deficient aryl iodide as shown in Table 3. In addition, the better results provided by the aromatic

Scheme 2. Possible Mechanism for Cu-Catalyzed Arylation of Imidazo[2,1-*b*]thiazoles



substrate compared to the aliphatic substrate can also be foreseen.

While monitoring the Cu(II)-catalyzed reaction, we observed that the purple reaction solution turned into a brown solution, just as the reaction with Cu(I) salt. This color change phenomenon can be understood on the basis of the catalytic cycle in Scheme 2. Cu(II) was initially transformed to Cu(I) and entered the cycle^{13c} to accumulate the reaction. It was also understood that Cu(II) showed somewhat low reactivity relative to Cu(I).

In summary, an efficient, ligandless copper-catalyzed method for the regioselective arylation of imidazo[2,1-*b*]thiazole was first developed. This protocol provided a new avenue for developing C–C bond-forming reactions of fused heteroarene. The best result was obtained with copper(I) catalyst, aryl iodide coupling partner, DMA solvent, and *t*-BuOLi base. Mechanistic investigations of the arylation process were also described. Further research will be focused on alkylation of imidazo[2,1-*b*]thiazole with aliphatic iodide in the presence of Cu(I).

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Supporting Information Available. Crystallographic data, experimental procedures, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.