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HETEROGENEOUS COPPER–CATALYZED SYNTHESIS OF *S*-ARYLATED 2-AMINOTHIOPHENOLS VIA RING OPENING OF BENZOTHIAZOLES AND C–S COUPLING USING ARYL HALIDES

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This paper is dedicated to Dr. Kiyoshi Tomioka, Professor of Doshisha Women's College of Liberal Arts and Professor Emeritus of Kyoto University for the occasion of his 70th birthday.

Abstract – Chelate resins, which are polystyrene-divinylbenezene-based polymers bearing iminodiacetic acids or polyamines as ligands, supported copper catalysts (Cu/CR11 or Cu/CR20) in effectively catalyzing the ring cleaving *S*-arylation of benzothiazole with aryl iodides or aryl bromides in the presence of lithium *tert*-butoxide in aqueous 2-propanol.

INTRODUCTION

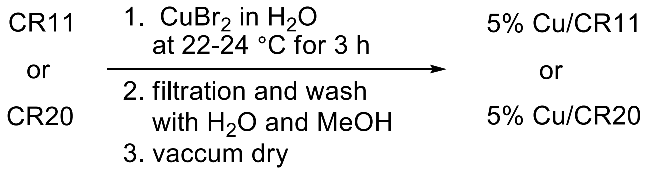
Aryl sulfide derivatives are ubiquitous fundamental skeletons of functional materials in natural and synthetic organic compounds.[1] Therefore, the development of a simple, widely applicable, and environmentally benign synthesis of aryl sulfide derivatives is important for preparing building blocks for organic synthesis. While a wide variety of preparation methods of aryl sulfides using transition metal-catalyzed C–S bond formation have been reported in the literature,[2] improved synthetic approaches that reduce the drawbacks of conventional methods are currently under investigation.[3] However, most of the reported methods require aprotic organic solvents, specific ligands for the catalyst metals, irradiation with UV or visible light, and homogeneous catalysts. In addition odiferous and oxygen sensitive thiols and their precursors are required. In 2012, Xu et al. reported a revolutionary CuCl-catalyzed synthesis of *S*-arylated 2-aminothiophenol derivatives using benzothiazole with aryl iodides via thiazole-ring-opening under basic aqueous conditions at 50 °C as a reasonably stable and less odorous precursor of 2-aminothiophenol.[4] Almost simultaneously, Han et al. reported a similar reaction catalyzed by copper nanoparticles derived from metallic copper in PEG-600 with Cs_2CO_3 at 140 °C.[5]

The use of the environmentally friendly methods has gained significant attention in modern organic synthetic chemistry. Since heterogeneous transition metal catalysts minimize the possibility of the residual metal in the final product and can possibly be reused, their application is an important for reducing the environmental burden of waste materials and synthetic cost.[6] We have previously developed a variety of reusable heterogeneous palladium catalysts for chemoselective hydrogenation.[7] In addition, we have reported a copper-catalyzed Huisgen 1,3-dipolar cycloaddition of azides to alkynes using a polystyrene-divinylbenzene-based polymer (DIAION HP20, Mitsubishi Chemical Corporation)[8]-supported copper catalyst, Cu/HP20,[9] and chelate resin (DIAION CR11 and CR20, Mitsubishi Chemical Corporation, polystyrene-divinylbenzene-based polymers bearing iminodiacetic acid and polyamine functionalities as the ligands, respectively)-supported copper catalysts, Cu/CR11 and Cu/CR20.[10] Since Cu/CR11 and Cu/CR20 possess iminodiacetic acid and polyamine moieties as chelate functionalities within the support, we expected that they could serve as intramolecular heterogeneous ligands of Cu species and accelerate the direct *S*-arylation of benzothiazole derivatives accompanied by thiazole-ring cleavage with aryl halides.

In this study, we describe the 5% Cu/CR11- or 5% Cu/CR20-catalyzed synthesis of *S*-arylated-2-aminothiophenols using benzothiazole and aryl iodide or aryl bromide in a 50% *i*-PrOH solution.

RESULTS AND DISCUSSION

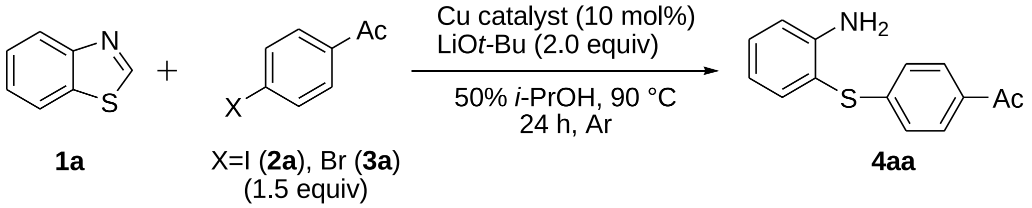
While Cu/CR11 and Cu/CR20 have been previously prepared as 12% Cu/CR11 and 7% Cu/CR20 using $Cu(NO)_2 \cdot 3H_2O$ in water,[10] herein the 5% Cu/CR11 and 5% Cu/CR20 were prepared from aqueous $CuBr_2$ solution adjusted to 5 weight% of Cu/CR11 and Cu/CR20. It was assumed that complete $CuBr_2$ absorption to CR11 and CR20 occurred at 22–24 °C over the course of 3 h (Scheme 1). Residual copper species were not detected in the aqueous filtrate after filter removal of the resulting Cu/CR11 and Cu/CR20 by atomic absorption spectrometry.



Scheme 1. Preparation of the 5% Cu/CR11 and 5% Cu/CR20

First, the efficiency of the catalyst supports was investigated using commercially available benzothiazole (**1a**) and 4'-bromo- or 4'-iodoacetophenone (**2a** or **3a**) as substrates in the presence of 5% Cu/CR11 or 5% Cu/CR20 (10 mol%) at 90 °C for 24 h under an argon atmosphere (Table 1). The 5% Cu/CR11 and 5% Cu/CR20 both exhibited good to excellent catalytic activities and the corresponding 2-(4-acetylphenylthio)aniline (**4aa**) was isolated from the reaction mixture (Entries 1–4). For comparison, 5% Cu/WA30 (Entry 5) was prepared using a similar method to that of the 5% Cu/CR11 and 5% Cu/CR20 using DIAION WA30 (Mitsubishi Chemical Corporation) bearing *N,N*-dimethylaminoalkyl functionalities on the polystyrene-divinylbenzene backbone as a support. The 5% Cu/CR20 exhibited efficient catalysis for the C-S coupling reaction of 4'-iodoacetophenone (**2a**) under the reaction conditions listed in Table 1 (Entry 2). Furthermore, 5% Cu/CR11 showed somewhat better catalytic activity towards the C-S coupling reaction using 4'-bromoacetophenone (**3a**) compared with 5% Cu/CR20 (Entries 3 versus 4). It should be noted that 5% Cu/CR11 and 5% Cu/CR20 could catalyze the C-S coupling of benzothiazole with 4'-bromoacetophenone (**3a**) as an aryl bromide. Previously reported coupling reactions using benzothiazole as a starting material have not been applied to aryl bromides.[4,5] Since the isolated yield of **4aa** was still approximately 60%, the reaction conditions were optimized.

Table 1. Efficiency of the various catalyst supports

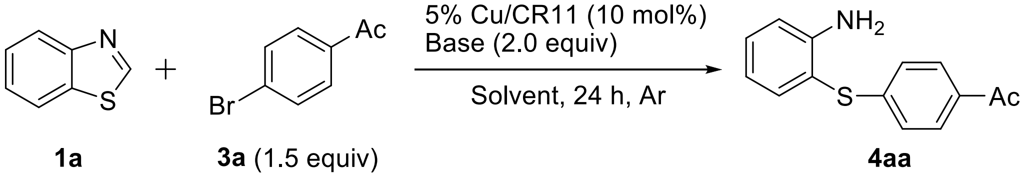


Entry	X (I or Br)	Cu catalyst	Yield (%)[a]
1	I	5% Cu/CR11	72
2	I	5% Cu/CR20	83
3	Br	5% Cu/CR11	62
4	Br	5% Cu/CR20	55
5	Br	5% Cu/WA30	9

[a] Isolated yield.

Although the 5% Cu/CR11-catalyzed reaction of **1a** and **3a** proceeded in a relatively smooth manner in 50% *i*-PrOH using LiO*t*-Bu as a base (Table 2, Entry 1), the use of NaO*t*-Bu and KO*t*-Bu significantly decreased the reaction efficiency (Entries 2 and 3) and LiOH, NaOH, Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3,

Table 2. Optimization of the reaction conditions

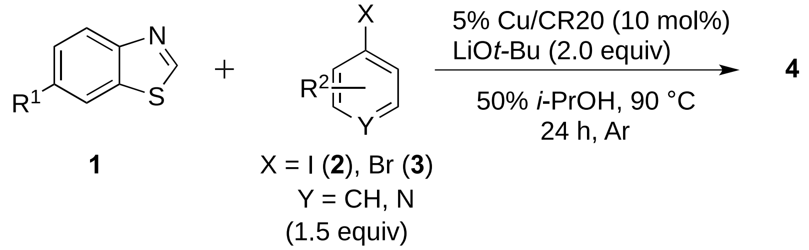


Entry	Base	Solvent	Yield (%)[a]
1	LiO*t*-Bu	50% *i*-PrOH	62
2	NaO*t*-Bu	50% *i*-PrOH	44
3	KO*t*-Bu	50% *i*-PrOH	37[b]
4	$LiOH·H_2O$	50% *i*-PrOH	9 (42)[b,c]
5	NaOH	50% *i*-PrOH	0[b]
6	Li_2CO_3	50% *i*-PrOH	0[b]
7	Na_2CO_3	50% *i*-PrOH	0[b]
8	K_2CO_3	50% *i*-PrOH	0[b]
9	Cs_2CO_3	50% *i*-PrOH	0[b]
10	K_3PO_4	50% *i*-PrOH	9[b]
11	Et_3N	50% *i*-PrOH	0[b]
12	LiO*t*-Bu	75% *i*-PrOH	62
13	LiO*t*-Bu	25% *i*-PrOH	60
14	LiO*t*-Bu	*i*-PrOH	1[b]
15	LiO*t*-Bu	H_2O	1[b]
16[d]	LiO*t*-Bu	50% *i*-PrOH	55[b]
17[e]	LiO*t*-Bu	50% *i*-PrOH	60[b]
18	LiO*t*-Bu	toluene	0[b]
19	LiO*t*-Bu	DMA	trace
20	LiO*t*-Bu	CPME[f]	0[b]
21	LiO*t*-Bu	MeCN	0[b]
22	LiO*t*-Bu	50% MeOH	32[b]
23	LiO*t*-Bu	50% EtOH	54[b]
24	LiO*t*-Bu	50% ethylene glycol	37[b]

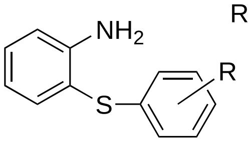
[a]Isolated yield unless otherwise noted. [b]The yield was determined by ^{1}H NMR of the crude mixture using 1,4-dioxane as an internal standard. [c]The number in parentheses indicated the yield determined by ^{1}H NMR after the reaction performed in the presence of 2 equiv of *t*-BuOH as an additive. [d]The reaction was performed at 120 °C. [e]NaI (30 mol%) was added. [f]Cyclopentyl methyl ether.

K_3PO_4, and Et_3N were impractical as bases (Entries 4–11). Since LiO*t*-Bu in 50% *i*-PrOH should be immediately and quantitatively converted to LiOH and *t*-BuOH, *t*-BuOH is expected to play a prominent role. Indeed, the addition of 2 equiv of *t*-BuOH into the reaction using LiOH as a base indicated the adequate accelerating effect although further effect was never identified by the increased use of *t*-BuOH. The concentration of aqueous *i*-PrOH solution (H_2O content) had a negligible effect on the reaction efficiency (Entry 1 versus 12 and 13), while the sole use of either *i*-PrOH or H_2O was not adequate (Entries 14 and 15). Elevated temperature (120 °C, Entry 16) and the addition of NaI (30 mol%, Entry 17) were also not effective for increasing reaction efficiency. Although the reaction did not proceed in an aprotic organic solvent, such as toluene, DMA, CPME, and MeCN (Entries 18–21, respectively), the reaction moderately proceeded in 50% aqueous alcoholic solvents other than 50% *i*-PrOH, such as 50% MeOH, 50% EtOH, and 50% ethylene glycol (Entries 22–24, respectively). Since we could not achieve a breakthrough for efficient reaction conditions to achieve the better isolated yield of **4aa** despite the detailed optimization study, the conditions described in Entry 1 were chosen for the substrate applicability study of aryl bromides.

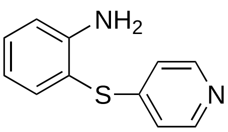
Table 3. Cu/CR11 or Cu/CR20-Catalyzed ring cleaving *S*-arylation using benzothiazole (**1**)



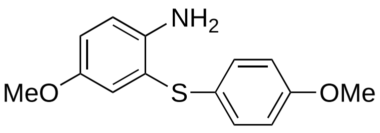
aryl iodides (**2**)



R= *p*-Ac (**4aa**), 83%
m-Ac (**4ab**), 76%
p-CF_3 (**4ac**), 76%
p-MeO (**4ad**), 97%
m-MeO (**4ae**), 80%
o-MeO (**4af**), 86%
p-Me (**4ag**), 54%
m-Me (**4ah**), 45%

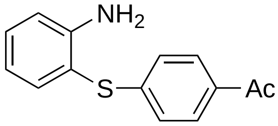


4ai,19%

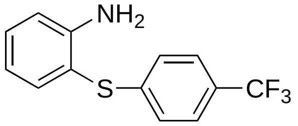


4bd, 19%

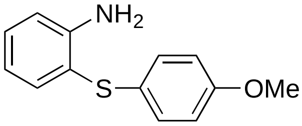
aryl bromides (**3**)



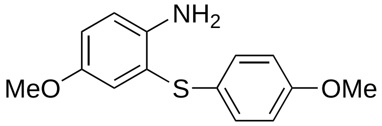
4aa, 62%[a)]



4ac, 17%[a)]



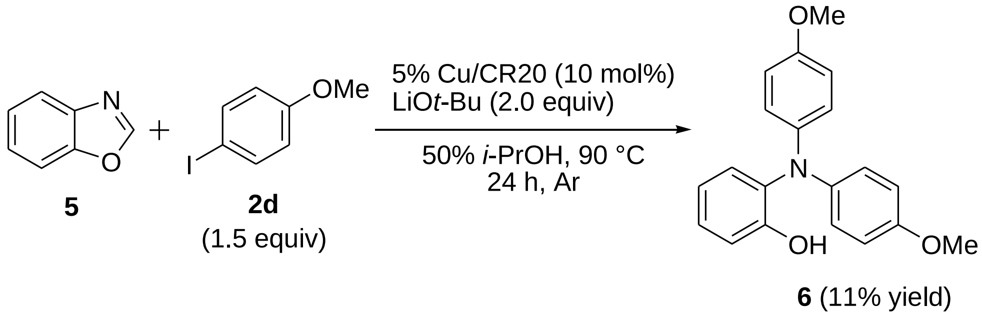
4ad, 26%[b)]



4bd, 9%[a)]

a) 10 mol% of 5% Cu/CR11 was used. b) 20 mol% of 5% Cu/CR11 was used.

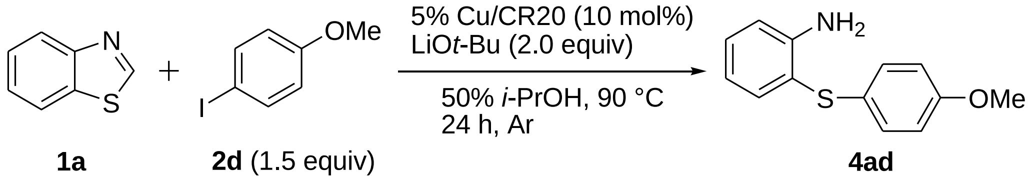
We explored the scope and limitations of a variety of aryl iodides (**2**) and aryl bromides (**3**) for use in the 5% Cu/CR20 or 5% Cu/CR11 (10 mol%)-catalyzed ring cleaving *S*-arylation using benzothiazole (**1**) as a starting material in the presence of LiO*t*-Bu (2.0 equiv) in 50% *i*-PrOH at 90 °C for 24 h under argon atmosphere (Table 3). When aryl iodides (**2**) were used as substrates, the reaction efficiently proceeded with the 5% Cu/CR20-catalyt, yielding the corresponding *S*-arylated 2-aminothiophenol (**4**) in good to excellent yields regardless of the electronic nature of the aromatic nuclei of **2** except for 4-iodopyridine (**2i**) and the reaction of **2b** with with 6-methoxy-1,3-benzothiazole (**1b**). Furthermore, aryl bromides (**3**) were also suitable substrates for ring cleaving *S*-arylation using 5% Cu/CR11 as a catalyst, although aryl bromides (**3**) exhibited lower reactivity relative to aryl iodides (**2**).



Scheme 2. The 5% Cu/CR20-Catalyzed ring cleaving reaction of benzoxazole

Next, the coupling of benzoxazole (**5**) instead of benzothiazole (**1a**) was investigated as a substrate with 4-iodoanisole (**2d**) under the same reaction conditions, and *N*-arylated 2-(bis(4-methoxyphenyl)amino)phenol (**6**) was obtained in an 11% yield (Scheme 2).[11] The arylation proceeded on the most basic nitrogen in this reaction although efficient *O*-arylation under the copper nanoparticle-catalyzed arylation of benzoxazole had been reported in the literature.[5,11]

Table 4. Reusability test of the 5% Cu/CR20 catalyst



Run	Recovery of 5% Cu/CR20 (%)	Yield of **4ad** (%)
1st	86	97
2nd	87	56[a]

[a] 16% of the unchanged starting material (**1a**) was recovered together with the desired **4ad**.

Subsequently, the reusability of the 5% Cu/CR20 catalyst was tested using benzothiazole (**1a**) and 4-methoxybenzenethiol (**2d**) as substrates. Although the reusability of the heterogeneous catalyst is beneficial in the formulation of environmentally friendly synthetic processes, the reaction efficiency was significantly reduced in the second run (Table 4). Furthermore, copper species leached into the filtrate during the 5% Cu/CR20-catalyzed C-S coupling reaction of benzothiazole (**1a**) with 4-iodoanisole (**2d**). This was determined after the addition of ethyl acetate and water to the resulting reaction mixture to remove the catalyst by simple filtration and subsequent extraction of the filtrate. As the result, approximately 2.1% of the total copper species (1.76 ppm in the aqueous layer and 0.41 ppm in the organic layer) was leached from 5% Cu/CR20 catalyst. The leaching and mechanical damage during the stirring are likely the main causes for the non-reusability of the catalyst.

CONCLUSIONS

A selective, efficient, and heterogeneous catalyst composed of copper bromide supported on a chelate resin for catalysis of C-S bond formation (*S*-arylation) of benzothiazole and various aryl halides was developed. The catalytic process was achieved with excellent efficiency by using aryl iodides as coupling partners via thiazole-ring-cleavage yielding the corresponding *S*-arylated 2-aminothiophenols bearing a free amino group at the *ortho*-position. Furthermore, aryl bromides are also suitable for the *S*-arylation reaction although decreased efficiency was unavoidable in some cases. Since the reaction can be performed in aqueous *i*-PrOH and benzothiazole as a substrate is reasonably stable, much less odor is generated than with thiophenol derivatives, or other related commercially available reagents. The catalytic system presented herein will find many practical applications for the preparation of *S*-arylated 2-aminothiophenols as synthetic precursors.

EXPERIMENTAL

General

All reactions were carried out under argon. All reagents and solvents were obtained from commercial sources and used without further purification. The DIAION CR11 and CR20 were obtained from Mitsubishi Chemical Corporation (Japan). Flash column chromatography was performed using silica gel 60N [spherical neutral (63–210 μm)] from Kanto Chemical Co., Inc. The ^{1}H and ^{13}C NMR spectra were recorded by a JEOL JNM AL-400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) or JEOL JNM ECA-500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometer. $CDCl_3$ was used as the solvent for NMR measurement. Chemical shifts (δ) are expressed in part per million and internally referenced (0.00 ppm for tetramethylsilane for ^{1}H NMR and 77.0 ppm for $CDCl_3$). High resolution mass spectrum was measured by Shimadzu hybrid LCMS-IT-TOF (LCMS-IT-TOF).

All products except for only 2-(3'-acetylphenylthio)aniline (**4ab**) were known compounds, and their ^{1}H and ^{13}C NMR spectral data were identical to those in the literature.

Preparation of the 5% Cu/CR11 and 5% Cu/CR20 catalysts

The 5% Cu/CR11 catalyst was prepared in a procedure similar to that previously reported in ref. 10. $CuBr_2$ was quantitatively immobilized by immersing granulated DIAION CR11 (1.00 g) in an aqueous solution (4 mL) of $CuBr_2$ (175 mg, 0.78 mmol) at 22–24 °C for 3 h. The resulting light blue granulated polymer was collected by filtration, washed with water and MeOH, and dried under reduced pressure overnight to yield copper on the DIAION CR11 (Cu/CR11). Atomic absorption spectrometry of the filtrate detected no residual copper species. Therefore, 5 wt% of the copper species was embedded on the granulated DIAION CR11. Granulated DIAION CR20 was subsequently treated with an aqueous solution of $CuBr_2$ in accordance with the procedure for the preparation of 5% Cu/CR11 to afford the 5% Cu/CR20 catalyst as a greenish solid.

General procedure for the investigation of the catalyst support (Table 1)

The suspension of benzothiazole (**1a**, 27.3 μL, 250 μmol), 4'-iodoacetophenone (**2a**, 92.3 mg, 375 μmol) or 4'-bromoacetophenone (**3a**, 74.6 mg, 375 μmol), LiO*t*-Bu (40.0 mg, 500 μmol), and 5% Cu/CR11, 5% Cu/CR20 or 5% Cu/WA30 (31.8 mg, 25.0 μmol) in 50% *i*-PrOH was stirred at 90 °C under argon atmosphere. After 24 h, the mixture was cooled to room temperature and filtered through a celite pad. The catalyst on the celite pad was washed with EtOAc (20 mL). The combined filtrates were washed with H_2O (20 mL) and the aqueous layer was further extracted with EtOAc (20 mL). The combined organic layers were washed with H_2O (20 mL × 3), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography using toluene/EtOAc (10 : 1) as a eluent to give spectrally pure 2-(4'-acetylphenylthio)aniline (**4aa**) in 72% yield (43.8 mg, 180 μmol). **2-(4'-Acetylphenylthio)aniline (4aa):**[12] Obtained in yields as indicated in Table 1 (Entries 1–5). ^{1}H NMR (400 MHz) δ 7.79 (2H, d, *J* = 8.0 Hz), 7.45 (1H, dd, *J* = 8.0, 1.5 Hz), 7.28 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz), 7.08 (2H, d, *J* = 8.0 Hz), 6.83–6.76 (2H, m), 4.30 (2H, br s), 2.52 (3H, s); ^{13}C NMR (100 MHz) δ 197.0, 149.0, 144.1, 137.6, 133.9, 131.8, 128.9, 125.2, 118.9, 115.5, 112.1, 26.4.

Preparation of 6-methoxy-1,3-benzothiazole (1b)[13]

A 20 mL-round bottom flask was charged with 2-amino-6-methoxy-1,3-benzothiazole (901 mg, 5.00 mmol) and 10 mL of 1,4-dioxane, and then isoamyl nitrite (1.5 mL, 10.0 mmol) was added slowly into the solution. The resulting mixture was stirred at 30 minutes, and poured into ice-water, and the resulting aqueous mixture was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated under decreased pressure. The residue was purified by silica-gel column chromatography using hexane/EtOAc (5 : 1) as an eluent to give 6-methoxy-1,3-benzothiazole (**1b**) in 60% yield (99.8 mg, 604 μmol).

^{1}H NMR (400 Hz) δ 8.34 (1H, s), 8.01 (1H, d, *J* = 9.6 Hz), 7.40 (1H, s), 7.13 (1H, d, *J* = 9.6 Hz), 3.89 (3H, s); ^{13}C NMR (100 Hz) δ 158.0, 151.4, 147.9, 135.4, 124.0, 115.8, 104.0, 55.8.

General procedure for the scope of substrate (Table 2)

The suspension of benzothiazole (**1**, 250 μmol), aryl halide (**2** or **3**, 375 μmol), LiO*t*-Bu (30.0 mg, 375 μmol), and 5% Cu/CR (31.8 mg, 25.0 μmol; 5% Cu/CR11 for **2**, 5% Cu/CR20 for **3**) in 50% *i*-PrOH (1 mL) was stirred at 90 °C under argon atmosphere. After 24 h, the mixture was cooled to room temperature and filtered through a celite pad. The catalyst on the celite pad was washed with EtOAc (20 mL). The combined filtrates were washed with H_2O (20 mL) and the aqueous layer was further extracted with EtOAc (20 mL). The combined organic layers were washed with H_2O (20 mL × 3), dried over Na_2SO_4 and concentrated under decreased pressure. The residue was purified by silica-gel column chromatography using toluene/EtOAc as an eluent to give a spectrally pure *S*-aryl-2-thioaniline (**4**).

2-(3'-Acetylphenylthio)aniline (4ab): Obtained in 74% yield (44.9 mg, 184 μmol) from **1a** (27.3 μL, 250 μmol) and 3'-iodoacetophenone (**2b**, 92.3 mg, 375 μmol). Slightly brown oil. ^{1}H NMR (500 MHz) δ 7.67 (1H, dd, *J* = 8.0, 1.5 Hz), 7.45 (1H, dd, *J* = 7.5, 1.5 Hz), 7.29 (1H, dd, *J* = 8.0, 1.5 Hz), 7.26 (1H, ddd, *J* = 7.5, 7.5, 1.5 Hz), 7.20 (1H, dd, *J* = 8.0, 1.5 Hz), 6.80 (1H, dd, *J* = 7.5, 1.5 Hz), 6.77 (1H, ddd, *J* = 7.5, 7.5, 1.5 Hz), 4.32 (2H, brs), 2.52 (3H, s); ^{13}C NMR (125 MHz) δ 197.6, 148.9, 148.1, 137.7, 137.5, 131.6, 130.5, 129.2, 126.1, 125.2, 118.9, 115.4, 113.3, 26.6; HRMS (LCMS-IT-TOF) calcd. for $C_{14}H_{14}NOS$ [(M+H)$^+$] 244.0791, found: 244.0804.

2-(4-Trifluoromethylphenylthio)aniline (4ac):[15] Obtained in 76% yield (51.0 mg, 169 μmol) from **1a** (27.3 μL, 250 μmol) and 4-iodobenzotrifluoride (**2c**, 102 mg, 375 μmol). ^{1}H NMR (400 MHz) δ 7.46–7.43 (3H, m), 7.28 (1H, ddd, *J* = 7.8, 7.8, 1.6 Hz), 7.11 (2H, d, *J* = 8.4 Hz), 6.82–6.76 (2H, m), 4.28 (2H, brs); ^{13}C NMR (125 MHz) δ 149.0, 142.2, 137.7, 131.9, 127.2 ($J_{C–F}$ = 25.7 Hz), 125.7 ($J_{C–F}$ = 2.80 Hz), 125.6, 124.1 ($J_{C–F}$ = 217 Hz), 119.0, 115.5, 112.3.

2-(4-Methoxyphenylthio)aniline (4ad):[14] Obtained in 97% yield (56.2 mg, 243 μmol) from **1a** (27.3 μL, 250 μmol) and 4-iodosnisole (**2d**, 87.8 mg, 375 μmol). ^{1}H NMR (500 MHz) δ 7.39 (1H, dd, *J* = 8.0, 2.0 Hz), 7.17 (1H, ddd, *J* = 8.0, 8.0, 2.0 Hz), 7.12 (2H, d, *J* = 9.5 Hz), 6.79 (2H, d, *J* = 9.5 Hz), 6.75–6.70 (2H, m), 4.19 (2H brs), 3.74 (3H, s); ^{13}C NMR (125 MHz) δ 158.2, 148.0, 136.3, 130.3, 129.6, 126.8, 118.6, 116.6, 115.3, 114.7, 55.3.

2-(3-Methoxyphenylthio)aniline (4ae):[14] Obtained in 80% yield (46.4 mg, 200 μmol) from **1a** (27.3 μL, 250 μmol) and 3-iodoanisole (**2e**, 87.8 mg, 375 μmol). ^{1}H NMR (500 MHz) δ 7.47 (1H, ddd, *J* = 8.0, 2.0 Hz), 7.26 (1H, ddd, *J* = 8.0, 8.0, 2.0 Hz), 7.11 (1H, ddd, *J* = 8.0, 8.0, 2.0 Hz), 6.87 (1H, dd, *J* = 8.0, 2.0 Hz), 6.82–6.77 (3H, m), 6.65 (1H, dd, *J* = 8.0, 2.0 Hz), 4.32 (2H, brs), 3.94 (3H, s); ^{13}C NMR (125 MHz) δ 155.5, 149.2, 137.8, 131.1, 126.1, 126.1, 124.9, 121.3, 118.8, 115.2, 113.0, 110.3, 55.8.

2-(2-Methoxyphenylthio)aniline (4af):[14] Obtained in 86% yield (49.9 mg, 215 μmol) from **1a** (27.3 μL, 250 µmol) and 2-iodoanisole (**2f**, 87.8 mg, 375 µmol). ^{1}H NMR (500 MHz) δ 7.46 (1H, d, *J* = 8.0 Hz), 7.24 (1H, dd, *J* = 8.0, 8.0 Hz) 7.14 (1H, dd, *J* = 8.0, 8.0 Hz), 6.80–6.75 (2H, m), 6.69–6.64 (3H, m), 4.29 (2H, brs), 3.73 (3H, s); ^{13}C NMR (125 MHz) δ 160.0, 148.8, 138.2, 137.5, 131.2, 129.8, 118.7, 118.6, 115.3, 114.0, 111.9, 110.9, 55.1.

2-(4-Tolylthio)aniline (4ag):[15] Obtained in 54% yield (29.1 mg, 135 µmol) from **1a** (27.3 µL, 250 µmol) and 4-iodotoluene (**2g**, 81.8 mg, 375 µmol). ^{1}H NMR (400 MHz) δ 7.43 (1H, dd, *J* = 8.0, 1.6 Hz), 7.21 (1H, ddd, *J* = 8.0, 8.0, 1.6 Hz), 7.04–6.79 (4H, m), 6.77–6.71 (2H, m), 4.25 (2H, brs), 2.27 (3H, s); ^{13}C NMR (100 MHz) δ 148.5, 137.0, 135.4, 133.0, 130.8, 129.8, 127.0, 118.6, 115.3, 115.2, 20.9.

2-(3-Tolylthio)aniline (4ah):[5] Obtained in 45% yield (24.3 mg, 113 µmol) from **1a** (27.3 µL, 250 µmol) and 3-iodotoluene (**2h**, 81.8 mg, 375 µmol). ^{1}H NMR (400 MHz) δ 7.44 (1H, dd, *J* = 7.6, 1.2 Hz), 7.22 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.09 (1H, dd, *J* = 8.0, 8.0 Hz), 6.63–6.91 (2H, m), 6,86 (1H, d, *J* = 8.0 Hz), 6.78–6.72 (2H, m), 4.26 (2H, m), 2.26 (3H, s); ^{13}C NMR (100 MHz) δ 148.7, 138.8, 137.3, 136.5, 130.1, 128.8, 127.1, 126.4, 123.6, 118.6, 115.3, 114.5, 21.4.

2-Aminophenyl-4'-pyridyl sulfide (4ai):[16] Obtained in 19% yield (9.7 mg, 47.9 µmol) from **1a** (27.3 µL, 250 µmol) and 4-iodopyridine (**2i**, 76.9 mg, 375 µmol). ^{1}H NMR (500 MHz) δ 8.34 (2H, m), 7.43 (1H, dd, *J* = 8.0, 1.5 Hz), 7.31 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz), 6.91 (2H, d, *J* = 6.5 Hz), 6.85–6.78 (2H, m), 4.29 (2H, brs); ^{13}C NMR (100 MHz) δ 149.4, 149.2, 148.7, 137.8, 132.2, 120.1, 119.0, 115.5, 110.6.

4-Methoxy-2-(methoxyphenylthio)aniline (4bd):[14] Obtained in 19% yield (12.4 mg, 47.4 µmol) from **1b** (27.3 µL, 250 µmol) and 4-iodoanisole (**2d**, 87.8 mg, 375 µmol). ^{1}H NMR (500 MHz) δ 7.16 (2H, d, *J* = 8.5 Hz), 6.94 (1H, d, *J* = 2.5 Hz), 6.81 (2H, d, *J* = 8.5 Hz), 6.79 (1H, dd, *J* = 8.5, 2.5 Hz), 6.72 (1H, d, *J* = 8.5 Hz), 3.98 (2H, brs), 3.77 (3H, s), 3.72 (3H, s); ^{13}C NMR (125 MHz) δ 158.5, 152.4, 141.7, 130.1, 126.3, 119.9, 118.1, 116.9, 116.6, 114.8, 55.8, 55.3.

Leaching test of copper species

A suspension of **1a** (139 µL, 1.27 mmol), **2d** (552 mg, 2.16 mmol), LiO*t*-Bu (252 mg, 3.14 µmol), and 5% Cu/CR20 (200 mg, 127 µmol) in 50% *i*-PrOH (6.0 mL) was stirred at 90 °C under an argon atmosphere for 24 h. The mixture was subsequently cooled to room temperature and filtered through a Kiriyama funnel using 1 µm filter paper. The catalyst remaining on the filter paper was washed with EtOAc (20 mL). The combined filtrates were washed with H_2O (20 mL) and the aqueous layer was further extracted with EtOAc (20 mL). The organic layers were combined and washed with H_2O (20 mL × 3). The organic layer was transferred to a 100 mL volumetric flask and further EtOAc was added exactly to a final volume of 100 mL. The corresponding atomic absorption analysis indicated that 0.414 ppm of copper species remained in the organic layer. The aqueous layer was also transferred to a 100 mL volumetric flask, diluted with H_2O to a final volume of 100 mL, and the corresponding atomic absorption analysis indicated that 1.762 ppm of copper species remained. Therefore, the total quantity of leached copper species in the reaction media was determined to be 217 μg (41.4 μg in the organic layer and 176 μg in the aqueous layer). Approximately 2.1% of the total amount of copper species was leached from 5% Cu/CR20 (200 mg, 127 μmol).

Reusability test of 5% Cu/CR20 (Table 3)

5% Cu/CR20 (31.8 mg, 25.0 μmol), **1a** (27.3 μL, 250 μmol), **2d** (87.8 mg, 375 μmol), LiO*t*-Bu (40.0 mg, 500 μmol) and 50% *i*-PrOH (1 mL) were placed in a test tube. The mixture was stirred at 90 °C under an argon atmosphere for 24 h using a liquid phase organic synthesizer, Chemist Plaza CP-1000 (Shibata Scientific Technology LTD.). The reaction mixture was filtered through a Kiriyama funnel using 1 μm filter paper. The catalyst remaining on the filter paper was washed with EtOAc (20 mL) and the combined filtrates were washed with H_2O (20 mL). The aqueous layer was further extracted with EtOAc (20 mL) and the combined organic layers were washed with H_2O (20 mL × 3), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography using toluene/EtOAc (10 : 1) as an eluent to give a spectrally pure **4ad** in 97% yield.

The recovered Cu/CR20, which was dried in a desiccator at room temperature under reduced pressure overnight (27 mg, 86%), was used for the second run. The reuse tests were carried out in proportion to the recovered quantity of Cu/CR20 in the same manner as the first run. The product **4ad** was obtained in 56% yield together with 16% of the recovered (unchanged) starting material (**1a**), and Cu/CR20 was recovered (87%).

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