Cu/Fe/O=PPh$_3$-Catalyzed Etherification for the Synthesis of Aryl 3-Benzo[*b*]thienyl Ethers

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Cu/Fe-cocatalyzed cross-coupling reactions between 3-bromobenzo[*b*]thiophene and hydroxyaryls are described herein. The combination of Cu and Fe catalysts is important for the progress of the reactions, and the use of triphenylphosphine oxide as a ligand suppresses the dehalogenation of 3-bromobenzo[*b*]thiophene, and proceeds promptly the reaction. The obtained aryl benzo[*b*]thienyl ethers can be converted to π-extended thienobenzofuran derivatives via Pd-catalyzed dehydrogenative cyclizations.

Keywords: Aryl thienyl ether, Cu/Fe-cocatalyst, Cross-coupling

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Diaryl ethers are known as common skeletal motifs of natural products and bioactive compounds, and several synthetic methods have been reported thus far.[1] Among the known diaryl ethers, aryl thienyl ethers are important because they can be used as precursors for π-extended thieno[3,2-*b*]furan derivatives,[2] which are potential candidates for organic materials.

While copper-mediated Ullmann couplings have been used for a long time for the synthesis of diaryl ethers, these reactions usually require the use of a stoichiometric amount of copper salts as well as high reaction temperatures.[3] Recently, a breakthrough was accomplished by the discovery of efficient ligands for Ullmann couplings.[4] These ligands realize catalytic Ullmann-type coupling under mild conditions. Another breakthrough is the use of an iron salt as a co-catalyst; several excellent works based on the combination of copper and iron catalysts were recently reported.[5] Thus, new possibilities have been reported for the synthesis of diaryl ethers; however, applying such reactions to the synthesis of diaryl ethers bearing an electron-rich heteroaryl, such as benzo[*b*]thiophene, is challenging because dehalogenation of the substrate often competes with the desired coupling reaction.[6] Buchwald and co-workers reported that picolinic acid was an efficient ligand for Cu-catalyzed Ullman-type etherifications.[7] They reported the reaction of 3-bromo-2-formyl-benzo[*b*]thiophene, but the reaction of 3-bromobenzo[*b*]thiophene, which could be used for thieno[3,2-*b*]furan, was not reported. Quite recently, Ma and co-workers reported CuI/*N*-(2-phenylphenyl)-*N*′-benzyl oxalamide-catalyzed diaryl ether syntheses.[8] While the catalytic system could be used for the synthesis of a wide variety of diaryl ethers, they used 3-iodobenzo[*b*]thiophene as the benzo[*b*]thiophene source. To the best of our knowledge, there has been no efficient method for a Cu-catalyzed etherification using 3-bromobenzo[*b*]thiophene, which is commercially available and cheaper than 3-iodobenzo[*b*]thiophene.

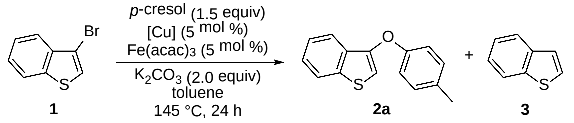
We considered that a fine-tuning of the reaction conditions could enhance the efficiency of the Ullmann-type coupling reaction of 3-bromobenzo[*b*]thiophene, which would be a powerful tool for the synthesis of aryl benzo[*b*]thienyl ethers. We examined the reaction conditions for an Ullmann-type reaction with 3-bromobenzo[*b*]thiophene, and found an efficient Cu/Fe catalytic system, using triphenylphosphine oxide as a ligand. To the best of our knowledge, there has been no report on a copper- or iron-catalyzed Ullmann-type reaction using triphenylphosphine oxide as a ligand.[9]

First, we chose 3-bromobenzo[*b*]thiophene (**1**) and *p*-cresol as model compounds and performed a screening of copper salts for the Cu/Fe-cocatalyzed etherification between them (Table 1). In the presence of a Cu source ([Cu], 5 mol %), Fe(acac)$_3$ (5 mol %), and K_2CO_3 (2.0 equiv), 3-bromobenzo[*b*]thiophene (**1**) was treated with *p*-cresol (1.5 equiv). Without the Cu source, only a trace amount of the desired product was obtained, and most of the starting material **1** was recovered (entry 1). In contrast, with copper powder, the coupling reaction between **1** and *p*-cresol proceeded smoothly to afford the coupling product **2a** in 55% yield with a considerable amount (41%) of the dehalogenated compound, benzo[*b*]thiophene (**3**) (entry 2). With Cu(I) salts such as CuCl, CuBr, and CuI,[5f,5h] **2a** was obtained in the respective yields of 48%, 50%, and 57% (entries 3–5). When the reaction was performed without Fe(acac)$_3$, the yield of **2** decreased and that of **3** increased (entry 4). Among several Cu(I) salts, copper thiophene-2-carboxylate (CuTC) provided the best result. With CuTC, the desired compound **2a** was obtained in 60% yield, but **3** was also obtained in 33% yield (entry 8). We then examined several Cu(II) salts (entries 9–13) and found that the use of Cu(acac)$_2$ afforded **2a** in the highest yield (62% yield, entry 13).

Then, we examined the effect of the iron source (Table 2) and Fe(acac)$_3$ was the best iron source among the studied sources. Using $FeCl_2$•$4H_2O$, $FeCl_3$, or $FeBr_3$, the yield of **2a** decreased to 43%–47% (entries 2–4).

The screening of the copper and iron sources revealed that the combination of Cu(acac)$_2$ and Fe(acac)$_3$ was efficient for the Cu/Fe-cocatalyzed etherification of **1** and *p*-cresol; however, dehalogenation of **1** to **3** was still problematic. Therefore, we investigated the effect of ligands (Table 3). Diamine ligands such as 2,2′-bipyridyl (bpy) and 1,10-phenanthroline (phen), which are commonly used with Cu, were ineffective for the reactions, and the yield of **2a** decreased (entries 1–2). We then evaluated oxygen ligands (entries 3 and 4) and found that with 1,1'-bi-2-naphthol (BINOL),[5i] the yield of **2a** increased to 51%, but **3** was also obtained in 41% yield (entry 3). The use of 2,2,6,6-tetramethylheptane-3,5-dione (TMHD)[5a,5j] provided a good result (72% yield, entry 4). The use of phosphine ligands was also investigated and found that the triphenylphosphine (PPh_3) was also effective, affording **2a** in 73% yield and a 15% suppression of the generation of **3** (entry 5). Further screening revealed that electron-donating phosphine ligands such as P(*p*-tol)$_3$ and PCy_3 were ineffective (entries 6 and 7). In contrast, the etherification proceeded smoothly with P(2-furyl)$_3$, which is a slightly electron-deficient ligand (79% yield), but afforded **3** in 18% yield (entry 8). Other electron-deficient ligands were not effective (entries 9–11). Finally, we found that dehalogenation of **1** was suppressed by the use of triphenylphosphine oxide ($O{=}PPh_3$), affording a 10% yield (entry 12). Using 10 mol % of $Cu(acac)_2$, and 10 mol % of $Fe(acac)_3$, the yield of **2a** increased to 82% (79% isolated yield) with 12 % yield of **3** (entry 13). The ratio of $O{=}PPh_3$ to $Cu(acac)_2$ and $Fe(acac)_3$ is singnificant. Increasing or decreasing the amount of $O{=}PPh_3$, the yields of **2a** decreased (entries 14 and 15). The temperature highly influenced the reaction, and the yield of **2a** decreased to 69% at 135 °C (entry 16). While the reason for the suppression of the dehalogenation of **1** is unclear, we assume that a catalyst bearing $O{=}PPh_3$ would be highly active and the cross-coupling reaction would proceed faster than the dehalogenation.

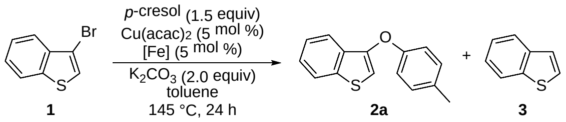
Table 1. Cu/Fe-Cocatalyzed etherification of 3-bromobenzo[*b*]thiophene using several catalysts [a]



Entry	[Cu]	Yield of 2a^b/%	Yield of 3^b/%
1	none	<1	<1
2	Cu powder	55	41
3	CuCl	48	25
4	CuBr	50 (42)^c	32 (45)^c
5	CuI	57	26
6	Cu_2O	54	17
7	CuCN	53	33
8	CuTC^d	60	33
9	$CuCl_2$	46	17
10	$CuBr_2$	54	40
11	CuO	60	23
12	$Cu(OAc)_2$	47	43
13	$Cu(acac)_2$	62	30

[a] Reaction conditions: **1** (0.5 mmol), *p*-cresol (0.75 mmol), [Cu] (5 mol %), $Fe(acac)_3$ (5 mol %), K_2CO_3 (2.0 equiv), toluene (0.63 M), 145 °C, 24 h. Performed in a sealed tube. [b] Determined by ^1H NMR. [c] Performed without $Fe(acac)_3$. [d] CuTC = copper thiophene-2-carboxylate.

Table 2. Effect of the Fe source on the Cu/Fe-cocatalyzed etherification reaction [a]

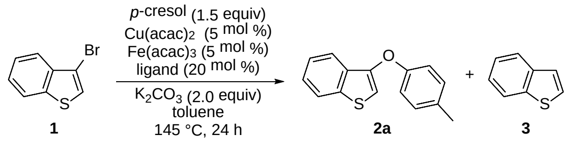


Entry	[Fe]	Yield of 2a^b/%	Yield of 3^b/%
1	$Fe(acac)_3$	62	30
2	$FeCl_2{\bullet}4H_2O$	43	17
3	$FeCl_3$	45	23
4	$FeBr_3$	47	28

[a] Reaction conditions: **1** (0.5 mmol), *p*-cresol (0.75 mmol), $Cu(acac)_2$ (5 mol %), [Fe] (5 mol %), K_2CO_3 (2.0 equiv), toluene (0.63 M), 145 °C, 24 h. Performed in a sealed tube. [b] Determined by ^1H NMR.

We then examined the scope of the etherification reactions. Several hydroxyaryls were terated with 3-bromobenzo[*b*]thiophene under optimized conditions (Table 4). The reaction with phenol afforded the corresponding coupling product **2b** in 73% yield. Not only *p*-cresol but also *o*- and *m*-cresol could be used for the reaction to give the corresponding coupling products **2c** and **2d** in the respective yields of 62% and 69%. Hydroxyaryls bearing electron-donating groups, such as *t*-Bu and methoxy groups, gave the coupling products in moderate to good yields (**2e**: 71%, **2f**: 56%). Reactions with hydroxyaryls bearing an electron-withdrawing group were also examined. Reactions with hydroxyaryls bearing a halogen atom, such as F and Cl, at the *p*-position gave the desired coupling products (**2g**: 76%, **2h**: 64%). Hydroxylaryls bearing much stronger electron-withdrawing groups at the *p*-position, such as trifluoromethyl or nitro groups, were unfortunately not applicable, probably due to their electronic effect. In contrast, the reaction with *m*-trifluoromethylphenol, which has an electron-withdrawing group at the *m*-position, proceeded smoothly to give the desired coupling product **2k** in 62% yield. We performed out the coupling reaction with more π-extended hydroxy aryls. *p*-Phenylphenol could be used for the reaction to afford **2l** in 71% yield. With 1-naphthol or 2-naphthol, the coupling products **2m** and **2n** were obtained in the respective yields of 15% and 54%.

Table 3. Optimization of ligands [a]

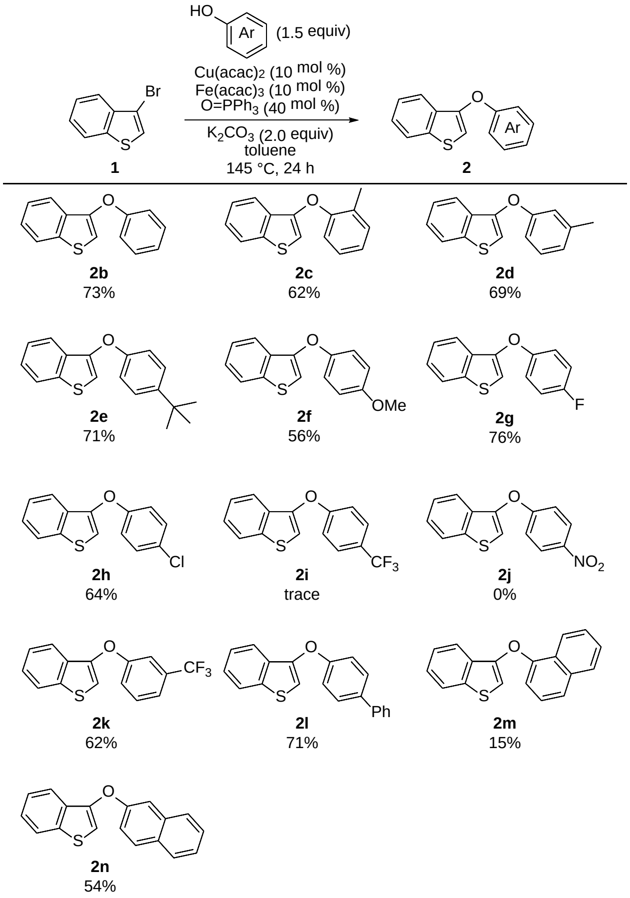


Entry	Ligand	Yield of 2a[b]/%	Yield of 3[b]/%
1	bpy[c]	41	35
2	phen[d]	39	50
3	BINOL	51	41
4	TMHD[e]	72	18
5	PPh_3	73	15
6	P(*p*-tol)	15	0
7	PCy_3	0	0
8	$P(2\text{-furyl})_3$	79	18
9	$P(C_6F_5)_3$	26	0
10	$P(C_6H_4\text{-}p\text{-}CF_3)$	56	14
11	$P(OPh)_3$	26	10
12	$O{=}PPh_3$	73	10
13[f]	$O{=}PPh_3$	82 (79)[g]	12
14[h]	$O{=}PPh_3$	68	8
15[i]	$O{=}PPh_3$	63	7
16[f,j]	$O{=}PPh_3$	69	9

[a] Reaction conditions: **1** (0.5 mmol), *p*-cresol (0.75 mmol), $Cu(acac)_2$ (5 mol %), $Fe(acac)_3$ (5 mol %), ligand (bidentate: 10 mol %, monodentate: 20 mol %), K_2CO_3 (2.0 equiv), toluene (0.63 M), 145 °C, 24 h. Performed in a sealed tube. [b] Determined by ^{1}H NMR. [c] bpy = 2,2′-bipyridyl. [d] phen = 1,10-phenanthroline. [e] TMHD = 2,2,6,6-tetramethylheptane-3,5-dione. [f] Performed with $Cu(acac)_2$ (10 mol %), $Fe(acac)_3$ (10 mol %), $O{=}PPh_3$ (40 mol %). [g] Isolated yield. [h] Performed with $Cu(acac)_2$ (10 mol %), $Fe(acac)_3$ (10 mol %), $O{=}PPh_3$ (20 mol %). [i] Performed with $Cu(acac)_2$ (10 mol %), $Fe(acac)_3$ (10 mol %), $O{=}PPh_3$ (60 mol %). [j] Performed at 135 ºC.

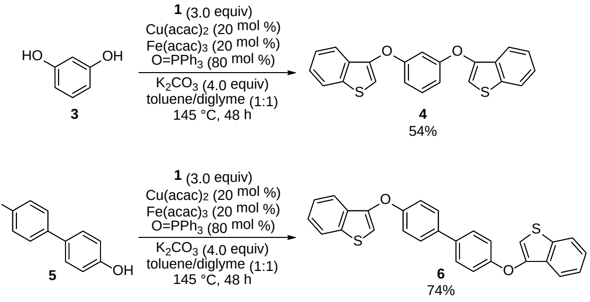
This reaction system could also be applied for the synthesis of diethers (Scheme 1). The Cu/Fe-catalyzed reaction between resorcinol and 3-bromobenzo[*b*]thiophene (**1**) afforded 1,3-bis(benzo[*b*]thiophen-3-yloxy)benzene (**4**) in 54% yield. Similarly, the reaction with (1,1′-biphenyl)-4,4′-diol (**5**) gave the corresponding diether **6** in 74% yield.

Table 4. Scope of the Cu/Fe-cocatalyzed etherification [a]



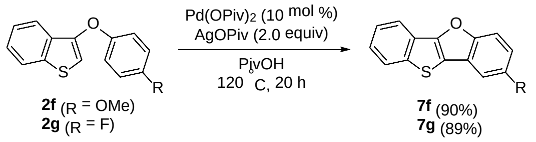
[a] Reaction conditions: **1** (0.5 mmol), hydroxyaryl (0.75 mmol), $Cu(acac)_2$ (10 mol %), $Fe(acac)_3$ (10 mol %), $O{=}PPh_3$ (40 mol %), K_2CO_3 (2.0 equiv), toluene (0.63 M), 145 °C, 24 h. Performed in a sealed tube. Isolated yield.

Scheme 1. Sequential double Cu/Fe-cocatalyzed etherification



As an application of the thus-obtained **2**, this compound was transformed into thienobenzofurans using a modified Pd-catalyzed dehydrogenative cyclization method, which was reported independently by Satoh and Miura,[10] and by Kanai and Kuninobu.[11] In the presence of $Pd(OPiv)_2$ (10 mol %) and AgOPiv (2.0 equiv) in PivOH, the cyclization of **2f** and **2g** was performed at 120 °C for 20 h (Scheme 2). The corresponding thienobenzofuran derivatives **7f** and **7g** were obtained in high yields from each precursor, which had an electron-donating or an electron-withdrawing group.[12]

Scheme 2. Representative examples of Pd-catalyzed dehydrogenative cyclization for the synthesis of thienobenzofuran derivatives 7 [a]



In summary, we developed Cu/Fe/O=PPh_3-catalyzed etherfication reactions for the synthesis of aryl benzo[*b*]thienyl ethers. The use of triphenylphosphine oxide as a ligand suppresses the dehalogenation of 3-bromobenzo[*b*]thiopehene, and enables an efficient synthesis of aryl benzo[*b*]thienyl ethers. Further applications of this strategy for other heteroaryl ethers are on-going in our laboratory.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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12 For the details of the dehydrogenative cyclization reactions, see the Supporting Information.

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Graphical Abstract

Textual Information

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Title(required)	Cu/Fe/O=PPh_3-Catalyzed Etherification for the Synthesis of Aryl 3-Benzo[*b*]thienyl Ethers
Authors' Names(required)	Koichi Mitsudo,* Takuya Asada, Tomohiro Inada, Yuji Kurimoto, Hiroki Mandai, and Seiji Suga*

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