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Integrated Synthesis of Thienyl Thioethers and Thieno[3,2-*b*]thiophenes via 1-Benzothiophen-3(2*H*)-ones

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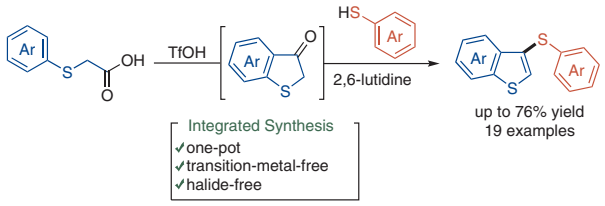

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Abstract A one-pot procedure for the synthesis of thienyl thioethers is described. Several thienyl thioethers were synthesized by a TfOH-promoted Friedel–Crafts-type cyclization, a subsequent nucleophilic attack by an arenethiol, and dehydration. This protocol was successfully applied to the synthesis of thienoacene derivatives by using a Pd-catalyzed dehydrogenative cyclization.

Key words thienyl thioethers, thioetherification, one-pot synthesis, metal-free, halide-free, thienoacenes

Hetaryl thioethers are important motifs in the fields of pharmaceuticals[1] and organic materials.[2] In particular, thienyl thioethers are potent candidates for bioactive compounds such as endothelin inhibitors[3a] and thrombin inhibitors[3b] (Figure 1). Hetaryl thioether moieties are also found in π-expanded thienoacene derivatives, such as [1]benzothieno[3,2-*b*][1]benzothiophene (**BTBT**), which are used as core units in high-performance semiconductors (Figure 1).[4]

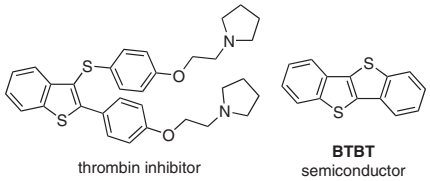
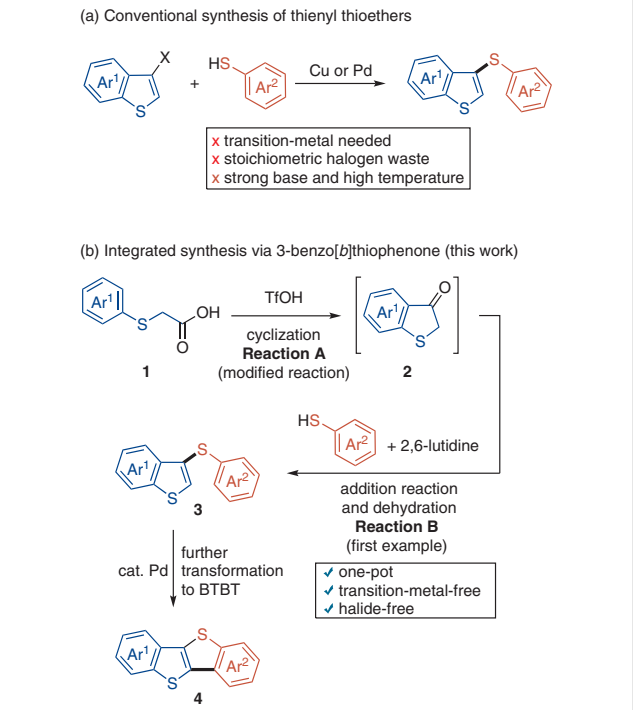


Figure 1 Thienyl thioether skeletons in a bioactive compound and an organic material

Conventional syntheses of thioethers involve transition-metal-catalyzed cross-coupling reactions between haloarenes and thiophenols, typically requiring the use of strong bases and high temperatures (Scheme 1a).[5] Several novel C–S coupling reactions have been explored to avoid the use of these harsh and toxic reaction conditions.[6–8] For example, Glorius and co-workers reported a Co-catalyzed dehydrogenative C–S coupling of indoles and thiols.[6a] Lei and co-workers established an electrochemical dehydrogenative C–S coupling reaction between indoles and thiols.[7a] Light-driven C–S coupling reactions have also been described;[8] for example, the Miyake group reported a visible-light-driven C–S coupling between aryl halides and arylthiols.[8a]



Scheme 1 Representative synthesis of thienyl thioethers

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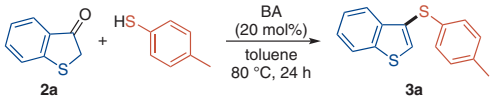
There have also been a few reports on halogen- and transition-metal-free C–S bond-formation reactions for the construction of thienyl thioethers.[9] For example, Johnson and co-workers reported a TsOH-promoted thioether synthesis from 7-bromo-3-hydroxybenzo[*b*]thiophenes.[9a] Procter and co-workers reported syntheses of thioethers, including thienyl thioethers, by Tf_2O-mediated C–H thiolations of arenes by methyl sulfoxides.[9b] Yorimitsu and co-workers developed acid-anhydride-promoted sulfanylation reactions of aryl sulfoxides.[9c] However, methods for synthesizing thienyl thioethers under halogen- and transition-metal-free conditions remain limited, and a novel and general method to access thienyl thioethers is attractive and in demand.

To accomplish this, we focused on 1-benzothiophen-3(2*H*)-ones **2**, which are known to be readily available from arylthioacetic acids **1** through intramolecular Friedel–Crafts cyclization (Scheme 1b, Reaction A),[10] and we designed a novel integrated sequential approach.[11] We expected that **2** could then be converted into 1-benzothien-3-yl thioethers **3** through Brønsted acid catalyzed addition of arylthiols and subsequent dehydration (Scheme 1b, Reaction B). Here, we report an integrated reaction system that combines Reactions A and B for the synthesis of thienyl thioethers. The products were successfully employed in Pd-catalyzed dehydrogenative cyclization reactions to give thienoacene derivatives **4**.

We first examined the thioetherification of 1-benzothiophen-3(2*H*)-one (**2a**) with 4-methylbenzenethiol (Reaction B) in the presence of various Brønsted acids, a key step to complete our strategy (Table 1). The desired reaction did not occur when acetic acid, trichloroacetic acid, or trifluoroacetic acid was used (Table 1, entries 1–3). Although thioetherification proceeded with H_3PO_4, the desired compound **3a** was obtained in only 6% yield (entry 4). Further optimization revealed that sulfonic acids were suitable for thioetherification and that MsOH, TfOH, and $TsOH·H_2O$ afforded **3a** in yields of 65, 63, and 70%, respectively (entries 5–7).

Because 1-benzothiophen-3(2*H*)-one (**2a**) is relatively unstable in air and gradually decomposes, we sought to prepare the reactant in situ, and we developed a one-pot reaction involving a Friedel–Crafts-type cyclization of **1a** to afford **2a** (Reaction A), followed by its thioetherification to give thioether **3a** (Reaction B) (Table 2). Among the Brønsted acids examined, only TfOH was effective for both Reaction A and Reaction B [Table 1 and Supporting Information (SI), Table S1]. Phenylthioacetic acid (**1a**) was treated with TfOH (8.0 equiv) at 40 °C for three hours to give 1-benzothiophen-3(2*H*)-one (**2a**). The reaction mixture was then cooled to 0 °C, 4-methylbenzenethiol and a base (7.6 equiv) were added, and the mixture was heated at 80 °C for 18 h. A base was essential for the formation of the desired product. Without the addition of a base, Reaction B did not proceed, and **3a** was not obtained (Table 2, entry 1), probably because the interaction of 4-methylbenzenethiol and the excess TfOH decreased the nucleophilicity of the thiol. To neutralize excess TfOH, we examined the addition of various bases (entries 2–6).[12] As expected, the addition of DIPEA promoted the desired reaction (entries 2 and 3). Aniline was not effective, probably because it was insufficiently basic (entry 4). The order of addition of the thiol and DIPEA

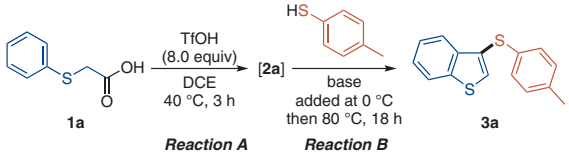
Table 1 Optimization of Reaction B: Thioetherification of 1-Benzothiophen-3(2*H*)-one (**2a**) with Various Brønsted Acids[a]



Entry	Brønsted acid	Conversion[b] (%)	Yield[b] (%) of **3a**
1	AcOH	9	ND[c]
2	CCl_3CO_2H	19	ND
3	CF_3CO_2H	9	ND
4	H_3PO_4	17	6
5	MsOH	>95	65
6	TfOH	>95	63
7	$TsOH·H_2O$	>95	70 (63)[d]

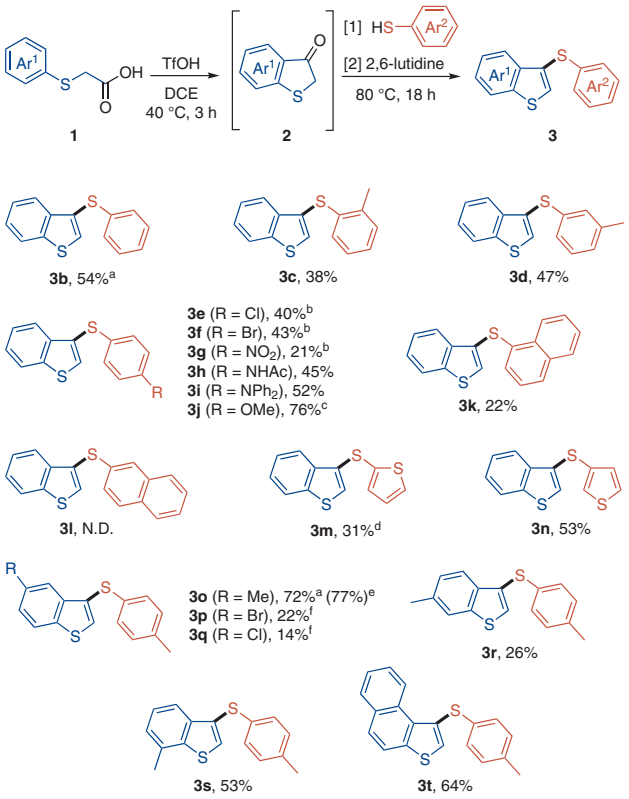
[a] Reaction conditions: **1a** (0.20 mmol), Brønsted acid (20 mol%), toluene (0.2 M), 80 °C, 24 h.
[b] Determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard.
[c] ND = Not detected.
[d] Isolated yield.

Table 2 One-Pot Synthesis of Thioether **3a** via 1-Benzothiophen-3(2*H*)-one (**2a**) with Various Bases[a]



Entry	Base	Yield[b] (%) of **3a**
1	none	ND[c]
2[d]	*i*-Pr_2NEt	32
3	*i*-Pr_2NEt	64
4	aniline	32
5	piperidine	65
6[e]	2,6-lutidine	67 (63)[f]

[a] Reaction conditions: Reaction A: **1a** (0.20 mmol), TfOH (8.0 equiv), DCE (0.66 M), 40 °C, 3 h. Reaction B: 4-methylbenzenethiol (1.0 equiv) and base (7.6 equiv) added at 0 °C, then 80 °C, 18 h.
[b] Yield from **1a**, determined by ^{1}H NMR.
[c] ND = not detected.
[d] Reaction B; base added before 4-methylbenzenethiol.
[e] Performed with TfOH (7.7 equiv).
[f] Isolated yield.



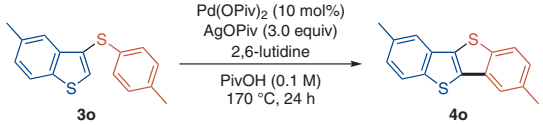
Scheme 2 One-pot syntheses of thienyl thioethers **3**. *Reagents and conditions*: Reaction A: **1** (0.20 mmol), TfOH (7.7 equiv), DCE (0.66 M), 40 °C, 3 h. Reaction B: arylthiol (1.0 equiv), 2,6-lutidine (7.4 equiv) added at 0 °C, then at 80 °C, 18 h. Yields are isolated yields based on **1**. [a] Thiol (1.2 equiv). [b] 2,6-lutidine (7.6 equiv). [c] 2,6-Lutidine was added before the thiol at –78 °C. [d] 2,6-Lutidine was added before the thiol at 0 °C. [e] 1.5 mmol scale. [f] 0.4 mmol scale.

affected the yield of the desired compound **3a** (SI; Scheme S1). When DIPEA was added first, **3a** was obtained in only 32% yield, due to the competing aldol condensation of **2a** to form the dimer 2,3′-bi-1-benzothiophene-3-ol (entry 2). When 4-methylbenzenethiol was added before DIPEA, the side reaction was suppressed, and the yield of **3a** increased to 64% (entry 3). We next examined several bases, and we found that 2,6-lutidine gave the best result (67% NMR yield and 63% isolated yield; entry 6).[13]

By using the optimized conditions, a series of thienyl thioethers were synthesized (Scheme 2). Thioetherification with phenylthiol gave thioether **3b** in 54% yield, whereas 2- and 3-methylbenzenethiol gave the corresponding thioethers **3c** and **3d** in moderate yields. Next, several *p*-substituted benzenethiols were used in the reaction (**3e–j**). 4-Chlorobenzenethiol and 4-bromobenzenethiol gave the halogenated thioethers **3e** and **3f** in yields of 40 and 43%, respectively. However, 4-nitrobenzenethiol, gave a low yield of thioether **3g** (21%), due to its low nucleophilicity. *N*-(4-Sulfanylphenyl)acetamide gave aryl thioether **3h** in 45% yield. Benzenethiols containing electron-donating groups were also effective reactants: 4-(diphenylamino)- and 4-methoxybenzenethiol gave the corresponding biaryl thioethers **3i** and **3j** in yields of 52 and 76%, respectively. Thioetherification also proceeded successfully with naphthalene-1-thiol (**3k**; 22% yield). In contrast, however, naphthalene-2-thiol failed to yield the desired compound; although the reason is unclear, nucleophilic attack by naphthalene-2-thiol did not proceed. Hetaryl thiols also reacted successfully. Thioetherification with thiophene-2-thiol and thiophene-3-thiol gave the corresponding dithienyl thioethers **3m** and **3n** in yields of 31 and 53%, respectively. One advantage of this reaction is that it is easy to introduce a substituent onto the benzothiophene skeleton because substituted precursors are readily available. Several substituted thienyl thioethers **3o–s** were obtained from the corresponding substituted precursors **1**. Beneficially, this protocol provides easy access to highly π-expanded thioethers, such as **3t**.

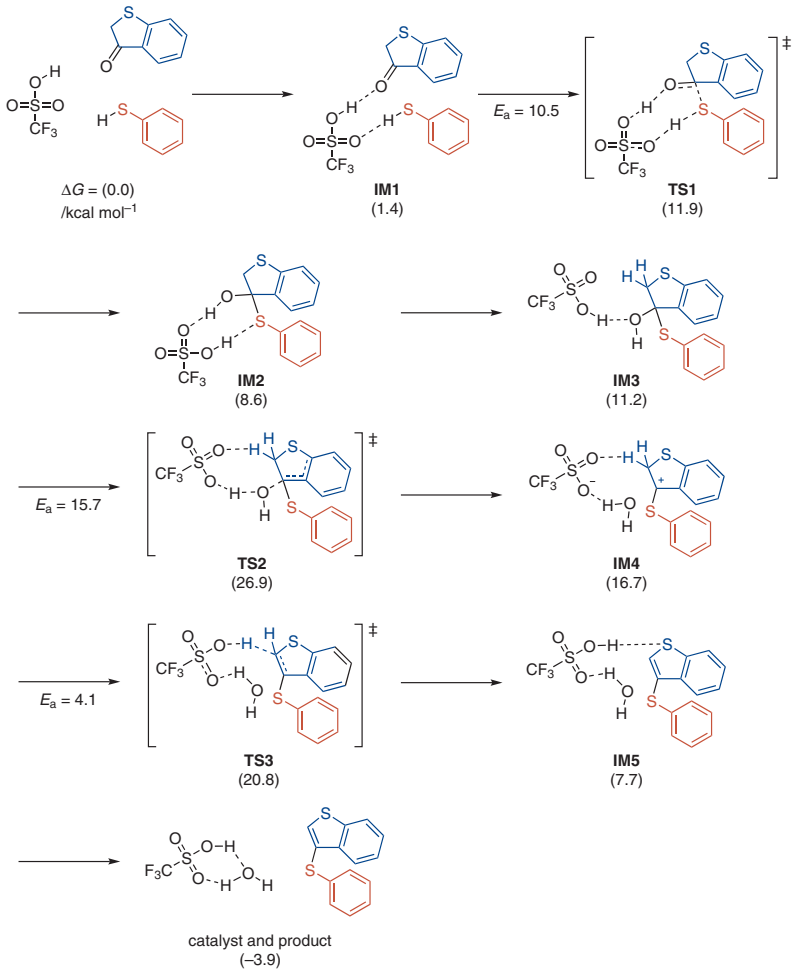
To clarify the mechanism of Reaction B, density functional theory (DFT) calculations were performed. Based on these calculations, a plausible mechanism is proposed (Scheme 3).[14] First, the carbonyl group of 1-benzothiophen-3(2*H*)-one is protonated by TfOH while a second oxygen atom of TfOH coordinates to the SH proton of benzenethiol to form complex **IM1**. Next, the benzenethiol sulfur atom attacks the carbonyl group to afford **IM2** via an eight-membered cyclic concerted transition state **TS1**.[15] TfOH-assisted dehydration of **IM3** proceeds via an eight-membered cyclic transition state **TS2** to afford the cationic intermediate **IM4**. Finally, **IM4** is deprotonated to form the desired thienyl thioether via transition state **TS3**. The calculated activation energy (E_a) of **TS2** (E_a = 15.7 kcal mol^{-1}) is higher than those of **TS1** (E_a = 10.5 kcal mol^{-1}) and **TS3** (E_a = 4.1 kcal mol^{-1}), suggesting that the C–O bond cleavage is the rate-determining step of this reaction.

Table 3 Effect of 2,6-Lutidine on the Pd-Catalyzed Dehydrogenative Cyclization of **3o**[a]



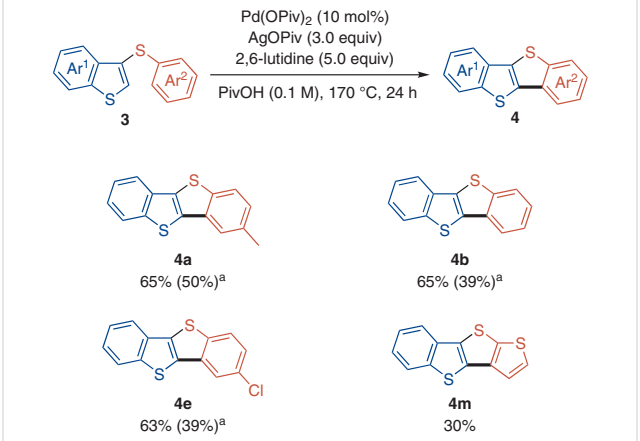
Entry	2,6-Lutidine (equiv)	Recovery[b] (%) of **3o**	Yield[b] (%) of **4o**
1	0	trace	35
2	1.0	ND[c]	54
3	3.0	ND	72
4	5.0	ND	88

[a] Reaction conditions: **3o** (0.15 mmol), $Pd(OPiv)_2$ (10 mol %), AgOPiv (3.0 equiv), 2,6-lutidine (0–5.0 equiv), PivOH (0.1 M), 170 °C, 24 h.
[b] Isolated yield.
[c] ND = not detected.

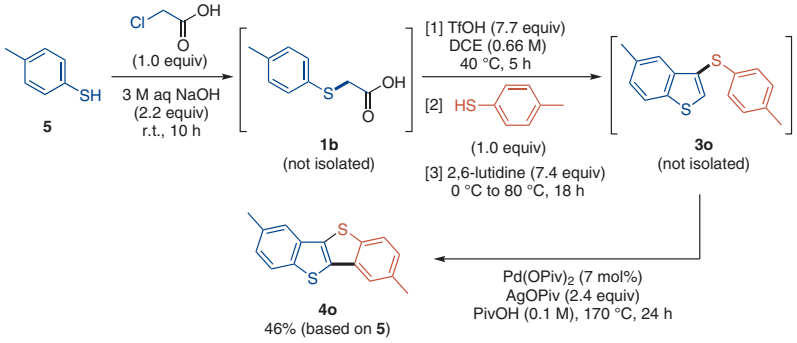


Scheme 3 A plausible mechanism for Reaction B. Gibbs free energies in kcal mol^{-1} are shown in parentheses.

We next focused on the transformation of thienyl thioethers into BTBT derivatives by Pd-catalyzed dehydrogenative cyclization. Pd-catalyzed dehydrogenative coupling has been established as a powerful method for the formation of heteroacenes.[16] However, to the best of our knowledge, this method has not been used for the efficient dehydrogenative construction of thiophene rings. Compound **3o** was used as a model to examine Pd-catalyzed dehydrogenative coupling (Table 3). Benzothiophene **3o** was heated at 170 °C for 24 hours in the presence of $Pd(OPiv)_2$ (10 mol%) and AgOPiv (3.0 equiv). We found that the addition of 2,6-lutidine was essential for the reaction. In the absence of 2,6-lutidine, the desired compound **4o** was obtained in only 35% yield (Table 3, entry 1).[17] The yield of **4o** increased as the amount of 2,6-lutidine increased. With 1.0 equivalents of 2,6-lutidine, the yield of **4o** was 54% yield (entry 2); this increased to 88% with 5.0 equivalents of 2,6-lutidine (entry 4). Although the role of 2,6-lutidine is not yet clear, it is likely to interact with the Pd catalyst and suppress C–S bond fission.



Scheme 4 Synthesis of several BTBT derivatives under the optimized conditions. [a] Performed with 1.0 equiv of 2,6-lutidine.



Scheme 5 Telescoped synthesis of **4o** from 4-methylbenzenethiol (**5**)

By using the optimized conditions, several BTBT derivatives were synthesized (Scheme 4). BTBT (**4b**) and substituted BTBTs **4a** and **4e** were readily obtained. The advantages of this method are (i) a ready introduction of substituents and (ii) easy replacement of the benzene ring by heterocycles such as thiophene (**4m**).

Finally, we examined a telescoped synthesis of **4o** from 4-methylbenzenethiol (**5**) (Scheme 5). A solution of **5** in 3 M aqueous NaOH was treated with chloroacetic acid to afford **1b**. The reaction was quenched with aqueous HCl and extracted with $CHCl_3$. After removal of the solvent, the crude product was used in the one-pot procedure without further purification to afford a crude solution of **3o**, which was quenched with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. After removal of the solvent, the crude mixture was used in the Pd-catalyzed dehydrogenative reaction to afford the desired BTBT derivative **4o** in an 46% overall yield.[18] This result suggests that our protocol can be used to prepare a variety of thienyl thioethers and BTBT derivatives from easily accessible chloroacetic acid and the appropriate arylthiol.

In conclusion, we have developed a transition-metal-free and halide-free one-pot synthesis of thienyl thioethers. Several novel thioethers were readily synthesized by using the optimized conditions. An efficient conversion of the thioethers into thienothiophenes was also established. We also demonstrated a telescoped synthesis of a thienothiophene from an arylthiol. This strategy permits the efficient and easy synthesis of 3-benzo[*b*]thienyl thioethers and thienothiophenes. Further applications of this strategy are currently being investigated in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707280.

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(12) Further details of the base optimizations, see SI, Table S6.

(13) **3-(4-Tolylsulfanyl)-1-benzothiophene (3a): One-Pot Synthesis; Typical Procedure**

TfOH (0.136 mL, 231 mg, 1.54 mmol) was added dropwise to a solution of (phenylsulfanyl)acetic acid (**1a**; 33.6 mg, 0.20 mmol) in anhyd DCE (0.3 mL), and the resulting mixture was stirred at 40 °C for 3 h then cooled to 0 °C. 4-Methylbenzenethiol (24.8 mg, 0.20 mmol) and 2,6-lutidine (0.18 mL, 1.5 mmol) were added, and the mixture was stirred at 80 °C for 18 h then cooled to r.t. The reaction was quenched with sat. aq $NaHCO_3$ (3 mL), and the mixture was extracted with $CHCl_3$ (3 × 5 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane) to give a colorless liquid; yield: 32.3 mg (0.13 mmol, 63%).

IR (neat): 3096, 3021, 1595, 1254, 1016 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 8.4 Hz, 2 H), 7.35–7.40 (m, 2 H), 7.62 (s, 1 H), 7.78–7.83 (m, 1 H), 7.86–7.90 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 122.9, 123.0, 124.7, 124.9, 125.0, 128.4, 129.8, 130.8, 132.5, 136.0, 138.8, 140.0.

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(18) For details, see SI.