Mild Copper(I) Iodide/β-Keto Ester Catalyzed Coupling Reactions of Styryl Bromides with Phenols, Thiophenols, and Imidazoles

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Abstract: An efficient and mild vinylation of *O*-, *S*-, and *N*-nucleophiles is reported. Copper(I) iodide/ethyl 2-oxocyclohexanecarboxylate is used as the catalytic system. The protocol tolerates a broad range of functional groups on the substrates, and gives the corresponding aryl styryl ethers, aryl styryl sulfides, and *N*-styrylimidazoles in moderate to excellent yields as well as with good stereoselectivity.

Key words: β-keto esters, Ullmann coupling reaction, copper catalysis, vinylation

Aryl vinyl ethers, vinyl sulfides, and *N*-vinylimidazoles are useful intermediates or building blocks in organic synthesis.[1] In addition, aryl vinyl ethers and vinyl sulfides have found application in the synthesis of biologically active molecules and natural product analogues.[2] *N*-Vinylimidazoles have also been used in medicine and agriculture.[3] Various methods for the synthesis of these compounds have been reported. The most straightforward of these involve the addition of phenols, thiophenols, and imidazoles to alkynes.[4] Although this protocol is particularly important, because the addition reaction proceeds in an atom-efficient way, without waste, it suffers from either harsh reaction conditions or lack of stereocontrol of the double-bond geometry. Another noteworthy methodology to gain aryl vinyl ethers, vinyl sulfides, and *N*-vinylimidazoles is copper-catalyzed Ullmann coupling.[5] However, these reactions usually proceed at relatively high temperatures or have been limited to vinyl iodides as substrates. More recently, a similar copper-catalyzed protocol enabled the O-vinylation of phenols under milder temperatures.[6] Unfortunately, only (*E*)-β-bromostyrene can be used as the substrate, and there was no example of a reaction of a substituted vinyl bromide with a phenol.

During the past few years, significant progress has been made on the development of a copper-catalyzed Ullmann-type coupling reaction.[7] This progress has relied greatly on the use of some special ligands, such as *N*,*N*-, *O*,*O*-, and *N*,*O*-bidentate compounds, as well as phosphines and carbenes. Ma and co-workers reported that the structures of α- and β-amino acids could induce acceleration of Ullmann-type aryl amination and the coupling reactions of amino acids with aryl halides could be carried out at relatively low temperatures.[8] Further exploration revealed that this catalytic system was applicable to the formation of C–N,[8b] C–O,[8c] C–S,[8d] and C–C[8e] bonds. Cristau and Taillefer et al. disclosed that copper-catalyzed arylation of pyrazoles with aryl halides was facilitated by oxime and Schiff base under mild conditions.[9] Buchwald and coworkers found that diamine- and diol-type compounds could serve as excellent supporting ligands in copper-catalyzed C–N bond-formation reactions.[10] Recently, they developed a highly selective copper-catalyzed C–N coupling reaction. The ligand they used was cyclic β-diketone and the reaction can be carried out at room temperature.[11] The abovementioned reports reveal that the selection of a proper ligand is of importance in Ullmann coupling and indicate the possibility to introduce new ligands to promote copper-catalyzed coupling reactions.

Recently, we reported that ethyl 2-oxocyclohexanecarboxylate is a very efficient ligand in the copper-catalyzed coupling reactions for the synthesis of *N*-arylamides, *N*-arylimidazoles, aryl ethers, and aryl thioethers.[12] This success prompted us to examine whether the new ligand is fit for the coupling of vinyl bromides with phenol, thiophenols, and imidazoles. Herein, we wish to report these results.

In our initial screening experiment, the coupling of (*E*)-β-bromostyrene with phenol was used as a model reaction to explore the suitable reaction conditions (Table 1). When the reaction was conducted under the action of copper(I) iodide and ethyl 2-oxocyclohexanecarboxylate at 60 °C in *N*,*N*-dimethylformamide, the corresponding product was obtained in 30% yield (Table 1, entry 1). Several solvents such as dimethyl sulfoxide, *N*-methylpyrrolidin-2-one, dioxane, toluene, acetonitrile, and 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) were tested. Dimethyl sulfoxide and *N*-methylpyrrolidin-2-one provided almost the same yields (Table 1, entries 3 and 5), but the other solvents were inferior (Table 1, entries 2, 4, 6, and 7). To our disappointment, although the reaction time was prolonged, poor conversion was observed when this coupling reaction was carried out at 45 °C (Table 1, entry 9). With regard to yield, copper(I) iodide is a better catalyst than copper(I) bromide in this reaction (Table 1, entries 5 and 8).

On the basis of the above studies, the optimized conditions can be set as follows: *N*-methylpyrrolidin-2-one as solvent, copper(I) iodide/ethyl 2-oxocyclohexanecarboxylate as catalytic system, and reaction temperature 60 °C. These reaction conditions were applied to the coupling of

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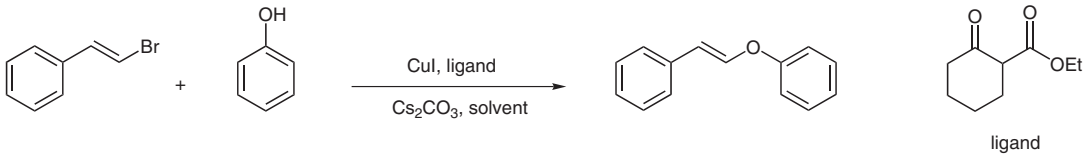
Table 1 Coupling Reaction of (*E*)-β-Bromostyrene and Phenol Catalyzed by Copper Salts and a β-Keto Ester[a]



Entry	Solvent	Catalyst	Temp (°C)	Time (h)	Yield[b] (%)
1	DMF	CuI	60	24	30
2	MeCN	CuI	60	24	40
3	DMSO	CuI	60	24	90
4	[Bmim]BF_4[c]	CuI	60	24	trace
5	NMP	CuI	60	24	95
6	dioxane	CuI	60	24	30
7	toluene	CuI	60	40	15
8	NMP	CuBr	60	24	55
9	DMSO	CuI	45	40	10

[a] Reagents and conditions: CuX (15 mol%), ligand (30 mol%), Cs_2CO_3 (2 mmol), (*E*)-β-bromostyrene (1 mmol), PhOH (1.2 mmol), solvent (2 mL).
[b] Isolated yield.
[c] Bmim = 1-butyl-3-methylimidazolium.

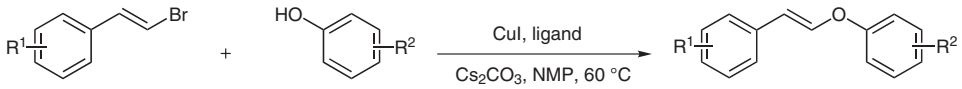
different phenols with different (*E*)-β-bromostyrenes (Table 2). The coupling reactions performed well for all the substrates examined, affording the target products in moderate to excellent yields. Electron-deficient (*E*)-β-bromostyrenes were generally superior to electron-rich ones, giving better yields (Table 2, compare entries 2, 3, and 4, as well as 7 and 8). Similar results were observed in the coupling of substituted (*E*)-β-bromostyrenes and 4-methylphenol (Table 2, entries 5, 7, and 8). Other phenols, whether electron-donating or electron-withdrawing, all worked well under these conditions (Table 2, entries 5 and 6). The stereoselectivity was good, as determined by ^{1}H NMR spectroscopy. With the exception of the reactions represented by entries 5 and 7 (Table 2), the stereochemistry of the double bond was retained under the reaction conditions.

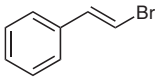
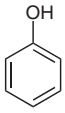
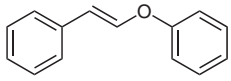
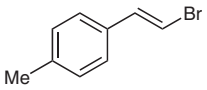
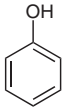
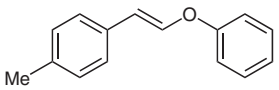
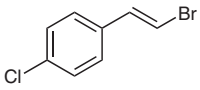
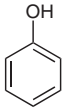
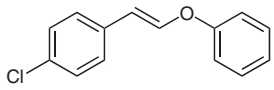
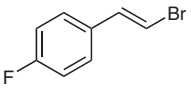
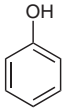
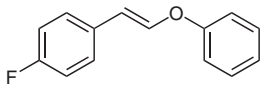
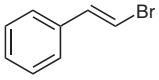
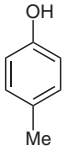
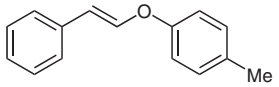
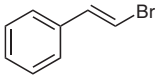
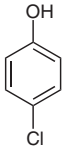
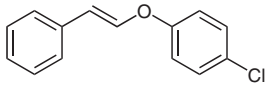
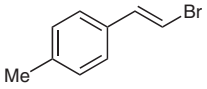
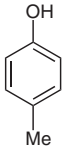
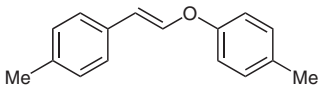
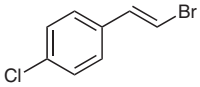
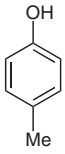
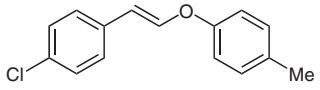
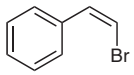
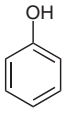
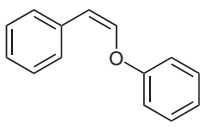
A second part of our work involved the application of the method to the synthesis of vinyl sulfides (Table 3). (*E*)-β-Bromostyrenes bearing an electron-withdrawing group on the benzene ring showed higher reactivity than those bearing an electron-donating group (Table 3, compare entries 2, 3, and 4). In addition, thiophenol with electron-withdrawing group worked well under the current conditions, giving the desired product in reasonable yield (Table 3, entry 5). Furthermore, this reaction is also applicable to (*E*)-β-bromostyrene and thiol (Table 3, entry 6). Fortunately, the conversion of (*E*)-β-bromostyrenes was remarkably stereoselective, giving (*E*)-vinyl sulfides; for example, when (*E*)-4-methyl-β-bromostyrene was coupled with thiophenol, the ratio of (*E*)-4-methylstyryl phenyl sulfide to the (*Z*)-isomer was 95:5 (by ^{1}H NMR; Table 3, entry 4). The reaction of (*E*)-4-chloro-β-bromostyrene with thiophenol gave the corresponding product with full retention of stereochemistry (Table 3, entry 2). The catalytic system is even milder than the L-proline/copper(I) iodide/ILs system we previously reported for the coupling of (*E*)-β-bromostyrenes and thiophenols.[5a]

The optimized reaction conditions were also used to examine the coupling of (*E*)-β-bromostyrenes with imidazoles (Table 4). Because the separation of product from the solvent *N*-methylpyrrolidin-2-one was difficult, we tried to use dimethyl sulfoxide as solvent instead. By this protocol, we were able to couple electron-rich and -poor (*E*)-β-bromostyrenes with imidazoles, producing the corresponding *N*-vinylimidazoles in good yields (Table 4, entries 2–4 and 6–8). The reaction was slightly disfavored by the steric hindrance of nucleophilic reagents. For example, when benzimidazole was used as the substrate, a higher reaction temperature than used with imidazole was necessary to ensure good conversion (Table 4, entries 5–8). Electron-rich (*E*)-4-(2-bromovinyl)toluene reacted well with benzimidazole, but a longer reaction time was required (Table 4, entry 6). Significantly, (*E*)-β-bromostyrenes furnished (*E*)-*N*-vinylimidazoles exclusively, except for the reaction shown in entry 7 (Table 4), which gave the product in an *E*/*Z* ratio of 97:3 (by ^{1}H NMR). The catalytic system for this reaction is even milder than that used in the L-proline/copper(I) iodide/ILs system we previously reported for the coupling of (*E*)-β-bromostyrenes and imidazoles.[5c]

Limitations in the method were found when (*Z*)-β-bromostyrene was used as substrate. For example, the cou-

Table 2 Coupling Reactions of (*E*)-β-Bromostyrenes with Phenols Catalyzed by Copper(I) Iodide/Ethyl 2-Oxocyclohexanecarboxylate[a]



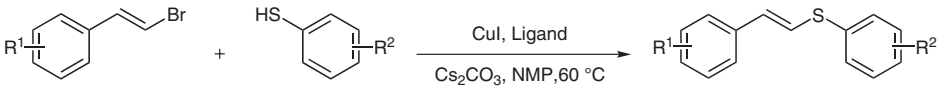
Entry	Bromostyrene	Phenol	Product	Yield[b] (%)	*E*/*Z*[c]
1				95	100:0
2				81	100:0
3				84	100:0
4				91	100:0
5				89	97:3
6				79	100:0
7				85	100:0
8				91	94:6
9				0[d]	

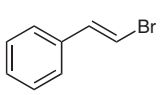
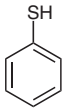
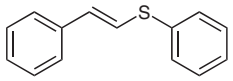
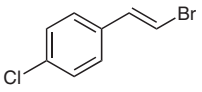
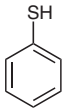
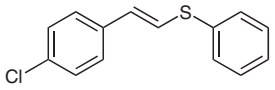
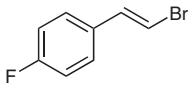
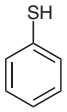
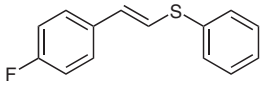
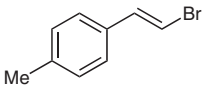
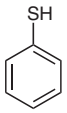
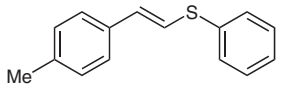
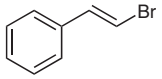
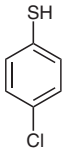
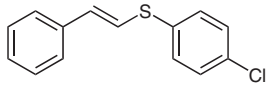
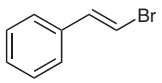
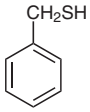
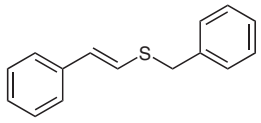
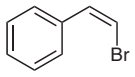
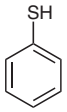
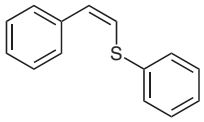
[a] Reagents and conditions: CuI (15 mol%), ligand (30 mol%), Cs_2CO_3 (2 mmol), (*E*)-β-bromostyrene (1 mmol), phenol (1.2 mmol), NMP (2 mL), 60 °C, 24 h.
[b] Isolated yield.
[c] The ratio was based on the ^1H NMR spectrum.
[d] Reaction performed at 90 °C.

pling of (*Z*)-β-bromostyrene with thiophenol proceeded well (Table 3, entry 7), but the reaction of (*Z*)-β-bromostyrene with phenol and imidazole failed to give any product, even at 90 °C (Table 2, entry 9 and Table 4, entry 9). We reason that this might result from the different nucleophilicity of these substrates.

In summary, we have reported here a mild and efficient catalytic system for the coupling reactions of phenols, thiols, and imidazoles with (*E*)-β-bromostyrenes at relatively low temperature, and which is applicable to a number of substrates. The yields are good to excellent, and the stereoselectivity is satisfactory.

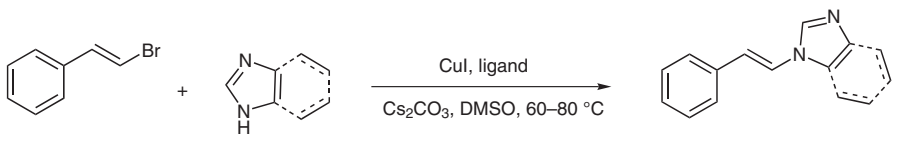
Table 3 Coupling Reactions of (*E*)-β-Bromostyrenes with Thiophenols Catalyzed by Copper(I) Iodide/Ethyl 2-Oxocyclohexanecarboxylate[a]



Entry	Bromostyrene	Thiophenol	Product	Yield[b] (%)	*E*/*Z*[c]
1				86	89:11
2				88	100:0
3				92	93:7
4				85	95:5
5				82	83:17
6				75	97:3
7				76	98:2

[a] Reagents and conditions: CuI (15 mol%), ligand (30 mol%), Cs_2CO_3 (2 mmol), (*E*)-β-bromostyrene (1 mmol), thiophenol (1.2 mmol), NMP (2 mL), 60 °C, 24 h.
[b] Isolated yield.
[c] The ratio was based on the ^1H NMR spectrum.

Table 4 Coupling Reactions of (*E*)-β-Bromostyrenes with Imidazoles Catalyzed by Copper(I) Iodide/Ethyl 2-Oxocyclohexanecarboxylate[a,b]



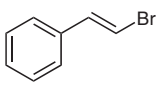
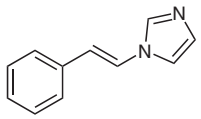
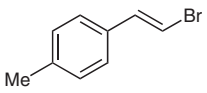
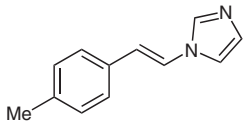
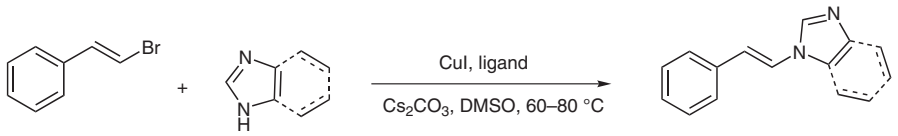
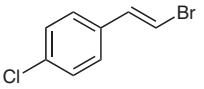
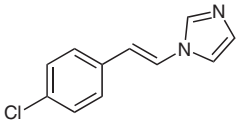
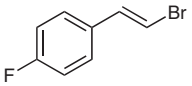
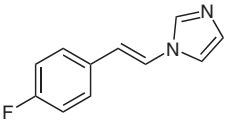
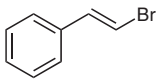
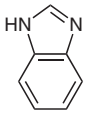
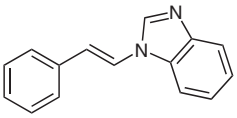
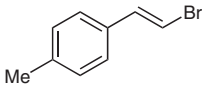
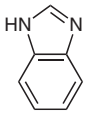
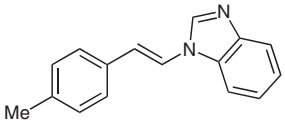
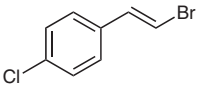
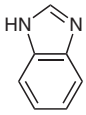
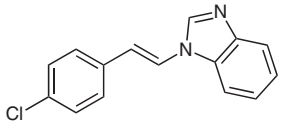
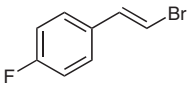
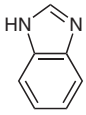
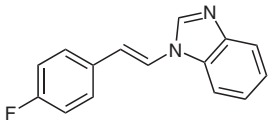
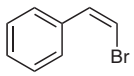
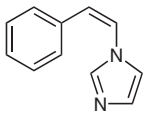
Entry	Bromostyrene	Imidazole	Product	Yield[c] (%)	*E*/*Z*[d]
1				88	100:0
2				85	100:0

Table 4 Coupling Reactions of (*E*)-β-Bromostyrenes with Imidazoles Catalyzed by Copper(I) Iodide/Ethyl 2-Oxocyclohexanecarboxylate[a,b] (continued)



Entry	Bromostyrene	Imidazole	Product	Yield[c] (%)	*E*/*Z*[d]
3				87	100:0
4				90	100:0
5				82	100:0
6				85[e]	100:0
7				84	97:3
8				88	100:0
9				0[f]	

[a] Reagents and conditions: CuI (15 mol%), ligand (30 mol%), Cs_2CO_3 (2 mmol), (*E*)-β-bromostyrene (1 mmol), imidazole (1.2 mmol), DMSO (2 mL), 24 h.
[b] Temp: imidazole, 60 °C; benzimidazole, 80 °C.
[c] Isolated yield.
[d] The ratio was based on the ^{1}H NMR spectrum.
[e] Reaction time: 40 h.
[f] Reaction performed at 90 °C.

All reactions were carried out in Schlenk or test tubes under a N_2 atmosphere. All the copper sources, ligands, and bases were commercially available. Organic solvents, also commercially available, were dried over 4-Å MS before use. All phenols, thiophenols, and imidazoles were used as received. TLC was carried out on 0.2-mm thick silica gel plates (GF 254) and visualized by UV light. The columns were packed with silica gel 60 (200–300). All products were confirmed by ^{1}H NMR and IR spectroscopy. Unknown compounds were additionally confirmed by ^{13}C NMR spectroscopy and elemental analysis. All melting points are uncorrected. The NMR spectra of samples in $CDCl_3$ with TMS as internal standard were recorded on a Bruker Avance 400-MHz NMR instrument. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer, and samples were prepared as KBr plates.

Coupling of Styryl Bromides with Phenols, Thiophenols, and Imidazoles; General Procedure

An oven-dried Schlenk tube was back-filled with N_2 and charged with Cs_2CO_3 (650 mg, 2.0 mmol), CuI (30 mg, 0.15 mmol, 15 mol%), ethyl 2-oxocyclohexanecarboxylate (50 mg, 0.30 mmol, 30 mol%), the appropriate (*E*)-β-bromostyrene (1 mmol), the nucleophilic reagent (phenol, thiophenol, or imidazole for C–O, C–S, or C–N coupling, respectively; 1.2 mmol), and anhyd solvent (2 mL) under a stream of N_2. The reaction tube was quickly sealed and the contents were stirred at the temperature indicated in Tables 2–4 for 24 h. The cooled reaction mixture was dissolved in H_2O and extracted with EtOAc. The combined organic layer was dried ($MgSO_4$). The product was further purified by column chromatography (silica gel, PE–EtOAc).

(*E*)-4-(2-Phenoxyvinyl)toluene (Table 2, entry 2)
Oil.

IR (KBr): 3045, 2922, 2855, 1657, 1592, 1231, 922, 799, 755, 691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 2 H), 7.25–7.08 (m, 8 H, Ar and vinyl), 6.36 (d, *J* = 12.4 Hz, 1 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.16, 142.62, 136.32, 132.09, 129.62, 129.30, 125.49, 123.03, 116.79, 113.59, 21.04.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71; Found: C, 85.55; H, 6.73.

(*E*)-4-(4-Methylstyryloxy)toluene (Table 2, entry 7)
Solid; mp 67–68 °C.

IR (KBr): 3013, 2915, 2857, 1654, 1504, 1242, 928, 815 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.8 Hz, 2 H), 7.17–7.11 (m, 5 H, Ar and vinyl), 6.97 (d, *J* = 8.8 Hz, 2 H), 6.31 (d, *J* = 12.4 Hz, 1 H), 2.35 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.05, 143.21, 136.18, 132.56, 132.26, 130.06, 129.29, 125.44, 116.78, 112.93, 21.04, 20.55.

Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19; Found: C, 85.67; H, 7.24.

(*E*)-4-(4-Chlorostyryloxy)toluene (Table 2, entry 8)
Solid; mp 47–48 °C.

IR (KBr): 3025, 2913, 2856, 1655, 1506, 1241, 1042, 927, 809 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.20 (m, 4 H), 7.16–7.12 (m, 3 H, Ar and vinyl), 6.96 (d, *J* = 8.4 Hz, 2 H), 6.24 (d, *J* = 12.8 Hz, 2 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.85, 144.50, 133.78, 132.95, 131.88, 130.12, 128.69, 126.62, 116.95, 111.57, 20.30.

Anal. Calcd for $C_{15}H_{13}ClO$: C, 73.62; H, 5.35; Found: C, 73.60; H, 5.34.

(*E*)-1-(4-Fluorostyryl)-1*H*-imidazole (Table 4, entry 4)
Solid; mp 78–79 °C.

IR (KBr): 3146, 3110, 3045, 2957, 1659, 1597, 1491, 1288, 931, 808 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.40–7.36 (m, 2 H), 7.30–7.26 (m, 2 H), 7.16 (s, 1 H), 7.09–7.05 (m, 2 H), 6.72 (d, *J* = 14.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.63, 161.11, 136.22, 130.40, 127.64, 127.55, 122.40, 117.63, 116.07, 115.91, 115.70.

Anal. Calcd for $C_{11}H_9FN_2$: C, 70.20; H, 4.82; N, 14.88; Found: C, 70.18; H, 4.82; N, 14.93.

(*E*)-1-(4-Fluorostyryl)-1*H*-benzo[*d*]imidazole (Table 4, entry 8)
Solid; mp 122–123 °C.

IR (KBr): 3089, 2964, 1659, 1610, 1492, 1290, 947, 808, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 7.86 (d, *J* = 7.0 Hz, 1 H), 7.61 (d, *J* = 7.0 Hz, 1 H), 7.48–7.44 (m, 3 H), 7.41–7.34 (m, 2 H), 7.11 (t, *J* = 12.4 Hz, 2 H), 6.95 (d, *J* = 14.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.79, 161.33, 144.01, 140.70, 132.66, 130.92, 127.84, 127.76, 123.91, 123.16, 120.81, 119.03, 116.11, 115.89, 110.24.

Anal. Calcd for $C_{15}H_{11}FN_2$: C, 75.62; H, 4.65; N, 11.76; Found: C, 75.63; H, 4.69; N, 11.71.

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