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A Very Active Cu-Catalytic System for the Synthesis of Aryl, Heteroaryl, and Vinyl Sulfides

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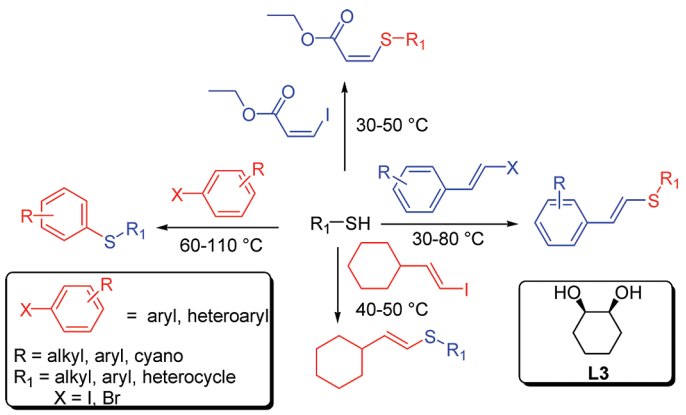

Conditions:
10 mol % CuI, 20 mol % **L3**, 1.5 equiv K_3PO_4, DMF, 30 min -15 h, 75-98 %

cis-1,2-Cyclohexanediol (**L3**) has been shown to be an efficient and versatile bidentate *O*-donor ligand that provides a highly active Cu-catalytic system. It was more effective than diols such as *trans*-1,2-cyclohexanediol or ethylene glycol. This commercially available *cis*-1,2-cyclohexanediol ligand facilitated the Cu-catalyzed cross-coupling reactions of alkyl, aryl, or heterocyclic thiols with either alkyl, aryl, heterocyclic, or substituted vinyl halides. This new catalytic system promoted the mild and efficient stereo- and regiospecific synthesis of biologically important vinyl sulfides. The yields obtained using electron-rich substituted vinyl sulfides with this catalyst system are generally 75−98%. Most importantly, this singular catalyst system is extremely versatile and provides entry into a wide range of sulfides. This method is particularly noteworthy given its mild reaction conditions, simplicity, generality, and exceptional level of functional group tolerance.

1. Introduction

The synthesis of vinyl and aryl sulfides has been an important objective in organic synthesis since both motifs are of value as important intermediates in the synthesis of biologically and pharmaceutically active molecules, as well as organic materials and intermediates.[1−32] Recent reports of the activity of aryl sulfides as anti-inflamatory agents and for the treatment of Alzheimer's and Parkinson's disease or

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as inhibitors for the treatment of human immunodeficiency virus (HIV), asthma, and obstructive pulmonary disease have demonstrated the potential of this class of compounds.[20−25] Additionally, increased interest in unsymmetrical aryl-alkyl disulfides has arisen because they are potent growth inhibitors of methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis*.[20−25] A recent report has illustrated the potential utility of vinyl sulfides against drug-resistant strains of tuberculosis and anthrax, in addition to many other drug-resistant Gram-positive bacteria [e.g., methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE)].[32]

In addition, from a chemical point of view, these vinyl sulfides can act as equivalents of enolate ions[26] and as Michael acceptors.[27] They are also important intermediates in the synthesis of oxetanes,[28] cyclopentanones,[29] and cyclopentanes.[30,31]

The metal-catalyzed formation of C−S bonds has played an important role in organosulfur chemistry.[19,33−51] During the past few years, metal-catalyzed methods for the preparation of aryl sulfides, in particular, with halide or pseudohalide derivatives facilitated by Pd, Ni, Co, Fe, and Cu catalysts, have been reported.[52−67] However, only a few reports have appeared which focus on the preparation of

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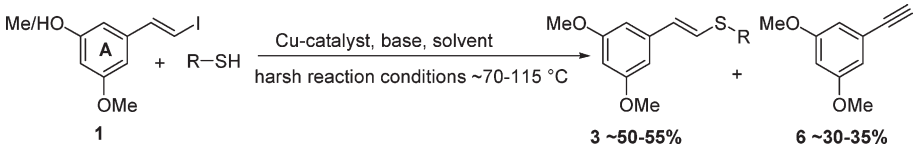
SCHEME 1. Adverse Effect of Harsh Reaction Conditions on the Thioetherifcation of Electron-Rich (EDG) 3,5-Dimethoxyvinyl Iodides with Thiols



vinyl sulfides via a cheap copper-catalytic method.[82−92] Although a number of methods for the preparation of vinyl sulfides are available in the literature, many are associated with limitations.[68−81] Among them, the most common is the addition of a thiol to an alkyne.[93−96] This process takes place only under radical conditions to afford the anti-Markovnikov product as a mixture of regioisomers. Other methods involve the use of transition-metal catalysts including Mo, Pd, Pt, Rh, and Ru. Vinyl sulfides have also been prepared from the cross-coupling of vinyl halides with Na or Li benzenethiolates or their Sn analogues.[19,97−104] This latter approach often requires the use of strong bases, and furthermore, the synthesis of this class of compounds via a Wittig approach can be problematic because of the synthesis of the appropriate Wittig reagent.[105]

With the current renaissance in Ullmann coupling processes over the past few years, the copper-catalyzed cross-coupling reactions of thiols and aryl halides have been shown to be a powerful tool in the formation of aryl C−S bonds,[52−67] while Cu-catalyzed formation of vinyl C−S bonds has received less attention.

Although a number of methods are available in the literature, many of the drawbacks of the classical Ullmann coupling, such as the use of a strong base or stoichiometric amounts of Cu salts, have recently been overcome, and the resulting application of Cu-catalyzed methods for the synthesis of diaryl sulfides has recently appeared in the literature.[52−67] However, these newer Cu-catalyzed methods still require high temperatures, harsh reaction conditions, or longer reaction times. Therefore, an active Cu-catalytic system which is effective at milder or at room temperatures had yet to be reported.[68−81] Methods aimed at improving processes with aryl halides have included Cu-catalytic systems which use Cs_2CO_3 as a base, but they often result in significant amounts of disulfides as side products. Recently, a few methods have appeared which have shown great improvement in the synthesis of diaryl sulfides.[52−54,61,90,106]

Previous to the use of *cis*-1,2-cyclohexanediol (**L3**) as a ligand, the most important Cu-catalytic method that had appeared for the preparation of vinyl sulfides was that of Venkataraman and co-workers, who employed a Cu-catalytic system.[19] However, this protocol required the use of an air- and moisture-sensitive Cu catalyst, which must be handled in a glovebox. In addition, this process required harsh reaction conditions (i.e., temperatures of 115 °C and reaction times of ~4 h) unsuitable for the electron-rich arylvinyl sulfides of interest here. In general, harsh reaction conditions have proven to be inefficient for electron-rich arylvinyl iodides in coupling reactions. In this regard, the major side product of the coupling process with electron-rich arylvinyl iodides is the elimination product, an arylacetylene, illustrated in Scheme 1. Furthermore, while this method was compatible with alkylvinyl iodides, it was incompatible with many substrates, especially with unstable electron-rich vinyl halides, as mentioned above.

Recently, we have begun to reinvestigate the use of copper catalysis for the preparation of arylvinyl, alkylvinyl, aryl, and heterocyclic sulfides employing milder conditions in order to synthesize vinyl sulfides substituted with electron-rich aryl rings in order to overcome the aforementioned elimination illustrated in Scheme 1. Initial success was obtained with the Cu-*cis*-1,2-cyclohexanediol system, which resulted in a mild and efficient Cu-catalyzed stereo- and regiospecific synthesis of arylvinyl and alkylvinyl sulfides from the corresponding vinyl iodides and thiols.[105] Advantage of the mild reaction conditions, inexpensive catalyst, and simple operational features of this method has now been taken to extend this process to the preparation of aryl and heterocyclic substituted sulfides, as well as vinyl sulfides, from their respective iodide and bromide progenitors. Illustrated below is the general, efficient, mild, and operationally simple Cu-catalyzed formation of arylvinyl, alkylvinyl, aryl, and heterocyclic substituted C−S bonds. As mentioned earlier, electron-rich vinyl iodides provided aryl acetylene side products under either strongly basic conditions or at higher temperatures. To avoid this elimination sequence, it was necessary to employ milder reaction conditions. Moreover, the expensive and less stable vinyl iodides were also replaced with the cheaper and more stable vinyl bromides as coupling partners, albeit the temperature

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required was higher in the case of the less reactive arylvinyl bromides. In all cases, broad substrate scope was realized with good to excellent yields. During the completion of this work, Chaozhong Li et al. reported an interesting Cu-catalyzed intramolecular S-vinylation of iodo vinyl thiols.[107] A few other approaches related to the Cu-catalytic process have been reported in the last 2 years while our work was in progress.[109−115]

2. Results and Discussion

2.1. Problems Encountered in the Synthesis of Electron-Rich Vinyl Sulfides. As mentioned in the Introduction, studies indicated that compounds which contain *N*-vinyl heterocycles, arylvinyl ethers, and arylvinyl thioethers were active against drug-resistant strains of tuberculosis, anthrax, and many other strains of drug-resistant Gram-positive bacteria including MRSA and VRE.[20−25] Many of these active agents required at least two or more electron-donating groups (EDGs) on at least one of the aryl rings of the molecule.[20−25,32] In order to exhibit the most potent activity, the location of these EDGs on these antibacterial agents must contain the EDGs on ring **A** of their structural framework, as illustrated by the two methoxy groups shown in Scheme 1. This electron-rich substitution pattern is a fundamental requirement for the potent activity of this new class of antibacterials.[20−25,32] Furthermore, the most potent agents contain a 3-hydroxy-5-methoxy pattern (see **5**) in ring **A** (Scheme 2).[32]

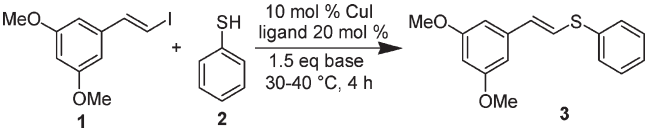
Initially, electron-rich 3-hydroxy-5-methoxystyryl phenyl thioethers and a variety of 3,5-dimethoxy analogues (see **3**, Scheme 1) were prepared using the catalytic conditions of Venkataraman (Table 1).[19] These conditions proved to be inefficient for the corresponding electron-rich arylvinyl iodides since a significant amount of aryl acetylene side products (approximately 30−35%) were observed in the reaction mixture due to the elimination process caused by the harsh reaction conditions.

In addition to the harsh reaction conditions, it was felt the use of a nitrogen-based bidentate ligand might also promote the unwanted elimination due to slightly higher basicity of the ligand. It had previously been reported that aryl acetylene formation occurred in the Cu-catalyzed cross-coupling reactions of unfunctionalized arylvinyl halides when nitrogen-based bidentate ligands were employed.[10]

2.2. Ligand Screening for the Cu-Catalyzed Vinylation of Thiols. A potential solution was envisioned by the use of an alternative Cu-catalytic system which would work for EDG-substituted substrates related to that of ring **A** in Scheme 1 under mild conditions. Initially, the coupling reaction of electron-rich 3,5-dimethoxyvinyl iodide **1** with thiophenol **2** (Figure 1) was selected in order to assess the catalytic activity of the best Cu-catalytic ligand−Cu complex (i.e., ligand screen). The prototypical reaction conditions utilized were 10 mol % of Cu(I)I, 20 mol % of the ligand, and 1.5 equiv of K_3PO_4 in reagent-grade DMF (without drying) at 30−40 °C. The structures of these ligands (**L1**−**L10**) and their resulting reaction yields are shown in Figure 1. Each reaction was conducted at 30−40 °C for 4 h with 20 mol % of ligand and 10 mol % of CuI. The yields of the desired vinyl sulfides **3** were determined by HPLC. As reported by Buchwald et al.,[8] the choice of the ligand can alter the selectivity of the cross-coupling reaction greatly. The coupling of either oxygen or nitrogen nucleophiles can be reversed by the choice of the ligand (oxygen- or nitrogen-based). In our estimation, the bidendate oxygen ligand rendered the copper softer in the transition state so it would be more prone to react with sulfur-based (soft nucleophile) substrates, which turned out to be the case.

Ligands chosen for screening with CuI included *O*-based bidentate ligands **L1**−**L7** and **L10** as well as mixed ligands **L8** and **L9** (Figure 1).[52,53,105] The complex from the CuI- and *O*-based bidentate ligand **L3** clearly generated the most active catalyst, affording full conversion to the arylvinyl sulfide in less than 4 h at a temperature of only 40 °C. The excellent catalytic activity of **L3** with CuI was, presumably, due to the proper geometry of the Cu catalyst itself and the relatively weak coordination of the Cu-**L3** complex. These factors, coupled with the suitable electron density provided by the substrate, presumably facilitated oxidative addition of the vinyl functionality of the substrate, which eventually resulted in the subsequent reductive elimination. Indeed, the *cis*-diol **L3** gave better yields than the corresponding diols **L1**, **L2**, or **L4**, which reinforced the importance of the aforementioned optimized coordination geometry of the hydroxyl functions of **L3** to the Cu metal cation. The *trans*-diol **L1** may have formed a tighter complex with Cu, which may

TABLE 1. Optimization of Cu-Catalyzed Coupling Reaction of 3,5-Dimethoxyphenylvinyl Iodide with Thiophenol



entry	catalyst	solvent	base	HPLC yield[b,c] (%)
1	CuI	DMF	K_3PO_4	0
2	CuI, phen[a] (1:2)	toluene	K_3PO_4	45[a]
3	CuI/phen[a]/PPh_3 (1:1:2)	toluene	K_3PO_4	65
4	CuI, **L3** (1:1)	toluene	K_3PO_4	63
5	CuI, **L3** (1:2)	toluene	K_3PO_4	68
6	CuI, **L3** (1:2)	*i*-PrOH	K_3PO_4	72
7	CuI, **L3** (1:2)	DME	K_3PO_4	63
8	**CuI, L3 (1:2)**	**DMF**	**K_3PO_4**	**99**
9	CuI, **L3** (1:2)	DMA	K_3PO_4	64
10	CuI, **L3** (1:2)	1,4-dioxane	K_3PO_4	72
11	CuI, **L3** (1:2)	DMF	Cs_2CO_3	93
12	CuI, **L3** (1:2)	DMF	K_2CO_3	91
13	CuI, **L3** (1:1)	DMF	K_3PO_4	94

[a]phen = 1,10-phenanthroline. [b]HPLC yields. [c]The reactions were performed at least two times and the yields are the average of at least two runs.

(107) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459.
(108) Fernandez-Rodriguez, M. A.; Hartiwg, J. F. *J. Org. Chem.* **2009**, *74*, 1663.
(109) Yong, W.; Yang, B. V. *Prog. Heterocycl. Chem.* **2009**, *21*, 261–295.
(110) Reddy, V. P.; Swapna, K. K.; Kumar, A. V.; Rao, K. R. *Synlett* **2009**, *17*, 2783.
(111) Jiang, Y.; Quin, Y; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org. Lett.* **2009**, *11*, 5250.
(112) Taylor, P. C. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2009**, *105*, 75.
(113) Luo, P.-S.; Wang, F. L.; Li, J.-H.; Tang, R.-Y.; Zhong, P. *Synthesis* **2009**, *6*, 921.
(114) Luo, P.-S.; Yu, M.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Tetrahedron Lett.* **2009**, *50*, 1066.
(115) Xu, H.-J.; Zhao, X.-Y.; Fu, Y.; Feng, Y.-S. *Synlett* **2008**, *19*, 3063.

have retarded the oxidative addition step. More work is required to determine why the *cis*-diol **L3** was more efficient than the *trans*-diol **L1** or ethylene glycol **L2**. In addition, use of the sterically hindered, electron-rich ligands **L5**, **L6**, and **L7** resulted in lower yields. Ligands which have been successfully employed for C−N (**L4**, **L9**, and **L10**) or C−C (**L8**) bond formation by others[52,53,105] also proved to be less effective in the formation of vinylic C−S bonds. These ligands routinely provided poor yields of the desired sulfides with increased amounts of aryl acetylene. In these latter cases, the poor results, presumably, occurred because of the high basicity of the ligand, unfavorable coordination of the copper cation, or disadvantageous electron density on the metal cation itself due to an unfavorable Cu-**L** geometry.[52,53,105] More work is necessary to determine which plays a greater role.

2.3. Optimization and Establishment of Reaction Conditions. Once the suitable catalytic system with ligand **L3** was established, an optimization study was conducted in order to determine the most suitable reaction conditions for the aforementioned electron-rich substrates. The experiments were conducted using 10 mol % of Cu(I)I and 20 mol % of **L3** with the mild bases K_2CO_3, Cs_2CO_3, or K_3PO_4 with various solvents at temperatures of 30−40 °C. These experiments employed the newly developed Cu-**L3** catalyst versus that which was reported with the 1,10-phenanthroline ligand.[52,53,105] The percent formation of the vinyl sulfide was determined after 4 h by HPLC (Table 1, entries 1−13).

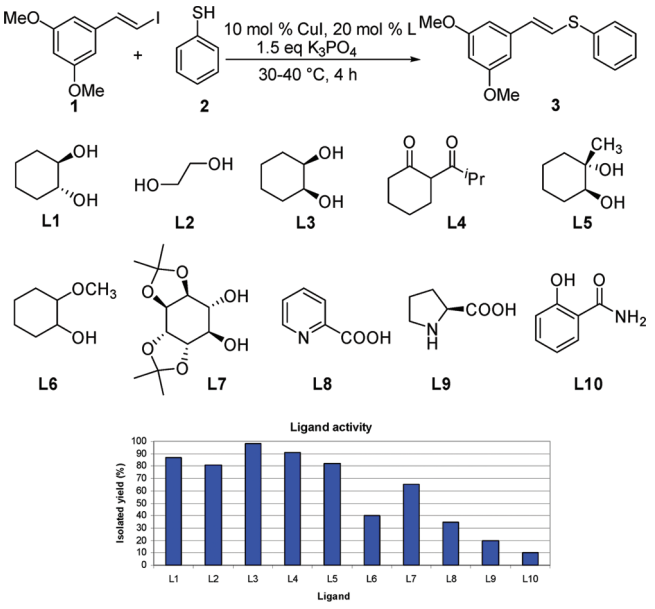
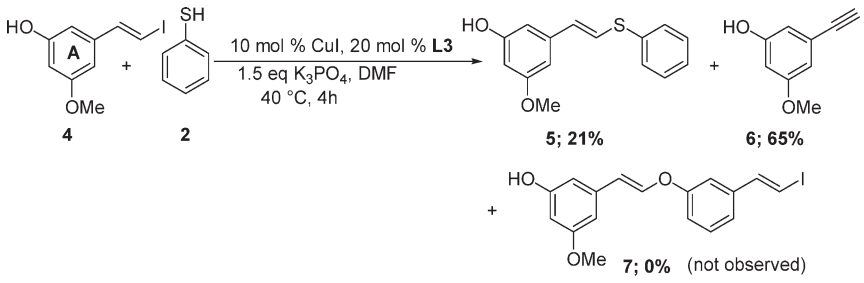


FIGURE 1. Effect of the ligand on the coupling of arylvinyl iodides with thiols. Reaction condtions: 3,5-dimethoxyphenylvinyl iodide (1 mmol), PhSH (1.1 mmol), CuI (10 mol %), **L3** (20 mol %), and K_3PO_4 (1.5 mmol) in DMF (5 mL) at 40 °C for 4 h.

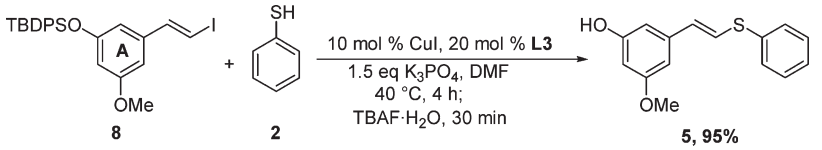
Several reactions were carried out by changing the catalyst loading and the concentration of the catalyst. The catalytic conditions with CuI (10 mol %) and **L3** (20 mol %) in dry DMF in the presence of K_3PO_4 (1.5 equivalent) proved to be the most efficient in the formation of the desired vinyl sulfides. Moreover, DME, *i*-PrOH, and 1,4-dioxane proved to be inefficient solvent systems at these lower temperatures because these processes required longer reaction times or higher temperature and produced a significant amount of aryl acetylene side product. Since this reaction went, presumably, through ionic intermediates, we assumed a solvent with a high dielectric constant would enhance the progress of the reaction. This was supported by the results presented in Table 1 (toluene, 2-propanol, DMF, DME, and 1,4-dioxane). The most common bases employed for Cu catalysis were screened and K_3PO_4 gave superior results compared to Cs_2CO_3 or K_2CO_3 (Table 1, entries 8, 11, and 12). Although the formation of aryl acetylene was observed in most cases, an optimal system was developed in which the elimination product (Table 1, entry 8) was not observed. It was noteworthy; this catalytic system did not yield any homocoupled product as well. As a final proof of concept with regard to this new alternative Cu-**L3** catalytic system, a comparison of the previously reported nitrogen-based bidentate ligand 1,10-phenanthroline was performed using traditional methods; the yields of the new alternative Cu-**L3** catalytic system proved superior to those requiring the traditional 1,10-phenanthroline ligand (Table 1, entries 2, 3, and 8).

2.4. Selectivity Issues for the Coupling of Arylvinyl Iodides with Arylphenols versus Thiophenols. Initially, 3-hydroxy-5-methoxyphenylvinyl sulfide analogues were of interest (Scheme 2), since this appears in this series to be a fundamental requirement for selective inhibition of Gram-positive bacteria.[32] Therefore, the coupling of the unprotected 3-hydroxy-5-methoxyphenylvinyl iodide **4** with thiophenol **2** with the optimized Cu-catalytic system was carried out (Scheme 2). The results (Scheme 2) of this key experiment indicated that no intermolecular coupling with the phenolic oxygen atom of 3-hydroxy-5-methoxyphenylvinyl iodide **4** had occurred. Instead, with the vinyl iodide **4**, the important chemoselectivity only with S-vinylation was demonstrated. Although the formation of the desired vinyl sulfide **5** was poor, a plausible explanation for the low yield of cross-coupled product can be attributed to the presence of the base in the reaction mixture which effected the deprotonation of the phenolic O−H of the vinyl iodide and generated the basic phenoxide ion. This phenoxide ion could accelerate the

SCHEME 2. Selective Coupling of the Vinyl Iodide with Thiols vs Phenols



SCHEME 3. Cu-Catalyzed Coupling of Protected 3-Hydroxy-5-methoxyvinyl Iodide with Thiophenol

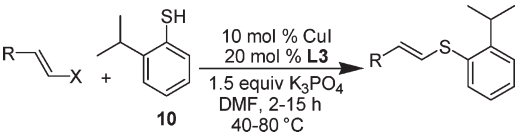


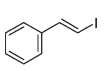
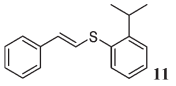
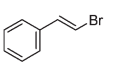
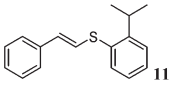
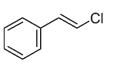
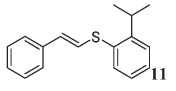
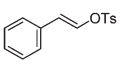
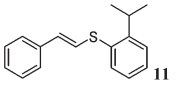
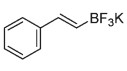
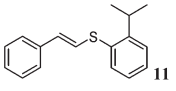
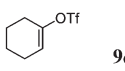
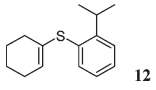
formation of the elimination side product 3-hydroxy-5-methoxyphenylacetylene **6** before the coupling reaction could take place between the requisite 3-hydroxy-5-methoxyphenylvinyl iodide **4** and thiophenol **2** (Scheme 2). Therefore, the side product, 3-hydroxy-5-methoxyphenylacetylene, appeared as a major product because it effectively consumed the vinyl iodide substrate. As expected, with this new method, the chemoselectivity of *S*-vinylation over *O*-vinylation was readily apparent; there was no product of intermolecular homocoupling obtained when unprotected 3-hydroxy-5-methoxyphenylvinyl iodide **4** was subjected to the coupling process with thiol **2**.

2.5. Requirement of the Protecting Group for (Phenolic C-3) the Hydroxy Group of the Arylvinyl Iodide. The important coupling of the 3-hydroxy-5-methoxyphenylvinyl iodide **4** with thiols by prevention of the unwanted elimination process was achieved in excellent yield when the phenolic hydroxyl group was protected as the *tert*-butyldiphenylsilyl (TBDPS) function. When the coupling process was carried out between this protected vinyl iodide **8** and thiophenol **2** using the optimized catalytic system (Cu-**L3**), as shown in Scheme 3, a very high yield of the thioether **5** was realized (see Scheme 3). In addition, upon completion of the coupling process the silyl group was removed in the same vessel in 30 min when the coupled product was treated with $TBAF \cdot H_2O$. The one-pot coupling and deprotection steps occurred to provide the 3-hydroxy-5-methoxy target **5** in an overall yield of 95%. Ultimately, these experiments indicated that the protection of the phenolic hydroxy group of 3-hydroxy-5-methoxyphenylvinyl iodide **4** and subsequent deprotection after the coupling process were required in order to accomplish successful cross-coupling reactions for the production of these biologically active phenolic vinyl sulfides in high yield. However, this was not necessary in the case of dimethoxy-substituted systems which underwent the coupling process with the Cu−**L3** catalytic system in very high yields as well.

2.6.1. Comparison of the Reactivity of Vinyl Iodides, Bromides, Chlorides, Tosylates, Borontrifluoride Salts, and Triflates in the Cu-Catalyzed Synthesis of Vinyl Sulfides. To compare reactivities, several vinyl halides which contained either different halogen atoms or other vinyl electrophiles were studied (Table 2). The coupling of various vinyl halides, a vinyl tosylate, a vinyl borontrifluoride potassium salt, and a vinyl triflate, were carried out using 2-isopropylthiophenol **10** as a model substrate. As typically observed in Cu-catalyzed cross-couplings, the phenylvinyl iodides were more reactive than their corresponding vinyl bromides in the newly optimized catalytic system (Cu-**L3**). Full conversion of phenylvinyl iodide **9** to the thioether **11** was observed in less than 2 h at 40 °C, while the corresponding bromide **9a** took 15 h at 80 °C for the complete consumption of the starting material. A slight variation in the yield of 91% from the vinyl bromide as compared to the arylvinyl iodide (97%) was observed in this case. It is important to reiterate here

TABLE 2. Comparison of the Reactivity of Vinyl Iodides vs Vinyl Bromides, Vinyl Chlorides, Vinyl Tosylates, Vinyl Tiflates, and Vinyl Boron Trifluoride Potassium Salts for the Cu-Catalyzed Cross-Coupling with 2-Isopropylthiophenol



entry	substrate	product	yield[a,b] (%)
1	 **9**	 **11**	97[c]
2	 **9a**	 **11**	91[d]
3	 **9b**	 **11**	0[d]
4	 **9c**	 **11**	0[d]
5	 **9d**	 **11**	0[d]
6	 **9e**	 **12**	0[d]

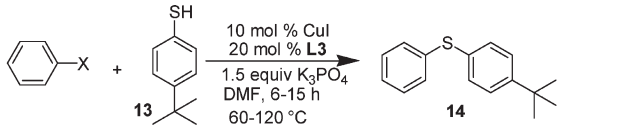
[a]Isolated yields, the average of at least two runs. [b]The starting arylvinyl iodides contained ∼9−12% *Z*-isomer; this led to ∼9−12% of the *cis*-isomer, reflected in the overall yield. [c]The reaction mixture was heated for 2 h at 40 °C. [d]The reaction mixture was heated for 15 h at 80 °C.

that vinyl bromides required higher temperatures and longer reaction times when compared to the vinyl iodides. This may have led to decomposition of some of the reactants in the case of the bromide, resulted in the 91% yield as compared to the 97% yield in the case of vinyl iodides.

Unfortunately, phenylvinyl chloride, the vinylic tosylate, and the vinylic boron trifluoride potassium salt did not provide the desired cross-coupled product. The same result was observed when a vinyl triflate was employed with the same thiol (Table 2, entry 6). Analysis of this set of experiments indicated that the catalytic system developed here could be useful for synthesis of various vinyl sulfides from any combination of vinyl iodides or bromides with various thiols.

2.6.2. Comparison of the Reactivity of Aryl Iodides, Bromides, Chlorides, Triflates, and Tosylates in the Cu-Catalyzed Synthesis of Diaryl Sulfides. To extend the scope of the newly

SCHEME 4. Comparison of the Reactivity of Aryl Iodides vs Aryl Bromides, Aryl Chlorides, Aryl Triflates, and an Aryl Boron Trifluride Potassium Salt in the Cu-Catalyzed Cross-Coupling with 4-*tert*-Butylthiophenol



X = I, Br, Cl, OTf, BF_3K

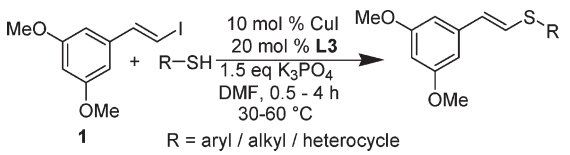
I = 95% at 60 °C for 6 h; Br = 91% at 100 °C for 15 h; Cl = 0% at 120 °C for 15 h; OTf = 0% at 120 °C for 15 h; BF_3K = 0 % at 120 °C for 15 h

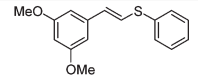
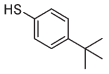
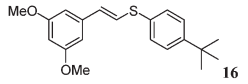
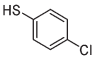
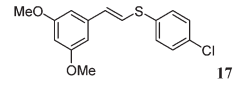
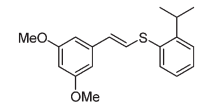
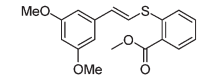
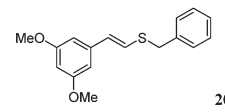
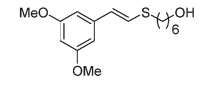
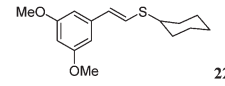
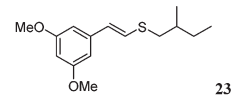
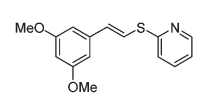
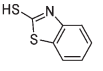
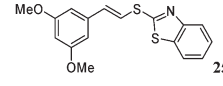
developed catalytic system (Cu-**L3**), various aryl halides, an aryl triflate, and an aryl tosylate were chosen as substrates to study the reactivity of the coupling process with 4-*tert*-butylthiophenol **13** (Scheme 4). The optimized catalytic system was applied to the above-mentioned system. The aryl iodide reacted faster (6 h) and under milder conditions (60 °C) as compared to the corresponding aryl bromide to provide the desired diaryl sulfide, as expected. The aryl bromide required an elevated temperature of 90−100 °C and 15 h for the complete consumption of the starting material to give the desired cross-coupled product **14**. The aryl chloride, aryl triflate, and aryl boron trifluoride salt did not yield any cross-coupled product. The trend of reactivity of this Cu-catalytic system with these different vinyl groups and aryl groups led to further investigation with regard to the substrate scope of the thiol moiety itself.

2.7. Scope of the Cu-Catalyzed Vinylation of Thiols. The cross-coupling of a series of vinyl iodides with aromatic, heteroaromatic, and aliphatic thiols was carried out using the aforementioned optimized reaction conditions in combination with CuI and 1,2-*cis*-cyclohexanediol ligand **L3** as a catalyst system. The results are summarized in the subsequent sections (see Tables 3−7).

2.7.1. Scope of the Cu-Catalyzed Vinylation of Electron-Rich Vinyl Iodides with Various Thiols. The reactions of aromatic thiols with electron-rich 3,5-dimethoxyphenylvinyl iodide **1** were conducted with the optimized catalyst loading (10 mol % of CuI and 20 mol % of **L3**) at 30−40 °C for 0.5−2 h. The coupling processes between 3,5-dimethoxyphenylvinyl iodide and a broad range of aromatic thiols provided good to excellent yields of the vinyl thioethers (Table 3, entries 1−5). In all cases, the desired vinyl sulfides were obtained under mild conditions (30−40 °C) with short reaction times (0.5−4 h); moreover, no aryl acetylene or homocoupled byproducts were observed. Analysis of the data in Table 3 demonstrated the effective use of the newly developed system to couple electron-rich vinyl iodides with hindered ortho-substituted aryl thiols (Table 3, entries 4−5). The base-sensitive ester group contained in the hindered ortho aryl thiol remained intact and gave thioether **19** in excellent yield (Table 3, entry 5) without hydrolysis of the ester group. Examination of these results indicated that the milder reaction conditions and shorter reaction times rendered this method robust for substrates which contained acid- or base-sensitive functional groups. The scope of this coupling reaction to 3,5-dimethoxyphenylvinyl iodide **1** was then extended to alkyl and heterocyclic substituted thiols. As expected, alkyl thiols gave the cross-coupled product in excellent yield but required slightly higher temperatures of

TABLE 3. Cu-catalyzed Cross-Coupling of Electron-Rich (*E*)-3,5-Dimethoxyvinyl Iodides with Aromatic, Aliphatic, and Heterocyclic Thiols

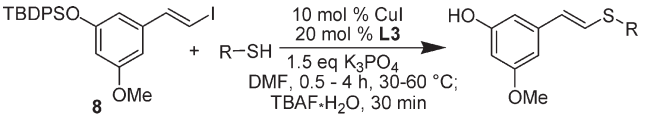


entry	thiol	product	yield[a,b] (%)
1		 **15**	96[c]
2		 **16**	97[c]
3		 **17**	95[c]
4		 **18**	97[c]
5		 **19**	84[c]
6		 **20**	88[e]
7		 **21**	90[d]
8		 **22**	95[e]
9		 **23**	93[e]
10		 **24**	97[d]
11		 **25**	93[d]

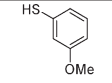
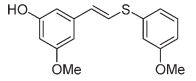
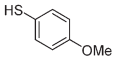
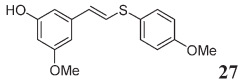
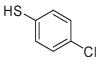
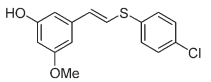
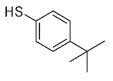
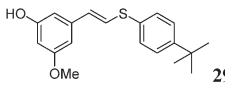
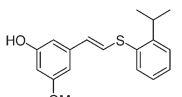
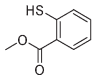
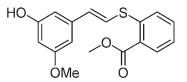
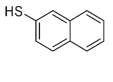
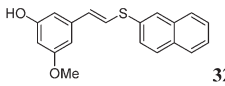
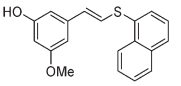
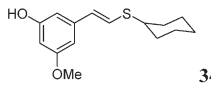
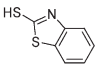
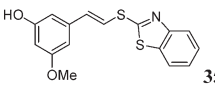
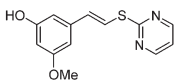
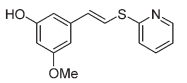
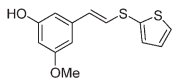
[a]Isolated yields, the average of at least two runs. [b]The starting arylvinyl iodides contained ∼9−12% of the *Z*-isomer, which led to ∼9−12% of the *cis*-isomer, reflected in the overall yield. [c]The reaction mixture was heated for 0.5−2 h at 30−40 °C. [d]The reaction mixture was heated for 8 h at 50−60 °C. [e]The reaction mixture was heated for 2−4 h at 40−50 °C.

40−50 °C and slightly longer reaction times of 2−4 h (Table 3, entries 6, 8, and 9). Presumably, the nucleophile generated from the alkyl thiol required a longer reaction time (2−4 h) and elevated temperatures (40−50 °C) as compared to aryl thiols (0.5−2 h and 30−40 °C). An exception was observed in the case of the alkyl thiol, 6-mercapto-1-hexanol, when reacted with 3,5-dimethoxyphenylvinyl iodide **1** to give the desired cross-coupled thioether **21** (Table 3, entry 7).

TABLE 4. Cu-catalyzed Cross-Coupling of Silyl-Protected Electron-Rich (*E*)-3-*tert*-Butyldiphenylsilyloxy-5-methoxy Vinyl Iodides with Aromatic, Aliphatic, and Heterocyclic Substituted Thiols



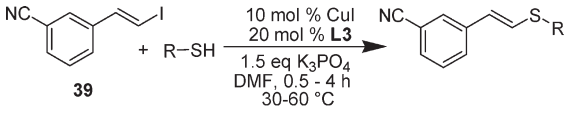
TBDPS = *tert*-Butyldiphenylsilyl; TBAF = *tert*-butylammoniumfluoride
R = aryl / alkyl / hetreocyclic

entry	thiol	product	yield[a,b,c] (%)
1		 **26**	84[d]
2		 **27**	95[c,d]
3		 **28**	96[d]
4		 **29**	97[d]
5		 **30**	96[d]
6		 **31**	83[d]
7		 **32**	92[d]
8		 **33**	91[d]
9		 **34**	96[e]
10		 **35**	92[f]
11		 **36**	87[f]
12		 **37**	92[e]
13		 **38**	86[e]

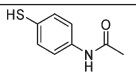
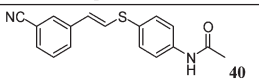
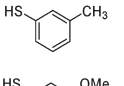
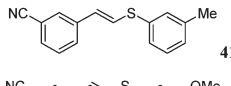
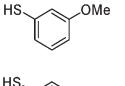
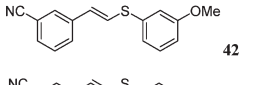
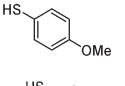
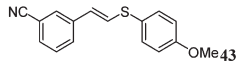
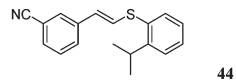
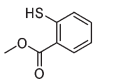
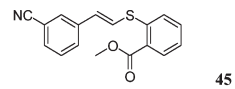
[a]Isolated yields, the average of at least two runs. [b]The starting arylvinyl iodides contained ~9−12% *Z*-isomer; this led to ~9−12% of the *cis*-isomer, reflected in the overall yield. [c]Treatment with TBAF·THF provided the desired phenol. [d]The reaction mixture was heated for 0.5−2 h at 30−40 °C. [e]The reaction mixture was heated for 4 h at 40−50 °C. [f]The reaction mixture was heated for 8 h at 50−60 °C.

This coupling process required a temperature of 60 °C and a reaction time of 8 h for complete consumption of starting material. This process gave **21** in 90% yield. Interestingly, the same chemoselectivity for *S*-vinylation was observed for *O*-vinylation. The heterocyclic thiols gave the corresponding cross coupled products **24** and **25**, respectively, in excellent yield when reacted with the electron rich 3,5-dimethoxyarylvinyl iodide **1** (Table 3, entries 10 and 11) as long as the conditions of elevated temperature and a longer reaction time (60 °C and 2−8 h) were employed.

TABLE 5. Cu-catalyzed Cross-Coupling of Electron Poor (EWG) (*E*)-3-Cyanophenylvinyl Iodides with Aromatic, Aliphatic, and Heterocyclic Substituted Thiols



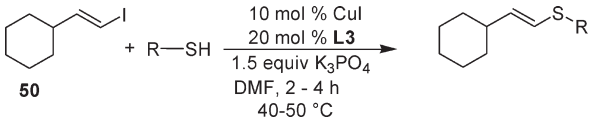
R = aryl / alkyl / heterocycle

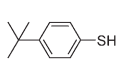
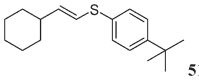
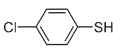
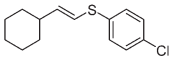
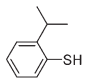
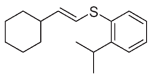
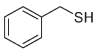
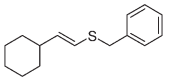
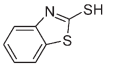
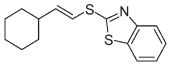
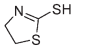
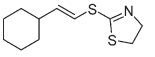
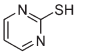
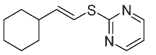
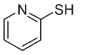
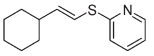
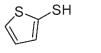
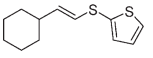
entry	thiol	product	yield[a] (%)
1		 **40**	87[c]
2		 **41**	84[c]
3		 **42**	84[c]
4		 **43**	86[c]
5		 **44**	93[c]
6		 **45**	87[c]
7		**46**	93[d]
8		**47**	90[e]
9		**48**	86[e]
10		**49**	90[d]

[a]Isolated yields, the average of at least two runs. [b]The starting arylvinyl iodides contained ~9−12% *Z*-isomer; this led to ~9−12% of the *cis*-isomer, reflected in the overall yield. [c]The reaction mixture was heated for 0.5−2 h at 30−40 °C. [d]The reaction mixture was heated for 2−4 h at 40−50 °C. [e]The reaction mixture was heated for 8 h at 50−60 °C.

2.7.2. Cu-Catalyzed Cross-Coupling of *O*-Protected Phenolic Vinyl Iodides with Various Thiols. As described in sections 2.4 and 2.5, the synthesis of the biologically active 3-hydroxy-5-methoxyvinyl sulfides was of interest here. The difficulties and problems associated with the synthesis of this class of vinyl sulfides have been described in sections 2.1 and 2.4 using previously reported methods.[68−81] Because of these difficulties, the inexpensive Cu-catalytic system (Cu-**L3**) was employed to couple the silyl-protected 3-hydroxy-5-methoxyphenylvinyl iodide **8** with aryl, alkyl, and heteroaryl thiols because this Cu−ligand catalyst system required

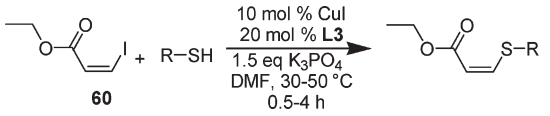
TABLE 6. Cu-catalyzed Cross-Coupling of (*E*)-3-Cyclohexylvinyl Iodides with Aromatic, Aliphatic, and Heterocyclic Substituted Thiols

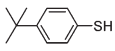
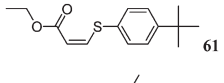
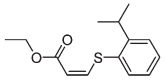
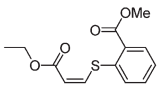
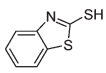
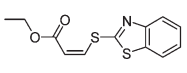
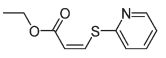
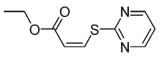
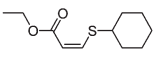


entry	thiol	product	yield[a,b] (%)
1		 **51**	98
2		 **52**	98
3		 **53**	97
4		 **54**	92
5		 **55**	93[b]
6		 **56**	91[b]
7		 **57**	89[b]
8		 **58**	93[b]
9		 **59**	88

[a]Isolated yields, the average of at least two runs. [b]The starting arylvinyl iodides contained ~9−12% *Z*-isomer; this led to ~9−12% of the *cis*-isomer, reflected in the overall yield.

TABLE 7. Cu-Catalyzed Cross-Coupling of (*Z*)-Ethyl-3-iodoacrylate with Aromatic, Aliphatic, and Heterocyclic Thiols



entry	thiol	product	yield[a] (%)
1		 **61**	98[b]
2		 **62**	98[b]
3		 **63**	93[b]
4		 **64**	95[c]
5		 **65**	97[c]
6		 **66**	93[c]
7		 **67**	94[c]

[a]Isolated yields, the average of at least two runs. [b]The reaction mixture was heated for 2 h at 30−40 °C. [c]The reaction mixture was heated for 4 h at 40−50 °C.

milder reaction conditions than the more classical methods.[19] It is noteworthy to mention that at higher temperatures (> 90 °C) the silyl group was cleaved and the phenolic group that was generated was responsible for the low yields of the desired thioether, as mentioned in sections 2.4 and 2.5 (Scheme 2) in part due to the formation of the arylacetylene side product. Therefore, the separation of the desired vinyl sulfide from unwanted acetylene **6** side product became difficult. In addition, the desired vinyl sulfides were obtained in only poor yields. In the presence of Cu-**L3** the silyl-protected 3-hydroxy-5-methoxyvinyl iodide reacted with aryl thiols under milder conditions (30−40 °C, 0.5−2 h). The catalyst loading was typically the same as that used in the earlier optimized conditions (i.e., 10 mol % of CuI and 20 mol % of **L3**). The coupled products (Table 4, entries 1−13) were obtained without cleavage of the silyl protecting group. Upon completion of the coupling reaction, the deprotection was carried out in the same reaction vessel by treatment with *tert*-butylammonium fluoride hydrate (TBAF·H_2O) for 30 min at room temperature. Ultimately, the desired vinyl sulfides were obtained in high yields (Table 4, entries 1−8). Excellent yields of the coupling product were obtained even when hindered ortho-substituted aryl thiols were employed (Table 4, entry 5). Base-sensitive ester groups which were contained in the ortho-hindered thiols also gave good yields (Table 4, entry 6). The alkyl thiol, cyclohexylmercaptan, gave excellent yields of **34** when reacted with the silyl-protected 3-hydroxy-5-methoxyphenylvinyl iodide **8** with the optimized catalytic system under the conditions of 50 °C for 4 h (Table 4, entry 9). The scope of the coupling reaction of the silyl-protected 3-hydroxy-5-methoxyvinyl iodide **8** with heterocyclic thiols was also extended with the same Cu-**L3** catalytic system using the same amount of catalyst loading, as mentioned previously. This generated heterocyclic substituted vinyl sulfides in good to excellent yields (Table 4, entries 10−13). The coupling process of only a few heterocyclic thiols (Table 4, entries 10 and 11) required elevated temperatures (60 °C) and longer reaction times (8 h). Gratifyingly, no disulfide side products were observed in any of these reactions.

The successful extension of this catalytic system, in particular, to the silyl-protected arylvinyl iodides, provided a simple process to access the biologically active 3-hydroxy-5-methoxystyrylthioaryl molecules required for potent antimicrobial activity against Gram-positive bacteria including anthrax, MRSA, VRE, and tuberculosis.[32]

2.7.3. Cu-Catalyzed Vinylation of *E*-Vinyl Iodides Substituted with Electron-Withdrawing Groups (EWG) with Thiols. The efficiency of this Cu-catalytic system prompted evaluation of coupling processes between electron-poor [arylvinyl iodides which contained an electron-withdrawing group (EWG)] arylvinyl iodides with various thiols. When the aromatic **A**-ring in the arylvinyl iodide was substituted with a cyano group at the 3-postion, 3-cyanophenylvinyl iodide **39**, and subjected to the coupling process with a broad spectrum of thiols including aryl, alkyl, and heterocyclic

thiols, this also provided high yields of the corresponding thioethers. The catalyst loading was kept constant using the aforementioned optimized reaction conditions. As expected, the 3-cyanophenylvinyl iodide **39** gave the coupled arylvinyl sulfides when treated with aryl thiols at 30−40 °C for 0.5−2 h (Table 5, entries 1−4). The thiols which were ortho-hindered or carried base sensitive functional groups again gave high yields of the corresponding vinyl sulfides under the same reaction conditions (Table 5, entries 5 and 6). Moreover, the electron poor 3-cyanophenylvinyl iodide **39** was subjected to coupling with alkyl thiols and heterocyclic thiols. The alkyl thiol, 2-methylbutanethiol, produced the corresponding coupled vinyl sulfide **46** in excellent yield at 40−50 °C in 4 h (Table 5, entry 7), while 6-mercapto-1-hexanol gave the chemoselective *S*-vinylated product **47** at 60 °C in 8 h (Table 5, entry 8). Heterocyclic substituted thiols gave the corresponding vinyl sulfides when subjected to the Cu-catalyzed coupling reaction with 3-cyanophenylvinyl iodide **39** at 60 °C, albeit a longer reaction time of 4−8 h (Table 5, entries 9 and 10) was required.

To date, the coupling process with arylvinyl iodides which contained either EDG or EWG groups underwent the Cu-catalyzed coupling reaction with various thiols in high yield. In general heterocyclic thiols are not as reactive as aryl thiols. Any combination of an arylvinyl iodide with an alkyl or heterocyclic substituted thiol required slightly higher temperatures and slightly longer reaction times, albeit the yields were still very good.

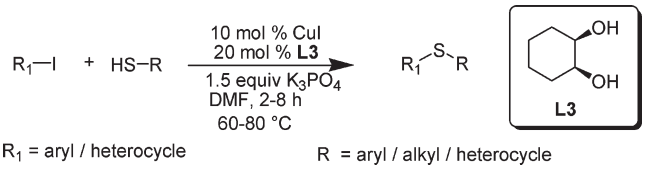
2.7.4. The Cu-Catalyzed Vinylation of *E*-Alkylvinyl Iodides with Thiols. Since the earlier focus had concerned only coupling of aromatic vinyl iodides, it was now decided to extend this process to the coupling of alkylvinyl iodides with thiols. The goal remained to broaden the substrate scope and the application of this Cu-catalytic system; hence the coupling between alkylvinyl iodides and various thiols was explored to prepare the corresponding alkylvinyl sulfides. The readily available alkylvinyl iodide, cyclohexylvinyl iodide **50**, was chosen as a standard alkylvinyl iodide for the coupling with various thiols. The ability to couple such an alkylvinyl iodide with thiols was investigated using aryl, alkyl and heterocyclic substituted thiols under the following reaction conditions: optimized catalyst loading [CuI 10 mol % and **L3** 20 mol %, temperature of 40−50 °C for 2−4 h]. Electron rich, electron poor, and ortho-hindered aryl thiols, alkyl thiols, as well as heterocyclic substituted thiols all gave alkylvinyl thioethers in good to excellent yields ranging from 88 to 98% (Table 6, entries 1−9). To the best of our knowledge, no Cu-catalytic systems have been published to date, with regard to vinylations of thiols which operate under such mild reaction conditions and work for both arylvinyl iodides and alkylvinyl iodides, which employ nearly the same substrate profile with such a wide variety of functionalized thiols.

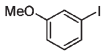
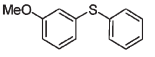
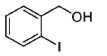
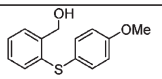
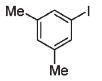
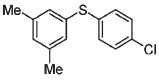
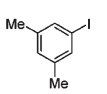
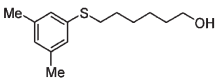
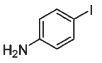
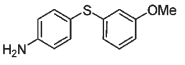
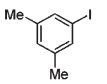
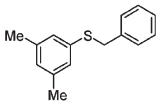
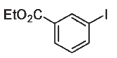
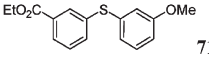
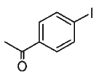
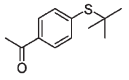
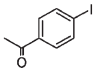
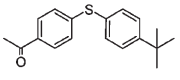
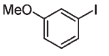
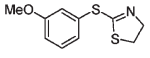
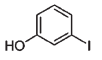
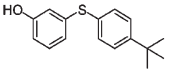
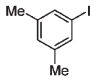
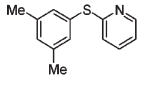
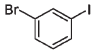
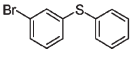
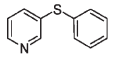
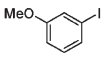
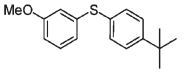
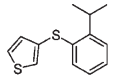
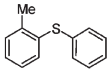
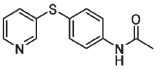
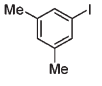
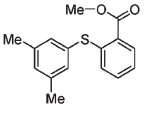
2.7.5. Cu-Catalyzed Vinylation of *Z*-Alkylvinyl Iodides with Thiols. The retention of regio- and stereochemistry in all products was observed in the cases of *E*-arylvinyl iodides. To ensure the coupling reaction proceeded in a regio- and stereospecific fashion, the coupling reaction was investigated using an electron-poor *Z*-vinyl iodide **60** which contained a base-sensitive group (ethyl *cis*-3-iodoacrylate) with various thiols. The results are summarized in Table 7. Analysis of the results indicated that the Cu-**L3** catalytic system worked well when the *Z*-vinyl iodide **60** was subjected to coupling with aryl-, alkyl-, or heterocyclic-substituted thiols (Table 7, entries 1−7). Electron-rich, electron-poor, and ortho-substituted hindered aromatic thiols gave excellent yields with full retention of double bond geometry when the reaction was carried out at 30−40 °C over a 2 h period (Table 7, entries 1−3). As expected from previous results, alkyl and heterocyclic thiols gave the corresponding vinyl sulfides at 40−50 °C in 4 h (Table 7, entries 4−7). In all cases, the catalyst loading, base, and solvent were the same as the optimized conditions previously described.

2.8. The Synthesis of Diaryl Sulfides from the Cu-Catalyzed Coupling of Aryl Iodides and Thiols. As referenced in the Introduction, the metal-catalyzed coupling of aryl halides with thiols was reported in the past few years and has been noted.[53] In addition, the application of the new catalytic system has been applied to the synthesis of diaryl sulfides and was described in a previous section (2.6.2, Scheme 3) from the coupling of aryl halides with thiols. Encouraged by the earlier results which concerned the coupling of vinyl halides with thiols using the Cu-**L3** catalytic system, attempts were undertaken to extend the scope of this reaction to include the synthesis of diaryl sulfides from the corresponding aryl iodides as well as bromides. Analysis of some reports indicated diaryl sulfides are of significance in the pharmaceutical industry.[108] The classical Ullmann-type Cu-catalyzed approach has been employed over the past few years for the synthesis of diaryl sulfides. Many of these approaches usually require either harsh reaction conditions or substrates with chelating functional groups in the ortho position. The most recent reports of the synthesis of diaryl sulfides which are Cu-catalyzed require either fairly harsh reaction conditions, a strong base such as NaO-*t*-Bu at 110 °C as in the case of Venkataraman,[60] or longer reaction times (18−22 h) as in the case of Buchwald.[17] Other routes lack efficiency and require the use of polyfunctionalized substrates which are cumbersome.[105]

To address the aforementioned issues, the new Cu-catalytic system was employed with various functionalized aryl iodides in combination with a nucleophilic thiol substrate. These reactions of aryl iodides were conducted between 60 and 80 °C for 2−8 h depending on the requirement of each substrate (see Table 8). In the cases of functionalized aryl iodides, the reaction went to completion within 2−4 h, while for heteroaryl-substituted aryl iodide substrates the coupling process required 6−8 h to finish. The coupling of a wide range of functionalized aryl iodides which contained potentially reactive ketones (CO), free anilino (NH_2), phenolic (OH), ester (COOR), ether (C−O−C), or alkyl moieties took place efficiently to form the corresponding diaryl sulfides in good to excellent yields (Table 8, entries 1−8). Again, the base-sensitive ester group (Table 8, entry 4) was maintained and gave the corresponding coupling product, diaryl sulfide **71**, in excellent yield. This process required a relatively shorter time (4 h) which minimized the hydrolysis of the ester group in the coupled product. The chemoselectivity of the *S*-nucleophile over the *O*-nucleophile and the relative reactivity of the iodo- and bromoaryl derivatives was clearly demonstrated (Table 8, entries 6 and 7). The phenolic aryl iodide gave the coupled product **73** only with the thiol as the sole coupling product, instead of any products generated from the intermolecular coupling at oxygen between two molecules

TABLE 8. Copper-Catalyzed Cross-Coupling of Various Aryl and Heterocyclic Substituted Iodides with Aromatic, Aliphatic, and Heterocyclic Thiols



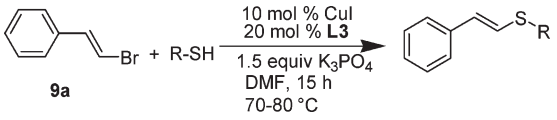
entry	vinyl iodide	product		yield[a] (%)	entry	vinyl iodide	product		yield[a] (%)
1			**68**	81[b]	12			**79**	93[c]
2			**69**	90[b]	13			**80**	95[d]
3			**70**	86[b]	14			**81**	96[c]
4			**71**	95[b]	15			**82**	95[c]
5			**72**	95[b]	16			**83**	85[c]
6			**73**	86[c]	17			**84**	93[d]
7			**74**	87[b]	18			**85**	97[d]
8			**75**	81[b]	19			**86**	86[c]
9			**76**	93[b]	20			**87**	90[d]
10			**77**	93[b]	21			**88**	93[d]
11			**78**	96[b]	22			**89**	95[d]

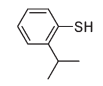
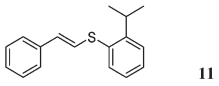
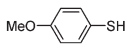
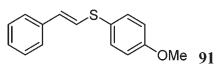
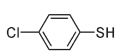
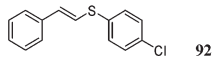
[a]Isolated yields, the average of at least two runs. [b]The reaction mixture was heated for 2−4 h at 60−70 °C. [c]The reaction mixture was heated for 4−6 h at 60−70 °C. [d]The reaction mixture was heated for 8 h at 80 °C.

of the phenolic aryl iodide (Table 8, entry 6). This result clearly demonstated the chemoselective nature again of this reaction for the coupling of thiols and phenolic aryl iodides. A coupling reaction between a bromo-substituted aryl iodide and aryl thiol also gave only the intended coupling product with no homocoupling regardless of the respective iodo and thiol progenitors. In essence, no unintended side products were observed despite the presence of the competing bromo functionality and thiols (Table 8, entry 7). Analysis of these results clearly differentiated the relative reactivity of bromo versus iodo groups and underscores the strong iodo selectivity of the reaction.

The next extension of this Cu-**L3** mediated process involved application of this protocol for the coupling of ortho-substituted aryl iodides and aryl thiols. As indicated in Table 8 (entires 9−12), the presence of functional groups in the ortho position of both aryl iodides and thiols was well tolerated. Substrates which contained *o*-hydroxymethyl, *o*-methyl, *o*-isopropyl, and *o*-carboxymethyl groups gave the corresponding diaryl sulfides **76**−**79**, respectively, in good to excellent yield (Table 8, entries 9−12). This demonstrated, this catalytic method could be applied to both electron-rich and electron-deficient substrates in the case of

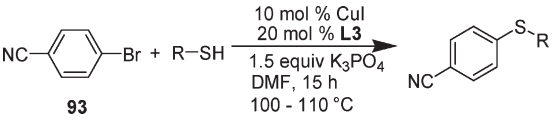
TABLE 9. Cu-Catalyzed Cross-Coupling of Phenylvinyl Bromide with Various Aromatic Thiols

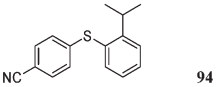
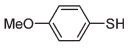
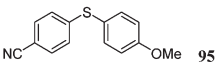
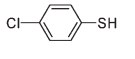
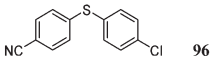


entry	thiol	product	yield[a,b] (%)
1		 **11**	84
2		 **91**	88
3		 **92**	84

[a]Isolated yields, the average of at least two runs. [b]The starting arylvinyl iodides contained ~9−12% *Z*-isomer, which led to ~9−12% of the *cis*-isomer, reflected in the overall yield.

TABLE 10. Copper-Catalyzed Cross-Coupling of Aryl Bromides with Various Aromatic Thiols



entry	thiol	product	yield[a] (%)
1		 **94**	92
2		 **95**	91
3		 **96**	93

[a]Isolated yields, the average of at least two runs.

either aryl iodides or thiols. The process was also extremely tolerant in terms of steric hindrance, although the reaction was, in some cases, slightly more demanding and required a little longer time or an elevated temperature. For example, the coupling of 2-isopropylthiophenol with 2-iodotoluene (Table 8, entry 11, **78**) required 4 h to go to completion (96% yield). In comparison, the reaction of *p*-methoxythiophenol with 2-hydoxymethyliodobenzene took 8 h to finish but still gave the desired diaryl sulfide **79** in 93% yield (Table 8, entry 12).

Alkanethiols were also found to be effective nucleophiles with the optimized reaction conditions (Table 8, entries 13−15). *tert*-Butyl thiol and benzylmercpatan gave the *S*-arylated products in excellent yields (Table 8, entries 14 and 15). In addition, the selective *S*-arylation was observed when 6-mercapto-1-hexanol was used as a nucleophile (Table 8, entry 13). Once again, the chemoselectivity of soft sulfur nucleophiles over the hard oxygen nucleophiles was clearly demonstrated. As seen in Table 8, entries 16 and 17, heterocyclic-substituted thiols gave the corresponding coupling product of the desired sulfides when reacted with aryl iodides in good to excellent yields, although as typically expected by now, these reactions required a longer reaction time (8 h) and a slightly elevated temperature of 80 °C.

Studies on the scope of the coupling of heterocyclic aryl iodides with electron-rich, electron-deficient, and ortho-hindered aryl thiols as well as alkyl thiols were conducted using the optimized reaction conditions (Table 8, entries 18−22). Again, very high yields were obtained in these cases using a relatively short reaction time without formation of any side products. All the reactions with heterocyclic-substituted aryl iodides were conducted at 80 °C for 6−8 h with the same amount of catalyst loading (CuI, 10 mol % and **L3**, 20 mol %).

2.9. The Synthesis of Diaryl Sulfides and Arylvinyl Sulfides from the Cu-Catalyzed Coupling of Their Respective Bromides and Thiols. As described in sections 2.6.1 (Table 1) and 2.6.2 (Scheme 3), the reactivity pattern of different vinyl halides and other pseudo halides indicated that diaryl sulfides and arylvinyl sulfides could also be synthesized from their respective bromo derivatives. Therefore, processes with aryl bromides and arylvinyl bromides were explored with this catalytic system for the synthesis of the corresponding sulfides from thiols. Examination of the experimental results indicated this catalytic system could be applied to more stable and less expensive arylvinyl bromides as well as aryl bromides compared to their iodo counterparts. The results of these studies are summarized in Tables 9 and 10.

The studies were carried out using the Cu-**L3** system and indicated arylvinyl bromides coupled well with the electron-rich, electron-poor, and ortho-hindered thiols when used in combination with 10 mol % of CuI, 20 mol % of **L3**, and a base K_3PO_4 (1.5 equiv). The results from these studies provided arylvinyl sulfides in good to excellent yields (Table 9). It is noteworthy to mention that the reaction with arylvinyl bromides required elevated temperatures (70−80 °C) as compared to those with arylvinyl iodides (40−60 °C). Furthermore, as expected, the completion of the reaction required a longer reaction time (15 h) for arylvinyl bromides as compared to arylvinyl iodides (0.5−2) h. In order to extend the scope of this catalytic system, the synthesis of diaryl sulfides from the corresponding aryl bromides was attempted as well. Again, the optimized catalytic conditions proved to be very effective when using aryl bromides to synthesize diaryl sulfides but again required slightly elevated reaction temperatures and longer reaction times (100−110 °C, 15 h), as compared to the corresponding aryl iodides (60−80 °C, 2−8 h). The results of the coupling reaction of aryl bromides with thiols are summarized in Table 10. Once again, the yields of each reaction were good to excellent with various thiols including electron-rich, electron-poor, and ortho-hindered thiophenols.

2.10. A Working Hypothesis of the Cu-Catalyzed Mechanistic Cycle for the Synthesis of Sulfides. To date, a pathway for palladium catalysis is better understood than the mechanism of the corresponding copper catalytic systems. According to recent mechanistic studies,[52,53,106] two possible mechanistic pathways may operate for the synthesis of these arylvinyl sulfides and diaryl sulfides. Both pathways begin with chelation of the CuI species by the 1,2-*cis*-cyclohexanediol ligand **L3** and solvent (Figure 2) to form a CuI tetrahedral species. The reactive CuI tetrahedral species is considered most likely in the case of this reaction. Nucleophilic substitution of the halide by the deprotonated thiol leads to a Cu^I tetrahedral complex ligated with solvent, as illustrated in path 1. The subsequent complexation followed by oxidative addition of an arylvinyl or aryl halide generates a square planar Cu^{III} complex (Figure 2).

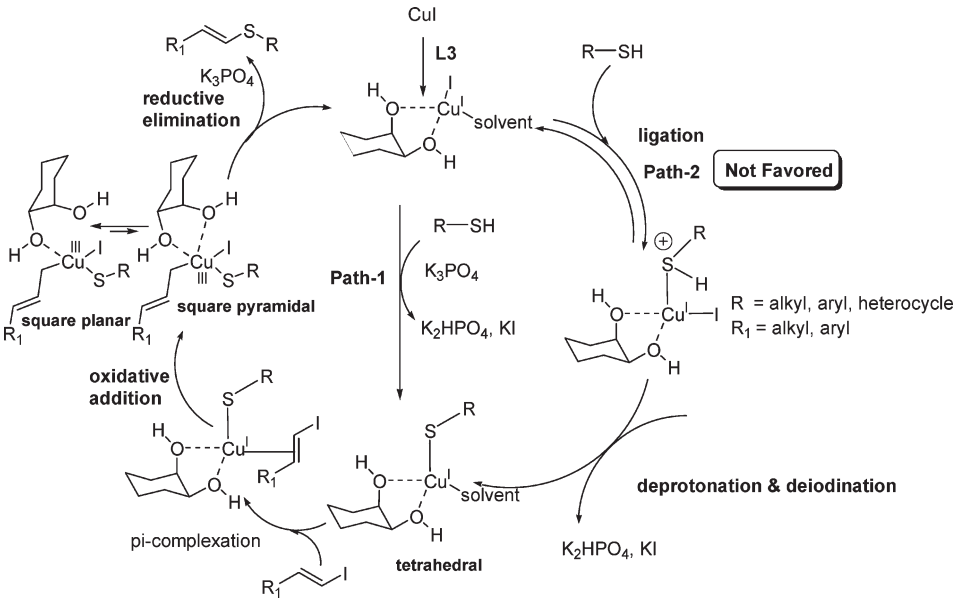


FIGURE 2. Working hypothesis of the mechanistic cycle for the synthesis of vinyl sulfides.

After this oxidative addition, the delivery of the cross-coupled product via reductive elimination occurs, which subsequently regenerates the Cu(I) species to take part in a new catalytic cycle. An alternative pathway (path 2, Figure 2) begins with the ligation of the nucleophile by substitution of the solvent and generation again of a CuI tetrahedral species. This is followed by the deprotonation of the cationic thiol-CuI complex to generate a neutral solvent-ligated CuI complex. This neutral solvent-ligated CuI complex then, in turn, undergoes an oxidative addition step, followed by a reductive elimination similar to path 1. This second pathway (i.e., path 2) can effectively be ruled out by following the recent mechanistic studies of Buchwald, Liu, Hartwig, and others.[52,53] It is important to note that both mechanistic possibilities proceed via Cu(I) and Cu(III).

3. Conclusion

In summary, it has been shown that CuI−**L3** complexes generated from 1,2-*cis*-cyclohexanediol are highly efficient catalysts for the coupling of vinyl, aryl, heteroaryl, and alkyl halides with thiols. Most importantly, this singular catalyst system is extremely versatile for the synthesis of a wide range of sulfides including arylvinyl sulfides, diaryl sulfides, heteroaryl sulfides, and alkyl sulfides. This method is particularly noteworthy given its mild reaction conditions, simplicity, generality, and exceptional level of functional group tolerance. The catalyst can be handled in open air, although it should be noted that all of the reaction vessels were evacuated and degassed when conducting the coupling reactions in order to prevent the formation of disulfides due to oxidation of starting thiols from the presence of air oxygen. This might well be achieved by addition of an inhibitor such as BHT to the reaction mixture. To the best of our knowledge, none of the Cu-catalytic methods which have been reported to date can operate under such mild conditions with such broad substrate scope. In the case of vinyl iodides, the regio- and stereochemistry of the vinyl sulfides was retained as in the starting vinyl halides. The broad functional group tolerance in this system, in part, is due to these milder reaction conditions. The relative reactivity for both vinyl and aryl halides followed the conventional trend of: vinyl iodide > vinyl bromide and aryl iodide > aryl bromide. The use of less reactive vinyl or aryl chlorides and pseudo halides did not prove to be effective for coupling with thiols when subjected to the newly developed catalytic system. In the case of electron-rich unstable vinyl iodides, the method gave exclusively the desired arylvinyl sulfides in high yield without any aryl acetylene side product or any other side product. The same results were observed with aryl and alkylvinyl halides.

4. Experimental Section

General Considerations. Copper(I) iodide (99.99% purity), ligands **L1**−**L10**, and *N*,*N*-dimethylformamide (DMF) (anhydrous, 99.8% purity) were purchased from commercial sources. All thiols were used as received from major laboratory chemical and biochemical supply firms without further purification. Cesium carbonate, potassium phosphate, and potassium carbonate were purchased from commercial suppliers and used as is. Silica gel (230−400 mesh) chromatography was utilized for purification of products. ^{1}H and ^{13}C NMR data were obtained on a 300 or 500 MHz NMR instrument with chemical shifts reported relative to TMS. Melting points were recorded on a electrothermal melting point apparatus and are uncorrected. Mass spectra and high-resolution mass spectra were performed by the mass spectroscopic laboratory from three different laboratories. The HRMS was performed by ESI on a PE SCIEX QSTAR, by APCI on a LCQ-DECA, and by EI on a GC−MS.

General Procedure A for the Synthesis of Aryl, Alkyl, and Vinyl Sulfides (Tables 3 and 5−10). An oven-dried round-bottom flask containing a magnetic stir bar was sealed with a rubber septum and then evacuated and backfilled with argon (the sequence was repeated three times) with cooling to rt. The round-bottom flask was then charged with anhydrous potassium phosphate (1.5 equiv), copper(I) iodide (10 mol %), *cis*-1,2-cyclohexanediol (20 mol %), and dry DMF (2 mL). The solution which resulted was stirred for 5−10 min at rt. The reaction mixture turned a light green color within 3−5 min. The reaction vessel was evacuated and backfilled with argon one more time before

adding the thiol and the aryl, alkyl, or vinyl iodide. This operation was done to prevent the formation of disulfides in the presence of oxygen inside the reaction vessel. The appropriate thiol (1.2 equiv) was added to the reaction mixture through a rubber septum and the mixture stirred for another 5 min at rt. The aryl or alkyl or vinyl iodide or bromide (1.0 equiv) of choice was dissolved in a minimum amount of dry DMF and was added to the resulting reaction mixture through a rubber septum. The contents of the reaction mixture were allowed to stir at 30−110 °C for 0.5−15 h depending on the substrate. The reaction mixture was then cooled to rt and filtered through a pad of silica gel to remove insoluble residues. The pad of silica gel was washed ethyl acetate (100 mL). The combined filtrate was washed with brine (4 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo on a rotatory evaporator. The concentrated crude oil was purified by flash column chromatography on silica gel using the eluent (2−10%) ethyl acetate and hexane (depending on the substrate) to obtain the pure product (75−98% yields).

General Procedure B for the Synthesis of Vinyl Sulfides (Table 4). An oven-dried round-bottom flask containing a magnetic stir bar was sealed with a rubber septum and then evacuated and backfilled with argon (the sequence was repeated three times) while cooling to rt. The round-bottom flask was then charged with anhydrous potassium phosphate (1.5 equiv), copper(I) iodide (10 mol %), *cis*-1,2-cyclohexanediol (20 mol %), and dry DMF (2 mL). The solution which resulted was stirred for 5−10 min at rt.The reaction mixture turned a light green color within 3−5 min. The reaction vessel was evacuated and backfilled with argon one more time before addition of the thiol and the vinyl iodide. This operation was done to prevent the formation of disulfides in the presence of oxygen or moisture inside the reaction vessel. The appropriate thiol (1.2 equiv) was added to the reaction mixture through a rubber septum and the mixture stirred for another 5 min at rt. The vinyl iodide (1.0 equiv) of choice in a minimum amount of dry DMF was added to the resulting reaction mixture through a rubber septum. The contents of the reaction mixture were heated to 30−60 °C for 0.5−8 h depending on the substrate. The reaction mixture was then cooled to rt, and TBAF·H_2O (1.5 equiv) was added to the reaction mixture. After being stirred at rt, the reaction mixture was filtered through a pad of silica gel to remove insoluble residues. The pad of silica gel was washed ethyl acetate (100 mL). The combined filtrate was washed with brine (4 × 50 mL) and dried (Na_2SO_4) after which it was concentrated in vacuo on a rotatory evaporator. The concentrated crude oil was purified by flash column chromatography on silica gel using the eluent (2−3%) ethyl acetate and hexane to obtain the pure product (83−97% yields).

Characterization Data for Products Shown in Table 3. (*E*)-3-[2-(Phenylsulfanyl)vinyl]-3,5-dimethoxybenzene (3) (Table 3, Entry 1). General procedure A was followed (1 h). Vinyl iodide **1** (50 mg, 0.17 mmol), benzenethiol (22.5 mg, 0.2 mmol), CuI (3.3 mg, 0.017 mmol), 1,2-*cis*-cyclohexanediol (4.0 mg, 0.034 mmol), K_3PO_4 (32 mg, 0.39 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **3** (44.4 mg, 96% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **3**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47−7.28 (5H, m), δ 6.90 (1H, d, J = 15.4 Hz), δ 6.67 (1H, d, J = 15.4 Hz), δ 6.52 (2H, d, J = 2.2 Hz), δ 6.40 (1H, t, J = 2.2 Hz), δ 3.82 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 138.4, 131.3, 130.0, 129.1, 126.9, 124.2, 106.6, 104.0, 99.8, 55.3. HRMS (ESI) $(M + H)^+$: calcd for $C_{16}H_{17}O_2S$ 273.0949, found 273.0947.

(*E*)-3-[2-(4-*tert*-Butylphenylsulfanyl)vinyl]-3,5-dimethoxybenzene (16) (Table 3, Entry 2). General procedure A was followed (30 min). Vinyl iodide **1** (100 mg, 0.34 mmol), 4-*tert*-butylbenzenethiol (68.2 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (8.0 mg, 0.069 mmol), K_3PO_4 (109 mg, 0.52 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **16** (108 mg, 97% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **16**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46−7.37 (4H, m), δ 6.90 (1H, d, J = 15.4 Hz), δ 6.63 (1H, d, J = 15.4 Hz), δ 6.51 (2H, d, J = 2.2 Hz), δ 6.39 (1H, t, J = 2.3 Hz), δ 3.81 (6H, s), δ 1.35 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 150.5, 138.5, 131.2, 130.3, 127.7, 126.2, 125.1, 106.6, 103.9, 99.7, 55.3, 31.2. HRMS (ESI) $(M + H)^+$: calcd for $C_{20}H_{25}O_2S$ 329.1575, found 329.1580.

(*E*)-3-[2-(4-Chlorophenylsulfanyl)vinyl]-3,5-dimethoxybenzene (17) (Table 3, Entry 3). General procedure A was followed (30 min). Vinyl iodide **1** (100 mg, 0.34 mmol), 4-chlorobenzenethiol (59.3 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (8.0 mg, 0.069 mmol), K_3PO_4 (109 mg, 0.52 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **17** (99 mg, 95% yield) as an off-white semisolid. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **17**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (4H, d, J = 2.8 Hz), δ 6.83 (1H, d, J = 15.4 Hz), δ 6.67 (1H, d, J = 15.6 Hz), δ 6.51 (2H, d, J = 2.2 Hz), δ 6.40 (1H, t, J = 2.2 Hz), δ 3.82 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 138.1, 133.0, 132.2, 131.1, 126.0, 123.3, 106.7, 104.1, 100.0, 55.3. HRMS (ESI) $(M + H)^+$: calcd for $C_{16}H_{16}ClO_2S$ 306.0481, found 306.0484

(*E*)-3-[2-(2-Isoproplyphenylsulfanyl)vinyl]-3,5-dimethoxybenzene (18) (Table 3, Entry 4). General procedure A was followed (30 min). Vinyl iodide **1** (100 mg, 0.34 mmol), 2-isopropylbenzenethiol (62.4 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (8.0 mg, 0.069 mmol), K_3PO_4 (109 mg, 0.52 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **18** (104 mg, 97% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **18**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (1H, d, J = 7.8 Hz), δ 7.38−7.28 (2H, m), δ 7.24−7.20 (1H, m), δ 6.85 (1H, d, J = 15.4 Hz), δ 6.53−6.49 (3H, m), δ 6.38 (1H, t, J = 2.2 Hz), δ 3.80 (6H, s), δ 3.54−3.49 (1H, m), δ 1.28 (6H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 149.3, 138.6, 132.3, 131.9, 130.1, 128.0, 126.5, 125.8, 125.2, 103.9, 99.6, 55.2, 30.5, 23.4. HRMS (ESI) $(M + H)^+$: calcd for $C_{19}H_{23}O_2S$ 315.1419, found 315.1420.

(*E*)-2-[2-(3,5-Dimethoxyphenyl)vinylsulfanyl]benzoic Acid Methyl Ester (19) (Table 3, Entry 5). General procedure A was followed (2 h). Vinyl iodide **1** (100 mg, 0.34 mmol), 2-mercaptobenzoic acid methyl ester (69 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (8.0 mg, 0.069 mmol), K_3PO_4 (109 mg, 0.52 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **19** (94 mg, 84% yield) as a colorless semisolid. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **19**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (1H, d, J = 7.8 Hz), δ 7.46−7.40 (2H, m), δ 7.28−7.22 (2H, m), δ 6.94 (2H, dd, J = 15.2 Hz, J = 23.8 Hz), δ 6.60 (1H, d, J = 2.2 Hz), δ 6.44 (1H, t, J = 2.3 Hz), δ 4.01 (6H, s), δ 3.83 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 160.9, 140.3, 137.7, 136.4, 133.0, 131.4, 127.6, 125.8, 124.9, 122.1, 104.5, 100.3, 55.3, 52.3. HRMS (ESI) $(M + Li)^+$: calcd for $C_{18}H_{18}O_4SLi$ 337.1086, found 337.1082.

(3,5-Dimethoxystyryl)(benzyl)sulfane (20) (Table 3, Entry 6). General procedure A was followed (2 h). Vinyl iodide **1** (100 mg, 0.34 mmol), benzylthiol (51 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (7.9 mg, 0.068 mmol), K_3PO_4 (108 mg, 0.51 mmol), and DMF (2.0 mL) were stirred at 40−50 °C to obtain the thioether **20** (87 mg, 88% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **20**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42−7.28 (5H, m), δ 6.75 (1H, d, J = 15.4 Hz), δ 6.50−6.44 (3H, m), δ 6.35 (1H, t, J = 2.3 Hz), δ 4.04 (2H, s), δ 3.81 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 138.9, 137.0, 128.7, 128.6, 127.6, 127.3, 125.1, 103.7, 99.2, 55.2, 37.2. HRMS (ESI) $(M + H)^+$: calcd for $C_{17}H_{19}O_2S$ 287.1106, found 287.1112.

(*E*)-6-[2-(3,5-Dimethoxyphenyl)vinylsulfanyl]hexan-1-ol (21) (Table 3, Entry 7). General procedure A was followed (8 h). Vinyl iodide **1** (100 mg, 0.34 mmol), 6-mercaptohexan-1-ol (55 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (8.0 mg, 0.069 mmol), K_3PO_4 (109 mg, 0.52 mmol), and DMF (2.0 mL) were stirred at 50−60 °C to obtain the thioether **21** (91 mg, 90% yield) as a colorless oil. Column chromatography solvent (3−5% EtOAc in hexane) provided pure **21**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (1H, m), δ 6.46 (2H, d, J = 2.2 Hz), δ 6.42−6.36 (1H, m), δ 6.34 (1H, t, J = 2.2 Hz), δ 3.81 (6H, s), δ 3.70−3.64 (2H, m, J = 7.3 Hz), δ 2.82 (2H, t, J = 7.3 Hz), δ 1.75−1.36 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 139.0, 126.4, 125.9, 103.5, 99.0, 62.7, 55.2, 32.5, 32.4, 29.2, 28.4, 25.2. HRMS (ESI) $(M+Li)^+$: calcd for $C_{16}H_{24}O_3SLi$ 303.1606, found 303.1608.

(*E*)-1-(2-Cyclohexylsulfanylvinyl)-3,5-dimethoxybenzene (22) (Table 3, Entry 8). General procedure A was followed (2 h). Vinyl iodide **1** (100 mg, 0.34 mmol), cyclohexyl thiol (48 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (7.9 mg, 0.068 mmol), K_3PO_4 (108 mg, 0.51 mmol), and DMF (2.0 mL) were stirred at 40−50 °C to obtain the thioether **22** (90 mg, 95% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **22**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (1H, d, J = 15.5 Hz), δ 6.53−6.43 (3H, m), δ 6.37−6.34 (1H, m), δ 3.81 (6H, s), δ 3.04−2.97 (1H, m), δ 2.09−1.58 (5H, m) δ 1.53−1.28 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 139.1, 128.2, 124.8, 103.7, 99.1, 55.2, 45.2, 33.5, 25.9, 25.6. HRMS (ESI) $(M + H)^+$: calcd for $C_{16}H_{23}O_2S$ 279.1419, found 279.1421.

(*E*)-1,3-Dimethoxy-5-[2-(2-methylbutylsulfanyl)vinyl]benzene (23) (Table 3, Entry 9). General procedure A was followed (4 h). Vinyl iodide **1** (100 mg, 0.34 mmol), 2-methylbutane-1-thiol (42.7 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (8.0 mg, 0.069 mmol), K_3PO_4 (109 mg, 0.52 mmol), and DMF (2.0 mL) were stirred at 40−50 °C to obtain the thioether **23** (84 mg, 93% yield) as a colorless oil. Column chromatography solvent (3−5% EtOAc in hexane) provided pure **23**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (1H, d, J = 15.6 Hz), δ 6.46 (2H, m), δ 6.42−6.37 (1H, m), δ 6.35−6.33 (1H, m), δ 3.81 (6H, s), δ 2.75 (2H, m), δ 1.80−1.63 (1H, m), δ 1.35−1.25 (2H, m), δ 1.05 (3H, d, J = 6.6 Hz), δ 0.95 (3H, t, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6, 144.8, 139.1, 126.7, 103.5, 98.9, 55.2, 39.7, 34.7, 28.6, 18.8, 11.2. HRMS (ESI) $(M + H)^+$: calcd for $C_{15}H_{23}O_2S$ 267.1419, found 267.1415.

(*E*)-2-[2-(3,5-Dimethoxyphenyl)vinylsulfanyl]pyridine (24) (Table 3, Entry 10). General procedure A was followed (8 h). Vinyl iodide **1** (100 mg, 0.34 mmol), pyridine-2-thiol (45.6 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (8.0 mg, 0.069 mmol), K_3PO_4 (109 mg, 0.52 mmol), and DMF (2.0 mL) were stirred at 50−60 °C to obtain the thioether **24** (90 mg, 97% yield) as a colorless oil. Column chromatography solvent (10% EtOAc in hexane) provided pure **24**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52−8.49 (1H, m), δ 7.57 (1H, t, J = 7.9 Hz), δ 7.50 (1H, d, J = 15.8 Hz), δ 7.29−7.24 (1H, m), δ 7.07 (1H, dd, J = 6.8 Hz, J = 7.8 Hz), δ 6.82 (1H, d, J = 15.8 Hz), δ 6.60 (2H, d, J = 2.2 Hz), δ 6.41 (1H, t, J = 2.2 Hz), δ3.83 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 157.8, 149.7, 138.4, 136.4, 131.6, 122.0, 120.4, 120.2, 104.3, 99.9, 55.3. HRMS (ESI) $(M + H)^+$: calcd for $C_{15}H_{16}NO_2S$ 274.0902, found 274.0904.

(*E*)-2-[2-(3,5-Dimethoxyphenyl)vinylsulfanyl]benzothiazole (25) (Table 3, Entry 11). General procedure A was followed (8 h). Vinyl iodide **1** (100 mg, 0.34 mmol), benzothiazole-2-thiol (68.5 mg, 0.41 mmol), CuI (6.5 mg, 0.034 mmol), 1,2-*cis*-cyclohexanediol (8.0 mg, 0.069 mmol), K_3PO_4 (109 mg, 0.52 mmol), and DMF (2.0 mL) were stirred at 50−60 °C to obtain the thioether **25** (104 mg, 93% yield) as an off-white solid. Column chromatography solvent (10% EtOAc in hexane) provided pure **25**. Mp: 77.2−78.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (1H, d, J = 8.2 Hz), δ 7.80 (1H, d, J = 8.0 Hz), δ 7.46 (1H, t, J = 7.6 Hz) δ 7.37−7.26 (3H, m), δ 6.99 (1H, d, J = 15.6 Hz), δ 6.63 (2H, d, J = 2.2 Hz), δ 6.47 (1H, t, J = 2.2 Hz), δ 3.85 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 153.5, 137.4, 136.6, 135.3, 126.2, 124.4, 121.9, 120.9, 118.0, 106.7, 104.8, 100.7, 55.4. HRMS (ESI) $(M + H)^+$: calcd for $C_{17}H_{16}NO_2S_2$ 330.0622, found 330.0624.

Characterization Data for Products Shown in Table 4. (*E*)-3-Methoxy-5-[2-(3-methoxyphenylsulfanyl)vinyl]phenol (26) (Table 4, Entry 1). General procedure B was followed (1 h).Vinyl iodide **8** (140 mg, 0.27 mmol), 3-methoxybenzenethiol (44.9 mg, 0.32 mmol), CuI (5.2 mg, 0.027 mmol), 1,2-*cis*-cyclohexanediol (6.3 mg, 0.054 mmol), K_3PO_4 (86 mg, 0.41 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **26** (65 mg, 84% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **26**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30−7.25 (2H, m), δ 7.03−6.96 (2H, m), δ 6.88 (1H, d, J = 15.4 Hz), δ 6.64 (1H, d, J = 15.4 Hz), δ 6.49 (1H, t, J = 1.6 Hz), δ 6.45 (1H, t, J = 13.6 Hz), δ 6.33 (1H, t, J = 2.2 Hz), δ 4.90 (1H, s), δ 3.83 (3H, s), δ 3.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 138.7, 131.1, 129.9, 126.6, 124.1, 122.0, 115.0, 113.2, 112.8, 105.4, 104.4, 100.8, 55.3. HRMS (ESI) $(M + H)^+$: calcd for $C_{16}H_{17}O_3S$ 289.0898, found 289.0895.

(*E*)-3-Methoxy-5-[2-(4-methoxyphenylsulfanyl)vinyl]phenol (27) (Table 4, Entry 2). General procedure B was followed (30 min to 1 h). Vinyl iodide **8** (100 mg, 0.27 mmol), 4-methoxybenzenethiol (44.9 mg, 0.32 mmol), CuI (5.2 mg, 0.027 mmol), 1,2-*cis*-cyclohexanediol (6.3 mg, 0.054 mmol), K_3PO_4 (86 mg, 0.41 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **27** (74 mg, 95% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **27**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (2H, d, J = 8.8 Hz), δ 6.93 (2H, d, J = 8.8 Hz), δ 6.81 (1H, d, J = 15.4 Hz), δ 6.43 (1H, t, J = 1.5 Hz), δ 6.38 (1H, d, J = 15.4 Hz), δ 6.38 (1H, t, J = 1.9 Hz), δ 6.29 (1H, t, J = 2.2 Hz), δ 4.84 (1H, s), δ 3.85 (3H, s), δ 3. 78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 159.6, 156.7, 138.9, 133.6, 129.3, 128.0, 126.8, 114.8, 105.2, 104.1, 100.4, 55.3. HRMS (ESI) $(M + H)^+$, Calcd. for $C_{16}H_{17}O_3S$ 289.0898; Found 289.0894.

(*E*)-3-[2-(4-Chlorophenylsulfanyl)vinyl]-5-methoxyphenol (28) (Table 4, Entry 3). General procedure B was followed (2 h). Vinyl iodide **8** (100 mg, 0.19 mmol), 4-chlorobenzenethiol (33 mg, 0.23 mmol), CuI (3.7 mg, 0.019 mmol), 1,2-*cis*-cyclohexanediol (4.4 mg, 0.038 mmol), K_3PO_4 (60 mg, 0.28 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **28** (53 mg, 96% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **28**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.28 (3H, m), δ 6.83 (1H, d, J = 14.8 Hz), δ 6.49−6.44 (2H, m), δ 6.39−6.36 (2H, m), δ 6.35 (1H, t, J = 2.2 Hz), 4.91 (1H, s), δ 3.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 156.6, 144.5, 139.7, 134.1, 131.6, 131.1, 129.3, 123.7, 108.1, 105.4, 101.5, 55.3. HRMS (ESI) $(M + H)^+$: calcd for $C_{15}H_{14}ClO_2S$ 293.0403, found 293.0402.

(*E*)-3-[2-(4-*tert*-Butylphenylsulfanyl)vinyl]-5-methoxyphenol (29) (Table 4, Entry 4). General procedure B was followed (30 min). Vinyl iodide **8** (100 mg, 0.19 mmol), 4-*tert*-butylbenzenethiol (38 mg, 0.23 mmol), CuI (3.7 mg, 0.019 mmol), 1,2-*cis*-cyclohexanediol (4.4 mg, 0.038 mmol), K_3PO_4 (60 mg, 0.28 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **29** (58 mg, 97% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **29**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.36 (2H, m), δ 7.30 (1H, d, J = 9.2 Hz), δ 6.85 (1H, dd, J = 15.0, J = 2.2 Hz), δ 6.57 (1H, d, J = 15.4 Hz), δ 6.47−6.36 (3H, m), δ 6. 37 (1H, t, J = 2.2 Hz), δ 5.11 (1H, s), δ 3.80 (3H, s), δ 1.35 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 156.7, 144.5, 138.9, 130.2, 129.8, 126.2, 125.4, 105.4, 104.4, 104.3, 101.5, 100.6, 55.3, 31.2. HRMS (ESI) $(M + H)^+$: calcd for $C_{19}H_{23}O_2S$ 315.1419, found 315.1421.

(*E*)-3-[2-(2-Isopropylphenylsulfanyl)vinyl]-5-methoxyphenol (30) (Table 4, Entry 5). General procedure B was followed (1 h).Vinyl

iodide **8** (140 mg, 0.27 mmol), 2-isopropylbenzenethiol (48.7 mg, 0.32 mmol), CuI (5.2 mg, 0.027 mmol), 1,2-*cis*-cyclohexanediol (6.3 mg, 0.054 mmol), K_3PO_4 (86 mg, 0.41 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **30** (78 mg, 96% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **30**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.21 (3H, m), δ 6.82 (1H, d, J = 14.8 Hz), δ 6.47−6.37 (4H, m), δ 6.31 (1H, t, J = 2.1 Hz), δ 5.05 (1H, br s), δ 3.80 (3H, s), δ 3.52−3.48 (1H, m), δ 1.27 (6H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 156.7, 148.8, 144.5, 138.9, 131.9, 129.6, 128.0, 126.5, 125.8, 125.5, 105.3, 104.2, 100.6, 55.3, 30.5, 23.4. HRMS (ESI) $(M + H)^+$: calcd for $C_{18}H_{21}O_2S$ 301.1262, found 301.1260.

(*E*)-2-[2-(3-Hydroxy-5-methoxyphenyl)vinylsulfanyl]benzoic Acid Methyl Ester (31) (Table 4, Entry 6). General procedure B was followed (30 min). Vinyl iodide **8** (100 mg, 0.19 mmol), benzenethiol-2-carboxylic acid methyl ester (38 mg, 0.23 mmol), CuI (3.7 mg, 0.019 mmol), 1,2-*cis*-cyclohexanediol (4.4 mg, 0.038 mmol), K_3PO_4 (60 mg, 0.28 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **31** (50 mg, 83% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **31**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (1H, d, J = 7.8 Hz), δ 7.46−7.38 (2H, m), δ 7.28−7.22 (1H, m), δ 6.97 (1H, d, J = 15.4 Hz), δ 6.88 (1H, d, J = 15.4 Hz), δ 6.60−6.57 (2H, m), δ 6.40 (1H, t, J = 2.2 Hz) δ 4.01 (1H, s), δ 3.97 (3H, s), δ 3.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 157.0, 140.9, 138.4, 136.1, 132.5, 131.2, 127.5, 125.8, 124.9, 122.1, 108.3, 105.9, 104.8, 101.3, 55.3, 52.3. HRMS (ESI) (M + H): calcd for $C_{17}H_{17}O_4S$ 317.0848, found 317.0850.

(*E*)-3-Methoxy-5-[2-(naphthalen-2-ylsulfanyl)vinyl]phenol (32) (Table 4, Entry 7). General procedure B was followed (1−2 h). Vinyl iodide **8** (100 mg, 0.19 mmol), 2-naphthylthiol (37 mg, 0.23 mmol), CuI (3.7 mg, 0.019 mmol), 1,2-*cis*-cyclohexanediol (4.4 mg, 0.038 mmol), K_3PO_4 (60 mg, 0.28 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **32** (54 mg, 92% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **32**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89−7.79 (4H, m), δ 7.53−7.49 (3H, m), δ 6.97 (1H, d, J = 15.4 Hz), δ 6.67 (1H, d, J = 15.4 Hz), δ 6.51 (1H, t, J = 1.6 Hz), δ 6.46 (1H, t, J = 1.9 Hz), δ 6.34 (1H, t, J = 2.2 Hz), δ 4.90 (1H, s, b), δ 3.80 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 156.8, 138.7, 133.7, 132.2, 131.1, 128.7, 128.4, 127.7, 127.2, 126.6, 126.1. 124.3, 105.4, 104.4, 100.9, 55.3. HRMS (EI): calcd for $C_{19}H_{16}O_2S$ 308.0871, found 308.0851.

(*E*)- 3-Methoxy-5-[2-(naphthalen-1-ylsulfanyl)vinyl]phenol (33) (Table 4, Entry 8). General procedure B was followed (1−2 h). Vinyl iodide **8** (100 mg, 0.19 mmol), 1-naphthylthiol (37 mg, 0.23 mmol), CuI (3.7 mg, 0.019 mmol), 1,2-*cis*-cyclohexanediol (4.4 mg, 0.038 mmol), K_3PO_4 (60 mg, 0.28 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **33** (53 mg, 91% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **33**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 8.3 Hz), δ 7.93−7.85 (2H, m), δ 7.72 (1H, d, J = 7.2 Hz), δ 7.60−7.56 (2H, m), δ 7.51−7.45 (1H, m), δ 6.87 (1H, t, J = 15.4 Hz), δ 6.49 (1H, d, J = 15.4 Hz), δ 6.43 (1H, s), δ 6.37 (1H, s), δ 6.30 (1H, t, J = 2.2 Hz), δ 5.16 (1H, s) δ 3.76 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 156.7, 138.8, 134.0, 130.4, 129.9, 128.9, 128.7, 128.5, 128.2, 126.8, 126.4, 125.7, 125.2, 125.1, 105.3, 104.3, 100.7, 55.3. HRMS (ESI) $(M + H)^+$: calcd for $C_{19}H_{17}O_2S$ 309.0949, found 309.0952.

(*E*)- 3-(2-Cyclohexylsulfanylvinyl)-5-methoxyphenol (34) (Table 4, Entry 9). General procedure B was followed (4 h). Vinyl iodide **8** (140 mg, 0.27 mmol), cyclohexanethiol (37.2 mg, 0.32 mmol), CuI (5.1 mg, 0.027 mmol), 1,2-*cis*-cyclohexanediol (6.3 mg, 0.054 mmol), K_3PO_4 (86 mg, 0.41 mmol), and DMF (2.0 mL) were stirred at 40−50 °C to obtain the thioether **34** (69 mg, 96% yield) as a colorless oil. Column chromatography solvent (3−5% EtOAc in hexane) provided pure **34**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (1H, d, J = 15.6 Hz), δ 6.49−6.40 (3H, m), δ 6.29 (1H, t, J = 2.1 Hz), δ 4.84 (1H, s), δ 3.80 (3H, s), δ 3.06−2.92 (1H, m), δ 2.08−1.65 (5H, m), δ 1.48−128 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6, 139.4, 127.7, 125.1, 105.0, 104.1, 101.5, 100.1, 55.3, 45.2, 33.5, 25.9, 25.5. HRMS (ESI) $(M + H)^+$: calcd for $C_{15}H_{21}O_2S$ 265.1262, found 265.1265.

(*E*)-3-[2-(Benzothiazol-2-ylsulfanyl)vinyl]-5-methoxyphenol (35) (Table 4, Entry 10). General procedure B was followed (8 h). Vinyl iodide **8** (140 mg, 0.27 mmol), benzothiazole-2-thiol (53.5 mg, 0.32 mmol), CuI (5.1 mg, 0.027 mmol), 1,2-*cis*-cyclohexanediol (6.3 mg, 0.054 mmol), K_3PO_4 (86 mg, 0.41 mmol) and DMF (2.0 mL) were stirred at 50−60 °C to obtain the thioether **35** (78 mg, 92% yield) as a light yellow solid. Column chromatography solvent (10% EtOAc in hexane) provided pure **35**. Mp: 137.6−142.2 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.93−7.86 (2H, m), δ 7.50 (1H, t, J = 7.2 Hz), δ 7.41−7.28 (2H, m), δ 7.05 (1H, d, J = 15.4 Hz), δ 6.60 (2 H, d, J = 6.1 Hz), δ 6.38 (1H, d, J = 2.2 Hz), 3.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 160.2, 157.7, 152.1, 137.4, 136.2, 133.9, 125.1, 123.3, 119.9, 115.1, 104.8, 102.4, 100.7, 100.0, 53.2. HRMS (ESI) $(M + H)^+$: calcd for $C_{16}H_{14}NO_2S_2$ 316.0466, found 316.0465.

(*E*)-3-Methoxy-5-[2-(pyrimidin-2-ylsulfanyl)vinyl]phenol (36) (Table 4, Entry 11). General procedure B was followed (8 h). Vinyl iodide **8** (140 mg, 0.27 mmol), pyrimidine-2-thiol (35.9 mg, 0.32 mmol), CuI (5.1 mg, 0.027 mmol), 1,2-*cis*-cyclohexanediol (6.3 mg, 0.054 mmol), K_3PO_4 (86 mg, 0.41 mmol), and DMF (2.0 mL) were stirred at 50−60 °C to obtain the thioether **36** (61 mg, 87% yield) as an yellow solid. Column chromatography solvent (10% EtOAc in hexane) provided pure **36**. Mp: 107.1−110.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (2H, d, J = 4.8 Hz), δ 7.56 (1H, d, J = 16.0 Hz), δ 7.06 (1H, t, J = 4.9 Hz), δ 6.75 (1H, d, J = 16.0 Hz), δ 6.55 (2H, d, J = 1.6 Hz), δ 6.35 (1H, t, J = 2.2 Hz) δ 6.09 (1H, s), δ 3.81 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 157.5, 157.0 138.4, 131.1, 119.9, 117.2, 106.7, 105.8, 104.6, 101.2, 55.3. HRMS (ESI) $(M + H)^+$: calcd for $C_{13}H_{13}N_2O_2S$ 261.0698, found 261.0696.

(*E*)- 3-Methoxy-5-[2-(pyridin-2-ylsulfanyl)vinyl]phenol (37) (Table 4, Entry 12). General procedure was B followed (4 h). Vinyl iodide **8** (100 mg, 0.19 mmol), pyridine-2-thiol (25 mg, 0.23 mmol), CuI (3.7 mg, 0.019 mmol), 1,2-*cis*-cyclohexanediol (4.4 mg, 0.038 mmol), K_3PO_4 (60 mg, 0.28 mmol), and DMF (2.0 mL) were stirred at 40−50 °C to obtain the thioether **37** (45 mg, 92% yield) as a colorless solid. Column chromatography solvent (10% EtOAc in hexane) provided pure **37**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (1H, d, J = 5.0 Hz), δ 7.59 (1H, t, J = 7.8 Hz), δ 7.38 (1H, d, J = 15.8 Hz), δ 7.29−7.27 (1H, m), δ 7.12−7.08 (1H, m), δ 6.77 (1H, d, J = 15.8 Hz) δ 6.51 (2H,d, J = 2.1 Hz), δ 6.34 (1H, t, J = 2.1 Hz), δ 6.14 (1H, br s), δ 3.79 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 157.9, 157.0, 149.6, 138.5, 136.6, 132.3, 122.3, 120.4, 120.0, 105.8, 104.5, 101.2, 55.2. HRMS (ESI) $(M + H)^+$: calcd for $C_{14}H_{14}NO_2S$ 260.0745, found 260.0744.

(*E*)- 3-Methoxy-5-[2-(thiophene-2-ylsulfanyl)vinyl]phenol (38) (Table 4, Entry 13). General procedure B was followed (4 h). Vinyl iodide **8** (100 mg, 0.19 mmol), 2-thiothiophene (27 mg, 0.23 mmol), CuI (3.7 mg, 0.019 mmol), 1,2-*cis*-cyclohexanediol (4.4 mg, 0.038 mmol), K_3PO_4 (60 mg, 0.28 mmol), and DMF (2.0 mL) were stirred at 40−50 °C to obtain the thioether **38** (43 mg, **86**% yield) as a colorless solid. Column chromatography solvent (10% EtOAc in hexane) provided pure **38**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (1H, m), δ 7.25 (1H, dd, J = 3.6, 1.3 Hz), δ 7.08 (1H, dd, J = 5.3, J = 3.6 Hz), δ 6.75 (1H, d, J = 15.4 Hz), δ 6.43−6.35 (3H, m), δ 6.30 (1H, t, J = 2.2 Hz), δ 5.21 (1H, s), δ 3.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 156.7, 138.5, 134.1, 130.3, 127.9, 127.8, 127.0, 125.3, 105.4, 104.3, 100.7, 55.3. HRMS (ESI) $(M + H)^+$: calcd for $C_{13}H_{13}O_2S_2$ 265.0357, found 265.0363.

Characterization Data for Products Shown in Table 5. (*E*)-*N*-[4-[2-(3-Cyanophenyl)vinylsulfanyl]phenyl]acetamide (40) (Table 5, Entry 1). General procedure A was followed (2 h). Vinyl iodide **39** (90 mg, 0.35 mmol), *N*-(4-mercaptophenyl)acetamide (70.2 mg, 0.42 mmol), CuI (6.7 mg, 0.035 mmol), 1,2-*cis*-cyclohexanediol (8.2 mg, 0.071 mmol), K_3PO_4 (112 mg, 0.53 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **40** (90 mg, 87% yield) as a light yellow solid. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **40**. Mp: 89.4−91.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (1H, s), δ 7.59−7.52 (3H, m), δ 7.49−7.37 (4H, m), δ 6.95 (1H, d, J = 15.4 Hz), δ 6.50−6.42 (1H, m), δ 2.21 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 138.1, 137.7, 132.5, 131.5, 130.2, 129.7, 129.4, 129.1, 128.7, 126.1, 123.9, 120.6, 118.6, 24.5. HRMS (ESI) (M + Li)$^+$: calcd for $C_{17}H_{14}N_2OSLi$ 301.0987, found 301.0988.

(*E*)-3-(2-*m*-Tolylsulfanylvinyl)benzonitrile (41) (Table 5, Entry 2). General procedure A was followed (1 h).Vinyl iodide **39** (90 mg, 0.35 mmol), 3-methylbenzenethiol (50.2 mg, 0.42 mmol), CuI (6.7 mg, 0.035 mmol), 1,2-*cis*-cyclohexanediol (8.2 mg, 0.071 mmol), K_3PO_4 (112 mg, 0.53 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **41** (74 mg, 84% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **41**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (1H, s), δ 7.55−7.48 (2H, m), δ 7.43 (1H, q, J=7.8 Hz, J=2.7 Hz), δ 7.31−7.28 (3H, m), δ 7.17−7.14 (1H, m), δ 7.01 (1H, d, J = 15.6 Hz), δ 6.57 (1H, d, J=15.6 Hz), δ 2.39 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 139.3, 137.8, 132.6, 131.4, 130.2, 129.7, 129.4, 129.1, 128.6, 127.9, 126.7, 124.1, 118.6, 112.8, 21.2. HRMS (EI) (M)$^+$: calcd for $C_{16}H_{13}NS$ 251.0769, found 251.0767.

(*E*)-3-[2-(3-Methoxyphenylsulfanyl)vinyl]benzonitrile (42) (Table 5, Entry 3). General procedure A was followed (2 h). Vinyl iodide **39** (100 mg, 0.39 mmol), 3-methoxybenzenethiol (66 mg, 0.47 mmol), CuI (7.4 mg, 0.039 mmol), 1,2-*cis*-cyclohexanediol (9.1 mg, 0.078 mmol), K_3PO_4 (124 mg, 0.59 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **42** (88 mg, 84% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **42**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (1H, s), δ 7.56−7.49 (2H, m), δ 7.44−7.39 (1H, m), δ 7.31 (1H, t, J = 8.1 Hz), δ 7.06−7.00 (3H, m), δ 7.02 (1H, d, J = 15.4 Hz), δ 6.61 (1H, d, J = 15.5 Hz), δ 3.84 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 137.7, 134.8, 132.7, 131.9, 130.4, 130.1, 129.8, 129.4, 129.1, 127.7, 127.3, 122.8, 116.1, 113.4, 55.3. HRMS (ESI) (M + Li)$^+$: calcd for $C_{16}H_{13}NOSLi$ 274.0878, found 274.0883.

(*E*)- 3-[2-(4-Methoxyphenylsulfanyl)vinyl]benzonitrile (43) (Table 5, Entry 4). General procedure A was followed (1 h). Vinyl iodide **39** (100 mg, 0.39 mmol), 4-methoxybenzenethiol (66 mg, 0.47 mmol), CuI (7.4 mg, 0.039 mmol), 1,2-*cis*-cyclohexanediol (9.1 mg, 0.078 mmol), K_3PO_4 (124 mg, 0.59 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **43** (90 mg, 86% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **43**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (1H, s), δ 7.49−7.43 (4H, m), δ 7.37 (1H, d, J = 7.6 Hz), δ 6.98−6.92 (3H, m), δ 6.33 (1H, d, J=15.5 Hz), δ 3.86 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 137.9, 134.4, 133.1, 132.0, 130.1, 129.9, 129.5, 129.3, 128.9, 124.6, 123.0, 115.0, 55.3. HRMS (ESI) (M + Li)$^+$: calcd for $C_{16}H_{13}NOSLi$ 274.0878, found 274.0881.

(*E*)-3-[2-(2-Isopropylphenylsulfanyl)vinyl]benzonitrile (44) (Table 5, Entry 5). General procedure A was followed (1 h). Vinyl iodide **39** (90 mg, 0.35 mmol), 2-isopropylbenzenethiol (64 mg, 0.42 mmol), CuI (6.7 mg, 0.035 mmol), 1,2-*cis*-cyclohexanediol (8.2 mg, 0.071 mmol), K_3PO_4 (112 mg, 0.53 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **44** (96 mg, 98% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **44**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55−7.46 (4H, m), δ 7.42−7.35 (3H, m), δ 7.28−7.22 (1H, m), δ 6.97 (1H, d, J = 15.4 Hz), δ 6.38 (1H, d, J = 15.4 Hz), δ 3.56−3.48 (1H, m), δ 1.28 (6H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.2, 137.9, 133.1, 130.1, 129.6, 129.3, 129.0, 128.9, 128.8, 126.7, 126.1, 125.8, 123.9, 118.6, 112.8, 30.7, 23.5. HRMS (EI) (M)$^+$: calcd for $C_{18}H_{17}NS$ 279.1082, found 279.1079.

(*E*)-2-[2-(3-Cyanophenyl)vinylsulfanyl]benzoic Acid Methyl Ester (45) (Table 5, Entry 6). General procedure A was followed (30 min). Vinyl iodide **39** (100 mg, 0.39 mmol), benzenethiol-2-carboxylic acid methyl ester (79 mg, 0.47 mmol), CuI (7.4 mg, 0.039 mmol), 1,2-*cis*-cyclohexanediol (9.1 mg, 0.078 mmol), K_3PO_4 (124 mg, 0.59 mmol), and DMF (2.0 mL) were stirred at 30−40 °C to obtain the thioether **45** (100 mg, 87% yield) as a colorless oil. Column chromatography solvent (2−3% EtOAc in hexane) provided pure **45**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (1H, d, J = 7.8 Hz), δ 7.71 (1H, s), δ 7.65−7.62 (1H, m), δ 7.58−7.47 (3H, m), δ 6.43−6.40 (1H, m), δ 7.32−7.28 (1H, m), δ 7.07−6.93 (2H, m), δ 3.96 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 139.6, 137.5, 132.5, 132.3, 131.2, 131.0, 130.3, 129.5, 129.2, 128.0, 126.0, 125.7, 125.5, 118.4, 113.0, 52.2. HRMS (ESI) (M + Li)$^+$: calcd for $C_{17}H_{13}NO_2SLi$ 302.0827, found 302.0821.

(*E*)-3-[2-(2-Methylbutylsulfanyl)vinyl]benzonitrile (46) (Table 5, Entry 7). General procedure A was followed (4 h). Vinyl iodide **39** (90 mg, 0.35 mmol), 2-methylbutane-1-thiol (43.8 mg, 0.42 mmol), CuI (55.0 mg, 0.035 mmol), 1,2-*cis*-cyclohexanediol (8.2 mg, 0.071 mmol), K_3PO_4 (112 mg, 0.53 mmol), and DMF (2.0 mL) were stirred at 40−50 °C to obtain the thioether **46** (75 mg, 93% yield) as a colorless oil. Column chromatography solvent (3−5% EtOAc in hexane) provided pure **46**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, s), δ 7.51−7.36 (3H, m), δ 6.86 (1H, d, J=15.6 Hz), δ 6.39 (1H, d, J = 15.4 Hz), δ 2.77 (2H, m), δ 1.77−1.70 (1H, m), 1.59−1.52 (1H, m), δ 1.36−1.26 (2H, m), δ 1.06−1.03 (3H m), δ 0.97−0.91 (3H m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 132.5, 129.8, 129.6, 129.3, 128.6, 123.0, 118.7, 112.7, 39.6, 34.7, 28.6, 18.8, 11.2. HRMS (ESI) (M + Li)$^+$: calcd for $C_{14}H_{17}NSLi$ 238.1242, found 238.1241.

(*E*)-3-[2-(6-Hydroxyhexylsulfanyl)vinyl]benzonitrile (47) (Table 5, Entry 8). General procedure A was followed (8 h).Vinyl iodide **39** (90 mg, 0.35 mmol), 6-mercaptohexan-1-ol (56.4 mg, 0.42 mmol), CuI (55.0 mg, 0.035 mmol), 1,2-*cis*-cyclohexanediol (8.2 mg, 0.071 mmol), K_3PO_4 (112 mg, 0.53 mmol), and DMF (2.0 mL) were stirred at 50−60 °C to obtain the thioether **47** (82 mg, 90% yield) as a colorless oil. Column chromatography solvent (3−5% EtOAc in hexane) provided pure **47**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (1H, s), δ 7.51−7.37 (3H, m), δ 6.86 (1H, d, J=15.6 Hz), δ 6.39 (1H, d, J= 15.6 Hz), δ 3.67 (2H, t, J = 6.4 Hz), δ 2.85 (2H, t, J = 7.2 Hz), δ 1.79−1.27 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 129.7, 129.3, 129.1, 128.6, 123.4, 118.2, 113.1, 62.7, 32.5, 32.3, 29.2, 28.4, 25.2. HRMS (ESI) (M + Li)$^+$: calcd for $C_{15}H_{19}NOSLi$ 268.1347, found 268.1344.

(*E*)-3-[2-(Pyrimidin-2-ylsulfanyl)vinyl]benzonitrile (48) (Table 5, Entry 9). General procedure A was followed (8 h). Vinyl iodide **39** (90 mg, 0.35 mmol), pyrimidine-2-thiol (47.1 mg, 0.42 mmol), CuI (6.7 mg, 0.035 mmol), 1,2-*cis*-cyclohexanediol (8.2 mg, 0.071 mmol), K_3PO_4 (112 mg, 0.53 mmol), and DMF (2.0 mL) were stirred at 50−60 °C to obtain the thioether **48** (72 mg, 86% yield) as an off-white solid. Column chromatography solvent (10% EtOAc in hexane) provided pure **48**. Mp: 85.0−87.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (2H, d, J=4.8 Hz), δ 7.84 (1H, d, J = 16.2 Hz), δ 7.75 (1H, s), δ 7.70−7.64 (1H, m), δ 7.56−7.53 (1H, m), δ 7.7 (1H, t, J=7.7 Hz), δ 7.10 (1H, t, J=4.8 Hz), δ 6.82 (1H, d, J=16.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 157.6, 137.6, 130.7, 130.3, 129.4, 129.3, 127.4, 123.5, 118.6, 117.4, 112.9. HRMS (ESI) (M + H)$^+$: calcd for $C_{13}H_{10}N_3S$ 240.0595, found 240.0598.

(*E*)-3-[2-(4,5-Dihydrothiazol-2-ylsulfanyl)vinyl]benzonitrile (49) (Table 5, Entry 10). General procedure A was followed (4 h). Vinyl

iodide **39** (90 mg, 0.35 mmol), 4,5-dihydrothiazole-2-thiol (50.1 mg, 0.42 mmol), CuI (6.7 mg, 0.035 mmol), 1,2-*cis*-cyclohexanediol (8.2 mg, 0.071 mmol), K_3PO_4 (112 mg, 0.53 mmol), and DMF (2.0 mL) were stirred at 40−50 °C to obtain the thioether **49** (78 mg, 90% yield) as a pale yellow solid. Column chromatography solvent (10% EtOAc in hexane) provided pure **49**. Mp: 72.0−74.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (1H, s), δ 7.62−7.53 (2H, m), δ 7.48 (1H, d, J = 3.0 Hz), δ 7.44 (1H, d, J = 5.2 Hz), δ 6.77 (1H, d, J = 16.0 Hz), δ 4.30 (2H, t, J = 8.1 Hz), δ 3.47 (2H, t, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.0, 131.1, 130.3, 129.6, 129.5, 129.4, 122.3, 118.4, 112.9, 64.3, 35.5, 29.6. HRMS (ESI) $(M + H)^+$: calcd for $C_{12}H_{11}N_2S_2$ 247.0364, found 247.0362.

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Supporting Information Available: Detailed experimental and characterization data for the compounds in Tables 6−10 including copies of the ^{1}H and ^{13}C for each (new and reported) compound. This material is available free of charge via the Internet at http://pubs.acs.org.