Mild, Efficient and Highly Stereoselective Synthesis of (*Z*)-Vinyl Chalcogenides from Vinyl Bromides Catalyzed by Copper(I) in Ionic Liquids Based on Amino Acids

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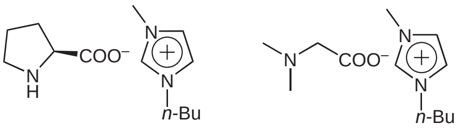
Abstract: A method for the synthesis of (*Z*)-vinyl chalcogenides by the coupling of vinyl bromides with thiols or diphenyl diselenide using copper(I) salts as catalysts in ionic liquids based on amino acids is reported. The desired vinyl chalcogenides were obtained in good to excellent yields with retention of stereochemistry. The ionic liquids play multiple roles in the reaction: they act as solvent, base, and excellent promoter for the copper-catalyzed coupling reactions.

Key words: ionic liquids, copper, coupling, stereoselective, vinyl chalcogenides

Vinyl sulfides and vinyl selenides are valuable synthetic intermediates in organic synthesis. They can be used as equivalents of carbonyl compounds[1] and Michael acceptors.[2] They are important intermediates in the stereoselective synthesis of functionalized alkenes.[3] Many natural products and compounds containing the vinyl sulfide or vinyl selenide moiety exhibit useful biological activities.[4] Conventionally, protocols for their preparations include the addition of heteroatom–hydrogen bonds to alkynes under free radical conditions[5] or catalyzed by transition metals,[6] Wittig olefination,[7] and direct nucleophilic substitution of vinyl halides.[8] Although these protocols provide access to vinyl chalcogenides, they suffer from harsh reaction conditions or lack of stereocontrol of the double bond geometry. The stereoselective synthesis of vinyl chalcogenides is of considerable interest to the academic world as well as to industry. Compared with the methods for the synthesis of (*E*)-vinyl chalcogenides,[5f,9,10] the strategies to obtain (*Z*)-vinyl chalcogenides are rather limited.[6d,11] One of the most valuable protocols to gain the stereospecific alkenes is the transition-metal-catalyzed cross-coupling reaction. The first example was reported by Murahashi and co-workers in 1979:[12] (*Z*)-β-bromostyrene was readily converted into the corresponding vinyl sulfides stereoselectively upon treatment with thiolate anions using tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] as catalyst. However, since then few reports have appeared in the literature for the formation of (*Z*)-vinyl chalcogenides bonds by cross-coupling of vinyl halides with thiols or selenols using transition-metal catalysts. Recently, Venkataraman reported a copper-catalyzed synthesis of (*E*)- and (*Z*)-vinyl sulfides via coupling reaction, but with vinyl iodides as substrates.[10] Ranu and co-workers also reported the synthesis of vinyl chalcogenides, using a simple one-pot procedure, which involved indium(I) iodide mediated cleavage of diphenyl diselenide and sulfide and subsequent reaction with vinyl bromides in the presence of Pd(0) catalyst.[11] Unfortunately, even though the conversion of (*E*)-vinyl bromides is remarkably stereoselective giving (*E*)-vinyl chalcogenides, the stereoselectivity of (*Z*)-vinyl bromides is not satisfactory. Thus a milder, more stereoselective and convenient methodology for the synthesis of (*Z*)-vinyl chalcogenides is worthy of exploration.

On the other hand, ionic liquids (ILs) as the novel ‘solutions’ for transition-metal catalysis have been extensively studied in recent years.[13] Various metal-catalyzed reactions including copper-catalyzed Ullmann reaction[14] and palladium-catalyzed Heck reaction,[15] have been demonstrated in ILs and excellent results have been obtained. As a continuation of our work in applications of ILs in Ullmann-type coupling reactions,[16] we report herein a mild, efficient and highly stereoselective synthesis of (*Z*)-vinyl chalcogenides from vinyl bromides catalyzed by copper(I) in ILs based on amino acids (Figure 1, **1** and **2**).



1 **2**

Figure 1 Structures of ILs based on amino acids

(*Z*)-β-Bromostyrene and thiophenol were selected as model partners for our first investigations on copper-catalyzed coupling reaction (Table 1). According to our previous experience in conducting coupling reactions of β-bromostyrene with imidazoles[16a] and thiols,[16b] we explored the coupling reaction initially by the following set of conditions: the coupling was conducted in IL [Bmim]BF_4 (Bmim: 1-butyl-3-methyl imidazolium) and catalyzed by 10 mol% of cuprous bromide (CuBr) and 20 mol% of L-proline at 110 °C in the presence of potassium carbonate. The reaction proceeded well and the vinyl sulfides were obtained in good yield, but the stereoselectivity was moderate (Table 1, entry 1, *Z*:*E* = 83:17).

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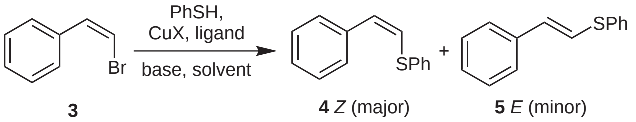
Table 1 Optimization of Reaction Conditions



Entry[a]	Solvent	CuX	Ligand	Temp (°C)	Product (*Z*:*E*)[c]	Yield (%)[d]
1	[Bmim]BF_4	CuBr	L-proline	110	83:17	82
2	[Bmim]BF_4	CuBr	L-proline	90	83:17	83
3	[Bmim]BF_4	CuBr	L-proline	60	83:17	80[e]
4	[Bmim]BF_4	CuI	L-proline	90	93:7	80
5	[Bmim]BF_4	CuI	*N*,*N*-dimethylglycine	90	93:7	87
6	[Bmim]BF_4	CuI	L-*N*-methylproline	90	90:10	60
7	[Bmim]BF_4	CuI	L-prolinol	90	96:4	65
8	[Bmim]BF_4	CuI	2-dimethylaminoethanol	90	86:14	80
9	DMF	CuI	*N*,*N*-dimethylglycine	90	85:15	56
10	1,4-dioxane	CuI	*N*,*N*-dimethylglycine	90	–	–[f]
11	**1**	CuI	–[b]	90	98:2	60
12	**2**	CuI	–[b]	90	98:2	90
13	**2**	CuBr	–[b]	90	95:5	85

[a] Reaction conditions: CuX (10 mol%), ligand (20 mol%), K_2CO_3 (2 mmol), vinyl bromide (1 mmol), thiol (1.1 mmol) in IL (2.4 g) for 16 h.
[b] The ligand and K_2CO_3 were not added.
[c] The ratio was based on the ^1H NMR spectrum (CH=CH).
[d] Isolated yield based on vinyl bromide.
[e] The reaction was run for 48 h.
[f] Very low amount coupling product was determined.

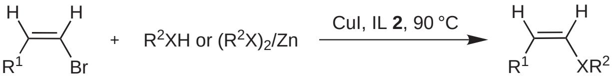
When the reaction was conducted at 90 °C, a similar result was obtained. Although the reaction took place smoothly at 60 °C, longer reaction time was needed and the yield was slightly lower (Table 1, entry 3). It seems that the different reaction temperatures have little effect on the stereoselectivity of the product. When copper(I) iodide (CuI) was used as a catalyst instead of CuBr, better stereoselectivity was detected (Table 1, entry 4). L-Proline was applied as an additive in this reaction at first and some other amino acids and their derivatives were also screened thereafter and proven effective (Table 1, entries 5–8). The best result was obtained with *N*,*N*-dimethylglycine (Table 1, entry 5). A slightly higher stereoselectivity was provided with L-prolinol but the reaction yield was only 65% (entry 7). Among the solvents tested, organic solvent *N*,*N*-dimethylformamide gave slightly lower yield and worse stereoselectivity of the product, while 1,4-dioxane delivered a very low amount of the desired coupling product (Table 1, entries 9 and 10). From the results exhibited above, it could be determined that the main factors affecting the reaction stereoselectivity were the kinds of CuX, ligand, and solvent used. The use of CuI as catalyst, *N*,*N*-dimethylglycine as ligand, and ionic liquid as solvent were the most efficient conditions for improving the reaction stereoselectivity. However, the results obtained with above conditions were not satisfactory. To simplify the catalyst system and facilitate the estimation of effects of other ions, we tried to use ionic liquids with amino acid as anion and imidazolium as cation (Figure 1, **1** and **2**) without the addition of other reagents. It was noteworthy that even though various ILs containing amino acid anions have been reported by Ohno and co-workers, their application in organic synthesis was not reported until now.[17] To the best of our knowledge, there has been only one example on the application of amino acid ILs in Diels–Alder reactions reported so far.[18] The ILs based on amino acids (**1** and **2**) were readily prepared according to the literature.[17a] Interestingly, when the reaction was conducted in IL **2** based on *N*,*N*-dimethylglycine, high stereoselectivity and excellent reaction yield were obtained (Table 1, entry 12). When IL **1** based on L-proline was used instead of **2**, the same stereoselectivity was obtained while a lower reaction yield was detected (entry 11). Compared with CuBr, the catalyst CuI gave the better results. Thus, CuI and IL **2** based on *N*,*N*-dimethylglycine at 90 °C is the most efficient and stereoselective catalytic conditions for this coupling reaction.

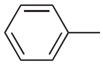
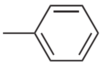
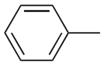
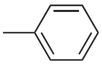
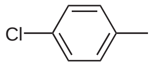
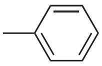
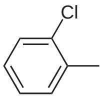
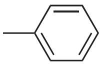
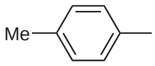
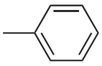
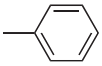
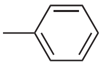
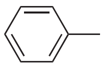
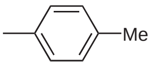
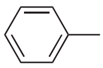
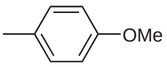
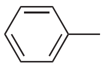
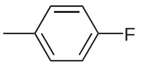
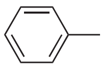
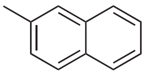
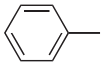
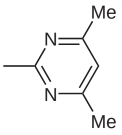
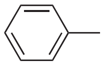
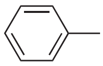
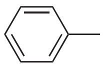
After optimized reaction conditions were set, the reaction scope was explored with various vinyl bromides and other thiols or diphenyl diselenide. The results are summarized in Table 2. Vinyl bromide coupled with both aromatic and aliphatic thiols in good to excellent yields, although longer reaction times were needed for the aliphatic thiols. Both electron-rich and electron-poor thiols were readily reacted with the vinyl bromide under this protocol. For the reaction of 2-mercapto-*N*-phenylacetamide with both amido and thiol groups, the thiol group coupled preferentially with vinyl bromide and no cross-coupling between vinyl bromide and amido group was observed (Table 2, entry 15), therefore amido-protection is not necessary. It was found that both the electron-rich and the electron-deficient vinyl bromides were suitable for this reaction, giving the desired coupling products in excellent yields and high stereoselectivities (Table 2, entries 3–5). Significantly, the alkyl vinyl bromide bearing aliphatic chain also gave good yields, though not as good as those with aryl derivatives (Table 2, entries 6 and 7). Since selenols are unstable, sensitive to air and possess high toxicity and that generally the diselenides are used in the organoselenation reactions, diphenyl diselenide was chosen as the starting material for the synthesis of vinyl selenides. Both aromatic and aliphatic vinyl bromides coupled with diphenyl diselenide in the presence of zinc powder in good yields and also high stereoselectivities (Table 1, entries 2 and 7).

Almost stereospecific (*Z*)-4-chloro-β-phenylthiostyrene was obtained when (*Z*)-4-chloro-β-bromostyrene was coupled with thiophenol (according to ^{1}H NMR spectra). For the coupling of (*Z*)-β-bromostyrene with phenylmethanethiol the product ratio of *Z* to *E* isomer was 98:2 (from ^{1}H NMR spectra). When diphenyl diselenide was used as the substrate, the *Z* to *E* product ratio was 96:4 (from ^{1}H NMR spectra).

Another merit of ILs in the metal-catalyzed reaction is that the metal catalysts immobilized in these media can be reused. To evaluate the possibility of recycling, (*Z*)-β-bromostyrene, thiophenol and CuI in IL **2** were allowed to react in the ionic solvent for 16 hours and then the products were extracted with diethyl ether (3 × 2 mL). After the recovered ionic solvent was concentrated in vacuo (5.0 torr for 1.5 h at 60 °C), further amounts of reactants were added and the process was repeated three times, until the by-product from hydrogen bromide neutralized by IL rendered the mixture in a solid-like state at room temperature. It seems that there was little effect on the rate or yield of the reaction during each cycle (Table 3). Further treatment of the solid-like mixture was as follows.[16d] The mixture was dissolved in acetone (8 mL) in the presence of potassium carbonate (6 mmol). After stirring for two hours, the solid was filtrated and then the acetone was evaporated under reduced pressure. The recovered ionic solvent was concentrated in vacuo (5.0 torr for 1.5 h at 60 °C), further amounts of reactions were added and the process was repeated. The reuse of IL–CuI system with selenide could be successfully achieved in a similar process.[16d]

Table 2 (*Z*)-Vinyl Chalcogenides Synthesized Using the Standard Protocol



Entry[a]	R^1	R^2	X	Product (Z:E)[c]	Time (h)	Yield (%)[d]
1			S	98:2	16	90
2			Se[b]	98:2	24	85
3			S	>99	16	93
4			S	98:2	16	91
5			S	94:6	16	87
6	*n*-Pr		S	92:8	16	76
7	*n*-Pr		Se[b]	96:4	24	70
8			S	96:4	16	89
9			S	95:5	16	90
10			S	94:6	16	85
11			S	98:2	16	90
12			S	>99	16	82
13		CH_2Ph	S	98:2	20	84
14		CH_2COOEt	S	94:6	20	88
15		$CH_2CONHPh$	S	>99	20	78

[a] Reaction conditions: CuI (10 mol%), vinyl bromide (1 mmol), thiol (1.1 mmol) in IL **2** (2.4 g) at 90 °C.

[b] Diphenyl diselenide (0.55 mmol) and Zn (1.5 mmol) were used instead of thiol.

[c] The ratio was based on the ^{1}H NMR spectrum (CH=CH).

[d] Isolated yield based on vinyl bromide.

Table 3 Reuse of CuI–IL Reaction System

Cycle[a]	Product (*Z*:*E*)[b]	Yield (%)[c]	Cycle	Product (*Z*:*E*)	Yield (%)
1	98:2	90	3	98:2	84
2	98:2	89	4	98:2	85[d]

[a] Reaction conditions: CuI (10 mol%), (*Z*)-β-bromostyrene (1 mmol), thiolphenol (1.1 mmol) in IL **2** (2.4 g) at 90 °C.
[b] The ratio was based on the ^{1}H NMR spectrum (CH=CH).
[c] Isolated yield based on (*Z*)-β-bromostyrene.
[d] Yield of the reaction after the IL–CuI system was treated with K_2CO_3 in acetone.

In summary, we have developed a mild, efficient and comparatively cheap methodology for the synthesis of (*Z*)-vinyl chalcogenides by coupling vinyl bromides with thiols or diphenyl diselenide in a highly stereoselective manner using CuI as catalyst. The reaction was conducted only in ionic liquids and no base or other additives were needed. The best results were obtained in the ionic liquid based on *N*,*N*-dimethylglycine with the retention of stereochemistry. The ionic liquid **2** played multiple roles in this reaction system, such as a high polar solvent to improve the reaction yield, an excellent promoter for the copper(I)-catalyzed coupling reaction, and a based to neutralize the by-product HBr. Additionally, the reaction avoided the use of palladium and/or expensive additives and vinyl iodides.

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