JOC*Note*

Stereoselective Hydroxycarbonylation of Vinyl Bromides to α,β-Unsaturated Carboxylic Acids in the Ionic Liquid [BMIM]PF_6

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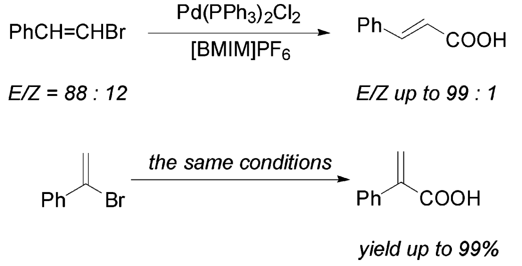

(*E*/*Z*)-Isomers containing vinyl bromides were stereoselectively carbonylated to the corresponding (*E*)-α,β-ethylenic carboxylic acids in the ionic liquid [BMIM]PF_6. Vinyl dibromides also underwent hydroxycarbonylation to give monoacids. The products are pure by proton NMR spectroscopic determination without purification by silica gel column chromatograghy or recrystallization.

(*E*)-α,β-Ethylenic carboxylic acids are not only versatile synthons, but also exist widely in natural products, for example, honeybee[1] and caffeir acid,[2] and in biologically active molecules such as (*E*)-2-methyl-3-(4-(myristyloxy)-phenyl)-prop-2-enoic acid.[3] Some methods have been developed to produce stereospecific α,β-unsaturated carboxylic acids from different substrates such as aldehydes,[4] alkynes,[5] aryl iodides,[6] and so on. Transition-metal-catalyzed carbonylation is of significant importance to form the carbonyl group in a wide range of molecules. Specifically, vinyl bromides were employed as starting materials, affording the corresponding α,β-unsaturated acids by transition-metal-catalyzed carbonylation, usually in the presence of water. For instance, Miura and co-workers realized the transformation of (*E*)- or (*Z*)-α,β-vinyl halides to (*E*)- or (*Z*)-α,β-unsaturated acids using nickel and cobalt complexes as the catalysts.[7] In 1989, our group successfully used phase-transfer catalysis to effect stereospecific carbonylation of (*E*)-α,β-vinyl bromides and some unsaturated chlorides to make (*E*)-α,β-unsaturated acids.[8] To our knowledge, until recently only a few stereospecific α,β-vinyl bromides had been used, and the reported catalysts could not be recycled in the reactions.

One of the increasing areas of green chemistry is focused on room-temperature ionic liquids to protect human health and the environment as a result of their features of low vapor pressure and ease of handling. Recently, many reactions have been carried out in ionic liquids, such as Heck,[9c,d] Suzuki,[9e] Sonogashira,[9f] Stille, Ullmann,[9g] Diels−Alder,[9h] Trost−Tsuji,[9i] aldol,[9j] hydrogenation,[9k] oxidation,[9l] carbonylation,[9m−o] and oligomerization reactions.[9] Although some satisfactory results were obtained, ionic liquids as attractive clean reaction media have not achieved their full potential. Transition-metal-catalyzed cross-coupling reactions in ionic liquids have been reported from our laboratories.[10] In this note, we describe the hydroxycarbonylation of vinyl bromides to the corresponding α,β-unsaturated carboxylic acids in the ionic liquid [BMIM]PF_6.

β-Bromostyrene (**1a**) containing (*E*)- and (*Z*)-isomers (*E*/*Z* = 88:12) was chosen as the model substrate to examine the hydroxycarbonylation reaction with 10 bar of CO using 3 mol % $Pd(PPh_3)_4$ as the catalyst in the ionic liquid [BMIM]PF_6 at 100 °C for 5 h. The product cinnamic acid (**2a**) was obtained in good yield (82%) with an *E*/*Z* = 96:4 molar ratio, as determined by ^1H NMR spectroscopy. Unfortunately, the catalyst cannot be recycled. Increasing the loading of the catalyst

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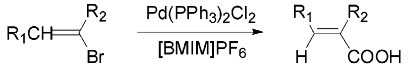
TABLE 1. Stereoselective Hydroxycarbonylation of Vinyl Bromides in [BMIM]PF$_6$

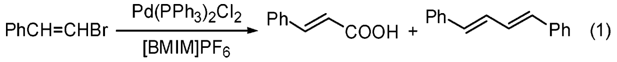


1 **2**

run^a	R$_1$ (R$_2$ = H)		E/Z^b in **1**	cycle no.	yield of **2** (%)	E/Z^b
1	Ph	**1a**	88:12	1	68	95:5
				2	79	97:3
				3	80	98:2
				4	55	99:1
				5	54	98:2
2	4-Me-C$_6$H$_4$	**1b**	95:5	1	84	E
				2	94	E
				3	99	E
				4	94	E
				5	53	E
3	thiophen-2-yl	**1c**	83:17	1	66	88:12
				2	80	99:1
				3	87	99:1
				4	63	97:3
				5	66	97:3

^{a} Reaction conditions: bromide (2 mmol); H_2O (0.18 mL, 10 mmol); Et_3N (0.57 mL, 4 mmol); catalyst, $Pd(PPh_3)_2Cl_2$ (5 mol %); CO (20 bar); 100 °C; [BMIM]PF$_6$ (2.0 g). Reaction times of cycles 1−5: 10, 10, 10, 16, and 24 h, respectively. After three runs, 0.5 g of fresh ionic liquid was added to the reaction system. ^{b} *E*/*Z* molar ratios were determined by ^{1}H NMR.

to 5 mol % to make the catalyst partially recyclable led to less than 60% yield for the desired product in the first and third runs. When the air-stable and less-active catalyst, $Pd(PPh_3)_2Cl_2$, was used, the hydroxycarbonylation reaction of **1a** had to be carried out with 20 bar of CO using 5 mol % of the catalyst in [BMIM]PF$_6$ at 100 °C for 10 h. The product, that is, the acid **2a**, was obtained in 68% yield (*E*/*Z* = 95:5; eq 1, Table 1, run 1). However, the yields were higher in the second and third runs than that in the first run with better *E*/*Z* molar ratios (97:3 and 98:2). In the fourth and fifth runs, the yields were reasonable and the *E*/*Z* molar ratios were still excellent (*E*/*Z* = 99:1 and 98:2). That unsaturated acid **2a** was only obtained in moderate to good yields (eq 1, runs 1−5 in Table 1), is attributed to the self-coupling of **1a** to 1,4-diphenyl-1,3-butadiene (**3a**; e.g., 18% yield in the first run, eq 1).[11] Along with recycling, the activity of the catalyst decreased in an ionic liquid so that the coupling of **1a** itself was reduced. The yields of **2a** in the fourth and fifth runs were lower than those in the second and third runs and attributed to incomplete conversion of **1a** by TLC analysis. Other substrates were also tested under the same reaction conditions. 4-Methylphenyl vinyl bromide (**1b**) was completely converted to the corresponding (*E*)-unsaturated acid (**2b**) in 84% yield (Table 1, run 2). When thiophen-2-yl vinyl bromide (*E*/*Z*, 83:17; **1c**) was treated by the same method, similar results were obtained (Table 1, run 3).



1a **2a** **3a**

E/Z = 88:12   E/Z = 95:5   (E, E)/(E, Z) = 96:4

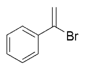
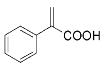
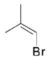
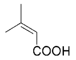
68%   18%

TABLE 2. Stereoselective Hydroxycarbonylation of Vinyl Bromides in [BMIM]PF$_6$

run^a	R$_1$	R$_2$		E/Z^b in **1**	cycle no.	yield of **2** (%)	E/Z^b
1	4-MeO−C$_6$H$_4$	H	**1d**	94:6	1	67	E
					2	99	E
					3	92	E
2^c	2-MeO−C$_6$H$_4$	H	**1e**	E	1	70	E
					2	92	E
3	4-Cl−C$_6$H$_4$	H	**1f**	93:7	1	48	E
					2	76	E
					3	26	E
4^c	2-Me-C$_6$H$_4$	H	**1g**	E	1	64	E
					2	91	E
					3	63	E
5	naphth-1-yl	H	**1h**	E	1	65	E
					2	92	E
					3	87	E
6^c	Ph	Me	**1i**	59:41	1	64	67:33

^{a} Reaction conditions: bromide (2 mmol); H_2O (5 equiv); Et_3N (2 equiv); catalyst, $Pd(PPh_3)_2Cl_2$ (5 mol %); CO (20 bar); 100 °C; reaction time, 10 h for each cycle; [BMIM]PF$_6$ (2.0 g). ^{b} *E*/*Z* molar ratios were determined by ^{1}H NMR. ^{c} Bromide concentration (1 mmol).

TABLE 3. Hydroxycarbonylation of Stereospecific Vinyl Bromides in [BMIM]PF$_6$

run^a	bromide		product		cycle no.	yield (%)
1		**4a**		**5a**	1	85
					2	90
					3	99
					4	98
					5	99
2		**4b**		**5b**	1	26
					2	56
					3	41

^{a} Reaction conditions: bromide (2 mmol); H_2O (0.18 mL, 10 mmol); Et_3N (0.57 mL, 4 mmol); catalyst, $Pd(PPh_3)_2Cl_2$ (5 mol %); CO (20 bar); 100 °C. Reaction times of cycles 1−5: 10, 10, 10, 16, and 24 h, respectively. [BMIM]PF$_6$ (2.0 g). After three runs, 0.5 g of fresh ionic liquid was added to the reaction system.

The hydroxycarbonylation of a number of other (*E*/*Z* or *E*) vinyl bromides was next investigated under similar conditions. The results are summarized in Table 2. The configuration of the acids is retained during the reaction in the ionic liquid (Table 2, runs 2, 4, and 5). When (*E*)- and (*Z*)-isomers containing vinyl bromides were carbonylated, they were efficiently transformed stereospecifically to the (*E*)-acids (Table 2, runs 1 and 3). However, it is difficult to afford α,*β*-unsaturated carboxylic acids in high *E*/*Z* molar ratios when the *E*/*Z* molar ratio of the isomers in the starting bromides is close to 3:2 (Table 2, run 6). The methodology was next extended to α-bromostyrene (**4a**) with CO under the stated conditions to give 2-phenyl-2-propenoic acid (**5a**) in excellent yield for each of five cycles (Table 3, run 1). In contrast, alkyl vinyl bromide **4b** was much less reactive to generate the corresponding α,*β*-unsaturated carboxylic acid **5b** (Table 3, run 2).

Previously, we obtained diacids from vinyl dibromides in excellent yields in the polar solvent, *t*-AmOH, by phase-transfer catalysis.[12] When this reaction was run in an ionic liquid to produce diacids, only monoacids instead of diacids were obtained in 2:1.0 to 3:1.0 = *E*/*Z* selectivity (Table 4). It is conceivable that the vinyl dibromides were initially carbonylated to the corresponding diacids **8** (eq 2), and under the relatively

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(11) After the reaction, the ionic liquid phase was extracted with diethyl ether. The solvent was dried under reduced pressure to give the crude residue. Compound **3a** was isolated in 18% yield by preparative TLC plate, using hexane/AcOEt (5:1, v/v) as the developer.

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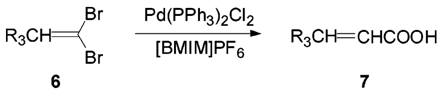
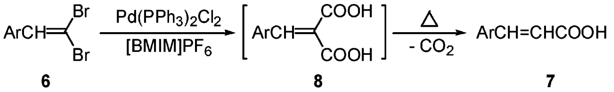
TABLE 4. Hydroxycarbonylation of Vinyl Dibromides in [BMIM]PF_6



run[a]	R_3		cycle no.	yield (%)	*E*/*Z*[b]
1	Ph	**6a**	1	66	69:31
			2	80	76:24
2	4-Me-C_6H_4	**6b**	1	62	73:27
			2	80	
			3	73	

[a] Reaction conditions: bromide (1 mmol); H_2O (5 equiv); Et_3N (4 equiv); catalyst, $Pd(PPh_3)_2Cl_2$ (5 mol %); CO (20 bar); 100 °C; reaction time, 10 h in each cycle; [BMIM]PF_6 (2.0 g). [b] *E*/*Z* molar ratios were determined by ^1H NMR.

harsh conditions, diacids **8** were easily decarboxylated to form the monoacids **7** in modest stereoselectivity.



(2)

In conclusion, vinyl bromides (isomeric *E*/*Z* ≥ 5:1) can be carbonylated in good yields to the corresponding α,β-unsaturated carboxylic acids with excellent *E*/*Z* stereoselectivity (up to 99:1) in the ionic liquid, [BMIM]PF_6. The products are pure by ^1H NMR spectroscopy without any column chromatography or recrystallization. Vinyl dibromides afforded only monoacids under the stringent conditions. Some of the reactions can be recycled up to five times (e.g., **4a**).

Experimental Section

Typical Procedure for the Hydroxycarbonylation of β-Bromostyrene in the Ionic Liquid [BMIM]PF_6. In a 45-mL autoclave containing a glass liner was added $Pd(PPh_3)_2Cl_2$ (5 mol %), [BMIM]PF_6 (2.0 g), β-bromostyrene (2 mmol), water (0.18 mL, 10 mmol), Et_3N (0.57 mL, 4 mmol), and a magnetic stirring bar. The autoclave was flushed three times with CO and then pressurized to 20 bar of CO. The mixture was heated at 100 °C for 10 h. The resulting solution was extracted with water (3 mL × 4). The aqueous phase was acidified with aqueous hydrochloric acid (0.25 M) and extracted with diethyl ether (20 mL × 3). The ether phases were combined, dried over anhydrous $MgSO_4$, and filtered through Celite. Concentration under reduced pressure gave the pure products. The ionic liquid phase was washed with 3 mL of diethyl ether, and fresh starting material was added to perform a second run reaction under the same conditions. The reaction times for runs 2−5 were 10, 10, 16, and 24 h, respectively. After three runs, 0.5 g of fresh ionic liquid was added. The products were characterized by NMR and MS, and a comparison was made with authentic samples. The *E*/*Z* molar ratios were determined by ^1H NMR spectroscopy.

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Supporting Information Available: General considerations, spectral data, and copies of ^1H and $^{13}C\{^1H\}$ NMR spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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