Palladium-Catalyzed Amidocarbonylation Improved by Recyclable Ionic Liquids

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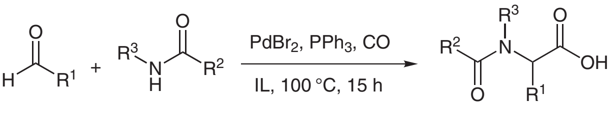
Abstract: Two types of ionic liquids (halide anion ionic liquids and Brønsted acidic ionic liquids) were first applied to improve the palladium-catalyzed amidocarbonylation. Both the palladium catalyst and the ionic liquids could be recycled at least five times without significant loss in catalytic activity.

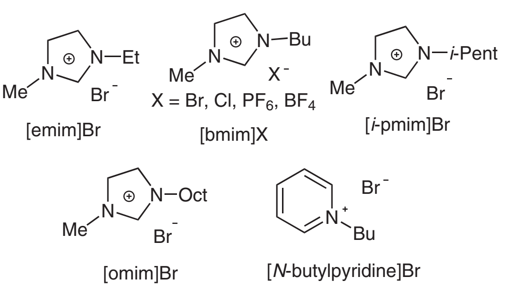
Key words: amidocarbonylation, ionic liquids, amino acids, palladium, catalysis



Equation 1

Amino acids and their derivatives are unequivocally one of the most important classes of organic compounds.[1] The transition-metal-catalyzed three-component reaction of aldehydes, amides, and carbon monoxide, so-called amidocarbonylation, is a versatile one step approach to the synthesis of racemic *N*-acyl-α-amino acids. Cobalt catalysts were originally discovered by Wakamatsu and coworkers[2] in the early 1970s, and then palladium catalyst systems consisting of main catalyst ($PdCl_2$ or $PdBr_2$), ligand (PPh_3), co-catalysts (LiBr and H_2SO_4) and polar solvent NMP (*N*-methylpyrrolidone) were revealed.[3] Recently, the catalytic activities of rhodium, iridium, ruthenium and platinum in amidocarbonylation were also reported.[4] Among these transition metals, the most active metal so far is palladium, although palladium catalysts are expensive and unrecoverable in many cases. To solve these problems the heterogeneous catalyst Pd/C in amidocarbonylation was reported by Beller et al.[5] and another heterogeneous catalyst (polymer-incarcerated palladium) was reported by Akiyama et al.[6] The heterogeneous catalyst can be recovered by filtering but there is no experimental evidence to show the reuse of these catalysts. Recently our group[7] has developed a new heterogeneous HZSM-5-supported palladium catalyst, which can be recovered and reused in amidocarbonylation by simple filtration. The other components of the catalyst system, however, could not be recycled. An attempt was made to search a novel environmentally benign and economic way to recycle the catalyst system for amidocarbonylation. The application of ionic liquids (ILs) would be a suitable choice.

Ionic liquids are emerging as a set of green solvents with unique properties such as good solvating ability, wide liquid range, tunable polarity, negligible vapor pressure, high thermal stability and ease of recyclability.[8] They are attractive especially for the immobilization of transition-metal-based catalysts, Lewis acids and enzymes.[9] Specifically functionalized ionic liquids, such as Brønsted acidic ionic liquids have been reported recently to serve as both reaction medium and catalysts.[10] The properties of ionic liquids can be tailored by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and the length of alkyl chain. Hence, there is significant interest in using ionic liquids as replacements of conventional organic solvents. However, there are no examples of the use of ionic liquids as solvents for the amidocarbonylation so far.



Scheme 1

In the present study, we would like to report, for the first time, the use of halide anion ionic liquids as solvent and halide ions co-catalyst, and the use of Brønsted acidic ionic liquids as strong acid co-catalyst instead of sulfuric acid in the palladium-catalyzed amidocarbonylation (Equation 1).

Several halide anion ionic liquids (Scheme 1) and Brønsted acidic ionic liquids (Scheme 2) were examined. Meanwhile the catalyst system, $PdBr_2$–PPh_3–ILs, could be directly reused after products separation.

Preliminary results to evaluate the performance of the two types of ionic liquids in amidocarbonylation are summarized in Table 1. The special significance of halide ions as co-catalyst for palladium-catalyzed amidocarbonylation[3]

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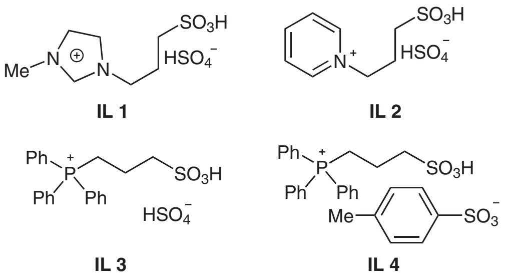
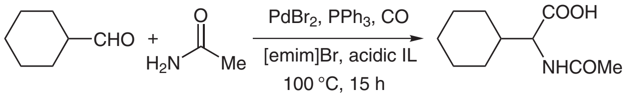


Scheme 2



Equation 2

suggests that ionic liquids with halide anions could be used as both reaction medium and halide ions co-catalyst. Investigations showed that the use of bromide anion ionic liquids, such as [emim]Br, as solvent afford activities as high as NMP in palladium-catalyzed amidocarbonylation. In the reaction of cyclohexanecarboxaldehyde with acetamide in [emim]Br (Equation 2), the corresponding *N*-acetylcyclohexylglycine can be obtained in 84% yield (Table 1, entry 1). The addition of 35 mol% lithium bromide to the catalyst system gave 85% yield (Table 1, entry 2); hence, the increase in yield was negligible. This demonstrated that the presence of halide ions co-catalyst could be omitted by using halide anion ionic liquids. Among the Brønsted acidic ionic liquids tested, Brønsted acidic IL **1** gave the best result (Table 1, entries 5–8). Brønsted acidic IL **2** showed good performance only when used with [*N*-butylpyridine]Br (Table 1, entry 11). When sulfuric acid was used as strong acid co-catalyst instead of Brønsted acidic ionic liquids, the amidocarbonylation yield decreased significantly (Table 1, entry 4). This indicated that Brønsted acidic ionic liquids showed much better compatibility with halide anion ionic liquids than sulfuric acid did. Ionic liquids with short alkyl-chain substituents displayed better performance, the order of activity is ranked as follows: [emim]Br > [bmim]Br, [*N*-butylpyridine]Br > [*i*-pmim]Br > [omim]Br (Table 1, entries 1, 5 and 9–11). The use of halide-free ionic liquids, for instance [bmim]PF_6 and [bmim]BF_4, as solvent resulted in no product, even though lithium bromide was added (Table 1, entries 13 and 14). In addition, the catalyst system showed no catalytic activity when Brønsted acidic ionic liquids, such as Brønsted acidic IL **1,** were used as solvent (Table 1, entry 15).

The major advantage of the use of ionic liquids as reaction media and co-catalysts is that this catalytic system can be easily recovered and recycled in subsequent runs. The reusability of the catalytic system was tested in the amidocarbonylation of cyclohexanecarboxaldehyde. The results are presented in Table 2.

Table 1 Amidocarbonylation of Cyclohexanecarboxaldehyde in Ionic Iiquids[a]

Entry	Solvent	Brønsted acidic IL	Additive	Yield (%)[b]
1	[emim]Br	IL **1**	–	84
2	[emim]Br	IL **1**	LiBr (35 mol%)	85
3	[emim]Br	IL **1**	*N*-acetylcyclohexylglycine (3 mol%)	87
4[c]	[bmim]Br	H_2SO_4	–	27
5	[bmim]Br	IL **1**	–	75
6	[bmim]Br	IL **2**	–	10
7	[bmim]Br	IL **3**	–	71
8	[bmim]Br	IL **4**	–	19
9	[*i*-pmim]Br	IL **1**	–	53
10	[omim]Br	IL **1**	–	38
11	[*N*-butylpyridine]Br	IL **2**	–	70
12	[bmim]Cl	IL **1**	LiBr (35 mol%)	29
13	[bmim]PF_6	IL **1**	LiBr (35 mol%)	–
14	[bmim]BF_4	IL **1**	LiBr (35 mol%)	–
15[d]	IL **1**	IL **1**	LiBr (35 mol%)	–

[a] Reagents and conditions: Cyclohexanal (20 mmol), acetamide (22 mmol), $PdBr_2$ (0.2 mmol), PPh_3 (0.2 mmol), Brønsted acidic IL (2 mmol), ionic liquids solvent (25 mL), CO (60 bar), at 100 °C for 15 h.
[b] Isolated yield.
[c] H_2SO_4 (0.6 mmol).
[d] Brønsted acidic IL **1** was used as solvent.

After each run, the *N*-acyl-α-amino acid products were removed by tetrahydrofuran extraction. The rest of the ILs and catalyst were recovered and reused in the next cycle without further addition of [emim]Br, $PdBr_2$ and PPh_3 in each alternative run. As shown in Table 2, the yields gradually increased from cycles 1 to 3 and then decreased from cycles 4 to 5. The maximum conversion was obtained in cycle 3. This is probably because the *N*-acyl-α-amino acid remaining in the ionic liquid solvent improved the reaction yield in the recycled runs. This is also in accordance with the result (Table 1, entry 3) that the addition of 3 mol% *N*-acetylcyclohexylglycine to the catalyst system gave increased yields. Compared to conventional solvents, the solubility of gases in ionic liquids is generally high.[11] The increased solubility of carbon monoxide in the ionic liquids is another advantage of the use of ionic liquids as solvent. Meanwhile the catalyst system remained yellow throughout the whole recycling, suggesting that the catalyst remained intact. The catalyst/ionic liquids solution could be reused at least five times without significant loss in catalytic activity.

To establish the generality of the present protocol, a variety of aldehydes was examined, and the obtained results

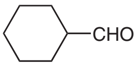
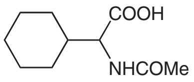
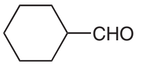
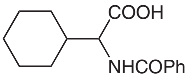
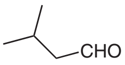
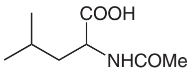
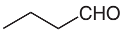
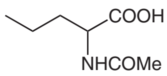
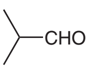
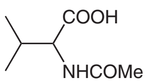
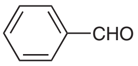
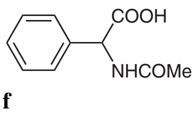
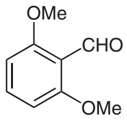
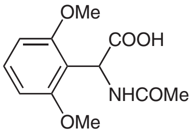
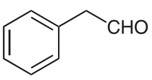
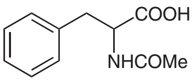
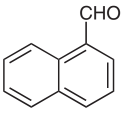
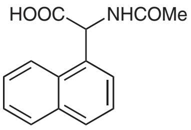
Table 2 Recyclability of $PdBr_2$–PPh_3–[emim]Br for Amidocarbonylation of Cyclohexanecarboxaldehyde[12]

Cycle	0	1	2	3	4	5
Yield (%)[a]	82 (84)	86	89	91	87	82

[a] Extracted yield; isolated yield is given in parentheses.

are summarized in Table 3. Under the optimized reaction conditions, a wide range of aldehydes underwent the catalytic amidocarbonylation in ionic liquids to produce the corresponding *N*-acyl-α-amino acids. All aliphatic and aromatic aldehydes tested here gave amidocarbonylation products in moderate to good yields.

Table 3 Amidocarbonylation of Aldehydes in [emim]Br[a]

Entry	Aldehyde	Product	Yield (%)[b]
1		 **a**	84
2		 **b**	82
3		 **c**	63
4		 **d**	56
5		 **e**	60
6		 **f**	53
7		 **g**	47
8		 **h**	41
9		 **i**	52

[a] Reagents and conditions: Aldehyde (20 mmol), amide (22 mmol), $PdBr_2$ (0.2 mmol), PPh_3 (0.2 mmol), Brønsted acidic IL **1** (2 mmol), [emim]Br (25 mL), CO (60 bar), at 100 °C for 15 h.
[b] Isolated yield.

In conclusion, the current study presents the realization of palladium-catalyzed amidocarbonylation improved by two types of ionic liquids. Halide anion ionic liquids were used as both the solvent and halogen source; environmentally friendly Brønsted acidic ionic liquids played a role of strong acid co-catalyst. Efficiencies comparable to non-IL are observed. This method is tolerant to a range of functional aldehydes and affords fairly good yields of N-acyl-α-amino acids. Recycling of the entire reaction media (IL solvent, palladium–phosphine catalyst, and IL halogen source) can be implemented by extraction of the product and remaining substrates. Of particular note is the fact that this novel protocol is economical and environmentally benign and shows potential utility in industry.

Acknowledgment

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(12) **General Procedure and Recycling Process**:
A 60-mL autoclave with a magnet-driven propeller stirrer was used for the high-pressure amidocarbonylation. Aldehyde (20 mmol), amide (22 mmol), $PdBr_2$ (0.2 mmol), PPh_3 (0.2 mmol), Brønsted acidic ionic liquid (2 mmol), and [emim]Br (25 mL) were transferred into the autoclave and allowed to react under 60 bar CO at 100 °C for 15 h. After the reaction the recycling process began with refluxing the reaction mixture with THF (3 × 30 mL). Then the THF phases were combined and the volatile components were removed in a rotary evaporator, and the residue was taken up in a sat. aq solution of $NaHCO_3$, and then washed with $CHCl_3$ and EtOAc. The aqueous phase was adjusted to pH 2 with phosphoric acid and extracted with EtOAc. Then the organic phases were combined and dried over $MgSO_4$, and the solvent was removed in vacuum. The product was purified by recrystallization with a suitable solvent mixture. The remaining ionic liquid was dried in vacuum and then poured into the autoclave reactor containing fresh aldehyde (20 mmol), amide (22 mmol) and Brønsted acidic ionic liquid (2 mmol) for the next run, but there was no need to add [emim]Br, $PdBr_2$ or PPh_3. Finally the reaction was restarted.

N-Benzoyl-α-cyclohexylglycine (**b**): white solid; mp 193–196 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.56 (s, 1 H), 8.42 (d, *J* = 7.6 Hz, 1 H), 7.88–7.90 (m, 2 H), 7.44–7.55 (m, 3 H), 4.32 (t, *J* = 7.6 Hz, 1 H), 1.59–1.87 (m, 6 H), 1.08–1.18 (m, 5 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.2, 166.9, 134.2, 131.3, 128.2, 127.7, 57.9, 29.4, 28.8, 25.7, 25.6. MS: *m*/*z* = 105 (100), 261 [M$^+$], 262 [M + 1]. IR (KBr): 3292, 2920, 2853, 1702, 1638, 1535, 1334, 1276, 932, 697 cm^{-1}.

N-Acetyl-α-norvaline (**d**): white solid; mp 111–114 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 (d, *J* = 7.6 Hz, 1 H), 4.17 (q, *J* = 7.6 Hz, 1 H), 1.83 (s, 3 H), 1.50–1.65 (m, 2 H), 1.26–1.31 (m, 2 H), 0.83–0.87 (t, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.0, 169.4, 51.6, 33.2, 22.3, 18.7, 13.5. MS: *m*/*z* = 72 (100), 159 [M$^+$], 160 [M + 1]. IR (KBr): 3345, 2962, 2936, 2875, 2456, 1928, 1717, 1595, 1543, 1237, 997, 612 cm^{-1}.

N-Acetyl-α-phenylglycine (**f**): white solid; mp 199–201 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.34 (s, 1 H), 8.65 (d, *J* = 7.6 Hz, 1 H), 7.32–7.42 (m, 5 H) 5.37 (d, *J* = 7.6 Hz, 1 H), 1.91 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.2, 169.3, 137.4, 128.7, 128.1, 127.8, 56.4, 22.4. MS: *m*/*z* = 106 (100), 193 [M$^+$], 194 [M + 1]. IR (KBr): 3342, 3032, 2484, 1922, 1716, 1602, 1544, 1258, 1179, 1003, 719, 614 cm^{-1}.

N-Acetyl-α-phenylalanine (**h**): white solid; mp 171–173 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.70 (s, 1 H), 8.21 (d, *J* = 8.0 Hz, 1 H), 7.18–7.30 (m, 5 H), 4.39–4.45 (m, 1 H), 3.03–3.07 (q, 1 H), 2.81–2.87 (q, 1 H), 1.79 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.2, 169.3, 137.8, 129.1, 128.2, 126.5, 53.6, 36.8, 22.4. MS: *m*/*z* = 148 (100), 207 [M$^+$], 208 [M + 1]. IR (KBr): 3331, 2913, 2458, 1699, 1621, 1553, 1437, 1244, 978, 908, 704 cm^{-1}.

N-Acetyl-α-(α-naphthyl)glycine (**i**): white solid; mp: 222–224 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.22 (d, 1 H), 7.90–8.08 (m, 3 H), 7.49–7.61 (m, 4 H), 6.12–6.14 (m, 1 H), 1.91 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.8, 170.3, 133.9, 133.7, 131.2, 129.2, 129.1, 127.3, 126.6, 126.1, 125.9, 123.7, 53.3, 22.6. MS: *m*/*z* = 156 (100), 243 [M$^+$], 244 [M + 1]. IR (KBr): 3348, 2878, 2787, 2486, 1916, 1704, 1615, 1535, 1289, 1261, 776, 663 cm^{-1}.