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Direct asymmetric α-amination of aldehydes with azodicarboxylates in ionic liquids catalyzed by imidazolium ion-tagged proline organocatalyst

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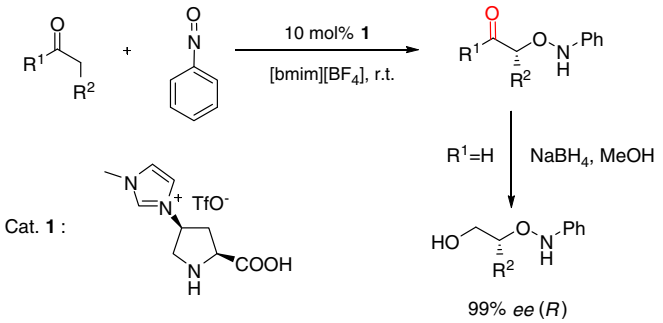
ABSTRACT

Direct asymmetric α-amination of unmodified aldehydes with azodicarboxylates in ionic liquids in the presence of imidazolium ion-tagged L-proline organocatalyst **1** gives excellent enantioselectivities (up to 98% ee) and high chemical yields. The system can be easily recycled and reused for at least four times without significant loss of yields and enantioselectivity.

Molecules containing an amino functional group are important building blocks used to construct many biologically active compounds. Therefore, many different diastereo-[1] and enantioselective[2] methods have been developed for the formation of carbon–nitrogen bonds which are highly attractive to many organic synthetic chemists. The first direct enantioselective α-amination of aldehydes with azodicarboxylates catalyzed by proline via enamine intermediate[3] was simultaneously and independently reported by List[4] and Jørgensen et al.[5] in 2002, in which moderate to high yields and excellent enantioselectivity were obtained. Shortly after those reports, Jørgensen and co-workers extended the scope of this reaction to ketone substrates.[6] Similar reaction conditions to those applied for aldehydes were used to obtain α-hydrazino ketones with high enantioselectivities. The substrate scope of the proline-catalyzed direct α-amination was also expanded to racemic α,α-disubstituted aldehydes to generate a quarternary stereocenter by Bräse[7] and Barbas[8] and their co-workers. Barbas and co-workers[9] combined α-amination of aldehydes with an acetone aldol reaction to produce optically active β-hydrazino alcohols. In addition, several organocatalysts other than proline have also been developed for α-amination of aldehydes and ketones.[10] Further developments in the α-amination also include that the reaction was carried out in ionic liquids instead of conventional organic solvents.[11] Unlike the case with conventional organic solvents, only a slight excess of aldehyde and a relatively short period of time are sufficient to obtain the aminated products.

Recently, chiral ionic liquids (CILS),[12] especially functional ionic liquids[13] or task specific ionic liquids have been introduced in many publications due to their unique characteristics and environmentally benign practices. But so far, there are very few reports on CILS as organocatalysts for asymmetric reactions and most of them were used as reaction media for inducing asymmetric synthesis.[14] In our previous studies, the novel imidazolium ion-tagged proline **1** was developed and successfully applied to catalyze α-aminoxylation of aldehydes and ketones with nitrosobenzene in ionic liquids, thus affording aminoxy alcohol or ketone with excellent enantioselectivity (Scheme 1).[15] In order to explore the further application of



Scheme 1. α-Aminoxylation of aldehydes and ketones in [bmim] [BF_4] catalyzed by **1**.

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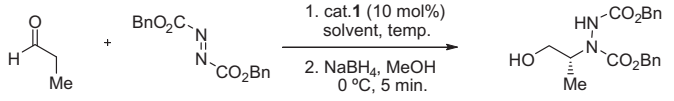
catalyst **1**, in this context, we decided to investigate its performance in the direct α-amination of aldehydes with azodicarboxylates in ionic liquids.

Initially, propionic aldehyde (**2a**) was selected as a model substrate for direct α-amination reaction with dibenzyl azodicarboxylate (**3a**) catalyzed by catalyst **1**. The results for the reaction carried out under various conditions are presented in Table 1. The aminated product was reduced to the primary alcohol with sodium borohydride because α-hydrazine aldehyde intermediate is configurationally labile. At first, the reaction was performed in different solvents at room temperature in the presence of 10 mol % **1** (Table 1, entries 1–9). In most conventional organic solvents, the chemical yields and enantioselectivities of α-hydrazine alcohol **4a** were disappointing (Table 1, entries 1–5). However, in acetonitrile the reaction proceeded in good yield and with satisfactory enantioselectivity (Table 1, entry 6). Ionic liquids have previously been used as solvents for organocatalytic reactions[15,16] due to the many advantages over traditional organic ones, such as non-volatility, easy recycling, and environmental friendliness. Catalyst **1** containing an ionic liquid unit could be well dissolved in the ionic liquid. We then investigated this reaction in both [bmim] $[BF_4]$ and [bmim] $[PF_6]$. High chemical yields and good enantioselectivities were obtained in these two kinds of ionic liquids in a short reaction time. The ionic liquid [bmim] $[BF_4]$ as solvent was a little better than [bmim] $[PF_6]$ under the same reaction conditions (Table 1, entries 8 and 9). Other green solvents such as brine were also examined but unfortunately, no reaction took place when brine was used as the reaction medium (Table 1, entry 7). The enantioselectivity increased to 95% when reaction temperature was lowered to 0 °C in [bmim] $[BF_4]$ and negligible reaction time was sacrificed (Table 1, entry 10). The effects of the catalyst amount on yield and enantioselectivity were also studied. Experimental results showed that the catalyst loading had a slight effect on enantioselectvty but greatly influenced catalytic activity. When a loading as low as 5 mol % **1** was used, the yield reduced from 96% to 76% in spite of a slight loss in enantioselectvity (Table 1, entry 11).[17]

Table 1
Optimizing reactions for the direct α-amination of **2a** with **3a** in the presence of **1**[a]



2a **3a** **4a** (*R*)

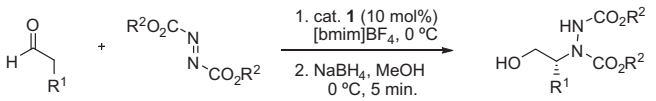
Entry	Solvent	Time (min)	Yield[b] (%)	ee[c] (%)
1	Hexane	360	56	25
2	CH_2Cl_2	15	83	55
3	THF	60	76	34
4	Dioxane	60	72	26
5	CH_3OH	30	65	34
6	CH_3CN	30	86	89
7	Brine	360	Trace	n.d.[d]
8	[bmim] BF_4	10	92	91
9	[bmim] PF_6	10	93	89
10[e]	[bmim] BF_4	20	96	95
11[f]	[bmim] BF_4	20	76	92

[a] Unless otherwise specified, in all cases **3a** (0.25 mmol) was added to a mixture of **2a** (0.5 mmol) and catalyst **1** (10 mol %) in various solvents (1.5 mL) at room temperature.
[b] Isolated yield.
[c] (*R*) configuration determined by chiral HPLC with a Chiralpak OD-H.
[d] Not determined.
[e] Performed with 10 mol % **1** at 0 °C.
[f] Performed with 5 mol % **1** at 0 °C.

To explore the potential and scope of catalyst **1** for direct enantioselective α-amination, we examined the reaction of a variety of alkyl-substituted aldehydes (**2a–f**) with azodicarboxylates (**3a–c**) under the optimized protocol, employing 10 mol % **1** in [bmim] $[BF_4]$ and followed by reduction with $NaBH_4$ at 0 °C. The results are summarized in Table 2. The desired α-aminated alcohols (**4a–g**) were obtained with high chemical yields (89–96%) and excellent enantioselectivities (92–98% ee). When the chain of the R^1 substituent changed from methyl to *n*-butyl, the reaction time was prolonged and the chemical yield of α-aminated alcohols was slightly decreased (Table 2, entries 1–4). The sterically crowded substrate **2e** reacted a little slowly but with the highest enantioselectivity (Table 2, entry 5). Diethyl and diisopropyl azodicarboxylates (**3b** and **3c**) were also used as nitrogen source for asymmetric α-amination of aldehyde (**2f**) which has benzene chromophore, facilitating HPLC analysis. Aminated products **4f** and **4g** were both obtained in high yields (93% and 95%, respectively) and with very excellent enantioselectivities (96% and 95%, respectively; Table 2, entries 6 and 7).

In addition, we have also examined the recyclability and reuse of the **1**/[bmim] $[BF_4]$ system under optimized reaction conditions. The direct asymmetric α-amination reaction of propionic aldehyde (**2a**) with dibenzyl azodicarboxylate (**3a**) was chosen as a model study. After the reaction had finished, the reaction system was extracted with ethyl ether to give the crude product (α-hydrazine

Table 2
The direct α-amination of various aldehydes **2a–f** with amine sources **3a–c** by catalyst **1**

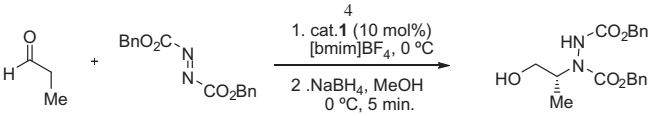


2a-f **3a-c** **4a-g** (*R*)

Entry	R^1	R^2	Time (min)	Yield[a] (%)	ee[b] (%)
1	Me (**2a**)	Bn (**3a**)	20	96 (**4a**)	95
2	Et (**2b**)	Bn (**3a**)	20	93 (**4b**)	94
3	Pr (**2c**)	Bn (**3a**)	40	90 (**4c**)	92
4	Bu (**2d**)	Bn (**3a**)	40	91 (**4d**)	96
5	*i*-Pr (**2e**)	Bn (**3a**)	40	89 (**4e**)	98
6	Bn (**2f**)	Et (**3b**)	30	93 (**4f**)	96
7	Bn (**2f**)	*i*-Pr (**3c**)	30	95 (**4g**)	95

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.

Table 3
Reuse of **1**/[bmim] BF_4 reaction system



2a **3a** **4a** (*R*)

Entry	Time (min)	Yield (%)[a]	ee (%)[b]
1	20	96	95
2	20	97	95
3	20	93	93
4	30	89	92

[a] Isolated yield.
[b] Determined by chiral HPLC with a Chiralpak OD-H.

aldehyde intermediate), whereas the ionic liquid residue containing **1** was dried under vacuum for about 60 min at 60 °C, and reused for the next run of reaction. This procedure could be repeated for four times and the product could be obtained without significant decrease in enantioselectivities and yields (Table 3).[18]

In summary, we successfully applied the imidazolium ion-tagged proline **1** to catalyze the direct asymmetric α-amination of unmodified aldehydes with azodicarboxylates. In ionic liquids as reaction solvents, the desired α-aminated alcohols were obtained with high chemical yields and excellent enantioselectivities in a short period of reaction time. Furthermore, it is remarkable that the catalyst **1**/[bmim] [BF_4] system could be easily recycled and retained similar reactivity as well as enantioselectivity after four recycles.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H NMR and HPLC reports of **4a**–**4g**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.036.

References and notes

1. (a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394; (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395; (c) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397–6399; (d) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030; (e) Harding, J. R.; Hughes, R. A.; Kelly, N. M.; Sutherlan, A.; Willis, C. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3406–3416; (f) Chao, C. S.; Cheng, C. K.; Li, S. H.; Chen, K. *Tetrahedron Lett.* **2009**, *50*, 333–336.
2. (a) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342–11343; (b) Mashiko, T.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2725–2728; (c) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565–4568; (d) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367–1369; (e) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421; (f) Dessole, G.; Bernardi, L.; Bonini, B. F.; Capito, E.; Fochi, M.; Herrera, R. P.; Ricci, A.; Cahiez, G. *J. Org. Chem.* **2004**, *69*, 8525–8528; (g) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598; (h) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9466–9468; (i) Liu, Y.; Melgar-Fernandez, R.; Juaristi, E. *J. Org. Chem.* **2007**, *72*, 1522–1525; (j) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044–16045; (k) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137–140; (l) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167–169; (m) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121; (n) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115–2118; (o) Gómez Aranda, V.; Barluenga, J.; Aznar, F. *Synthesis* **1974**, 504; (p) Li, G.; Wei, H. X.; Kim, S. H.; Carducci, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277–4280.
3. Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978.
4. List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657.
5. Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790–1793.
6. Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255.
7. (a) Vogt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun.* **2003**, 2448–2449; (b) Baumann, T.; Vogt, H.; Bräse, S. *Eur. J. Org. Chem.* **2007**, 266–282; (c) Baumann, T.; Bächle, M.; Hartmann, C.; Bräse, S. *Eur. J. Org. Chem.* **2008**, 2207–2212.
8. Suri, J. T.; Steiner, D. D.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 3885–3888.
9. Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2003**, *5*, 1685–1688.
10. (a) Dahlin, N.; Bøgevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101–1105; (b) Chowdari, N. S.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 867–870; (c) Franzén, J.; Marigo, M.; Fielenbach, S.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; (d) Thomassigny, C.; Prim, D.; Greck, C. *Tetrahedron Lett.* **2006**, *47*, 1117–1119; (e) Liu, T. Y.; Cui, H. L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z. Q.; Chen, Y. C. *Org. Lett.* **2007**, *9*, 3671–3674; (f) Hayashi, Y.; Aratake, S.; Imai, Y.; Hibino, K.; Chen, Q. Y.; Yamaguchi, J.; Uchimaru, T. *Chem. Asian J.* **2008**, *3*, 225–232; (g) Liu, P. M.; Chang, C.; Reddy, R. J.; Ting, Y. F.; Kuan, H. H.; Chen, K. *Eur. J. Org. Chem.* **2010**, 42–46.
11. Kotrusz, P.; Alemayehu, S.; Toma, S.; Schmalz, H. G.; Adler, A. *Eur. J. Org. Chem.* **2005**, 4904–4911.
12. (a) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D. A.; Gaumont, C.; Plaquevent, J. C. *Tetrahedron: Asymmetry* **2003**, *14*, 3081–3093; (b) Ding, J.; Armstrong, D. W. *Chirality* **2005**, *17*, 281–292; (c) Baudequin, C.; Bregeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J. C. *Tetrahedron: Asymmetry* **2005**, *16*, 3921–3945; (d) Bica, K.; Gaertner, P. *Eur. J. Org. Chem.* **2008**, *19*, 3235–3250; (e) Winkel, A.; Reddy, P. V. G.; Wilhelm, R. *Synthesis* **2008**, 999–1016; (f) Domínguez de María, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6960–6968.
13. (a) Davis, J. H. *Chem. Lett.* **2004**, *33*, 1072–1077; (b) Fei, Z.; Geldbach, T. J.; Zhao, D.; Dyson, P. J. *Chem. Eur. J.* **2006**, *12*, 2122–2130; (c) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Cheng, J. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093–3097; (d) Miao, W.; Chan, T. H. *Adv. Synth. Catal.* **2006**, *348*, 1711–1718; (e) Zhou, L.; Wang, L. *Chem. Lett.* **2007**, *36*, 628–629; (f) Luo, S. Z.; Zhang, L.; Mi, X. L.; Qiao, Y. P.; Cheng, J. P. *J. Org. Chem.* **2007**, *72*, 9350–9352; (g) Lombardo, M.; Pasi, F.; Easwar, S.; Trombini, C. *Adv. Synth. Catal.* **2007**, *349*, 2061–2065; (h) Yacob, Z.; Shah, J.; Leistner, J.; Liebscher, J. *Synlett* **2008**, 2342–2344; (i)*Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2008; Vol. 2, pp 488–527; (j) Ni, B.; Zhang, Q. Y.; Dhungana, K.; Headley, A. D. *Org. Lett.* **2009**, *11*, 1037–1040; (k) Lombardo, M.; Easwar, S.; Pasi, F.; Trombini, C. *Adv. Synth. Catal.* **2009**, *351*, 276–282.
14. Toma, Š.; Mečiarová, M.; ebesta, R. Š. *Eur. J. Org. Chem.* **2009**, 321–327.
15. Ding, X.; Tang, W. M.; Cheng, Y. X.; Zhu, C. J. *Adv. Synth. Catal.* **2010**, *352*, 108.
16. (a) Kotrusz, P.; Kmentová, I.; Gotov, B.; Toma, S.; Solcániová, E. *Chem. Commun.* **2002**, 2510–2511; (b) Loh, T. P.; Feng, L. C.; Yang, H. Y.; Yang, J. Y. *Tetrahedron Lett.* **2002**, *43*, 8741–8743; (c) Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44*, 5351–5353.
17. *General procedure for the direct asymmetric α-amination in [bmim] [BF_4]*: To a test-tube equipped with a magnetic stirring bar and charged with ionic liquid (1.5 mL) was added catalyst **1** (10 mol %) and aldehyde (0.5 mmol). The mixture was stirred for 2 min at 0 °C followed by addition of azodicarboxylates (0.25 mmol). The resulting solution was then stirred until the yellow color of the mixture disappeared and the completion of amination reaction was determined by TLC. The reaction mixture was then extracted with ethyl ether (6 × 5 mL) followed by solvent evaporation using a rotary evaporator. To the crude α-hydrazine aldehyde intermediate was added methanol (2 mL). The mixture was cooled to 0 °C and sodium borohydride (0.55 mmol) was added. After 5 min, the reaction was quenched with saturated aqueous ammonium chloride solution (0.5 mL) and the resulting mixture was extracted with ethyl acetate (4 × 3 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under vacuum after filtration. Purification by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:3–1:10) gave pure α-aminated products as white solids.
18. *Procedure for the recycle and reuse of* ***1****/[bmim] [BF_4]*. The mixture of catalyst **1**, propionic aldehyde **2a,** and dibenzyl azodicarboxylate **3a** (0.1:1:2) in [bmim] BF_4 (1.5 mL) were stirred for 20 min at 0 °C and then extracted with ethyl ether (6 × 5 mL). The residue was dried under vacuum for about 60 min at 60 °C, and reused for the next run of reaction. This procedure could be repeated for four times at least.