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An ionic liquid influenced L-proline catalysed asymmetric Michael addition of ketones to nitrostyrene

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Abstract

L-Proline in ionic liquid was employed for Michael addition of ketones to nitrostyrene. Optically active γ-nitroketones were obtained in good yields up to 80%. The reaction offers high *syn* selectivity (90%). The most striking feature is that the ionic liquid has been found to enhance the enantioselectivity, wherein enantiomeric excess approaches 75%. The system of ionic liquid and catalyst has proved to be an efficient recyclable medium.

Keywords: L-Proline; Ionic liquid; Michael addition; Enantioselectivity; Recyclability

1. Introduction

The need for enantiomerically enriched compounds had triggered an extensive development in the field of catalytic asymmetric synthesis. The enantioselective Michael reaction has been one of the most studied C–C bond forming reactions in synthetic organic chemistry [1–4]. An impressive number of efficient metal based catalytic systems have been established which are complementary to each other with respect to applicable Michael acceptors and donors [5]. However, relatively few asymmetric transformations have been reported which employ small organic molecules as catalysts. Very recently, metal-free catalysts (e.g. alkaloids and simple peptides) are gaining importance for enantioselective Michael additions [6–9].

Nitroalkenes are of special interest as excellent Michael acceptors due to their low tendency for 1,2- additions and the strong stabilizing effect of the nitro group. The nitro group is particularly versatile in synthesis since it may be transformed into diverse functionalities. Seebach et al. have extensively studied Michael addition of preformed enamines of ketones to nitroolefins [10,11]. Though direct addition of non-activated ketones to nitroolefins via amino-catalysis seems to hold potential, very few reports have been described in the literature [12–16].

After the pioneering work by Stork et al. [17], who employed enamines as nucleophiles in Michael reaction, very recently Barbas and co-workers, have extensively studied a wide spectrum of enamine related reactions of high synthetic importance such as intermolecular aldol reaction, Mannich reaction etc., using pyrrolidine type amines [18–20]. Amongst these pyrrolidine type amines, proline [21–23] is no doubt the most easily accessible chiral catalyst, which is environmentally safe and available in both the enantiomeric forms. Asymmetric aldol reaction, in particular, has been quite successful with L-proline [24,25].

Several protic and aprotic solvents have been used for the Michael reaction. It has been observed that solvents do have a substantial role in determining the overall outcome of the reaction [13]. Ionic liquids are upcoming new generation designer solvents, which are backed by various striking

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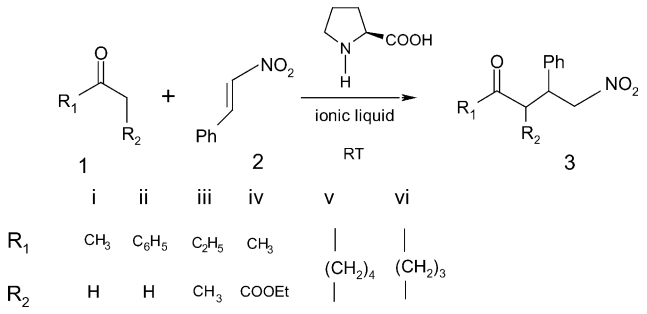

Scheme 1. L-Proline catalysed Michael addition of ketones to nitrostyrene in ionic liquid.

features such as negligible vapour pressure, high thermal stability, recyclability, etc. [26,27]. Ionic liquids have until now been shown to be much superior to conventional organic solvents where activity, selectivity and stability of the catalyst are concerned besides being environmentally benign [28]. L-Proline in combination with ionic liquids has proved to be an efficient system for direct asymmetric aldol reaction [29], cross-aldol reaction [30] as well as Mannich reaction [31]. As a part of our ongoing research in the field of ionic liquids [32–37], we were highly interested in studying the influence of ionic liquids on L-proline catalysed Michael addition of ketones to nitrostyrene. In pursuit of achieving enhanced enantioselectivity, several groups have attempted this Michael addition using structurally modified L-proline [38,39]. We herein report an efficient methodology for the synthesis of nitro-alkylated compounds employing unmodified L-proline in ionic liquids with high enantiomeric excess (Scheme 1).

2. Experimental

2.1. Materials

Ionic liquids were prepared by the procedures given in the literature. All other chemicals and reagents were of analytical grade and used as obtained.

2.2. General experimental procedure for the L-proline catalysed Michael addition of ketones to nitrostyrene in neutral ionic liquids

To 2 mmol of nitrostyrene **2**, 20 mmol of the substrate **1** was added. To this, 1 ml of ionic liquid and 0.4 equivalents of L-proline were added. The reaction mixture was stirred at room temperature until TLC showed complete disappearance of **2**. The work up was simple as the crude product could be easily extracted from the ionic liquid with diethyl ether for all the ionic liquids or with ethyl acetate for [MOEMIM]OMs. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product. The product was purified by column chromatography. The absence of enamine adduct was confirmed by ^{1}H NMR. Optical rotations were measured on a Jasco digital polarimeter P-1020.

2.3. General experimental procedure for the recycling of ionic liquids and L-proline

The system of ionic liquid and L-proline was thoroughly extracted with diethyl ether to remove all organic impurities and was recharged with a new batch of substrates. The reaction was carried out as per the above given procedure.

3. Results and discussions

The salient feature of the present study is that ionic liquid enhances enantioselectivity of the reaction manifold in comparison to that reported in conventional organic solvents [12]. The reaction of cyclohexanone and nitrostyrene was explored as a model conversion in different ionic liquids having structural diversity. The reaction proceeded smoothly to furnish the Michael adduct in good yield. The methodology offered a high degree of diastereoselectivity in all the ionic liquids employed for the present study. The diastereoselectivity was in accordance with the Seebach's model [10]. The *syn* diastereomer predominates over the *anti* isomer. Both hydrophobic as well as hydrophilic ionic liquids have been employed in the present study (Table 1).

Table 1
L-Proline catalysed Michael addition of cyclohexanone to nitrostyrene in various ionic liquids and organic solvents

Entry	Equivalence of L-proline	Solvent	Time (h)	Yield[a] (%)	de[b] (%)	ee[c] (%)
1	0.2	[MOEMIM]OMs	68	74	90	73
2	0.4	[MOEMIM]OMs	60	75	90	75
3	0.8	[MOEMIM]OMs	47	78	85	68
4	1.6	[MOEMIM]OMs	36	80	82	65
5	0.4	[bmim]PF_6	55	74	85	31
6	0.4	[bmim]BF_4	55	76	88	33
7	0.4	[hmim]BF_4	55	76	90	32
8	0.4	[bmim]Cl	30	71	88	50
9	0.4	DMSO	70	65	85	20
10	0.4	MeOH	65	85	90	50

[a] Isolated yields.
[b] Diastereomeric excess of the *syn* isomer, determined by ^{1}H NMR.
[c] Enantiomeric excess of the *syn* isomer. Optical rotations were measured on Jasco digital polarimeter P-1020.

Table 2
L-Proline catalysed Michael addition of ketones to nitrostyrene in ionic liquids

Substrate	Equivalence of L-proline	Ionic liquid	Time (day)	Yield[a] (%)	de[b] (%)	ee[c] (%)
I	1.6	[bmim]PF_6	5	58	–	–
ii [40]	1.6	[hmim]BF_4	3.5	51	–	26
iii[13]	0.8	[bmim]PF_6	6.5	68	90:10	45
iv	0.4	[hmim]BF_4	6	53	60:40	–
v [10]	0.4	[MOEMIM]OMs	2.5	75	90:10	75
vi	0.4	[MOEMIM]OMs	4.5	71	85:15	–

[a] Isolated yields including *anti* isomer.
[b] Diastereomeric excess of the *syn* isomer, determined by either ^{1}H NMR or GC analysis.
[c] Enantiomeric excess of the *syn* isomer.

We observed that the ionic liquids exerted a remarkable effect on the enantioselectivity of the reaction. Amongst the ionic liquids studied by us, 1-butyl-3-methylimidazolium chloride, [bmim]Cl, and 1-methoxyethyl-3-methylimidazolium methanesulphonate, [MOEMIM]OMs, are the only ionic liquids which gave moderate to good enantiomeric excess of the product. These ionic liquids are miscible with catalytic amounts of L-proline. However, cyclohexanone was partially miscible with [bmim]Cl but immiscible with [MOEMIM]OMs. It was observed that the reaction was slower in [MOEMIM]OMs than that in [bmim]Cl. On the other hand, the Michael adduct was obtained in good enantiomeric excess in case of [MOEMIM]OMs as compared to that obtained from the reaction carried out in [bmim]Cl. Thus, [MOEMIM]OMs appeared to be the most suitable ionic liquid for the current investigation with respect to yield as well as stereoselectivity. Interestingly, 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim]BF_4 is also hydrophilic in nature but immiscible with L-proline in all proportions. The enantioselectivity obtained in [bmim]BF_4 was comparatively poor. The enantiomeric excess of the final product obtained by employing hydrophobic ionic liquids namely 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim]PF_6 and 1-hexyl-3-methylimidazolium tetrafluoroborate, [hmim]BF_4 were equivalent to that obtained with [bmim]BF_4. The results are presented in Table 1.

The amount of catalyst was varied from 0.2 eq. to 1.6 eq. to investigate its influence on the course of the reaction. The enantioselectivity was not much affected with increasing quantity of L-proline. An excellent enantioselectivity was observed with 0.4 eq. of L-proline.

To extend the present methodology, we studied the reaction with other ketones as well as 1,3-dicarbonyl compounds. We initially chose [MOEMIM]OMs for further study due to its miscibility with the catalyst and good results were obtained with cyclic ketones such as cyclohexanone and cylopentanone. However, [MOEMIM]OMs did not prove to be an efficient ionic liquid for any of the acyclic ketones chosen, as the yields were poor. Hence, we screened all the other ionic liquids used in the present study for other ketones to achieve optimum results. Likewise, the amount of the catalyst was also optimized as per the substrate. As evident from the results presented in Table 2, hydrophobic ionic liquids viz. [bmim]PF_6 and [hmim]BF_4 showed better performance in view of conversion as well as selectivity in case of acyclic ketones.

Table 3
Study of the recyclability of ionic liquid and L-proline

Run	Yield (%)[a]	ee (%)
1	75	73
2	74	47
3	74	26

[a] Isolated yields.

Cyclohexanone proved to be an excellent substrate for the current reaction in terms of yield and stereoselectivity. The solubility of L-proline in ionic liquid could be the likely reason for better enantioselectivity than that obtained in conventional organic solvents [12,13].

One noteworthy feature of the present study is the reusability of ionic liquid as well as the catalyst. The ionic liquid acted as a reservoir for the catalyst. [MOEMIM]OMs containing L-proline was used for three runs consecutively. Though the yield of the product was comparable to that obtained in the first run, we observed a decrease in %ee in subsequent runs. The results are presented in Table 3.

4. Conclusion

In conclusion, we have demonstrated that ionic liquids can act as an efficient media for enhancing the selectivity of L-proline catalysed Michael reaction. The results are a definite improvement over those previously reported for this particular reaction with L-proline in organic solvents. We have also successfully explored the possibility of catalyst recovery and solvent reusability. The catalytic activity was strongly dependent on the nature of the ionic liquid, which influenced the yield and selectivity of the reaction. The study points out the fact that the structure of ionic liquid can be well modulated to meet the needs of a specific process.

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References

[1] E.D. Bergan, D. Ginsburg, R. Pappo, Org. React. 10 (1959) 179.
[2] N. Krause, A. Gerold, Angew. Chem. Int. Ed. Eng. 36 (1997) 186.
[3] R.D. Little, M.M. Masjedizah, O. Wallquist, J.I. McLoughlin, Org. React. 47 (1995) 315.
[4] P. Perlmutter, Conjugate Addition Reactions in Organic Synthesis, Pergamon Press, Oxford, 1992.
[5] N. Krause, A. Hoffmann-Röder, Synthesis (2001) 171.
[6] S. Saito, M. Nakadai, H. Yamamoto, Synlett (2001) 1245.
[7] F.-Y. Zhang, E.J. Corey, Org. Lett. 2 (2000) 1097.
[8] T.E. Horstmann, D.J. Guerin, S.J. Miller, Angew. Chem. 112 (2000) 3781.
[9] T.E. Horstmann, D.J. Guerin, S.J. Miller, Angew. Chem. Int. Ed. Engl. 39 (2000) 3635.
[10] S.J. Blarer, W.B. Schweizer, D. Seebach, Helv. Chim. Acta 65 (1982) 1637.
[11] D. Seebach, M. Missbach, G. Calderari, M. Eberle, J. Am. Chem. Soc. 112 (1990) 7625.
[12] B. List, P. Pojarliev, H.J. Martin, Org. Lett. 3 (2001) 2423.
[13] D. Enders, A. Seki, Synlett (2002) 26.
[14] J.M. Betancort, K. Sakthivel, R. Thayumanavan, C.F. Barbas III, Tetrahedron Lett. 42 (2001) 4441.
[15] A. Alexakis, O. Andrey, Org. Lett. 4 (2002) 3611.
[16] K. Sakthivel, W. Notz, T. Bui, C.F. Barbas III, J. Am. Chem. Soc. 123 (2001) 5260.
[17] G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, R. Terrel, J. Am. Chem. Soc. 85 (1963) 207.
[18] J.M. Betancort, C.F. Barbas III, Org. Lett. 3 (2001) 3737.
[19] A. Córdova, W. Notz, C.F. Barbas III, J. Org. Chem. 67 (2002) 301.
[20] A. Córdova, S.-I. Watanabe, F. Tanaka, W. Notz, C.F. Barbas III, J. Am. Chem. Soc. 124 (2002) 1866.
[21] B. List, P. Pojarliev, W.T. Biller, H.J. Martin, J. Am. Chem. Soc. 124 (2002) 827.
[22] B. List, J. Am. Chem. Soc. 122 (2000) 2395.
[23] K.A. Ahrendt, C.J. Borths, D.W.C. Macmillan, J. Am. Chem. Soc. 122 (2000) 4243.
[24] A. Bøgevig, N. Kumaragurubaran, K.A. Jørgensen, Chem. Commun. (2002) 620.
[25] Y.-Y. Peng, Q.-P. Ding, Z. Li, P.G. Wang, J.-P. Cheng, Tetrahedron Lett. 44 (2003) 3871.
[26] J. Dupont, R.F. de Souza, P.A.Z. Suarez, Chem. Rev. 102 (2002) 3667.
[27] S.-G. Lee, J.H. Park, J. Kang, J.K. Lee, Chem. Commun. (2001) 1698.
[28] C.E. Song, W.H. Shim, E.J. Roh, S.-G. Lee, J.H. Choi, Chem. Commun. (2001) 1122.
[29] T.-P. Loh, L.-C. Feng, H.-Y. Yang, J.-Y.T. Yang, Tetrahedron Lett. 43 (2002) 8741.
[30] A. Córdova, Tetrahedron Lett. 45 (2004) 3949.
[31] N.S. Chowdari, D.B. Ramchary, C.F. Barbas III, Synlett (2003) 1906.
[32] M.K. Potdar, S.S. Mohile, M.M. Salunkhe, Tetrahedron Lett. 42 (2001) 9285.
[33] J.R. Harjani, S.J. Nara, M.M. Salunkhe, Tetrahedron Lett. 42 (2001) 1979.
[34] S.J. Nara, J.R. Harjani, M.M. Salunkhe, J. Org. Chem. 66 (2001) 8616.
[35] M.C. Uzagare, Y.S. Sanghvi, M.M. Salunkhe, Green Chem. 5 (2003) 370.
[36] R.T. Dere, R.R. Pal, P.S. Patil, M.M. Salunkhe, Tetrahedron Lett. 44 (2003) 5351.
[37] M.S. Rasalkar, M.K. Potdar, M.M. Salunkhe, J. Mol. Catal. B: Enzym. 27 (2004) 267.
[38] A.J.A. Cobb, D.A. Longbottom, D.M. Shaw, S.V. Ley, Chem. Commun. (2004) 1808.
[39] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, J. Am. Chem. Soc. 126 (2004) 9558.
[40] Schionato, S. Paganelli, C. Botteghi, J. Mol. Catal. 50 (1989) 11.