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Short Communication

Choline chloride based eutectic solvents: Magical catalytic system for carbon–carbon bond formation in the rapid synthesis of β-hydroxy functionalized derivatives

Balvant Shyam Singh, Hyacintha Rennet Lobo, Ganapati Subray Shankarling *

Department of Dyestuff Technology, Institute of Chemical Technology, N. P. Marg, Matunga, Mumbai, 400019, India

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ABSTRACT

Significant β-hydroxy functionalized derivatives including nitroaldols, β-hydroxy nitriles and β-hydroxy carboxylic acids were successfully prepared, for the first time, by catalytic use of deep eutectic solvents (DES). This paper explores the versatility and effectiveness of DES as catalyst in three different carbon–carbon bond formation reactions. The uniqueness of this catalyst lies in its simplicity since it avoids expensive catalysts and multi-step synthesis as reported in literature. The compounds, which are potent intermediates for innumerable useful products, were synthesized in excellent yields within very short reaction times. The catalyst prepared from choline chloride and urea, is biodegradable, non-toxic, cost-effective and recyclable.

1. Introduction

β-Hydroxy functionalized derivatives prepared by classical carbon–carbon bond forming reaction could be versatile intermediates for the preparation of variety of compounds like nitroalkenes, 2-aminoalcohols, 2-nitroketones [1], etc. A short diagrammatic summary is shown in Fig. 1.

One of the extremely significant β-hydroxy functionalized compound includes nitroaldol or β-hydroxy nitroalkanols that have found increasing applications in pharmaceutical industries [2], synthesis of natural products [3], synthesis of biological compounds including fungicides, insecticides [4,5] certain antibiotics [6], polyaminoalcohols and polyhydroxylated amides [7].

Nitroaldols can be extensively prepared by Henry reaction in presence of bases [4] such as sodium methoxide, sodium hydroxide, triethylamine, LDA and butyl lithium. However, the basic reagents often lead to side reactions such as aldol condensation, Cannizzaro reaction and elimination. Apart from bases, some other reports explain use of lanthanide [8] and rhodium based metal complexes [9], enzymatic catalysts [10], chloroaluminate ionic liquids as reaction media [11], microwave technique [12] etc. These methods either involve difficult catalyst preparation, longer reaction time, expensive catalysts or higher equivalents of nitroalkylating agent.

Also, the toxic reagents, harsh bases, volatile organic solvents have negative effects on the environment. Hence, it is important to replace these systems with milder one that will not only be environmentally benign but would be as effective as the above stated reagents.

Deep eutectic mixtures belong to an interesting set of eutectics which have been recently explored in important organic reactions [13,14]. Deep eutectic solvents (DES) are a special type of ionic solvent composed of quaternary salt like choline chloride (CHCl) and neutral molecules like urea, glycerol, etc. The melting point of such mixtures is much lower than either of the individual components [15]. Although they are somewhat similar in features to conventional ionic liquids, but their advantages can be justified through the major differences that lie between them. These eutectics are cost-effective, non-toxic and easy to store than the most ionic liquids owing to the fact that choline is a naturally occurring bio-compatible compound and choline chloride is also commercially produced on a large scale as a chicken feed additive.

In addition to being eco-friendly, another advantage of using deep eutectic of choline chloride and urea is the ability of the urea component to catalyze nitroaldol reactions via hydrogen bond catalysis [16]. Several urea [17] and thiourea [18] based catalyst have been investigated in the past for such reactions owing to their efficient hydrogen bonding activity. However, we have limited our reaction to urea based DES since choline chloride:thiourea based DES (freezing point 69 °C) is not liquid [19] at our reaction temperature (room temperature).

Therefore, we explored the catalytic activity of deep eutectic solvent (CHCl:Urea) in methanol media for rapid and eco-friendly synthesis of nitroaldol compounds. Its catalytic role is observed from the fact that the reaction does not initiate at all in methanol but rapidly progresses once DES catalyst is added to it.

We further extended the methodology towards synthesis of other important β-hydroxy derivatives like β-hydroxynitriles and

* Corresponding author at: Department of Dyestuff Technology, Institute of Chemical Technology, N. P. Marg, Matunga, Mumbai, 400019, India. Tel.: +91 22 33612708; fax: +91 22 33611020.
E-mail addresses: gsshankarling@gmail.com, gs.shankarling@ictmumbai.edu.in (G.S. Shankarling).

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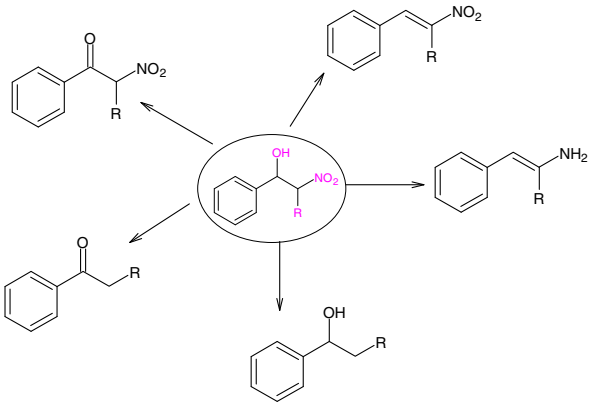


Fig. 1. Versatile applications of nitroaldol compounds in organic synthesis.

β-hydroxy carboxylic acids. Such molecules are important building blocks in most natural product synthesis [20] especially because groups like nitrile and acids provide rapid access to much useful functionalities and also nitriles are much stable towards handling [21].

Conventionally, β-hydroxynitriles are synthesized by deprotonation of α proton of acetonitrile or benzyl nitrile with equivalent amount of strong alkali metal base [22]. Some other reports show catalytic use of quaternary ammonium salts like TBAF [23] or use modified form of acetonitrile like trimethylsilylacetonitrile in presence of Lewis base catalysts [24]. However, these methods suffer from demerits like either low yield [22], requirement of harshly basic conditions, multi-step procedures, side reactions like oxidation of aldehydes to acids [23], etc. β-Hydroxy carboxylic acids are also difficult to prepare directly via aldol condensation owing to difficult deprotonation of α proton due to carboxylic acid group. Some reports suggest use of Mukaiyama aldol reactions [25] but cannot prepare β-hydroxy carboxylic derivatives, of reactants like 4-nitrobenzaldehyde by direct aldol reaction with acetic acid. We have devised a method by which such derivatives are prepared via catalytic application of deep eutectic solvents not only in single step but also without use of complicated procedures or reagents and in an environmentally benign manner.

Hence, our present study highlights the first catalytic use of deep eutectics in successful synthesis of β-hydroxy functionalized derivatives. In addition, optimization and recycling studies are also discussed.

Table 1
Optimization of catalyst/organic solvent in nitroaldol reaction.[a]

Sr. no.	Catalyst	Organic solvent	Yields[b] (%)
1.	–	Hexane	–
	10% DES	Hexane	30
2.	–	Toluene	–
	10% DES	Toluene	55
3.	–	Methanol	–
	10% DES	Methanol	70
4.	15% DES	Methanol	80
5.	20% DES	Methanol	95
6.	25% DES	Methanol	94

[a] Reaction conditions: 4-Nitrobenzaldehyde (1.0 eq) and nitromethane (5.0 eq), 20% DES in MeOH (10 vol), room temperature, reaction time = 8 min.
[b] Isolated yields.

2. Experimental

2.1. General

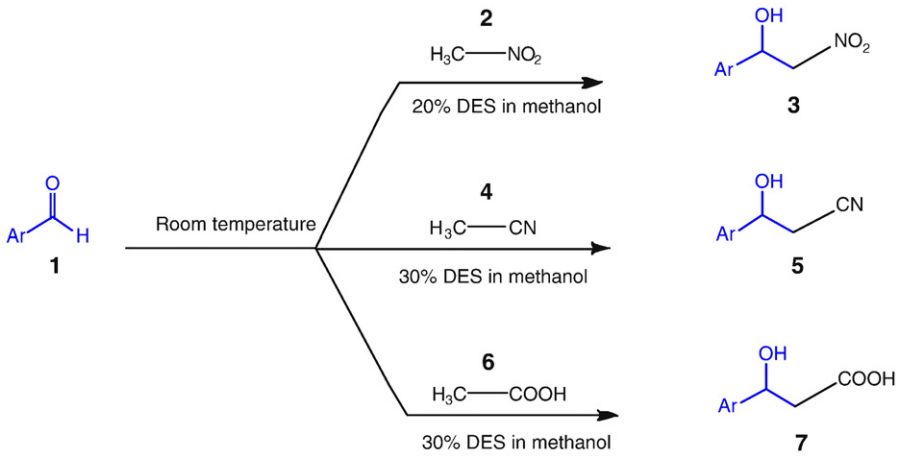
FT-IR spectrums were recorded on a Bomem Hartmann and Braun MB-Series FT-IR spectrometer. ^{1}H NMR spectrums were recorded on Varian 300 MHz mercury plus spectrometer. Mass spectral data were obtained with a micromass-Q-TOF (YA105) spectrometer. Common reagent grade chemicals were procured from M/s S.D. Fine Chemical Ltd. India and were used without further purification.

Spectral data for representative compounds:

2-Nitro-1-(4-nitrophenyl)ethanol (3b). IR(KBr): ν_{max} cm^{-1} 3508, 2921, 2851, 1552, 1515, 1416, 1379,1347, 1080, and 855 cm^{-1}; ^{1}H NMR (300 MHz; CDCl3; Me_4Si) δppm 8.31–8.27 (m, 2H), 7.65–7.63 (m, 2H), 5.62 (m, 1H), 4.65–4.55 (m, 2H), 3.09 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 148.0, 145.0, 126.9, 124.1, 80.6, and 69.9; m/z (EI) 213.1(M + 1); $C_8H_7N_2O_5$ calculated m/z: 212.04.

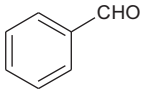
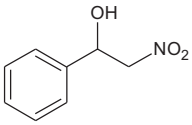
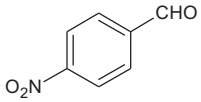
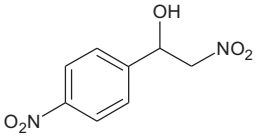
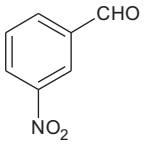
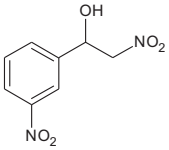
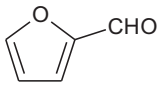
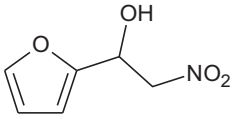
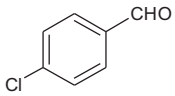
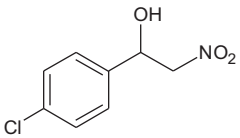
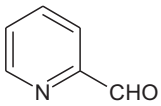
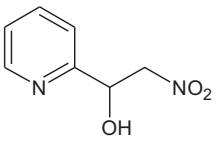
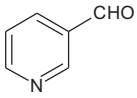
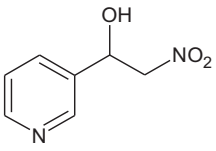
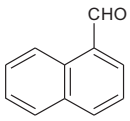
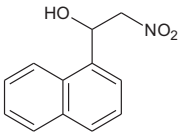
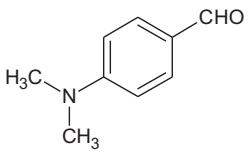
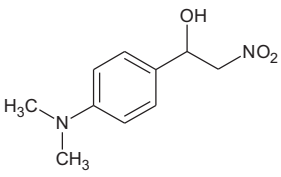
3-Hydroxy-3-(3′-nitrophenyl)propanenitrile (5). IR(KBr): ν_{max} cm^{-1} 3504, 2251, 1665, 1598, 1547, 1381, 1104, 855 cm^{-1}; ^{1}H NMR (300 MHz; CDCl3; Me_4Si) δppm 8.30–8.20 (m, 2H), 7.76–7.60 (m, 2H), 5.18 (s, 1H), 3.09 (s, 1H), 2.81–2.83 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) 148.4, 143.4, 130.7, 129.1, 123.5, 120.2, 116.7, 69.9, 29.2; m/z (EI) 193.1(M + 1); $C_8H_7N_2O_5$ calculated m/z: 192.04.

3-Hydroxy-3-(4-nitrophenyl)propanoic acid (7). IR(KBr): ν_{max} cm^{-1} 3457, 3307, 1650, 1639, 1599, 1550, 1346,1275, 1107, 854 cm^{-1}; ^{1}H NMR (300 MHz; CDCl3; Me_4Si) δppm 11.2 (s, IH) 8.30–8.25 (m, 2H), 7.75–7.60 (m, 2H), 5.31 (m, 1H), 2.81 (m,



Scheme 1. Synthesis of β-hydroxy derivatives using deep eutectic solvent as a catalyst.

Table 2
Nitroaldol reaction of nitromethane with functionalized aromatic aldehydes catalyzed by deep eutectic solvents in methanol.

Entry no.	Reactants	Products[a]	Reaction time (min)	Yield[b] (%)	Physical constants	
					Found	Literature
3a			30	83	B.P.: 140	142–143 [27]
3b			5	95	86	83–85 [28]
3c			7	93	74–76	75–77 [28]
3 d			8	89	B.P.: 128	130–131 [29]
3e			12	86	40	35–37 [28]
3f			9	90	66	68 [30]
3 g			10	88	120	116–117 [31]
3 h			35	78	62	59–61 [32]
3i			60	69	112	110–111 [33]

[a] Reaction conditions: Aromatic aldehyde (1.0 eq) and nitromethane (5.0 eq), 20% DES in MeOH (10 vol), room temperature.
[b] Isolated yields.

2H), 2.74 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) 171.3, 151.1, 147.3, 127.0, 123.3, 68.2, 43.4; m/z (EI) 212.1(M + 1); $C_8H_7N_2O_5$ calculated m/z: 211.04.

2.2. Preparation of deep eutectic solvent (DES)

In this study, deep eutectic solvents (DES) were synthesized according to the procedures reported in the literature [26].

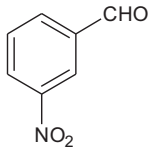
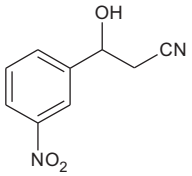
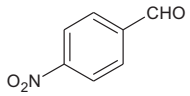
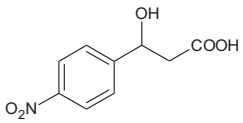
The preparation involved reaction of choline chloride (1 mol) with urea (2 mol) at 74 °C till a clear solution was obtained which was used for reactions without any purification. This method gives deep eutectic solvent with 100% atom economy without any other by-product formation (Scheme 1).

2.3. Typical experimental procedure

2.3.1. Deep eutectic solvent catalyzed reaction for synthesis of nitroaldol derivatives

Aromatic aldehyde (1.0 eq) and nitromethane (5.0 eq) were mixed together in a 50 mL round bottom flask. This was followed by

Table 3
Optimization for quantity of DES catalyst in synthesis of β-hydroxynitriles and β-hydroxy carboxylic acids.

Compd. no.	Reactant	Product	Catalyst	Solvent	Yields[c] (%)	Melting point	
						Found	Literature
5[a]			–	Methanol	–	90	86–89 [34]
			10% DES	Methanol	80		
			20% DES	Methanol	85		
			30% DES	Methanol	95		
			40% DES	Methanol	94		
7[b]			–	Methanol	–	108–110	112–114 [34]
			10% DES	Methanol	77		
			20% DES	Methanol	83		
			30% DES	Methanol	90		
			40% DES	Methanol	91		

[a] Reaction conditions: 3-Nitrobenzaldehyde (1.0 eq) and acetonitrile (5.0 eq), DES in MeOH (10 vol), room temperature, reaction time = 2 h.
[b] Reaction conditions: 4-Nitrobenzaldehyde (1.0 eq) and acetic acid (3.0 eq), DES in MeOH (10 vol), room temperature, reaction time = 3 h.
[c] Isolated yields.

addition of catalytic system containing 20% DES catalyst in methanol. The reaction mixture was then stirred at room temperature for an appropriate time (Table 2). The progress of the reaction was monitored by TLC. The reaction mixture was then extracted with ethyl acetate and the DES layer was separated off. The ethyl acetate layer was washed with water and concentrated. The residue was chromatographed on silica gel column (hexane: ethyl acetate = 9:1) to afford pure nitroaldol derivatives.

2.3.2. Deep eutectic solvent catalyzed reaction for synthesis of β-hydroxynitriles [3-hydroxy-3-(3-nitrophenyl)propanenitrile]

3-Nitrobenzaldehyde (1.0 eq) and acetonitrile (5.0 eq) were mixed together in a 50 mL round bottom flask. This was followed by addition of catalytic system containing DES catalyst (quantity optimized in Table 3) in methanol. The reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was then extracted with ethyl acetate and the DES layer was separated off. The ethyl acetate layer was washed with water and concentrated. The residue was chromatographed on silica gel column (hexane: ethyl acetate = 8:2), to afford pure β-hydroxynitrile derivative.

2.3.3. Deep eutectic solvent catalyzed reaction for synthesis of β-hydroxy carboxylic acids [3-hydroxy-3-(4-nitrophenyl)propanoic acid]

4-Nitrobenzaldehyde (1.0 eq) and acetic acid (3.0 eq) were mixed together in a 50 mL round bottom flask. This was followed by addition of catalytic system containing DES catalyst (quantity optimized in Table 3) in methanol. The reaction mixture was stirred at room temperature for 3 h. The completion of the reaction was monitored by TLC. Water was added to the reaction mass which resulted in formation of precipitate. The precipitate was filtered off and the filtrate was subjected to evaporation of water/methanol under vacuum to obtain DES. The solid product was chromatographed on silica gel column (hexane: ethyl acetate = 8:2 to 5:5), to afford pure β-hydroxy carboxylic derivative.

3. Results and discussion

3.1. Influence of catalyst and solvent on nitroaldol reaction

In order to understand the importance of deep eutectic solvent in nitroaldol reaction, the optimization studies were performed as depicted in Table 1. For this purpose, the reaction of 4-nitrobenzaldehyde with nitromethane was taken as standard. Initially, the reaction was conducted in the presence and the absence of DES in different organic solvents. It was observed that the reaction does not proceed at all in absence of DES. However, the progress in reaction was observed soon after addition of DES. This highlights the catalytic effect of DES in this reaction. Also, the catalytic system of DES–methanol gave best results. Hence, the reaction was also checked to know the optimum amount of DES required for the reaction. It was found that 20% DES in methanol is the most effective combination.

3.2. Nitroaldol reaction of nitromethane with functionalized aromatic aldehydes

Various functionalized aromatic aldehydes including heterocylcic systems were reacted with nitromethane in the presence of DES–methanol mixture as summarized in Table 2. The reaction proceeded very fast in cases of electron deactivating groups. However, electron activating systems gave results not so fast but within 1 h. The method gave extremely interesting results in terms of yield as well as time as compared to many of the reported methods that proceeded in 24–50 h. One more interesting aspect is that this method used only 5 eq of nitromethane as against conventional methods that use more 20–30 eq of nitromethane.

3.3. Extension of the methodology towards synthesis of other β-hydroxy derivatives

To explore the versatility of the DES catalyst towards other important β-hydroxy compounds, we performed the reaction of nitrobenzaldehyde with acetonitrile or acetic acid to obtain β-hydroxynitriles and β-hydroxy carboxylic acids (Table 3). To our surprise, we got extremely

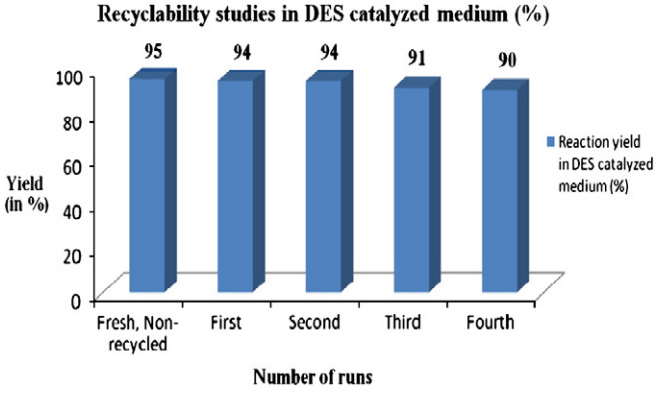
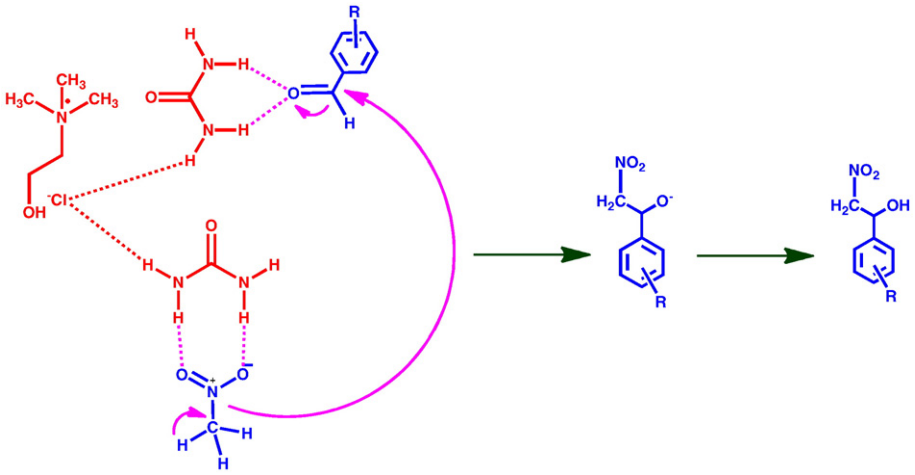


Fig. 2. Recyclability tests of DES catalyst in reaction of 4-nitrobenzaldehyde with nitromethane.



Scheme 2. Proposed mechanism for nitroaldol reaction in DES-catalyzed medium.

better results in both the cases than reported literature that use multi-step synthesis and expensive reagents. Once again, the quantity of DES was optimized to know the effective quantity.

3.4. Scale-up batch and recyclability studies

The reaction of 4-nitrobenzaldehyde with nitromethane was scaled-up to obtain a yield of 95%. The DES recycled after the scale-up batch was re-used further for further batches as depicted in Fig. 2. No significant decrease in yields was observed even after four runs.

3.5. Proposed mechanism

Since it is the first report on use of DES as catalyst, the exact role of DES as catalyst needs to be confirmed. However, urea based catalysts are known to work in such reactions by hydrogen bonding catalysis [16]. We wish to propose that the DES catalyst might play an important role in promoting nitroaldol reaction through hydrogen bonding interactions (Scheme 2) of urea hydrogens with nitromethane and aldehyde group. This bonding not only makes methyl group in nitromethane more reactive but also increases electrophilicity of aldehydic carbon atom.

4. Conclusion

In summary, we have developed a simple, green and efficient catalytic system using deep eutectic mixtures for rapid synthesis of nitroaldol compounds. The reaction gave excellent yields in very short reaction times. The reaction was also extended towards synthesis of β-hydroxynitriles and β-hydroxy carboxylic acids that showed a marked improvement over reported methods. To the best of our knowledge, this is the first report of a catalyst that can effectively catalyze these three important C – C bond formation reactions. In addition to having good catalytic potency, the DES catalyst could also be easily recycled and reused at least up to four runs without any considerable loss in yields.

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References

[1] Nitro Group in Organic Synthesis, Noboru Ono, Chapter 3, Wiley VCH, 2001, p. 30.
[2] H. Sasai, S. Arai, Y. Tahara, M. Shibasaki, Journal of Organic Chemistry 60 (1995) 6656.
[3] R.J. Heffner, J. Jiang, M.M. Jouillie, Journal of the American Chemical Society 114 (1992) 10181.
[4] F.A. Luzzio, Tetrahedron 57 (2001) 915.
[5] G. Mikite, K. Jakucs, F. Darvas, A. Lopata, Pestic Science 13 (1982) 557.
[6] O. Sakanaka, T. Ohmorti, S. Kazaki, T. Suami, T. Ishii, S. Ohba, Y. Saito, Bulletin of the Chemical Society of Japan 59 (1986) 1753.
[7] F.M. Kie, P. Poggendorf, S. Picasso, V. Jagerger, Journal of the Chemical Society (1998) 119.
[8] Wen-Bin Yi, Xin Wang, Chun Cai, Catalysis Communications 8 (2007) 1995.
[9] S. Kiyooka, T. Tsutsui, H. Maeda, Y. Kaneko, K. Isobe, Tetrahedron Letters 36 (1995) 6531.
[10] M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc, H. Griengl, Advanced Synthesis and Catalysis 349 (2007) 1445.
[11] A. Kumar, S.S. Pawar, Journal of Molecular Catalysis A: Chemical 235 (2005) 244.
[12] C. Gan, X. Chen, G. Lai, Z. Wang, Synlett 3 (2006) 387.
[13] B. Singh, H. Lobo, G. Shankarling, Catalysis Letters 141 (2011) 178.
[14] P.M. Pawar, K.J. Jarag, G.S. Shankarling, Green Chemistry 13 (2011) 2130.
[15] A. Abbott, G. Capper, D. Davies, R. Rasheed, V. Tambyrajah, Chemical Communications (2003) 70.
[16] W.R. Zheng, J.L. Xu, T. Huang, Q. Yang, Z.C. Chen, Research on Chemical Intermediates 37 (2011) 31.
[17] K. Lang, J. Park, S. Hong, Angewandte Chemie International Edition 51 (2012) 1620.
[18] Y. Sohtome, Y. Hashimoto, K. Nagasawaa, Advanced Synthesis and Catalysis 347 (2005) 1643.
[19] M.C. Gutierrez, M.L. Ferrer, C.R. Mateo, F. Monte, Langmuir 25 (2009) 5509.
[20] E.J. Corey, Y.J. Wu, Journal of the American Chemical Society 115 (1993) 8871.
[21] Z. You, H. Lee, Tetrahedron Letters 37 (1996) 1165.
[22] E.W. Kaiser, C.R. Hauser, Journal of the American Chemical Society 89 (1967) 4566.
[23] E.Y. Ko, C.H. Lim, K.H. Chung, Bulletin of the Korean Chemical Society 27 (2006) 432.
[24] K. Wadhwa, J.G. Verkade, Journal of Organic Chemistry 74 (2009) 5683.
[25] C.W. Downey, M.W. Johnson, D.H. Lawrence, A.S. Fleisher, K.J. Tracy, Journal of Organic Chemistry 75 (2010) 5351.
[26] A. Abbott, G. Capper, D. Davies, H. Munro, R.K. Rasheed, V. Tambyrajah, Chemical Communications (2001) 2010.
[27] K. Biswajit, N.C. Barua, B. Maitreyee, B. Ghanashyam, Synlett 9 (2001) 1411.
[28] L. Guoyin, G. Fengfeng, Z. Yueqin, et al., Chemistry A European Journal 17 (2011) 1114.
[29] M.N. Elinson, A.I. Ilovaisky, V.M. Merkulova, F. Barba, B. Batanero, Tetrahedron 64 (2008) 5915.
[30] V.E. Profft, F. Schneider, H. Beyer, Journal fur Praktische Chemie 4 (1955) 147.
[31] Zymalkowski, Archiv der Pharmazie 291 (1958) 12.
[32] D.A. Evans, D. Seidel, M. Rueping, H.W. Lam, J.T. Shaw, C.W. Downey, Journal of the American Chemical Society 125 (2003) 12692.
[33] Rumjancev Rumjanceva, Journal of organic chemistry of the USSR 4 (1968) 804.
[34] A. Haribabu, Z. Dunming, Y. Yan, B. Edward, R.H. Ling, Journal of Organic Chemistry 74 (2009) 1658.