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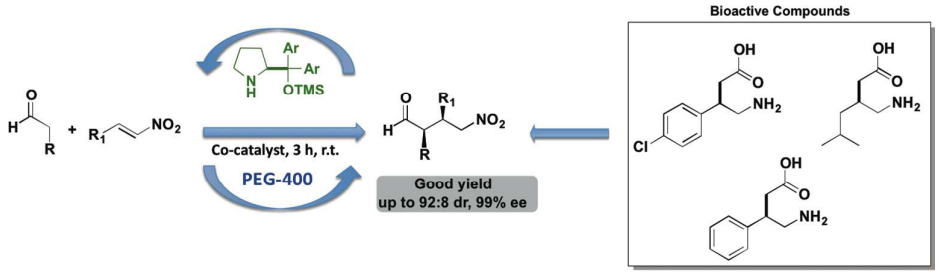

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ARTICLE

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A highly stereoselective organocatalytic Michael addition of aldehydes to trans-β-nitrostyrenes using PEG as recyclable solvent medium is presented. The scope of this organocatalytic system is demonstrated by the formation of several Michael adducts in good yields and stereoselectivities. Furthermore, applying this new protocol to acetaldehyde, we have disclosed an easy formal synthesis of (R)-Pregabalin, (R)-Phenibut and (R)-Bacoflen with good yieds and outstanding enantioselectivities.

Introduction

Environmental concerns associated with synthetic organic chemistry have posed stringent and compelling demands for greener processes. The development of cost-efficient and environmentally benign catalytic systems has become one of the main subjects in modern chemistry.[1] In many chemical processes, organic solvents are widely used and had been a cause of major environmental concern due to their hazards.[2] A recent benchmarking study performed by the Pharmaceutical Industry[3] unveiled that solvents are the foremost contributor to the amount of waste produced in pharmaceutical manufacturing processes - the so-called E-Factor.[4] Therefore, the social and economical imperative for sustainability has prompted the scientific community to search for alternative reaction media in place of volatile, pyrophoric, often toxic and of difficult recover solvents.[5] To overcome these limitations, attempts have been made in the development of new protocols having water and/or other aqueous solutions as greener solvent.[6] Furthermore, similar alternatives also include: (a) supercritical fluids,[7] (b) ionic liquids,[8] (c) fluorous based system,[7b,9] (d) and more recently the use of liquid polymers.[10] To address the concerns raised by volatile organic solvents, liquid PEGs have been subjected to an increasing number of scientific investigations.[11] Chemical reactions carried out in PEGs have a different thermodynamic and kinetic behaviour with respect to those in conventional solvents, and, in addition, PEGs have a number of intrinsic proprieties that may be of importance for industrial application. Therefore, PEGs could be an attractive greener option due to its non-toxic and non-hazardous characteristics, its lack of measurable vapour pressure associated to their air and moisture stability propriety.[12] However, relatively few articles have been focused on the use of PEG solutions in catalytic asymmetric synthesis.

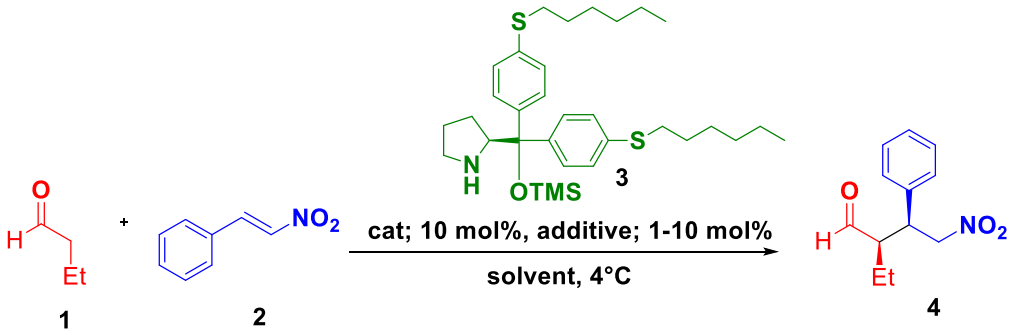
Over the past few years, especially with the conception of the organocatalysis field, many organic reactions that were conventionally believed to occur only in traditional organic solvents have been successfully performed in an environmentally benign reaction medium. Among all the methods developed, the asymmetric organocatalytic Michael reaction[13] is an excellent example and has strongly contributed to the green chemistry perspective. This elegant and atom-economic methodology proves to be one of the most versatile tools for carbon-carbon and carbon-heteroatom bonds formation,[14] as exemplified by the large number of publications in this field over the last few years.[15] Moreover, the addition products are important synthetic intermediates, which can be further manipulated into a range of different classes of biologically active compounds.

A pressing challenge facing organic chemists, therefore, is to advance new asymmetric catalytic processes that are not only efficient, by-product free, and high yielding but also eco-compatible. On account of these factors, herein we report the application of PEG 400 as a recyclable reaction medium in the asymmetric organocatalytic Michael addition of aldehydes to *trans*-β-nitrostyrenes.

Results and discussion

The directed Michael addition of butyraldehyde **1** to *trans*-*β*-nitrostyrene **2** was selected as the model reaction to evaluate the feasibility of our organocatalytic system in environmentally benign solvents (Table 1). In order to optimize the reaction conditions, different solvents, catalysts and catalytic additives were carefully evaluated. We started the screening studies, by using 10 mol% derivative catalyst of proline with sulphur alkyl chain, **3**, recently described in our group[16,17] and benzoic acid (10 mol %) as catalytic additive.

Table 1: Optimization of Reaction Conditions: Solvent and Additive Studies[a]



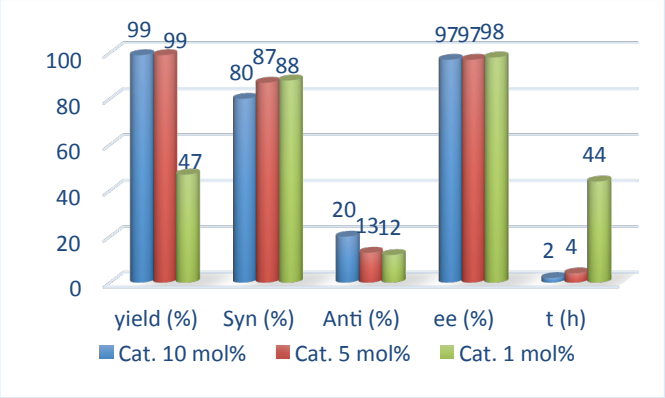
Entry	Solvent	Additive	Time (h)	Yield (%)[b]	Diastereomeric ratio (*dr*) [c]	Enantiomeric excess (*ee* %)[d]
1	EtOH	Benzoic acid	48	68	64:36	94
2	H_2O	Benzoic acid	48	46	60:40	94
3	Glycerol	Benzoic acid	48	57	60:40	95
4	Toluene	Benzoic acid	48	92	67:33	97
5	Diethylene Glycol	Benzoic acid	2	96	88:12	97
6	**PEG-400**	**Benzoic acid**	**2**	**99**	**80:20**	**97**
7[e]	PEG-400	Benzoic acid	1	92	65:35	95
8	PEG-400	4-Nitrophenol	5	93	84:16	95
9	PEG-400	*L*-Tartaric acid	3	85	78:22	96
10	PEG-400	*L*- Malic acid	2	92	84:16	96
11	PEG-400	CSA	24	-	-	-
12[f]	PEG-400	CSA	3	89	77:23	94
13	PEG-400	4-Nitrobenzoic acid	2	98	77:23	96
14	PEG-400	------	11	84	90:10	96

[a] Unless otherwise specified, all reactions were performed using *trans*-*β*-nitrostyrene (0.3 mmol), butylraldehyde (0.6 mmol), additive (10 mol %) and organocatalyst (10 mol %) in environmentally begin solvent (0.15 mL) at 4ºC. [b] Isolated yield. [c]Determined by ^{1}H NMR. [d] Determined by chiral-phase HPLC analysis for *syn*- product. [e] The reaction was carried out at room temperature. [f] 1 mol% of additive was used.

When the reactions were carried out in EtOH, water or glycerol, the desired products were obtained with moderate chemical yields as well as diastereoseletivities, and high enantioselectivities (Table 1, entries 1, 2 and 3). Having toluene as solvent, an increment on the chemical yield was observed, with no variation in the diastereo- and enantioselectivity (entry 4). Moreover, diethylene glycol provided the product after only 2h, with higher yield and stereoselectivities than those evaluated before. These results have prompted us to evaluate a greener, non-volatile and recoverable solvent such as PEG-400 (entry 6). To our delight, the desired product **4** was smoothly obtained within 2 h in quantitative yield and excellent enantioselectivity (entry 6 *vs* 5). In order to further optimize the protocol, different parameters were also varied. When the reaction temperature was raised to 30ºC, a decrease in yield, *ee* and *dr* was noted compared to the reaction at 4ºC (entry 7). Encouraged by these results, a set of cocatalytic additives was screened for further optimization. In doing so, when the reactions were performed in the presence of 10 mol% of 4-nitrophenol, *L*-tartaric acid or *L*-maleic acid (entries 8 - 10), a slight decrease on the reaction yield and on the stereoselectivities were observed. Changing the additive to 10 mol% of CSA led to a complete degradation of the product (entry 11). On the order hand, decreasing the loading of CSA to 1 mol % achieved the formation of the Michael adduct in lower yield (89%), maintaining good stereoselectivities (entry 12). Compared to benzoic acid, the accomplishment of the reaction with 4-nitrobenzoic acid did not affect significantly the yield and stereoselectivities (entry 13) indicating that, among all tested additives, benzoic acid provides optimal yield, *ee* and *dr*. As expected, in absence of cocatalytic additive, the reaction yield has dropped to 84%, maintaining good selectivity (entry

14). Having optimized both solvent and additive, we turned our attention to study the amount of organocatalyst and additive in the reaction. Lowering the loading of both organocatalyst and additive to 5 mol %, the desired product was obtained in quantitative yield with excellent enantioselectivity in a longer reaction time; nevertheless, better diastereoisomeric ratio was obtained. Unfortunately, decreasing the catalytic loading from 5 to 1 mol % produced erosion in terms of yield (47%), albeit without substantial changes in the *dr* and *ee* (Chart 1).

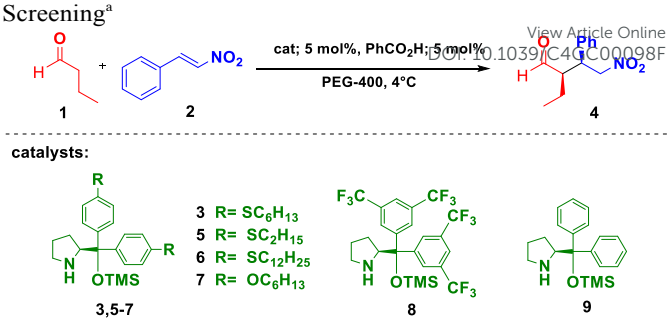
Chart 1- Optimization of catalyst loading



We next investigated the architecture of diarylprolinol silyl ether based organocatalysts, to further increase the reactivity and selectivity of the catalytic system. All evaluated organocatalysts were able to promote the Michael addition under environmentally benign reaction medium, although the reaction outcome varies as a function of the alky side-chain length. Thus, when the length of the hydrophobic alkyl chain was decreased to ethyl (**5**), the desired Michael adduct was obtained with slight erosion on the chemical yield along with a longer reaction time (Table 2, entry 1). Increasing the alkyl chain to dodecyl (**6**) led to a dramatic drop in the chemical efficiency of Michael addition, however the degree of stereocontrol remained high (entry 3). Similar yield, *ee* and *dr* were obtained using an oxygen-based analogue of the organocatalyst **3,** within 4 h (entries 1 *vs* 4). Despite the extended reaction time, catalysts **8** and **9** proved to be less effective, reaching the desired Michael adduct in only 16% and 62% yields, respectively (Table 4, entry 5 and 6).

In order to conclude the optimization studies of this catalytic system, the reaction was carried out in different concentrations. In the absence of solvent, the product was obtained in a lower yield with higher diastereomeric ratio (Table 2, entry 7). Furthermore, diluting the reaction media to 0.6M (Table 2, entry 8), notwithstanding the longer time (19h), the reaction proceeded with excellent selectivities (92:8 *dr* and 97% *ee*) and these results indicate that no further improvements in yield or selectivity were observed for lower concentrations.

Table 2: Optimization of the reaction conditions: Catalyst Screening[a]



Entry	Cat.	[mol L^{-1}]	Time (h)	Yield [b] (%)	*ee* [c] (%)	dr[d]
1	**4**	2	4	99	97	87:13
2	**5**	2	19	99	97	90:10
3	**6**	2	19	52	98	91:09
4	**7**	2	4	98	95	86:14
5	**8**	2	19	16	97	93:07
6	**9**	2	19	62	97	72:28
7	**4**	-	2	67	97	91:09
8	**4**	0.6	19	99	97	92:08
9	**4**	0.3	19	73	96	89:11

[a] Unless otherwise specified, all reactions were performed using *trans-β*-nitrostyrene (0.3 mmol), butylraldehyde (0.6 mmol), benzoic acid (0.015 mmol-5 mol %) and organocatalyst (0.015 mmol – 5 mol %) in PEG 400 (0.15 mL- 2 mol.L^{-1}). [b] Isolated yield. [c]The *ee* values were determined by chiral HPLC. [d]The *dr* values were determined by chiral HPLC and NMR of the crude mixture.

With these notably improved reaction conditions in hand, we explored the scope of the Michael addition of aldehydes to nitroolefins mediated by organocatalyst **3** in PEG 400 as solvent (Scheme 1). Initially, a representative selection of nitroolefins was evaluated to establish the generality of this asymmetric catalytic system. As depicted in Scheme 1, nitrostyrenes bearing *β*-aryl substituents with either electron-donating (e.g. methoxyl) or electron-withdrawing groups (e.g. chloro, bromo, fluoro, and nitro) are almost equally tolerated, thus giving the desired Michael adducts in excellent chemical yield with good diastereomeric ratios and *ee* values within the range of 91-99%, **10 a-g**. Even *β*-alkyl-substituted nitroolefins participate in this catalytic system to give the desired adduct with good *dr* as well as *ee*, albeit in modest chemical yield, **10 j** and **10k**. When valeraldehyde was used as donor, the reaction proceeded very efficiently, affording the corresponding product **10h** in 83%, with high levels of stereoselectivities.

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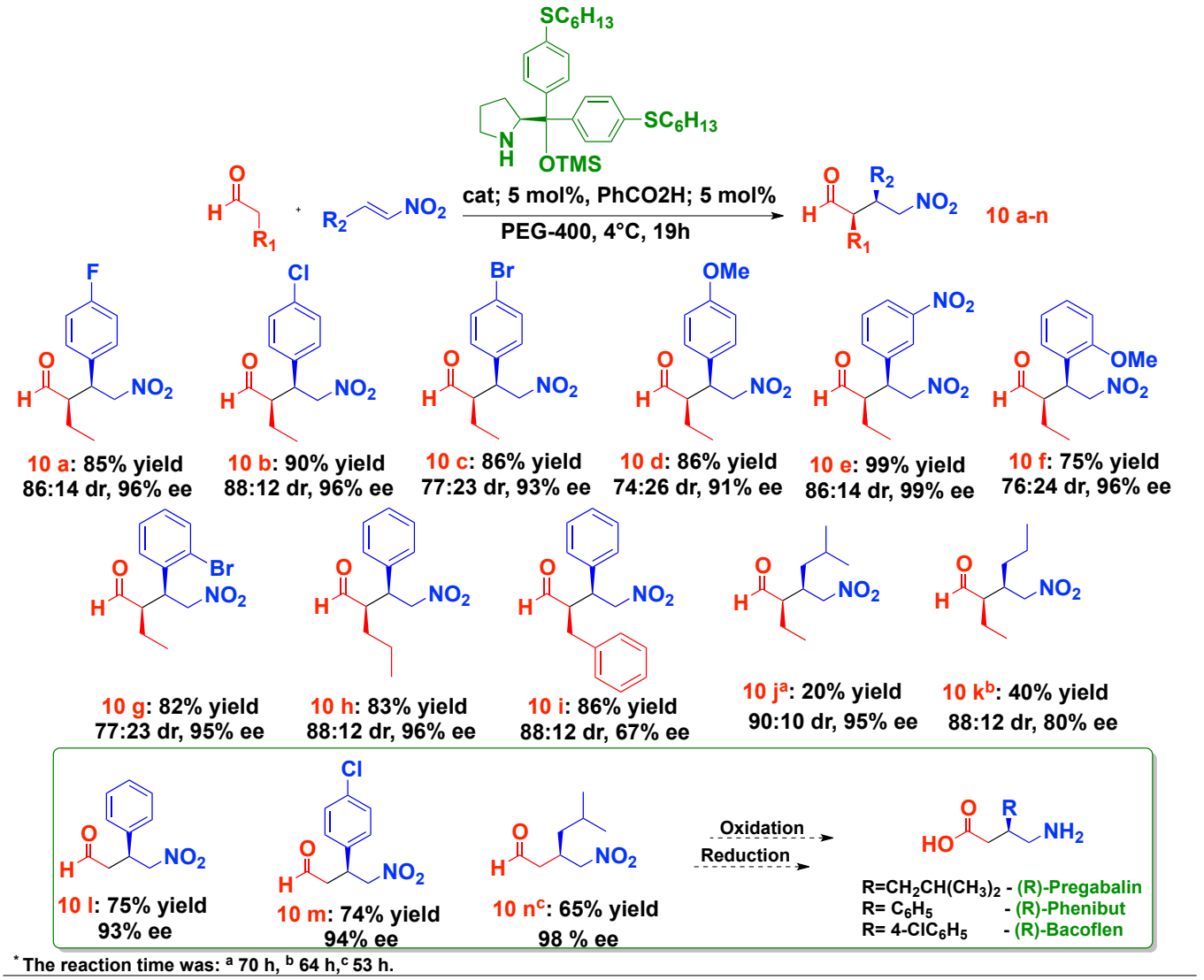
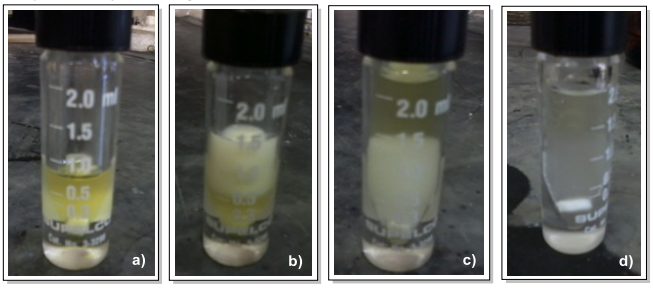


Scheme 1

A sterically hindered aldehyde provoked a decrease on the enantioselectivity, keeping good yield and dr, **10i**. Furthermore, aliphatic nitroolefines - reacted in a Michel fashion in excellent enantioselectivities, however the chemical yield of the product was low compared to the other substrates (products **10j** and **10k**)

Recently, the Michael-type addition involving acetaldehyde has emerged as a versatile, yet challenging, transformation in asymmetric catalysis.[18] However, examples including it as donor are scarcely described. It could be explained, since acetaldehyde is very reactive and volatile. For these reasons, it needs to be carefully manipulated and the reactions normally involve inert atmosphere and highly catalyst loading to delivered the desired product with acceptable yield. The nitroaldehyde products are versatile synthetic intermediates, easily transformed into γ-aminobutyric acid derivatives (GABAs), which are very important inhibitors of the neurotransmission in the brain. Gratifyingly, when we applied our optimized reaction conditions to promote the Michael reaction of acetaldehyde with β-nitrostryrene, *p*-chloro-nitrostyrene and β-alkyl-substituted nitroolefins, these reactions proceeded smoothly, leading to the desired products in 60-75% yields, with excellent enantiomeric excess, **10l-n**, (Scheme 1).

Those excellent results can be explained due to the use of PEG-400 (green and recoverable solvent), which might play an important role in the retention of the acetaldehyde in solution.
The recyclability of the solvent in the catalytic system was also evaluated for the reaction of *trans*-*β*-nitrostyrene and *n*-butyraldehyde (Figure 1).



a) reaction mixture at the end time, b) 0.25 mL of water was added – emulsion appears, c) extraction with ether, d) the emulsion disappears – with totally recovery of PEG .

Figure 1 – PEG recovering

Hence, we attempted to reuse the PEG, which was one of the prime objectives in our quest. In this regard we performed a set of experiments to explore whether the PEG can be reused for further reactions (Table 3). After completion of the reaction, task specific PEG was recovered and subjected to another run, affording the product in almost same yield, *dr* and *ee*. This process was repeated four more times, affording the product in excellent yields, *dr* and *ee*. In order to verify the reproducibility of runs, the standard deviation (σ) and also correlation coefficient (C.V.) were calculated (Table 3). Consequently, as the C.V. was less than 5%, the experimental values are acceptable. The simple experimental and product isolation procedures combined with the easy recovery and reuse of PEG is expected to contribute to the development of a green strategy for the Michael addition reactions.

Table 3- Recyclability of PEG for the conjugate addition.[a]

Runs	1	2	3	4	5	σ	C.V.
Yield (%)[b]	99	95	95	94	89	3.2	3.38%
ee (%)[c]	97	97	96	97	97	0.4	0.41%

[a]Reactions were performed using *trans*-*β*-nitrostyrene (0.3 mmol), butylraldehyde (0.6 mmol), benzoic acid (0.015 mmol-5 mol %) and organocatalyst (0.015 mmol – 5 mol %) in PEG 400 (0.5 mL- 0.6 mol.L^{-1}). [b] Isolated yield. [c]The *ee* values were determined by chiral HPLC.

Experimental

General Information:

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 (400 and 100 MHz respectively). All NMR spectra were obtained with $CDCl_3$.
HPLC chromatograms of Michael adduct were obtained on a Shimadzu apparatus, LC-20AT Pump, SPD-M20A UV-Vis Detector, CBM-20A System Controller, using a Chiralcel OD-H (4.6 mmØ x 250 mmL, particle size 5 µm), Chiralpak AD-H (4.6 mmØ x 250 mmL, particle size 5 µm) and a Chiralcel AS-H (4.6 mmØ x 250 mmL, particle size 5 µm).
Optical rotations were measured with a Schmidt + Haensch Polartronic H Polarimeter, at 589 nm, 23 °C, using a 1 mL cell with a 1 dm path length and reported as follows: $[\alpha]_D^{23}$ (c in g per mL of solvent).
All the compounds synthesized in the manuscript are known. The relative and absolute configurations of the products were determined by comparison with the known ^{1}H and ^{13}C NMR, chiral HPLC analysis, and optical rotation values.
Column chromatography was performed using Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with $KMnO_4$ solution.

General procedure for Michael Addition:

The aldehyde (0.6 mmol), nitroolefin (0.3 mmol) and benzoic acid (0.015 mmol) were added to a solution of the catalyst (0.015 mmol) in PEG-400 (0.5 mL). The reaction mixture was stirred for 19h and then was direct purified by flash column chromatography on silica gel using n-hexane/EtOAc as the eluent. The enantiomeric excess was determined by chiral-stationary-phase HPLC analysis through comparison with the authentic racemic material. Assignment of the stereoisomers was performed by comparison with literature data.

Conclusions

In conclusion, taking advantage of the benign nature of PEG 400, we have developed a highly efficient organocatalised asymmetric Michael addition of aldehydes to trans-*β*-nitrostyrenes, allowing a faster and high stereoselective reaction when compared with other eco-friendly solvents. The explanation of this innovative and good result can be due to a host-guest complex, PEG-nitrostyrene, which will facilitate the nucleophilic addition of enamine resultant from the reaction between aldehyde and organocatalyst. Moreover and noteworthy, after Michael addition product extraction with ether, PEG was efficiently totally recovered and reused. Regarding the architecture of the diaril prolinol silyl ether organocatalyst, we have concluded that hydrophobic alkyl side chains greatly influence the reaction, being the better organocatalysts the ones which possess ethyl and hexyl chains on their structure. The best catalytic system (with organocatalyst 3) in PEG proved to be very effective for the enamine based Michael reactions, providing good yields and stereoselectivities for a broad range of aldehydes and trans-*β*-nitroolefins. When this system is applied to acetaldehyde, which is known to be very difficult to handle and highly reactive (translated into undesired side reactions and moderate yields), we have found, to our delight, good yields and excellent *ee*, proving to be an excellent and easy methodology for the formal synthesis of three pharmaceuticals: (R)-enantiomer of Pregabalin, (R)-Phenibut and (R)-Bacoflen. In fact, eco-friendly procedure, high yields and stereoselectivities,

easy work up, efficient synthesis of Pregabalin, Phenibut and Bacoflen precursors and the total recyclability of PEG are the very notable features of this work.

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Notes and references

1 For selected recent reviews and monographs on green chemistry, see "*Green Chemistry: Designing Chemistry for the Environment*": *ACS Symp. Ser*., ed. P. T. Anastas and T. C. Williamson, 1996, ch. 1, vol. 626, pp. 1-17; (b) *Green Chemistry: Theory and Practice*, ed. P. T. Anastas and J. Warner, Oxford University Press, New York, 1998; (c) *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*, ed. P. T. Anastas and T. C. Williamson, Oxford University Press, New York, 1999; (d) P. T. Anastas and J. B. Zimmerrman, *Environ. Sci. Technol*., 2003, **37**, 95.

2 K. Shanab, C. Neudorfer, E. Schirmer and H. Spreitzer, *Curr. Org. Chem.,* 2013, **9**, 1179.

3 (a) D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem*., 2002, **4**, 521; (b) *Green Chemistry in the Pharmaceutical Industry*, ed. P. J. Dunn, A. S. Wells and M. T. Williams,Wiley-VCH 2010, p.333.

4 (a) R. A. Sheldon, C. R. Acad. Sci., Ser. IIc: Chim., 2000, 3, 541-551; (b) R. A. Sheldon, *Chem. Ind*., 1997, 12; (c) R. A. Sheldon, *Pure Appl. Chem*., 2000, **72**, 1233; (d) R. A. Sheldon, *Russ. Chem. J.*, 2000, **44**, 9. (e) R. A. Sheldon, *Green Chem*., 2007, **9**, 1273; (f) P. J. Dunn., *Chem. Soc. Rev.,* 2012, **1**, 1452; (g) R. A. Sheldon, *Chem. Soc. Rev*., 2012, **41**, 1437.

5 A. Chaudhary, D. Kumar and R. Singh*, Environ. Sci.Indian J.*, 2008, **3**, 277.

6 (a) Y. Gu and F. Jérôme, *Chem. Soc. Rev*., 2013, **42**, 9550; (b) S Toma, R. Sebesta and M. Meciarova, *Curr. Org. Chem*., 2011, **15**, 2257; (c) N. Mase and C. F. Barbas, *Org. Biomol. Chem*., 2010, **8**, 4043; (d) M. Raj and V. K. Singh, *Chem. Commun*., 2009, **44**, 6687; (e) M. Gruttadauria, F. Giacalone and R. Noto, *Adv. Synth. Catal*., 2009, **351**, 33; (f) A. P. Brogan, T. J. Dickerson and K. D. Janda, *Angew. Chem*., 2006, **118**, 8278; (g) A. P. Brogan, T. J. Dickerson and K. D. Janda, *Angew. Chem. Int. Ed*., 2006, **45**, 8100; (h) Y. Hayashi, *Angew. Chem*., 2006, **118**, 8281; (i) Y. Hayashi, *Angew. Chem. Int. Ed.*, 2006, **45**, 8103; (j) S. Duce, A. Mateo, I. Alonso, J. L. G. Ruano and M. B. Cid, *Chem. Commun*., 2012, **48**, 5184; (k) P. G. Jessop, *Green Chem*., 2011, **13**, 1391; (l) M-O. Simon and C-J. Li, *Chem. Soc. Rev*., 2012, **41**, 1415.

7 (a) *Handbook of Green Chemistry–Green Solvents*, Vol. 4: *Supercritical Solvents*, ed. P. T. Anastas, P. Jessop and W. Leitner, Wiley-VCH, 2010; (b) R. A. Sheldon, *Green Chem*., 2005, **7**, 267-278.

8 *Handbook of Green Chemistry–Green Solvents*, Vol. 6: *Ionic Liquids*, ed. P. T. Anastas, P. Wasserscheid and A. Stark, Wiley-VCH, 2010.

9 (a) I. T. Horváth and J. Rabai, *Science*, 1994, **266**, 72: (b) I. T. Horváth, *Acc. Chem. Res*., 1998, **31**, 641; (c) I. T. Horváth, G. Kiss, R. A. Cook, J. E. Bond, P. A. Stevens, J. Rábai and E. J. Mozeleski, *J. Am. Chem. Soc*., 1998, **120**, 3133; (d) *Handbook of Fluorous Chemistry*, ed. J. A. Gladysz, D. P Curran and I. T. Horváth, Willey, Weinheim, 2004.

10 (a) *Green Polymer Chemistry: Biocatalysis and Biomaterials – Green Polymer Chemistry: Enzymatic Functionalization of Liquid Polymers in Bulk,* ch. **28**, vol. 1043, J. E. Puskas and M. Y. Sen, *ACS Symp. Ser*, 2010; (b) P. Li, D. R. Paul, T-S. Chung, *Green Chem*., 2012, **14**, 1052.

11 (a) V. V. Namboodiri, R. S. Varma. *Green Chem*., 2001, **3**, 141. (b) S. Chandrasekhar, C. Narsihmulu, S. S. Sultana, N. R. Reddy, *Org. Lett.*, **2002**, *4*, 4399. (c) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem*., 2005, **7**, 64; (d) R. Kumar, P. Chaudhary, S. Nimesha, R.Chandra, *Green Chem*., 2006, **8**, 356; (e) B. Thierry and H. J. Griesser, *J. Mat. Chem*., 2012, **22**, 8810; (f) H. Xu, Y. H. Deng, D. W. Chen, W. W. Hong, Y. Lu and X. H. Dong, *J. Control. Release*, 2008, **130**, 238; (g) H. Ihre, O. L. P. de Jesus and J. M. J. Frechet, *J. Am. Chem. Soc*., 2001, **123**, 5908; (h) L. Kong, H. Xing, B. Su, Z. Bao, Z. Zhang, Y. Yang, Q. Ren, *Green Chem*., 2014, 16, 102.

12 (a) K. Knop, R. Hoogenboom, D. Fisher and U. S. Schubert, *Angew. Chem. Int. Ed*., 2010, **49**, 6288. (b) L. C. C. Vieira, M. W. Paixão and A. G. Corrêa, *Tetrahedron Lett*., 2012, **53**, 2715.

13 (a) *Conjugative Additions in Organic Synthesis*, A. Perlmutter, Pergamon Press: Oxford, 1992; (b) M. Yamaguchi, *Conjugate Addition of Stabilized Carbanions* in : *Comprehensive Asymmetric Catalysis*, eds:, E. N. Jacobsen, A. Pfaltz, H. Yammamoto, Springer Berlin, 1999, vol. 3; (c) M. P. Sibi and S. Manyem, *Tetrahedron,* 2000, **56**, 8033; (d) N. Krause and A. Hoffmann-Röde, *Synthesis*, 2001, **2**, 171; (e) S. B. Tsogoeva, *Eur. J. Org. Chem*., 2007, **11**, 1701; (f) D. Almasi, D. A. Alonso and C. Najera,*Tetrahedron Asymmetry*, 2007, **18**, 299; (g) J. L. Vicario, D. Badia and L. Carrillo, *Synthesis*, 2007, **14**, 2065;(h) M. Thirumalaikumar, *Org. Prep. Proced. Int.*, 2011, **43**, 67; (i) K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach and Y. Hayashi, *Helv. Chim. Acta*, 2011, **94**, 719; (j) Y. Zhang and W. Wang, *Catal. Sci. Technol*., 2012, **2**, 42.

14 (a) H. Pellissier,*Tetrahedron*, 2007, **63**, 9267; (b) S. Brandau, A.Landa, J. Franzen, M. Marigo and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2006, **45**, 4305; (c) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem. Int. Ed*., 2007, **46**, 8431; (d) C. Bhanja, S. Jena, S. Nayak, S. Mohapatra and Beilstein *J. Org. Chem*., 2012, **8**, 1668; (e) D. Almasi, D. A. Alonso and D. Najera, *Tetrahedron Asymmetry*, 2007, **18**, 299.

15 (a) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi and K. Maruoka, *Angew. Chem. Int. Ed*., 2003, **42**, 3796; (b) Y. Yamamoto, N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.,* 2004, **126**, 5962; (c) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc*., 2005, **127**, 6964; (d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri and M. Petrini, *Chem. Rev*., 2005, **105**, 933; (e) F. Wu, R. Hong, J. Khan, X. Liu and L. Deng, *Angew. Chem. Int. Ed*., 2006,**45**, 4301; (f) Y. K. Chen,M. Yoshida and D. W. C. MacMillan*, J. Am. Chem. Soc*., 2006, **128**, 9328; (g) D. Almas¸ D. A. Alonso and C. Nájera, *Tetrahedron Asymmetry*, 2007, **18**, 299; (h) G. Guillena, D. J. Ramón and M. Yus, *Tetrahedron Asymmetry,* 2007, **18**, 693;(i) D. Enders, K. Lüttgen and A. A. Narine, *Synthesis*, 2007, **7**, 959; (j) D. Almas ¸i, D. A. Alonso, E. Gómez-Bengoa, Y. Nagel and C. Nájera, *Eur. J. Org. Chem.,* 2007, **14**, 2328; (k) H. Pellissier, *Tetrahedron* 2007,**63**, 9267; (l) S. B. Tsogoeva, *Eur. J. Org. Chem*.,2007, **11**, 1701; (m) J. L. Vicario, D. Badia and L. Carrillo, *Synthesis,* 2007, **14**, 2065; (n) B. Tan, X. Zeng, Y. Lu, P. J. Chua and G. Zhong, *Org. Lett*., 2009, **11**, 1927; (o) Y. Liu, B. Sun, B. Wang, M. Wakem and L. Deng, *J. Am. Chem. Soc*., 2009, **131**, 418; (p) Y.-F. Sheng, Q. Gu, A.-J. Zhang, S.-L. You*, J. Org. Chem*., 2009, **74**, 6899; (q) S. Chandrasekhar, K. Mallikarjum, G. Pavankumarreddy, K. V. Rao and B. Jagadeesh, *Chem. Commun*., 2009, **33**, 4985; (r) S. Syu, T.-T. Kao and W. Lin, *Tetrahedron*, 2010, **66**, 891; (s) G.-L. Zhao, A. Córdova, *Tetrahedron Lett*., 2007, **48**, 5976; (t) Y. Wang, P. Li, X. Liang and J. Ye, *Adv. Synth. Catal*., 2008, **350**, 1383; (u) I. Fleischer and A. Pfaltz, *Chem. Eur. J*., 2010, **16**, 95; (v) R. Baran, E. Veverková, A. Skorcová and R. Sebesta, *Org. Biomol. Chem.,* 2013, **11**, 7705; (w) Y. Qiao and A. D. Headley, *Green Chem*., 2013, **15**, 2690.

16 (a) K. S. Feu, A. M. Deobald, S. Narayanaperumal, A. G. Corrêa and M. W. Paixão, *Eur. J. Org. Chem*., 2013, **26**, 5917. (b) A. M.

Deobald, A. G. Corrêa, D. G. Rivera and M. W. Paixão, *Org. Biomol. Chem*., 2012,**10**, 7681.
17 C. Moberg, *Angew. Chem. Int. Ed*., 2013, **52**, 2160.
18 (a) Y. Hayashi, T. Itoh, M. Ohkubo and H. Ishikawa, *Angew. Chem. Int. Ed.*, 2008, **47**, 4722; (b) P. Garcia-Garcia, A. Ladépêche, R. Halder, B. List, *Angew. Chem. Int. Ed.*, 2008, **47**, 4719; (c) Y. Qiao, J. he, B. Ni and A. D. Headley, *Adv. Synth. Catal*. 2012, **354**, 2849; (d) E. M. Geertsema, Y. Miao, P. G. Tepper, P. de Haan, E. Zandvoort and G. J. Poelarends, *Chem. Eur. J.,* 2013, **19**, 14407; (e) X. Fan, C. Rodríguez-Escrich, S. Sayalero and M. A. Pericàs, *Chem. Eur. J*., 2013, **19**, 10814.

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