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Development and Scale-up of an Organocatalytic Enantioselective Process to Manufacture (*S*)-Pregabalin

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Supporting Information

ABSTRACT: Herein is reported the development of a new process to manufacture (*S*)-pregabalin. The method comprises six steps, run under the catalysis of a recyclable polymer bound phase transfer catalyst, and afforded (*S*)-pregabalin in overall 54% yield, starting from building blocks acetylacetone, isovaleraldehyde, and nitromethane.

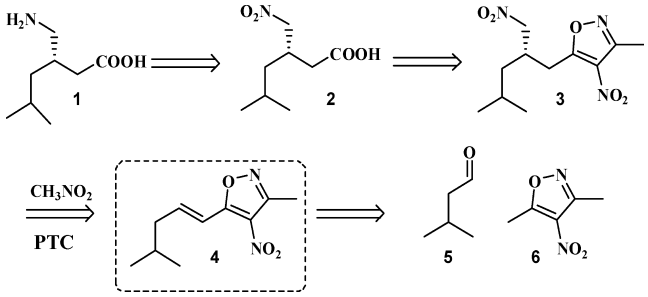
1. INTRODUCTION

(*S*)-Pregabalin **1** is currently manufactured by the originator (Pfizer) as well as by other generic pharmaceutical producers.[1−9] The original Pfizer process involved six steps, the enantioselective one relying on a Rh(DUPHOS) catalyzed hydrogenation.[1] Rhodium and chiral phosphines are becoming increasingly expensive, and in order to gain competitiveness, Pfizer has recently developed and patented a new process in which the chirality was generated via an enzymatic step.[2] Many other generic producers have recently filed patents describing their processes to manufacture (*S*)-pregabalin **1**.[3] A vast proportion of these technologies gave (*RS*)-pregabalin as a racemate, from which (*S*)-**1** was then obtained via diastereoisomeric crystallization. This limited the theoretical yield of (*S*)-**1** at 50% with concomitant discard of 50% in mass of the unwanted (*R*)-isomer. Recently, Piramal developed a method to racemise (*R*)-pregabalin-**1** to (*RS*)-pregabalin-**1** in order to recycle the unwanted isomer.[4] Other methodologies have been described to produce (*S*)-**1**. These relied either on bioenzymatic steps,[5] diastereoselective synthesis from natural biomass (D-mannitol),[6] organocatalysis,[7,8] and flow chemistry.[9] Although these methodologies provided (*S*)-**1** in high enantiomeric excess,[5−9] no evidence has been provided on the reliability of these syntheses in a multikilogram context. Therefore, the suitability of these to manufacture (*S*)-**1** at a large scale is still uncertain.

Phase transfer catalysis (PTC) has been effectively used to manufacture drugs intermediates and unnatural α-amino acids and drug intermediates at scale.[10a] *Cinchona* derived phase transfer catalysts, used to perform these transformations, can be prepared in a single step from inexpensive *Cinchona* alkaloids which could be recovered and recycled at the end of reaction.[10b−d] In this context, it is noteworthy the immobilization of *Cinchona* derived phase transfer catalysts on polystyrene beads, which could be used to perform an enantioselective step and recycled.[11] Importantly, the reactions carried out with the polystyrene bound catalysts gave similar conversion and enantioselectivity as the one carried out using the unbound agents. Therefore, on the bases of cost of reagents, chemical efficiency and precedents for large scale manufactures, Phase transfer catalysis (PTC) was selected as the technology of choice for the development of a new process to prepare (*S*)-**1**.

As part of their research, the Adamo's group has developed alkenes **4** as optimal Michael acceptors (Scheme 1).[12]

Scheme 1. Retrosynthetic Analysis for the Preparation of (*S*)-Pregabalin 1



Compounds **4** underwent highly enantioselective addition when reacted with nitromethane[13,14] (Scheme 1), as well as with bromomalonates[15] under phase transfer catalysis. With this in mind, the synthesis of (*S*)-**1** was planned around the PTC catalyzed addition of nitromethane to compounds **4**. In retrosynthetic fashion (Scheme 1), (*S*)-**1** could be obtained via reduction of nitroacid **2**, which is also an intermediate for the synthesis of racemic and enantiopure pregabalin.[16] In turn, nitroacid **2** could be prepared from hydrolysis of nitroisoxazole **3** via the Sarti−Fantoni reaction,[15] a procedure in which the 4-nitroisoxazole core could be opened to display a carboxylate by treatment with excess hydroxide. Compound **3** was then accessible via PTC catalyzed addition of nitromethane to alkene **4**, which, in turn, could be made by condensation of aldehyde **5** and 4-nitroisoxazole **6**.[14]

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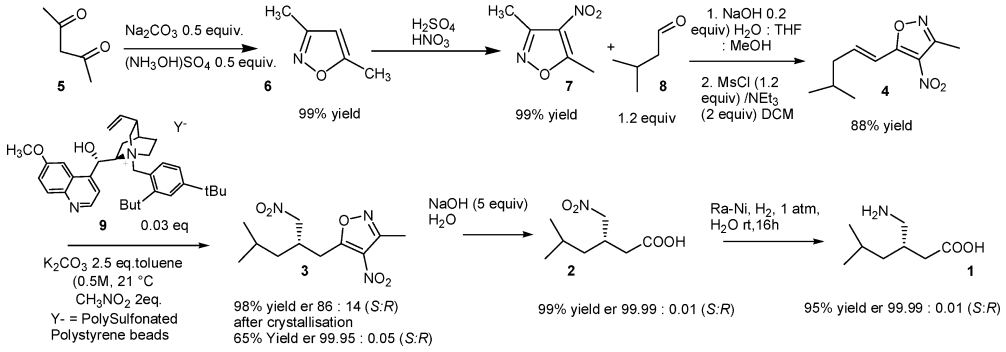
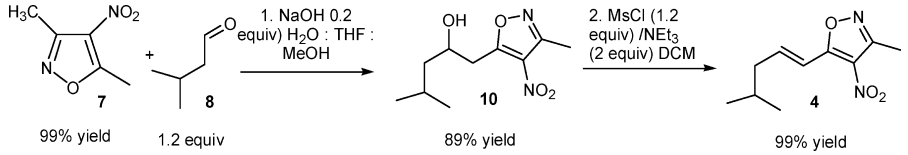
Scheme 2. Preparation of (*S*)-Pregabalin 1



Scheme 3. Preparation of Michael Acceptor 4



2. RESULTS AND DISCUSSION

In forward sense, the preparation of (*S*)-**1** has been accomplished starting from acetylacetone **5**, aldehyde **8** and nitromethane as the carbon containing building blocks.[17] Hence, acetylacetone **5** was reacted with hydroxylamine to obtain 3,5-dimethylisoxazole **6** in excellent isolated yields compound **6**, in turn was nitrated to 3,5-dimethyl-4-nitro-isoxazole **7** which was equally obtained in quantitative yields. The next step involved a two-phase procedure to condensate **7** and aldehyde **8** to desired Michael acceptor **4**. Compound **4**, which was obtained in 88% optimized yield, was then subjected to enantioselective Michael addition with nitromethane, a reaction which proceeded under the catalysis of *Cinchona* based ammonium salt **9** to provide adduct **3** in excellent yield and good enantioselectivity (from 72 to 86% ee, vide infra). Compound **3** could be recrystallized to enantiopure (99.7% ee) and then subjected to the Sarti−Fantoni reaction to access nitroacid **2**. Final reduction of the nitro group in **2** provided (*S*)-pregabalin **1**. The conditions highlighted in Scheme 2 are optimized and proved to work at kilogram scale. This required optimization of each step and development of opportune methods of purification. The development and the optimization of each synthetic steps described in Scheme 2 will be described below.

The condensation of acetylacetone and hydroxylamine is a well-known reaction that has been described in many papers.[18] This reaction takes place in water and involves dissolving an opportune hydroxylamine salt and a base to make an aqueous solution of hydroxylamine (pH ≈ 8) to which acetylacetone **5** was slowly added under vigorous stirring. The addition of acetylacetone **5** to a solution of hydroxylamine is exothermic, and on a 10 kg scale the temperature of the solution went from 18 °C to 35−40 °C (**5** added in portions during a period of 1 h). We have described the preferred use of hydroxylamine carbonate as this was, to our knowledge, the cheapest source of hydroxylamine. However, we have tested other salts, for example hydroxylamine hydrochloride, which worked equally well. The reaction of **5** and hydroxylamine gave in our hands almost quantitative yields which could be explained as follows. First, the resulting 3,5-dimethylisoxazole **6** is insoluble in water and upon cooling of the reaction mixture separated out as an oily supernatant that was decanted. This procedure assured ≈85% weighted yield of **6**, which was augmented by subjecting the water layer to distillation under reduced pressure (T = 58 °C, P = 37 mmHg). This operation, at R&D lab scale, could be performed well using a rotavapor. Compound **6** was distilled off from the water layer to provide an additional 10−14% in mass. Key to optimization of this step was the concentration at which this reaction should be performed. Hence, using a 3 M molar concentration ensured separation of the oily phase of **6** as a supernatant, which would not occupy promptly when the reaction was performed in a diluted media. Compound **6** obtained from this step and purified as described above could be carried through the next step without further purification.

Nitration of compound **6** to provide 3,5-dimethyl-4-nitro-isoxazole **7**, which occurred under conventional aromatic nitration condition. This involved dissolving compound **6** in cold (0−5 °C) sulfuric acid then adding nitric and then excess of sulfuric acid keeping the temperature below 15−20 °C. The subsequent heating of the reaction mixture generated an exotherm which brought the temperature from 50 to 58 °C. This data is in line with observation recorded for other aromatic nitrations which is explained considering the generation of a $^{+}NO_2$ ion. Quenching of reaction using water ice bath gave almost quantitative yield of desired **7**, which is highly water insoluble and precipitated immediately. Noteworthy, to obtain acid free **7**, suitable for the next step, the acidic reaction mixture should be poured into a vortex formed by fast stirring of an cooled aqueous bath media. This ensured fast precipitation of water insoluble **7** that was obtained as a fine powder. Filtration of the cake of **7** and its washing with cold water gave compound **7** pure enough to be carried out in the next step. The high yield observed in the preparation of **7** therefore is a reflection of its extremely low solubility in water. It should be noted that nitration of **6** to **7** could also be performed using ammonium nitrate and trifluoroacetic acid[12a] and that the sulfonitric mixture was selected based on low cost of these reagents.

The condensation of compound **7** and aldehyde **8** (Scheme 3) to provide aldol compound **10** was studied under a vast number of conditions which included variation of temperature,

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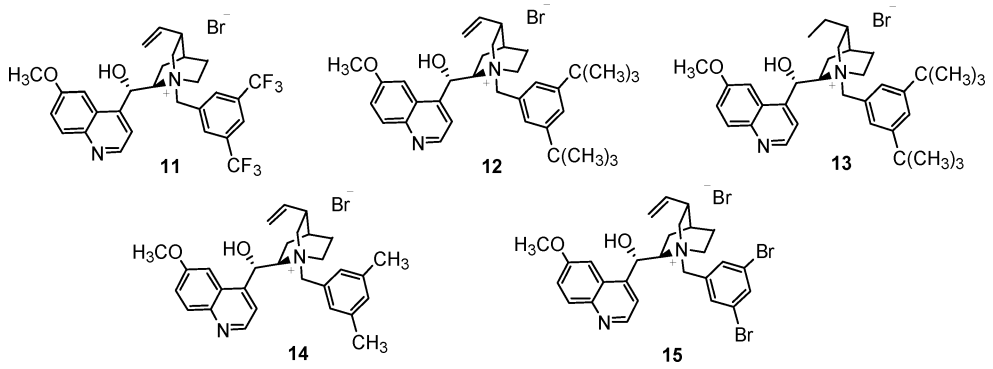
Table 1. Catalyst Screening



entry[a]	catalyst	conv % of **4**	yield % of **3**	ee % of **3**	er *S*:*R* of **3**
1	**11**	100	95	72	86:14
2	**12**	100	97	86	93:7
3	**13**	100	96	85	92:8
4	**14**	100	97	64	82:18
5	**15**	100	91	62	81:19

[a]Alkene **4** (20 mg, 0.096 mmol) toluene (9.6 mL), catalyst **11**−**15** (0.1 equiv, 10 mol %), and nitromethane (30 mg, 0.48 mmol, 5 equiv), temperature 0 °C, K_2CO_3 (66 mg, 0.48 mmol, 5 equiv) added in one portion. The reaction was stirred for 32 h, then quenched with sat NH_4Cl (10 mL), extracted with toluene (2 × 10 mL), dried over $MgSO_4$, filtered over Celite, and evaporated to give pure compound in yield and ee listed.

solvent, amount of hydroxide base, order of addition of reagents, and concentration. The nucleophilic addition of deprotonated **7** to aldehyde **8** is thermodynamically favored. However, there is a remarkable difference in the solubility of these reagents. Compound **7** lithium or sodium salt is very soluble in water but virtually insoluble in most organic solvents. On the other hand, aldehyde **8** is very soluble in most organic solvents but very poorly soluble in water. For this reason, the optimization of this step required, principally, a careful selection of the solvent media. After several attempts, a ternary mixture of water, tetrahydrofuran, and methanol was identified as the best media to ensure high yields of aldol compound **10**. The use of substoichiometric amounts of sodium hydroxide allowed limiting the loading of **8** to 1.2 equiv. The limited amount of base reduced the extent of self-condensation of **8** and allowed obtaining compound **10** in higher yields and purity. We have shown that the preparation of **10** could be performed in a range of temperatures varying from −5 °C to ambient (20 °C). However, when run at 0−5 °C, the self-condensation of aldehyde **8** was suppressed and compound **10** obtained in 89% yield. The crude ^{1}H NMR of this reaction showed, after work up, that **10** contained starting materials **7** (7%) and **8** (5%) together with a small amount of alkene **4** (8%) as the only contaminants. Therefore, the reaction of **7** and **8** under this condition was an equilibrium reaction which cleanly produced desired **10** and small amounts of dehydrated **4**. Crude compound **10** could be used in the next step without further purification. Therefore, compound **10** was dissolved in dichloromethane and treated with mesyl chloride and triethylamine. The optimized procedure involved using 1.2 equiv of mesyl chloride and two equivalents of triethylamine. It should be noted that the addition of the first equivalent of triethylamine was exothermic and therefore this first part of the reaction must be conducted with control of temperature. Also, while the mesyl chloride could be charged in one portion, the addition of triethylamine has to occur within a range of time (typically 1 h when the reaction was conducted on a 10 kg scale, but this may be variable with the design of the reactor). Noteworthy, this step was equally fast when run at −30 °C and at 20 °C, and in all cases only the *E*-stereoisomer could be detected.[12a] Compound **4** could be obtained in 96% purity (NMR) by a simple wash with water and diluted hydroxide which served to eliminate the remainder traces of compound **7** and **8** brought through from the previous step. This product was pure enough to be carried through the enantioselective to prepare **3**. It should be noted that the following step is robust enough to allow using samples of alkene **4** containing up to 15−20% impurities. These low grade samples reacted equally providing desired Michael adduct **3** in identical enantioselectivity and reaction rates as a pure sample. Although not necessary, compound **4** could be obtained in purity higher that 99.9% by (a) distilling crude **4** (120 °C at 0.2 mb) and (b) performing a treatment with DMF and water which retained the traces of unreacted **7** and **8**.

The following step involved the optimization of the enantioselective procedure to obtain compound **3**. The optimization of this step has been achieved in three phases, which involved: (a) the selection of an optimal catalyst, (b) the adjustment of condition to perform the addition of nitromethane to **4** at 0.5 M concentration; (c) the preparation of a polymer bound catalyst and its recycling.

We have first determined that *Quinidinium* salts were providing the desired (*S*)-**3** over the unwanted (*R*)-**3**. This was established by converting (*S*)-**3** to desired (*S*)-**1** and measuring the optical rotation of the final compound. In addition, toluene and potassium carbonate were found as the best media to perform this reaction. Therefore, a number of quinidinium ammonium salts were subsequently screened. A short list of the most relevant catalysts **11**−**15** is described in Table 1 alongside the enantioselectivity of compounds **3** obtained. The addition of nitromethane to alkene **4** was also performed under the catalysis of Maruoka's catalysts.[10a] These experiments gave desired adduct **3** in almost racemic mixtures (3−8% ee).

As evidenced in Table 1, catalysts **12**−**13** holding two ^{t}butyl groups ensured the highest enantioselectivity. Compound **3** was

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therefore obtained in up to 86% ee when the reaction was conducted at 0 °C and in diluted media. Reactions carried out at lower temperatures (up to −28 °C) provided desired **3** in significantly lower ee's. With the best catalyst in hand, we have then studied the variation of enantioselectivity of **3** as a function of temperature and reagent concentration.

The results collected in Table 2 pointed out that reaction rate increased with the concentration; however, the enantioselectivity of **3** dropped from 86% at 0.01 M to 72% at 0.5 M. This data identified 0.08 M as a threshold for the concentration to still obtain high enantioselectivity and it also showed that complete conversion was only obtained with high catalyst loading. In order to reduce the catalyst loading further, we have conducted a series of experiments at room temperature. This set of experiments showed that compound **4** was fully converted in 24 h and with only 0.03 equiv of 0 °C **12** affording compound **3** in high yields and in 72% ee's. Importantly under this new set of condition, the amount of nitromethane could be reduced to only two equivalents. It has been found beneficial to purity of compound **3** to prepare a solution of nitromethane and catalyst **12** and then add this dropwise to a suspension of alkene **4** and base in toluene. This limited the time of contact between base and nitromethane which suffered of base-catalyzed polymerization.

Table 2. Effect of Concentration on the Enantioselectivity of 3

entry[c]	conc. of **4**	conv. of **4** (h)	ee % of **3**
1[a]	0.01 M	100% (96 h)	86%
2[b]	0.01 M	90% (96 h)	86%
5[b]	0.04 M	75% (40 h)	85%
6[b]	0.08 M	80% (20 h)	83%
7[b]	0.16 M	83% (20 h)	80%
8[b]	0.32 M	92% (19 h)	74%
9[b]	0.50 M	100% (24 h)	72%
10[d]	0.50 M	60% (96 h)	72%

[a]Reaction conducted with 0.1 equiv of **12**. [b]Reaction conducted with 0.05 equiv of **12**. [c]Alkene **4** (20 mg, 0.096 mmol) toluene, catalyst **12** (0.05 equiv, 5 mol %), nitromethane (5 equiv), temperature 0 °C, K_2CO_3 (5 equiv) added in one portion. The reaction was stirred for the time listed, then quenched with sat. NH_4Cl, extracted with toluene, dried over $MgSO_4$, filtered over Celite, and evaporated to give compound **3** in ee listed. [d]Reaction conducted with 0.03 equiv of **12**.

Finally, with the aim of recycling catalyst **12** and show this could be used in additional cycles, we have immobilized **12** on a sulfonylated polystyrene matrix as described by Itsuno.[11] Hence compound **12** was reacted with *p*-sulfonylstyrene, and the ammonium sulfonate salt so obtained was subsequently subjected to radical polymerization. The catalyst loading was determinated by elemental analysis and resulted to be of 0.57 mmol/g. The resulting material was employed in the reaction of **4** with nitromethane under the optimized conditions identified (Scheme 2). Delightfully, the reaction proceeded under the catalysis of 0.03 equiv of polystyrene bound **12** providing compound **3** in the high yields and 72% ee. In relation to polymer-bound **12**, we have found the following experimental facts: (a) the polymerized product must be washed with toluene before being employed; indeed unpurified material obtained via the Itsuno procedure may still contain dimethyformamide which interferes with the reaction of **4**, leading in the first cycle to compound **3** in a decreased ee's; (b) the polymer-bound catalyst could be reused up to 10 times without loss of enantioselectivity and of conversion; (c) as reported by others,[11] the polymer elemental content of nitrogen remained constant at each run, hence demonstrating no loss of ammonium salt from the polymer. Hence, polymer-bound catalyst **12** was a robust and practical catalyst that promoted the formation of desired adduct **3** and could be separated via simple filtration and reused.

Compound **3** could be recrystallysed to >99% ee and then carried through to final (*S*)-pregabalin **1**. In alternative, enantioenriched compound **3** (72% ee) cold be carried through the two following steps to give (*S*)-**1** in identical 72% ee. This latter could be then subjected to partial resolution via reported methodology.[3]

Compound **3** was then subjected to the Sarti−Fantoni reaction,[14] which entailed mixing neat compound **3** with a 5 N NaOH solution and then heating to reflux for 2 h. This reaction gave excellent yields of compound **2**, which was fully characterized. However, compound **2** is remarkably acid sensitive, and it is prone to decompose rapidly if heated or if brought to a pH < 3. On the contrary, sodium carboxylate salt of **2** is very stable and could be isolated and stored for long periods. We have found that the best procedure to obtain high yield of desired (*S*)-**1** involved submitting an aqueous solution of **2** sodium salt to reduction using Ni/Ra and hydrogen.

The reduction of acid **2** to (*S*)-**1** has been reported in a number of papers and patents[19] and could be conducted with loadings of Ni/Ra in dependence of the pressure of H_2 employed and of the quality and make of the catalyst. With the low grade Ni/Ra available to us and in order to operate at 1 atm, 2 equiv of Ni/Ra were necessary to obtain quantitative yields of compound **1**. The high loading of Ni/Ra was required to avoid the formation of products of partial reduction. We have observed that the starter nitroacid **2** disappeared just after 2 h; however, the purity and quantity of the reduced compound, i.e., pregabalin **1**, increased with elongation of reaction time. We have also verified that Ni/Ra could be reused for at least 8 cycles before it lost in part its activity and required regeneration. We have also demonstrated that Pd/C and H_2 or ammonium formate are equally good reductants allowing to obtain desired (*S*)-**1**.

3. CONCLUSION

In conclusion, we have developed and reported a new process for the manufacture of (*S*)-**1** in six steps and in overall 54% yields. The method made use of a recyclable organocatalyst and employed acetylacetone, isovaleraldehyde, and nitromethane as the carbon-containing building blocks. The *Chincona* alkaloids could be sourced at average 25−30 €$/kg from the Asian market and are a cheap source of chirality mostly when considering their recyclability up to 10-fold. Therefore, they compare well, price-wise with the phosphines normally employed in the synthesis of γ-amino acids, which price range from $40.000 to $80.000 per kg. In addition, the best methods of resolution of pregabalin gave only 25−30% yields.[1−4] Therefore, the present method that provides (*S*)-**1** in 65% yield is competitive when benchmarked against resolution. Considering that all the reagents could be sourced at cheap price and the solvents and catalysts recycled, this is a cost-efficient and competitive method for the large-scale manufacture of (*S*)-**1**.

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4. EXPERIMENTAL SECTION

General Experimental Details. ^{1}H, ^{13}C, and NMR spectra were recorded on a Varian AS 300 and Bruker 400 and 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR (^{1}H NMR: 7.26 ppm for $CDCl_3$; ^{13}C NMR: 77.0 ppm for $CDCl_3$. ^{13}C NMR spectra were acquired with ^{1}H broad band decoupled mode. DMSO-d_6 (referenced to 2.52 and 3.35 ppm for ^{1}H and 40.0 for ^{13}C). Coupling constants (J) are in Hz. Multiplicities are reported as follows: s, singlet, d, doublet, dd, doublets of doublets, t, triplet, q, quartet, m, multiplet, c, complex, and br, broad. ^{1}H NMR spectral assignments are supported by $^{1}H-^{1}H$ COSY and $^{13}C-^{1}H$-COSY where necessary. Carbon spectra are supported by DEPT analysis where necessary.

Melting points were determined using a Stuart scientific melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded as KBr discs using a Bruker Tensor27 FT-IR instrument. Absorption maximum (ν_{max}) was reported in wave numbers (cm^{-1}), and only selected peaks are reported. High-resolution mass spectra were obtained on a Waters Micro mass LCT, and low-resolution mass spectra were recorded on Waters Micro mass Quattro LC-MS spectrometers at 70 eV. Tetrahydrofuran was freshly distilled over sodium benzophenone prior to use according to standard procedure. All other reagents and solvents were used as purchased from Aldrich. Reactions were checked for completion by TLC (EM Science, silica gel 60 F254) which were visualized by quenching of u.v. fluorescence (λ_{max} = 254 nm) or by staining with either 10% (w/v) ammonium molybdate in 2 M sulfuric acid or basic potassium permanganate solution (followed by heat) as appropriate. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD, Chiracel OJ, Chiracel OD, Chiralpak AS columns), using a UV detector operating at 254 nm. Retention factors (R_f) are reported to ±0.05.

Preparation of 3,5-Dimethylisoxazole ***6***. In a round bottomed flask (20 L) fitted with a magnetic stirrer were put 7 L of deionized water, followed by $(NH_3OH)_2SO_4$ (1710.2 g, M_w = 164, 10.44 mol) followed by addition of small portions of $Na_2CO_3 \cdot 10H_2O$ (3000 g, M_w = 286, 10.48 mol). After evolution of CO_2 ceased and pH was ~8, acetylacetone **5** (2070 g, M_w = 101, 20.7 mol) was added in one portion and the reaction mixture heated at 65 °C for 16 h. At the end of this time an oily supernatant was noted which was decanted and proven to be pure 3,5-dimethylisoxazole (1730 g). The water layer was loaded in a rotary evaporator, heated at 58 °C, and kept at a pressure of 37 mmHg to distill a second fraction of 3,5-dimethylisoxazole (360 g). The combined fractions could be used in the next step without further purification. Optionally they could be purified by distillation using a rotavapor (58 °C, 37 mmHg), to give pure title compound (2040 g, 99% yield). 3,5-Dimethylisoxazole **6** so obtained is stable at room temperature and did not show signs of decomposition after 12 months.

Preparation of 3,5-Dimethyl-4-nitroisoxazole ***7***. In a round bottomed flask (20 L), fitted with overhead stirrer and kept at −5 to 0 °C by an ice salt bath, was put H_2SO_4 (95−98% ACS reagent, 3240 mL; d = 1.83) then 3,5-dimethylisoxazole (1200 g). This addition must be carried out slowly to ensure that the temperature stays close to 0 °C. Then HNO_3 conc. previously cooled at temperature between 0 and 5 °C (1200 mL; d = 1.413) was added, and then additional H_2SO_4 conc. (5064 mL) was added in small portions. The solution was then heated at 60−65 °C for 6 h, then allowed to reach room temperature and poured dropwise in a basin (30 L) containing ice and water under vigorous stirring. A fine precipitate was obtained then filtered, washed (suspended in 20 L of water and stirred vigorously for 10 min, then filtered (operation to be repeated until water is neutral) and dried (1720 g; yield 99%). This product could be used in next step without further purification and stored at room temperature for long periods (over 24 months).

Preparation of 4-Methyl-1-(3-methyl-4-nitro-isoxazol-5-yl)-pentan-2-ol ***10***. In a 10 L round bottomed flask fitted with a magnetic stirrer were put 3,5-dimethyl-4-nitroisoxazole (1000 g, M_w = 142, 7.042 mol) and 800 mL of THF and the resulting solution stirred at 0 °C. To this solution, were then added 2000 mL of MeOH−H_2O (7:3). A freshly made solution of NaOH (56 g, M_w = 40, 1.4 mol, 0.2 equiv) in 500 mL of H_2O was then charged in a dropping funnel and added dropwise over 10 min. Upon this addition, the solution becomes yellow to dark brown. It was noted the formation of a precipitate of sodium 3,5-dimethyl-4-nitroisoxazolate that will dissolve during the course of the reaction. At this point, a solution of isovaleraldehyde (726 g, M_w = 86, 8.45 mol, 1.2 equiv) in 200 mL of THF was added dropwise at 0 °C, over the period of 50 min. After this period the ice bath was removed, and the reaction allowed reaching room temperature under vigorous stirring. Conversion was monitored after 5 h (60%), 10 h (83%), and 16 h (92%) since end of addition of aldehyde. A sample of the reaction mixture was kept under stirring for further 2 h and conversion measured again (92%) indicating the reaction mixture had reached the equilibrium. The reaction was quenched by addition of distilled H_2O (5000 mL), stirred for 10 min, then extracted twice with DCM (first extraction 3000 mL; second extraction 2000 mL). The organic layers were combined, washed with H_2O (3000 mL at least to avoid formation of emulsion), then with sat. $NaHSO_3$ (2000 mL) then again with H_2O (3000 mL). The organic layer was evaporated at the rotavapor (49 °C, 44mb) to give 1610g of material which contains the title compound alongside 7% of alkene **4** (vide infra), 8% of unreacted 3,5-dimethyl-4-nitroisoxazole **7**, and 5% of isovaleraldehyde **8**. Estimated weight in title alcohol was 1430 g (89% yield). Colorless liquid; R_f = 0.2 (petroleum ether/ethyl acetate, 90:10); δH (400 MHz, $CDCl_3$) 4.23−4.20 (1H, m), 3.36 (1H, dd, J = 15, J = 4), 3.29 (1H, dd, J = 15, J = 7), 2.55 (3H, s), 1.87−1.76 (1H, m), 1.58−1.53 (1H, m), 1.40−1.34 (1H, m), 0.95 (3H, d, J = 7), 0.93 (3H, d, J = 7); δC (100.6 MHz, $CDCl_3$) 172.9, 155.8, 130.9, 68.0, 46.8, 36.1, 24.8, 23.3, 22.0, 11.8. HRMS: m/z found $[M + H]^+$ 229.1154, $C_{10}H_{17}N_2O_3$ requires 229.1188.

Synthesis of 3-Methyl-5-(4-methyl-pent-1-enyl)-4-nitro-isoxazole ***4***. In a 20 L round bottomed flask fitted with an overhead stirrer (to overcome difficult stirring caused by formation of solid $HNEt_3Cl$ during the reaction) were loaded 800g of 4-methyl-1-(3-methyl-4-nitro-isoxazol-5-yl)-pentan-2-ol (about 90% pure, 720g, 3.165 mol, M_w = 229) and 10 L of DCM. The solution was cooled at 0 °C by ice water, then mesyl chloride (433.1 g, M_w = 114, 3.8 mol, 1.2 equiv) was added dropwise over 30 min. To the resulting solution was then added NEt_3 (638.5 g, 6.33 mol, M_w = 101, 2.0 equiv) dropwise over the period of 2 h 30 min. It should be noted that addition of the first equivalent of NEt_3 is exothermic; therefore, addition should be carried out at such a rate to keep temperature between 0 and 10 °C maximum. This is to avoid formation of

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side products and ensure high purity of alkene product. After the addition was completed, the reaction was allowed to reach room temperature and stirred for 2 h (from the end of addition of NEt_3). The reaction was quenched with H_2O (3000 mL), washed with additional H_2O (2 × 5000 mL), then with 5% NaOH in water, the organic layer dried over Na_2SO_4 and then evaporated under reduced pressure to give 1390g of crude product that could be used in the next step (estimated purity 96% by ^1H NMR). The product so obtained could be taken through the next step without further purification. Optionally, the crude product (1390g) could be thinned with 500 mL of petroleum ether (40−60 °C) and passed through a plug of silica gel (flash type) (100g) to give 1320g of title compound. Pale yellow liquid; R_f = 0.8 (petroleum ether/ethyl acetate, 90:10); δ_H (400 MHz, $CDCl_3$) 7.12- 7.00 (2H, m), 2.56 (3H, s), 2.29−2.26 (2H, m), 1.89−1.82 (1H, m), 0.97 (6H, d, J = 6), δ_C (100.6 MHz, $CDCl_3$) 167.0, 156.0, 130.1, 115.6, 43.0, 28.3, 22.5, 12.0. HRMS: m/z found $[M]^+$ 196.0815, $C_9H_{14}N_2O_3$ requires 196.0848.

Note 1: While the next step proceeds well with alkene containing variable levels of impurities (1−15%), product **4** can be obtained over 99.9% pure via distillation, collecting the fraction boiling over 120 °C at 0.2 mb. The yield was ca. 65−70% of pure alkene.

Note 2: For purification via DMF wash, the alkene may be obtained over 99.9% pure by dissolving it in a DMF−H_2O (20:80) mixture and then extracting with petroleum ether. Typically, 120 g of crude material were dissolved in 100 mL of DMF; then 400 mL of water were added, and the resulting yellow solution was extracted with petroleum ether (40:60), (2× 500 mL). Optionally, the alkene (20 g) was dissolved in petroleum ether (40:60, 50 mL), then treated with 3 mL of DMF, stirred for 20 min, then washed with water (2 × 50 mL).

*Synthesis of (S)-3-Methyl-5-(4-methyl-2-nitromethyl-pentyl)-4-nitro-isoxazole **3** Using a Solution of Catalyst **12**.* In a 20 L round bottomed flask fitted with an overhead stirrer were charged toluene (6600 mL) and K_2CO_3 (1518 g, 11 mol, 2.5 equiv). A solution of alkene **4** (924g, 4.4 mol), nitromethane (536g, 8.8 mol, 2 equiv), and catalyst **12** (217.8 g, 0.03 equiv) in toluene (2200 mL) was charged in a dropping funnel and added dropwise over a 2 h period. The reaction was stirred at room temperature (21 °C) until conversion is completed (8−24 h) (Note: Conversion rates have been found variable depending on the particle size of potassium carbonate. Smaller particle size gave faster reactions). Then the organic liquid phase was filtered, washed with NH_4Cl dil solution (1000 mL) then with water (2000 mL). The organic layers were evaporated to give compound **3** in 98% yield (1168 g) as a sticky liquid and in enantiomeric ratio (*S*:*R*). The ee of the product was determined by CSP-HPLC using a Chiralcel OD column (*n*-hexane/*i*-PrOH 90:10, flow rate 1 mL/min). Retention times: (*S*)-**3**, 34.4 min, (*R*)-**3** 32.1 min.

Recrystallization of compound **3** from 72% ee to enantiopure +99 ee: pure compound **3** (400 g) was dissolved in minimum amounts of hot isopropanol or hot mixtures of isopropanol petroleum ether (1:1), the second typically 1000 mL. The resulting solution was cooled at 0 °C to give compound **3** as needles, which were filtered, dried, and weighted 280 g (70%) and were 99.95% ee. Colorless solid, mp 55 °C (isopropanol/hexane); δ_H (400 MHz, $CDCl_3$) 4.38 (2H, d, J = 6), 3.35 (1H, dd, J = 15, J = 6), 3.28 (1H, dd, J = 15, J = 7), 2.87 (1H, sept, J = 7), 2.56 (3H, s), 1.68 (1H, sept, J = 7), 1.36−1.23 (2H, m), 0.92 (3H, d, J = 4), 0.90 (3H, d, J = 4), δ_C (100.6 MHz, $CDCl_3$) 172.1, 122.9, 78.5, 40.9, 33.9, 30.0, 25.1, 22.4, 22.3, 11.7. HRMS: m/z found $[M + H]^+$ 272.1212, $C_{11}H_{18}N_3O_5$ requires 272.1246.

*Synthesis of (S)-3-Methyl-5-(4-methyl-2-nitromethyl-pentyl)-4-nitro-isoxazole **3** Using Polymer-Supported **12**.* In a 20 L round bottomed flask fitted with an overhead stirrer were charged toluene (6600 mL) and K_2CO_3 (1518 g, 11 mol, 2.5 equiv), toluene (2200 mL), alkene **4** (924g, 4.4 mol), nitromethane (536g, 8.8 mol, 2 equiv), and polymer-supported catalyst **12** (429 g, 0.03 equiv). The reaction was stirred at room temperature (21 °C) until conversion is completed (8−24 h). (Note: Conversion rates have been found variable depending on the particle size of potassium carbonate. A smaller particle size gave faster reactions.) Then the organic phase was separated, the solids were washed with water to dissolve the inorganic salts to give 428 g of polymer bound catalyst (99% recovery). Ten consecutive runs using the same catalyst gave compound **3** in identical yields and enantiomeric ratio.

*Preparation of Sodium 5-Methyl-3-nitromethyl-hexanoate **2**.* Neat compound **3**, (392g, 1.44 mol) was charged in a 5 L round bottomed flask and treated with a freshly made aqueous solution (5N, 1440 mL, 5 equiv) of NaOH (288g, 7.2 mol). The resulting dark solution was heated (T = 60−65 °C) for 2 h, then allowed to reach room temperature. The dark aqueous solution of **2** sodium salt was carried through the following reduction without requirement for isolation. Isolation and purification of free acid **2** involved: cooling the aqueous solution of **2** sodium salt, adjustment of pH ≈ 3, and extraction with EtOAc. Dark yellow liquid, ^1H NMR (400 MHz, $CDCl_3$) δ_H 4.50 (1H, dd, J = 12, J = 7), 4.44 (1H, dd, J = 12, J = 6) 2.67 (1H, sept, J = 6), 2.49 (2H, d, J = 6), 1.66 (1H, sept, J = 7), 1.28 (2H, m), 0.93 (3H, d, J = 7), 0.91 (3H, d, J = 7). ^{13}C NMR δ_C (100.1 MHz, $CDCl_3$) 177.6, 78.4, 40.3, 35.6, 31.7, 24.9, 22.3, 22.0.

*Preparation of (S)-Pregabalin **1**.* In a 10 L round bottomed flask were charged Raney-Ni (2 equiv, 493 g of slurry 50% Raney-Ni in water) and methanol (2500 mL). To this suspension was added a solution of nitroacid **2** in water and base obtained via hydrolysis of compound **3** (1.44 mol). The suspension obtained was stirred at room temperature under H_2 (1 atm) for 6 h, then the liquid phase decanted, the solid Ra−Ni rinsed with methanol and reused 10 times. The methanolic aqueous solution was evaporated to give an aqueous solution of (*S*)-pregabalin **1**, which was precipitated by adjustment of pH ≈ 6 via addition of diluted hydrochloric acid (95% yield) as a colorless solid and in enantiomeric ratio of (*S*:*R*) of 99.99:0.01. The optical purity of (*S*)-**1** was assessed via HPLC. Compound **1** was reacted with *N*-α-5-fluoro-2,4-dinitrophenyl-5-L-alanine amide. The two diastereoisomers so obtained could be separated by an ordinary chromatography column (Inertsil ODS-2.5 μm, 250 mm × 4.6 mm i.d.). Phosphoric acid buffer and acetonitrile (55:45, v/v) were used as mobile phase, the separation carried out at 1.0 mL/min flow rate, at room temperature, and the detector wavelength fixed at 340 nm. Procedure: 8 mg of (*S*)-pregabalin **1** were accurately weighted in a 10 mL calibrated flask and dissolved in 1 N HCl. The pH of the system was adjusted to 7 by addition of 1N NaOH in water. The volume was brought to 10 mL by addition of distillated water. A portion of 50 μL of this solution was mixed with 200 μL of the FDNPAA solution (100.0 mg of FDNPAA was dissolved by acetone into a 10 mL calibrated flask and stored in the refrigerator) and 20 μL of 1N $NaHCO_3$. The

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solution was closed and heated for 1 h at 40 °C, then 10 μL 2 N HCl was added, and the solution evaporated under vacuum. The residue was dissolved in 4 mL of dimethyl sulfoxide (DMSO) (equivalent to 10.0 μg/mL pregabalin sample). The sample solution was filtered through a membrane filter, and an aliquot (20 μL) of the sample was injected for HPLC analysis. Retention times: derivative of (*S*)-**1**, 9.3 min; derivative of (*R*)-**1** 10.2 min.

Preparation of N-(3,5-Di-tert-butylbenzyl)quinidinium Bromide ***12***.[18] in a round bottomed flask fitted with a magnetic stirrer and a reflux condenser were put sequentially quinidine (1.0 equiv), acetone to make a 0.18−0.20 M solution and finally 3,5-di-*tert*-butylbenzyl bromide (1.05 equiv). The resulting solution was heated at 60−65 °C for 2 h. The reaction mixture was then allowed to reach room temperature, the solvent evaporated to give a solid which was suspended in petroleum ether, stirred for 30 min, then filtered and dried to give pure catalyst (NMR). Optionally the crude product may be dissolved in the minimum quantity of DCM and then precipitated by addition of Et_2O. Yield 94−98%. Note 1: Commercial sources of quinidine always contain variable amounts of dihydroquinidine. This implies that catalysts may contain variable amounts of the corresponding dihydroquinidinium salt. Dihydroquinidinium salts performed equally well in the synthesis of **3** as the quinidinium salts. Note 2: Catalysts may form sticky viscous oils when in the presence of small amounts of organic solvents (e.g., acetone, DCM, or Et_2O); drying under reduce pressure (rotavapor) gave compound **12** as a fine powder. Colorless powder; δ_H (400 MHz, $CDCl_3$) 8.61−8.59 (1H, m), 7.97−7.94 (1H, m), 7.68−7.67 (1H, m), 7.60−7.59 (1H, m), 7.53−7.51 (1H, m), 7.3−7.26 (2H, m), 6.79−6.77 (1H, m), 6.58−6.55 (1H, m), 6.00−5.92 (1H, m), 5.83−5.80 (1H, m), 5.19−5.15 (2H, m), 4.85−4.76 (1H, m), 4.62−4.57 (1H, m), 4.10−4.04 (1H, m), 3.93 (3H, s), 3.88−3.83 (1H, m), 3.50−3.44 (1H, m), 3.07−3.02 (1H, m), 1.89−1.85 (1H, m), 1.80−1.75 (1H, m), 1.08−1.01 (1H, m);); δ_C (100.6 MHz, $CDCl_3$) 157.9, 152.0, 147.4, 144.2, 143.0, 135.8, 131.8, 128.3, 126.2, 126.1, 124.4, 121.0, 120.5, 118.1, 102.2, 68.4, 65.3, 64.3, 56.8, 56.0, 54.2, 38.3, 35.0, 31.4, 30.9, 27.8, 24.2, 21.5.

General Preparation of Quinidium Bromides ***11−15***. In a round bottomed flask fitted with a magnetic stirrer and a reflux condenser were put sequentially quinidine (1.0 equiv), a suitable benzyl bromide (1.05 equiv), and acetone to make a 0.18−0.20 M solution. It was noted that at 50−55 °C the reaction became clear. The resulting solution was heated at 60−65 °C for 2−8 h depending on scale. The reaction mixture was then allowed to reach room temperature, the solvent evaporated to give a solid which was suspended in petroleum ether, stirred for 30 min, then filtered, and dried to give pure quinidinium bromides **11−15**. Optionally compounds **11−15** may be dissolved in the minimum quantity of DCM and then precipitated by addition of Et_2O.

Note 1: Commercial sources of quinidine always contain variable amounts of dihydroquinidine. This implies that catalysts **11−12** and **14−15** may contain variable amounts of the corresponding dihydroquinidinium salt.

Note 2: In the synthesis of compounds **13−15**, it was noted the formation of a precipitate from hot acetone, minutes from refluxing at 60−65 °C.

Note 3: Compounds **11−12** may form sticky viscous oils when wet (acetone, DCM, or Et_2O); drying under reduce pressure (rotavapor) gave compounds **11−15** as a fine powder.

N-(3,5-Ditrifluoromethylbenzyl)quinidinium Bromide ***11***. Light yellow powder; δ_H (400 MHz, $CDCl_3$) 8.39−8.36 (1H, m), 8.25−8.24 (2H, m), 7.74 (1H, s), 7.67 (1H, d, J = 8 Hz), 7.61 (1H, d, J = 4 Hz), 7.49 (1H, d, J = 4 Hz), 6.95−6.92 (1H, m), 6.48−6.47 (1H, m), 6.12−6.09 (1H, m), 6.10 (1H, d, J = 8 Hz), 5.82 (1H, d, J = 8 Hz), 5.80−5.74 (1H, m), 5.16−5.10 (2H, m), 4.56−4.50 (1H, m), 4.34−4.29 (1H, m), 4.15−4.10 (1H, m), 3.68 (3H, s), 3.08−3.02 (1H, m), 2.64−2.59 (1H, m), 2.39−2.19 (2H, m), 1.77−1.73 91H, m), 0.85−0.82 (1H, m); δ_C (100.6 MHz, $CDCl_3$) 157.9, 147.0, 144.0, 142.0, 134.9, 133.9, 132.6, 132.3, 131.6, 130.4, 126.0, 123.9, 121.2, 120.4, 120.0, 118.5, 103.2, 68.1, 67.1, 60.4, 60.2, 56.5, 56.3, 54.5, 37.9, 27.0, 23.8, 21.9.

N-(3,5-Di-tert-butylbenzyl)dihydroquinidinium Bromide ***13***. Colorless powder; δ_H (400 MHz, $CDCl_3$) 8.69−8.68 (1H, m), 8.03−8.00 (1H, m), 7.75−7.74 (1H, m), 7.59−7.58 (2H, m), 7.54−7.53 (1H, m), 7.63−7.29 (2H, m), 6.82−6.80 (1H, m), 6.66−6.62 (1H, m), 4.76−4.73 (1H, m), 4.42−4.36 (1H, m), 3.94 (3H, s), 3.74−3.65 (2H, m) 3.55−3.46 (1H, m), 3.14−3.06 (1H, m), 2.54−2.48 (1H,m), 1.94−1.88 (1H, m), 1.81−1.77 (1H, m), 1.69−1.55 (3H, m), 0.88−0.84 (1H, m);); δ_C (100.6 MHz, $CDCl_3$) 158.0, 152.1, 147.7, 144.3, 143.1, 132.2, 128.3, 126.2, 126.0, 124.5, 120.6, 120.5, 102.3, 68.9, 64.9, 64.6, 57.1, 56.0, 55.9, 36.2, 35.0, 31.4, 31.3, 24.9, 24.6, 24.3, 21.3, 11.4.

N-(3,5-Dimethylbenzyl)quinidinium Bromide ***14***. Colorless powder; δ_H (400 MHz, $CDCl_3$) 8.45−8.43 (1H, m), 7.89−7.86 (1H, m), 7.71−7.70 (1H, m), 7.20−7.19 (1H, m), 7.20−7.17 (2H, m), 6.89−6.88 (1H, m), 6.69−6.67 (1H, m), 6.47−6.45 (1H, m), 5.89−5.81 (1H, m), 5.73−5.69 (1H, m), 5.17−5.12 (2H, m), 4.53−4.48 (1H, m), 3.91−3.86 (1H, m), 3.80 (3H, s), 3.43−3.38 (1H, m), 2.93−2.90 (1H, m), 2.39−2.34 92H, m), 2.30 (6H, s), 1.80−1.65 (4H, m), 0.93−0.80 (1H, m); δ_C (100.6 MHz, $CDCl_3$) 157.8, 147.3, 144.3, 142.6, 138.7, 135.6, 131.9, 131.7, 131.4, 126.8, 126.4, 120.7, 120.6, 118.0, 102.8, 68.0, 66.9, 62.9, 56.6, 56.0, 54.0, 38.2, 27.2, 24.0, 21.7, 21.3.

N-(3,5-Dibromobenzyl)quinidinium Bromide ***15***. Colorless powder; δ_H (400 MHz, $CDCl_3$) 8.36−8.35 (1H, m), 7.82−7.74 (4H, m), 7.66−7.65 (1H, m), 7.04−7.01 (1H, m), 6.58−6.56 (1H, m), 6.44−6.40 (1H, m), 6.17−6.15 (1H, m), 5.86−5.79 (1H, m), 5.64−5.59 (1H, m), 5.28−5.22 (2H, m), 4.55−4.52 (1H, m), 4.27−4.25 (2H, m), 3.70 (3H, s), 3.23−3.20 (1H, m), 2.79−2.76 (1H, m), 2.40−2.38 (1H, m), 2.25−2.21 (1H, m), 1.85−1.77 (3H, m), 0.93−0.85 (1H, m);); δ_C (100.6 MHz, CDCl3)157.7, 147.0, 144.1, 142.0, 136.2, 135.1, 135.0, 131.6, 131.1, 126.3, 123.5, 120.5, 119.5, 118.2, 103.8, 67.7, 59.8, 56.3, 56.0, 54.2, 37.9, 27.0, 23.8, 22.0, 15.3.

Preparation of Polymer-Supported ***12***. This was prepared following the procedure reported by Itsuno.[11] Typically, compound **12** (12.12 g, 20 mmol) was dissolved in DCM (10 mL) and styrene sodium sulfonate added (1 equiv, 20 mmol). The resulting solution was stirred for 20 min, then washed with water (2 × 10 mL), and the organic phase evaporated to give the correspondent ammonium sulfonate salt (M_w = 710, 14.19 g, 99.99% yield). The ammonium sulfonate (14.19 g, 20 mmol) was then dissolved in DMF (5 g), the solution charged in a round bottomed flask fitted with a magnetic stirrer and styrene (18.7 g, M_w = 104, 9 equiv), divinylbenzene **13** (520 mg, M_w = 130, 0.2 equiv), and AIBN (660 mg, 0.05 equiv) consecutively added. Copolymerization was run at 60 °C for 6 h;, then the polymer was collected and washed with toluene and methanol to remove the DMF to give polymer supported **12** (33.3 g, 99% yield).

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The loading of the catalyst was established by elemental analysis: Elem. Anal. Calculated for $C_{11.6}H_{11.7}N_{0.2}O_{0.4}S_{0.1}$: C, 85.20%; H, 7.21%; N, 1.71%. Found: C, 82.66%; H, 7.19%; N, 1.58%. Corresponding at 0.57 mmol N/g.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00160.

Copies of ^{1}H NMR, ^{13}C NMR of compounds **11**−**15**, **4**, **10**, **3**, **2**, **1**; HPLC of compounds **3** and **1**; additional table of results for the optimization of the preparation of **3** using other phase transfer catalysts (PDF)

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Notes

The authors declare no competing financial interest.

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