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Short Communication

Polystyrene-supported organocatalysts for α-selenenylation and Michael reactions A common post-modification approach for catalytic differentiation

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ABSTRACT

Three different resin-supported catalysts have been prepared by using the well established post-modification approach by means of thiol-ene coupling reaction. Two catalysts were tested for the first time in the asymmetric α-selenenylation of propanal, while the third catalyst was used in the Michael addition reaction. While the preliminary results are not encouraging in the case of supported Jørgensen' catalyst, interesting data have been collected with both for the supported MacMillan and prolyl-prolinol catalysts. In fact, these catalysts displayed good activity and selectivity. A reversed enantioselectivity in the α-selenenylation was observed by changing the polarity of the solvent. Finally, these materials were easily recovered, and used four and five times, respectively.

1. Introduction

The supporting of homogeneous chiral organocatalysts is of great interest since it allows to obtain heterogeneous catalytic materials which can be easily manipulated. Particularly, polymers, in insoluble bead form, offer a great advantage in recovery of the supported chiral catalyst by filtration [1–4]. In fact, the main reason that prompted chemists to immobilize chiral organocatalysts lies in the synthetic advantages for larger scale production of cheap, easily available and recoverable materials, able to be reused for several cycles. The organic catalyst, or its precursor, can be introduced after the macromolecular synthesis (polymerization), or before it. The first case is described as post-modification strategy whereas the second approach is referred as a bottom-up strategy. Recently, a discussion on such approaches has been reported [5]. In the last years, our research group has devoted efforts to the development of recyclable polystyrene-supported organocatalysts employing the post-modification strategy. In this way, several proline and prolinamide-supported catalysts were synthesized starting from commercially available mercaptomethylpolystyrene (1% cross-linked with DVB). The proper organic catalysts were immobilized using a styrene functionality as anchorage moiety through the thiol-ene coupling protocol. Starting from this common immobilization strategy, we got a set of diversified catalysts, which were successfully employed in the enantioselective aldol reaction [6–9] and non-enantioselective α-selenenylation [10] and Baylis–Hillman reactions [11]. In order to show the general applicability of our approach (Fig. 1) we have decided to synthesize other polystyrene-supported organocatalysts employing the same strategy. In this communication, we report preliminary results on the synthesis and use of three different resin-supported catalysts. Two catalysts were tested in the asymmetric α-selenenylation of propanal, being this the first example in which the title reaction is performed using a supported catalyst. The third catalyst was employed in the Michael addition between nitrostyrene and aldehydes. These reactions furnish useful intermediates that could be converted into valuable chiral building blocks [12, 13].

2. Experimental

2.1. General

2-(Phenylselenyl)propanal [14] and Michael products [15,16] are known compounds and showed spectroscopic and analytical data in agreement with their structures. The configurations of the products were assigned by comparison with literature data. Derivatives **9**, **10** [17] and **12**[9] are known compounds and have been prepared as reported in the literature. Chiral HPLC analyses for ee determinations were performed by using a Shimadzu LC-10 AD apparatus equipped with an SPD-M10 A UV detector and Daicel columns (OD-H, AD-H, AS-H) by using hexane/2-propanol as the eluent. Semi-solid NMR spectra were recorded with a Bruker Avance 2 400 MHz spectrometer at 300 K by using the CPMG pulse sequence with a proton pulse of 8.77 μs and MAS rate 5 KHz. Samples (ca. 5 mg) were swollen in $CDCl_3$ 50 μL.

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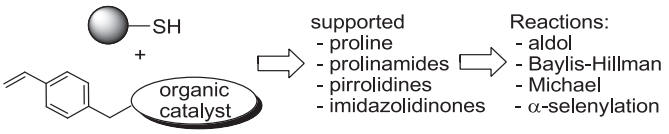


Fig. 1. Catalytic differentiation by post-modification strategy based on thiol-ene coupling.

2.2. General procedure for immobilization of catalysts

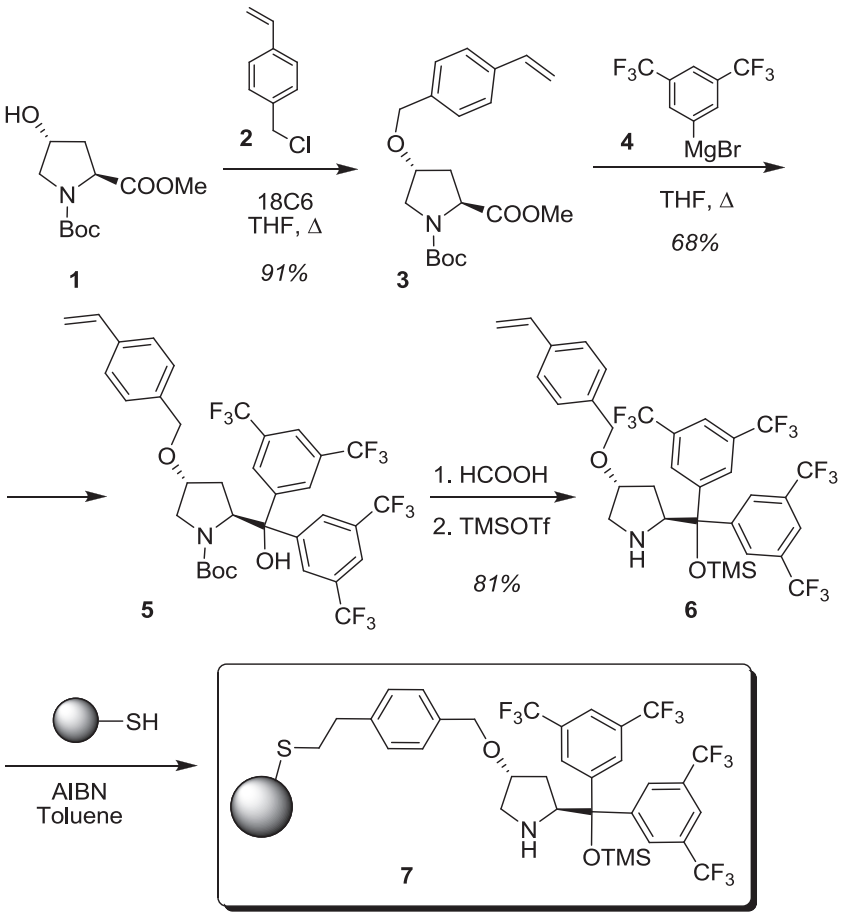
Mercaptomethylpolystyrene (1% cross-linked with DVB, spherical beads, particle size 100–200 mesh, 2.5 mmol/g of -SH; 400 mg, 1 mmol) was added to precursors **6**, **10** or **14** (2–3 mmol) and AIBN (2–5 mol%) in toluene (25 mL) and the solution was degassed bubbling argon. The mixture was stirred at 110 °C overnight under argon. After cooling to room temperature, the resin was filtered and washed with dichloromethane, methanol and diethyl ether. The weight increase serves as an estimation on catalyst precursor covalently attached to the resin [18]. When Boc deprotection was needed, the resin was suspended in HCOOH (1.4 mL, for **7**) or in CH_2Cl_2/TFA 5:1 v/v and stirred for 20 h. After this time, water was added and the mixture was filtered off. The resin was washed with a saturated solution of $NaHCO_3$, water, methanol and diethyl ether. Hence, the resin was dried in oven at 60 °C for 2 h. The weight difference corresponds to the amount of Boc removed, which is identical to the amount of available catalyst (**7**: 0.47 mmol/g; **11**: 0.91 mmol/g; **15**: 1.0 mmol/g).

2.3. Typical procedure for α-selenenylation of propanal

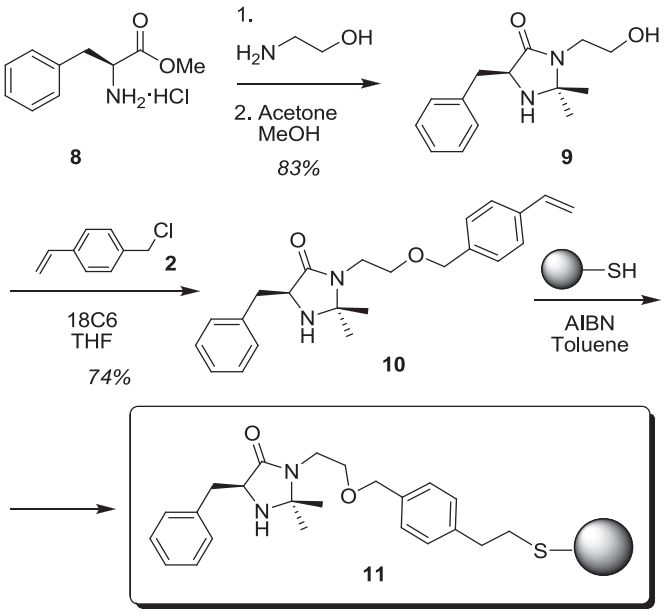
To a mixture of the propanal (0.4 mmol) and *N*-(phenylseleno) phthalimide (80%, 0.44 mmol) in the solvent of choice (0.8 mL), catalyst **7** or **11** and the co-catalyst were added (0.04 mmol of each) and the reaction mixture was stirred at rt for 2 h. The mixture is filtered off in order to recover the catalyst and washed with CH_2Cl_2, methanol and diethyl ether. The solvent was concentrated under reduced pressure and the residue was quickly purified by a short column chromatography (SiO_2, petroleum ether/ethyl acetate) gave 2-(phenylselanyl)propanal. Enantiomeric ratio has been determined by means of HPLC analysis by using a chiral AD-H column (80/20 hexanes/*i*-PrOH; 0.75 mL/min; λ = 214 nm).

2.4. Typical procedure for Michael reaction

A mixture of nitrostyrene (75 mg, 0.5 mmol), benzoic acid (3.4 mg, 0.025 mmol) and catalyst **15** (24 mg, 0.025 mmol) in the proper solvent, was stirred for 20 minutes. After this period the aldehyde (1.5 mmol) was added and the mixture was further stirred. Then the solution was filtered off and the catalyst was washed with ethyl acetate and diethyl ether. The organic phase was concentrated under reduced pressure and the residue was purified by a column chromatography (SiO_2, petroleum ether/ethyl acetate) to give the corresponding known Michael adduct.



Scheme 1. Synthesis of supported Jørgensen catalyst 7.



Scheme 2. Synthesis of supported MacMillan catalyst 11.

3. Results and discussion

3.1. Synthesis and test of supported catalysts for asymmetric α-selenenylation

Supported Jørgensen catalyst has been prepared by following the synthetic strategy depicted in Scheme 1. Starting from commercially available *trans*-*N*-Boc-4-hydroxy-L-proline methyl ester, the corresponding derivative endowed with a styrene moiety **3** has been easily prepared. This can react with freshly prepared 3,5-bis(trifluoromethyl)phenylmagnesium bromide **4** to afford diaryl prolinol **5** with good yield. The carbamate deprotection followed by silylation leads to key intermediate **6**, which was in turn immobilized onto a cross-linked mercaptomethylpolystyrene through a thiol-ene coupling protocol to give resin **7** with a loading of 0.47 mmol/g.

Analogously, the same protocol has been used to covalently anchor MacMillan catalyst's precursor **10**[17], which led to the final catalyst with a loading of 0.91 mmol/g (Scheme 2). The lowest loading showed by resin **7** may be due to the major steric hindrance of the precursor **6** with respect to **10**, which make more difficult the right orientation during the coupling. However, we think that the remaining unreacted SH groups on the resin surface are not able to affect the catalytic process.

Catalysts **7** and **11** were characterized by semi-solid ^{1}H NMR. In Figs. 2 and 3 are reported ^{1}H NMR spectra.

Next, we tested the so-obtained catalytic materials in the asymmetric α-selenenylation reaction of propanal, employing *N*-(phenylseleno) phthalimide (NPSP) as selenenylating agent. Unfortunately, applying the best reaction conditions reported for this reaction [14], catalyst **7** revealed to work worst and slowest even compared with the precursor **6** itself (Table 1, entry 5). Probably, both the presence of the support and that of the styrenic linker negatively affects the catalytic activity.

Better results were obtained with catalyst **11** (Table 2) [19]. In fact, this time it was possible carry out reactions in only 2 h. A screening of solvent revealed dichloromethane as the best one (entry 6), but it is noteworthy to note that in acetonitrile a decrease in enantioselectivity was observed (entry 3) while in DMSO or DMF (entries 4–5), a change in enantioselectivity was observed. This finding has been already noticed, but only just explained in terms of influence of solvent dielectric constant [20,21]. We think this behavior deserves for a more in depth investigation due to its mechanistic implications and further experiments are currently underway.

The temperature has a minor influence in the stereochemical outcome (entries 6–8). In fact, cooling down the reaction mixture results in a slightly increase in enantioselectivity, although longer reaction times are needed. In dichloromethane, the presence of TFA as co-catalyst has been proved to be necessary, in order to achieve better

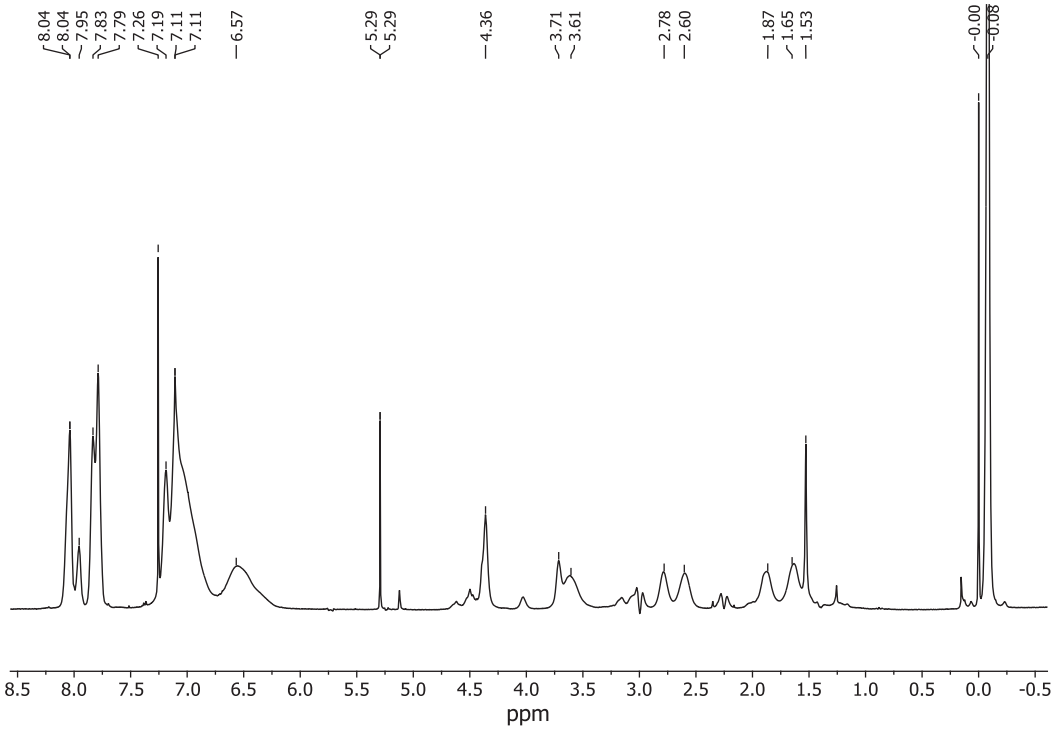


Fig. 2. Semi-solid ^{1}H CPMG NMR spectra of resin **7**.

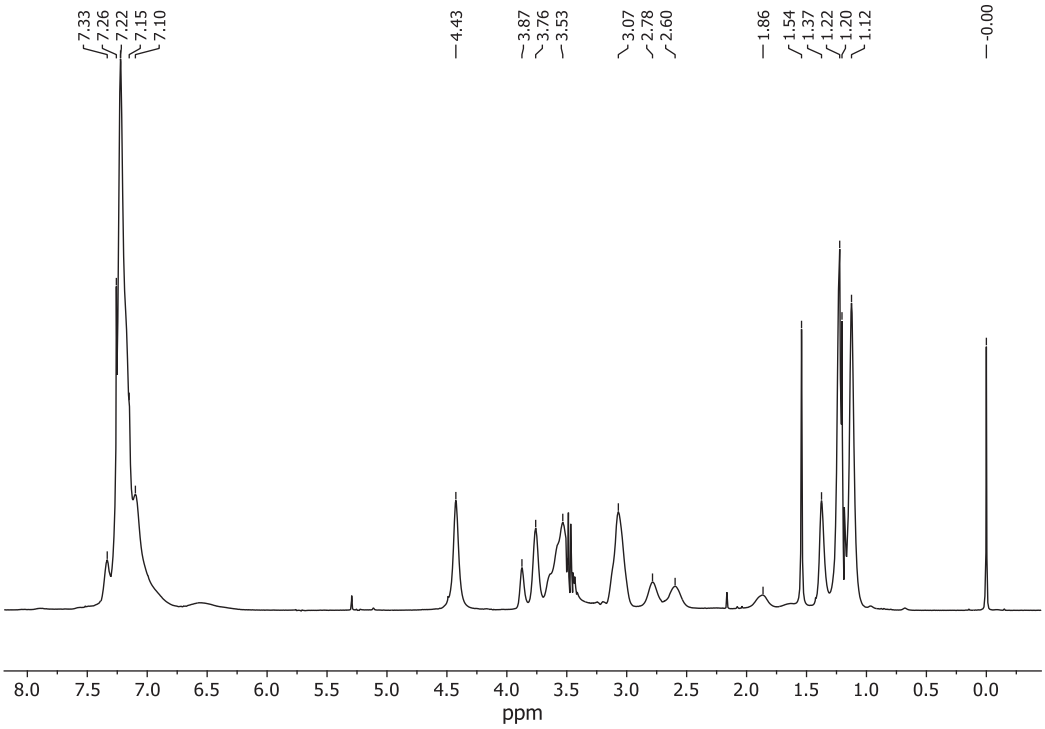
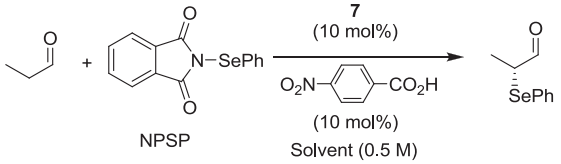


Fig. 3. Semi-solid ^{1}H CPMG NMR spectra of resin **11**.

yield and enantiomeric ratio (entry 9). Finally, we carried out recycling studies (entries 10–12). After reactions took place, the catalyst has been recovered by filtration, washed with CH_2Cl_2, methanol and diethyl ether, dried and reused. Interestingly its selectivity remains almost unaffected after 4 cycles with only a slight decrease in activity. It is also interesting to note that, the levels of activity and selectivity displayed in homogeneous conditions by using monomer **10** have been matched with resin **11** (compare entries 13 and 6–8) indicating that in this case the post-modification approach is a good choice. Finally, resin used in DMF in the first cycle (entry 5) was used in a second cycle employing CH_2Cl_2. Er value (entry 14) indicated the reproducibility of the catalyst.

Table 1
Asymmetric α-selenenylation reaction between propanal and *N*-(phenylseleno)phthalimide (NPSP) employing **7** as catalyst.[a]



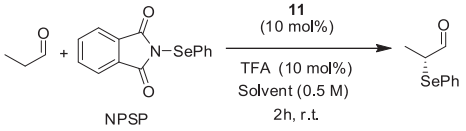
Entry	Cycle	Solvent	T (°C)	t (h)	Yield[(b)] (%)	Er[(c)] (%)
1	1	Toluene	0	22	–	–
2	1	Toluene	25	22	76	51/49
3	2	CH_2Cl_2	0	24	20	87/13
4	2	CH_2Cl_2	25	22	30	75/25
5[(c)]	–	CH_2Cl_2	25	22	82	80/20

[a]Reaction conditions: propanal (0.4 mmol), NPSP (0.44 mmol), **7** (0.04 mmol), 4-nitrobenzoic acid (0.04 mmol), solvent (0.8 mL).
[b]Isolated yields.
[c]Enantiomeric ratio determined by HPLC.
[d]Reaction carried out using 0.04 mmol of **6** as catalyst.

3.2. Synthesis and test of supported catalysts for asymmetric Michael reaction

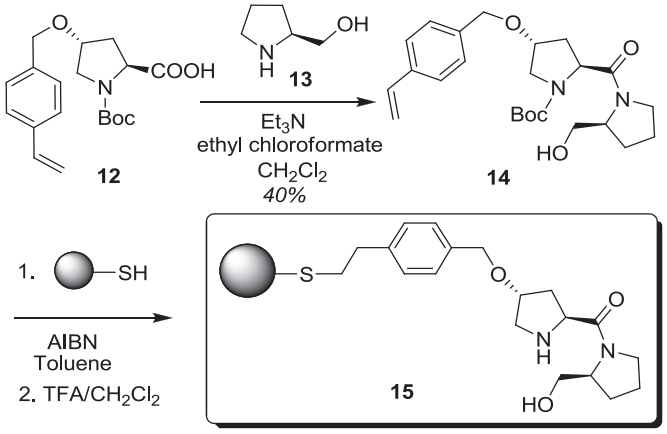
The post-modification strategy has been also followed in order to prepare resin-supported prolyl-prolinol (Scheme 3). In this case, condensation between proline-derivative **12** and L-prolinol afforded the

Table 2
Asymmetric α-selenenylation reaction between propanal and *N*-(phenylseleno)phthalimide employing **11** as catalyst.[a]



Entry	Cycle	Solvent	T (°C)	t (h)	Yield[b] (%)	Er[c] (%)
1	1	THF	25	2	29	70/30
2	1	Toluene	25	2	58	73/27
3	1	MeCN	25	2	67	62/28
4	1	DMSO	25	2	35	39/61
5	1	DMF	25	2	41	30/70
6	1	CH_2Cl_2	25	2	86	85/15
7	1	CH_2Cl_2	0	24	75	86/14
8	1	CH_2Cl_2	−20	24	72	88/12
9[d]	1	CH_2Cl_2	25	2	67	73/27
10	2	CH_2Cl_2	25	2	66	85/15
11	3	CH_2Cl_2	25	2	70	83/17
12	4	CH_2Cl_2	25	2	64	83/17
13[e]	1	CH_2Cl_2	25	2	82	88/12
14[f]	2	CH_2Cl_2	25	2	75	85/15

[a] Reaction conditions: propanal (0.4 mmol), NPSP (0.44 mmol), **11** (0.04 mmol), trifluoroacetic acid (0.04 mmol), solvent (0.8 ml).
[b] Isolated yields.
[c] Enantiomeric ratio determined by HPLC.
[d] Reaction carried out without TFA.
[e] Reaction carried out using 0.04 mmol of **10** as catalyst.
[f] This cycle was carried out with resin used in DMF (entry 5).



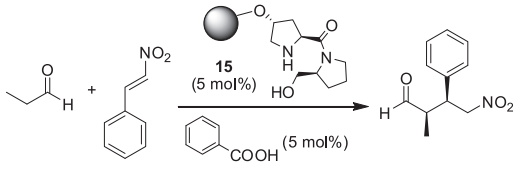
Scheme 3. Synthesis of supported prolyl-prolinol catalyst 15.

expected prolinamide **14** in not good yield, although such procedure has not been optimized. Once again, thiol-ene coupling reaction with mercaptomethyl resin followed by Boc deprotection successfully led to the new catalytic material **15** with a loading of 1.0 mmol/g (see supporting information for semi-solid ^{1}H NMR spectrum).

Once prepared, catalyst **15** has been used in the Michael reaction between propanal and nitrostyrene (Table 3). As a starting point we applied the best reaction condition found for the homogeneous catalyst [22], namely 0.2 M of nitrostyrene in CH_2Cl_2 with 5 mol% of **15** and 5 mol% of benzoic acid (entry 1). Although selectivity was good, after 45 h only a 33% yield was obtained. Then we employed more concentrated solutions (2 M) in which the low surface area catalyst performed better with or without the presence of water (entries 2–3). In order to see the real effect of water [23–24], reaction time was shortened from 45 to 24 h, and this helped to discriminate the beneficial presence of water both on the yield and in the selectivity (entries 4–5). A third cycle with the same catalyst resulted in a decrease of activity, which was completely restored in the forth cycle after an easy regeneration step (entries 6–7) [7–9].

Next, we extended the scope of the reaction employing a set of different aliphatic aldehydes (Table 4). Excellent results have been also obtained with butyraldehyde although between the first and the third cycles a regeneration step has been needed in order to restore

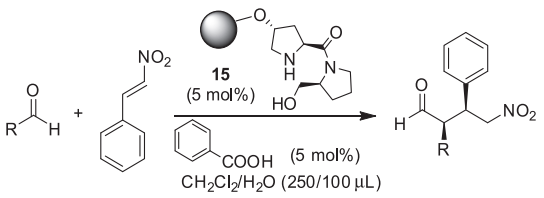
Table 3
Asymmetric Michael reaction between propanal and nitrostyrene catalyzed by **15**.

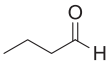
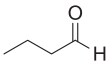
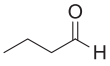
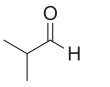
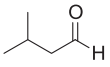
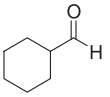
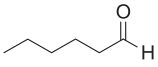
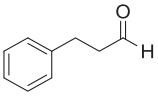
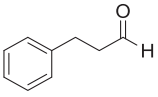


Entry	Solvent	t (h)	Cycle	Yield[b]	Syn/Anti[c]	Er[d] (%)
1	CH_2Cl_2 (2.5 mL)	45	1	33	91/9	95/5
2	CH_2Cl_2 (250 μL)	45	1	95	88/12	96/4
3	CH_2Cl_2/H_2O (250/100 μL)	45	1	98	87/13	96/4
4	CH_2Cl_2 (250 μL)	24	2	64	87/13	95/5
5	CH_2Cl_2/H_2O (250/100 μL)	24	2	82	92/8	96/4
6	CH_2Cl_2/H_2O (250/100 μL)	24	3	48	92/8	96/4
7[e]	CH_2Cl_2/H_2O (250/100 μL)	24	4	99	91/9	96/4

[a]Reaction conditions: propanal (1.5 mmol), nitrostyrene (0.5 mmol), **15** (0.025 mmol), benzoic acid (0.025 mmol), solvent, room temperature.
[b]Isolated yields.
[c]Determined by ^{1}H NMR spectroscopic analysis of the crude product.
[d]Enantiomeric ratio determined by HPLC.
[e]Reaction carried out with catalyst regenerated with 200 μL of formic acid during 2.5 h.

Table 4
Asymmetric Michael reaction between nitrostyrene and aldehydes catalyzed by **15**: substrate scope.



Entry	Aldehyde	t (h)	Cycle	Yield[B]	Syn/Anti[c]	Ee[d] (%)
1		24	1	96	92/8	92/8
2		24	2	78	93/7	92/8
3[e]		24	3	97	92/8	92/8
4		72	3	–	–	–
5		24	1	33	97/3	92/8
6[e]		72	3	–	–	–
7[e]		24	4	72	77/23	100/0
8[e]		24	4	54	92/8	80/20
9[f]		48	5	64	97/3	80/20

[a]Reaction conditions: aldehyde (1.5 mmol), nitrostyrene (0.5 mmol), **15** (0.025 mmol), benzoic acid (0.025 mmol), CH_2Cl_2 (250 μL), water (100 μL), room temperature.
[b]Isolated yields.
[c]Determined by ^{1}H NMR spectroscopic analysis of the crude product.
[d]Enantiomeric ratio determined by HPLC.
[e]Reaction carried out with catalyst regenerated with 200 μL of formic acid during 2.5 h.
[f]Reaction carried out with catalyst regenerated two times.

catalyst activity (entries 1–3). No products, even with longer reaction time, were achieved from branched aldehydes such as isobutyraldehyde and cyclohexanecarboxaldehyde (entries 4 and 6, respectively), whilst isovaleraldehyde reacted slowly (entry 5). Excellent enantioselectivity has been showed by hexanal, while hydrocinnamic aldehyde needed an extended reaction time for improving the yield (entries 7–9). It is worth mentioning that resin **15** worked nicely for 5 cycles, being the regeneration protocol able to restore the catalytic activity several times. Moreover, in some case, better performances than in homogeneous conditions have been achieved with the supported catalyst [22].

4. Conclusions

In summary, three different supported organocatalysts have been prepared employing the useful post-grafting strategy. In doing so, catalyst precursors were covalently linked by means of thiol-ene coupling protocol. Whilst the supported Jørgensen catalyst does not reach similar levels of activity and selectivity than their unsupported

version, MacMillan' supported catalyst worked nicely in the asymmetric α-selenenylation of propanal, resulting easily recoverable and recyclable at least for four cycles. This is the first example of asymmetric α-selenenylation reaction carried out in the presence of a supported organocatalyst. Moreover, it appears to be interesting the reversal in enantioselectivity observed by changing the solvent.

Analogously, the supported version of prolyl-prolinol efficiently promoted the asymmetric Michael reaction between nitrostyrene and aliphatic aldehydes just in 5 mol%. Moreover, in some case the catalyst displayed better performances than its homogeneous counterpart. Finally, **15** resulted to be recyclable with no loss in activity and selectivity at least for 5 cycles, and can be easily regenerated.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2011.08.040.

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