DOI: 10.1002/chem.201101730

Polystyrene-Supported Diarylprolinol Ethers as Highly Efficient Organocatalysts for Michael-Type Reactions

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Abstract: α,α-Diphenylprolinol methyl- and trimethylsilyl ethers anchored onto a polystyrene resin have been prepared by a copper-catalyzed azide–alkyne cycloadditions (CuAAC). The catalytic activity and enantioselectivity displayed by the *O*-trimethylsilyl derivative are comparable to those exhibited by the best known homogeneous catalysts for the addition of aldehydes to nitroolefins and of malonates or nitromethane to α,β-unsaturated aldehydes. The combination of the catalytic unit, the triazole linker, and the polymeric matrix provides unprecedented substrate selectivity, in favor of linear, short-chain aldehydes, when the organocatalyzed reaction proceeds by an enamine mechanism. High versatility is noted in reactions that proceed via an iminium ion intermediate. The catalytic behavior of polystyrene-supported α,α-diphenylprolinol methyl ether was also evaluated in asymmetric Michael addition reactions. As a general trend, the CuAAC immobilization of diarylprolinol ethers onto insoluble polystyrene resins offers important operational advantages, such as high catalytic activity, easy recovery from the reaction mixture by simple filtration, and the possibility of extended reuse.

Keywords: aldehydes · asymmetric catalysis · Michael addition · organocatalysis · solid-phase catalysts

Introduction

The covalent immobilization of chiral catalytic species onto polymer supports has become an important research area over the last decade,[1] mainly due to the inherent properties of the polymer backbone, which allows easy recovery by simple filtration, recycling, reuse, and even application in continuous-flow processes. However, this strategy sometimes leads to a decrease in catalytic activity with respect to the monomeric species because of a deficient interaction between the reactants and the supported catalyst. This is accompanied by a decrease in enantioselectivity due to perturbation of the transition state of the enantiodetermining step by the polymer chain. Thus, appropriate design and preparation of the heterogeneous catalytic systems is essential to achieve catalytic activities and selectivities comparable to those provided by their homogeneous counterparts. Besides proper selection of the position on the homogeneous catalyst to be modified to create an anchoring point, the nature of the linker, spacer (if any), and polymer support plays also a fundamental role in determining the catalytic activity and stereoselectivity of the supported species. The more widely used supports that allow homogeneous conditions to be closely approached are highly swellable, yet insoluble, resins made of slightly cross-linked polystyrene-based polymers. Such polymers are readily available, can be easily functionalized by various methods, and have high chemical inertness.[2] Among them, Merrifield resins and their derivatives are ideal carriers for catalytic species due to their easy handling, optimal physical properties, and modularity.[3]

The continued and ever-growing interest in organocatalysis over the past two decades has led to the development of many different types of organocatalyzed reactions that provide enantiomerically pure compounds through very simple reaction setups.[4] However, many of these reactions lead to rather polar products, so isolation and purification become the main sources of solvent consumption and waste generation. Taking into account factors such as separation, catalyst recovery, and ease of purification of the reaction products, the immobilization of organocatalytic species appears a promising strategy.

In a continued effort towards the development of chemical processes with improved sustainability characteristics, we have introduced a variety of organocatalysts synthesized from pyrrolidine derivatives and anchored onto insoluble polystyrene resins[5a–g] by copper-catalyzed azide–alkyne cycloaddition (CuAAC).[6] The nature of the catalytic species, the presence of the triazole linker, and the environment pro-

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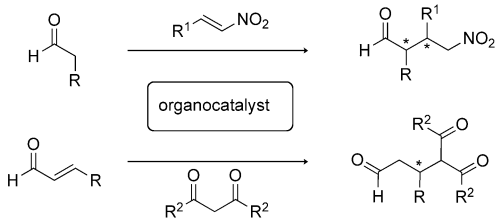
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101730.

vided by the polymer backbone have shown a synergistic effect, which has led to remarkably high catalytic activity and enantioselectivity.[5a–g]

Catalysis mediated by primary or secondary amines include reactions that take place via enamine and iminium ion intermediates.[7] Among these processes, Michael reactions[8] represent a powerful synthetic tool for the assembly of 1,5-difunctionalized compounds (Scheme 1). Within the wide



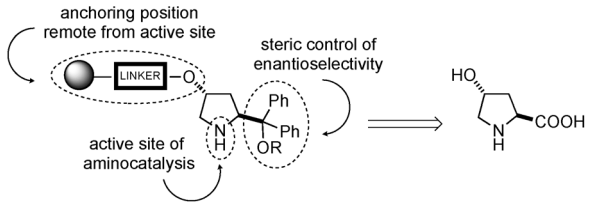
Scheme 1. Michael reaction of aldehydes with nitroolefins and malonates via enamine and iminium ion intermediates, respectively.

application range of these chemical transformations, their use as the first step in cascade processes,[9] or use of a combination of the two catalysis mechanisms in tandem sequences, has aroused a great deal of interest because complex molecular frameworks can be constructed in simple, one-pot operations. Of particular interest are catalysts derived from (*S*)-α,α-diarylprolinol silyl ethers,[10] independently introduced by Jørgensen and Hayashi for the enantioselective organocatalyzed α-sulfenylation of aldehydes and asymmetric Michael addition of aldehydes to nitroalkenes, respectively.[11] The steric effect caused by the bulky substituent placed at C2 on the pyrrolidine ring controls the enantioselectivity of the reactions very efficiently.

We have recently reported[5f] the development of a new immobilized, enantiopure (*S*)-α,α-diphenylprolinol trimethylsilyl ether (**4**)—supported onto polystyrene by a CuAAC reaction—that displays an unprecedented selectivity in favor of linear, short-chain aldehyde donors in the highly enantioselective Michael addition to nitroolefins. The same strategy was subsequently employed by Mager and Zeitler for the attachment of the same monomer to soluble methoxy polyethyleneglycol polymers.[5h] Herein, we report a full account of the design and synthesis of **4**, the chemical modification of this species as a methyl ether to obtain an extended life cycle, and the use of these catalysts in a variety of Michael reactions with aldehyde, malonate, or nitromethane donors and nitroolefin or α,β-unsaturated aldehyde acceptors.

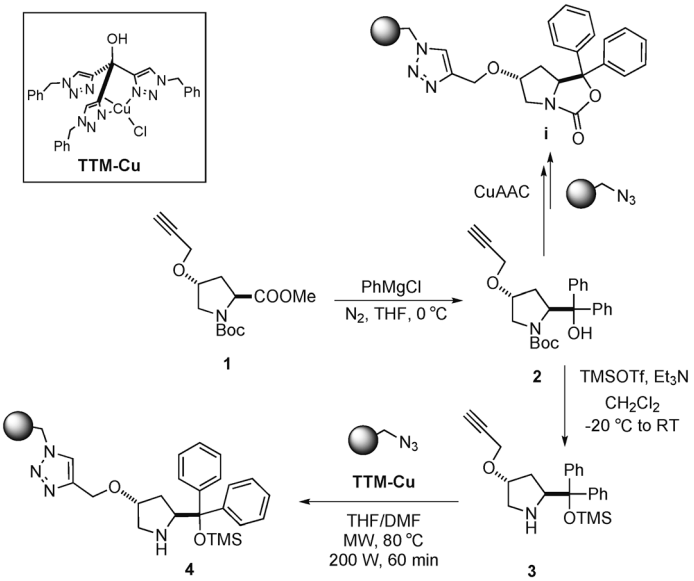
Results and Discussion

Design and synthesis of polystyrene-supported (*S*)-α,α-diphenylprolinol trimethylsilyl ether (4) and its evaluation in the Michael addition of aldehydes to nitroolefins: The asymmetric organocatalytic Michael addition[12] has emerged as one of the most important carbon–carbon bond-forming reactions and aldehydes have proven to be very reactive and convenient donors in this process. Catalysts derived from (*S*)-α,α-diarylprolinol silyl ethers have provided excellent results in terms of activity and selectivity for aminocatalytic enantioselective Michael reactions. For the design of a widely applicable polymer-supported Jørgensen–Hayashi-type organocatalyst, we reasoned that the immobilization strategy should involve the functionalization of these systems at the most remote position from the catalytic active amine moiety and the chiral C2 atom, to avoid perturbation of the enantiodetermining transition state by the linker and the polymeric backbone (Scheme 2).



Scheme 2. Supported organocatalyst design.

We selected natural hydroxyproline as our starting material and a CuAAC reaction as the covalent strategy to anchor the pyrrolidine moiety onto Merrifield resin (Scheme 3). This well-established atom-economic immobilization approach[5] required some synthetic effort to prepare the key intermediate **3** from the propargyloxy derivative (**1**) of commercially available *N*-Boc-(2*S*,4*R*)-4-hydroxyproline methyl ester (Boc = *tert*-butoxycarbonyl). The silylation, with concomitant carbamate deprotection of **2**, afforded the desired intermediate **3**,[5f] ready to be attached to the support by the selected methodology. The CuAAC reaction planned for the



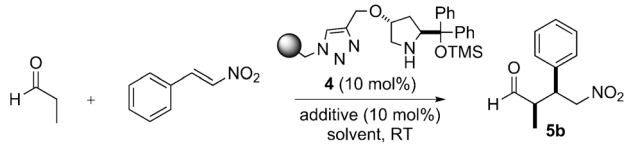
Scheme 3. Immobilization reaction to obtain polystyrene-supported (*S*)-α,α-diphenylprolinol trimethylsilyl ether (**4**).

conjugation step represented an important synthetic challenge because common Cu^I catalysts employed for the cycloaddition were incompatible with the free amino group present in the substrate. Notably, the immobilization of **3** onto azidomethylpolystyrene was efficiently catalyzed by the tris(triazolyl)methanol–copper complex (**TTM-Cu**),[13] which allowed the easy and highly reproducible synthesis of the catalytic resin **4**.

Notably, when the immobilization was performed at an earlier stage (immobilization of **2** to give resin **i**) the unavoidable formation of a cyclic carbamate was observed. Hydrolysis of this class of intermediates is feasible in homogeneous phase, however, it posed severe experimental difficulties on polymer substrates.

Recently, significant progress in the development of the organocatalytic Michael reaction has been achieved through the introduction of a variety of catalytic species and reaction conditions. These include reaction in aqueous media or in less-conventional environments, such as ionic liquids.[14] In this context, the Michael addition of propionaldehyde to β-nitrostyrene was selected as a model reaction for optimization of the reaction conditions with **4** as a catalyst (Table 1).

Table 1. Screening of reaction conditions for the Michael addition of propionaldehyde to (*E*)-β-nitrostyrene.[a]



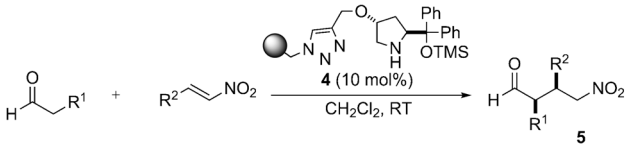
	Solvent	Additive[b]	*t* [h]	Conv [%][c]	*syn*/*anti*[c]	*ee* [%][d]
1[e]	hexane/THF	none	36	40	97:3	97
2[e]	CH_2Cl_2	none	7	>99	96:4	>99
3[e]	CH_2Cl_2	DMAP	24	>99	81:19	99
4[e]	CH_2Cl_2	PhCOOH	24	>99	77:23	97
5	CH_2Cl_2	none	7	>99	>99:1	>99
6	CH_2Cl_2	DMAP	23	>99	86:14	>99
7	CH_2Cl_2	PhCOOH	2	>99	87:13	99
8	H_2O	diMePEG	24	97	96:4	99
9	CH_2Cl_2	TFA	48	none	–	–

[a] General conditions: (*E*)-β-nitrostyrene (0.2 mmol), propionaldehyde (0.3 mmol), and **4** (0.02 mmol), solvent (1 mL), RT. [b] Additive (0.02 mmol). [c] Conversion determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Propionaldehyde (2 mmol).

It was established that CH_2Cl_2 was the optimal solvent for the reaction. Although different additives were tested (Table 1, entries 3, 4, 6–8), optimal results were recorded with the use of 10 mol% catalyst in the absence of any additive (Table 1, entry 5). Notably, these optimal conditions involve the use of a 1.5:1.0 molar ratio of aldehyde/nitrostyrene, much more convenient than the usually employed 10:1 ratio. Indeed, Michael adducts were obtained in this manner with better diastereoselectivity and from cleaner crude reaction products due to the suppression of aldehyde self-condensation reactions. When volatile substrates were used, the direct isolation of the pure products was possible by simple filtration of the catalyst and evaporation of the solvent. In any case, it is also important to emphasize the excellent performance of **4** in water; this reaction is the first example of an insoluble organocatalyst successfully promoting reaction with aldehydes in an aqueous medium.[5c]

The scope of the Michael addition between aldehydes and nitroolefins mediated by **4** was next studied. The results are presented in Table 2. As a general trend, the *syn* Michael

Table 2. Screening of substrates in the Michael addition of aldehydes to nitroolefins catalyzed by **4**.[a]



	R^1	R^2	**5**	*t* [h]	Conv[b] [%]	Yield[c] [%]	d.r.[b]	*ee*[d] [%]
1	H	Ph	**5a**	72	50	44	–	96
2	Me	Ph	**5b**	7	>99	98	>99:1	>99
3	Et	Ph	**5c**	5	>99	93	90:10	>99
4	Pr	Ph	**5d**	27	>99	98	82:18	99
5	n-pent	Ph	**5e**	48	99	91	75:25	98
6	*i*Pr	Ph	**5f**	96	<10	–	n.d.[e]	n.d.
7	Ph	Ph	**5g**	48	<5	–	n.d.	n.d.
8	$(CH_3)_2$	Ph	**5h**	120	0	–	n.d.	n.d.
9	Me	4-BrC_6H_4	**5i**	4	>99	98	91:9	98
10	Me	4-$MeOC_6H_4$	**5j**	8	>99	94	89:11	99
11	Me	2-furyl	**5k**	4	>99	96	85:15	90
12	Me	$(CH_2)_2C_6H_5$	**5l**	24	>99	94	81:19	95
13	Me	C_6H_{11}	**5m**	64	>99	89	70:30	97
14	Me	*i*Pr	**5n**	96	88	84	70:30	99

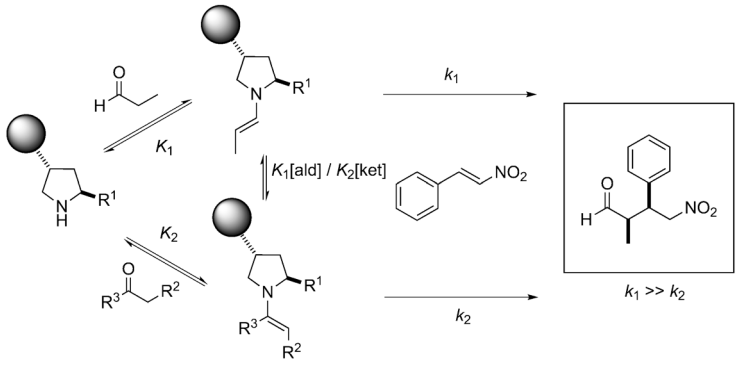
[a] General conditions: nitroolefin (0.2 mmol), aldehyde (0.3 mmol), **4** (0.02 mmol), solvent (1 mL), RT. [b] Conversion and diastereomeric ratio (d.r.) determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] n.d. = not determined.

products **5** were obtained with excellent diastereo- and enantioselectivity. Even in the challenging Michael reaction of acetaldehyde with β-nitrostyrene (Table 2, entry 1) resin **4** compares favorably with α,α-diphenylprolinol trimethylsilyl ether, which avoids the use of a large excess of acetaldehyde and employs a halved catalyst loading.[15] Thus, adduct **5a** can be prepared in 96% enantiomeric excess (*ee*), which deserves special comment given the reported interest in α-unsubstituted-γ-nitroaldehydes and general interest in the organocatalytic reactions of acetaldehyde.[15,16]

The catalytic activity of **4** showed a remarkable dependency on the structure of the aldehyde donor. Thus, fast reactions were observed for linear, short-chain aldehydes propionaldehyde and butanal (Table 2, entries 2 and 3), whereas the reaction time increased significantly with chain length (Table 2, entries 4 and 5). In all of these cases, the yields and enantioselectivities of the major *syn* products were excellent. Branching at the β position of the aldehyde had a detrimental effect on reaction rate (Table 2, entries 6 and 7) and α branching (Table 2, entry 8) completely blocked the

reaction. Ketones, such as acetone and cyclohexanone, were also tested as Michael donors but they were found to be completely unreactive.

With respect to the Michael acceptor, various substituted nitroolefins were tested. Under the optimized conditions, the addition of propionaldehyde to β-substituted aromatic nitroalkenes gave the expected *syn* adducts in excellent yields and enantioselectivities after short reaction times, independent of the electronic properties of the aryl or heteroaryl substituent (Table 2, entries 9–11). Reaction time increased notably when the aromatic substituent was not conjugated with the nitroolefin (Table 2, entry 12) and for aliphatic nitroolefins (Table 2, entries 13 and 14), although the Michael products **5l–n** were obtained in high yield and excellent enantioselectivity.



Scheme 5. Origin of the substrate selectivity [aldehydes (ald) versus ketones (ket)] in the Michael addition of carbonyl compounds to β-nitrostyrene catalyzed by **4**.

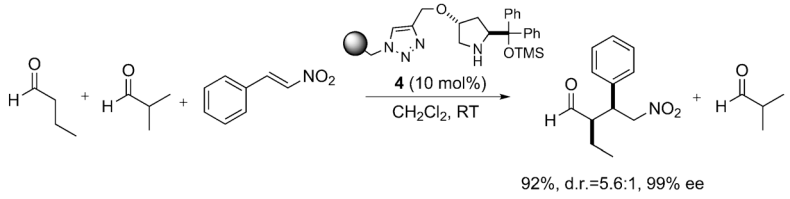
To ascertain if selectivity for linear aldehydes could be achieved in the presence of branched ones, we tested resin **4** in the Michael reaction of a mixture of butanal and 2-methylpropanal, with the composition that resulted from the Rh-catalyzed hydroformylation of propene and β-nitrostyrene in the presence of **4** (**4**/β-nitrostyrene/butanal/2-methylpropanal 0.1:1.0:2.4:1.5; see Scheme 4). Gratifyingly, under these conditions, only the linear aldehyde underwent Michael addition with no decrease in enantioselectivity (99% *ee*, compared to Table 2, entry 3).

However, the reaction time required for complete conversion (92% isolated yield) under these conditions was substantially extended (24 vs. 5 h), which suggested that unproductive enamines of 2-methylpropanal could be formed during the reaction and lead to a decrease in the concentration of the viable enamine intermediate. This suggestion is reinforced by the results of competition experiments that involved pentanal and cyclohexanone. When an equimolar mixture of these substrates was treated with β-nitrostyrene, the required time for the complete conversion of pentanal extended from 27 to 55 h. Even more noteworthy, when the cyclohexanone/pentanal ratio was changed to 13:1, the reaction time increased to 7 d. The retardation effect exerted by branched aldehydes or ketones can be rationalized through the equilibria represented in Scheme 5.

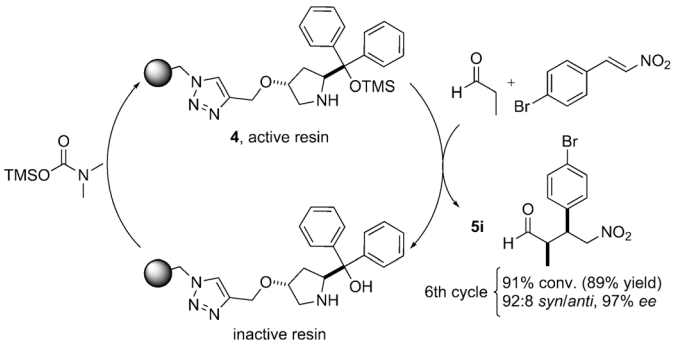
As already mentioned, the insoluble nature of the polymer allows for catalyst recovery by simple filtration. However, the recycling process can be limited by deactivation effects and, in the case of α,α-diphenylprolinol silyl ethers, the lability of the silyl ether group towards hydrolysis[12r] makes the reuse of the organocatalyst sometimes difficult. In our case, a complete absence of catalytic activity was observed in the Michael reaction of a resin that bore free hydroxyl groups on the α,α-diphenylprolinol moiety.

After extensive experimentation, we were able to address the deactivation problem of catalyst **4** by selective reprotection of the hydroxyl groups of inactive diphenylprolinol-type resins through brief treatment with trimethylsilyl *N,N*-dimethylcarbamate[17] in hexane/acetonitrile. This simple procedure leads to full recovery of the catalytic activity of the supported organocatalyst **4** and makes its reuse possible. Thus, in six consecutive cycles of reaction/reconditioning, the excellent performance of resin **4** in the Michael addition of propionaldehyde to 4-bromo-β-nitrostyrene remained intact (Scheme 6). Interestingly, the reactivation procedure does not represent any significant inconvenience from a practical point of view. Because the only byproduct formed in the process is dimethylamine, the reactivated resin can be directly reused after washing out any excess silylating reagent.

Synthesis and evaluation of polystyrene-supported (*S*)-α,α-diphenylprolinol methyl ether (11) in the Michael reaction of aldehydes and nitroalkenes: Although the origin of the deactivation of resin **4** was elucidated and properly solved, we were interested in the development of more robust polymer-supported diphenylprolinol-type catalysts with the ultimate goal of performing the present reaction in a continuous-flow manner. Therefore, we aimed

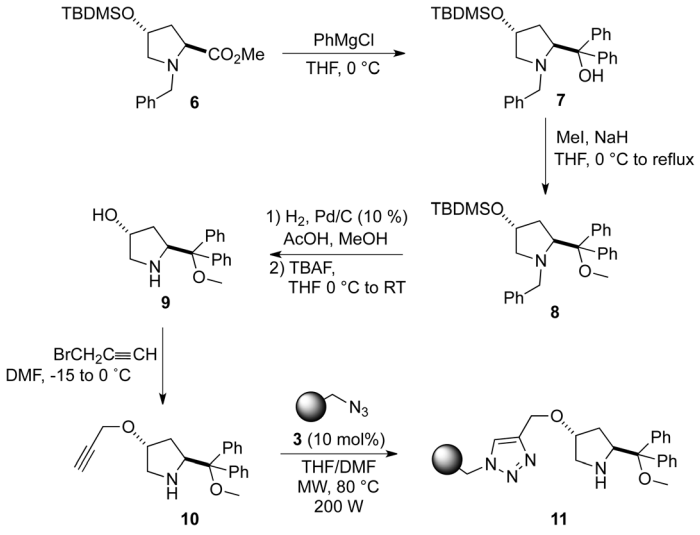


Scheme 4. Selective Michael addition of butanal to β-nitrostyrene in the presence of 2-methylpropanal catalyzed by **4**.



Scheme 6. Reconditioning and reuse of resin **4**.

to prepare and evaluate polymer-supported diphenylprolinol methyl ether (**11**), which should be stable under the standard reaction and recycling conditions, and not show hydrolytic deactivation. The synthesis of resin **11** is explained in detail in the Supporting Information and summarized in Scheme 7.

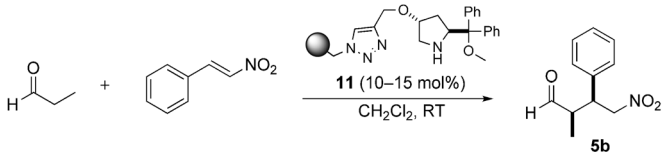


Scheme 7. Synthesis of the polymer-supported organocatalyst **11**.

To avoid the difficulties associated with the small-scale preparation of a non-supported counterpart,[18] our synthetic approach started with the preparation of compound **6** by selective protection of commercially available (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride. Grignard addition and subsequent methylation of the resulting tertiary alcohol provided the intermediate **8**, which was sequentially deprotected to give key intermediate 4-hydroxy diphenylprolinol methyl ether (**9**). Propargylation of **9** led to the required derivative **10**, suitable for a **TTM-Cu**-mediated click reaction with azidomethyl polystyrene.

Resin **11** was evaluated in the Michael addition of propionaldehyde to (*E*)-β-nitrostyrene (Table 3). Under the previously optimized conditions for catalyst **4** (Table 3, entry 1), the reaction proceeded slowly and with lower selectivity than with the silylated resin **4**. The addition of benzoic acid as a co-catalyst (Table 3, entry 2) led to a slight improvement in the activity of catalyst **11**, although deactivation was observed (after approximately 48 h) before full conversion could be achieved.

Table 3. Evaluation of organocatalyst **11** in the Michael addition of propionaldehyde to (*E*)-β-nitrostyrene.[a]



	Additive (10 mol %)	*t* [h]	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	none	96	51	80:20	85
2	PhCOOH	48	63	79:21	92
3[e]	PhCOOH[f]	48	53	82:18	90
4	4-NO_2PhCOOH	48	35	2:1	82
5[g]	PhCOOH	48	55	93:7	93
6[h]	PhCOOH	60	72	95:5	93

[a] General conditions: (*E*)-β-nitrostyrene (0.2 mmol), propionaldehyde (0.3 mmol), **11** (0.02 mmol), solvent (1 mL), RT. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Catalyst **11** (0.03 mmol). [f] Benzoic acid (15 mol %). [g] (*E*)-β-nitrostyrene (1.5 equiv). [h] (*E*)-β-nitrostyrene (3 equiv).

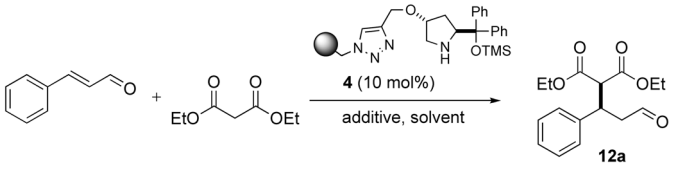
On the other hand, the addition of benzoic acid had a positive effect on the enantioselectivity of the process, which increased from 85 to 92 % *ee*, whereas the diastereoselectivity did not experience any change. The use of an additional 5 mol % of catalyst and co-catalyst did not change the results significantly (Table 3, entry 3). In turn, addition of the more acidic *p*-nitrobenzoic acid had a negative effect on both the conversion and stereoselectivity (Table 3, entry 4). In light of recently published kinetic studies, which revealed that the rate-limiting steps in the case of peptide-organocatalyzed conjugate addition reactions between aldehydes and nitroolefins are both the reaction of the enamine with the electrophile and the hydrolysis of the resulting imine,[19] we decided to perform the Michael addition of propanal to (*E*)-β-nitrostyrene with 1.0:1.5 and 1:3 molar ratios of aldehyde/nitroolefin (Table 3, entries 5 and 6, respectively). In these cases, the excess of nitrostyrene led to the Michael adduct **5b** with good enantioselectivity and highly improved diastereoselectivity relative to the previous results, even increasing the reaction time, although complete conversion was not achieved. Based on these initial experiments, we can envisage that although polystyrene-supported methyl ether **11** does not present the problem of ether cleavage under mild reaction conditions, it would show worse performance as a catalyst in the Michael addition of aldehydes to nitroolefins relative to **4**. This demonstrates, once again, the crucial role exerted by the *O*-silyl protecting group in the control of catalytic activity and selectivity of diarylprolinol ether derivatives.

Conjugate additions of malonates to α,β-unsaturated aldehydes catalyzed by 4: Secondary amines readily experience

condensation reactions with aldehydes or ketones to form intermediate iminium cations. These species are characterized by a low-lying LUMO and can often be trapped by nucleophiles before proton loss converts them into imines (primary amines) or enamines (secondary amines). This nucleophilic trapping is the fundamental event in iminium-type aminocatalysis. Focusing on conjugate addition reactions, a broad range of nucleophilic intermediates, such as nitroalkanes, nitroesters, malonates, and ketoesters, among others, have been used for conjugate addition to α,β-unsaturated systems assisted by iminium-type aminocatalysis.[20] The modularity of the products that arise from this process makes them valuable building blocks in organic chemistry. Chiral secondary amines, such as imidazolidinone derivatives[21] and *O*-TMS-protected diarylprolinols,[22] have shown high efficiency as catalysts by activating α,β-unsaturated systems through iminium-type mechanisms. Through the use of recoverable organocatalysts, positive economic and environmental aspects could complement this synthetic efficiency.

In view of our recent results obtained with dimethyl 3-oxoglutarate,[5g] we decided to test the **4** in the reaction of α,β-unsaturated aldehydes with dialkyl malonates.[23] The addition of diethyl malonate to cinnamaldehyde was selected as a model reaction and the results from the preliminary screening of the reaction conditions are shown in Table 4. Initially, we chose dichloromethane as the solvent because of its good swelling properties for resin **4** and the optimal performance of this solvent in the Michael addition of aldehydes to nitroalkenes discussed above. When the reaction was performed in the absence of additives, poor activity was recorded, with only 24% of conversion after 96 h (Table 4, entry 1), although enantioselectivity was high (90% *ee*). Benzoic acid (30 mol%), a commonly employed acidic cocatalyst for iminium-catalyzed processes, was tested as an additive to promote conversion, but no improvement was observed (Table 4, entry 2). As an alternative, we attempted to increase the activity of catalyst **4** by Lewis base/Brønsted base co-operative catalysis.[23c] Thus, when lithium acetate was used as a Brønsted base to activate the malonate reagent complete conversion was recorded after 36 h and enantioselectivity was preserved (Table 4, entry 3). To investigate the effect of the aldehyde/malonate ratio in the reaction, we tried the same reaction with diethyl malonate (1.0 equiv), cinnamaldehyde (1.5 equiv) and lithium acetate (10 mol%). No change in enantioselectivity was observed, but conversion suffered a dramatic decrease and only 25% of the starting material had reacted after 24 h (Table 4, entry 4). Tetrahydrofuran was tested as a solvent for the optimal swelling of **4** but, surprisingly, resulted in total loss of catalytic activity (Table 4, entry 5). Water was also tested as a solvent, but after 96 h conversion was only 49% and the *ee* had decreased to 53% (Table 4, entry 6). Thus, the possible environmental advantages presented by this solvent are outbalanced by its probable negative effect on iminium ion formation and malonate reactivity. Finally, to mitigate the requirement for long reaction times, we decided to perform the reaction under low-power microwave (MW) irradiation, in line with our previous experience in other reactions catalyzed by polystyrene-supported species.[5e,24] Gratifyingly, a notable acceleration of the reaction was observed (Table 4, entry 7).

Table 4. Optimization of the reaction conditions for the asymmetric addition of diethyl malonate to cinnamaldehyde catalyzed by **4**.[a]



	Solvent	Additive (30 mol%)	*t* [h]	Conv[b] [%]	*ee*[c] [%]
1	CH_2Cl_2	none	96	24	90
2	CH_2Cl_2	PhCOOH	24	8	n.d.
3	CH_2Cl_2	LiOAc	36	>99	90
4[d]	CH_2Cl_2	LiOAc[e]	24	25	90
5	THF	LiOAc	48	0	n.d.
6	H_2O	LiOAc	96	49	53
7[f]	CH_2Cl_2	LiOAc	6	93	90

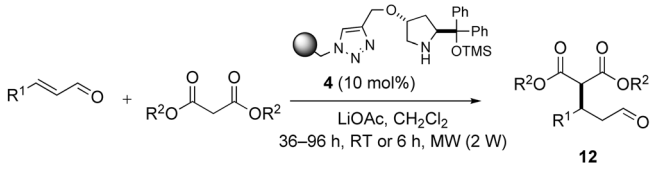
[a] General conditions: cinnamaldehyde (0.2 mmol), diethyl malonate (0.6 mmol), **4** (0.02 mmol), solvent (1 mL), RT. [b] Conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Reaction carried out with a 1:1.5 molar ratio of aldehyde/malonate. [e] LiOAc (10 mol%). [f] Reaction carried out under MW irradiation (2 W) in CH_2Cl_2 (0.3 mL).

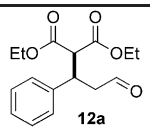
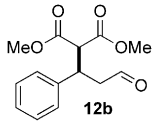
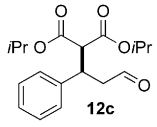
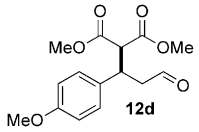
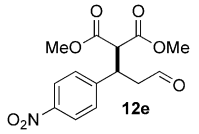
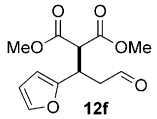
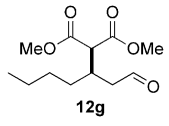
Under low-power MW irradiation (2 W), the reaction temperature increased from 23 to 30°C and the reaction time was reduced by a factor of six (Table 4, entry 7 versus 3), although no change in enantioselectivity was noticed. Under these optimized conditions, the scope of the reaction was studied. A series of dialkyl malonates and α,β-unsaturated aldehydes were tested and the results are presented in Table 5.

The addition of dimethyl, diethyl, or diisopropyl malonates to cinnamaldehyde was studied at room temperature and under MW irradiation (2 W, 6 h). In all cases, the expected products **12a–c** were obtained with full conversion and very high enantioselectivities (Table 5, entries 1–3). Branching in the alkyl moiety of the malonate ester (Table 5, entry 3) resulted in an extended reaction time for complete conversion to be achieved. Given the excellent enantioselectivity recorded from reaction with dimethyl malonate (Table 5, entry 2), we evaluated the addition of this nucleophile to a small family of α,β-unsaturated aldehydes. Good yields and high enantioselectivities were obtained from the reactions of cinnamaldehyde derivatives with either an electron-donating or electron-withdrawing group on the *para* position of the ring (Table 5, entries 4 and 5).

Full conversion was again observed in the addition of dimethyl malonate to heterocyclic α,β-unsaturated aldehyde 3-(2-furyl)acrolein, but the enantioselectivity was substantially lower than for previous examples (Table 5, entry 6). To exemplify enals lacking extended conjugation, 2-heptenal was also tested as an electrophile in the reaction (Table 5, entry 7) and afforded the addition product **12g** with good yield and enantioselectivity. As a general observation, the

Table 5. Substrate scope in the asymmetric addition of dialkyl malonates to α,β-unsaturated aldehydes organocatalyzed by **4**.[a]



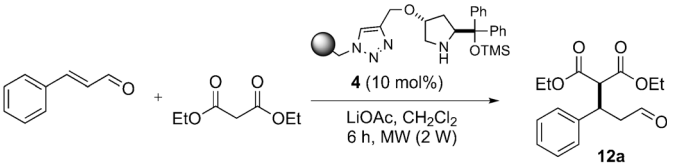
	Product	*t* [h]	Yield[b,c] [%]		*ee*[b,d] [%]	
1	 **12a**	36	81	(88)	91	(90)
2	 **12b**	36	86	(80)	99	(99)
3	 **12c**	72	85	(63)	90	(90)
4	 **12d**	96	87	(85)	94	(92)
5	 **12e**	36	90	(89)	92	(90)
6	 **12f**	96	75	(82)	77	(78)
7	 **12g**	96	85	(76)	79	(83)

[a] General conditions: α,β-unsaturated aldehyde (0.2 mmol), dialkyl malonate (0.6 mmol), LiOAc (0.06 mmol), **4** (0.02 mmol), CH_2Cl_2 (0.3 mL), RT or MW irradiation (6 h, 2 W). [b] The results of the experiments performed under MW irradiation are shown in parentheses. [c] Isolated yield. [d] Determined by chiral HPLC analysis.

results obtained from this screening showed that the co-operative catalytic system **4**/LiOAc is highly efficient for the addition of malonates to α,β-unsaturated aldehydes with the advantage of easy separation of the polymer-supported catalyst from the obtained products. Experimentally, activation of the reactions with low-power microwave irradiation (2 W) is clearly advantageous over execution of the reactions at room temperature.

The possibility of recycling and reusing resin **4** was next studied. As shown in Table 6, conversion decreased considerably when the catalytic system **4**/LiOAc was directly reused after separation of the reaction mixture and a dichloromethane wash (Table 6, cycle 2). Addition of fresh LiOAc in the next cycle did not improve the catalytic activity (Table 6, cycle 3); nevertheless, enantioselectivity remained unchanged over the three runs. As already mentioned, we could reactivate resin **4** in the Michael addition of aldehydes to nitroolefins by reprotection of the inactive polymer-supported diphenylprolinol with trimethylsilyl *N,N*-dimethylcarbamate.[17] In this particular case, such treatment had a positive effect but did not lead to complete recovery of the catalytic activity of **4** (Table 6, cycle 4).

Table 6. Recycling experiments of catalyst **4** in the asymmetric addition of diethyl malonate to cinnamaldehyde.[a]



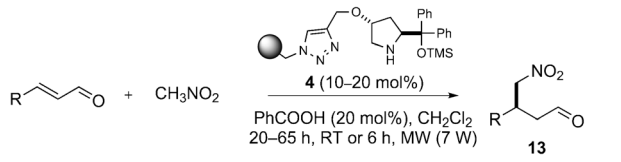
Cycle	*t* [h]	Conv[b] [%]	*ee*[c] [%]
1	6	93	90
2	6	73	90
3[d]	6	53	90
4[e]	6	77	90

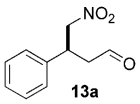
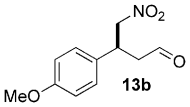
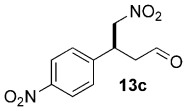
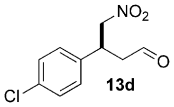
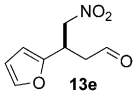
[a] General conditions: cinnamaldehyde (0.2 mmol), diethyl malonate (0.6 mmol), LiOAc (0.06 mmol), **4** (0.02 mmol), CH_2Cl_2 (0.3 mL), MW irradiation (2 W). [b] Conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Additional LiOAc (0.06 mmol) was added. [e] Resin reconditioned by treatment with trimethylsilyl *N,N*-dimethylcarbamate (see reference [5f].

To test the performance of polystyrene-supported methyl ether **11** in reactions taking place via iminium ion intermediates, **11** (10 mol%) was also tested as catalyst in the addition of diethyl malonate to cinnamaldehyde in the presence of LiOAc (30 mol%) in CH_2Cl_2 under MW irradiation (2 W) to accelerate the reaction. After 6 h, **12a** could be isolated in 27% yield and 86% *ee*. This result confirmed our initial impression (see above) on the lower catalytic efficiency of **11** relative to **4**.

Addition of nitromethane to α,β-unsaturated aldehydes catalyzed by 4: Further proof of the effectiveness of resin **4** in reactions that take place through iminium ion activation could be obtained from its notable performance in the iminium-catalyzed enantioselective synthesis of γ-nitro aldehydes by a Henry-type reaction of nitromethane with α,β-unsaturated aldehydes.[5h,25] Preliminary experiments in the addition of nitromethane to cinnamaldehyde under the optimal reaction conditions reported for α,α-diphenylprolinol-type catalysts[5h,25] [MeOH, catalyst (10 mol%), benzoic acid co-catalyst (10–20 mol%)] resulted in poor conversions. Much better results were obtained in dichloromethane, an optimal swelling media for **4**, which was adopted as the solvent for this study (Table 7). On the other hand, the use of LiOAc (20 mol%) as a co-catalyst in the addition of nitromethane to cinnamaldehyde resulted in a significant reduction of activity, therefore its use was no longer considered. Thus, the selected reaction conditions were a combination of **4** and benzoic acid in dichloromethane.

Table 7. Evaluation of organocatalyst **4** in the Michael addition of nitromethane to α,β-unsaturated aldehydes.[a]



	Product	T [°C]	t [h]	Conv[b] [%]	Yield[c] [%]	*ee*[d] [%]
1[e]	 **13a**	RT	65	75	52	96
2		RT	56	>99	86	96
3		45	20	83	75	95
4[e]		45	30	64	51	93
5[f]		45	6	>99	61	96
6[f]	 **13b**	45	6	>99	80	91
7[f]	 **13c**	45	6	>99	88	90
8[f]	 **13d**	45	6	>99	85	90
9[f]	 **13e**	45	6	>99	31	94
10[g]		30	7	85	52	95

[a] General conditions: α,β-unsaturated aldehyde (0.2 mmol), nitromethane (0.6 mmol), benzoic acid (0.04 mmol), **4** (0.04 mmol), CH_2Cl_2 (0.5 mL). [b] Conversion determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield. [d] Determined by chiral GC or HPLC analysis. [e] Catalyst **4** (10 mol%). [f] Reaction performed under MW irradiation (7 W). [g] Reaction performed under MW irradiation (3 W).

When **4** (10 mol%) and benzoic acid (20 mol%) were used to promote the reaction at room temperature, only moderate conversion to **13a** was recorded after 65 h (Table 7, entry 1). However, the enantioselectivity compared very favorably with that recorded when soluble α,α-diphenylprolinol trimethylsilyl ethers were used.[5h,25] Increasing the catalyst loading (20 mol%) was enough to ensure complete conversion, high yield, and excellent enantiomeric excess after a reasonable reaction time (Table 7, entry 2). Importantly, we also found that heating the reaction mixture at 45°C accelerated the reaction but compromised both the yield and enantioselectivity (Table 7, entries 3 and 4). Interestingly, when the reaction was performed at this temperature under MW irradiation (7 W), we were able to significantly reduce the reaction time and achieve total conversion of cinnamaldehyde without any detriment to the enantioselectivity (Table 7, entry 5). The observed decrease in the isolated yield under these conditions can be attributed to poor stability of the aldehyde product.[25b]

The beneficial effect of MW activation in this reaction was additionally confirmed when a representative set of α,β-unsaturated aldehydes was evaluated under the same reaction conditions. High yields and selectivities were recorded with both electron-poor and electron-rich substituted cinnamaldehydes (Table 7, entries 6–8). With 3-(2-furyl)acrolein (Table 7, entries 9 and 10) the reaction proceeded more satisfactorily when run under MW irradiation at 30°C, and gave γ-nitro aldehyde **13e** in moderate yield but with excellent enantioselectivity.

Conclusion

An insoluble polystyrene-supported diarylprolinol silyl ether (**4**) was prepared and used as a highly efficient, reusable organocatalyst for Michael additions that proceed by enamine or iminium ion catalysis. In reactions via enamine intermediates, **4** exhibits a remarkable preference for linear aldehyde donors; this preference can be used in practice for the differentiation between linear and branched aldehydes in their reactions with nitroolefins. In reactions taking place via iminium ion intermediates, **4** efficiently mediates the addition of dialkyl malonates and nitromethane to α,β-unsaturated aldehydes. As a general observation, **4** exhibits a catalytic performance comparable, or superior, to monomeric, soluble diarylprolinol silyl ethers and offers the additional advantages of simplified reaction workup, easy catalyst recovery, and the possibility of catalyst reuse. In an attempt to extend the life cycle of **4** for repeated use, a polystyrene-supported diarylprolinol methyl ether (**11**) was also prepared and evaluated. However, the catalytic characteristics of this species are inferior to those of **4**.

Experimental Section

General procedure for the Michael addition of aldehydes to nitroolefins catalyzed by 4 or 11 (GP1): Nitroolefin (0.2 mmol) and catalyst **4** (46.1 mg, 10 mol% according to the functionalization (f) = 0.462 mmol g^{-1}) or **11** (45.1 mg, 10 mol%, f = 0.443 mmol g^{-1}) were mixed with the aldehyde (0.3 mmol) in CH_2Cl_2 (1.0 mL). The suspension was stirred at RT for the time specified in Table 2 and filtered to separate the solid catalyst. The resin was washed with CH_2Cl_2 and the combined organic extracts were concentrated under reduced pressure. A ^{1}H NMR spectrum was recorded to calculate the conversion and d.r. For volatile starting aldehydes, the Michael adduct was obtained as the evaporation residue without further purification. In other cases, purification by flash chromatography on silica gel (EtOAc/hexane) afforded the Michael adduct. The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak IB or Chiralcel AD-H columns).

All of the prepared products are known and spectroscopic data are, in all cases, in agreement with the published data. Compounds **5a–k** have been described in a preliminary communication of this work.[5f]

Starting nitroolefins (*E*)-(4-nitrobut-3-en-1-yl)benzene, (*E*)-(2-nitrovinyl)cyclohexane, and (*E*)-3-methyl-1-nitrobut-1-ene were prepared by literature procedures.[26]

(2*R*, 3*R*) 2-Methyl-3-nitromethyl-5-phenyl-pentanal (51):[27] Compound **51** was prepared from *E*-(4-nitrobut-3-en-1-yl)benzene and propionaldehyde according to **GP1** in 94% yield (44.2 mg, 0.188 mmol) as an inseparable mixture of two diastereomers. 95% *ee* by HPLC: IB (hexane/*i*PrOH 95:5, 1.0 mL min^{-1}, λ = 220 nm); retention time (t_R) (major) = 18.6 min, t_R(minor) = 21.3 min.

(2*R*, 3*R*)-3-Cyclohexyl-2-methyl-4-nitrobutyraldehyde (5m):[12c] Compound **5m** was prepared from *E*-(2-nitrovinyl)cyclohexane and propionaldehyde according to **GP1** in 89% yield (38 mg, 0.178 mmol) as an inseparable mixture of two diastereomers. 97% *ee* by HPLC: AD-H (hexane/*i*PrOH 99:1, 1.0 mL min^{-1}, λ = 213 nm); t_R(major) = 13.3 min, t_R(minor) = 16.7 min.

(2*R*, 3*R*)-2,4-Dimethyl-3-nitromethylpentanal (5n):[28] Compound **5n** was prepared from *E*-3-methyl-1-nitrobut-1-ene and propionaldehyde according to **GP1** in 84% yield (29 mg, 0.168 mmol) as an inseparable mixture of two diastereomers. 99% *ee* by HPLC: AD-H (hexane/*i*PrOH 99:1, 0.8 mL min^{-1}, λ = 210 nm); t_R(major) = 12.6 min, t_R(minor) = 13.9 min.

General procedure for the addition of malonates to α,β-unsaturated aldehydes (GP2): Resin **4** (10 mol%, f = 0.462 mmol g^{-1}) and lithium acetate (30 mol%) were placed in a vial. CH_2Cl_2 (1 mL) was added, followed by the α,β-unsaturated aldehyde (0.2 mmol) and dialkyl malonate (0.6 mmol). The mixture was stirred at RT for the time indicated in Table 4, until total conversion was confirmed by ^{1}H NMR spectroscopy. The resin was filtered off and rinsed with CH_2Cl_2 (3 mL). The combined organic extracts were concentrated under reduced pressure and the crude product purified by flash chromatography on silica gel (hexane/diethyl ether, 10:1).

General procedure for the addition of malonates to α,β-unsaturated aldehydes under MW irradiation (GP3): Resin **4** (10 mol%, f = 0.462 mmol g^{-1}), lithium acetate (30 mol%), and CH_2Cl_2 (0.3 mL) were added to a MW vial. α,β-Unsaturated aldehyde (0.2 mmol) and dialkyl malonate (0.6 mmol) were added. The mixture was irradiated at 2 W power (30 °C) for 6 h. The resin was filtered off and rinsed with CH_2Cl_2 (3 mL). The combined organic extracts were concentrated under reduced pressure and the crude product purified by flash chromatography (hexane/diethyl ether, 10:1). Products **12a–g** are known compounds, and the spectroscopic data are in agreement with the published data.[23c–g,29]

(*R*)-Diethyl 2-(3-oxo-1-phenylpropyl)malonate (12a):[23c] Compound **12a** was obtained from (*E*)-cinnamaldehyde and diethyl malonate with catalyst **4** after 36 h in 81% yield (47.4 mg, 0.162 mmol) following **GP2**. When **GP3** was followed, **12a** was obtained in 88% yield (51.5 mg, 0.176 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mL min^{-1}, λ = 210 nm); t_R(major) = 17.5 min, t_R(minor) = 21.9 min.

(*R*)-Dimethyl 2-(3-oxo-1-phenylpropyl)malonate (12b):[23c] Compound **12b** was obtained from (*E*)-cinnamaldehyde and dimethyl malonate with catalyst **4** after 36 h in 86% yield (45.5 mg, 0.172 mmol) following **GP2**. When **GP3** was followed, **12b** was obtained in 80% yield (42.3 mg, 0.16 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mL min^{-1}, λ = 210 nm); t_R(major) = 20.4 min, t_R(minor) = 23.8 min.

(*R*)-Diisopropyl 2-(3-oxo-1-phenylpropyl)malonate (12c):[23c] Compound **12c** was obtained from (*E*)-cinnamaldehyde and diisopropyl malonate with catalyst **4** after 72 h in 85% yield (54.5 mg, 0.17 mmol) following **GP2**. When **GP3** was followed, **12c** was obtained in 63% yield (40.3 mg, 0.126 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mL min^{-1}, λ = 210 nm); t_R(major) = 14.4 min, t_R(minor) = 17.6 min.

(*R*)-2-Isopropyl 3-methyl 2-((*R*)-1-(4-methoxyphenyl)-3-oxopropyl)malonate (12d):[23g] Compound **12d** was obtained from (*E*)-3-(4-methoxyphenyl) acrylaldehyde and dimethyl malonate with catalyst **4** after 96 h in 87% yield (56 mg, 0.174 mmol) following **GP2**. When **GP3** was followed, **12d** was obtained in 85% yield (54.8 mg, 0.17 mmol). HPLC: AD-H (hexane/*i*PrOH 90:10, 0.8 mL min^{-1}, λ = 210 nm); t_R(major) = 25.3 min, t_R(minor) = 27.1 min.

(*R*)-1-Isopropyl 3-methyl 2-((*R*)-1-(4-nitrophenyl)-3-oxopropyl)malonate (12e):[23g] Compound **12e** was obtained from (*E*)-3-(4-nitrophenyl)acrylaldehyde and dimethyl malonate with catalyst **4** after 36 h in 90% yield (61 mg, 0.18 mmol) following **GP2**. When **GP3** was followed, **12e** was obtained in 89% yield (60 mg, 0.178 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.8 mL min^{-1}, λ = 210 nm); t_R(major) = 23.8 min, t_R(minor) = 25.4 min.

(*R*)-1-Isopropyl 3-methyl 2-((*R*)-1-(furan-2-yl)-3-oxopropyl)malonate (12f):[23g] Compound **12f** was obtained from (*E*)-3-(2-furyl)acrylaldehyde and dimethyl malonate with catalyst **4** after 96 h in 75% yield (42.7 mg, 0.15 mmol) following **GP2**. When **GP3** was followed, **12f** was obtained in 82% yield (46.3 mg, 0.164 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.8 mL min^{-1}, λ = 210 nm); t_R(minor) = 20.3 min, t_R(major) = 22.2 min.

(*R*)-1-Isopropyl 3-methyl 2-((*R*)-1-oxoheptan-3-yl)malonate (12g):[29] Compound was obtained from (*E*)-hept-2-enal and dimethyl malonate with catalyst **4** after 96 h in 85% yield (46.3 mg, 0.17 mmol) following **GP2**. When **GP3** was followed **12g** was obtained in 76% yield (41.4 mg, 0.152 mmol). HPLC: IC (heptane/*i*PrOH 90:10, 1 mL min^{-1}, mass-APCI(−)); t_R(major) = 13.3 min, t_R(minor) = 14.1 min.

General procedure for the Michael addition of nitromethane to cinnamaldehyde (GP4): Catalyst **4** (10–20 mol%, f = 0.462 mmol g^{-1}) and benzoic acid (4.87 mg, 0.04 mmol) were placed in a vial. CH_2Cl_2 (0.5 mL), cinnamaldehyde (0.2 mmol, 25 mL), and nitromethane (0.6 mmol, 32 mL) were added successively. The mixture was stirred at the indicated temperature for the time noted in Table 7. The resin was filtered and rinsed with CH_2Cl_2. The combined organic extracts were concentrated under reduced pressure and the crude product purified by flash chromatography (silica gel, hexane/EtOAc 10:1).

General procedure for the Michael addition of nitromethane to α,β-unsaturated aldehydes under MW irradiation (GP5): Catalyst **4** (86.6 mg, 0.04 mmol, f = 0.462 mmol g^{-1}) and benzoic acid (4.87 mg, 0.04 mmol) were placed in a MW vial. CH_2Cl_2 (0.5 mL), α,β-unsaturated aldehyde (0.2 mmol), and nitromethane (0.6 mmol, 32 mL) were added successively. The mixture was irradiated at 7 W (45 °C) for 6 h in a MW reactor. The resin was filtered and rinsed with CH_2Cl_2. Evaporation of the solvent under reduced pressure afforded the desired product, which was purified by flash chromatography (silica gel, hexane/EtOAc 10:1). Products **13a–e** are known compounds and the spectroscopic data are in agreement with the published data.[5h,25a]

(*S*)-4-Nitro-3-phenylbutanal (13a):[25a] Compound **13a** was obtained from cinnamaldehyde in 86% yield following **GP4**, and in 61% yield following **GP5**. GC-MS: Chiraldex G-TA (130 °C isotherm, 1.5 mL min^{-1}); t_R(minor) = 133.4 min, t_R(major) = 139.4 min.

(*S*)-3-(4-Methoxyphenyl)-4-nitrobutanal (13b):[25a] Compound **13b** was obtained from 3-(4-methoxyphenyl)propenal in 80% yield following **GP5**. HPLC: IB (hexane/*i*PrOH 85:15, 1.0 mL min^{-1}, λ = 254 nm); t_R(minor) = 11.9 min, t_R(major) = 12.5 min.

(*S*)-4-Nitro-3-(4-nitrophenyl)butanal (13c):[5h] Compound **13c** was obtained from 3-(4-nitrophenyl)propenal in 88% yield following **GP5**. HPLC: IC (hexane/*i*PrOH 90:10, 1.0 mL min^{-1}, λ = 254 nm); t_R(minor) = 41.3 min, t_R(major) = 44.4 min.

(*S*)-3-(4-Chlorophenyl)-4-nitrobutanal (13d):[25a] Compound **13d** was obtained from 3-(4-chlorophenyl)propenal in 85% yield following **GP5**. HPLC: IC (hexane/*i*PrOH 10:1, 1.0 mL min^{-1}, λ = 240 nm); t_R(minor) = 18.9 min, t_R(major) = 20.8 min.

(*S*)-3-(2-Furyl)-4-nitrobutanal (13e):[25a] Compound **13e** was obtained from 3-furyl-propenal in 52% yield following a modified version of **GP5** with irradiation at 3 W for 7 h. GC-MS: Chiraldex G-TA (130 °C isotherm, 1.5 mL min^{-1}); t_R(minor) = 49.9 min, t_R(major) = 54.0 min.

For general methods and for the synthesis and characterization of **11**, see the Supporting Information.

Acknowledgements

This work was funded by MICINN (Grant CTQ2008–00947/BQU and Consolider Ingenio 2010 Grant CSD2006–0003), DIUE (Grant 2009SGR623), and ICIQ Foundation. E.A. thanks the ICIQ Foundation for a pre-doctoral fellowship. P.K. thanks MICINN for a pre-doctoral FPI-fellowship. The authors gratefully acknowledge S. Curreli for her help with HPLC-MS and GC-MS analysis.

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Received: June 7, 2011
Published online: September 1, 2011

