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A Highly Selective, Polymer-Supported Organocatalyst for Michael Additions with Enzyme-Like Behavior

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Abstract: A polymer-supported α,α-diarylprolinol silyl ether displays catalytic activity and enantioselectivity comparable to the best homogeneous catalysts in the Michael addition of aldehydes to nitroolefins. Above all, the combination of polymer backbone, triazole linker, and catalytic unit confers to it an unprecedented substrate selectivity in favor of linear, short-chain aldehydes.

Keywords: asymmetric catalysis; Michael addition; nitroolefins; organocatalysis; synthetic enzymes

The design and preparation of immobilized catalysts[1] that keep intact the characteristics (activity and selectivity) of their homogeneous counterparts represents a major goal in view of more efficient chemical production. When enantioselective processes are concerned,[1c] the opportunities offered by this approach (recovery and reuse of expensive catalytic species, highly simplified work-up, implementation of continuous flow processing) become even more evident.

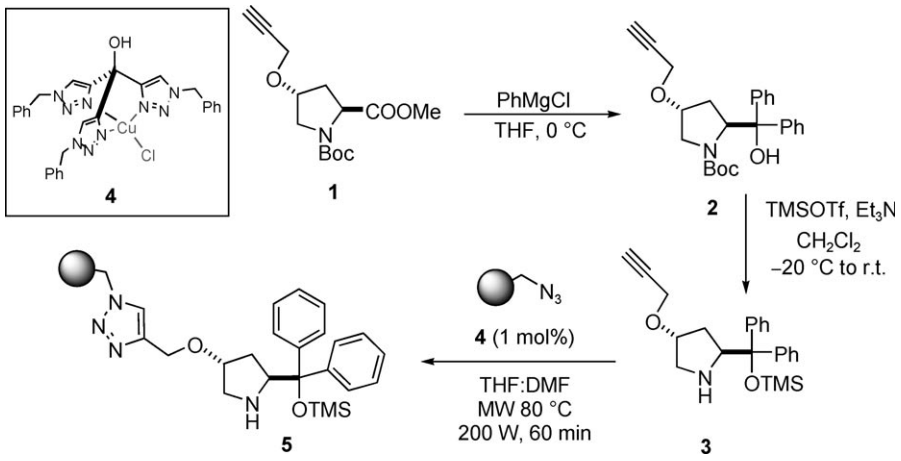
In a continued effort towards this goal, we have shown that a variety of organocatalytic processes can be most efficiently mediated by proline derivatives supported onto polystyrene resins through 1,2,3-triazole linkers.[2] Synergistic effects between polymer backbone, triazole linker and catalytic unit leading to very high catalytic activity and enantioselectivity have been observed.[2a,d] Most remarkably, the behavior of some of these catalytic resins is reminiscent of that of polypeptides with enzyme activity.[2d] The Michael addition of carbon nucleophiles to nitroolefins is a convenient entry to versatile synthetic intermediates.[3] The reaction has been widely used as the first step in cascade processes,[4] and the most successful enantioselective versions of it are based on organocatalytic approaches.[5] Among them, those mediated by enantiopure pyrrolidines bearing a bulky C-2 substituent have found wide application[6] and, in particular, (*S*)-α,α-diarylprolinol silyl ethers (Jørgensen–Hayashi catalysts) exhibit optimal performance for a variety of donors and acceptors.[7]

Herein we report the preparation of a polystyrene-supported, enantiopure (*S*)-α,α-diphenylprolinol trimethylsilyl ether (**5**) displaying high catalytic activity and enantioselectivity in the Michael addition of aldehydes to nitroolefins with unprecedented, enzyme-like substrate selectivity.

The preparation of **5** from commercially available *N*-Boc-(2*S*,4*R*)-4-hydroxyproline methyl ester *via* its propargyloxy derivative (**1**) is shown in Scheme 1 (see Supporting Information for details).

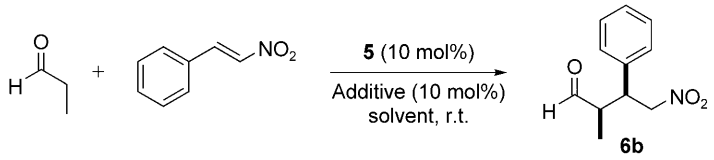
The silylation with concomitant carbamate deprotection of **2** leads to the key intermediate **3**, already containing the functional arrangement of the target catalyst. The immobilization of **3** onto azidomethylpolystyrene using click chemistry, in turn, posed an important synthetic challenge, since common catalysts for the cycloaddition were deactivated by the free amino group in the substrate. Gratifyingly enough, the recently developed tris(triazolyl)methanol-copper complex **4**[8] efficiently catalyzed the immobilization reaction, thus allowing the easy and highly reproducible synthesis of the catalytic resin **5**.

The Michael addition[9] of propanal to β-nitrostyrene was selected as a model for the evaluation of **5** and was studied under a variety of experimental conditions (Table 1). In the initial set of experiments (entries 1–4) a ten-fold excess of aldehyde donor was used, according to the usual practice in this organocatalytic process with homogeneous catalysts.[7b] Under these conditions, dichloromethane proved itself as the optimal solvent, reactions in it being faster and more stereoselective in the absence of additives (entry 2). Quite interestingly, the use of a much more conven-



Scheme 1. Synthesis of the polymer-supported organocatalyst **5**.

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



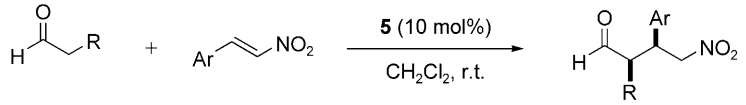
Entry	Solvent	Additive[b]	*t* [h]	Conversion [%][c]	*syn/anti*[c]	*ee* [%][d]
1[e]	hexane:THF	none	36	40	97:3	97
2[e]	CH_2Cl_2	none	7	>99	96:4	>99
3[e]	CH_2Cl_2	DMAP	24	>99	81:19	99
4[e]	CH_2Cl_2	PhCOOH	24	>99	77:23	97
5	CH_2Cl_2	none	7	>99	>99:1	>99
6	CH_2Cl_2	DMAP	23	>99	86:14	>99
7	CH_2Cl_2	PhCOOH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

[a] All reactions performed with 0.2 mmol of (*E*)-β-nitrostyrene, 0.3 or 2.0 mmol of propanal, and 0.02 mmol of **5** in 1 mL of solvent at room temperature.
[b] 0.02 mmol.
[c] Determined by ^{1}H NMR of the reaction crude.
[d] Determined by chiral HPLC analysis.
[e] 2 mmol of propanal were used.

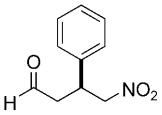
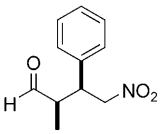
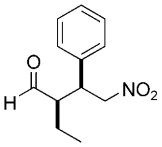
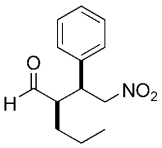
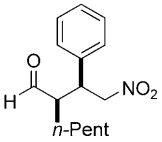
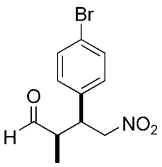
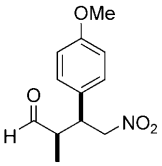
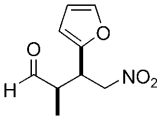
ient 1.5:1 propanal to β-nitrostyrene ratio (entries 5–9) led to cleaner reaction crudes (aldehyde self-aldol reaction was efficiently suppressed) with increased diastereoselectivity. The straightforward isolation of the Michael adducts in the absence of additives, simply involving catalyst separation by filtration and concentration of the reaction crude (entry 5), strongly favors these reaction conditions. On the other hand, it is worth noting that **5** is also able to induce a highly enantioselective Michael addition in water (entry 8), and this represents the first example of an insoluble catalyst successfully dealing with aldehydes in this solvent.[2c]

The scope of the Michael addition mediated by **5** was next investigated. The results of this study have been summarized in Table 2. As a general trend, diastereo- and enantioselectivities achieved with **5** compare well with those recorded with the most efficient homogeneous organocatalysts. Quite unexpectedly, the catalytic activity of resin **5** was remarkably dependent on the aldehyde donor. Thus, a fast reaction was observed for linear, short chain aldehydes like propanal and butanal (entries 2 and 3), while further increases in the chain length (entries 4 and 5) resulted in significant extension of reaction time. In all these cases, yield and enantioselectivity of the major *syn* adducts were excellent. Branching in the β position of the aldehyde (**6i** and **6j**, Figure 1) is deletereous for conversion, while α-branching (**6k**, Figure 1) completely blocks the reaction. Ketones like acetone and

Table 2. Scope of the Michael addition of aldehydes to nitroolefins catalyzed by **5**.[a]



6a – h

Entry	Product		*t* [h]	Conversion[b] [%] (Yield [%])[c]	*syn/anti*[b]	*ee*[d] [%]
1		**6a**	72	50 (44)	–	96
2		**6b**	7	>99 (98)	>99:1	>99
3		**6c**	5	>99 (93)	90:10	>99
4		**6d**	27	>99 (98)	82:18	99
5		**6e**	48	99 (91)	75:25	98
6		**6f**	4	>99 (98)	91:9	98
7		**6g**	8	>99 (94)	89:11	99
8		**6h**	4	>99 (96)	85:15	90

[a] All reactions performed with 0.2 mmol of nitroolefin, 0.3 mmol of aldehyde, and 0.02 mmol of **5** in 1 mL of CH_2Cl_2 at room temperature.
[b] Determined by ^1H NMR of the reaction crude.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.

cyclohexanone, in turn, are completely unreactive. With respect to Michael acceptors, nitroethylenes bearing β-aryl or hetaryl substituents with different electronic characters were studied, the corresponding *syn*-adducts being obtained in excellent yields and selectivities after short reaction times (Table 2, entries 6–8). Finally, resin **5** was also tested in the more demanding Michael addition of acetaldehyde to β-nitrostyrene (Table 2, entry 1), with results comparable to those reported in the literature for homogeneous

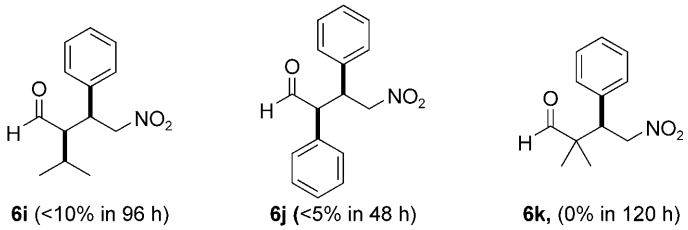
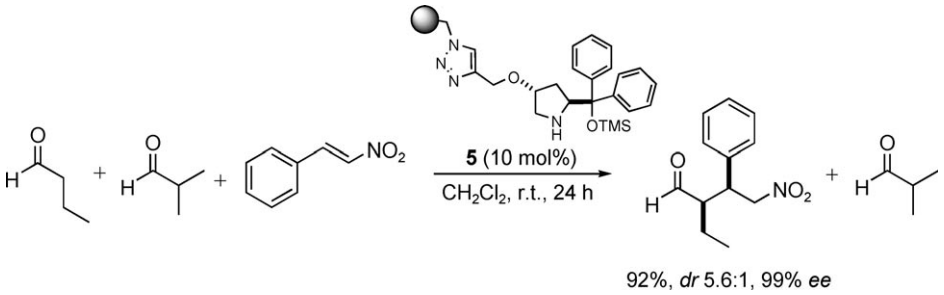


Figure 1. Michael adducts whose formation is not efficiently mediated by resin **5**.

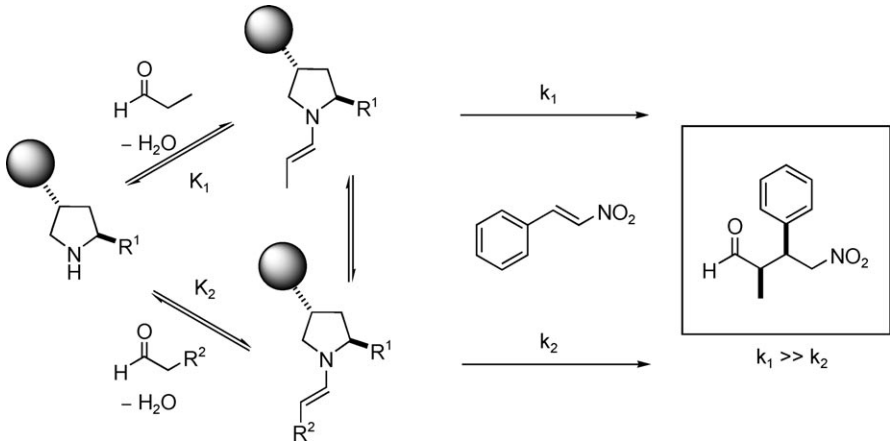
catalysts,[10] but using in the present case a much smaller excess of acetaldehyde and half catalyst loading.[10b]

In view of the high substrate selectivity exhibited by resin **5**, we envisaged a possible application in the discrimination between linear and α-branched aldehyde donors for Michael additions. To test this possibility, the 1.6:1 mixture of butanal and 2-methylpropanal obtained in the Rh-catalyzed hydroformylation of propene[11] was treated with β-nitrostyrene in the presence of **5** (**5**/β-nitrostyrene/butanal/2-methylpropanal: 0.1/1/2.4/1.5; see Scheme 2). Under these conditions, *only the linear aldehyde underwent Michael addition*. While the enantioselectivity of the reaction with butanal alone was preserved (99%, see Table 2, entry 3), the reaction time required for complete conversion (92% isolated yield) was substantially extended (24 *vs.* 5 h), and this suggested that unproductive enamines involving 2-methylpropanal can be formed during the reaction. The suggestion that substrate selectivity in reactions mediated by **5** finds its origin in the different reactivity of equilibrating enamine intermediates is reinforced by the results of an experiment where an equimolar mixture of pentanal and cyclohexanone is treated with β-nitrostyrene (see Supporting Information for details). As anticipated, cyclohexanone did not participate in the addition process, but its presence in the reaction media extended the required time for complete conversion from 27 h to 55 h. When the cyclohexanone:pentanal ratio was changed to 13:1, the reaction time increased to 7 days.

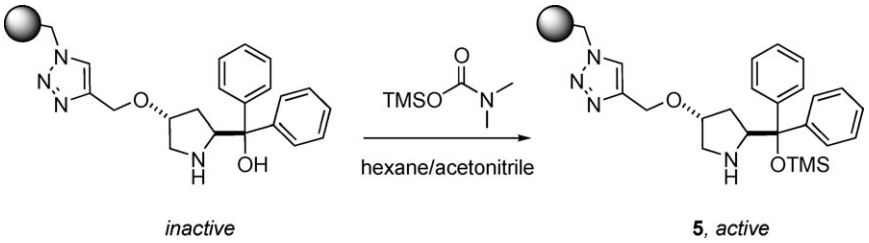
We have summarized in Scheme 3 our interpretation on the origin of the selectivity in the reactions mediated by resin **5**. First, the observed *syn* selectivity and the sign of enantioselection are indicative of the intermediacy of conformationally biased enamines, with the bulky R^1 substituent on the pyrrolidine blocking one of the enamine faces. With respect to substrate selectivity, the retardant effect of bulky aldehydes (or ketones) is strongly indicative of the participation of these reagents in the reversible forma-



Scheme 2. Selective Michael addition of butanal to β-nitrostyrene in the presence of 2-methylpropanal catalyzed by **5**.



Scheme 3. Origin of the substrate-selectivity in the Michael addition of aldehydes to β-nitrostyrene catalyzed by **5**.



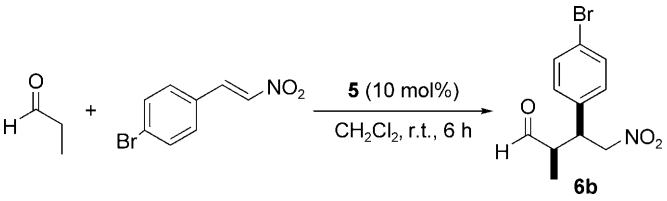
Scheme 4. Reconditioning conditions for supported organocatalyst **5.**

tion of unreactive enamine intermediates. The reason why even very similar enamines based on resin **5** could exhibit so strikingly different reactivities in front of β-nitrostyrene must result from the topology of the reaction cavity defined by the combination of polymer backbone, triazole linker, and catalytic unit. Thus, the enzyme-like selectivity exhibited by **5** would obey to restrictions in the achievement of the required transition state geometry for C–C bond formation whenever a *bulky* aldehyde is involved in the formation of the putative enamine intermediate.

As already mentioned, one of the main advantages associated to heterogenized catalysts is the possibility of its easy recovery and reuse. While recovery can be easily achieved by simple filtration when insoluble polymers are employed, the possibility of catalyst reuse is normally limited by deactivation processes. In the case of α,α-diarylprolinol silyl ethers, deactivation is triggered by hydrolysis of the labile silyl ether.[9r] More precisely, we have observed that a resin analogous to **5**, but bearing free hydroxy substituents instead of trimethylsilyl ethers is completely inactive in the considered Michael reactions. We accordingly devoted some effort to the development of a simple procedure for *error correction* on resin **5**. After testing a variety of silylating agents, we found that a brief treatment of an inactive diphenylprolinol-type resin with trimethylsilyl *N,N*-dimethylcarbamate[12] in hexane/acetonitrile leads to the selective protection of the hydroxy groups with full recovery of catalytic activity (Scheme 4). From a practical point of view, the re-conditioning process leaves dimethylamine as the only by-product, so that the resin can be immediately reused after washing out any excess of silylating agent. In practice, the intercalation of catalytic and re-conditioning cycles leads to complete preservation of the catalytic activity and stereoselectivity, thus allowing effective reuse over six consecutive runs (Table 3).

In summary, a highly efficient, polymer-supported organocatalyst for Michael additions of aldehydes to nitroolefins (**5**) has been prepared. Besides very high catalytic activity and enantioselectivity, comparable to those depicted by the best homogeneous catalysts in the same process, **5** displays unprecedented substrate selectivity that allows, in practice, inducing the completely selective reaction of a linear aldehyde in the presence of its α-branched regioisomer. Extension of the use of **5** to tandem processes is currently underway in our laboratories.

Table 3. Recycling experiments of catalyst **5** in the Michael addition of propanal to 4-bromo-β-nitrostyrene.[a]



Cycle	Conversion[b] [%] (Yield [%])[c]	*syn:anti*[b]	*ee* [%][d]
1	>99 (98)	93:7	99
2	>99 (96)	93:7	99
3	98 (96)	92:8	97
4	96 (94)	92:8	97
5	94 (92)	93:7	98
6	91 (89)	92:8	97

[a] All the experiments were performed using the general method with the resin recovered from the previous run and reconditioned before its use with trimethylsilyl *N,N*-dimethylcarbamate in 0.1 M hexane solution.
[b] Determined by ^{1}H NMR of the reaction crude.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.

Experimental Section

Typical Experimental Procedure

Propionaldehyde (22 μL, 0.3 mmol) was added to a mixture of *trans*-β-nitrostyrene (30 mg, 0.2 mmol) and **5** (46 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The suspension was stirred for 7 h and then directly filtered off. The solid resin was washed with CH_2Cl_2 and the organic filtrate was concentrated under reduced pressure. The Michael adduct **6b** was obtained without further purification as a clear oil; yield: 40.2 mg (98%); *syn/anti* 99:1 (by ^{1}H NMR spectroscopy), 99% *ee* by HPLC on a chiral phase (Chiralpak IC column, λ = 214 nm, ethanol/hexane 95:5, 0.8 mL min^{-1}): t_R = 30.7 min (minor, *syn*), 36.8 min (major, *syn*).

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