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Highly Enantioselective Michael Additions in Water Catalyzed by a PS-Supported Pyrrolidine

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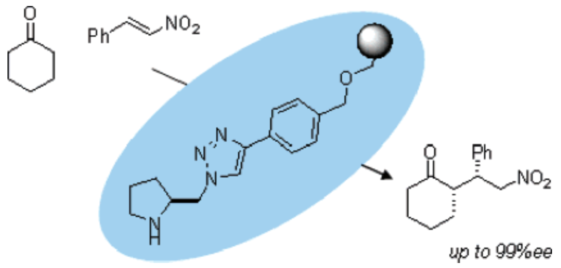
ABSTRACT



The development of a highly efficient, polymer-supported organocatalyst for the Michael addition of ketones to nitroolefins is described. A 1,2,3-triazole ring, constructed through a *click* 1,3-cycloaddition, plays the double role of grafting the chiral pyrrolidine monomer onto the polystyrene backbone and of providing a structural element, complementary to pyrrolidine, key to high catalytic activity and enantioselectivity. Optimal operation in water and full recyclability make the triazole linker attractive for the immobilization of organocatalysts.

C–C bond-forming reactions occupy the central position in the playground of organic synthesis because they are key to the construction of molecular frameworks of increasing complexity. In recent times, a growing interest has arisen in achieving this goal in an enantioselective manner through the use of purely organic, metal-free catalysts. As a result, different catalytic systems (quite often based on proline) have been developed providing very useful solutions for almost every reaction involving classical carbonyl chemistry.[1]

Organocatalytic processes are generally considered as environmentally benign because the use of metals is avoided. However, their catalytic efficiency is usually lower than in metal-catalyzed processes in terms of turnover number. To circumvent this difficulty, the development of immobilized, easily recoverable, and reusable catalysts appears as one of the most promising strategies.[2]

For optimal performance, ligands to be supported must be designed to allow anchoring through positions remote from the catalytic sites because, in this way, interference by the bulky polymer backbone is avoided. Working according to this principle, we have developed polystyrene-supported ligands for organometallic reactions which keep intact the catalytic activity and enantioselectivity of their homogeneous counterparts.[3] Quite recently, we have shown that *trans*-4-hydroxyproline can be properly immobilized onto polystyrene (PS) resins through copper-mediated 1,3-dipolar cycloaddition between azides and alkynes (*click chemistry*)[4] and that the resulting resins show improved catalytic properties over homogeneous counterparts in the direct aldol

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reaction in water[5] and in the α-aminoxylation of ketones and aldehydes,[6] while offering important operational advantages.[7]

In the context of our efforts toward the implementation of copper-mediated 1,3-dipolar cycloadditions as a general immobilization strategy for organocatalysis, we turned our attention to the catalytic enantioselective Michael addition of ketones to nitrostyrenes.[8] This reaction is a powerful synthetic tool that provides access to synthons of many interesting types[9] and has been studied from the perspective of organocatalysis following two different approaches: (i) the use of bifunctional catalysts that simultaneously activate the ketone and nitroolefin partners[10] and (ii) the use of simple 2-substituted cyclic amines (mostly pyrrolidines), where the side chain is believed to act as a steric controller that directs the reactivity toward the less hindered diastereotopic face of the intermediate enamine.[11] Within this category, systems bearing highly nitrogen-rich substituents such as tetrazoles and 1,2,3-triazoles have shown promising activity–selectivity profiles in the asymmetric Michael reactions.[11d,e,g,h]

However, in spite of the interest of the reaction, the first efforts toward the development of recyclable catalysts have only been published quite recently,[12] and nothing has been known until now on the use of insoluble, polymer-supported organocatalysts in this process.

In this paper, we report on the preparation of new immobilized organocatalysts (Figure 1) through Cu-catalyzed 1,3-dipolar cycloadditions between (*S*)-2-azidomethylpyrrolidine and alkynyl-functionalized Merrifield resins and on the development of optimal conditions for the use of these resins as highly efficient catalysts for the asymmetric Michael addition.

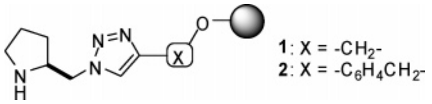
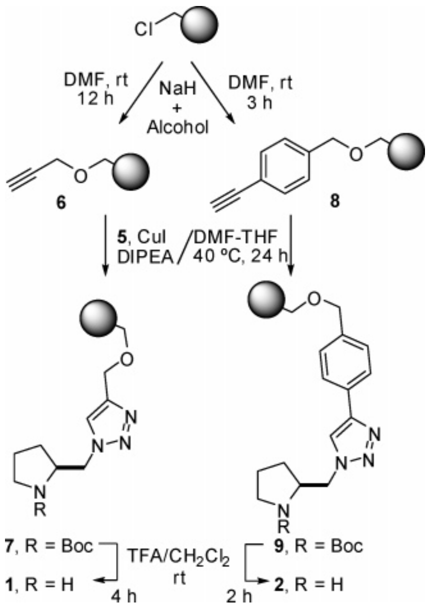


Figure 1. Structure of the supported catalysts.

The catalysts were prepared by a straightforward route as shown in Scheme 1 and the Supporting Information. Azidomethylpyrrolidine **5** was prepared from L-proline by reduction with lithium aluminum hydride and subsequent protection of the unstable aminoalcohol with di-*tert*-butyl dicarbonate. The alcohol **3** was then activated as a tosylate, and azide was introduced via S_N2 substitution.[13]

Scheme 1. Functionalization of the PS Resin



On the other hand, a Merrifield resin (1% DVB, $f_o = 0.74$ mmol/g) was treated with propargyl alcohol under basic

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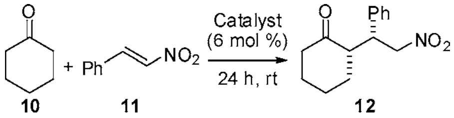
conditions (NaH in DMF) to provide the alkyne-functionalized resin **6**. Azide **5** was grafted onto this resin by a Cu-catalyzed Huisgen cycloaddition to afford, upon deprotection with TFA, the immobilized catalyst **1**. In a similar manner, catalyst **2** was prepared from the same Merrifield resin, through intermediate functionalization with 4-ethynylbenzyl alcohol (resin **8**).

Both resins were tested as catalysts for the Michael addition of cyclohexanone to β-nitrostyrene in a variety of solvents (Table 1). As a general trend, resin **1** was clearly more active but less enantioselective than **2**.

The best conversion with resin **1** was achieved with trifluoroacetic acid (TFA) as an additive under neat conditions (entry 1).[14] In turn, the highest ee was recorded when water (no TFA) was used as the solvent (79% ee, entry 6), although conversion was significantly lower under these conditions. Quite interestingly, conversion increased to 66% by simply increasing the amount of cyclohexanone employed in the reaction (compare entries 6 and 7). It is thus strongly suggested that the role of TFA in these reactions is limited to facilitating the formation and hydrolysis of the intermediate enamine and that 2-triazolylmethylpyrrolidines do not behave as bifunctional catalysts.[15]

Table 1. Optimization of the Reaction Conditions*

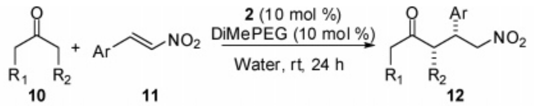


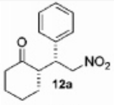
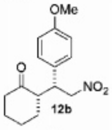
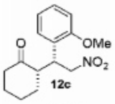
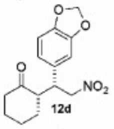
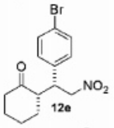
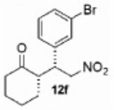
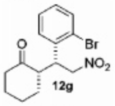
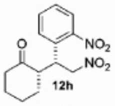
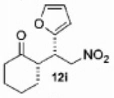
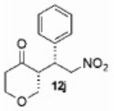
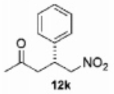
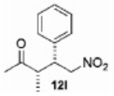
entry	catalyst	solvent	additive	% conv^{e}	d.r.^{e,f}	% ee^{g}
1^{a}	**1**	–	TFA^{c}	80	94:6	67
2^{a}	**1**	H_2O	TFA^{c}	55	96:4	60
3^{a}	**1**	DMF	TFA^{c}	31	97:3	75
4^{a}	**1**	THF	TFA^{c}	67	93:7	67
5^{a}	**1**	toluene	TFA^{c}	72	93:7	62
6^{a}	**1**	H_2O	–	27	93:7	79
7^{b}	**1**	H_2O	–	66	95:5	77
8^{b}	**2**	H_2O	–	35	94:6	85
9^{b}	**2**	brine	–	19	95:5	84
10^{b}	**2**	–	TFA^{c}	42	94:6	82
11^{b}	**2**	DMF	TFA^{c}	17	97:3	76
12^{b}	**2**	H_2O	TFA^{c}	84	95:5	87
13^{b}	**2**	H_2O	DiMePEG^{d}	87	95:5	89
14^{b}	**2**	H_2O	TFA^{c} + DiMePEG^{d}	77	90:10	87
15^{b}	**2**	toluene^{h}	–	15	95:5	85
16^{b}	**2**	toluene^{i}	TFA^{c}	19	91:9	83
17^{b}	**2**	toluene^{j}	DiMePEG^{d}	23	93:7	84

* All reactions performed with 0.5 mmol of nitrostyrene and 6 mol % of catalyst in 2 mL of solvent. ^{a} 5 equiv of cyclohexanone. ^{b} 20 equiv of cyclohexanone. ^{c} 2.5 mol %. ^{d} 10 mol %. ^{e} Determined by ^{1}H NMR of the crude material. ^{f} Diasteromeric ratio, anti/syn. ^{g} Determined by HPLC. ^{h} 79 ppm of water. ^{i} 579 ppm of water. ^{j} 560 ppm of water.

As already mentioned, resin **2** behaved as much more enantioselective in the considered process, and water (no TFA additive) turned out to be the solvent of choice for the reactions where it was used. In sharp contrast with what is

Table 2. Michael Addition of Ketones to Nitrostyrenes*



entry	product	% conv^{a} (yield^{b})	*syn:anti*^{a}	% ee^{c}
1	 **12a**	>99 (85)	95:5 100:0^{d}	90 99.9^{d}
2	 **12b**	>99 (84)	95:5	>99
3	 **12c**	>99 (83)	95:5	91
4	 **12d**	>99 (77)	93:7	94
5	 **12e**	>99 (84)	96:4	90
6	 **12f**	98 (78)	95:5	92
7	 **12g**	94 (76)	>99:1	95
8	 **12h**	>99 (81)	98:2	93
9	 **12i**	>99 (80)	90:10	79
10	 **12j**	98 (62)	94:6	85
11	 **12k**	91 (40^{e})	-	26
12	 **12l**	>99 (64^{f})	89:11	70

* All reactions performed with 0.25 mmol of the nitroolefin, 20 equiv of the ketone, 10 mol % of DiMePEG, and 10 mol % of catalyst **2** in 1 mL of water, at room temperature for 24 h. ^{a} Determined by ^{1}H NMR of the crude products. ^{b} Isolated yield. ^{c} Determined by HPLC. ^{d} After a single recrystallization. ^{e} 19% of the double addition product also observed. ^{f} 31% of attack by the primary carbon also observed.

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[14] For a review, see: Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 1758.

[15] The configuration of the chiral center in the cyclohexanone ring of **9a** indicates that attack to β-nitrostyrene by the intermediate enamine takes place by the face opposite to the triazolylmethyl substituent.

observed with **1**, the use of organic solvents was deleterious for conversion with this resin (compare entries 1/10, 3/11, and 5/16).

The catalytic performance of resin **2** in water could be improved by addition of two different additives. On one hand, and in contrast with **1**, addition of TFA (2.5 mol %) led to increased catalytic activity without deterioration in enantioselectivity (compare entries 2 and 6 for **1**, and 8 and 12 for **2**). On the other hand, the use of DiMePEG as an additive in the reactions led to an even greater improvement both in conversion and in ee (entry 13). Those were in fact the conditions of choice for the reaction because the simultaneous use of both additives, TFA and DiMePEG (entry 14), did not lead to any synergistic effect. Results for the test reaction in water (entries 12−14) are particularly remarkable when compared with the corresponding ones in toluene (entries 15−17) because resin **2** swells in toluene but not in water.

When the structures of resins **1** and **2** are compared, the *p*-phenylene group present in the linker in resin **2** possesses increased size and hydrophobicity with respect to the corresponding linker in **1**. Hence, the presence in **2** of a single, small hydrophilic moiety (the pyrrolidine−triazole system) embedded in a vast hydrophobic domain (the polymer backbone and the linker) appears to be key to the high enantioselectivity shown by this resin in the presence of water.

This is the same phenomenon already observed for a PS-supported hydroxyproline catalyst[5] and suggests the presence of combined hydrophobic−hydrophilic effects that might stabilize the transition states leading to products, thus speeding up the reaction. We suggest that the combination of both effects might be a general activation mode in organocatalysis and particularly important with polymer-supported organocatalysts.

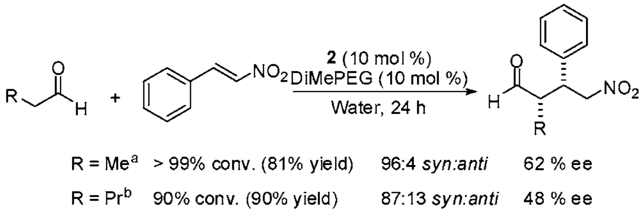
To establish the scope of the reaction with resin **2**, a series of substrates (nitroolefins and ketones) were tested under the optimized reaction conditions (Table 2).

β-Nitrostyrenes with different substitution patterns on the phenyl ring, including electron-releasing and electron-withdrawing groups, were tested as Michael acceptors. All the addition products where obtained in good yields and with excellent diastereo- and enantioselectivities, with no significant dependence on the electronic or steric properties of the substrate (entries 1 to 8). Recycling of the catalyst was tested with the reagent combination of entry 2. After three consecutive uses, no decrease was observed in the isolated yield of adduct **12b** or in the stereoselectivity parameters.

When major structural changes were introduced on the Michael acceptor (entry 9), a slight decrease was observed in diastereo- and enantioselectivity, whereas the reaction yield remained high. On the other hand, use of ketones other than cyclohexanones had a detrimental effect on the performance of the catalyst. Thus, the use of acetone as a Michael donor (entry 11) resulted in a dramatic drop in both yield and ee, a mixture of the single and double addition products being obtained. With 2-butanone (entry 12), in turn, a mixture of regioisomers was obtained. The regioisomer arising from the most substituted enamine could be isolated in 64% yield and with 70% ee.

The resin was also tested in the Michael addition of aldehydes to nitrostyrene (Scheme 2). High conversions and diastereoselectivities were obtained for linear aldehydes, although ee's were only moderate. A *β*-branched aldehyde such as isovarelaldehyde gave poor conversion and ee. Cyclohexanecarbaldehyde, in turn (α-branched), did not react at all.

Scheme 2. Michael Addition of Aldehydes to Nitrostyrene



[a] At 4 °C. [b] At rt.

In summary, a highly efficient, polymer-supported organocatalyst for the highly diastereo- and enantioselective Michael addition of nitroolefins to ketones has been developed. This catalytic system, constructed through the use of *click chemistry*, represents the first insoluble mediator for this reaction and approaches the performance of referable, soluble catalysts for the same process. The exact role of water and the hydrophobic polymer backbone in the reaction is being studied, and results will be reported in due course.

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Supporting Information Available: Experimental procedures and preparation and characterization of resins **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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