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Polymer-Supported Thiourea Catalysts for Enantioselective Michael Reaction

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Among the large number of reactions involving the formation of carbon-carbon bond, the addition of ketones to nitroolefins is a powerful tool for the synthesis of γ-nitro-carbonyl compounds, useful intermediates for pharmaceutical industry. Our recently reported primary amine-thioureas based on *tert*-butyl esters of natural amino acids exhibit excellent performance for the Michael reaction of ketones with nitroolefins providing the products quantitatively and almost stereospecifically (>99% *ee*).[1,2] Using this methodology, enantiopure baclofen and phenibut (analogs of GABA) have been synthesized.[2] Polymer-supported organocatalysts constitute a great challenge for the Michael reaction. In the current study, we report the immobilization of amine-thiourea catalysts containing (1*S*,2*S*)- or (1*R*,2*R*)-diphenylethylenediamine and *tert*-butyl aspartate, on various polymer supports, either directly or through spacer units. The solid-supported catalysts evaluated in the reaction between acetone and β-nitrostyrene and highlighted the importance of the choice of the polymer as well as the presence of the spacer or not. The direct attachment of the primary amine-thiourea-aspartate to a crosslinked polystyrene-divinyl benzene resin containing a uniform distribution of aminomethyl groups provides a supported catalyst that affords the product of the reaction between acetone and β-nitrostyrene quantitatively and in high enantioselectivity (91% *ee*).

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POLYMER-SUPPORTED THIOUREA CATALYSTS FOR ENANTIOSELECTIVE MICHAEL REACTION

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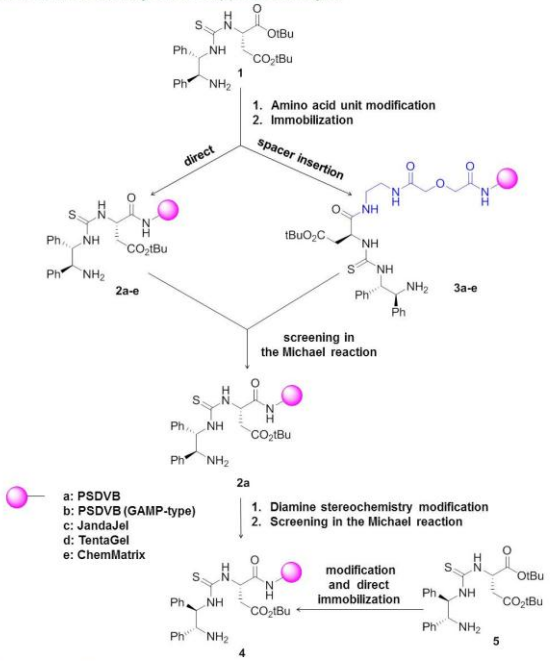
INTRODUCTION

Among the large number of reactions involving the formation of carbon-carbon bond, the addition of ketones to nitroolefins is a powerful tool for the synthesis of γ-nitro-carbonyl compounds, useful intermediates for pharmaceutical industry.[1] Our recently reported primary amine-thioureas based on *tert*-butyl esters of natural amino acids exhibit excellent performance for the Michael reaction of ketones with nitroolefins providing the products quantitatively and almost stereospecifically (>99% *ee*).[2,3] Using this methodology, enantiopure baclofen and phenibut (analogs of GABA) have been synthesized.[3] Polymer-supported organocatalysts constitute a great challenge for the Michael reaction. In the current study, we report the immobilization of amine-thiourea catalysts containing (1*S*,2*S*)- or (1*R*,2*R*)-diphenylethylenediamine and *tert*-butyl aspartate on various polymer supports, and the evaluation of the resulting supported organocatalysts in the reaction between acetone and *trans*-β-nitrostyrene.

RESULTS AND DISCUSSION

Our previously reported primary amine-thiourea **1**[2,3] was initially attached to various aminomethylated polymers either directly or by inserting a relatively long spacer unit based on ethylenediamine and 2,2'-oxydiacetic acid, preceded suitable modification of the amino acid segment (Scheme1). Uniformly-distributed cross-linked polystyrene-divinylbenzene (PSDVB), JandaJel, TentaGel and ChemMatrix resins were used for the immobilization of the catalyst. An aminomethylated PSDVB resin that exhibits a gradual increase of functional groups from the inside to the outside of the polymeric bead (Gradually Aminomethylated Polystyrene Resins, GAMPs) was also used, in order to examine the effect of the enhanced surface-exposed catalytic centers in the reactivity of the supported catalyst.



Scheme 1. *Optimization of polymer-supported primary amine-thiourea catalysts based on tert-butyl aspartate and 1,2-diphenylethylenediamine.*

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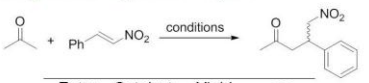
The activity of all the catalysts that were synthesized was evaluated in the Michael reaction between acetone and *trans*-β-nitrostyrene, under previously reported conditions, utilizing toluene or chloroform as the reaction medium and AcOH, H_2O as additives at ambient temperature (Table 1).[2,3] The uniformly-distributed PSDVB-supported catalyst **2a** provides the product in satisfactory yield and enantioselectivity (entry 2, Table 1), while the derivative **2b** leads to diminished yield, indicating that the highly shell-functionalized resin, slows down the reaction (entry 3, Table 1). The introduction of a longer and more flexible cross-linker than divinylbenzene between polystyrene chains in supported catalyst **2c**, further restricts product formation, while deteriorates the enantioselectivity as well (entry 4, Table 1). The insertion of PEG units between the PSDVB matrix and the thiourea catalyst (**2d**), restores somehow the results provided by the so far optimum supported derivative **2a** (entry 5, Table 1), while the ChemMatrix-supported thiourea resin **2e** maintains the yield obtained with the Tentagel resin **2d**, decreasing slightly however the enantioselectivity (entry 6, Table 1).

Table 1. Asymmetric Michael reaction between acetone and *trans*-β-nitrostyrene using various supported catalysts.



Entry	Catalyst	Yield (%)[a]	ee (%)[b]
1[c]	**1**	100	91(*R*)
2[d]	**2a**	76	76(*R*)
3[d]	**2b**	31	73(*R*)
4[d]	**2c**	22	38(*R*)
5[d]	**2d**	54	75(*R*)
6[d]	**2e**	56	61(*R*)
7[d]	**3a**	24	67(*R*)
8[d]	**3b**	22	64(*R*)
9[d]	**3c**	77	70(*R*)
10[d]	**3d**	10	37(*R*)
11[d]	**3e**	16	46(*R*)
12[d]	**4a**	100	91(*S*)
13[e]	**4a**	100	91(*S*)
14[f]	**4a**	100	77(*S*)
15[g]	**5**	96	99(*S*)

[a] Isolated yield after column chromatography, [b] The enantiomeric excess (*ee*) was determined by chiral HPLC, [c] Conditions: **1** (15 mol%), PhMe, AcOH (15 mol%), H_2O (2 equiv.), r.t., 48h,[2] [d] Conditions: catalyst (15 mol%), PhMe, AcOH (15 mol%), H_2O (2 equiv.), r.t., 72h, [e] Conditions: **4** (15 mol%), $CHCl_3$, AcOH (15 mol%), 72h [f] Conditions: **4** (15 mol%), $CHCl_3$, 72h, [g] Conditions: **5** (10 mol%), $CHCl_3$, AcOH (10 mol%), 48h.[3]

The insertion of the spacer leads in the case of the **3a** and **3b** derivative in low product yield with respect to the directly attached analogues **2a** and **2b**, without affecting the stereoselectivity (entry 7 and 8 vs 2 and 3, Table 1). Compared to Tentagel and ChemMatrix derivatives (**2d**, **2e**), resins **3d** and **3e** further reduce product yield, while degrade seriously the enantioselectivity of the reaction (entry 10 and 11, vs 4 and 5, Table 1). Surprisingly, JandaJel derivative **3c** exhibits a clear superiority both among the thiourea catalysts attached *via* the spacer unit and the direct immobilized analogue **2c** (entry 9 vs 4, 7, 8, 10 and 11, Table 1). The replacement of the (1*S*,2*S*)-diphenylethylenediamine unit of the supported catalyst **2a** with the (1*R*,2*R*)-enantiomer in the diastereomer **4**, leads to quantitative yield, while the opposite enantiomer of the product becomes predominant with high selectivity (entry 12, Table 1). Chloroform maintains the results obtained with toluene (entry 13, Table 1), while the absence of the acid additive decreases enantioselectivity (entry 14, Table 1).

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