Bottom-up Synthesis of Novel Supported Thioureas and Their Use in Enantioselective Solvent-free Aza-Henry and Michael Additions.

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Abstract

Two sets of supported chiral thioureas, which differ in the length of the tether connecting the chiral appendage to the polymer structure and the effective functionalization, have been prepared by co-polymerization of styrene, novel styryl thioureas derived from (L)-valine, and divinylbenzene. The efficiency of these polymeric thioureas has been tested in two different enantioselective transformations such as aza-Henry and nitro-Michael reactions in neat reaction conditions. The obtained results show that it is possible to recycle, and they are able to promote the reactions with good enantioselectivity in low catalyst loading.

Introduction

One of the most important problems that suffer the organocatalytic processes refers to the recovering of the catalysts from the final reaction mixtures. In general, they can be recovered by flash chromatography, but the isolation remains difficult. The anchorage of a chiral catalyst on polymeric materials has recently flourished as a solution of recovering and recycling the catalysts,[1] and an additional advantage of the polymer-supported organocatalysts is related with their use in continuous-flow enantioselective procedures.[2]

The support of proline derivatives on different solid materials has been extensively developed, but other privileged catalysts, such as bifunctional thioureas, have attracted less attention. The most popular supports for these kind of catalysts are polystyrene derivatives,[3] although mesoporous silica[4] and magnetic nanoparticles[5] have been used as solid supports for bifunctional thioureas. The preparation of all these catalysts is based on the grafting of the thiourea onto a functionalized preformed support (generally commercially available).

More interesting, although synthetically demanding, is the synthesis bottom-up of the supported catalyst by co-polymerization of two monomers, one of them functionalized with the thiourea, with or without a cross-linker. This method allows for the control of the degree of functionalization of the polymer and its physical properties, although only a few antecedents have been previously described. In that way, achiral polymeric amino thioureas have been prepared by co-polymerization of styrene-derived tertiary amines and thioureas,[6] whereas attempts to prepare co-polymers derived from cinchona thioureas failed because extensive decomposition of the monomer occurred under the radical polymerization conditions.[7] On the contrary, cinchona-derived thioureas co-polymers have been obtained by immobilization using thiol-ene chemistry.[8]

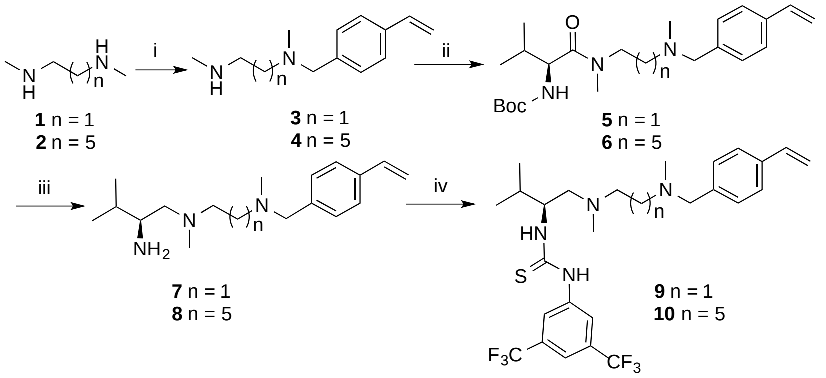
Our interest in the synthesis of novel supported[9] and unsupported[10] bifunctional organocatalysts and their use in different enantioselective transformations, lead us to consider the bottom-up synthesis of chiral bifunctional thioureas by co-polymerization of styrene, 4-vinyl benzylamine derivatives, and divinyl benzene as a cross-linker (Figure 1). This approach has been previously used for the immobilization of different chiral ligands,[11] and organocatalysts such as 4-hydroxyproline,[12] and prolinamides.[13] Because our previous results indicated that the best results were obtained with thioureas prepared from 1,2-diamines derived from (*L*)-valine,[14] we decided the incorporation of that chiral appendage to the monomer, and to study the best conditions for polymerization and the effect of the length of the tether connecting the thiourea group and the polymer chain on the activity of the catalysts.

Results and discussion

Styryl thioureas **9** and **10** were easily prepared[15] from commercially available N,N´-dimethyl ethylene diamine **1** and N,N´-dimethyl -1,6-hexane diamine **2** as summarized in Scheme 1. Amines **1** and **2** were alkylated, as previously described for benzylation of ethylene diamine,[16] by reaction with 4-vinylbenzyl chloride in DCM at rt leading to monoalkylated amines **3** and **4**, respectively, with good yields.

These amines were coupled with Boc-L-valine activated with dicyclohexyl carbodiimide (DCC) to amides **5** and **6**, which after quimioselective reduction of the amide group with lithium aluminum hydride (LAH) in THF at 0 ^{o}C, and deprotection by treatment with trifluoro acetic acid (TFA) in DCM yielded triamines **7** and **8**.

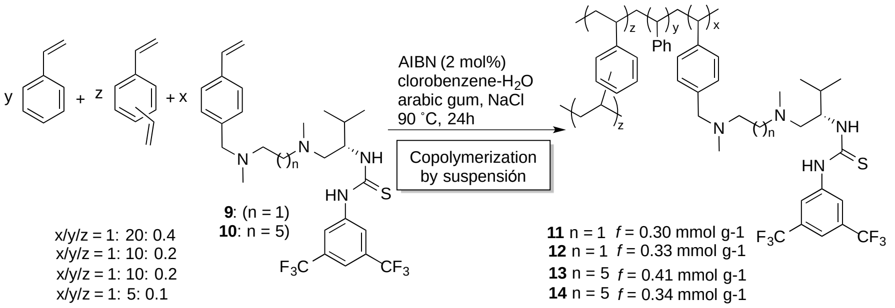
Thioureas **9** and **10** were obtained, in excellent yields from **7** and **8** by reaction with 3,5-(bis)trifluoromethyl isotiocyanate in DCM at rt.



Scheme 1. *Reagents and conditions*: (i) 4-CH_2=$CHC_6H_4CH_2Cl$, CH_2Cl_2, rt, 4h. (ii) Boc-L-valine, DCC, CH_2Cl_2, 0 ºC to rt. (iii) 1. LAH, THF, 0 ºC, 1h. 2. TFA, CH_2Cl_2, rt. (iv) 3,5-$(CF_3)_2C_6H_3NCS$, CH_2Cl_2,rt.

With the styryl thioureas in hand, we studied the co-polymerization with styrene and divinyl benzene as cross-linker in aqueous phase, with AIBN as initiator (Scheme 2). Initially, a mixture of Thiourea **9** (x), styrene (y) and divinyl benzene (z) in a ratio 1: 20: 0.4 (x: y: z), and arabic gum was heated in a mixture of chlorobenzene-water at 90 ^{o}C for 24 h in the presence of 2 mol% of AIBN. The formed polymer **11** was separated by filtration, thoroughly washed successively with methanol, water and methanol, and dried under vacuum. This material was characterized by the IR absorption at 1131, 1386, and 1276 cm^{-1}, corresponding to the thiourea group, and the Ar-N and C-F bonds, respectively. The analytical data of the nitrogen and sulfur atoms allowed the calculation of the degree of incorporation of the thiourea to the polymer to be 17-18% and the effective functionalization (*f*) 0.30 mmol g^{-1}. Looking for increasing the effective functionalization, the polymerization procedure was repeated by using twice thiourea content in the initial mixture (x: y: z = 1: 10: 0.2). The analytical data shown that the obtained material (**12**) increased its effective functionalization to *f* = 0.33 mmol g^{-1}.

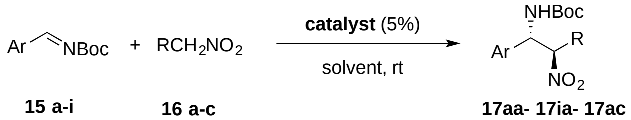
By using the described methodology, two experiments of polymerization were done for thiourea **10**. In the first one, with a ratio of monomers x: y: z = 1: 10: 0.2, the polymer **13** incorporated 24-26% of thiourea (*f* = 0.41), whereas an increase in the ratio of thiourea to x: y: z = 1: 5: 0.1 gave polymer **14** with lower effective functionalization (*f* = 0.34 mmol g^{-1}), pointing to that, under the studied conditions, the maximum degree of incorporation of the thiourea to the final catalysts is about 25%.



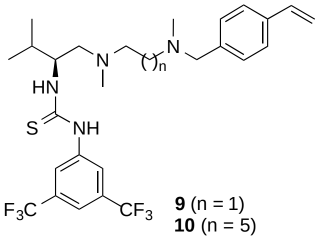
Scheme 2. Bottom-up synthesis of supported catalyst by co-polymerization.

The ability of the novel prepared catalysts to promote stereoselective transformations was first tested for the aza-Henry reaction.[17] The reaction of N-Boc benzaldimine **15a** with nitromethane **16a** was taken as a model to find the best catalyst and reaction conditions (Table 1, entries 1-8). The reactions were done by stirring a mixture of imine and nitroalkane (6 equiv.) in the presence of 5 mol% of the corresponding catalyst at rt.

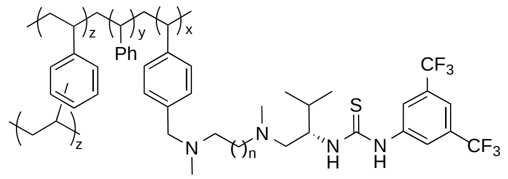
Table 1. Enantioselective Aza-Henry reactions organocatalyzed by **9-14**.



	a	b	c	d	e	f	g	h	i
Ar (15)	Ph	4-NO$_2$Ph	4-CF$_3$Ph	4-ClPh	4-MeOPh	4-MePh	1-Naphtyl	2-Naphtyl	2-Furyl
R (16)	H	Me	Et						



9 (n = 1)
10 (n = 5)



11, 12 (n = 1)
13, 14 (n = 5)

Entry[a]	Solvent	Catalyst	Reagents	t (h)	Product	Yield (%)[b]	Dr[c] *anti/syn*	Er[c]
1	DCM	**13**	**15a/16a**	7	**17aa**	68	-	92/8
2	Toluene	**13**	**15a/16a**	8	**17aa**	70	-	92/8
3	Neat	**13**	**15a/16a**	2	**17aa**	94	-	94/6
4	Neat	**14**	**15a/16a**	2	**17aa**	95	-	94/6
5	Neat	**11**	**15a/16a**	8	**17aa**	67	-	92/8
6	Neat	**12**	**15a/16a**	2	**17aa**	98	-	91/9
7	Neat	**9**	**15a/16a**	5	**17aa**	80	-	93/7
8	Neat	**10**	**15a/16a**	3	**17aa**	95	-	96/4
9	Neat	**13**	**15b/16a**	2	**17ba**	52	-	94/6
10	Neat	**13**	**15c/16a**	2	**17ca**	78	-	93/7
11	Neat	**13**	**15d/16a**	2	**17da**	66	-	93/7
12	Neat	**13**	**15e/16a**	8	**17ea**	51	-	92/8
13	Neat	**13**	**15f/16a**	4	**17fa**	84	-	93/7
14	Neat	**13**	**15g/16a**	3	**17ga**	60	-	91/9
15	Neat	**13**	**15h/16a**	2	**17ha**	57	-	94/6
16	Neat	**13**	**15i/16a**	1	**17ia**	53	-	86/14
17	Neat	**13**	**15a/16b**	2	**17ab**	84	76:24	94/6[d]
18	Neat	**13**	**15a/16c**	2	**17ac**	75	91:9	94/6[d]
19	2nd cycle	**13**	**15a/16a**	2	**17aa**	90	-	94/6
20	3th cycle	**13**	**15a/16a**	4	**17aa**	95	-	94/6

[a]Reaction was conducted at 0.3 mmol scale in 0.1 mL of nitroalkane (6 equiv). [b] Isolated yield. [c] Diastereomeric and enantiomeric ratio determined by chiral HPLC analysis and the absolute configuration was determined by comparison of the HPLC retention time with that of the literature data. [d]Er ratio refers to the major *anti* diastereoisomer.

When the reaction of **15a** and **16a** was carried out in two different apolar solvents such as DCM and toluene, the addition product **17aa** was obtained in good yield (68-70%) and very good enantiomeric ratio (er: 92/8) (entries 1, 2 in Table 1), but the reaction was quicker in neat conditions, decreasing the reaction time to 2 h, and increasing both the yield (94%) and enantioselection (er: 94/6) (entry 3 in Table 1). In these conditions, the same results were obtained by using supported thiourea **14** as organocatalysts (entry 4). The influence of the effective functionalization of the polymeric thioureas was tested in the reactions catalyzed by **11** (f = 0.30 mmol g^{-1}) and **12** (f = 0.33 mmol g^{-1}). The results shown that the higher functionalization of **12** makes the reaction occurred easier and in higher yield, although with near the same enantioselection (entries 5,6 in Table 1). It is also interesting to note that, contrary to previously observed for thioureas supported on sulfonylpolystyrene,[9a] the length of the tether connecting the catalyst and the polymer only play a marginal role on both the yield and the enantioselection of the process (compare entries 6 *versus* 3 or 4).

For comparative purposes, reactions catalyzed by monomeric thioureas **9** and **10** were also studied, observing that only small difference exists in the reaction catalyzed by supported (**13**) and unsupported (**10**) 1,6-hexane diamine-derived thioureas (compare entries 3 *versus* 8), whereas better yield was obtained with the supported (**12**) than unsupported (**9**) ethylene diamine-derived thioureas (entries 6 and 7 in Table 1).

The best reaction conditions found for the reaction catalyzed by **13** were used to extend the aza-Henry reaction to N-Boc aldimines derived from different aromatic aldehydes and nitroalkanes (Table 1, entries 9-18).

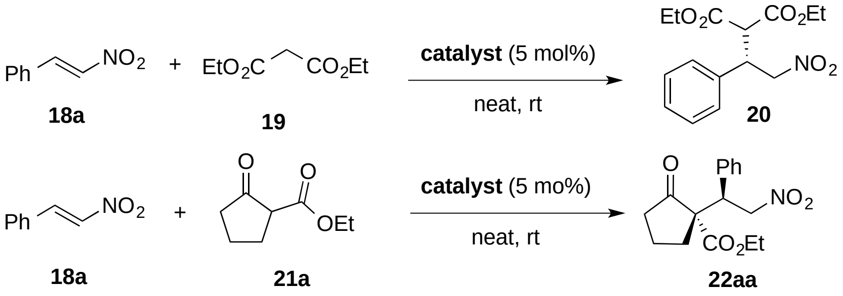
The reaction of nitromethane **16a** with imines derived from activated and nonactivated benzaldehydes (**1a-f**) proceeded with excellent enantioselectivities, which are independent on the electronic character of the substituent at *para*-position (entries 9-13 in Table 1). On the contrary, the yields of the isolated α-nitroamines were very good for *p*-trifluoromethyl- (**15c**), *p*-methyl- (**15f**), and *p*-chloro- (**15d**) derivatives (entries 10, 11, and 13), but only moderate for *p*-nitrobenzaldimine **15b** (entry 9), probably as a consequence of a competing hydrolytic reaction. As expected, the less reactive aldimine derived from *p*-methoxybenzaldehyde (**15e**) reacted slower leading to the addition product **17ea** in moderate yield (entry 12 in Table 1). A modest yield and enantioselectivity were achieved in the reaction of nitromethane and 2-furylaldehyde (entry 16).

In order to obtain α-nitroamines with two contiguous stereocenters, we tested the reaction of N-Boc benzaldimine **15a** with nitroethane **16b** and nitropropane **16c**. In both cases the reactions were completed after 2 h of stirring at rt, leading to the *anti*-addition products **17ab** and **17ac** in good yields and enantioselection, but only with moderate diastereoselectivity for the reaction with nitroethane (entries 17 and 18 in Table 1).

Finally, we focused our attention on the recovery and reuse of the supported catalyst **13**. To this end, the crude reaction mixture of **15a** and **16a** was filtered in order to separate the insoluble catalyst, the solid was thoroughly washed with methanol, dried under vacuum to constant weight, and reused in the next cycle. The yield of the recovered catalyst was in the range 80-90%. After three consecutive cycles, both the yield and enantioselection were maintained nearly constant, but the reaction time increased to 4h in the third cycle (entries 3, 19, 20).

In a different approach, we have extended the use of the polymeric thioureas to the enantioselective Michael addition of different, easily enolizable, substrates to nitroalkenes. The interest of that reaction is based on the possibility to obtain highly functionalized enantioenriched products with one or two contiguous stereocenters, specially if one of them is quaternary.[18] Bifunctional thioureas derived from *trans*-1,2-diaminocyclohexane,[19] *Cinchona* alkaloids,[20] and diamines derived from aminoacids[21] have been used to achieve that goal.

Table 2. Screening of the catalysts for the stereoselective nitro Michael addition



Entry[a]	Catalyst	Product	t (h)	Yield (%)[b]	dr[c]	er[d]
1	**9**	**20**	14	90	-	70:30
2	**10**	**20**	5	93	-	90:10
3	**11**	**20**	96	78	-	82:18
4	**13**	**20**	6	98	-	90:10
5	**9**	**22aa**	3	85	86:14	86:14
6	**10**	**22aa**	0.5	90	87:13	90:10
7	**11**	**22aa**	0.5	80	89:11	88:12
8	**12**	**22aa**	0.5	95	87:13	88:12
9	**13** (1st cycle)	**22aa**	0.5	89	89:11	93:7
10	**13** (2nd cycle)	**22aa**	0.5	83	88:12	93:7
11	**13** (3th cycle)	**22aa**	0.5	84	87:13	93:7
12	**13**[e]	**22aa**	0.5	90	89:11	93:7
13	**14**	**22aa**	0.5	94	89:11	93:7

[a]Unless otherwise specified, the reaction was carried out with 2 equiv of nucleophile in the presence of 5 mol% of catalyst at room temperature. [b] Isolated yield. [c] Determined by ^{1}H-NMR analysis. [d] Determined by chiral HPLC. [e] Only 2 mol% of catalyst was used

Searching for a green process[22] we first investigated the nitro Michael reaction at rt, with 5 mol% catalyst in neat conditions by using a twofold excess of the nucleophile. Two different sets of reactions were proposed to search for the best catalyst. In the first one, we studied the addition of diethylmalonate (**19**) to *trans*-nitrostyrene (**1**8a) in the presence of monomeric (**9**, **10**) and polymeric (**11**, **13**) thioureas searching for the most effective organocatalysts. In the second, the addition of 2-ethoxycarbonylcyclopentanone **21a** to the same nitroalkene, in the presence of the catalysts **9-14**, was used to establish the enantio- and diastereoselectivity formation of two contiguous tertiary-quaternary stereocenters.

The reaction of *trans*-β-nitrostyrene with ethyl malonate lead diethyl (*S*)-2-(2-nitro-1-phenylethyl)malonate[23] **20** as major enantiomer in good to excellent yield, but the reactivity and the enantioselection is highly dependent on the catalyst used. Unsupported and supported catalysts **10** and **13**, respectively, derived from 1,6-hexanediamine behave in a similar way with respect to their activity, but they are able to promote a more enantioselective transformation than those derived from ethylene diamine (**9** and **11**) (compare entries 2, 4 *versus* 1, 3 in Table 2). Additionally, no differences was observed when using monomeric thiourea **10** and its polymeric counterpart **13** (compare entries 1, 3), whereas the reaction promoted by polymeric ethylene-derived thiourea **11** was much more slow, obtaining the addition product in low yield, although in better enantioselection (compare entries 2,4 in Table 2).

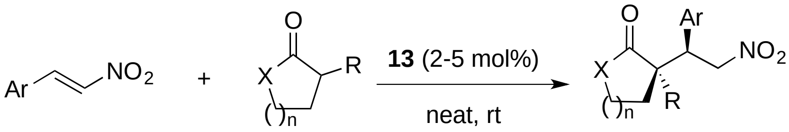
A different behavior with respect to the catalyst was observed in the reaction of *trans*-β-nitrostyrene with 2-ethoxycarbonylcyclopentanone (**21a**) leading to ethyl (2*S*, 3*R*)-ethyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate[24] (**22aa**) (entries 5-13 in Table 2). In those cases, the reactions were finished after 0.5 h of stirring leading to the addition product with excellent yield, good diastereoselectivity and good to very good enantioselectivity. It is interesting to note that the diastereoselectivity was nearly independent on the nature of the catalyst, but once again, the best enantioselection was obtained for reactions catalyzed by polymeric 1,6-hexanediamine-derived thioureas **13** and **14**. The loading of catalyst **13** can be diminished to only 2 mol% without affecting the yield or stereoselectivity (entry 12 in Table 2), and catalyst **13** was also recycled for three times with only a slight variation of the yield, but maintaining the level of stereocontrol (entries 9, 11 in Table 2).

The excellent catalytic activity showed by the polymeric thioureas led us to extend the reaction to different nitroolefins (**18a-d**) and nucleophiles (**21a-f**), which differ both in the size of the cyclic structure and the nature of the activating groups. The reactions were carried out at rt, with only 2 mol% catalyst **13** (5 mol% in entries 5 and 6) in neat conditions by using a twofold excess of the nucleophile, and the results are summarized in Table 3.

The electronic nature of the aryl ring in the nitrostyrene derivative was studied by reacting **18a-d** with cyclopentanone derivative **21a** (entries 1-4 in Table 3). Addition products **22aa**-**22da** were formed with uniform good yield and diatereoselectivity, and very good enantioselectivity. The only difference refers to the longer reaction time observed for the reaction of styrene derivative bearing a methoxy group with high donating character (entry 4).

The reaction was extended to different α-substituted cicloalkanones and related compounds to test the generality of the process. To this end, compounds **21a-f** were reacted with *trans*-β-nitrostyrene (**18a**) in the above conditions (etries 5-9 in Table 3). 2-Ethoxycarbonylcyclohexanone **21b** behaved in a similar way than its homolog derived from cyclopentanone **21a** did, leading to **22ab** in good yield and diastereoselectivity and excellent enantioselectivity (compare entries 1 and 5 in Table 3). On the contrary, the reaction of α-substituted cycloheptanone **21c** was much less diastereoselective, although maintaining the enantioselection level (entry 6). 2-Acetylcyclopentanone **21d** quickly reacted with the nitroolefin, yielding the addition product **22ad** with moderate stereoselection, and the reaction of α-acetyl-γ-lactone **21e** occurred with excellent yield and enantioselectivity but moderate diastereoselectivity (entry 8 in Table 3). Interestingly, the reaction of the more acidic α-nitrocyclohexanone with **18a** was slow (12h) leading to **22af** as a single diastereoisomer but in moderate yield and enantioselection.

Table 3. Stereoselective nitro Michael addition of **21a-f** to nitroolefins **18a-d** catalyzed by supported thiourea **13**.



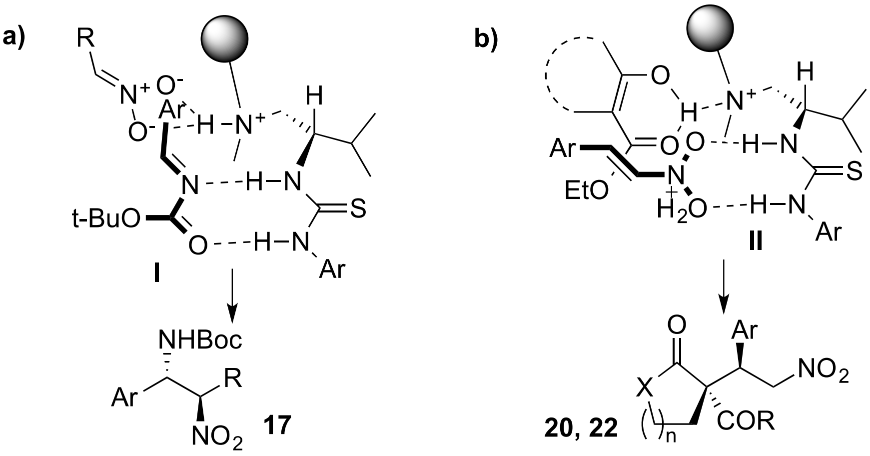
18a-d **21a-f** **22aa-af, 22ba-da**

Entry[a]	n	X	R	Ar	t (h)	Product	Yield (%)[b]	dr[c]	er[d]
1	1	CH_2	CO_2Et	Ph	0.5	**22aa**	89	89:11	93:7
2	1	CH_2	CO_2Et	*p*-ClPh	0.5	**22ba**	84	89:11	94:6
3	1	CH_2	CO_2Et	*p*-FPh	3	**22ca**	80	91:9	93:7
4	1	CH_2	CO_2Et	*p*-MeOPh	10	**22da**	79	88:12	93:7
5[e]	2	CH_2	CO_2Et	Ph	5	**22ab**	81	90:10	96:4
6[e]	3	CH_2	CO_2Me	Ph	7	**22ac**	91	78:22	95:5
7	1	CH_2	COMe	Ph	1	**22ad**	90	80:20	87:13
8	1	O	COMe	Ph	5	**22ae**	95	75:25	95:5
9[f]	2	CH_2	NO_2	Ph	12	**22af**	70	>98:<2[g]	85:15

[a] The reaction was carried out with 2 equiv of dicarbonyl compound in the presence of 2 mol% of catalyst at room temperature. [b] Isolated yield. [c] Determined by ^{1}H-NMR analysis. [d] Determined by chiral HPLC. [e] 5 mol% of catalyst was used. [f] Reaction performed in MeCN. [g] The given value means that only one diastereoisomer was detected in the ^{1}HNMR of the mixture

The sense of the stereoselection observed in both the aza-Henry and the nitro-Michael reactions can be explained by accepting the formation of the ternary complexes depicted in Scheme 3 (figures a an b respectively). It is well known that thioureas behave as bifunctional catalysts able to activate both the electrophile and nucleophile. The high degree of enantioselection observed in the aza-Henry reaction could be explained by accepting the formation of a highly coordinated ternary complex **I** (Scheme 3a) by thiourea activation of the nitro group followed by deprotonation by the tertiary amine to the corresponding nitronate, and subsequent coordination of the imine carbamate.[25] The major diastereomers **17**should be formed by addition of the *si*-face of the nitronate to the *re*-face of the imine.

The mechanism and stereochemical outcome for the nitro-Michael addition is also well known. [26] In that case, the tertiary amine will be the responsible of deprotonation of the acidic hydrogen and the thiourea will activate the nitroalkene by hydrogen bonding leading to a ternary complex summarized in Scheme 3b. The addition of the *re*-face of the enolate to the *si*-face of the nitroolefin yielded compounds **20** and**22** as major diastereoisomers.



Scheme 3. Plausible ternary complexes that explain the stereoselection for the aza-Henry (a), and nitro-Michael (b) reactions.

Conclusions

In summary, we have prepared two different styryl thioureas derived from (L)-valine and commercially available diamines. The co-polymerization of these thioureas with styrene and divinylbenzene, in different conditions, allowed for the synthesis of four different polymeric materials, which was used as chiral organocatalysts in enantioselective aza-Henry and nitro-Michael additions. The best results were obtained with catalyst **13**, derived from 1,6-hexanediamine, which is able to promote both reactions in high stereoselectivity and excellent enantioselectivity in neat conditions. The catalyst can be recycled without modification of the catalytic activity.

Acknowledgements.

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References and Notes

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