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Novel Bifunctional Chiral Urea and Thiourea Derivatives as Organocatalysts: Enantioselective Nitro-Michael Reaction of Malonates and Diketones

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The ability of chiral hydrogen-bond donors to catalyze useful enantioselective transformations constitutes an increasing area of interest, and diverse types of structures have been described to this end.[1] An important class of species are urea and thiourea compounds[2] which have frequently been used in several transformations, such as Henry or aza-Henry,[3] Mannich,[4] Strecker,[5] and Friedel–Crafts[6] reactions or Michael[7] and nitro-Michael[8] additions.

The modular design of these types of catalysts requires the possibility to introduce different urea and thiourea moieties and the modification of the structure with the chiral information. Most of the described catalysts until now are aryl or diaryl ureas or thioureas with electron withdrawing groups, although some relatively electron rich derivatives have proved to catalyze a variety of enantioselective transformations.[9]

The chiral information in the catalyst has been placed at both the nitrogen terminus in the urea or thiourea or in the central chiral core. In this respect, a few structures are used in the preparation of the catalysts, namely chiral diamines,[10] both enantiomers of *trans* cyclohexane-1,2-diamine,[10,11] binaphthylamines,[12] diamines derived from cinchona alkaloids,[13] amino alcohols,[14] and very recently, sugars.[15]

In our opinion, the development of novel chiral scaffolds to be incorporated into urea and thiourea derivatives, capable to act as bifunctional organocatalyts, is necessary. Because, in general, 1,2-diamines are the structures that lead to the best results, we planned to prepare these compounds taking into account three facts: i) The starting material would have be commercially available and cheap; ii) both enantiomers of the amine must be accessible; and iii) the synthesis should be able to provide the ability to fine-tune the substituents at the nitrogen atoms.

We envisioned that natural α-amino acids would be the starting material of choice and we describe here the synthesis of chiral diamines derived from them and their use as organocatalysts in nitro-Michael additions of stabilized carbanions. The generality of the synthesis was demonstrated in the preparation of catalysts **4a–i** in three steps from commercially available N-Boc protected α-amino acids. The nature of the substituent at the stereocenter is dictated by the election of the starting amino acid, the substituents at the nitrogen atom can be varied in the formation of the α-amino amide, and the structure of the urea–thiourea component is selected depending on the isocyanate–isothiocyanate used in the last step.

In this way, N-Boc protected L-valine, L-isoleucine, L-phenylalanine, and L-*tert*-leucine were converted into **1a–h** by reaction with the corresponding amines,[16] which were transformed into **2a–h** by deprotection with TFA in methylene chloride. Lithium aluminum hydride reduction to **3a–g** and condensation with the corresponding isocyanate or isothiocyanate yielded the final urea or thiourea derivatives **4a–h** in good yields.[17] The same protocol allowed the preparation of *ent*-**4a** starting from D-valine, and **4i**, regioisomer of **4a**, was obtained from L-valinamide hydrochloride by dimethylation, lithium aluminum hydride reduction and reaction with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (Scheme 1).

The catalytic activity of **4a–i** was first evaluated in the reaction of *trans* β-nitrostyrene **5a** with diethyl malonate **6a** in the presence of 10 mol% of catalyst at room temperature, and the results are collected in Table 1. A set of five different solvents was tested as reaction media (entries 1–5 in Table 1) showing that the reactions occurred in good yields and moderate to good *ee*. Only in the case of methanol (entry 1) the enantioselectivity decreased to 40% *ee*, probably because the competitive establishment of hydrogen activation of the solvent with the catalyst,[8a] and the enantioselectivity increased when less polar solvents were used (compare entries 1–5), or if the reaction was carried out without

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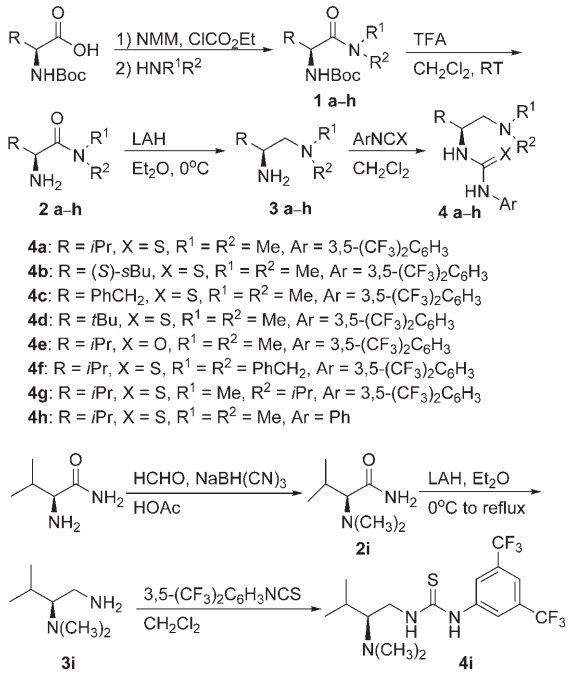
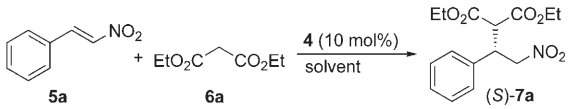


Scheme 1. Synthesis of urea and thioureas **4a–i**.

Table 1. Nitro-Michael reaction of trans-nitrostyrene with **6a** catalyzed by **4a–i**.



Entry	Catalyst	Solvent	t [h]	Yield [%][b]	*ee* [%][c] (Config.)[d]
1	**4a**	CH_3OH	28	73	40 (*S*)
2	**4a**	CH_3CN	30	82	79 (*S*)
3	**4a**	THF	31	64	85 (*S*)
4	**4a**	CH_2Cl_2	32	77	86 (*S*)
5	**4a**	toluene	25	83	88 (*S*)
6	**4a**	neat	23	81	84 (*S*)
7[e]	**4a**	toluene	48	85	88 (*S*)
8[f]	**4a**	toluene	48	55	89 (*S*)
9	**4b**	toluene	29	87	87 (*S*)
10	**4c**	toluene	30	93	85 (*S*)
11	**4d**	toluene	22	83	87 (*S*)
12	**4e**	toluene	22	93	87 (*S*)
13	**4f**	toluene	48	–	–
14	**4i**	toluene	46	44	14 (*S*)
15[g]	**4a**	toluene	44	90	95 (*S*)
16[g]	**4b**	toluene	46	88	93 (*S*)
17[g]	**4c**	toluene	46	67	89 (*S*)
18[g]	**4d**	toluene	43	94	92 (*S*)
19[g]	**4e**	toluene	19	91	92 (*S*)
20[g]	**4g**	toluene	48	97	94 (*S*)
21[g]	**4h**	toluene	96	65	85 (*S*)
22[g]	*ent*-**4a**	toluene	48	90	93 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1 equiv of **5a** and 2 equiv of **6a** in the presence of 10 mol% of catalyst at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **7a** using a chiral column. [d] Absolute configuration was determined by comparing the optical rotation of **7a** with that of the literature data. [e] 5 mol% of the catalyst was used. [f] 2 mol% of the catalyst was used. [g] The reaction was carried out at −18°C.

solvent (entry 6). Further optimization of this process shown that the reaction could be performed with 5 mol% (entry 7) or 2 mol% (entry 8) of catalyst loading without decreasing the enantioselectivity, although in the last case the yield decreased for the same reaction time.

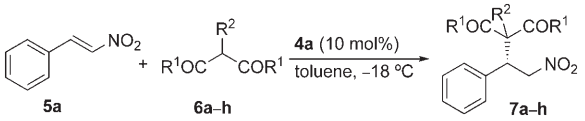
The effect of the modification of the core chiral structure of ureas and thioureas on the enantioselectivity was sudied by using **4b–i** as catalysts in toluene as solvent. In general, the modification of the alkyl substituent has little influence on the reaction enantioselectivity (85–88% *ee*, entries 5, 9–11), with valine-derived catalyst providing the best results. Interestingly, the use of urea **4e** as catalyst gave excellent yield and very good *ee* (entry 12).

On the contrary, the substituents at the amine nitrogen atom or the stereogenic nature of the carbon atom where the thiourea environment is attached were observed to exert a very significant effect on both the yield and the enantioselectivity of the reaction. In this way, *N*,*N*-dibenzyl derivative **4f** was unable to promote the reaction after 48 h at RT (entry 13). Catalyst **4i**, regiosisomer of **4a** where the thiourea substituent is attached to a non-stereogenic carbon atom, led to the addition product in low yield and very low enantioselectivity (entry 14).

The reaction temperature also plays an important effect on the enantioselectivity. The reactions carried out in toluene with 10 mol% of the catalyst at −18°C (entries 15–22) demonstrated that at low temperature the enantioselectivity increased to 95% *ee* without decreasing the yield, although in same cases the reaction time must be increased to 48 h. In these conditions, the *N*-methyl-*N*-isopropyl derivative **4g** lead to the addition product in excellent yield (97%) and *ee* (94%), and the phenylthiourea **4h** which has a greater pK_a than the 3,5-bis(trifluoromethyl) derivatives, and consequently with decreased H-bond donating ability,[17] also promotes the reaction with moderate yield (65%) and good *ee* (85%) although for a long period of time (entry 21). Catalysts **4a–i**, derived from L-amino acids gave addition products with *S* configuration at the created stereocenter, and as expected thiourea *ent*-**4a**, derived from D-valine yielded the addition product with *R* configuration with excellent yield and *ee* (entry 22).

We next studied the effect of the variations of the nucleophilic structure on the addition reaction. To this end, *trans* β-nitrostyrene was treated with different malonates or acetylacetone (**6a–h**) in toluene at −18°C and 10 mol% of catalyst **4a**, and the results are summarized in Table 2. It is noteworthy that the ease of the reaction is dependent upon the size of the alcoxy group of the unsubstituted malonates (entries 1-4 in Table 2). The reaction with dimethyl malonate **6b** was completed after 24 h, and the addition product was obtained in excellent 95% yield and 93% *ee* (entry 2), and the reaction time increased, and the yield diminished with the bulk of the alcoxy substituent. The bulkiest di-*tert*-butyl malonate did not react in the described conditions after 120 h of stirring.

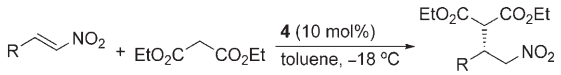
Table 2. Enantioselective nitro-Michael reaction of **5a** with malonates **6a–h** in the presence of **4a**.



Entry	R^1	R^2	t [h]	Yield [%][b]	Product (*ee* [%])[c] (Config.)[d]
1	OEt (**6a**)	H	44	90	**7a** (95) (*S*)
2	OMe (**6b**)	H	24	95	**7b** (93) (*S*)
3	O*i*Pr (**6c**)	H	96	64	**7c** (91) (*S*)
4	O*t*Bu (**6d**)	H	120	n.r.	–
5	Me (**6e**)	H	4	99	**7e** (93) (*S*)
6	OMe (**6f**)	Me	72	57	**7f** (96) (−)[e]
7	OMe (**6g**)	Cl	1	86	**7g** (99) (+)[e]
8	OEt (**6h**)	NHBoc	72	53	**7h** (79) (−)[e]

[a] The reactions were carried out with 1 equiv of **5a** and 2 equiv of **6** in the presence of 10 mol% of catalyst at −18°C. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **7** using a chiral column. [d] Absolute configuration was determined by comparing the optical rotation of **7** with that of the literature data. [e] Not determined.

Table 3. Enantioselective Michael reaction of nitroolefins **5a–f** with diethyl malonate **6a** in the presence of **4a–e**.



Entry	Cat.	R	t [h]	Yield [%][b]	Product (*ee* [%])[c] (Config.)[d]
1	**4a**	C_6H_5 (**5a**)	44	90	**8a** (95) (*S*)
2	**4a**	4-Cl-C_6H_4 (**5b**)	47	96	**8b** (93) (*S*)
3	**4b**	4-Cl-C_6H_4 (**5b**)	48	94	**8b** (92) (*S*)
4	**4d**	4-Cl-C_6H_4 (**5b**)	27	98	**8b** (93) (*S*)
5	**4e**	4-Cl-C_6H_4 (**5b**)	24	94	**8b** (91) (*S*)
6	**4a**	4-MeO-C_6H_4 (**5c**)	72	94	**8c** (94) (+)[e]
7	**4a**	2-NO_2-C_6H_4 (**5d**)	48	>99	**8d** (87) (+)[e]
8	**4a**	2-furyl (**5e**)	46	94	**8e** (95) (−)[e]
9	**4a**	$C_6H_5CH_2CH_2$ (**5f**)	144	69	**8f** (81) (−)[e]

[a] The reaction was carried out with 1 equiv of **5** and 2 equiv of **6a** in the presence of 10 mol% of catalyst at −18°C. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **8** using a chiral column. [d] Absolute configuration was determined by comparing the optical rotation of **8** with that of the literature data. [e] Not determined.

Acetylacetone **6e** easily reacted with nitrostyrene yielding the addition product **7e** in 99% yield and 93% *ee* within 4 h (entry 5). More interesting are the additions of substituted malonates because of the formation of a quaternary carbon center in the final products. In this way, 2-methyl dimethyl malonate yielded the addition product **7f** in moderate yield (57%) but excellent 96% *ee* after 72 h of reaction (entry 6), whereas the protected 2-amino diethyl malonate also reacted in moderate yield and *ee* (entry 8). In contrast, the reaction of 2-chlorodimethyl malonate was completed after only 1 h leading to **7g** in excellent 86% yield and complete enantioselectivity (entry 7).

Finally, we screened a series of reactions of diethyl malonate with nitroolefins **5a–f** bearing different β-substituents promoted by catalysts **4a–e** in toluene at −18°C. As illustrated in Table 3, *p*-chloronitrostyrene **5b** underwent conjugate addition of diethyl malonate in the presence of catalysts **4a–e** in excellent yields and *ee* values; the results are almost independent of the nature of the catalyst. The reaction promoted by urea **4e** was faster than those carried out with thiourea catalysts, although the *ee* was slightly lower (entry 5). The addition of diethyl malonate to *p*-methoxynitrostyrene **5c** in the presence of **4a** proceeded with high yield and enantioselectivity, but the rate of the reaction was somewhat decreased, probably due to the electron-rich characteristics of the substituent, whereas the *o*-nitro substituted nitrostyrene and the nitroolefin with a 2-furyl substituent behaves in a similar way as β-phenylnitrostyrene do (entries 7, 8 in Table 3). In contrast to this general behavior, the nitroolefin with a saturated substituent at β-position (**5f**) slowly reacted with diethyl malonate, yielding the addition product **8f** in moderate yield (69%) and *ee* (81%) after 144 h of stirring in toluene at −18°C (entry 9).

In summary, we have successfully developed a modular synthesis of novel bifunctional urea and thiourea organocatalysts derived from cheap, easily accessible natural and non-natural amino acids. The method allowed the preparation of both enantiomers of the catalysts starting from L- or D-amino acid series. Taking the Michael addition of malonates or dicarbonyl compounds to nitroolefins as a model we have tested the ability of these structures as enantioselective organocatalysts, proving the generality of their use. Among the tested catalysts, **4a** and *ent*-**4a**, thioureas derived from L- or D-valine respectively, are the most promising in terms of cost, yield and enantioselectivity. The enantioselective additions in presence of these catalysts occurred with excellent yield and *ee*, and they are compatible with a variety of nitroolefins and donors. In this way, they can be efficiently used to create tertiary and quaternary carbon center.

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