Tetrahedron 66 (2010) 3655–3661

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Doubly stereocontrolled asymmetric conjugate addition of acetylacetone to nitroolefins catalyzed by bifunctional tertiary amine–thiourea catalysts derived from both acyclic α-amino acids and carbohydrates

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ARTICLE INFO

Article history:
Received 21 January 2010
Received in revised form 18 March 2010
Accepted 23 March 2010
Available online 27 March 2010

Dedicated to Professor Albert S.C. Chan on the occasion of his 60th birthday

Keywords:
Catalyst design
Conjugate addition
Doubly stereocontrolled
α-Amino acids
Carbohydrates

ABSTRACT

A novel class of easily preparative, cheap, and fine-tunable bifunctional chiral tertiary amine–thiourea organocatalysts have been developed by combining both acyclic diamines derived from acyclic α-amino acids and carbohydrates. These organocatalysts promoted the enantioselective conjugate addition of acetylacetone to various nitroolefins in good yields (up to 93%) with good enantioselectivities (up to 91% ee). The present research demonstrates the advantages of incorporating two stereocontrolling structures into a single catalyst. Notably, it offers a simple and convenient doubly stereocontrolled approach for the catalytic asymmetric synthesis of a chiral organic molecule.

1. Introduction

Design of new chiral organocatalysts for efficient asymmetric transformations has become a focal point of attention in asymmetric organocatalysis.[1] In particular, development of a novel approach for asymmetric synthesis of both enantiomers[2] would be very useful by designing novel multitasking chiral organocatalysts.

In the past few years, bifunctional tertiary amine–(thio)urea organocatalysts have emerged as new and efficient organocatalysts for asymmetric reactions.[3,4] Despite their tremendous utility, these organocatalysts are derived from a very limited range of chiral structural scaffolds, including cyclohexane-1,2-diamine, 1,1′-binaphthyl-2,2′-diamine, and cinchona alkaloids. Moreover, the potential application of these organocatalysts in doubly stereocontrolled asymmetric reactions[5] has been less explored. Therefore, development of bifunctional tertiary amine–thiourea organocatalysts with novel chiral scaffolds for doubly stereocontrolled asymmetric transformations would be highly desirable.

As part of our interest in developing novel types of bifunctional organocatalysts for asymmetric processes,[6,7] and in developing new approaches for doubly stereocontrolled asymmetric catalysis,[8] herein we first report a class of easily preparative, cheap, and fine-tunable chiral bifunctional tertiary amine–thiourea organocatalysts by combining both acyclic diamines derived from acyclic α-amino acids and carbohydrates, and their application in the doubly stereocontrolled catalytic conjugate addition of acetylacetone to a variety of nitroolefins under mild conditions.[9,10]

Acyclic α-amino acids have received growing attention in organocatalysis as chiral scaffolds.[11] In contrast, carbohydrates have received less attention in the development of chiral organocatalysts although they are potential chiral scaffolds for the synthesis of chiral organocatalysts.[12] Carbohydrates, i.e., monosaccharides, are conformationally stable, cheap, and readily available. In addition, they possess multiple chiral centers and functional groups for catalyst performance optimization. Therefore, rational assembly of two stereocontrolling units into a single molecule would lead to a series of novel cost-effective and fine-tunable chiral organocatalysts.[13] Surprisingly, despite the enormous potential utility of this organocatalyst design strategy, few organocatalysts have been developed with this combining strategy. Recently, Kunz and co-workers preliminarily explored the utility of this organocatalyst

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doi:10.1016/j.tet.2010.03.081

design strategy by designing an elegant class of bifunctional Schiff base organocatalysts, which catalyzed enantioselective Strecker and Mannich reactions.[12a] In this pioneering work, only one α-amino acid (L-*tert*-leucine) was used. Both for scientific interest and for practical applications, it is desirable to investigate further full potentials of this organocatalyst design strategy by developing other types of chiral organocatalysts such as bifunctional tertiary amine–thiourea organocatalysts (Fig. 1). In particular, it is highly attractive to explore the new role of carbohydrate motif in the doubly stereocontrolled asymmetric catalysis.

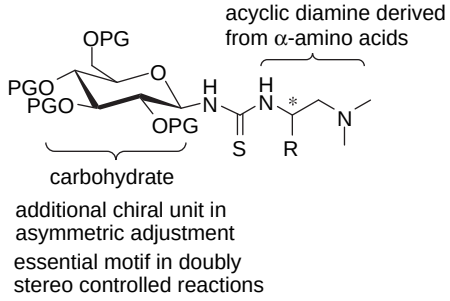


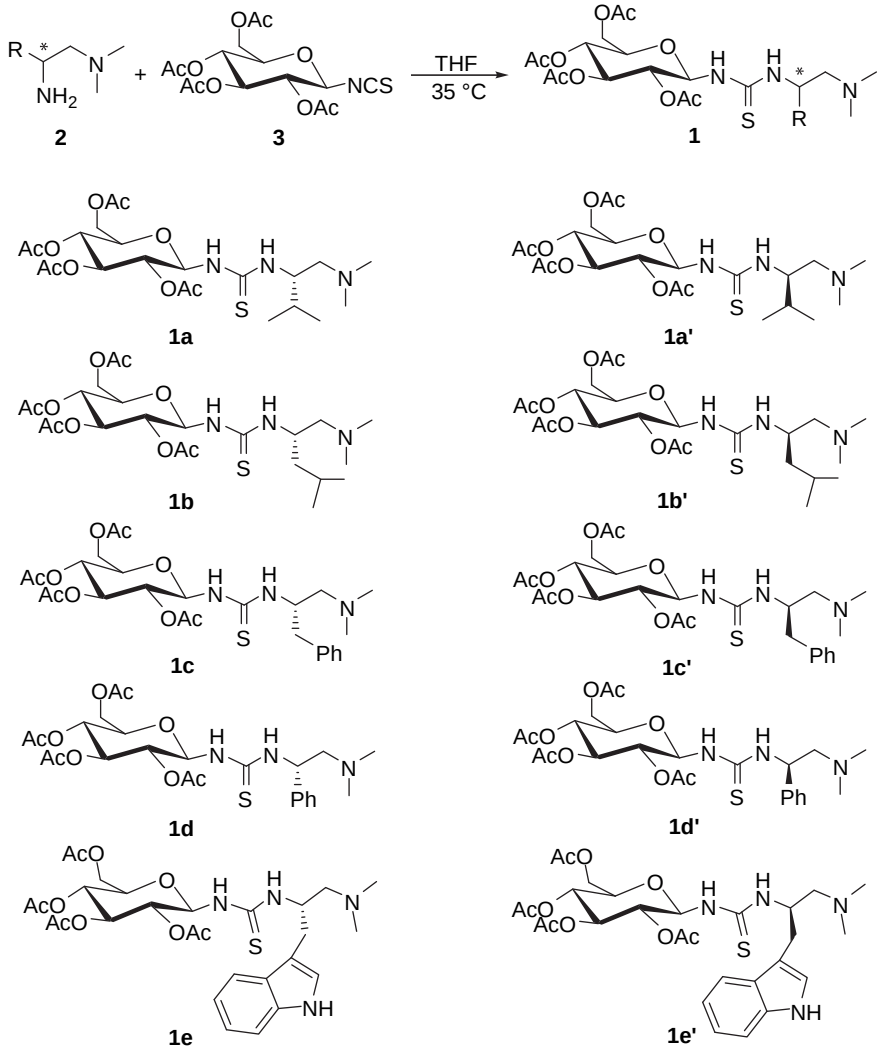
Figure 1. Key design elements of a new class of bifunctional chiral tertiary amine–thiourea organocatalysts.

2. Results and discussion

2.1. Synthesis and activity of bifunctional chiral tertiary amine–thiourea catalysts 1

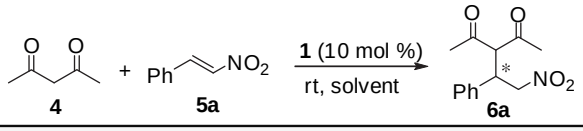
The chiral organocatalysts **1** were easily synthesized by reaction of the primary–tertiary diamine **2**[14] derived from acyclic α-amino acids with the isothiocyanate **3**[15] derived from D-glucopyranose (Scheme 1).

The catalytic activities of these chiral tertiary amine–thioureas **1** were initially evaluated in the conjugate addition reaction of acetylacetone **4** to *trans*-β-nitrostyrene **5a** in the presence of 10 mol% of catalyst loading at room temperature, and the results are summarized in Table 1. Several different solvents with the chiral organocatalyst **1a** derived from L-valine and D-glucopyranose were examined to find optimum reaction media, and the conjugate addition reaction with the organocatalyst **1a** in *THF* afforded the best enantioselectivity (85% ee, entry 6). Next, the effect of the variation of α-amino acid moieties was studied. The conjugate addition reactions with other organocatalysts **1b**–**e** derived from L-leucine, L-phenylalanine, L-phenylglycine, and L-tryptophan in THF resulted in lower enantiomeric excess (entries 7–10). Then the conjugate addition with the organocatalyst **1a**′ derived from D-valine and D-glucopyranose in THF was examined. The use of



Scheme 1. Synthesis of bifunctional tertiary amine–thiourea organocatalysts **1**.

Table 1
Enantioselective conjugate addition of acetylacetone **4** to *trans*-β-nitrostyrene **5a** catalyzed by **1**[a]



Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**1a**	DCM	84	82 (*S*)
2	**1a**	$PhCH_3$	90	82 (*S*)
3	**1a**	Et_2O	72	73 (*S*)
4	**1a**	DMF	75	27 (*S*)
5	**1a**	MeOH	69	34 (*S*)
6	**1a**	*THF*	88	*85* (*S*)
7	**1b**	THF	89	80 (*S*)
8	**1c**	THF	90	74 (*S*)
9	**1d**	THF	85	72 (*S*)
10	**1e**	THF	89	81 (*S*)
11	**1a′**	THF	87	76 (*R*)
12	**1b′**	THF	86	74 (*R*)
13	**1c′**	THF	80	70 (*R*)
14	**1d′**	THF	81	61 (*R*)
15	**1e′**	THF	85	61 (*R*)

[a] The reaction was performed with acetylacetone **4** (2 equiv) and *trans*-β-nitrostyrene **5a** (1 equiv) in the presence of catalyst **1** (10 mol %) at room temperature.
[b] Yields of isolated products.
[c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H).

Table 2
Enantioselective conjugate addition of acetylacetone **4** to *trans*-β-nitrostyrene **5a** catalyzed by the organocatalysts **1** in THF and $PhCH_3$[a]

Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**1a**	*THF*	88	*85* (*S*)
2	**1a**	$PhCH_3$	90	82 (*S*)
3	**1a′**	THF	87	76 (*R*)
4	**1a′**	*$PhCH_3$*	90	*86* (*R*)
5	**1b**	THF	89	80 (*S*)
6	**1b**	$PhCH_3$	90	78 (*S*)
7	**1b′**	THF	86	74 (*R*)
8	**1b′**	$PhCH_3$	89	79 (*R*)
9	**1c**	THF	90	74 (*S*)
10	**1c**	*$PhCH_3$*	89	*89* (*S*)
11	**1c**	*$PhCH_3$*	88	*90* (*S*)[d]
12	**1c′**	THF	80	70 (*R*)
13	**1c′**	*$PhCH_3$*	90	*87* (*R*)
14	**1c′**	*$PhCH_3$*	87	*90* (*R*)[d]
15	**1d**	THF	85	72 (*S*)
16	**1d**	$PhCH_3$	87	87 (*S*)
17	**1d′**	THF	81	61 (*R*)
18	**1d′**	$PhCH_3$	90	84 (*R*)
19	**1e**	THF	89	81 (*S*)
20	**1e**	$PhCH_3$	91	80 (*S*)
21	**1e′**	THF	85	61 (*R*)
22	**1e′**	$PhCH_3$	85	77 (*R*)

[a] The reaction was performed with acetylacetone **4** (2 equiv) and *trans*-β-nitrostyrene **5a** (1 equiv) in the presence of catalyst **1** (10 mol %) at room temperature.
[b] Yields of isolated products.
[c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H).
[d] At 0 °C.

organocatalyst **1a′** in THF provided the product **6a** with lower enantioselectivity (76% ee, entry 11), as well as with a reversal of the absolute configuration. Moreover, all other chiral tertiary amine–thiourea organocatalysts **1b′**–**e′** derived from D-α-amino acids exhibited an opposite sense of asymmetric induction (entries 12–15). Interestingly, all these chiral tertiary amine–thiourea organocatalysts derived from D-α-amino acids gave lower enantioselectivity in THF than those derived from the corresponding L-α-amino acids in THF (entries 6–10 vs 11–15). These results indicate clearly that the chiral moiety from α-amino acids predominated the absolute configuration of the product **6a**. On the other hand, it seems to indicate that the L-configuration of α-amino acid moiety matched the D-glucopyranose scaffold of thioureas, enhancing the stereochemical control in this conjugate addition reaction, whereas D-configuration of α-amino acid moiety mismatched the D-glucopyranose scaffold of thioureas.

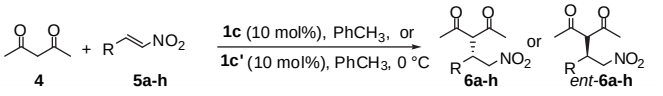
However, we were pleased to find that the conjugate addition reaction with the 'mismatched' organocatalyst **1a′** in *$PhCH_3$* gave the desired product **6a** in almost the same enantiomeric excess with opposite absolute configuration (entry 4 vs entry 1, Table 2). Triggered by these interesting observations, we made further investigations. It was found that while the chiral tertiary amine–thiourea organocatalyst **1c** derived from L-phenylalanine in *THF* (the optimized solvent, see Table 1) provided lower enantioselectivity (74% ee, entry 8, Table 1 or entry 9, Table 2), the conjugate addition reaction with this 'useless' organocatalyst **1c** in $PhCH_3$ gave the desired product **6a** with higher enantioselectivity (89% ee, entry 10, Table 2). Moreover, the corresponding organocatalyst **1c′** from D-phenylalanine in *$PhCH_3$* provided the desired product **6a** with the almost same high enantioselectivity with opposite absolute configuration (87% ee, entry 13, Table 2). Decreasing the reaction temperature to 0 °C improved the enantioselectivities slightly. Both enantiomers of the desired product **6a** were obtained in the same enantiomeric excess (90% ee) by using the organocatalyst **1c**, **1c′** in *$PhCH_3$* at 0 °C, respectively (entries 11, 14, Table 2). Interestingly, all the organocatalysts **1a′**–**e′** derived from D-α-amino acids in *$PhCH_3$* afforded the product **6a** with high enantioselectivities than in *THF* (Table 2).

Development of a novel approach for asymmetric synthesis of both enantiomers is highly useful in organic synthesis and in the pharmaceutical industry.[2] However, organocatalytic methods for such a purpose are few.[16] On the other hand, reutilization of the 'useless' organocatalysts is very attractive in the chiral organocatalyst development because of cost-effectiveness and environmental benefits.[17] Our findings might offer not only a simple and convenient route for the reutilization of the 'useless' organocatalysts in the chiral organocatalyst development, but also a new approach for doubly stereocontrolled catalytic synthesis.

2.2. Enantioselective conjugate addition of acetylacetone to nitroolefins in a doubly stereocontrolled manner catalyzed by bifunctional thiourea catalysts 1c and 1c′ *in same solvent*

The generality of doubly stereocontrolled asymmetric conjugate addition of acetylacetone **4** to a variety of nitroolefins **5a**–**h** was examined in the presence of organocatalysts **1c** and **1c′** in $PhCH_3$, respectively, and the results are summarized in Table 3. It is seen that all reactions of nitroolefins proceed smoothly affording the desired products of the (*S*) or (*R*) configuration[9g] with good enantioselectivities ((*S*)-adducts, 86–91% ee, (*R*)-adducts, 84–91% ee, Table 3). It appears that the position and the electronic property of the substituents for aromatic rings of nitroalkenes **5a**–**g** are well tolerated by the enantioselective conjugate addition reactions. Whether electron-withdrawing (entries 2–4, Table 3), electron-donating (entries 5–7, Table 3), or electron-neutral (entry 1, Table 3) groups on aromatic rings were used, the reactions proceeded smoothly to give the desired adducts in good yields (80–90%) with good enantioselectivity (85–91% ee). Notably, the conjugate addition of challenging aliphatic nitroolefins such as 4-methyl-1-nitropent-1-ene **5h** with acetylacetone **4** afforded the desired product **6h** with 88% ee and *ent*-**6h** with 84% ee in the presence of chiral organocatalysts **1c** and **1c′** in $PhCH_3$, respectively (entry 8). Few examples of the asymmetric addition of acetylacetone to aliphatic nitroolefins have been described so far due to lower reactivity of aliphatic nitroolefins than aromatic nitroolefins[7b,9n,s] The

Table 3
Organocatalytic enantioselective conjugate addition of acetylacetone **4** to various nitroolefins **5a–h** promoted by tertiary amine–thioureas **1c** and **1c′** in same solvent[a]

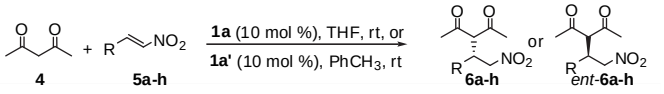


4 5a-h 6a-h ent-6a-h

Entry	R	Catalyst	Product	*t* (h)	Yield[b] (%)	ee[c] (%)
1	Ph (**5a**)	**1c**	**6a**	19	88	90
		1c′	*ent*-**6a**	19	87	90
2	4-ClC_6H_4 (**5b**)	**1c**	**6b**	14	83	91
		1c′	*ent*-**6b**	16	84	85
3	4-BrC_6H_4 (**5c**)	**1c**	**6c**	17	81	89
		1c′	*ent*-**6c**	15	80	86
4	2-$CF_3C_6H_4$ (**5d**)	**1c**	**6d**	19	90	86
		1c′	*ent*-**6d**	16	87	90
5	4-MeC_6H_4 (**5e**)	**1c**	**6e**	45	83	88
		1c′	*ent*-**6e**	43	81	87
6	4-$MeOC_6H_4$ (**5f**)	**1c**	**6f**	40	81	91
		1c′	*ent*-**6f**	39	80	89
7	2-$BnOC_6H_4$ (**5g**)	**1c**	**6g**	60	84	90
		1c′	*ent*-**6g**	64	86	91
8	*i*-Bu (**5h**)	**1c**	**6h**	64	84	88[d]
		1c′	*ent*-**6h**	60	80	84[d]

[a] The reaction was performed with acetylacetone **4** (2 equiv) and nitroolefins **5a–h** (1 equiv) in the presence of organocatalyst **1c** or **1c′** (10 mol %) at 0 °C.
[b] Yields of isolated products.
[c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H, AD-H and Chiralcel OD-H).
[d] At room temperature.

Table 4
Organocatalytic enantioselective conjugate addition of acetylacetone **4** to various nitroolefins **5a–h** promoted by tertiary amine–thioureas **1a** and **1a′** in different solvents[a]



4 5a-h 6a-h ent-6a-h

Entry	R	Catalyst	Product	*t* (h)	Yield[b] (%)	ee[c] (%)
1	Ph (**5a**)	**1a**	**6a**	17	88	85
		1a′	*ent*-**6a**	14	90	86
2	4-ClC_6H_4 (**5b**)	**1a**	**6b**	18	80	88
		1a′	*ent*-**6b**	15	92	86
3	4-BrC_6H_4 (**5c**)	**1a**	**6c**	20	84	86
		1a′	*ent*-**6c**	15	93	88
4	2-$CF_3C_6H_4$ (**5d**)	**1a**	**6d**	18	80	83
		1a′	*ent*-**6d**	14	87	88
5	4-MeC_6H_4 (**5e**)	**1a**	**6e**	20	86	86
		1a′	*ent*-**6e**	20	90	88
6	4-$MeOC_6H_4$ (**5f**)	**1a**	**6f**	18	82	90
		1a′	*ent*-**6f**	15	89	87
7	2-$BnOC_6H_4$ (**5g**)	**1a**	**6g**	36	80	85
		1a′	*ent*-**6g**	32	87	88
8	*i*-Bu (**5h**)	**1a**	**6h**	40	81	80
		1a′	*ent*-**6h**	48	85	81

[a] The reaction was performed with acetylacetone **4** (2 equiv) and nitroolefins **5a–h** (1 equiv) in the presence of organocatalyst **1a** or **1a′** (10 mol %) at room temperature.
[b] Yields of isolated products.
[c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AS-H, AD-H and Chiralcel OD-H).

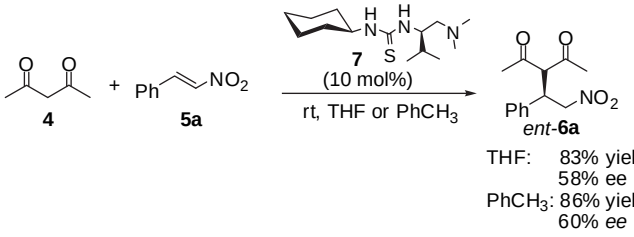
previous highest enantioselectivty in the asymmetric addition of acetylacetone to aliphatic nitroolefins reported by Najera's group in 2009 is 86% ee.[9s] During the course of our study,[10a] Zhou's group reported the nice application of chiral tertiary amine–thiourea organocatalysts derived from *trans*-cyclohexane-1,2-diamine and D-glucopyranose in the asymmetric conjugate addition of acetylacetone to aromatic nitroolefins.[9p] However, their organocatalysts could NOT catalyze the enantioselective addition of acetylacetone to aliphatic nitroolefins. *These results might indicate the advantage of incorporating acyclic diamines derived from α-amino acids into chiral tertiary amine–thiourea organocatalysts.*

2.3. Enantioselective addition of acetylacetone to nitroolefins in a doubly stereocontrolled manner catalyzed by bifunctional thiourea catalysts 1a and 1a′ *in different solvents*[10a]

The asymmetric conjugate addition reactions of acetylacetone **4** to various nitroolefins **5a–h** were investigated in the presence of organocatalysts **1a** and **1a′** in THF and $PhCH_3$, respectively, and the results are summarized in Table 4. Both organocatalysts exhibited good enantioselectivity in the conjugate addition reactions. Generally, both enantiomers of all the desired products can be achieved in almost the same enantiomeric excess with the organocatalyst **1a** in THF and with organocatalyst **1a′** in $PhCH_3$, respectively (entries 1–8, Table 4). The use of chiral organocatalyst **1a** always gave the conjugate adducts **6a–h** with (*S*)-configuration,[9g] while the use of organocatalyst **1a′** afforded *ent*-**6a–h** with the (*R*)-configuration.[9g]

2.4. Reaction mechanism

To gain an insight into the reaction mechanism of the conjugate addition of acetylacetone to nitroolefins catalyzed by the chiral tertiary amine–thiourea organocatalysts derived from both α-amino acids and carbohydrates, the role of sugar motif was investigated. The new chiral tertiary amine–thiourea **7** without sugar motif was synthesized and evaluated in the conjugate addition of acetylacetone **4** to *trans*-β-nitrostyrene **5a**. The product **6a** was obtained with lower enantioselectivity (Scheme 2). *The results might demonstrate the advantage of incorporating carbohydrate into chiral tertiary amine–thiourea organocatalysts. Moreover, these results might highlight the important role of the carbohydrate motif in the doubly stereocontrolled catalytic conjugate addition reaction of acetylacetone to nitroolefins.* To the best of our knowledge, this is the first example of catalytic asymmetric reaction in a doubly stereocontrolled manner catalyzed by chiral organocatalysts possessing the carbohydrate scaffold.



Scheme 2. Conjugate addition of acetylacetone **4** to *trans*-β-nitrostyrene **5a** catalyzed by the chiral tertiary amine–thiourea organocatalyst **7**.

On the basis of previous literatures[18] and the observations made in the present research, a tentative model representing the prototypical addition of acetylacetone **4** to *trans*-β-nitrostyrene **5a** in the presence of organocatalyst **1a** derived from L-valine and D-glucopyranose is shown in Figure 2, in which a thiourea moiety of the catalyst **1a** interacts through hydrogen bonding with a nitro group of the nitroalkene and enhances their electrophilicity while the tertiary amine deprotonates an acidic proton of acetylacetone, generating a ternary complex. The *re*-face approach of the nitroolefin accounts for the observed absolute configuration (*S*) of the conjugate adduct. As to the results that the 'mismatched' catalyst **1a′** derived from D-valine and D-glucopyranose in *THF* gave almost the same enantiomeric excess with opposite absolute configuration in *$PhCH_3$*, the solvents might play an important role in the stereochemistry of transition state.[19] Probably the interesting solvent effects come from the introduction of acylated sugar moiety. The

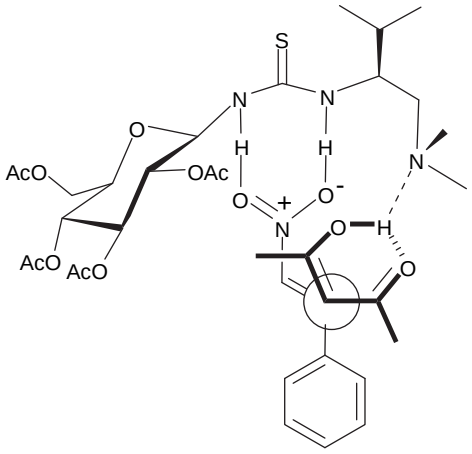


Figure 2. Proposed transition state model.

sugar moiety of bifunctional tertiary amine–thiourea catalysts might be mainly responsible for the different chiral induction in different solvents.

3. Conclusion

In summary, two classes of important compounds acyclic α-amino acids and carbohydrates *in life* have been used for the development a class of easily preparative, cheap, and fine-tunable bifunctional tertiary amine–thiourea organocatalysts *in chemistry*. These bifunctional thiourea organocatalysts promoted the enantioselective conjugate addition of acetylacetone to various nitroolefins at room temperature in good yields (up to 93%) with good enantioselectivity (up to 91% ee). The present research demonstrates the advantages of incorporating two stereocontrolling structures into a single catalyst. Notably, it offers a simple and efficient doubly stereocontrolled approach for the asymmetric synthesis of a chiral organic molecule. Doubly stereocontrolled catalytic conjugate addition of nitroolefins has been achieved with bifunctional thiourea catalysts **1c** and **1c′** in same solvent ($PhCH_3$), and **1a** and **1a′** in different solvents ($PhCH_3$ and THF), respectively. Further investigation of the efficacy of these organocatalysts in other catalytic asymmetric reactions and development of other chiral organocatalysts by this organocatalyst design strategy are in progress in our laboratory.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded at Bruker Avance 300 spectrophotometer. Chemical shifts (δ) are expressed in parts per million, and *J* values are given in hertz. The enantiomeric excess was determined by HPLC using Chiralpak AS-H, or AD-H and Chiralcel OD-H column with n-hexane and *i*-propanol as eluents. HRMS data were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. Optical rotations were determined on a JASCO J-20C polarimeter with 0.2 dm tube using 589 nm at 20 °C. All chemicals and solvents were used as received without further purification unless otherwise stated. Flash column chromatography was performed on silica gel (230–400 mesh).

4.2. General procedure for preparation of bifunctional tertiary amine–thiourea catalysts 1

To a solution of the primary–tertiary diamine **2** derived from α-amino acids (1 mmol) in dry THF (5 mL) was added dropwise a solution of the isothiocyanate **3** derived from D-glucopyranose (1.2 mmol) in dry THF (10 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 35 °C, and the reaction was monitored by TLC. After removal of solvent, the residue was purified through column chromatography on silica gel to give the amine–thiourea catalysts.

*4.2.1. (4S,5S,6R)-2-(Acetoxymethyl)-6-(3-((S)-1-(dimethylamino)-3-methylbutan-2-yl) thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1a**).* Yield 431 mg (83%); $[\alpha]_D^{20}$ −9.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=6.15 (br s, 1H), 5.74 (t, *J*=8.8 Hz, 1H), 5.32 (t, *J*=9.5 Hz, 1H), 5.07 (t, *J*=9.7 Hz, 1H), 4.93 (t, *J*=9.3 Hz, 1H), 4.26 (dd, *J*=4.1, 3.9 Hz, 1H), 4.15 (dd, *J*=2.0, 2.3 Hz, 1H), 3.88 (m, 1H), 3.28 (br s, 1H), 2.50–2.46 (m, 2H), 2.32 (s, 6H), 2.04 (s, 6H), 2.02 (s, 6H), 1.83 (m, 1H), 0.96 (d, *J*=6.9 Hz, 3H), 0.95 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=184.0, 170.5, 170.1, 169.8, 83.9, 73.3, 71.3, 68.5, 63.5, 61.9, 59.7, 44.9, 31.5, 20.8, 20.6, 18.1, 18.0; HRMS (FAB^+) calcd for $C_{22}H_{38}N_3O_9S$ $[M+1]^+$ 520.2329, found 520.2330.

*4.2.2. (4S,5S,6R)-2-(Acetoxymethyl)-6-(3-((R)-1-(dimethylamino)-3-methylbutan-2-yl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1a′**).* Yield 420 mg (81%); $[\alpha]_D^{20}$ +44.0 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=5.76 (m, 1H), 5.23 (t, *J*=9.4 Hz, 1H), 5.01 (t, *J*=9.6 Hz, 1H), 4.87 (t, *J*=9.4 Hz, 1H), 4.18 (d, *J*=12.3 Hz, 1H), 4.06 (d, *J*=12.4 Hz, 1H), 3.76 (m, 1H), 2.63–2.37 (m, 2H), 2.24 (s, 6H), 1.99 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.19 (m, 1H), 0.88 (d, *J*=4.5 Hz, 3H), 0.81 (d, *J*=2.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=185.1, 170.6, 170.3, 169.9, 169.7, 83.6, 76.6, 73.5, 73.4, 71.3, 68.4, 62.0, 45.1, 31.6, 20.8, 20.7, 20.6, 18.1; HRMS (FAB^+) calcd for $C_{22}H_{38}N_3O_9S$ $[M+1]^+$ 520.2329, found 520.2330.

*4.2.3. (4S,5S,6R)-2-(Acetoxymethyl)-6-(3-((S)-1-(dimethylamino)-4-methylpentan-2-yl) thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1b**).* Yield 426 mg (80%); $[\alpha]_D^{20}$ −9.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=6.16 (br s, 1H), 5.71 (br s, 1H), 5.33 (t, *J*=9.5 Hz, 1H), 5.08 (t, *J*=9.7 Hz, 1H), 4.94 (t, *J*=9.5 Hz, 1H), 4.28 (dd, *J*=3.6, 3.4 Hz, 1H), 4.15 (d, *J*=12.3 Hz, 1H), 3.88 (m, 1H), 3.53 (br s, 1H), 2.57–2.41 (m, 2H), 2.33 (s, 6H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.68 (m, 1H), 1.36–1.22 (m, 2H), 0.93 (d, *J*=6.5 Hz, 3H), 0.90 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=185.0, 170.6, 169.8, 168.7, 168.6, 83.8, 73.3, 73.1, 71.3, 68.5, 66.9, 61.9, 53.4, 45.1, 42.5, 24.7, 22.7, 20.7; HRMS (FAB^+) calcd for $C_{23}H_{40}N_3O_9S$ $[M+1]^+$, 534.2485, found 534.2457.

*4.2.4. (4S,5S,6R)-2-(Acetoxymethyl)-6-(3-((R)-1-(dimethylamino)-4-methylpentan-2-yl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1b′**).* Yield 426 mg (80%); $[\alpha]_D^{20}$ +41.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ5.81 (m, 1H), 5.33 (t, *J*=9.4 Hz, 1H), 5.08 (t, *J*=9.7 Hz, 1H), 4.96 (t, *J*=9.1 Hz, 1H), 4.28 (dd, *J*=4.3, 4.3 Hz, 1H), 4.12 (d, *J*=12.3 Hz, 1H), 3.86 (m, 1H), 2.70–2.18 (m, 8H), 2.07 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.69 (m, 1H), 1.26 (m, 2H), 0.94 (d, *J*=6.4 Hz, 3H), 0.87 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=185.4, 170.6, 169.9, 169.7, 83.2, 73.4, 71.2, 68.5, 66.1, 62.0, 52.8, 45.2, 42.6, 24.9, 22.7, 20.7, 20.6; HRMS (FAB^+) calcd for $C_{23}H_{40}N_3O_9S$ $[M+1]^+$, 534.2485, found 534.2457.

*4.2.5. (4S,5S,6R)-2-(Acetoxymethyl)-6-(3-((S)-1-(dimethylamino)-3-phenylpropan-2-yl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1c**).* Yield 442 mg (78%); $[\alpha]_D^{20}$ +11.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.23 (m, 3H), 7.19–7.17 (m, 2H), 6.48 (br s, 1H), 5.71 (m, 1H), 5.32 (t, *J*=9.5 Hz, 1H), 5.06 (t, *J*=9.8 Hz, 1H), 4.92 (t, *J*=9.3 Hz, 1H), 4.28 (dd, *J*=3.8, 3.7 Hz, 1H), 4.14 (m, 1H), 3.84 (m, 1H), 2.74 (m, 1H), 2.72 (m, 1H), 2.51 (m, 1H), 2.36 (m, 1H), 2.21 (s, 6H), 2.03 (s, 6H), 2.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.3, 170.3, 170.0, 169.6, 169.5, 136.6, 129.0, 128.7, 127.0, 83.6, 73.1, 73.0,

71.2, 68.4, 64.8, 61.7, 55.9, 44.7, 39.0, 20.9, 20.6, 20.4; HRMS (ESI) calcd for $C_{26}H_{37}N_3O_9S$ $[M+1]^+$, 568.2323, found 568.2320.

*4.2.6. (4S,5S,6R)-2-(Acetoxymethyl)-6-(3-((R)-1-(dimethylamino)-3-phenylpropan-2-yl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1c′**).* Yield 431 mg (76%); $[\alpha]_D^{20}$ +14.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.29–7.27 (m, 2H), 7.22–7.19 (m, 3H), 7.07 (br s, 1H), 5.84 (m, 1H), 5.34 (t, *J*=9.4 Hz, 1H), 5.07 (t, *J*=9.7 Hz, 1H), 4.95 (m, 1H), 4.35 (dd, *J*=4.1, 3.8 Hz, 1H), 4.08 (m, 1H), 3.87 (d, *J*=9.9 Hz, 1H), 2.99 (m, 2H), 2.47 (m, 2H), 2.17 (s, 6H), 2.04 (s, 6H), 2.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.6, 170.5, 170.3, 169.8, 169.5, 137.2, 129.4, 128.5, 126.6, 82.8, 73.3, 71.1, 68.3, 61.8, 53.5, 45.1, 38.6, 20.9, 20.5, 20.4; HRMS (ESI) calcd for $C_{26}H_{37}N_3O_9S$ $[M+1]^+$, 568.2323, found 568.2320.

*4.2.7. (4S,5S,6R)-2-(Acetoxymethyl)-6-(3-((S)-2-(dimethylamino)-1-phenylethyl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1d**).* Yield 448 mg (81%); $[\alpha]_D^{20}$ +28.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.31 (m, 3H), 7.25–7.23 (m, 2H), 6.65 (br s, 1H), 5.76 (m, 1H), 5.33 (t, *J*=9.5 Hz, 1H), 5.09 (t, *J*=9.9 Hz, 1H), 4.95 (t, *J*=9.4 Hz, 1H), 4.30 (dd, *J*=4.2, 4.1 Hz, 1H), 4.12 (m, 1H), 3.87 (m, 1H), 2.90 (m, 1H), 2.53 (dd, *J*=1.7, 1.7 Hz, 1H), 2.35 (s, 6H), 2.06 (s, 3H), 2.04 (s, 3H), 2.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.4, 170.5, 170.3, 169.8, 169.6, 139.4, 129.2, 128.5, 126.5, 83.6, 73.4, 73.2, 71.1, 68.4, 66.6, 61.8, 58.8, 45.1, 20.6, 20.5; HRMS (ESI) calcd for $C_{25}H_{35}N_3O_9S$ $[M+1]^+$, 554.2167, found 554.2178.

*4.2.8. (4S,5S,6R)-2-(Acetoxymethyl)-6-(3-((R)-2-(dimethylamino)-1-phenylethyl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1d′**).* Yield 448 mg (81%); $[\alpha]_D^{20}$ +3.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.19 (m, 5H), 5.74 (m, 1H), 5.26 (t, *J*=9.5 Hz, 1H), 4.97 (t, *J*=9.6 Hz, 1H), 4.86 (m, 1H), 4.20 (dd, *J*=4.2, 4.1 Hz, 1H), 4.02 (m, 1H), 3.76 (m, 1H), 2.71 (m, 1H), 2.34 (dd, *J*=3.8, 3.7 Hz, 1H), 2.19 (s, 6H), 1.97 (s, 3H), 1.94 (s, 3H), 1.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.7, 170.8, 170.6, 169.8, 169.6, 139.9, 128.8, 127.8, 126.5, 82.9, 73.3, 73.0, 71.1, 68.4, 68.2, 67.8, 65.1, 61.8, 56.6, 45.0, 20.6, 20.5; HRMS (ESI) calcd for $C_{25}H_{35}N_3O_9S$ $[M+1]^+$, 554.2167, found 554.2178.

*4.2.9. (3R,5S,6R)-2-(Acetoxymethyl)-6-(3-((S)-1-(dimethylamino)-3-(1H-indol-3-yl)propan-2-yl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1e**).* Yield 467 mg (77%); $[\alpha]_D^{20}$ −10.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.83 (br s, 1H), 7.47 (br s, 1H), 7.32 (d, *J*=7.9 Hz, 1H), 7.15–7.03 (m, 2H), 6.97 (br s, 1H), 6.42 (br s, 1H), 5.64 (d, *J*=8.6 Hz, 1H), 5.24 (t, *J*=9.5 Hz, 1H), 5.01 (t, *J*=9.8 Hz, 1H), 4.87 (m, 1H), 4.17 (dd, *J*=3.7, 3.4 Hz, 1H), 4.05 (d, *J*=11.5 Hz, 1H), 3.77 (m, 2H), 2.81 (br s, 2H), 2.48 (m, 2H), 2.19 (s, 6H), 1.96 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.5, 170.6, 169.9, 169.8, 136.6, 126.9, 123.3, 122.2, 119.5, 118.2, 111.6, 110.0, 83.8, 73.2, 71.2, 68.4, 68.2, 67.9, 65.9, 61.8, 54.6, 44.9, 29.6, 20.6; HRMS (ESI) calcd for $C_{28}H_{38}N_4O_9S$ $[M+1]^+$, 607.2423, found 607.2438.

*4.2.10. (3R,5S,6R)-2-(Acetoxymethyl)-6-(3-((R)-1-(dimethylamino)-3-(1H-indol-3-yl)propan-2-yl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**1e′**).* Yield 484 mg (80%); $[\alpha]_D^{20}$ +30.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.85 (br s, 1H), 7.58 (br s, 1H), 7.36 (d, *J*=7.7 Hz, 1H), 7.17–7.05 (m, 2H), 6.99 (br s, 1H), 6.52 (br s, 1H), 5.77 (d, *J*=5.8 Hz, 1H), 5.29 (t, *J*=9.2 Hz, 1H), 5.03 (t, *J*=9.7 Hz, 1H), 4.76 (m, 1H), 4.25 (d, *J*=7.3 Hz, 1H), 4.08 (m, 1H), 3.79 (m, 2H), 2.96 (br s, 2H), 2.49 (br s, 2H), 2.09 (s, 6H), 2.03 (s, 6H), 2.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.2, 171.2, 170.7, 169.9, 169.7, 136.4, 127.4, 123.3, 122.2, 119.6, 118.6, 111.5, 110.3, 83.2, 73.3, 71.2, 68.4, 68.2, 65.0, 61.9, 53.5, 45.1, 29.6, 20.7, 20.5; HRMS (ESI) calcd for $C_{28}H_{38}N_4O_9S$ $[M+1]^+$, 607.2423, found 607.2438.

4.3. Typical procedure for asymmetric conjugate addition reaction of acetylacetone 4 to nitroolefins 5 catalyzed by catalyst 1

Catalyst **1a** (10.4 mg, 0.02 mmol, 10 mol %) was added to a vial containing acetylacetone **4** (40 mg, 0.4 mmol) and nitroolefins **5** (0.2 mmol) in dry THF (0.6 mL) at room temperature. The resulting mixture was stirred at room temperature, and the reaction was monitored by TLC. The reaction mixture was quenched with 1 M aqueous HCl solution, extracted with EtOAc, and dried over Na_2SO_4. The crude product was purified by flash silica gel chromatography to give the desired adducts **6**. The ee values were determined by chiral HPLC analysis.

*4.3.1. (S)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (**6a**)*[9g]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.26 (m, 3H), 7.20–7.17 (m, 2H), 4.67–4.62 (m, 2H), 4.37 (d, *J*=10.8 Hz, 1H), 4.28–4.24 (m, 1H), 2.30 (s, 3H), 1.94 (s, 3H); HPLC (Chiralpak AS-H, *i*-propanol/hexane=15/85, flow rate 1.0 mL/min, λ=210 nm): $t_{R,major}$=15.5 min, $t_{R,minor}$=24.3 min.

*4.3.2. (S)-3-(1-(4-Chlorophenyl)-2-nitroethyl)pentane-2,4-dione (**6b**)*[9g]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J*=6.5 Hz, 2H), 7.14 (d, *J*=6.5 Hz, 2H), 4.62 (d, *J*=6.6 Hz, 2H), 4.33 (d, *J*=10.7 Hz, 1H), 4.27–4.25 (m, 1H), 2.30 (s, 3H), 1.98 (s, 3H); HPLC (Chiralpak AS-H, *i*-propanol/hexane=15/85, flow rate 1.0 mL/min, λ=210 nm): $t_{R,major}$=15.8 min, $t_{R,minor}$=33.7 min.

*4.3.3. (S)-3-(1-(4-Bromophenyl)-2-nitroethyl)pentane-2,4-dione (**6c**)*[9g]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J*=6.6 Hz, 2H), 7.07 (d, *J*=6.7 Hz, 2H), 4.62–4.60 (m, 2H), 4.34 (d, *J*=10.7 Hz, 1H), 4.26–4.23 (m, 1H), 2.30 (s, 3H), 1.98 (s, 3H); HPLC (Chiralpak AS-H, *i*-propanol/hexane=15/85, flow rate 1.0 mL/min, λ=210 nm): $t_{R,major}$=16.9 min, $t_{R,minor}$=32.0 min.

*4.3.4. (S)-3-(2-Nitro-1-(2-(trifluoromethyl)phenyl)ethyl)pentane-2,4-dione (**6d**)*[9g]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, *J*=7.6 Hz, 1H), 7.46 (t, *J*=7.2 Hz, 1H), 7.37 (t, *J*=7.6 Hz, 1H), 7.20 (d, *J*=7.5 Hz, 1H), 4.81–4.75 (m, 1H), 4.62–4.55 (m, 3H), 2.25 (s, 3H), 1.94 (s, 3H); HPLC (Chiralcel OD-H, *i*-propanol/hexane=10/90, flow rate 1.0 mL/min, λ=210 nm): $t_{R,major}$=15.9 min, $t_{R,minor}$=17.8 min.

*4.3.5. (S)-3-(2-Nitro-1-p-tolylethyl)pentane-2,4-dione (**6e**)*[9g]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, *J*=8.0 Hz, 2H), 7.06 (d, *J*=8.2 Hz, 2H), 4.62–4.59 (m, 2H), 4.5 (d, *J*=10.9 Hz, 1H), 4.22 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.94 (s, 3H); HPLC (Chiralpak AS-H, *i*-propanol/hexane=15/85, flow rate 1.0 mL/min, λ=210 nm): $t_{R,major}$=12.5 min, $t_{R,minor}$=19.4 min.

*4.3.6. (S)-3-(1-(4-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (**6f**)*[9g]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, *J*=6.8 Hz, 2H), 6.84 (d, *J*=6.8 Hz, 2H), 4.60 (d, *J*=6.9 Hz, 2H), 4.34 (d, *J*=10.9 Hz, 1H), 4.12 (m, 1H), 3.78 (s, 3H), 2.29 (s, 3H), 1.94 (s, 3H); HPLC (Chiralpak AD-H, *i*-propanol/hexane=5/95, flow rate 0.8 mL/min, λ=210 nm): $t_{R,major}$=40.6 min, $t_{R,minor}$=66.5 min.

*4.3.7. (S)-3-(1-(2-(Benzyloxy)phenyl)-2-nitroethyl)pentane-2,4-dione (**6g**)*[9g]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.40 (m, 5H), 7.26 (m, 1H), 7.10 (m, 1H), 6.98–6.91 (m, 2H), 5.13 (s, 2H), 4.80–4.77 (m, 1H), 4.57–4.53 (m, 3H), 2.18 (s, 3H), 1.91 (s, 3H); HPLC (Chiralpak AS-H, *i*-propanol/hexane=10/90, flow rate 0.8 mL/min, λ=210 nm): $t_{R,major}$=20.2 min, $t_{R,minor}$=22.1 min.

*4.3.8. (R)-3-(4-Methyl-1-nitropentan-2-yl)pentane-2,4-dione (**6h**)*[7b]. ^1H NMR (300 MHz, $CDCl_3$): δ 4.51 (m, 2H), 3.99 (d, *J*=8.4 Hz, 1H), 2.90 (m, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 1.69 (m, 1H), 1.35 (m, 1H),

0.98 (m, 1H), 0.94 (m, 6H); HPLC (Chiralpak AS-H, *i*-propanol/hexane=4/96, flow rate 1.0 mL/min, λ=210 nm): $t_{R,major}$=10.4 min, $t_{R,minor}$=12.8 min.

Acknowledgements

We thank National Natural Science Foundation of China (20702044, 20962023) and the Program for New Century Excellent Talents in University for support of this research.

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