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Asymmetric construction of spirocyclohexanonerhodanines catalyzed by simple diamine derived from chiral tert-leucine†

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A diamine-catalyzed asymmetric tandem reaction between α,β-unsaturated ketones and rhodanine derivatives has been developed to synthesize various spirocyclic compounds with high stereoselectivities (up to 99% ee and >20 : 1 dr). The products obtained contain two pharmaceutically relevant features: the biologically active rhodanine moiety embedded in a spirocyclic unit.

Spirocompounds, which have received increasing interest from synthetic organic chemists, feature in a large number of natural products, new ligands and catalysts due to the unique structural properties of spirocycles.[1] Particularly, heterocyclic spiro-type molecules are very attractive to pharmacological scientists. Recently, 2-thioxo-1,3-thiazolidin-4-one (rhodanine), 1,3-thiazolidine-2,4-dione and 2-thioxoimidazolidin-4-one have become a very important group of heterocyclic compounds in drug discovery and development.[2] The rhodanine derivative epalrestat, thiazolidine-2,4-dione derivatives, glitazones (Avandia, Rezulin, and Actos) and the 2-thioxoimidazolidin-4-one derivative dilantin have been introduced to clinical use for treatment of diabetic complications, type II diabetes, mellitus and epilepsy, respectively.[3] 5-substituted benzyl thiazolidine-2,4-dione and 5-octylthiazolidine-2,4-dione have demonstrated potential applications as GPR40 agonists.[4] Interestingly, the 5*S* enantiomers of glitazone compounds with the methyl group in the 5-position have been found to have enhanced anti-inflammatory activity over the corresponding 5*R* enantiomers.[5] The relationship between the biological and pharmacological activities and the stereoconfiguration prompted us to focus on developing new methodologies for the direct construction of novel, stereoriched and architecturally complex molecular scaffolds with these biologically attractive heterocyclic backbones.[6]

Since the elegant tandem reaction of α,β-unsaturated ketones was reported by Barbas III and Cabal,[7] enones have been employed in the synthesis of spirocyclic compunds. In 2009, Melchiorre[8] demonstrated that the organocascade reaction of α,β-unsaturated ketones proceeded *via* a tandem iminium and enamine activation sequence catalyzed by a cinchona alkaloid hydroquinine-derived primary amine catalyst and this strategy was applied in the asymmetric synthesis of spirocyclic oxindoles.[9] Later, Gong's group[10] developed an approach for the direct construction of spiro-[4-cyclohexanone-1,3′-oxindoline] derivatives *via* the bifunctional organocatalytic [4 + 2] cycloaddition of Nazarov reagents. Shortly after, chiral spiro[cyclohexane-1,3′-indoline]-2′,3-diones and spirocyclic benzofuranone cyclohexanones were synthesized by Wang[11] and Melchiorre,[12] respectively, employing somewhat similar strategies.

In our initial study, a series of chiral primary amines were chosen as catalysts to evaluate the reaction. Moderate diastereoselectivities and enantioselectivities were observed using 10 mol% (*R*,*R*)-1,2-cyclohexanediamine and (*R*,*R*)-1,2-diphenylethylenediamine as catalysts, coordinating with 20 mol% benzoic acid. When the quinidine-derived catalyst 9-amino(9-deoxy)*epi*-quinine **3** was employed in the reaction, the desired spiro product was afforded with a good yield, while only with 75% ee and 3 : 1 dr.

We envisaged that a catalyst with neighboring bulky substituents of the primary amine group could improve the enantioselectivity based on the above results. Diamine (primary-secondary or primary-tertiary) was chosen as the catalyst backbone, which was readily available from inexpensive amino acids.[13] Initially, the *tert*-butyl group was introduced into the catalyst scaffold to investigate the effects of secondary and tertiary amines. Dimethylamine and piperidine derived catalysts **4a** and **4b** gave poor results (Table 1, entries 4 and 5), while cyclohexylamine derived catalyst **4c** revealed excellent controlling ability in regulating the enantioselectivity, affording 99% ee and 69/31 dr. Comparing the effect of neighboring substituents of the primary amine group, *tert*-butyl was obviously much better than the isopropyl and benzyl groups in catalysts **4d** and **4e** (Entries 6–8). To our delight, the diastereoselectivity was dramatically improved through acid screening. Satisfactory results (90% yield, 98% ee and >20 : 1 dr) were obtained when the combination of 10 mol% catalyst **4c** and 20 mol% 2-methoxybenzoic acid or *N*-Boc-L-tryptophan was employed, and the reaction was performed in toluene at 30 °C for 24 hours.

After the optimal conditions had been established, the generality of the tandem reaction was investigated by using

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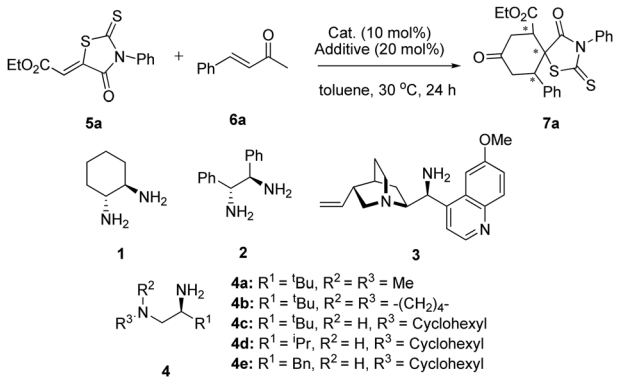
Table 1 Screening of chiral amino catalysts and acidic additives[a]



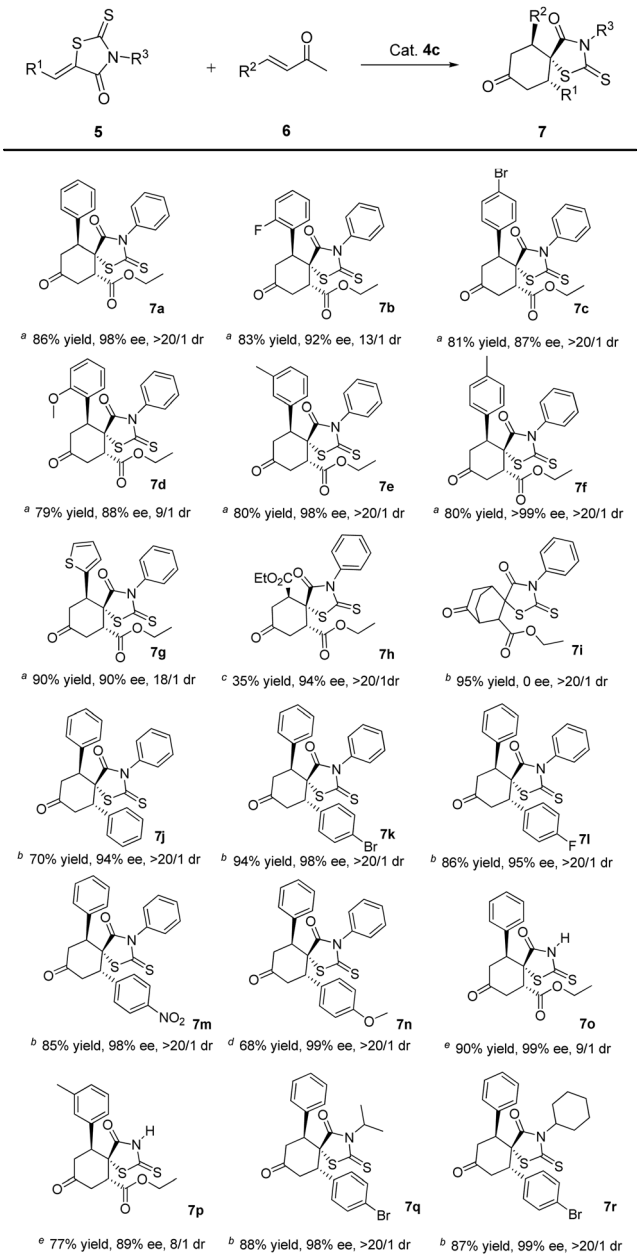
Entry	Cat.	Additive	Yield[b] (%)	ee[c] (%)	dr[d]
1	**1**	$PhCO_2H$	52	−23	70/30
2	**2**	$PhCO_2H$	69	−22	73/27
3	**3**	$PhCO_2H$	86	75	3/1
4	**4a**	$PhCO_2H$	46	−15	75/25
5	**4b**	$PhCO_2H$	27	−27	76/24
6	**4c**	$PhCO_2H$	89	99	69/31
7	**4d**	$PhCO_2H$	83	−9	3/1
8	**4e**	$PhCO_2H$	87	70	3/1
9	**4c**	*N*-Boc-L-Phg	88	83	10/1
10	**4c**	*N*-Boc-L-Trp	87	98	>20/1
11	**4c**	*o*-F-$C_6H_4CO_2H$	88	93	6/1
12	**4c**	*o*-CH_3O-$C_6H_4CO_2H$	90	98	>20/1
13	**4c**	*p*-NO_2-$C_6H_4CO_2H$	92	98	13/1

[a] Reaction conditions: **5a** (0.10 mmol, 1.0 eq), **6a** (0.15 mmol, 1.5 eq), catalyst (10 mol %) and acid (20 mol%) in toluene (C = 0.5 M) at 30 °C for 24 h. [b] Yield of isolated product after chromatography. [c] Enantiomeric excess was determined by chiral HPLC. [d] Determined by ^{1}H NMR and chiral HPLC of the crude reaction mixture.

rhodanine derivatives (compound **5**). As summarized in Table 2, α,β-unsaturated ketones with electron-withdrawing and electron-donating substituents at different positions on the aromatic ring and neutral and heteroaromatic α,β-unsaturated ketones turned out to be tolerant of the reaction, affording up to >99% ee and >20 : 1 dr. When (*E*)-ethyl 4-oxopent-2-enoate was involved in the tandem reaction, the yield decreased to 35%. Unexpectedly, the enantioselectivity of the cascade product of the cyclic α,β-unsaturated ketone dropped to 0. Changing the ester group into aromatic groups decreased the reactivity of the rhodanine derivatives because of the weaker electron attraction. In spite of this, substrates with different electron-withdrawing aromatic substituents at the terminal carbon atom of the double bond yielded the desired products with 94–99% ee and >20 : 1 dr by extending the reaction time to 48 hours and increasing the temperature to 50 °C. In contrast, the electron-donating aromatic substituted substrates afforded poor yields because the reaction rate of the first-step Michael addition was greatly influenced. The relative and absolute configurations of the sequential reaction products were assigned on the basis of X-ray crystal structural analysis of the product **7c** (see the ESI†).

Next, the attention was turned to evaluate the substituents on the nitrogen atom of substrates **5**. The reactivity of substrates **5** with different substituents (phenyl, isopropyl, cyclohexyl or hydrogen) on the nitrogen atom were almost

Table 2 Generality of organocatalytic tandem reactions

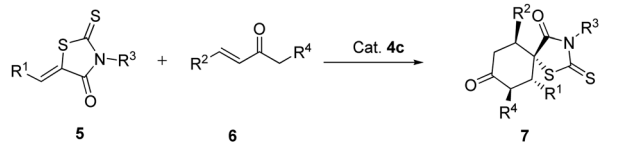


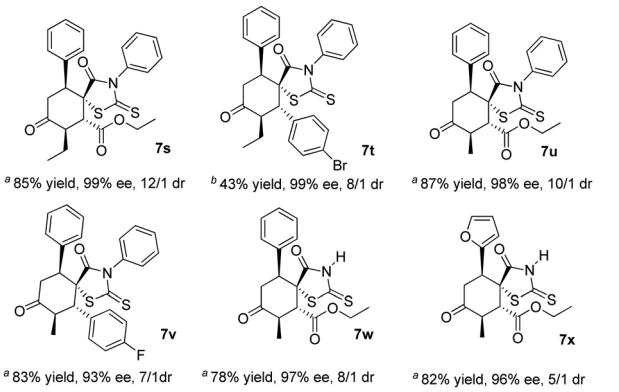
Reaction conditions. [a] **5** (0.30 mmol, 1.0 eq), **6** (0.45 mmol, 1.5 eq), Cat. **4c** (10 mol%) and *o*-CH_3O-$C_4H_6CO_2H$ (20 mol%) in $PhCH_3$ (C = 0.5 M) at 30 °C for 24 h. [b] Cat. **4c** (10 mol%) and *N*-Boc-L-Trp (20 mol%) in $CHCl_3$ (C = 0.5 M) at 50 °C for 48 h. [c] 50 °C for 72 h. [d] Cat. **4c** (30 mol%) and *N*-Boc-L-Trp (60 mol%) for 72 h. [e] **5** (0.30 mmol, 1.0 eq), **6** (0.60 mmol, 2.0 eq), Cat. **4c** (10 mol%) and *N*-Boc-L-Trp (20 mol%) in $CHCl_3$ (C = 0.5 M) at 50 °C for 72 h.

the same and the reaction proceeded smoothly, giving the desired products with satisfactory results (**7a**, **7o** to **7r**).

In the further exploration, the construction of spirocyclohexanonerhodanines with four chiral consecutive centers was focused upon, which remains challenging in asymmetric synthesis. As shown in Table 3, introducing alkyl groups such as methyl and ethyl into the fourth chiral center of the spiro-backbone gave 43 to 87% yields, 93 to 99% ee and 5 : 1 to 12 : 1 dr.

Table 3 Construction of spirocompounds with four consecutive chiral centers

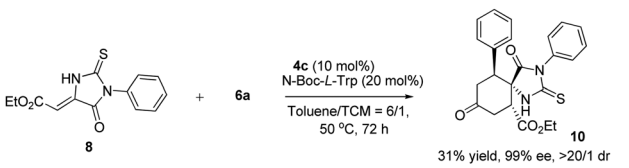




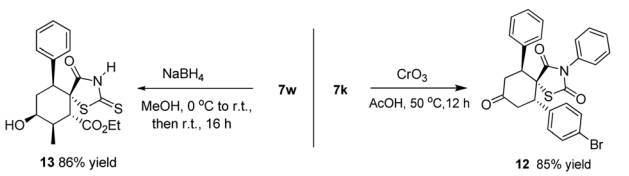
[a] 85% yield, 99% ee, 12/1 dr [b] 43% yield, 99% ee, 8/1 dr [a] 87% yield, 98% ee, 10/1 dr

[a] 83% yield, 93% ee, 7/1dr [a] 78% yield, 97% ee, 8/1 dr [a] 82% yield, 96% ee, 5/1 dr

Reaction conditions. [a] **5** (0.30 mmol, 1.0 eq), **6** (0.45 mmol, 1.5 eq), Cat. **4c** (10 mol%) and *N*-Boc-L-Trp (20 mol%) in $CHCl_3$ (C = 0.5 M) at 50 °C for 72 h. [b] Cat. **4c** (20 mol%) and *N*-Boc-L-Trp (40 mol%) in $CHCl_3$ (C = 0.5 M) at 50 °C for 72 h.



Scheme 1 Investigation of the heterocyclic moiety.



Scheme 2 Synthetic transformations of the spirocyclohexanone-rhodanines.

An investigation of possible variations at the heterocyclic moiety of the acceptor substrate was undertaken (Scheme 1). Using a 2-thioxoimidazolidin-4-one derivative (compound **8**), the tandem reaction turned out to be slow, while excellent enantioelectivity and diastereoselectivity (99% ee and >20 : 1 dr) remained. Surprisingly, the aza-Michael addition product (**11**) was observed using (*Z*)-ethyl 2-(2,4-dioxothiazolidin-5-ylidene)-acetate in 93% yield (see the ESI†).

Finally, we tried to demonstrate the synthetic transformation of these products. The rhodanine moiety was easily oxidized to 2-thioxoimidazolidin-4-one in 85% yield, using chromium trioxide as the oxidant. Furthermore, the carbonyl was easily converted to chiral alcohol by reduction with $NaBH_4$ (Scheme 2).

In summary, rhodanine derivatives **5** were successfully applied in cascade reactions for the construction of spiro-cyclohexanonerhodanines with multiple consecutive chiral centers catalyzed by a simple diamine, providing products in good yields and high stereoselectivities (up to 99% ee and >20 : 1 dr).

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