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Asymmetric Michael Addition of Substituted Rhodanines to α,β-Unsaturated Ketones Catalyzed by Bulky Primary Amines

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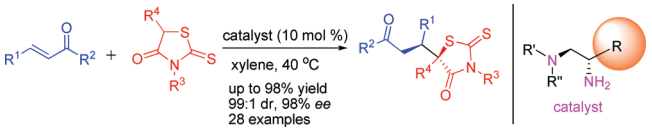
ABSTRACT



A bulky group was introduced by design into a diamine catalyst, and a series of robust and tunable bulky chiral primary amine catalysts were developed and successfully applied in the direct conjugate addition of substituted rhodanines to α,β-unsaturated ketones. High yields (up to 99%) and excellent diastereoselectivities (up to 99:1 dr) and enantioselectivities (up to 98% ee) were observed.

It has been discovered that five-membered rhodanines and structurally analogous scaffolds play an important role in medicinal chemistry and drug discovery, behaving as small molecule inhibitors of numerous targets because of their wide range of pharmacological activities. Several rhodanine derivatives have entered into clinical trials showing antibacterial, antiviral, antimalarial, and antitumor activities.[1] A schematic representation of the 5-arylidene rhodanine skeleton is provided in Scheme 1A. Epalrestat is one of the most well-known examples of a drug product containing a 5-arylidene rhodanine moiety, and the compound is currently commercially available for the treatment of diabetic neuropathy. A schematic representation of the corresponding nonconjugated structure, which contains a stereocenter at the 5-position of the heterocyclic system, is shown in Scheme 1B.[2] Rosiglitazone and pioglitazone are both derived from 4-thiazolidonedione and show great therapeutic effects in type 2 diabetes mellitus. A challenging problem for the nonconjugated rhodanines and analogous 4-thiazolidinone systems is the relative ease with which enolization can occur at the 5-position under physiological conditions, which makes the stereochemistry difficult to maintain at this position. Kawamatsu[3] and Oschkinat[2a] have successively demonstrated that the enantiomers of ciglitazone and 5-aryl-2-thioxo-4-thiazolidinones can easily racemize. Only one enantiomer, however, showed biological activity. We were intrigued by the challenges presented by these idiosyncratic defects and developed a great interest in the development of reliable and highly stereoselective methods for the synthesis of chiral rhodanine structures.[4]

Inspired by several excellent privileged ligands and catalysts containing large bulky groups, such as the bisoxazoline ligand with its bulky *tert*-butyl group (*t*-Bu-Box),[5] Jacobsen's thiourea catalysts with their *tert*-leucine amide

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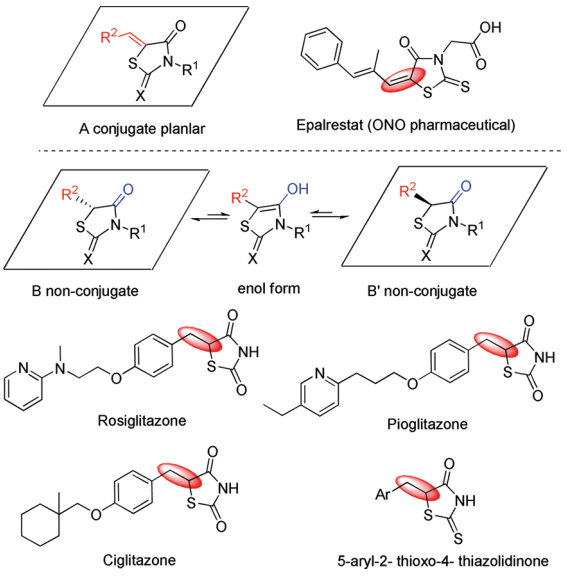
Scheme 1. Several Pharmaceutically Active Molecules That Contain the Fragments of Rhodanine and Thiazolidonedione Derivatives



structural motifs,[6] MacMillan's imidazolidinone with its *tert*-butyl group[7] and Jørgensen and Hayashi's diarylprolinol silyl ether catalyst,[8] we were interested in incorporating bulky groups into diamine catalysts. Furthermore, we were interested in integrating iminium activation, availability, and tunability. Frequently used diamines, such as 1,2-diaminocyclohexane and 1,2-diphenyl-ethylenediamine are rigid *trans*-diamines.[9] In recent years, 9-amino-9-deoxy-epi-cinchona alkaloids have emerged as one of the most successful primary amine catalysts.[10] However, it is very difficult to introduce bulky groups into all three of the backbones present within these systems to allow for the introduction of tunable reactivity and stereoselectivity.

Diamines derived from amino acids are attractive compounds for catalyst design because of the rich availability of the chiral amino acid starting materials.[11] We therefore prepared a series of diamines from L-valine (**1a**), L-phenylalanine (**1b**), L-*tert*-leucine (**1c**−**1f**), and D-serine (**1g**−**1i**).

A series of chiral primary amine catalysts were first applied in the conjugate addition of substituted rhodanine **3a** to benzalacetone. The results are summarized in Table 1. Catalysts **1a**−**c**, which contained a tertiary amine moiety derived from piperidine, clearly demonstrated behavior consistent with catalytic activity and produced some encouraging results. These catalysts provided the anticipated products in near complete conversion with excellent diastereomeric ratios. Interestingly, the enantioselectivity of the reaction was observed to be greatly dependent on the steric hindrance around the primary amine group (Table 1, entries 1−3, from 0 to 70%). In contrast to catalysts containing the piperidine moiety, the use of the more hindered diisopropylamine moiety, as in catalyst **1e**, destroyed the catalytic activity, and only trace conversion was observed (Table 1, entry 5). The use of the secondary diamine derived from cyclohexamine, as in catalysts **1f** and **1i**, also gave poor diastereoselectivity results (Table 1, entries 6 and 9). Pleasingly, replacement of the *tert*-butyl group with the more hindered methoxy-diphenylmethyl group led to significant improvements in the levels of enantioselectivity observed. For example, catalysts **1g** and **1h** provided the product with an enantioselectivity of 88% ee in both cases. At the same time, the diastereomeric ratios were maintained (dr 96:4), and moderate to good levels of conversion were observed in both cases (Table 1, entries 7 and 8). It is worthy of note that extended reaction times were needed to obtain a good levels of conversion. On the basis of these results, a 10 mol % loading of catalyst **1h** was selected for further screening. Several different reaction solvents were assessed, and dichloroethane (DCE), methyl *t*-butyl ether (MTBE), hexane, dioxane, and xylene were all found to be suitable for the model reaction. In contrast, the polar solvent *i*-PrOH did not provide good levels of stereoselectivity (Table 1, entry 15). Xylene was found to be the best solvent with an enantioselectivity of 96% ee and a diastereoselectivity of 99:1 dr (Table 1, entry 14). The addition of an acidic cocatalyst to the catalytic system also produced the same high level of stereoselectivity in the Michael product at a similar reaction rate (Table 1, entry 16), and the enantioselectivity was slightly lower when compared with the corresponding reaction performed without the acid.

Under the optimized reaction conditions, which included a 10 mol % loading of catalyst **1h** at 40 °C in xylene, the scope of the reaction between different α,β-unsaturated ketones **2** and rhodanine derivatives **3** was investigated (Table 2). A variety of different substituents and different positions of the aromatic rings on the enones were well

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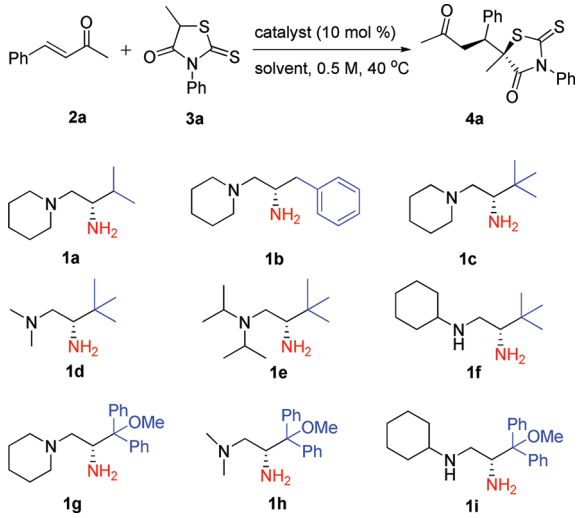
Table 1. Optimization of Reaction Parameters[a]

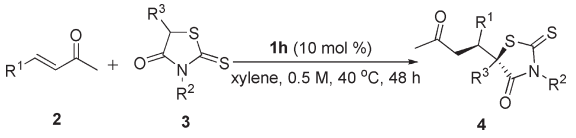


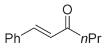
entry	cat	*t*/h	solvent	conv (%)[b]	dr[c]	ee (%)[d]
1	**1a**	24	$CHCl_3$	99	97:3	0
2	**1b**	24	$CHCl_3$	99	94:6	33
3	**1c**	24	$CHCl_3$	99	97:3	70
4[e]	**1d**	24	$CHCl_3$	99	97:3	68
5	**1e**	72	$CHCl_3$	trace		
6	**1f**	24	$CHCl_3$	99	65:35	56
7	**1g**	48	$CHCl_3$	62	96:4	88
8	**1h**	48	$CHCl_3$	82	96:4	88
9	**1i**	72	$CHCl_3$	42	76:24	77
10	**1h**	48	DCE	79	96:4	91
11	**1h**	48	MTBE	95	98:2	92
12	**1h**	48	hexane	90	96:4	93
13	**1h**	48	EtOAc	94	96:4	92
14	**1h**	48	xylene	96	>99:1	96
15	**1h**	48	*i*-PrOH	90	87:13	66
16[e]	**1h**	48	xylene	96	99:1	94

[a] Unless otherwise stated, all reactions were carried out using 1.0 equiv of **3a** (0.20 mmol), 2.0 equiv of **2a** (0.40 mmol), and 0.10 equiv of catalyst in 0.4 mL of solvent. [b] Conversion was determined by GC. [c] Diastereomeric ratios (dr) were determined by GC and confirmed by ^{1}H NMR of the crude reaction mixture. [d] Enantiomeric excess (ee) values were determined by chiral HPLC. [e] With 10 mol % addition of benzoic acid.

tolerated, furnishing the corresponding Michael addition products in good yields with excellent diastereo- and enantioselectivities (Table 2, entries 2−7). Slightly higher reaction activities were observed for the enones bearing electron-withdrawing groups (Table 2, entries 4−6) compared with those functionalized with electron-donating groups (Table 2, entries 2 and 3). Heterocyclic thiophene and furan enones also worked well without any loss in the diastereo- or enantioselectivities (Table 2, entries 8, 9). When aliphatic enones were employed, moderate yields and good ee values were obtained (Table 2, entries 10 and 11). It is worthy of note that the functionalized enone containing an alkenyl moiety reacted with **3a** in good yield and high diastereo- and enantioselectivity (Table 2, entry 12). This alkylated adduct is of great value because the C=C bond provides a good handle for further transformations and the generation of other useful functional groups.

Table 2. Scope of Direct Conjugate Addition of Various α,β-Unsaturated Ketones[a]



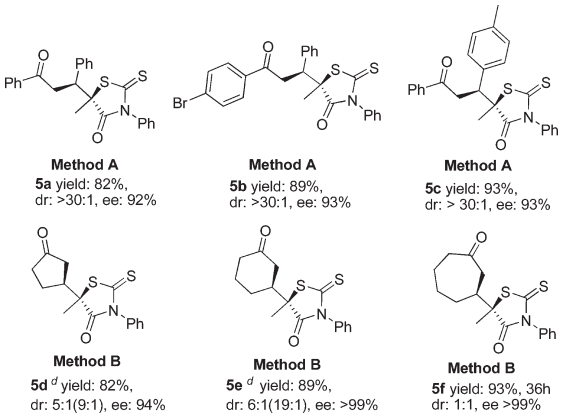
entry	cat.	R_1	R_2	R_3	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	Ph	Ph	Me	95(**4a**)	99:1	96
2[h]	**1b**	*p*-CH_3Ph	Ph	Me	75(**4b**)	97:3	93
3[h]	**1c**	*m*-CH_3OPh	Ph	Me	81(**4c**)	99:1	94
4	**1d**	*m*-BrPh	Ph	Me	92(**4d**)	99:1	93
5	**1e**	*p*-Cl Ph	Ph	Me	95(**4e**)	99:1	96
6[f]	**1f**	*o*-NO_2Ph	Ph	Me	89(**4f**)	99:1	95
7	**1g**	Nap	Ph	Me	93(**4g**)	98:2	91
8	**1h**	2-thiophenyl	Ph	Me	96(**4h**)	97:3	98
9	**1i**	2-furanyl	Ph	Me	84(**4i**)	99:1	95
10[e,h]	**1h**	CH_3	Ph	Me	64(**4j**)	95:5	80
11[e,h]	**1h**	$PhCH_2CH_2$	Ph	Me	60(**4k**)	97:3	87
12[g]	**1h**	*E*-PhCH=CH	Ph	Me	83(**4l**)	93:7	96
13	**1h**	Ph	*i*-Pr	Me	97(**4m**)	99:1	90
14	**1h**	Ph	Bn	Me	94(**4n**)	98:2	95
15	**1h**	Ph	*p*-MeOPh	Me	98(**4o**)	99:1	96
16[e]	**1h**	*p*-ClPh	Bn	Me	97(**4p**)	97:3	95
17	**1h**	*p*-BrPh	*p*-MeOPh	Me	96(**4q**)	99:1	95
18[e]	**1h**		Ph	Me	82(**4r**)	99:1	95
19	**1h**	Ph	Ph	Et	91(**4s**)	98:2	97
20	**1h**	Nap	Ph	Et	96(**4t**)	99:1	91
21	**1h**	*p*-NO_2 Ph	Ph	Et	98(**4u**)	97:3	92
22[e,h]	**1h**	Ph	Ph	*i*-Pr	68(**4v**)	93:7	71

[a] All reactions were carried out using 1.0 equiv of 3 (0.20 mmol), 2.0 equiv of α,β-unsaturated ketone **2** (0.40 mmol), and 0.10 equiv of the catalyst **1h** in xylene (0.4 mL). [b] Isolated yield. [c] Determined by GC and confirmed by ^{1}H NMR of the crude reaction mixture. [d] Determined by chiral HPLC. [e] Catalyst loading of 20 mol %. [f] Reaction time:24 h. [g] Reaction time:72 h. [h] Reaction time:96 h.

Other nucleophiles bearing different R^2 group, including *i*-Pr, Bn, and *p*-methoxyphenyl were also compatible with the reaction conditions (Table 2, entries 13−17). Increasing the steric hindrance of the enone group by introducing an *n*-propyl group adjacent to the carbonyl carbon led to a reduction in activity, although a good yield and high diastereo- and enantioselectivities were still obtained with a 20 mol % loading of catalyst **1h** (Table 2, entry 18). The results obtained for the ethyl-substituted rhodanine **3e** were excellent (Table 2, entries 19−21). When a rhodanine substrate with a branched alkyl chain (*i*-Pr) was used, a slower rate of reaction was observed, and a moderate enantioselectivity (71% ee) with a good diastereoselectivity (dr 93:7) was obtained when a 20 mol % loading of catalyst was used (Table 2, entry 22).

To further expand the scope of the process, other types of α,β-unsaturated ketones were investigated for the Michael reaction with **3a** (Scheme 2). The more sterically hindered chalcone led to a sluggish reaction under the optimized reaction conditions, and it was speculated that the rate of formation of the iminium intermediate with catalyst **1h** was reduced by the steric interaction occurring between the bulky methoxy-diphenylmethyl group of catalyst and the phenyl group of chalcone. Therefore, we switched our attention back to the diamine catalyst derived from L-*tert*-leucine, which contained the less hindered

Scheme 2. Scope of Direct Michael Reation of Chalcones and Cyclic Enones[a,b,c]



[a] Experimental condition: 1.0 equiv of **3a** (0.20 mmol) and 2.0 equiv of α,β-unsaturated ketone (0.40 mmol) in xylene (0.40 mL). [b] Diastereomeric ratios (dr) were determined by GC and confirmed by ^{1}H NMR of the crude reaction mixture. [c] Enantiomeric excess (ee) values were determined by chiral HPLC. [d] The dr values in parentheses were obtained after silica gel chromatography. Method A: 20 mol % catalyst **1c** with 20 mol % Boc-L-*tert* -leucine, 40 °C; Method B: 10 mol % catalyst **1f** with 10 mol % Boc-L-*tert*-leucine, 0 °C.

tert-butyl group. Fortunately, catalyst **1c** promoted the reaction dramatically, and the addition product **5a** was obtained in good yield with a high level of stereocontrol (dr 30:1, 93% ee). Furthermore, it was observed that the addition of a suitable acid facilitated the formation of the iminium ion. Several differentially substituted chalcones were well tolerated by the catalytic system, and high yields and excellent diastereo- and enantioselectivities were achieved (Scheme 2; **5b** and **5c**). The cyclic enones effectively containing *Z*-alkenes showed different behavior from the acyclic enones, which effectively contained *E*-alkenes, and the tertiary diamine catalyst **1c** provided poor results. Pleasingly, the secondary diamine catalyst **1f** performed much more effectively when used in conjunction with an additional proper organic acid in a 1:1 ratio (10 mol %) (Scheme 2, **5d**−**f**). The reactions proceeded smoothly at 0 °C to give the corresponding products with satisfying results in terms of efficiency and enantioselectivity. The diastereoselectivities varied from 1:1 to 6:1 for different cyclic enones. The absolute configuration of the asymmetric Michael addition products **4a** and **5e** were determined by X-ray crystallographic analysis (see the Supporting Information).

The Michael reaction between the substituted rhodanines and various α,β-unsaturated ketones has been developed with satisfactory results, and the chiral center at the C-5 position of the heterocycle was successfully constructed in a highly efficient and stereoselective manner. Further efforts to demonstrate the utility of the current method were carried out (Scheme 3). The 4-thiazolidonedione core has also been

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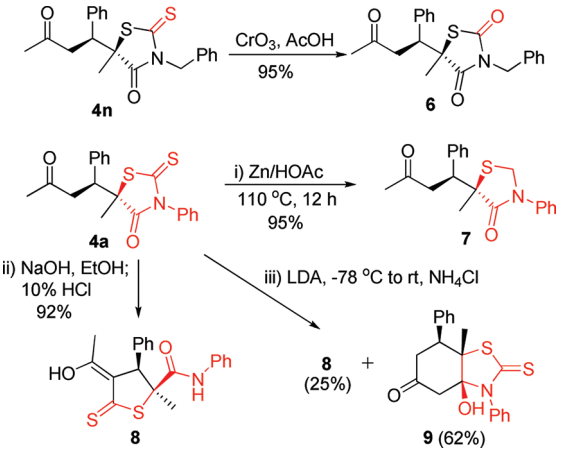
Scheme 3. Derivatization of the Michael Addition Product



recognized as a privileged scaffold for drug discovery.[1a] The reaction between the 4-thiazolidonedione substrate and benzalacetone was slow under the optimized reaction conditions, whereas compound **6** was easily obtained in a high yield of 95% following oxidization of the corresponding rhodanine product **4n** with CrO_3 in acetic acid.[12] This also provided an effective and indirect method to access the chiral 4-thiazolidone core compounds. Thus, the thiocarbonyl group of **4a** could be effectively reduced by zinc dust in acetic acid, affording the compound **7** containing the chiral skeleton of thiazolidinone.[13] The substituted tetrahydrothiophene **8** was obtained in 92% yield following treatment of **4a** with aqueous basic NaOH through thermodynamic control of enolization.[14] Interestingly, when **4a** was treated with the strong base LDA at −78 °C, a fused heterocyclic product **9** bearing two adjacent quaternary stereocenters was obtained in 62% yield by means of a kinetically controlled enolization. Crystals of the products **8** and **9** were subjected to X-ray analysis to determine the absolute configuration.

In conclusion, a strategy of steric hindrance has been successfully applied to the design of a series of novel chiral diamines from amino acids, and a series of robust and tunable bulky chiral primary amine catalysts have been developed and applied in the direct diastereo- and enantioselective Michael addition of substituted rhodanines to α,β-unsaturated ketones. The reactions proceeded well, and a variety of different enones were well tolerated, providing access to a wide range of enantioenriched rhodanine derivatives, which were proven to be valuable scaffolds in biochemistry and medicinal chemistry.

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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms of the products and CIF files demonstrating the enantiopurity. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.