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Organocatalytic enantioselective transient enolate protonation in conjugate addition of thioacetic acid to α-substituted *N*-acryloyloxazolidinones

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ABSTRACT

Organocatalytic conjugate addition of thioacetic acid to a series of α-substituted *N*-acryloyloxazolidin-2-ones followed by enantioselective protonation has been studied in the presence of thiourea catalysts derived from cinchona alkaloids. Conjugate addition/protonation adducts have been obtained up to 97% ee and high yields. The methodology could serve as an easy and practical route to the syntheses of useful biologically active molecules.

Optically active molecules having tertiary carbon stereocenter are extremely common structural motif in valuable biologically active natural products and pharmaceutical agents.[1] Enantioselective protonation of a prostereogenic enolate derivative has been shown to be a convenient and practical method for the preparation of enantiomerically enriched carbonyl compounds having a tertiary asymmetric carbon at the α-position.[2] The importance of such building blocks in biology and organic synthesis makes it a worthwhile goal to achieve. Several strategies have emerged for enantioselective protonation by exploiting various means of enantiocontrol through different mechanisms. The earlier methods were based on the protonation of lithium enolates in the presence of an excess of chiral proton source.[3] Recent approaches involve the catalytic protonation of pre-formed enolates.[4] An attractive alternative is the generation of a transient enolate involving conjugated addition reaction of a nucleophile to an α-substituted α,β-unsaturated carbonyl compound followed by an in situ enantioselective protonation of the resulting transient enolate which enables the installation of different functional groups at the β-position.[5] In particular, such molecules containing sulfur functional group are integral part of many drug molecules and important intermediates for the syntheses of physiologically active natural products.[6] Therefore, a great deal of recent interest has been focused to prepare and manipulate chiral organosulfur species with chirality residing at sulfur, at carbon, or at both. Asymmetric sulfa-Michael addition has gained a lot of interest for the construction of carbon–sulfur bond due to the availability of diversity of electrophilic and nucleophilic partners. Much of these studies have been directed to asymmetric sulfa-Michael addition of different sulfur centered nucleophiles to β-substituted activated olefins.[7] Despite considerable advance in this field, the scope of sulfa-Michael addition to α-substituted acrylates followed by enantioselective protonation reactions is reasonably narrow.[8] Specifically, the catalytic conjugate addition of thioacids to a range of α-substituted Michael acceptors has not been utilized yet. Although, quite efficient enantioselective protonation in conjugate addition of thioacids to methacryloyl substrate with chiral auxiliary is reported, the substrate scope for this reaction is relatively low.[9]

The catalytic conjugate addition of thioacids to α-substituted acrylates is highly desirable because the resulting thioesters could easily be hydrolyzed in mild conditions to give synthetically and therapeutically useful compounds having free mercapto group. Therefore, further advances toward the development of organocatalytic processes capable of promoting high level of asymmetric induction with substrate generality remain to be accomplished.

Cinchona alkaloid derived thiourea catalysts, in particular, have been found very efficient for several enantioselective transformations.[10] In our previous report on asymmetric protonation in sulfa-Michael addition of thiols, we have found that quinine derived thiourea **1a** was an efficient bifunctional catalyst for the reaction (Scheme 1).[11] Also α-substituted *N*-acryloyloxazolidinone was found to be an excellent acyclic template for asymmetric protonation in conjugate addition of thiols[11] and malonates.[5i] We have envisioned that the replacement of thiol with thioacid as a

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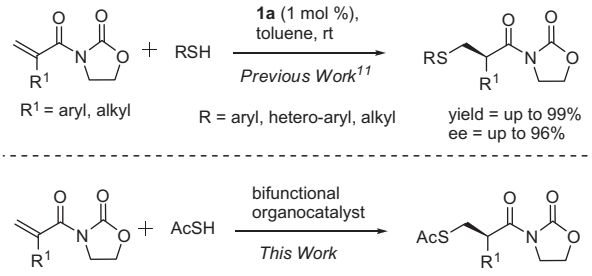
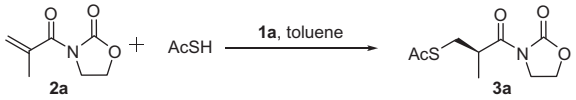


Scheme 1. Asymmetric protonation in conjugate addition of sulfa-Michael addition to α-substituted acrylate derivatives.

nucleophile would work in a similar fashion in the conjugate addition to α-substituted acrylate derivatives in the catalytic influence of *cinchona* alkaloid derived thiourea (Scheme 1) and, if successful, would be an excellent and easy route to the synthesis of biologically active captopril and cysteine derivatives. Very few catalytic literature reports for the preparation of such valuable scaffold with high enantiopurity are available to date.[12] Here, we wish to demonstrate a catalytic enantioselective transient enolate protonation in the conjugate addition of thioacetic acid to α-substituted *N*-acryloyloxazolidinones with bifunctional organocatalyst derived from *cinchona* alkaloid.

Initial attempts were made to test our hypothesis by carrying out the conjugate addition of thioacetic acid to *N*-methacryloyloxazolidinone, an excellent template for asymmetric protonation found previously, in the catalytic influence of quinine derived thiourea **1a** (10 mol %). We were pleased to find that the product was obtained in excellent yield and impressive enantioselectivity (Table 1, entry 1). Lowering the reaction temperature to 0 °C led to an increase in enantioselectivity to some extent (Table 1, entry 2). However, further lowering of temperature resulted in lower chemical yield and enantioselectivity of the reaction (Table 1, entries 3 and 4). Thus, to improve the asymmetric induction, further optimization studies were conducted by keeping the reaction temperature constant at 0 °C.

Table 1
Optimization of reaction conditions[a]



Entry	**1a** Mol %	Temp (°C)	Time (d)	Yield (%)	ee[b] (%)
1	10	rt	1	98	59
2	10	0	2	98	67
3	10	−5	2	90	63
4	10	−20	2	75	51
5	5	0	3	98	72
6	2	0	3	95	77
7	1	0	3	90	78
8	0.5	0	3	82	80
9	0.1	0	3	80	77
10[c]	0.5	0	3	77	77
11[d]	0.5	0	3	90	82
12[e]	0.5	0	3	96	78
13[f]	0.5	0	3	99	75
14[g]	0.5	0	3	99	69

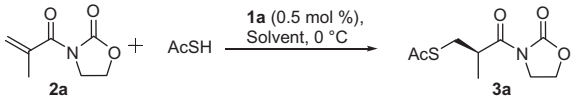
[a] All reactions were carried out on 0.2 mmol of **2a** and 0.24 mmol of thioacetic acid in 1 mL toluene, unless noted otherwise.
[b] Determined by HPLC using chiral column.
[c] 0.2 mmol of thioacetic acid.
[d] 0.3 mmol of thioacetic acid.
[e] 0.4 mmol of thioacetic acid.
[f] 0.6 mmol of thioacetic acid.
[g] 0.8 mmol of thioacetic acid.

We were delighted to observe that the enantioselectivity of the reaction increased to a greater extent when the catalyst loading was decreased from 10 to 0.5 mol % (Table 1, entry 8). However, further lowering of the catalyst loading to 0.1 mol % causes a slight decrease in enantioselectivity. It has been found that 1.5 equiv of thioacetic acid was optimum in terms of both yield and enantioselectivity (Table 1, entry 11). Subsequently, the influence of the solvent on the stereochemical outcome of the reaction was examined. Less polar solvents proved to be more effective. Among several less polar solvents screened, toluene was found to be the best and the product was obtained in 84% ee (Table 2, entry 16).

After initial optimization of the reaction conditions with catalyst **1a**, various *cinchona* alkaloid derived (thio) urea catalysts (Fig. 1) were employed in the above reaction, and the results are summarized in Table 3. Intensive screening of catalysts disclosed the significant impact of the substituent and catalyst's chiral scaffold on the enantioselectivity. Thiourea catalysts were found to be more efficient over corresponding urea derivatives having same chiral environment (Table 3, entries 1–4). Very low enantioselectivity with *epi-quinine* derived catalyst **1e** emphasizes the importance of the correct relative orientation of thiourea and quinuclidine functional groups in the catalyst's chiral scaffold (Table 3, entry 5). It is interesting to note that the antipode of **3a** was obtained up to 87% ee when pseudoenantiomeric catalysts **1f–g** were used, as per our expectation (Table 3, entries 6 and 7). To our delight, catalyst **1h** derived from cinchonidine afforded products with 90% ee (Table 3, entries 8 and 10). However, when 6′-*cinchona* thiourea **1i** was used for the reaction, poor enantioselectivity was observed (Table 3, entry 9). Replacing thioacetic acid with thiobenzoic acid as a nucleophile, it was noticed that the corresponding addition/protonation product **3aa** was afforded only in moderate enantioselectivity (Table 3, entry 11).

In search for a suitable prochiral template, several methacryloyl derivatives **2b–d** were tested under the optimized conditions and

Table 2
Solvent screening[a]



Entry	Solvent	Time (d)	Yield (%)	ee[b] (%)
1	Toluene	3	90	82
2	*m*-Xylene	3	96	77
3	*o*-Xylene	3	92	71
4	Mesitylene	3	95	74
5	*n*-Hexane	3	72	37
6	CH_3CN	3	66	27
7	DMF	3	96	0
8	THF	3	65	53
9	Et_2O	3	95	65
10	CH_2Cl_2	3	79	51
11	$CHCl_3$	3	85	53
12	DCE	3	78	67
13[c]	1,4-Dioxane	1	74	9
14[c]	*p*-Xylene	1	98	78
15[c]	Benzene	1	85	75
16[d]	Toluene	3	86	84
17[e]	Toluene	3	73	82
18[f]	Toluene	3	91	79
19[g]	Toluene	3	95	71

[a] All reactions were carried out on 0.2 mmol of **2a** and 0.3 mmol of thioacetic acid in 1 mL solvent, unless noted otherwise.
[b] Determined by HPLC using Chiralpak IA3 column.
[c] At room temperature.
[d] In 1.5 mL toluene.
[e] In 2 mL toluene.
[f] In 0.5 mL toluene.
[g] In 250 μL toluene.

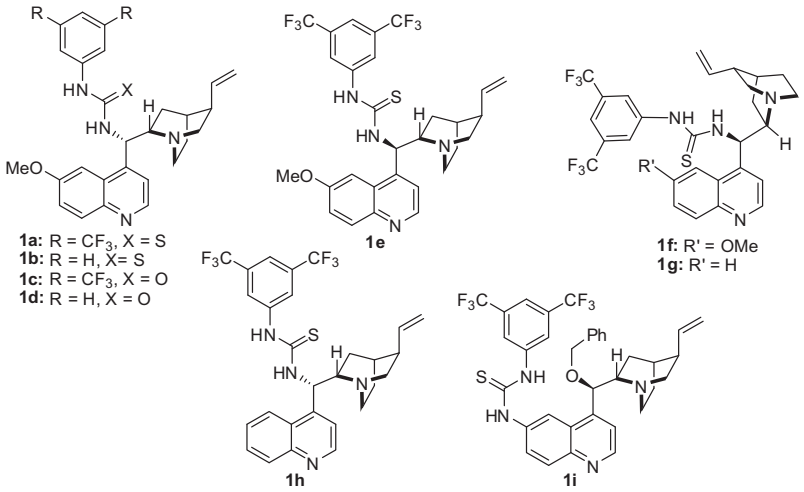
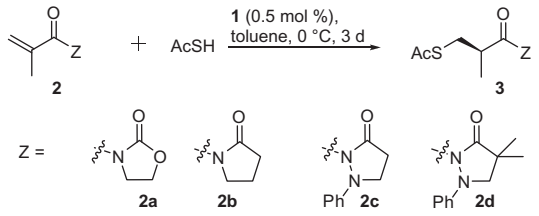


Figure 1. *Cinchona* alkaloid derived (thio) urea catalysts.

Table 3
Screening of different chiral catalysts and prochiral templates[a]



Entry	Catalyst	2	Yield (%)	ee[b] (%)
1	**1a**	**2a**	86	84
2	**1b**	**2a**	74	77
3	**1c**	**2a**	79	67
4	**1d**	**2a**	75	46
5	**1e**	**2a**	78	7
6	**1f**	**2a**	75	77
7	**1g**	**2a**	73	87
8	**1h**	**2a**	84	90
9	**1i**	**2a**	78	11
10[c]	**1h**	**2a**	92	90
11[d]	**1h**	**2a**	98	53
12[c]	**1h**	**2b**	88	69
13[c]	**1h**	**2c**	80	14
14[c]	**1h**	**2d**	99	50

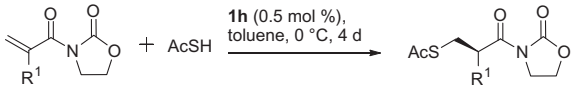
[a] All reactions were carried out on 0.2 mmol of **2** and 0.3 mmol of thioacetic acid in 1.5 mL of toluene, unless noted otherwise.
[b] Determined by HPLC using chiral column.
[c] 4 days.
[d] Thiobenzoic acid as nucleophile.

it was found that *N*-methacryloyloxazolidinone eventually came out as an efficient template (Table 3, entries 12–14).

Having identified the optimized reaction conditions, a series of α-substituted *N*-acryloyloxazolidinones were investigated in the conjugate addition with thioacetic acid. Most of the substrates underwent the reaction smoothly and the corresponding products were obtained in excellent yields and enantioselectivities (Table 4). The aliphatic substituted templates as Michael acceptors furnished excellent enantioselectivities in general (Table 4, entries 1–3). We were delighted to observe that the products with aryl substitution were also obtained in high to excellent enantiopurity with high yields (Table 4, entries 4–13). The electronic nature of the substitution at the aromatic ring of the Michael acceptors had no effect as such on yield and enantioselectivities (Table 4, entries 4–13). Interestingly, 2-(*o*-methoxyphenyl) acryloyloxazolidin-2-one **2m** furnished the corresponding product in 97% ee (Table 4, entry 10). However, α-substituted *N*-acryloyloxazolidinones having naphthyl group had a considerable impact on the enantioselectivities. The addition/protonation adducts containing 2-naphthyl derivatives were formed in moderate ees (Table 4, entries 14 and 16). On the other hand, 1-naphthyl substituted Michael acceptor afforded product with excellent enantioselectivity (97% ee, Table 4, entry 15). It is important to note that, due to their crystalline nature, a few of the products were recrystallized from dichloromethane and hexane to achieve up to 99.9% ee (Table 4, entries 4, 7–10, and 14)

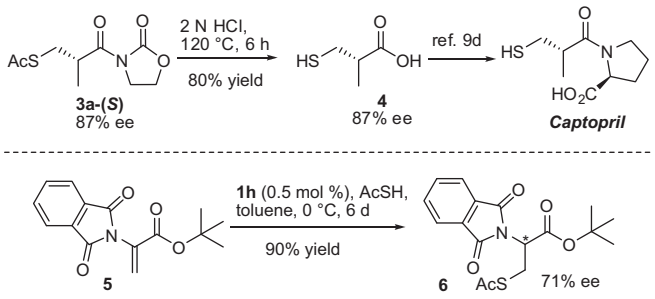
Finally, the synthetic potential of the protonated adduct was studied. The adduct **3a**-(***S***) was readily converted into (*S*)-3-mercapto-2-methylpropanoic acid **4** in high yield without the loss of optical purity. It could be transformed to orally active angiotensin-converting enzyme inhibitor captopril, which is widely pre-

Table 4
Substrate scope of conjugate addition followed by enantioselective protonation[a]



Entry	R^1	3	Yield (%)	ee[b] (%)
1	Me (**2a**)	**3a**	92	90
2	^{n}Bu (**2e**)	**3e**	82	90
3	$PhCH_2$ (**2f**)	**3f**	98	90
4[c]	Ph (**2g**)	**3g**	98 (47)	86 (99)
5	4-F-C_6H_4 (**2h**)	**3h**	99	85
6	4-Cl-C_6H_4 (**2i**)	**3i**	95	84
7	4-Me-C_6H_4 (**2j**)	**3j**	98 (50)	86 (98)
8	3-Me-C_6H_4 (**2k**)	**3k**	99 (56)	90 (99)
9	4-MeO-C_6H_4 (**2l**)	**3l**	97 (56)	86 (97)
10	2-MeO-C_6H_4 (**2m**)	**3m**	99 (76)	97 (99.9)
11	4-^{n}Bu-C_6H_4 (**2n**)	**3n**	93	85
12	4-^{t}Bu-C_6H_4 (**2o**)	**3o**	92	85
13	4-^{i}Bu-C_6H_4 (**2p**)	**3p**	96	90
14	2-Naphthyl (**2q**)	**3q**	95 (25)	75 (97)
15	1-Naphthyl (**2r**)	**3r**	98	97
16	2-(6-MeO-naphthyl) (**2s**)	**3s**	94	75

[a] All reactions were carried out on 0.2 mmol of **2** and 0.3 mmol of thioacetic acid in 1.5 mL of toluene, unless noted otherwise.
[b] Determined by HPLC using chiral column and data in the parenthesis were obtained after recrystallization.
[c] Absolute configuration of **3g** was determined to be (*R*) by single crystal X-ray analysis.



Scheme 2. Applications of the addition/protonation products.

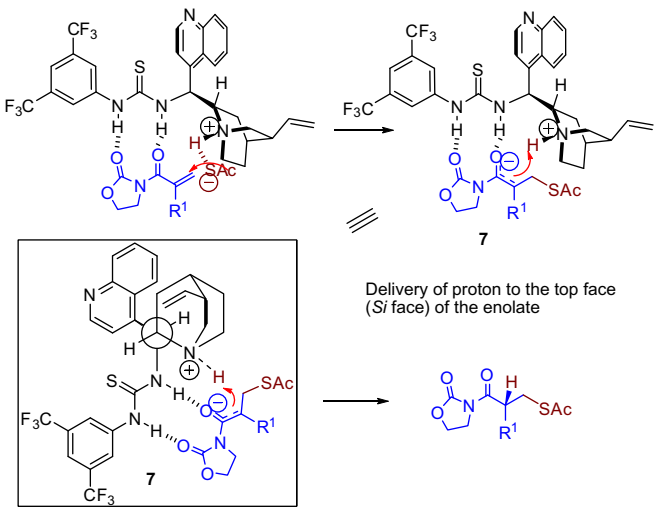


Figure 2. Possible transition state model.

scribed for the treatment of hypertension (Scheme 2).[9d] Reaction between 2-phthalimidoacrylate derivative **5** and thioacetic acid under optimized conditions yielded the corresponding product **6** in good enantiomeric excess (71% ee) enabling a direct access to enantioenriched cysteine derivative (Scheme 2).

A plausible transition state model to explain the high stereochemical outcome of the reaction is shown in Figure 2. We believe that the bifunctional catalyst simultaneously activates thioacetic acid through acid–base interaction and Michael acceptor **2** via double H-bondings. Initial conjugate addition of nucleophile to **2** generates a transient ion pair **7**. Subsequent delivery of the proton from the quinuclidine nitrogen to the top face (*Si* face) of the generated prochiral enolate leads to the formation of the major stereoisomer (Fig. 2).

In conclusion, we have developed an effective catalytic conjugate addition of thioacetic acid to a range of α-substituted *N*-acryloyloxazolidin-2-ones **2** followed by enantioselective protonation using thiourea catalyst **1h** derived from *cinchona* alkaloid. This approach offers several advantages such as operational simplicity, low catalyst loading (0.5 mol %), and the products were obtained in high to excellent enantioselectivities (up to 97% ee) with almost quantitative yields. It is noteworthy that both enantiomers of addition/protonation products could be obtained with the same level of enantioselectivities. The synthetic utility of the present catalytic asymmetric protonation reaction was established by transforming the products to useful intermediates of biological importance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.004.

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