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Enantioselective Enolate Protonation in Sulfa–Michael Addition to α-Substituted *N*-Acryloyloxazolidin-2-ones with Bifunctional Organocatalyst

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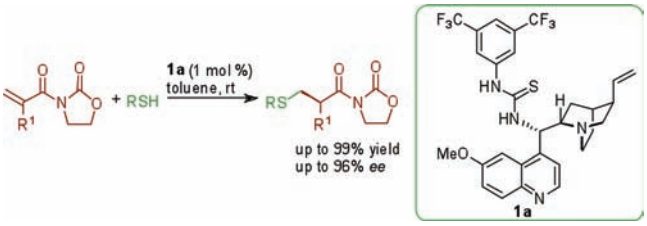
ABSTRACT



Organocatalytic conjugate addition of thiols to α-substituted *N*-acryloyloxazolidin-2-ones followed by asymmetric protonation has been studied in the presence of *cinchona* alkaloid derived thioureas. Both of the enantiomers are accessible with the same level of enantioselectivity using pseudoenantiomeric quinine/quinidine derived catalysts. The addition/protonation products have been converted to useful biologically active molecules.

Enantioselective protonation of a prostereogenic enol(ate) derivative is a fundamental concept and has been shown to be a powerful practical method for the preparation of enantiomerically enriched carbonyl compounds which possess a tertiary asymmetric carbon at the α-position.[1] Tertiary carbon stereocenters are extremely common structural motifs in valuable biologically active natural products and pharmaceutical agents.[2] The creation of a stereogenic center by the formation of a C–H bond using enantioselective transfer of a proton to an enolate intermediate remains a worthwhile goal. A number of chemical methods exist for enantioselective protonation by exploring various means of enantiocontrol in different mechanisms. The majority of work in this area has been directed toward the use of isolated enolate precursors, such as silyl enol ethers,[3] and a stoichiometric amount of chiral proton sources.[4] Enol ethers (or enolate) derived from α-substituted cyclic ketones have been widely investigated. However, the employment of preformed acyclic enolate derivatives for this reaction are sparse.[5] An attractive alternative is the generation of a transient enolate by the conjugate addition of a nucleophile to an α-substituted

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α,β-unsaturated carbonyl compound followed by an *in situ* enantioselective protonation of the resulting transient enolate.[6] In particular, the Michael addition of thiols to α-substituted acrylates followed by enantioselective protonation has been a challenging target.[7] Sulfur-containing chiral frameworks are useful building blocks in many naturally occurring compounds and therapeutically active molecules.[8] Implication of a sulfur functional group in synthetic organic chemistry is extremely high because it can be selectively removed or subjected to late stage transformations.[7c] *Cinchona* derivatives have recently emerged as efficient organocatalysts for different reactions.[9] Quite efficient catalytic asymmetric sulfa-Michael addition reactions using a *cinchona* alkaloid derived catalyst have been achieved.[10] In contrast, the organocatalytic asymmetric protonation *via* sulfa-Michael addition has not yet been achieved to a synthetically useful level.[11] The success in enantioselective protonation of a transient acyclic enolate solely depends on rotamer control of the enolate configuration.[12] Thus, the appropriate choice of a prochiral template and chiral catalyst is important. Here, we report an effective catalytic sulfa-Michael addition to α-substituted *N*-acryloyloxazolidin-2-ones followed by enantioselective protonation by using *cinchona* alkaloid derived thioureas.

Our initial studies began to identify the combination of prochiral template and chiral catalyst that could provide high reactivity and selectivity in sulfa-Michael addition/protonation to α-methyl acrylate acceptors. After screening different prochiral templates for the reaction using **1a** as a catalyst, 3-methacryloyloxazolidin-2-one **2b** was found to be the best in terms of selectivity. Therefore, further optimization was carried out using **2b** as a model template. Several reaction parameters were examined to improve the selectivity, and it was found that **2b** gave a promising enantioselectivity (85% *ee*) and excellent yield (99%) with catalyst **1a** (1 mol %) in toluene at rt.[13]

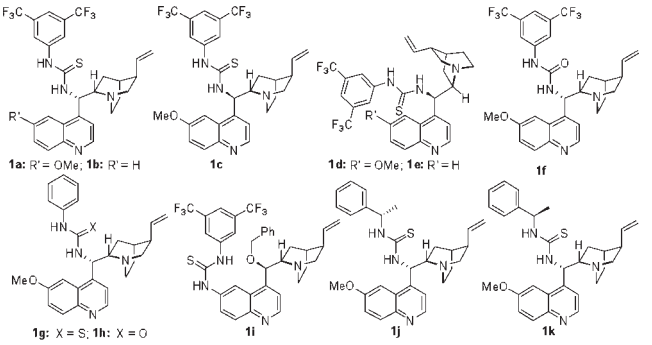

Figure 1. Cinchona alkaloid derived thiourea catalysts.

After initial optimization of the reaction conditions with **1a**, various *cinchona* alkaloid derived thiourea catalysts (Figure 1) were screened in the above reaction, and the results are summarized in Table 1. The enantioselectivities varied greatly depending on the organocatalysts used. Moderate enantioselectivity with catalysts **1c** emphasizes the importance of the correct relative orientation of thiourea and quinuclidine functional groups in the catalyst's chiral scaffold (Table 1, entry 3). Sulfa-Michael addition/protonation product **3b**, enriched in the opposite enantiomer, was obtained with catalyst **1d**–**e** (Table 1, entries 4 and 5). Thus, access to both enantiomers was found to be possible with the same level of enantioselectivity. The thiourea catalyst **1a** was found to be superior over the corresponding urea **1f**. The moderate enantiomeric excess with catalysts **1g**–**h** clearly indicates that the CF_3 substituent on the aromatic ring is crucial for high ee. When 6′-*cinchona* thiourea **1i** was used for the reaction, a low *ee* was observed. The result indicates that the appropriate distance between acidic and basic groups is important for a high *ee*. Catalysts **1j**–**k** having an additional chiral center were also tested in the above reaction, but poor enantioselectivities were observed. Mixing the racemic **3b** in optimum reaction conditions did not show any *ee* even after 24 h, suggesting that the kinetic control is probably responsible for the observed results.[14] Next, we tried to recover the catalyst. Yet, it was unsucessful for such a small scale reaction.

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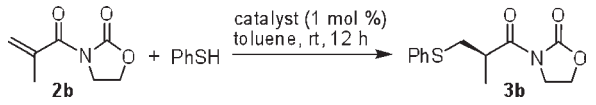
(13) For details, see Supporting Information.

(14) A control experiment was performed according to a reviewer's comment. We thank the reviewer for his valuable suggestion.

Table 1. Screening of Different Chiral Catalysts[a]



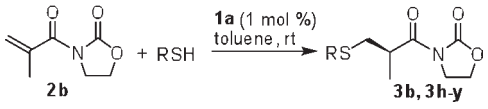
entry	catalyst	yield (%)	ee (%)[b]
1[c]	**1a**	99	85
2	**1b**	97	83
3	**1c**	95	70
4[d]	**1d**	99	84
5[d]	**1e**	97	83
6	**1f**	93	63
7	**1g**	90	50
8	**1h**	97	42
9	**1i**	98	30
10	**1j**	96	20
11	**1k**	96	36

[a] Reactions were carried out on 0.2 mmol of **2b** and 0.24 mmol of thiophenol in 1 mL of toluene with 0.002 mmol of catalyst **1** at rt, unless noted otherwise. [b] Determined by HPLC using a chiral column. [c] Absolute stereochemistry was determined to be (*R*). [d] Opposite enantiomer as major was obtained.

Having identified the optimized conditions for this reaction, a variety of thiols were then tested by using **2b** as a Michael acceptor (Table 2). Next, we investigated the scalability of the reaction. A 10-fold increase in the scale resulted in comparable yields and enantioselectivity (Table 2, entry 2). Then we conducted the reaction of **2b** with a variety of thiols. Good to high enantioselectivities were obtained in almost all the cases. It is noteworthy that the electronic nature and the steric hindrances of the substituents on the aromatic ring of thiols have little effect on the enantioselectivity. Less reactive aliphatic thiols were also employed for this reaction, and high *ee*'s were achieved in all the cases (Table 2, entries 16–19). Yet, a longer reaction time was required for the completion of the reaction. A heteroaromatic thiol, namely 2-pyrimidine thiol, was reacted smoothly with **2b** and furnished the product **3y** with 82% *ee* (Table 2, entry 20).

To extend the scope of the reaction, Michael addition/protonation of thiophenol with structurally different α-substituted *N*-acryloyl oxazolidinones (**4a**–**n**) were studied. Useful enantioselectivities were achieved with a wide variety of substituents (Table 3). The electronic nature of the substituent on the aromatic ring of Michael acceptors has little effect on the product *ee* (Table 3, entries 7–9).

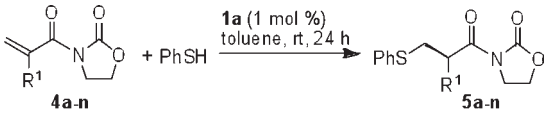
Table 2. Conjugate Addition of Different Thiols to Prochiral Template **2b** Followed by Enantioselective Protonation[a]



entry	R	time (h)	product	yield (%)	ee[b] (%)
1	Ph	12	**3b**	99	85
2[c]	Ph	12	**3b**	97	81
3	4-MeO-C_6H_4	12	**3h**	95	78
4	2-MeO-C_6H_4	12	**3i**	94	76
5	4-Me-C_6H_4	12	**3j**	96	80
6	2-Me-C_6H_4	12	**3k**	94	81
7	4-^{t}Bu-C_6H_4	12	**3l**	98	86
8	4-F-C_6H_4	9	**3m**	99	80
9	2-F-C_6H_4	10	**3n**	99	73
10	4-Cl-C_6H_4	9	**3o**	99	76
11	2-Cl-C_6H_4	10	**3p**	99	70
12	4-Br-C_6H_4	12	**3q**	98	84
13	2-Naphthyl	14	**3r**	97	83
14	2-Et-C_6H_4	14	**3s**	94	85
15	2-H_2N-C_6H_4	8	**3t**	98	65
16[d]	$PhCH_2$	72	**3u**	94	82
17[d]	4-^{t}Bu-$C_6H_4CH_2$	72	**3v**	92	79
18[d]	4-MeO-$C_6H_4CH_2$	72	**3w**	85	89
19[d]	furfuryl	72	**3x**	86	90
20	2-pyrimidine	18	**3y**	98	82

[a] Reactions were carried out on a 0.2 mmol scale with 0.24 mmol of thiol in 1 mL of toluene at rt, unless noted otherwise. [b] Determined by HPLC using chiral column. [c] Reaction was carried out on a 2 mmol scale. [d] 3 equiv of thiol were used.

Table 3. Conjugate Addition of Thiol to Different α-Substituted *N*-Acryloyl Oxazolidinones Followed by Enantioselective Protonation[a]

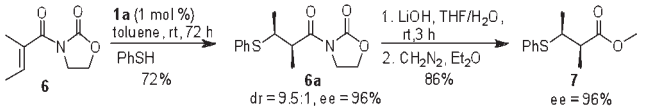


entry	R^1 **4**	product	yield (%)	ee[b] (%)
1	Ph **4a**	**5a**	99	88
2[c]	Ph **4a**	**5a′**	98	87
3	4-Cl-C_6H_4 **4b**	**5b**	99	73
4	4-F-C_6H_4 **4c**	**5c**	99	82
5	4-MeO-C_6H_4 **4d**	**5d**	97	77
6	3-MeO-C_6H_4 **4e**	**5e**	97	80
7	2-MeO-C_6H_4 **4f**	**5f**	98	96
8[d]	2-MeO-C_6H_4 **4f**	**5f′**	98	94
9[e]	2-MeO-C_6H_4 **4f**	**5f″**	82	95
10	4-Me-C_6H_4 **4g**	**5g**	98	80
11	3-Me-C_6H_4 **4h**	**5h**	96	82
12	4-^{t}Bu-C_6H_4 **4i**	**5i**	98	84
13	4-^{n}Bu-C_6H_4 **4j**	**5j**	98	83
14	4-^{i}Bu-C_6H_4 **4k**	**5k-(*R*)**	98	89
15[f]	4-^{i}Bu-C_6H_4 **4k**	**5k-(*S*)**	98	92
16	2-naphthyl **4l**	**5l**	98	83
17	1-naphthyl **4m**	**5m**	95	93
18	2-(6-MeO-naphthyl) **4n**	**5n-(*R*)**	96	81
19[f]	2-(6-MeO-naphthyl) **4n**	**5n-(*S*)**	96	83

[a] Reactions were carried out on a 0.2 mmol scale with 0.24 mmol of thiol in 1 mL of toluene at rt, unless noted otherwise. [b] Determined by HPLC using chiral column. [c] 2-Aminothiophenol was used. [d] 2-Naphthylthiol was used. [e] 4-Methoxytoluenethiol (3 equiv) was used, and reaction was continued for 72 h. [f] Catalyst **1d** was used.

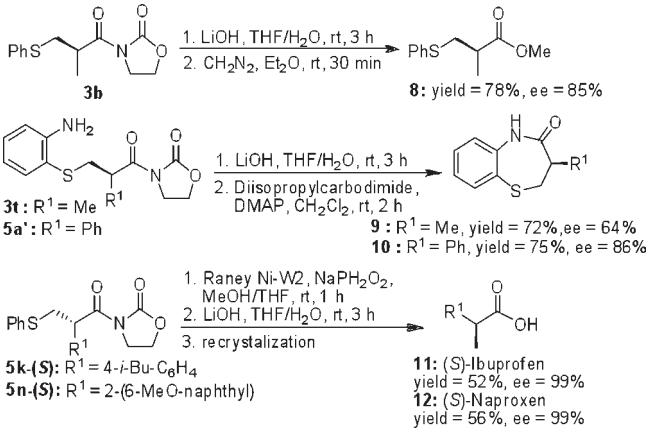
However, the position of the substituents on the aromatic ring has a dramatic effect on enantioselectivity. Interestingly, 2-(*o*-methoxyphenyl) acryloyloxazolidin-2-one **4f** furnished the corresponding products in excellent enantioselectivities (up to 96% *ee*) (Table 3, entries 7−9). For two typical cases, both enantiomers were achieved with the same level of enantioselectivity by using two pseudoenantiomeric catalysts **1a** and **1d** (Table 3, entries 15 and 19). Then, we challenged the method by testing its efficiency with an α,*β*-substituted α,*β*-unsaturated carbonyl compound. Reaction of thiophenol with **6**, sulfa-Michael addition, and ptotonation led to the desired product **6a** with moderate dr and excellent *ee* of the major diastereomer. The product was later transformed to the corresponding methyl ester **7** without any detectable epimerization (Scheme 1).[13]

Scheme 1. Catalytic Asymmetric Sulfa-Michael Addition/Protonation



Finally, the synthetic potential of the protonated products was demonstrated. The adduct **3b** was converted to **8** in high yield without compromising the optical purity. The transformation also led us to determine the absolute configuration of **3b** (*R*)[13] (Scheme 2). Addition/protonation products **3t** and **5a′** were successfully converted to the corresponding cyclic amides **9** and **10**, the core structure of diltiazem,[8a] without affecting the *ee*'s. Desulfurization with Raney Nickel W-2 followed by basic hydrolysis of **5k-(*S*)** and **5n-(*S*)** gave the corresponding chiral acids without racemization. Recrystallization of these chiral acids from benzene enabled us to obtain analytically pure (*S*)-Ibuprofen[2b] and (*S*)-Naproxen,[2c] nonsteroidal anti-inflammatory drugs (NSAIDs) in 99% enantiopure form in good yields (Scheme 2).

Scheme 2. Applications of the Sulfa-Michael Addition/Protonation Products



The proposed transition state models to explain the stereochemical outcome of the reaction are shown in Figure 2. We believe that 3-methacryloyloxazolidin-2-one is activated by the thiourea moiety through double hydrogen bonding, while the aromatic thiol is activated by the tertiary nitrogen of the quinuclidine. Michael addition of thiolate to **2b** generates a transient ion pair. Subsequent delivery of the proton from the quinuclidine nitrogen to the *Si* face of the generated prochiral enolate leads to the formation of the major stereoisomer.[11a,12]

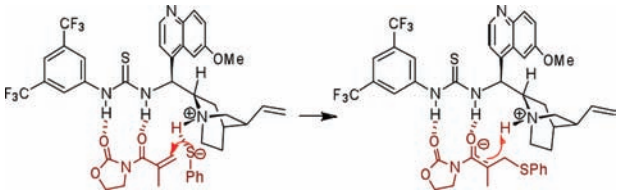


Figure 2. Proposed transition state models.

In conclusion, we have developed an effective catalytic sulfa-Michael addition to α-substituted *N*-acryloyloxazolidin-2-ones followed by enantioselective protonation by using *cinchona* alkaloid derived thiourea catalysts. This protocol offers several advantages such as operational simplicity, mild reaction conditions, low catalyst loading (1 mol %), good to excellent enantioselectivities (up to 96% *ee*), and quantitative yields. Both enantiomers of addition/protonation products could be achieved with the same level of enantioselectivity. The synthetic utility of the present catalytic asymmetric protonation reaction was established by transforming the products to useful molecules, such as (*S*)-Ibuprofen and (*S*)-Naproxen, used clinically as NSAIDs. Further studies focusing on the full scope of the catalytic system are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org