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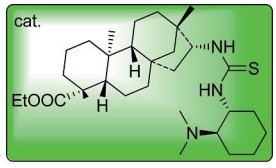
SHORT COMMUNICATION

Asymmetric Organocatalysis



Compounds containing both a pyrazole motif and a masked amino acid structure were obtained through the asymmetric Michael addition/aromatization of azlactones to α,β-unsaturated pyrazolones. The reaction proceeds with C-4 regioselectivity by using an isosteviol-derived thiourea organocatalyst and provides the products in good yields with good diastereoselectivities and good enantioselectivities.

Keywords: Organocatalysis / Asymmetric synthesis / Amino acids / Nitrogen heterocycles / Azlactones

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Asymmetric Michael/Aromatization Reaction of Azlactones to α,β-Unsaturated Pyrazolones with C-4 Regioselectivity Catalyzed by an Isosteviol-Derived Thiourea Organocatalyst

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Keywords: Organocatalysis / Asymmetric synthesis / Amino acids / Nitrogen heterocycles / Azlactones

Pyrazoles are an important class of molecular structures with significant biological and pharmaceutical activities. Herein, heterocyclic compounds containing both a pyrazole motif and a masked amino acid structure are synthesized through the asymmetric Michael/aromatization of azlactones to α,β-unsaturated pyrazolones by using isosteviol-derived amine thiourea as the organocatalyst. The products are obtained in good yields (up to 93 %) with good diastereoselectivities and good enantioselectivities (up to >10:1 *dr*, 97 % *ee*).

Introduction

Pyrazoles and pyrazolones, which are five-membered heterocyclic compounds containing two adjacent nitrogen atoms, are important motifs found in a number of organic molecules that possess a wide range of agricultural and pharmaceutical activities. Particularly, 3-hydroxypyrazole derivatives, obtained by aromatization of pyrazolones, are extensively studied as potent biological enzyme inhibitors and activators. For example, some aryl-substituted 3-(3-dimethylaminopropyloxy)-1*H*-pyrazoles demonstrate potent activation of soluble guanylate cyclase and potent inhibition of platelet aggregation. Remogliflozin etabonate plays an important role in renal glucose reabsorption and is a remarkable transporter as a molecular target for the treatment of diabetes (Figure 1).[1] Therefore, the development of new methods for the efficient synthesis of optically active pyrazoles and pyrazolones is highly desirable. From 2011, Rios, Wang, and our group successively reported organocatalytic cascade reactions to synthesize spiropyrazolones by using α,β-unsaturated pyrazolones or pyrazolones as starting materials.[2]

The use of azlactones as precursors for the enantioselective synthesis of quaternary α-amino acid derivatives[3] found in many biologically active compounds was pioneered by the groups of Fu and Trost (Figure 1).[4–6] Ten years later, Jørgensen and co-workers first reported the organocatalytic enantioselective Michael addition of 4-substituted azlactones to α,β-unsaturated aldehydes with complete C-4 regioselectivity.[7] Shortly thereafter, Hayashi and co-workers also reported a similar enantioselective transformation.[8] Subsequently, Jørgensen, Rios and Ooi individually reported the organocatalyzed Michael additions of 4-substituted azlactones to nitrostyrenes,[9] unsaturated acyl phosphonates,[10] phenylsulfonyl-substituted ethylenes,[11] maleimides,[12] unsaturated amides,[13] electron-deficient triple bonds,[14] and di- and trienyl *N*-acylpyrroles[15] to provide either masked quaternary α-amino acid derivatives (C-4 regioselectivity) or chiral oxyaminals (C-2 regioselectivity).

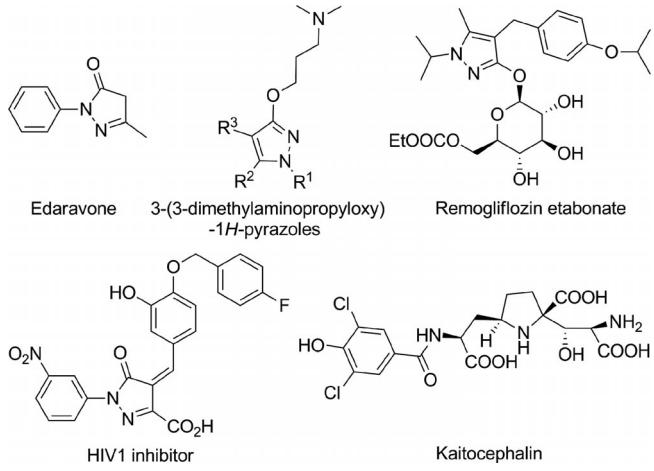

Figure 1. Some biologically active pyrazole, pyrazolone, and α-amino acid derivatives.

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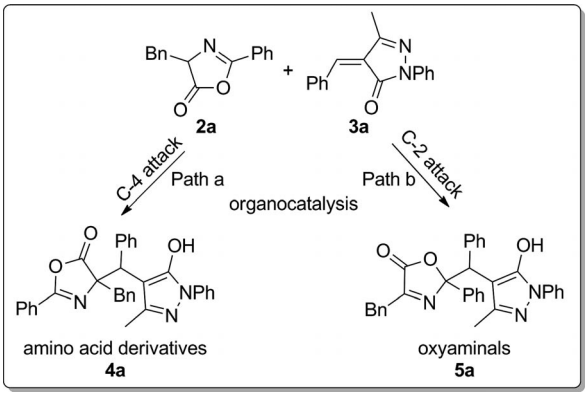
Generally, the relative nucleophilicities of 2,4-disubstituted azlactones were greatly affected by several factors, including substituents on the azlactones, electrophiles, catalysts, and reaction conditions. In the reported literature, many reactions showing C-4 regioselectivity were performed with the use of azlactones derived from phenylglycines as the donors of the Michael addition reactions. Given that azlactones and pyrazolones are highly practical synthetic blocks, herein we report the organocatalytic enantioselective Michael addition/aromatization reactions between alkyl-substituted azlactones and α,β-unsaturated pyrazolones to provide enantiomerically enriched heterocyclic products containing both a 3-hydroxypyrazole motif and a masked amino acid structure. These reactions are efficiently catalyzed by an isosteviol-derived bifunctional thiourea organocatalyst, originally devised by the Tao group for enantioselective catalysis,[16] in excellent yields with good to excellent enantioselectivities (Scheme 1).



Scheme 1. The Michael/aromatization reaction of azlactones **2** to α,β-unsaturated pyrazolones **3**. Path a: C-4 regioselectivity and Path b: C-2 regioselectivity; Bn = benzyl.

Results and Discussion

Initially, the reaction between 4-benzyl-2-phenyl-2-oxazoline-5-one (**2a**) and α,β-unsaturated pyrazolone **3a** was selected as the model reaction to examine a series of bifunctional organic catalysts **1a**–**l** (Figure 2) in dichloromethane at room temperature (Table 1, entries 1–12). Quinine and its derivatives **1a**–**d** were firstly tested (Table 1, entries 1–4). When quinine-derived tertiary amino–thiourea organocatalyst **1d** (10 mol-%) was employed,[17] the Michael addition of **2a** with **3a** provided desired product **4a** in 70% yield with 43%*ee* (Table 1, entry 4). Encouraged by these promising results, (1*R*,2*R*)-cyclohexane-1,2-diamine (DACH) and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (DPEN) derived bifunctional thiourea tertiary amine catalysts **1e**–**i** were investigated for this transformation (Table 1, entries 5–9). We found that organocatalysts **1h** and **li** with (*R*)- and (*S*)-α-phenylethylamine motifs increased the enantioselectivity of product **4a** to 71 and 72%*ee*, respectively, with over 10:1 *dr* (Table 1, entries 8 and 9). Furthermore, several chiral isosteviol-derived bifunctional thiourea organocatalysts **1j**–**l** were synthesized and examined in this reaction (Table 1, entries 10–12). To our delight, if **1j** (10 mol-%) was used in this transformation, product **4a** was obtained in 92% yield with >10:1 *dr* and 81%*ee* (Table 1, entry 10). Notably, a trace amount up to 9% yield of **6a** was detected in all of the above tentative reactions, which might be produced by Michael/ring opening or a concerted Diels–Alder process,

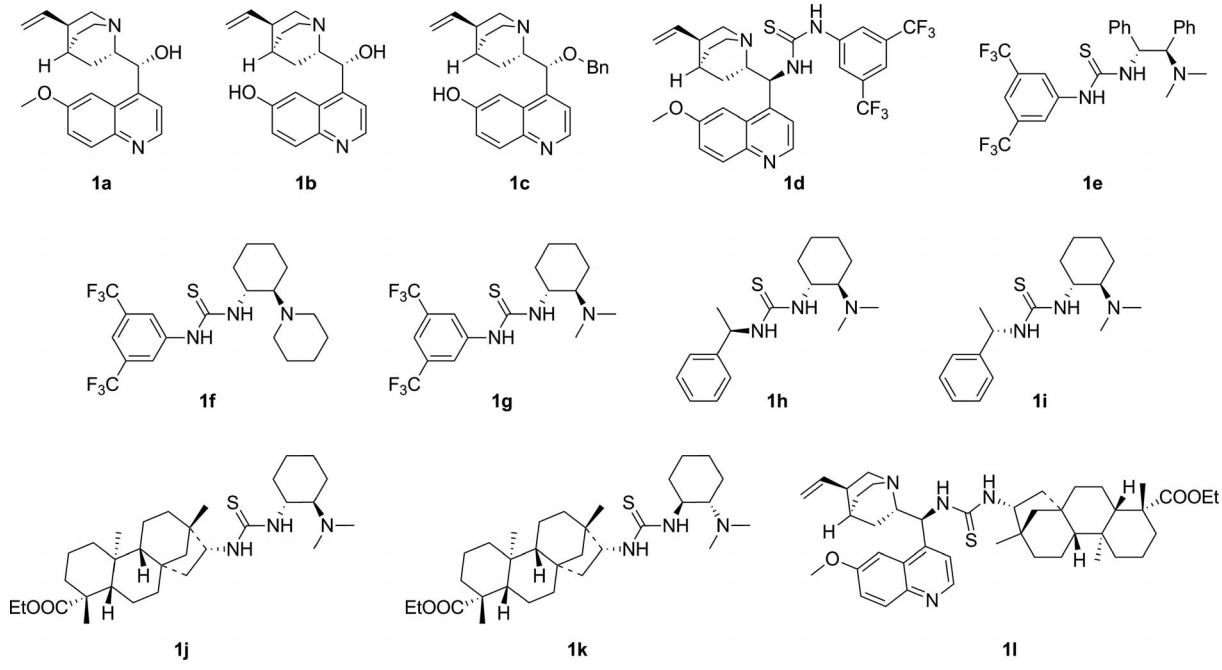
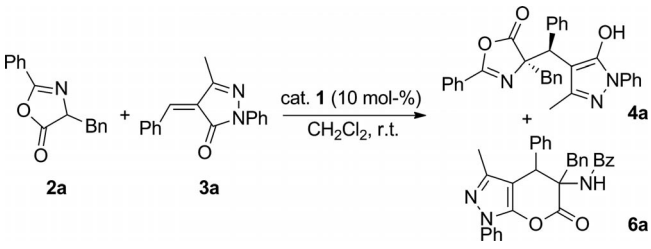


Figure 2. Structures of bifunctional organocatalysts **1a**–**l**.

and **5a** resulting from C-2 regioselectivity was not detected. With **1j** as the organocatalyst, less than 5% yield of **6a** was obtained (Table 1, entry 10). So, **1j** turned out to be the optimal organocatalyst in terms of both enantioselectivity and reactivity.

Table 1. Optimization of the catalysts.[a]

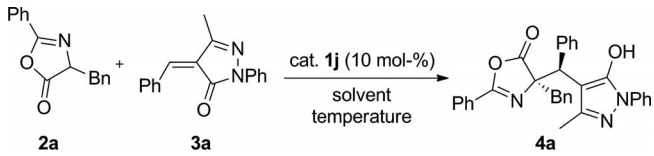


Entry	Catalyst	*t* [min]	Yield[b] [%]	**4a**/**6a**[c]	*dr*[c]	*ee*[d] [%]
1	**1a**	5	88	–	–	–15
2	**1b**	180	60	–	–	–4
3	**1c**	15	81	–	–	37
4	**1d**	45	70	–	–	–43
5	**1e**	180	50	–	–	45
6	**1f**	25	78	–	–	21
7	**1g**	15	75	–	–	49
8	**1h**	15	93	16:1	>10:1	71
9	**1i**	15	91	13:1	>10:1	72
10	**1j**	30	92	17:1	>10:1	81
11	**1k**	30	89	10:1	>10:1	–73
12	**1l**	180	46	–	–	–51

[a] Unless noted, reactions were carried out with **2a** (0.13 mmol), **3a** (0.1 mmol), and **1** (10 mol-%) in CH_2Cl_2 (1.0 mL) at r.t.; Bz = benzoyl. [b] Isolated yield of **4a**; isomers **4a** and **6a** could be easily separated. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis.

Having identified **1j** as a potent catalyst for this transformation, the reaction conditions were further optimized by examination of the effects of solvent, temperature, additive, substrate concentration, as well as the catalyst loading, and the results are shown in Table 2. The effect of solvent was first examined in the presence of **1j** (10 mol-%), and several common solvents, such as CH_2Cl_2, Et_2O, toluene, and PhCl, all exhibited similar reactivity, enantioselectivity, and diastereoselectivity at the same substrate concentration at room temperature (Table 2, entries 1–4). If the reaction was carried out at –40 °C in CH_2Cl_2, 91% enantioselectivity was obtained (Table 2, entry 7). To our delight, the enantioselectivity could be further improved to 95% by adding activated 4 Å molecular sieves (MS) at –40 °C in toluene (Table 2, entry 9). If the temperature was increased to –20 °C, the enantioselectivity decreased slightly (Table 2, entry 12 vs. 9). Thus, –40 °C was selected as the optimal reaction temperature. Afterwards, the effects of substrate concentration and catalyst loading for this reaction were investigated (Table 2, entries 15–20). The highest enantioselectivity was obtained if the substrate concentration was 0.025 M (Table 2, entry 17). The enantioselectivity slightly dropped by increasing or decreasing the catalyst loading (Table 2, entry 17 vs. entries 18–20).

Table 2. Optimization of the reaction conditions.[a]

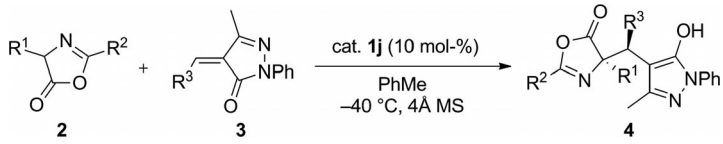


Entry	Solvent	*T* [°C]	Conc. [M]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	CH_2Cl_2	r.t.	0.1	0.5	92	81
2	Et_2O	r.t.	0.1	5[d]	90	80
3	PhMe	r.t.	0.1	5[d]	91	80
4	PhCl	r.t.	0.1	0.25	94	78
5	PhMe	–40	0.1	8	91	86
6	PhCl	–40	0.1	8	94	88
7	CH_2Cl_2	–40	0.1	8	97	91
8	Et_2O	–40	0.1	8	87	82
9[e]	PhMe	–40	0.1	8	94	95
10[e]	PhCl	–40	0.1	8	94	92
11[e]	CH_2Cl_2	–40	0.1	8	95	93
12[e]	PhMe	–20	0.1	1	93	93
13[e]	PhCl	–20	0.1	1	93	90
14[e]	CH_2Cl_2	–20	0.1	1	88	92
15[f]	PhMe	–40	0.20	8	88	91
16[g]	PhMe	–40	0.05	8	92	96
17[h]	PhMe	–40	0.025	8	93	97
18[i]	PhMe	–40	0.025	8	95	96
19[j]	PhMe	–40	0.025	8	91	96
20[k]	PhMe	–40	0.025	8	87	96

[a] Unless noted, reactions were carried out with **2a** (0.13 mmol), **3a** (0.1 mmol), and **1j** (10 mol-%) in solvent (1.0 mL) at r.t. In all cases, the products were obtained with >10:1 *dr*, as determined by ^{1}H NMR spectroscopy. [b] Isolated yield of **4a**; isomers **4a** and **6a** could be easily separated. [c] Determined by chiral HPLC analysis. [d] Time is given in minutes. [e] With the addition of 4 Å MS (100 mg). [f] With toluene (0.5 mL), 4 Å MS (50 mg). [g] With toluene (2.0 mL), 4 Å MS (200 mg). [h] With toluene (4.0 mL), 4 Å MS (400 mg). [i] 20 mol-% of the catalyst was used. [j] 5 mol-% of the catalyst was used. [k] 2.5 mol-% of the catalyst was used.

Having established the optimized reaction conditions, the scope and limitations of the substrate were then explored with isosteviol-derived thiourea **1j** (10 mol-%) as the catalyst in toluene at –40 °C with 4 Å molecular sieves as an additive, and the results are summarized in Table 3. With the use of **2a** as the nucleophilic reagent, α,β-unsaturated pyrazolones **3** were investigated to study the effects of the electronic properties and the steric hindrance of the R^3 group on enantioselectivity, diastereoselectivity, and reactivity (Table 3, entries 1–9). For aryl-substituted α,β-unsaturated pyrazolones **3** bearing electron-donating groups (4-Me, 4-MeO, 4-SMe) or electron-withdrawing groups (4-F, 4-Cl, 4-Br) on the phenyl ring, all the reactions proceeded smoothly to provide the desired products in 81–91% yield with 91–97% *ee* (Table 3, entries 2–7). 2-Naphthyl-substituted α,β-unsaturated pyrazolone **3h** showed quite good performance and desired product **4h** in 92% yield with 94% *ee*, although a prolonged reaction time was required (Table 3, entry 8). A lower enantioselectivity (66%) was observed for 2,4-dichloro-substituted α,β-unsaturated pyrazolone **3i** probably as a result of steric hindrance (Table 3, entry 9). The Michael addition reactions of α,β-unsaturated

Table 3. Substrate scope.[a]



2 3 4

Entry	R^1, R^2	R^3	Product, yield [%][b]	*ee* [%][c]
1	Bn, C_6H_5 (**2a**)	C_6H_5 (**3a**)	**4a**, 93	97
2	Bn, C_6H_5 (**2a**)	4-MeC_6H_4 (**3b**)	**4b**, 87	97
3	Bn, C_6H_5 (**2a**)	4-MeOC_6H_4 (**3c**)	**4c**, 90	96
4	Bn, C_6H_5 (**2a**)	4-MeSC_6H_4 (**3d**)	**4d**, 91	91
5	Bn, C_6H_5 (**2a**)	4-FC_6H_4 (**3e**)	**4e**, 86	94
6	Bn, C_6H_5 (**2a**)	4-ClC_6H_4 (**3f**)	**4f**, 81	93
7	Bn, C_6H_5 (**2a**)	4-BrC_6H_4 (**3g**)	**4g**, 83	91
8	Bn, C_6H_5 (**2a**)	2-naphthyl (**3h**)	**4h**, 92	94
9	Bn, C_6H_5 (**2a**)	2,4-$Cl_2C_6H_3$ (**3i**)	**4i**, 87	66
10	Bn, 4-FC_6H_4 (**2b**)	C_6H_5 (**3a**)	**4j**, 89	84
11	Bn, 4-ClC_6H_4 (**2c**)	C_6H_5 (**3a**)	**4k**, 88	94
12	Bn, 4-ClC_6H_4 (**2c**)	4-FC_6H_4 (**3e**)	**4l**, 93	84
13	Bn, 4-MeC_6H_4 (**2d**)	C_6H_5 (**3a**)	**4m**, 92	95
14	Bn, 4-MeC_6H_4 (**2d**)	4-FC_6H_4 (**3e**)	**4n**, 90	94
15	*i*Bu, 4-MeC_6H_4 (**2e**)	C_6H_5 (**3a**)	**4o**, 90	80
16	*i*Pr, C_6H_5 (**2f**)	C_6H_5 (**3a**)	**4p**, 76	84
17	2-(methylthio)ethyl, C_6H_5 (**2g**)	C_6H_5 (**3a**)	**4q**, 80	94
18	*i*Pr, *t*Bu (**2h**)	C_6H_5 (**3a**)	**4r**, <5	–
19[d]	*i*Pr, *t*Bu (**2h**)	C_6H_5 (**3a**)	**4r**, <5	–

[a] Unless noted, reactions were carried out with **2** (0.13 mmol), **3** (0.1 mmol), **1j** (10 mol-%), and 4 Å MS (400 mg) in toluene (4.0 mL) at –40 °C for 8–12 h. In all cases, the products were obtained with >10:1 *dr*, as determined by ^{1}H NMR spectroscopy. [b] Isolated yield of **4**. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out with **2h** (1.0 mmol), **3** (0.1 mmol), **1j** (30 mol-%), and 4 Å MS (100 mg) in toluene (1.0 mL) at r.t. for 36 h.

pyrazolones **3a** and **3e** with azlactones **2b–h** were also examined under otherwise identical conditions. It was observed that varying the R^2 substituent on the benzene ring also led to some changes in the enantioselectivities (Table 3, entries 10–14). Substrates with bulkier R^1 groups provided decreased enantioselectivities (Table 3, entry 15 vs. 13, entry 16 vs. 1). A good result was obtained with a methylthioethyl group at the R^1 position (Table 3, entry 17). Azlactone **2h** with alkyl groups at the R^1 and R^2 positions failed to give the product even at room temperature with 30 mol-% catalyst loading (Table 3, entries 18 and 19). In all of the above cases, good yields (76–93%) and diastereoselectivities (>10:1 *dr*) were obtained. Fortunately, a single crystal of **4d** was obtained by recrystallization from petroleum ether/*n*-hexane/CH_2Cl_2, and the configuration of the two contiguous stereocenters was unambiguously determined by X-ray analysis (Figure 3).[18]

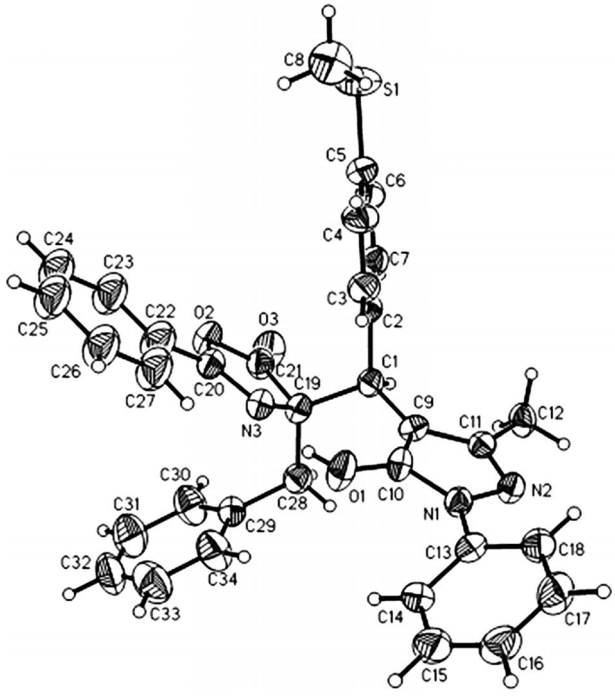


Figure 3. X-ray crystal structure of chiral compound **4d**.

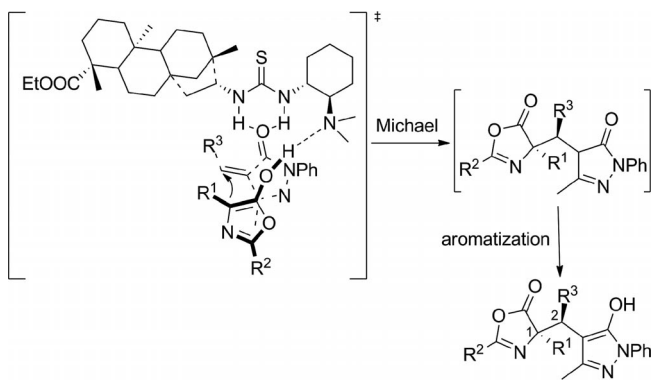


Figure 4. Proposed transition state and mechanism.

On the basis of the X-ray analysis of compound **4d**, a possible transition state and mechanism are proposed and shown in Figure 4. The tertiary amine of the catalyst deprotonates the azlactone, and the thiourea moiety activates the α,β-unsaturated pyrazolone through hydrogen bonding, which provides the intermediate. Subsequently, aromatization of the intermediate gives the desired chiral product with a (1*R*,2*S*) configuration.

Conclusions

In summary, we have developed the asymmetric Michael/aromatization reactions of azlactones to α,β-unsaturated pyrazolones with complete C-4 regioselectivity by using isosteviol-derived amine thiourea as a catalyst. A series of heterocyclic compounds containing both a 3-hydroxypyrazole motif and a masked amino acid structure were synthesized in good yields with moderate to excellent enantioselectivities.[19] The development of new chiral organocatalysts to obtain cyclic compound **6** as the major product is now in progress in our laboratory.

Experimental Section

General Procedure for the Asymmetric Michael Addition/Aromatization Reaction of Azlactones to α,β-Unsaturated Pyrazolones: In an ordinary tube equipped with a magnetic stirring bar, a solution of azlactone **2** (0.13 mmol), 4 Å MS (400 mg), and catalyst **1j** (10 mol-%) in toluene (4.0 mL) was stirred at –40 °C for 30 min, and then α,β-unsaturated pyrazolone **3** (0.10 mmol) was added. The reaction mixture was stirred for 8–12 h at –40 °C. The reaction mixture was directly loaded onto silica gel and purified by flash chromatography (petroleum ether/dichloromethane = 1:1–1:2) to give desired products **4a**–**q**.

Supporting Information (see footnote on the first page of this article): Experimental details and spectroscopic data.

Acknowledgments

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