Organic LETTERS

Letter

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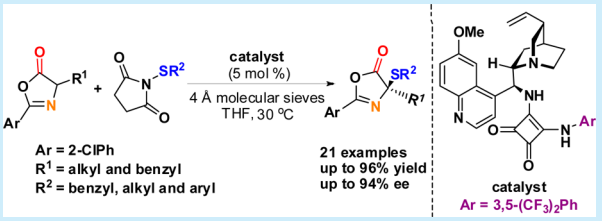
Highly Enantioselective Organocatalytic α-Sulfenylation of Azlactones

Baokun Qiao,[†,§] Xinfei Liu,[‡,§] Shaobo Duan,[‡] Lin Yan,[†] and Zhiyong Jiang*[,†,‡]

[†]Institute of Chemical Biology and [‡]Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Kaifeng, Henan, China, 475004

Supporting Information

ABSTRACT: The first asymmetric α-sulfenylation of azlactones with *N*-(sulfanyl)succinimides has been developed by using *cinchona* alkaloid-derived squaramide as a catalyst and 4 Å molecular sieves as an additive. The reaction conditions were suitable to 4-alkyl and benzyl-substituted azlactones as well as *N*-(benzyl/alkyl/arylthio)succinimides, affording adducts with high enantioselectivities (81−94% ee).



Due to their extensive applications in numerous areas, chiral sulfur-containing compounds have attracted increasing interest from chemists.[1] Various protocols on their asymmetric synthesis have been well established in recent decades.[2,3] In particular, asymmetric α-sulfenylation has been demonstrated as a direct method to introduce a sulfur-substituted heteroquaternary stereogenic center to the α-position of carbonyl compounds, which are main frameworks in many bioactive compounds.[3] To date, several asymmetric α-sulfenylations have been established; the reported nucleophiles included cyclic β-keto esters, lactams and phosphonates, 1,3-dicarbonyl compounds, aldehydes, diketopiperazines, and 3-substituted oxindoles.[3] Nevertheless, the extension of α-sulfenylation to unprecedented nucleophiles to afford more types of valuable synthetic building blocks is still highly desirable.

In recent years, azlactones have been recognized as the most common nucleophilic reagents to introduce a heteroquaternary carbon stereocenter on the α-position of α-amino acid derivatives.[4] A variety of catalytic asymmetric transformations of azlactones have been established, such as Steglich rearrangement, Michael reaction, oxyamination, allylation, benzylation, thiolysis, Mannich reaction, and cycloaddition.[4] To the best of our knowledge, asymmetric α-sulfenylation of azlactones has not been reported yet. In our recent research programs, we are focusing on organocatalytic asymmetric reactions to assemble chiral quaternary and heteroquaternary centers.[3l,5] Especially, the enantioselective α-sulfenylation of oxindoles has been successfully addressed with excellent enantioselectivity.[3l] As an extension of these works, we herein report an unprecedented asymmetric α-sulfenylation of azlactones to furnish the first highly enantioselective synthesis of α-sulfur-substituted α-amino acid derivatives,[6] which are important frameworks in many natural and non-natural products with crucial biological and medicinal properties (Figure 1).[7]

In our initial investigation on reaction conditions for α-sulfenylation, azlactone **1a** and *N*-(benzylthio)succinimide **2a**

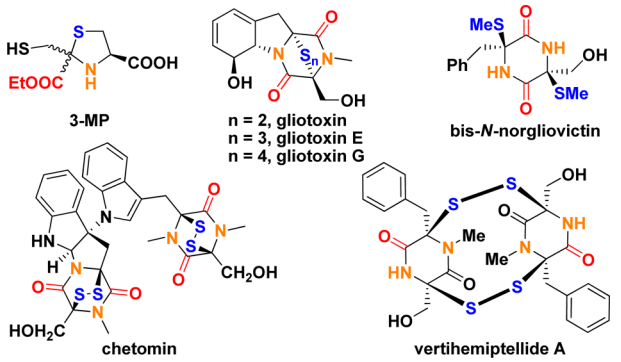


Figure 1. Selected natural and non-natural products.

were chosen as model substrates (Table 1). *Cinchona* alkaloid-derived thiourea **I** (from quinine, Figure 2) was attempted as the catalyst for its well-established versatility in many reactions.[8] It was found that, in the presence of 10 mol % catalyst **I** in THF at 30 °C, the desired adduct **3aa** could be obtained in 53% yield with 20% ee after 14 h (entry 1). The results indicated that the framework of the *cinchona* alkaloid should benefit the enantioselectivity; modification of the acid moiety of the catalyst becomes feasible. Therefore, a series of *cinchona* alkaloid-derived squaramides[9] were prepared and examined (**II**−**V**, Figure 2). We delighted that the enantioselectivity increased remarkably (entries 2−5), and an 88% ee for **3aa** was obtained when catalyst **II** was utilized (entry 2). Further optimization of the reaction conditions was carried out by examining different solvents in the presence of 10 mol % **II** (entries 6−9); the ideal solvent was still determined to be THF from regarding the yield and enantioselectivity (entry 2). 4 Å Molecular sieves as an additive were subsequently investigated to improve the reactivity and enantioselectivity (entries 10−

Received: November 15, 2013

   dx.doi.org/10.1021/ol403303k | *Org. Lett.* XXXX, XXX, XXX−XXX

Table 1. Optimization of the Reaction Conditions[a]

entry	1	catalyst	solvent	t (h)	3	yield (%)[b]	ee (%)[c]
1	**1a**	**I**	THF	14	**3aa**	53	20
2	**1a**	**II**	THF	14	**3aa**	67	88
3	**1a**	**III**	THF	14	**3aa**	59	−87
4	**1a**	**IV**	THF	14	**3aa**	63	−86
5	**1a**	**V**	THF	14	**3aa**	48	83
6	**1a**	**II**	toluene	14	**3aa**	trace	N.D.
7	**1a**	**II**	CH_2Cl_2	14	**3aa**	trace	N.D.
8	**1a**	**II**	EtOAc	14	**3aa**	40	86
9	**1a**	**II**	Et_2O	14	**3aa**	43	85
10[d]	**1a**	**II**	THF	14	**3aa**	65	88
11[e]	**1a**	**II**	THF	14	**3aa**	73	88
12[f]	**1a**	**II**	THF	14	**3aa**	78	89
13[g]	**1a**	**II**	THF	14	**3aa**	86	89
14[g]	**1b**	**II**	THF	16	**3ba**	71	88
15[g]	**1c**	**II**	THF	14	**3ca**	64	89
16[g]	**1d**	**II**	THF	16	**3da**	68	89
17[g]	**1e**	**II**	THF	12	**3ea**	82	89
18[g]	**1f**	**II**	THF	16	**3fa**	61	90
19[g]	**1g**	**II**	THF	16	**3ga**	67	91
20[g]	**1h**	**II**	THF	20	**3ha**	85	92
21[g]	**1i**	**II**	THF	20	**3ia**	97	90
22[g]	**1j**	**II**	THF	20	**3ja**	32	91
23[g]	**1k**	**II**	THF	11	**3ka**	70	89
24[g]	**1l**	**II**	THF	14	**3la**	75	90
25[g,h]	**1h**	**II**	THF	20	**3ha**	78	91
26[g,i]	**1h**	**II**	THF	20	**3ha**	70	91
27[g,j]	**1h**	**II**	THF	12	**3ha**	91	92
28[g,k]	**1h**	**II**	THF	14	**3ha**	80	92
29[g,l]	**1h**	**II**	THF	14	**3ha**	64	90

[a]Reactions were performed with 0.05 mmol of **1a**, 0.055 mmol of **2a**, and 0.005 mmol of catalyst in 1.0 mL of solvent. [b]Yield of isolated product. [c]Determined by HPLC on a chiral stationary phase. [d]5 mg of 4 Å molecular sieves were used. [e]25 mg of 4 Å molecular sieves were used. [f]50 mg of 4 Å molecular sieves were used. [g]100 mg of 4 Å molecular sieves were used. [h]T = 20 °C. [i]T = 10 °C. [j]20 mol % of **II** were used. [k]5 mol % of **II** were used. [l]2.5 mol % of **II** were used.

13).[10] It was found that the molecular sieves could accelerate the reaction rate without compromising the ee value. When 100 mg of molecular sieves were used, the adduct **3aa** was obtained in 86% yield with 89% ee (entry 13).

We next examined the influence of the aryl group of azlactones (**1b**−**l**) on the 2-position in affecting stereoselectivity (entries 14−24). We found that azlactones **1b**−**c** with substituent groups at the *para* position of the phenyl ring gave similar enantioselectivities (entries 14−15). When substituent groups were introduced at the *meta* position of the phenyl ring (**1d**−**e**), ee values were maintained (entries 16−17). A series of azlactones with different substituent groups at the *ortho* position of the phenyl ring (**1f**−**j**) were then prepared and investigated (entries 18−22). It was observed that the enantioselectivity was improved slightly and adduct **3ha** with an *o*-chlorophenyl group was obtained with the best results (85% yield, 92% ee, entry 20). A lower temperature could not promote the enantioselectivity and made the reaction sluggish (entries 25−26). The influence of number of equivalents of catalyst **II** was also evaluated (entries 27−29). When 20 mol % of **II** were used, the reaction was finished in 91% yield with 92% ee within 12 h (entry 27). 5 mol % of **II** gave the same enantioselectivity and a slightly decreased reaction rate, which could be addressed with more suitable conditions from the

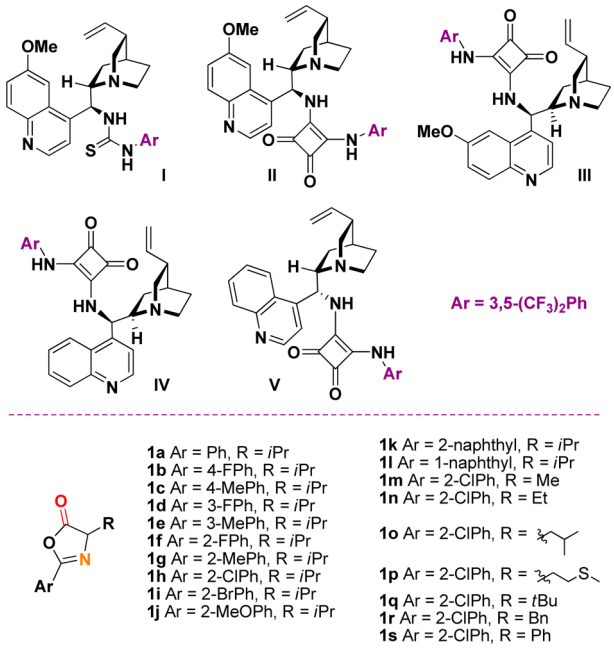


Figure 2. Structures of catalysts **I**−**V** and azlactones **1a**−**s**.

standpoint of economizing the catalyst (entry 28). A slightly compromising ee was detected when 2.5 mol % of **II** were utilized (entry 29).

With the optimal conditions established, the scope of the reaction was investigated with a variety of azlactones **1** and *N*-(sulfanyl)succinimides **2** in the presence of 5 mol % **II** as the catalyst and using 4 Å molecular sieves as the additive (Table 2). The reactions of azlactone **1f** and *N*-(benzylthio)succinimides (**2a**−**j**) afforded the adducts **3ha**−**hj** in 72−86% yield with 86−93% ee within 14−45 h (entries 1−10). The results revealed that the introduction of substituent groups on the *ortho*-position of the aromatic ring of *N*-(benzylthio)succinimides should decrease the reactivity and enantioselectivity slightly; 10 mol % of **II** were necessary and 86−88% ee for the adducts (**3hh**−**hj**) were obtained (entries 8−10). Furthermore, we found that the reaction conditions were also applicable to *N*-(alkylthio)succinimides (**2k**−**o**, entries 11−15), giving adducts in 75−94% yield with 90−93% ee as well as similarly good reactivity except for **2o** due to the steric effect (entry 15). The use of *N*-(2-naphthylthio)succinimide **2p** resulted in an excellent yield and good enantioselectivity (entry 16). Other azlatones (**1m**−**q**), containing different alkyl groups on the 4-position, also provided the corresponding adducts **3ma**−**qa** with good to excellent enantioselectivities (entries 17−21); the best enantioselectivity was obtained when **1q** with the bulkiest *tert*-butyl group was used, but the reaction was sluggish (entry 21). When the benzyl group was embedded on the 4-position of azlatone (**1r**) under the established conditions, the adduct **3ra** could be obtained in good yield and enantioselectivity (entry 22). Furthermore, under the established conditions, the α-sufenylation of 4-phenyl-substituted azlatone **1s** and *N*-(benzylthio)succinimide **2a** could be finished within 18 h but in moderate yield and ee, which remains a challenging task (entry 23).

To demonstrate the utility of this methodology, the synthetic transformations of α-sulfenylation adducts were subsequently processed (Scheme 1). When the hydrolysis of **3ha** was conducted in the presence of 5.0 equiv of hydrochloric acid

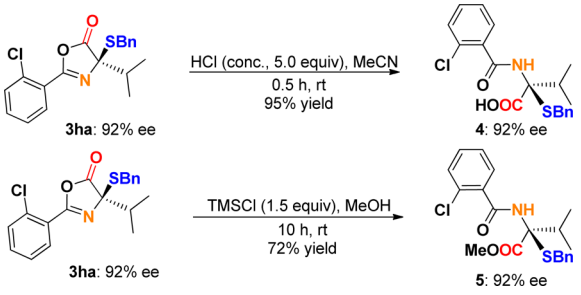
dx.doi.org/10.1021/ol403303k | *Org. Lett.* XXXX, XXX, XXX−XXX

Table 2. Sulfenylation of Azlactones 1 to *N*-(Sulfanyl)succinimide 2 Catalyzed by II[a]

entry	1	R^2 (2)	t (h)	3	yield (%)[b]	ee (%)[c]
1	**1h**	Bn (**2a**)	14	**3ha**	84	92
2	**1h**	4-FPhCH_2 (**2b**)	15	**3hb**	79	90
3	**1h**	4-ClPhCH_2 (**2c**)	20	**3hc**	74	90
4	**1h**	4-BrPhCH_2 (**2d**)	22	**3hd**	78	91
5	**1h**	4-MePhCH_2 (**2e**)	25	**3he**	79	93
6	**1h**	4-*t*BuPhCH_2 (**2f**)	18	**3hf**	78	93
7	**1h**	3-MePhCH_2 (**2g**)	20	**3hg**	86	91
8[d]	**1h**	2-ClPhCH_2 (**2h**)	35	**3hh**	83	86
9[d]	**1h**	2-BrPhCH_2 (**2i**)	18	**3hi**	72	88
10[d]	**1h**	2-MePhCH_2 (**2j**)	45	**3hj**	78	87
11	**1h**	Et (**2k**)	13	**3hk**	83	90
12	**1h**	*n*Pr (**2l**)	25	**3hl**	91	90
13	**1h**	1-dodecane (**2m**)	50	**3hm**	94	92
14	**1h**	*n*Bu (**2n**)	20	**3hn**	89	93
15	**1h**	*i*Pr (**2o**)	65	**3ho**	75	92
16	**1h**	2-naphthyl (**2p**)	14	**3hp**	96	82
17	**1m**	Bn (**2a**)	8	**3ma**	93	87
18	**1n**	Bn (**2a**)	8	**3na**	90	90
19	**1o**	Bn (**2a**)	6	**3oa**	84	85
20	**1p**	Bn (**2a**)	8	**3pa**	80	87
21	**1q**	Bn (**2a**)	78	**3qa**	43	94
22	**1r**	Bn (**2a**)	12	**3ra**	82	81
23	**1s**	Bn (**2a**)	18	**3sa**	68	40

[a]All reactions were performed with 0.10 mmol of **1**, 0.11 mmol of **2**, 200 mg of 4 Å molecular sieves, and 0.005 mmol of **II** in 2.0 mL of THF. [b]Yield of isolated product. [c]Determined by HPLC on a chiral stationary phase. [d]10 mol % of **II** were used.

Scheme 1. Synthetic Transformation of Adduct 3ha



(conc.) in acetonitrile as solvent at room temperature after 0.5 h, an α-sulfur-substituted α-amino acid **4** was obtained in 95% yield with 92% ee. Alternatively, an α-sulfur-substituted α-amino methyl ester **5** could be achieved when **3ha** is treated with 1.5 equiv of TMSCl using methanol as the solvent at room temperature. The results indicated the reaction finished smoothly after 10 h, affording **5** in 72% yield without compromising the ee value.

In conclusion, we have developed the first example of an asymmetric α-sulfenylation of azlactones. *Cinchona* alkaloid-derived squaramide was demonstrated as an efficient catalyst to promote the reaction using 4 Å molecular sieves as the additive, affording adducts with excellent enantioselectivities (81−94% ee). The reaction conditions were most suitable to 4-alkyl and benzyl-substituted azlactones as well as *N*-(benzyl/alkyl/arylthio)succinimides. From the obtained adducts, the important α-sulfur-substituted α-amino acid derivatives, containing a chiral α-heteroquaternary center, could be readily prepared with satisfactory results after a simple process, representing the first example of their synthesis with excellent enantioselectivity. Further investigations into organocatalytic asymmetric α-sulfenylation with other novel nucleophiles to access various compounds with significant biological activity are still in progress.

■ ASSOCIATED CONTENT

Supporting Information

General information, typical experimental procedures, characterization, HPLC and NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chmjzy@henu.edu.cn.

Author Contributions

[§]B.Q. and X.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC (Nos. 21072044, 21202034), NCET-11-0938, and Excellent Youth Foundation of Henan Scientific Committee (114100510003).

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