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Organocatalytic Asymmetric Neber Reaction for the Synthesis of 2*H*-Azirine Carboxylic Esters

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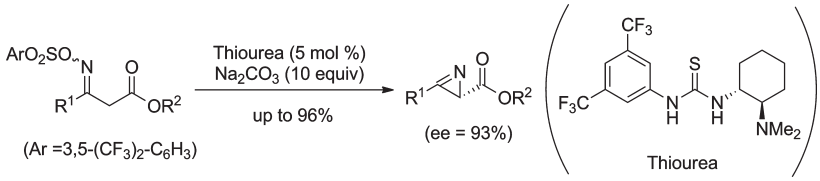
ABSTRACT



The first enantioselective Neber reaction of β-ketoxime sulfonates catalyzed by a bifunctional thiourea has been developed. The reaction proceeds stereoselectively with 5 mol % of the catalyst to give the 2*H*-azirine carboxylic esters in good yields with up to 93% ee. In addition, the resulting azirines can be successfully employed in the stereoselective synthesis of di- and trisubstituted aziridines.

2*H*-Azirines are the smallest heterocycles that contain a C=N double bond in a three-membered ring. Several naturally occurring 2*H*-azirines such as azirinomycin and dysidazirine have been isolated as promising antibiotics (Figure 1).[1]

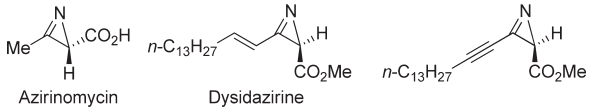


Figure 1. Biologically active 2*H*-azirines.

Due to the unique structural and chemical properties, these strained molecules have been extensively studied as synthetic intermediates as well as for theoretical and biological applications.[2] Although the reactivity of 2*H*-azirines is highly dependent on the nature of the substituents, chiral 2*H*-azirine-2-carboxylic acid derivatives are of particular interest as nonproteinogenic amino acids. So far, enantiomerically enriched 2*H*-azirines have been prepared by either a β-elimination of chiral nonracemic *N*-substituted aziridines[3] or an asymmetric Neber reaction of ketoxime sulfonates (Figure 2).[4]

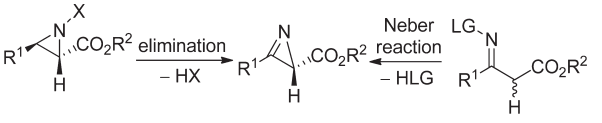


Figure 2. Synthetic strategy for 2*H*-azirines.

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The former method provides the desired compounds with high ee, but the preparation of the chiral aziridines is sometimes rather cumbersome. In contrast, the latter route is more concise and practical. However, except for a highly diastereoselective synthesis using a chiral amino acid as a chiral auxiliary, no asymmetric reactions which proceed in a highly enantioselective manner have been achieved with a stoichiometric or catalytic amount of chiral ligands (the reported ee's are up to 82%).[4] Therefore, development of the catalytic enantioselective Neber reaction would be highly desireable.

We have developed several organocatalyzed asymmetric reactions[5] with bifunctional thioureas in the past decade.[6] In these reactions, the catalysts were designed to work as a dual activator of both nucleophile and electrophile in bimolecular reactions, guiding the two reactants to get close in a restricted manner and enabling them to react smoothly and stereoselectively [(i) in Figure 3]. After our work, similar bifunctional thioureas bearing an amino or phosphine group were applied to intramolecular reactions of some multifunctional substrates.[7] The reaction was considered to proceed via the same dual activation mechanism as seen in the bimolecular reactions.

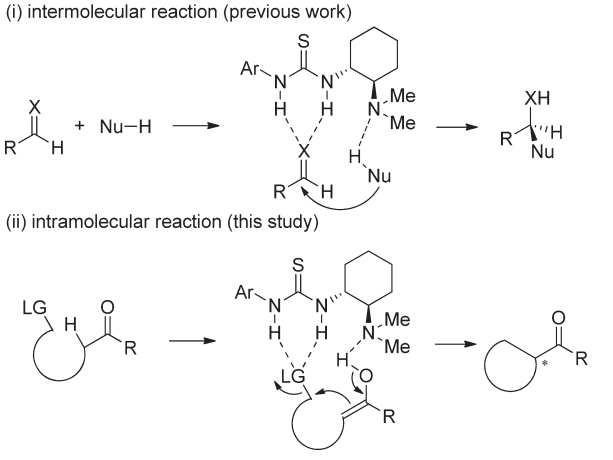

Figure 3. Dual activation of bifunctional thioureas.

We then envisaged that the same amino thiourea catalyst might be used effectively in the Neber reaction, if the thiourea and amine moieties of the catalyst interact with the leaving group (LG) and ester of the substrate, respectively, through triple hydrogen-bonding interaction [(ii) in Figure 3]. In this paper, we describe the first catalytic asymmetric Neber reaction of ketoxime sulfonates in the presence of bifunctional thiourea **2a** (5 mol %) to give 2*H*-azirines as well as the asymmetric synthesis of related aziridine derivatives.

We selected *O*-Ts-oxime *tert*-butyl ester **1aa**, prepared as an inseparable mixture of *E*/*Z* isomers in a ratio of 65/35, for the optimization of the reaction conditions (Table 1). The reactions of **1aa** were carried out in toluene with 10 mol % of **2a** in the presence of more than a stoichiometric amount of base to trap the generated TsOH (entries 1–6). We found that the desired product **3a** was obtained in comparable yields in all cases, but the enantioselectivity was significantly affected by the base used. Inorganic bases generally gave better results than organic base and biphasic conditions (entries 1 and 6). In contrast, the solvents examined had no significant effect on the ee (entries 7 and 8). We therefore chose Na_2CO_3 and toluene for further examination. Although various types of bifunctional organocatalysts **2b**–**g** were investigated to enhance the stereoselectivity, **2a** was revealed to be the best catalyst in terms of the ee (entries 9–14). Neither cyclic tertiary amines **2b** and **2c** nor other types of hydrogen-bond donors **2e**–**2g**[8] exhibited higher reactivity and improved stereoselectivity. The poor results of the same reaction with amide **2h** and sulfonamide **2i** strongly suggested the importance of the thiourea moiety of the catalysts for the high enantioselectivity (entries 15 and 16).

We next examined substituent effects of the ketoxime sulfonates **1ab**–**1df** (Table 2). Regarding the leaving group, electron-withdrawing substituents tend to give improved enantioselectivities (entries 1–6) and the 3,5-bis(trifluoromethyl)benzenesulfonate proved to be the best one, furnishing **3a** in 72% ee. It is noteworthy that an *ortho*-substitution with a nitro group dramatically increased the reaction rate in the case of *O*-2-Ns-oxime **1ac**, whereas the reaction of *O*-2-Ts-oxime **1ad** led to a decrease in ee (entry 2 vs 3). Moreover, the use of mesitylsulfonate completely suppressed the Neber reaction, resulting in the recovery of the starting material.[9] These results are reasonable, if the oxygen atom of the sulfonate group is considered to coordinate to the thiourea of the catalyst in the transition state. We next investigated other esters and amides as substrates. Tertiary amide **1ba** and esters **1ca** or **1da** gave comparable or slightly improved outcomes (entries 6–8). By lowering the reaction temperature to −20 °C, the corresponding product **3d** was obtained in 78%

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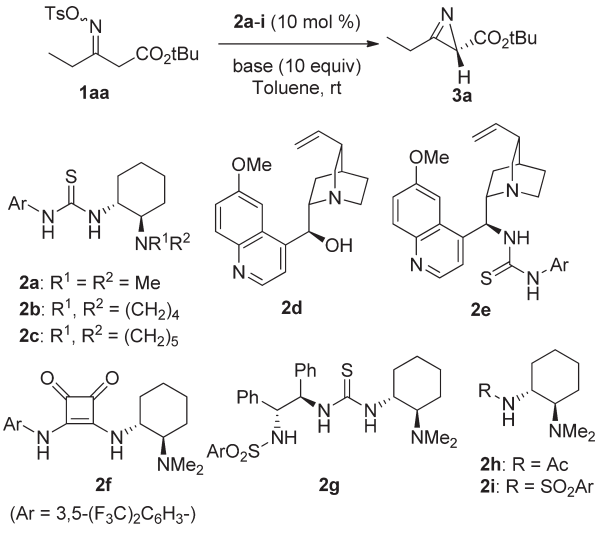
(9) The reaction of the similar substrate which bears the mesitylsulfonate moiety as a leaving group resulted in completely no reaction. The spectral data of this substrate are shown in the Supporting Information.

Table 1. Optimization of the Reaction Conditions[a]



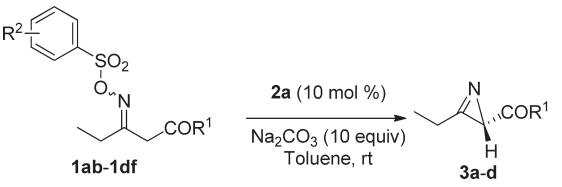
entry	**2**	base	time (h)	yield (%)[b]	ee (%)[c]
1	**2a**	Et_3N[d]	6	78	10
2	**2a**	Cs_2CO_3	24	80	45
3	**2a**	K_2CO_3	24	78	52
4	**2a**	Na_2CO_3	24	79	64
5	**2a**	$NaHCO_3$	24	63	62
6[e]	**2a**	Na_2CO_3[f]	24	81	38
7[g]	**2a**	Na_2CO_3	24	75	64
8[h]	**2a**	Na_2CO_3	24	78	63
9	**2b**	Na_2CO_3	12	81	51
10	**2c**	Na_2CO_3	48	80	56
11	**2d**	Na_2CO_3	24	72	22
12	**2e**	Na_2CO_3	24	75	57[i]
13	**2f**	Na_2CO_3	24	56	28
14	**2g**	Na_2CO_3	24	72	56
15	**2h**	Na_2CO_3	24	56	8[i]
16	**2i**	Na_2CO_3	24	21	5

[a] Unless otherwise noted, the reaction was performed with **1aa**, catalyst **2** (10 mol %) and base (10 equiv) in toluene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] 1 equiv of base was used. [e] Water was added (toluene/H_2O = 10:1). [f] 2 equiv of base was used. [g] TBME was used as a solvent. [h] CH_2Cl_2 was used as a solvent. [i] The antipode of (*S*)-**3a** was obtained.

yield and 81% ee (entry 9). In addition, the Neber reaction proceeded equally well with 5 mol % of **2a** without decreasing the enantioselectivity (entry 10). Finally, when we used substrate **1df**, which was designed by the combination of the two most positive substituent effects, the first high enantioselectivity (86% ee) was achieved by the catalytic asymmetric Neber reaction (entry 11).

After optimizing the substrates, our attention was directed toward the scope of the reactions (Table 3). Azirine **5a** bearing a propyl group was synthesized in 71% yield with 86% ee from *O*-3,5-bis(trifluoromethyl)benzenesulfonyl oxime **4a** (entry 1). When the reaction was applied to the substrates with longer alkyl chains, the enantioselectivity slightly increased (entries 2 and 3). In the cases of ketoximes **4d** and **4e** possessing secondary alkyl groups,

Table 2. Effect of the Substituents (R^1 and R^2)[a]



1ab: R^1 = O^{t}Bu, R^2 = 4-NO_2
1ac: R^1 = O^{t}Bu, R^2 = 2-NO_2
1ad: R^1 = O^{t}Bu, R^2 = 2-Me
1ae: R^1 = O^{t}Bu, R^2 = 3,5-Me_2
1af: R^1 = O^{t}Bu, R^2 = 3,5-$(CF_3)_2$
1ba: R^1 = NPh_2, R^2 = 4-Me
1ca: R^1 = OBn, R^2 = 4-Me
1da: R^1 = OEt, R^2 = 4-Me
1df: R^1 = OEt, R^2 = 3,5-$(CF_3)_2$

entry	**1**	time (h)	**3**	yield (%)[b]	ee (%)[c]
1	**1ab**	24	**3a**	78	68
2	**1ac**	4	**3a**	78	62
3	**1ad**	24	**3a**	78	49
4	**1ae**	24	**3a**	81	54
5	**1af**	24	**3a**	80	72
6	**1ba**	13	**3b**	80	64
7	**1ca**	24	**3c**	81	67
8	**1da**	24	**3d**	81	68
9[d]	**1da**	48	**3d**	78	81
10[d,e]	**1da**	48	**3d**	75	82
11[d,e]	**1df**	48	**3d**	72	86

[a] Unless otherwise noted, the reaction was performed with **1**, thiourea **2a** (10 mol %), and Na_2CO_3 (10 equiv) in toluene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out at −20 °C [e] 5 mol % of **2a** was used.

the corresponding (trifluoromethyl)benzenesulfonyl oxime could not be synthesized; however the corresponding *p*-toluenesulfonyl oxime gave **5d** and **5e** in good enantioselectivities (entries 4 and 5). The reaction of alkenyl-substituted ketoximes **4f**–**h** generally occurred with high enantioselectivity, providing the cyclized products **5f**–**h** (entries 6–8). However, the same treatment of alkynyl-substituted ketoxime **4i** resulted in a somewhat lower ee of azirine **5i** (entry 9). Azirine **5j**, which can be an important synthetic intermediate of pleurocybellaziridine,[10] could be prepared from **4j** (entry 10).[11]

Finally, we explored the synthetic versatility of the products obtained in the asymmetric Neber reaction. As shown in Scheme 1, the asymmetric synthesis of (*S*)-dysidazarine, antipode of the natural product, was accomplished in five steps from commercially available compound **6**. β-Keto ester **7** was prepared by the successive treatment of **6** with *N*,*N*′-carbonyldiimidazole (CDI) and $Mg(OCOCH_2CO_2Me)_2$ in one pot. Subsequently, **7** was transformed into dysidazirine by the standard three-step procedure. The reaction of **7** with hydroxylamine, sulfonylation of the resulting oxime with 3,5-bis$(CF_3)_2$-$C_6H_3SO_2Cl$, and asymmetric Neber reaction provided the

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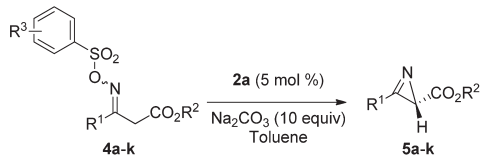
Table 3. Scope of the Substrates[a]

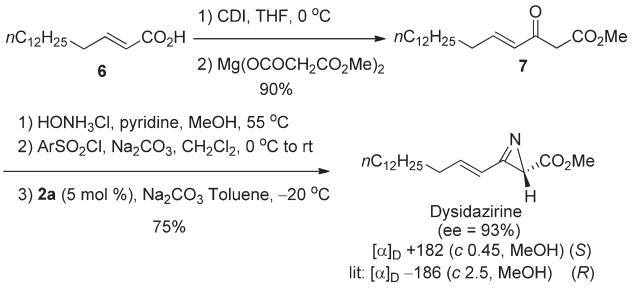


4a: R^1 = nPr, R^2 = Et, R^3 = 3,5-$(CF_3)_2$
4b: R^1 = Bn, R^2 = Et, R^3 = 3,5-$(CF_3)_2$
4c: R^1 = $Ph(CH_2)_2$, R^2 = Et, R^3 = 3,5-$(CF_3)_2$
4d: R^1 = iPr, R^2 = Et, R^3 = 4-Me
4e: R^1 = Cy, R^2 = Et, R^3 = 4-Me
4f: R^1 = (*E*)-PhCH=CH, R^2 = Et, R^3 = 3,5-$(CF_3)_2$
4g: R^1 = (*E*)-4-$MeOC_6H_4CH$=CH, R^2 = Et, R^3 = 3,5-$(CF_3)_2$
4h: R^1 = (*E*)-4-FC_6H_4CH=CH, R^2 = Et, R^3 = 3,5-$(CF_3)_2$
4i: R^1 = PhC≡C, R^2 = Et, R^3 = 3,5-$(CF_3)_2$
4j: R^1 = Me, R^2 = $CHPh_2$, R^3 = 3,5-$(CF_3)_2$

entry	4	temp (°C)	time (h)	5	yield (%)[b]	ee (%)[c]
1	**4a**	−10	48	**5a**	71	86
2	**4b**	−10	48	**5b**	78	93
3	**4c**	−10	48	**5c**	82	88
4	**4d**	−20	72	**5d**	82	85
5	**4e**	−20	72	**5e**	73	88
6	**4f**	−20	24	**5f**	96	90
7	**4g**	−20	24	**5g**	73	93
8	**4h**	−20	24	**5h**	77	90
9	**4i**	−20	72	**5i**	81	82
10	**4j**	−20	72	**5j**	64	80

[a] Unless otherwise noted, the reaction was performed with **4** (1.0 equiv), thiourea **2a** (5 mol %), and Na_2CO_3 (10 equiv) in toluene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

Scheme 1. Asymmetric Synthesis of (+)-Dysidazirine

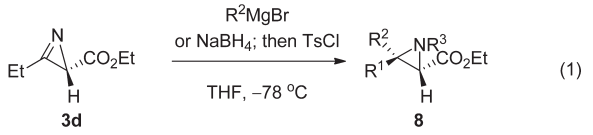


desired (*S*)-azirine in 75% yield with 93% ee. The ee value of the synthetic product is comparable to the one reported for the same product obtained by diastereoselective aziridination using a chiral sulfoxide auxiliary.[3d]

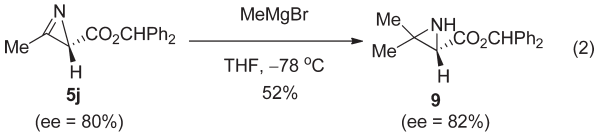
Furthermore, various tri- and disubstituted chiral aziridines **8a**−**c** could be prepared from **3d** by the diastereoselective nucleophilic addition of methyl, alkynyl, and hydride groups according to the reported methods (Scheme 2, eq 1).[2]

The azirine **5j** was successfully converted into the aziridine **9**, which is the synthetic precursor of *Pleurocybella porrigens*. During the course of the Neber reaction and Grignard reaction, the enantiomeric excess did not decrease and comparison of the specific rotation of **9** with that of the reported data also supported that the Neber reaction catalyzed by **2a** gave an (*S*)-configuration (Scheme 2, eq 2).[10]

Scheme 2. Transformation of the Azirines



8a: R^1 = Et, R^2 = Me, R^3 = H (83%, dr = >95:5)
8b: R^1 = Et, R^2 = C≡CPh, R^3 = H (87%, dr = >95:5)
8c: R^1 = H, R^2 = Et, R^3 = Ts (73%, dr = >95:5)



[α]D = +20 (*c* 1.1, $CHCl_3$) (*S*)
lit: [α]D = +24 (*c* 1.0, $CHCl_3$) (*S*)

In conclusion, we have developed the first highly enantioselective catalytic Neber reaction for the synthesis of chiral 2*H*-azirines. The reaction requires the bifunctional aminothiourea **2a** as a chiral catalyst. In addition we found that it is effective to use the 3,5-bis(trifluoromethyl)-benzenesulfonyl group as a leaving group for high enantioselectivity. In particular, the thiourea moiety of catalyst **2a** is important, and use of amide and sulfonamide catalysts possessing no thiourea results in a dramatic decrease in ee. Research to clarify the detailed mechanism of the asymmetric Neber reaction is currently underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.