Communication

Organocatalytic Kinetic Resolution of Sulfoximines

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Organocatalytic Kinetic Resolution of Sulfoximines

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Supporting Information Placeholder

ABSTRACT: An efficient kinetic resolution of sulfoximines with enals was realized using chiral *N*–heterocyclic carbene (NHC) catalysts. The stereoselective amidation proceeds without additional acyl transfer agent. Both enantiomers of the sulfoximines can be obtained with excellent ee values (up to 99% ee and –97% ee, respectively). Performing the catalysis on a gram scale allowed using the recovered sulfoximine (+)-**1j** in an asymmetric synthesis of FXa inhibitor **F**.

Sulfoximines,[1] the monoaza analogues of sulfones, have been widely used in organic synthesis as reagents,[2] chiral auxiliaries,[3] chiral ligands,[4] and directing groups in C–H activations.[5] Moreover, sulfoximines have attracted attention in agricultural science[6] and medicinal chemistry[1e] (compounds **A**-**F**; Figure 1). In most of these applications the stereochemistry at sulfur proved important.

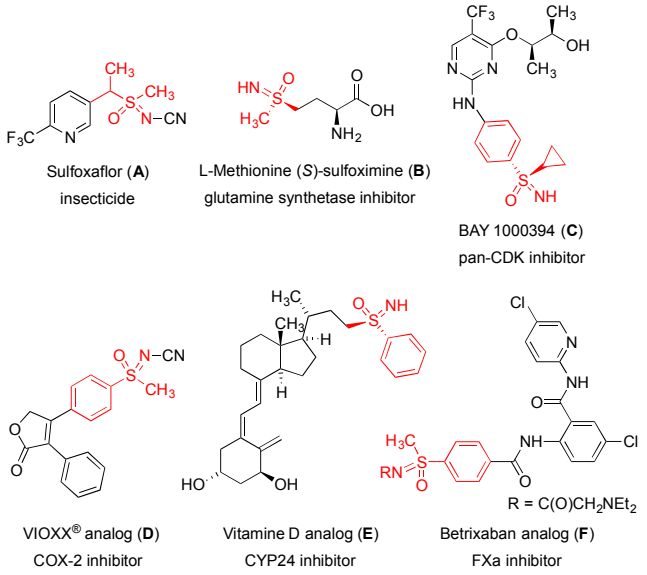
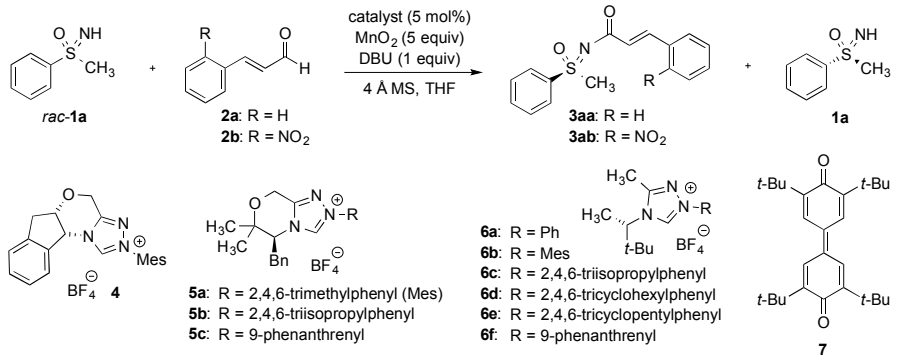


Figure 1. Structures of selected bioactive sulfoximines

Although sulfoximines can be readily synthesized by various methods, their preparation in enantioenriched form is still challenging. Besides resolution,[7] which is only applicable to a small number of sulfoximines, the most prominent strategies are stereospecific imidations of optically active sulfoxides[8a-c] and oxidations of enantioenriched sulfimides.[8d-f] However, those approaches are multi-step transformations with undesirable protection/deprotection sequences.[9] For the preparation of other important compound classes, catalytic kinetic resolution (KR) is often the method of choice.[10] In this context, we recently reported an iron-catalyzed imidative KR of racemic sulfoxides, leading to *N*-Ts protected sulfoximines in enantiomerically enriched form.[11] However, the low yield (15%) of a product with high ee (94% ee) limited the utility of this method. Although acylative KR reactions of amines have been well-established,[10] a direct chemocatalytic KR of sulfoximines has not been realized to date.[12] Herein, we describe the first process of such type using chiral NHCs as catalysts leading to various sulfoximines with excellent ee values for both enantiomers (up to 99% ee and –97% ee, respectively).

The slightly distorted tetrahedral arrangement at sulfur[1a] presented a particular challenge for the KR of sulfoximines. The initial results were disappointing. Well-established chiral acyl transfer catalysts[13] such as benzotetramizoles[13a] and thiourea/DMAP combinatons[13b] only gave racemic *S*-methyl-*S*-phenyl sulfoximine (**1a**). Inspired by Zhao's work,[14] we attempted the use of chiral NHCs.[15] The common need of an additive such as imidazole or 1-hydroxy-7-azabenzotriazole in NHC-catalyzed amide formations was foreseen as potential difficulty.[16] To our delight, however, even without such additive,[17] the reaction of sulfoximine (±)-**1a** with cinnamaldehyde (**2a**) proceeded smoothly in the presence of 5 mol% of NHC catalyst **4**, MnO_2 (5 equiv), 4 Å MS, and DBU (1 equiv), resulting in amide **3aa** in 53% yield with 39% ee. Unreacted **1a** was isolated in 44% yield with 45% ee (s = 4, Table 1, entry 1). Encouraged by this result, the effects of other NHCs were investigated.[18] Triazolium **5a** gave a better result, providing the recovered sulfoximine with opposite configuration (entry 2, –45% ee for **3aa** and –62% ee for **1a**, s = 5). Then, different enals were used, and it was found that 2-nitrocinnamaldehyde (**2b**) showed enhancements in both reactivity and enantioselectivity (entry 3).[18] A search for alternative NHC catalysts led to chiral triazolium **6a** developed by Enders.[19] Pleasingly, an s factor of 8 was achieved with this (*S*)-3,3-dimethylbutan-2-amine-based catalyst, albeit the reactivity was low. Subjecting a series of structurally related *N*-substituted triazolium salts to the model reaction[18] showed that *N*-mesityl-substituted **6b**[20] did not only lead to good ee values, but also to a high catalytic activity (s = 10, Table 1, entry 5). Catalyst **6c** bearing a bulkier *N*-2,4,6-*i*-$Pr_3C_6H_2$ substituent performed even better (s = 12, Table 1, entry 6). Increasing the steric bulk further, for example, by using tricyclohexyl- or tricyclopentyl-substituted **6d** or **6e**, respectively, gave no improvement (Table 1, entries

Table 1. Optimization of the Reaction Conditions[a]



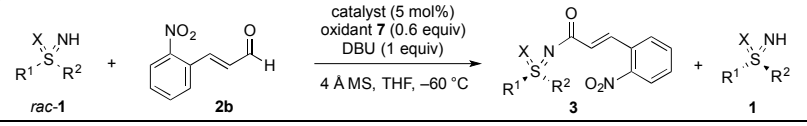
entry	catalyst	T (°C)	t (h)	yield of **3** (%)	ee of **3** (%)[b]	yield of **1a** (%)	ee of **1a** (%)[b]	*s*[c]
1[d]	**4**	–20	48	53 (**3aa**)	39	44	45	4
2[d]	**5a**	–20	48	58 (**3aa**)	–45	40	–62	5
3	**5a**	–20	24	42 (**3ab**)	–68	50	–50	9
4	**6a**	–20	48	30 (**3ab**)	72	65	32	8
5	**6b**	–20	48	45 (**3ab**)	70	52	57	10
6	**6c**	–20	48	54 (**3ab**)	67	42	81	12
7	**6d**	–20	48	57 (**3ab**)	63	40	84	11
8	**6e**	–20	48	50 (**3ab**)	70	45	70	12
9	**6f**	–20	48	54 (**3ab**)	67	41	80	12
10	**5b**	–20	48	51 (**3ab**)	–70	46	–70	12
11	**5c**	–20	72	51 (**3ab**)	–68	45	–70	11
12	**6c**	–45	72	38 (**3ab**)	78	58	50	13
13[e]	**6c**	–45	72	59 (**3ab**)	64	38	94	15
14[e,f]	**6c**	–60	96	53 (**3ab**)	81	43	91	30
15[e]	**5b**	–60	96	56 (**3ab**)	–75	42	–95	25

[a] Unless otherwise noted, all reactions were carried out with the catalyst (5 mol%), **1a** (31 mg, 0.20 mmol), **2b** (21 mg, 0.12 mmol), DBU (30 μL, 0.20 mmol), 4 Å MS (30 mg) and MnO_2 (87 mg, 1.0 mmol) in THF (1 mL). [b] Determined by CSP-HPLC analysis [c] Selectivity factors (*s*), calculated according to the following equation: $s = \ln[(1-C)*(1-ee_1)]/\ln[(1-C)*(1+ee_1)]$, $C = (ee_1)/(ee_1+ee_3)$. [d] Use of **2a** (19 μL, 0.15 mmol) instead of **2b**. [e] 3,3',5,5'-tetra-*tert*-butyl-[1,1'-bi(cyclohexylidene)]-2,2',5,5'- tetraene-4,4'-dione (**7**, 49 mg, 0.12 mmol) was used as the oxidant instead of MnO_2. [f] The absolute configuration of the major enantiomer **1a** was (*S*) by comparing the specific rotation with the reported value.[7b]

7 and 8). Triazolium **6f** bearing an *N*-9-phenanthrenyl substituent performed equally well (*s* = 12, entry 9), indicating a possible π-π stacking interaction between the catalyst and the substrates. The same trend could be deduced from the data obtained with triazoliums **5b** (with an *N*-2,4,6-*i*-$Pr_3C_6H_2$ substituent) and **5c** (bearing an *N*-9-phenanthrenyl moiety) (Table 1, entries 10 and 11 vs entry 3). With this promising lead, the reaction conditions were systematically screened.[18] Lowering the temperature from –20 °C to –45 °C led to a slight improvement of the s factor, but at the expense of the reactivity (entry 12 vs entry 6). When MnO_2 was replaced by quinone **7** as the oxidant, both the selectivity (*s* = 15) and the reactivity increased (entry 13). Further, lowering the temperature to –60 °C improved the *s* value to 30 (Table 1, entry 14), and unreacted **1a** was recovered in 43% yield with 91% ee. Using **5b**, the enantiomer of sulfoximine **1a** was formed in preference with –95% ee (Table 1, entry 15).

Having the optimized reaction conditions established, the scope of the kinetic resolution of sulfoximines was studied with **5b** or **6c** as catalysts (Table 2). A broad range of sulfoximines bearing different aryl substituents reacted smoothly affording the desired amides **3ab** and **3b–k** with moderate to high enantioselectivities (41–59% yield, 67–93% ee for **6c**, and 41–57% yield, –52 to –96% ee for **5b**). Unreacted **1a–k** were recovered in yields of 38–55% with 65–99% ee and in 40–53% yields with –65 to –97% ee (Table 2, entries 1–22). Notably, substrates with 4-CF_3, 4-SF_5, and 2-naphthyl substituents (**1l–n**) were also suitable (Table 2, entries 23–28). 2-Pyridyl-substituted **1o** gave low *s* factors (Table 2, entries 29 and 30). Sulfoximines **1p** and **1q** with cyclopropyl and benzyl substituents also underwent the KR processes with *s* factors of 16–60 (Table 2, entries 31–34). Product **3ab** was readily hydrolyzed with aqueous HCl to give **1a** stereospecifically under retention of configuration.[18] Finally, sulfondiimide **1r** was reacted, giving product **3r** with 58% ee (for **6c**) and –75% ee (for **5b**). In both cases, however, unreacted **1r** was recovered with low ee values (Table 2, entries 35 and 36).

Table 2. Substrate Scope for Kinetic Resolutions of Sulfoximines and a Sulfondiimide with Enal 2b[a]

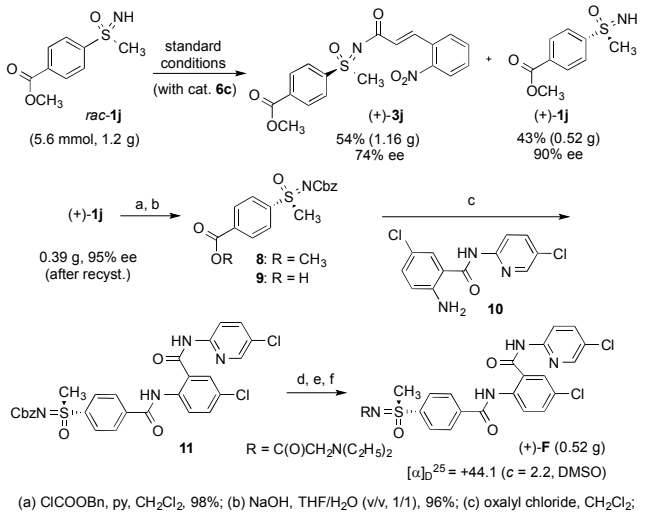


entry	R^1	R^2	X	t (h)	yield of **3** (%)	ee of **3**(%)[b]	yield of **1** (%)	ee of **1** (%)[b]	*s*
1	C_6H_5	CH_3	O	96	53 (**3ab**)	81	43 (**1a**)	91	30
2[c]	C_6H_5	CH_3	O	96	56 (**3ab**)	−75	42 (**1a**)	−95	25
3	2-BrC_6H_4	CH_3	O	96	54 (**3b**)	78	43 (**1b**)	92	26
4[c]	2-BrC_6H_4	CH_3	O	96	57 (**3b**)	−67	40 (**1b**)	−90	16
5	3-BrC_6H_4	CH_3	O	96	59 (**3c**)	67	38 (**1c**)	99	25
6[c]	3-BrC_6H_4	CH_3	O	96	56 (**3c**)	−74	42 (**1c**)	−93	22
7	4-BrC_6H_4	CH_3	O	96	56 (**3d**)	73	41 (**1d**)	96	24
8[c]	4-BrC_6H_4	CH_3	O	96	54 (**3d**)	−77	42 (**1d**)	−94	27
9	2-ClC_6H_4	CH_3	O	96	53 (**3e**)	80	45 (**1e**)	92	29
10[c]	2-ClC_6H_4	CH_3	O	96	56 (**3e**)	−69	40 (**1e**)	−85	14
11	4-ClC_6H_4	CH_3	O	96	52 (**3f**)	81	45 (**1f**)	94	33
12[c]	4-ClC_6H_4	CH_3	O	96	54 (**3f**)	−76	43 (**1f**)	−90	22
13	4-FC_6H_4	CH_3	O	108	54 (**3g**)	72	42 (**1g**)	85	16
14[c]	4-FC_6H_4	CH_3	O	108	53 (**3g**)	−75	42 (**1g**)	−88	20
15	4-$CH_3C_6H_4$	CH_3	O	96	52 (**3h**)	82	44 (**1h**)	94	35
16[c]	4-$CH_3C_6H_4$	CH_3	O	96	54 (**3h**)	−80	43 (**1h**)	−95	33
17	4-$CH_3OC_6H_4$	CH_3	O	96	52 (**3i**)	78	42 (**1i**)	89	24
18[c]	4-$CH_3OC_6H_4$	CH_3	O	96	57 (**3i**)	−73	41 (**1i**)	−97	26
19	4-$CH_3OC(O)C_6H_4$	CH_3	O	108	52 (**3j**)	78	42 (**1j**)	87	23
20[c]	4-$CH_3OC(O)C_6H_4$	CH_3	O	108	55 (**3j**)	−52	42 (**1j**)	−65	6
21[d]	4-$NO_2C_6H_4$	CH_3	O	108	41 (**3k**)	93	55 (**1k**)	65	54
22[c,d]	4-$NO_2C_6H_4$	CH_3	O	108	41 (**3k**)	−96	53 (**1k**)	−69	101
23	4-$CF_3C_6H_4$	CH_3	O	96	54 (**3l**)	76	44 (**1l**)	91	23
24[c]	4-$CF_3C_6H_4$	CH_3	O	96	52 (**3l**)	−80	47 (**1l**)	−87	25
25	4-$SF_5C_6H_4$	CH_3	O	96	53 (**3m**)	75	43 (**1m**)	88	20
26[c]	4-$SF_5C_6H_4$	CH_3	O	96	56 (**3m**)	−73	41 (**1m**)	−93	21
27	2-naphthyl	CH_3	O	96	54 (**3n**)	79	43 (**1n**)	96	33
28[c]	2-naphthyl	CH_3	O	96	54 (**3n**)	−80	44 (**1n**)	−95	33
29	2-pyridyl	CH_3	O	120	52 (**3o**)	43	44 (**1o**)	48	4
30[c]	2-pyridyl	CH_3	O	120	54 (**3o**)	−53	44 (**1o**)	−63	6
31	C_6H_5	cyclopropyl	O	96	54 (**3p**)	84	44 (**1p**)	99	60
32[c]	C_6H_5	cyclopropyl	O	96	54 (**3p**)	−79	44 (**1p**)	−93	29
33	C_6H_5	$C_6H_5CH_2$	O	96	53 (**3q**)	78	45 (**1q**)	90	25
34[c]	C_6H_5	$C_6H_5CH_2$	O	96	56 (**3q**)	−69	40 (**1q**)	−90	16
35	C_6H_5	CH_3	NC_6H_5	96	16 (**3r**)	58	82 (**1r**)	11	4
36[c]	C_6H_5	CH_3	NC_6H_5	96	18 (**3r**)	−75	80 (**1r**)	−17	8

[a] Unless otherwise noted, all reactions were carried out with **6c** (5 mol%), **1** (0.20 mmol), **2b** (21 mg, 0.12 mmol), DBU (30 μL, 0.20 mmol), 4 Å MS (30 mg) and oxidant **7** (49 mg, 0.12 mmol) in THF (1.0 mL) at −60 °C. . [b] Determined by CSP-HPLC analysis. [c] Catalyst **5b** was used instead of **6c**. [d] Use of 10 mol% of catalyst.

To further evaluate the synthetic potential of the catalytic system, the reaction was conducted on a gram scale, giving (+)-**1j** in 43% yield with 90% ee. Sulfoximine **1j** was selected as target here because it represented a key fragment of compound **F**, which as racemate revealed a strong human FXa inhibitory activity (IC_{50}= 2.1 nM) and anticoagulant effects. Using recrystallized sulfoximine (+)-**1j** (with 95% ee) prepared by the aforementioned kinetic resolution process allowed for the first time the preparation of optically active compound **F** (with a total yield of 50%; Scheme 1).[21]

Scheme 1. Scale-up Experiment and Its Application



(a) ClCOOBn, py, CH_2Cl_2, 98%; (b) NaOH, THF/H_2O (v/v, 1/1), 96%; (c) oxalyl chloride, CH_2Cl_2; then **10**, 94%; (d) H_2SO_4; (e) $ClCH_2C(O)Cl$, TEA, THF; (f) $HNEt_2$, KI, DMF, 56% over 3 steps.

In summary, catalytic resolutions of racemic sulfoximines have been accomplished by chiral NHC-catalyzed enantioselective amidation reactions with enals. Both enantiomers of various sulfoximines could be obtained with excellent ee values. The utility of this strategy was demonstrated in the asymmetric synthesis of human Factor Xa inhibitor **F**.

ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(17) We assume that this behavior is due to the low nucleophilicity and basicity of the NH group of sulfoximine **1a** (with a pK_a value of 24 in DMSO).

(18) For details, see the Supporting Information and the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif where the data can be obtained free of charge.

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