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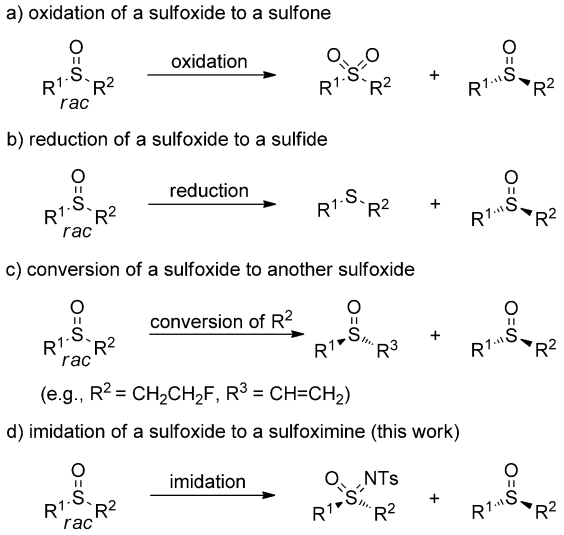
Kinetic Resolution

Iron-Catalyzed Imidative Kinetic Resolution of Racemic Sulfoxides

Jun Wang,[a, b] Marcus Frings,[a] and Carsten Bolm*[a]

Abstract: Kinetic resolution of racemic sulfoxides requires either custom substrates or shows moderate enantioselectivity, leading to achiral coproducts (such as sulfones) as an intrinsic part of the process. A new strategy is demonstrated that allows the resolution of racemic sulfoxides through catalytic asymmetric nitrene-transfer reactions. This approach gives rise to both optically active sulfoxides and highly enantioenriched sulfoximines. By using a chiral iron catalyst and a readily available iodinane reagent, high selectivity factors have been achieved under very practical reaction conditions. With respect to the substrate scope, it is noteworthy that this unprecedented imidative kinetic resolution of racemic sulfoxides provides access to both aryl–alkyl and dialkyl sulfoximines in highly enantioenriched forms.



Scheme 1. Strategies for the kinetic resolution of racemic sulfoxides.

When a racemic compound reacts with an enantiopure reagent, the two enantiomers of the former can convert at very different reaction rates. Such kinetic resolutions can also occur with achiral reaction partners when enzymes or chiral catalysts are applied.[1] In both academia and industry, kinetic resolutions have great significance in the preparation of enantiopure products. With respect to sulfoxides, three strategies have been reported to date.[2] The first two have in common that one sulfoxide enantiomer of a racemic mixture is preferentially transformed into an achiral product. This can either be a sulfone[3] or a sulfide,[4] depending on the use of oxidative or reductive methods, respectively (Scheme 1, a and b). Both routes have carefully been investigated, but often the efficiency of the reaction is low and the observed enantioselectivities are moderate. The preferential conversion of one sulfoxide enantiomer into a different sulfoxide is the third strategy (Scheme 1, c). Unfortunately, this pathway is limited to some very specific substrates.[5] Herein, we present a new approach to kinetic sulfoxide resolutions by using iron-catalyzed asymmetric nitrene-transfer reactions (Scheme 1, d). As a result, both sulfoximines and sulfoxides can be obtained in enantiomerically enriched forms.[6]

Owing to their potential synthetic applications and interesting biological activities, sulfimides[7] and sulfoximines[8] attract continuous attention. The synthesis of these compounds usually involves the imidation of sulfides or sulfoxides;[9] however, only a few of these methods are enantioselective. Recently, we described a method for the synthesis of sulfimides and sulfoximines that involves the application of a chiral iron complex, leading to high enantioselectivities in imidative sulfide-to-sulfimide conversions.[10,11] Encouraged by those results, we wondered how this catalyst system would work in a kinetic-resolution process starting from racemic sulfoxides.

Initially, racemic methylphenylsulfoxide *rac*-**1a** was employed as the model substrate and *N*-tosyliminophenyliodinane (PhI=NTs) was employed as the nitrene precursor. The reactions were conducted with *rac*-**1a** (1 equivalent), PhI=NTs (0.5 equivalents), and 5 mol% of catalyst (with respect to *rac*-**1a**), in acetone at 0 °C. Preliminary studies revealed that the catalyst, generated in situ from [Fe(acac)$_3$] (acac = acetylacetonate) (**3a**) and (*R*,*R*)-2,6-bis(4-phenyl-2-oxazolinyl)pyridine, (*R*,*R*)-Ph-PyBOX (**4a**), showed a good ability to differentiate the two enantiomers of the sulfoxide. Hence, sulfoximine **2a** was isolated with an enantiomeric ratio (e.r.) of 88:12 (*R*/*S*), in 19% yield after 15 h (Table 1, entry 1).

[a] Dr. J. Wang, M. Frings, Prof. Dr. C. Bolm
Institute of Organic Chemistry
RWTH Aachen University
Landoltweg 1, 52056 Aachen (Germany)
Fax: (+49) 241-8092391
E-mail: carsten.bolm@oc.rwth-aachen.de
Homepage: http://bolm.oc.rwth-aachen.de

[b] Dr. J. Wang
Current address: School of Chemistry and Chemical Engineering
Sun Yat-Sen University
Guangzhou 510275 (P.R. China)

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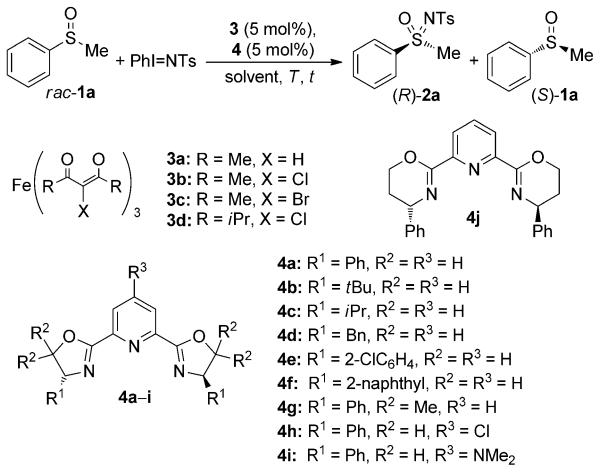
Table 1. Optimization of the reaction conditions.[a]



Entry	Iron salt	Ligand	Solvent	T [°C]	t [h]	Yield of **2a** [%][b]	e.r. of **2a**[c]	s[d]
1	**3a**	**4a**	acetone	0	15	19	88:12	8.7
2	**3b**	**4a**	acetone	0	15	28	93:7	18.4
3	**3c**	**4a**	acetone	0	15	29	92:8	16.1
4	**3d**	**4a**	acetone	0	15	18	89:11	9.6
5	**3b**	**4a**	CH_2Cl_2	0	15	35	83:17	6.9
6	**3b**	**4a**	MeCN	0	3	44	90:10	17.0
7	**3b**	**4a**	acetone	−20	15	32	95:5	28.8
8	**3b**	**4a**	**acetone**	**−20**	**22**	**37**	**94:6**	**26.2**
9	**3b**	**4a**	acetone	−45	38	15	97:3	38.0
10	**3b**	**4a**	*i*PrCN	−20	15	42	93:7	25.1
11	**3b**	**4b**	*i*PrCN	−20	21	36	71:29	3.1
12	**3b**	**4c**	*i*PrCN	−20	21	37	65:35	2.2
13	**3b**	**4d**	*i*PrCN	−20	21	39	64:36	2.1
14	**3b**	**4e**	*i*PrCN	−20	21	48	79:21	6.3
15	**3b**	**4f**	*i*PrCN	−20	21	42	88:12	12.6
16	**3b**	**4g**	*i*PrCN	−20	21	42	89:11	14.2
17	**3b**	**4h**	*i*PrCN	−20	21	41	89:11	13.8
18	**3b**	**4i**	*i*PrCN	−20	15	29	93:7	18.7
19	**3b**	**4j**	*i*PrCN	−20	21	34	93:7	20.5

[a] Reaction conditions: Iron(III) salt (**3**, 5 mol%), ligand (**4**, 5 mol%), *rac*-**1a** (1 equivalent), PhI=NTs (0.5 equivalents), solvent. [b] Based on the amount of *rac*-**1a**. [c] Determined by high-performance liquid chromatography (HPLC) analysis by using a chiral stationary phase. [d] Selectivity factors (s), calculated according to the following equation: $s = \ln[1-C(1+ee_{2a})]/\ln[1-C(1-ee_{2a})]$, in which C = conversion (yield of **2a**) and ee_{2a} = enantiomeric excess of **2a**.

Subsequently, various iron(III) acetylacetonate derivatives were examined. Notably, both the steric and electronic effects of the 1,3-diketonate moiety influenced the outcome of the reaction. Thus, with iron(III)-3-chloroacetylacetonate, [Fe(acacCl)$_3$] (**3b**), the catalytic activity and the enantioselectivity were greatly enhanced, leading to sulfoximine **2a** with an e.r. of 93:7, in 28% yield. In other words, the selectivity factor (s)[12] had increased from 8.7 to 18.4 (Table 1, entry 2). Assuming that the increased Lewis acidity of the iron(III) center played a role in enhancing the enantioselectivity, iron(III)-3-bromoacetylacetonate, [Fe(acacBr)$_3$] (**3c**), was tested; as hypothesized, **3c** led to a result comparable to that of **3b** (Table 1, entry 3). In contrast, the use of iron(III)-4-chloro-2,6-dimethyl-3,5-heptanedionate, [Fe(dmhdCl)$_3$] (**3d**), with two bulky R groups (isopropyl instead of methyl) in each 1,3-diketonate, diminished both the reactivity and enantioselectivity (Table 1, entry 4 versus entry 2).[13] When the reaction was performed in other solvents (e.g., dichloromethane or acetonitrile), inferior results were obtained (Table 1, entries 5 and 6). Lowering the reaction temperature from 0 to −20 °C (Table 1, entry 7) increased the selectivity factor (s = 28.8), and sulfoximine **2a** was obtained with an e.r. of 95:5, in 32% yield. When the reaction time was increased from 15 to 22 h, the yield of **2a** increased to 37%, but the e.r. slightly decreased from 95:5 to 94:6 (Table 1, entry 8). Performing the reaction at −45 °C was beneficial for the enantioselectivity, but the reaction rate was dramatically reduced. After 38 h sulfoximine **2a** was isolated with an e.r. of 97:3, but with only 15% yield (Table 1, entry 9).

Various other PyBOX ligands, as well as an analogue thereof, have been screened with *i*PrCN as solvent. Under the same reaction conditions, PyBOX ligands **4b**–**d**, with aliphatic or benzylic substituents, gave poor enantioselectivities (Table 1, entries 11–13 versus entry 10). Replacing the phenyl groups in PyBOX **4a** by 2-chlorophenyl or 2-naphthyl substituents resulted in decreased enantioselectivities (Table 1, entries 14 and 15). Introducing two methyl groups at the 5-position of each oxazoline moiety also diminished the enantioselectivity (Table 1, entry 16). PyBOX ligands containing substituents with distinct electronic properties on the pyridine ring were also tested. The enantioselectivity slightly decreased when the ligand had a chloride group at the 4-position of the PyBOX pyridine ring (Table 1, entry 17). However, PyBOX **4i**, containing a 4-dimethylamino substituent, gave the same enantioselectivity as **4a**, but a lower reactivity was observed (Table 1, entry 18). Thus, the basicity of the pyridine moiety influenced the catalytic process. Interestingly, ligand **4j**, with two six-membered 4*H*-1,3-oxazine rings, gave the same enantioselectivity as PyBOX **4a** (Table 1, entry 19). Taking all of our findings into consideration, PyBOX **4a** was identified as the best ligand of those tested.

Other reaction parameters were also varied[14] and the optimal reaction conditions were found to be: [Fe(acacCl)$_3$] (**3b**, 5 mol%), (*R*,*R*)-Ph-PyBOX (**4a**, 5 mol%), racemic sulfoxide **1a** (1 equivalent), and PhI=NTs (0.5 equivalents), in acetone (0.2 M) at −20 °C. Neither moisture nor air had to be excluded.

Table 2. Investigation using different amounts of the nitrene precursor.[a]

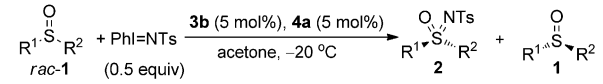
Entry	PhI=NTs [equiv]	**2a** Yield [%]	**2a** e.r.[b]	**1a** Yield [%]	**1a** e.r.[b]	s[c]
1	0.5	37	94:6	56	78:22	27.5 (26.2)
2	0.6	46	93:7	45	84:16	26.9 (29.1)
3	0.75	48	91:9	47	87:13	22.3 (22.9)
4	1.0	49	91:9	47	85:15	21.1 (24.1)

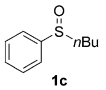
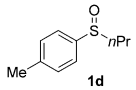
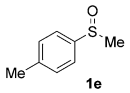
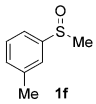
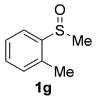
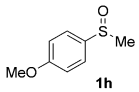
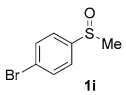
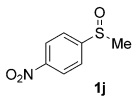
[a] Reaction conditions: [Fe(acacCl)$_3$] (**3b**, 5 mol%), (*R*,*R*)-Ph-PyBOX (**4a**, 5 mol%), *rac*-**1a** (1 equivalent), PhI=NTs (0.5–1 equivalent), in acetone at −20 °C, 18 h. [b] Determined by HPLC by using a chiral stationary phase. [c] As in Table 1, footnote [d], $C = (ee_{1a})/(ee_{1a}+ee_{2a})$. In parentheses: yields of **2a** were used as conversions for calculations.

To investigate the effect of the sulfoxide conversion on the outcome of the kinetic resolution, reactions were performed under identical conditions, but with various amounts (0.5–1 equivalent) of the nitrene precursor (Table 2). As expected, on increasing the amount of PhI=NTs, the yield of sulfoximine **2a** improved (from 37 to 49%), but the e.r. decreased (from 94:6 to 91:9). For (recovered) sulfoxide **1a**, the opposite trend was observed. The selectivity factor gradually decreased from 27.5 to 21.1 as the conversion increased.

Next, the conversion of various racemic sulfoxides, under the optimized conditions, (Table 1, entry 8) was studied. Pleasingly, the catalyst was capable of accommodating a number of aryl alkyl sulfoxides. Extending the alkyl chain linearly, from C_1 (methyl) to C_4 (butyl), had no influence on the e.r. (94:6) of the resulting sulfoximines **2a**–**d**, and their yields (ranging from 37 to 44%) remained essentially the same (Table 3, entries 1–4). To evaluate the impact of the arene substitution pattern, reactions with three methyltolyl sulfoxides **1e**–**g** were examined (Table 3, entries 5–7); *para*- and *meta*-substituted **1e** and **1f**, respectively, gave similar results to those of the model substrate **1a**, whereas, *ortho*-substituted sulfoxide **1g** showed poor selectivity ($s=$ 3.9) and very low conversion (4% yield after 24 h). Thus, the presence of an *ortho*-methyl group seriously hampered the catalytic process. Raising the temperature from −20 to 0 °C did not positively affect the reaction rate. Electronic effects were studied by examining aryl–methyl sulfoxides **1h**–**j**, which possess *para*-MeO, *para*-Br, and *para*-NO_2 substituents, respectively. The yields (41 and 43%) and e.r. values (93:7) of the corresponding sulfoximines (**2h** and **2i**) of **1h** and **1i** were essentially the same (Table 3, entries 8 and 9), whereas the results achieved with **1j**, which has a strong electron-withdrawing group, NO_2, were unsatisfying (Table 3, entry 10). Even after 24 h (at −20 °C), only 6% of sulfoximine **2j** (with an e.r. of 90:10) was obtained, even at 0 °C

Table 3. Substrate scope of the imidative kinetic resolution.



Entry	Sulfoxide	*t* [h]	Yield of **2** [%]	e.r. of **2**[a]	*s*[c]
1	 **1a**	22	37	94:6	26.2
2	 **1b**	22	39	94:6	27.6
3	 **1c**	22	37	94:6	26.2
4	 **1d**	24	40	94:6	28.3
5	 **1e**	24	35	94:6	25.0
6	 **1f**	24	35	93:7	21.0
7[b]	 **1g**	24 (21)	4 (6)	79:21 (72:28)	3.9 (2.6)
8	 **1h**	24	41	93:7	24.3
9	 **1i**	24	43	93:7	25.9
10[b]	 **1j**	24 (21)	6 (18)	90:10 (84:16)	9.5 (6.1)
11	 **1k**	24	35	86:14	9.0

[a] As determined by HPLC by using a chiral stationary phase. The absolute configurations of the major enantiomers of **2a** and **2e** were determined to be *R* by comparing the respective optical rotations with reported data. [b] The data in parentheses were obtained when reactions were conducted at 0 °C. [c] As in Table 1, footnote [d].

the yield remained low (18%; e.r. = 84:16). As exemplified by the imidation of cyclohexylmethylsulfoxide **1k**, nonaromatic substrates were also tolerated in this reaction (Table 3, entry 11). Accordingly, sulfoximine **2k** was obtained in 35% yield, with an e.r. of 86:14 (corresponding to a selectivity factor of 9.0).

In summary, the catalytic imidative kinetic resolution of racemic sulfoxides is a new strategy for the synthesis of optically active sulfoximines. High selectivity factors (up to 38.0) have been reached by using an easily accessible chiral iron complex, providing sulfoximines in enantiomerically enriched form (up to 97:3 e.r.).[6]

Experimental Section

General procedure for the iron-catalyzed imidation of racemic sulfoxides

$[Fe(acacCl)_3]$ (**3b**, 5 mol%, 0.01 mmol, 4.6 mg), (*R*,*R*)-Ph-PyBOX (**4a**, 5 mol%, 0.01 mmol, 3.7 mg), and acetone (1 mL) were added to a test tube. The mixture was stirred for 30 min at room temperature and then racemic sulfoxide **1** (1 equivalent, 0.2 mmol) was added. After cooling the mixture to −20 °C, PhI=NTs (0.5 equivalents, 0.1 mmol, 37.5 mg) was added in one portion. The resulting mixture was stirred at −20 °C. After the time indicated in Table 3, the reaction mixture was directly subjected to silica-gel column chromatography. The resulting sulfoximine, **2**, was isolated and the e.r. was determined by HPLC by using a chiral stationary phase.

Acknowledgements

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Keywords: iron catalysis · kinetic resolution · nitrene transfer · sulfoxides · sulfoximines

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[6] As indicated in Table 2, the kinetic-resolution process also leads to enantiomerically enriched sulfoxides. In this study, these sulfoxides were not isolated (except for **1a**) owing to difficulties during purification of the product by column chromatography (the sulfoxides had similar R_f values to the PyBOX ligand).

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[13] Interestingly, in the previously studied enantioselective imidation of sulfides (ref. [10]), **3d** provided a better result than **3b**.

[14] For example, different imidation reagents, containing alternative sulfonyl groups were tested and, furthermore, nitrene precursors generated in situ by combining the corresponding sulfonamides ($ArSO_2NH_2$) with iodosylbenzene (PhI=O) were applied. None of these attempts led to improved enantioselectivities or better yields. For details, see the Supporting Information.

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