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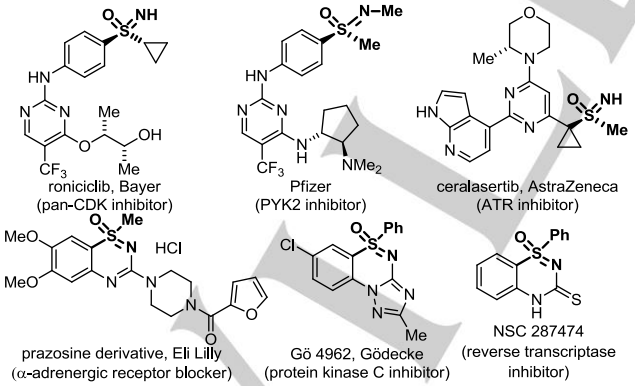
Efficient Kinetic Resolution of Sulfur-Stereogenic Sulfoximines Exploiting Cp^xRh^{III}-Catalyzed C-H Functionalization

Marcus Brauns and Nicolai Cramer[*]

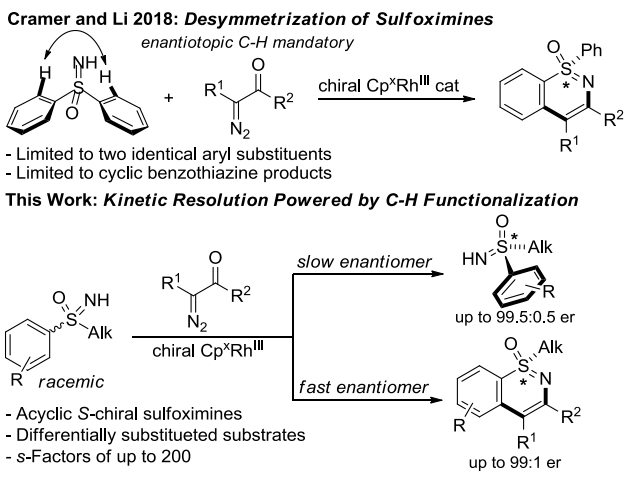
Abstract: Chiral sulfoximines with stereogenic sulfur atoms are promising motifs in drug discovery. We report an efficient method to access chiral sulfoximines by a C-H functionalization-based kinetic resolution. A rhodium(III) complex equipped with a chiral Cp^x-ligand selectively participates in conjunction with phthaloyl phenyl alanine in the C-H activation of just one of the two sulfoximine enantiomers. The intermediate reacts with various diazo compounds, providing access to chiral 1,2-benzothiazines with synthetically valuable substitution patterns. Both sulfoximines and 1,2-benzothiazines were obtained in high yields and excellent enantioselectivities with *s*-values of up to 200. The utility of the method is illustrated by the synthesis of the key intermediates of two pharmacologically relevant kinase inhibitors.

Already discovered in the late 1940s,[1] the sulfoximine functional group had largely been undervalued and underutilized. More recently, it has received a tremendous increase in attention, especially in the last decade.[2] Improved access by new synthetic methods reported by Bolm and others have reinforced this trend.[3] Sulfoximines are a chemically robust functional group, displaying configurationally stable *S*-stereogenicity.[2d, 4] In medicinal chemistry, they often show significant bioactivity, indicating a high potential as active pharmaceutical ingredients.[2c, 5] Compared to sulfones and sulfonamides, sulfoximines can provide strategic advantages related to improved solubility properties or higher metabolic stability.[5a, 6] Due to these benefits, an increasing number of sulfoximine-containing bioactive compounds have been disclosed and entering clinical trials. For example, kinase inhibitors like roniciclib,[6b] ceralasertib[3e] or Pfizer's PYK2 inhibitor[7] bear an acyclic chiral sulfoximine moiety. Lilly's prazosine analog,[8] Gö 4962[9] and NSC 287474 are representative examples for cyclic benzannulated sulfoximines.[10] The chirality of the sulfoximine group has proven important, with each enantiomer of the stereogenic sulfur atom having different properties.[11] For instance, the (*R*)-configuration of the sulfur atom in ceralasertib leads to a slightly higher bioactivity as well as enjoys a significantly higher solubility compared to the corresponding (*S*)-sulfur epimer.[6a] Although the situation for the synthesis of this compound class has greatly improved,[3] the selective preparation of chiral sulfoximines and corresponding motifs remains challenging. While processes for selective imination and oxidation,[12] as well as organo- and metal-catalyzed kinetic resolutions[13] have been reported by Bolm *et al.*, the number of broadly useful tools for the synthesis of chiral sulfoximines remains limited. Sulfoximines have emerged as suitable directing group for catalytic C-H functionalizations.[14, 15] Very recently, we[16] and independently Li *et al.*[17] reported the desymmetrization of prochiral sulfoximines *via* an enantioselective C(sp^2)-H bond functionalization[18] providing access to broad range of cyclic benzannulated sulfoximines (Scheme 1). However, the method has conceptual limitations requiring two identical aryl groups in starting material, thus precluding its application for the synthesis of acyclic aryl alkyl substituted sulfoximines, like the one featured in roniciclib, for instance.

Figure 1. Biologically active compounds with a stereogenic sulfoximine.



Scheme 1. Access to chiral sulfoximines by C-H functionalization technology.



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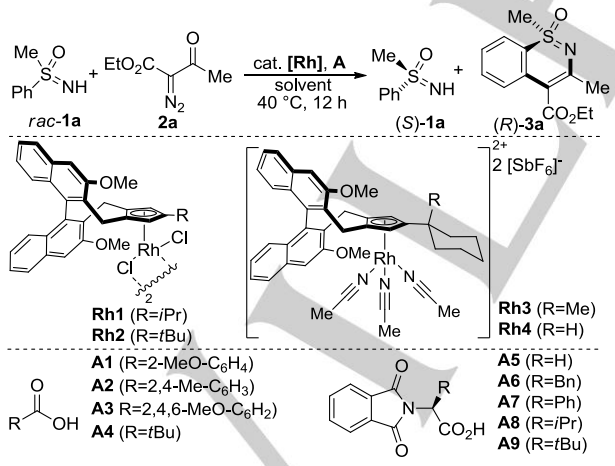
We envisioned that a kinetic resolution based on a C-H functionalization[19, 20] would allow to address this void. Herein, we report an efficient kinetic resolution of differentially substituted sulfoximines, enabling access to acyclic enantioenriched aryl alkyl sulfoximines, as well as cyclic benzothiazines. Our investigation of the kinetic resolution of sulfoximines started with phenyl methyl sulfoximine (**1a**) and diazoketoester **2a** as model substrates (Table 1). Evaluation of a small set of 3-substituted Cp^{x}Rh(III)-complexes[21] in DCE revealed **Rh3** as promising lead, providing an *s*-value of 18 (91:9 *er* for **1a** and 87.5:12.5 *er* for **3a**, entry 3). While the addition of achiral carboxylic acid significantly improved the reaction rate, allowing lowering the reaction temperature to 40 °C and shortening the reaction time, it almost completely levelled the selectivity (entries 5-8). Methanol as solvent partly restored the selectivity (*s*=10 for pivalic acid and **Rh4**, entry 11). It should be noted that the addition of **A2** and **A3** inverted the selectivity (See SI for details).[17] Subsequently, we investigated the potential synergistic effect of chiral carboxylic acids.[22] In this respect, phthalimido-protected amino acids **A5**-**A9**[16, 23] showed the best performance in conjunction with **Rh4** (entries 12-16). Achiral glycine-derived **A5** resulted in an *s*-value of 28 (entry 12). Both phenylalanine and *tert*-leucine derived acids **A6** and **A9** displayed an equally good performance with an *s*-value of 45 (entries 13, 16). Subsequently **A6** was selected for its low cost and availability. Notably, the enantioselectivity and efficiency could be further increased by the reduction of the amount of acid **A6** to 10 mol% (entry 17). Now, the reaction reliably stalled at 50 % conversion, resulting in the formation of **1a** in 99.5 *er* and **3a** in 95:5 *er* translating to an *s*-value of 99. The dramatic influence of the acid on the reaction performance becomes even clearer when **A6** was switched for its enantiomer *ent*-**A6** (entry 18). The resolution process lost almost all performance, with the *s*-value dropping sharply to 11, and benzothiazine **3a** formed with only 82:18 *er*.

Table 1. Reaction optimization for the kinetic resolution of *rac*-**1a**.[a]



Entry	[Rh]	A (Equiv.)	Solvent	% Conv.[b]	*er* **1a**[c]	*er* **3a**[c]	*s*-value[d]
1[e,f]	**Rh1**	$AgSbF_6$	DCE	38	67:33	78:22	5
2[e,f]	**Rh2**	$AgSbF_6$	DCE	42	77:23	88:12	13
3[f]	**Rh3**	-	DCE	52	91:9	88:12	18
4[f]	**Rh4**	-	DCE	46	77:23	82:18	8
5	**Rh3**	**A1** (1.0)	DCE	45	68:32	72:28	4
6	**Rh3**	**A2** (1.0)	DCE	42	39:61	35:65	2
7	**Rh3**	**A3** (1.0)	DCE	38	45:55	42:58	2
8	**Rh3**	**A4** (1.0)	DCE	60	71:29	64:36	3
9	**Rh3**	**A2** (1.0)	MeOH	42	39:61	35:65	2
10	**Rh3**	**A4** (1.0)	MeOH	50	82:I8	82:18	9
11	**Rh4**	**A4** (1.0)	MeOH	37	72:28	87:13	10
12	**Rh4**	**A5** (1.0)	MeOH	56	98:2	88:12	28
13	**Rh4**	**A6** (1.0)	MeOH	53	98:2	92:8	45
14	**Rh4**	**A7** (1.0)	MeOH	52	92:8	89:11	21
15	**Rh4**	**A8** (1.0)	MeOH	53	92:8	88:12	19
16	**Rh4**	**A9** (1.0)	MeOH	53	98:2	92:8	45
17	**Rh4**	**A6** (0.1)	MeOH	52	>99:1	95:5	99
18	**Rh4**	*ent*-**A6** (0.1)	MeOH	55	90:10	82:18	11

[a] 0.1 mmol *rac*-**1**, 0.06 mmol **2a**, 3 mol% [**Rh**], 10 mol% **A6**, 0.3 M; [b] determined by ^{1}H-NMR; [c] determined by chiral HPLC; [d] calculated according to: $s = \ln[(1-C) * (1-ee^{1a})] / \ln[(1-C) * (1+ee^{1a})]$, $C = (ee^{1a}) / (ee^{1a}+ee^{3a})$; [e] with 12 mol% $AgSbF_6$; [f] at 60 °C for 16 h.

Next, we investigated the scope for the kinetic resolution with respect to the sulfoximine (Table 2). The developed catalytic system proved to be robust for the selective conversion of *ortho-, meta-* and *para*-substituted aryl sulfoximines (entries 1-7). Both electron-donating (**1b**-**1c**) and electron-withdrawing groups (**1d**-**1f**) on the arene were well tolerated. In all cases, the resolution performed well and allowed for the isolation of both the residual resolved sulfoximine **1** as well as benzothiazine **3** in 39-50 % yield with an enantiomeric ratio from 94:6 to 99.5:0.5 *er*. Remarkably, *para*-nitrophenyl methyl sulfoximine **1e**[24] (entry 5) and 1-naphthyl methyl sulfoximine **1g** (entry 7) were particularly suited, resulting in *s*-values of >200 and 149, respectively. Next, the tolerance for the different substituents R was tested. Besides the methyl group (**1a**), benzyl-substitution (**1h**) was smoothly resolved with a comparable *s*-value. Sterically demanding branched alkyls such as *i*Pr (**1h**) or cyclohexyl (**1j**) were tolerated and reacted well. However, their respective *s*-values range from 38-42. Nevertheless, the yields are very good and the obtained enantioselectivity never drop below 93:7. In contrast, the valuable cyclopropyl substituent (**1k** and **1l**) behaved remarkably different resulting in excellent *s*-values (entries 11 and 12). Synthetically attractive substrates with heteroatom-containing saturated six-membered ring substituents such as 4-tetrahydro-pyranyl (**1m**, entry 13) and *N*-Boc-4-piperidinyl (**1n**, entry 14) reacted more selectively than the parent cyclohexyl group. In particular, **1n** was smoothly resolved, with an *s*-value of 62, translating to the formation of **3n** in 49 % yield and 95:5 *er* and 46 % for unreacted starting material **1n** with 96:4 *er*.

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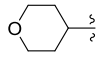
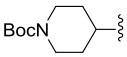
Table 2. Scope for the kinetic resolution of different racemic sulfoximines.[a]

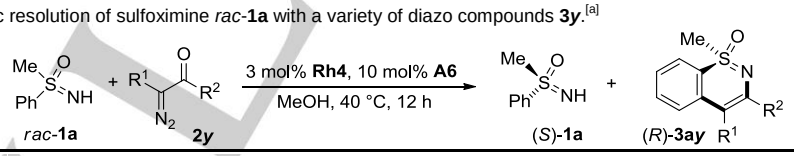
Entry	*rac*-**1*x***	R	Ar	% Conv.	% Yield **1*x***	*er* **1*x***	% Yield **3*x***	*er* **3*x***	*s*-value
1	**1a**	Me	Ph	52	45	>99:1	48	95:5	99
2	**1b**	Me	3-Me-C_6H_4	49	39	93:7	47	94:6	43
3	**1c**	Me	4-MeO-C_6H_4	48	47	94.5:5.5	47	97:3	97
4	**1d**	Me	4-Cl-C_6H_4	50	46	95:5	49	96:4	74
5	**1e**	Me	4-NO_2-C_6H_4	49	47	98:2	47	98.5:1.5	>200
6	**1f**	Me	2-Br-C_6H_4	50	41	94:6	48	94.5:5.5	50
7	**1g**	Me	1-naphthyl	51	42	99:1	42	97:3	149
8	**1h**	Bn	Ph	50	46	97:3	49	96.5:3.5	98
9	**1i**	*i*Pr	Ph	49	42	93:7	43	94:6	43
10	**1j**	Cy	Ph	50	45	93.5:6.5	45	93:7	38
11	**1k**	cyclopropyl	Ph	52	41	>99:1	49	95:5	99
12	**1l**	cyclopropyl	4-NO_2-C_6H_4	49	46	97:3	47	98:2	175
13	**1m**		Ph	50	40	95.5:4.5	49	95:5	60
14	**1n**		Ph	51	46	96:4	49	95:5	62

[a] 0.3 mmol *rac*-**1**, 0.156 mmol **2a**, 3 mol% **Rh4**, 10 mol% **A6**, 0.3 M in MeOH.

Subsequently, a range of diazo interceptors **2*y*** were tested for the kinetic resolution of *rac*-**1a** (Table 3). In addition to the sterically demanding *tert*-butyl ester (**3ab**), a tosyl group (**3ag**) was suitable as electron-withdrawing group R^1. Substituents R^2 could be varied as well to accommodate an aryl (**3ac**),[24] a heteroaryl (**3ae**) or a styryl group (**3ae**). Moreover, a methyl (**3ag**) or cyclopropyl unit (**3af**) were well tolerated.

High *s*-values were obtained, except for diazo compounds **3ac** and **3ad,** which provided *s*-values between 48 and 52. This clearly indicates that the diazo intermediate plays a non-innocent role. Nevertheless, the method reliably provided excellent yields and enantioselectivities throughout the complete sulfoximine and diazo substrate spectrum.

Table 3. Scope for the kinetic resolution of sulfoximine *rac*-**1a** with a variety of diazo compounds **3*y***.[a]



Entry	**2*y***	R^1	R^2	% Conv.	% yield **1a**	*er* **1a**	% yield **3ay**	*er* **3ay**	*s*-value
1	**2b**	CO_2tBu	Me	53	47	>99:1	50	94:6	81
2	**2c**	CO_2Et	Ph	55	41	>99:1	49	91:9	52
4	**2d**	CO_2Et	(*E*)-styryl	51	45	95:5	46	94:6	48
5	**2e**	CO_2Et	2-furyl	50	39	97:3	47	97:3	115
6	**2f**	CO_2Et	cyclopropyl	49	47	95:5	44	97:3	100
7	**2g**	Ts	Me	49	49	96:4	47	97:3	106

[a] 0.3 mmol *rac*-**1a**, 0.165 mmol **2*y***, 3 mol% **Rh4**, 10 mol% **A6**, 0.3 M in MeOH.

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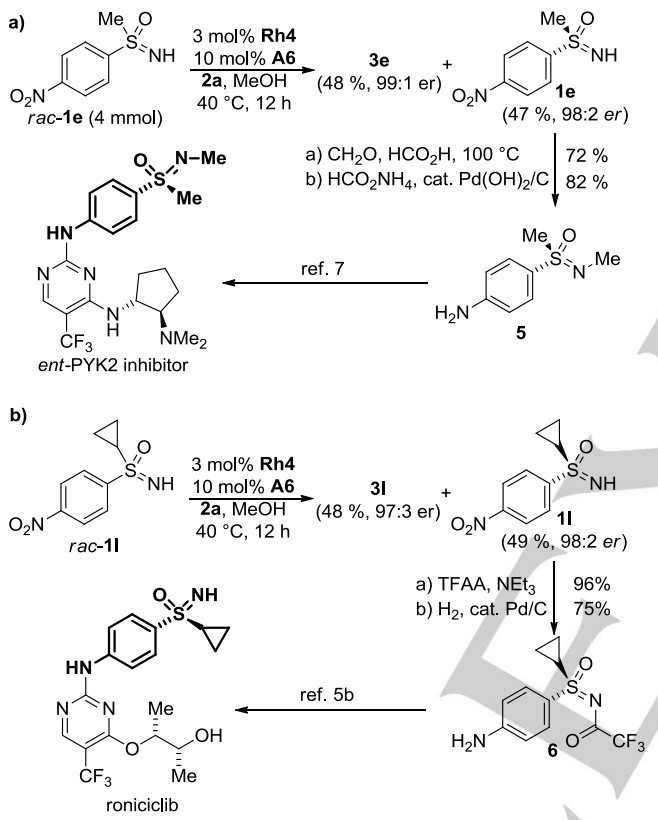
To illustrate the relevance of our method, we performed the resolution of *rac*-**1e** on a 4 mmol (800 mg) scale (Scheme 2). Optically enriched (*S*)-**1e** and (*R*)-**3e**[24] were obtained in 47 % yield with 98:2 *er* and 48 % yield and 99:1 *er*, respectively. Sulfoximine (*S*)-**1e** was *N*-methylated and its nitro group was subsequently hydrogenated catalytically. Obtained aniline **5** is a key precursor for the synthesis of the proline-rich tyrosine kinase 2 (PYK2) inhibitor which may represent an anabolic therapy for osteoporosis patients.[7] Resolution of cyclopropyl-containing *rac*-**1l** provided access to (*S*)-**1l** in 49 % yield and 98:2 *er*. *N*-acylation and reduction gave aniline **6** which is a direct precursor for roniciclib.[6b]

Scheme 2. Application of the kinetic resolution for bioactive compounds.



To gain insight into the reaction, we obtained sets of reaction kinetics by ^{1}H-NMR (Figure 2). The kinetics for both enantiomers of **1a** with one equivalent of diazoester **2a** were separately measured. Complete conversion for the fast reacting *R*-enantiomer (red line) is reached at 6.5 hours. The conversion of the slow reacting *S*-enantiomer (blue line) was very sluggish. After 10 hours, more than 90 % of (*S*)-**1a** remained. This roughly equals to a rate difference of 20, well matching to the observed resolution selectivities. The reaction of *rac*-**1a** (black line) with *a full equivalent* of **2a** shows a significant decrease in reaction rate after the 6.5 hour mark. This 50 % substrate conversion corresponds to a complete consumption of the matching enantiomer. Due to usage of one full equivalent of **2a** it keeps reacting with the mismatched enantiomer, resulting in a slow increase in conversion. For the preparative kinetic resolutions, reduction of the amount of **2** to 0.52 equivalents mitigated this slow selectivity erosion over time avoiding the necessity for exact timing of the reaction quench. For comparison, a reaction of *rac*-**1a** in the *absence* of **A6** (dotted grey line) is displayed. Virtually no substrate is converted, once again evidencing the critical importance of the carboxylic acid for the success of the transformation.

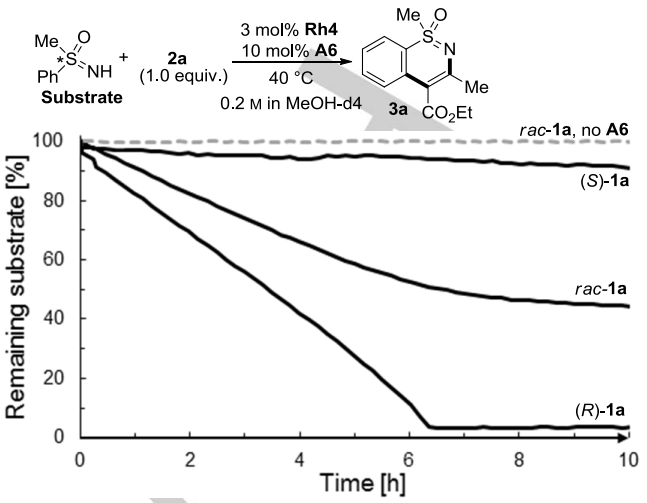


Figure 2. Reaction kinetics of substrate **1a**.

In conclusion, we developed an efficient kinetic resolution of racemic sulfoximines based on a C-H functionalization. A powerful synergistic Interplay of chiral trisubstituted Cp^x ligand Rh^{III}-complex with a phthaloyl phenyl alanine enabled a strong kinetic differentiation between the two enantiomers of stereogenic sulfur atoms of the substrates. The kinetic resolution proceeds with high yields and enantioselectivities for the product as well as the remaining substrate, ensuring *s*-values of up to >200. The transformation is tolerant to a range of differently substituted sulfoximines and is shown to be compatible with a selection of diazo interceptors. The utility of the transformation is showcased by the formal synthesis of two kinase inhibitors.

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Keywords: Asymmetric Catalysis • Chiral Cp Ligands • Kinetic Resolution • Sulfoximine • Rhodium

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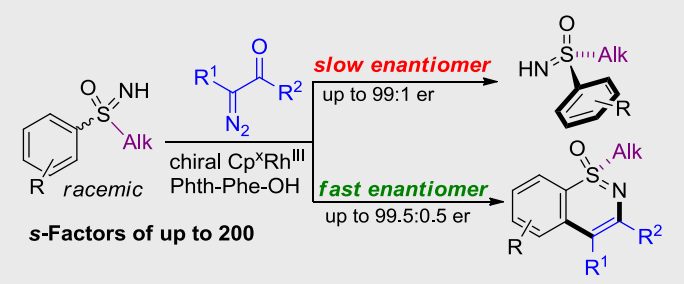
Efficient Kinetic Resolution of Sulfur-Stereogenic Sulfoximines Exploiting Cp^xRh^{III}-Catalyzed C-H Functionalization



An efficient method to access chiral sulfoximines by a C-H functionalization-based kinetic resolution is disclosed. Together, phthaloyl phenyl alanine and a Cp^xRh^{III} complex participate in the selective C-H activation of just one of the two sulfoximine enantiomers and its reaction with diazo compounds to benzothiazines. Excellent enantioselectivities with s-values of up to >200 are obtained.