Kinetic Resolution of 2-Substituted Indolines via *N*-Sulfonylation using an Atropisomeric 4-DMAP-*N*-oxide Organocatalyst

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Abstract: The first catalytic kinetic resolution by *N*-sulfonylation is described. 2-Substituted indolines are resolved (*s* = 2.6–19) using an atropisomeric 4-dimethylaminopyridine-*N*-oxide (4-DMAP-*N*-oxide) organocatalyst. Use of 2-isopropyl-4-nitrophenylsulfonyl chloride is critical to the stereodiscrimination and enables facile deprotection of the sulfonamide products with thioglycolic acid. A qualitative model that accounts for the stereodiscrimination is proposed.

The global demand for enantiomerically pure alcohols and amines is steadily increasing^[1] and kinetic resolution (KR) of racemates provides a useful and scalable approach to accessing such compounds.^[2,3] Whilst several efficient non-enzymatic methods for the Lewis base (LB) catalysed^[4] KR of alcohols *via* acylation,^[5] silylation,^[5,6–9] phosphorylation^[5,10,11] and sulfonylation^[5,8,12] have been developed, analogous protocols for the KR of amines are less common.^[5,13,14] This situation mainly reflects the challenge in achieving efficient catalysis, as most amines are themselves significantly Lewis basic.^[5,13]

Optically active 2-substituted and 2,3-disubstituted indolines^[15] occur in many natural products,^[16] drugs,^[17] and drug candidates.^[18] This and the proximity of the moderately Lewis basic indoline nitrogen to the C2/C3 stereogenic centres, makes them attractive for KR^[19] *via* LB-catalysed *N*-functionalisation. So far, only Arp and Fu^[20] have achieved this, using planar chiral LB catalyst **1** to effect KR *via* *N*-acylation (Scheme 1A), although others, notably Hou and Zheng^[21] and Akiyama *et al.*,^[22] have reported non-acylative KRs (Scheme 1B–C). Asymmetric hydrogenation of indoles also provides efficient access to this type of indoline.^[23]

Our laboratory has developed atropisomeric 3-aryl-4-DMAP derivatives as LB catalysts for the acylative KR of *sec*-alcohols^[24] and amines.^[25] Recently, we also reported a comparative study of

amines vs. *N*-oxides as catalysts for the acylation, sulfonylation and silylation of alcohols, revealing that *N*-oxides are generally more efficient catalysts for sulfonylation and silylation.^[26] Cognisant that 4-DMAP-*N*-oxide promotes the sulfonylation of aniline with benzene sulfonyl chloride ~20 fold faster than 4-DMAP,^[27] we envisioned that a suitable chiral pyridine-*N*-oxide derivative would catalyse sulfonylative KR of indolines. Herein, we report the development of such a process employing an atropisomeric 2-aryl-4-DMAP-*N*-oxide catalyst (**4**) with 2-isopropyl-4-nitrophenylsulfonyl chloride as the sulfonylating agent (Scheme 1D).

Scheme 1. Comparison of previous KRs of indolines with this work.^[21,22]

The challenge of achieving chirality transfer *via* an sulfonyloxypyridinium salt intermediate during *N*-oxide catalysed sulfonylation as compared to *via* an acylpyridinium salt intermediate during pyridine catalysed acylation (*i.e.* **I** vs. **II**, Scheme 2A), accrues from two key differences. Firstly, there is an additional rotatable bond between the pyridine ring and the electrophilic sulfur atom (*cf.* the carbonyl carbon atom). Secondly, the trajectory of the incoming nucleophile relative to the S–O bond in the asynchronous S_N2 transition state is linear (*cf.* the Bürgi–Dunitz trajectory towards the C=O bond).^[28] Our design of catalysts **4a** and **4b** incorporated an atropisomeric axis at the 2-position of the pyridine to address these challenges, as well as an

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electron deficient 2,4-bis(perfluoroalkyl)phenyl motif to impart high reactivity by analogy with achiral congeners as catalysts for O-phosphorylation (Scheme 2B).^[29]

Scheme 2. A) Schematic comparison of reaction trajectories for sulfonylation vs. acylation, B) structures of atropisomeric catalysts **4a** and **4b**.

We began our investigations using the *bis*-trifluoromethyl catalyst (-)-**4a** and ($\pm$)-2-methylindoline (**5a**, Table 1, see *Supporting Information* for full details).

Table 1. Optimisation of *N*-sulfonylative KR of ($\pm$)-2-methylindoline **5a**.

Entry	Cat.	R	T (°C)	Time (h)	Conv. (%) ^[a]	<i>s</i> ^[a]
1	(-)- 4a	4-NO ₂	0	4	100	N.D.
2	(-)- 4a	2-NO ₂	0	3	60	1.3
3	(-)- 4a	2-NO ₂	-40	4	53	1.4
4	(-)- 4a	2-NO ₂	-60	3	23	1.9
5	(-)- 4a	2-NO ₂	-78	3	15	5.7
6	(-)- 4a	2- <i>i</i> -Pr, 4-NO ₂	-60	3	54	8.9
7	(-)- 4a	2- <i>i</i> -Pr, 4-NO ₂	-78	3	52	13.8 ^[b]
8	(+)- 4b	2- <i>i</i> -Pr, 4-NO ₂	-78	3	<5	N.D. ^[c]
9	(+)- 4b	2- <i>i</i> -Pr, 4-NO ₂	-78	24	48	8.2 ^[c]
10	(-)- 4a	2- <i>i</i> -Pr, 6-NO ₂	-78	3	0	N.D.
11	(-)- 4a	2- <i>i</i> -Pr, 6-NO ₂	r.t.	3	0	N.D.

^[a]Conversions and *s* values calculated from chiral HPLC data. Absolute configuration of recovered SM **5a** established as (2*R*) by comparison with literature data, see *Supporting Information*. ^[b]There is no detectable conversion in the absence of catalyst under these optimised conditions. ^[c]Gives enantiomeric SM and P to those depicted [*i.e.* (S)-**5a** and (R)-**6a**]. N.D. = not determined.

Initial evaluation of the sulfonylating agent revealed that 4-nitrophenylsulfonyl chloride (4-NsCl) was reactive but unselective whereas 2-NsCl was similarly reactive and delivered *s* = 1.3 at 0 °C (entries 1 and 2, Table 1). Lowering the reaction temperature resulted in increased selectivity^[3] (*s* = 5.7 at -78 °C, entries 3–5, Table 1). Encouraged by these results and aiming to combine a bulky 2-substituent capable of relaying stereochemical information^[30] with favourable reactivity imparted by the nitro group, we next investigated the use of 2-isopropyl-6-NsCl and 2-isopropyl-4-NsCl as sulfonylating agents. Whilst the former proved unreactive (entries 10 and 11, Table 1), the latter resulted in a significant increase in selectivity at -78 °C (*s* = 13.8, entry 7,

Table 1). We also examined the performance of *bis*-perfluorobutyl catalyst (+)-**4b** under these conditions; this catalyst promoted reaction of the opposite indoline enantiomer as expected but the reaction was slower and offered no advantage in terms of selectivity (*s* = 8.2 after 24 h, entries 8 and 9, Table 1). The efficiency of several additives commonly used in LB-catalysed KRs were also evaluated,^[23b-c,31] but to no avail (see *Supporting Information*).

Next, we evaluated the substrate scope of this sulfonylative KR (Table 2).

Table 2. Evaluation of scope of indoline sulfonylative KR.

Entry (substrate)	R	R ¹	Time (h)	Conv. (%) ^[a]	<i>s</i> ^{[a][b]}
1 (5a)	Me	H	3	52	13.8(<i>R</i>) ^[c]
2 (5b)	CH ₂ OTES	H	6	34	14.8
3 (5c)	CH ₂ OTIPS	H	5	33 ^[d]	10.1 ^[e]
4 (5d)	CH ₂ OTBS	H	5	47 ^[d]	17.2(<i>S</i>)
5 (5e)	<i>i</i> -Pr	H	6	40	16.2(<i>S</i>) ^[e]
6 (5f)	<i>n</i> -Bu	H	3	56	12.9(<i>R</i>)
7 (5g)	Ph	H	4	<1	N.D.
8 (5h)	CO ₂ Me	H	4	<1	N.D.
9 (5i)	Me	5-Cl	2	46	13.8(<i>R</i>)
10 (5j)	Me	5-Me	6	41	11.0(<i>R</i>) ^[e]
11 (5k)	Me	5-OMe	1	52	4.8
12 (5l)	Me	6-	2	69	2.6

^[a]Conversions and *s* values calculated from chiral HPLC data. ^[b]Indicated absolute configurations are of recovered SMs established by comparison with literature data, see *Supporting Information*. *NB*. Although the CIP designations vary, all entries using catalyst (-)-**4a** give the configuration depicted. ^[c]Same experiment as Table 1, entry 7. ^[d]Conversion measured by ¹H NMR, *s* determined by chiral HPLC of SM or P. ^[e]Catalyst (+)-**4a** was used and gave enantiomeric SM and P to those depicted. N.D. = not determined.

2-Alkyl- and 2-siloxymethylindolines were found to undergo sulfonylative KR with good selectivity (*s* = 10.1–17.2, entries 1–6, Table 2). 2-Alkyl-5-substituted indolines were also resolved efficiently (entries 9–11, Table 2), although 2-Me-5-OMe indoline **5k** was resolved with the lowest selectivity (*s* = 4.8), likely because of the relatively high nucleophilicity of this derivative due to conjugation between the OMe and NH groups. Similarly, the 6-NMe₂ derivative **5l** displayed high reactivity but low selectivity (*s* = 2.6, entry 12, Table 2). Unfortunately, sterically encumbered 2-Ph and 2-CO₂Me substituted indoline derivatives proved unreactive both under standard conditions and at elevated temperature (entries 7 and 8, Table 2). 7-Substituted indolines also proved unreactive, presumably due to steric hindrance of the reactive nitrogen centre (data not shown).

Figure 2. A) Lowest free energy conformer of catalyst (+)-**4a** with S_a configuration by DFT at the B3LYP+D3BJ/6-311G(2df,p)/SCRF=chloroform level (see Supporting Information).^[32] B) Lowest free energy, potentially stereodiscriminating conformer of chiral sulfonoxypyridinium salt (S_a)-**9a** (H atoms removed for clarity) by DFT at the B3LYP+D3BJ/6-311++G(2df,p)/SCRF=toluene level (see Supporting Information).^[32] C) Qualitative model for stereodiscrimination illustrated for the reactive (2R) enantiomer of indoline **5a** with the (+)-**4a** derived sulfonoxypyridine salt (S_a)-**9a**.

Preparative sulfonylative KR of 2-methylindoline was performed using catalyst (-)-**4a**, affording similar selectivity and conversion after 3 h as the analytical run ($s = 11.6$, $C = 61\%$, cf. entry 1, Table 2). The enantioenriched sulfonylated product (2R)-**6a** underwent facile deprotection with thioglycolic acid^[33] and DBU in MeCN (93%) with no detectable erosion of its enantiopurity. Concomitantly, catalyst (-)-**4a** was recovered quantitatively as a single enantiomer (see Supporting Information).

The absolute configuration of the dextrorotatory enantiomer of catalyst **4a** was assigned by comparison of its optical rotation value and electronic and vibrational circular dichroism (ECD and VCD) spectra with those computed by DFT.^[34] All three datasets led to (+)-**4a** being assigned the (S_a) configuration.^[32] The VCD data was most compelling as the match in the 1000–1250 cm^{-1} region was largely independent of conformation (Figure 1).

Figure 1. Experimental VCD spectrum for (+)-**4a** (blue) and computed VCD spectrum for (S_a)-**4a** (orange) [at the ω B97XD/Def2-TZVP/SCRF=chloroform level, weighted by the Boltzmann conformer populations calculated using B3LYP+D3BJ/6-311G(2df,p)/SCRF=chloroform free energies].^[32] For further details see Supporting Information.

The lowest energy potentially stereodiscriminating conformer of the chiral sulfonoxypyridinium salt **9a**, derived from (+)-**4a**/2-isopropyl-4-NsCl, as computed by DFT, was used to construct a qualitative model to rationalize the sense and scope of the indoline KR reactions (Figure 2A–B). This conformer provides a chiral 'pocket' for which the phenyl ring of the arylsulfonate forms the base, the 2-isopropyl group of the arylsulfonate forms one side (*element A*), and the *ter*-phenyl group of the catalyst forms the other side (*element B*, Figure 2C). The approach of the indoline nitrogen lone pair to the $\sigma^*_{\text{S-O}}$ orbital such that the C2/C3 positions can avoid clashing with *elements A/B* then leads to the preferred sulfonylation of (2R)-**5a** as shown in Figure 2C. The 2-substituents of indolines **5a–f** are presumably able to rotate to avoid a steric clash with *element B*, allowing them to be resolved efficiently (entries 2–6, Table 2). By contrast, the less flexible 2-Ph and 2-CO₂Me substituents in indolines **5g** and **5h** (entries 7 and

8, Table 2) cannot avoid clashing with *element B*, making them poor substrates for KR. 7-Substituted indolines are also poor substrates for this resolution due to steric interactions with *element A*.

This qualitative model predicts that 2,3-disubstituted indolines will require *cis*-stereochemistry for efficient KR and that *trans* derivatives will resolve poorly as one alkyl group would necessarily protrude into *element B*. To test these hypotheses, we investigated the sulfonylative KR of *cis* and *trans* 2,3-dimethylindolines **5m** and **5n** and tricyclic indolines **5o–q** (Table 3).

Table 3. Sulfonylative KR of 2,3-disubstituted indolines **5m–q**.

Entry	Cat.	Substrate	Time (h)	Conv. (%) ^[a]	s ^{[a][b]}
1	(+)- 4a		3	62	9.7(2S,3S)
2	(+)- 4a		3	6	2.1
3	(-)- 4a		3	35	7.2
4	(-)- 4a		2	37	11.7(4aR,9aR)
5	(-)- 4a		4	54 ^[c]	19.0

^[a]Conversions and s values calculated from chiral HPLC data. ^[b]Absolute configurations of unreacted SM established by comparison with literature data, see Supporting Information. ^[c]Conversion measured by ¹H NMR, s determined by chiral HPLC of SM or P.

As predicted, *cis*-2,3-dimethylindoline undergoes efficient KR ($s = 9.7$, entry 1, Table 3) whereas the analogous *trans* derivative is a poor substrate ($s = 2.1$, entry 2, Table 3). Given the prevalence of the tricyclic indoline motif in natural products,^[19a,35] we were pleased to find that these substrates also undergo efficient KR with good selectivity ($s = 7.2$ –18.9, entries 3–5, Table 3). Congruent with the model, increasing the aliphatic ring size resulted in increased selectivity (cf. entries 3 and 4, Table 3) and *N*-Boc- β -carboline provided the highest selectivity yet obtained in this *N*-sulfonylative KR ($s = 19.0$, entry 5, Table 3).

In summary, we have developed the first protocol for catalytic KR of amines by sulfonylation and demonstrated its utility for the preparation of enantiomerically enriched 2-substituted and 2,3-disubstituted indolines. The use of an atropisomeric 2-aryl-4-DMAP-*N*-oxide catalyst **4a** in combination with a 2-substituted-4-nitrophenylsulfonyl chloride is crucial for achieving enantioselectivity and allows for facile deprotection of the sulfonamide products using thioglycolic acid. A qualitative model has been developed to rationalise the substrate scope and to aid further development, which is ongoing in our laboratory.

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Kinetic Resolution of 2-Substituted Indolines via N -Sulfonylation using an Atropisomeric 4-DMAP- N -oxide Organocatalyst

The kinetic resolution of 2-substituted indolines by catalytic N -sulfonylation is reported using an atropisomeric 4-dimethylaminopyridine- N -oxide (4-DMAP- N -oxide) organocatalyst. VCD is used to assign the absolute configuration of the catalyst and a qualitative model that accounts for the stereodiscrimination is proposed.