Asymmetric Ortholithiation of Amides by Conformationally Mediated Chiral Memory: An Enantioselective Route to Naphtho- and Benzofuranones

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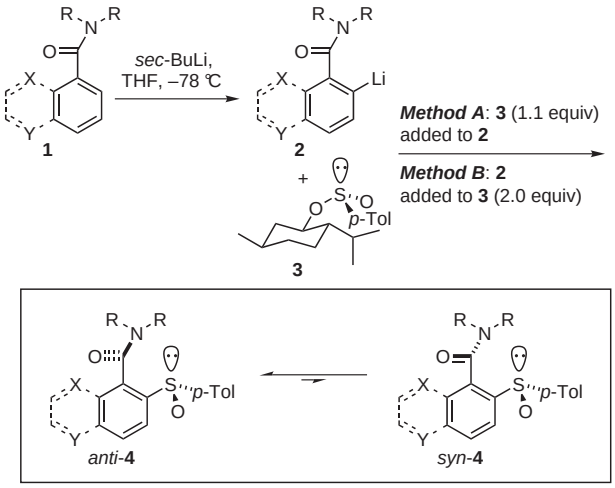
Abstract: An enantiomerically pure sulfinyl group *ortho* to an aromatic amide imposes absolute stereochemistry on the conformation of its Ar–CO axis. Sulfoxide–lithium exchange followed by addition to an aldehyde relays the chirality of the amide axis to the new hydroxyl-bearing stereogenic centre with good stereochemical fidelity. Lactonisation of the hydroxyamide gives naphthofuranones and benzofuranones, including the fungal metabolite isoochracein, but with substrate-dependent stereoselectivity.

Key words: chiral memory, amide, sulfoxide, directed metallation, benzofuranone

Ortholithiation is a powerful method for the regioselective functionalisation of an aromatic ring,[1] but attempts to use it to introduce *ortho*-substituents enantioselectively by, for example, using chiral metallation directing groups, have generally failed.[2] Chiral versions of several classes of metallation directing groups[3] – including amides,[4] oxazolines,[5] hydrazides,[6] sulfonamides,[7] and sulfoxides[8] – have all been examined, but only the last two have been able to show good, though substrate-dependent, levels of diastereoselectivity on addition to prochiral electrophiles. We have reported that an aromatic tertiary amide group, which may possess a stereogenic Ar–CO axis,[9] is capable of directing the diastereoselective formation of a new hydroxyl-bearing centre via ortholithiation and reaction with an aldehyde.[10] In this paper we report the extension of this work to the synthesis of enantiomerically enriched alcohols by using the conformation of a slowly-rotating amide Ar–CO axis to store a record of the configuration of a pre-existing stereogenic centre, with its stereochemistry later being regenerated in the guise of an enantiomerically enriched chiral alcohol.

Several classes of stereogenic centre have proved to be capable of imposing an orientational preference upon a nearby amide group,[11] but for the purpose of this work we required a chiral substituent removable at a temperature low enough to allow the amide to retain its axial conformation. A sulfinyl group appears to fit this requirement perfectly.[12]

We therefore made a range of enantiomerically pure or enriched amidosulfoxides **4**, following the method of Andersen.[13] Lithiation of the tertiary amides **1** with *s*-BuLi in THF[14] gave ortholithiated amides **2** which reacted with (1*R*, 2*S*, 5*R*, S*S*)-(–)-menthyl toluenesulfinate **3**[15] (Scheme 1) to yield sulfoxides **4**.[7] Two alternative protocols were employed: initially the sulfinate was added to the lithiated amide ('Method A'). Products of high ee were obtained with this method when the amide was relatively hindered (**4a**,**b**,**d** were all formed in > 95% ee). In other cases, however, this method gave less than complete enantiospecificity: in the case of **4e** the product was racemic. Reasoning that ee at the sulfoxide centre was being eroded by multiple invertive substitution at sulfur by the excess nucleophile,[16] we repeated these reactions using Method B, in which the ortholithiated amide was added by cannula to a two-fold excess of the sulfinate. The enantiomeric excesses of **4c** and **4e** were dramatically improved, and using 10 equivalents of sulfinate increased the ee of **4e** from 0% (by Method A) to 92% (Table 1, Method B, entries 7–9).



Scheme 1 Synthesis of enantiomerically enriched amidosulfoxides

NMR indicated that the amidosulfoxides adopt a single diastereoisomeric conformation, to the limit of detection (>95:5), about their Ar–CO axis (which in related compounds is sufficiently labile to equilibrate rapidly to the more stable of the two possible axial conformations). The preferred orientation of the amide group adjacent to a sulfoxide has previously been shown to be *anti*, with an (*S*)-sulfoxide stereogenic centre inducing *P* stereochemistry at the amide axis.[17]

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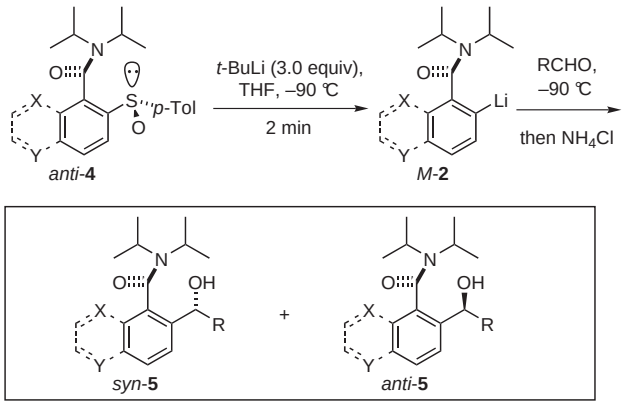
Table 1 Amidosulfoxides by Ortholithiation

Entry	Starting material	R =	X =	Y =	Method	Yield *anti*-**4** (%)	ee *anti*-**4** (%)
1	**1a**	*i*-Pr	Benzo[a]		A	74	> 95[b]
2	**1b**	*i*-Pr	MeO	MeO	A	62	> 95
4	**1c**	*i*-Pr	MeO	H	A	48	70[b]
5	**1c**	*i*-Pr	MeO	H	B	83	> 95
6	**1d**	*i*-Pr	*i*-Pr_3SiO	H	A	56	96
7	**1e**	Et	Benzo[a]		A	65	0[b]
8	**1e**	Et	Benzo[a]		B	60	88
9	**1e**	Et	Benzo[a]		B[c]	55	92
10	**1f**	Et	Me_2N	H	B	55	72
11	**1g**	*i*-Pr	H	H	B	86	> 95

[a] 1-Naphthamide.
[b] Previously reported in ref.[7] but ee not determined.
[c] With 10 equiv sulfinate **3**.

The amidosulfoxides *anti*-**4** were submitted to sulfoxide-lithium exchange[12] by treatment with *t*-BuLi (3.0 equiv). A reaction temperature of –90 °C was employed to minimise Ar–CO rotation after formation of the presumed enantiomerically enriched organolithium *M*-**2**. After two minutes (the minimum time consistent with complete substitution of the sulfinyl group) an aldehyde electrophile was added. The product was quenched with water and kept cool and the results are shown in Scheme 2 and Table 2.

The diastereoselectivities obtained were high – typically 10:1 or better[18] – with the major product in all cases being the *syn*-diastereoisomer. Chiral HPLC indicated that the enantiomeric excess of this major *syn*-diastereoisomer was also typically high, in the region of 90–95% (entries 1–6).[19] Given that the only stereogenic centre in the



Scheme 2 Chiral memory in additions to aldehydes

Table 2 Additions to Aldehydes

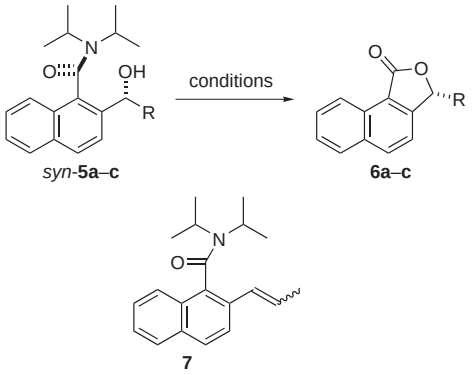
Entry	Starting material[a]	X =	Y =	R =	Product, yield (%)	*syn*-**5**:*anti*-**5**	ee of *syn*-**5**
1	**4a**	Benzo[b]		Et	**5a**, 94	93:7	88
2	**4a**	Benzo		*i*-Pr	**5b**, 79	95:5	93
3	**4a**	Benzo		Ph	**5c**, 88	90:10	> 95
4	**4b**	MeO	MeO	*c*-Hx	**5d**, 46	> 85:15	96
5	**4b**	MeO	MeO	$Ph(CH_2)_2$	**5e**, 59	> 90:10	93
6	**4c**	MeO	H	Et	**5f**, 89	95:5	95
7	**4g**	H	H	Ph	**5g**, 89	60:40[c]	0

[a] All starting materials > 95% ee.
[b] 1-Naphthamide.
[c] Thermodynamically-controlled ratio of interconverting conformers.

starting material is destroyed before the aldehyde is added, the most likely explanation for this result is that the axial conformation of the amide has mediated the transfer of stereochemical information from the old sulfoxide centre to the new hydroxyl-bearing centre. The fact that a substituent *ortho* to the amide (in addition to the sulfinyl group) is essential for any level of asymmetry in the product supports this hypothesis: compound **4g** (entry 7) lacks this substituent and in this case the lithiated amide 'forgets' the stereochemistry of the sulfoxide as a result of fast bond rotation.[20,21]

Slow rotation has been invoked as the controlling feature in other 'chiral memory' sequences, most notably the asymmetric alkylation reactions of amino acids developed by Kawabata and Fuji,[22] where the orientation of a carbamate group stores a record of a stereogenic centre which is destroyed by enolisation and then recreated faithfully, controlled by the carbamate conformation, in a subsequent alkylation. Both this method and the one we now describe are special cases of the phenomenon described by Seebach as 'self-regeneration of stereocentres':[23] in his pioneering work, the configuration of a temporary stereogenic centre was employed as the mediator of chiral memory. The linking feature of all chiral memory sequences is the formation, under thermodynamic control, of a temporary stereochemical feature, which is no longer present in the final product of the sequence.

In order to convert them to useful chiral products, and to bring the chiral memory sequence to completion, we sought to lactonise the alcohols **5a–c** to naphthofuranones **6** (Scheme 3).[24] However, protic and Lewis acids converted the hydroxyamide **5a** to only poor yields of **6a** (Table 3, entries 1–3 give some examples) and pose the risk of rapid racemisation via carbocationic intermediates. We therefore turned to more neutral conditions, and found by chance that by heating the alcohols **5** with sodium *p*-toluenesulfinate, or, better, sodium or potassium acetate in refluxing xylene, gave good yields of the naphthofuranones **6** (entries 4–7) The cyclisation varied in the degree of its stereospecificity, although interestingly it was always to some degree retentive, suggesting that the principal mechanism for cyclisation is nucleophilic substitution at the amide carbonyl group rather than S_N1-style displacement of the hydroxyl group by the nucleophilic amide oxygen atom (Figure 1).[25]



Scheme 3 Ring-closure to enantiomerically enriched naphthofuranones

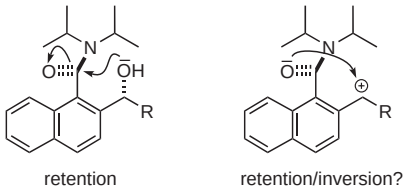


Figure 1 Mechanisms for lactonisation

With a small, aliphatic R substituent (entry 4), ee was preserved intact in the product. However, with a more bulky or an aryl substituent (entries 5 and 6), selectivity was significantly lower, presumably because of competitive cyclisation via an invertive or non-stereospecific substitution of the hydroxyl group by the amide carbonyl group.

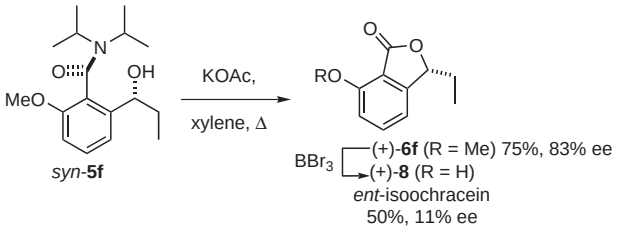
Using KOAc, cyclisation of **5f** gave **6f** (Scheme 4 and Table 3 entry 7) which was deprotected with BBr_3 to yield the simple fungal metabolite isoorchracein[26] in 50% yield, but unfortunately with only 11% ee as a result of

Table 3 Cyclisation to Yield Naphtho- and Benzofuranones **6**

Entry	Starting material, ee (%)	R =	Conditions[a]	Product	Yield	ee (%)
1	**5a**, n/d	Et	A	6a	–[b]	–
2	**5a**, n/d	Et	B	6a	Trace[b]	–
3	**5a**, 88	Et	C	6a	25	88
4	**5a**, 88	Et	D	6a	72	89
5	**5b**, 93	*i*-Pr	D	6b	70	73
6	**5c**, >95	Ph	D	6c	70	17
7	**5f**, 95	Et	D	6f	75	83

[a] Conditions: A: $MeSO_3H$, toluene, Δ; B: PPTS, xylene, Δ; C: silica, toluene, Δ; D: KOAc, xylene, Δ.
[b] Significant quantities of elimination product **7** formed.

racemisation during the deprotection step. Nonetheless, this represents the first synthesis of **8** with any enantioselectivity and (subject to the limits of our certainty about the stereospecificity of the cyclisation[25]) confirms that the natural product, which is laevorotatory, has the *S* configuration.[26]



Scheme 4 Synthesis of *ent*-isoochracein

In summary, we have shown that a transiently chiral Ar–CO axis in an ortholithiated amide may mediate the transfer of chirality from a sulfoxide to a hydroxyl-bearing centre, providing a route to enantiomerically enriched benzofuranones, useful compounds lacking more direct synthetic approaches.

(*R*)-2-(1-Hydroxypropyl)-*N*,*N*-diisopropyl-6-methoxybenzamide (5f).

t-BuLi (4.2 mmol of a 1.4 M solution in hexane, 3 equiv) was added dropwise to a stirred solution of sulfoxide **4c**[7] (522 mg, 1.40 mmol) in dry THF (20 mL) under nitrogen at –90 °C. After 2 min, propionaldehyde (0.806 mL, 11.12 mmol) was added dropwise at –90 °C and the mixture was allowed to warm to r.t. The THF was removed under reduced pressure and the mixture diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl solution (3 × 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a residue which was purified by flash chromatography (SiO_2; petroleum ether–EtOAc, 50:50) give the alcohol **5f** (365 mg, 89%) as white crystals; R_f = 0.26 (60:40 petroleum ether–EtOAc); >95:5 *syn*:*anti* diastereoisomers, >95% ee *syn*-isomer; $[\alpha]_D$ +67.8 (*c* 0.33, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (3 H, t, *J* = 8 Hz, CH_3), 1.07 (3 H, d, *J* = 7 Hz, CH_3), 1.22 (3 H, d, *J* = 7 Hz, CH_3), 1.60 (3 H, d, *J* = 7 Hz, CH_3), 1.62 (3 H, d, *J* = 7 Hz, CH_3), 1.85–2.06 (2 H, m, CH_2), 3.56 (1 H, sept, *J* = *7* Hz, NCH), 3.74 (1 H, sept, *J* = 7 Hz, NCH), 3.84 (3 H, s, OCH_3), 4.52 (1 H, t, *J* = 7 Hz, CHOH), 6.84 (1 H, d, *J* = 8 Hz, ArH), 7.12 (1 H, d, *J* = 8 Hz, ArH), 7.35 (1 H, t, *J* = 8 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 20.5, 20.6, 20.8, 21.1, 27.3, 46.3, 51.5, 55.6, 72.4, 109.8, 118.2, 127.9, 129.8, 142.3, 155.1, 168.8. MS (CI): *m/z* (%) = 294 (30) [M + H], 69 (100). HRMS: *m/z* calcd for $C_{17}H_{27}NO_3$ [M]: 293.1985; found [M^+]: 293.1986.

(*R*)-3-Ethyl-7-methoxyisobenzofuran-1(3*H*)-one (6f).

Amide *syn*-**5f** (290 mg, 1.09 mmol) and potassium acetate (4.0 g, 1.71 mmol) were heated at reflux for 18 h in xylene (10 mL). The mixture was diluted with Et_2O (20 mL), washed with sat. NH_4Cl solution (3 × 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue which was purified by flash chromatography (SiO_2; petroleum ether–EtOAc, 80:20) to give the lactone **6f**[27] (185 mg, 95%) as a clear oil; R_f = 0.31 (70:30 petroleum ether–EtOAc); 83% ee by HPLC; $[\alpha]_D$ +69.1 (*c* 0.11, acetone).

(*R*)-3-Ethyl-7-methoxyisobenzofuran-1(3*H*)-one [(*R*)-(+)-isoochracein] (8).

Boron tribromide (0.83 mL of a 1 M solution in CH_2Cl_2, 0.83 mmol) was added dropwise to a solution of lactone **6f** in CH_2Cl_2 (3 mL) at r.t. After 3 h, the solution was quenched with 0.1 M aq HCl and the mixture diluted with CH_2Cl_2 (15 mL), washed with sat. NH_4Cl solution (3 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. NMR spectrum of the crude residue showed the phenol (90%). Flash chromatography (SiO_2; petroleum ether–EtOAc, 80:20) gave the ring-opened product (50%) plus the lactone (36 mg, 47%) as white crystals, mp 80–81 °C (lit.[26] mp 78–79 °C); R_f = 0.55 (70:30 petroleum ether–EtOAc); 11% ee by HPLC; $[\alpha]_D$ +48.6 (*c* 0.43, $CHCl_3$). IR: ν_{max} = 3429 (O–H), 2972 (C–H), 1735 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (3 H, t, *J* = 7 Hz, CH_3), 1.88 (1 H, m, CH_2), 2.15 (1 H, m, CH_2), 5.50 (1 H, dd, *J* = 4, 7 Hz, CH), 6.90 (1 H, d, *J* = 8 Hz, ArH), 6.92 (1 H, d, *J* = 8 Hz, ArH), 7.58 (1 H, t, *J* = 8 Hz, ArH), 7.82 (1 H, br s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.1, 27.8, 84.1, 111.6, 113.4, 115.6, 137.1, 150.3, 156.8, 172.5. MS (CI): *m/z* (%) = 196 (100) [M + NH_4^+], 179 (30) [M + H]. HRMS: *m/z* calcd for $C_{10}H_{10}O_3$ [M]: 178.0624. Found [M^+]: 178.0621.

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(15) A convenient synthesis of (–)-menthyl sulfinate on a 100 g scale has been described, see: Solladié, G.; Hutt, J.; Girardin, A. *Synlett* **1987**, 173.

(16) A similar loss of absolute stereochemistry for this reason plagues the analogous synthesis of ferrocenyl *p*-tolyl sulfoxide. See: Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511; and references therein.

(17) See ref. 7h. The level of conformational selectivity has recently been determined in related compounds to be of the order of 200:1 (Clayden, J.; Helliwell, M.; Mitjans, D.; Regan, A. C. manuscript in preparation).

(18) In our earlier work on the addition of racemic organolithiums to aldehydes (ref. 10), we reported somewhat lower diastereoselectivities, although those reactions were carried out at –78 °C. Repeating some of the earlier racemic reactions at –90 °C confirmed that it is simply the temperature, and not the enantiomeric purity of the organolithiums, which improves the diastereoselectivity. Racemic ortholithiated amides are heterochiral dimers (at least in the solid state: see Clayden, J.; Davies, R. P.; Hendy, M. A.; Snaith, R.; Wheatley, A. E. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1238), and some differences in reactivity between organolithiums of different ee are therefore to be expected.

(19) The major diastereoisomer was identified by comparison with known compounds whose structure had been confirmed by X-ray crystallography (ref. 10). Absolute stereochemistry was deduced from the preferred orientation of amides adjacent to enantiomerically pure sulfoxides and from the absolute stereochemistry of comparable atropisomeric amides obtained by quenching with simple, 'non-prochiral' electrophiles (see ref. 7h).

(20) An alternative explanation, that the sulfoxide by-product of the reaction, *tert*-butyl tolyl sulfoxide, which may be generated in enantiomerically pure form, could mediate the asymmetric formation of the new centre, seems unlikely, given this dependence on amide structure.

(21) Attempts to extend this application of chiral memory to the control of stereogenic centres formed by lateral lithiation were hampered by the remarkably fast racemisation of laterally lithiated amides. See: (a) Clayden, J.; Helliwell, M.; Pink, J. H.; Westlund, N. *J. Am. Chem. Soc.* **2001**, *123*, 12449. (b) Clayden, J.; Pink, J. H.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 901. (c) See also: Clayden, J.; Stimson, C. C.; Keenan, M.; Wheatley, A. E. H. *Chem. Commun.* **2004**, 228.

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(24) Ortholithiation, addition to aldehydes, and lactonisation under acid conditions is an established way of making benzofuranones from aromatic amides: see ref. 1b and references therein, and ref. 27.

(25) It is of course possible that chiral memory effects operate during the cyclisation, and we cannot rule out retentive cyclisation via a benzylic carbocation. Our confidence in the absolute stereochemistry of the products is based upon the fact that simple 3-alkylbenzofuranones with reported optical rotations are laevorotatory if *S* and dextrorotatory if *R*. See: ref. 5 and: (a) Watanabe, M.; Hashimoto, N.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1992**, *57*, 742. (b) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205. (c) Kawasaki, T.; Kimachi, T. *Tetrahedron* **1999**, *55*, 6847. In a previous publication (ref. 7h) we got this wrong: we claimed, erroneously, the opposite dependence of optical activity on stereochemistry (though in mitigation we suggest that the experimental section of ref. 25b invites misinterpretation!), and the proposed cationic mechanism for the lactonisation reported in ref. 7h is consequently probably wrong.

(26) (–)-Isoochracein is a fungal metabolite isolated from *Hypoxylon spp.* See: Anderson, J. R.; Edwards, R. L.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2185.

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