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Using amide conformation to 'project' the stereochemistry of an (−)-ephedrine-derived oxazolidine: a pair of pseudoenantiomeric chiral amido-phosphine ligands

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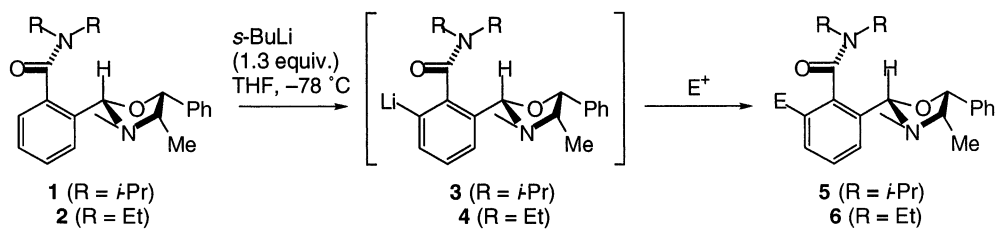
Abstract—Protection of a tertiary 2-formylbenzamide as an (−)-ephedrine-derived oxazolidine both forces the amide's stereogenic Ar–CO axis to adopt one of two possible diastereoisomeric conformations and protects the formyl group from attack during amide *ortho*-lithiation. By functionalising the amide in the 6-position, reactive sites (such as –CHO, –SR, $-PR_2$ groups) may be introduced which fall under the stereochemical influence, relayed by the amide, of the (−)-ephedrine-derived oxazolidine. This 'projection' of stereochemistry is exemplified by a pair of amido-phosphines, members of the first ever class of non-biaryl atropisomeric ligands, which are made functionally pseudoenantiomeric by the intervention of either one or two amide groups between the (−)-ephedrine-derived oxazolidine and the PPh_2 group. The pseudoenantiomeric amido-phosphines promote the palladium-catalysed asymmetric allylation of dimethyl malonate in 82 and −53% e.e., respectively. © 2001 Published by Elsevier Science Ltd.

We recently introduced[1] the use of (−)-ephedrine as a resolving agent for the dynamic resolution of atropisomers. Formation of an (−)-ephedrine-derived oxazolidine adjacent to the stereogenic Ar–CO axis of a tertiary aromatic amide gives the oxazolidine thermodynamic control over the conformation of the amide. We now expand upon this finding, exploiting the apparent compatibility of the ephedrine-derived oxazolidine with *ortho*-lithiation chemistry[2] to make enantiomerically pure functionalised atropisomeric amides by a short sequence of lithiation/electrophilic quench steps. We also demonstrate that the conformation of the amide, itself under the influence of (−)-ephedrine, is able to control further stereoselective reactions, relaying (or 'projecting') the stereochemistry of the (−)-ephedrine-derived oxazolidine onto reaction sites both within the amide molecule and in other molecules.

Oxazolidines **1** and **2**, which are apparently single Ar–CO conformers in solution,[1] were made from the aldehydes and (−)-ephedrine, as described previously. Lithiation with *s*-BuLi (1.3 equiv.) gave organolithiums **3** and **4**, which reacted cleanly with methyl iodide to yield **5a** (E = Me) and **6a** (E = Me) as single atropisomers (by ^{1}H NMR), with the preferred conformation of the amide now locked in place by the second *ortho*-substituent (Scheme 1).[3] An X-ray crystal structure of **5a** (E = Me) (Fig. 1) confirmed the stereochemistry of the product, and hence the conformational preference of the starting material **1**. The ephedrine-derived oxaz-



Scheme 1. Ortholithiation of ephedrine-protected amido-aldehydes.

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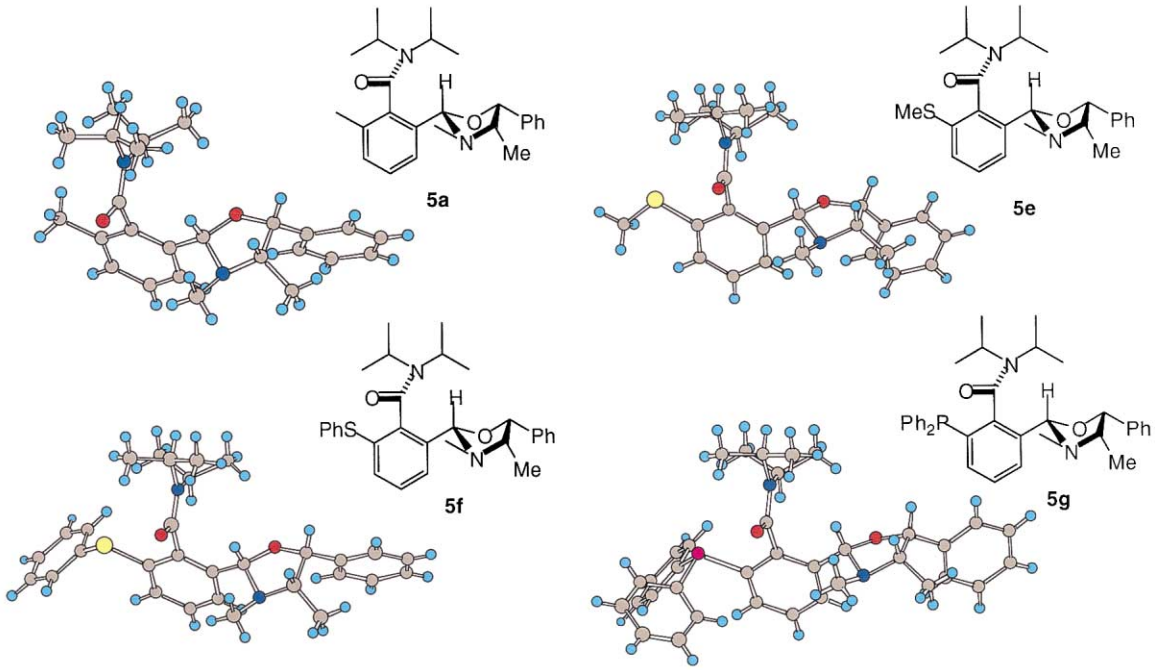


Figure 1. X-Ray crystal structures of **5a**, **5e**, **5f** and **5g**.

olidine functions both as a source of stereocontrol and as a useful protecting group during the lithiation step.[4]

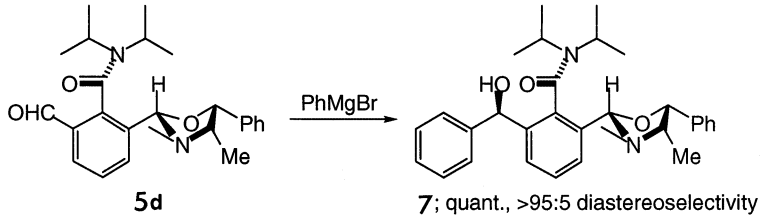
We repeated the lithiation–quench sequence of Scheme 1 with a series of electrophiles (Table 1). In each case, a single atropisomer (by NMR) of the products **5** or **6** was obtained, and the structure and stereochemistry of the sulfides **5e** and **5f** and phosphine **5g** were confirmed by X-ray crystallography (Fig. 1). This atroposelective synthesis of amides **5** and **6** is conceptually similar to our published use of a 1-silylethyl group as a source of stereocontrol,[5] but it is easier to construct an (–)-ephedrine derived oxazolidine than to carry out an enantioselective silylation reaction.[6,7]

The new substituents *ortho* to the amide group in **5** and **6**, while relatively remote from the chirality of the oxazolidine, still fall under the oxazolidine's stereochemical influence because of the control the oxazolidine exerts over amide conformation. We have shown, in a series of papers,[8] that the stereogenic axis of tertiary aromatic amides is a powerful director of stereoselective reactions, and in **5** and **6** we expected the amide to relay, or *project*,[9] a stereochemical influence from the oxazolidine onto the new *ortho*-substituent. To demonstrate this effect, we treated the aldehyde **5d** with phenylmagnesium bromide, a reaction similar to a known[10,11] atroposelective transformation of 2-formyl-1-naphthamides, and obtained a single diastereoisomer (>95:5 by NMR) of the alcohol **7** in quantitative yield (Scheme 2).[12] In essence, this is an instance of 1,7-stereocontrol, in which stereochemistry is relayed from ephedrine to the new stereogenic centre via the configuration at the stereogenic centre in the oxazolidine ring and the conformational preference of the amide axis.

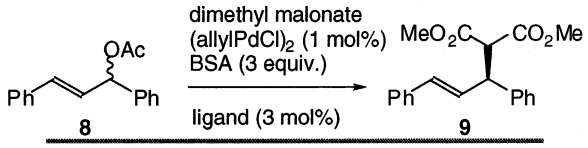
In **5e**–**5g**, a potential metal-coordinating site (the sulfide or phosphine) should similarly be under the projected stereochemical influence of the (–)-ephedrine-derived oxazolidine. The *ortho*-lithiation route to these compounds (Scheme 1) represents a highly efficient synthesis of a series of potential chiral ligands for metals, and we set out to establish the utility of phosphine **5g** by employing it in a palladium-catalysed allylic substitution reaction.[13] Racemic 1,3-diphenylallyl acetate **8** was treated with dimethylmalonate, allylpalladium chloride

Table 1. Functionalised atropisomeric amido-oxazolidines produced by the method of Scheme 1

Entry	R	E^+	E	Oxazolidine product	Yield (%)
1	*i*-Pr	MeI	Me	**5a**	55
2	Et	MeI	Me	**6a**	58
3	*i*-Pr	EtI	Et	**5b**	69
4	Et	EtI	Et	**6b**	58
5	*i*-Pr	Me_2CO	$C(OH)Me_2$	**5c**	89
6	*i*-Pr	Me_2NCHO	CHO	**5d**	89
7	*i*-Pr	Me_2S_2	SMe	**5e**	39
8	*i*-Pr	Ph_2S_2	SPh	**5f**	53
9	*i*-Pr	$ClPPh_2$	PPh_2	**5g**	44



Scheme 2. Projecting the stereochemistry of the oxazolidine onto a new stereogenic centre.



Entry	ligand	**9**, yield (%)	**9**, ee (%)
1	**5g**	93	82 (*S*)-(−)
2	**13**	85	53 (*R*)-(+)

Scheme 3. Allylic substitution reactions with atropisomeric amido-phosphine ligands.

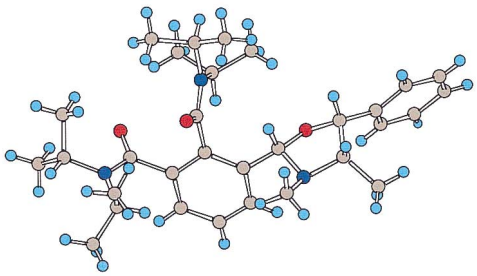


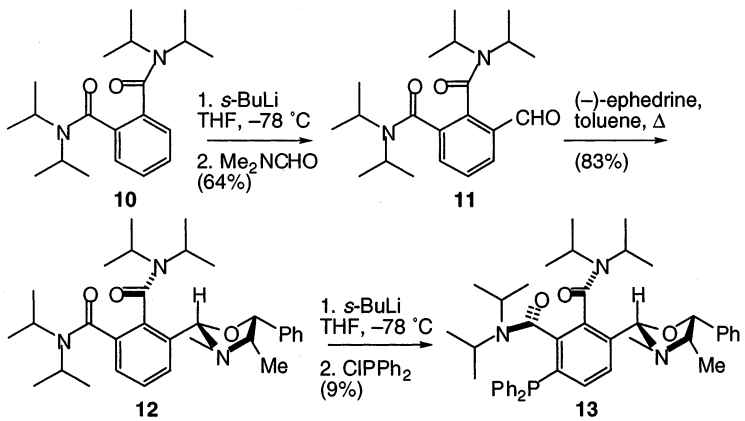
Figure 2. X-Ray crystal structure of **12**.

dimer (1 mol%), phosphine **5g** (3 mol%) and *N*,*O*-bis(trimethylsilyl)acetamide (3 equiv.) and the mixture stirred at 20°C for 24 hours. The product (*S*)-(−)-**9** was obtained in 93% yield, with an enantiomeric excess of 82% (HPLC on chiral stationary phase: Whelk-O1) (Scheme 3).

It is not yet possible to be precise about the mode of coordination between palladium and the ligand, but we assume Pd–P complexation is involved, with the amide system projecting the stereochemistry of the ephedrine-derived oxazolidine onto the phosphorus atom. Nonetheless, it seems conceivable that the asymmetric induction observed in these reactions arises not from the stereochemistry of the rotationally restricted amide group but from direct complexation of palladium by the oxazolidine ring. To rule out this possibility, we made a ligand still containing ephedrine, but whose phosphorus atom is in a local environment pseudo-enantiomeric with that of **5g**.

We know that *ortho*-disposed tertiary carboxamides align their carbonyl groups *anti*, presumably to avoid steric interactions between the NR_2 groups, and we have used such conformational interlocking of two amide groups to relay stereochemistry around an aromatic ring[14] or from one ring to another.[15] The stereochemistry of the second amide is inverted relative to that of the first. We *ortho*-lithiated *N*,*N*,*N*′,*N*′-tetraisopropylbenzene-1,2-dicarboxamide **10**[16] and converted it to the aldehyde **11**. This aldehyde reacted with ephedrine under the usual conditions to give the oxazolidine **12** which was isolated in 83% yield, and whose X-ray crystal structure (Fig. 2) clearly displays an *anti* arrangement between the two amide groups. The oxazolidine-containing diamide **12** was lithiated and quenched with chlorodiphenylphosphine to give, in low yield, but as an easily purified white solid, the bis(amido)phosphine **13** (Scheme 4).

The allylic substitution reaction (Scheme 3) was repeated with the phosphine **13** and gave, as expected, the (*R*)-(+) enantiomer of the product **9**, with an e.e. of 53%. The local environment at the oxazolidine is the



Scheme 4. Asymmetric synthesis of a chiral bis(amido)phosphine.

same in both ligands, while the environment at phosphorus is pseudoenantiomeric, so we are confident that the asymmetric induction observed with atropisomeric amido-phosphine ligands is due to the stereochemistry of the Ar–CO axis.[17]

Acknowledgements

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2. Clayden, J.; Lai, L. W. *Tetrahedron Lett*., submitted.
3. On addition of a second *ortho* substituent, the thermodynamically stable but kinetically labile Ar–CO axis of **1** or **2** becomes both thermodynamically and kinetically stable in **5** and **6**. For discussion of this matter, see Ref. 5.
4. We had previously had difficulties *ortho*-lithiating amides bearing aldehydes protected as lithiohemiaminals (Comins, D. L.; Brown, J. D. *J. Org. Chem*. **1984**, *49*, 1078), acetals, or aminals (Clayden, J.; Lai, L. W.; Westlund, N.; Youssef, L. H., unpublished observations), presumably due to competing complexation of *s*-BuLi to the protected aldehyde. Irrespective of stereochemical features, condensation with (−)-ephedrine is currently our favoured method for protecting aldehydes during *ortho*-lithiation.
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7. Removal of (−)-ephedrine from the amide as though it were an auxiliary (by the method of Ref. 1) was not successful: oxazolidines **5a**, **5b**, or **5e** were hydrolysed (CF_3CO_2H) and reduced immediately at low temperature to alcohols, but the enantiomeric excesses obtained were only 8, 28 and 0%, respectively. Presumably, racemisation of a configurationally unstable intermediate aldehyde is responsible: atropisomeric amides with trigonal 2-substituents (2-formyl or 2-acyl, in particular) have very poor resistance to racemisation by bond rotation: see Ref. 16 and Clayden, J.; Westlund, N.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1351.
8. For a review, see: Clayden, J. *Synlett* **1998**, 810. For further leading references, see: Clayden, J.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1379; Clayden, J.; Helliwell, M.; McCarthy, C.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3232; Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett*. **1999**, *40*, 3329; Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett*. **1999**, *40*, 3331; Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett*. **1998**, *39*, 6103; Clayden, J.; Pink, J. H. *Tetrahedron Lett*. **1997**, *38*, 2561.
9. We feel that the term '*projecting* stereochemistry' carries some useful implications absent from '*relaying* stereochemistry'. *Projection* implies the representation, at a distance, of a three-dimensional object on a two dimensional surface. It also implies inversion (by use of a lens). These three features—distance, planarity, inversion—are all aspects of the amide's role in these reactions: the essential steric features of the gross, three-dimensional stereochemistry of the oxazolidine are reproduced, with inversion, in the conformation of the amide in the two-dimensional plane perpendicular to the aromatic ring. Inversion occurs because the amide places its bulk *anti* to the bulk of the oxazolidine, and a second inversion is apparent when two amides are placed in sequence, continuing the lens analogy.
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17. The local environment of the phosphorus atom in **5g** is homochiral with that of the phosphorus atom in our previously published amido-phosphine ligand (Ref. 5), and a similar degree and sense of enantioselectivity arise from both ligands.