Pergamon

Tetrahedron Letters 42 (2001) 3163–3166

TETRAHEDRON LETTERS

(–)-Ephedrine as an auxiliary for the asymmetric synthesis of atropisomeric amides by dynamic resolution under thermodynamic control

Jonathan Clayden* and Lai Wah Lai

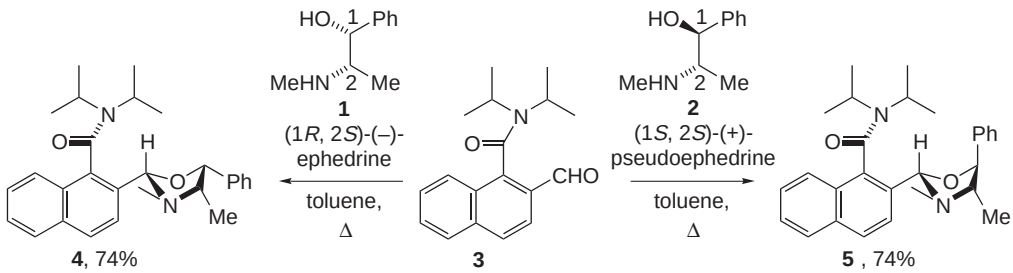
Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Received 20 December 2000; revised 29 January 2001; accepted 12 March 2001

Abstract—*N*,*N*-Dialkyl-2-formylbenzamides and *N*,*N*-dialkyl-2-formyl-1-naphthamides condense with (–)-ephedrine in refluxing toluene to give oxazolidines both as single diastereoisomers with respect to the new stereogenic centre and as single conformers with respect to the slowly-rotating Ar–$CONR_2$ bond. In the naphthamide series, removal of the ephedrine auxiliary by hydrolysis returns the starting aldehyde (isolated by reduction to the more stable alcohol) in enantiomerically enriched form (up to 94% ee). Overall, the two-step sequence amounts to a dynamic resolution under thermodynamic control.

We[1] and others,[2] have recently demonstrated that non-biaryl atropisomers (such as hindered aromatic amides and anilides) are powerful agents of intramolecular stereocontrol. The development of reactions employing non-biaryl atropisomers for intermolecular control of stereochemistry has been hampered by the shortage of effective methods for their asymmetric synthesis. A handful of methods for the asymmetric synthesis of axially chiral aromatic amides (with varying degrees of generality) have now been described,[3–7] including one involving dynamic resolution under thermodynamic control,[5] and one of these allowed us to demonstrate for the first time a non-biaryl atropisomer acting as a chiral ligand in an asymmetric metal-promoted reaction.[6]

In this Letter, we report that thermodynamic control over amide conformation may be achieved more simply and directly by using (–)-ephedrine-derived oxazolidines formed in one-step by condensation of commercially available (–)-ephedrine with 2-formyl benzamides and naphthamides.[8] It is well established that that (1*R*,2*S*)-(–)-ephedrine **1**[9] and (1*S*,2*S*)-(+)-pseudoephedrine **2**[10] condense with aromatic aldehydes diastereoselectively (with respect to the 'aminal' centre) to form oxazolidines. In order to establish the ability of ephedrine and pseudoephedrine to control not only the configuration of a new stereogenic centre in the ring but also that of an adjacent stereogenic axis, we condensed them with *N*,*N*-diisopropyl-2-formyl-1-naphthamide **3**[11,12] in refluxing toluene under a Dean–Stark condenser (Scheme 1). In each case, we obtained single diastereoisomers **4** and **5**, with no trace (in the NMR spectrum of the crude reaction mixture) of epimers at either the new stereogenic centre in the oxazolidine ring or at the rotationally restricted Ar–CO axis. The oxazo-



Scheme 1. Condensation of (–)-ephedrine and (+)-pseudoephedrine with a 2-formyl-1-naphthamide.

* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00416-6

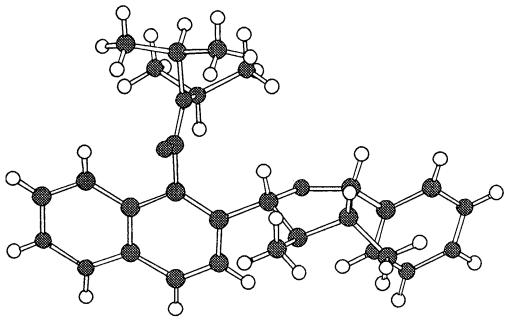


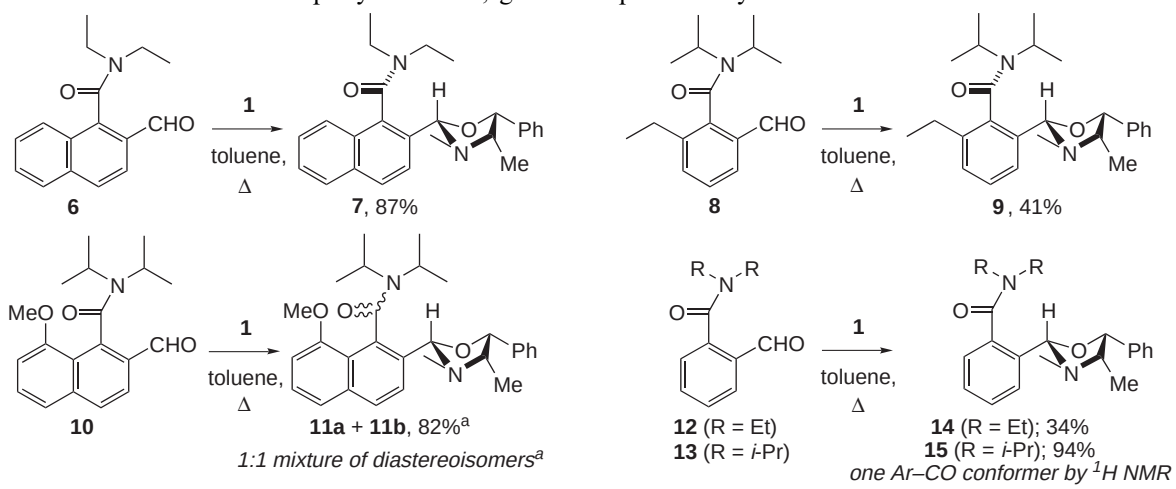
Figure 1. X-ray crystal structure of **4**.

lidines were isolated in 70–80% yield after purification by recrystallisation, and the stereochemistry of **4** was determined by X-ray crystallography (Fig. 1).

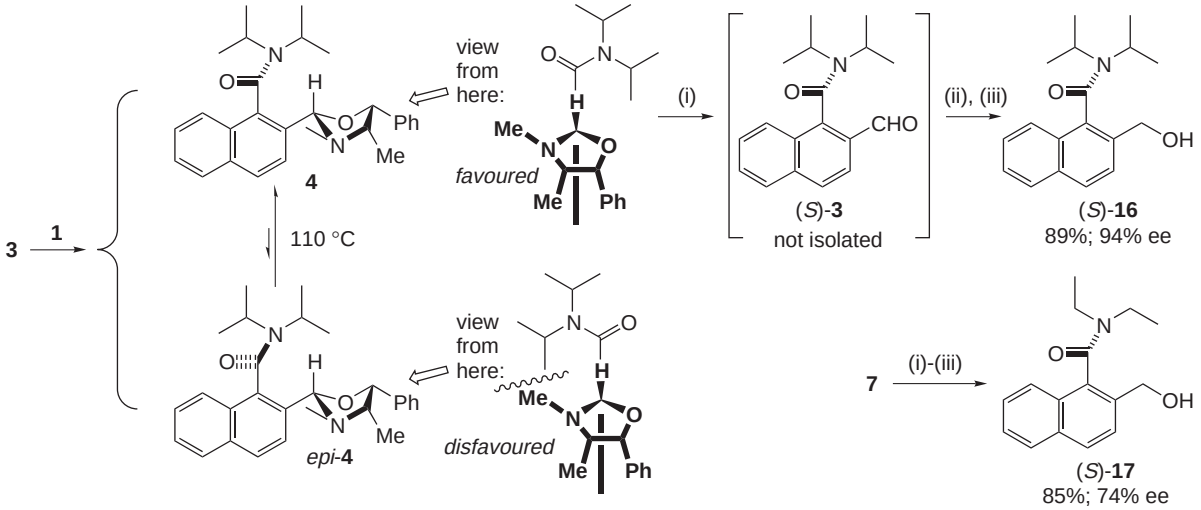
Similar reactions of four further aldehydes **6**, **8**, **10** and **12** (Scheme 2) illuminate the mechanism by which (−)-ephedrine gains control of the stereogenic Ar–CO axis of **4**. Like **3**, amides **6**[12] and **8**[13] reacted with ephedrine to give single diastereoisomers of the oxazolidines **7** and **9**. Given that the aldehydes **3**, **6** and **8** are racemic, atropisomeric compounds,[14] the formation of **4**, **7** and **9** as single diastereoisomers in >50% yield can be explained only by a dynamic resolution of some kind. Dynamic resolution implies interconversion of stereoisomers, and the temperature of the reaction (110°C) provides easily enough thermal energy to racemise **3**, **6** and **8**,[11] so dynamic kinetic resolution during the oxazolidine formation (one atropisomeric enantiomer reacting faster than the other) is certainly feasible. However, several features of the reactions of **3**, **6**, **8**, and also **10**, **12** and **13** lead us to believe that the stereoselective formation of **4**, **7** and **9** is under thermodynamic control, as illustrated in Scheme 3. Firstly, typical barriers to epimerisation of *N*,*N*-dialkyl-1-naphthamides bearing chiral, branched 2-substituents lie between 105 and 115 kJ mol^{-1}.[11,15] At 110°C, a kinetically-determined ratio of such products will be irrelevant to the outcome of a reaction lasting more than 10 min; the stereoselectivity will be determined by equilibration to the most stable epimer. Secondly, the amide **10**, which should also racemise rapidly at 110°C, gives a 1:1 mixture of stereoisomeric oxazolidines **11a** and **11b** under these conditions.[16,17] 8-Heterosubstituted naphthamides epimerise much more slowly than 8-unsubstituted naphthamides,[18] and presumably the epimers **11a** and **11b** do not interconvert under the conditions of the reaction. Thirdly, while the amides **12** and **13** form oxazolidines **14** and **15** which, without a second aromatic *ortho* substituent, cannot exist as two atropisomers,[11,15] **14** and **15** appear (by ^{1}H NMR) to exist as single conformers about the Ar–CO bond.[19] Their conformations must be under thermodynamic control, and if one Ar–CO conformer of **14** or **15** is significantly more stable than the other, it seems reasonable to propose the same for one atropisomer of **4**, **7** or **9**.

Scheme 3 illustrates the way this dynamic resolution under thermodynamic control (or 'dynamic thermodynamic resolution'[20,5]) is achieved with aldehyde **3**. Condensation of **3** with (−)-ephedrine **1** gives an initial, kinetically controlled mixture of diastereoisomers **4** and *epi*-**4** which rapidly equilibrate (within minutes) at the temperature of the reaction. *epi*-**4** Is significantly less stable than **4**, which is the only isolable product of the reaction. The crystal structure of **4** (Fig. 1) gives an indication of the origin of its relative stability: as usual,[6,21,22] the stereogenic centre at the *ortho*-position prefers its smallest substituent (H) more or less to eclipse the Ar–CO bond, so that the plane of the naphthamide ring bisects the oxazolidine ring. Steric crowding is significantly lessened if the N*i*-Pr$_2$ group lies *anti* across the ring to the N–Me group, and this is the arrangement observed in **4**.

In order to complete the resolution of **3** and **6**, the ephedrine auxiliary must be removed from **4** and **7**. In each case, acid-catalysed hydrolysis returned the enantiomerically-enriched aldehyde, but given the low barriers to racemisation of 1-naphthamides bearing carbonyl groups in their 2-positions[11,5,23] we found it necessary to reduce the product aldehydes rapidly to alcohols **16** and **17** to prevent rapid racemisation of the products.[24] Loss of enantiomeric purity, particularly from **17**, is presumably due to the ease of racemisation of the



Scheme 2. Condensation of (−)-ephedrine with amidoaldehydes. [a] Taken from Refs. 8 and 9.



Scheme 3. Dynamic thermodynamic resolution of atropisomeric 2-formylnaphthamides. (i) CF_3CO_2H (20 equiv.), THF, H_2O; (ii) NaOMe (25 equiv.); (iii) $NaBH_4$ (10 equiv.).

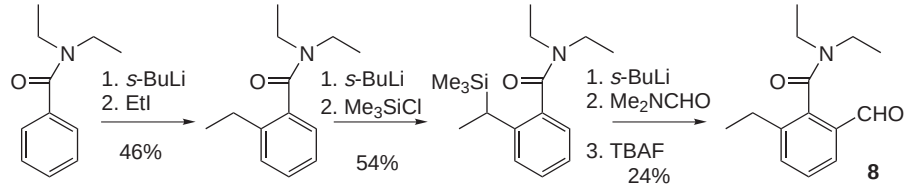
aldehyde intermediate. We are currently developing new applications for enantiomerically pure non-biaryl atropisomers, particularly as chiral ligands for metals, and these will be reported in due course.

Acknowledgements

We are grateful to the EPSRC and to GlaxoWellcome for a CASE award (to L.W.L.), to Dr. Andrew Craven for many helpful discussions, and to Dr. Madeleine Helliwell for determining the X-ray crystal structure of **4**.

References

1. Clayden, J. *Synlett* **1998**, 810.
2. For leading references, see: (a) Curran, D. P.; Geib, S.; DeMello, N. *Tetrahedron* **1999**, *55*, 5681; (b) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955; (c) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131; (d) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295; (e) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607; (f) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 1108; (g) Kitagawa, O.; Momose, S.-i.; Fushimi, Y.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 8827; (h) Fujita, M.; Kitagawa, O.; Izawa, H.; Dobashi, A.; Fukaya, H.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 1949; (i) Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447; (j) Bach, T.; Schröder, J.; Harms, K. *Tetrahedron Lett.* **1999**, *40*, 9003.
3. Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899.
4. Koide, H.; Uemura, M. *J. Chem. Soc., Chem. Commun.* **1998**, 2483.
5. Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2556.
6. Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033.
7. Clayden, J.; Johnson, P.; Pink, J. H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 371.
8. This ephedrine-based method has a number of advantages over our previously-described method based on diamine-derived aminals (Ref. 5). (–)-Ephedrine, unlike the diamine, is cheap and commercially available as both enantiomers, and the oxazolidines are more stable to purification than animals.
9. (a) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2256; (b) Agami, C.; Rizk, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1485; (c) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537.
10. Santiesteban, F.; Grimaldo, C.; Contreras, R.; Wrackmeyer, B. *J. Chem. Soc., Chem. Commun.* **1983**, 1486.
11. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.
12. Clayden, J.; McCarthy, C.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1363.
13. The synthesis of 2-formyl-6-alkyl benzamides such as **8** by ortholithiation is complicated by the need either to protect the aldehyde from nucleophilic attack during the introduction of the alkyl group, or to protect the alkyl group from lateral lithiation (Court, J. J.; Hlasta, D. J. *Tetrahedron Lett.* **1996**, *37*, 1335) during introduction of the formyl group. Our route to **8** (below) employed silyl-protection of



the ethyl group (Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372) during the formylation step.

14. In general, 2,6-disubstituted tertiary benzamides and 2-substituted tertiary naphthamides may exist as two atropisomeric enantiomers which interconvert only slowly, see Ref. 15.
15. Bowles, P.; Clayden, J.; Helliwell, M.; McCarthy, C.; Tomkinson, M.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2607.
16. Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett.* **2000**, *41*, 3279.
17. Clayden, J.; Helliwell, M.; McCarthy, C.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3232.
18. Clayden, J.; McCarthy, C.; Helliwell, M. *J. Chem. Soc., Chem. Commun.* **1999**, 2059.
19. The Ar–CO axis of a benzamide bearing only one *ortho* substituent is not usually stereogenic, but may appear so on the NMR timescale: for example, 2-substituted benzamides containing a stereogenic centre typically display two sets of signals in the NMR spectrum at ambient temperature due to the two slowly-interconverting Ar–CO conformers. For further discussion, see Refs. 22 and 6.
20. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.
21. Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1999**, *40*, 3331.
22. Clayden, J.; Pink, J. H.; Yasin, S. A. *Tetrahedron Lett.* **1998**, *39*, 105.
23. Clayden, J.; Darbyshire, M.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1997**, *38*, 8587.
24. Enantiomeric excesses were determined by HPLC on chiral stationary phase (Whelk-O1 from Regis).