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Diastereoselective Enolate Chemistry using Atropisomeric Amides

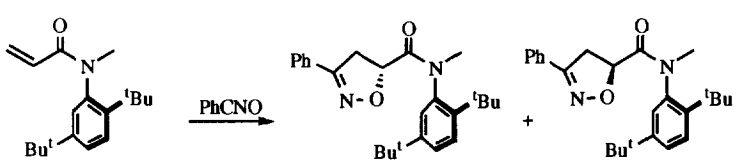
Adam D. Hughes, David A. Price, Oleg Shishkin and Nigel S. Simpkins*

Department of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

Abstract: The alkylations and aldol reactions of certain atropisomeric amides, derived from *ortho-tert*-butyl aniline, are highly diastereoselective. Copyright © 1996 Elsevier Science Ltd

The selective synthesis of organic compounds in enantiomerically pure form continues to present the organic chemist with a major challenge. Despite the recent advances in chiral reagents and asymmetric catalysis, the chiral auxiliary method remains the most well-developed, effective and reliable approach for the asymmetric synthesis of many types of compound.[1] A typical example is in enolate chemistry involving carboxylic acid derivatives, where a range of amides and imides, typified by the excellent Evans systems,[2] allows for highly efficient and diastereoselective alkylation and aldol chemistry.

Notably, the vast majority of such auxiliary systems rely on chiral pool materials, and involve diastereoselective reactions in which the control (for example facial control in an enolate alkylation) originates from asymmetric *centres* in the auxiliary. In contrast, auxiliary methods which rely on control originating from an element of *axial* chirality, especially non-biaryl types, are very rare.[3] A recent report from the group of Curran illustrated the potential of such systems for asymmetric synthesis, e.g. Scheme 1.[4]



(1) (2) (3)

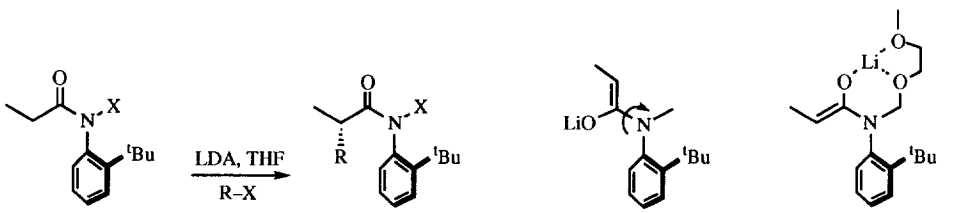
Scheme 1

Thus, the benzonitrile oxide cycloaddition of **1** generates a mixture of atropisomeric products (stable at room temperature) in which one isomer greatly predominates. The stereochemical outcome of this reaction was assumed to be as shown, with reaction occurring *anti* to the amide face shielded by the *ortho-tert*-butyl group,[5] to give **2** as the major product. Free radical reactions, and other types of cycloaddition, conducted with such amides were found to be similarly stereoselective. Although these studies demonstrate potentially useful levels of diastereocontrol, the amide and imide systems examined were either prochiral or racemic (one atropisomeric series is shown for clarity).

We became interested in testing the utility of this type of atropisomeric anilide in enolate reactions, and

herein describe our preliminary results in this area, which show that good diastereocontrol is possible in alkylation and aldol reactions, and which provide further information on the stability of the atropisomers to isomerisation, and on the sense of stereoinduction in their reactions.[6]

Our initial experiments involved alkylation reactions of the lithium enolate derived from anilide **4** by treatment with LDA. These reactions gave the desired products **6** in good chemical yield but with very modest diastereoselectivities of around 2–4:1.[7]



(**4**) X = Me
(**5**) X = MEM

(**6**) X = Me
(**7**) X = MEM

(**8**)

(**9**)

Scheme 2

We attributed this poor level of selectivity to the possibility of rotation around the amide C–N bond in the intermediate enolate, as illustrated by **8**.[8] An obvious approach to controlling the conformation of such enolates would be to introduce a metal co-ordinating group X into the *N*-substituent. Initial attempts, using imide type derivatives with X = Boc or CO^{t}Bu were unrewarding, these compounds not forming enolates, but instead acting as acylating agents. We turned instead to the *N*-MEM derivative **5**, which we hoped might fix the conformation of the enolate by co-ordination, as shown in **9**.

Pleasingly, the enolate reactions of **5**, with simple electrophiles, such as alkyl halides, proved much more stereoselective than those involving **4**, Table 1.[9]

Table 1: yields and diastereoselectivities in enolate reactions of amide 5

electrophile	$PhCH_2Br$	$H_2C{=}CHCH_2Br$	EtI	$PhCH{=}CHCH_2Cl$	$PhSSO_2Ph$
yield **7** (%)	83	82	89	69	84
diastereomer ratio	25:1	15:1	15:1	>25:1*	>25:1*

* Only one diastereoisomer observed by NMR

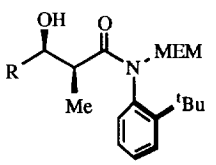
In each case we assume that the major product is **7**, corresponding to reaction on the face of the enolate not shielded by the *ortho-tert*-butyl group, in each case we were able to identify the minor diastereoisomer by thermal atropisomerisation.[10]

We also examined the aldol reactions of **5**, involving addition of achiral aldehydes to the lithium enolate in THF, Table 2.

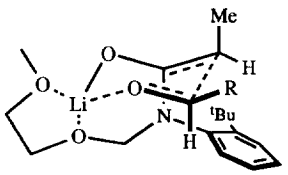
Table 2: yields and diastereoselectivities in aldol reactions of amide 5

aldehyde	PhCHO	Me_2CHCHO	$C_6H_{11}CHO$	Me_3CCHO	EtCHO
yield **10** (%)	87	85	86	84	83
diastereomer ratio	*syn* aldol product only observed, all atropselectivities > 25:1[11]				

With a range of bulky or branched chain aldehydes, and even with propanal, the aldol products **10** are obtained with very good diastereoselectivity.[11] The lability of the MEM group in the starting amide **8** precluded the use of alternative aldol strategies, involving the use of $TiCl_4$ or Bu_2BOTf.[12] In each case we assume that the major aldol product is the *syn*-isomer **10** resulting from reaction of a *(Z)*-lithium enolate, via a transition state such as **11**, in which the bulky *ortho-tert*-butyl group in the enolate is orientated away from the approaching aldehyde.



(10)



(11)

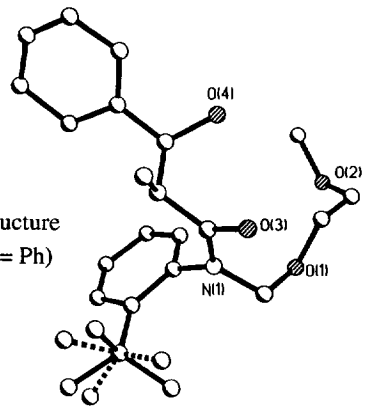
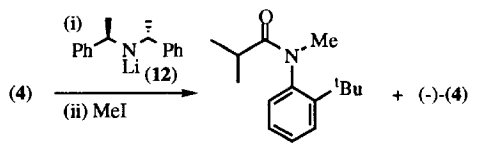


Figure 1
X-ray structure of **10** (R = Ph)

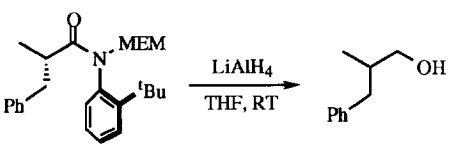
As shown, this result was confirmed for the aldol product (**10**, R = Ph) resulting from the reaction with PhCHO, by a single crystal X-ray structure determination, Figure 1.

Having demonstrated useful levels of diastereocontrol in enolate reactions of atropisomeric amides, two further problems relating to their potential in auxiliary chemistry need to be addressed, namely their availability in enantiomerically pure form, and the release of chiral products from the anilide. Whilst we have not studied either area in detail, Schemes 3 and 4 indicate some preliminary findings.



(13)

Scheme 3



(7) R = Bn

(14) (80%)

Scheme 4

Thus, treatment of *N*-methyl amide **4** with a deficiency of the chiral lithium amide base **12**, followed by quenching with MeI, allowed recovery of the unreacted (-)-**4** in enantiomerically enriched form.[13] This unprecedented kinetic resolution has not been optimised, and is at present inefficient, the enantiomer selectivity being only about 3:1, but the reaction allowed us to isolate small quantities of (-)-**4** in up to 88% ee, and to show that this material is fairly stable to thermal racemisation.[14]

Finally, attempts to hydrolyse the highly hindered product anilides, such as **7**, under a range of conditions have not uncovered an efficient procedure to date, however, as shown, the reduction of the benzyl substituted anilide **7** (R = Bn), by reaction with $LiAlH_4$ in THF at room temperature gave the primary alcohol **14** in good chemical yield.[15]

The results described above move closer the realisation of effective auxiliary chemistry based on atropisomeric systems. We are actively pursuing a range of approaches to these types of compound in enantiomerically pure form, as well as examining alternative axially chiral motifs, which may offer even better levels of stereocontrol, combined with improved auxiliary removal.

Acknowledgements

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References and Footnotes

1. Houben-Weyl, Methods of Organic Chemistry, Vol E21, Thieme, Stuttgart, 1995.
2. See for example, Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.
3. For a list of examples, see reference 6a. See also (a) Seebach, D.; Wasmuth, D. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 971. (b) Atkinson R. S.; Barker, E.; Price, C. J.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1994**, 1159.
4. Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131. The work described in this paper was inspired by a lecture delivered by Professor Curran at the 6th Brazilian Meeting on Organic Synthesis, Sao Paulo, 5–9 September 1994.
5. The *meta-tert*-butyl group was present simply out of synthetic expediency and was not thought to influence the stereochemical outcome of these reactions.
6. Related publications have appeared recently, see (a) Bowles, P.; Clayden, J.; Tomkinson, M. *Tetrahedron Lett.* **1995**, *36*, 9219. (b) Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899.
7. Professor Curran has informed us of his similar findings, from unpublished work conducted by his co-workers H. Qi and A. Balog.
8. The preferred conformations of the anilides themselves are well established to be as shown, see for example Stewart, W. E.; Siddall III, T. H. *Chem. Rev.* **1970**, *70*, 517. However, we expect that the loss of amide resonance on formation of the lithium enolate results in greatly increased conformational mobility around the CO–N bond.
9. In a typical procedure the starting amide **5** was added to a slight excess of LDA in THF at -78 °C, and after 30 min an excess of alkylating agent was added. The mixture was then allowed to warm slowly to room temperature, and when TLC indicated complete reaction the product was isolated following usual aqueous work-up and column chromatography. The diastereoisomer ratios indicated were determined from integration of high field ^{1}H NMR spectra of crude products.
10. Purification of samples of products **7**, by bulb-to-bulb distillation (at *ca.* 220 °C), resulted in extensive epimerisation, allowing identification of minor atropisomers. Variable temperature NMR studies showed that the isomer ratio of **7** (R = Bn) changed from 25:1 to 2:1 after 65 min at 95 °C.
11. The atropselectivities indicated are with respect to the anilide aryl C–N axis, the aldol products also showed additional minor signals attributed to *amide* C–N rotamers.
12. Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.
13. For example, treatment of **4** with 0.9 equivalents of the chiral base **12**, followed by addition of an excess of MeI resulted in about 90% conversion to **13** (the ee of which was not precisely determined), the remaining **4** having 88% ee as estimated by HPLC using a chiralpak AD column, and pentane–^{i}PrOH (96:4) as eluant. Amide (-)-**4** of 63% ee had $[\alpha]_D^{29}$ -23 (*c* 0.48 in $CHCl_3$).
14. Maintaining a solution of non-racemic (-)-**4** at 50 °C for 5h resulted in no change in enantiomeric excess, as monitored by HPLC.
15. Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343.

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