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A Study of 4-Substituted 5,5-Diaryl Oxazolidin-2-ones as Efficacious Chiral Auxiliaries

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Abstract

A series of three 5,5-diaryl substituted oxazolidin-2-ones (diphenyl, dinaphthyl and ditolyl) have been prepared and shown to be particularly effective chiral auxiliaries to afford high yields and diastereoselectivities for alkylation and azidations of their N-acyl derivatives. The 5,5-ditolyl oxazolidin-2-one proved to be particularly efficacious in terms of diastereoselectivity, yield and solubility. © 1998 Elsevier Science Ltd. All rights reserved.

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The use of stoichiometric chiral auxiliaries to effect asymmetric transformations continues to be an important area of asymmetric synthesis. In this context, the seminal work of Evans in the development of chiral oxazolidin-2-ones has proved to be a particularly effective methodology. These, so called, Evans auxiliaries have been utilized in a particularly wide variety of highly diastereoselective reactions of attached N-acyl groups including alkylation, amination, azidation, bromination, hydroxylation, aldol additions, Diels-Alder cycloadditions and conjugate additions [1].

One of the drawbacks of the Evans methodology involves the removal of the auxiliary. If the N-acyl group is sterically demanding or α -branched then the unwanted endocyclic hydrolysis can predominate to give a ring opened amide rather than the required exocylic cleavage to afford the carboxylic acid derivative and the recovered chiral auxiliary [2]. The endocyclic hydrolysis can be suppressed by the use of lithium hydroperoxide, however, the use of this reagent on a large scale may be hazardous. Consequently, Davies *et al.* have developed an elegant solution in the form of the "super Quats" which are 4-substituted 5,5-dimethyl oxazolidin-2-ones 1. These auxiliaries do not suffer from the undesired endocyclic cleavage and give good to excellent diastereoselectivities in alkylation and conjugate addition reactions [3].

We anticipated that increasing the steric requirements of the 5-substituents in 5,5-diaryl oxazolidin-2-ones 2 would have a beneficial effect on the diastereoselectivity in reactions utilizing such auxiliaries. Furthermore, we hoped that the enolate chemistry of N-acyl derivatives of 5,5-diaryl oxazolidin-2-ones 2 would be more efficient than observed for other 5,5-disubstituted oxazolidin-2-ones. After our work was initiated, other 5,5-disubstituted oxazolidin-2-ones were reported but these auxiliaries were not utilized in

diastereoselective alkylations [4]. At the conclusion of our work we became aware of the work of Isobe and Fukuda who had prepared a number of 5,5-diphenyl oxazolidin-2-ones 3 [5]. The 4-benzyl-5,5-diphenyloxazolidin-2-one 3 ($R^1 = CH_2Ph$; $R^2 = Ph$) was studied in diastereoselective alkylations and provided only moderate de's for methylation (87% de) and gave very poor chemical yields in benzylation studies (25%). These findings prompted us to disclose our results for the 5,5-diaryl oxazolidin-2-ones 2 where the nature of the 5-aryl substituent is important for the diastereoselectivity of alkylation reactions and the efficiency of these alkylations as well as the efficacy in the preparation of the acylated 5,5-diaryl oxazolidin-2-ones 6.

 $\begin{array}{c} 0 \\ 0 \\ 0 \\ R^2 \\ R^2 \\ R^2 \\ R^1 \end{array} = Me, Ph, PhCH_2 \text{ or } Me_2CH; R^2 = Me \\ \mathbf{2} \\ R^1 = Me_2CH; R^2 = Ph, 4-MeC_6H_4 \text{ or } 2-naphthyl \\ \mathbf{3} \\ R^1 = Me_2CH, Me_2CHCH_2, PhCH_2, Ph, Me_3C; R^2 = Ph \end{array}$

The 4-isopropyl-5,5-diaryloxazolidin-2-ones 2a-c [6,7] and their N-acylated counterparts **6a-f** were readily prepared from valine methyl ester hydrochloride **4** as detailed in scheme 1. Thus, reaction of ester 4 with excess aryl Grignard reagents afforded the amino alcohols 5a (Ar = Ph, 54%), 5b (Ar = 2-naphthyl, 60%) and 5c (Ar = 4-tolyl, 52%). Subsequent reaction of the amino alcohols **5a-c** with triphosgene in toluene with KOH provided the corresponding oxazolidin-2-ones 2a (Ar = Ph, 73%), 2b (Ar = 2-naphthyl, 59%) and 2c (Ar = 4-tolyl, 54%). The oxazolidin-2-one 2c could also be prepared in 62% using triethylamine in THF. N-Acylations of the oxazolidin-2-ones **2a-c** were carried out by deprotonation with BuLi followed by treatment with the appropriate acid chlorides to afford the corresponding N-acyl products **6a-f** (Table 1). Alternatively, the N-acyl oxazolidin-2ones 6a and 6c could be generated in 84% and 100% yield (entries 1 and 3, Table 1), respectively, using triethylamine as the base in the presence of N,N-dimethylamino-4pyridine [8]. Surprisingly, the 2-naphthyl **2b** and 4-tolyl **2c** substituted oxazolidin-2-ones were consistently N-acylated in considerably higher yield (82-100%) in comparison to the phenyl analogue 2a (46-70%). This is a consequence of the fact that the auxiliaries 2b, c are fully soluble in THF at -78°C whilst 2a is not.



With access to the N-acylated oxazolidin-2-ones **6a-f** in hand they were subjected to diastereoselective alkylations (Scheme 2, Table 1). Thus, the hydrocinnamoyl oxazolidin-2-ones **6a-c** were subjected to diastereoselective methylation by enolate formation with sodium bis(trimethylsilyl)amide at -78°C followed by reaction with methyl iodide to give the oxazolidin-2-ones **7a-c** in excellent de's (82-94% de, entries 1-3). The diastereoselectivity achieved for the methylation of **6c** (94% de, entry 3) is in line with the most efficient Davies "super Quat" **6g** (95% de, entry 7) [3] but shows improvement over the 4-benzyl-5,5-diphenyloxazolidin-2-one of Isobe and Fukuda (87% de) [5].

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Entry	6	Ar	R	Yield of 6	R1	Yield of 7	de of 7
				(%)		(%)	(%) ^b
1	a	Ph	PhCH ₂	46 (84) ^a	Me	69	91
2	b	2-naphthyl	PhCH ₂	97	Me	58 (68) ^c	82 (86) ^c
3	с	4-tolyl	PhCH ₂	82 (100) ^a	Me	52	94
4	d	Ph	Me	70	PhCH ₂	46	97
5	e	2-naphthyl	Me	90	PhCH ₂	55	91
6	f	4-tolyl	Me	97	PhCH ₂	66	96
7	g	Me	PhCH ₂	-	Me	68d	95d
8	ĥ	Me	Me	-	PhCH ₂	22d	97d

Table 1 Synthesis of oxazolidin-2-ones 7a-f from oxazolidin-2-ones 2a-c

^aYield in parentheses for acylation using Et₃N/DMAP; ^b% de determined by ¹H nmr; ^cdata for enolate formation with LDA at 0°C; ^ddata taken from reference 3.



A complimentary set of diastereomers 7d-f were available by the benzylation of the corresponding N-propionyl oxazolidin-2-ones 6d-f. This was achieved by enolate formation with LDA at 0°C followed by treatment with benzyl bromide to give the benzylated products 7d-f in outstanding de's (91-97% de, entries 4-6). The diastereoselectivity observed for the benzylation of the 5,5-ditolyl oxazolidin-2-one 6f (96% de, entry 6) is in line with the Davies "super Quat" 6h (97% de, entry 8) [3]. Moreover, the efficiency of the benzylation of 6f (66%, entry 6) compares favourably with the 4-benzyl-5,5-diphenyloxazolidin-2-one of Isobe and Fukuda (22% yield) [5].

With both diastereomeric series in hand 7a-c and 7d-f, the de's were established by ¹H nmr analysis of the benzyl methylene and methyl resonances of the alkylated N-acyl portions of 7a-f.



Removal of the oxazolidin-2-one auxiliaries from 7a and 7d was achieved by treatment with lithium hydroxide to give, gratifyingly, the chiral auxiliary 2a (94% and 95%) together with the alkylated acids 8a (94%, 89% ee) and 8b (60%, 98% ee), respectively (Scheme 3). The absolute configurations and ee's of the enantiomeric acids 8a and 8b were established by the use of (R,R)-diphenyldiaminoethane [9] and from their specific rotations. The absolute configurations of acids 8a and 8b were consistent with those anticipated from delivery of the alkylating agent to the 2Si face of a carbonyl-metal-carbonyl Z-enolate of **6a** and **6d**, in accord with the Evans [1] and Davies [3] auxiliaries.

The N-hydrocinnamoyl oxazolidin-2-one 6c was also subjected to complementary diastereoselective azidations using the methodology of Evans [1]. Thus, enolate formation from oxazolidin-2-one 6c using potassium bis(trimethysily)amide followed by treatment with trisyl azide then acetic acid afforded the azide 9 (65% yield, 85% de) (Scheme 4). Alternative treatment of 6c with dibutylboron triflate and Hünig's base followed by reaction with N-bromosuccinimide gave the bromide 10. The crude bromide 10 was reacted with tetramethyguanidinium azide to give the diastereomeric azide 11 (55%, 91% de).



Scheme 4 (Ar = p-tolyl) *Reagents and conditions:* (a) KN(SiMe₃)₂, -78°C, THF; (b) Trisyl azide; (c) AcOH; (d) Bu₂BOTf, Pr_2NEt , -78°C; (e) NBS, -78°C, CH₂Cl₂; (f) Tetramethylguanidinium azide, -78°C, CH₂Cl₂

In conclusion, a series of three 5,5-diaryl oxazolidin-2-ones **2a-c** were prepared and found to be effective chiral auxiliaries for diastereoselective alkylations and azidations of attached N-acyl portions. The 5,5-ditolyl oxazolidin-2-one **2c** proved to be the most efficacious in terms of solubility, yield and stereodirecting influence. The auxiliaries could also be removed in \geq 94% yield so enhancing their recyclability.

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References and Notes

- For reviews of the use of oxazolidin-2-ones as chiral auxiliaries see: Ager. D. J.; Prakash, J.; Schaad, D. R. Aldrichimica Acta, 1997, 30, 3. Ager, D. J.; Prakash, J.; Schaad, D. R. Chem. Rev., 1996, 96, 835. Evans, D. A. Aldrichimica Acta. 1982, 15, 23.
- [2] Evans, D. A.; Britton, T. C.; Ellman, J. A. Tetrahedron Lett., 1987, 28, 6141.
- [3] Davies, S. G.; Sanganee, H. J. *Tetrahedron: Asymmetry*, 1995, 6, 671. Bull, S. G.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Prasad, R. S.; Sanganee, H. J. *Synlett*, 1998, 519.
- [4] Delair, P.; Einhorn, C.; Luche, J. J. Org. Chem., 1994, 59, 4680. Delaunay, D.; Le Corre, M. Chem. Comm., 1994, 3041. Cardillo, G.; Gentilucci, L.; Tomasini, C.; Tomasoni, L., Tetrahedron: Asymmetry, 1995, 6, 1947.
- [5] Isobe, T.; Fukuda, K. Japanese Patent JP09143173, 1995; Chem. Abstr., 1997, 127, 50635.
- [6] All new compounds gave satisfactory ir, ¹H nmr, ¹³C nmr. accurate mass and/or elemental analysis.
- [7] The 5,5-diaryl oxazolidin-2-ones 2a-c are now commercially available from Hickson & Welch Ltd.
- [8] Ager, D. J.; Allen, D. R.; Froen, D. E.; Schaad, D. R. Synthesis, 1996, 1283.
- [9] Parker, D.; Fulwood, R. Tetrahedron: Asymmetry, 1992. 3, 25.