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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.

Keywords: Asymmetric synthesis; diastereoselection; oxazolidinones

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

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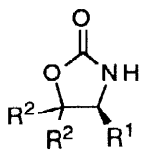
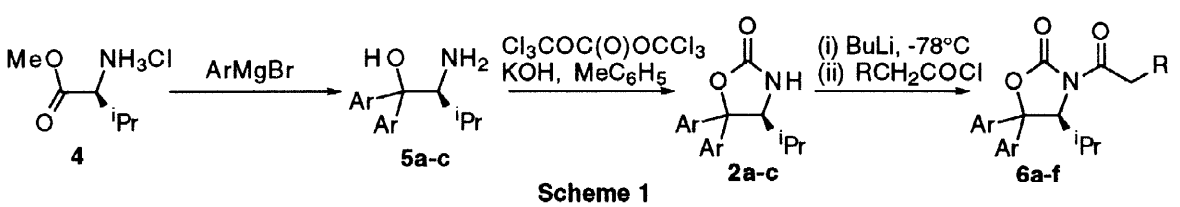
diastereoselective alkylations [4]. At the conclusion of our work we became aware of the work of Isobe and Fukuda who had prepared a number of 5,5-diphenyl oxazolidin-2-ones **3** [5]. The 4-benzyl-5,5-diphenyloxazolidin-2-one **3** (R^1 = CH_2Ph; R^2 = Ph) was studied in diastereoselective alkylations 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**.



1 R^1 = Me, Ph, $PhCH_2$ or Me_2CH; R^2 = Me
2 R^1 = Me_2CH; R^2 = Ph, 4-MeC_6H_4 or 2-naphthyl
3 R^1 = Me_2CH, Me_2CHCH_2, $PhCH_2$, Ph, Me_3C; R^2 = Ph

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-2-ones **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-4-pyridine [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.



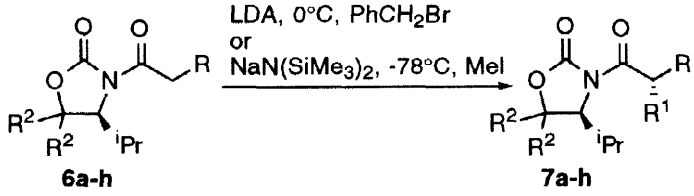
Scheme 1

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].

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

Entry	6	Ar	R	Yield of 6 (%)	R^1	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	c	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	68[d]	95[d]
8	h	Me	Me	-	$PhCH_2$	22[d]	97[d]

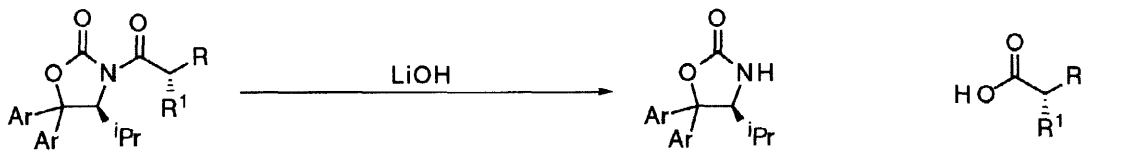
[a]Yield in parentheses for acylation using Et_3N/DMAP; [b]% de determined by ^1H nmr; [c]data for enolate formation with LDA at 0°C; [d]data taken from reference 3.



Scheme 2

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**.

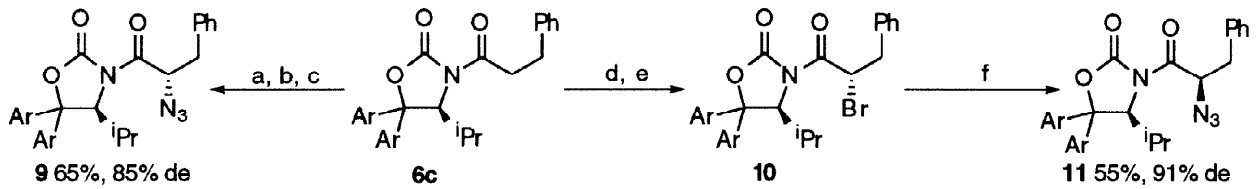


Scheme 3

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 2*Si* 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(trimethysilyl)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).



9 65%, 85% de **6c** **10** **11** 55%, 91% de

Scheme 4 (Ar = p-tolyl) *Reagents and conditions:* (a) $KN(SiMe_3)_2$, -78°C, THF; (b) Trisyl azide; (c) AcOH; (d) Bu_2BOTf, $^iPr_2NEt$, -78°C; (e) NBS, -78°C, CH_2Cl_2 ; (f) Tetramethylguanidinium azide, -78°C, CH_2Cl_2

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 ≥94% yield so enhancing their recyclability.

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References and Notes

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[6] All new compounds gave satisfactory ir, ^1H nmr, ^{13}C 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.

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