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4-Substituted-5,5-Dimethyl Oxazolidin-2-ones as Effective Chiral Auxiliaries for Enolate Alkylations and Michael Additions.

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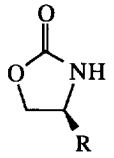
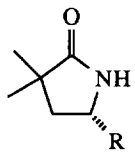
Abstract: 4-(Methyl, phenyl, benzyl, and *i*-propyl)-5,5-dimethyl-oxazolidin-2-ones, readily available from α-amino acids, are shown to be effective chiral auxiliaries for stereoselective enolate alkylations and conjugate additions of attached N-acyl moieties.

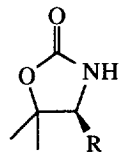
One of the most popular and reliable methods of asymmetric synthesis has proved to be *via* stoichiometric chiral auxiliaries.[1-4] In this area the homochiral 4-substituted oxazolidin-2-ones **1** developed by Evans have proved particularly effective for controlling a variety of reactions of attached acyl fragments.[5] Recently we reported the synthesis[6] and applications[7] of an analogous series of "Quat" auxiliaries, 5-substituted-3,3-dimethyl-2-pyrrolidinones **2** which had the advantage of completely clean removal and recycling of the auxiliary while maintaining effective stereocontrol in a variety of reactions. We describe herein a second series of "Quat" auxiliaries **3** which are equally effective in terms of stereocontrol and cleavage but more accessible than our original "Quats".



1 R = ^{i}Pr, Bn

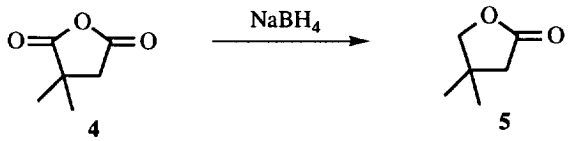


2 R = Me, Et, $CH_2OSiMe_2{}^{t}Bu$, CH_2OCPh_3



3 R = (a) Me, (b) Ph, (c) Bn, (d) ^{i}Pr

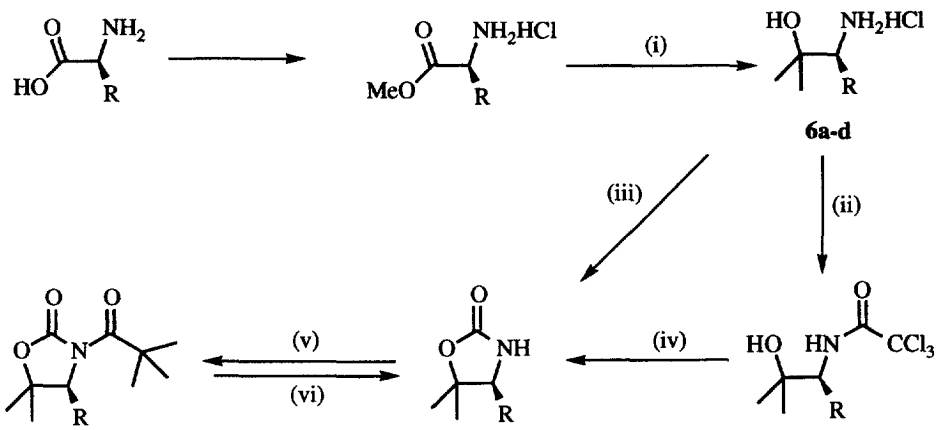
The rationale behind the "Quat" auxiliaries **2** was that the *gem*-dimethyl groups would protect the ring carbonyl from nucleophilic attack and hence promote the desired exocyclic cleavage *vs* endocyclic cleavage in the removal of elaborated *N*-acyl fragments. The *gem*-dimethyl groups in the auxiliaries **3** were expected to be even more effective in this respect given the known reduction of the anhydride **4** to the lactone **5**, i.e. in a five membered ring a carbonyl group is more effectively shielded by *gem*-dimethyl groups in the 3- rather than the 2-position.[8] In addition the *gem*-dimethyl groups were expected to control the conformation of the 3-substitutents, such as phenyl, benzyl or *i*-propyl, thus enhancing the face-stereoselective shielding of attached acyl fragments.



4 **5**

A recent report[9] of a 4,5,5-trisubstituted oxazolidine-2-one of type **3** prompts us to report our work on these compounds as chiral auxiliaries.

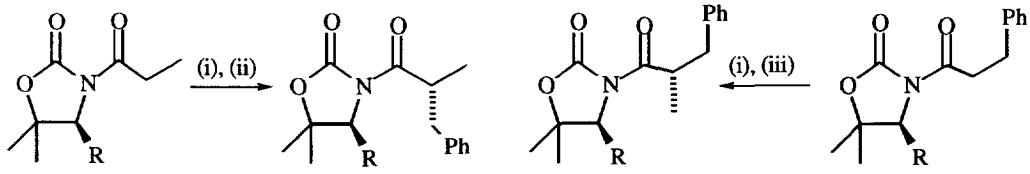
The 4-substituted-5,5-dimethyl oxazolidin-2-ones **3a-d** are readily available from the corresponding α-amino acids as shown in Scheme 1. Esterification (MeOH/HCl) and Grignard addition generated the amino alcohols **6a-d**. Formation of the oxazolidin-2-ones was achieved using the trichloroacetyl chloride[10] or carbonyldiimidazole as carbonyl equivalents.



Scheme 1: Reagents: (i) $MeMgI/Et_2O$, (ii) CCl_3COCl/Pyridine, (iii) CDI/ CH_2Cl_2, (iv) K_2CO_3/EtOH, (v) BuLi/^{t}BuCOCl, (vi) LiOH, THF/H_2O (3:1), 0°C-RT.

N-Acylations of the auxiliaries **3a-d** were achieved *via* deprotonation with BuLi followed by quenching with the appropriate acid chloride (87-100% yield). The effectiveness of these auxiliaries for promoting exocyclic acyl hydrolysis may be illustrated first by the pivaloyl derivatives **7a-d** where treatment with LiOH in THF/H_2O at 0°C-RT regenerated the auxiliaries **3a-d** completely with no detectable endocyclic cleavage.

Having established that *N*-propionyl (**8a-d**) and *N*-hydrocinnamoyl (**10a-d**) derivatives could be formed in good yields, diastereoselective reactions were attempted. Diastereoselective alkylations were achieved with excellent d.e.'s employing lithium di-isopropylamide (LDA; 1.1 equiv, 0°C for 1 h) in tetrahydrofuran, followed by the addition of the alkylating agents. In each case complementary diastereoisomers were formed in the benzylations of the propionyl derivatives and in the methylations of the dihydrocinnamoyl derivatives. With both diastereoisomers in hand assessment of the diastereomeric excesses was readily achieved by 500MHz ^{1}H NMR spectroscopic analysis of the crude products. In each case indicated a single crystallisation increased the d.e. to >99%. The absolute configurations were assigned by chemical correlation[11] of the organic moiety generated on cleavage of the *N*-acyl moiety and confirmed by an X-ray crystal structure analysis of compound **11c**. In common with the Evans auxiliaries, the asymmertic induction can be rationalised by a carbonyl-metal-carbonyl chelation model giving a Z-enolate where the C-4 substituent controls the diastereofacial bias.



8a-d

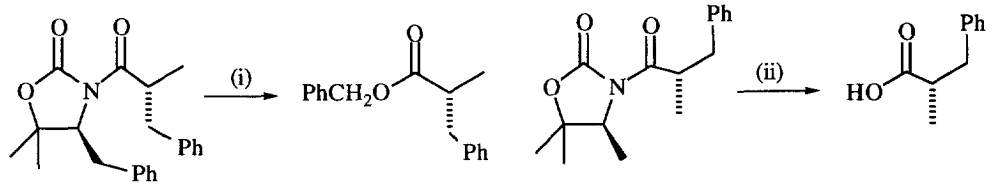
9, R	%Yield	%d.e.
a Me	85	90
b Ph	63	81
c Bn	51	95
d ^{i}Pr	22	97

11, R	%Yield	%d.e.
a Me	82	85
b Ph	88	75
c Bn	65	92
d ^{i}Pr	68	95

10a-d

Scheme 2: Reagents: (i) LDA, 0°C (ii) $PhCH_2Br$ (iii) MeI

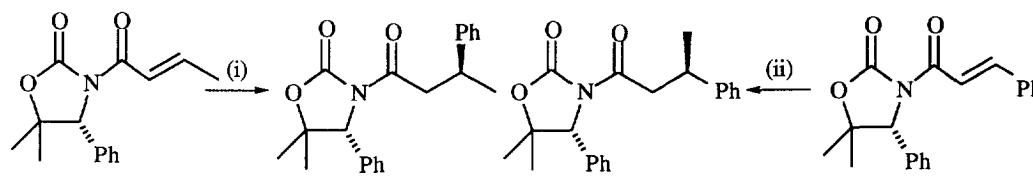
As illustrated in Scheme 3, removal of the chiral auxiliary without compromising the stereochemical integrity was achieved by the use of lithium benzyloxide and lithium hydroxide giving ester (*R*)-(-)-**12** {$[\alpha]_D^{24}$ = -24.5 (c 0.95 in CH_2Cl_2, Lit.[12] $[\alpha]_D^{21}$ = -26.9 (c 6.12 in CH_2Cl_2)} and acid (*R*)-(-)-**13** {$[\alpha]_D^{21}$ = +30.4 (c 1 in $CHCl_3$), Lit.[11] $[\alpha]_D^{22}$ = -30.1 (c 1 in $CHCl_3$)} repectively. As expected, no products from endocyclic cleavage were observed in the reactions. The absolute configurations and enantiomeric excesses were determined by comparison of their specific rotations with literature values and/or by ^{1}H NMR spectroscopic analysis using the chiral shift reagent {tris[3-(heptafluoropropylhydroxymethylene)-(+)-campharato]Eu(III)}.



9c, 94% d.e. **12**, 89%, 94% e.e **11c**, 99% d.e. **13**, 100%, 99% e.e

Scheme 3: Reagents: (i) $PhCH_2OLi$/THF, -78°C, (ii) LiOH, 0°C-RT, THF/H_2O (3:1)

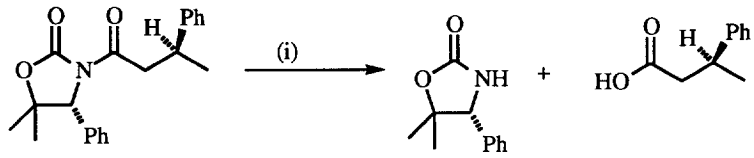
Diastereoselective Michael additions were accomplished using the conditions of Hruby *et al* [13] with organocuprates being added to the *N*-crotonyl and *N*-cinnamoyl oxazolidinones **14** and **15** (Scheme 4). In both cases good yields and diastereoselectivities were obtained and again recrystallisation gave products with >99% d.e.



14 **16**, 67%, 95% d.e. **17**, 87%, 92% d.e. **15**

Scheme 4: Reagents: (i) CuBr.$(CH_3)_2S$ / PhMgBr, THF/$(CH_3)_2S$ (2:1), (ii) CuBr.$(CH_3)_2S$ / MeMgBr, THF/$(CH_3)_2S$ (2:1)

In order to ascertain the sense of asymmetric induction, the hydrolysis of **16** to homochiral (*S*)-3-phenylbutanoic acid {$[\alpha]_D^{23}$ = +53.3 (c 0.3 in benzene), Lit.[14] (*R*)-(-)-**18** $[\alpha]_D^{20}$ = -57 (c 9.8 in benzene)}, was performed. The absolute configuration of the product (*S*)-3-phenylbutanoic acid was established by comparison of the specific rotation with the literature values and the material was shown to be homochiral by ^{1}H NMR spectroscopic analysis in the presence of the chiral shift reagent (*R*,*R*)-diphenyldiaminoethane.[15] The sense of asymmetric induction is consistent with addition to the unhindered face of the acceptor in the chelation controlled *s-cis* or non-chelation controlled *s-trans* conformations.



16, 99% d.e **3b**, 97% **18**, 80%, 99% e.e

Scheme 5: Reagents: (i) LiOH, THF/H_2O, 0°C-RT

In conclusion we have demonstrated 4-substituted-5,5-dimethyl-oxazolidin-2-ones, readily available from α-amino acids, are effective chiral auxiliaries for stereoselective enolate alkylations and conjugate additions of attached *N*-acyl moieties with the elaborated *N*-acyl moieties being very easily and efficiently removed allowing the auxiliaries to be recycled.

All compounds described have been fully characterised.

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