A Practical Procedure for the Multigram Synthesis of the SuperQuat Chiral Auxiliaries

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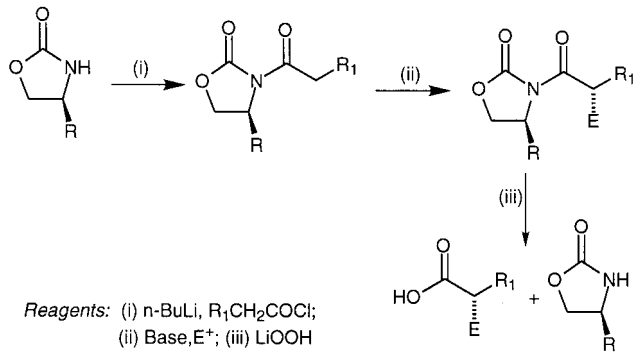
Received 4 February 1998

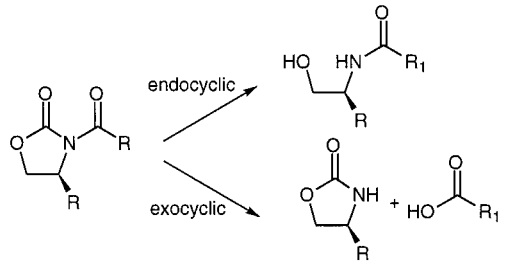
Abstract: An efficient and simple synthesis of oxazolidin-2-one SuperQuat chiral auxiliaries is described which provides rapid access to multigram quantities of the auxiliaries.

The versatile oxazolidin-2-one based methodology developed by Evans *et al* has been widely used in asymmetric synthesis for the preparation of highly functionalised homochiral molecules.[1] This methodology generally involves coupling the auxiliary to an acyl fragment which is then chemically derivatised to afford ideally a single diastereoisomer with one or more new stereocentres. Subsequent cleavage and purification of the transformed acyl fragment affords the desired homochiral product and the chiral auxiliary which may be recycled as required (Scheme 1).



Scheme 1

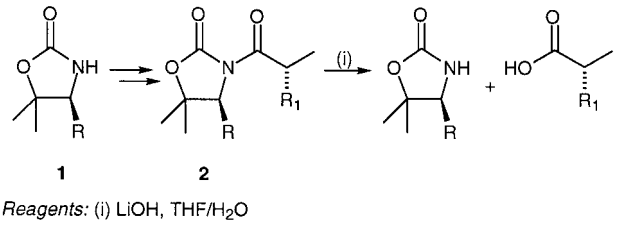
The range of chemistry to which these acylated auxiliaries has been subjected is highly impressive,[2] but there are problems associated with its use. The major problem concerns its recyclability due to the tendency of the oxazolidinone ring of large branched acylated auxiliaries to undergo endocyclic ring opening under the alkaline cleavage conditions (Scheme 2).[3]



Scheme 2

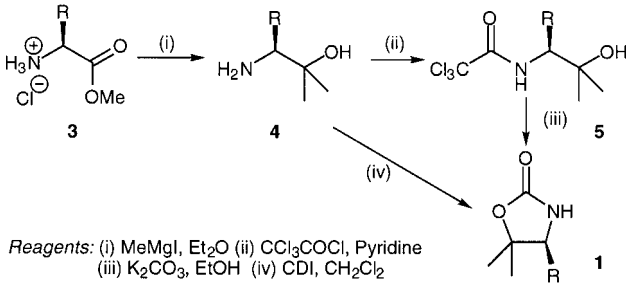
This deviation from the desired exocyclic cleavage pathway results in loss of product, difficulty in purification, and loss of recyclability. Although these endocyclic cleavage problems may be overcome using the more nucleophilic reagent LiOOH,[3] the use of large volumes of peroxide on a large scale is clearly undesirable.

We have recently reported on the development of a new family of oxazolidinone based auxiliaries, the 'SuperQuats',[4] which successfully address these problems. The salient features of these auxiliaries are the presence of the geminal dimethyl groups at C-5 which completely suppress the endocyclic cleavage pathway and also convey a high degree of crystallinity to both the auxiliaries themselves and the acylated derivatives, enabling simple purification of intermediates and products by recrystallisation (Scheme 3).



Scheme 3

Work carried out within these laboratories has clearly demonstrated that the repertoire of chemistry which ensured the popularity of Evans' auxiliary is equally accessible using the SuperQuat methodology[5] and we now report on a new synthesis of these auxiliaries which enables their preparation on a multigram scale. The original preparation of SuperQuat auxiliaries involved the addition of methylmagnesium bromide to an α-amino acid methyl ester **3** to afford amino alcohol **4**, followed by direct treatment with carbonyl diimidazole.[4] An alternative procedure was developed based on conversion of alcohol **4** to trichloroacetamide derivative **5** followed by base promoted cyclisation to the desired auxiliary **1** (Scheme 4).[4]

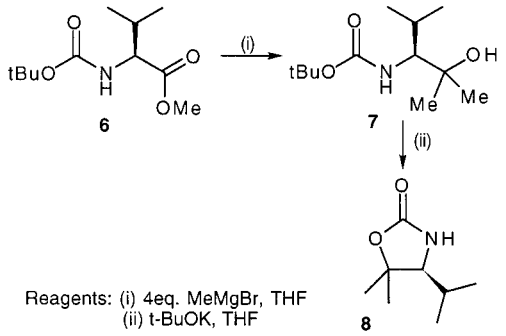


Scheme 4

While these methods were amenable to small scale synthesis, attempts at scale-up were either low yielding, or resulted in partial racemisation of the target auxiliary. In order to address these problems we proposed a new synthetic protocol involving addition of MeMgBr to the *N*-Boc methyl esters of α-amino acids to afford *N*-Boc-protected amino alcohols. The presence of the Boc protecting group was central to our synthetic strategy since initial deprotonation of the acidic carbamate proton results in the formation of an anion which disfavours any further deprotonation/racemisation of the stereogenic centre by excess Grignard reagent.[6] Subsequent base catalysed cyclisation of the resulting amino alcohols would afford the desired auxiliary invoking a strategy whereby the *N*-Boc protecting group acts as a sacrificial carbonyl equivalent.

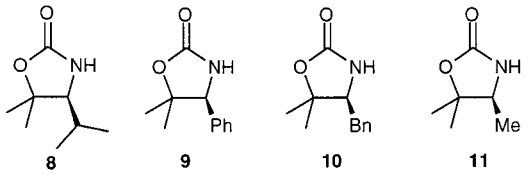
Treatment of BOC-(L)-valine methyl ester **6** in THF with 4 equivalents of methylmagnesium bromide gave the desired tertiary alcohol **7** in good yield without the need for purification. The crude alcohol **7** was treated with potassium t-butoxide in THF to give an alkoxide species which cyclised smoothly *in situ* to afford SuperQuat **8** which was easily

isolated in high yield by simple recrystallisation of the crude product mixture (Scheme 5).[7]



Scheme 5

The versatility of this methodology was demonstrated by preparing a known range of SuperQuats **9-11** derived from (L)-phenylglycine, (L)-phenylalanine, and (L)-alanine respectively in good yields (Figure 1). The stereochemical integrity of each auxiliary was confirmed by chiral gas chromatography[8] and found to be homochiral (≥98% e.e.) by direct comparison with authentic racemic samples.



	8	9	10	11
[a]Yield	62%	81%	40%	55%
[b] $[\alpha]_D^{23}$	+21.3 (*c* 0.8)	+79.0 (*c* 0.5)	-103.5 (*c* 0.6)	+0.5 (*c* 2.0)

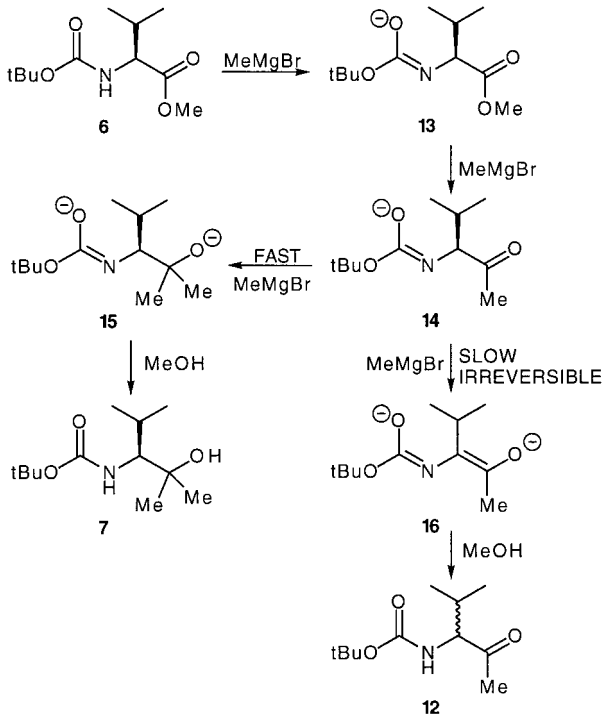
(a) Yields quoted from *N*-Boc-α-amino acids; (b) Specific rotations in chloroform

Figure 1

While addition of Grignard reagent to the Boc methyl esters of the various α-amino acids always afforded the desired tertiary alcohol in high yield, a small quantity of ketone impurity (<5%) was always observed in the ^{1}H NMR spectra of the crude reaction mixture. Purification of the crude reaction mixture obtained from addition of MeMgBr to *N*-Boc-Valine-methyl ester, and examination of the optical rotation of ketone **12** revealed that the stereogenic centre had been totally racemised. This observation led us to propose that the following mechanism was operating during Grignard addition.

Initial addition of the first equivalent of methylmagnesium bromide to *N*-Boc-ester **6** deprotonates the acidic urethane NH proton resulting in the generation of an anion α to the stereogenic centre. The second equivalent of MeMgBr attacks the ester functionality of **13** to afford ketone **14** which is then free to react via one of two possible pathways. The major reaction pathway involves nucleophilic addition of a third equivalent of MeMgBr to the ketone to afford the desired homochiral alkoxide **15**. The minor reaction pathway involves the Grignard reagent acting as a base which irreversibly deprotonates ketone **14** at the stereogenic centre to afford enolate **16** (Scheme 6).

It follows from examination of the enantiomeric excess of the resulting homochiral SuperQuat auxiliary **7** that this enolisation process is irreversible since any transenolisation processes would result in excess Grignard reagent reacting with *racemic* ketone **12** thus compromising the stereochemical integrity of both the alcohol **7** and the final SuperQuat auxiliary product **8**. Upon quenching the reaction mixture magnesium enolate **16** is reprotonated to afford the observed racemic



Scheme 6

ketone **12**, thus ensuring that racemic ketone **12** is never exposed to Grignard reagent.

In conclusion, we have developed an improved synthesis of SuperQuat family of chiral auxiliaries which is rapid and affords good yields of the desired product. The method is amenable to scale up and has been used routinely for the synthesis of 100g batches of the auxiliaries.

Acknowledgements

We are grateful to Oxford Asymmetry Ltd (S. D. B.) for funding.

References and Notes

1. Evans, D. A. *Aldrichimica Acta*, **1982**, *15*, 23.
2. Ager, D. J.; Prakash, I; Scaad, D. R. *Aldrichimica Acta*, **1997**, *30*, 3.
3. Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.*, **1987**, *28*, 6141.
4. Davies, S. G.; Sanganee, H. J. *Tetrahedron: Asymmetry*, **1995**, *6*, 671.
5. Sanganee, H. J. *D. Phil thesis*, Oxford, 1997.
6. A similar racemisation process has been reported during addition of phenyl lithium to the benzyl carbamates of α-amino acids; Buckley III, T. F.; Rapoport H. *J. Am. Chem. Soc.* **1981**, *103*, 6157; Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *J. Org. Chem.*, **1994**, *59*, 4680.
7. Typical procedure for the preparation of the SuperQuat auxiliaries:
(S)-N-(t-Butylcarboxy)-3-amino-2,4-dimethylpentan-2-ol **7**
BOC-(L)-Valine methyl ester **6** (16.0g, 0.069mol) was dissolved in freshly distilled THF (400mL) and cooled to 0°C. Methyl magnesium bromide (92mL, 0.276mol, 3.0M solution in ether) was added dropwise under nitrogen (**Care!** Initial addition results in evolution of methane) over 30 minutes and the reaction left to stir at room temperature for 36 hours. The reaction was cooled to 0°C and methanol (200mL) added cautiously, followed by water

(50mL). A fine white precipitate formed which was filtered through Celite and washed with ethyl acetate (2x100mL). The combined filtrates were evaporated, redissolved in ether (100mL), filtered through Celite and evaporated again to provide the dimethyl alcohol **7** as an oil (13.84g, 87%); $[\alpha]^{23}_D$= -6.0 (c 1.0, $CHCl_3$); (Found: MH^+ 232.1913. $C_{12}H_{25}NO_3$ requires MH^+ 232.1913);.υ_{max} (Film)/cm^{-1} 3446 (OH), 1694 (C=O); δ_H (200MHz, $CDCl_3$) 4.88 (1H, d (br), J 10.4, NHCH), 3.35 (1H, dd,J 10.4, J 2.4, NHCH), 2.07-2.17 (1H, m, CH$(CH_3)_2$), 2.04 (1H, s (br), OH), 1.42 (9H, s, 3xCH_3), 1.23 (3H, s, CH_3C), 1.19 (3H, s, CH_3C), 0.89 (6H, m, CH$(CH_3)_2$); δ_C (50MHz; $CDCl_3$) 157.2 (C=O), 78.9 (OC$(CH_3)_3$), 73.6 (COH), 61.7 (CHNH), 28.8 (CH_3CH), 28.2 (3xCH_3), 28.1 (CH_3C), 26.9 (CH_3C), 22.2 (CH_3CH), 16.8 (CH_3CH); m/z (CI^+) 232 (MH^+, 10%), 176 (42), 158 (76), 132 (100), 114 (68).

(S)-4-i-Propyl-5,5-dimethyloxazolidin-2-one **8**

Potassium t-butoxide (7.18g, 0.064mol) was added in one portion to a stirred solution of (*S*)-*N*-(t-Butylcarboxy)-3-amino-2,4-dimethyl pentan-2-ol **7** (12.39g, 0.054 mmol) in freshly distilled THF (250mL) at 0°C. After 30 minutes, saturated NH_4Cl solution (100mL) and ethyl acetate (100mL) were added and the layers separated. The aqueous layer was extracted with ethyl acetate (2x100mL), washed with brine (50mL) and dried over $MgSO_4$. The solvent was evaporated to give a crude oil, which was recrystallised from petroleum ether (40-60) / diethyl ether (6.06g, 71%) to give the desired SuperQuat **8** as needles; m.p. 88-89°C; $[\alpha]^{23}_D$= +21.3 (c 0.8, $CHCl_3$); (Found MH^+ 158.1187. $C_8H_{15}NO_2$ requires MH^+ 158.1181); υ_{max} (KBr) 1732 (C=O); δ_H (500MHz; $CDCl_3$) 6.30 (1H, s (br), NH), 3.19 (1H, d, J 8.7, CHNH), 1.80-1.87 (1H, m, CH_3CH), 1.48 (3H, s, CH_3C), 1.39 (3H, s, CH_3C), 1.00 (3H, d, J 6.6, CH_3CH), 0.92 (3H, d, J 6.6, CH_3)CH); δ_C (50MHz; $CDCl_3$) 155.9 (C=O), 83.9 (OC$(CH_3)_3$), 68.5 (CHNH), 28.4 (CH_3CH), 28.3 (CH_3C), 21.1 (CH_3C), 20.9 (CH_3CH) 19.8 (CH_3CH); m/z (CI^+) 315 (M_2H^+, 20%), 271 (5), 158 (MH^+, 70), 128 (5), 114 (100).

(RS)-N-(t-butylcarboxy)-3-amino-4-methylpentan-2-one **12**

Ketone **13** was separated from the crude reaction for the preparation of the valine dimethyl alcohol **7** by column chromatography (1:5 ether / petrol) (341mg, 1.59mmol, 2%) as colourless needles; m.p. 71-74°C; $[\alpha]^{23}_D$= +0.4 (c 1.0, $CHCl_3$); (Found: C, 61.05; H, 9.80; N, 6.1. $C_{11}H_{21}NO_3$ requires C, 61.4; H, 9.8; N, 6.5%); υ_{max} (KBr)/cm^{-1} 3292 (NH), 1736 (C=O), 1678 (N-CO); δ_H (200MHz; $CDCl_3$) 5.13 (1H, m, NH), 4.31 (1H, m, CHNH), 2.22 (3H, s, CH_3CO), 1.60 (1H, s, CH_3CH), 1.46 (9H, s, 3xCH_3), 1.03 (3H, d, J 6.8, CH_3CH), 0.80 (3H, d, J 6.8, CH_3)CH); δ_C (50MHz, $CDCl_3$) 207.8 (CH_3CO), 156.2 (C=O), 79.7 (OC$(CH_3)_3$), 64.6 (CHNH), 29.9 (CH_3CO), 28.3 (3xCH_3), 27.9 (CH_3CH), 19.8 (CH_3CH), 16.4 (CH_3CH); m/z (CI^+) 160 (35%, MH^+-C_4H_8).

8. Gas chromatographic analysis was carried out over a Chirasil valine stationary phase.