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Enantioselective Synthesis of α-Amino Acetals (aldehydes) *via* Nucleophilic 1,2-Addition to Chiral 1,3-Oxazolidines

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Abstract: *A general procedure for the diastereoselective addition of Grignard reagents to chiral 2-(4,4,6,6-tetramethyl-1,3-dioxan-2-yl)-4-substituted-1,3-oxazolidines* **4** *is described. Chemical yields and diastereoselectivities are generally excellent (91–100% de). The resulting amino alcohols* **6** *may be oxidatively or reductively cleaved to enantiomerically enriched α-amino acetals* **3** *which are useful chiral building blocks.*

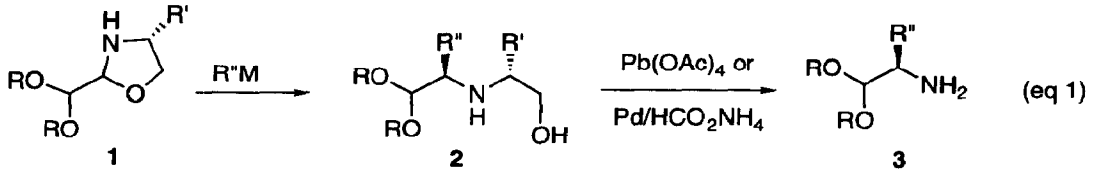
We have previously reported how one may employ magnesium chelated secondary 1,3-oxazolidines to effect useful levels of asymmetric induction leading to the synthesis of nearly enantiomerically pure α-alkyl(aryl)methylamines,[1,2] β-amino esters,[3] 1,2-disubstituted-1,2-dihydronapthalenes,[4] γ-substituted phenylpropanols,[4] and 1,1,2-trisubstituted-1,2-dihydronapthalenes[5] *via* the nucleophilic addition of organoceriums, organolithiums, or Grignards to chiral 2-substituted-4-phenyl-1,3-oxazolidines. The original concept to employ *secondary* chiral 1,3-oxazolidines as a chelate bound template for synthesis of enantiopure primary amines was initially reported by Takahashi in 1986,[6] but until now has not been thoroughly explored.

As an extension of our work, we sought to explore the range of functionalized oxazolidines that would tolerate the above mentioned organometallics while not adversely altering diastereoselectivity. This would thereby greatly enhance the overall utility of this procedure by providing facile access to enantiopure multifunctional primary amines.

Since enantiomerically pure α-amino aldehydes are rapidly attaining importance as chiral building blocks,[7] we decided to explore the applicability of this procedure to their synthesis first. Chiral α-amino aldehydes are usually synthesized by reduction of esters or amides of chiral α-amino acids or oxidation of chiral α-amino alcohols.[8] An asymmetric approach to their synthesis employed by Enders and Denmark independently utilized the α-SAMP or RAMP chiral hydrazone acetal in a 1,2-nucleophilic organocerium addition to the hydrazone double bond.[9,10] While the reported chemical yields were normally excellent, high diastereoselectivities (~95% de) could only be achieved

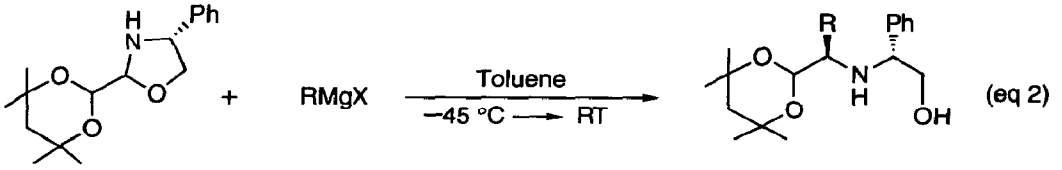
employing addition temperatures around –100 °C. In addition, removal of the chiral auxiliary resulted in some racemization as observed by both laboratories.

Our organometallic addition approach employed 2-acetal-1,3-oxazolidines similar to **1** (eq 1).



1 **2** **3**

It was quickly determined that simple diethyl acetals and cyclic acetals derived from either 2,2-dimethyl-1,3-propanediol, 2,2,4-trimethyl-1,3-pentanediol, or 2,4-pentanediol[11] were not suitable as the aldehyde protecting group using this procedure because of the poor selectivity of the Grignard addition, yielding diastereomeric ratios ranging from 1:1 to 10:1. In those reactions, three equivalents of the organometallic reagent was added at –45 °C to **1** in THF and allowed to warm to ambient temperature over 18 h. Optimum results were eventually obtained employing oxazolidine **4** where the cyclic acetal was derived from 2,4-dimethyl-2,4-pentanediol. Grignard addition in toluene at –45 °C gave results superior to those conducted in THF at the same temperature (eq 2, Table I).[12]

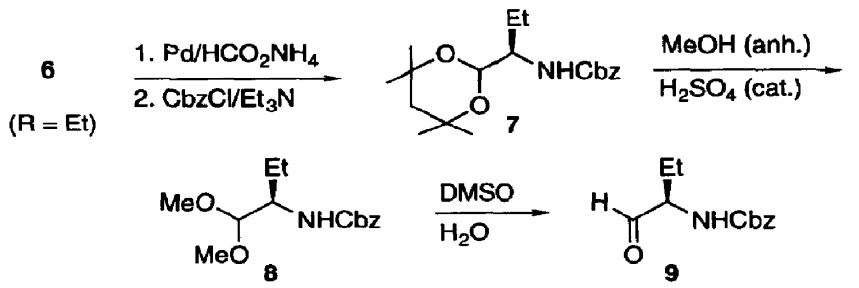


4 **5** **6**

The mode of addition of the Grignard reagent to **4** appears to parallel that of our other reported examples, *i.e.* (*R*) configured α-amino adducts are obtained when the chiral auxiliary is (*R*).[2–5] The failure of the simpler acetals to provide high selectivity is most probably due to less steric demand in the transition state when compared to the tetramethyl substituted dioxane **4**. In support of that contention, the diisopropyl acetal analog of **1** yielded results comparable to **4** but the difficulty of preparing it in quantity precluded its use. The metal of choice is the strong chelator magnesium as exemplified by entries 4, 12 and 13 of Table I. The *tert*-leucinol derived auxilary yields slightly better selectivity than the phenylglycinol derived one. However, the current commercial availability of the latter in both antipodal forms makes its use more attractive.

Conversion of **6** to Cbz protected α-amino acetals may be accomplished **without racemization** by employing standard palladium catalyzed hydrogenolysis conditions. Because we could not find conditions that allowed us to proceed directly and cleanly to aldehyde **9**, conversion *via* the α-amino dimethyl acetal **8** was accomplished with only slight epimerization (98 vs 92% ee; eqn 3). Recrystallization, however, improves the enantiomeric purity to > 99% ee. Hydrolysis to *N*-protected α-amino aldehydes was accomplished, again without racemization, using aqueous DMSO.[13]

The above protocol also allows for access to chiral unnatural or other less accessible amino alcohols, *e.g. tert*-leucinol in either enantiomeric forms.[14]



(eq 3)

Table I. Organometallic Additions to 1,3-Oxazolidine **4**.[12]

Entry	RM	Reaction Conditions[b]	Yield, **6**[d] (%)	de, **6**[e] (%)
1	MeMgCl	–45 °C (4 h) → rt (18 h)	92	98
2	EtMgCl	–45 °C (2 h)	95	98
3	^{i}PrMgCl	–45 °C (18 h) → rt (1 h)	94	94
4	^{t}BuMgCl	Reflux (4 h)	92	96
5	VinylMgCl	–45 °C (4 h) → rt (18 h)	88	91
6	PhMgCl	–45 °C (48 h) → rt (24 h)	92	> 98
7	PhMgCl	Reflux (2 h)	97[f]	> 98
8	EtMgCl	–45 °C (2h)	95[c]	90
9	EtMgCl[a]	–45 °C (1.5 h)	95[f]	> 98
10	EtMgCl[a]	–45 °C (3 h)	97[c,f]	> 98
11	EtMgCl/$CeCl_3$ (6:1)	–45 °C (1 h) → rt (18 h)	89[c,f]	60
12	^{t}BuLi/$CeCl_3$ (1:1)	–45 °C (18 h)	96[c]	75
13	^{t}BuLi	–78 °C (4 h)	97[c,f]	67

[a] Oxazolidine was derived from (*S*)-*tert*-leucine. [b] Standard condition: 3 equiv Grignard in toluene. [c] THF as solvent. [d] Yields are after flash chromatography, except where noted. [e] Crude de's were determined by ^{1}H NMR integrations (300 or 400 MHz). [f] Crude yields.

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12. **Typical addition procedure**: Oxazolidine **4** was prepared by stirring the corresponding glyoxal monoacetal[11] with 1 equiv of the appropriate amino alcohol and $MgSO_4$ (1.5 equiv) in toluene at ambient temperature for 18 h.[4] To a stirred solution of oxazolidine **4** (0.58g, 0.002 mol) in toluene (10 mL) under Argon was added 3 equiv of MeMgCl (2.0 M THF soln) dropwise at –45 °C. The resulting solution was stirred at –45 °C for 2 h, warmed to room temperature and then allowed to stir for 24 h. Water (0.25 mL) was added dropwise and the mixture was diluted with 10 mL of ether and 10 mL of 15% aqueous ammonium hydroxide. The resulting suspension was stirred for 30 min at room temperature and extracted with 3 x 50 mL of ether. The combined organic phase was dried ($MgSO_4$) and the volatiles were removed *in vacuo*. The crude product was purified by flash chromatography to afford 0.57 g (92%) of a colorless oil. **Hydrolysis procedure**: To a solution of Cbz protected acetal **7** (150 mg, 0.45 mmol) in anhydrous methanol (freshly distilled, 20 mL) was added one drop of conc. sulfuric acid. The resulting solution was heated under reflux for 48h. The reaction mixture was neutralized with aqueous sodium bicarbonate and was then extracted with 3x50 mL ether. The ethereal layer was dried ($MgSO_4$) then concentrated *in vacuo*. The % ee of the product was determined to be 92% by chiral HPLC (Chiralcel OD column; 12% IPA/hexanes, 0.5 mL/min.). The dimethyl acetal **8** was purified by flash chromatography to afford 118 mg (98%) of a white crystalline product. Recrystallization from EtOAC/hexanes afforded pure enantiomer (>99% ee). The pure dimethyl acetal **8** (20 mg, 0.07 mmol) was dissolved in DMSO (2mL). Water (0.1 mL) was added to this solution which was then heated under reflux for 1h.[13] The reaction mixture was extracted with 2x25 mL ether, and the ethereal layer was dried ($MgSO_4$) then concentrated to afford a pale yellow oil. The % ee of the product was determined to be 99% by chiral HPLC (12% IPA/hexanes, 1 mL/min.) by comparison to a 2:1 isomeric mix. Purification by flash chromatography afforded the pure N-Cbz protected aldehyde **9** (95%). All new materials gave satisfactory combustion and/or spectral data.
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