Asymmetric Synthesis of β-Substituted α-Amino Acids Using 2*H*-Azirine-2-carboxylate Esters. Synthesis of 3,3-Disubstituted Aziridine-2-carboxylate Esters†

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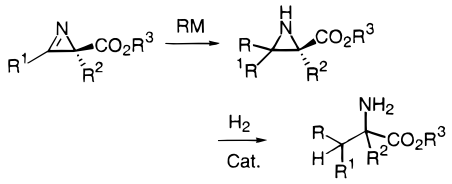
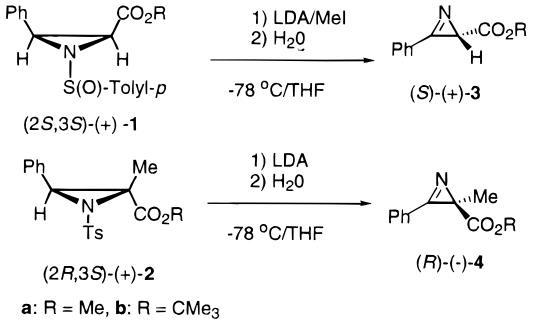
The asymmetric synthesis of nonprotein β-substituted α-amino acids is an area of considerable current interest because these amino acids are constituents of antibiotics and peptides.[1] Moreover, incorporation of these amino acids, along with their α-alkylated analogs, into peptides results in modification of the peptide's steric, conformational, and stereoelectronic properties.[2] One method for the asymmetric syntheses of β-substituted α-amino acids is the conjugate addition of organometallic reagents to α,β-unsaturated chiral amides with subsequent incorporation of the α-amino functionality.[3,4] Methylphenylalanine was prepared by conjugate addition of a chiral glycine unit to a vinyl sulfone,[5] and addition of phenylmagnesium bromide to an oxazolidinone methyl ester afforded diphenylalanine.[6] A few other methods have also been described.[7]

N-Activated aziridine-2-carboxylate esters undergo stereoselective ring opening with nucleophiles to give β-substituted α-amino acids.[8,9] However, most of these examples were with heteronucleophiles,[10] and the few studies with organometallic reagents employed unsubstituted aziridines.[10a,11] In this paper, we report that addition of Grignard reagents to 2*H*-azirine-2-carboxylate esters results in new methodology for the asymmetric synthesis of 3,3-disubstituted aziridine-2-carboxylate esters, which on stereoselective hydrogenolysis afford β-substituted α-amino acid esters (Scheme 1).

Scheme 1



Scheme 2



N-Sulfinylaziridine-2-carboxylate esters such as **1** and **2** are important chiral building blocks for the asymmetric synthesis of α-amino acids and their derivatives.[9,12−14] Furthermore, treatment of **1a** with LDA/MeI affords enantiomerically pure 2*H*-azirine-2-carboxylate ester **3a** and resulted in the first asymmetric synthesis of the cytotoxic antibiotic (*R*)-(−)-dysidazirine (**3a**, Ph = *n*-$C_{13}H_{27}$-CH=CH−) (Scheme 2).[15] However, an attempt to extend this methodology to the synthesis of the 2-methyl-3-phenyl analog **4** by reaction of the corresponding *N*-sulfinyl derivative of **2a** with LDA resulted in a complex mixture of products consisting of **4**, diisopropyl-*p*-tolylsulfinamide (*p*-tolylS(O)NPr^i_2), and the N-unsubstituted aziridine **2**. Significantly, treatment of the *N*-tosylaziridine **2a**[12] with 1.25 equiv of LDA at −78 °C afforded (*R*)-(−)-**4a**, $[\alpha]^{20}_D$ −163.2 (*c*, 0.434 $CHCl_3$), in 87% isolated yield following flash column chromatography. The *tert*-butyl ester derivatives **3b** and **4b** were prepared in a similar manner from the corresponding aziridines **1b** and **2b**[16] in 54 and 74−80% yield, respectively.[17]

We next turned our attention to the reaction of organometallic reagents to azirines **3** and **4**. The few reports of the addition of Grignard reagents to 2*H*-azirines revealed that the aziridine product is formed by attack at the least hindered face.[18] Since there are no reports of the reaction of organometallic reagents to 2*H*-azirine-2-carboxylate esters, it was unclear whether the C−N bond or the ester functionality would be the more reactive site. Moreover, there was the possibility that deproto-

† This paper is dedicated to Professor Carl R. Johnson on the occasion of his 60th birthday.

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(16) *N*-Sulfonylaziridines were prepared as previously described. See refs 12 and 13.

(17) Selected physical properties: **1b** mp 79−80 °C, $[\alpha]^{20}_D$ +24.6 (*c* 1.6, $CHCl_3$); **2b**, oil, $[\alpha]^{20}_D$ +43.4 (*c* 1.32, $CHCl_3$); **3b**, mp 72−3 °C, $[\alpha]^{20}_D$ +219.9 (*c* 0.7, $CHCl_3$); **4a**, oil, $[\alpha]^{20}_D$ −163.2 (*c* 0.434, $CHCl_3$); **4b**, oil, $[\alpha]^{20}_D$ −139.4 (*c* 0.71, $CHCl_3$); **5a**, oil, $[\alpha]^{20}_D$ +206.2 (*c* 0.31, $CHCl_3$); **5b**, oil, $[\alpha]^{20}_D$ +165.2 (*c* 0.51, $CHCl_3$); **6a**, mp 55−56 °C, $[\alpha]^{20}_D$ −142.0 (*c* 1.26, $CHCl_3$); **6b**, mp 35−36, $[\alpha]^{20}_D$ −135.0 (*c* 0.30, $CHCl_3$); **7b**, oil, $[\alpha]^{20}_D$ +4.54 (*c* 1.04, $CHCl_3$); **8b**, oil, $[\alpha]^{20}_D$ +11.0 (*c* 0.51, $CHCl_3$).

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Scheme 3

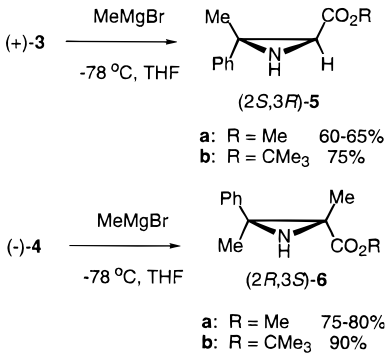


Table 1. Hydrogenation of Aziridines 5 and 6 over 20% Palladium Hydroxide on Carbon

		product: retention/inversion (% isolated yield)[a] in solvent	
entry	aziridine	CH_2Cl_2	hexane
1	**5a** (R = Me)	**7a**: 86:14[b] (88)	65:35 (85)
2	**5b** (R = *t*-Bu)	**7b**: 96:4 (84)	79:21 (90)
3	**6a** (R = Me)	**8a**: 67:33 (97)	10:90 (90) [52][c]
4	**6b** (R = *t*-Bu)	**8b**: 90:10 (88) [80][d]	40:60 (95)

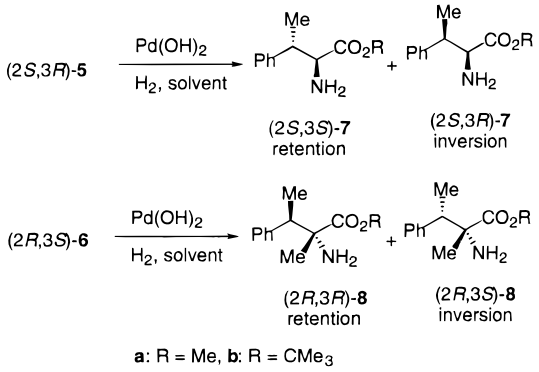
[a] Combined yields of isomers. [b] Retention/inversion as determined by ^{1}H NMR. [c] Isolated yield of pure major amino acid. [d] Isolated yield of pure major isomer.

nation at C-2 in (+)-**3** could result in lower yields and loss of enantiomeric purity.

Attempts to add methyllithium to the azirine **3** and **4** gave complex mixtures of products resulting mainly from reaction at the carbonyl group. Gratifyingly, reaction of (+)-**3a** and (−)-**4a** with methylmagnesium bromide (MeMgBr) in THF at −78 °C gave (+)-**5a** and (−)-**6a** in 60−65% and 75−80% yield, respectively (Scheme 3). The yields of **5b** and **6b** were 75 and 90% when the bulky *tert*-butoxy ester derivatives, (+)-**3b** and (−)-**4b**, were employed. No other isomers could be detected in the crude mixture by ^{1}H NMR. For **5a** and **6a**, irradiation at the C-3 methyl groups resulted in 2% and 1% NOE's with the carbomethoxy groups, respectively, but no NOE's were detected for the corresponding C-2 hydrogen and C-2 methyl groups. Since NOE experiments on **5b**/**6b** were inconclusive, assignment of their stereochemistry was based on the fact that their ^{1}H NMR spectra were nearly identical to aziridines **5a**/**6a**; e.g., the CMe and CH are shielded to the same extent by the adjacent phenyl group. Thus, addition of MeMgBr occurs syn to the carbomethoxy group or from the more hindered face of the azirine. These results, which contradict previous reports,[18] are likely a consequence of prechelation of the Grignard reagent with the carboxyl ester group.

Hydrogenation of aziridines **5** and **6** was accomplished under an atmosphere of H_2 (balloon) over 20% palladium hydroxide on carbon for 3 h (Table 1, Scheme 4). The ratio of retention/inversion products was determined by ^{1}H NMR of the crude reaction mixtures before purification by flash chromatography. The assignment of stereochemistry to the isomers of **7a** (R = Me) was based on the fact that the *erythro* product has the larger coupling constant (7.5 vs 7.1 Hz)[19] and for (2*R*,3*S*)-**8a** by comparison with literature values.[2c] These assignments were confirmed by 6 N HCl hydrolysis of the major isomers of **7b**/**8b** (R = CMe_3), purified by ion-exchange column (Dowex, H^+), to give *erythro*-(2*S*,3*S*)-(−)-3-methylphenylalanine[20] and (2*R*,3*R*)-(+)-2,3-dimethylphenylalanine[2c] in

Scheme 4



86 and 95% isolated yield, respectively, and >96% ee. Attempts to separate the isomers of **7a/8a** (R = Me) by preparative TLC were unsuccessful. Diastereomerically pure (2*R*,3*S*)-(−)-2,3-dimethylphenylalanine[2c] was obtained in 52% yield from (2*R*,3*S*)-**8a** (Table 1, entry 3) by hydrolysis with 6 N HCl and crystallization of the hydrochloride salts.

In related experiments, hydrogenation of optically active 2-methyl-2-phenylaziridine over $Pd(OH)_2$ occurs predominately with inversion of configuration (86:14), but with retention in the presence of NaOH.[21] These results were interpreted by Mitsui and Sugi in terms of the affinity of the catalysts for the nitrogen atom with a low affinity leading to inversion. As can be seen from the results summarized in Table 1, the stereoselectivity for the hydrogenolysis of aziridines **5** and **6** is highly dependent upon the solvent and the substitution pattern of the substrate. For aziridines **5** hydrogenation gives **7** primarily with retention of configuration regardless of the solvent (Table 1, entries 1 and 2). On the other hand, the presence of the C-2 methyl group in **6** results in addition of hydrogen with retention in methylene chloride but inversion of configuration in *n*-hexane (see Table 1, entries 3 and 4). The carbonyl groups in **5** and **6**, which may provide an additional site for palladium chelation, and the added complication of steric factors make interpretation of these results difficult and is under active investigation.

In summary, the highly stereoselective addition of MeMgBr to 2*H*-azirines **3** and **4** results in the first asymmetric synthesis of unsymmetrical 3,3-disubstituted aziridine-2-carboxylate esters and is a potentially general route to these valuable materials. Selective hydrogenation of the aziridines **5** and **6** results in new methodology for the enantioselective synthesis of β-substituted α-amino acid esters **7** and **8**.

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Supporting Information Available: Experimental procedures for the synthesis of compounds **3**−**8** and spectral data for aziridines **1b**, **2b**, **5a**,**b**, and **6a**,**b**, aziridines **3b** and **4a**, and amino acid esters **7b** and **8b** (4 pages).

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