Tetrahedron: Asymmetry Vol. 2, No. 3, pp. 183-186, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

ASYMMETRIC SYNTHESIS OF R-β-AMINO BUTANOIC ACID AND S-β-TYROSINE: HOMOCHIRAL LITHIUM AMIDE EQUIVALENTS FOR MICHAEL ADDITIONS TO α,β-UNSATURATED ESTERS.

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(*Received* 14 *February* 1991)

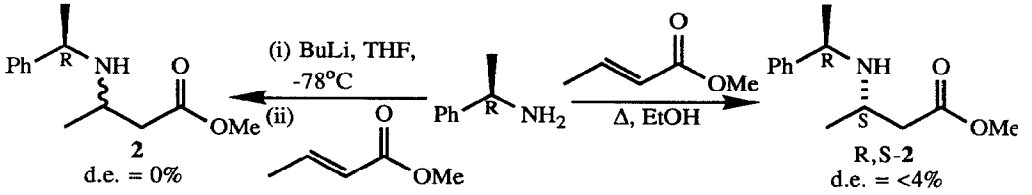
Abstract: Michael addition of the lithium amide derived from R-N-(α-methylbenzyl)benzylamine to benzyl E-crotonate is highly stereoselective (95% d.e.) giving after debenzylation and crystallisation homochiral R-β-amino butanoic acid. A similar addition to methyl E-(*p*-benzyloxy)cinnamate is completely stereoselective giving after debenzylation and acid hydrolysis homochiral S-β-tyrosine as its HCl salt.

β-Amino acids are constituents of many classes of natural products, for example, terpenes, alkaloids, peptides, β-lactam antibiotics, etc., as well as being important for the synthesis of compounds of pharmaceutical interest. Some homochiral (enantiomerically pure) β-amino acids have been made available *via* manipulation of the chiral pool,[1] while approaches to their asymmetric synthesis have, to date, generally been centred on chiral auxiliaries providing homochiral enolate and homochiral α,β-unsaturated acid equivalents for additions to imines[2] and Michael additions[3] respectively.

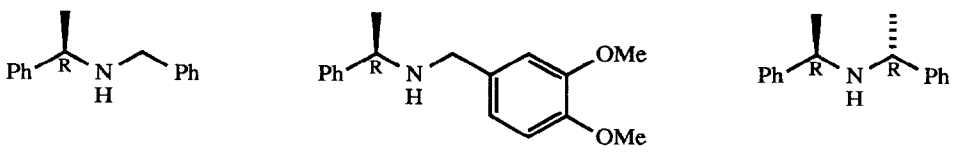
Although the basic properties of homochiral lithium amides have been extensively studied for application to asymmetric synthesis their potential as homochiral nucleophiles in Michael additions has received little attention.[4] The highly stereoselective (97% d.e.) Michael addition of the 1,1'-binaphthyl derived lithium amide of 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine to methyl crotonate has been described[5], however, the subsequent release of the β-amino acid has not been reported.

We recently described good chiral recognition in the Michael addition reaction between lithium N-(3,4-dimethoxybenzyl)α-methylbenzylamide and the chiral iron crotonyl complex E-[$(C_5H_5)Fe(CO)(PPh_3)$(COCH=CHMe)], which allowed the kinetic resolution of the latter.[6] Implicit in the chiral recognition is that both the iron and the α-methylbenzyl chiral auxiliaries must each be exerting powerful stereochemical control over the formation of the β-chiral centre. We reasoned, therefore, that high stereoselectivities should be expected in the addition of lithium N-(3,4-dimethoxybenzyl)α-methylbenzylamide to simple E-crotonate esters.

The Michael addition of α-methylbenzylamine to methyl crotonate in alcohol solvents proceeds in reasonable yield but with poor diastereoselectivity (6-20% d.e.).[7,8] In our hands addition of R-α-methylbenzylamine **1** to methyl crotonate in ethanol at reflux gave the R,S-β-amino derivative **2** in 35% yield with <4% d.e. Addition of the lithium amide derived from **1** to methyl crotonate at -78°C in THF gave R,R-**2**, but with no discernible stereoselectivity (yield 28%; 0% d.e.): The low yield was due to extensive formation of N-α-methylbenzyl crotonamide (35%).



In contrast to the primary amine **1**, the derived secondary amines **3**, **4** and **5** do not yield any Michael adducts with methyl crotonate in ethanol at reflux. The corresponding lithium amides **6**, **7** and **8** respectively, however, do add giving, after protonation, the Michael adducts in high yield and with high diastereoselectivity: All these additions were essentially instantaneous.



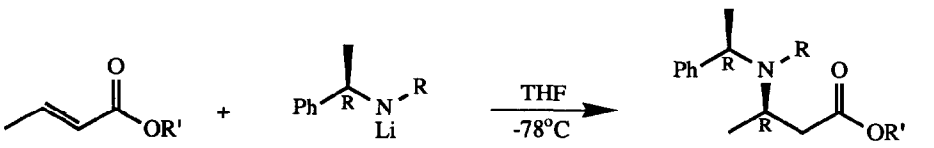
3 **4** **5**

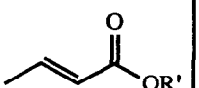
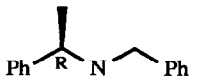
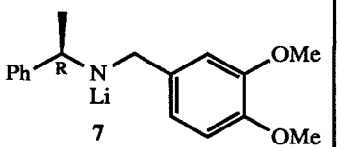
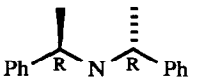
The diastereoselectivities and yields for the Michael additions of the lithium amides derived from R-**3**, R-**4** and R,R-**5** to alkyl crotonates are listed in the Table. In two cases the configuration of the major product diastereoisomer was unambiguously assigned as R,R, *vide infra*, and all others were assigned by analogy. Characteristically, in the ^{1}H n.m.r. spectra the β-methyl doublet for the major R,R-diastereoisomer in each case appeared between δ1.0-1.2, whereas that of the minor R,S-diastereoisomer appeared between δ0.8-0.9.

General procedure for the Michael additions: Butyl lithium (1.4M in hexanes; 2.0 mmol) was added to the secondary amine (2.0 mmol) in tetrahydrofuran (15ml) at 0°C. The resulting red solution was stirred at 0°C for 15 min and cooled to -78°C. The crotonate ester (1.0 mmol) in tetrahydrofuran (4ml) was added dropwise and the mixture stirred for 15 min at -78°C before quenching with saturated ammonium chloride (2 ml). The mixture was allowed to warm and poured into saturated aqueous sodium chloride solution. Extraction of the aqueous layer with ether (2 x 20 ml), drying ($MgSO_4$), filtration and evaporation gave a mixture of the adduct and the excess amine as a pale yellow oil. ^{1}H n.m.r. spectroscopic analyses of these oils were used to determine the diastereomeric excesses. Column chromatography (silica: 40/60 petrol : ether, 4 : 1) gave the pure adducts as colourless oils with no change in d.e. Elemental microanalyses were obtained for the adducts or for the corresponding crystalline HCl salts.

Table

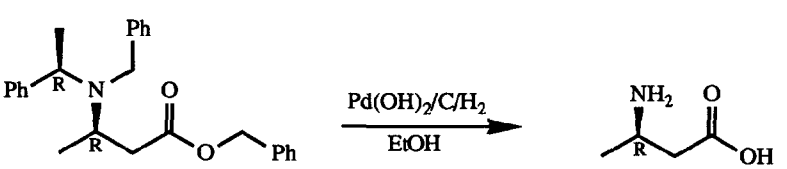
Diastereomeric excesses (and yields) for the addition of secondary lithium amides to E-crotonate esters



	 6	 7	 8
R' = Me	95 (85)	95 (68)	>99*(57)
CH_2Ph	95 (88)	96 (74)	98(23)**
^tBu	>99*(82)	>99*(83)	>99*(27)

* >99% d.e. indicates that none of the minor diastereoisomer was detected **0°C (no reaction at -78°C)

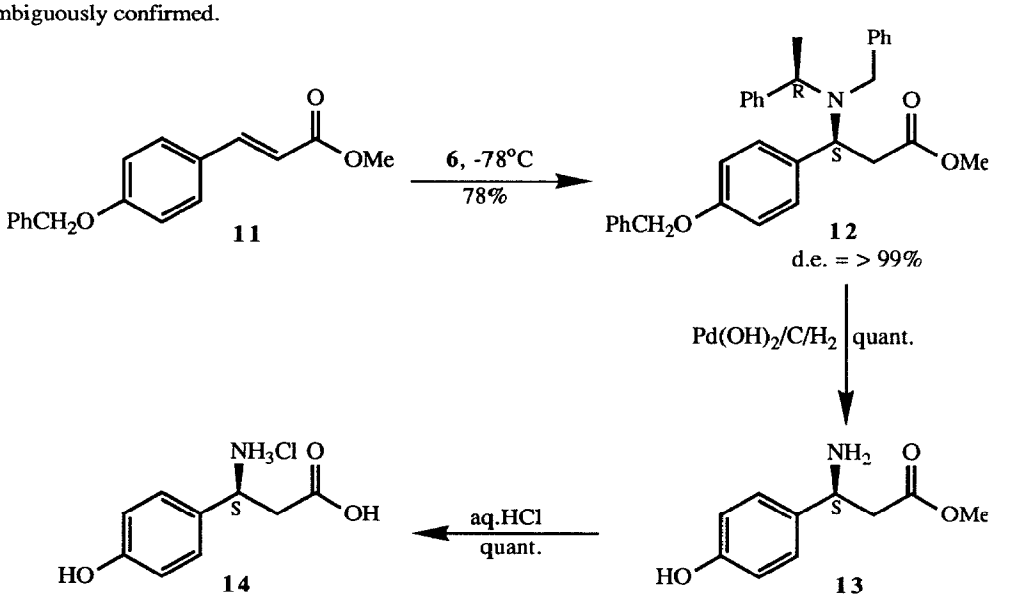
The reaction of methyl crotonate with lithium amide **8** could be performed at 0°C without compromising the complete stereoselectivity while at 40°C the diastereomeric excess of the adduct dropped to 93%. Debenzylation of the above adducts could be achieved with Pearlman's catalyst under 1-5 atmospheres of hydrogen. Thus the hydrogenolysis of R,R-**9** (95% d.e.; 516 mg, 1.33 mmol) in EtOH (15 ml) with $Pd(OH)_2$ on charcoal (20%) under *ca.* 5 atmospheres of hydrogen at 20°C for 22h gave, after removal of the catalyst by filtration and evaporation to dryness, β-amino butanoic acid as a colourless solid in quantitative yield. A single crystallisation from methanol gave homochiral R-β-amino butanoic acid R-**10** (64%) $[\alpha]_D^{19}$ -39.8 (c = 0.47, H_2O) Lit.[9] for S-**10** $[\alpha]_D^{18}$ +38.8 (c = 0.48, H_2O).



9 R-**10**

Treatment of methyl *p*-benzyloxycinnamate **11** with the lithium amide **6** generated the corresponding adduct **12** as a single diastereoisomer. Debenzylation of **12** following a modification of a literature procedure[8] (1.3g, 2.8 mmol) in MeOH (20ml), water (2ml) and acetic acid (0.5ml) in the presence of palladium hydroxide on charcoal (20%) under hydrogen (1 atm.) at 20°C for 18h gave, after filtration and evaporation, the

homochiral methyl ester of S-β-tyrosine **13** as an oil in quantitative yield. The enantiomeric purity (>99%) was confirmed by ^1H n.m.r. spectroscopy in the presence of S-2,2,2-trifluoro-1-(9-anthryl)ethanol in comparison with a racemic sample. Compound **13** was fully characterised as the HCl salt $[\alpha]_D^{20}$ +10.55 (c = 1.9, H_2O). Homochiral S-β-tyrosine.HCl **14** $[\alpha]_D^{25}$ +3.55 (c = 1.38, H_2O)[10] was available by acid hydrolysis (aq. HCl, reflux 16h) of the methyl ester **13**. The absolute configuration of **14** was assigned by comparison with the literature data[10] and hence the absolute configuration of **13** and relative configurations within **12** were unambiguously confirmed.



We thank Idemitsu Petrochemical Co., Ltd. (Japan) for support (to OI).

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