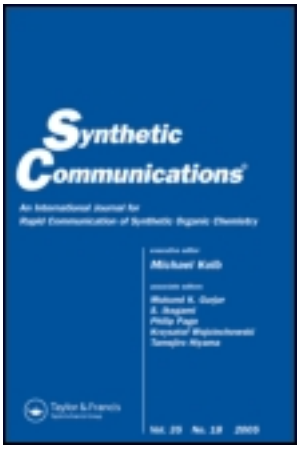


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# A Chiral, Oxidatively Cleavable Auxiliary in Conjugate Additions of Lithium Amides. Preparation of Enantiomerically Pure β-Amino Acid Derivatives

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# A CHIRAL, OXIDATIVELY CLEAVABLE AUXILIARY IN CONJUGATE ADDITIONS OF LITHIUM AMIDES. PREPARATION OF ENANTIOMERICALLY PURE β-AMINO ACID DERIVATIVES

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**Abstract:** Addition of enantiomerically pure 4-methoxyphenethyl-substituted lithium amides to α,β-unsaturated esters leads to β-amino acid derivatives **4 – 7** with selectivities > 95 : 5. The auxiliary can be cleaved by oxidation with cerium(IV) ammonium nitrate (CAN) and subsequent hydrolysis of the resulting mixture of imines.

Several methods for the stereoselective synthesis of β-amino acids have been presented during the last decades.[1,2] Davies *et al.* used chiral lithium amides in conjugate additions to α,β-unsaturated carboxylic esters. Excellent selectivities (up to > 99 : 1) could be achieved with phenethyl-substituted secondary lithium amides like benzylphenethylamide, allylphenethylamide[3,4] or 3,4-dimethoxybenzylphenethylamide.[5] Similar work in this direction was published by Sewald *et al.*, who used chiral amido cuprates.[6]

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Recently, we presented a variation of the Staudinger reaction leading to β-lactams starting from amino acid derived diazoketones. To improve selectivities in this reaction, we used chiral imines prepared from *para*-methoxyphenethylamine (PMPE-amine, **1**).[7] These enantiomerically pure, chiral amines are easily accessible by enzymatic kinetic resolution using lipases.[8]

In this paper, we present the utilisation of the PMPE-auxiliary in the formation of enantiomerically pure β-amino acids. Since this auxiliary is easily cleaved using oxidative conditions, it should be useful for the preparation of substrates, which do not tolerate hydrogenolytical conditions (which have to be used for the cleavage of phenethyl-substituents).

We prepared PMPE-substituted, secondary amines in analogy to a published procedure,[9] reacting equimolar portions of PMPE-amine **1** and allyl- or 4-methoxybenzyl (PMB-) bromide, respectively, in hexahydro-1,3-dimethyl-pyrimidin-2-one (DMPU), using potassium carbonate as a base. Thus we obtained allyl-4-methoxyphenethylamine (**2**) and 4-methoxybenzyl-4-methoxyphenethylamine (**3**) in 85 % and 77 % yield, respectively.

The secondary amines were deprotonated with *n*BuLi at –78 °C and reacted with cinnamates and crotonates yielding the corresponding β-amino acid derivatives after work-up. In $^1$H NMR spectra of the crude products only one isomer could be observed (d. r. > 95 : 5). The addition to *tert*butyl cinnamates gave products **4** and **5** after chromatography in excellent 84 and 88 % yield, respectively (scheme 1 and table, entry 1,2). The usage of methyl cinnamate or ethyl crotonate as Michael acceptors led to yields up to 45 %.

**Scheme 1**

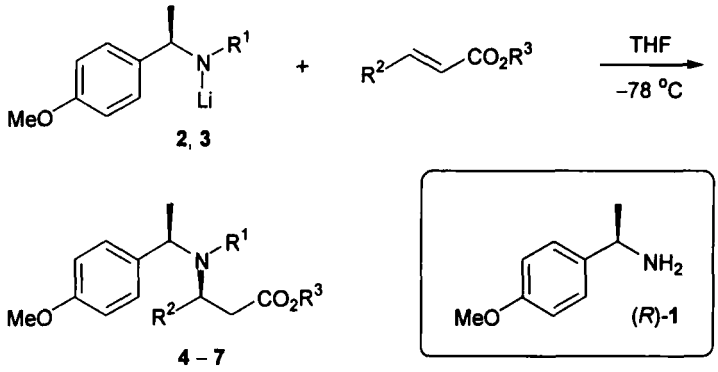



**Table:** Addition of PMPE-Substituted Amides to α,β-Unsaturated Esters.

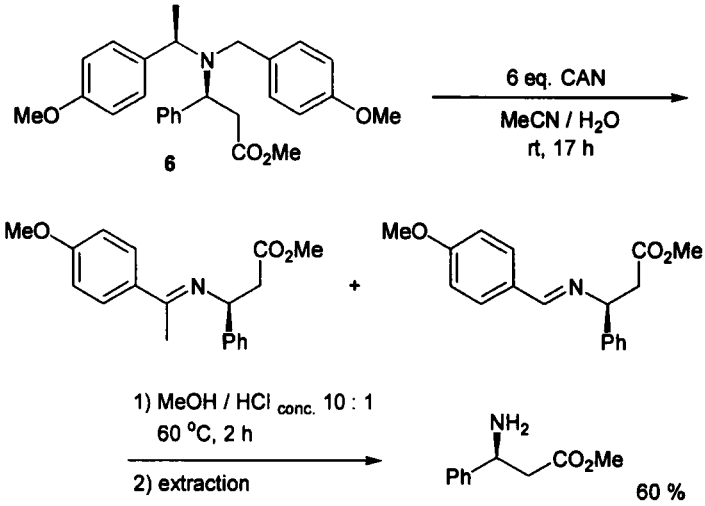
| Entry | Amine | $R^1$ | $R^2$ | $R^3$ | Product | Yield | d. r. |
|---|---|---|---|---|---|---|---|
| 1 | **2** | Allyl | Ph | *t*Bu | **4** | 84 % | > 95 : 5 |
| 2 | **3** | PMB | Ph | *t*Bu | **5** | 88 % | > 95 : 5 |
| 3 | **3** | PMB | Ph | Me | **6** | 44 % | > 95 : 5 |
| 4 | **3** | PMB | Me | Et | **7** | 41 % | > 95 : 5 |

The protective group and the auxiliary could be cleaved using CAN as oxidizing agent (scheme 2). In this reaction an oxidation of the intermediately formed secondary amines to a mixture of imines was observed;[10] they can be readily hydrolyzed using hydrochloric acid in methanol. The β-amino acid[11] is separated from its by-products (4-methoxyacetophenone and anisaldehyde) by appropriate aqueous work-up (taking the amine in the aqueous phase and extraction).

The conjugate addition of PMPE-substituted lithium amides proceeds with excellent selectivities and is therefore a useful extension to the work presented by Da-

vies *et al.* The utilisation of PMPE-amines in other organic reactions is currently under investigation in our laboratories.

**Scheme 2**




## Experimental Section

PMPE-amine (**1**) and similar enantiopure amines can be purchased from Lancaster. $^{1}H$- and $^{13}C$-NMR spectra were recorded with a *Bruker* ARX 500 spectrometer at room temp. in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded using a *Finnigan* MAT 95 [FAB or CI ($CH_4$ or $NH_3$)-technique] or a *Varian* MAT 711 instrument (EI). IR spectra were recorded with a *Bruker* IFS 28 or a *Perkin-Elmer* 283 instrument. Elemental analyses were performed by the service of the Institut für Organische Chemie, Stuttgart.

### Typical procedure for the preparation of the amines 2 and 3:[9]

(*R*)-*N*-Allyl-1-(4-methoxyphenyl)ethylamine (**2**): 2.99 g (19.8 mmol) (*R*)-1-(4-methoxyphenyl)ethylamine (*R*)-**1** was dissolved in DMPU (30 ml) under a nitro-

gen atmosphere and treated with 4.20 g (39.6 mmol) $Na_2CO_3$. To the resulting suspension was added dropwise 1.71 ml (19.8 mmol) allyl bromide and the mixture was heated to 65 °C for 3 h. The mixture was cooled and water was added. After extraction with $Et_2O$, the organic layers were re-extracted with water, dried ($MgSO_4$) and concentrated. Flash column chromatography (light petroleum / ethyl acetate / $NEt_3$ 500 : 50 : 3 → 100 : 100 : 1) yielded pure amine **2** (2.81 g, 85 %) as a yellowish liquid: IR (film) 3322 $cm^{-1}$ (NH), 2960, 2834 (CH), 1611 (C=C); $[\alpha]_D^{20}$ +66 (*c* 1.7, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 1.34 (d, *J* 6.5 Hz, 3 H, $CHCH_3$), 3.08 (dq, *J* 6.0, 1.6 Hz, 2 H, $NCH_2$), 3.76 (q, *J* 6.6 Hz, 1 H, $CHCH_3$), 3.79 (s, 3 H, $OCH_3$), 5.06 (dq, *J* 10.2, 1.6 Hz, 1 H, $CH=CH_2$-*trans*), 5.12 (dq, *J* 17.2, 1 H, $CH=CH_2$-*cis*), 5.88 (ddt, *J* 17.1, 10.3, 6.0 Hz, 1 H, $CH=CH_2$), 6.86 (d, *J* 8.7 Hz, 2 H, arom. CH), 7.23 (d, *J* 8.5 Hz, 2 H, arom. CH), NH covered; $^{13}C$ NMR ($CDCl_3$, 126 MHz) $\delta$ 24.2 (q, $CHCH_3$), 50.2 (t, $N\text{-}CH_2$), 55.2 (q, $O\text{-}CH_3$), 56.8 (d, $CHCH_3$), 113.8 (d, arom. CH), 115.6 (t, $CH=CH_2$), 127.6 (d, arom. CH), 137.0 (d, $CH=CH_2$), 137.6 (s, arom. C), 158.5 (s, arom. C); MS (EI, 70 eV): *m/z* (%) 191 (8, $M^+$), 176 [100, $(M - CH_3)^+$], 135 [23, $(M - C_3H_6N)^+$]; Anal. calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.44; H, 9.04; N, 7.27.

(*R*)-*N*-Benzyl-1-(4-methoxyphenyl)ethylamine (**3**): $[\alpha]_D^{20}$ +53 (*c* 1.1, $CHCl_3$); Anal. calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.00; H, 7.84; N, 5.11.

**Typical procedure for the preparation of the adducts 4 – 7:**[4]

*tert*Butyl (3*S*,1'*R*)-3-[Allyl-1-(4-methoxyphenyl)ethylamino]-3-phenylpropanoate (**4**): A solution of (*R*)-allyl-1-(4-methoxyphenyl)ethylamine **2** (191 mg, 1.00

mmol) in anhydrous THF (3.5 ml) was cooled to –78 °C and *n*BuLi (589 µl, 0.94 mmol) was added. The pink solution was stirred for 30 min and a solution of *tert*-butyl cinnamate (178 mg, 871 µmol) in THF (0.5 ml) was added *via* syringe. Stirring was continued for 2 h at –78 °C and satd. $NH_4Cl$-soln. (1 ml) was added. After warming to room temp. the mixture was extracted with $CH_2Cl_2$. The organic layers were dried ($MgSO_4$), concentrated and chromatographied (light petroleum / ethyl acetate 20 : 1) to yield adduct **4** (289 mg, 84 %) as a yellowish oil, $R_f$ 0.33 (tlc, light petroleum / ethyl acetate 1 : 9); IR (film) 2976 $cm^{-1}$, 2934, 2835 (CH), 1730 (C=O); $[\alpha]_D^{20}$ +11 (*c* 0.6, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 1.14 (d, *J* 6.9 Hz, 3 H, $CHCH_3$), 1.29 [s, $C(CH_3)_3$], 2.57 (dd, *J* 14.6, 8.9 Hz, 1 H, H-$2_a$), 2.75 (dd, *J* 14.7, 6.0 Hz, 1 H, H-$2_b$), 3.12 (dd, *J* 5.8, 1.2 Hz, 2 H, $NCH_2$), 3.78 (s, $OCH_3$), 3.97 (q, *J* 6.7 Hz, 1 H, $CHCH_3$), 4.42 (dd, *J* 8.9, 6.1 Hz, 1 H, H-3), 5.02 (dd, *J* 10.2, 1.3 Hz, 1 H, CH=C$H_2$-*trans*), 5.13 (dd, *J* 17.3, 1.4, CH=C$H_2$-*cis*), 5.77 (ddt, *J* 17.3, 10.2, 6.2 Hz, 1 H, $CH$=$CH_2$), 6.85 (d, *J* 8.9 Hz, 2 H, arom. CH), 7.21 – 7.37 (m, 7 H, arom. CH); $^{13}C$ NMR ($CDCl_3$, 126 MHz) $\delta$ 16.4 (q, $CHCH_3$), 27.9 [q, $C(CH_3)_3$], 39.2 (t, C-2), 49.5 (t, $NCH_2$), 55.2 (q, $OCH_3$), 55.5 (d, $CHCH_3$), 59.1 (d, C-3), 80.1 [s, $C(CH_3)_3$], 113.3 (d, arom. CH), 115.6 (t, CH=$CH_2$), 127.0, 128.1, 128.1 128.6 (4 d, arom. CH), 136.9 (s, arom. C), 139.1 (d, $CH$=$CH_2$), 141.7, 158.2 (2 s, arom. C), 171.3 (s, C-1); MS (EI, 70 eV) *m/z* (%) 395 (2, $M^+$), 380 [8, $(M - CH_3)^+$], 280 [12, $(M - C_6H_{11}O_2)^+$], 260 [37, $(M - C_9H_{11}O)^+$], 204 (27, $C_{13}H_{16}O_2^+$), 135 (100, $C_9H_{11}O^+$); Anal. calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.71; H, 8.43; N, 3.44.

*tert*Butyl (3*S*,1'*R*)-3-[4-methoxybenzyl-1-(4-methoxyphenyl)ethylamino]-3-phenylpropanoate (**5**): $[\alpha]_D^{20}$ +21 (*c* 0.4, $CHCl_3$). Anal. calcd for $C_{30}H_{37}NO_4$: C, 75.76; H, 7.84; N, 2.94. Found: C, 75.61; H, 7.97; N 2.88.

Methyl (3*S*,1'*R*)-3-[4-methoxybenzyl-1-(4-methoxyphenyl)ethylamino]-3-phenylpropanoate (**6**): $[\alpha]_D^{20}$ +16 (*c* 1.1, $CHCl_3$). Anal. calcd for $C_{27}H_{31}NO_4$: C, 75.80; H, 7.21; N, 3.23. Found: C, 74.57; H, 7.26; N 3.15.

Ethyl (3*S*,1'*R*)-3-[Allyl-1-(4-methoxyphenyl)ethylamino]butenoate (**7**): $[\alpha]_D^{20}$ +22 (*c* 0.9, $CHCl_3$). Anal. calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.58; H, 8.11; N 3.63.

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