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Highly stereoselective alkylation of (*S*)-proline-based chiral auxiliaries

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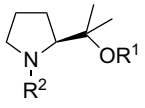
Abstract—Alkylation of the enolates of the propanoylamides of two chiral auxiliaries (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol **1a** and (*S*)-(−)-2-(2-methoxypropan-2-yl)pyrrolidine **1b**, derived from (*S*)-proline, with benzyl bromide and *n*-butyl iodide has been studied. The auxiliaries **1a** and **1b** induced opposite selectivity that is (*R*)- and (*S*)-configuration, respectively, at the newly created stereogenic centre. The diastereoselectivities and conversion yields in these alkylations were moderate to excellent. When Cp_2ZrCl_2 was used as an enolate coordinating agent, benzylation of propanoylated **1b** gave an excellent diastereomeric ratio of 99:1. The benzylated diastereomeric products from either propanoylated **1a** or **1b** were easily separated by liquid chromatography.

1. Introduction

The use of chiral auxiliaries in asymmetric alkylation reactions, has been important for a very long time for organic chemists, for constructing synthetic building blocks of high stereoisomeric purity. The need for such building blocks has inspired many researchers to develop a large number of chiral auxiliaries and reagents for the induction of asymmetry in a wide variety of reactions.[1]

Some examples of known auxiliaries are derivatives of (*S*)-proline with some of them being successfully used in asymmetric alkylation reactions. In 1980, Evans and Takacs[2] and Sonnet and Heath[3] independently reported that dianions of amides of (*S*)-prolinol furnished diastereomeric mixtures of alkylated products in ratios of up to 97:3. They also reported reversed diastereoselectivity after alkylation of Me-, MOM- and TBDMS-ethers of (*S*)-prolinolamides.[2,3] In comparison with the results obtained with the corresponding (*S*)-prolinol auxiliaries, the diastereoselectivity obtained with these ether auxiliaries was low. Similar results, that is, reversed and lower diastereoselectivity, were also reported by Norin in 1985 when using an (*S*)-proline-based auxiliary, where the substituent on the pyrrolidine ring was an *iso*-propenyl moiety.[4] A bulkier (*S*)-prolinolamide derivative **2a** (Fig. 1) was elaborated by Lin et al.,[5] that slightly improved the diastereomeric ratios in alkylation reactions of its amide enolate. The methyl ether **2b** of this derivative has recently been used in a benzylation reaction of its amide enolate and as mentioned above the diastereoselectivity appeared to be reversed and very low (∼40:60).[6] Some (*S*)-prolinol derivatives have also been used in stereoselective aldol reactions[7] and for the preparation of chiral building blocks for insect pheromone synthesis[4,8] as well as other natural products.[9]



1a R^1 = H, R^2 = H
1b R^1 = Me, R^2 = H
2a R^1 = H, R^2 = Propanoyl
2b R^1 = Me, R^2 = Propanoyl

Figure 1. (*S*)-Proline based chiral auxiliaries used in the alkylation reactions.

Herein, we report our investigation of the diastereoselectivity in alkylation reactions of the chiral propanoyl amide enolates of **2a** and **2b** under varying reaction conditions. By comparing the reactions of hydroxyamide **2a** with those of the methyl ether amide **2b** at different temperatures, we found some support for the probable mechanisms behind the reversal in diastereoselection.[10]

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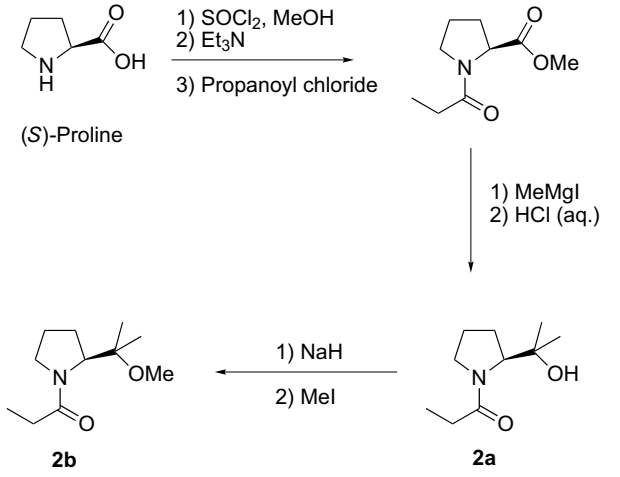
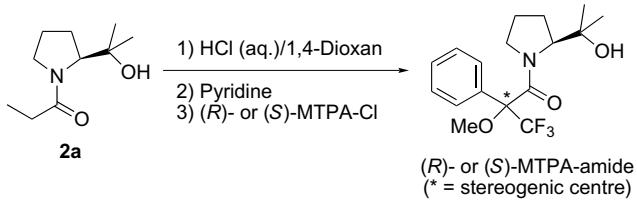
2. Results and discussion

The propanoylated auxiliaries 1-[(*S*)-(−)-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl]propan-1-one **2a** and 1-[(*S*)-(−)-2-(2-methoxypropan-2-yl)pyrrolidin-1-yl]propan-1-one **2b** were prepared from (*S*)-proline following the procedures reported earlier (Scheme 1).[11]



Scheme 1. Synthesis of the propanoylated chiral auxiliaries **2a** and **2b**.

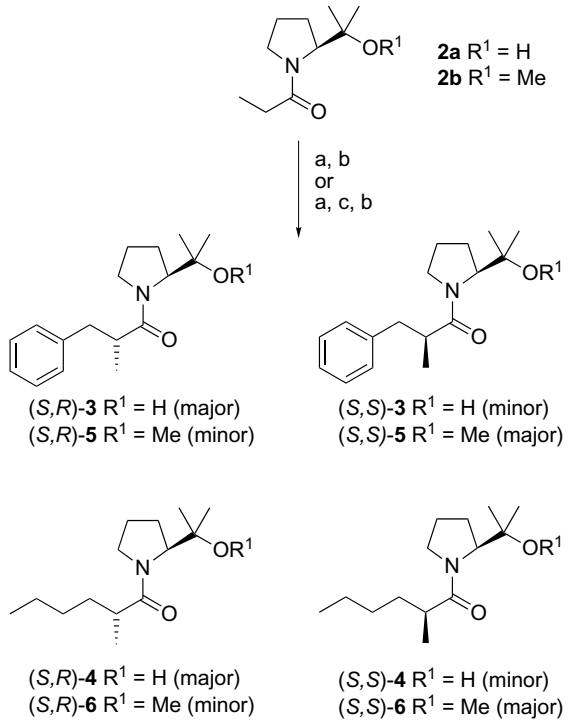
The enantiomeric purities of the obtained propanoylated auxiliaries **1a** and **1b** were both >99% ee. This was determined from GC analyses of the corresponding (*R*)- and (*S*)-MTPA amides of **1a**, prepared via hydrolysis[5] of hydroxyamide **2a** and acylation[12] of **1a** with (*R*)- and (*S*)-MTPA-Cl, respectively (Scheme 2).



Scheme 2. Preparation of (*R*)- and (*S*)-MTPA derivatives of the auxiliary **1a** for determination of enantiomeric purity.

The general method used for the alkylation reactions of hydroxyamide **2a** and methyl ether amide **2b** was the addition of one of these amides to freshly prepared LDA or LiHMDS or commercial NaHMDS for the generation of a *Z*-metal amide enolate.[2,10] Then, either the electrophile (benzyl bromide or *n*-butyl iodide) was added to the enolate, or an additive (Tables 1 and 2) was added before addition of the electrophile (Scheme 3).

Most alkylations reported in the literature proceed via the lithium enolates. We also investigated the use of some other coordinating agents (e.g., Na^+, Cp_2TiCl_2, Cp_2ZrCl_2 and excess of Li^+ from LiCl) to see the effect on the diastereoselection. Such modified reactions resulted in diastereomeric mixtures of alkylated products **3**–**6** (Scheme 3). The diastereomeric ratios were determined by GC analyses and, in some entries, also by ^{1}H NMR measurements (Tables 1 and 2).



Scheme 3. Reagents and conditions for alkylations of amides **2a** and **2b**: (a) LDA, LiHMDS or NaHMDS (2.25 or 1.25 equiv), THF, 0 °C; (b) benzyl bromide or *n*-butyl iodide (2.50 equiv), reaction temperatures and conversions: see Tables 1 and 2; (c) Cp_2ZrCl_2 or Cp_2TiCl_2 (1.05 equiv), 0 °C.

From alkylations of the *Z*-enolate of hydroxyamide **2a** with benzyl bromide or *n*-butyl iodide, we obtained (*SR*)-**3** or (*SR*)-**4**, respectively, as the major diastereomer (entries 1 and 7, Table 1), probably via a rigid chelated amide enolate (Fig. 2).[10] As earlier reported, the diastereomers of **3**, as well as those of **4**, were distinguishable by differences in chemical shifts from ^{1}H NMR data.[5] The diastereomers of amide **3** displayed a significant shift difference for the two methyl groups in the auxiliary moiety [1.00 and 1.16 ppm for (*SR*)-**3** and 0.71 and 1.12 ppm for (*SS*)-**3**], whereas those of amide **4** displayed a small shift difference for one of the two methyl groups in the auxiliary moiety [1.04 ppm for (*SR*)-**4** and 1.05 ppm for (*SS*)-**4**].

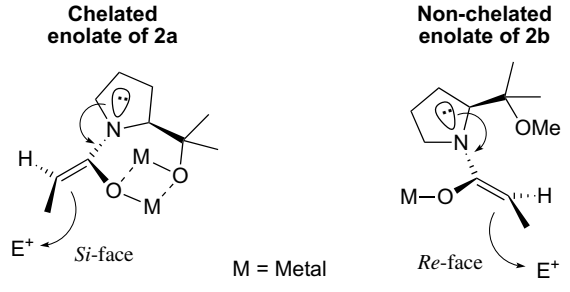


Figure 2. Possible mechanisms for the electrophilic attack on the enolates of **2a** and **2b**.

Table 1. Alkylation of hydroxyamide **2a**, favouring an (*R*)-configuration at the newly created stereogenic centre

Entry	Coordinating agent (equiv)	Electrophile	Reaction conditions	Conv.[d] (%)	Diastereomeric ratio (*S*,*R*:*S*,*S*)	
					GC	^{1}H NMR
1	Li^+ (2.25)[a]	BnBr	−78 °C (2 h)–2 h → −50 °C	84	78:22[e]	77:23
2	LiCl (6.50)	BnBr	−78 °C (2 h)–2 h → −50 °C	89	89:11[e]	88:12
3	Li^+ (2.25)[b]	BnBr	−78 °C (2 h)–3 h → −50 °C	69	87:13[e]	86:14
4	Na^+ (2.25)[c]	BnBr	−78 °C (2 h)–3 h → −50 °C	56	78:22[e]	77:23
5	Cp_2ZrCl_2 (1.05)	BnBr	−42 °C (4 h)	52	92:8[e]	92:8
6	Cp_2TiCl_2 (1.05)	BnBr	−42 °C (4 h)	44	77:23[e]	76:24
7	Li^+ (2.25)[a]	*n*-BuI	0 °C (2 h)	97	93:7[f]	
8	Li^+ (2.25)[a]	*n*-BuI	−42 °C (2 h)–1 h → −20 °C (1 h)	75	94:6[f]	
9	LiCl (6.50)	*n*-BuI	0 °C (2 h)	100	92:8[f]	
10	LiCl (6.50)	*n*-BuI	−42 °C (2 h)–1 h → −20 °C (1 h)	79	90:10[f]	
11	Li^+ (2.25)[b]	*n*-BuI	0 °C (2.5 h)	98	94:6[f]	
12	Na^+ (2.25)[c]	*n*-BuI	0 °C (4 h)	42	88:12[f]	
13	Cp_2ZrCl_2 (1.05)	*n*-BuI	0 °C (4 h)	15	82:18[f]	
14	Cp_2TiCl_2 (1.05)	*n*-BuI	0 °C (4 h)	15	66:34[f]	

[a] From LDA.
[b] From LiHMDS.
[c] From NaHMDS.
[d] Determined by GC (EC-5 capillary column) of the crude product.
[e] Determined by GC (EC-1 capillary column) of the crude product.
[f] Determined by GC (β-dex 225 chiral phase capillary column) of the crude product.

Table 2. Alkylation of methylether amide **2b**, favouring an (*S*)-configuration at the newly created stereogenic centre

Entry	Coordinating agent (equiv)	Electrophile	Reaction conditions	Conv.[d] (%)	Diastereomeric ratio (*S*,*R*:*S*,*S*) GC
15	Li^+ (1.25)[a]	BnBr	−78 °C (1.5 h)	100	3:97[e]
16	LiCl (6.50)	BnBr	−78 °C (1.5 h)	100	3:97[e]
17	Li^+ (1.25)[b]	BnBr	−78 °C (4 h)	82	9:91[e]
18	Na^+ (1.25)[c]	BnBr	−78 °C (4 h)	46	8:92[e]
19	Cp_2ZrCl_2 (1.05)	BnBr	−15 °C (4 h)	47	1:99[e]
20	Cp_2TiCl_2 (1.05)	BnBr	−15 °C (4 h)	19	6:94[e]
21	Li^+ (1.25)[a]	*n*-BuI	0 °C (2 h)	100	12:88[f]
22	Li^+ (1.25)[a]	*n*-BuI	−42 °C (2 h)	100	9:91[f]
23	Li^+ (1.25)[a]	*n* BuI	−78 °C (2 h)	90	8:92[f]
24	LiCl (6.50)	*n*-BuI	0 °C (2 h)	91	6:94[f]
25	LiCl (6.50)	*n*-BuI	−42 °C (2 h)	97	4:96[f]
26	LiCl (6.50)	*n*-BuI	−78 °C (2 h)	96	3:97[f]
27	Li^+ (1.25)[b]	*n*-BuI	−78 °C (2 h)–2 h → −35 °C	72	6:94[f]
28	Na^+ (1.25)[c]	*n*-BuI	−78 °C (2 h)–2 h → −35 °C	18	7:93[f]
29	Cp_2ZrCl_2 (1.05)	*n*-BuI	−42 °C (1.5 h) → −15 °C (1.5 h)	0	—
30	Cp_2TiCl_2 (1.05)	*n*-BuI	−42 °C (1.5 h) → −15 °C (1.5 h)	0	—

[a] From LDA.
[b] From LiHMDS.
[c] From NaHMDS.
[d] Determined by GC (EC-5 capillary column) of the crude product.
[e] Determined by GC (EC-1 capillary column) of the crude product.
[f] Determined by GC (β-dex 225 chiral phase capillary column) as the enantiomeric ratio of the corresponding 2-methylhexanol.

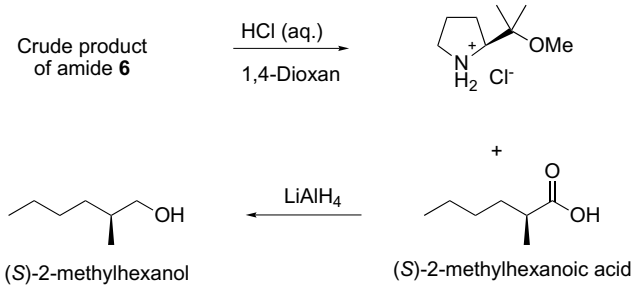
We were unable to reproduce the high diastereomeric ratio (94:6 and 95:5, from the benzylation and butylation reaction, respectively) obtained previously by Lin et al.[5] However, when an excess of LiCl was used as an additive, we obtained a significantly higher diastereomeric ratio in the benzylation reaction (entry 2). Generally, the presence of an excess of LiCl has been demonstrated to be essential for accelerating the rate in alkylation reactions and in suppressing *O*-alkylations without affecting the diastereoselectivity.[13] However, it has been reported that lithium chloride influences on the diastereoselectivity.[14] When the *Z*-enolate was generated with LiHMDS (entry 3), we also obtained a higher diastereoselectivity (cf. entry 1) but a lower conversion. The produced 1,1,1,3,3,3-hexamethyldisilazane in this reaction probably plays a significant role as a coordinating agent to the enolate, making it more sterically demanding than the less bulky diisopropylamine in entry 1. Therefore, we expected a similar diastereoselection when using NaHMDS (entry 4). However, the diastereomeric ratio was lowered to the same level as that in entry 1 and with a lower conversion. The mixed lithium/zirconium enolate gave the highest diastereomeric ratio (92:8, entry 5); this result was probably due to the steric hindrance exerted

by the bulky cyclopentadienyl ligands. However, when Cp_2TiCl_2 was used as an additive (entry 6) the same effect was not observed. This may be due to either the titanium complex being a poor chelating agent in this case or that no transmetallation was obtained in the reaction. A by-product was noticed in some cases (entries 5 and 6) and was identified as benzyl chloride, obtained via a halide exchange reaction. This might explain the low conversions also obtained in entries 13 and 14 (Table 1) and entries 19 and 20 (Table 2, alkylations of amide **2b**).

In the butylation reactions (entries 7–14, Table 1) we were unable to improve upon the results from the reactions performed under standard conditions (entries 7 and 8). However, it is noteworthy that the selectivity did not significantly change when performing the reactions at different temperatures (entries 7 and 8 and entries 9 and 10). This supports the idea that the alkylation reactions most likely take place from the *Si*-face of the chelated enolate of **2a** and that probably the nitrogen lone pair plays an important role as a director,[15] since steric hindrance does not seems to be the only important factor for obtaining high diastereoselectivity[10] (Fig. 2). When NaHMDS (entry 12) instead of LiHMDS (entry 11) was used as the base for the generation the enolate, lower diastereoselectivity and a lower conversion were obtained (cf. entries 3 and 4). Lithium cations probably form stronger chelates with the two charged oxygens when compared to sodium cations. This difference in diastereoselectivity is not observed in entries 17, 18, 27 and 28 (Table 2) when the methylether amide **2b** was used as the chiral inducer. The conversion was, however, lowered in these entries, as for all entries, when NaHMDS was used as base. The use of Cp_2ZrCl_2 and Cp_2TiCl_2 (entries 13 and 14, Table 1) in the reactions at low temperatures resulted in very slow reactions while elevated temperatures were required to obtain measurable conversions. The diastereoselectivities also proved to be very low. The low conversions in these entries can probably be explained by the observed background reaction that emerged as a competing reaction to the alkylation reaction, that is formation of butylated cyclopentadiene.

Alkylations of (*S*)-methylether amide **2b** with either benzyl bromide or *n*-butyl iodide furnished either (*S*,*S*)-**5** or (*S*,*S*)-**6**, respectively, as the major diastereomer, probably via a nonchelated amide enolate (Fig. 2).[10] As described earlier, the diastereomers of **5** were distinguishable by the differences in their ^1H chemical shifts,[16] while **6** were not. Removal of the chiral auxiliary from **6** by acid hydrolysis[5] furnished the nonracemic 2-methylhexanoic acid. The positive sign of the specific rotation of the obtained acid[5] verified (*S*,*S*)-**6** as the major diastereomer produced in the alkylation reaction while the diastereomeric ratio of amide **6** was determined as the enantiomeric ratio of 2-methylhexanol, after $LiAlH_4$-reduction of the nonracemic acid (Scheme 4).

This was expected when compared with results from previous studies on the alkylation of ethers of prolinol-amides,[2,3,6] that is, reversal from (*R*)- to (*S*)-configuration at the newly created stereogenic centre. Surprisingly, in contrast to the results obtained by others,[2,3,6] we obtained these alkylated amides in very high diastereomeric ratios. In the benzylation reaction under standard conditions (entry 15, Table 2), we obtained (*S*,*S*)-**5** in a very high diastereomeric ratio, which could be increased to an excellent ratio of 99:1 by the use of Cp_2ZrCl_2 as an additive (entry 19). In contrast to the results obtained in entries 2 and 3 (Table 1, alkylations of amide **2a**), no improvement in diastereoselectivity was obtained when LiCl (entry 16) or LiHMDS (entry 17) was used as an additive.



Scheme 4. Preparation of 2-methylhexanoic acid and 2-methylhexanol for the determination of the configuration at the newly created stereogenic centre and the diastereomeric ratio in the crude product of amide **6**.

When *n*-butyl iodide was used as the electrophile (entries 21–28, Table 2), we also obtained alkylated amides in high diastereomeric ratios while again the use of LiCl as an additive increased the diastereoselectivity (entries 24–26 in comparison with 21–23). These entries also indicated that lowering the temperature resulted in a higher diastereoselectivity, both in the presence or absence of LiCl as additive. This temperature dependence of the reaction implies that the reaction takes place from *Re*-face of the nonchelated enolate of **2b** (Fig. 2). The lower diastereoselectivity at higher temperature may depend on the higher flexibility of the enolate due to *C*–*N* rotation,[10] that is several conformations of the enolate may be present. No product was obtained when using Cp_2ZrCl_2 and Cp_2TiCl_2 as additives at low temperatures (entries 29 and 30, Table 2), most probably explained by the observed halide exchange reaction as mentioned above for entries 5 and 6 (Table 1, alkylations of amide **2a**).

In contrast to the diastereomeric butylated amides **4** and **6**, benzylated amides **3** and **5** were separable by liquid chromatography (EtOAc/cyclohexane) to give each of the diastereomers [(*S*,*R*)-**3**, (*S*,*S*)-**3**, (*S*,*S*)-**5** and (*S*,*R*)-**5**] in high diastereomeric purity (>99.5:0.5 dr).

3. Conclusion

In summary, we have shown that the diastereomeric ratios in alkylation reactions, using proline derivatives as chiral auxiliaries, can be improved upon by using various additives and conditions. The most surprising

results herein were the high level of facial selectivity in the reaction of the enolate of **2b** in comparison with **2a**. Alkylated amides of opposite configurations could be obtained and isolated in high diastereomeric purities, that is, the benzylated amides **3** and **5**, by a proper choice between the auxiliaries **1a** and **1b** derived from the same chiral source, (*S*)-proline.

4. Experimental

4.1. General

Unless otherwise stated, the starting materials and solvents were used as received from their commercial suppliers. Dry THF (benzophenone and potassium), Et_2O ($LiAlH_4$), CH_2Cl_2 (CaH_2), Et_3N (CaH_2), diisopropylamine (CaH_2), pyridine (CaH_2), ethyl acetate (CaH_2), benzylbromide ($CaCl_2$) and *n*-butyliodide (K_2CO_3) were distilled from the indicated drying agents and used either immediately or stored under argon. LiCl was oven dried before use. Unless otherwise stated, all reactions were performed under an argon atmosphere. NMR spectra were recorded on a Bruker DMX 250 instrument and all shifts are reported in ppm. GC analyses were carried out using a 30 m × 0.32 mm id capillary column coated with EC-1, $d_f = 0.25\,\mu m$, carrier gas: N_2 (6 psi), split ratio: 1/20 and a 30 m × 0.25 mm id capillary column coated with β-dex 225, $d_f = 0.25\,\mu m$, carrier gas: He (19 psi), split ratio: 1/100. Mass spectra were recorded on a Varian SATURN 2000 GC/MS instrument. Optical rotations were carried out on a Perkin–Elmer 241 Polarimeter in a 1 dm cell and specific rotations are reported in units of $10^{-1}\,deg\,cm^2\,g^{-1}$. Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM) was used in liquid chromatography (LC) using distilled EtOAc in distilled cyclohexane as eluent. Thin layer chromatography (TLC) was performed on silica gel plates (Merck 60, pre-coated aluminium foil) eluted with EtOAc (100%), and developed in UV-light and sprayed with vanillin in sulfuric acid or phosphomolybdic acid in aqueous sulfuric acid followed by heating with a heat gun. Boiling points are uncorrected, and are given as air-bath temperatures in a bulb-to-bulb (Büchi-GKR-51) apparatus.

4.2. Syntheses and analyses of the enantiomeric purities of the propanoylated auxiliaries 2a and 2b

The propanoylated auxiliaries **2a** and **2b** were prepared according to the literature procedure.[11] **2a** and **2b** were both >99% ee according to GC analyses on the corresponding (*R*)- and (*S*)-MTPA amides of **1a**, prepared from hydrolysis[5] of **2a** followed by acylation[12] of **1a** with (*R*)- and (*S*)-MTPA-Cl, respectively. GC retention times (EC-1 capillary column: 170 °C, 2 min, then programmed 1 °C/min up to 190 °C), t_R(2*S*,*S**/2*R*,*R**) 17.15 min and t_R(2*S*,*R**/2*R*,*S**) 17.77 min. An asterisk denotes configuration of the MTPA moiety.

4.2.1. 1-[(*S*)-(−)-2-(2-Hydroxypropan-2-yl)pyrrolidin-1-yl]propan-1-one 2a. 2a: bp 155 °C/0.6 mbar (lit.,[11] 110–120 °C/0.01 mbar); $[\alpha]_D^{20} = -92.2$ (*c* 5.30, MeOH) {lit.,[7] $[\alpha]_D^{25} = -96.5$ (*c* 5.40, MeOH)}; ^1H NMR (250 MHz; $CDCl_3$; Me_4Si), ^{13}C NMR (62.9 MHz; $CDCl_3$; Me_4Si) and MS(EI) spectral data were similar to those reported.[7]

4.2.2. 1-[(*S*)-(−)-2-(2-Methoxypropan-2-yl)pyrrolidin-1-yl]propan-1-one 2b. 2b: bp 105 °C/0.6 mbar (lit.,[11] 85 °C/0.001 mbar); $[\alpha]_D^{20} = -79.1$ (*c* 1.04, $CHCl_3$) {lit.,[11] $[\alpha]_D = -74.4$ (*c* 1.039, $CHCl_3$)}; ^1H NMR (250 MHz; $CDCl_3$; Me_4Si) and ^{13}C NMR (62.9 MHz; $CDCl_3$; Me_4Si) spectral data were similar to those reported.[11] MS (EI) *m*/*z* (relative intensity): 200 (MH^+, 100%), 184 (1), 168 (12), 127 (37), 112 (12), 73 (15), 70 (37), 57 (3).

4.3. Alkylation reactions of amide 2a. General procedure

Hydroxyamide **2a** (150 mg, 0.81 mmol) dissolved in THF (0.8 mL) was added to freshly prepared LDA or Li-HMDS in THF [prepared from a THF (0.4 mL) solution of diisopropylamine (0.26 mL, 1.86 mmol) or HMDS (0.39 mL, 1.86 mmol) and 1.55 M *n*-butyllithium in hexanes (1.18 mL, 1.82 mmol) at 0 °C] or to commercial 1.0 M NaHMDS in THF (1.82 mL, 1.82 mmol) at 0 °C. After 0.3 h the reaction solution was cooled to the indicated temperature (see Table 1) and the electrophile [benzyl bromide (0.24 mL, 2.02 mmol) or *n*-butyl iodide (0.23 mL, 2.02 mmol)] dissolved in THF (0.6 mL) added or alternatively an additive (Table 1, LiCl was added to the LDA solution) was added before the addition of the electrophile. After the indicated reaction time and temperature (Table 1), the reaction was quenched with dilute hydrochloric acid. Extraction of the aqueous phase with CH_2Cl_2 was followed by drying over $MgSO_4$ of the pooled organic phases and concentration by evaporation of the solvent afforded the crude alkylation products **3** or **4**. Final conversion and the diastereomeric ratio was determined by GC and NMR.

GC retention times (EC-1 capillary column; 180 °C, 2 min, then programmed 2 °C/min up to 210 °C), t_R[(*S*,*R*)-**3**] 14.26 min and t_R[(*S*,*S*)-**3**] 15.06 min. GC retention times (β-dex 225 capillary column; 125 °C, 20 min, then programmed 0.5 °C/min up to 165 °C), t_R[(*S*,*S*)-**4**] 92.62 min and t_R[(*S*,*R*)-**4**] 93.60 min.

4.3.1. 2-Benzyl-1-[2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl]propan-1-one 3. (*S*,*R*)-**3** and (*S*,*S*)-**3** was obtained from the diastereomeric mixture as single isomers by LC.

(*S*,*R*)-**3** (major isomer): 100% chemical purity and >99.5:0.5 dr; bp 185–188 °C/0.6 mbar (lit.,[5] 170–175 °C/0.1 mmHg); $[\alpha]_D^{20} = -147$ (*c* 1.71, MeOH) {lit.,[5] $[\alpha]_D^{19} = -133.4$ (*c* 1.730, MeOH)}; ^1H NMR (250 MHz; $CDCl_3$; Me_4Si): δ 1.00 (3H, s), 1.16 (3H, s), 1.24 (3H, d, $J = 6.4$ Hz), 1.10–1.25 (1H, m), 1.41–1.56 (1H, m), 1.60–1.73 (1H, m), 1.83–1.96 (1H, m), 2.68 (1H, dd, $J = 9.8$, 17.0 Hz), 2.88–3.02 (2H, m), 3.09–3.20 (1H, m), 3.23–3.32 (1H, m), 4.03 (1H, t, $J = 7.8$ Hz), 4.86 (1H, br s), 7.16–7.31 (5H, m); ^{13}C NMR (62.9 MHz; $CDCl_3$; Me_4Si): δ 18.35, 23.15, 24.09, 27.73, 28.61, 40.29, 40.72, 48.83, 67.95, 73.36, 126.36, 128.39 (2C),

128.89 (2C), 139.69, 177.87; MS (EI) *m/z* (relative intensity): 276 (MH^+, 100%), 258 (51), 126 (63), 91 (10), 70 (14).

(*S*,*S*)-**3** (minor isomer): 100% chemical purity and >99.5:0.5 dr; bp 190–193 °C/0.8 mbar (lit.,[5] 185–190 °C/0.1 mmHg); $[\alpha]_D^{20} = +29.9$ (*c* 1.39, MeOH) {lit.,[5] $[\alpha]_D^{19} = +30.8$ (*c* 1.145, MeOH)}; ^{1}H NMR (250 MHz; $CDCl_3$; Me_4Si): δ 0.71 (3H, s), 1.12 (3H, s), 1.18 (3H, d, $J = 6.5$ Hz), 1.47–1.74 (2H, m), 1.77–1.90 (1H, m), 1.97–2.08 (1H, m), 2.69 (1H, dd, $J = 5.2$, 12.4 Hz), 2.87–3.17 (3H, m), 3.62–3.71 (1H, m), 4.09 (1H, t, $J = 7.6$ Hz), 5.24 (1H, br s), 7.13–7.31 (5H, m); ^{13}C NMR (62.9 MHz; $CDCl_3$; Me_4Si): δ 17.11, 22.80, 24.39, 27.83, 28.59, 40.57, 40.92, 48.80, 68.17, 73.38, 126.22, 128.35 (2C), 129.00 (2C), 139.60, 177.52; MS (EI) *m/z* (relative intensity): 276 (MH^+, 76%), 258 (45), 126 (100), 91 (25), 70 (37).

4.3.2. 1-[2-(2-Hydroxypropan-2-yl)pyrrolidin-1-yl]-2-methylhexan-1-one 4. (*S*,*R*)-**4** (major isomer) and (*S*,*S*)-**4** (minor isomer) were obtained as a diastereomeric mixture. MS (EI) *m/z* (relative intensity) on a diastereomeric mixture: 242 (MH^+, 100%), 225 (5), 182 (1), 127 (10), 126 (5), 70 (8), 59 (2). ^{1}H NMR (250 MHz; $CDCl_3$; Me_4Si) spectral data was similar to those reported for (*S*,*R*)-**4** and (*S*,*S*)-**4**.[5]

4.4. Alkylation reactions of amide 2b. General procedure

Methylether amide **2b** (125 mg, 0.63 mmol) dissolved in THF (0.6 mL) was added to freshly prepared LDA or LiHMDS in THF [prepared from a THF (0.4 mL) solution of diisopropylamine (0.11 mL, 0.82 mmol) or HMDS (0.17 mL, 0.82 mmol) and 1.55 M *n*-butyllithium in hexanes (0.51 mL, 0.79 mmol) at 0 °C] or to commercial 1.0 M NaHMDS in THF (0.79 mL, 0.79 mmol) at 0 °C. After 0.3 h the reaction solution was cooled to the indicated temperature (see Table 2) and the electrophile [benzyl bromide (0.19 mL, 1.58 mmol) or *n*-butyl iodide (0.18 mL, 1.58 mmol)] dissolved in THF (0.6 mL) was added or alternatively an additive (Table 2, LiCl was added to the LDA solution) was added before addition of the electrophile. After the indicated reaction time and temperature (Table 2), the reaction was quenched with dilute hydrochloric acid. Extraction of the aqueous phase with CH_2Cl_2 was followed by drying over $MgSO_4$ of the pooled organic phases with concentration by evaporation afforded the crude alkylation products **5** or **6**. Final conversion and diastereomeric ratio was determined by GC. GC retention times (EC-1 capillary column: 180 °C, 2 min, then programmed 2 °C/min up to 210 °C), t_R[(*S*,*R*)-**5**] 13.85 min and t_R[(*S*,*S*)-**5**] 14.49 min.

4.4.1. 2-Benzyl-1-[2-(2-methoxypropan-2-yl)pyrrolidin-1-yl]propan-1-one 5. (*S*,*S*)-**5** and (*S*,*R*)-**5** was obtained from the diastereomeric mixture as single isomers by LC.

(*S*,*S*)-**5** (major isomer): 100% chemical purity and >99.5:0.5 dr; bp 160–164 °C/0.7 mbar; $[\alpha]_D^{20} = +39.5$ (*c* 1.44, $CHCl_3$) {lit.,[16] $[\alpha]_D = +42.5$ (*c* 1.051, $CHCl_3$)}; ^{1}H NMR (250 MHz; $CDCl_3$; Me_4Si; Two rotamers, ~3:2): δ 0.87 (1.8H, s), 0.96 (1.2H, s), 1.00 (1.2H, s), 1.06 (1.8H, s), 1.11 (1.8H, d, $J = 6.5$ Hz), 1.24 (1.2H, d, $J = 6.5$ Hz), 1.29–1.83 (2.6H, m), 1.92–2.07 (1.4H, m), 2.61–3.06 (3H, m), 3.07 (1.8H, s), 3.11 (1.2H, s), 3.22–3.38 (1.4H, m), 3.55–3.64 (0.6H, m), 3.77 (0.4H, ddd, $J = 5.6$, 9.1, 12.2 Hz), 4.34 (0.6H, dd, $J = 2.1$, 8.8 Hz), 7.14–7.29 (5H, m); ^{13}C NMR (62.9 MHz; $CDCl_3$; Me_4Si; Asterisk denotes minor rotamer peaks): δ 16.87, 18.20*, 19.34*, 21.59*, 21.95, 22.28*, 23.22, 24.69, 25.08, 26.30*, 39.95*, 40.16, 40.73, 42.20*, 46.03*, 47.75, 49.06*, 49.27, 62.67, 65.09*, 77.96*, 78.23, 126.06 (2C)*, 126.06 (2C), 128.20 (2C)*, 128.20 (2C), 128.76*, 129.05, 140.06, 140.27*, 175.45, 176.62*; MS (EI) *m/z* (relative intensity): 290 (MH^+, 73%), 274 (5), 258 (28), 217 (33), 126 (43), 91 (51), 73 (39), 70 (100).

(*S*,*R*)-**5** (minor isomer): >96% chemical purity and >99.5:0.5 dr; $[\alpha]_D^{20} = -82.5$ (*c* 1.45, $CHCl_3$) {lit.,[16] $[\alpha]_D = -97$ (*c* 1.071, $CHCl_3$)}; ^{1}H NMR (250 MHz; $CDCl_3$; Me_4Si): δ 1.10 (3H, s), 1.14 (3H, s), 1.20 (3H, d, $J = 6.5$ Hz), 1.28–1.40 (1H, m), 1.49–1.63 (1H, m), 1.76–2.00 (2H, m), 2.61 (1H, dd, $J = 5.2$, 12.0 Hz), 2.85–3.04 (2H, m), 3.15 (3H, s), 3.17–3.32 (2H, m), 4.35 (1H, dd, $J = 2.3$, 8.7 Hz), 7.14–7.29 (5H, m); ^{13}C NMR (62.9 MHz; $CDCl_3$; Me_4Si): δ 18.58, 22.07, 22.86, 24.48, 24.83, 40.00, 40.37, 47.48, 49.26, 62.59, 78.48, 126.08, 128.28 (2C), 128.98 (2C), 140.31, 175.83; MS (EI) *m/z* (relative intensity): 290 (MH^+, 23%), 274 (4), 258 (11), 217 (68), 126 (34), 91 (56), 73 (40), 70 (100).

4.4.2. 1-[2-(2-Methoxypropan-2-yl)pyrrolidin-1-yl]-2-methylhexan-1-one 6. (*S*,*S*)-**6** (major isomer) and (*S*,*R*)-**6** (minor isomer) were obtained as a diastereomeric mixture.

MS (EI) *m/z* (relative intensity): 256 (MH^+, 100%), 240 (5), 183 (15), 127 (68), 73 (33), 70 (93).

4.4.3. Determination of the diastereomeric ratio and assignment of the configuration at the newly created stereogenic centre in the alkylated amide 6 (entries 21–28 in Table 2). The diastereomeric mixture of amide **6** was dissolved in aqueous 3 M HCl/1,4-dioxan (15 mL/mmol amide, 1/1) and heated to 90–95 °C. After complete conversion of amide **6**, the reaction mixture was cooled to room temperature and extracted with Et_2O. The pooled organic phases were dried over $MgSO_4$ and concentrated by evaporation to yield nonracemic 2-methylhexanoic acid. The specific rotation of this acid[5] dissolved in Et_2O was measured with the positive sign indicating an excess of (*S*)-2-methylhexanoic acid, that is (*S*,*S*)-**6** is the major isomer in the alkylation reaction. The diastereomeric ratio of the starting amide **6** was then calculated as the determined enantiomeric ratio of (*S*)-2-methylhexanol [obtained from $LiAlH_4$-reduction of the (*S*)-acid] by GC analysis and ranged from 76% de to 94% de.

GC retention times (β-dex 225 capillary column: 65 °C, 1 min, then programmed 0.5 °C/min up to 70 °C), 20 min, t_R[(*R*)-2-methylhexanol] 25.10 min and t_R[(*S*)-2-methylhexanol] 25.96 min.

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