Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 527–534

TETRAHEDRON: *ASYMMETRY*

Enantioselective butylation of aliphatic aldehydes by mixed chiral lithium amide/*n*-BuLi dimers

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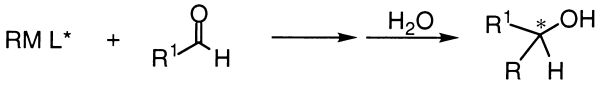
Received 14 December 1998; accepted 26 January 1999

Abstract

The enantioselective butylation of aliphatic aldehydes with mixtures of *n*-butyllithium and chiral lithium amides in a diethyl ether–dimethoxymethane solvent mixture is described. Enantiomeric excesses ranging from 91 to 98.5% were observed for several aliphatic alcohols. The asymmetric butylation of the prochiral aldehydes proceeds much faster by the mixed lithium amide/*n*-BuLi complexes than by tetrameric *n*-BuLi. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Nucleophilic addition to carbonyl carbon utilizing organometallic reagents, e.g. R_2Zn, RMgX and RLi, is a central reaction in organic synthesis allowing formation of new carbon–carbon bonds.[1–3] This addition reaction, shown in Scheme 1, also provides a reliable route to optically active secondary alcohols, when chiral auxiliaries or ligands are used.[4–7]



Scheme 1. Enantioselective nucleophilic addition of organometallic reagents to carbonyl compounds. L*=chiral inducer

Despite the wide use of organolithium reagents in organic synthesis, only a few examples of asymmetric alkylation reactions using alkyllithium reagents and non-covalently bound chiral auxiliaries have been reported. One reason for the meager exploration of alkyllithium reagents in such reactions is their high reactivity and propensity to assemble in aggregates. It has even been suggested that the products may form mixed aggregates with the reagent,[8,9] thereby changing the reaction conditions. The aggregates of organolithium reagents generally show large structural diversity and undergo various dynamic processes

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PII: S0957-4166(99)00033-6

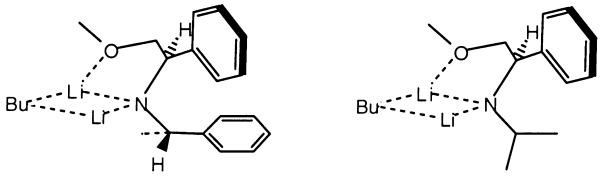
in solution.[10–12] We and others have shown that mixed aggregates are formed in mixtures of alkyllithium reagents and homochiral lithium amides or lithium alkoxides.[13–19] The property of alkyllithium reagents to form mixed aggregates is potentially useful for asymmetric synthesis since it allows introduction of a chiral environment at the alkyllithium moieties.

The first report of asymmetric induction in nucleophilic addition of organolithium reagents to benzaldehyde **3** came in 1968 from Nozaki et al. Using an *n*-BuLi/sparteine complex they obtained 1-phenyl-1-pentanol in 6% ee.[20] Since then, the groups of Mukaiyama,[21] Cram[22] and Hogeveen[23] have each described chiral additives that yield enantioselectivities above 90% for 1-phenyl-1-pentanol in the asymmetric alkylation of **3** with *n*-butyllithium (*n*-BuLi). The chiral inducers in these studies were a chiral lithium alkoxide, a chiral diamine, or a chiral lithium amide, respectively. Only modest asymmetric induction values (40–50% ee) were obtained in the butylation of non-aromatic aldehydes using these or other chiral inducers.[21,22,24]

In this paper we wish to report on the enantioselective addition of *n*-BuLi to aliphatic prochiral aldehydes in the presence of the chiral lithium amide bases lithium (*R*)-*N*-2-methoxy-1-phenyl-(*S*)-α-methylbenzylamide Li-**1** and lithium (*R*)-*N*-2-methoxy-1-phenyl-*i*-propylamide Li-**2**, respectively. These chiral lithium amide bases were the most successful among a series of analogues previously investigated for use in asymmetric butylation of **3**.[13]

2. Results and discussion

In 1984, Hogeveen and Eleveld reported the use of the chiral lithium amide base Li-**1** in the enantioselective addition of *n*-BuLi to **3** in diethyl ether (DEE).[23] Recently, we showed that the structurally more simple ligand Li-**2**, containing only one stereogenic center gave approximately the same enantiomeric excess (74% ee) as Li-**1** (72% ee) under the same reaction conditions.[13] NMR spectroscopic studies have shown that the reagent solution consists of three species in equilibrium, homo-aggregated *n*-BuLi, lithium amide dimers, i.e. (Li-**1**)$_2$ or (Li-**2**)$_2$ and a mixed 1:1 complex between the lithium amide and *n*-BuLi, i.e. Li-**1**/*n*-BuLi or Li-**2**/*n*-BuLi shown in Scheme 2.[14]



Li-**1**/*n*-BuLi Li-**2**/*n*-BuLi

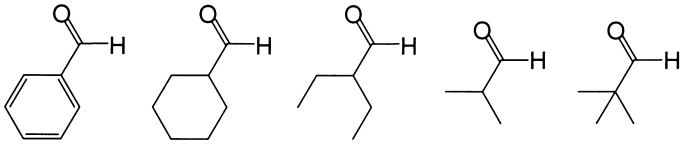
Scheme 2. Schematic representation of Li-**1**/*n*-BuLi and Li-**2**/*n*-BuLi (coordinating solvent molecules are excluded for clarity)

The chiral lithium amide Li-**2** showed strong solvent dependence in the asymmetric alkylation of **3** with *n*-BuLi as a butylating reagent. Butylation at −116°C gave the product (*S*)-1-phenyl-1-pentanol in 74% ee when DEE was used as solvent. However, under the same reaction conditions, with the exception of using a 1:1 diethyl ether–dimethoxy methane (DEE–DMM) mixture as solvent, the same alcohol was obtained with 90% ee.[13] The reaction gave quantitative yields (GC) in both solvents.

Steric interactions between the R-group of the aldehyde and bulky groups of the ‘chiral’ lithium complex constitute the basis for design of chiral lithium amide bases to be used as chiral inducers in the asymmetric butylation of aldehydes. However, the earlier success, in terms of enantioselectivity, with **3** but failure with aliphatic aldehydes suggests that also π–π and Li–π interactions could be important in the asymmetric butylation of **3** using amide bases with aromatic substituents, e.g. Li-**1**. If π–π and/or

Li–π interactions between the phenyl group of the aldehyde and the phenyl group and/or the lithium in the lithium amide are crucial for the asymmetric induction, replacement of the phenyl group with a non-aromatic group would have a dramatic effect on the stereoselectivity.

In order to address this 'proposal' we conducted a series of experiments using non-aromatic aldehydes (Scheme 3). The chiral lithium amides Li-**1** and Li-**2** were used as chiral inducers, i.e. employed to form mixed complexes with the nucleophile *n*-BuLi, in the butylation of the aldehydes in 1:1 DEE–DMM solutions. As a comparison we also included **3** in these asymmetric butylation reactions. Based on previous studies we used 1.45 equiv. *n*-BuLi to 1.0 equiv. of the chiral amine. Thus, 1 equiv. of *n*-BuLi is used to form the lithium amide, i.e. lithiate the amine, and the remaining 0.45 equiv. is available for the formation of the hetero-complexes Li-**1**/*n*-BuLi and Li-**2**/*n*-BuLi, respectively. The aldehyde (0.25 equiv.) was added to the chiral lithium amide/*n*-BuLi mixture at −116°C. The reaction mixture was quenched after 15 min by addition of methanol and the mixtures were analyzed using capillary gas chromatography on a chiral stationary phase. The results of the asymmetric butylation of prochiral aldehydes using the chiral lithium amide bases Li-**1** and Li-**2**, respectively, are summarized in Table 1. The chemical yields in all reactions were quantitative (GC). Use of the Li-**1**/*n*-BuLi and Li-**2**/*n*-BuLi complexes gives excellent enantioselectivities in the butylation of these aliphatic aldehydes. Tentatively, we conclude that the π–π and Li–π interactions are of minor importance for obtaining high enantioselectivity in this alkylation reaction.



3 **4** **5** **6** **7**

Scheme 3.

The asymmetric butylation of aldehydes is likely to proceed through an activated complex in which the aldehyde is coordinated to one of the two stereogenic lithium atoms in the lithium amide/*n*-BuLi/aldehyde hetero-complex. In this hetero-complex the steric requirements of the aldehydes are important for the asymmetric induction. The aldehydes in Table 1 differ in their steric requirements at the α- and β-carbons. Replacing the phenyl ring in **3** for a cyclohexyl group yields 1-cyclohexyl carboxaldehyde **4** which increases the steric requirements of the aldehyde. This is reflected in an increased enantiomeric excess of the product 1-cyclohexyl-1-pentanol, 91% and 96% using Li-**1** and Li-**2**, respectively. An even more sterically demanding aldehyde is obtained by removing the C4-carbon in the cyclohexyl ring of **4**, yielding 2-ethyl-butyraldehyde **5**. This modification gave a low enantiomeric excess of the product 3-ethyl-4-octanol using Li-**2** as a chiral ligand. The lower enantiomeric excess obtained with **5**, compared to **4**, is presumably due to an alternative reaction route competing effectively with the former when congested aldehydes are used. Removal of the two additional carbons in the above aldehydes yield *i*-butyraldehyde **6**. Since this is a less sterically demanding aldehyde the enantiomeric excess of the product 2-methyl-3-heptanol is again high, >98.5% using Li-**2** and 96% with Li-**1**.

Both Li-**1** and Li-**2** are efficient in selecting between the *Re*- and *Si*-faces of the carbonyl group in the above aldehydes. However, for pivaldehyde **7**, having a *t*-butyl group attached to the carbonyl group, the enantiomeric excess of the resulting 2,2-dimethyl-3-heptanol dropped to 58% and 11% for Li-**1** and Li-**2**, respectively. Similar results were also observed in an attempt to butylate acetophenone in the presence of Li-**2**. The resulting product, 2-phenyl-2-hexanol, was only obtained in 10% ee. Thus, it is clear that the enantioselectivity in the addition reaction is extremely sensitive to the steric requirements of the R-groups attached to the carbonyl carbon.

Table 1
Enantioselective addition of *n*-BuLi (0.45 equiv.) to prochiral aldehydes (0.25 equiv.) in the presence of chiral lithium amide, Li-**1** or Li-**2** (1 equiv.) in (50/50 v/v) DEE–DMM solution at −116°C

Entry	Lithium amide	aldehyde	product	ee (%)
1	Li-**1**	**3**	1-phenyl-1-pentanol	72
2	Li-**2**	"	"	91
3	Li-**1**	**4**	1-cyclohexyl-1-pentanol	91
4	Li-**2**	"	"	>98.5
5	Li-**1**	**5**	3-ethyl-4-octanol	90[a]
6	Li-**2**	"	"	65[a]
7	Li-**1**	**6**	2-methyl-3-heptanol	96
8	Li-**2**	"	"	>98.5
9	Li-**1**	**7**	2,2-dimethyl-3-heptanol	58
10	Li-**2**	"	"	11

a) The peaks are not fully resolved, and reported values are estimates of enantiomeric excess.

The reactivity of organolithium reagents has been observed to increase upon deaggregation, i.e. dimers of *n*-BuLi are known to be more reactive than their tetrameric analogues.[8] Thus, it seems likely that the *n*-BuLi within the hetero-dimer Li-**2**/*n*-BuLi would be more reactive than *n*-BuLi present as dimeric and tetrameric aggregates. To test this hypothesis, we estimated approximate reaction rates at −116°C for the butylation of **4** and **6** from the observed half-life of the aldehydes, in the absence and presence of Li-**2**. The rate of butylation using the mixed complex Li-**2**/*n*-BuLi was found to be too fast to be determined using conventional methods ($t_{1/2}$<15 s). However, the butylation of **4** and **6** without added Li-**2**, i.e. with dimeric and/or tetrameric *n*-BuLi, is much slower ($t_{1/2}$>10 min).

The high rate constant for the asymmetric butylation of **4** and **6** with Li-**2**/*n*-BuLi suggests that Li-**2** catalyzes the reaction. To prove this hypothesis, a series of experiments was performed. To different reaction flasks containing aldehyde (0.25 equiv.) and lithium amide (1.0 equiv.), was added 0.2, 2.5, 5.1 and 11 equiv. homo-aggregated *n*-BuLi, respectively (Table 2). We obtained enantioselectivities ranging from 98.5 to 67%, establishing that *n*-BuLi in the mixed hetero-complex Li-**2**/*n*-BuLi reacts substantially faster with the aldehyde than homo-aggregated *n*-BuLi.

The relationship between the observed enantioselectivity and the equivalents of homo-aggregated *n*-BuLi in the butylation reaction shows that the enantioselectivity for an ideal reaction mixture without any homo-aggregated *n*-BuLi would be 100% (Table 2). Thus, the Li-**2**/*n*-BuLi hetero-complex may yield 100% ee in the reaction. However, homo-aggregated *n*-BuLi is always present in the reaction mixtures due to the equilibrium between Li-**2**, homo-aggregated *n*-BuLi and Li-**2**/*n*-BuLi. This homo-aggregated *n*-BuLi lowers the ee of 2-methyl-3-heptanol to >98.5%.

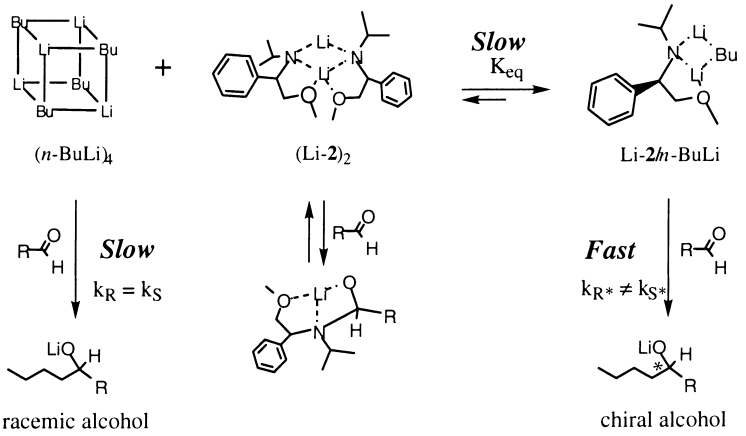
Performing the asymmetric butylation of **4** and **6** under catalytic conditions (1 equiv. Li-**2**, 5 equiv. *n*-BuLi and 5 equiv. aldehyde) gave the product alcohols in high enantioselectivities but low chemical yields. Prolonging the reaction time increased the chemical yield at the expense of the selectivity. These

Table 2
Nucleophile addition of *n*-BuLi (0.2 to 11 equiv.) to **6** (0.25 equiv.) in the presence of Li-**2** (1.0 equiv.) at −116°C in DEE–DMM

Entry	Li-**2** /equiv.	*n*-BuLi /equiv.	**6** /equiv.	2-methyl-3-heptanol / ee (%)
1	1.0	0.2	0.25	>98.5
2	1.0	2.5	0.25	96
3	1.0	5.1	0.25	91
4	1.0	11.0	0.25	67

[a]) The mixture of chiral amide and *n*-BuLi in DEE-DMM was frozen on liquid nitrogen prior to the addition of the aldehyde in order to minimize the chances of warming up the reaction mixture by addition of a large volume of the aldehyde.

results may indicate that the formation of the mixed complex Li-**2**/*n*-BuLi is comparable or slower than the racemic alkylation by homo-aggregated *n*-BuLi (Scheme 4).



Scheme 4. The chiral lithium amide dissociates the tetramers of *n*-BuLi into hetero-dimers Li-**2**/*n*-BuLi, which are more reactive towards the aldehydes than the *n*-BuLi tetramers. The formation of Li-**2**/*n*-BuLi is slower than the reaction between the aldehydes and Li-**2**/*n*-BuLi. The lithium amide dimer, $(\text{Li-}\mathbf{2})_2$, undergoes 1,2-addition to the aldehyde in the absence of *n*-BuLi

Only modest enantioselectivity (<40% ee) and chemical yield (40% GC) were obtained when *n*-BuLi was added to a mixture of Li-**2** and **4** at −116°C. Thus, the rate of formation of Li-**2**/*n*-BuLi from Li-**2** and *n*-BuLi is comparable to the rate of homo-aggregated *n*-BuLi addition to aldehyde, the reason for this being a slow equilibrium or the loss of amide through a 1,2-addition reaction with the aldehyde.

1,2-Addition of lithium amides to aldehydes, yielding hemiaminal-like intermediates has previously been reported. Such a reaction would also explain the lower yield and selectivity observed under catalytic conditions. We therefore added 1 equiv. of **3** to a DEE solution of Li-**2** at −90°C. Both the ^{13}C and ^{6}Li NMR spectra showed broad and unresolved signals. No signals for dimers of the lithium amide could be detected. After addition of methanol, the reaction mixture only contained unreacted aldehyde and chiral amine (GC–MS). The above results support the reversible formation of a hemiaminal-like intermediate as reported by Duhamel et al.[18] and others.[25–28]

Turnover for the asymmetric butylation was demonstrated by a repetitive cycle comprised of: (1)

formation of the mixed complex Li-**2**/*n*-BuLi at room temperature (by the addition of 0.5 equiv. *n*-BuLi to Li-**2**); and (2) cooling down to −116°C followed by addition of **4** (0.5 equiv.). This cycle was repeated 5 times to yield 1-cyclohexyl-1-pentanol in quantitative chemical yield (GC) and 82% ee using sub-stoichiometric amount of Li-**2**. Furthermore, since the chemical yield and enantioselectivity were found to be high, there does not seem to be any interference from the product.

3. Summary

In this paper we have demonstrated that asymmetric butylation of prochiral aldehydes is possible in both high yields and excellent stereoselectivities using *n*-BuLi as a butylating agent in the form of mixed Li-**1**/*n*-BuLi or Li-**2**/*n*-BuLi hetero-complexes. We conclude that the use of these chiral lithium amides, e.g. Li-**1** and Li-**2**, in asymmetric synthesis is a promising alternative to other organometallic reagents, especially due to the ease of recycling the chiral amine and the use of the cheap and common organolithium reagent, i.e. *n*-BuLi as an alkyl donor. The very high enantiomeric excesses obtained in this asymmetric C–C bond formation originate from the increased reactivity of *n*-BuLi when complexed to the chiral lithium amides Li-**1** or Li-**2** in the form of hetero-dimers, compared to the reactivity of homo-aggregated *n*-BuLi. Unfortunately, the formation of mixed dimers is slower or comparable to the racemic butylation reaction by homo-aggregated *n*-BuLi. This hampers turnover in a one-pot synthesis.

4. Experimental

4.1. General

Glassware and syringes were dried at 50°C in a vacuum oven before transfer into a glove box (Mecaplex GB 80 equipped with a gas purification system that removes oxygen and moisture) containing a nitrogen atmosphere. Typical moisture content was less than 0.5 ppm. All manipulations concerning the alkylation reactions were carried out using gas-tight syringes. Ether solvents, distilled under nitrogen from sodium and benzophenone, were kept over 4 Å molecular sieves in a septum sealed flask inside the glove box. The concentrations of commercially available *n*-butyllithium solutions (1.6 M or 2.5 M solution in hexanes, Aldrich) were determined by double Gilman titration.[29]

Chromatographic analyses were carried out using a Varian Star 3400 CX gas chromatograph. All GC analyses were run on a chiral stationary phase column (CP-Chirasil-DEX CB, 25 m, 0.32 mm) from Chrompack. Analyses were performed using He (1.5 mL/min) as carrier gas (injector 225°C, detector 250°C). Mass spectra (MS) were recorded on a Varian Saturn 2000 GC–MS/MS operating in electronic ionization (EI) or chemical ionization (CI) mode. Methane was used as reagent gas for CI operation. The GC column connected to the mass analyzer was a DB-5MS (J & W Scientific). Routine 1D ^{1}H and ^{13}C NMR spectra were recorded using a Varian Unity 400 MHz spectrometer. The ^{13}C and ^{6}Li NMR spectra indicating a reaction of Li-**2** with **3** were recorded on a Varian Unity 500 spectrometer using a 5 mm ^{1}H, ^{13}C, ^{6}Li, ^{15}N quad resonance probe head custom built by Nalorac.

The chiral amines **1** and **2**, precursors to the lithiated amides Li-**1** and Li-**2**, respectively, were prepared according to previously published procedures.[13]

4.2. Asymmetric butylation reactions

A septum sealed flask containing a magnet, the amine (0.20 mmol) and a dry 1:1 DEE–DMM solution (1.6 mL) was assembled inside the glove box. The flask was taken out and directly fitted with a dry argon inlet. The flask was cooled to 0°C and *n*-BuLi (0.29 mmol as solution in hexane) was added via a syringe. After stirring for 15 min at 0°C, the flask was moved to a DEE/liquid N_2 bath (−116°C). The aldehyde (0.05 mol; as a 25% solution in DEE–DMM) was added via a syringe after allowing the flask to temperature equilibrate at −116°C for 30 min. (For the catalytic reactions and reactions with more than 4 equiv. of aldehyde and *n*-BuLi, the mixture of *n*-BuLi and lithium amide was frozen down to −196°C in liquid nitrogen before adding the aldehyde. After 5 min the reaction vessel was transferred to the −116°C cooling bath and allowed to thaw and react.) The reaction was quenched after 15 min by addition of methanol (0.5 mL). The crude mixture containing the alkylation product was analyzed using chiral stationary phase GC and GC–MS. The chromatograms showed that the reactions were quantitative, with the amines and alcohols being the only detected compounds.

4.3. Preparation and characterization of racemic alcohols

Racemic alcohols were prepared by addition of *n*-BuLi (1.4 mmol) to a solution of the aldehyde (0.7 mmol) in DEE (2 mL) kept under an argon atmosphere at −78°C. The reaction was quenched after 15 min by addition of MeOH (1 mL). The mixture was diluted with DEE (2 mL) after warming to room temperature. The solution was washed with brine (0.5 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave pure racemic alcohols in about 85% yield.

4.3.1. 1-Phenyl-1-pentanol

^{1}H NMR 400 MHz ($CDCl_3$): δ (ppm): 0.80 (3H, t, *J*=6.74 Hz), 1.1–1.36 (4H, m), 1.56–1.76 (2H, m), 1.86 (1H, br), 4.56 (1H, t, *J*=6.11 Hz), 7.15–7.30 (5H, m); ^{13}C NMR 100 MHz ($CDCl_3$): δ (ppm): 14.2, 22.8, 28.2, 39.0, 74.9, 126.1, 127.6, 128.6, 145.1; MS (CI) *m/z* 165 (M^++1); MS (EI) *m/z* 164 (15), 147 (19), 107 (100), 79 (70), 51 (14); GC on chiral stationary phase: 125°C, 17.8 (*S*) and 18.5 (*R*) min.

4.3.2. 1-Cyclohexyl-1-pentanol

^{1}H NMR 400 MHz ($CDCl_3$): δ (ppm): 0.80 (3H, t, *J*=7.11 Hz), 0.86–1.43 (12H, m), 1.55 (2H, m), 1.62–1.72 (4H, m), 3.25 (1H, m); ^{13}C NMR 100 MHz ($CDCl_3$): δ (ppm): 14.3, 23.1, 26.5, 26.6, 26.8, 27.9, 28.4, 29.5, 34.0, 43.8, 76.4; MS (CI) *m/z* 170 (M^++1); MS (EI) *m/z* 169 (1), 152 (9), 124 (4), 113 (26), 95 (93), 87 (17), 69 (100), 55 (35); GC on chiral stationary phase: 115°C, 23.7 and 24.8 min.

4.3.3. 2-Ethyl-4-octanol

^{1}H NMR 400 MHz ($CDCl_3$): δ (ppm): 0.82–0.86 (9H, m), 1.12 (1H, m), 1.17–1.43 (10H, m), 3.54 (1H, m); ^{13}C NMR 100 MHz ($CDCl_3$): δ (ppm): 12.0, 12.1, 14.3, 21.4, 22.3, 23.0, 28.7, 34.0, 47.0, 73.4; MS (CI) *m/z* 158 (M^++1); MS (EI) *m/z* 157 (1), 141 (3), 99 (8), 87 (19), 69 (100), 55 (21); GC on chiral stationary phase: 85°C, 32.8 and 33.1 min, no baseline separation.

4.3.4. 2-Methyl-3-heptanol

^{1}H NMR 400 MHz ($CDCl_3$): δ (ppm): 0.78–0.98 (10H, m), 1.16–1.43 (6H, m), 1.60 (1H, m), 3.30 (1H, m); ^{13}C NMR 100 MHz ($CDCl_3$): δ (ppm): 14.3, 17.3, 19.0, 23.0, 28.4, 33.6, 34.0, 78.8; MS (CI) *m/z* 130 (M^+); MS (EI) *m/z* 129 (1), 113 (7), 87 (15), 69 (100), 55 (27); GC on chiral stationary phase: 95°C, 6.5 and 6.7 min.

4.3.5. 2,2-Dimethyl-3-heptanol

^{1}H NMR 400 MHz ($CDCl_3$): δ (ppm): 0.80–0.88 (12H, m), 1.13–1.38 (5H, m), 1.54–1.41 (2H, m), 3.12 (1H, m); ^{13}C NMR 100 MHz ($CDCl_3$): δ (ppm): 14.3, 23.0, 25.9, 29.5, 31.4, 35.1, 80.2; MS (CI) *m/z* 144 (M^+); MS (EI) *m/z* 127 (3), 87 (25), 69 (100), 57 (33); GC on chiral stationary phase: 95°C, 8.6 and 9.1 min.

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