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Double Asymmetric Alkylation Reactions Using C_2-symmetric Benzene Based Bis(2-amino-2-oxazolines) Chiral Auxiliaries

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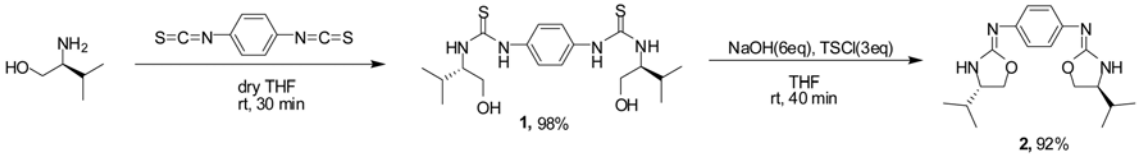
Chiral auxiliary-derived asymmetric alkylations have been extensively studied and are now important and general methods for asymmetric carbon-carbon bond formation.[1] Recently, we developed 2-amino-2-oxazoline chiral auxiliaries which exhibited excellent levels of stereoselectivity control, high stability and recyclability.[2-4] To develop more effective chiral auxiliaries, bifunctional C_2-symmetric auxiliaries were investigated,[5-7] allowing for two diastereoselective reactions to occur with the same sense of asymmetric induction on a single substrate molecule; therefore, two molecules of the enantiomerically enriched product can be obtained per molecule of the auxiliary. Given our success in single asymmetric alkylation reactions and the advantage of bifunctional chiral auxiliaries, in this study, we attempted to investigate double asymmetric alkylation reactions by developing C_2-symmetric benzene based bis(2-amino-2-oxazolines) chiral auxiliaries having the following characteristic features. Each of the 2-amino-2-oxazoline rings should exhibit equivalent functions either sterically or stereoelectronically and act as an independent chiral-directing group.

Results and Discussion

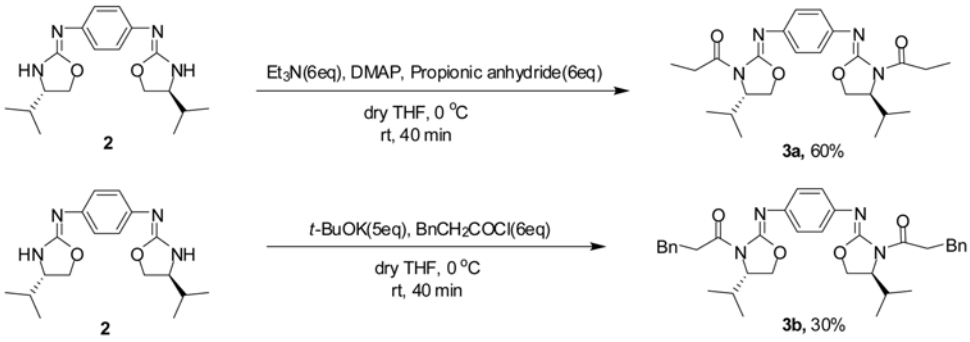
The benzene based bis(thiourea) **1** was synthesized from (*S*)-2-amino-3-methyl-1-butanol and *p*-phenylene diisothiocyanate in good yield (98%). The cyclization of compound **1** according to the previously reported procedure using TsCl/NaOH[2] gave the C_2-symmetric benzene based bis(2-amino-2-oxazoline) chiral auxiliary **2** in 97% yield (Scheme 1).

The *N*-acylations were first carried out by the deprotonation of chiral auxiliary **2** with potassium *tert*-butoxide, and then treated with acyl halides. However, following this procedure, the required products **3a** and **3b** were obtained in low yield (30%). Therefore, we tried to improve this reaction by changing the reaction condition such as using DMAP (1.2 eq.) and Et_3N (6 eq.), and propionic anhydride (6 eq.) at 0 °C. Pleasingly, in this case, the compound **3a** was obtained in 60% yield. Our effort to improve the yield of compound **3b** was unsuccessful (Scheme 2). Theoretically, after acylation reactions, the three regioisomeric *N*,*N*′-endo-endo, *N*,*N*′-endo-exo and *N*,*N*′-exo-exo-acylated products might be formed. The ^{1}H NMR spectra of compounds **3** confirmed the formation of only the *N*,*N*′-endo-endo-acylated products, **3a** and **3b**.[3]

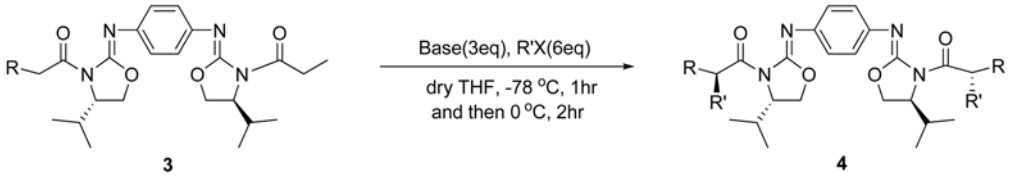
Next, the asymmetric alkylation reactions using **3a** and **3b** were investigated. The formation of the metal enolate at −78 °C using LiHMDS or NaHMDS occurred within 1 h in THF and the subsequent addition of the alkyl halide led to the



Scheme 1. Synthesis of benzene based bis(2-amino-2-oxazolines).



Scheme 2. Acylation of benzene based bis(2-amino-2-oxazolines).



Scheme 3. Asymmetric alkylations using benzene based bis(2-amino-2-oxazolines) chiral auxiliary.

Table 1. Asymmetric alkylations using benzene based bis(2-amino-2-oxazolines)

Entry	Substrate	Base	R	R'	Product	Yield (%)[a]	d.e (%)[b]
1	**3a**	LiHMDS	Me	Bn	**4a**	84	> 99
2	**3a**	LiHMDS	Me	Allyl	**4b**	75	> 99
3	**3a**	NaHMDS	Me	Et	**4c**	17	98
4	**3b**	LiHMDS	Bn	Allyl	**4d**	74	> 99
5	**3b**	LiHMDS	Bn	Me	**4e**	78	70

[a]Isolated yields after column chromatography. [b]Determined by HPLC using chiralcell OD-H column after purification.

formation of the alkylation product with good diastereoselectivity (Scheme 3, Table 1). As the results in Table 1 reveal, the allyl bromide and benzyl bromides proceeded very well to give the required products in high yield and excellent diastereoselectivity (d.e. > 99%) (entries 1-2 and 4). On the other hand, although a somewhat low yield (17%) was observed with ethyl iodide, the diastereoselectivity was found to be almost complete after the treatment with NaHMDS (d.e. 98%) (entry 3). The yield of the ethylation reaction was greatly improved from 17% to 70% by the addition of HMPA (10% v/v) as a co-solvent. However, this resulted in a very low diastereoselectivity of 49:50 in HPLC. In addition, unexpectedly, the methylation reaction, in which it was difficult to control the stereoselectivity, yielded the product **4e** with a d.e. value of 70%. Compared with the same model in the single chiral auxiliary,[3] each of the 2-amino-2-oxazoline rings of the benzene based bis(2-amino-2-oxazolines) chiral auxiliaries **3**, as expected, exhibited equivalent functions, either sterically or stereoelectronically, and acted as an independent chiral-directing group in the cases of benzylation, allylation and ethylation. However, it was more difficult to control the stereoselectivity in the case of methylation.

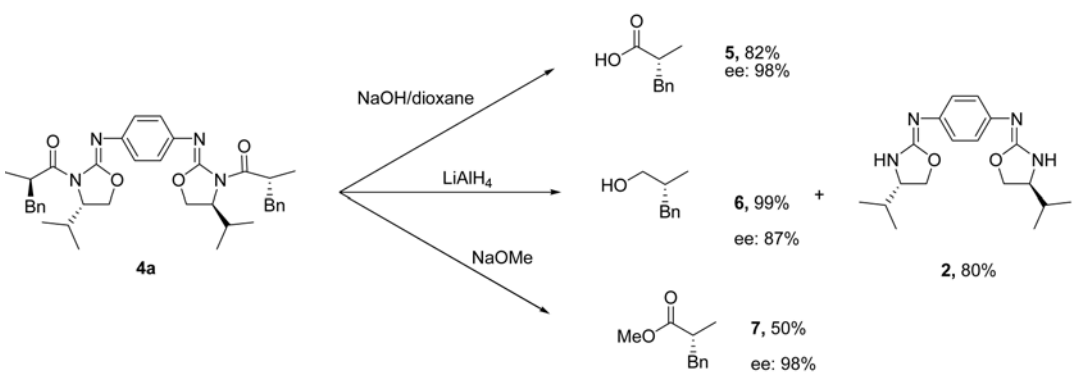
The alkylated product **4a** can be converted to the two stoichiometric ratio derivatives **5-7** (Scheme 4). The treatment with NaOH yielded the chiral carboxylic acid **5** with an e.e. value of 98%, while the treatment with $LiAlH_4$ yielded the chiral alcohol **6** with an e.e. of 87%. The formation of the chiral ester **7** with an excellent e.e value of 98% was also achieved by treating the alkylated products **4a** with sodium methoxide. No racemization occurred under NaOH and NaOMe cleavage conditions. However, using $LiAlH_4$ gave rise to some degree of epimerization in this chiral auxiliary, **4a**.

Conclusions

In summary, the C_2-symmetric benzene based bis(2-amino-2-oxazolines) chiral auxiliaries allowed for high diastereoselectivity control (d.e. > 99%), as in the case of the single chiral auxiliary, except for the methylation reaction (d.e. 70%). After the removal reactions, the two molecules of the enantiomerically enriched chiral acid, alcohol and ester products can be produced per molecule of the auxiliary. No racemization occurred under NaOH and NaOMe cleavage conditions. However, using $LiAlH_4$ gave rise to some epimerization.

Experimental Section

Preparation of Benzene Based Bis(thiourea) 1. To a stirred solution of (*S*)-2-amino-3-methyl-1-butanol (2.2 eq.) in THF under N_2 at room temperature was added a solution of *p*-phenylene diisothiocyanate dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and the solvent evaporated. The crude product was purified by column chromatography to yield product **1** as a white solid. Yield 98%; $[\alpha]_D = -120.1$ (c = 0.1 g/100 mL, CH_3OH); ^1H



Scheme 4. Removal reactions.

NMR (CD_3OD, 300 MHz) δ 7.41 (2H, s), 4.38 (1H, m), 3.71 (2H, d, J = 4.5 Hz), 2.01 (1H, m), 1.01 (6H, t, J = 6.9 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 182.90, 137.37, 126.48, 62.79, 30.32, 20.06, 19.40. HRMS $[M+H]^+$ *m/z* expected for 399.1888, obtained 399.1813.

Preparation of Benzene Based bis(2-amino-2-oxazoline) Chiral Auxiliary 2. To a stirred solution of compound **1** in THF under N_2 at room temperature were added dropwise a solution of NaOH (6 eq.) in H_2O and *p*-toluenesulfonyl chloride (3 eq.) in THF. The resulting mixture was stirred at room temperature for 40 min, quenched with H_2O and extracted with ethyl acetate (30 mL × 3). The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography to yield product **2** as a white solid. Yield 92%; $[\alpha]_D$ = +73.4 (c = 0.1 g/100 mL, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (4H, s), 4.38 (2H, dd, J_1 = 6.8 Hz, J_2 = 8.4 Hz), 4.07 (2H, dd, J_1 = 6.8 Hz, J_2 = 8.4 Hz), 3.74 (2H, dd, J_1 = 6.8 Hz, J_2 = 14.8 Hz), 1.73 (2H, m), 1.01 (6H, d, J = 6.8 Hz), 0.88 (6H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.93, 121.26, 70.28, 65.35, 32.98, 18.64, 17.98; HRMS $[M+H]^+$ *m/z* expected for 331.2134, obtained 331.2136.

Preparation of Benzene Based Bis(*N*-acyl-2-amino-2-oxazoline) 3a. To a solution of compound **2** in dry THF were added DMAP (1.2 eq.) and Et_3N (6 eq.), then propionic anhydride (6 eq.) was added dropwise to the reaction mixture at 0 °C and stirred at 0 for 20 min. The reaction was quenched with saturated aqueous NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (30 mL × 3). The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography to yield product **3a** as a yellow oil. Yield 60%; $[\alpha]_D$ = +141.1 (c = 0.26 g/100 mL, CH_3Cl); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.00 (4H, s), 4.50 (2H, m), 4.18 (4H, d, J = 4.2 Hz), 3.13 (4H, m), 2.32 (2H, m), 1.14 (6H, t, J = 6.0 Hz), 0.93 (12H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.89, 146.66, 141.24, 123.07, 65.34, 59.05, 29.76, 29.19, 18.29, 15.41, 8.74; HRMS $[M+H]^+$ m/z expected for 443.2658, obtained 443.2651.

Preparation of Benzene Based Bis(*N*-acyl-2-amino-2-oxazolines) 3b. To a solution of compound **2** in dry THF was added *t*-BuOK (6 eq.), and then hydrocinnamoyl chloride (6 eq.) was added dropwise to the reaction mixture at 0 °C and stirred at this temperature for 40 min. The reaction was quenched with saturated aqueous NH_4Cl and the organic layer was separated. The aqueous layer was extracted with diethyl ether (30 mL × 3). The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography to yield product **3b** as a yellow oil. Yield 30%; $[\alpha]_D$ = +101.8 (c = 0.19 g/100 mL, CH_3Cl); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (14H, m), 4.76 (2H, m), 4.42 (4H, m), 3.80 (2H, m), 3.66 (2H, m), 3.29 (4H, m), 2.57 (2H, m), 1.18 (12H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.37, 146.64, 141.27, 141.09, 128.55, 128.35, 126.00, 123.23, 65.45, 59.18, 37.65, 31.09, 29.25, 18.40, 15.49; HRMS $[M+H]^+$ *m/z* expected for 595.3284, obtained 595.3269.

Typical Procedure for 'double' Asymmetric Alkylations. To a solution of compound **3** was added dry THF. The solution was cooled to −78 °C, a 1 M solution of the base LiHMDS or NaHMDS (4 eq.) was added, and the solution was stirred at −78 °C for 1 h. Then, the mixture was treated with the alkyl halide (6 eq.). After stirring successively for 1 h at −78 °C and 2 h at −0 °C, the reaction was quenched with saturated aqueous NH_4Cl and the organic layer was separated. The aqueous layer was extracted with diethyl ether (30 mL × 3). The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography to yield the alkylated products **4**.

Compound 4a: Yield 84%; Yellow oil; $[\alpha]_D$ = +100.7 (c = 0.24 g/100 mL, CH_3Cl); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.16 (10H, m), 6.98 (4H, s), 4.60 (2H, m), 4.47 (2H, m), 3.25 (2H, dd, J_1 = 6.9 Hz, J_2 = 13.2 Hz), 2.53 (2H, dd, J_1 = 6.9 Hz, J_2 = 13.2 Hz), 2.12 (2H, m), 1.06 (6H, d, J = 6.9 Hz), 0.81 (6H, d, J = 6.9 Hz), 0.73 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.39, 146.37, 141.31, 139.78, 129.28, 128.13, 126.01, 123.24, 65.17, 59.11, 40.03, 38.83, 29.19, 18.31, 16.02, 15.31; HRMS $[M+H]^+$ *m/z* expected for 623.3597, obtained 623.3588; diastereomeric excess 99% determined by HPLC using chiralcell OD-H column, eluent *n*-hexane/*i*-PrOH 10:1 v/v, flow rate 0.5 mL/min, detection at 254 nm, retention time 15.8 min (major) and 19.9 min (minor).

Compound 4b: Yield 75%; Yellow oil; $[\alpha]_D$ = +151.1 (c = 0.215 g/100 mL, CH_3Cl); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.03 (4H, s), 5.86 (2H, m), 5.06 (4H, m), 4.54 (2H, dd, J_1 = 4.6 Hz, J_2 = 9.0 Hz), 4.33 (2H, m), 4.24 (4H, d, J = 4.6 Hz), 2.63 (2H, m), 2.23 (4H, m), 1.16 (6H, d, J = 6.8 Hz), 0.92 (12H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.32, 146.20, 141.26, 136.10, 123.23, 116.49, 65.26, 59.09, 38.25, 36.82, 29.29, 18.37, 15.92, 15.52; HRMS $[M+H]^+$ *m/z* expected for 523.3284, obtained 523.3254; diastereomeric excess 99% determined by HPLC using chiralcell OD-H column, eluent *n*-hexane/*i*-PrOH 10:1 v/v, flow rate 0.4 mL/min, detection at 254 nm, retention time 13.2 min (major) and 16.8 min (minor).

Compound 4c: Yield 17%; Yellow oil; $[\alpha]_D$ = +175.3 (c = 0.047 g/100 mL, CH_3Cl); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.03 (4H, s), 4.56 (2H, dd, J_1 = 4.5 Hz, J_2 = 9.3 Hz), 4.17 (6H, m), 2.30 (2H, m), 1.91 (2H, m), 1.49 (2H, m), 1.16 (6H, d, J =6.9 Hz), 0.96 (18H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.13, 146.24, 141.36, 123.21, 65.26, 59.09, 38.56, 29.37, 27.19, 18.40, 15.83, 15.56, 11.54; HRMS $[M+H]^+$ *m/z* expected for 499.3284, obtained 499.32221; diastereomeric excess 99% determined by HPLC using chiralcell OD-H column, eluent *n*-hexane/*i*-PrOH 30:1 v/v, flow rate 0.3 mL/min, detection at 254 nm, retention time 24.2 min (minor) and 28.2 min (major).

Compound 4d: Yield 74%; Yellow oil; $[\alpha]_D$ = +97.0 (c = 0.12 g/100 mL, CH_3Cl); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22 (10H, m), 6.98 (4H, s), 5.91 (2H, m), 5.10 (4H, m), 4.97 (2H, m), 4.30 (2H, m), 4.0 (2H, dd, J_1 = 1.0 Hz, J_2 = 8.7 Hz),

3.73 (2H, q, J = 8.7 Hz), 2.95 (2H, dd, J_1 = 7.2 Hz, J_2 = 13.2 Hz), 2.83 (2H, dd, J_1 = 7.2 Hz, J_2 = 13.2 Hz), 2.61 (2H, m), 2.35 (2H, m), 2.2 (2H, m), 0.87 (12H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.14, 146.34, 141.16, 139.73, 135.81, 129.10, 128.17, 126.10, 123.18, 116.64, 65.30, 59.24, 43.11, 38.38, 36.72, 29.44, 18.37, 15.71; HRMS $[M+H]^+$ m/z expected for 675.3910, obtained 675.3915; diastereomeric excess 99% determined by HPLC using chiralcell OD-H column, eluent *n*-hexane/*i*-PrOH 20:1 v/v, flow rate 0.5 mL/min, detection at 254 nm, retention time 16.5 min (minor) and 17.3 min (major).

Compound 4e: Yield 78%; Yellow oil; $[\alpha]_D$ = +86.7 (c = 0.09 g/100 mL, CH_3Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (14H, m), 4.72 (21H, m), 4.34 (2H, m), 4.05 (2H, dd, J_1 = 1.2 Hz, J_2 = 8.7 Hz), 3.84 (2H, t, J = 8.7 Hz), 3.04 (2H, dd, J_1 = 8.1 Hz, J_2 = 13.2 Hz), 2.71 (2H, dd, J_1 = 8.1 Hz, J_2 = 13.2 Hz), 2.25 (2H, m), 1.27 (6H, d, J = 7.0), 0.90 (12H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.50, 146.46, 141.29, 139.93, 129.10, 128.21, 126.09, 123.19, 65.37, 59.30, 40.28, 38.73, 29.44, 18.40, 17.40, 15.69; HRMS $[M+H]^+$ *m/z* expected for 623.3597, obtained 623.3599; diastereomeric excess 70% determined by HPLC using chiralcell OD-H column, eluent *n*-hexane/*i*-PrOH 10:1 v/v, flow rate 0.5 mL/min, detection at 254 nm, retention time 15.6 min (minor) and 18.1 min (major).

Preparation of Chiral Acid 5. To a solution of compound **4a** in 1,4 dioxane was added excess 2 M NaOH in H_2O. The reaction mixture was refluxed for 20 min at 100 °C. After that, the reaction mixture was extracted with ethyl acetate (30 mL × 3) to recover the chiral auxiliary. The aqueous layer was acidified with 30 wt % HCl to pH ~ 2 and extracted with ethyl acetate (30 mL × 3) to obtain the requisite product **5** as a colorless oil after purifying by column chromatography. Yield 82%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (5H, m), 3.08 (1H, dd, J_1 = 6.8 Hz, J_2 = 13.1 Hz), 2.72 (2H, m), 1.18 (3H, d, J = 6.8 Hz); The enantiomeric purity was determined by HPLC to be 98% after conversion to **7** with CH_2N_2.

Preparation of Chiral Alcohol 6. To a solution of compound **4a** in dry THF was added 1 M $LiAlH_4$ (4 eq) in THF at 0 °C. Then, the reaction mixture was warmed to room temperature and allowed to react for 12 hr. The excess of $LiAlH_4$ was quenched with water, aqueous 2 M sodium hydroxide, and water in sequence. The reaction mixture was filtered off and washed with dichloromethane. The filtrate was dried over magnesium sulfate and the solvent evaporated. The crude product was purified by column chromatography to give the requisite product **6** as a colorless oil. Yield 99%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (5H, m), 3.51 (2H, m), 2.76 (1H, dd, J_1 = 6.3 Hz, J_2 = 13.4 Hz), 2.43 (1H, dd, J_1 = 8.0 Hz, J_2 = 13.4 Hz), 1.95 (1H, m), 0.92 (3H, d, J = 6.3 Hz); enantiomeric excess 87% determined by HPLC using chiralcell OD-H column, eluent *n*-hexane/*i*-PrOH 10:1 v/v, flow rate 0.5 mL/min, detection at 254 nm, retention time 10.4 min (minor) and 11.8 min (major).

Preparation of Chiral Ester 7. To a solution of compound **4a** in dry THF was added 0.5 M $LiAlH_4$ (4 eq) in MeOH at 0 °C. Then, the reaction mixture was warmed to room temperature and reacted for 12 h. The reaction mixture was quenched by adding saturated NH_4Cl, filtered and the filtrate was evaporated to remove the THF and extracted with dichloromethane. The filtrate was dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography to give the requisite product **8** as a colorless oil. Yield 50%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (5H, m), 3.64 (3H, s), 3.03 (1H, dd, J_1 = 6.2 Hz, J_2 = 12.7 Hz), 2.70 (2H, m), 1.15 (3H, d, J = 6.2 Hz); enantiomeric excess 98% determined by HPLC using chiralcell OD-H column, eluent *n*-hexane/*i*-PrOH 10:1 v/v, flow rate 0.3 mL/min, detection at 254 nm, retention time 15.3 min (minor) and 17.0 min (major).

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