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New Bifunctional Substrates for Copper-Catalyzed Asymmetric Conjugate Addition Reactions with Trialkylaluminium

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Trialkylaluminium reagents have been found to undergo a copper-catalyzed asymmetric conjugate addition (ACA) reaction with oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylates with the simultaneous creation of two stereocenters. Different types of ligands were tested, and chiral phosphoramidite ligands allowed the reaction to proceed with good yields and good to excellent enantioselectivity. The *syn* substitution product observed by X-ray analysis suggests an *exo* attack of the nucleophile. Herein we report the results obtained in the development of this copper-catalyzed ACA methodology, which affords an all-carbon quaternary center with unsubstituted and substituted oxacyclic Michael acceptors. The study was completed by mechanistic investigations performed to elucidate the original reaction pathway.

Introduction

The asymmetric conjugate addition (ACA) reaction is nowadays a mature methodology.[1] In particular, the rhodium-[1c] and copper-catalyzed ACA reactions are very efficient with both cyclic and acyclic Michael acceptors and either Zn, Al, or Mg organometallic reagents.[2] However, there are still some aspects that need to be clarified, for example, difunctionalized substrates have scarcely been studied. Although geminally difunctionalized substrates, such as alkylidenemalonates, afford good yields and enantioselectivities,[3] there is only a single example of the reaction of an alkene with the electron-withdrawing groups at both ends of the double bond, for example, fumarates or related substrates.[4]

Fumarates are excellent substrates for Diels–Alder reactions. It was expected that they would be particularly suitable for copper-catalyzed ACA reactions. Indeed, when diethyl fumarate (**1**) was treated with diethylzinc with just $Cu(OTf)_2$ as the catalyst for racemate formation, a quantitative yield was obtained at –40 °C in toluene. When the reaction was tested with a chiral phosphoramidite ligand (see Figure 1), the reaction was slower, and the best enantioselectivity (33% *ee*) was obtained with **L6**. As we suspected a competitive radical achiral pathway,[5] we repeated these experiments in the presence of isopropyl iodide as a radical probe.[6] Two thirds of the resulting adducts were the isopropyl adduct, instead of the ethyl adduct (Scheme 1).

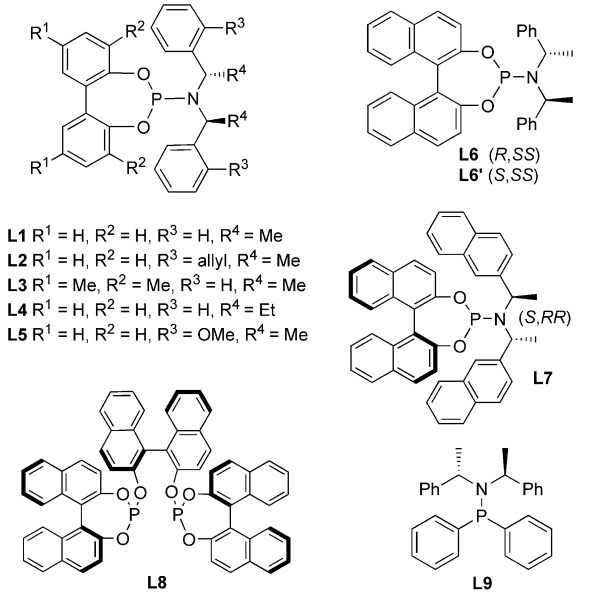
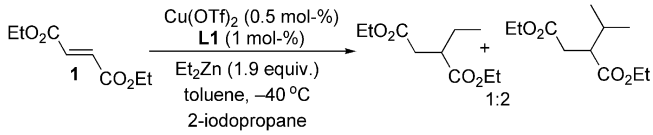


Figure 1. Chiral ligands **L1**–**L9**.



Scheme 1. Addition of diethylzinc to diethyl malonate: radical pathway.

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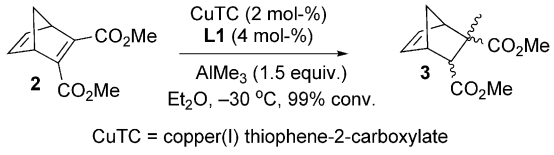
The same reaction with diethyl maleate gave similar results, but it was a much slower reaction in which the (*Z*) double bond was isomerized to an (*E*) double bond, as detected by GC–MS analysis.[7]

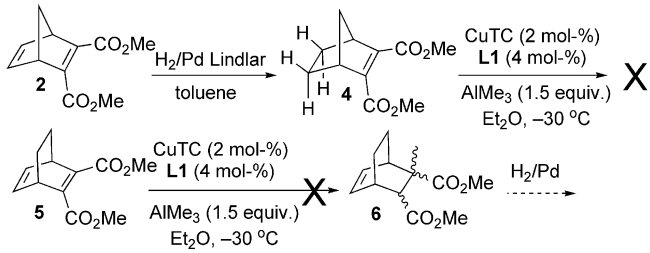
As fumarate-type substrates were not as reactive as expected, we turned our attention to more strained compounds in the hope of higher reactivity. Norbornadiene-type substrates offer such an opportunity. Substrate **2** was easily synthesized by Diels–Alder reaction of cyclopentadiene and dimethyl acetylenedicarboxylate, and was submitted to our previously described reaction conditions in the presence of diethylzinc and a copper catalyst.[8] However, only the reduced product was obtained, probably through a single-electron transfer (SET) process. To overcome this problem, alkylaluminium reagents were used instead of organozinc reagents. R_3Al reagents have been used in our group to overcome the steric hindrance in multisubstituted substrates by Lewis acid activation.[9] The copper-catalyzed 1,4-addition of trimethylaluminium to substrate **2** (Scheme 2) proceeded with complete conversion to afford **3** as a mixture of isomers as a result of the nonselective *endo*/*exo* attack of the nucleophile followed by a nonselective protonation.



Scheme 2. Addition of trimethylaluminium to **2**.

The same experiment was repeated in the presence of 6 equiv. of isopropyl iodide to determine whether the reaction proceeded by a radical pathway. The absence of the isopropyl adduct confirmed a non-radical pathway. A reaction under similar conditions without the copper/ligand system did not lead to the product, and the starting material was recovered, which shows that the catalyst was needed. Note that this reaction afforded an all-carbon quaternary center, a synthetic challenge in ACA.[10]

To increase the steric bias between the *endo* and *exo* face, **2** was partially hydrogenated to **4** with the Pd/Lindlar catalyst. The two axial hydrogen atoms should prevent an *endo* attack of the nucleophile. However, no reaction took place when the addition reaction was performed (Scheme 3). It seems that a partial release of the ring-strain in **4** could explain such a lack of reactivity. Another way to overcome the problem of selectivity between the *endo*/*exo* faces was to test a slightly different substrate such as **5** (Scheme 3). In this case, the potential adduct **6** obtained after the conjugate addition could be hydrogenated with loss of the *endo*/*exo* notion. However, here again no conjugate addition took place at all.



Scheme 3. Conjugate addition to hydrogenated norbornadiene substrates.

As the *endo*/*exo* attack of the nucleophile could not be controlled by steric hindrance, we thought that coordination effects could be more effective. If the bridging methylene group could be replaced by an oxygen atom, we could expect an efficient coordination to Al, which would favor an *exo* approach of the nucleophile (Figure 2).

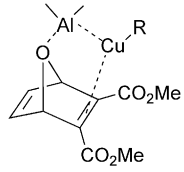
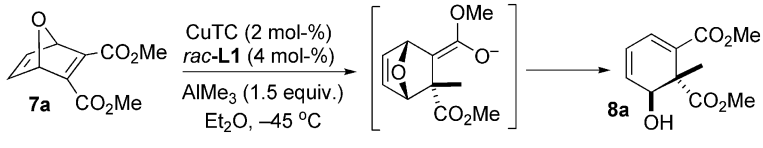


Figure 2. Coordination of Al to an oxanorbornadiene substrate.

Results and Discussion

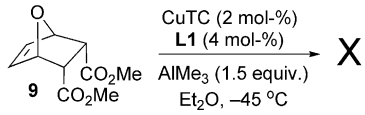
To the best of our knowledge, the asymmetric conjugate addition reaction with oxygen-bridged substrates has not been reported previously. However, some examples of the asymmetric copper-catalyzed ring-opening of oxabicyclo[2.2.1]alkenes, leading to an *anti* stereoselectivity as a result of *endo* attack of the nucleophile, have been reported.[11] Mechanistically, these results represent an *anti* γ-allylic substitution of the heterobicyclic alkene, which is typical in organocopper chemistry.[12] Most other transition-metal-catalyzed reactions afford the *syn* substitution product.[13]

Substrate **7a** was easily prepared by a Diels–Alder reaction between furan and dimethyl acetylenedicarboxylate, and was submitted to our ACA standard reaction conditions (Scheme 4). The reaction afforded, after quenching with an acidic aqueous solution, a single product **8a**, which is a result of the conjugate addition of a methyl group followed by opening of the oxacycle.



Scheme 4. ACA reaction of oxygen-bridged substrate **7a**.

The *syn* relationship of the incoming methyl group and the hydroxy moiety corresponds to our anticipated coordination of the oxygen bridge and Me_3Al. This product **8a** cannot arise from an allylic substitution mechanism because the stereochemical relationship should be opposite.[12] Neither was any product arising from attack on the least-substituted double bond detected. Additional proof was sought by performing the reaction with substrate **9** (Scheme 5), which lacks the double bond between the two ester functionalities. No reaction took place at all.



Scheme 5. Addition of $AlMe_3$ to substrate **9**.

In an effort to optimize this reaction, several copper salts and ligands were tested for the asymmetric addition of trimethylaluminium to substrate **7a**. First the reaction was performed with different copper salts in the presence of chiral phosphoramidite ligand **L1** (Table 1). Diethyl ether was used as the solvent at –45 °C, which is the optimum temperature for this reaction. Although the ACA reaction could be performed in THF, in some cases this solvent did not lead to complete conversion at this temperature, and the enantioselectivity was lower. Although the use of copper(I) chloride or bromide (Entries 1 and 2) allowed complete conversion of **7a** to **8a** in 30 min, the enantiomeric excesses were less than 60%. The use of copper(II) acetate or triflate (Entries 3 and 4) led to 70% *ee*, with the best enantiomeric excess of 73% being obtained in the presence of 2 mol-% of $Cu(CH_3CN)_4BF_4$.

Table 1. Optimisation of the copper catalyst with **L1**.

Entry	Copper salt	Conversion [%][a]	*ee* [%][b]
1	CuCl	99	56
2	CuBr	99	59
3	$Cu(OAc)_2 \cdot H_2O$	99	71
4	$Cu(OTf)_2$	99	70
5	CuTC	98	70
6	$Cu(CH_3CN)_4BF_4$	99	73
7	$Cu(CH_3CN)_4PF_6$	99	71

[a] Determined by GC–MS analysis. [b] Determined by chiral GC analysis.

The previously described reaction conditions were then used with different ligands to increase the enantioselectivity (Table 2). Different phosphoramidite ligands were tested (Entries 1–10) in a 2:4 copper/ligand ratio (other ratios did not give better results). These experiments demonstrated that substitution at the *ortho* position of the biphenol group (**L1** vs. **L3**) led to a decrease in the enantioselectivity. The presence of a methoxy group on the amine part of the ligand also led to a decrease in the enantioselectivity (**L1** vs. **L5**). When binaphthol ligands were used (**L6**/**L6′**) a match/mismatch effect was observed: The (*R*,*SS*) diastereoisomer afforded 90% *ee*, whereas the (*S*,*SS*) diastereoisomer led to complete conversion but to an enantiomeric excess of 48%. Replacing the phenyl group with a 2-naphthyl group on the amine part of the ligand (**L7**) increased this enantiomeric excess to 93%. Other types of ligands were also tested in this reaction, for example, the Simplephos ligand **L9**,[14] which has already been reported in the copper-catalyzed asymmetric conjugate addition of triethylaluminium to cyclohexenone, and the phosphite ligand **L8** described by Chan and co-workers.[15] However, the desired product **8a** was obtained with enantiomeric excesses of only 19 and 31%, respectively.

Table 2. Optimisation of the ligand with the $Cu(CH_3CN)_4BF_4$ catalyst.

Entry	Ligand	Conversion [%][a]	*ee* [%][b]
1	**L1**	99	73
2	**L2**	73	6
3	**L3**	91	45
4	**L4**	98	53
5	**L5**	99	11
6	**L6**	98	90
7	**L6′**	99	48
8	**L7**	99	93
9	**L8**	99	31
10	**L9**	99	19

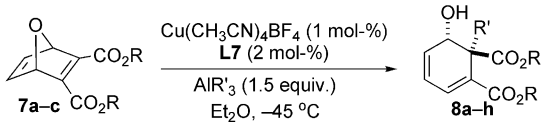
[a] Determined by GC–MS analysis. [b] Determined by GC chiral analysis.

These optimized reaction conditions were then applied to different oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate substrates **7** to establish the scope of this methodology; the results are summarized in Table 3. Several esters were tested with trimethylaluminium as nucleophile. The best enantiomeric excesses were obtained with methyl ester **7a** (Entry 1) and ethyl ester **7b** (Entry 2), which gave 93 and 96% *ee*, respectively, and isolated yields of 95 and 81%. Although the reaction performed with triethylaluminium allowed the products **8e** and **8h** to be obtained in yields of up to 90%, the enantiomeric excesses were lower than those obtained with trimethylaluminium. The addition of triisobutylaluminium to **7a** enabled the isolation of **8g** in 73% yield but with a disappointing 60% *ee*. Commercially available $Al(n\text{Pr})_3$ and $Al(n\text{Bu})_3$ were also used in this methodology, giving good yields and moderate enantioselectivities (Entries 6 and 7).

The product **8a** had to be derivatized with a heavy atom to determine its absolute stereochemistry. The corresponding *p*-chlorobenzoate **10** could be formed, but the crystals were not suitable for X-ray analysis. Finally, a Diels–Alder reaction of **10** to form 4*H*-1,2,4-triazole-3,5-dione **11** allowed us to obtain this information (Figure 3). The structure clearly shows the *syn* relative stereochemistry between the hydroxy and methyl groups.

Other similar substrates were also tested. Thus, **7a** was partially hydrogenated to **12** with the H_2/Pd Lindlar catalyst. However, as for **4**, no subsequent ACA reaction took place (Scheme 6). This result again stresses the importance of ring-strain in these substrates.

Table 3. Scope of the reaction.



Entries	R	Substrate	R′	Product, yield [%]	*ee* [%][a]
1	Me	**7a**	Me	**8a**, 95	93 (*SS*)
2	Et	**7b**	Me	**8b**, 81	96 (*SS*)
3	*i*Pr	**7c**	Me	**8c**, 73	67 (*SS*)
4	Me	**7a**	Et	**8d**, 90	73 (*SS*)
5[b]	Me	**7a**	*n*Pr	**8e**, 82	55 (*RR*)
6[b]	Me	**7a**	*n*Bu	**8f**, 79	74 (*RR*)
7[b]	Me	**7a**	*i*Bu	**8g**, 73	60 (*RR*)
8	Et	**7b**	Et	**8h**, 92	68 (*SS*)

[a] Determined by chiral GC. [b] (*S*,*RR*)-**L7**.

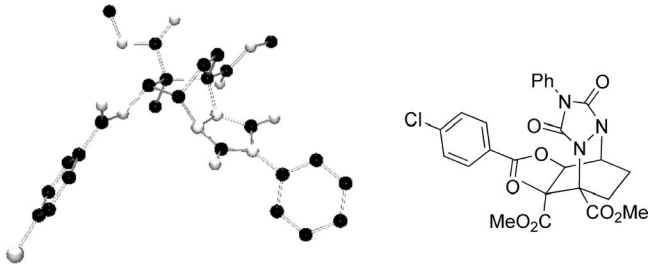
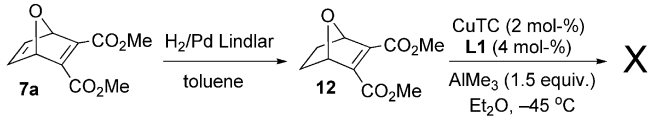
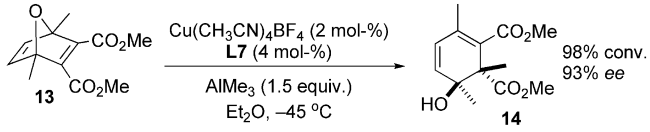


Figure 3. ORTEP diagram of compound **11**.[16]



Scheme 6. ACA reaction of partially hydrogenated **7a**.

On the other hand, the sterically more crowded substrate **13**, with two Me groups at the bridgehead but with the same ring-strain, reacted in quantitative yield and excellent (93%) enantioselectivity (Scheme 7). Only one diastereomer was observed. Interestingly, **14** has two adjacent quaternary centers!



Scheme 7. ACA reaction of **13**.

As this adduct was isolated as a solid, the *syn* relative relationship between the hydroxy and methyl groups was confirmed by X-ray analysis (Figure 4).

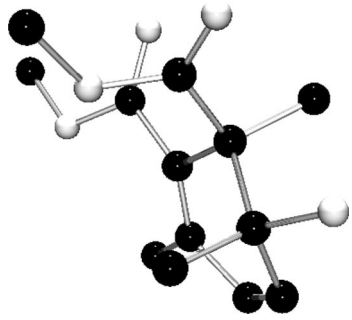
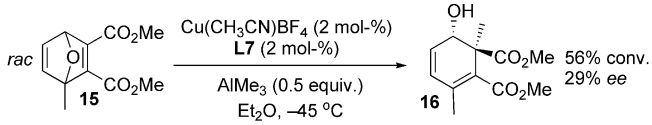


Figure 4. ORTEP diagram of compound **14**.[16]

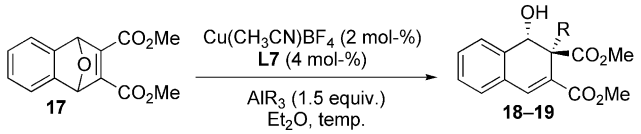
The application of the ACA methodology to the corresponding monosubstituted substrate was more problematic. The substrate **15** (Scheme 8), synthesized by a Diels–Alder reaction, presents one stereogenic center, so the only way to obtain an enantiomerically enriched reaction product was by kinetic resolution of the racemic mixture. Unfortunately, the ACA of 0.5 equiv. of trimethylaluminium to compound **15** (Scheme 8) gave only 50% conversion and a poor 29% *ee*. However, the reaction was completely regioselective, the ACA occurring at the least-substituted position.



Scheme 8. ACA reaction of substrate **15**.

To complete this study, the aromatic bicyclic compound **17** was tested. This substrate retains the same ring-strain, but proved quite unreactive at –45 °C (Table 4, Entry 1). However, complete conversion could be obtained with an enantiomeric excess of 74% (Entry 2) by raising the temperature to –10 °C. The optimum conditions for this substrate were obtained when the temperature was increased to 0 °C, giving the best enantiomeric excess (Entry 3). Under the same reaction conditions, triethylaluminium gave product **19** in 82% yield and with a moderate 56% *ee* (Entry 4). Finally, it should be mentioned that under these reaction

Table 4. ACA to substrate **17**.



Entry	R	Temperature [°C]	Product, conversion [%][a]	*ee* [%][b]
1	Me	–45	0	–
2	Me	–10	**18**, 98	74
3	Me	0	**18**, 98 (85)	80
4	Et	0	**19**, 98 (82)	56

[a] Isolated yields are given in parentheses. [b] Determined by chiral HPLC or chiral SFC.

conditions with trimethylaluminium no addition took place with simple oxabenzonorbornadiene (that is, without the ester groups).[17]

Conclusions

We have reported herein a new class of substrates for the copper-catalyzed asymmetric conjugate addition reaction. The methodology allows the generation of two or more stereocenters, one of which is quaternary, in one step. The reaction gives good yields and enantiomeric excesses. We have demonstrated that the ring-strain is necessary for the reaction, and we realized control experiments to illustrate the mechanistic pathway. Finally, the *syn* relative stereochemistry of the products indicates a conjugate addition/elimination mechanism rather than an allylic substitution.

Experimental Section

General: ^{1}H (400 or 300 MHz) and ^{13}C (100 or 300 MHz) NMR spectra were recorded with a Bruker 400 FT or 300 FT NMR spectrometer in $CDCl_3$. The chemical shifts (δ) are given in ppm relative to residual $CHCl_3$, and coupling constants are reported in Hz. The multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), br. s (broad singlet). Mass spectra (MS) were obtained by EI (70 eV) and high-resolution mass spectrometry. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter at 20 °C in a 10 cm cell in $CHCl_3$. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentrations c are given as g/100 mL). IR spectra were recorded neat with a Perkin–Elmer Spectrum One IR spectrometer. Enantiomeric excesses were determined by chiral GC with either an HP6890 or an HP6850 apparatus with the stated column and H_2 as the vector gas. Temperature programs are described as follows: Initial temperature [°C]–initial time [min]–temperature gradient [°C min^{-1}]–final temperature [°C]; retention times (T) are given in min. Enantiomeric excesses were in some cases determined by chiral-SFC measurements with the stated column, except for product **18** which was analyzed by HPLC. Gradient programs are described as follows: Initial methanol concentration [%]–initial time [min]–percent gradient of methanol (% min^{-1})–final methanol concentration [%]; retention times (T) are given in min. Flash chromatography was performed by using silica gel 60 Å. All the reactions were performed in anhydrous solvents, dried by filtration over activated alumina.

General Protocol for the Copper-Catalyzed Asymmetric Conjugate Addition of Trialkylaluminium: The copper salt (0.001 mmol) and ligand (0.002 mmol) were suspended in dry diethyl ether (1 mL) under nitrogen. The suspension was stirred at room temperature for 30 min and then cooled to –45 °C. Trialkylaluminium (1.5 mmol) was added, and then the substrate (1 mmol) in diethyl ether (1 mL) was added dropwise. The reaction mixture was stirred for 1 h and then warmed to room temperature. The reaction mixture was cooled to 0 °C and quenched with a solution of 1 N HCl (0.5 mL). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography by using the indicated solvent.

Procedure for the Synthesis of the 4-Phenyl-4*H*-1,2,4-triazole-3,5-dione Diels–Alder Adduct of Dimethyl 6-(4-Chlorobenzoyloxy)-1-methylcyclohexa-2,4-diene-1,2-dicarboxylate (11): Triethylamine (20 mL, 1.42 mmol) in dry dichloromethane (5 mL) was added to dimethyl 6-hydroxy-1-methylcyclohexa-2,4-diene-1,2-dicarboxylate (**8a**; 1.146 g, 0.65 mmol) under nitrogen. The solution was cooled to 0 °C, and 4-chlorobenzoyl chloride (0.09 mL, 0.65 mmol) was added dropwise over 2 min. The mixture was stirred at 0 °C for 30 min and then at reflux temperature for 5 h. The solution was then stirred at room temperature overnight. Additional 4-chlorobenzoyl chloride (0.05 mL, 0.36 mmol) was then added dropwise over 2 min, and the resulting mixture was heated at reflux 1 h. The solution was then poured into water, and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried with $MgSO_4$, and the solvent was evaporated under reduced pressure to give 0.331 g of a brown paste. The crude product was purified by flash chromatography on silica gel (diethyl ether/pentane, 4:6) to afford 193 mg (81% yield) of **10** (R_f = 0.35). Dimethyl 6-(4-chlorobenzoyloxy)-1-methylcyclohexa-2,4-diene-1,2-dicarboxylate (45 mg, 0.12 mmol) and 4-phenyl-4*H*-1,2,4-triazole-3,5-dione (21.6 mg, 0.12 mmol) were dissolved in toluene. The mixture was stirred at room temperature for 4 h and heated at 62 °C overnight. The product was purified by flash chromatography on silica gel, and the white solid was recrystallized in ethyl acetate. One suitable crystal was submitted to X-ray diffraction analysis.

Dimethyl 6-Hydroxy-1-methylcyclohexa-2,4-diene-1,2-dicarboxylate (8a): The title compound was prepared from dimethyl 7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**7a**; 0.210 g, 1.00 mmol) according to the ACA general procedure.[18] The desired alcohol was obtained as a yellow oil (0.214 g, 95% yield) after flash chromatography (diethyl ether/pentane, 4:6). R_f = 0.60. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96–6.94 (m, 1 H), 6.05–5.96 (m, 2 H), 5.06 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 1.84 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 1.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 166.8, 137.4, 133.2, 132.4, 122.7, 74.5, 52.9, 52.2, 52.2, 11.8 ppm. HRMS: calcd. for $C_{11}H_{14}O_5Na$ 247.0733; found 249.0726. $[\alpha]_D^{20}$ = +8.16 (c = 1.02, $CHCl_3$). Enantiomer separation: Hydrodex-B-6-TBDM (25 m, H_2, 40 cm s^{-1}): 80–0-1–170–25; T_1 = 70.9, T_2 = 71.46.

Diethyl 6-Hydroxy-1-methylcyclohexa-2,4-diene-1,2-dicarboxylate (8b): The title compound was prepared from diethyl 7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**7b**; 0.238 g, 1.00 mmol) according to the ACA general procedure.[19] The desired alcohol was obtained as a yellow oil (0.211 g, 83% yield) after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.65. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94–6.92 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 6.03–5.94 (m, 1 H), 5.97–5.94 (m, 1 H), 5.04–5.02 (m, 1 H), 4.25–4.13 (m, 4 H), 1.88–1.86 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 1.35 (s, 3 H), 1.29–1.23 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2, 166.1, 136.4, 133.3, 131.6, 122.5, 74.3, 61.3, 60.8, 51.9, 14.2, 14.1, 11.5 ppm. IR (neat): $\tilde{\nu}$ = 3460, 2982, 1706, 1257, 1102, 1024, 643 cm^{-1}. HRMS calcd. for $C_{13}H_{18}O_5Na$ 277.1046; found 277.1049. $[\alpha]_D^{20}$ = +19.8 (c = 0.7, $CHCl_3$). Enantiomer separation: Hydrodex-B-6-TBDM (25 m, H_2, 40 cm s^{-1}): 80–0-1–170–25; T_1 = 77.44, T_2 = 78.58.

Diisopropyl 6-Hydroxy-1-methylcyclohexa-2,4-diene-1,2-dicarboxylate (8c): The title compound was prepared from diisopropyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[20] (**7c**; 0.266 g, 1.00 mmol) according to the ACA general procedure. The desired alcohol was obtained as a yellow oil (0.206 g, 73% yield) after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.60.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88–6.87 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 6.02–5.97 (m, 1 H), 5.96–5.92 (m, 1 H), 5.10–5.01 (m, 2 H), 4.99–4.97 (m, 1 H), 1.82 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 1.34 (s, 3 H), 1.27–1.21 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 165.7, 135.9, 133.6, 131.1, 122.6, 74.3, 68.6, 68.3, 51.9, 21.9, 21.8, 21.8, 21.6, 11.6 ppm. IR (neat): $\tilde{\nu}$ = 3460, 2971, 1703, 1257, 1099, 1010, 715 cm^{-1}. HRMS: calcd. for $C_{15}H_{23}O_5$ 283.1540; found 283.1548. $[\alpha]_D^{20}$ = +3.89 (c = 1.5, $CHCl_3$). Enantiomer separation: Hydrodex-B-6-TBDM (25 m, H_2, 40 cm s^{-1}): 80–0-1–170–25; T_1 = 78.65, T_2 = 79.42.

Dimethyl 1-Ethyl-6-hydroxycyclohexa-2,4-diene-1,2-dicarboxylate (8d): The title compound was prepared from dimethyl 7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**7a**; 0.210 g, 1.00 mmol) according to the ACA general procedure.[17] The desired alcohol was obtained as a yellow oil (0.216 g, 90% yield) after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.62. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 6.01–5.90 (m, 2 H), 5.18 (br. s, 1 H), 3.74 (s, 3 H), 3.73 (m, 3 H), 2.25–2.12 (m, 1 H), 1.96–1.84 (m, 2 H), 0.91 (t, $^3J_{H,H}$ = 3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2, 166.1, 136.4, 133.3, 131.6, 122.5, 74.3, 61.3, 60.8, 51.9, 14.2, 14.1, 11.5 ppm. IR (neat): $\tilde{\nu}$ = 3471, 2975, 1699, 1255, 1095, 718 cm^{-1}. $[\alpha]_D^{20}$ = +29.76 (c = 1.36, $CHCl_3$). Enantiomer separation: Hydrodex-B-6-TBDM (25 m, H_2, 40 cm s^{-1}): 80–0-1–170–25; T_1 = 74.73, T_2 = 76.71.

Dimethyl 6-Hydroxy-1-propylcyclohexa-2,4-diene-1,2-dicarboxylate (8e): The title compound was prepared from dimethyl 7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**7a**; 0.210 g, 1.00 mmol) according to the ACA general procedure.[18] The desired alcohol was obtained as a yellow oil (0.208 g, 82% yield) after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.58. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 5.99–5.91 (m, 2 H), 5.17 (br. s, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 2.07 (td, $^3J_{H,H}$ = 4, $^3J_{H,H}$ = 14 Hz, 1 H), 1.89 (br. s, 1 H), 1.84 (td, $^3J_{H,H}$ = 4, $^3J_{H,H}$ = 14 Hz, 1 H), 1.54–1.45 (m, 1 H), 1.36–1.27 (m, 1 H), 0.86 (t, $^3J_{H,H}$ = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 166.7, 137.6, 133.6, 130.4, 122.1, 74.8, 54.6, 52.5, 51.9, 29.8, 18.6, 15.0 ppm. IR (neat): $\tilde{\nu}$ = 3466, 2953, 1712, 1435, 1264, 1064, 759 cm^{-1}. HRMS: calcd. for $C_{13}H_{18}O_5Na$ 277.1046; found 277.1040. $[\alpha]_D^{20}$ = –5.4 (c = 1.06, $CHCl_3$). Enantiomer separation: SFC OD-H (30 °C, 200 bar, 2 mL min^{-1}): 5–2–1–15%; T_1 = 3.85, T_2 = 4.76.

Dimethyl 1-Butyl-6-hydroxycyclohexa-2,4-diene-1,2-dicarboxylate (8f): The title compound was prepared from dimethyl 7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**7a**; 0.210 g, 1.00 mmol) according to the ACA general procedure.[17] The desired alcohol was obtained as a yellow oil (0.211 g, 79% yield) after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.58. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 6.00–5.90 (m, 2 H), 5.17 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 2.16–2.06 (m, 1 H), 1.90–1.76 (m, 2 H), 1.29–1.18 (m, 3 H), 0.86 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6, 166.7, 137.6, 133.6, 130.4, 122.1, 74.7, 54.6, 52.5, 51.9, 27.3, 27.2, 23.7, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 3489, 2956, 1709, 1434, 1253, 1064, 727 cm^{-1}. HRMS: calcd. for $C_{14}H_{20}O_5Na$ 291.1202; found 291.1208. $[\alpha]_D^{20}$ = –29.0 (c = 0.7, $CHCl_3$). Enantiomer separation: SFC OD-H (30 °C, 200 bar, 2 mL min^{-1}): 5–2–1–15; T_1 = 3.87, T_2 = 4.93.

Dimethyl 6-Hydroxy-1-isobutylcyclohexa-2,4-diene-1,2-dicarboxylate (8g): The title compound was prepared from dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**7a**; 0.210 g, 1.00 mmol) according to the ACA general procedure.[18] The desired alcohol was obtained as a yellow oil (0.195 g, 73% yield) after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.59. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, $^3J_{H,H}$ = 4 Hz, 1 H), 6.03–5.94 (m, 2 H), 5.15 (br. s, 1 H), 3.73 (s, 6 H), 2.00–1.77 (m, 4 H), 0.90 (d, $^3J_{H,H}$ = 6 Hz, 3 H), 0.82 (d, $^3J_{H,H}$ = 6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.9, 167.0, 138.0, 134.0, 131.3, 122.6, 75.4, 55.0, 52.8, 52.3, 35.0, 25.7, 25.6, 24.3 ppm. IR (neat): $\tilde{\nu}$ = 3489, 2956, 1709, 1434, 1253, 1064, 727 cm^{-1}. HRMS: calcd. for $C_{14}H_{20}O_5$ 268.1307; found 268.1310. $[\alpha]_D^{20}$ = –3.87 (c = 1.06, $CHCl_3$). Enantiomer separation: Hydrodex-B-6-TBDM (25 m, H_2, 40 cm s^{-1}): 80–0-1–170–25; T_1 = 79.24, T_2 = 79.95.

Diethyl 1-Ethyl-6-hydroxycyclohexa-2,4-diene-1,2-dicarboxylate (8h): The title compound was prepared from diethyl 7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[19] (**7b**; 0.238 g, 1.00 mmol) according to the ACA general procedure. The desired alcohol was obtained as a yellow oil (0.246 g, 92% yield) after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.62. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11–7.10 (d, $^3J_{H,H}$ = 5 Hz, 1 H), 5.99–5.90 (m, 2 H), 5.16 (s, 1 H), 4.22–4.14 (m, 4 H), 2.23–2.14 (m, 1 H), 1.96–1.87 (m, 2 H), 1.29–1.23 (m, 6 H), 0.92 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 166.4, 137.2, 133.4, 130.4, 122.0, 74.6, 61.2, 60.7, 54.9, 20.6, 14.2, 14.1, 10.0 ppm. IR (neat): $\tilde{\nu}$ = 3479, 2980, 1704, 1249, 1028, 631 cm^{-1}. HRMS: calcd. for $C_{14}H_{20}O_5Na$ 291.1202; found 291.1191. $[\alpha]_D^{20}$ = +5.5 (c = 1.02, $CHCl_3$). Enantiomer separation: Hydrodex-B-6-TBDM (25 m, H_2, 40 cm s^{-1}): 80–0-1–170–25; T_1 = 82.32, T_2 = 83.86.

Dimethyl 6-Hydroxy-1,3,6-trimethylcyclohexa-2,4-diene-1,2-dicarboxylate (14): The title compound was prepared from dimethyl 1,4-dimethyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[18] (**13**; 0.127 g, 0.5 mmol) according to the ACA general procedure. The desired alcohol was obtained as a solid after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.54. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (q, $^3J_{H,H}$ = 9 Hz, 2 H), 3.72 (s, 3 H), 3.72 (s, 3 H), 2.00 (s, 3 H), 1.58 (s, 3 H), 1.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 169.1, 137.1, 136.6, 128.0, 126.6, 75.0, 57.1, 52.13, 51.2, 24.8, 19.9, 16.5 ppm. Enantiomer separation: SFC OD-H (30 °C, 200 bar, 2 mL min^{-1}): 5–2–1–15; T_1 = 2.25, T_2 = 2.79.

Dimethyl 6-Hydroxy-1,3-dimethylcyclohexa-2,4-diene-1,2-dicarboxylate (16): The title compound was prepared from dimethyl 1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[18] (**15**; 0.224 g, 1.00 mmol) according to the ACA general procedure. The desired alcohol was obtained as a yellow oil after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.60. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (d, $^3J_{H,H}$ = 9 Hz, 1 H), 5.82 (d, $^3J_{H,H}$ = 9 Hz, 1 H), 4.88 (s, 1 H), 3.70 (s, 6 H) 2.08 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 168.1, 140.33, 134.4, 129.1, 127.3, 73.7, 53.9, 52.5, 52.3, 51.3, 20.4, 12.1 ppm. Enantiomer separation: Hydrodex-B-6-TBDM (25 m, H_2, 40 cm s^{-1}): 50–0-1–170–25; T_1 = 104.38, T_2 = 106.10.

Dimethyl 1,2-Dihydro-1-hydroxy-2-methylnaphthalene-2,3-dicarboxylate (18): The title compound was prepared from dimethyl 1,4-epoxy-1,4-dihydronaphthalene-2,3-dicarboxylate[21] (**17**; 0.130 g, 0.5 mmol) according to the ACA general procedure at 0 °C. The desired alcohol was obtained as a solid after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.54 (s, 1 H), 7.50–7.46 (m, 1 H), 7.37–7.28 (m, 1 H), 5.44 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 3.85 (s, 6 H), 2.19 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 1.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 166.7, 137.4, 136.1, 133.1, 131.2, 130.2, 128.7, 128.1, 124.6, 74.6, 52.9, 52.3, 27.2, 12.9 ppm. Enantiomer separation: HPLC Chiralpak AD (Agilent 1100 series

instrument; eluents: hexane/isopropanol, grad. 99+1, 90+10, 1 mL, 60 min, 254 nm): T_1 = 39.34, T_2 = 49.32.

Dimethyl 2-Ethyl-1,2-dihydro-1-hydroxynaphthalene-2,3-dicarboxylate (19): The title compound was prepared from dimethyl 1,4-epoxy-1,4-dihydronaphthalene-2,3-dicarboxylate[21] (**17**; 0.130 g, 0.5 mmol) according to the ACA general procedure at 0 °C. The desired alcohol was obtained as a solid after flash chromatography on silica gel (diethyl ether/pentane, 4:6). R_f = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1 H), 7.59 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.35–7.26 (m, 2 H), 5.54 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 3.84 (s, 6 H), 2.22 (br. s, 1 H), 1.83–1.65 (m, 2 H), 0.74 (t, $^3J_{H,H}$ = 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 166.7, 138.0, 137.3, 131.0, 130.3, 130.0, 128.4, 127.7, 123.7, 74.8, 55.1, 52.5, 52.1, 20.9, 9.5 ppm. Enantiomer separation: SFC OJ-H (30 °C, 200 bar, 2 mL min^{-1}): 5–2–1–15; T_1 = 6.63, T_2 = 10.35.

Supporting Information (see footnote on the first page of this article): NMR spectra and enantiomeric separations.

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[1] For reviews, see: a) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196; c) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844; d) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279–1300.

[2] For reviews, see: a) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221–3236; b) A. Alexakis, J. E. Backvall, N. Krause, O. Pamies, M. Dieguez, *Chem. Rev.* **2008**, *108*, 2796–2823; c) T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2009**, *38*, 1039–1075.

[3] a) A. Alexakis, C. Benhaim, *Tetrahedron: Asymmetry* **2001**, *12*, 1151–1157; b) T. Watanabe, T. F. Knöpfel, E. M. Carreira, *Org. Lett.* **2003**, *5*, 4557–4558; c) J. Shuppan, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2004**, 792–793; d) E. Fillion, A. Wilsily, *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775; e) A. W. Wird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989.

[4] M. K. Brown, T. L. May, C. A. Baxter, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2007**, *46*, 1097–1098.

[5] K. Li, A. Alexakis, *Angew. Chem. Int. Ed.* **2006**, *45*, 7600–7603.

[6] M. P. Bertrand, L. Feray, R. Nouguier, P. Perfetti, *J. Org. Chem.* **1999**, *64*, 9189–9193.

[7] M. Vuagnoux-d'Augustin, A. Alexakis, *Eur. J. Org. Chem.* **2007**, 5852–5860.

[8] A. Alexakis, C. Benhaim, S. Rosset, M. Human, *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263.

[9] a) M. d'Augustin, L. Palais, A. Alexakis, *Angew. Chem. Int. Ed.* **2005**, *44*, 1376–1378; b) N. Fuchs, M. d'Augustin, M. Humam, A. Alexakis, R. Taras, S. Gladiali, *Tetrahedron: Asymmetry* **2005**, *16*, 3143–3146; c) M. Vuagnoux-d'Augustin, A. Alexakis, *Chem. Eur. J.* **2007**, *13*, 9647–9662.

[10] For reviews, see: a) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; b) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396.

[11] a) F. Bertozzi, M. Pineschi, F. Macchia, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2002**, *4*, 2703–2705; b) R. Gómez Arrayás, S. Cabrera, J. C. Carretero, *Org. Lett.* **2003**, *5*, 1333–1336; c) R. Gómez Arrayás, S. Cabrera, J. C. Carretero, *Synthesis* **2006**, *7*, 1205–1219; d) W. Zhang, L.-X. Wang, W.-J. Shi, Q.-L. Zhou, *J. Org. Chem.* **2005**, *70*, 3734–3736; e) W. Zhang, S.-F. Zhu, X.-Ch. Qiao, Q.-L. Zhou, *Chem. Asian J.* **2008**, *3*, 2105–2111; f) R. Millet, T. Bernardez, L. Palais, A. Alexakis, *Tetrahedron Lett.* **2009**, *50*, 3474–3477; g) R. Millet, L. Gremaud, T. Bernardez, L. Palais, A. Alexakis, *Synthesis* **2009**, 2101–2112.

[12] For reviews, see: a) A. Alexakis, C. Malan, L. Lea, K. Tissot-Croset, D. Polet, C. Falciola, *Chimia* **2006**, *60*, 124–130; b) C. Falciola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765–3780.

[13] For reviews, see: a) M. Lautens, *Synlett* **1993**, 177–185; b) M. Lautens, K. Fagnou, S. Hiebert, *Acc. Chem. Res.* **2003**, *36*, 48–58.

[14] L. Palais, I. S. Mikhel, C. Bournaud, L. Micouin, C. A. Falciola, M. Vuagnoux-d'Augustin, S. Rosset, G. Bernardinelli, A. Alexakis, *Angew. Chem. Int. Ed.* **2007**, *46*, 7462–7465.

[15] L. Liang, M. Yan, Y.-M. Li, A. S. C. Chan, *Tetrahedron: Asymmetry* **2003**, *14*, 1865.

[16] See the Supporting Information for a full color figure.

[17] a) R. Millet, T. Bernardez, L. Palais, A. Alexakis, *Tetrahedron Lett.* **2009**, *50*, 3474–3477; b) R. Millet, L. Gremaud, T. Bernardez, L. Palais, A. Alexakis, *Synthesis* **2009**, 2101–2112.

[18] Y. D. Xing, N. Z. Huang, *J. Org. Chem* **1982**, *47*, 140–142.

[19] R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945–4948.

[20] L. Delaude, A. Demonceau, A. Noels, *Macromolecules* **1999**, *32*, 2091–2103.

[21] J. G. Smith, G. Kruger, *J. Org. Chem.* **1985**, *50*, 5759–5760.

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