Stereospecific Reaction of α-Carbamoyloxy-2-alkenylboronates and α-Carbamoyloxy-alkylboronates with Grignard Reagents – Synthesis of Highly Enantioenriched Secondary Alcohols

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Abstract: Highly enantioenriched secondary alcohols were synthesized by treatment of α-carbamoyloxy-2-alkenylboronates and α-carbamoyloxy-alkylboronates with Grignard reagents. An intermediary boronate complex was transformed stereospecifically to the corresponding secondary 2-alkenyl- and alkylboronates by migration of an introduced residue. Oxidative workup furnished the enantioenriched secondary alcohols.

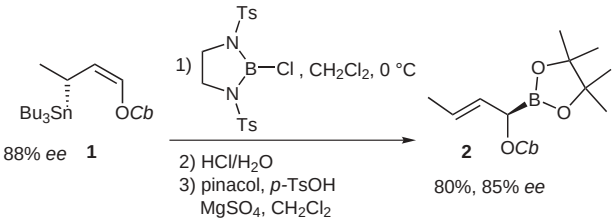
Key words: boron, asymmetric synthesis, alcohols, chirality, stereoselectivity

Enantioenriched secondary alcohols are important intermediates in organic chemistry. They are key structures in the synthesis of several natural products.[1]

So far, several methods have been developed for the synthesis of enantioenriched secondary alcohols such as enantioselective reduction of the corresponding ketones[2] or addition of organometallic compounds to aldehydes using chiral ligands or chiral Lewis acids.[3]

Herein we report a new method for the synthesis of enantioenriched secondary alcohols starting from simple primary alcohols, which are transformed to highly enantioenriched α-carbamoyloxy-substituted boronates.

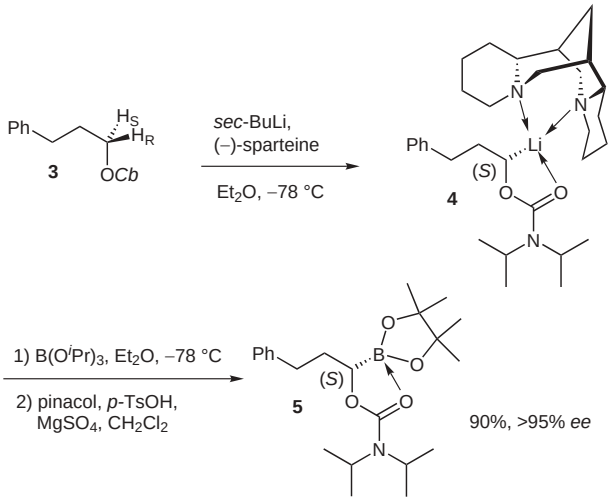
α-Carbamoyloxy-crotylboronate (**2**, Scheme 1) can be synthesized from the enantioenriched γ-stannylated alkenyl carbamate **1**.[4]



Scheme 1

The analoguous α-carbamoyloxy-alkylboronate (**5**) was synthesized from the corresponding alkyl carbamate **3** by enantioselective deprotonation with the chiral base *sec*-butyllithium/(–)-sparteine (Scheme 2). The *pro*-(*S*)-proton is abstracted preferentially[5] resulting in the *S*-configured lithium species **4**, which is configurationally stable at –78 °C. Reaction with tri*iso*propyl borate followed by acidic workup and transesterification with pinacol led to the desired α-carbamoyloxy-alkylboronate (**5**).[6]

The α-carbamoyloxy-substituted boronates **2** and **5** were subjected to a stereospecific substitution reaction by treatment with Grignard reagents.



Scheme 2

Organoborane chemistry offers the possibility of stereospecific ligand migration from boron to carbon, which is of great value in asymmetric synthesis.[7–9] In general, α-halogenated alkylboranes **6** (Scheme 3) react with Grignard reagents stereospecifically in a nucleophilic substitution process. The Grignard reagent adds to borane **6** forming borate complex **7**, which rearranges by migration of a ligand R^1 from boron to an electron deficient carbon via transition state **8** to form product **9**. The leaving group X is replaced by the ligand R^1 under inversion of configuration.[7]

There are many examples for the utility of this efficient process, especially for chain extension of α-halo-boronic esters developed by Matteson et al.[8,9]

This method has also been utilized in asymmetric synthesis employing chiral boronates **10** (Scheme 4).[10] Upon treatment of **10** with dichloromethyllithium the *ate*-complex **11** is formed. This was treated with zinc chloride to

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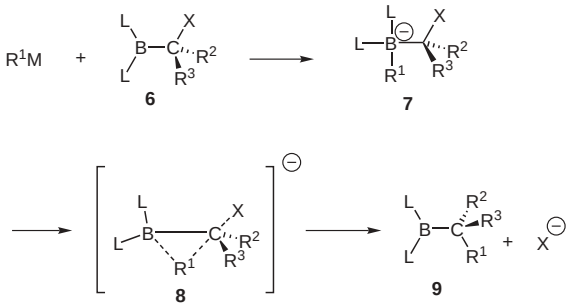
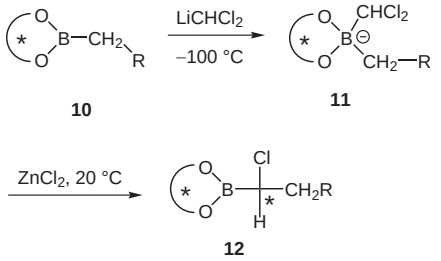


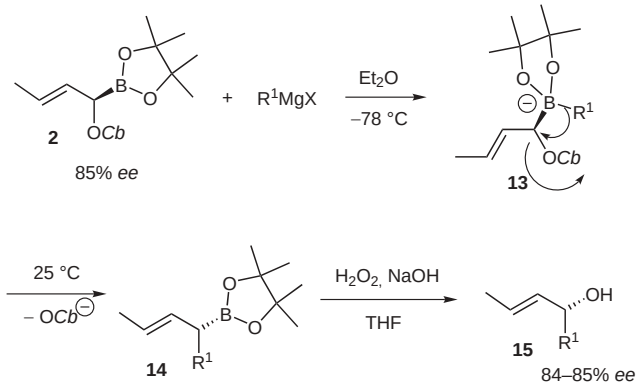
Scheme 3



Scheme 4

form the diastereomeric homologation product **12** which can be further transformed to several highly enantioenriched products. However, without addition of zinc chloride to the reaction mixture, the homologation reaction proceeds very slowly and inefficiently.[10]

For this kind of reaction an electron deficient carbon with a leaving group in α-position to the boron is required. As we found out, these conditions are fulfilled by the α-carbamoyloxy-substituted boronates **2** and **5**.

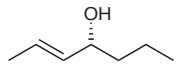
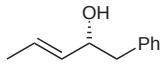
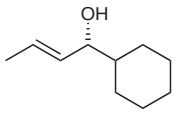
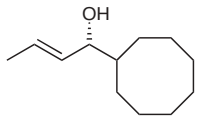


Scheme 5

α-Carbamoyloxy-crotylboronate (**2**) was treated with Grignard reagents at –78 °C to form the boronate complex **13** (Scheme 5). Upon warming to room temperature the substituent R^1 migrates to the electron deficient α-carbon atom with substitution of the carbamoyloxy moiety under inversion of configuration at the chiral centre.[11]

The resulting secondary allylic boronates **14** were prone to hydrolysis on the attempt of purification and, thus, were directly oxidized to the corresponding secondary allylic alcohols **15**[12] (Scheme 5) with retention of configuration.[13] The reaction proceeds under complete stereotransfer and in 58–62% yield with respect to the carbamoyloxy-alkenylboronate (**1**, Table 1).

Table 1 Preparation of Enantioenriched Secondary Allylalcohols

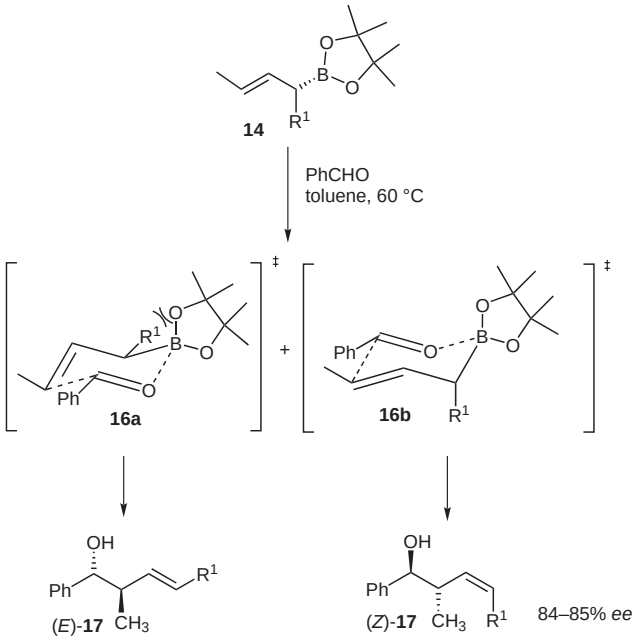
Entry	Grignard reagent	Product	Yield (%)[a]	ee (%)
1	PrMgCl	 **15a**	62	85[b]
2	BnMgCl	 **15b**	58	84[c]
3	$C_6H_{11}MgBr$	 **15c**	62	85[d]
4	$C_8H_{15}MgCl$	 **15d**	60	85[b]

[a] Yield based on **2**.
[b] Determined by ^1H NMR shift experiment with 40 mol% of $Eu(hfc)_3$.
[c] Determined by chiral HPLC (column: chiragrom 2, 60 × 2 mm; solvent: *i*-PrOH–hexane = 1:600).
[d] Determined by comparison of optical rotation.[14]

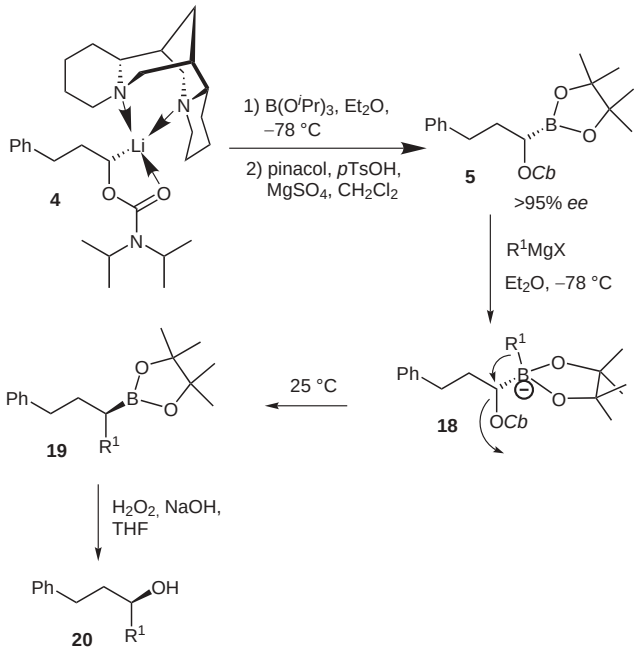
The allylic boronates **14** can also be employed in a stereoselective addition to aldehydes (Scheme 6). The reaction with benzaldehyde via transition state **16a** or **16b** furnishes the *anti*-(*E*)- and (*Z*)-homoallylic alcohols **17**of opposite absolute configuration.[15] This was already found for **17a** (Table 2, entry 1).[16] However, separation of (*E*)- and (*Z*)-**17** on a preparative scale turned out to be difficult.

The assumption, that a larger substituent R^1 could improve the *E*:*Z* ratio, could not be verified (Table 2). However, the enantioenrichment of the starting material is completely transferred to the product **17**.

If an organolithium reagent such as *n*-butyllithium (Table 2, entry 2) is used for the preparation of allylboronate **14** the yield drops dramatically. This is consistent with the observations of Matteson et al. for the reaction of organolithium reagents with boronates.[10] Obviously, the typical features of Grignard reagents play an important role in this reaction which is also underlined by the fact that two equivalents are needed for a smooth reaction.[11] Presumably one Grignard reagent acts as a Lewis acid making the carbamoyloxy moiety a better leaving group, which results in a higher reaction rate.

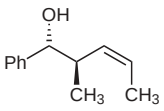
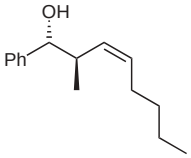
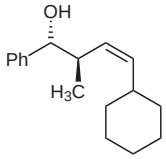
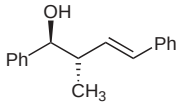
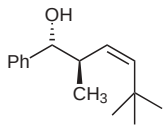


Scheme 6



Scheme 7

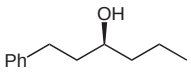
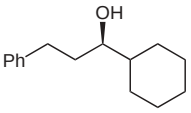
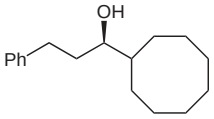
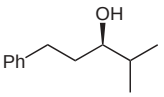
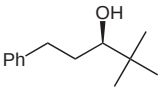
Table 2 Preparation of Enantioenriched Homoallylic Alcohols

Entry	Organometal reagent	Main product[a]	Yield (%)[b]	*E*:*Z*	ee (%) [c]
1	MeMgBr	 **17a**	51	20:80	84
2	*n*-BuLi	 **17b**	28	25:75	85
3	$C_6H_{11}MgBr$	 **17c**	57	33:67	83
4	PhMgBr	 **17d**	46	89:11	84
5	*t*-BuMgCl	 **17e**	59	28:72	85

[a] From all unknown compounds, correct CHN analyses were obtained.
[b] Yield based on **2**.
[c] The *ee* value of the main product; determined by chiral HPLC (column: chiragrom 2, 250 × 2 mm; solvent: *i*-PrOH–hexane = 1:400).

The reaction of α-carbamoyloxy-alkylboronate (**5**) with Grignard reagents proceeds in the same way as described above. Formation of the boronate complex **18** (Scheme 7) leads to migration of the substituent R^1 to the electron-deficient α-carbon upon warming to room temperature. The carbamoyloxy moiety is replaced stereospecifically, and subsequent oxidation of the hydrolytically labile intermediate **19** furnishes the secondary alcohols **20** in greater than 95% ee and 50–70% overall yield (Table 3).[17]

Table 3 Preparation of Enantioenriched Secondary Alcohols

Entry	Grignard reagent	Product	Yield (%)[a]	ee (%)[b]
1	PrMgCl	 **20a**	50	>95
2	$C_6H_{11}MgBr$	 **20b**	70	>95
3	$C_8H_{15}MgCl$	 **20c**	61	>95
4	*i*-PrMgCl	 **20d**	56	>95
5	*t*-BuMgCl	 **20e**	64	>95

[a] Yield based on **5**.
[b] Determined by chiral HPLC (column: chiragrom 2, 250 × 2 mm; solvent: *i*-PrOH–hexane = 1:400).

In summary, we have developed a method for the synthesis of highly enantioenriched secondary alcohols, which should be applicable to a diversity of α-carbamoyloxy-alkylboronates and α-carbamoyloxy-2-alkenylboronates. With this approach it is even possible to synthesize secondary alcohols with very similar substituents in high enantiomeric excess, which is not possible by enantioselective reduction.

An additional advantage is the fact that starting from one enantioenriched precursor a wide variety of products is accessible by simply changing the Grignard reagent. There is no loss of stereoinformation as the reaction occurs via the intermediary borate complex, which rearranges with loss of the carbamoyloxy group. The displacement proceeds with inversion of configuration at the chiral center.

This method significantly broadens the scope of application of lithiated alkyl carbamates **4** for the synthesis of chiral secondary alcohols, since the alkylation reaction of **4** is limited to few primary alkyl iodides[5c] and 2-alkenyl halides.[18]

For the synthesis of the opposite enantiomers, less available (+)-sparteine would be required.[19] Here, the use of a (+)-sparteine surrogate, developed by O'Brien et al. can close the gap.[20]

Acknowledgment

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(6) **Experimental Procedure:** The amount of 1.315 g (5.0 mmol, 1.0 equiv) of **3** and 1.490 g (6.0 mmol, 1.2 equiv) of (–)-sparteine were dissolved in 10 mL of anhyd Et_2O and the mixture was cooled to –78 °C. To this mixture 5.0 mL (6.0 mmol, 1.2 equiv) of a 1.2 M solution of *sec*-butyllithium in cyclohexane were added slowly within 15 min with a syringe pump. After a deprotonation time of 5 h 1.410 g (7.5 mmol, 1.5 equiv) tri*iso*propyl borate were added at –78 °C and the reaction mixture was stirred for an additional hour. The reaction was quenched with 5 mL of 2 M HCl at –78 °C and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL), the combined organic extracts were dried with $MgSO_4$ and the solvent was removed in vacuum.

The crude product was dissolved in 10 mL of CH_2Cl_2 and added to a flask charged with 885 mg (7.5 mmol, 1.5 equiv) of pinacol, 0.050 g of *p*-toluenesulfonic acid and $MgSO_4$. This mixture was stirred at r.t. for 24 h, the solid material was filtered off and the solvent was removed. After purification of the crude product by flash column chromatography (SiO_2, cyclohexane–EtOAc = 5:1) we obtained 1.788 g (4.5 mmol, 90%) of compound **5** as a colorless oil. The ee was determined by ^{1}H NMR shift experiment using 30 mol% of Eu(hfc)$_3$. R_f = 0.24 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +36.7 (*c* 0.97, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 [s, 12 H, CH_3 (pinacol)], 1.29–1.35 [m, 12 H, CH_3 (*Cb*)], 1.94–2.19 (m, 2 H, CH_2), 2.75–2.98 (m, 2 H, CH_2), 3.85, 4.14 [sep, 2 H, CH(*Cb*), ^3J = 7.0 Hz)], 3.92 (dd, 1 H, CH, ^3J = 4.2 Hz, ^3J = 10.3 Hz), 7.21–7.38 [m, 5 H, CH(Ar)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 20.3, 20.6 [CH_3 (pinacol) + CH_3(*Cb*)], 26.9 (CH_2), 33.3 (CH_2), 46.7, 48.4 [CH(*Cb*)], 79.8 (CH), 125.6 [C_q(pinacol)], 128.2, 128.5 [CH(Ar)], 142.5 [C_q(Ar)], 162.7 [C=O(*Cb*)] ppm. Anal. Calcd for $C_{22}H_{36}BNO_4$ (389.27): C, 67.87; H, 9.32; N, 3.60. Found: C, 67.76; H, 9.36; N, 3.85.

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(11) **Experimental Procedure:** The amount of 163 mg (0.5 mmol, 1.0 equiv) of **2** was dissolved in 5 mL of anhyd Et_2O and cooled to –78 °C. To this mixture 1.0 mmol (2.0 equiv) of the Grignard reagent as solution in Et_2O was slowly added. The mixture was stirred for 1 h at –78 °C and then warmed to r.t. for an additional hour. The solution was quickly filtered over ca. 5 g of silica gel with pentane and the solvent was removed carefully at 800 mbar to furnish the crude product **14**, which was subjected to the subsequent reactions without further purification.

(12) The crude product **14** was dissolved in 5.00 mL of THF. At r.t., 1.20 mL (0.6 mmol, 1.2 equiv) of 0.5 M NaOH was added dropwise and after 5 min, 0.07 mL (0.7 mmol, 1.4 equiv) H_2O_2 (35%) was added. The mixture was stirred for 30 min at r.t., then diluted with 5.00 mL of H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL), the combined organic extracts were washed with sat. $FeSO_4$ solution to destroy the peroxides and then dried with $MgSO_4$. After removal of the solvent in vacuum the crude product was purified by flash column chromatography (SiO_2, Et_2O–pentane = 1:6) to furnish the alcohols **15** as colorless liquids. Compound **15a**:[21] R_f = 0.44 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ –8.3 (*c* 0.85, $CHCl_3$). The ee was determined by ^{1}H NMR shift experiment with 40 mol% of Eu(hfc)$_3$. Compound **15b**:[22] R_f = 0.46 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ –7.4 (*c* 0.76, $CHCl_3$). The ee was determined by chiral HPLC (column: chiragrom 2, 60 × 2 mm; solvent: *i*-PrOH–hexane = 1:600). Compound **15c**: R_f = 0.52 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ –11.8 (*c* 2.4, EtOH). The ee was determined by comparison of optical rotation.[14] Compound **15d**: R_f = 0.59 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ –3.3 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19–1.71 [m, 19 H, CH_2 (oct), CH(oct), CH_3, OH], 3.81 [t, 1 H, CH(OH), ^3J = 6.2 Hz], 5.46 (ddq, 1 H, CH, ^4J = 1.0 Hz, ^3J = 7.0 Hz, ^3J = 15.2 Hz), 5.63 (ddq, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 (CH_3), 25.7, 29.6, 30.0, 37.8 [CH_2 (oct)], 42.3 [CH(oct)], 75.2 [CH(OH)], 127.0, 133.8 (CH=CH) ppm. Anal. Calcd for $C_{12}H_{22}O$ (182.17): C, 79.06; H, 12.16. Found: C, 78.67; H, 12.44. The ee was determined by ^{1}H NMR shift experiment with 40 mol% of Eu(hfc)$_3$.

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(15) The crude product **14** was dissolved in 5 mL of anhyd toluene and 106 mg (1.0 mmol, 2.0 equiv) of benzaldehyde were added. The mixture was heated to 60 °C for 12 h and then cooled to r.t. The toluene was removed in vacuo, the residue was dissolved in 5 mL of Et_2O, and 90 mg (0.6 mmol, 1.2 equiv) of triethanolamine were added. After one hour of stirring at r.t. the precipitate was filtered off and the solvent was removed. Flash column chromatography of the crude product (SiO_2, Et_2O–pentane = 1:5) furnished the homoallyl alcohols **17** as colorless liquids. The *E*:*Z*-ratios of the compounds were determined by ^{1}H NMR of the crude products. The ee were determined by HPLC using a chiral column (chiragrom 2, 250 × 2 mm) and the solvent mixture *i*-PrOH–hexane = 1:400. Compound **17a**: *E*:*Z* = 80:20; R_f = 0.54 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +24.3 (*c* 0.67, $CHCl_3$). Compound **17b**: *E*:*Z* = 25:75; R_f = 0.57 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +4.7 (*c* 0.50, $CHCl_3$). Compound **17c**: *E*:*Z* = 33:67; R_f = 0.69 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +26.5 (*c* 1.12, $CHCl_3$). Compound **17d**: *E*:*Z* = 89:11; R_f = 0.58 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +30.1 (*c* 1.00, $CHCl_3$). Compound **17e**: *E*:*Z* = 28:72; R_f = 0.69 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +74.2 (*c* 1.21, $CHCl_3$). Compound (*E*)-**17e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, 3 H, CH_3, ^3J = 6.9 Hz), 1.01 (s, 9 H, CH_3), 2.17 (d, 1 H, OH, ^3J = 2.4 Hz), 3.36–3.49 [m, 1 H, CH(CH_3)], 4.27 [dd, 1 H, CH(OH), ^3J = 2.4 Hz, ^3J = 7.9 Hz], 5.25 (dd, 1 H, CH, ^3J = 8.6 Hz, ^3J = 15.9 Hz), 5.63 (d, 1 H, CH, ^3J = 15.9 Hz), 7.23–7.35 [m, 5H, CH(Ar)] ppm. Compound (*Z*)-**17e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (d, 3 H, CH_3, ^3J = 6.8 Hz), 1.14 (s, 9 H, CH_3), 2.14 (d, 1 H, OH, ^3J = 1.7 Hz), 2.97–3.10 [m, 1 H, CH(CH_3)], 4.23 [dd, 1 H, CH(OH), ^3J = 1.7 Hz, ^3J = 8.4 Hz], 5.09 (dd, 1 H, CH, ^3J = 11.0 Hz, ^3J = 11.9 Hz), 5.59 (d, 1 H, CH, ^3J = 11.9 Hz), 7.23–7.35 [m, 5 H, CH(Ar)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 [CH(CH_3)], 29.8, 31.6, 33.5 (CH_3), 41.2 [CH(CH_3)], 79.0 [CH(OH)], 127.0, 127.1, 127.7, 128.2, 130.5 [CH(Ar), CH], 142.4 (CH), 143.1 [C_q(Ar)] ppm. Anal. Calcd for $C_{15}H_{22}O$ (218.17): C, 82.52; H, 10.16. Found: C, 82.17; H, 10.22.

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(17) **Experimental Procedure:** The amount of 195 mg (0.5 mmol, 1.0 equiv) of **5** was dissolved in 5.00 mL of anhyd Et_2O and the solution was cooled to –78 °C. To this mixture 1.0 mmol (2.0 equiv) of the Grignard reagent as solution in Et_2O was slowly added. The mixture was stirred for 1 h at –78 °C and then warmed to r.t. for an additional hour. The solution was quickly filtered over ca. 5 g of silica gel with pentane and the solvent was removed carefully at 800 mbar. The residue was dissolved in 5.00 mL of THF. At r.t. 1.20 mL (0.6 mmol, 1.2 equiv) of 0.5 M NaOH were added dropwise and after 5 min 0.07 mL (0.7 mmol, 1.4 equiv) H_2O_2 (35%) were added. The mixture was stirred for 30 min at r.t., then diluted with 5.00 mL of H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL), the combined organic extracts were washed with sat. $FeSO_4$ solution to destroy the peroxides and then dried with

$MgSO_4$. After removal of the solvent in vacuum the crude product was purified by flash column chromatography (SiO_2, Et_2O–pentane = 1:6) to furnish the alcohols **20**. The ee were determined by HPLC using a chiral column (chiragrom 2, 250 × 2 mm) and the solvent mixture *i*-PrOH–hexane = 1:400. Compound **20a**:[23] colorless liquid; R_f = 0.43 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +11.9 (*c* 1.00, $CHCl_3$). Compound **20b**:[24] white solid; mp 96 °C; R_f = 0.53 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +28.7 (*c* 0.91, $CHCl_3$). Compound **20c**: colorless liquid; R_f = 0.55 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +15.8 (*c* 0.92, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29–1.82 [m, 16 H, CH_2 (oct), CH(oct), OH], 2.67 (ddd, 2 H, CH_2, ^3J = 7.0 Hz, ^3J = 9.4 Hz, ^3J = 13.5 Hz), 2.86 (ddd, 2 H, CH_2, ^3J = 5.7 Hz, ^3J = 9.4 Hz, ^3J = 13.5 Hz), 3.48 [m, 1 H, CH(OH)], 7.17–7.34 [m, 5 H, CH(Ar)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.1, 27.5, 26.0, 30.0, 32.7 [CH_2(oct), CH_2], 36.47 (CH_2), 48.1 [CH(oct)], 75.0 [CH(OH)], 127.9, 128.4, 130.0 [CH(Ar)], 141.1 [C_q(Ar)] ppm. Anal. Calcd for $C_{17}H_{26}O$ (246.20): C, 82.87; H, 10.64. Found: C, 82.51; H, 10.86. Compound **20d**:[25] colorless liquid; R_f = 0.54 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +27.5 (*c* 0.85, $CHCl_3$). Compound **20e**:[26] colorless liquid; R_f = 0.55 (Et_2O–pentane = 1:1); $[\alpha]_D^{20}$ +50.0 (*c* 1.15, $CHCl_3$).

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