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Straightforward Synthesis of Chiral Hydroxy Isocyanides

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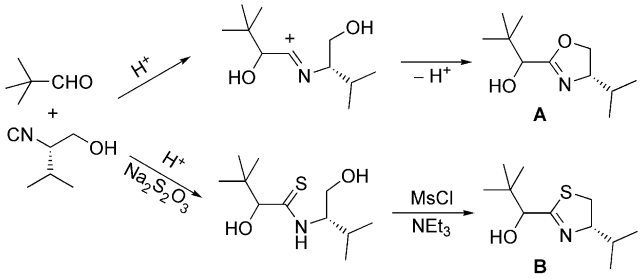
Various types of hydroxy isocyanides have been prepared from the corresponding amino alcohols. These hydroxy isocyanides are interesting building blocks for multicomponent reactions and the synthesis of (hydroxyalkyl)oxazoline ligands. The isocyanides are susceptible to cyclization, giving rise to oxazolines. Therefore, they should be prepared freshly before use or be stored below –30 °C.

Introduction

Isocyanides are a highly interesting class of compounds because of the unique nature and reactivity of this functional group. The coordinatively unsaturated terminal carbon atom reacts easily with electrophiles and nucleophiles, providing so-called α-adducts. Therefore, they are ideal candidates for multicomponent reactions (MCRs), as reviewed recently by Ramón and Yus[1] and Dömling.[2] Probably the most popular MCRs were developed by Passerini (3-CR)[3] and later by Ugi and co-workers (4-CR),[4] opening up the field for combinatorial chemistry. In particular, functionalized isocyanides, which are extremely well suited to the generation of molecular complexity, have been used in the synthesis of peptides and depsipeptides, natural products as well as a wide range of drug-like molecules.[2,5] Also many examples of the synthesis of a wide range of heterocycles have been reported.[6]

In the past we have also taken advantage of the Ugi reaction to synthesize linear and cyclic peptides,[7] as well as heterocyclic amino acid derivatives.[8] Recently, we reported the synthesis of chiral (hydroxyalkyl)oxazolines (**A**)[9] and -thiazolines (**B**)[10] based on a Passerini-type reaction (Scheme 1). The key step in our ligand synthesis was the nucleophilic attack of a hydroxy isocyanide on an aldehyde, giving rise to an ionic intermediate that directly undergoes cyclization to give the required (hydroxyalkyl)oxazoline. To synthesize the corresponding thiazolines, $Na_2S_2O_3$ was added to generate a thioamide,[11] which could be cyclized by using mesyl chloride/NEt_3.

These functionalized heterocycles are themselves excellent ligands for asymmetric carbonyl addition reactions[9,10] and also suitable precursors for even more complex ligands such as phosphite–[12] or phosphoramidite–oxazolines.[13]



Scheme 1. Synthesis of (hydroxyalkyl)oxazolines and -thiazolines.

The reaction of the hydroxy group with a wide range of dialkylchlorophosphanes[14] allows the ligand properties to be modified, and a combination of this process with the advantages of MCRs is ideally suited to the generation of libraries of ligands in only a few steps. To exploit the full potential of this combinatorial approach, a straightforward protocol towards hydroxy isocyanides is required. In principle, the isocyanides can be obtained by epoxide ring opening with R_3SiCN[15] or by the aldol addition of α-metallated isocyanides. Unfortunately, under the latter conditions the deprotonated hydroxy isocyanides directly undergo cyclization to the corresponding isoxazolines.[16] Herein, we describe the synthesis of a wide range of different substituted hydroxy isocyanides and the properties of these compounds.

Results and Discussion

Simple amino acid derived hydroxy isocyanides can easily be obtained from the corresponding amino alcohols by *N*-formylation and subsequent dehydration (Table 1). The *N*-formylation proceeded nearly quantitatively by heating the amino alcohols at reflux in ethyl formate, giving rise to *N*-(hydroxyalkyl)formamides **1** as crystalline solids.[17] In general, formamides can be dehydrated to isocyanides by using $POCl_3/NEt_3$ or $COCl_2/NEt_3$,[18] but in the reaction with **1** the yields were below 20% owing to several side-

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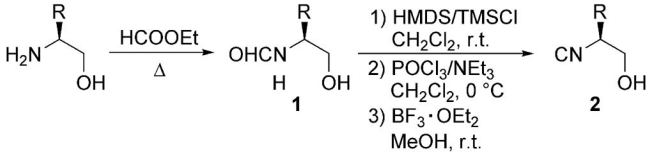
reactions initiated by the OH functionality. These problems can be solved by switching to the corresponding TMS ether, which can be generated prior to isocyanide formation by stirring the alcohol in CH_2Cl_2 in the presence of HMDS and a catalytic amount of TMSCl. After complete protection, $POCl_3/NEt_3$ was added at 0 °C (the TMS group proved to be stable under these conditions) and finally, after complete conversion of the formamide, the silyl ether was cleaved by using $BF_3{\cdot}OEt_3$. This one-pot protocol allowed the synthesis of isocyanides **2a**–**d** in acceptable to good overall yields and can be carried out on a multigram scale. These isocyanides are clear colorless liquids with a strong odor, which should be stored below –30 °C to avoid cycloisomerization.

Table 1. Synthesis of hydroxy isocyanides from simple amino alcohols.



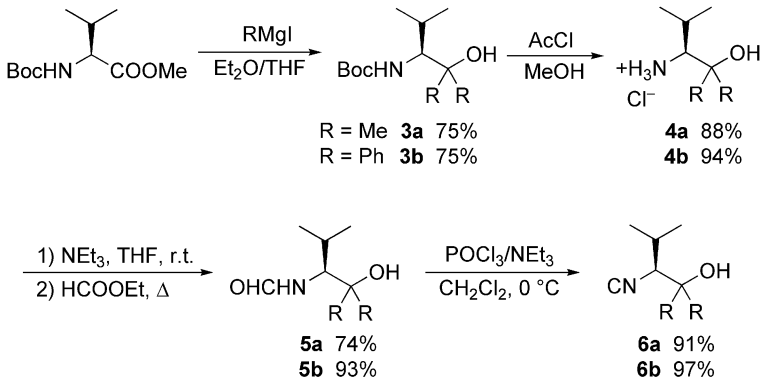
Entry	R	1	Yield [%]	2	Yield [%]
1	*i*Pr	**1a**	99	**2a**	76
2	*t*Bu	**1b**	99	**2b**	81
3	Bn	**1c**	98	**2c**	64
4	Ph	**1d**	99	**2d**	54

In principle, this synthetic route should be suitable for all kinds of primary alcohols. Owing to the sensitivity of oxazolines towards nucleophilic ring opening at the 5-position, we next focused on the synthesis of higher substituted substrates. The desired disubstituted hydroxy isocyanides can easily be obtained from Boc-protected amino acid esters, as illustrated for the isocyanides **6** (Scheme 2).

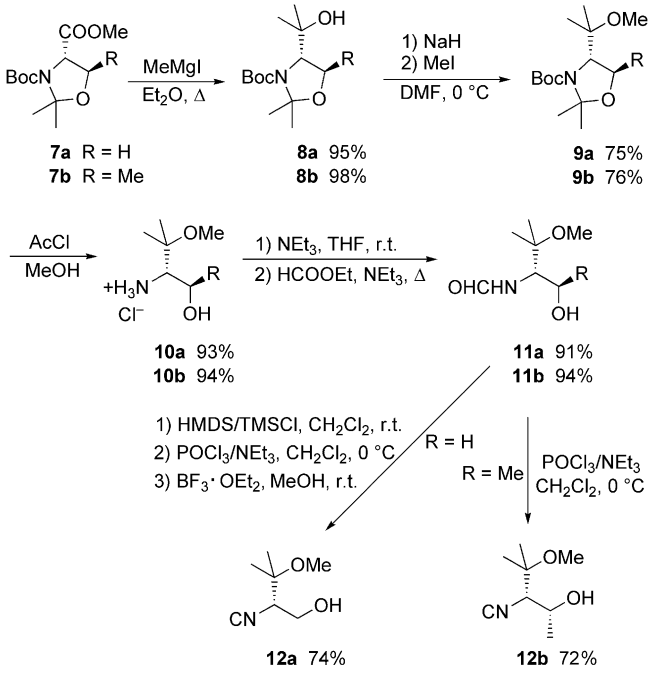
Grignard reactions, for example, of the valine ester, provided the tertiary alcohols **3**. The Boc-protecting group could be cleaved (without elimination of the OH group) by in situ generated HCl in CH_3OH, providing the amino alcohol salts **4**. These salts had to be deprotonated first, otherwise the *N*-formylation would not occur. The formamides **5** could be directly dehydrated without silyl protection, and the isocyanides **6a** and **6b** were obtained in nearly quantitative yield. In principle, this route should allow the introduction of a wide range of substituents at the 5-position of oxazolines.

To vary the substitution pattern of the side-chain, we developed a third approach starting from serine and threonine derivatives. The known fully protected derivatives **7**[19] were subjected to a Grignard reaction, giving rise to the tertiary alcohols **8**,[20] which were subjected to *O*-methylation (Scheme 3). Subsequently, the Boc- and ketal-protecting groups were removed with in situ generated HCl to give the amino alcohol salts **10** in excellent yields. The *N*-formylation was carried out as reported for **1**, but in the presence of NEt_3 for deprotonation. In the final step, the serine-derived primary alcohol had to be protected prior to dehydration, whereas the secondary alcohol of the threonine-based formamide did not require protection.

A common feature of all the synthesized hydroxy isocyanides is their high tendency to undergo thermal isomerization to the corresponding oxazolines **13** (Table 2). Therefore, these isocyanides should be stored at –30 °C to avoid this cyclization reaction. At room temperature, some isocyanides (**2b** and **2c**) underwent such a fast isomerization so that we were not able to record clean NMR spectra (Entries 2 and 3). In these cases, the products were contaminated with 1–5% oxazoline. This effect was even more dramatic with other analytical methods. To prove the *ee* of our isocyanides, we first used GC with different chiral columns, but in most cases only the oxazoline could be detected. Interestingly, the isomerization was complete for the primary isocyano alcohols, whereas the tertiary alcohols seemed to undergo cyclization more slowly, allowing the identification of both isomers (Entry 5). The sharp peaks observed in the gas chromatograms indicate that isomerization has probably already occurred in the injector of the GC apparatus. In contrast, no significant isomerization (except **2c**) was observed during HPLC analysis. Despite the cycloisomerization reaction, both analytical methods clearly indicate that no epimerization occurred during isocyanide formation.

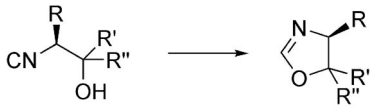


Scheme 2. Synthesis of highly substituted hydroxy isocyanides.



Scheme 3. Synthesis of hydroxy isocyanides with sterically demanding side-chains.

Table 2. Formation of oxazolines from hydroxy isocyanides.



Entry	Isocyanide	Yield of **13** [%]		
		By NMR	By GC	By HPLC
1	**2a**	0	100	n.d.
2	**2b**	1	100	n.d.
3	**2c**	5	n.d.	20
4	**2d**	0	n.d.	5
5	**6a**	0	38	n.d.
6	**6b**	0	n.d.	0
7	**12a**	1	100	n.d.
8	**12b**	0	100	n.d.

Conclusions

We have shown that chiral hydroxy isocyanides can easily be prepared from various types of amino alcohols. Depending on the alcohol used, different approaches have to be used to generate the isocyanide functionality. The hydroxy isocyanides should be used directly or be stored at –30 °C to avoid cyclization to the corresponding oxazolines.

Experimental Section

General Remarks: All air- or moisture-sensitive reactions were carried out under argon in oven-dried glassware (65 °C), which was freshly heated under vacuum before use. Dry solvents were distilled before use: THF was distilled from $LiAlH_4$, CH_2Cl_2 and NEt_3 from CaH_2, and MeOH from Na. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel, silica gel 60, 50–200 μm). Analytic TLC was performed on precoated silica gel plates (Macherey-Nagel Polygram Sil G/UV_{254}), and UV, $KMnO_4$ solution, or iodine was used for visualization. Melting points were determined with a Dr. Tottoli (Büchi) melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance II [400 (^1H) and 100 MHz (^{13}C)] and DRX-500 [500 (^1H) and 125 MHz (^{13}C)] spectrometers by using (in general) $CDCl_3$ as solvent. Chemical shifts are reported in ppm (δ), and $CDCl_3$ was used as a reference. HRMS data were recorded with a Finnigan MAT 95 spectrometer by using the CI technique. Elemental analyses were performed at the Saarland University.

General Procedure for the Synthesis of Formamides (GP 1): A solution of the corresponding amino alcohol (30 mmol) in ethyl formate (3.25 mL, 40 mmol) was heated at reflux for 1–8 d. The progress of the reaction was monitored by TLC. After complete consumption of the amino alcohol, the solvent was removed in vacuo, and the crude product was purified by washing with Et_2O or by flash chromatography (silica). In the case that the hydrochloride of the amino alcohol was used, NEt_3 (1 equiv.) was added as proton scavenger.

General Procedure for Isocyanide Formation (GP 2)

With Protection of the Hydroxy Functionality (GP 2a): A solution of the corresponding formamide (*n* mmol) was dissolved in CH_2Cl_2 (*n* mL), hexamethyldisilazane (1.1*n* mmol) and Me_3SiCl (1 drop) were added, and the mixture was stirred at room temp. After completion of the reaction (1–4 h, TLC), the solution was cooled to 0 °C, before NEt_3 (2.5*n* mmol) was added. A solution of $POCl_3$ (*n* mmol) in CH_2Cl_2 (0.5*n* mL) was added slowly at such a rate that the reaction temperature remained below 5–10 °C. After the addition, the cooling bath was removed, and, after completion of the reaction (TLC control), an Na_2CO_3 solution (20%) was added dropwise. After stirring at room temp. for 10 min, H_2O was added, and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The resulting brown oil was dissolved in MeOH, $BF_3{\cdot}OEt_2$ (0.1*n* mol) was added, and the reaction mixture was stirred at room temp. After completion of the reaction (TLC), the solvent was removed in vacuo, and the crude product was purified by distillation or flash chromatography (silica).

Without Protection of the Hydroxy Functionality (GP 2b): A solution of the corresponding formamide (*n* mmol) in CH_2Cl_2 (*n* mL) was cooled in an ice bath to 0 °C, before NEt_3 (2.5*n* mmol) and $POCl_3$ (*n* mol) in CH_2Cl_2 (0.5*n* mL) were added (reaction temperature: 5–10 °C). After complete addition, the ice bath was removed, and the solution was warmed to room temp. A solution of Na_2CO_3 (20%) was added at a temperature of 27–29 °C. After stirring at room temp. for 10 min, H_2O was added, and the layers were separated. The aqueous layer was washed twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (silica).

General Procedure for the Cleavage of the Boc and Ketal Groups (GP 3): A solution of the protected compound (*n* mmol) was dissolved in dry MeOH at 0 °C under Ar. AcCl (2.5–3*n* mol) was added slowly at such a rate that the reaction temperature remained below 10 °C. After stirring at room temp. overnight, the solvent was evaporated in vacuo. The solid residue was suspended in Et_2O, stirred for 2 h, filtered, and dried in vacuo.

(+)-(2*S*)-2-(Formylamino)-3,3-dimethyl-1-butanol (1b): According to GP 1, **1b** was obtained from (+)-(*S*)-*tert*-leucinol (3.95 g,

33.7 mmol) and ethyl formate (3.26 mL, 40.4 mmol) as a colorless solid in 99% yield (4.84 g, 33.3 mmol). M.p. 82 °C. $[\alpha]_D^{20}$ = +38.4 (*c* = 3.0, $CHCl_3$). The NMR spectra showed signals of the (*Z*)- and (*E*)-formamide in an (*Z*)/(*E*) ratio of 56:44. **(*Z*)-1b:** ^{1}H NMR (500 MHz): δ = 0.94 (s, 9 H), 3.50 (dd, *J* = 11.3, 9.1 Hz, 1 H), 3.60 (br. s, 1 H), 3.83 (dd, *J* = 11.3, 3.3 Hz, 1 H), 3.87 (ddd, *J* = 12.3, 9.1, 3.3 Hz, 1 H), 6.46 (d, *J* = 12.3 Hz, 1 H), 8.26 (d, *J* = 1.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 26.8, 33.4, 58.3, 61.9, 162.8 ppm. **(*E*)-1b:** ^{1}H NMR (500 MHz): δ = 0.93 (s, 1 H), 3.04 (td, *J* = 10.0, 3.2 Hz, 1 H), 3.50 (dd, *J* = 11.7, 10.0 Hz, 1 H), 3.80 (dd, *J* = 11.7, 3.2 Hz, 1 H), 3.94 (br. s, 1 H), 6.46 (dd, *J* = 11.7, 10.0 Hz, 1 H), 7.95 (d, *J* = 11.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 26.7, 33.1, 61.0, 64.3, 166.3 ppm. HRMS (CI): calcd. for $C_7H_{16}NO_2$ $[M + H]^+$ 146.1181; found 146.1168. $C_7H_{15}NO_2$ (145.20): C 57.90, H 10.41, N 9.65; found: C 57.85, H 10.32, N 9.59.

(–)-(2*S*)-2-(Formylamino)-3-phenyl-1-propanol (1c): According to GP 1, **1c** was obtained from (–)-(*S*)-phenylalaninol (5.25 g, 34.7 mmol) and ethyl formate (3.36 mL, 41.7 mmol) as a colorless solid in 98% yield (6.10 g, 34.0 mmol). M.p. 59–63 °C. $[\alpha]_D^{20}$ = –31.2 (*c* = 0.5, $CHCl_3$). The NMR spectra showed signals of the (*Z*)- and (*E*)-formamide in an (*Z*)/(*E*) ratio of 75:25. **(*Z*)-1c:** ^{1}H NMR (500 MHz): δ = 2.84 (dd, *J* = 13.9, 7.2 Hz, 1 H), 2.88 (dd, *J* = 13.9, 7.3 Hz, 1 H), 3.55 (dd, *J* = 11.2, 5.2 Hz, 1 H), 3.60 (br. s, 1 H), 3.65 (dd, *J* = 11.2, 3.8 Hz, 1 H), 4.23 (m, 1 H), 6.32 (d, *J* = 7.4 Hz, 1 H), 7.20–7.23 (m, 3 H), 7.29 (t, *J* = 7.2 Hz, 2 H), 8.06 (d, *J* = 1.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 36.9, 51.7, 63.4, 126.7, 128.6, 129.2, 137.4, 161.7 ppm. **(*E*)-1c:** ^{1}H NMR (500 MHz): δ = 2.71 (dd, *J* = 13.8, 8.3 Hz, 1 H), 2.75 (dd, *J* = 13.8, 8.4 Hz, 1 H), 3.54 (dd, *J* = 10.6, 6.4 Hz, 1 H), 3.59 (m, 1 H), 3.67 (dd, *J* = 10.6, 3.7 Hz, 1 H), 6.72 (dd, *J* = 11.9, 10.6 Hz, 1 H), 7.14 (d, *J* = 7.6 Hz, 2 H), 7.72 (d, *J* = 11.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 38.4, 56.4, 64.4, 126.8, 128.7, 129.3, 137.1, 165.0 ppm. HRMS (CI): calcd. for $C_{10}H_{14}NO_2$ $[M + H]^+$ 180.1025; found 180.1016. $C_{10}H_{13}NO_2$ (179.22): calcd. C 67.02, H 7.31, N 7.82; found C 66.98, H 7.28, N 7.73.

(+)-(2*S*)-2-(Formylamino)-2-phenylethanol (1d): According to GP 1, **1d** was obtained from (+)-(*S*)-α-phenylglycinol (6.36 g, 46.4 mmol) and ethyl formate (4.49 mL, 55.7 mmol) as a colorless solid in 99% yield (7.62 g, 46.1 mmol). M.p. 95–96 °C. $[\alpha]_D^{20}$ = +104.1 (*c* = 1.2, $CHCl_3$). The NMR spectra showed signals of the (*Z*)- and (*E*)-formamide in an (*Z*)/(*E*) ratio of 84:16. **(*Z*)-1d:** ^{1}H NMR (500 MHz, $CDCl_3$ + 10% $[D_6]$DMSO): δ = 3.51 (m, 1 H), 3.56 (m, 1 H), 4.30 (t, *J* = 5.9 Hz, 1 H), 4.84 (dt, *J* = 7.1, 4.8 Hz, 1 H), 7.00–7.14 (m, 5 H), 7.61 (d, *J* = 7.1 Hz, 1 H), 7.94 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ + 10% $[D_6]$DMSO): δ = 53.8, 64.7, 126.2, 126.7, 127.8, 139.0, 161.0 ppm. **(*E*)-1d:** ^{1}H NMR (500 MHz, $CDCl_3$ + 10% $[D_6]$DMSO): δ = 3.46 (m, 2 H), 4.32 (m, 1 H), 4.50 (t, *J* = 5.9 Hz, 1 H), 7.00–7.14 (m, 5 H), 7.38 (dd, *J* = 11.7, 9.1 Hz, 1 H), 7.86 (d, *J* = 11.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ + 10% $[D_6]$DMSO): δ = 58.0, 65.1, 126.1, 127.1, 128.1, 138.7, 164.7 ppm. HRMS (CI): calcd. for $C_9H_{12}NO_2$ $[M + H]^+$ 166.0868; found 166.0894. $C_9H_{11}NO_2$ (165.19): C 65.44, H 6.71, N 8.48; found C 65.07, H 6.66, N 8.42.

(+)-(2*S*)-2-Isocyano-3-methyl-1-butanol (2a): According to GP 2a, **2a** was obtained from **1a**[17] (39.4 g, 300 mmol), HMDS (70.1 mL, 330 mmol), NEt_3 (105 mL, 750 mmol), $POCl_3$ (27.4 mL, 300 mmol), and $BF_3{\cdot}OEt_2$ (3.77 mL, 30.0 mmol) after flash chromatography (silica, Et_2O) and distillation ($b.p._{0.005}$ = 38 °C) as a colorless oil in 76% yield (25.8 g, 228 mmol). $[\alpha]_D^{20}$ = +0.8 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 1.00 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.93 (m, 1 H), 2.96 (s, 1 H), 3.48 (m, 1 H), 3.68–3.73 (m, 2 H) ppm. ^{13}C NMR (125 MHz): δ = 17.2, 19.4, 28.5, 62.8, 63.5 (t, *J* = 5.7 Hz), 155.8 (t, *J* = 4.5 Hz) ppm. HRMS (CI): calcd. for $C_6H_{12}NO$ $[M + H]^+$ 114.0919; found 114.0917.

(+)-(2*S*)-2-Isocyano-3,3-dimethyl-1-butanol (2b): According to GP 2a, **2b** was obtained from **1b** (3.49 g, 24.0 mmol), HMDS (5.61 mL, 26.4 mmol), NEt_3 (8.43 mL, 60.0 mmol), $POCl_3$ (2.19 mL, 24.0 mmol), and $BF_3{\cdot}OEt_2$ (301 μL, 2.40 mmol) after distillation ($b.p._{0.016}$ = 52 °C) as a colorless oil in 81% yield (2.47 g, 19.4 mmol). $[\alpha]_D^{20}$ = +48.7 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 1.02 (s, 9 H), 2.82 (dd, *J* = 7.6, 5.5 Hz, 1 H), 3.41 (ddt, *J* = 9.0, 3.4, 1.7 Hz, 1 H), 3.68 (m, 1 H), 3.77 (m, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 26.2, 33.0, 61.6, 67.8 (t, *J* = 5.6 Hz), 155.9 (t, *J* = 5.4 Hz) ppm. Traces of oxazoline **13b** were observed by NMR spectroscopy. ^{1}H NMR (500 MHz, selected signals): δ = 3.86 (ddd, *J* = 10.3, 8.4, 1.9 Hz, 1 H), 4.01 (dd, *J* = 8.7, 8.4 Hz, 1 H), 4.14 (dd, *J* = 10.3, 8.7 Hz, 1 H), 6.87 (d, *J* = 1.9 Hz, 1 H) ppm. HRMS (CI): calcd. for $C_7H_{14}NO$ $[M + H]^+$ 128.1076; found 128.1087.

(–)-(2*S*)-2-Isocyano-3-phenyl-1-propanol (2c): According to GP 2a, **2c** was obtained from **1c** (6.10 g, 34.0 mmol), HMDS (7.94 mL, 37.4 mmol), NEt_3 (11.9 mL, 85.0 mmol), $POCl_3$ (3.10 mL, 34.0 mmol), and $BF_3{\cdot}OEt_2$ (427 μL, 3.40 mmol) after flash chromatography (silica, Et_2O) as a colorless oil in 64% yield (3.51 g, 21.8 mmol). $[\alpha]_D^{20}$ = –47.3 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 2.83 (s, 1 H), 2.89 (m, 1 H), 2.93 (m, 1 H), 3.60 (m, 1 H), 3.66 (m, 1 H), 3.78 (m, 1 H), 7.19 (d, *J* = 7.3 Hz, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.29 (t, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR (125 MHz): δ = 37.4, 58.4 (t, *J* = 6.1 Hz), 63.4, 127.2, 128.7, 129.2, 135.7, 156.4 (t, *J* = 4.5 Hz) ppm. Traces of oxazoline **13c** could be observed by NMR spectroscopy. ^{1}H NMR (500 MHz, selected signals): δ = 2.64 (dd, *J* = 13.8, 8.2 Hz, 1 H), 3.03 (dd, *J* = 13.8, 5.8 Hz, 1 H), 3.91 (dd, *J* = 8.8, 7.7 Hz, 1 H), 4.13 (dd, *J* = 9.1, 8.8 Hz, 1 H), 4.35 (m, 1 H), 6.82 (d, *J* = 1.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, selected signals): δ = 41.5, 66.0, 70.7, 126.6, 128.5, 129.1, 137.4, 155.5 ppm. HPLC (OD-H, hexane/*i*PrOH, 90:10, 0.5 mL/min): t_R[(*R*)-**13c**] = 14.30 min, t_R[(*S*)-**13c**] = 15.38 min, t_R[(*R*)-**2c**] = 20.30 min, t_R[(*S*)-**2c**] = 21.59 min.[21] HRMS (CI): calcd. for $C_{10}H_{12}NO$ $[M + H]^+$ 162.0918; found 162.0925.

(+)-(2*S*)-2-Isocyano-2-phenylethanol (2d): According to GP 2a, **2d** was obtained from **1d** (3.30 g, 19.8 mmol), HMDS (4.67 mL, 22.0 mmol), NEt_3 (7.03 mL, 50.0 mmol), $POCl_3$ (1.83 mL, 20.0 mmol), and $BF_3{\cdot}OEt_2$ (251 μL, 2.00 mmol) after flash chromatography (silica, Et_2O) as a colorless oil in 54% yield (1.58 g, 10.7 mmol). $[\alpha]_D^{20}$ = +70.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 2.61 (t, *J* = 6.1 Hz, 1 H), 3.84 (br. s, 2 H), 4.83 (t, *J* = 6.1 Hz, 1 H), 7.35–7.45 (m, 5 H) ppm. ^{13}C NMR (125 MHz): δ = 61.1 (t, *J* = 6.7 Hz), 67.0, 126.3, 128.9, 129.0, 133.4, 157.8 (t, *J* = 4.6 Hz) ppm. HPLC (OD-H, hexane/*i*PrOH, 90:10, 0.5 mL/min): t_R[(*R*)-**2d**] = 16.62 min, t_R[(*S*)-**2d**] = 18.39 min.[21] HRMS (CI): calcd. for $C_9H_{10}NO$ $[M + H]^+$ 148.0762; found 148.0742. C_9H_9NO (147.18): calcd. C 73.45, H 6.16, N 9.52; found C 73.12, H 6.21, N 9.51.

(–)-(3*S*)-3-(Formylamino)-2,4-dimethyl-2-pentanol (5a): According to GP 1, **5a** was obtained from **4a**[22] (1.61 g, 9.60 mmol), ethyl formate (3.26 mL, 40.4 mmol), and NEt_3 (1.35 mL, 9.60 mmol) after 24 h. Flash chromatography (silica, CH_2Cl_2/MeOH, 8:2) gave rise to **5a** as a colorless solid in 74% yield (1.08 g, 6.78 mmol). M.p. 73 °C. $[\alpha]_D^{20}$ = –24.0 (*c* = 0.2, $CHCl_3$). The NMR spectra showed signals of the (*Z*)- and (*E*)-formamide in an (*Z*)/(*E*) ratio of 71:29. **(*Z*)-5a:** ^{1}H NMR (500 MHz): δ = 0.92 (d, *J* = 6.8 Hz, 6 H), 1.20 (s, 3 H), 1.28 (s, 3 H), 2.14 (qqd, *J* = 6.8, 6.8, 2.4 Hz, 1 H), 2.24 (s, 1 H), 3.83 (dd, *J* = 10.4, 2.4 Hz, 1 H), 6.23 (d, *J* = 10.4 Hz, 1

H), 8.32 (d, J = 1.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 16.8, 22.2, 27.2, 28.0, 29.3, 58.8, 73.1, 161.8 ppm. **(*E*)-5a:** ^{1}H NMR (500 MHz): δ = 0.91 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 1.22 (s, 3 H), 1.27 (s, 3 H), 2.14 (m, 1 H), 2.54 (s, 1 H), 2.90 (dd, J = 10.8, 2.3 Hz, 1 H), 6.42 (dd, J = 11.9, 10.8 Hz, 1 H), 7.92 (d, J = 11.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 16.6, 22.2, 27.0, 27.6, 28.9, 64.9, 72.6, 165.3 ppm. HRMS (CI): calcd. for $C_8H_{18}NO_2$ [M + H]$^+$ 160.1337; found 160.1337. $C_8H_{17}NO_2$ (159.23): C 60.35, H 10.76, N 8.80; found C 60.75, H 10.49, N 8.74.

(–)-(2*S*)-(Formylamino)-3-methyl-1,1-diphenyl-1-butanol (5b): According to GP 1, **5b** was obtained from **4b**[23] (543 mg, 1.86 mmol), ethyl formate (7.4 mL, 92 mmol), and NEt_3 (261 μL, 1.86 mmol) after 24 h. Flash chromatography (silica, CH_2Cl_2/MeOH, 8:2) gave rise to **5b** as a colorless solid in 93% yield (491 mg, 1.73 mmol). M.p. 145–146 °C. $[\alpha]_D^{20}$ = –97.7 (c = 0.9, $CHCl_3$). The NMR spectra showed signals of the (*Z*)- and (*E*)-formamide in an (*Z*)/(*E*) ratio of 86:14. **(*Z*)-5a:** ^{1}H NMR (400 MHz): δ = 0.90 (d, J = 6.7 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 1.85 (qqd, J = 6.7, 6.7, 2.1 Hz, 1 H), 3.05 (s, 1 H), 5.05 (dd, J = 10.2, 2.1 Hz, 1 H), 6.21 (d, J = 10.2 Hz, 1 H), 7.18 (t, J = 7.4 Hz, 1 H), 7.21 (t, J = 7.4 Hz, 1 H), 7.28 (t, J = 7.4 Hz, 2 H), 7.32 (t, J = 7.4 Hz, 2 H, 8′-H), 7.46 (d, J = 7.4 Hz, 2 H), 7.48 (d, J = 7.4 Hz, 2 H), 8.06 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 17.6, 22.8, 28.7, 56.6, 82.0, 125.1, 125.3, 126.9, 127.1, 128.45, 128.47, 145.2, 145.9, 161.3 ppm. **(*E*)-5a:** ^{1}H NMR (400 MHz, selected signals): δ = 2.01 (qqd, J = 6.8, 6.8, 1.4 Hz, 1 H), 3.03 (s, 1 H), 4.06 (dd, J = 10.7, 1.4 Hz, 1 H), 7.70 (d, J = 11.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, selected signals): δ = 17.0 (C-5), 22.4, 28.1, 62.8, 81.5, 125.43, 125.48, 127.25, 127.28, 128.55, 128.59, 144.3, 145.0, 164.7 ppm. HRMS (CI): calcd. for $C_{18}H_{22}NO_2$ [M + H]$^+$ 284.1650; found 284.1644. $C_{18}H_{21}NO_2$ (283.37): calcd. C 76.30, H 7.47, N 4.94; found C 75.90, H 7.42, N 4.84.

(–)-(3*S*)-3-Isocyano-2,4-dimethyl-2-pentanol (6a): According to GP 2b, **6a** was obtained from **5a** (1.04 g, 6.53 mmol), NEt_3 (2.29 mL, 16.3 mmol), and $POCl_3$ (0.6 mL, 6.55 mmol) after flash chromatography (silica, Et_2O) as a colorless oil in 91% yield (836 mg, 5.92 mmol). $[\alpha]_D^{20}$ = –23.6 (c = 0.9, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 1.05 (d, J = 6.5 Hz, 3 H), 1.07 (d, J = 6.5 Hz, 3 H), 1.30 (s, 3 H), 1.34 (s, 3 H), 1.93 (s, 1 H), 2.09 (m, 1 H), 3.37 (dt, J = 4.5, 2.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 17.0, 22.5, 26.0, 27.8, 27.4, 70.7 (t, J = 5.4 Hz), 71.9, 157.3 (t, J = 5.2 Hz) ppm. HRMS (CI): calcd. for $C_8H_{16}NO$ [M + H]$^+$ 142.1232; found 142.1232.

(–)-(2*S*)-2-Isocyano-3-methyl-1,1-diphenyl-1-butanol (6b): According to GP 2b, **6b** was obtained from **5b** (220 mg, 77.6 μmol), NEt_3 (273 μL, 1.94 mmol), and $POCl_3$ (73 μL, 77.6 μmol) after flash chromatography (silica, hexanes/EtOAc, 9:1) as colorless needles in 97% yield (200 mg, 75.4 μmol). $[\alpha]_D^{20}$ = –33.8 (c = 0.2, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 1.00 (d, J = 6.7 Hz, 3 H), 1.06 (d, J = 6.7 Hz, 3 H), 1.73 (m, 1 H), 2.66 (s, 1 H), 4.53 (d, J = 1.2 Hz, 1 H), 7.20–7.42 (m, 8 H), 7.54 (d, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR (125 MHz): δ = 17.0, 22.5, 27.6, 67.3 (t, J = 5.3 Hz), 79.7, 125.3, 125.9, 127.3, 127.7, 128.5, 128.6, 142.3, 145.0, 159.0 (t, J = 4.5 Hz) ppm. HPLC (OD-H, hexane/*i*PrOH, 90:10, 0.5 mL/min): t_R[(*S*)-**2b**] = 9.30 min. HRMS (CI): calcd. for $C_{18}H_{20}NO$ [M + H]$^+$ 266.1544; found 266.1523. $C_{18}H_{19}NO$ (265.35): calcd. C 81.48, H 7.22, N 5.28; found C 80.99, H 7.20, N 5.24.

(–)-(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-4-(1-hydroxy-1-methylethyl)-2,2,5-trimethyloxazolidine (8b): A solution of MeI (14.9 mL, 240 mmol) was added slowly to Mg filings (4.86 g, 200 mmol) in Et_2O (200 mL). After complete consumption of the Mg, **7b**[19] (21.9 g, 80 mmol) in dry Et_2O (80 mL) was added at such a rate that the solution started to reflux. After complete addition, the reaction mixture was stirred for a further 10 min, before satd. NH_4Cl was added carefully. The layers were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (silica, Et_2O) provided **8b** (21.9 g, 89 mmol, 98%) as a yellow oil. $[\alpha]_D^{20}$ = –30.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 1.16 (s, 3 H), 1.17 (s, 3 H), 1.39 (d, J = 6.2 Hz, 3 H), 1.49 (s, 12 H), 1.60 (s, 3 H), 3.71 (d, J = 5.2 Hz, 1 H), 3.97 (br. s, 1 H), 5.86 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 22.6, 24.6, 26.6, 27.7, 28.3, 29.3, 72.3, 73.4, 73.6, 81.5, 94.7, 155.6 ppm. HRMS (CI): calcd. for $C_{14}H_{28}NO_4$ [M + H]$^+$ 274.2018; found 274.2005. $C_{14}H_{27}NO_4$ (273.37): C 61.51, H 9.96, N 5.12; found C 61.01, H 9.56, N 5.64.

(–)-(4*S*)-3-(*tert*-Butoxycarbonyl)-4-(1-methoxy-1-methylethyl)-2,2-dimethyloxazolidine (9a): A solution of **8a**[20] (8.22 g, 31.7 mmol) in dry DMF (30 mL) was cooled to 0 °C, before MeI (3.95 mL, 63.4 mmol) and NaH (1.71 g, 43 mmol, 60% suspension in oil) were added. The colorless suspension was stirred at room temp. for 2 h, before MeOH (5 mL) was added to quench the reaction. The solution was diluted with CH_2Cl_2 (100 mL) and washed twice with H_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (silica, hexanes/Et_2O, 9:1) gave rise to **9a** (6.41 g, 23.5 mmol, 75%) as a colorless oil, which crystallized on standing. M.p. 53–55 °C. $[\alpha]_D^{20}$ = –5.1 (c = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 1.12 (s, 3 H), 1.17 (s, 3 H), 1.47 (s, 9 H), 1.48 (s, 3 H), 1.59 (s, 3 H), 3.20 (s, 3 H), 3.85 (dd, J = 9.2, 6.4 Hz, 1 H), 4.05 (br. s, 1 H), 4.13 (d, J = 9.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 21.0, 23.2, 24.4, 26.8, 28.3, 49.4, 62.6, 64.2, 77.4, 80.1 ppm. HRMS (CI): calcd. for $C_{14}H_{28}NO_4$ [M + H]$^+$ 274.2018; found 274.2032. $C_{14}H_{27}NO_4$ (273.37): calcd. C 61.51, H 9.96, N 5.12; found C 61.46, H 9.76, N 5.10.

(–)-(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-4-(1-methoxy-1-methylethyl)-2,2,5-trimethyloxazolidine (9b): Methyl ether **9b** was obtained from **8b** (10.9 g, 40.0 mmol), NaH (2.16 g, 54.0 mmol), and MeI (5.0 mL, 80.0 mmol) in analogy to ether **9a** as a colorless oil. Yield: 76% (8.70 g, 30.3 mmol). $[\alpha]_D^{20}$ = –7.6 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 1.13 (s, 3 H, 9-H), 1.14 (s, 3 H), 1.29 (d, J = 6.6 Hz, 3 H), 1.46 (s, 9 H), 1.52 (s, 3 H), 1.60 (s, 3 H), 3.18 (s, 3 H), 3.81 (br. s, 1 H), 4.41 (qd, J = 6.6, 1.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 21.0, 22.9, 23.6, 27.8, 28.3, 30.1, 49.2, 70.2, 72.9, 77.4, 79.9, 95.5, 154.0 ppm. HRMS (CI): calcd. for $C_{15}H_{30}NO_4$ [M + H]$^+$ 288.2175; found 288.2169. $C_{15}H_{29}NO_4$ (287.40): C 62.69, H 10.17, N 4.87; found C 62.38, H 10.05, N 5.03.

(–)-(2*S*)-2-Amino-3-methoxy-3-methyl-1-butanol Hydrochloride (10a): According to GP 3, **10a** was obtained from **9a** (6.37 g, 23.3 mmol) and AcCl (4.14 mL, 58.3 mmol) as a colorless, hygroscopic powder in 93% yield (3.77 g, 22.2 mmol). M.p. 135°°C (decomp.). $[\alpha]_D^{20}$ = –20.1 (c = 0.8, MeOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.12 (s, 3 H), 1.17 (s, 3 H), 3.06 (dd, J = 7.4, 3.7 Hz, 1 H), 3.10 (s, 3 H), 3.51 (ddd, J = 11.4, 7.4, 4.2 Hz, 1 H), 3.66 (ddd, J = 11.4, 3.8, 3.7 Hz, 1 H), 5.37 (dd, J = 4.2, 3.8 Hz, 1 H), 7.95 (br. s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 20.1, 21.7, 48.6, 58.4, 59.5, 73.8 ppm. HRMS (CI): calcd. for $C_6H_{16}NO_2$ [M – Cl]$^+$ 134.1181; found 134.1191. $C_6H_{16}ClNO_2$ (169.65): calcd. C 42.48, H 9.51, N 8.26; found C 42.79, H 9.02, N 8.16.

(–)-(2*R*,3*S*)-3-Amino-4-methoxy-4-methyl-2-pentanol Hydrochloride: (10b): According to GP 3, **10b** was obtained from **9b** (7.19 g, 25.0 mmol) and AcCl (4.44 mL, 62.5 mmol) as a colorless, hygroscopic powder in 94% yield (4.33 g, 23.6 mmol). M.p. 108–110 °C. $[\alpha]_D^{20}$ = –1.1 (c = 0.8, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.31 (s, 3 H), 1.44 (d, J = 6.5 Hz, 3 H), 3.08 (m, 1 H),

3.21 (s, 3 H), 4.15 (qd, J = 6.5, 2.6 Hz, 1 H), 4.45 (br. s, 1 H), 8.01 (br. s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 22.2, 49.0, 63.5, 64.1, 75.4 ppm. HRMS (CI): calcd. for $C_7H_{18}NO_2$ [M – Cl]$^+$ 148.1337; found 148.1335. $C_7H_{18}ClNO_2$ (183.68): calcd. C 45.77, H 9.88, N 7.63; found C 45.77, H 9.68, N 7.51.

(+)-(*S*)-2-(Formylamino)-3-methoxy-3-methyl-1-butanol (11a): According to GP 1, **11a** was obtained from **10a** (2.54 g, 15.0 mmol), ethyl formate (30 mL, 370 mmol), and NEt_3 (2.11 mL, 15.0 mmol) after 16 h. Flash chromatography (silica, EtOAc/EtOH, 9:1) gave rise to **11a** as a colorless oil in 91% yield (2.21 g, 13.7 mmol). $[\alpha]_D^{20}$ = +19.5 (c = 1, $CHCl_3$). The NMR spectra gave signals of the (*Z*)- and (*E*)-formamide in an (*Z*)/(*E*) ratio of 83:17. **(*Z*)-11a:** ^{1}H NMR (500 MHz): δ = 1.18 (s, 3 H), 1.25 (s, 3 H), 3.18 (s, 3 H), 3.51 (d, J = 7.7 Hz, 1 H), 3.64 (ddd, J = 11.2, 7.7, 3.3 Hz, 1 H), 3.90 (dd, J = 11.2, 4.0 Hz, 1 H), 3.93 (ddd, J = 7.8, 4.0, 3.3 Hz, 1 H), 6.62 (br. s, 1 H), 8.23 (d, J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 21.96, 22.01, 49.1, 56.1, 62.4, 77.9, 161.6 ppm. **(*E*)-11a:** ^{1}H NMR (500 MHz): δ = 1.15 (s, 3 H), 1.19 (s, 3 H), 3.16 (s, 3 H), 3.21 (ddd, J = 10.5, 6.9, 4.0 Hz, 1 H), 3.56 (br. s, 1 H), 3.68–3.76 (m, 2 H), 6.46 (dd, J = 11.9, 10.7 Hz 1 H), 7.99 (d, J = 11.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 21.8, 21.9, 49.2, 61.5, 61.8, 76.3, 165.3 ppm. HRMS (CI): calcd. for $C_7H_{16}NO_3$ [M + H]$^+$ 162.1130; found 162.1122.

(+)-(2*R*,3*S*)-3-(Formylamino)-4-methoxy-4-methyl-2-pentanol (11b): According to GP 1, **11b** was obtained from **10b** (3.67 g, 20.0 mmol), ethyl formate (40 mL, 500 mmol), and NEt_3 (2.81 mL, 20.0 mmol) after 72 h. Flash chromatography (silica, EtOAc/EtOH, 9:1) gave rise to **11b** as a colorless oil in 94% yield (3.25 g, 18.6 mmol). $[\alpha]_D^{20}$ = +16.5 (c = 1.4, $CHCl_3$). The NMR spectra showed signals of the (*Z*)- and (*E*)-formamide in an (*Z*)/(*E*) ratio of 92:8. **(*Z*)-11b:** ^{1}H NMR (500 MHz): δ = 1.09 (dd, J = 6.3, 0.9 Hz, 3 H), 1.19 (s, 3 H), 1.34 (s, 3 H), 3.21 (s, 3 H), 3.74 (s, 1 H), 3.76 (d, J = 10.4 Hz, 1 H), 4.38 (q, J = 6.3 Hz, 1 H), 6.45 (d, J = 10.2 Hz, 1 H), 8.35 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 19.8, 22.1, 22.2, 49.1, 58.1, 65.7, 79.4, 161.4 ppm. **(*E*)-11b:** ^{1}H NMR (500 MHz): δ = 1.11 (dd, J = 6.3, 0.7 Hz, 3 H), 1.33 (s, 3 H), 2.83 (d, J = 10.6 Hz, 1 H), 3.22 (s, 3 H), 3.59 (s, 1 H), 6.28 (dd, J = 12.1, 10.6 Hz, 1 H), 7.97 (d, J = 12.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 20.1, 22.2, 22.5, 49.2, 63.5, 65.4, 78.9, 164.5 ppm. HRMS (CI): calcd. for $C_8H_{17}NO_3$ [M + H]$^+$ 176.1287; found 176.1284. $C_8H_{17}NO_3$ (175.23): calcd. C 54.84, H 9.78, N 7.99; found C 54.40, H 9.59, N 8.21.

(+)-(2*S*)-2-Isocyano-3-methoxy-3-methylbutanol (12a): According to GP 2a, **12a** was obtained from **11a** (2.21 g, 13.7 mmol), HMDS (3.21 mL, 15.1 mmol), NEt_3 (4.82 mL, 34.3 mmol), $POCl_3$ (1.25 mL, 13.7 mmol), and $BF_3{\cdot}OEt_2$ (172 μL, 1.37 mmol) after flash chromatography (silica, hexanes/Et_2O, 1:1) as a colorless oil in 74% yield (1.45 g, 10.1 mmol). $[\alpha]_D^{20}$ = –7.6 (c = 1.2, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 1.28 (s, 3 H), 1.31 (s, 3 H), 3.04 (t, J = 6.4 Hz, 1 H), 3.24 (s, 3 H), 3.63 (m, 1 H), 3.79 (m, 1 H), 3.88 (m, 1 H_b) ppm. ^{13}C NMR (125 MHz): δ = 20.3, 22.5, 49.7, 61.7, 63.9 (t, J = 6.4 Hz), 76.1, 157.8 (t, J = 5.1 Hz) ppm. Traces of oxazoline **13a** could be observed by NMR spectroscopy. ^{1}H NMR (500 MHz, selected signals): δ = 4.10 (ddd, J = 9.6, 8.2, 1.9 Hz, 1 H), 4.16 (dd, J = 9.6, 8.7 Hz, 1 H), 4.22 (dd, J = 8.7, 8.2 Hz, 1 H), 6.87 (d, J = 1.9 Hz, 1 H) ppm. HRMS (CI): calcd. for $C_7H_{14}NO_2$ [M + H]$^+$ 144.1025; found 144.1032.

(+)-(2*R*,3*S*)-3-Isocyano-4-methoxy-4-methyl-2-pentanol (12b): According to GP 2b, **12b** was obtained from **11b** (2.38 g, 13.6 mmol), NEt_3 (4.78 mL, 34.0 mmol), and $POCl_3$ (1.24 mL, 13.6 mmol) after flash chromatography (silica, Et_2O) as a colorless oil in 72% yield (1.53 g, 9.73 mmol). $[\alpha]_D^{20}$ = +32.5 (c = 0.7, $CHCl_3$). ^{1}H NMR (500 MHz): δ = 1.28 (d, J = 6.3 Hz, 3 H), 1.29 (s, 3 H), 1.38 (s, 3 H), 3.25 (s, 1 H), 3.27 (s, 3 H), 3.58 (s, 1 H), 4.23 (s, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 20.7, 22.17, 22.24, 49.8, 64.3, 68.0 (t, J = 6.3 Hz), 158.7 ppm. HRMS (CI): calcd. for $C_8H_{16}NO_2$ [M + H]$^+$ 158.1181; found 158.1205.

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