Improved Synthesis of C₂-Symmetrical Pyridinediols and Synthesis of C₃-Symmetrical Pyridinediols


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Base-induced reaction of 2,6-dimethylpyridine (2,6-lutidine) (1) with two equivalents of various ketones has been reported to provide C₂-symmetrical pyridine diols 3. Closer examination reveals that competitive di-addition to a single methyl group can occur providing C₂-symmetrical pyridine diols 7. By varying the lithiation times, the formation of this side product could be maximized or minimized on the basis of a mechanistic proposal for the competing pathways. The formation of the C₃-diol 7 could be excluded completely by using potassium diisopropylamide as base; high yields of C₂-symmetrical pyridine diols 3 are obtained. Regioselective additions of 1 to (R)-fenchone and (−)-menthone were also achieved.

Introduction

The achievements over the past few decades in developing new chiral non-racemic reagents[1] and asymmetric synthetic methodologies[2] have been remarkable. For example, the synthesis of many chiral non-racemic receptor molecules is now a relatively simple matter. In the past, we have developed a synthetic approach to chiral non-racemic pyridine thioethers and dithiols,[3] and have, for example, applied the thioethers thereof in palladium-catalyzed allylic substitution.[4]

Sterically bulky C₂-symmetrical pyridine diol ligands like 3 obtained by condensation of ketones with lutidine 1 are of special interest as complexing agents for the development of new homogeneous catalysts. The combination of two hydroxy groups and the pyridine nitrogen atom leads to ligands capable, for example, of stabilizing high-valent osmium alkoxide complexes.[5] With Zr and W good polymerization catalysts are formed.[6] Biomimetic studies of enzymes have been conducted with some Mo complexes.[7] Well-defined complexes with Ti,[8] Zn,[9] Co,[9] Si,[10] and Ru[11] have also been reported in the literature.

The synthesis of this class of compounds was first reported by Tilford and Van Campen[12] and further explored by Berg and Holm[7b] in the synthesis of pyridine diol 3a. These compounds have been of interest in our group as model systems for zinc-alcohol dehydrogenase,[9b] carboxypeptidase,[13] and for preparation of silicon alkoxides.[10a] Several derivatives have been prepared making use of the described methodology for the synthesis of pyridine diols 3a (Scheme 1).[7b,9b] This approach consists of a one-pot, two-step synthesis. Yields are moderate; the benzophenone-based pyridine diol 3a is obtained in 35% yield, whereas C₂-symmetrical derivatives 3b, 3c, 3d, and 3e (based on adamantanol,[14] acetone,[9b] camphor, and fluorenone,[9b] respectively) are obtained in yields of 51, 34, 45, and 13%, respectively. We shall discuss some additional factors that can have a major effect on the synthetic outcome.

Scheme 1. Reagents and conditions: i) nBuLi (1.1 equiv.), THF, −60 °C; ii) R¹¹R²²C=O; iii) nBuLi (1.1 equiv.), −80 °C; iv) R¹¹R²²C=O; v) 2 N HCl; vi) nBuLi (2.1 equiv.), THF, room temp.

Synthesis

Yields could be improved substantially by applying a two-pot reaction in which the monoadduct 2 is first isolated, and then converted into the C₂-symmetrical di-adduct 3 by adding slightly more than two equivalents of base, followed by the addition of the ketone (Scheme 1). Mixed combinations can be prepared as shown by Nakayama et. al.[6a] However, there is more to this than meets the eye, as will be discussed in the following paragraphs. The monoadducts 2 formed by addition of monolithiated lutidine to benzophenone, adamantanol, and camphor can be isolated in 85, 88, and 89% yields, respectively. The second reaction step, however, is less straightforward. The time that the mixture is stirred after lithiation and before...
addition of the ketone (lithiation time) strongly influences the yield of the desired C₃-symmetrical product. Using this two-pot synthetic approach, it was found that if a lithiation time of 4 h was applied for the adamantane derivative 2b, after which one equivalent of adamantane was added, followed by work up with 2 N HCl, the adamantane-based C₃-symmetrical pyridine diol 3b could be isolated in 70% yield (overall yield 62%). However, when adamantane was added after a lithiation time of only 30 min, a second product, C₃-symmetrical pyridine diol 7b, was also isolated. The formation of 7b must involve deprotonation of the CH₂ group forming the dilithiated intermediate 5b instead of deprotonation at the presumably sterically less hindered methyl group, which gives rise to the intermediate 6b (Scheme 2).

Experiments at different temperatures and with different lithiation times were conducted in order to obtain further mechanistic insight. In these experiments, monosubstitution product 2b was treated with two equivalents of n-butyllithium under the given conditions. The ratios of the C₂-symmetrical adduct 7b to C₃-symmetrical adduct 3b were determined, after quenching the reaction with adamantane and workup with 2 N HCl, by means of ¹H-NMR spectroscopy. The results are given in Table 1; t₁ is the time between the addition of n-butyllithium and the addition of the adamantane, and t₂ is the time the mixture is stirred after the addition of the ketone and before it is quenched with HCl.

At −80 °C lithiation is slow (Entries 1, 2) and even at −40 °C complete lithiation requires several hours (Entries 3—5). Lithiation is far more rapid at 0 °C, and there is a clear tendency with short lithiation times for 7b to predominate over 3b, although the ratio tends towards the latter at longer lithiation times (Entries 6—9). This trend is even clearer at room temperature; fairly long lithiation times lead to a striking reversal of the ratio 7b over 3b (Entries 10—14). From these results it seems justified to conclude that the lithium alkoxide 4b first formed is deprotonated at the CH₂ group to form 5b more rapidly than at the methyl group to form 6b. In other words, k₅ > k₆ (Scheme 2). This effect is assumed to arise from coordination of the second equivalent of n-butyllithium to the electron-rich oxygen atom in the (presumed) chelate ring of 4b, followed by facile intermolecular deprotonation at the CH₂ group as shown in Figure 1. A second conclusion is that 6b is thermodynamically more stable than 5b. Whether the slow conversion of 5b to 6b is due to inter- or intramolecular processes cannot be concluded from the data of Table 1.

**Scheme 2.** Reagents and conditions: i) nBuLi (1.1 equiv.), THF; ii) 2 N HCl

**Figure 1.** Six-membered intermediate

Using the data of Table 1 as guide, the reaction conditions were optimized for formation of the C₃-diol 7b. This entailed lithiation and quenching at room temperature after a lithiation time of 30 s.

When similar temperature- and time-dependent lithiation experiments were carried out with the diphenylcarbinol 2a, only C₂-symmetrical diol 3a and some starting materials in the reaction mixture were detected. However, when longer lithiation times were used at room temperature, starting material was still recovered, despite the fact that lithiation at this temperature and with these reaction times should be complete. It was also observed that the yield of the C₂-symmetrical diol 3a increased with prolonged lithiation times. These observations can be explained by the formation of intermediate 5a, although no trace of the C₃-adduct 7a was detected. Only on modification of the workup procedure was the C₃-symmetrical diol 7a obtained. When 2 N NH₄Cl was used in the workup, C₃-symmetrical diol 7a could be isolated in moderate to low yield (5—35%) de-
pending on the reaction conditions applied (−80 °C to room temp.). The usual workup with 2 N HCl is, apparently, too acidic to keep the diol 7a intact. Experiments with various lithiation times and at different temperatures followed by workup with 2 N NH₄Cl showed the same phenomenon as observed for the adamantanone adduct. Initially, lithiation of the alkoxide 4a is preferred at the CH₂ group forming dilithio species 5a, which is converted into 6a at prolonged lithiation times. When the C₆-diol 7a was stirred with 2 N HCl it indeed reverted to the benzophenone monoadduct 2a and benzophenone (Scheme 3).

![Scheme 3. Retro aldol reaction](image)

This retro aldol reaction is probably initiated by protonation of the pyridine nitrogen atom of 8, after which the benzophenone is expelled, affording intermediate 9, which tautomerizes to the pyridine. The retro aldol reaction can also be induced by sonication or heat, and also occurs upon purification of the product by means of column chromatography on silica. This reaction is also observed for the C₆-diol 7b under acidic conditions at higher temperatures.

The best conditions for the formation of the C₆-diol 7a (35% yield) were found to be 0 °C with a lithiation time of 1 min. The optimal conditions for the formation of the C₆-diol 3a involve a lithiation time of 4 h at room temp. to afford 3a in 67% yield.

When the time- and temperature-dependent lithiation was carried out for the camphor adduct 2d, again an increase in the formation of the camphor-based C₆-diol 3d upon longer lithiation times was observed. Recovery of starting material at room temperature was substantial. The C₆-diol 7d, however, could not be detected, even when a mild workup procedure was applied. The best preparative results for the C₆-diol 3d were at −40 °C; at higher temperatures more side products are obtained. This diol adduct probably is too unstable to be isolated. The fact that double addition can take place at one methyl group is established probably is too unstable to be isolated. The fact that double addition reaction at this position can and does take place, and that in some cases the C₆-symmetrical diols 7 can be isolated, provided that they are sufficiently stable to survive retro aldol reaction.

The almost exclusive synthesis of the C₆-diols 3 as single product is possible, although long lithiation times (lithiation time of at least 4 h) are required to ensure that all the kinetic product is converted into the thermodynamic product. Another possibility is to make use of the understanding that was gained in conducting the time-dependent lithiatiations, of the intermediates. If a base is used that less readily leads to the six-membered intermediate chelate (Figure 1), the deprotonation at the CH₂ group should not be kinetically favored, and deprotonation should only take place at the less hindered methyl group. When the adamantanone-based alcohol 2b was deprotonated with 2.1 equivalents of potassium disopropylamide (KDA) and quenched with adamantanone after only 15 min of stirring, the C₆-diol 3b was obtained as sole product in 95% yield (Scheme 5). KDA is a very strong base, and the potassium does not strongly coordinate with the nitrogen and oxygen atoms. After deprotonation of the hydroxy group, the second attack apparently occurs at the sterically less hindered methyl group, and no reaction at the CH₂ group is observed. This approach is very selective and provides the C₆-diols exclusively after stirring for a short time. Sterically more hindered lithium bases such as sBuLi and tBuLi were not investigated to see whether they would lead to increased selectivity.

When this new approach was applied in the synthesis of the benzophenone- and camphor-based C₆-diols 3a and 3d, the products were isolated in high yields (Table 2).

The C₆-diols also have interesting features, as they are known to coordinate several metals. It would thus be de-
Efforts to add, facially selective if possible, the mono-adduct of 15 to another chiral ketone like (±)-menthene were less successful. Addition to (R)-fenchone afforded inseparable exo and endo adducts in equal amounts. Addition of the lithio species 15 to (±)-menthone gave the cis and trans isomers 2g in a ratio of 16:5 in favor of the cis adduct (Scheme 7). These isomers could be separated by means of column chromatography.

The configurations of the isomers were deduced from the HETCOR, COSY, and NOESY NMR spectral data (not shown). An NOE interaction of the equatorial benzylic CH3 protons (Figure 2a) with proton Hf and the axial proton Hs for the cis isomer was observed, whereas for the trans isomer interaction of the axial benzylic proton (Figure 2b) with either one of these protons is absent.

When the cis-2g isomer was lithiated with two equivalents of n-butyllithium and allowed to react with (±)-menthene, the bis-product was formed as a mixture of the isomers cis-cis-3g and cis-trans-3g in a ratio of 6:1. The cis-cis-3g isomer could be selectively crystallized from a mixture of water/ethanol.

Better facial selectivity for the (R)-fenchene derivative was obtained when the lithium in the monolithio species 15 was replaced by CeCl3, followed by the addition of (R)-fenchene. Alkylcerium reagents are known to give clean 1,2-addition to “difficult” ketones.[18] This is presumed to be due to the reduced basicity and the oxaphilicity of the alkylcerium reagent.[19] Furthermore, complexation of the cerium to the carbonyl functionality, and subsequent attack
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of the alkyl group to the carbon atom enhances selectivity. We thought that complexation of the alkyl reagent to the carbonyl group could improve the regioselectivity of the addition reaction to (R)-fenchone and (−)-menthone. Indeed, some improvement was found when the cerium species 16 was synthesized from the lithio species 15 and allowed to react with (R)-fenchone. However, although the endo/exo isomer ratio for this reaction improved to 1:2 at −50 °C in THF, a mixture of the two isomers was obtained. When the reaction temperature was lowered to −80 °C, a small improvement of the ratio to 1:4 was found. Addition of the cerium species 16 to (−)-menthone, however, led to far better results. When (−)-menthone was allowed to react with 16 at −80 °C only the cis isomer 2g was formed (Scheme 8).

Scheme 8. Reagents and conditions: i) nBuLi (1.1 equiv.), THF, −70 °C; ii) CeCl$_3$/THF; iii) (−)-menthone; iv) 2 $\equiv$ NH$_2$Cl

Conclusions

Aided by the understanding of the lithiation process, an approach has been developed that allows the preparation of chiral as well as achiral C$_2$-symmetrical pyridine diols in high yields. The synthetic approach to C$_2$-symmetrical pyridine diols opens up a route to interesting new ligands of which is currently under investigation. The use of CeCl$_3$ in the addition reaction of 2,6-lutidine to (−)-menthone gave a regiospecific addition to the cis-pyridine diol. The application of CeCl$_3$ in the addition reactions opens up a new perspective for regioselective addition to chiral ketones, as shown for (−)-menthone.

Experimental Section

General Remarks: All reactions were carried out under Ar. The following solvents were distilled prior to use: THF was distilled from Na wire, acetonitrile and dichloromethane were distilled from CaH$_2$, and diethyl ether and hexane were distilled from P$_2$O$_5$. – Column chromatography was performed on alumina (Merck 90, II/III, 0.063–0.200 mm) or silica gel (Alrich 60, 230–400 mesh). – Elemental microanalyses were carried out in the analytical department of this laboratory. – $^1$H- and $^{13}$C-NMR spectra were recorded using a Varian Unity Plus 500, a Varian VXR 300 instrument or a Genuine 200 instrument. The chemical shifts are expressed relative to CDCl$_3$ for $^1$H-NMR (at δ = 7.26) and $^{13}$C-NMR (at δ = 76.91). NOESY [20] and COSY [21] spectra were performed using standard Varian pulse programs. – Deuterated solvents were dried with an Al$_2$O$_3$ (activity I) column just prior to use. All other reagents were obtained from Aldrich or Acros Chimica and used as received, unless otherwise noted.

2-(6-Methyl-2-pyridinyl)-1,1-diphenyl-1-ethanol (2a): 2.6-Lutidine (1) (10.0 g, 93.3 mmol) was dissolved in 200 mL of THF and cooled to −60 °C. n-Butyllithium (1.6 M in hexane, 59.4 mL, 95.0 mmol) was added under stirring. The mixture was warmed to −50 °C and stirring was continued for 1 h before benzophenone (17.3 g, 95.0 mmol) in 25 mL of THF was added by means of a cannula. The mixture was allowed to reach ambient temperature overnight, and was acidified to pH = 1 with 2 $\equiv$ HCl. After stirring for 1 h, the mixture was neutralized with 2 $\equiv$ NaOH. The aqueous layer was extracted with ethyl acetate twice and the organic layers were dried with MgSO$_4$. After concentration in vacuo, the product was recrystallized from methanol yielding a colorless solid (2.3 g, 79.5 mmol, 85%) with m.p. 124–125 °C. – IR (KBr): $\tilde{v}$ = 3250, 2900, 1610, 1600, 1450, 1100, 800, 700, 550 cm$^{-1}$. – $^1$H NMR (300 MHz, CDCl$_3$): δ = 2.47 (s, 3 H), 3.67 (s, 2 H), 6.90 (m, 2 H), 7.15 (m, 2 H), 7.23 (m, 4 H), 7.40 (m, 1 H), 7.49 (m, 4 H), 8.17 (br, OH). – $^{13}$C NMR (300 MHz, CDCl$_3$): δ = 24.1 (q), 46.7 (t), 78.2 (s), 120.9 (d), 121.4 (d), 126.1 (d), 126.2 (d), 127.7 (d), 137.0 (d), 147.3 (s), 156.7 (s), 158.4 (s). – HRMS: calcld. 289.147; found 289.147. – C$_{20}$H$_{16}$NO (289.4): calcld. C 83.93, H 6.24, N 5.48; found C 83.93, H 6.34, N 5.47.

2-(6-Methyl-2-pyridinyl)ethyl]-2-adamantanone (2b): 2.6-Lutidine (1) (3.84 g, 35.8 mmol) was dissolved in 100 mL of THF and cooled to −50 °C. Subsequently, n-butyllithium (1.6 M in hexane, 22.6 mL, 36.2 mmol) was added and stirring was continued for 30 min. A solution of adamantanone (5.4 g, 36 mmol) in 10 mL of THF was added slowly and stirring was continued overnight allowing the mixture to reach room temp. slowly. The solution was quenched with 2 $\equiv$ HCl and stirred for 15 min before it was neutralized with 2 $\equiv$ NaOH. The solution was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried with MgSO$_4$. After being dried under vacuum, the product was recrystallized from hexane yielding a colorless solid (8.1 g, 31.5 mmol, 88%) with m.p. 131–132 °C. – IR (KBr): $\tilde{v}$ = 3250, 2900, 1610, 1600, 1450, 700 cm$^{-1}$. – $^1$H NMR (200 MHz, CDCl$_3$): δ = 1.4–2.0 (m, 12 H), 2.28 (m, 2 H), 2.50 (s, 3 H), 3.08 (s, 2 H), 6.48 (s, OH), 6.94 (d, J = 11.7 Hz, 1 H), 6.98 (d, J = 11.7 Hz, 1 H), 7.49 (dd, J = 11.7 Hz, J = 11.7 Hz, 1 H), 7.50 (m, 2 H), 7.52 (s), 120.9 (d), 121.4 (d), 126.1 (d), 126.2 (d), 126.4 (d), 157.2 (s), 158.8 (s). – HRMS: calcld. 275.178; found 275.179. – C$_{25}$H$_{22}$NO (275.4): calcld. C 79.33, H 9.01, N 5.44; found C 79.86, H 9.05, N 5.45.

1(1R,2S)-1,7,7-Trimethyl-2-[6-(6-methyl-2-pyridinyl)ethyl]-bicyclo-[2.2.1]heptan-2-ol (2d): To a solution of 2,6-lutidine (1) (6.0 g, 56 mmol) in 20 mL of THF at −60 °C was added n-butyllithium (1.6 M in hexane, 38.5 mL, 61.6 mmol). The mixture was stirred at −60 °C for 30 min and (R)(+)-camphor (5.4 g, 56 mmol) in 20 mL of THF was added. Stirring was continued for 1 h at −60 °C. The mixture was quenched with 1 $\equiv$ HCl and stirred for 30 min and neutralized with 2 $\equiv$ NaOH. The solution was extracted with ethyl acetate twice and the combined organic layers were washed with brine and dried with MgSO$_4$. After removal of the solvents in vacuo, the product was purified by means of kugelrohr distillation (75 °C, 0.4 Torr) yielding 2d as a colorless solid (13.0 g, 51 mmol, 90%) with m.p. 38–39 °C. – $^1$H NMR (300 MHz, CDCl$_3$): δ = 0.45 (s, 3 H), 1.05 (m, 1 H), 1.07 (s, 3 H), 1.30 (m, 1 H), 1.41 (m, 2 H), 1.63 (m, 2 H), 1.90 (m, 1 H), 2.44 (s, 3 H), 2.88 (s, 2 H), 6.65 (br, OH), 6.91 (d, J = 7.7 Hz, 1 H), 6.94 (d, J = 7.7 Hz, 1 H), 7.45 (dd, J = 7.7 Hz, J = 7.7 Hz, 1 H), 7.50 (m, 2 H), 7.52 (s), 120.9 (d), 121.4 (d), 126.1 (d), 126.2 (d), 126.4 (d), 157.2 (s), 158.8 (s). – HRMS: calcld. 259.194; found 259.194.
C$_{12}$H$_{22}$NO (259.4): calcd. C 78.72, H 9.71, N 3.56; found C 78.75, H 9.78, N 3.54.

2-[(6-[(2-Hydroxy-2-adamantyl)methyl]-2-pyridinyl)methyl]-2-adaman- tanol (3b) with n-Butyllithium: The mono-adduct 2b (1.1 g, 3.4 mmol) was dissolved in 50 mL of THF and n-butyllithium (1.6 m in hexane, 5.6 mL, 9.0 mmol) was added to deprotonate the starting material. The mixture was stirred for 4 h before adamantanone (0.7 g, 4.3 mmol) in 5 mL of THF was added. After stirring for 1 h 1 N HCl was added and after stirring for 30 min it was neutralized with 2 N NaOH. The solution was extracted with dichlormethane twice and the combined organic layers were washed with brine and dried with MgSO$_4$. After removal of the solvent, the product was recrystallized from ethanol yielding 3b as colorless needles (1.2 g, 3.0 mmol, 70%) with m.p. 194°C, m/z 274 (M$^+$), 238 (M$^+$-C$_3$H$_5$), 215 (M$^+$-C$_3$H$_5$-OH). IR (KBr): δ = 3500, 3300, 2923, 2850, 2500, 1600, 1450, 700 cm$^{-1}$. – H NMR (300 MHz, CDCl$_3$): δ = 1.4–1.9 (m, 20 H), 2.00 (m, 4 H), 2.14 (m, 4 H), 3.13 (s, 4 H), 4.21 (s, 2 OH), 7.07 (d, $J$ = 7.7 Hz, 2 H), 7.55 (s, 1 H). – 13C NMR (300 MHz, CDCl$_3$): δ = 23.7 (d), 32.7 (t), 34.6 (t), 37.2 (d), 38.3 (t), 44.6 (t), 75.4 (s), 122.5 (d), 136.8 (d), 158.3 (s). – HRMS: calcd. 472.2822; found 472.2822. – C$_{23}$H$_{29}$NO$_2$ (472.6): calcd. C 84.05, H 5.99, N 2.96.}

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was added by syringe. Stirring was continued for 3 h allowing the mixture to reach room temp. The mixture was quenched with 2 N NH₄Cl and extracted twice with ethyl acetate, after which the combined organic layers were washed with brine and dried with MgSO₄. After removal of the solvent, the product was purified by kugelrohr distillation (120 °C, 0.1 Torr) yielding 10d as a colorless oil (6.2 g, 25 mmol, 72%). νₒ (KBr) = 3200, 3000, 1600, 1580, 1450, 1100, 850, 800, 700 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 0.48 (s, 3 H), 0.81 (s, 3 H), 0.98 (d, J = 13.2 Hz, 1 H), 1.09 (m, 1 H), 1.11 (s, 3 H), 1.41 (m, 3 H), 1.70 (m, 2 H), 2.06 (d, J = 13.2 Hz, 1 H), 2.91 (s, 2 H), 6.31 (br, OH), 7.17 (m, 2 H). 7.61 (t, J = 7.7 Hz, 1 H), 8.45 (d, J = 4.0 Hz, 1 H). 13C NMR (300 MHz, CDCl₃): δ = 11.0 (q), 20.9 (q), 21.3 (q), 27.1 (t), 30.6 (t), 44.9 (d), 45.1 (t), 47.3 (t), 49.4 (s), 52.8 (s), 81.1 (s), 121.3 (d), 124.2 (d), 136.7 (d), 147.8 (d), 160.4 (s). 13C NMR: calcd. 245.178; found 245.178 – C₂H₅N₂O (245.4); calcd. C 78.32, H 9.45, N 5.71; found C 78.33, H 9.54, N 5.44.

Reaction of (10d) with n-Butyllithium and Benzophenone to Obtain 10a: To a stirred solution of 10d (0.7 g, 2.7 mmol) in 50 mL of THF at −60 °C was added n-butyllithium (1.6 mol in hexane, 3.5 mL, 5.6 mmol) followed after 5 min by the addition of benzophenone (0.5 g, 2.7 mmol). The mixture was stirred for 1 h, allowing it to reach ambient temperature, and was quenched with 2 N NH₄Cl. The solution was extracted with dichloromethane twice and the combined organic layers were washed with brine and dried with Na₂SO₄. After removal of the solvents, the product was purified by kugelrohr distillation (120 °C, 0.1 Torr) yielding 10a as a colorless solid (10.8 g, 39.4 mmol, 94%). All spectroscopic data are in full accordance with those described in previous paragraphs.

Preparation of KDA: To a stirred solution of potassium tert-butoxide (0.9 g, 8.0 mmol) in 50 mL of THF was added disopropylamine (0.8 g, 8.0 mmol), and the mixture was cooled to −100 °C. n-Butyllithium (1.6 mol in hexane, 5.0 mL, 8.0 mmol) was added over a period of 10 min and the solution was stirred for 30 min before use. 2-({6-[[(2-Hydroxy-2-adamantyl)methyl]-2-pyridinyl}methyl]-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)ethanol (3b) with KDA: 2-({6-[[(2-Hydroxy-2-adamantyl)methyl]-2-pyridinyl}methyl]-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)ethan-2-ol (3d) with KDA: Mono-adduct 2d (0.5 g, 1.9 mmol) was dissolved in 50 mL of THF and a solution of KDA (0.16 mol in THF, 25 mL, 4.0 mmol) was added at −50 °C. After stirring for 15 min, a solution of (Z)-(+)-camphor (0.3 g, 2.0 mmol) in 5 mL of THF was added. Stirring was continued for 2 h while the solution was allowed to reach ambient temperature. The mixture was quenched with 2 N NH₄Cl and extracted twice with dichloromethane. The combined organic layers were washed with brine and dried with MgSO₄. The product was recrystallized from ethanol/water (2:1) (0.8 g, 1.8 mmol, 95%). All experimental data are in full accordance with those described in previous paragraphs.

2-Methyl-1-[(2-pyridinyl)ethen-2-propanol (10c): To a solution of 2-picoline (13) (3.9 g, 42 mmol) in 100 mL of THF at −60 °C was added n-butyllithium (1.6 mol in hexane, 26.3 mL, 42.1 mmol) and the mixture was stirred for 30 min. A solution of benzophenone (7.6 g, 42 mmol) in 10 mL of THF was added. Stirring was continued for 1 h allowing the mixture to reach ambient temperature. The mixture was quenched with 2 N NH₄Cl, extracted twice with ethyl acetate and the combined organic layers were dried with MgSO₄. The product was recrystallized from ethanol yielding a colorless solid (10.8 g, 9.9 mmol, 94%). All spectroscopic data are in accordance with those described in previous paragraphs.

1,1-Diphenyl-2-[(2-pyridinyl)ethyl]ethan-1-ol (3a): To a solution of 2-picoline (13) (3.9 g, 42 mmol) in 100 mL of THF at −60 °C was added n-butyllithium (1.6 mol in hexane, 26.3 mL, 42.1 mmol) and the mixture was stirred for 30 min. A solution of benzophenone (7.6 g, 42 mmol) in 10 mL of THF was added. Stirring was continued for 1 h allowing the mixture to reach ambient temperature. The mixture was quenched with 2 N NH₄Cl, extracted twice with ethyl acetate and the combined organic layers were dried with MgSO₄. The product was purified by column chromatography [silica, hexane/diethyl ether (3:1)] yielding 10b as a colorless solid (1.6 g, 7.4 mmol, 74%) with mp. 87−88 °C. IR (KBr): ν = 3300, 2900, 1600, 1590, 1400, 950, 800 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 1.4−2.0 (mol, 12 H), 2.33 (d, J = 11.0 Hz, 2 H), 3.14 (s, 2 H), 6.05 (br, OH), 7.15 (m, 2 H), 7.61 (t, J = 7.7 Hz, 1 H), 8.50 (d, J = 5.5 Hz, 1 H). 13C NMR (300 MHz, CDCl₃): δ = 27.3 (s), 27.4 (d), 27.4 (t), 34.6 (t), 37.2 (d), 38.4 (t), 43.6 (t), 75.4 (s), 121.3 (d), 124.4 (d), 136.6 (d), 148.3 (d), 159.6 (s). HRMS: calcd. 243.16; found 243.16. C₁₆H₂₁NO (243.4); calcd. C 78.79, H 8.70, N 5.67; found C 78.95, H 8.79, N 5.81.

2-Methyl-1-[(2-pyridinyl)methyl]-2-propanol (10c): To a solution of 2-picoline (13) (0.7 g, 7.4 mmol) in 50 mL of THF at −50 °C was added n-butyllithium (1.6 mol in hexane, 5.0 mL, 8.1 mmol) followed by the addition of acetone (0.6 g, 10 mmol) after stirring for 15 min. Stirring was continued for another 15 min, and the solution was quenched with NH₄Cl and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried with MgSO₄. The product was obtained after distillation by means of kugelrohr (60 °C, 0.05 Torr) affording 10c (0.6 g, 3.8 mmol, 51%). IR (KBr): νₜ = 1761, 1715, 1640, 1242, 1048, 728 cm⁻¹.
2,5,6 (br, OH), 5.65 (d, 1H), 7.05 (d, 1H), 7.55 (t, 1H), 8.10 (d, 1H), 8.42 (d, 1H). – \(^1^C\)C NMR (300 MHz, CDCl\(_3\)): \(\delta = 29.3\) (q), 48.5 (t), 70.6 (s), 121.3 (d), 124.2 (d), 136.6 (s), 148.2 (d), 159.8 (s).

1.1,3,3-Tetraphenyl-2-(2-pyridinyl)-1,3-propanediol (14a): To a solution of the mono-adduct 10a (1.0 g, 3.6 mmol) in 50 mL of THF at room temp. was added 2-n-butylthiophene (1.6 mL in hexane, 4.8 mL, 7.7 mmol). The mixture was stirred for 15 min and benzophenone (0.7 g, 3.6 mmol) in 5 mL of THF was added. The mixture was stirred overnight. The mixture was quenched with 2 N HCl and extracted with dichloromethane, and the organic layer dried with MgSO\(_4\). The mixture was concentrated in vacuo, the solid was washed with hot methanol and recrystallized from ethyl acetate/hexane yielding a colorless solid (0.6 g, 1.2 mmol, 33%) with m.p. 143 °C. After stirring of the mono-adduct 10a (1.0 g, 3.6 mmol) in 50 mL of THF at –60 °C was added 2-n-butylthiophene (1.6 mL in hexane, 4.1 mL, 6.5 mmol). After stirring for 10 min, (–)-menthone (1.0 g, 6.5 mmol) in 5 mL of THF was added. Stirring was continued for 1 h at –60 °C before the mixture was quenched with NH\(_4\)Cl and extracted with ethyl acetate. The organic layer was washed with brine and dried with MgSO\(_4\). The cis and trans products in the mixture with a ratio of 2:1 were separated by means of column chromatography (silica, hexane/diethyl ether 10:1) yielding the pure isomers.

trans-2g (0.5 g, 2.0 mmol, 30%), m.p. 60–62 °C. – \([\alpha]_D^{23} = +67\) (c = 0.8, acetone). – \(^1^H\) NMR (500 MHz, CDCl\(_3\)): \(\delta = 0.72\) (d, 1H, J = 6.5 Hz, 3H), 0.87 (d, J = 7.0 Hz, 1H), 0.91 (m, 2H), 1.03 (d, J = 7.0 Hz, 3H), 1.33 (m, 2H), 1.37 (m, 2H), 1.67 (m, 1H), 1.73 (m, 1H), 2.44 (d, J = 7.0 Hz, 7.0 Hz, 1H), 2.52 (s, 3H), 2.94 (dd, J = 14.0 Hz, 14.0 Hz, 2H), 6.91 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.51 (dd, J = 7.0 Hz, J = 7.8 Hz, 1H). – \(^1^C\)NMR (300 MHz, CDCl\(_3\)): \(\delta = 19.2\) (q), 22.3 (q), 23.4 (t), 24.86 (q), 24.78 (q), 30.3 (d), 35.0 (t), 38.9 (t), 47.8 (t), 51.9 (d), 75.6 (s), 120.8 (d), 121.2 (d), 136.9 (s), 159.4 (s). – HRMS: calcld. 261.209; found 261.209.

cis-2g (1.0 g, 3.8 mmol, 59%), m.p. 64–66 °C. – \([\alpha]_D^{23} = -121\) (c = 0.6, acetone). – \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.67\) (d, J = 6.2 Hz, 3H), 0.75 (m, 2H), 0.88 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 1.05 (m, 1H), 1.15 (m, 1H), 1.52 (m, 2H), 1.67 (m, 2H), 2.19 (dq, J = 6.9 Hz, J = 6.9 Hz, 1H), 2.44 (d, J = 3.9, 1H), 2.45 (s, 3H), 3.31 (d, J = 13.9 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 6.9 Hz, J = 7.7 Hz, 1H). – \(^1^C\)NMR (300 MHz, CDCl\(_3\)): \(\delta = 18.0\) (q), 20.8 (t), 22.4 (q), 23.8 (q), 24.2 (q), 26.2 (d), 27.7 (d), 35.4 (t), 46.1 (t), 47.4 (t), 51.1 (d), 74.7 (s), 120.6 (d), 121.5 (d), 136.8 (s), 157.1 (s), 159.9 (s). – HRMS: calcld. 261.209; found 261.209. – \(\text{C}_12\text{H}_22\text{NO}_2\) (261.4): calcld. C 78.11 H 10.41, N 5.36; found C 78.12 H 10.57, N 5.12.

1.2.5.5.5-2-Isopropyl-5-methyl-1-[(6-methyl-2-pyridinyl)-methyl]cyclohexanol (2g): To a solution of 2,6-lutidine (0.4 g, 2.5 mmol) in 3 mL of THF at –14 °C was added menthone (1.0 g, 6.5 mmol) in 5 mL of THF. After stirring for 10 min, (–)-menthone (1.0 g, 6.5 mmol) in 5 mL of THF was added. After stirring for 1 h the mixture was quenched with NH\(_4\)Cl and extracted with ethyl acetate. The organic layer was washed with brine and dried with MgSO\(_4\). The cis and trans products in the mixture with a ratio of 2:1 were separated by means of column chromatography (silica, hexane/diethyl ether 10:1) yielding the pure isomers.
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(300 MHz, CDCl3): δ 0.67 (d, J = 6.4 Hz, 6 H), 0.8 (m, 4 H), 0.89 (d, J = 6.9 Hz, 6 H), 0.94 (d, J = 6.6 Hz, 6 H), 1.05 (m, 2 H), 1.4–1.8 (m, 10 H), 2.20 (m, 2 H), 2.49 (d, J = 13.2 Hz, 2 H), 3.32 (d, J = 13.2 Hz, 2 H), 3.75 (br, 2 OH), 6.99 (d, J = 7.7 Hz, 2 H), 7.50 (t, J = 7.7 Hz, 1 H). – 13C NMR (300 MHz, CDCl3): δ = 18.1 (q), 20.8 (t), 23.3 (q), 23.7 (q), 26.1 (d), 27.6 (d), 35.1 (t), 47.1 (t), 47.4 (t), 51.0 (d), 74.7 (s), 122.3 (d), 136.8 (d), 159.2 (s). – HRMS: calcld. 415.345; found 415.345. – C2H15NO2 (395.5): calcld. C 78.02, H 10.91, N 3.37; found C 77.91, H 10.99, N 3.37.

Dichloro(6-methyl-2-pyridinyl)methyl]cerium (16): To a stirred solution of 2,6-lutidine (1) (0.1 m solution in THF, 10 mL, 1.0 mmol) at 70 °C was added n-butyllithium (0.6 mL, 1.0 mmol). After stirring for 15 min, this solution was added to CeCl3·nH2O, 0.1 mmol) in THF, 10 mL, 1.0 mmol) at 70 °C. The solution was stirred for 1 h at –50 °C and used as such for the addition reactions to ketones.

General Procedure for the Addition of 16 to Ketones: To a stirred solution of 16 (0.05 m solution in THF, 20 mL, 1.0 mmol) at 70 °C was added a solution of the ketone (1.0 mmol) in 2 mL of THF. Stirring was continued for 3 h after which the solution was quenched with NH4Cl and extracted with ethyl acetate twice. The combined layers were washed with brine and dried with MgSO4.

(1R,2R)-1,3,5-Trimethyl-2-[(6-methyl-2-pyridinyl)methyl]bicyclo-[2.2.1]heptan-2-ol (2f) with CeCl3: According to the above general procedure starting from 16 (0.05 m solution in THF, 22 mL, 1.1 mmol) and (R)-p-fenchone (0.2 g, 1.1 mmol), a mixture of endo and exo isomers 2f was obtained in a ratio of 4:1 (0.2 g, 0.6 mmol, 54%). The spectra for these isomers are in accordance with those described in previous paragraphs.

(1R,2S,5S)-2-Isopropyl-5-methyl-1-[(6-methyl-2-pyridinyl)methyl]cyclohexanol (cis-2g) with CeCl3: According to the above general procedure starting from 16 (0.05 m solution in THF, 36 mL, 1.8 mmol) and (S)-p-henlenethione (0.3 g, 1.8 mmol) cis-2g was obtained as a colorless solid after column chromatography (silica, hexane/diethyl ether 9:1) (0.2 g, 0.8 mmol, 45%). Spectra were in full accordance with those described in previous paragraphs.

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