New pyridine-derived *N*-oxides as chiral organocatalysts in asymmetric allylation of aldehydes

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Abstract

New chiral pyridine-type *N*-oxides **5a**–**e** have been synthesized from (+)-α-pinene (+)-**6** in four steps including photochemical oxidation, followed by Kröhnke annulation, α-alkylation, and *N*-oxidation. The methoxy derivative (+)-**5d** exhibited the highest enantioselectivity as a catalyst in the title reaction, producing (*S*)-(–)-**3** of 68% e.e.
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1. Introduction

The asymmetric allylation of aldehydes with allyltrichlorosilanes, catalyzed by chiral Lewis bases (Scheme 1), is a newly developed powerful method for the synthesis of optically active homoallylic alcohols [1–3]. Particularly high enantioselectivities (≤92% e.e.) have been attained with 2,2′-bipyridine-type bis-*N*,*N*-oxides and related catalysts, characterized by strongly donating oxygen atoms [1h,2].

We have recently reported on the new terpene-derived bipyridine *N*-monoxide **4a** (PINDOX) and its dimethyl analogue **4b** (Scheme 2), which exhibited a further enhanced enantioselectivity (≤98% e.e.) in the allylation of benzaldehyde and its congeners (Table 1,

entries 1 and 2) [4]. Herein, we report on the catalytic activity of their monopyridine analogues **5a**–**e**.

2. Experimental

2.1. Materials and methods

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in CHCl₃ at 25 °C unless otherwise indicated, with an error of ≤±0.1. The $[\alpha]_D$ values are given in $10^{-1\circ}\,cm^3\,g^{-1}$. The NMR spectra were recorded in CDCl₃, ¹H at 400 MHz and ¹³C at 100.6 MHz with chloroform-d_1 (δ 7.26, ¹H; δ 77.0, ¹³C) as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for CHCl₃ solutions. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of

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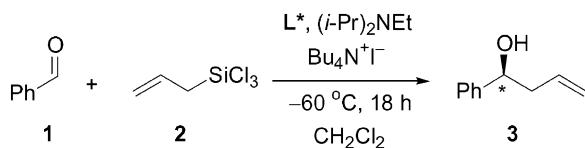
Scheme 1.

dry, oxygen-free nitrogen in oven-dried glassware, twice evacuated and filled with inert gas. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use (dichloromethane from calcium hydride). Petroleum ether refers to the fraction boiling in the range of 60–80 °C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures. (+)-α-Pinene (+)-6 was purchased from Aldrich; according to GC analysis on a Supelco β-DEX 120 column the e.e. was 90%. (−)-Pinocarvone (−)-7 was obtained on a 40 g scale from (+)-α-pinene (+)-6 via the photochemical oxidation (99%) according to the Mihelich procedure [5]. The Kröhnke salts 8a–d were prepared from the corresponding acetophenones by iodination in the presence of pyridine by refluxing in ethyl acetate; 8a, 8c, and 8d were known compounds [6–8]. Allyltrichlorosilane was used as purchased.
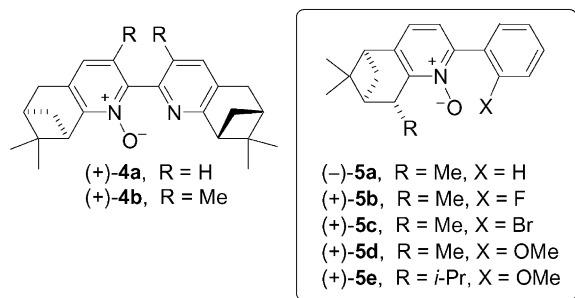
Scheme 2.

2.2. Procedures

2.2.1. Kröhnke salt 8b

2-Fluoroacetophenone (5.0 g, 36.2 mmol) was added dropwise to a solution of I_2 (9.1 g, 36.2 mmol) in pyridine (15 ml), the resulting solution was refluxed for 2 h, and then cooled to room temperature. The brownish precipitate was filtered off, successively washed with absolute ethanol (2 × 5 ml), pyridine (4 ml), and again absolute ethanol (2 × 5 ml) to give 8b as a pale yellow solid (5.8 g, 47%): mp 202–203 °C (dec); ^1H NMR δ (DMSO-d_6) 6.31 (d, $J = 3.3$ Hz, 2H), 7.48 (t, $J = 8.1$ Hz, 1H), 7.55 (dd, $J = 11.8$, 8.4 Hz, 1H), 7.86 (m, 1H), 8.01 (td, $J = 7.6$, 1.8 Hz, 1H), 8.28 (dd, $J = 7.8$, 6.6 Hz, 2H), 8.75 (t, $J = 7.8$ Hz, 1H), 8.98 (d, $J = 6.6$ Hz, 2H); ^{13}C NMR δ (DMSO-d_6) 69.22 (d, $J = 13.6$ Hz, CH_2), 117.52 (d, $J = 23.1$ Hz, CH), 122.13 (d, $J = 12.6$ Hz, C), 125.73 (d, $J = 2.9$ Hz, CH), 128.12 (CH), 130.79 (CH), 137.47 (d, $J = 9.6$ Hz, CH), 146.73 (d, $J = 20.6$ Hz, CH), 162.26 (d, $J = 255.0$ Hz, CF), 188.58 (CO); HRMS (EI) 215.0741 [$C_{13}H_{10}FNO$ $(M–H)^+$ requires 215.0746].

2.2.2. General procedure for the condensation of Kröhnke salts 8a–d with (−)-pinocarvone (−)-7: Method A

A suspension of the respective Kröhnke salt 8a–d (8.00 mmol), anhydrous ammonium acetate (10.0 g), and (−)-pinocarvone-(−)-7 (7.00 mmol), in acetic acid (10 ml) was heated at 100 °C for 3 h. Water (20 ml) was then added and the mixture was extracted with ethyl acetate (3 × 50 ml). The combined organic layers were washed successively with water (3 × 50 ml) and brine (30 ml), and dried ($MgSO_4$). The solvent was removed in vacuo to afford an oil that was purified via flash chromatography on silica gel (25 g) using petroleum ether, followed by a 9:1 mixture of petroleum ether and ethyl acetate to give pure (+)-9a–d as dense yellowish/orange oils; the yields are given below.

(+)-9a (65%): $[\alpha]_D$ +82.5 (c 0.8, CHCl₃) {literature [9] gives $[\alpha]_D$ +90.5 (c 1.8, CHCl₃)}; ^1H NMR δ 0.71 (s, 3H), 1.34 (d, $J = 9.5$ Hz, 1H), 1.45 (s, 3H), 2.42 (m, 1H), 2.73 (dt, $J = 9.5$ and 5.7 Hz, 1H), 2.81 (t, $J = 5.7$ Hz, 1H), 3.21 (d, $J = 2.8$ Hz, 2H), 7.28, (d, $J = 7.7$ Hz, 1H), 7.37–7.54 (m, 4H), 7.97 (dd, $J = 7.1$ and 1.9 Hz, 1H) in accordance with

the literature [9]; ^{13}C NMR δ 21.7 (CH$_3$), 26.5 (CH$_3$), 32.4 (CH$_2$), 37.2 (CH$_2$), 39.9 (C), 40.7 (CH), 46.7 (CH), 117.6 (CH), 127.1 (CH), 128.6 (CH), 129.0 (CH), 134.0 (CH), 140.4 (C), 140.8 (C), 155.2(C), 157.2(C).

(+)-**9b** (83%): $[\alpha]_D$ +95.0 (c 1.0, CH$_2$Cl$_2$) {an authentic sample of the opposite enantiomer had $[\alpha]_D$ −75.2 (c 0.8, CHCl$_3$) [7c]}; ^{1}H NMR δ 0.69 (s, 3H), 1.32 (d, $J = 9.6$ Hz, 1H), 1.42 (s, 3H), 2.39 (m, 1H), 2.70 (dt, $J = 9.6$, 5.7 Hz, 1H), 2.79 (t, $J = 5.7$ Hz, 1H), 3.18 (d, $J = 2.8$ Hz, 2H), 7.12 (ddd, $J = 11.3$, 8.1, and 1.2 Hz, 1H), 7.23 (ddd, $J = 7.7$, 7.7, and 1.2 Hz, 1H), 7.25 (d, $J = 7.8$ Hz, 1H), 7.32 (m, 1H), 7.46 (dd, $J = 7.8$ and 2.4 Hz, 1H) 7.96 (ddd, $J = 7.9$, 7.9, and 1.9 Hz, 1H); ^{13}C NMR δ 21.8 (CH$_3$), 26.5 (CH$_3$), 32.3 (CH$_2$), 37.1 (CH$_2$), 39.9 (C), 40.6 (CH), 46.7 (CH), 116.4 (d, $J_{C–F} = 23.2$ Hz, CH), 121.5 (d, $J_{C–F} = 8.8$ Hz, CH), 124.8 (d, $J_{C–F} = 3.1$ Hz, CH), 128.4 (d, $J_{C–F} = 12.2$ Hz, C), 130.0 (d, $J_{C–F} = 8.5$ Hz, CH), 131.4 (d, $J_{C–F} = 3.4$ Hz, CH), 133.5 (CH), 141.1 (C), 150.7 (C), 157.3 (C), 160.8 (d, $J_{C–F} = 248.8$ Hz, CF); IR ν 3030, 3007, 2935, 1585, 1492, 1447 cm^{-1}; HRMS (EI) 267.1422 (C$_{18}$H$_{18}$FN requires 267.1423).

(+)-**9c** (82%): $[\alpha]_D$ +35.8 (c 1.2, CHCl$_3$); ^{1}H NMR δ (400 MHz) 0.64 (s, 3H), 1.28 (d, $J = 9.6$ Hz, 1H), 1.36 (s, 3H), 2.32 (m, 1H), 2.62 (m, 1H), 2.74 (t, $J = 5.7$ Hz, 1H), 3.11 (d, $J = 2.8$ Hz, 2H), 7.16–7.30 (m, 3H), 7.40 (td, $J = 7.5$ and 1.0 Hz, 1H), 7.57 (dd, $J = 7.6$ and 1.7 Hz, 1H), 7.67 (dd, $J = 8.0$ and 1.0 Hz, 1H); ^{13}C NMR δ 21.7 (CH$_3$), 26.4 (CH$_3$), 32.3 (CH$_2$), 37.0 (CH$_2$), 39.9 (C), 40.6 (CH), 46.7 (CH), 121.5 (CH), 122.5 (CH), 127.8 (CH), 129.6 (CH), 131.8 (CH), 133.1 (CH), 133.6 (CH), 138.5 (C), 141.0 (C), 155.7 (C), 155.0 (C); MS (EI) m/z (%) 327 ($M^{\bullet+}$, 82), 312 (53), 314 (50), 286 (100), 284 (84); HRMS (EI) 327.0625 (C$_{18}$H$_{18}$BrN requires 327.0623).

(+)-**9d** (40%): $[\alpha]_D$ +76.9 (c, 1.0, CH$_2$Cl$_2$); ^{1}H NMR δ 0.72 (s, 3 H), 1.36 (d, $J = 9.5$, 1H), 1.44 (s, 3H), 2.41 (m, 1H), 2.71 (td, $J = 9.4$ and 5.7 Hz, 1H), 2.80 (t, $J = 5.8$ Hz, 1H), 3.20 (d, $J = 2.8$ Hz, 2H), 3.87 (s, 3H), 7.00 (d, $J = 8.2$ Hz, 1H), 7.09, (t, $J = 7.0$ Hz, 1H), 7.24 (d, $J = 7.8$ Hz, 1H) 7.35 (t, $J = 7.8$ Hz, 1H), 7.52 (d, $J = 7.8$ Hz, 1H), 7.80 (dd, $J = 7.7$ and 1.8 Hz, 1H); ^{13}C NMR δ 21.8 (CH$_3$), 26.5 (CH$_3$), 32.4 (CH$_2$), 37.1 (CH$_2$), 40.0 (C), 40.7 (CH), 46.7 (CH), 55.9 (OCH$_3$), 111.7 (CH), 121.4 (CH),

121.9 (CH), 129.6 (CH), 130.0 (C), 131.6 (CH) 132.9 (CH) 140.1 (C) 153.3 (C) 156.7 (C) 157.3 (C); MS (EI) m/z (%) 279 ($M^{\bullet+}$, 100), 264 (52), 236 (35); HRMS (FAB) 280.1700 ($M + 1$) (C$_{19}$H$_{21}$NO + H requires 280.1701).

2.2.3. Alkylation of (+)-*9a*–*d*: Method A

n-Butyllithium (1.6 M in hexane, 5.4 ml, 8.70 mmol) was added dropwise to a solution of (+)-**9a**–**d** (1.0 g, 2.90 mmol) in THF (30 ml) at −35 °C, turning the color from pale yellow to deep red. The solution was stirred for 1 h at that temperature and then the neat alkyl iodide (8.70 mmol) was added dropwise at −35 °C and the mixture was then stirred at room temperature overnight. Aqueous 1 M NaOH was added and the mixture was extracted with CH$_2$Cl$_2$ (3 × 30 ml). The organic layers were combined, washed with brine (30 ml), and dried (MgSO$_4$) and the solvent was evaporated under vacuum. The crude product was purified using flash chromatography on silica gel (40 g) with a petroleum ether–ethyl acetate mixture (10:1) to give pure (+)-**10a**–**e** as white solids. The yield are given below.

2.2.4. Method B

A solution of *n*-butyllithium (1.6 M in hexane, 13.9 ml, 21.8 mmol) was added dropwise to a solution of diisopropylamine (3.35 ml, 23.98 mmol) in THF (30 ml) at −40 °C, the mixture was brought to 0 °C, stirred for 30 min, and cooled to −40 °C. A solution of (+)-**9a**–**d** (2.5 g, 7.24 mmol) in THF (30 ml) was added at −40 °C, turning the solution dark red (for **9a** and **9d**) or dark brown (**9c**), and the mixture was stirred at that temperature for 2 h. Alkyl halide (21.8 mmol) was then added dropwise and the mixture was stirred overnight at room temperature. Water (30 ml) was added and the mixture was extracted with CH$_2$Cl$_2$ (3 ml × 30 ml). The organic layers were combined and washed with brine (30 ml) and dried (MgSO$_4$) and the solvent was removed under reduced pressure. The crude product was purified using flash chromatography on silica gel (80 g) with a mixture of petroleum ether and ethyl acetate 9:1) to give pure (+)-**10a**–**e** as white solids.

(+)-**10a** (68%; Method B): $[\alpha]_D$ +79.3 (c 0.7, CHCl$_3$); ^{1}H NMR δ 0.60 (s, 3H), 1.26 (d, $J = 9.7$ Hz,

1H), 1.35 (s, 3H), 1.39 (d, $J = 7.0$ Hz, 3H), 2.10 (td, $J = 6.0$ and 2.5 Hz, 1H), 2.50 (m, 1H), 2.73 (t, $J = 5.6$ Hz, 1H), 3.19 (qd, $J = 7.0$ and 2.4 Hz, 1H), 7.16 (d, $J = 7.7$ Hz, 1H), 7.26–7.39 (m, 4H), 7.93 (m, $J = 7.2$ Hz, 2H); ^{13}C NMR δ 18.7 (CH$_3$), 21.3 (CH$_3$), 23.5 (CH$_3$), 26.7 (CH$_2$), 29.1 (C), 39.4 (CH), 41.8 (CH), 47.2 (CH), 47.4 (CH), 117.4 (CH), 127.0 (CH), 128.6 (CH), 129.0 (CH), 133.7 (CH), 140.4 (C), 140.6 (C), 154.8 (C), 161.0 (C); HRMS (EI) m/z (%) 263 ($M^{\bullet+}$, 65), 248 (100); HRMS (EI) 263.1674 (C$_{19}$H$_{21}$N requires 263.1674).

(+)-**10b** (70%; Method A): $[\alpha]_D$ +32.1 (c 0.83, CHCl$_3$) {an authentic sample of the opposite enantiomer had $[\alpha]_D$ –39.5 (c 1.3, CHCl$_3$) [7c]}; ^{1}H NMR δ 0.68 (s, 3H), 1.34 (d, $J = 9.8$ Hz, 1H), 1.42 (s, 3H), 1.45 (d, $J = 7.0$ Hz, 3H), 2.17 (td, $J = 6.1$, 2.5 Hz, 1H), 2.57 (dt, $J = 9.8$, 5.7 Hz, 1H), 2.78 (t, $J = 5.7$ Hz, 1H), 3.26 (qd, $J = 7.0$ and 2.5 Hz, 1H), 7.12 (ddd, $J = 11.5$, 8.1, and 1.2 Hz, 1H), 7.24 (m, 2H), 7.31 (m, 1H), 7.49 (dd, $J = 7.7$ and 2.3 Hz, 1H) 8.06 (ddd, $J = 7.9$, 7.9, and 1.9 Hz, 1H); ^{13}C NMR δ 18.7 (CH$_3$), 21.4 (CH$_3$), 26.7 (CH$_3$), 29.0 (CH$_2$), 39.3 (CH), 41.8 (C), 47.2 (CH), 47.4 (CH), 116.4 (d, $J_{C-F} = 23.3$ Hz, CH), 121.5 (d, $J_{C-F} = 9.7$ Hz, CH), 124.8 (d, $J_{C-F} = 3.8$ Hz, CH), 128.3 (d, $J_{C-F} = 11.7$ Hz, C), 130.0 (d, $J_{C-F} = 8.7$ Hz, CH), 131.4 (d, $J_{C-F} = 3.0$ Hz, CH), 133.3 (CH), 141.0 (C), 150.4 (C), 160.9 (d, $J_{C-F} = 248.9$ Hz, CF), 161.1 (C); IR ν 2961, 2920, 2865, 1585, 1497, 1446 cm^{-1}; MS (EI) m/z (%) 281 ($M^{\bullet+}$, 30), 266 (87); HRMS (EI) 281.1577 (C$_{19}$H$_{20}$FN requires 281.1580).

(+)-**10c** (72%; Method B): $[\alpha]_D$ +31.2 (c 1.2, CHCl$_3$); ^{1}H NMR δ 0.61 (s, 3H), 1.31 (d, $J = 9.8$ Hz, 1H), 1.36 (d, $J = 7.0$ Hz, 3H), 1.37 (s, 3H), 2.11 (td, $J = 6.1$ and 2.6 Hz, 1H), 2.52 (m, 1H), 2.72 (t, $J = 5.8$ Hz, 1H), 3.18 (dq, $J = 7.1$ and 2.4 Hz, 1H), 7.12–7.22 (m, 3H), 7.33 (m, 1H), 7.49 (dd, $J = 7.6$ and 1.7 Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR δ 15.2 (CH$_3$), 21.0 (CH$_3$), 26.3 (CH$_3$), 28.6 (CH$_2$), 35.2 (CH), 42.0 (C), 47.4 (CH), 47.7 (CH), 122.8 (CH), 124.6 (CH), 127.6 (CH), 128.4 (CH), 129.9 (CH), 130.6 (CH), 133.1 (C), 138.5 (C), 145.7 (C), 148.2 (C); MS (EI) m/z (%) 341 ($M^{\bullet+}$, 47), 327 (100); HRMS (EI) 341.0776 (C$_{19}$H$_{20}$BrN requires 341.0779).

(+)-**10d** (98%; Method A): $[\alpha]_D$ +18.8 (c, 1.0, CH$_2$Cl$_2$); ^{1}H NMR δ 0.66 (s, 3H), 1.35 (d, $J =$ 9.8 Hz, 1H), 1.42 (s, 3H), 1.45 (d, $J = 7.1$ Hz, 3H), 2.16 (td, $J = 6.0$ and 2.5 Hz, 1H), 2.56 (dt, $J = 9.8$ and 5.7 Hz, 1H), 2.75 (t, $J = 5.8$ Hz, 1H), 3.18 (qd, $J = 6.9$ and 2.4 Hz, 1H), 3.86 (s, 3H), 6.99 (d, $J = 8.2$ Hz, 1H), 7.07, (t, $J = 7.0$ Hz, 1H), 7.20 (d, $J = 7.8$ Hz, 1H) 7.32 (t, $J = 7.8$ Hz, 1H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.88 (dd, $J = 7.7$ and 1.8 Hz, 1H); ^{13}C NMR, δ 17.3 (CH$_3$), 20.0 (CH$_3$), 25.4 (CH$_3$), 27.6 (CH$_2$), 37.9 (CH), 40.3 (C), 45.6 (CH), 45.9 (CH), 54.5 (OCH$_3$), 110.4 (CH), 119.9 (CH), 120.5 (CH), 128.2 (CH), 128.5 (C), 130.1 (CH), 131.3 (CH), 138.5 (C), 151.5 (C), 155.9 (C), 159 (C); MS (EI) m/z (%) 293 ($M^{\bullet+}$, 72), 278 (100), 250 (69); HRMS (EI) 293.1779 (C$_{20}$H$_{23}$NO requires 293.1780).

(+)-**10e** (68%; Method B): $[\alpha]_D$ +80 (c 0.9, CHCl$_3$); ^{1}H NMR δ 0.59 (s, 3H), 0.79 (d, $J = 6.9$ Hz, 3H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.34 (d, $J = 9.4$ Hz, 1H), 1.35 (s, 3H), 2.30 (t, $J = 6.0$, 1H), 2.50 (dt, $J = 9.4$ and 5.9 Hz, 1H), 2.66 (t, $J = 5.9$ Hz, 1H), 2.84 (m, 1H), 2.91 (m, 1H), 3.79 (s, 3H), 6.91 (d, $J = 8.5$ Hz, 1H) 7.00 (td, $J = 7.5$ and 1.0 Hz, 1H), 7.13 (dd, $J = 7.8$ and 1.4 Hz, 1H), 7.25 (td, $J = 7.9$ and 1.8 Hz, 1H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.82 (dd, $J = 7.6$ and 1.5 Hz, 1H); ^{13}C NMR δ 20.4 (CH$_3$), 21.5 (CH$_3$), 22.6 (CH$_3$), 26.8 (CH$_3$), 29.9 (CH$_2$), 30.6 (CH), 41.6 (C), 42.3 (C), 47.00 (CH), 49.5 (CH), 56.0 (CH$_3$), 111.9 (CH), 121.4 (CH), 121.8 (CH), 129.6 (CH), 130.1 (C), 131.6 (CH), 132.8 (CH), 140.6 (C), 152.7 (C), 157.5 (C), 159.1 (C); MS m/z (%) 321 ($M^{\bullet+}$, 27), 306 (37), 279 (98), 278 (100), 264 (35), 236 (99); HRMS (EI) 321.2094 (C$_{22}$H$_{27}$NO requires 321.2093).

2.2.5. N-Oxidation of pyridine derivatives (+)-**10a–e**

m-Chloroperoxybenzoic acid (70%, 167 mg, 0.68 mmol) was added portion-wise to a solution of the respective pyridine derivative (+)-**10a–e** (0.68 mmol) in dichloromethane (5 ml) at 0 °C and the mixture was stirred at room temperature for 4 h. The reaction mixture was then diluted with ether (30 ml) and washed successively with satd. NaHCO$_3$ (3 × 10 ml) and brine (10 ml). The ethereal solution was dried over Na$_2$SO$_4$ and the solvent was evaporated in vacuo. The resulting solid was purified by column chromatography on silica gel (10 cm × 2.5 cm) with a mixture of petroleum ether and ethyl acetate (10:1) to elute the unreacted starting material, followed

by ethyl acetate to give pure **5a–e**, respectively, as pale/white-yellowish solids.[3]

(–)-**5a** (63%): $[\alpha]_D$ −25.9 (*c* 1.6, CHCl$_3$); ^{1}H NMR δ 0.61 (s, 3H), 1.36 (s, 3H), 1.39 (d, J = 10.0 Hz, 1H), 1.45 (d, J = 6.6 Hz, 3H), 2.11 (m, 1H), 2.50 (dt, J = 10.0 and 5.7 Hz, 1H), 2.73 (t, J = 5.6 Hz, 1H), 3.37 (qd, J = 6.6 and 2.8 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.35 (m, 3H), 7.71 (m, 2H); ^{13}C NMR δ 15.2 (CH$_3$), 21.0, (CH$_3$), 26.3 (CH$_3$), 28.6 (CH$_2$), 35.5 (CH), 42.0 (C), 47.3 (CH), 47.9 (CH), 123.3 (CH), 124.4 (CH), 128.4 (CH), 129.3 (CH), 129.9 (CH), 135.0 (C), 144.7 (C), 148.2 (C), 151.0 (C); HRMS (EI) 279.1623 (C$_{19}$H$_{21}$NO requires 279.1623).

(+)-**5b** (95%): $[\alpha]_D$ +48 (*c* 0.5, CH$_2$Cl$_2$); ^{1}H NMR δ 0.61 (s, 3H), 1.35 (s, 3H), 1.39 (d, J = 10.0 Hz, 1H), 1.47 (d, J = 6.6 Hz, 3H), 2.11 (td, J = 6.0 and 2.5 Hz, 1H), 2.51 (dt, J = 10.0 and 5.7 Hz, 1H), 2.75 (t, J = 5.6 Hz, 1H), 3.44 (qd, J = 6.6 and 2.8 Hz, 1H), 6.95 (dd, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.31–7.40 (m, 3H), 7.77 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ 15.4 (CH$_3$), 20.9 (CH$_3$), 26.2 (CH$_3$), 28.6 (CH$_2$), 35.5 (CH), 42.0 (C), 47.3 (CH), 47.8 (CH), 116.0 (CH), 123.6 (CH), 124.4 (CH), 128.4 (CH), 128.6 (C), 129.3 (CH), 130.0 (CH), 134.0 (C), 144.8 (C); 149.5 (d, J_{C-F} = 251.5 Hz, CF); MS (EI) *m/z* (%) 279 (MH$^{\bullet+}$–F, 9), 262 (12), 220 (16); HRMS (FAB) 280.1700 (C$_{19}$H$_{22}$NO requires 280.1701).

(+)-**5c** (88%): $[\alpha]_D$ +15.6 (*c*, 1.5, CHCl$_3$); ^{1}H NMR δ 0.61 (s, 3H), 1.36 (s, 3H), 1.42 (m, 1H), 1.43 (d, J = 6.6 Hz, 3H), 2.10 (td, J = 6.1 and 2.9 Hz, 1H), 2.50 (dt, J = 10.0 and 5.6 Hz, 1H), 2.73 (t, J = 5.7 Hz, 1H), 3.35 (qd, J = 6.5 and 2.8 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 7.19 (m, 1H), 7.29–7.38 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 15.0 (CH$_3$), 20.9 (CH$_3$), 26.2 (CH$_3$), 28.5 (CH$_2$), 35.2 (CH), 42.0 (C), 47.5 (CH), 47.9 (CH), 122.3 (CH), 124.6 (CH), 127.6 (CH), 128.3 (C), 129.9 (CH), 130.5 (CH), 133.1 (CH), 136.0 (C), 145.5 (C), 148.1 (C), 150.6 (C); MS (EI) *m/z* 357 (M$^{\bullet+}$, 12), 278 (100); HRMS (EI) 278.1544 (C$_{19}$H$_{20}$NO requires 278.1545).

(+)-**5d** (85%): mp 115–117 °C (ethyl acetate); $[\alpha]_D$ +30.9 (*c*, 1.0, CH$_2$Cl$_2$); ^{1}H NMR δ 0.60 (s, 3H), 1.36 (s, 3H), 1.41 (d, J = 9.9 Hz, 1H), 1.42 (d, J = 6.5 Hz, 3H), 2.09 (td, J = 6.0 and 2.9 Hz, 1H), 2.49 (dt, J = 9.9 and 5.7 Hz, 1H), 2.70 (t, J = 5.7 Hz, 1H), 3.35 (qd, J = 6.5 and 2.8 Hz, 1H), 3.73 (s, 3H), 6.76 (d, J = 7.7 Hz, 1H), 6.92, (d, J = 8.1 Hz, 1H), 6.98 (t, J = 7.7 Hz, 1H) 7.02 (d, J = 7.7 Hz, 1H), 7.32 (m, 2H); ^{13}C NMR δ 15.1 (CH$_3$), 21.0 (CH$_3$), 26.3 (CH$_3$), 28.6 (CH$_2$), 35.3 (CH), 42.0 (C), 47.3 (CH), 47.9 (CH), 56.2 (OCH$_3$), 111.6 (CH), 120.8 (CH), 122.4 (CH), 123.6 (C), 125.1 (CH), 130.7 (CH), 131.4 (CH), 144.5 (C), 146.5 (C), 150.2 (C), 157.8 (C); MS (EI) *m/z* (%) 309 (M$^{\bullet+}$, 11), 293 (18) 278 (100), 250 (22); HRMS (FAB) 309.1730 (C$_{20}$H$_{23}$NO$_2$ requires 309.1729).

(+)-**5e** (75%): mp 120–121 °C (CH$_2$Cl$_2$); $[\alpha]_D$ +52.0 (*c* 1.0, CHCl$_3$); ^{1}H NMR δ 0.56 (s, 3H), 0.91 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 7.1 Hz, 3H), 1.34 (s, 3H), 1.55 (d, J = 9.9 Hz, 1H), 2.31 (td, J = 6.0 and 2.6 Hz, 1H), 2.47 (dt, J = 9.9 and 5.7 Hz, 1H), 2.68 (t, J = 5.6 Hz, 1H), 3.10 (m, 1H), 3.17 (m, 1H), 3.71 (s, 3H), 6.77 (d, J = 7.6 Hz, 1H), 6.91–7.00 (m, 3H), 7.27–7.33 (m, 2H); ^{13}C NMR δ 20.9 (CH$_3$), 21.1 (CH$_3$), 21.9 (CH$_3$), 26.2 (CH$_3$), 28.5 (CH), 28.6 (CH$_2$), 42.8 (C), 43.6 (CH), 45.6 (CH), 47.0 (CH), 56.1 (CH$_3$), 111.6 (CH), 120.9 (CH), 122.4 (CH), 124.0 (C), 124.9 (CH), 130.6 (CH), 130.1 (CH), 145.2 (C), 146.8 (C), 149.3 (C), 157.7 (C); MS (EI) *m/z* (%) 337 (M$^{\bullet+}$, 33), 320 (37), 295 (73), 279 (62), 278 (100), 220 (86); HRMS (EI) 337.2043 (C$_{22}$H$_{27}$NO$_2$ requires 337.2042).

2.2.6. General procedure for the reaction of allyltrichlorosilane with aldehydes

Allyltrichlorosilane (75 μl, 0.47 mmol) was added to a solution of the catalyst **10** (0.04 mmol), diisopropylethylamine (0.35 ml, 2 mmol), tetra-*n*-butylammonium iodide (175.4 mg, 0.47 mmol) and aldehyde (0.4 mmol) in dichloromethane (2 ml) under nitrogen at –60 °C. The mixture was stirred at the same temperature until completion (TLC monitoring; see Table 1 for the reaction times), and then quenched with aqueous satd. NaHCO$_3$ (1 ml). The aqueous layer was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and the solvent was removed in vacuo. The residue was purified by flash chromatography on a silica gel column (15 cm × 2 cm; petroleum

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[3] Since no crystallization or other purification methods capable of altering the ee of the intermediates has been employed, the final products **5a–e** are assumed to reflect the enantiopurity of the starting (+)-α-pinene, i.e. 90% ee.

ether–ethyl acetate, 95:5). Product **3** was identical with an authentic sample [4]. The absolute configuration of **3** was determined from the sense of the optical rotation [4]. The enantiopurity of **3** was determined by chiral GC, using a Supelco β-DEX 120 column (oven: 100 °C for 5 min, then 1 ° min^{-1} to 200 °C, 10 min at that temperature); $t_R = 31.06$ min, $t_S = 31.49$ min.

3. Results and discussion

3.1. General considerations

In the transition state of the allylation reaction, the strongly donating oxygen of the *N*-oxide group of **4a,b** is assumed to coordinate to the silicon in a *trans*-fashion with respect to the allyl group (**A**; Scheme 3) in order to increase its nucleophilicity through the stereoelectronic effect [1,4]. We proposed that the remaining nitrogen of the bipyridine unit should be *trans*-coordinated toward the incoming carbonyl oxygen in order to retain the Lewis acidity at Si [4].

If this model is correct, other weekly coordinating groups with affinity to silicon can be anticipated to mimic the properties of the pyridine nitrogen and to have a beneficial effect on the reaction course. If successful, this approach would not only shed more light on the mechanism of these intriguing organocatalysts but may lead to the design of new catalysts whose synthesis might be simpler than the approaches developed for the existing ones. Therefore, we set out to prepare a series of monopyridine-type catalysts **5**, where the original second pyridine unit is replaced by a substituted benzene ring, with a suitable *ortho*-substituent (X = H, F, Br, and OMe). Herein, we report on their application as chiral organocatalysts
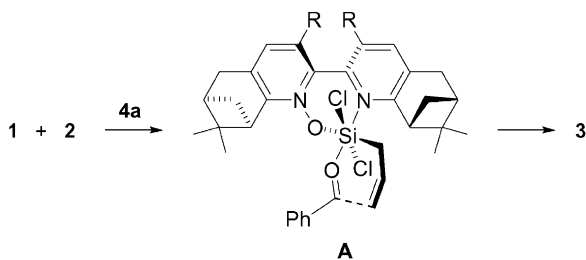
Scheme 3.
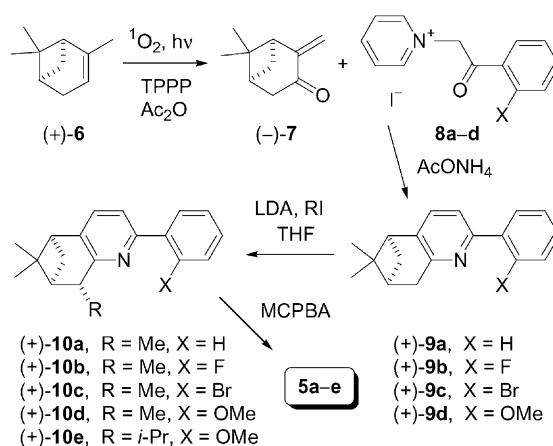
Scheme 4.

in the asymmetric allylation of benzaldehyde with allyl trichlorosilane.

3.2. Catalyst synthesis

The synthesis of pyridine-*N*-oxides 5a–e (Scheme 4) commenced with the ene-reaction of (+)-α-pinene (+)-**6** with singlet oxygen [5] that afforded pinocarvone [5] (−)-**7** (O$_2$, tetraphenylporphine, Ac$_2$O, DMAP, CH$_2$Cl$_2$, 20 °C, 18 h; 99%). Condensation of (−)-**7** with ammonium acetate and the respective Kröhnke salt **8a–d** [6], prepared from acetophenone and its ortho-substituted congeners via iodination in the presence of pyridine (I$_2$, pyridine, reflux 2 h) [7,8], led to the pyridine derivatives (+)-**9a–d** (AcONH$_4$, AcOH, 115 °C, overnight; 65, 83, 82, and 40%, respectively). Deprotonation of the latter products in the benzylic position (LDA, THF, −40 °C, 2 h), followed by alkylation [10] with MeI (−40 °C to RT, overnight), afforded the monomethyl derivatives (+)-**10a–d** (68, 70, 72, and 98%, respectively) with high stereoselectivity [11].[4] An analogous reaction of the deprotonated **9d** with *i*-PrI produced the isopropyl analogue (+)-**10e** (68%). The latter reaction proceeded less efficiently, which is undoubtedly associated with the increased steric bulk of the alkylating agent [10,11]. Oxidation of the latter pyridine

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[4] Only traces of the corresponding epimers could be detected by TLC. Pure alkylated derivatives **10a**–**e** were obtained from the crude produts by flash chromatography. For analogous observations, see ref. [10].

Table 1
Allylation of benzaldehyde **1** with allylsilane **2** to produce (*S*)-(–)-**3**, catalyzed by **4a**,**b** and **5a**–**e** (Scheme 1)[a]

Entry	Catalyst	X	Yield (%)[b]	e.e. (%)[c,d]
1[e]	**4a**	–	78	90
2[e]	**4b**	–	72	98
3	**5a**	H	66	41
4	**5b**	F	15	16
5	**5c**	Br	20	7
6	**5d**	OMe	55	68
7	**5e**	OMe	51	67

[a] The reactions were carried out at 1.0 mmol scale in CH_2Cl_2 with 1.1 eq. of **2**, in the presence of the catalyst (7 mol%) and Bu_4NI (1 eq.) at –60 °C for 18 h.

[b] Isolated yield (note the volatility of the product).

[c] Determined by chiral HPLC or GC.

[d] The absolute configuration of **3** was established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data [2].

[e] Reference [4].

derivatives **10a**–**e** with MCPBA [4] (CH_2Cl_2, RT, 4 h) afforded the corresponding *N*-oxides **5a**–**e** (64, 75, 88, 85, and 75%, respectively).

3.3. Asymmetric allylation catalyzed by **5a**–**e**

In the allylation reaction (Scheme 1), the new catalysts **5a**–**e** exhibited lower enantioselectivities (Table 1; entries 3–7) than their bipyridine counterparts **4a**,**b** (entries 1 and 2) but a clearly increasing trend from *X* = F or Br (entries 4 and 5) to *X* = OMe (entries 6 and 7) has been observed. The *o*-haloderivatives **5b**,**c** afforded the lowest enantioselectivities (16 and 7% e.e., respectively; entries 4 and 5) and low conversion rates, whereas the highest asymmetric induction was observed for the *o*-methoxy compounds **5d**,**e** (68% and 67% e.e.; entries 6 and 7).[5] The latter result seems to be indicative of the involvement of silicon coordination by the methoxy group as a significant factor in the reaction course. However, the relatively high asymmetric induction

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[5] Since the catalysts **5** are only of ca. 90% ee (Footnote 2), the absolute values of the asymmetric induction may be slightly higher than those shown in entries 3, 6, and 7 (Table 1). On the other hand, catalysts **4a**,**b** were enantiopure as their synthesis involved crystallizations, which enhanced the original enantiopurity of the chiral pool.

in the case of the unsubstituted phenyl derivative **5a** (41% e.e.; entry 3), in conjuction with the very low induction by **5b**,**c**, suggests that the electronic properties of the phenyl group also play a role, presumably via a favorable π-stacking [2c] of the electron-rich aryl (**5d**,**e**) with the incoming, electron-poor aldehyde. If correct, this hypothesis could be used as a lead in designing more efficient catalysts, whose synthesis would still be straightforward and even shorter than the syntheses of **4a**,**b** recently developed by us [4].

4. Conclusion

In conclusion, we have designed new promising catalysts **5a**–**e** for the allylation of aromatic aldehydes (Scheme 1) with up to 68% e.e. (obtained for **5d**). The catalysts were synthesized in four steps from the non-expensive chiral pool (**6**), employing Kröhnke annulation as the key transformation (Scheme 4).

Acknowledgements

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