Supporting Information

Azaphilic versus Carbophilic Coupling at C=N Bonds: Key Steps in Titanium-Assisted Multicomponent Reactions

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1. General Information

All manipulations, except those indicated, were carried out under exclusion of air and moisture using standard Schlenk and glove box techniques. As inert gas, Argon 5.0, purchased from Messer Group GmbH, was used after drying over Granusic® phosphorpentoxide granulate. Solvents were dried over activated alumina columns using a solvent purification system (M. Braun SPS 800) or according to standard literature methods\(^1\) and stored in glass ampules under an argon atmosphere. Diethyl ether and n-pentane were distilled from sodium/potassium alloy, tetrahydrofuran, benzene and n-hexane from potassium, methanol from magnesium, dichloromethane, chloroform and triethylamine from calcium hydride and toluene from sodium. The same procedures were used to dry the deuterated solvents. NMR spectra were recorded on Bruker Avance (400 MHz, 600 MHz) instruments. Chemical shifts (\(\delta\)) are reported in parts per million (ppm) and are referenced to residual proton solvent signals or carbon resonances.\(^2\) \(\text{H}_3\text{PO}_4\) (\(^{31}\text{P}\)) and \(\text{CCl}_3\text{F}\) (\(^{19}\text{F}\)) were used as external standards. The following abbreviations were used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), br (broad signal). High-resolution mass spectra were acquired on Bruker ApexQe hybrid 9.4 T FT-ICR (ESI) and JEOL JMS-700 magnetic sector (FAB, EI, LIFDI) spectrometers at the mass spectrometry facility of the Institute of Organic Chemistry, of the University of Heidelberg. Elemental analyses were carried out in the Microanalysis Laboratory of the Heidelberg Chemistry Department on a vario MICRO cube (Elementar). IR spectra were acquired on a Varian 3100 FT IR spectrometer (Excalibur series) of a nujol mull of the compounds at room temperature using a KBr cell. HPLC analyses were conducted on a Agilent 1200 Series chromatograph using chiral Daicel columns (AD-H, OD-H or OJ-H). Notably, due to the multicomponent setup of the reactions, the highly reactive nature of the reactants and the variability of the concentrations of the Grignard solutions the yields were found to vary considerably in several cases. All other chemicals were obtained from commercial suppliers, dried under high vacuum or over molecular sieves and stored under an inert atmosphere.
2. Preparation of starting materials

The cyclohexyl allenol was prepared following a standard literature method starting from 1-ethynyl-1-cyclohexanol, paraformaldehyde, dicyclohexylamine and anhydrous CuBr in dioxane.\textsuperscript{[3]}

$^1\text{H-NMR}$ (CDCl\textsubscript{3}, 399.89 MHz, 295 K): $\delta$ [ppm] = 5.29 (t, $J$ = 6.7 Hz, 1H, H-3), 4.87 (d, $J$ = 6.7 Hz, 2H, H-1), 1.68-1.56 (m, 6H, H-5 + H-5' + H-6), 1.50-1.40 (m, 3H, H-6' + H-7), 1.39-1.30 (m, 1H, H-7');

$^{13}\text{C}^\{^1\text{H}\}$-NMR (CDCl\textsubscript{3}, 100.55 MHz, 295 K): $\delta$ [ppm] = 206.36 (s, C-2), 99.52 (s, C-3), 78.31 (s, C-1), 70.62 (s, C-4), 38.40 (s, C-5), 25.60 (s, C-7), 22.65 (s, C-6);
3. Preparation of \(N\)-aryl benzhydrylamines (\(\text{Ar} = \text{Ar}'\))

**General procedure 1 (GP 1):** To a solution of the indicated heteroaromatic nitrile (5.19 mmol, 1 eq) in dry THF (24 mL) at 0 °C was added a solution of the indicated Grignard reagent in THF (0.5-2 M, 3 eq) and the mixture was stirred 1 h at room temperature. Next, titanium(IV) isopropoxide (1.54 mL) was added and the reaction mixture was placed in an oil bath and heated to 60 °C for 18 h. The reaction was quenched by the addition of sat. \(\text{NH}_4\text{Cl(aq)}\) solution and filtered to remove insoluble metal salts. The residue was extracted with ethyl acetate and dichloromethane and the combined organic extracts were evaporated. Purification by column chromatography yielded the corresponding (2-pyridylmethyl)amines as oils or solids. Solid products can be obtained by crystallization from hot \(n\)-hexane:ethyl acetate mixtures at −30 °C.

5.19 mmol scale from 2-pyridinecarbonitrile, 4-fluorophenylmagnesium bromide (1 M in THF) and titanium(IV) isopropoxide (1.54 mL). 1a was obtained as a yellow oil (63%)

\(^1\text{H}-\text{NMR}\) (CDCl\(_3\), 600.13 MHz, 295 K): \(\delta\) [ppm] = 8.61-8.58 (m, 1H, H-5), 7.70-7.66 (m, 1H, H-3), 7.45-7.41 (m, 2H, H-8), 7.35 (d, \(J=7.9\) Hz, 1H, H-2), 7.23-7.20 (m, 1H, H-4), 7.03-6.99 (m, 2H, H-9), 6.85-6.80 (m, 2H, H-13), 6.57-6.53 (m, 2H, H-12), 6.10-4.99 (bs, 1H, NH), 5.55 (s, 1H, H-6);

\(^{13}\text{C}\{^1\text{H}\}-\text{NMR}\) (CDCl\(_3\), 150.90 MHz, 296 K): \(\delta\) [ppm] = 162.36 (d, \(J=245.9\) Hz, C-10), 160.42 (m, C-1), 156.12 (d, \(J=235.6\) Hz, C-14), 148.83 (m, C-5), 143.18 (d, \(J=1.8\) Hz, C-11), 137.91 (m, C-7), 137.69 (m, C-3), 129.10 (d, \(J=8.2\) Hz, C-8), 122.73 (s, C-4), 122.25 (s, C-2), 115.95 (d, \(J=21.6\) Hz, C-9), 115.75 (d, \(J=22.4\) Hz, C-13), 114.68 (d, \(J=7.4\) Hz, C-12), 62.91 (s, C-6);

\(^{19}\text{F}\{^1\text{H}\}-\text{NMR}\) (CDCl\(_6\), 376.27 MHz, 295 K): \(\delta\) [ppm] = −114.57 (s, 1F, F-10), −127.49 (s, 1F, F-14);

**Elemental analysis:**

|  | found: | calculated: |
|---|---|---|
| C | 72.71% | 72.96% |
| H | 4.90% | 4.76% |
| N | 9.44% | 9.45% |

**MS (HR-ESI(+)):**

| m / z | Calculated: |
|---|---|
| 297.1200 | \(\text{C}_{18}\text{H}_{15}\text{N}_{3}\text{F}_{2}\text{O} \, [\text{M+H}]^+\) |

S4
2.67 mmol scale from 2-pyrimidinecarbonitrile in THF (8 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (0.79 mL). Purification by column chromatography ($n$-pentane:ethyl acetate = 20:1 to 3:1) (60 %) and recrystallization from hot $n$-hexane at $-30 \, \text{°C}$ yielded colorless crystals of 1b.

$^1$H-NMR (CDCl$_3$, 399.89 MHz, 297 K): $\delta$ [ppm] = 8.71 (d, $J$= 4.9 Hz, 2H, H-2), 7.58-7.50 (m, 2H, H-6), 7.17 (t, $J$= 4.9 Hz, 1H, H-3), 7.03-6.95 (m, 2H, H-7), 6.87-6.80 (m, 2H, H-11), 6.62-6.55 (m, 2H, H-10), 6.17-5.00 (bs, 1H, NH), 5.70 (s, 1H, H-4);

$^{13}$C{$^1$H}-NMR (CDCl$_3$, 100.55 MHz, 299 K): $\delta$ [ppm] = 169.12 (m, C-1), 162.25 (d, $J$= 246.0 Hz, C-8), 157.29 (s, C-2), 155.86 (d, $J$= 235.4 Hz, C-12), 142.64 (d, $J$= 1.8 Hz, C-9), 136.67 (d, $J$= 3.1 Hz, C-5), 128.84 (d, $J$= 8.2 Hz, C-6), 119.51 (s, C-3), 115.70 (d, $J$= 8.9 Hz, C-7/11), 115.48 (d, $J$= 8.0 Hz, C-11/7), 114.42 (d, $J$= 7.5 Hz, C-10), 63.13 (s, C-4);

$^{19}$F{$^1$H}-NMR (CDCl$_3$, 376.23 MHz, 297 K): $\delta$ [ppm] = −114.84 (s, F-8), −127.72 (s, F-12);

$^{15}$N-NMR (CDCl$_3$, 40.52 MHz, 297 K): $\delta$ [ppm] = 285.4 (m, N$_{\text{pyrimidine}}$), 68.5 (m, NH);

MS (HR-ESI(+)): $m / z$ 298.1152 ([M+H]$^+$)
calculated: 298.1156 (C$_{17}$H$_{14}$N$_3$F$_2$ $✓$ [M+H]$^+$)

2.67 mmol scale from 6-methoxy-2-quinolinecarbonitrile in THF (24 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (0.79 mL). Purification by column chromatography ($n$-pentane:ethyl...
acetate = 50:1 to 10:1) (54 %). Crystallization from hot n-hexane at −30 °C yielded colorless crystals of 1c suitable for X-ray diffraction analysis.

\[ ^1H-NMR \text{ (CDCl}_3, 600.13 \text{ MHz, 295 K): } \delta \text{ [ppm] = 8.12-8.03 (m, 1H, H-8), 7.98 (d, } J= 8.3 \text{ Hz, 1H, H-3), 7.53-7.46 (m, 2H, H-13), 7.42-7.38 (m, 1H, H-7), 7.32 (d, } J= 7.9 \text{ Hz, H-2), 7.06-7.04 (m, 1H, H-5), 7.03-6.98 (m, 2H, H-14), 6.86-6.81 (m, 2H, H-18), 6.64-6.60 (m, 2H, H-17), 6.01 (bs, 1H, NH), 5.63 (s, 1H, H-11), 3.92 (s, 3H, H-10); \]

\[ ^1H-NMR \text{ (CDCl}_3, 600.13 \text{ MHz, 295 K): } \delta \text{ [ppm] = 8.12-8.03 (m, 1H, H-8), 7.98 (d, } J= 8.3 \text{ Hz, 1H, H-3), 7.53-7.46 (m, 2H, H-13), 7.42-7.38 (m, 1H, H-7), 7.32 (d, } J= 7.9 \text{ Hz, H-2), 7.06-7.04 (m, 1H, H-5), 7.03-6.98 (m, 2H, H-14), 6.86-6.81 (m, 2H, H-18), 6.64-6.60 (m, 2H, H-17), 6.01 (bs, 1H, NH), 5.63 (s, 1H, H-11), 3.92 (s, 3H, H-10); \]

\[ ^1H-NMR \text{ (CDCl}_3, 600.13 \text{ MHz, 295 K): } \delta \text{ [ppm] = 8.12-8.03 (m, 1H, H-8), 7.98 (d, } J= 8.3 \text{ Hz, 1H, H-3), 7.53-7.46 (m, 2H, H-13), 7.42-7.38 (m, 1H, H-7), 7.32 (d, } J= 7.9 \text{ Hz, H-2), 7.06-7.04 (m, 1H, H-5), 7.03-6.98 (m, 2H, H-14), 6.86-6.81 (m, 2H, H-18), 6.64-6.60 (m, 2H, H-17), 6.01 (bs, 1H, NH), 5.63 (s, 1H, H-11), 3.92 (s, 3H, H-10); \]

\[ ^13C{^1H}-NMR \text{ (CDCl}_3, 150.90 \text{ MHz, 295 K): } \delta \text{ [ppm] = 162.33 (d, } J= 246.1 \text{ Hz, C-15), 158.09 (s, C-6), 157.56 (s, C-1), 155.96 (d, } J= 235.1 \text{ Hz, C-19), 143.35 (s, C,H), 143.07 (bs, C,H), 138.25 (bs, C,H), 136.19 (bs, C-3), 130.46 (bs, C-8), 129.25 (d, } J= 8.1 \text{ Hz, C-13), 128.45 (s, C-4), 122.71 (bs, C-7), 120.26 (s, C-2), 115.93 (d, } J= 21.5 \text{ Hz, C-14), 115.72 (d, } J= 22.4 \text{ Hz, C-18), 114.57 (d, } J= 7.4 \text{ Hz, C-17), 105.28 (s, C-5), 62.93 (s, C-11), 55.73 (s, C-10); \]

\[ ^19F{^1H}-NMR \text{ (CDCl}_3, 376.27 \text{ MHz, 295 K): } \delta \text{ [ppm] = -114.75 (s, F-15), -127.98 (s, F-19); }\]

\[ \text{MS (HR-ESI(+)): } \text{m} / \text{z} \quad 377.1463 \quad (\text{M+H})^+ \]

3.00 mmol scale from 1-isoquinolinecarbonitrile in THF (10 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (888 μL). Purification by column chromatography (n-pentane:ethyl acetate = 30:1) (59 %) gave 1d as a pale brown solid.

\[ ^1H-NMR \text{ (CDCl}_3, 399.89 \text{ MHz, 295 K): } \delta \text{ [ppm] = 8.58 (d, } J= 5.7 \text{ Hz, 1H, H-1), 8.37 (d, } J= 8.1 \text{ Hz, 1H, H-4/7), 7.85-7.80 (m, 1H, H-4/7), 7.70-7.60 (m, 2H, H-5 + H-6), 7.62-7.53 (m, 3H, H-2 + H-12), 7.02-6.94 (m, 2H, H-13), 6.96-6.88 (m, 2H, H-17), 6.79-6.72 (m, 2H, H-16), 6.45 (s, 1H, H-10), 6.05 (bs, 1H, NH); \]

\[ ^13C{^1H}-NMR \text{ (CDCl}_3, 100.55 \text{ MHz, 297 K): } \delta \text{ [ppm] = 161.97 (d, } J= 246.1 \text{ Hz, C-14), 159.11 (s, C-9), 155.89 (d, } J= 235.2 \text{ Hz, C-18), 143.22 (d, } J= 1.7 \text{ Hz, C-15), 141.31 (s, C-1), 137.52 (d, } J= 3.1 \text{ Hz, C-11), 136.76 (s, C-3/8), 130.32 (s, C-5/6), 129.29 (d, } J= 8.2 \text{ Hz, C-12), 127.82 (s, C-4/7), 127.78 (s, C-5/6), 125.67 (s, C-3/8), 124.23 (s, C-4/7), 120.76 (s, C-2), 115.71 (d, } J= 22.3 \text{ Hz, C-13/17), 115.58 (d, } J= 21.50 \text{ Hz, C-13/17), 114.64 (d, } J= 7.4 \text{ Hz, C-16), 58.09 (s, C-10); \]

S6
$^{19}$F$^1$H-NMR (CDCl$_3$, 376.27 MHz, 296 K): $\delta$ [ppm] = $-127.56$ (s, F-18), $-114.73$ (s, F-14);

$^{15}$N-NMR (CDCl$_3$, 40.52 MHz, 296 K): $\delta$ [ppm] = $294.2$ (m, N$_{isoquinoline}$), $74.3$ (m, NH);

**MS (HR-DART(+))**:
- $m / z$ 347.1351 ([M+H]$^+$)
- Calculated: 347.1360 (C$_{22}$H$_{17}$N$_2$F$_2$ [M+H]$^+$)

8.64 mmol scale from 4-methylthiazole-2-carbonitrile in THF (30 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (2.56 mL). Purification by column chromatography (n-pentane:ethyl acetate:triethylamine = 50:1:1) (60 %). Crystallization from hot n-hexane at $-30$ °C yielded colorless crystals of 1e suitable for X-ray diffraction analysis.

$^1$H-NMR (CDCl$_3$, 399.89 MHz, 297 K): $\delta$ [ppm] = 7.48-7.42 (m, 2H, H-7), 7.08-7.02 (m, 2H, H-8), 6.88-6.82 (m, 2H, H-12), 6.81-6.80 (m, 1H, H-3), 6.59-6.53 (m, 2H, H-11), 5.70-5.66 (m, H-5), 4.87-4.77 (m, 1H, NH), 2.44-2.43 (m, 3H, H-4);

$^{13}$C$^1$H-NMR (CDCl$_3$, 100.55 MHz, 298 K): $\delta$ [ppm] = 172.76 (s, C-1), 162.58 (d, $J$= 247.2 Hz, C-9), 156.44 (d, $J$= 236.5 Hz, C-13), 153.15 (s, C-2), 142.92 (d, $J$= 2.0 Hz, C-10), 136.81 (d, $J$= 3.2 Hz, C-6), 129.08 (d, $J$= 8.3 Hz, C-7), 116.02 (d, $J$= 21.6 Hz, C-8), 115.70 (d, $J$= 22.4 Hz, C-12), 114.83 (d, $J$= 7.5 Hz, C-11), 114.16 (s, C-3), 61.05 (s, C-5), 17.20 (s, C-4);

$^{19}$F$^1$H-NMR (CDCl$_3$, 376.27 MHz, 297 K): $\delta$ [ppm] = $-113.40$ (s, F-9), $-126.26$ (s, F-13);

$^{15}$N-NMR (CDCl$_3$, 40.52 MHz, 296 K): $\delta$ [ppm] = 316.1 (m, N$_{thiazole}$), 76.3 (m, NH);

**Elemental analysis**: found: C 64.80%, H 4.70%, N 8.93%,
- Calculated: C 64.54%, H 4.46%, N 8.85%.

**MS (HR-ESI(+))**:
- $m / z$ 339.0742 ([M+Na]$^+$)
- Calculated: 339.0743 (C$_{17}$H$_{14}$N$_2$F$_2$SNa [M+Na]$^+$)
2.66 mmol scale from 1,3-oxazole-2-carbonitrile in THF (10 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (787 μL). Purification by column chromatography (n-pentane:ethyl acetate = 20:1) (55 %). If was obtained as a yellow oil.

$^1$H-NMR (C$_6$D$_6$, 600.13 MHz, 295 K): \(\delta [ppm] = 7.23-7.19 \) (m, 2H; H-6), 7.02-7.00 (m, 1H, H-1/2), 6.78-6.68 (m, 5H, H-1/2 + H-7 + H-11), 6.38-6.33 (m, 2H, H-10), 5.45 (d, \(J = 6.1 \) Hz, 1H, H-4), 5.19-5.15 (m, 1H, N-H);

$^{13}$C\{$^1$H\}-NMR (C$_6$D$_6$, 100.55 MHz, 299 K): \(\delta [ppm] = 163.89 \) (s, C-3), 162.84 (d, \(J = 246.2 \) Hz, C-8), 156.69 (d, \(J = 235.5 \) Hz, C-12), 143.07 (d, \(J = 1.8 \) Hz, C-9), 139.34 (s, C-1/2), 135.01 (d, \(J = 3.1 \) Hz, C-5), 129.24 (d, \(J = 8.2 \) Hz, C-6), 127.26 (s, C-1/2), 115.91 (d, \(J = 22.4 \) Hz, C-7/11), 115.89 (d, \(J = 21.6 \) Hz, C-7/11), 114.97 (d, \(J = 7.4 \) Hz, C-10), 56.52 (s, C-4);

$^{19}$F\{$^1$H\}-NMR (C$_6$D$_6$, 376.27 MHz, 298 K): \(\delta [ppm] = -113.76 \) (m, 1F, F-8), -126.52 (m, 1H, F-12);

MS (HR-EI(+)): \(m / z\) 286.0914 ([M$^+$])
calculated: 286.0918 (C$_{16}$H$_{12}$N$_2$F$_2$O $\equiv$ [M$^+$])
4. Preparation of N-aryl benzhydrylamines (Ar ≠ Ar’))

**General procedure 2 (GP 2):** To a solution of the indicated N-heteroaromatic nitrile (5.19 mmol, 1 eq) in dry THF (24 mL) at 0 °C was added a solution of the indicated Grignard reagent in THF (0.5-2 M, 1 eq) and the mixture was stirred 1 h at room temperature. Next, titanium(IV) isopropoxide (1.54 mL) was added and the reaction mixture was stirred for 10 min. Then, the second Grignard reagent was added as a solution in THF (0.5-2 M, 2 eq) and the mixture was placed in an oil bath and heated to 60 °C for 18 h. The reaction was quenched by the addition of sat. NH₄Cl(aq) solution and filtered to remove insoluble salts. The residue was extracted with ethyl acetate and dichloromethane and the combined organic extracts were evaporated. Purification by column chromatography on SiO₂, yielded the corresponding (2-pyridylmethyl)amines as oils or solids. Solid products can be obtained by crystallization from hot n-hexane:ethyl acetate mixtures at −30 °C.

2.67 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (10 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (790 μL, 1 eq) and 4-chlorophenylmagnesium bromide (1 M in Et₂O, 2 eq). Purification by column chromatography (SiO₂, n-pentane:ethyl acetate:triethylamine = 50:1:1) (53 %). 2a was obtained as a colorless solid.

**¹H-NMR** (CDCl₃, 399.89 MHz, 295 K): δ [ppm] = 8.61-8.57 (m, 1H, H-5), 7.66-7.60 (m, 1H, H-3), 7.43-7.37 (m, 2H, H-8), 7.29 (d, J= 8.2 Hz, 1H, H-2), 7.21-7.16 (m, 1H, H-4), 7.08-7.04 (m, 2H, H-13, 7.03-6.98 (m, 2H, H-9), 6.56-6.51 (m, 2H, H-12), 5.64 (bs, 1H, NH), 5.51 (s, 1H, H-6);

**¹³C{¹H}-NMR** (CDCl₃, 100.55 MHz, 295 K): δ [ppm] = 162.32 (d, J= 246.1 Hz, C-10), 160.14 (s, C-1), 149.34 (s, C-5), 145.43 (s, C-11), 137.99 (d, J= 3.2 Hz, C-7), 137.14 (s, C-3), 129.12 (s, C-13), 128.98 (d, J= 8.1 Hz, C-8), 122.62 (s, C-4), 122.34 (s, C-14), 122.08 (s, C-2), 115.95 (d, J= 21.6 Hz, C-9), 114.82 (s, C-12), 62.43 (s, C-6);

**¹⁹F{¹H}-NMR** (CDCl₃, 376.27 MHz, 295 K): δ [ppm] = −114.71 (s, F-10);
MS (HR-ESI(+)):  

\[
\begin{align*}
\text{m / z} & \quad 313.0905 \quad ([M+H]^+) \\
\text{calculated:} & \quad 313.0908 \quad (C_{18}H_{15}N_2FCl \ [M+H]^+) \\
\end{align*}
\]

5.34 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (20 mL), 4-chlorophenylmagnesium bromide (1 M in Et₂O, 1 eq), titanium(IV) isopropoxide (1.58 mL, 1 eq) and 4-fluorophenylmagnesium bromide (1 M in THF, 2 eq). Purification by column chromatography (SiO₂, n-pentane:ethyl acetate:triethylamine = 30:1:1) (57 %). 2b was obtained as a yellow oil.

\[\text{1H-NMR (CDCl}_3, 399.89 \text{ MHz, 295 K): } \delta \text{ [ppm] = 8.59 (d, } J= 4.7 \text{ Hz, } 1\text{H, H-5)}, 7.65-7.58 (m, 1\text{H, H-3}), 7.40 (d, } J= 8.3 \text{ Hz, } 2\text{H, H-8)}, 7.32-7.27 (m, 3\text{H, H-2 + H-9)}, 7.20-7.14 (m, 1\text{H, H-4)}, 6.87-6.80 (m, 2\text{H, H-13)}, 6.58-6.52 (m, 2\text{H, H-12)}, 5.75-5.24 (bs, 1\text{H, NH}), 5.49 (s, 1\text{H, H-6});\]

\[\text{13C}\{\text{1H}\}-\text{NMR (CDCl}_3, 100.55 \text{ MHz, 295 K): } \delta \text{ [ppm] = 160.07 (s, C-1)}, 155.96 (d, } J= 235.1 \text{ Hz, C-14)}, 149.29 (s, C-5), 143.18 (d, } J= 1.7 \text{ Hz, C-11)}, 140.99 (s, C-7), 137.06 (s, C-3), 133.38 (s, C-10), 129.10 (s, C-9), 128.73 (s, C-8), 122.57 (s, C-4), 122.03 (s, C-2), 115.67 (d, } J= 22.3 \text{ Hz, C-13)}, 114.48 (d, } J= 7.4 \text{ Hz, C-12)}, 62.99 (s, C-6);\]

\[\text{19F}\{\text{1H}\}-\text{NMR (CDCl}_3, 376.27 \text{ MHz, 295 K): } \delta \text{ [ppm] = -127.60 (s),}\]

\[\text{15N-NMR (CDCl}_3, 40.52 \text{ MHz, 295 K): } \delta \text{ [ppm] = 302.7 (m, N}_\text{pyridine)}, 71.4 (m, NH);\]

MS (HR-ESI(+)):  

\[
\begin{align*}
\text{m / z} & \quad 647.1547 \quad ([2\text{M+Na}]^+) \\
\text{calculated:} & \quad 647.1557 \quad (C_{36}H_{28}N_4F_2Cl_2Na \ [2\text{M+Na}]^+) \\
\end{align*}
\]
10.4 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (30 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (3.07 mL, 1 eq) and 4-methoxyphenylmagnesium bromide (0.5 M in THF, 2 eq). Purification by column chromatography (SiO₂, n-pentane:ethyl acetate = 100:1 to 9:1) (49 %). 2c was obtained as a yellow oil.

¹H-NMR (CDCl₃, 399.89 MHz, 296 K): δ [ppm] = 8.62-8.58 (m, 1H, H-5), 7.64-7.57 (m, 1H, H-3), 7.48-7.41 (m, 2H, H-H-8), 7.36-7.32 (m, 1H, H-2), 7.18-7.13 (m, 1H, H-4), 7.05-6.98 (m, 2H, H-9), 6.78-6.73 (m, 2H, H-13), 6.4-6.59 (m, 2H, H-12), 5.54 (d, J = 4.3 Hz, 1H, H-6), 5.22 (d, J = 4.3 Hz, 1H, NH), 3.71 (s, 3H, H-15);

¹³C{¹H}-NMR (CDCl₃, 100.55 MHz, 298 K): δ [ppm] = 162.09 (d, J = 245.9 Hz, C-10), 160.92 (s, C-1), 152.19 (s, C-11/14), 149.25 (s, C-5), 141.15 (s, C-14/11), 138.49 (d, J = 3.1 Hz, C-7), 136.89 (s, C-3), 129.01 (d, J = 8.1 Hz, C-8), 122.30 (s, C-4), 121.85 (s, C-2), 115.64 (d, J = 21.5 Hz, C-9), 114.90 (s, C-12/13), 114.79 (s, C-13/12), 63.37 (s, C-6), 55.66 (s, C-15);

¹⁹F{¹H}-NMR (CDCl₃, 376.27 MHz, 297 K): δ [ppm] = −114.95 (s, F-10);

¹⁵N-NMR (CDCl₃, 60.81 MHz, 295 K): δ [ppm] = 304.0 (m, Npyridine), 70.2 (m, NH);

Elemental analysis:  
found:  
C 73.99%   
H 5.86%   
N 9.00%  
calculated:  
C 74.01%   
H 5.56%   
N 9.08%  

MS (HR-ESI(+)):  
m / z 309.1399 ([M+H]+)  
calculated: 309.1403 (C₁₀H₁₉N₂FO ≈ [M+H]+)
5.2 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (20 mL), 3-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (1.54 mL, 1 eq) and 2-methoxyphenylmagnesium bromide (1 M in THF, 2 eq). Purification by column chromatography (SiO2, n-pentane:ethyl acetate:triethylamine = 100:1:1) (52 %). 2d was obtained as a pale yellow oil.

$^1$H-NMR (CDCl$_3$, 399.89 MHz, 297 K): $\delta$ [ppm] = 8.63 (d, $J$ = 4.7 Hz, 1H, H-5), 7.66-7.60 (m, 1H, H-3), 7.39 (d, $J$ = 7.8 Hz, 1H, H-2), 7.32-7.27 (m, 2H, H-11 + H-12), 7.23-7.15 (m, 2H, H-4 + H-8), 6.98-6.91 (m, 1H, H-10), 6.82 (d, $J$ = 7.8 Hz, 1H, H-15), 6.79-6.73 (m, 1H, H-17), 6.72 6.66 (m, 1H, H-16), 6.44 (d, $J$ = 7.7 Hz, 1H, H-18), 5.84 (d, $J$ = 4.7 Hz, 1H, NH), 5.61 (d, $J$ = 4.7 Hz, 1H, H-6), 3.91 (s, 3H, H-19);

$^{13}$C$^{1}$H-NMR (CDCl$_3$, 100.55 MHz, 299 K): $\delta$ [ppm] = 163.25 (d, $J$ = 246.2 Hz, C-9), 160.71 (s, C-1), 149.55 (s, C-5), 147.20 (s, C-14), 145.36 (d, $J$ = 6.6 Hz, C-7), 137.01 (s, C-3), 136.77 (s, C-13), 130.35 (d, $J$ = 8.2 Hz, C-11), 123.13 (d, $J$ = 2.8 Hz, C-12), 122.46 (s, C-4), 121.80 (s, C-2), 121.13 (s, C-17), 117.10 (s, C-16), 114.52 (d, $J$ = 21.3 Hz, C-10), 114.33 (d, $J$ = 22.0 Hz, C-8), 111.13 (s, C-18), 109.50 (s, C-15), 63.04 (d, $J$ = 1.6 Hz, C-6), 55.54 (s, C-19);

$^{19}$F$^{1}$H-NMR (CDCl$_3$, 376.27 MHz, 298 K): $\delta$ [ppm] = −112.35 (s, F-9);

$^{15}$N-NMR (CDCl$_3$, 40.52 MHz, 297 K): $\delta$ [ppm] = 304.7 (m, N$_{\text{pyridine}}$), 63.9 (m, NH);

MS (HR-ESI(+)): m / z 309.1399 ([M+H]$^+$); calculated: 309.1403 (C$_{19}$H$_{18}$N$_2$FO $\equiv$ [M+H]$^+$)
5.2 mmol scale according to GP 2, from 2-pyrimidinecarbonitrile in THF (15 mL), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 1 eq), titanium(IV) isopropoxide (1.65 mL, 1 eq) and 3-fluorophenylmagnesium bromide (1 M in THF, 2 eq). Purification by column chromatography (SiO₂, n-pentane:ethyl acetate:triethylamine = 90:10:1) (56 %). **2e** was obtained as a pale yellow/brown oil.

**1H-NMR** (CDCl₃, 399.89 MHz, 295 K): δ [ppm] = 8.71 (d, J = 4.8 Hz, 2H, H-2), 7.48 (d, J = 8.5 Hz, 2H, H-6), 7.15 (t, J = 4.8 Hz, 1H, H-3), 7.08-7.01 (m, 1H, H-14), 6.85 (d, J = 8.5 Hz, 2H, H-7), 6.48-6.43 (m, 1H, H-15), 6.38-6.31 (m, 2H, H-11 + H-13), 5.70 (s, 1H, H-4), 3.75 (s, 3H, H-9);

**13C{1H}-NMR** (CDCl₃, 100.55 MHz, 295 K): δ [ppm] = 169.38 (s, C-1), 164.07 (d, J = 242.2 Hz, C-12), 159.25 (s, C-8), 157.43 (s, C-2), 148.40 (d, J = 10.9 Hz, C-10), 132.81 (s, C-5), 130.30 (d, J = 10.2 Hz, C-14), 128.43 (s, C-6), 119.55 (s, C-3), 114.28 (s, C-7), 109.55 (d, J = 2.1 Hz, C-15), 103.95 (d, J = 21.6 Hz, C-11/13), 100.44 (d, J = 25.4 Hz, C-13/11), 62.68 (s, C-4), 55.32 (s, C-9);

**19F{1H}-NMR** (CDCl₃, 376.27 MHz, 295 K): δ [ppm] = −112.91 (s);

**15N-NMR** (CDCl₃, 40.52 MHz, 295 K): δ [ppm] = 285.4.0 (m, Npyrimidine), 73.7 (m, NH);

**MS (HR-ESI):**

\[
\begin{align*}
&\text{m / z} \quad 641.2440 \quad ([2M+Na]^+) \\
&\text{calculated:} \quad 641.2453 \quad (C_{36}H_{32}N_6F_2O_2Na \ \sharp \ [2M+Na]^+))
\end{align*}
\]
3.1 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (15 mL), 4-
fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (0.92 mL, 1 eq) and
3,5-bis(trifluoromethyl)phenylmagnesium bromide (0.5 M in THF, 2 eq). Purification by column
chromatography (SiO₂, n-pentane:ethyl acetate:triethylamine = 50:1:1) (28 %). 2f was obtained as a
pale yellow oil. Pale yellow bushy crystals are obtained upon cooling a hot saturated solution of the
compound in n-hexane to −30 °C.

¹H-NMR (CDCl₃, 399.89 MHz, 295 K): δ [ppm] = 8.61 (d, J= 4.8 Hz, 1H, H-5), 7.69-7.63 (m, 1H, H-
3), 7.47-7.41 (m, 2H, H-8), 7.27-7.20 (m, 2H, H-2 + H-4), 7.12 (s, 1H, H-14), 7.07-7.01 (m, 2H, H-9),
6.99 (s, 2H, H-12), 6.56 (bs, 1H, NH), 5.57 (s, 1H, H-6);

¹³C{¹H}-NMR (CDCl₃, 150.90 MHz, 295 K): δ [ppm] = 162.49 (d, J= 246.6 Hz, C-10), 158.75 (s, C-
1), 149.08 (s, C-5), 147.38 (s, C-11), 137.29 (s, C-3), 137.13 (d, J= 3.2 Hz, C-7), 132.36 (q, J=
32.8 Hz, C-13), 128.90 (d, J= 8.2 Hz, C-8), 123.62 (q, J= 272.7 Hz, C-15), 122.88 (s, C-2/4), 122.33
(s, C-4/2), 116.21 (d, J= 21.7 Hz, C-9), 112.86 (m, C-12), 110.45 (m, C-14), 61.41 (s, C-6);

¹⁹F{¹H}-NMR (CDCl₃, 376.27 MHz, 295 K): δ [ppm] = −63.23 (s, 6F, F-15), −114.02 (s, 1F, F-10);

¹⁵N-NMR (CDCl₃, 60.81 MHz, 295 K): δ [ppm] = 300.3 (m, Npyridine), 78.3 (m, NH);

Elemental analysis:  
found:  C 58.20%, H 3.44%, N 6.50%,
calculated: C 57.98%, H 3.16%, N 6.76%.

MS (HR-ESI(+)):  m / z 415.1040 ([M+H]⁺)
calculated: 415.1045 (C₂₀H₁₂N₂F₇⁺)

5.2 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (20 mL), 4-
fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (1.54 mL, 1 eq) and
methylmagnesium chloride (22 wt% in THF, 2 eq). Purification by column chromatography (SiO₂, n-
pentane:ethyl acetate = 6:1) (28 %). 2g was obtained as a yellow/orange oil.
$^1$H-NMR (CDCl$_3$, 399.89 MHz, 295 K): $\delta$ [ppm] = 8.56 (d, $J$ = 4.7 Hz, 1H, H-5), 7.63-7.57 (m, 1H, H-3), 7.42-7.36 (m, 2H, H-8), 7.26 (d, $J$ = 7.8 Hz, 1H, H-2), 7.15-7.11 (m, 1H, H-4), 7.03-6.96 (m, 2H, H-9), 4.78 (s, 1H, H-6), 2.40 (s, 3H, H-11);

$^{13}$C$^{1}$H-NMR (CDCl$_3$, 100.55 MHz, 295 K): $\delta$ [ppm] = 162.28 (s, C-1), 162.19 (d, $J$ = 245.4 Hz, C-10), 149.40 (s, C-5), 138.29 (d, $J$ = 3.2 Hz, C-7), 136.78 (s, C-3), 129.36 (d, $J$ = 8.0 Hz, C-8), 122.23 (s, C-4), 121.89 (s, C-2), 115.48 (d, $J$ = 21.3 Hz, C-9), 69.75 (s, C-6), 34.91 (s, C-11);

$^{19}$F$^{1}$H-NMR (CDCl$_3$, 376.27 MHz, 295 K): $\delta$ [ppm] = −115.50 (s);

MS (HR-ESI(+)): $m/z$ 217.1136 ([M+H]$^+$)
calculated: 217.1141 (C$_{13}$H$_{14}$N$_2$F$^+$) [M+H]$^+$

2 mmol scale according to GP 2, from 6-methylpyridine-2-carbonitrile in THF, 4-methoxyphenylmagnesium bromide (0.5 M in THF, 1 eq), titanium(IV) isopropoxide (0.6 mL, 1 eq) and para-tolylmagnesium chloride (2M in THF, 2 eq). Purification by column chromatography (SiO$_2$, $n$-pentane:ethyl acetate = 30:1) (56 %). 2h was obtained as a colorless solid.

$^1$H-NMR (CDCl$_3$, 600.13 MHz, 295 K): $\delta$ [ppm] = 7.55-7.51 (m, 1H, H-3), 7.48-7.45 (m, 2H, H-9), 7.23 (d, $J$ = 7.8 Hz, 1H, H-4), 7.06-7.02 (m, 3H, H-2 + H-15), 6.95-6.92 (m, 2H, H-10), 6.69-6.65 (m, 2H, H-14), 5.60 (s, 1H, H-7), 5.46 (bs, 1H, NH), 3.80 (s, 3H, H-12), 2.66 (s, 3H, H-6), 2.31 (s, 3H, H-17);

$^{13}$C$^{1}$H-NMR (CDCl$_3$, 150.90 MHz, 295 K): $\delta$ [ppm] = 160.57 (s, C-5), 158.77 (s, C-11), 157.74 (s, C-1), 144.90 (s, C-16), 136.93 (s, C-3), 134.92 (s, C-8), 129.54 (s, C-15), 128.54 (s, C-9), 126.27 (s, C-13), 121.57 (s, C-2), 118.66 (s, C-4), 114.02 (s, C-10), 113.72 (s, C-14), 62.73 (s, C-7), 55.08 (s, C-12), 24.47 (s, C-6), 20.38 (s, C-17);

$^{15}$N-NMR (CDCl$_3$, 60.81 MHz, 295 K): $\delta$ [ppm] = 303.5 (m, N$_{pyridine}$), 73.9 (m, NH);
10.4 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (30 mL), 2-thienylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (3.07 mL, 1 eq) and 4-fluorophenylmagnesium bromide (1 M in THF, 2 eq). Purification by column chromatography (SiO₂, n-pentane:ethyl acetate:triethylamine = 30:1:1 to 9:1:1) (50%). 2i was obtained as a yellow/brown oil that crystallizes upon standing as an ochre solid. Crystals suitable for X-ray diffraction analysis were obtained from a saturated solution of the compound in n-hexane at −30 °C.

1H-NMR (CDCl₃, 399.89 MHz, 297 K): δ [ppm] = 8.61 (d, J= 4.7 Hz, 1H, H-5), 7.66-7.7.60 (m, 1H, H-3), 7.40 (d, J= 7.9 Hz, 1H, H-2), 7.22-7.15 (m, 2H, H-4 + H-8/10), 7.06-7.03 (m, 1H, H-10/8), 6.97-6.93 (m, 1H, H-9), 6.90-6.82 (m, 2H, H-13), 6.68-6.61 (m, 2H, H-12), 5.82 (d, J= 5.1 Hz, 1H, H-6), 5.48 (d, J= 5.1 Hz, 1H, NH);

13C{1H}-NMR (CDCl₃, 100.55 MHz, 298 K): δ [ppm] = 160.07 (s, C-1), 156.09 (d, J= 235.7 Hz, C-14), 149.16 (s, C-5), 146.90 (s, C-7), 143.13 (d, J= 1.9 Hz, C-11), 137.05 (s, C-3), 126.87 (s, C-9), 125.24 (s, C-8/10), 125.09 (s, C-10/8), 122.63 (s, C-4), 121.71 (s, C-2), 115.59 (d, J= 22.3 Hz, C-13), 114.80 (d, J= 7.4 Hz, C-12), 59.61 (s, C-6);

19F{1H}-NMR (CDCl₃, 376.27 MHz, 297 K): δ [ppm] = −127.07 (s);

Elemental analysis: found: C 67.85%, H 4.47%, N 9.98%; calculated: C 67.58%, H 4.61%, N 9.85%.

MS (HR-ESI(+)): m / z  591.1461 ([2M+Na]+) calculated: 591.1465 (C₁₂H₂₆Na₂F₂S₂Na ≡ [2M+Na]+).
5.2 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (20 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (1.54 mL, 1 eq) and phenyllithium (1.8 M in Bu₂O, 2 eq). Purification by column chromatography (SiO₂, n-pentane:ethyl acetate:triethylamine = 50:1:1) (63 %). 2j was obtained as a colorless oil.

\[^{1}H\text{-NMR} \quad (\text{CDCl}_3, 600.13 \text{ MHz, } 295 \text{ K}): \delta \text{ [ppm]} = 8.64-8.61 \text{ (m, } 1\text{H, H-5)}, 7.66-7.61 \text{ (m, } 1\text{H, H-3)}, 7.49-7.44 \text{ (m, } 2\text{H, H-8)}, 7.36 \text{ (d, } J = 7.9 \text{ Hz, } 1\text{H, H-2)}, 7.20-7.15 \text{ (m, } 3\text{H, H-4 + H-13)}, 7.06-7.01 \text{ (m, } 2\text{H, H-9)}, 6.76-6.71 \text{ (m, } 1\text{H, H-14)}, 6.69-6.65 \text{ (m, } 2\text{H, H-12)}, 5.61 \text{ (s, } 1\text{H, H-6)}, 5.55 \text{ (bs, } 1\text{H, NH});\]

\[^{13}C\text{-NMR} \quad (\text{CDCl}_3, 150.90 \text{ MHz, } 295 \text{ K}): \delta \text{ [ppm]} = 162.15 \text{ (d, } J = 245.9 \text{ Hz, C-10)}, 160.59 \text{ (s, C-1)}, 149.30 \text{ (s, C-5)}, 146.88 \text{ (s, C-11)}, 138.36 \text{ (d, } J = 3.1 \text{ Hz, C-7)}, 136.99 \text{ (s, C-3)}, 129.22 \text{ (s, C-13)}, 128.99 \text{ (d, } J = 8.1 \text{ Hz, C-8)}, 122.41 \text{ (s, C-4)}, 121.93 \text{ (s, C-2)}, 117.68 \text{ (s, C-14)}, 115.75 \text{ (d, } J = 21.5 \text{ Hz, C-9)}, 113.67 \text{ (s, C-12)}, 62.49 \text{ (s, C-6)};\]

\[^{19}F\text{-NMR} \quad (\text{CDCl}_3, 376.27 \text{ MHz, } 297 \text{ K}): \delta \text{ [ppm]} = -114.91 \text{ (s, F-10)};\]

**MS (HR-ESI(+))**: 

\[
\begin{array}{ccc}
\text{m / z} & 279.1294 & ([M+H]^+) \\
\text{calculated:} & 279.1298 & (C_{18}H_{16}N_{2}F \quad [M+H]^+) \\
\end{array}
\]

5.2 mmol scale according to GP 2, from 2-pyridinecarbonitrile in THF (20 mL), 2-thienyllithium (1 M in THF, 1 eq), titanium(IV) isopropoxide (1.54 mL, 1 eq) and phenyllithium (1.8 M in Bu₂O, 2 eq). Purification by column chromatography (SiO₂, n-pentane:ethyl acetate:triethylamine = 50:1:1) (43 %). 2k was obtained as a yellow oil.
$^1$H-NMR (CDCl$_3$, 600.13 MHz, 295 K): \( \delta \) [ppm] = 8.65-8.63 (m, 1H, H-5), 7.68-7.64 (m, 1H, H-3), 7.46 (d, \( J = 7.9 \) Hz, 1H, H-2), 7.24-7.22 (m, 1H, H-10), 7.22-7.16 (m, 3H, H-4 + H-13), 7.08-7.05 (m, 1H, H-8), 6.99-6.96 (m, 1H, H-9), 6.78-6.72 (m, 3H, H-12 + H-4), 5.93-5.90 (m, 1H, H-6), 5.54-5.49 (m, 1H, NH);

$^{13}$C\{$^1$H\}-NMR (CDCl$_3$, 150.90 MHz, 295 K): \( \delta \) [ppm] = 160.34 (s, C-1), 149.24 (s, C-5), 146.99 (s, C-7), 146.74 (s, C-11), 137.07 (s, C-3), 129.20 (s, C-13), 126.87 (s, C-9), 125.21 (s, C-8/10), 125.07 (s, C-10/8), 122.60 (s, C-4), 121.65 (s, C-2), 118.05 (s, C-14), 113.86 (s, C-12), 59.11 (s, C-6);

$^{15}$N-NMR (CDCl$_3$, 60.81 MHz, 295 K): \( \delta \) [ppm] = 304.0 (m, N$_{pyridine}$), 78.1 (m, NH);

**MS (HR-EI(+))**: m / z 266.0895 ([M$^+$]

**calculated**: 266.0878 (C$_{16}$H$_{14}$N$_2$S \( \equiv \) [M$^+$])
5. Alternative procedure

For several N-heterocyclic aromatics the desired nitrile compounds are conveniently accessible by a wide range of methods. Nevertheless, a complementary route is outlined below, relying on simple aromatic nitriles and metallated (Mg, Li) heterocycles. The latter may be prepared *in situ*, e.g. by direct or directed metalation or halogen-metal exchange, thus extending the scope of this procedure considerably. However, since this route requires a correct stoichiometry for four components, yields may decrease on smaller reaction scales.

**Method A:**

\[
\text{N} = \text{CN} + \text{F} + \text{MgBr} \xrightarrow{\text{THF, 18 h, 60 °C}} \text{H}_{2}\text{O} \xrightarrow{} \text{HN} \text{N} + \text{F} + \text{F}
\]

(1 eq.) (3 eq.) (1 eq.)

**Method B:**

\[
\text{N} = \text{M} + \text{CN} + \text{MgBr} \xrightarrow{\text{THF, 18 h, 60 °C}} \text{H}_{2}\text{O} \xrightarrow{} \text{HN} \text{N} + \text{F} + \text{F}
\]

\((\text{M = Mg, Li})\) (1 eq.) (1 eq.) (2 eq.) (1 eq.)
To a solution of 2-pyrimidinecarbonitrile (5.6 mmol, 1 eq) in dry Et₂O (24 mL) at 0 °C was added a solution of the 4-fluorophenylmagnesium bromide in THF (1 M, 1 eq) and the mixture was stirred 1 h at room temperature. Next, titanium(IV) isopropoxide (1.65 mL, 1 eq) was added and the reaction mixture was stirred for 10 min. Then, 4-methoxyphenylmagnesium bromide was added as a solution in THF (0.5 M in THF, 2 eq) and the mixture was placed in an oil bath and heated to 40 °C for 18 h. To the reaction mixture dry paraformaldehyde (5 eq) was added in one portion and heating at 40 °C was continued overnight. The reaction was quenched by the addition of dest. water and filtered to remove insoluble metal salts. The byproduct 4-methoxybenzyl alcohol was removed from the reaction mixture by distillation in vacuo. The residue was purified by column chromatography (SiO₂, n-pentane:ethyl acetate:triethylamine = 9:1:1) and 5a was obtained as a yellow oil (33 %). Single crystals suitable for X-ray diffraction analysis were obtained from a saturated solution of the compound in n-hexane at −30 °C.

H-NMR (CDCl₃, 600.13 MHz, 295 K): δ [ppm] = 8.69 (d, J=4.7 Hz, 2H, H-2), 7.45-7.41 (m, 2H, H-8), 7.10 (t, J= 4.7 Hz, 1H, H-3), 7.06-7.01 (m, 2H, H-9), 6.60 (d, J= 8.6 Hz, 2H, H-13), 6.38 (d, J= 8.6 Hz, 2H, H-12), 5.40 (s, 1H, H-6), 5.35 (s, 1H, H-6'), 5.11 (d, J= 8.0 Hz, 1H, H-5), 4.40 (d, J= 8.0 Hz, 1H, H-5'), 3.66 (s, 3H, H-15);

13C{1H}-NMR (CDCl₃, 150.90 MHz, 295 K): δ [ppm] = 169.89 (s, C-1), 161.89 (d, J= 246.3 Hz, C-10), 156.69 (s, C-2), 151.90 (s, C-14), 137.49 (s, C-11), 136.22 (d, J= 3.1 Hz, C-7), 130.23 (d, J= 8.0 Hz, C-8), 119.25 (s, C-3), 115.42 (s, C-12), 114.67 (d, J= 21.3 Hz, C-9), 114.09 (s, C-13), 84.72 (s, C-5), 84.04 (s, C-6), 73.84 (s, C-4), 55.44 (s, C-15);

19F{1H}-NMR (CDCl₃, 376.27 MHz, 298 K): δ [ppm] = −115.71 (s);

15N-NMR (CDCl₃, 60.81 MHz, 295 K): δ [ppm] = 295.75 (m, Npyrimidine), 85.68 (m, Noxazolidine);

MS (HR-ESI(+)): m / z 352.1480 ([M+H]⁺)  
  calculated: 352.1461 (C₂₀H₂₀N₃FO₂ [M+H]⁺)
To a solution of 2-pyridinecarbonitrile (5.2 mmol, 1 eq) in dry THF (24 mL) at 0 °C was added a solution of the 2-thienylmagnesium bromide in THF (1 M, 1 eq) and the mixture was stirred 1 h at room temperature. Next, titanium(IV) isopropoxide (1.54 mL, 1 eq) was added and the reaction mixture was stirred for 10 min. Then, 4-methoxyphenylmagnesium bromide was added as a solution in THF (0.5 M in THF, 2 eq) and the mixture was placed in an oil bath and heated to 60 °C for 18 h. To the reaction mixture dry paraformaldehyde (5 eq) was added in one portion and stirring at room temperature was continued overnight. The reaction was quenched by the addition of dest. water and filtered to remove insoluble metal salts. The byproduct 4-methoxybenzyl alcohol was removed from the reaction mixture by distillation \(\text{in vacuo}\). The residue was purified by column chromatography (SiO\(_2\), n-pentane:ethyl acetate = 50:1 to 9:1) and \(5b\) was obtained as a yellow oil (35 %).

\(^1\text{H-NMR}\) (CDCl\(_3\), 399.89 MHz, 295 K): \(\delta\) [ppm] = 8.73-8.70 (m, 1H, H-1), 7.65-7.59 (m, 1H, H-3), 7.42-7.38 (m, 1H, H-4), 7.25-7.19 (m, 2H, H-2 + H-10/12), 6.99-6.96 (m, 1H, H-10/12), 6.90-6.87 (m, 1H, H-11), 6.70-6.64 (m, 2H, H-15), 6.35-6.30 (m, 2H, H-14), 5.40 (d, \(J= 2.1\) Hz, 1H, H-8), 5.34 (d, \(J= 2.1\) Hz, 1H, H-8'), 4.69 (d, \(J= 8.3\) Hz, 1H, H-7), 4.44 (d, \(J= 8.3\) Hz, 1H, H-7'), 3.69 (s, 3H, H-17).

\(^{13}\text{C\{^1\text{H}\}}\)-NMR (CDCl\(_3\), 100.55 MHz, 295 K): \(\delta\) [ppm] = 160.69 (s, C-5), 152.02 (s, C-16), 148.92 (s, C-1), 144.27 (s, C-9), 136.91 (s, C-13), 136.70 (s, C-3), 127.42 (s, C-10/12), 126.26 (s, C-11), 126.01 (s, C-10/12), 122.53 (s, C-2), 122.29 (s, C-4), 115.57 (s, C-14), 114.37 (s, C-15), 84.82 (s, C-7), 83.64 (s, C-8), 70.94 (s, C-6), 55.58 (s, C-17).

\(^{15}\text{N-NMR}\) (CDCl\(_3\), 40.52 MHz, 295 K): \(\delta\) [ppm] = 310.2 (m, N\(_\text{pyridine}\)), 83.2 (m, N/H);

\(\text{MS (HR-DART(+))}:\ m/z\quad 339.1164\quad ([M+H]^{+})\)

\(\text{calculated:}\quad 339.1167\quad (C_{19}H_{19}N_2O_2S \quad [M+H]^{+})\)
To a solution of 2-pyridinecarbonitrile (0.5 mL, 5.2 mmol, 1 eq) in THF (20 mL) at 0 °C was added a solution of 4-fluorophenylmagnesium bromide (1 M in THF, 5.2 mL, 1 eq) in THF and the resulting mixture was stirred 1 h at room temperature. To the resulting suspension was added [Ti(OiPr)₄] (1.54 mL, 1 eq) and, after 10 min, a solution of 4-fluorophenylmagnesium bromide (1 M, 10.4 mL, 2 eq) in THF and subsequently allyl bromide (0.9 mL, 2 eq). The reaction mixture was heated to 60 °C overnight (ca. 18 h) and then quenched by the addition of an aqueous saturated NH₄Cl solution. Filtration, evaporation of the solvent and purification by column chromatography (SiO₂, petrol ether:ethyl acetate:triethylamine = 100:1:1) gave 6a (1.01 g, 58 %) as a pale yellow oil.

¹H-NMR (CDCl₃, 399.89 MHz, 295 K): δ [ppm] = 8.59-8.56 (m, 1H, H-1), 7.60-7.53 (m, 3H, H-3 + H-11), 7.16-7.12 (m, 1H, H-2), 7.09-7.00 (m, 3H, H-4 + H-12), 6.77-6.70 (m, 2H, H-16), 6.58 (bs, 1H, NH), 6.41-6.35 (m, 2H, H-15), 5.45-5.33 (m, 1H, H-8), 4.87-4.82 (m, 1H, H-9), 4.74-4.67 (m, 1H, H-9), 3.56-3.48 (m, 1H, H-7), 3.18-3.11 (m, 1H, H-7');

¹³C{¹H}-NMR (CDCl₃, 100.55 MHz, 295 K): δ [ppm] = 162.70 (s, C-5), 161.95 (d, J= 246.3 Hz, C-13), 155.73 (d, J= 234.9 Hz, C-17), 147.22 (s, C-1), 141.61 (d, J= 1.9 Hz, C-10/14), 141.50 (d, J= 3.2 Hz, C-14/10), 136.85 (s, C-3), 132.63 (s, C-8), 128.99 (d, J= 7.9 Hz, C-11), 122.24 (s, C-4), 121.84 (s, C-2), 118.77 (s, C-9), 116.21 (d, J= 7.2 Hz, C-15), 115.74 (d, J= 21.2 Hz, C-12), 115.34 (d, J= 22.1 Hz, C-16), 64.00 (s, C-6), 40.74 (s, C-7);

¹⁹F{¹H}-NMR (CDCl₃, 376.27 MHz, 295 K): δ [ppm] = −115.62 (s, F-13), −128.47 (s, F-17);

¹⁵N-NMR (CDCl₃, 40.52 MHz, 295 K): δ [ppm] = 300.6 (m, Npyridine), 72.5 (m, NH);

MS (HR-DART(+)): m / z 337.1508 ([M+H]+)
calculated: 337.1516 (C₂₁H₁₉N₂F₂ [M+H]+)
To a solution of 2-pyridinecarbonitrile (0.5 mL, 5.2 mmol, 1 eq) in THF (20 mL) at 0 °C was added a solution of 4-fluorophenylmagnesium bromide (1 M in THF, 5.2 mL, 1 eq) in THF and the resulting mixture was stirred 1 h at room temperature. To the resulting suspension was added [Ti(OiPr)₄] (1.54 mL, 1 eq) and, after 10 min, a solution of 4-methoxyphenylmagnesium bromide (0.5 M, 20.8 mL, 2 eq) in THF and subsequently cinnamyl bromide (1.54 mL 2 eq). The reaction mixture was heated to 60 °C overnight (ca. 18 h) and then quenched by the addition of an aqueous saturated NH₄Cl solution. Filtration, evaporation of the solvent and purification by column chromatography (SiO₂, petrol ether:ethyl acetate:triethylamine = 100:1:1) gave 6b (34 %) as a yellow foam.

**1H-NMR** (CDCl₃, 600.13 MHz, 295 K): δ [ppm] = 8.72-8.70 (m, 1H, H-1), 7.80-7.76 (m, 2H, H-15), 7.73-7.69 (m, 1H, H-3), 7.39-7.35 (m, 2H, H-12), 7.34-7.23 (m, 5H, H-2 + H-4 + H-11 + H-13), 7.23-7.18 (m, 2H, H-16), 6.83-6.80 (m, 2H, H-20), 6.60-6.57 (m, 2H, H-19), 6.42 (bs, 1H, NH), 6.15 (d, J= 15.9 Hz, 1H, H-9), 5.96-5.89 (m, 1H, H-8), 3.86 (s, 3H, H-22), 3.82-3.77 (m, 1H, H-7), 3.48-3.43 (m, 1H, H-7');

**13C{1H}-NMR** (CDCl₃, 150.90 MHz, 295 K): δ [ppm] = 163.11 (s, C-5), 161.85 (d, J= 246.2 Hz, C-17), 152.01 (s, C-21), 147.38 (s, C-1), 141.91 (d, J= 3.1 Hz, C-14), 139.48 (s, C-18), 137.61 (s, C-10), 136.72 (s, C-3), 133.64 (s, C-9), 129.12 (d, J= 7.9 Hz, C-15), 128.44 (s, C-12), 127.10 (s, C-13), 126.13 (s, C-11), 124.77 (s, C-8), 122.19 (s, C-2/4), 121.75 (s, C-4/2), 117.14 (s, C-19), 115.60 (d, J= 21.2 Hz, C-16), 114.49 (s, C-20), 64.80 (s, C-6), 55.70 (s, C-22), 40.07 (s, C-7);

**19F{1H}-NMR** (CDCl₃, 376.27 MHz, 295 K): δ [ppm] = −115.87

**15N-NMR** (CDCl₃, 60.81 MHz, 295 K): δ [ppm] = 301.9 (m, Npyridine), 72.1 (m, NH);

**MS (HR-DART(+))**: m / z  425.2024 ([M+H]⁺)
    calculated:  425.2029 (C₂₈H₂₆N₂FO [M+H]⁺)

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To a solution of 2-pyridinecarbonitrile (0.5 mL, 5.19 mmol, 1 eq) in THF (24 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (1 M, 1 eq) in THF and the mixture was stirred for 1 h at room temperature. [Ti(OiPr)₄] (1.54 mL, 5.19 mmol, 1 eq) was added and stirring was continued for 10 min. Then, a solution of 4-fluorophenylmagnesium bromide (1 M, 2 eq) in THF and subsequently 1-(bromomethyl)-4-(tert-butyl)benzene (3.3 mL, 3.5 eq) were added. The mixture was heated to 60 °C for 18 h and then quenched by the addition of a sat. NH₄Cl solution. Filtration and purification by column chromatography (SiO₂, petrol ether:ethyl acetate = 100:1) gave 6c as a pale yellow solid (43 %). Single crystals suitable for X-ray diffraction were obtained from a saturated solution of the compound in n-hexane at room temperature by slow evaporation of the solvent.

$^1$H-NMR (CDCl₃, 399.89 MHz, 296 K): $\delta$ [ppm] = 8.40-8.37 (m, 1H, H-1), 7.66-7.60 (m, 1H, H-3), 7.37 (d, $J$ = 8.1 Hz, 1H, H-4), 7.31-7.26 (m, 2H, H-15/16/17), 7.14 (dd, $J$ = 7.5 Hz, $J$ = 5.1 Hz, 1H, H-2), 7.04 (dd, $J$ = 5.1 Hz, $J$ = 3.7 Hz, 1H, H-15/16/17), 7.01-6.97 (m, 2H, H-10), 6.84-6.77 (m, 2H, H-20), 6.66-6.38 (m, 3H, NH + H-19), 6.34-6.28 (m, 2H, H-9), 4.04 (d, $J$ = 13.3 Hz, 1H, H-7), 3.55 (d, $J$ = 13.3 Hz, 1H, H-7’), 1.22 (s, 9H, H-13);

$^{13}$C($^1$H)-NMR (CDCl₃, 100.55 MHz, 298 K): $\delta$ [ppm] = 161.54 (s, C-5), 155.73 (d, $J$ = 235.0 Hz, C-21), 151.90 (m, C-14), 149.32 (s, C-11), 146.94 (s, C-1), 141.57 (d, $J$ = 1.7 Hz, C-18), 136.74 (s, C-3), 132.47 (s, C-8), 130.07 (s, C-9), 126.84 (s, C-15/16/17), 126.49 (s, C-15/16/17), 124.75 (s, C-15/16/17), 124.58 (s, C-10), 122.12 (s, C-2/4), 122.00 (s, C-2/4), 116.32 (d, $J$ = 7.1 Hz, C-19), 115.47 (d, $J$ = 22.1 Hz, C-20), 64.42 (s, C-6), 43.60 (s, C-7), 34.43 (s, C-12), 31.45 (s, C-13);

$^{19}$F($^1$H)-NMR (CDCl₃, 376.27 MHz, 296 K): $\delta$ [ppm] = −128.42 (s, F-21);

MS (HR-DART(+)): m/z 431.1952 ([M+H]+)
calculated: 431.1957 (C₂₇H₂₈N₂FS $\equiv$ [M+H]+)
To a solution of 2-pyridinecarbonitrile (0.5 mL, 5.2 mmol, 1 eq) in THF (20 mL) was added a solution of 2-thienylmagnesium bromide (1 M, 5.2 mL, 1 eq) in THF and the mixture was left stirring for 1 h. Then, [Ti(OiPr)₄] (1.54 mL, 5.2 mmol, 1 eq) was added and stirring was continued for 10 min. After that, a solution of 4-fluorophenylmagnesium bromide (1 M, 10.4 mL, 2 eq) in THF was added at room temperature. To this flask was added a solution of the lithium alkoxide of 2-methylbut-3-en-2-ol (5 eq) in THF. The latter was separately prepared from the corresponding allylic alcohol (2.72 mL, 5 eq) and n-butyllithium (2.5 M in hexane, 5 eq) in THF (8 mL) at −78 °C followed by warming to room temperature and stirring for 1 h. The reaction mixture was heated to 60 °C for 2 d and then quenched by the addition of sat. NH₄Cl solution. Solid materials were filtered off and the residue was directly purified by column chromatography (SiO₂, n-pentane:ethyl acetate = 100:1). 7a was obtained as a colorless solid (37 %). Single crystals suitable for X-ray diffraction were obtained from a hot solution of the compound in n-hexane after slow cooling to −78 °C.

¹H-NMR (CDCl₃, 399.89 MHz, 295 K): δ [ppm] = 8.58 (d, J= 4.7 Hz, 1H, H-5), 7.63-7.56 (m, 1H, H-3), 7.30-7.25 (m, 2H, H-2 + H-Thiophene), 7.24-7.21 (m, 1H, H-Thiophene), 7.19-7.14 (m, 1H, H-4), 7.02-6.99 (m, 1H, H-Thiophene), 6.80-6.72 (m, 2H, H-18), 6.52-6.45 (m, 2H, H-17), 4.71-4.64 (m, 1H, H-8), 3.45-3.35 (m, 1H, H-7), 3.08-2.98 (m, 1H, H-7'), 1.50 (s, 3H, H-11), 1.14 (s, 3H, H-10);

¹³C{¹H}-NMR (CDCl₃, 100.55 MHz, 295 K): δ [ppm] = 162.26 (s, C-1), 155.89 (d, J= 235.5 Hz, C-19), 152.62 (s, C-12), 147.11 (s, C-5), 141.82 (d, J= 2.0 Hz, C-16), 136.76 (s, C-3), 135.59 (s, C-9), 126.73 (s, C-Thiophene), 126.16 (s, C-Thiophene), 124.23 (s, C-Thiophene), 121.83 (s, C-4), 121.61 (s, C-2), 117.50 (s, C-8), 116.84 (d, J= 7.2 Hz, C-17), 115.17 (d, J= 22.0 Hz, C-18), 63.88 (s, C-6), 37.09 (s, C-7), 25.99 (s, C-11), 17.56 (s, C-10)

¹⁹F{¹H}-NMR (CDCl₃, 376.27 MHz, 295 K): δ [ppm] = −127.89 (s);

¹⁵N-NMR (CDCl₃, 40.52 MHz, 295 K): δ [ppm] = 300.5 (m, Npyridine), 76.7 (m, NH);

Elemental analysis:

|          | found     | calculated |
|----------|-----------|------------|
| C        | 71.58%    | 71.56%     |
| H        | 5.65%     | 6.01%      |
| N        | 8.02%     | 7.95%      |
To a solution of 2-pyridinecarbonitrile (120 μL, 1.24 mmol, 1 eq) in THF (10 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (1 M, 1.24 mL, 1 eq) in THF and the mixture was left stirring for 1 h. After that, [Ti(OiPr)4] (368 μL, 1 eq) was added and, after 10 min, a solution of 4-fluorophenylmagnesium bromide (1 M, 2.5 mL, 2 eq) in THF. In a second flask, a solution of (S)-1-phenyl-2-propen-1-ol (500 mg, 3 eq, enantiopurity: >97:3 e.r.) in THF (5 mL) was cooled to −78 °C and tert-butyllithium (1.9 M in pentane, 3.1 eq) was added dropwise. The mixture was slowly warmed to room temperature over 1.5 h. Then, the solution of the lithium alkoxide was added to the reaction mixture and the combined solution was first stirred 4 h at room temperature and then heated to 60 °C for 2 d. Addition of sat. NH4Cl solution, filtration and purification by column chromatography (SiO2, n-pentane:ethyl acetate = 40:1) gave 7b as a colorless foam in 45 % yield (89.9:10.1 e.r.). The product slowly decomposed in CDCl3 solution. Colorless crystals suitable for X-ray diffraction analysis were obtained from a saturated solution of the compound in n-hexane at room temperature.

1H-NMR (CDCl3, 600.13 MHz, 295 K): δ [ppm] = 8.64-8.61 (m, 1H, H-1), 7.69 (t, J = 7.4 Hz, 1H, H-3), 7.43-7.36 (m, 1H, H-4), 7.34-7.32 (m, 1H, H-15/17), 7.30-7.18 (m, 5H, H-2 + H-12 + H-13 + H-15/17), 7.14-7.11 (m, 2H, H-11), 7.08-7.06 (m, 1H, H-16), 6.84-6.80 (m, 2H, H-20), 6.58-6.54 (m, 2H, H-19), 6.05 (d, J = 15.8 Hz, 1H, H-9), 5.76-5.70 (m, 1H, H-8), 3.68 (dd, J = 13.9 Hz, J = 7.6 Hz, 1H, H-7), 3.23 (dd, J = 13.9 Hz, J = 7.1 Hz, 1H, H-7');

13C{1H}-NMR (CDCl3, 150.90 MHz, 295 K): δ [ppm] = 161.79 (s, C-5), 156.24 (d, J = 235.8 Hz, C-21), 151.53 (bs, C-14), 147.22 (s, C-1), 141.33 (s, C-18), 137.37 (m, 2C, C-3 + C-10), 134.30 (s, C-9), 128.52 (s, C-12), 127.33 (s, C-13), 126.92 (s, C-16), 126.50 (s, C-15/17), 126.21 (s, C-11), 124.70 (s, C-14), 123.79 (s, C-8), 122.33 (s, C-2), 121.85 (s, C-4), 117.29 (m, C-19), 115.35 (d, J = 22.1 Hz, C-20), 64.24 (s, C-6), 42.36 (s, C-7);
**19F{1H}-NMR** (CDCl₃, 376.27 MHz, 295 K): \( \delta \) [ppm] = −127.49 (s, F-21);

**MS (HR-DART(+))**: 

| m / z | ([M+H]+) | calculated: |
|-------|-----------|-------------|
| 401.1484 | ([M+H]+) | 401.1488 (C₂₅H₂₁N₂FS [M+H]+) |

**HPLC**: Column: AD-H, n-hexane:iso-propanol = 98:2, \( \lambda = 254 \) nm, flow rate 1 mL/min, 20 °C, \( t(1) = 15.4 \) min, \( t(2) = 19.7 \) min. \((S)-1\)-Phenyl-2-propen-1-ol yields the product \( t(1) \) as major species.

The isolated and characterized \((E)\)-isomer was found to be the major product of this reaction and no minor isomeric species could be unambiguously identified in the proton NMR spectrum of the crude product.

To a solution of 2-pyridinecarbonitride (193 μL, 2.0 mmol, 1 eq) in THF (10 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (1 M, 1 eq) in THF and the mixture was left stirring for 1 h. After that, \([\text{Ti(OiPr)}₄]\) (1 eq) was added and, after 10 min, a solution of 4-fluorophenylmagnesium bromide (1 M, 2 eq) in THF. In a second flask, a solution of 1-octen-3-ol (3 eq) in THF (10 mL) was cooled to −78 °C and \(\text{tert}-\text{butyllithium} \) (1.9 M in pentane, 3.1 eq) was added dropwise. The mixture was slowly warmed to room temperature over 1 h. Then, the solution of the lithium alkoxide was added to the reaction mixture and the combined solutions were first stirred 4 h at room temperature and then heated to 60 °C for 2 d. Addition of sat. \(\text{NH}_4\text{Cl} \) solution, filtration and purification by column chromatography (SiO₂, \( n\)-pentane:ethyl acetate = 100:1) gave 7c as a pale yellow solid in 41 % yield. The reaction was also conducted at room temperature for 4 days using chiral \((S)-1\)-octen-3-ol (enantiopurity: >99:1 e.r.) to afford the corresponding enantioenriched product (87.7:12.3 e.r.).

**1H-NMR** (CDCl₃, 399.89 MHz, 295 K): \( \delta \) [ppm] = 8.61-8.56 (m, 1H, H-1), 7.65-7.58 (m, 1H, H-3), 7.31-7.24 (m, 2H, H-4 + H-16/18), 7.21-7.14 (m, 2H, H-2 + H-16/18), 7.02-6.98 (m, 1H, H-17), 6.80-6.73 (m, 2H, H-21), 6.51-6.45 (m, 2H, H-20), 5.14-5.04 (m, 1H, H-9), 4.97-4.86 (m, 1H, H-8), 3.45-3.37 (m, 2H, H-19), 3.06-2.98 (m, 2H, H-22), 2.46-2.38 (m, 2H, H-15), 2.34-2.26 (m, 2H, H-13), 2.25-2.17 (m, 2H, H-14), 1.64-1.56 (m, 1H, H-10), 1.50-1.42 (m, 1H, H-6), 1.33-1.26 (m, 1H, H-7), 0.88 (t, J = 6.5 Hz, 3H, CH₃-14).
To a solution of 2-pyridinecarbonitrile (2.0 mmol, 1 eq) in THF (10 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (1 M, 1 eq) in THF and the mixture was left stirring for 1 h. After that, [Ti(OiPr)₄] (1 eq) was added and, after 10 min, a solution of 4-fluorophenylmagnesium bromide (1 M, 2 eq) in THF. In a second flask, a solution of 1-(propa-1,2-dien-1-yl)cyclohexan-1-ol (see section 2) (3 eq) in THF (10 mL) was cooled to −78 °C and tert-butyllithium (1.9 M in pentane, 3.05 eq) was added dropwise. The mixture was slowly warmed to room temperature over 1 h. Then,
the solution of the lithium alkoxide was added to the reaction mixture and the combined solutions were heated to 60 °C for 2 d. Addition of dest. water, filtration and purification by column chromatography (SiO₂, n-pentane:ethyl acetate = 50:1 to 5:1) gave 8a as a pale brown solid in 41 % yield.

\(^1\)H-NMR (CDCl₃, 399.89 MHz, 297 K): \(\delta \ [ppm] = 8.57-8.51 \ (m, \ 1H, \ H-1)\), 7.61-7.55 \ (m, \ 1H, \ H-3)\), 7.28-7.23 \ (m, \ 2H, \ H-4 + H-15/17)\), 7.22 \ (d, \ J= 3.6 Hz, \ J= 1.0 Hz, \ 1H, \ H-15/17)\), 7.16-7.11 \ (m, \ 1H, \ H-2)\), 7.00 \ (dd, \ J= 5.0 Hz, \ J= 3.6 Hz, \ 1H, \ H-16)\), 6.80-6.73 \ (m, \ 2H, \ H-20)\), 6.56-6.49 \ (m, \ 2H, \ H-19)\), 5.28-5.15 \ (m, \ 2H, \ H-8 + H-9)\), 3.56-3.48 \ (m, \ 1H, \ H-7)\), 3.04-2.97 \ (m, \ 1H, \ H-7')\), 1.59-1.15 \ (m, \ 10H, \ H-11 + H-11' + H-12 + H-12' + H-13 + H-13')\);

\(^1^3\)C\(^{\text{1}}\)H-NMR (CDCl₃, 100.55 MHz, 299 K): \(\delta \ [ppm] = 161.85 \ (s, \ C-5)\), 155.88 \ (d, \ J= 235.7 Hz, \ C-21)\), 152.08 \ (s, \ C-14)\), 146.91 \ (s, \ C-1)\), 142.22 \ (s, \ C-9)\), 141.45 \ (d, \ J= 1.8 Hz, \ C-18)\), 137.00 \ (s, \ C-3)\), 126.77 \ (s, \ C-16)\), 126.24 \ (s, \ C-15/17)\), 124.24 \ (s, \ C-15/17)\), 121.99 \ (s, \ C-2)\), 121.62 \ (s, \ C-4)\), 120.97 \ (s, \ C-8)\), 116.83 \ (d, \ J= 7.2 Hz, \ C-19)\), 115.17 \ (d, \ J= 22.1 Hz, \ C-20)\), 71.12 \ (s, \ C-10)\), 63.66 \ (s, \ C-6)\), 41.02 \ (s, \ C-7)\), 37.77 \ (s, \ C-11)\), 37.60 \ (s, \ C-11')\), 25.43 \ (s, \ C-13)\), 22.07 \ (s, \ C-12)\), 22.03 \ (s, \ C-12')\);

\(^{19}\)F\(^{\text{1}}\)H-NMR (CDCl₃, 376.27 MHz, 298 K): \(\delta \ [ppm] = −127.37 \ (s, \ F-21)\);

\(^{15}\)N-NMR (CDCl₃, 40.52 MHz, 297 K): \(\delta \ [ppm] = 298.1 \ (m, \ N_{\text{pyridine}})\), 76.3 \ (m, \ NH);\n
MS (HR-DART(+) ): \(m / z \ 423.1926 \ ([M+H]^+)\)   
calculated: 423.1906 \ (C\(_{33}\)H\(_{29}\)N\(_2\)FOS \(\cong [M+H]^+)\)

8a-d₁ was prepared following the same procedure as described for 8a in a 36 % yield. For the aqueous workup, D\(_2\)O was used instead.

\(^1\)H-NMR (CDCl₃, 399.89 MHz, 297 K): \(\delta \ [ppm] = 8.57-8.51 \ (m, \ 1H, \ H-1)\), 7.61-7.55 \ (m, \ 1H, \ H-3)\), 7.28-7.23 \ (m, \ 2H, \ H-4 + H-15/17)\), 7.22 \ (d, \ J= 3.6 Hz, \ J= 1.0 Hz, \ 1H, \ H-15/17)\), 7.16-7.11 \ (m, \ 1H, \ H-2)\), 7.00 \ (dd, \ J= 5.0 Hz, \ J= 3.6 Hz, \ 1H, \ H-16)\), 6.80-6.73 \ (m, \ 2H, \ H-20)\), 6.56-6.49 \ (m, \ 2H, \ H-19)\), 5.28-5.15 \ (m, \ 2H, \ H-8 + H-9)\), 3.56-3.48 \ (m, \ 1H, \ H-7)\), 3.04-2.97 \ (m, \ 1H, \ H-7')\), 1.59-1.15 \ (m, \ 10H, \ H-11 + H-11' + H-12 + H-12' + H-13 + H-13');
2), 7.00 (dd, J = 5.0 Hz, J = 3.6 Hz, 1H, H-16), 6.80-6.73 (m, 2H, H-20), 6.56-6.49 (m, 2H, H-19), 5.17 (1, 1H, H-9), 3.52 (d, J = 13.7 Hz, 1H, H-7), 3.00 (d, J = 13.7 Hz, 1H, H-7'), 1.59-1.15 (m, 10H, H-11 + H-11' + H-12 + H-12' + H-13 + H-13');

$^2$D$^1$H-NMR (CDCl$_3$, 92.12 MHz, 295 K): δ [ppm] = 5.26 (s, D-8);

$^{13}$C$^1$H-NMR (CDCl$_3$, 100.55 MHz, 299 K): δ [ppm] = 161.85 (s, C-5), 155.88 (d, J = 235.7 Hz, C-21), 152.08 (s, C-14), 146.91 (s, C-1), 142.08 (s, C-9), 141.45 (d, J = 1.8 Hz, C-18), 137.00 (s, C-3), 126.77 (s, C-16), 126.24 (s, C-15/17), 124.24 (s, C-15/17), 121.99 (s, C-2), 121.62 (s, C-4), 120.75 (t, J = 15.1 Hz, C-8), 116.83 (d, J = 7.2 Hz, C-19), 115.17 (d, J = 22.1 Hz, C-20), 71.20 (s, C-10), 63.60 (s, C-6), 40.87 (s, C-7), 37.77 (s, C-11), 37.60 (s, C-11'), 25.43 (s, C-13), 22.07 (s, C-12), 22.03 (s, C-12');

$^{19}$F$^1$H-NMR (CDCl$_3$, 376.27 MHz, 298 K): δ [ppm] = −127.53 (s, F-21);

$^{15}$N-NMR (CDCl$_3$, 40.52 MHz, 297 K): δ [ppm] = 298.1 (m, N$_{pyridine}$), 76.3 (m, NH);

MS (HR-DART(−)): m / z 422.1822 ([M−H]$^-$)  
 calculated: 422.1813 (C$_{25}$H$_{25}$DN$_2$FOS$^-$ [M−H]$^-$)

To a solution of 2-pyridinecarbonitrile (5.2 mmol, 1 eq) in THF (20 mL) at 0 °C was added a solution of 4-fluorophenylmagnesium bromide (1 M, 1 eq) in THF and the mixture was left stirring for 1 h. After that, [Ti(OiPr)$_4$] (1 eq) was added and, after 10 min, a solution of 4-methoxyphenylmagnesium bromide (0.5 M, 2 eq) in THF. In a second flask, a solution of 1-(propa-1,2-dien-1-yl)cyclohexan-1-ol (see section 2) (5 eq) in THF (10 mL) was cooled to −78 °C and tert-butyllithium (1.9 M in pentane, 5.25 eq) was added dropwise. The mixture was slowly warmed to room temperature over 1 h. Then,
the solution of the lithium alkoxide was added to the reaction mixture and the combined solutions were heated to 60 °C for 2 d. Addition of dest. water, filtration and purification by column chromatography (SiO2, n-pentane:ethyl acetate:triethylamine = 50:1:1 to 9:1:1) gave 8b as a yellow oil in 38 % yield.

_1H-NMR_ (CDCl3, 399.89 MHz, 297 K): \( \delta \text{ [ppm]} = 8.56-8.52 \text{ (m, 1H, H-1)}, 7.63-7.49 \text{ (m, 3H, H\textsubscript{Ar} + H-3)}, 7.13-7.08 \text{ (m, 1H, H-2)}, 7.07-6.99 \text{ (m, 3H, H\textsubscript{Ar} + H-4)}, 6.66-6.60 \text{ (m, 2H, H-21/22)}, 6.43-6.37 \text{ (m, 2H, H-21/22)}, 6.34 \text{ (brs, 1H, N-H)}, 5.34-5.23 \text{ (m, 1H, H-8)}, 5.19-5.12 \text{ (m, 1H, H-9)}, 3.68 \text{ (s, 3H, H-24)}, 3.54-3.44 \text{ (m, 1H, H-7)}, 3.13-3.02 \text{ (m, 1H, H-7\textsuperscript{'})}, 1.61-1.15 \text{ (m, 11H, H\textsubscript{Alkyl})}; The product shows traces of an inseparable impurity.

_13C\{1H\}-NMR_ (CDCl3, 100.55 MHz, 298 K): \( \delta \text{ [ppm]} = 163.13 \text{ (s, C-5)}, 161.82 \text{ (d, J= 246.1 Hz, C-19)}, 151.88 \text{ (s, C-20/23)}, 147.08 \text{ (s, C-1)}, 141.97 \text{ (d, J= 3.1 Hz, C-16)}, 141.63 \text{ (s, C-9)}, 139.43 \text{ (s, C-20/23)}, 136.67 \text{ (s, C-3)}, 129.07 \text{ (d, J= 7.9 Hz, C-17)}, 122.27 \text{ (s, C-2/4)}, 121.91 \text{ (s, C-8)}, 121.65 \text{ (s, C-2/4)}, 116.90 \text{ (s, C-21/22)}, 115.52 \text{ (d, J= 21.2 Hz, C-18)}, 114.50 \text{ (s, C-21/22)}, 71.26 \text{ (s, C-10)}, 64.51 \text{ (s, C-6)}, 55.68 \text{ (s, C-24)}, 39.29 \text{ (s, C-7)}, 37.89 \text{ (s, C-11/15)}, 37.57 \text{ (s, C-21/22)}, 25.52 \text{ (s, C-13)}, 22.19 \text{ (s, C-12/14)}, 22.15 \text{ (s, C-12/14)}; The product shows traces of an inseparable impurity.

_19F\{1H\}-NMR_ (CDCl3, 376.27 MHz, 297 K): \( \delta \text{ [ppm]} = -115.87 \text{ (s, F-19)}.

**MS (HR-DART(+))**: m / z 447.2443 ([M+H]⁺) 
**calculated**: 447.2448 (C\textsubscript{28}H\textsubscript{32}N\textsubscript{2}FO\textsubscript{2} \( \equiv \) [M +H]⁺)
7. Control reactions

Control reactions were conducted using 5-(4-chlorophenyl)-2-furonitrile and naphthalene-2-carbonitrile. Notably, both reactions yielded solely the trityl amine product.

This reaction was set up in analogy to GP 1 to elucidate the effect of an O-heterocycle in the vicinity of the nitrile function.

Following GP 1, 5-(4-chlorophenyl)-2-furonitrile (1 g, 1 eq), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) tetraisopropoxide (1.45 mL, 1 eq) gave the corresponding trityl amine in 67 % yield after purification by column chromatography (SiO2, n-pentane:ethyl acetate = 9:1).

\[ \text{1H-NMR (CDCl}_3, 399.89 \text{ MHz, 295 K): } \delta [\text{ppm}] = 7.53 (\text{d, } J= 8.5 \text{ Hz, 2H, H-11}), 7.36-7.29 (\text{m, 6H, H-7 + H-12}), 7.05-6.98 (\text{m, 4H, H-8}), 6.58 (\text{d, } J= 3.3 \text{ Hz, 1H, H-3}), 6.01 (\text{d, } J= 3.3 \text{ Hz, 1H, H-2}), 2.46 (\text{bs, 2H, NH}_2); \]

\[ \text{13C{1H}-NMR (CDCl}_3, 100.55 \text{ MHz, 295 K): } \delta [\text{ppm}] = 161.90 (\text{d, } J= 246.5 \text{ Hz, C-9}), 159.40 (\text{s, C-1}), 152.74 (\text{s, C-4}), 141.87 (\text{d, } J= 2.9 \text{ Hz, C-6}), 133.06 (\text{s, C-10/13}), 129.14 (\text{d, } J= 8.0 \text{ Hz, C-7}), 129.13 (\text{s, C-13/10}), 128.89 (\text{s, C-12}), 124.91 (\text{s, C-11}), 119.43 (\text{d, } J= 21.3 \text{ Hz, C-8}), 110.61 (\text{s, C-2}), 105.97 (\text{s, C-3}), 62.22 (\text{s, C-5}); \]

\[ \text{19F{1H}-NMR (CDCl}_3, 376.27 \text{ MHz, 295 K): } \delta [\text{ppm}] = -115.10 (\text{s}); \]

\[ \text{MS (HR-ESI(+)): } \text{m / z } 379.0693 (\text{[M−NH}_2^+]^{+}) \]

\text{calculated: } 379.0696 (\text{C}_{25}\text{H}_{14}\text{F}_{2}\text{OCl} \text{[M−NH}_2^+]^{+})
Following GP 1, 2-naphthonylimine (0.514 g, 1 eq), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) tetraisopropoxide (2.96 mL, 3 eq) gave the corresponding trityl amine in 86 % yield after purification by column chromatography (SiO₂, n-pentane:ethyl acetate = 30:1 to 9:1 + 0.5 % triethylamine).

$^1\text{H-NMR}$ (CDCl₃, 399.89 MHz, 296 K): $\delta$ [ppm] = 7.86-7.78 (m, 2H, H₉), 7.77-7.72 (m, 1H, H₈), 7.64-7.62 (m, 1H, H₇), 7.52-7.44 (m, 2H, H₆), 7.42-7.37 (m, 1H, H₅), 7.32-7.25 (m, 4H, H-13), 7.05-6.97 (m, 4H, H-14), 2.40 (bs, 2H, NH);

$^{13}\text{C}^\{1\text{H}\}$-NMR (CDCl₃, 100.55 MHz, 298 K): $\delta$ [ppm] = 161.73 (d, $J$ = 246.2 Hz, C-15), 145.78 (s, C₃), 144.11 (d, $J$ = 3.2 Hz, C-12), 132.97 (s, C₅), 132.31 (s, C₆), 129.92 (d, $J$ = 7.9 Hz, C-13), 128.42 (s, C₂), 127.99 (s, C₃), 127.55 (s, C₄), 126.62 (s, C₅), 126.41 (s, C₆), 126.34 (s, C₇), 126.29 (s, C₈), 114.93 (d, $J$ = 21.2 Hz, C-14), 65.71 (s, C-11);

$^{19}\text{F}^\{1\text{H}\}$-NMR (CDCl₃, 376.27 MHz, 297 K): $\delta$ [ppm] = −116.01 (s, F-15);

Elemental analysis: found: C 79.71%, H 4.92%, N 4.25%,
calculated: C 79.98%, H 4.96%, N 4.06%.

MS (HR-ESI(+)): m / z 329.1137 ([M−NH₂]+)
calculated: 329.1142 (C₂₃H₁₅F₂ + [M−NH₂]+).

It should be noted, that Gregg et al. already employed similar reaction conditions for the preparation of α-trisubstituted amines starting from 4-pyridinecarbonitrile or 1-piperidineacetonitrile. These reactions demonstrated that (i) the pyridyl nitrogen has to be directly adjacent to the nitrile function and (ii) a potentially chelating 1,4-diaza motif is not sufficient to ensure azaphilic addition.
In addition, we investigated whether the reaction occurs via a tritylamine intermediate which subsequently rearranges to the N-aryl species. For this experiment a pyridyl-substituted trityl amine was prepared: starting from ethyl 2-picolinate:

\[
\begin{align*}
\text{N} & \quad \text{OEt} \quad + \quad \text{ArMgBr} \quad \rightarrow \quad \text{N} & \quad \text{OH} \quad \text{Ar} \\
\text{(Ar} & \quad = \quad 4-\text{F-C}_6\text{H}_4) \\
\end{align*}
\]

Reaction conditions: (i) THF, 0 °C C, rt over night; (ii) SOCl\textsubscript{2} (excess), n-hexane, reflux, 3 h; (iii) NH\textsubscript{3} (0.5 M in dioxane, 100 mL), NEt\textsubscript{3} (10 Åq.), CH\textsubscript{3}CN, rt, 24 h.

To a solution of 4-fluorophenylmagnesium bromide (0.05 mol, 2.5 eq) in THF (140 mL) at 0 °C a solution of ethyl 2-picolinate (3.02 g, 0.02 mol, 1 eq) in THF (50 mL) was slowly added. The mixture was warmed to room temperature overnight. Then, sat. NH\textsubscript{4}Cl(aq) solution was added and the mixture was extracted with Et\textsubscript{2}O. The combined organic extracts were dried over anhydrous MgSO\textsubscript{4}, filtered, evaporated and further purified by column chromatography (SiO\textsubscript{2}, n-pentane:ethyl acetate = 20:1 to 10:1). The product was obtained as a colorless oil (95 %, 5.63 g).

\[1^H\text{-NMR (CDCl}_3, 399.89 \text{ MHz, 296 K): } \delta \text{ [ppm]} = 8.60-8.56 (m, 1H, H-5), 7.68-7.62 (m, 1H, H-3), 7.28-7.19 (m, 5H, H-4 + H-8), 7.07-7.03 (m, 1H, H-2), 7.01-6.94 (m, 4H, H-9), 6.26 (s, 1H, OH);\]

\[13^C\{^1H\}-\text{NMR (CDCl}_3, 100.55 \text{ MHz, 296 K): } \delta \text{ [ppm]} = 162.94 (s, C-1), 162.20 (d, J = 246.6 Hz, C-10), 148.05 (s, C-5), 141.91 (d, J = 3.2 Hz, C-7), 136.79 (s, C-3), 129.96 (d, J = 8.1 Hz, C-8), 122.76 (m, C-2 + C-4), 114.93 (d, J = 21.4 Hz, C-9), 80.19 (s, C-6);\]

\[19^F\text{-NMR (CDCl}_3, 188.09 \text{ MHz, 295 K): } \delta \text{ [ppm]} = -115.10--115.27 (m, F-10);\]

\[\text{MS (HR-ESI(−)): } \text{m/z} \quad 296.0890 \quad ([\text{M-}\text{H}]^-) \quad \text{calculated: } \quad 296.0887 \quad (\text{C}_{18}\text{H}_{12}\text{NF}_2\text{O} \quad \text{[M-\text{H}]^-})\]
To a solution of the alcohol from the previous reaction (5.5 g, 18.5 mmol, 1 eq) in dry n-hexane (100 mL) at room temperature was added an excess of SOCl₂ (30 mL) and the mixture was stirred for 30 min. Then the reaction mixture was heated to reflux for 3 h, cooled to room temperature and the excess of SOCl₂ was removed *in vacuo* to yield a yellow foam. Subsequently, dry CH₃CN (300 mL), dry NEt₃ (25 mL, 10 eq) and a solution of NH₃ in dioxane (0.5 M, 100 mL) was added. The mixture was left stirring at room temperature for 24 h, evaporated to dryness and purified by column chromatography (SiO₂, n-pentane:ethyl acetate = 3:1 to dichloromethane:methanol 95:5). The pyridyl-substituted tritylamine was obtained as a brown oil that solidified on standing to give a pale brown solid (1.95 g, 36 %).

**1H-NMR** (CDCl₃, 399.89 MHz, 296 K): δ [ppm] = 8.65-8.62 (m, 1H, H-5), 7.61-7.55 (m, 1H, H-3), 7.23-7.15 (m, 5H, H-4 + H-8), 7.03-6.94 (m, 5H, H-2 + H-9), 2.75 (bs, 2H, NH);

**13C{1H}-NMR** (CDCl₃, 150.90 MHz, 295 K): δ [ppm] = 165.56 (s, C-1), 161.83 (d, J = 246.4 Hz, C-10), 149.24 (s, C-5), 143.52 (d, J = 3.2 Hz, C-7), 136.28 (s, C-3), 130.05 (d, J = 8.0 Hz, C-8), 122.67 (s, C-2), 121.99 (s, C-4), 114.98 (d, J = 21.2 Hz, C-9), 67.01 (s, C-6);

**19F-NMR** (CDCl₃, 188.11 MHz, 295 K): δ [ppm] = −115.87−−116.05 (m, F-10);

**Elemental analysis:**

| Found   | Calculated |
|---------|------------|
| C 73.04% | C 72.96%   |
| H 5.04%  | H 4.76%    |
| N 9.39%  | N 9.45%    |

**MS (HR-EI(+)):**

| m / z     | ([M⁺])            |
|-----------|--------------------|
| 296.1137  | (C₁₈H₁₄N₂F₂)⁺     |
| calculated| 296.1125 (C₁₈H₁₄N₂F₂)⁺ |

However, subjecting this tritylamine product to the reaction conditions showed no signs of conversion. A second indication, that a carbon-to-nitrogen-shift mechanism is not feasible is the observed regioselectivity of the transformation (i.e. no preference for either electron-withdrawing or electron-donating aromatic units).
8. Characterization of byproducts

In the procedures GP 1 and GP 2 described above, the second Grignard species is added in excess (generally 2 eq) to obtain higher yields. As a result, small amounts of biphenyl byproducts are formed in less than 10% yield. To allow identification, the spectroscopic data of two biphenyl compounds is given below.

![Diagram of biphenyl molecule]

Colorless crystals.

\(^1\text{H-NMR}\) (CDCl\(_3\), 600.13 MHz, 295 K): \(\delta\) [ppm] = 7.51-7.48 (m, 4H, H-2), 7.14-7.10 (m, 4H, H-3);

\(^{13}\text{C}\{^1\text{H}\}-\text{NMR}\) (CDCl\(_3\), 150.90 MHz, 295 K): \(\delta\) [ppm] = 162.55 (d, \(J = 246.5\) Hz, C-4), 136.53 (d, \(J = 3.3\) Hz, C-1), 128.72 (d, \(J = 8.2\) Hz, C-2), 115.83 (d, \(J = 21.4\) Hz, C-3);

\(^{19}\text{F}\{^1\text{H}\}-\text{NMR}\) (CDCl\(_3\), 376.27 MHz, 298 K): \(\delta\) [ppm] = -115.74 (s);

\textbf{MS (HR-EI(+))}: \\
\begin{tabular}{l|l|l}
 m / z & 190.0584 & ([M]^+) \\
 calculated: & 190.0594 & (C\(_{12}\)H\(_8\)F\(_2\) \[M]^+)
\end{tabular}

Colorless crystals.

\(^1\text{H-NMR}\) (CDCl\(_3\), 399.89 MHz, 296 K): \(\delta\) [ppm] = 7.50-7.45 (m, 4H, H-2/3), 6.98-6.93 (m, 4H, H-2/3), 3.84 (s, 6H, H-5);

\(^{13}\text{C}\{^1\text{H}\}-\text{NMR}\) (CDCl\(_3\), 100.55 MHz, 298 K): \(\delta\) [ppm] = 158.84 (C\(_\text{Ar}\)), 133.64 (C\(_\text{Ar}\)), 127.88 (C\(_\text{Ar}\)H), 114.31 (C\(_\text{Ar}\)H), 55.50 (C-5);
Other minor byproducts include the mono-arylated primary amines and the corresponding ketones and imines. For each class of compounds a fully characterized example is given below.

Brown oil.

$^1$H-NMR (CDCl$_3$, 399.89 MHz, 296 K): $\delta$ [ppm] = 8.58-8.54 (m, 1H, H-5), 7.63-7.57 (m, 1H, H-3), 7.40-7.34 (m, 2H, H-8), 7.24 (d, $J$ = 7.8 Hz, 1H, H-2), 7.16-7.11 (m, 1H, H-4), 7.02-6.95 (m, 2H, H-9), 5.22 (s, 1H, H-6), 2.28 (bs, 2H, NH);

$^{13}$C{$^1$H}-NMR (CDCl$_3$, 100.55 MHz, 298 K): $\delta$ [ppm] = 163.29 (s, C-1), 162.06 (d, $J$ = 245.7 Hz, C-10), 149.20 (s, C-5), 140.48 (d, $J$ = 3.1 Hz, C-7), 136.75 (s, C-3), 128.76 (d, $J$ = 8.0 Hz, C-8), 122.17 (s, C-4), 121.56 (s, C-2), 115.45 (d, $J$ = 21.4 Hz, C-9), 60.45 (s, C-6);

$^{19}$F{$_^1$H}-NMR (CDCl$_3$, 376.27 MHz, 297 K): $\delta$ [ppm] = −115.64 (s, F-10);

MS (HR-ESI(+)): m / z 203.0979 ([M+H]$^+$)

Calculated: 203.0985 (C$_{12}$H$_{11}$N$_2$F $\Leftrightarrow$ [M+H]$^+$)

Colorless solid.

$^1$H-NMR (CDCl$_3$, 600.13 MHz, 295 K): $\delta$ [ppm] = 8.72-8.70 (m, 1H, H-5), 8.19-8.14 (m, 2H, H-8), 8.07-8.04 (m, 1H, H-2), 7.93-7.89 (m, 1H, H-3), 7.51-7.48 (m, 1H, H-4), 7.18-7.13 (m, 2H, H-9);

$^{13}$C{$_^1$H}-NMR (CDCl$_3$, 150.90 MHz, 295 K): $\delta$ [ppm] = 192.18 (s, C-6), 165.85 (d, $J$ = 255.2 Hz, C-10), 155.08 (s, C-1), 148.59 (s, C-5), 137.31 (s, C-3), 133.95 (d, $J$ = 9.3 Hz, C-8), 132.66 (d, $J$ = 3.0 Hz, C-7), 126.42 (s, C-4), 124.81 (s, C-2), 115.44 (d, $J$ = 21.8 Hz, C-9);

$^{19}$F{$_^1$H}-NMR (CDCl$_3$, 376.27 MHz, 295 K): $\delta$ [ppm] = −105.25 (s, F-10);
Elemental analysis: found: C 71.79%, H 4.09%, N 6.95%, calculated: C 71.64%, H 4.01%, N 6.96%.

MS (HR-EI(+)): m / z 201.0600 ([M]^+)  
calculated: 201.0590 (C_{12}H_{8}NFO \[M]^+)

In solution a mixture of cis- and trans-isomers of the imine is present. The two isomers (ratio 1 : 0.6) are labeled A and B for the major and minor isomer, respectively.

$^1$H-NMR (C$_6$D$_6$, 600.13 MHz, 295 K): $\delta$ [ppm] = 8.49 (d, $J$= 8.0 Hz, 1H, H$_{B-1/4}$), 8.44-8.41 (m, 1H, H$_{A-1}$), 8.38-8.34 (m, 1H, H$_{B-1/4}$), 7.88-7.83 (m, 2H, H$_A$-8/9), 7.20-7.16 (m, 1H, H$_B$-2/3), 7.03-6.98 (m, 2H, H$_B$-12/13), 6.89-6.84 (m, 2H, H$_A$-12), 6.82-6.75 (m, 3H, H$_A$-3 + H$_A$-8/9), 6.82-6.75 (m, 2H, H$_A$), 6.69-6.65 (m, 3H, H$_B$-2/3 + H$_B$-12/13), 6.64-6.61 (m, 1H, H$_A$), 6.64-6.61 (m, 2H, H$_B$-13), 6.60-6.56 (m, 2H, H$_A$-13), 6.50-6.47 (m, 1H, H$_A$-2), 3.21(s, 3H, H$_B$-15), 3.17 (s, 3H, H$_A$-15);  

$^{13}$C$^1$H-NMR (C$_6$D$_6$, 150.90 MHz, 295 K): $\delta$ [ppm] = 166.13 (s, C$_{B-Ar}$), 164.79 (s, C$_{A-Ar}$), 164.73 (d, $J$= 250.9 Hz, C$_{A-10}$), 162.82 (d, $J$= 247.6 Hz, C$_B$-10), 157.92 (s, C$_{B-Ar}$), 157.02 (s, C$_{A-Ar}$), 156.81 (s, C$_{A-Ar}$), 156.36 (s, C$_{A-Ar}$), 149.62 (s, C$_A$-1), 148.67 (s, C$_B$-1), 144.52 (s, C$_{A-Ar}$), 144.13 (s, C$_{B-Ar}$), 136.08 (s, C$_B$-11), 135.73 (s, C$_A$-3), 135.51 (d, $J$= 3.1 Hz, C$_A$-7), 132.47 (d, $J$= 8.1 Hz, C$_B$-8$^\prime$), 132.27 (d, $J$= 3.6 Hz, C$_B$-7), 131.64 (d, $J$= 8.6 Hz, C$_A$-8), 124.50 (s, C$_{A-II}$), 124.31 (s, C$_{B-II}$), 123.20 (s, C$_{B-II}$), 123.10 (s, C$_{A-12}$), 123.08 (s, C$_{B-II}$), 122.84 (s, C$_A$-2), 115.31 (d, $J$= 21.6 Hz, C$_A$-9), 114.93 (d, $J$= 21.5 Hz, C$_B$-9), 114.32 (s, C$_{B-II}$), 114.19 (s, C$_A$-13), 54.80 (s, C$_{B-II}$), 54.73 (s, C$_A$-15);  

$^{19}$F$^1$H-NMR (CDCl$_3$, 376.27 MHz, 295 K): $\delta$ [ppm] = −109.67 (s, F$_A$), −111.51 (s, F$_B$);  

MS (HR-DART(+)): m / z 307.1237 ([M+H]$^+$)  
calculated: 307.1247 (C$_{19}$H$_{15}$N$_2$FO$_2$ \[M+H]$^+$) (For [M])

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9. Preparation of the homo- and heterometallic reaction intermediates

To a solution of 2-pyridinecarbonitrile (0.9 mL, 1 eq) in dry THF (25 mL) at 0 °C was added 4-fluorophenylmagnesium bromide in THF (1 M, 1.05 eq) and the mixture was warmed to room temperature over night. The supernatant was removed by filtration and the residue was washed with THF (2 x 6 mL). Drying \textit{in vacuo} afforded 7 as a bright yellow solid (90 %, 2.55 g). Multinuclear NMR spectra show a multitude of resonances hinting at the presence of a number of metallic species in solution. Single crystals suitable for X-ray diffraction analysis were obtained from a solution of the compound in dichloromethane after layering with toluene and \textit{n}-pentane.

\textbf{Elemental Analysis:} found: C 51.17%, H 4.37%, N 7.55%, calc.: C 51.17%, H 4.29%, N 7.46%. (For [M+THF])

\textbf{IR (Nujol, KBr, room temperature):} relevant region: 1621 cm\textsuperscript{-1}, 1601 cm\textsuperscript{-1}, 1592 cm\textsuperscript{-1}, 1569 cm\textsuperscript{-1}, 1506 cm\textsuperscript{-1}.

\textbf{MS (LIFDI(+))}: \begin{align*}
m/z & \quad 199.4 \quad ([\text{py-ketimide}]^+) \\
calc. & \quad 199.1 \quad (C_{12}H_8N_2F \rightleftharpoons [\text{py-ketimide}]^+)
\end{align*}
To a solution of [TiBr(O\text{Pr})_3] (610 mg, 1 eq) in a THF/toluene/n-pentane solvent mixture was added the Mg-pyridylketimido complex 7 (751 mg, 1 eq). The mixture was stirred at room temperature for 30 min and filtered through Celite. The clear solution was carefully layered with toluene and n-pentane. 8 was obtained as a pale yellow solid (417 mg, 25 %). Multinuclear NMR spectra show a multitude of resonances hinting at the presence of a number of metallic species in solution.

**Elemental analysis:**
- found: C 49.36\%, H 4.91\%, N 7.09\%
- calculated: C 49.76\%, H 4.67\%, N 6.83\%

**MS (LIFDI(+)):**
- m / z 199.4 ([py-ketimide]^+)
- calc.: 199.1 (C_{12}H_{10}N_{2}F = [py-ketimide]^+)

**IR (Nujol, KBr, room temperature):** relevant region: 1632 cm\(^{-1}\), 1617 cm\(^{-1}\), 1596 cm\(^{-1}\), 1570 cm\(^{-1}\), 1504 cm\(^{-1}\).

For comparison: Reeves et al. reported the IR analysis a titanium(IV) ketimine complex which was formed in situ from acetophenone, ammonia and [Ti(O\text{Pr})_4]. A band at 1626 cm\(^{-1}\) was observed and attributed to the C=N bond: J. T. Reeves, Z. Tan, Z. S. Han, G. Li, Y. Zhang, Y. Xu, D. C. Reeves, N. C. Gonnella, S. Ma, H. Lee, B. Z. Lu, C. H. Senanayake, *Angew. Chem.* **2012**, *124*, 1429-1433.
10. Deuteration experiments

In the preparation of benzhydryle amine 1a-d₁, D₂O was used for quenching the reaction mixture. After column chromatography the dibenzylic position was found to be (almost) quantitatively deuterated (~92 %).

\[ \text{HN} \]

\[ 1H \text{ NMR spectra of 1a (bottom) and 1a-d₁ (top) in CDCl₃.} \]
In the preparation of the multicomponent reaction product \(8a\)-d\(_1\), D\(_2\)O was used for quenching the reaction mixture. After column chromatography the vinylic position (H-8) was found to be (almost) quantitatively deuterated (~94 %). In the \(^1\)H-NMR spectra the deuteration has a pronounced effect on the H-7 protons (shown on the right).

Left: \(^1\)H NMR spectra of \(8a\) (bottom) and \(8a\)-d\(_1\) (top) in CDCl\(_3\). Right: Section of the \(^1\)H NMR spectra displaying the coupling pattern of H-7 in \(8a\) and \(8a\)-d\(_1\).
11. X-ray Crystal Structure Determinations

Crystal data and details of the structure determinations are compiled in Tables S1-S2. Full shells of intensity data were collected at low temperature with a Bruker AXS Smart 1000 CCD diffractometer (Mo-\(K_\alpha\) radiation, sealed X-ray tube, graphite monochromator; compounds 2\(i\), 6\(c\), 7\(a\) and 7\(b\)) or an Agilent Technologies Supernova-E CCD diffractometer (Mo- or Cu-\(K_\alpha\) radiation, microfocus X-ray tube, multilayer mirror optics; all other compounds). Data were corrected for air and detector absorption, Lorentz and polarization effects;\(^{5,6}\) absorption by the crystal was treated analytically,\(^{6,7}\) numerically (Gaussian grid)\(^{6,8}\) or with a semiempirical multiscan method\(^{9,10,11}\)

The structures were solved by direct methods with dual-space recycling (compound 7\(b\)),\(^{12}\) by intrinsic phasing (compound 3)\(^{13}\) or by the charge flip procedure (all other compounds)\(^{14}\) and refined by full-matrix least squares methods based on \(F^2\) against all unique reflections.\(^{15}\) All non-hydrogen atoms were given anisotropic displacement parameters. Hydrogen atoms were generally input at calculated positions and refined with a riding model. When justified by the quality of the data the positions of some hydrogen atoms were taken from difference Fourier syntheses and refined. When found necessary, disordered groups where subjected to suitable geometry and adp restraints. Due to severe disorder and fractional occupancy, some electron density attributed to solvent (dichloromethane) of crystallization was removed from the structures of 3 with the BYPASS procedure,\(^{16}\) as implemented in PLATON (SQUEEZE).\(^{17}\) Partial structure factors from the solvent masks were included in the refinement as separate contributions to \(F_{\text{obs}}\).

Supporting Information Available: CIF files giving crystallographic data for compounds 1\(c\), 1\(e\), 2\(i\), 3, 4, 5\(a\), 6\(c\), 7\(a\), 7\(b\), 8\(a\).
Table S1. Details of the crystal structure determinations.

|          | 1e   | 1e   | 2i   | 3    | 4    |
|----------|------|------|------|------|------|
| formula  | C₁₆H₁₃FN₂S | C₂₃H₁₈F₂N₂O | C₁₇H₁₄F₂N₂S | C₁₀₀H₇₂B₈Cl₈F₈M | C₁₁H₁₄Br₃F₆MgN₉O₄Ti |
| Mᵣ      | 284.34 | 376.39 | 316.36 | 2767.09 | 820.71 |
| crystal system | monoclinic | monoclinic | monoclinic | monoclinic | triclinic |
| space group | P 2₁/n | C 2/c | P 2₁/c | P 2₁/c | P 1 |
| a /Å      | 10.195(4) | 15.759(3) | 18.0092(2) | 22.4267(3) | 9.8718(3) |
| b /Å      | 9.490(4)  | 9.65061(16) | 10.00543(13) | 16.2143(2) | 10.4703(4) |
| c /Å      | 13.914(7) | 24.0594(4) | 17.4500(3) | 32.7617(5) | 17.5861(5) |
| α /°      | 97.588 | 91.837(11) | 97.0396 | 101.0556 | 94.438(2) |
| β /°      | 99.211 | 98.5049 | 97.0396 | 101.0556 | 94.438(2) |
| γ /°      | 95.282 | 98.240(17) | 97.0396 | 101.0556 | 94.438(2) |
| V /Å³     | 1345.6 | 3617.63 | 3120.61 | 11692.1 | 1786.75 |
| Z         | 4     | 8     | 8     | 4     | 2     |
| F₀₀₀      | 592   | 1568  | 1312  | 5472  | 832   |
| d₀ /mm⁻¹  | 1.404 | 1.382 | 1.347 | 1.572 | 1.525 |
| X-radiation, λ /Å | Mo-Kα, 0.71073 | Mo-Kα, 0.71073 | Cu-Kα, 1.5418 | Mo-Kα, 0.71073 | Mo-Kα, 0.71073 |
| μ /mm⁻¹   | 0.8623, 0.8209 | 1.0000, 0.9394 | 0.935, 0.728 | 0.835, 0.547 | 0.852, 0.687 |
| max., min. transmission factors | 0.8623, 0.8209 | 1.0000, 0.9394 | 0.935, 0.728 | 0.835, 0.547 | 0.852, 0.687 |
| data collect. temper. /K | 100(2) | 110(1) | 110(2) | 120(1) | 120(1) |
| θ range /° | 2.4 to 32.5 | 3.3 to 32.6 | 4.9 to 70.8 | 3.2 to 27.1 | 3.3 to 28.7 |
| index ranges h,k,l | -14...14, -14...14, -20...20 | -23...23, -14...14, -36...36 | -21...21, -12...12, -20...20 | -28...28, -20...20, -41...41 | -13...13, -14...14, -23...23 |
| reflections measured | 33321 | 68525 | 66994 | 202860 | 39199 |
| unique [Rint] | 4627 [0.0449] | 6575 [0.0789] | 5972 [0.0512] | 25754 [0.0792] | 9238 [0.0662] |
| observed [I2θ(2θ)] | 3685 | 4573 | 4963 | 19620 | 6606 |
| parameters refined | 221 | 301 | 467 | 1343 | 428 |
| GoF on F² | 1.044 | 1.047 | 1.013 | 1.036 | 1.044 |
| R indices [F>4σ(F)] | R(F), wR(F²) | 0.0443, 0.1060 | 0.0505, 0.1179 | 0.0337, 0.0852 | 0.0590, 0.1277 |
| | R indices (all data) | R(F), wR(F²) | 0.0604, 0.1172 | 0.0804, 0.1327 | 0.0459, 0.0914 |
| | Difference density: max, min /e·Å⁻³ | 0.551, -0.264 | 0.357, -0.230 | 0.267, -0.202 | 2.113, -1.780 | 1.553, -0.464 |
Table S2. Details of the crystal structure determinations.

|       | 5a            | 6c            | 7a            | 7b            | 8a            |
|-------|---------------|---------------|---------------|---------------|---------------|
| formula         | C₉H₁₃FN₃O₂   | C₁₀H₁₈FN₃S   | C₁₀H₁₈FN₃S   | C₁₀H₁₈FN₃S   | C₁₀H₁₈FN₃O₈   |
| M_r            | 351.37        | 430.56        | 352.46        | 400.50        | 422.54        |
| crystal system  | monoclinic    | monoclinic    | monoclinic    | monoclinic    | monoclinic    |
| space group     | C 2/c         | P -1          | P 2₁/n        | P -1          | P -1          |
| a /Å            | 20.3079(8)    | 10.526(3)     | 12.052(6)     | 8.573(3)      | 10.25396(16)  |
| b /Å            | 7.57317(19)   | 11.253(5)     | 11.172(5)     | 11.492(4)     | 13.4798(2)    |
| c /Å            | 23.5113(8)    | 11.792(6)     | 13.492(7)     | 11.507(5)     | 16.1777(3)    |
| a /°            | 96.617(15)    | 98.667(10)    | 77.201(6)     | 100.671(13)   | 91.6383(14)   |
| β /°            | 113.312(4)    | 113.902(11)   | 98.667(10)    | 77.201(6)     | 100.671(13)   |
| γ /°            | 109.266(16)   | 113.902(11)   | 99.201(6)     | 100.671(13)   | 91.6383(14)   |
| V /Å³           | 3353.4(2)     | 1154.3(10)    | 1795.9(16)    | 1017.6(7)     | 2186.89(6)    |
| Z               | 8             | 2             | 4             | 2             | 4             |
| F₀₀₀           | 1472          | 456           | 744           | 420           | 896           |
| d₀, Mg m⁻³      | 1.392         | 1.239         | 1.304         | 1.307         | 1.283         |
| X-radiation, λ /Å | Cu-Kα, 1.5418 | Mo-Kα, 0.71073 | Mo-Kα, 0.71073 | Mo-Kα, 0.71073 | Mo-Kα, 0.71073 |
| μ /mm⁻¹         | 0.819         | 0.165         | 0.195         | 0.181         | 0.176         |
| max., min. transmission factors | 0.930, 0.873 | 0.8623, 0.8137 | 0.7462, 0.6722 | 0.8623, 0.8031 | 0.991, 0.968 |
| data collect. temperat. /K | 110(1) | 100(1) | 100(1) | 120(1) | 120(1) |
| θ range /°      | 4.1 to 70.4   | 2.0 to 30.5   | 2.1 to 31.1   | 1.8 to 32.5   | 3.3 to 28.9   |
| index ranges h,k,l | -21 ... 24, -9 ... 28 ... 28 | -15 ... 15, -16 ... 16, -16 ... 16 | -17 ... 17, -16 ... 16, -19 ... 19 | -12 ... 12, -17 ... 17, -17 ... 17 | -13 ... 13, -17 ... 18, -21 ... 21 |
| reflections measured | 38825 | 28265 | 44346 | 26274 | 62602 |
| unique [Rint]   | 3161 [0.0886] | 7025 [0.0329] | 5760 [0.0587] | 6868 [0.0235] | 10753 [0.0459] |
| observed [I>2σ(I)] | 2824 | 5164 | 4304 | 5965 | 9252 |
| parameters refined | 282 | 318 | 266 | 326 | 558 |
| Goof on F²     | 1.115         | 1.026         | 1.057         | 1.055         | 1.137         |
| R indices [F>4σ(F)] | R(F), wR(F²) | 0.0421, 0.0902 | 0.0699, 0.1895 | 0.0450, 0.1106 | 0.0457, 0.1225 |
| R indices (all data) | R(F), wR(F²) | 0.0502, 0.0942 | 0.0932, 0.2096 | 0.0683, 0.1240 | 0.0526, 0.1291 |
| Difference density: max, min /e·Å⁻³ | 0.194, -0.184 | 1.037, -0.395 | 0.547, -0.305 | 0.754, -0.313 | 0.591, -0.743 |
12. Solid State Structures

Molecular structure of compound 1c, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(2)-H and the benzylic C(11)-H, have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.3150(16), C(1)-C(11) 1.5274(18), C(11)-N(2) 1.4456(16), N(1)-C(1)-C(11)-N(2) 8.40(16).

Molecular structure of compound 1e, thermal ellipsoids set at the 50 % probability level. The other enantiomer and H-atoms, except N(2)-H and the benzylic C(1)-H, have been omitted for clarity. Selected bond lengths [Å] and angles [°] (values in square brackets refer to the second independent molecule): N(1)-C(2) 1.3019(19) [1.3026(19)], C(1)-C(2) 1.513(2) [1.516(2)], C(1)-N(2) 1.4516(19) [1.4540(18)], N(1)-C(2)-C(1)-N(2) 174.04(13) [-167.30(13)].
Molecular structure of compound 2i, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(1)-H and the benzylic C(1)-H, have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.4659(16), C(1)-C(6) 1.5259(17), C(6)-N(2) 1.3426(17), N(1)-C(1)-C(6)-N(2) 40.78(14).

Molecular structure of compound 3, thermal ellipsoids set at the 50 % probability level. H-atoms and cocrystallized solvent molecules have been omitted for clarity. Left: The central Mg$_4$Br$_4$ cube has been colored for emphasis. Selected avg. bond lengths [Å] and angles [°]: $N_{Py}$-Mg 2.163±0.007, $N_{imide}$-Mg (chelat) 2.098±0.009, $N_{imide}$-Mg (bridging) 2.055±0.010, $C_{Py}$-$C_{imide}$ 1.263±0.004.
1.514±0.005, Mg···Mg 3.494±0.021, Mg-Br (terminal) 2.514±0.020, NPy-Mg-Nimide 79.31±0.36, MgImide-N-MgImide 114.57±0.91.

Molecular structure of compound 4, thermal ellipsoids set at the 50 % probability level. H-atoms have been omitted for clarity, iso-propyl groups are drawn as wireframes. Selected bond lengths [Å] and angles [°]: Br(1)-Ti 2.6938(8), Br(2)-Mg 2.5448(13), Ti-Mg 3.1656(13), Ti-O(1) 1.808(3), Ti-O(2) 1.798(3), Ti-N(1) 2.140(3), Ti-N(2) 2.245(3), Ti-N(3) 2.028(3), Mg-O(3) 2.073(3), Mg-N(1) 2.102(3), Mg-N(3) 2.163(3), Mg-N(4) 2.192(3), N(1)-C(1) 1.277(4), N(2)-C(2) 1.350(5), N(3)-C(13) 1.275(5), N(4)-C(14) 1.348(5), C(1)-C(2) 1.502(5), C(13)-C(14) 1.506(6), Br(1)-Ti-Mg 71.23(3), O(1)-Ti-Br(1) 88.53(9), O(1)-Ti-Mg 148.58(10), O(1)-Ti-N(1) 158.19(12), O(1)-Ti-N(2) 89.95(13), O(1)-Ti-N(3) 111.61(13), O(2)-Ti-Br(1) 168.89(9), O(2)-Ti-Mg 97.92(9), O(2)-Ti-O(1) 102.34(13), O(2)-Ti-N(1) 91.68(12), O(2)-Ti-N(2) 89.41(12), O(2)-Ti-N(3) 94.14(13), N(1)-Ti-Br(1) 78.62(8), N(1)-Ti-N(2) 73.38(11), N(2)-Ti-Br(1) 92.92(8), N(2)-Ti-N(1) 79.52(9), N(2)-Ti-N(3) 83.52(11), N(3)-Ti-N(2) 156.73(12), Br(2)-Mg-Ti 119.34(4), O(THF)-Mg-Br(2) 102.56(8), O(THF)-Mg-Ti 129.03(8), N(1)-Mg-Br(2) 108.96(9), N(1)-Mg-N(3) 81.25(12), N(1)-Mg-N(4) 154.08(13), N(3)-Mg-Br(2) 109.14(9), N(3)-Mg-N(4) 75.83(12), N(4)-Mg-Br(2) 90.08(9), Mg-N(1)-Ti 96.52(12), C(1)-N(1)-Ti 119.7(2), C(1)-N(1)-Mg 143.6(3), C(2)-N(2)-Ti 115.3(2), Ti-N(3)-Mg 98.08(13), C(13)-N(3)-Ti 144.1(3), C(13)-N(3)-Mg 115.9(3), C(14)-N(4)-Mg 112.7(2), N(1)-C(1)-C(2) 117.4(3), N(2)-C(2)-C(1) 112.9(3), Ti-N(1)-C(1)-C(2) 1.1(4), Ti-N(2)-C(2)-C(1) -12.5(4), Mg-N(1)-C(1)-C(2) -173.5(3), Mg-
N(3)-C(13)-C(14) -3.1(4), Mg-N(4)-C(14)-C(13) -21.6(4), N(1)-C(1)-C(2)-N(2) 7.9(5), N(3)-C(13)-C(14)-N(4) 17.1(5).

Molecular structure of compound 5a, thermal ellipsoids set at the 50 % probability level. H-atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(2)-C(4) 1.341(2), C(1)-C(4) 1.538(2), C(1)-N(1) 1.4637(19), N(2)-C(4)-C(1)-N(1) 50.15(17), N(1)-C(1)-C(2)-O(1) 27.84(15).

Molecular structure of compound 6c, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(1)-H, and the disorder within the tert-butyl group have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.459(2), C(1)-C(17) 1.536(3), N(2)-C(17) 1.333(2), N(1)-C(1)-C(17)-N(2) 17.87(19).
Molecular structure of compound 7a, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(1)-H, have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.4615(18), C(1)-C(12) 1.542(2), C(12)-N(2) 1.3378(19), N(1)-C(1)-C(12)-N(2) 23.22(16).

Molecular structure of compound 7b, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(1)-H, are omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.4517(14), C(1)-C(2) 1.5614(16), C(1)-C(11) 1.5152(15), C(1)-C(15) 1.5431(15), C(3)-C(4) 1.3322(16), N(1)-C(1)-C(15)-N(2) 17.72(12).
Molecular structure of compound 8a, thermal ellipsoids set at the 50 % probability level. H-atoms, except O(1)-H and N(1)-H, have been omitted for clarity. Only one of the two independent molecules is shown. Selected bond lengths [Å] and angles [°] (values in square bracket refer to the second independent molecule): O(1)-C(5) 1.439(3) [1.444(3)], N(1)-C(1) 1.464(3) [1.483(3)], N(2)-C(15) 1.339(3), C(1)-C(15) 1.546(3) [1.546], C(2)-C(3) 1.498(3) [1.501(3)], C(3)-C(4) 1.321(3) [1.324(3)], C(4)-C(5) 1.512(3) [1.512(3)], C(1)-C(11) 1.525(3) [1.524(3)], N(1)-C(20) 1.402(3) [1.410(3)], C(20)-N(1)-C(1) 122.76(19) [121.5(2)], N(1)-C(1)-C(2) 113.16(18) [112.16(19)], N(1)-C(1)-C(15) 109.53(18) [111.1(2)], N(1)-C(1)-C(15) 108.40(18) [106.40(19)], C(11)-C(1)-C(2) 108.77(18) [108.63(19)], C(11)-C(1)-C(15) 109.71(18) [107.04(19)], C(15)-C(1)-C(2) 107.22(18) [111.4(2)], C(3)-C(2)-C(1) 113.68(18) [112.68(19)], C(4)-C(3)-C(2) 123.5(2) [124.7(2)], C(3)-C(4)-C(5) 125.8(2) [125.6(2)], O(1)-C(5)-C(4) 111.00(18) [110.75(18)], N(1)-C(1)-C(15)-N(2) -23.7(3), C(3)-C(4)-C(5)-O(1) -13.3(3) [13.2(3)].
13. Computational Details

Geometry optimizations have been performed with the Gaussian09 package\textsuperscript{18} at the PBE0 level of hybrid density functional theory.\textsuperscript{19} The atoms (Ti, C, H, N, O, Br, Mg) were represented by a svp basis set.\textsuperscript{20} The solvent (thf) influence was taken into consideration through single point calculations on the gas-phase optimized geometry with SCRF calculations within the SMD model.\textsuperscript{21} For the SCRF calculations the atoms were treated with a tzvp basis set.\textsuperscript{22} All energies reported in the present work are Gibbs free energies obtained by summing the SMD energy and the gas-phase Gibbs contribution at 333 K (see Table below for the corresponding values in atomic units). The NBO analysis were carried out, using NBO 6.0,\textsuperscript{23} on wavefunctions computed with PBE0 in gas phase with a tzvp basis set for all the atoms.

|                | E(smd/tzvp) | G(333 K) |
|----------------|-------------|----------|
| A-cyc          | -4970.068903| 0.304339 |
| TS-A-C-cyc     | -4970.06041 | 0.303527 |
| C-cyc          | -4970.066043| 0.305864 |
| TS-C-D-cyc     | -4970.032508| 0.305857 |
| D-cyc          | -4970.086525| 0.305461 |
| TS-A-B-cyc     | -4970.023162| 0.307102 |
| B-cyc          | -4970.094863| 0.304412 |
| A              | -4970.042019| 0.297799 |
| TS-A-C         | -4970.031993| 0.30192  |
| C              | -4970.036047| 0.302822 |
| TS-C-D         | -4970.002343| 0.302217 |
| D              | -4970.06148 | 0.309079 |
| TS-A-B         | -4970.003427| 0.300543 |
| B              | -4970.067191| 0.302399 |
| E-cyc          | -4970.099608| 0.306302 |
| Mg(Br)(Ar)     | -3104.545986| 0.041257 |
| Ti-solo-cyc    | -1865.466189| 0.234209 |
| Ti-solo        | -1865.45455 | 0.227282 |
14. NMR Spectra

1a \(^{(1}H\) NMR, CDCl\(_3\), 600.13 MHz, 295 K)

\[ \text{NMR Spectra} \]

1a \(^{(13}C\{^{1}H\})\) NMR, CDCl\(_3\), 150.90 MHz, 296 K

\[ \text{NMR Spectra} \]
1a ($^{19}$F $^{1}$H NMR, CDCl$_3$, 376.27 MHz, 296 K)

$$\begin{align*}
\text{HN} & \quad \text{F} \\
\text{N} & \quad \text{F}
\end{align*}$$

1b ($^{1}$H NMR, CDCl$_3$, 399.89 MHz, 297 K)

$$\begin{align*}
\text{HN} & \quad \text{F} \\
\text{N} & \quad \text{F}
\end{align*}$$
$1b$ ($^{13}\text{C}\{^1\text{H}\}$ NMR, CDCl$_3$, 100.55 MHz, 299 K)

$1b$ ($^{19}\text{F}\{^1\text{H}\}$ NMR, CDCl$_3$, 376.27 MHz, 297 K)
1c ($^1$H NMR, CDCl$_3$, 399.89 MHz, 295 K)

1c ($^{13}$C {$^1$H} NMR, CDCl$_3$, 150.90 MHz, 295 K)
1c (¹⁹F {¹H} NMR, CDCl₃, 376.27 MHz, 295 K)

![NMR spectrum for 1c](image)

1d (¹H NMR, CDCl₃, 399.89 MHz, 295 K)

![NMR spectrum for 1d](image)
1d ($^{13}$C-$^1$H NMR, CDCl$_3$, 100.55 MHz, 297 K)

1d ($^{19}$F-$^1$H NMR, CDCl$_3$, 376.27 MHz, 296 K)
1e (¹H NMR, CDCl₃, 399.89 MHz, 297 K)

1e (¹³C{¹H} NMR, CDCl₃, 100.55 MHz, 298 K)
1e \((^{19}F\{^1H\} \text{NMR, CDCl}_3, 376.27 \text{ MHz, 297 K})\)

![NMR spectrum of 1e](image1)

1f \((^1H \text{NMR, CDCl}_3, 399.89 \text{ MHz, 296 K})\)

![NMR spectrum of 1f](image2)
$^{13}$C-$^1$H NMR, C$_6$D$_6$, 100.55 MHz, 297 K

$^{19}$F-$^1$H NMR, CDCl$_3$, 376.27 MHz, 298 K
$2a \ (^1H \text{ NMR, CDCl}_3, 399.89 \text{ MHz, 295 K})$

$2a \ (^{13}C\{^1H\} \text{ NMR, CDCl}_3, 100.55 \text{ MHz, 295 K})$
2a ($^{19}$F $^1$H NMR, CDCl$_3$, 376.27 MHz, 295 K)

2b ($^1$H NMR, CDCl$_3$, 399.89 MHz, 295 K)
2b ($^{13}$C–$^{1}$H NMR, CDCl$_3$, 100.55 MHz, 295 K)

2b ($^{1}$H NMR, CDCl$_3$, 399.89 MHz, 296 K)
$2c$ ($^{13}$C-$^1$H NMR, CDCl$_3$, 100.55 MHz, 298 K)

$2c$ ($^{13}$C-$^1$H NMR, CDCl$_3$, 376.27 MHz, 297 K)
2d \(^{1}H\) NMR, CDCl\(_3\), 399.89 MHz, 297 K

\[
\begin{align*}
\text{H}_3\text{C} & \text{O} \quad \text{N} \\
\text{HN} & \quad \text{F} \\
\text{N} & \quad \text{HN} \\
\text{O} & \quad \text{F} \\
\text{H}_3\text{C} & \text{O}
\end{align*}
\]

2d \(^{13}C\) \(^{1}H\) NMR, CDCl\(_3\), 100.55 MHz, 299 K

\[
\begin{align*}
\text{H}_3\text{C} & \text{O} \quad \text{N} \\
\text{HN} & \quad \text{F} \\
\text{N} & \quad \text{HN} \\
\text{O} & \quad \text{F} \\
\text{H}_3\text{C} & \text{O}
\end{align*}
\]
2d \(^{19}F\{^1H\}\) NMR, CDCl\(_3\), 376.27 MHz, 298 K

\[
\begin{align*}
\text{H}_3\text{C} & \text{-O} & \text{-NH} & \text{-N} & \text{-F} \\
\text{N} & \text{H} & \text{N} & \text{O} & \text{F}
\end{align*}
\]

2e \(^1H\) NMR, CDCl\(_3\), 399.89 MHz, 295 K

\[
\begin{align*}
\text{N} & \text{-HN} & \text{-F} & \text{-O} & \text{CH}_3 \\
\text{N} & \text{H} & \text{F} & \text{O} & \text{CH}_3
\end{align*}
\]
2e \(^{13}C\{^1H\} \text{NMR, CDCl}_3, 100.55 \text{ MHz, 295 K}\)

\[
\text{HN} \quad \text{F} \\
\text{N} \\
\text{HN} \quad \text{F} \\
\text{N}
\]

2e \(^{19}F\{^1H\} \text{NMR, CDCl}_3, 376.27 \text{ MHz, 295 K}\)

\[
\text{HN} \quad \text{F} \\
\text{N} \\
\text{HN} \quad \text{F} \\
\text{N}
\]

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$2f$ (¹H NMR, CDCl₃, 399.89 MHz, 295 K)

$2f$ ($^{13}$C-¹H NMR, CDCl₃, 100.55 MHz, 295 K)
$2f$ ($^{19}$F $^{1}$H NMR, CDCl$_3$, 376.27 MHz, 295 K)

$2g$ ($^{1}$H NMR, CDCl$_3$, 399.89 MHz, 295 K)
2g ($^{13}$C/$^1$H NMR, CDCl$_3$, 100.55 MHz, 295 K)

2h ($^1$H NMR, CDCl$_3$, 600.13 MHz, 295 K)
2h ($^{13}$C{$^1$}H NMR, CDCl$_3$, 150.90 MHz, 295 K)

![NMR spectrum of 2h]

2i ($^1$H NMR, CDCl$_3$, 399.89 MHz, 297 K)

![NMR spectrum of 2i]
2i ($^{13}$C/$^1$H NMR, CDCl$_3$, 100.55 MHz, 298 K)

2j ($^1$H NMR, CDCl$_3$, 600.13 MHz, 295 K)
2j ($^{13}$C{^1}H NMR, CDCl$_3$, 150.90 MHz, 295 K)

2k (^1H NMR, CDCl$_3$, 600.13 MHz, 295 K)
$2k$ ($^{13}\text{C}^{(1)}\text{H}$ NMR, CDCl$_3$, 150.90 MHz, 295 K)

\[
\text{HN} \quad \text{HN} \\
\text{S} \\
\text{N} \quad \text{O} \\
\text{H3C} \\
\text{F}
\]

$5a$ ($^1\text{H}$ NMR, CDCl$_3$, 600.13 MHz, 295 K)

\[
\text{HN} \quad \text{HN} \\
\text{S} \\
\text{N} \quad \text{O} \\
\text{H3C} \\
\text{F}
\]
5a \(^{13}\text{C}^{1}\text{H}\) NMR, CDCl\(_3\), 150.90 MHz, 295 K

\[
\begin{align*}
\text{H}_3\text{C} & \text{O} \\
\text{N} & \text{N} \\
\text{O} & \\
\end{align*}
\]

5a \(^{19}\text{F}^{1}\text{H}\) NMR, CDCl\(_3\), 376.27 MHz, 298 K

\[
\begin{align*}
\text{H}_3\text{C} & \text{O} \\
\text{N} & \text{N} \\
\text{O} & \\
\end{align*}
\]
$5b$ ($^1H$ NMR, CDCl$_3$, 399.89 MHz, 295 K)
6a ($^1$H NMR, CDCl$_3$, 399.89 MHz, 295 K)

6a ($^{13}$C{$^1$H} NMR, CDCl$_3$, 100.55 MHz, 295 K)
6a $^{19}$F $^1$H NMR, CDCl$_3$, 376.37 MHz, 295 K

6b $^1$H NMR, CDCl$_3$, 600.13 MHz, 295 K
6b (\(^{13}\)C\(^{1}\)H NMR, CDCl\(_3\), 150.90 MHz, 295 K)

6c (\(^{1}\)H NMR, CDCl\(_3\), 399.89 MHz, 296 K)
6c ($^{13}$C-$^1$H NMR, CDCl$_3$, 150.90 MHz, 295 K)

6c ($^{19}$F-$^1$H NMR, CDCl$_3$, 376.27 MHz, 296 K)
7a $^{1}H$ NMR, CDCl$_3$, 600.13 MHz, 295 K

7a $^{13}C$ $^{1}H$ NMR, CDCl$_3$, 100.55 MHz, 295 K
7a ($^{19}$F ($^1$H) NMR, CDCl$_3$, 376.27 MHz, 295 K)

![NMR spectrum of 7a](image)

7b ($^1$H NMR, CDCl$_3$, 600.13 MHz, 295 K)

![NMR spectrum of 7b](image)
7b $^{13}$C $^{1}$H NMR, CDCl$_3$, 150.90 MHz, 295 K

7b $^{19}$F $^{1}$H NMR, CDCl$_3$, 376.27 MHz, 295 K
7e (1H NMR, CDCl₃, 399.89 MHz, 295 K)

![1H NMR spectrum of 7e](image)

7e (13C{1H} NMR, CDCl₃, 100.55 MHz, 295 K)

![13C{1H} NMR spectrum of 7e](image)
8a (1H NMR, CDCl₃, 399.89 MHz, 297 K)

8a (13C{1H} NMR, CDCl₃, 100.55 MHz, 299 K)
8a-d₁ (¹H NMR, CDCl₃, 600.13 MHz, 295 K)

8a-d₁ (¹³C{¹H} NMR, CDCl₃, 150.90 MHz, 295 K)
$8a-d$ ($^1$H NMR, CDCl$_3$, 376.27 MHz, 297 K)

$8b$ ($^1$H NMR, CDCl$_3$, 399.89 MHz, 297 K)
8b (\({\text{\textsuperscript{13}C}}\{\text{\textsuperscript{1}H}\}\) NMR, CDCl\(_3\), 100.55 MHz, 298 K)

8b (\({\text{\textsuperscript{19}F}}\{\text{\textsuperscript{1}H}\}\) NMR, CDCl\(_3\), 376.27 MHz, 297 K)
15. HPLC data

7b: HPLC: Column: AD-H, $n$-hexane:$iso$-propanol = 98:2, $\lambda = 254$ nm, flow rate 1 mL/min, 20 °C, $t_{(1)} = 15.4$ min, $t_{(2)} = 19.7$ min. (S)-1-Phenyl-2-propen-1-ol yields the product $t_{(1)}$ as major species.

7b from (S)-1-phenyl-2-propen-1-ol:

![Graph showing HPLC data for 7b from (S)-1-phenyl-2-propen-1-ol.]

7b from (R)-1-phenyl-2-propen-1-ol:

![Graph showing HPLC data for 7b from (R)-1-phenyl-2-propen-1-ol.]

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7c: HPLC: Column: AD-H, \( n \)-hexane:iso-propanol = 98:2, \( \lambda = 254 \) nm, flow rate 1 mL/min, 20 °C, 
\( t_{1(1)} = 6.3 \) min, \( t_{2(2)} = 6.8 \) min. (S)-1-Octen-3-ol yields the product \( t_{(1)} \) as major species.

7c from racemic 1-octen-3-ol

7c from (S)-1-octen-3-ol
16. Empirical model

Micalizio *et al.* proposed an empirical model for the prediction of (**E**)- and (**Z**)-selectivity in titanium-mediated coupling reactions. The selectivity is governed by A-1,2 and A-1,3 strain interactions. However, since only monosubstituted allylic alkoxides were used in this study, only the axial and equatorial orientation of the alkoxide R-group was considered. Based on the model depicted below, and the isolation and characterization of the (**E**)-products 7b and 7c an equatorial orientation of the phenyl or pentyl group in the transition state seems likely.

A further discussion of the reaction mechanism, e.g. the mechanism for the partial chirality transfer in the reactions leading to 7b and 7c is not feasible at this point.
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