Supporting Information

for

Electron-rich triarylphosphines as nucleophilic catalysts for oxa-Michael reactions

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Experimental details, data in tabular form, NMR spectra
Experimental details

Synthesis of (4-methoxyphenyl)diphenylphosphine (MMTPP)

The synthesis was performed according to a literature procedure. Under a nitrogen atmosphere, a 100 mL Schlenk tube was charged with dry THF (30 mL) and 4-bromoanisole (1.56 g, 8.34 mmol). The tube was cooled to −80 ºC with an acetone–N₂ bath for 30 min before n-butyllithium (5.7 mL, 1.6 M in hexanes, 8.9 mmol, 1.1 equiv) was added. The reaction mixture was stirred for 1 h. Then, chlorodiphenylphosphine (2.51 g, 11.4 mmol, 1.33 equiv) dissolved in THF (6 mL) was added and the reaction mixture was stirred for another 4 h at −80 ºC before it was warmed to room temperature overnight. The reaction was quenched with saturated NH₄Cl solution (15 mL) and water (15 mL). The organic phase was separated and subsequently washed with saturated NaCl solution (30 mL) and water (30 mL). The solvent was removed under reduced pressure whereupon a yellow, oily liquid remained. The crude product was purified by silica gel column chromatography with cyclohexane/dichloromethane 4:1 as eluent to give the product as colorless crystals (0.886 g, 3.03 mmol, 35.5% yield).

Reactions with acrylonitrile as Michael acceptor

Conversion of acrylonitrile was determined by integration of the signals deriving from the residual Michael acceptor (6.26–6.20 ppm, ¹H) and the CH₂ group in the β-position to the cyano group. NMR spectra of 1a–d are exemplarily shown in Figure S1, Figure S2, Figure S3, and Figure S4.

Table S1: Conversion of acrylonitrile (%) in the oxa-Michael reaction with alcohols a–d after 1 h and 24 h catalyzed by 1 mol % phosphine at room temperature (23 ºC).

| Alcohol (Product) | TPP | MMTPP | TMTPP |
|-------------------|-----|-------|-------|
| Propan-2-ol (1a)  | 1 h | 24 h  | 1 h   | 24 h |
| Propan-1-ol (1b)  | 2.4 | 26.7  | 16.3  | 65.9 |
| Prop-2-en-1-ol (1c)| 6.1 | 37.2  | 29.6  | 75.8 |
| Prop-2-yn-1-ol (1d)| 23.1| 97.0  | 24.5  | 98.7 |

3-Isopropyloxypropanenitrile¹ (1a):
Propan-2-ol (2.10 equiv, 0.238 g, 3.96 mmol), acrylonitrile (1.00 equiv, 124 µL, 1.89 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00674 g, 0.0191 mmol).

¹H-NMR (300.36 MHz, CDCl₃): δ 3.66 – 3.61 (m, 3H, O-CH-(CH₃)₂, O-CH₂-CH₂), 2.57 (t, 2H, CH₂-CN), 1.20 (d, 6H, O-CH-(CH₃)₂).

3-Propoxypropanenitrile² (1b):
Propan-1-ol (2.10 equiv, 0.244 g, 4.06 mmol), acrylonitrile (1.00 equiv, 124 µL, 1.89 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00652 g, 0.0185 mmol).

¹H-NMR (300.36 MHz, CDCl₃): δ 3.66 – 3.60 (m, 2H, O-CH₂-CH₂-CN), 3.44 (t, 2H, O-CH₂-CH₂), 2.59 (t, 2H, CH₂-CN), 1.60 (m, 2H, CH₂-CH₃), 0.93 (t, 3H, CH₃-CH₂).
3-(Allyloxy)propanenitrile\(^3\) (1c):

Prop-2-en-1-ol (2.00 equiv, 0.219 g, 3.78 mmol), acrylonitrile (1.00 equiv, 124 µL, 1.89 mmol), tris(4-methoxyphenyl)phosphine (0.00668 g, 0.01 equiv, 0.0190 mol).

\(^1\)H-NMR (300.36 MHz, CDCl\(_3\)): \(\delta\) 5.86-5.78 (m, 1H, \(\text{CH}_2=\text{CH}-\text{CH}_2\)), 5.27-5.13 (dd, 2H, \(\text{CH}_2=\text{CH}-\text{CH}_2\)), 3.98 (d, 2H, O-\(\text{CH}_2\)-CH), 3.60 (t, 2H, O-\(\text{CH}_2\)-CH), 2.55 (t, 2H, O-\(\text{CH}_2\)-CH)

3-(Prop-2-yn-1-yloxy)propanenitrile\(^4\) (1d):

Prop-2-yn-1-ol (2.00 equiv, 0.223 g, 3.98 mmol), acrylonitrile (1.00 equiv, 124 µL, 1.89 mmol), tris(4-methoxyphenylphosphine (0.01 equiv, 0.00670 g, 0.0190 mmol).

\(^1\)H-NMR (300.36 MHz, CDCl\(_3\)): \(\delta\) 4.22 (d, 2H, O-\(\text{CH}_2\)-C-), 3.76 (t, 2H, O-\(\text{CH}_2\)-CH), 2.65 (t, 2H, \(\text{CH}_2\)-CN), 2.48 (dt, 1H, \(\text{CH}\)-C-).

Figure S1: \(^1\)H-NMR spectrum (300 MHz, CDCl\(_3\)) of 1a after 24 h reaction time; as catalyst TMTPP was used; conversion was calculated from the integral ratio of the peaks at 6.26–6.20 and the peak at 2.57.
Figure S2: $^1$H-NMR spectrum (300 MHz, CDCl$_3$) of 1b after 1 h reaction time; as catalyst TMTPP was used; conversion was calculated from the integral ratio of the peaks at 6.26–6.20 and the peak at 2.59.
Figure S3: $^1$H-NMR spectrum (300 MHz, CDCl$_3$) of 1c after 24 h reaction time; as catalyst TPP was used; conversion was calculated from the integral ratio of the peaks at 6.26–6.20 and the peak at 2.61.
Figure S4: $^1$H-NMR spectrum (300 MHz, CDCl$_3$) of 1d after 1 h reaction time; as catalyst MMTPP was used; conversion was calculated from the integral ratio of the peaks at 6.26–6.20 and the peak at 2.65 ppm.

Reactions with acrylamide as Michael acceptor

Conversion of acrylamide was determined by integration of the signals deriving from the residual Michael acceptor (5.61–5.57 ppm, $^1$H) and the newly formed CH$_2$ group. NMR spectra are exemplarily shown in Figure S5, Figure S6, Figure S7, and Figure S8.

Table S2: Conversion of acrylamide (%) in the oxa-Michael reaction with various alcohols after 1 h and 24 h catalyzed by 1 mol% phosphine at room temperature (23 °C)

| Alcohol (Product) | TPP 1 h | TPP 24 h | MMTPP 1 h | MMTPP 24 h | TMTPP 1 h | TMTPP 24 h |
|------------------|---------|----------|------------|-------------|-----------|------------|
| Propan-2-ol (2a) | 0       | 0        | 0          | 3.3         | 0         | 9.0        |
| Propan-1-ol (2b) | 0       | 7.6      | 0          | 19.0        | 3.6       | 60.6       |
| Prop-2-en-1-ol (2c) | 1.6   | 25.3     | 3.6        | 45.7        | 5.5       | 74.4       |
| Prop-2-yn-1-ol (2d) | 1.3   | 16.0     | 1.6        | 15.8        | 1.6       | 16.9       |

3-Isopropoxypropanamide (2a):

Propan-2-ol (2.00 equiv, 217 µL, 2.81 mmol), acrylamide (1.0 equiv, 0.101 g, 1.43 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00498 g, 0.0141 mmol).

$^1$H-NMR (300 MHz, DMSO-d6) δ 7.26 (bs, 1H, NH$_2$), 6.76 (bs, 1H, NH$_2$), 3.55 (m, 3H, CH-O-CH$_2$), 2.23 (t, 2H, O=C=CH$_2$-CH$_2$), 1.05 (d, 6H, CH$_3$)
3-Propan-1-ol (2.00 equiv, 211 µL, 2.81 mmol), acrylamide (1.00 equiv, 0.0999 g, 1.40 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00472 g, 0.0134 mmol).

\[^1\text{H-NMR}\ (300 \text{ MHz, DMSO-d}_6)\ \delta\ 7.27\ (\text{bs, 1H, NH}_2),\ 6.78\ (\text{bs, 1H, NH}_2),\ 3.54\ (t, 2\text{H, O-CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3),\ 3.31\ (t, 2\text{H, O-CH}_2-\text{CH}_2-\text{CH}_2),\ 1.47\ (\text{m, 2H, O-CH}_2-\text{CH}_2),\ 0.84\ (\text{t, 3H, CH}_3)\]

\[^{13}\text{C-NMR}\ (75.53\ \text{ MHz, DMSO-d}_6)\ \delta\ 172.25\ (\text{C=O}),\ 71.57\ (\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{O}),\ 66.34\ (\text{O-CH}_2-\text{CH}_2-\text{C}=\text{O}),\ 35.89\ (\text{O-CH}_2-\text{CH}_2-\text{CH}_2-\text{O}),\ 10.48\ (\text{CH}_3)\]

3-(Allyloxy)propenamide (2c):

Prop-2-en-1-ol (2.00 equiv, 191 µL, 2.81 mmol), acrylamide (1.00 equiv, 0.104 g, 1.46 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00509 g, 0.0141 mmol).

\[^1\text{H-NMR}\ (300 \text{ MHz, DMSO-d}_6)\ \delta\ 7.29\ (\text{bs, 1H, NH}_2),\ 6.79\ (\text{bs, 1H, NH}_2),\ 5.92-5.79\ (\text{m, 1H, CH}_2=\text{CH}_2),\ 5.27-5.11\ (\text{dd, 2H, CH}_2=\text{CH}_2),\ 3.91\ (\text{d, 2H, CH}_2=\text{CH}_2),\ 3.56\ (\text{t, 2H, O-CH}_2-\text{CH}_2),\ 2.29\ (\text{t, 2H, O-CH}_2-\text{CH}_2)\]

\[^{13}\text{C-NMR}\ (75.53\ \text{ MHz, DMSO-d}_6)\ \delta\ 172.17\ (\text{C=O}),\ 135.27\ (\text{CH}_2=\text{CH}_2),\ 116.20\ (\text{CH}_2=\text{CH}_2),\ 70.78\ (\text{CH}_2=\text{CH}_2),\ 66.01\ (\text{O-CH}_2-\text{CH}_2),\ 35.81\ (\text{O-CH}_2-\text{CH}_2)\]

3-(Prop-2-yn-1-ylloxy)propenamide (2d):

Prop-2-yn-1-ol (2.00 equiv, 166 µL, 2.81 mmol), acrylamide (1.00 equiv, 0.101 g, 1.42 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00509 g, 0.0144 mmol).

\[^1\text{H-NMR}\ (300 \text{ MHz, DMSO-d}_6)\ \delta\ 7.31\ (\text{bs, 1H, NH}_2),\ 6.82\ (\text{bs, 1H, NH}_2),\ 4.09\ (\text{d, 2H, CH}-\text{C-CH}_2),\ 3.62\ (\text{t, 2H, O-CH}_2-\text{CH}_2),\ 3.39\ (\text{t, 1H, CH}=\text{C-CH}_2),\ 2.29\ (\text{t, 2H, O-CH}_2=\text{CH}_2)\]

\[^{13}\text{C-NMR}\ (75.53\ \text{ MHz, DMSO-d}_6)\ \delta\ 172.06\ (\text{C=O}),\ 80.34\ (\text{C-CH}_2-\text{CH}_2),\ 76.98\ (\text{CH}=\text{C-CH}_2),\ 65.69\ (\text{O-CH}_2-\text{CH}_2),\ 57.32\ (\text{CH}=\text{C-CH}_2),\ 35.51\ (\text{O-CH}_2=\text{CH}_2)\]
**Figure S5:** $^1$H-NMR spectrum (300 MHz, DMSO-$d_6$) of 2a after 24 h reaction time; as catalyst TMTPP was used; conversion was calculated from the integral ratio of the peaks at 5.61–5.58 and the peak at 3.53.
Figure S6: $^1$H-NMR spectrum (300 MHz, DMSO-$d_6$) of 2b after 24 h reaction time; as catalyst TMTPP was used; conversion was calculated from the integral ratio of the peaks at 5.61–5.58 and the peak at 3.54.
Figure S7: $^1$H-NMR spectrum (300 MHz, DMSO-$d_6$) of 2c after 24 h reaction time; as catalyst TMTPP was used; conversion was calculated from the integral ratio of the peaks at 5.61–5.58 and the peak at 3.56.
Figure S8: $^1$H-NMR spectrum (300 MHz, DMSO-$d_6$) of 2d after 24 h reaction time; as catalyst TMTPP was used; conversion was calculated from the integral ratio of the peaks at 5.61–5.58 and the peak at 3.61.

Reactions with divinyl sulfone as Michael acceptor

Conversion of divinyl sulfone was determined by integration of the signals deriving from the residual Michael acceptor (6.42–6.37 ppm, 1H) and the CH$_2$ group in β-position. NMR spectra are exemplarily shown in Figure S9, Figure S10, Figure S11, and Figure S12.

Mono/di ratios were determined from the integral ratio of the signals deriving from the protons adjacent to the sulfur atom (details see figures).

Table S3: Conversion of divinyl sulfone and corresponding product ratios mono/di [%] in the oxa-Michael reaction with alcohols a–d after 1 h and 24 h catalyzed by 1 mol % phosphine at room temperature (23 °C)

| Alcohol (Product) | TPP 1 h | TPP 24 h | MMTTP 1 h | MMTTP 24 h | TMTTP 1 h | TMTTP 24 h |
|-------------------|---------|---------|------------|------------|-----------|------------|
| Propan-2-ol (3a)  | 53/3    | 52/48   | 58/3       | 33/67      | 65/5      | 17/83      |
| Propan-1-ol (3b)  | 28/72   | 0/100   | 28/72      | 0/100      | 30/70     | 0/100      |
| Prop-2-en-1-ol (3c)| 29/70  | 0/100   | 42/58      | 11/89      | 21/79     | 0/100      |
| Prop-2-yn-1-ol (3d)| 40/60  | 0/100   | 52/48      | 0/100      | 31/69     | 0/100      |
2-(2-((2-Isopropoxyethyl)sulfonyl)ethoxy)propane (3a):
Propan-2-ol (3.00 equiv, 194 µL, 2.54 mmol), divinyl sulfone (1.00 equiv, 85.1 µL, 0.847 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00305 g, 0.00866 mmol)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 3.84 (t, 4H, CH$_2$-S-CH$_2$), 3.63 (m, 2H, CH), 3.31 (t, 4H, -CH$_2$-CH$_2$-S-), 1.16 (d, 12H, CH$_3$).

1-(2-((2-Propoxethyl)sulfonyl)ethoxy)propane (3b):
Propan-1-ol (3.00 equiv, 191 µL, 2.54 mmol), divinyl sulfone (1.00 equiv, 85.1 µL, 0.847 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00292 g, 0.00828 mmol)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 3.85 (dd, 4H, -CH$_2$-CH$_2$-S-), 3.42 (t, 4H, CH$_3$-CH$_2$-CH$_2$-), 3.32 (t, 4H, -CH$_2$-CH$_2$-S-), 1.70-1.43 (m, 4H, CH$_3$-CH$_2$-), 0.91 (t, 6H, CH$_3$-).

$^{13}$C-NMR (75.53 MHz, CDCl$_3$) $\delta$ 73.15 (CH$_3$-CH$_2$-CH$_2$-), 64.30 (-CH$_2$-CH$_2$-S-), 55.03 (-CH$_2$-CH$_2$-S-), 22.81 (CH$_3$-CH$_2$-), 10.65 (CH$_3$-).

3-(2-((2-(Allyloxy)ethyl)sulfonyl)ethoxy)prop-1-ene (3c):
Prop-2-en-1-ol (3.00 equiv, 174 µL, 2.54 mmol), divinyl sulfone (1.0 equiv, 85.1 µL, 0.847 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00298 g, 0.00846 mmol)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 5.91 – 5.82 (m, 2H, CH$_2$-CH$_2$-), 5.22 (m, 4H, CH$_3$-CH$_2$-), 4.03 (d, 4H, -CH-CH$_2$-O-), 3.88 (t, 4H, -CH$_2$-CH$_2$-S-), 3.36 (t, 4H, -CH$_2$-CH$_2$-S-).

3-(2-((2-(Prop-2-yn-1-yloxy)ethyl)sulfonyl)ethoxy)prop-1-yne (3d):
Prop-2-yn-1-ol (3.0 equiv, 152.2 µL, 2.54 mmol), divinyl sulfone (1.0 equiv, 85.1 µL, 0.847 mmol), tris(4-methoxyphenyl)phosphine (0.01 equiv, 0.00290 g, 0.00823 mmol)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 4.27 (d, 4H, -C-CH$_2$-), 3.98 (t, 4H, -CH$_2$-CH$_2$-S-), 3.36 (t, 4H, -CH$_2$-CH$_2$-S-), 2.48 (d, 2H, CH-C-).
Figure S9: $^1$H-NMR spectrum (300 MHz, CDCl$_3$) of 3a after 24 h reaction time; as catalyst TMTPP was used; mono/di ratio was calculated from the peak at 3.19 and the peak at 3.29 ppm.
Figure S10: $^1$H-NMR spectrum (300 MHz, CDCl$_3$) of 3b after 1 h reaction time; as catalyst MMTPP was used; mono/di ratio was calculated from the peak at 3.23 and the peak at 3.32 ppm.
Figure S11: $^1$H-NMR spectrum (300 MHz, CDCl$_3$) of 3c after 24 h reaction time; as catalyst TMTPP was used; mono/di ratio was calculated from the peak at 3.26 (not visible in this spectrum) and the peak at 3.35 ppm.
Figure S12: $^1$H-NMR spectrum (300 MHz, CDCl$_3$) of 3d after 24 h reaction time; as catalyst TPP was used; mono/di ratio was calculated from the peak at 3.27 and the peak at 3.35 ppm.
Figure S13: Heat-map plot of all reactions
Oxa-Michael addition polymerization of 2-hydroxyethyl acrylate (HEA)

Calculation of double bond conversion of 2-hydroxyethyl acrylate:

\[
\text{Double bond conversion} \ [\%] = \frac{\text{integral} \ 2.62 \ \text{ppm} / 2}{\text{integral} \ 5.85 + \text{integral} \ 2.62 / 2} \times 100
\]

Calculation of Rauhut–Currier share:

\[
\text{Rauhut} – \text{Currier share} \ [\%] = \frac{\text{integral} \ 5.61}{\text{integral} \ 2.62 - 4 \times \text{integral} \ 5.61 / 2} \times 100
\]

Table S4: Conversion of 2-hydroxyethyl acrylate [%] after 24 h, molecular weight \( M_n \) of the formed polymers, polydispersity index (D) and Rauhut–Currier share [%]

| Catalyst | T [°C] | conversion [%] | \( M_n \) [g/mol] | D | Rauhut-Currier share [%] |
|----------|--------|----------------|-------------------|---|-------------------------|
| TPP      | 23     | 74             | 660               | 1.5 | 5                      |
| TPP      | 80     | 89             | 680               | 1.6 | 20                     |
| MMTPP    | 23     | 87             | 910               | 1.7 | 6                      |
| MMTPP    | 80     | 97             | 820               | 1.7 | 17                     |
| TMTPP    | 23     | 95             | 1160              | 1.8 | 6.5                    |
| TMTPP    | 80     | 99             | 890               | 1.8 | 17                     |

\(^{1}\text{H-NMR (300 MHz, CDCl}_3\) \delta 6.47 (d, 1H), 6.20 (s, 6H), 5.84 (d, 1H), 4.33-4.21 (m, 76 H), 3.82-3.56 (m, 141 H), 2.61 (t, 70H).

\(^{13}\text{C-APT NMR (75.53 MHz, CDCl}_3\) \delta 171.4, 126.6, 72.27, 70.39, 68.96, 66.80-66.15, 64.07, 63.88, 63.62, 62.33, 61.66, 60.98, 34.99.\)
Figure S14: $^1$H-NMR spectrum (300 MHz, CDCl$_3$) of poly4 after 24 h at 80°C with TMTPP (5 mol %) as catalyst
Figure S15: $^{13}$C-APT spectrum (300 MHz, CDCl$_3$) of poly4 after 24 h at 80 °C with TMTPP (5 mol %) as catalyst

Figure S16: HSQC of poly4 after 24 h at 80 °C with TMTPP (5 mol %) as catalyst
Oxidation experiments ($^{31}$P-NMR)

Table S5: $^{31}$P-NMR shifts (in CDCl$_3$) of TPP, MMTPP and TMTPP and their corresponding phosphine oxides relative to 85% H$_3$PO$_4$

|       | TPP  | MMTPP | TMTPP |
|-------|------|-------|-------|
| phosphine      | -5.02 | -6.69 | -9.82 |
| phosphine oxide | 29.42 | 29.24 | 28.96 |

Figure S17: $^1$H-NMR (300 MHz, CDCl$_3$) spectrum of TPP
Figure S18: $^{31}$P-NMR (202.55 MHz, CDCl$_3$) spectrum of TPP

Figure S19: $^1$H-NMR (500 MHz, CDCl$_3$) spectrum of MMTPP
Figure S20: $^{31}$P-NMR (202.55 MHz, CDCl$_3$) spectrum of MMTPP

Figure S21: $^1$H-NMR (500 MHz, CDCl$_3$) spectrum of TMTPP
Figure S22: $^{31}$P-NMR (202.55 MHz, CDCl$_3$) spectrum of TMTPP
Computational details

Figure S23: Visual representation of the HOMOs of TPP, MMTPP and TMTPP, calculated on B3LYP/def2-TZVPPD level

Table S6: Theoretical data for TPP, MMTPP, TMTPP, MCA values from Ref.5, pKₐ values from Ref.6, HOMO and SOMO energies were calculated on B3LYP/def2-TZVPPD level

|        | MCA [kJ/mol] | pKₐ  | HOMO [eV] | SOMO [eV] |
|--------|--------------|------|-----------|-----------|
| TPP    | +618.7       | 1.31 | -5.911    | -9.596    |
| MMTPP  | -            | 2.85 | -5.728    | -9.175    |
| TMTPP  | +651.0       | 4.20 | -5.418    | -8.589    |

Scheme S1: Reaction for the Michael acceptor affinity (MAA) of a phosphine

Table S7: Calculated Michael acceptor affinities (MAA in kJ/mol) for phosphines PMe₃, TPP, MMTPP and TMTPP and Michael acceptors acrylonitrile, acrylamide and divinyl sulfone on B3LYP/def2-TZVPPD level

|       | R = acrylonitrile | R = acrylamide | R = divinyl sulfone |
|-------|-------------------|----------------|---------------------|
| R¹ = Me | -74.6             | -78.5          | -64.6               |
| R¹ = Ph | -96.4             | -103.9         | -85.6               |
| R¹ = 2-(CH₃O)C₆H₄ | -94.2             | -103.9         | -84.9               |
| R¹ = 2,4,6-(CH₃O)₃C₆H₂ | -87.7             | -95.3          | -76.7               |

References:
1 Bergbreiter, D.E.; Yang, Y.-C.; Variable-Temperature NMR Studies of Soluble Polymer-Supported Phosphine-Silver Complexes, J. Org. Chem., 2010, 75, 873-878.
2 Heller, B.; Sundermann, B.; Buschmann, H.; Dextler, H.-J.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G.; Photocatalyzed [2+2+2]-cycloaddition of nitriles with acetylene: an effective method for the synthesis of 2-pyridines under mild conditions, J. Org. Chem., 2002, 67(13), 4414-4422.
3 Luu, H.-T.; Wiesler, S.; Frey, G.; Streuff, J.; A Titanium(III)-Catalyzed Reductive Umpolung Reaction for the Synthesis of 1,1-Disubstituted Tetrahydroisoquinolines, *Org. Lett.*, **2015**, *17*(10), 2478-2481.

4 Golobokova, T. V.; Pokatilov, F. A.; Proidakov, A. G.; Vereshchagin, L. I.; Kizhnyaev, V. N.; Synthesis of polynuclear azoles linked by ether tethers, *Russ. J. Org. Chem.*, **2013**, *49*(1), 130-137.

5 Lindner, C.; Tandon, R.; Maryasin, B.; Larionov, E.; Zipse, H. Cation Affinity Numbers of Lewis Bases. *Beilstein J. Org. Chem.* **2012**, *8*, 1406-1442.

6 calculated using the pKa prediction platform (neural network result for solvent H2O) available at www.pka.luo-group.com see: Yang, Q.; Li, Y.; Yang, J.-D.; Liu, Y.; Zhang, L.; Luo, S.; Cheng, J.-P. Holistic Prediction of pKa in Diverse Solvents Based on Machine Learning Approach, *Angew. Chem. Int. Ed.* **2020**, *59*, 19282-19291.