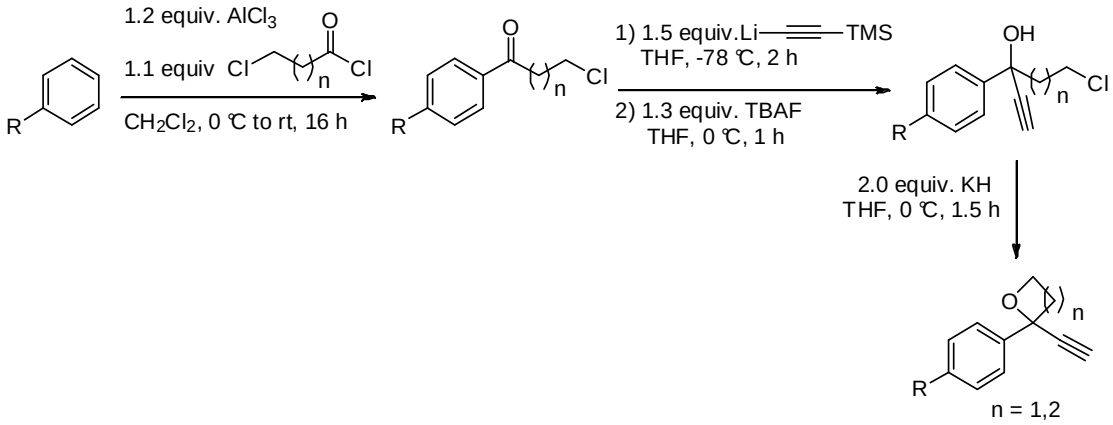
Copper-catalyzed oxidative cyclisation of alkynyl oxetanes

1. General procedures

General Procedure 3.1:[1]



To a dry flask under argon atmosphere were added $AlCl_3$ (1.2 equiv) and dichloromethane (0.75 M compared to arene). The mixture was cooled to 0 °C. Then the acyl chloride (1.1 equiv) was added followed by addition of the arene. The reaction was stirred 30 minutes at 0 °C. The ice bath was removed and the reaction stirred for a total of 16 hours. After cooling to 0 °C, the reaction was slowly quenched with water. The mixture was poured into a separatory funnel containing water and dichloromethane. The phases were separated and the aqueous extracted twice with dichloromethane. The combined organic phases were washed with water and sat. $NaHCO_3$ (aq.), then dried over Magnesium sulfate. The solvent was removed *in vacuo* and the crude purified by flash chromatography (Diethyl ether in petroleum ether) yielding the ketone.

To a dry flask under argon atmosphere were added THF (0.4 M compared to ketone) and TMS-acetylene (1.5 equiv) and the mixture cooled to -78 °C. Then *n*BuLi (2.5 M in hexanes, 1.5 equiv) was added and the reaction stirred for 30 minutes. To this mixture was slowly added the ketone and the reaction left stirring for 2 hours at -78 °C. The reaction was quenched with sat. NH_4Cl (aq.), then allowed to heat to room temperature before it was transferred to a separatory funnel containing water and Diethyl ether. The phases were separated and the aqueous extracted twice with Diethyl ether. The combined organic phases were washed with water and brine, then dried over Magnesium sulfate. The solvents were removed *in vacuo* and the crude product carried forward without further purification.

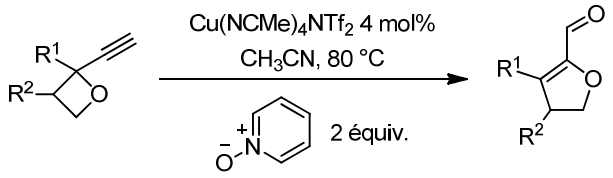
A flask containing the alcohol and THF (0.2 M compared to alcohol) was cooled to 0 °C. Then TBAF (1 M in THF, 1.3 equiv) was added and the reaction stirred 1 hour at 0 °C. The reaction mixture was poured into a separatory funnel containing water and Diethyl ether. The phases were separated and the aqueous extracted twice with Diethyl ether. The combined organic phases were washed with

[1] Lo, M. M.-C.; Fu, G. C. *Tetrahedron*, **2001**, *57*, 2621.

water and brine, then dried over Magnesium sulfate. The solvent was removed *in vacuo* and the crude purified by flash chromatography (Diethyl ether in petroleum ether) yielding the propargylic alcohol.

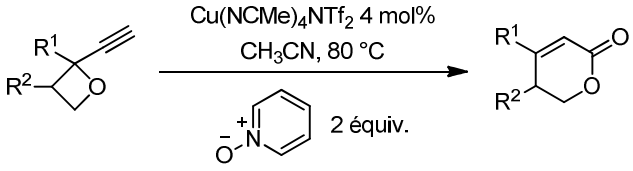
To a dry flask were added KH (30% weight dispersion in mineral oil, 2.0 equiv.) and THF (0.1 M compared to alcohol) and the mixture cooled to 0 °C. Then the alcohol was slowly added. The reaction was stirred 10 minutes at 0 °C, then allowed to heat to room temperature. The reaction was stirred for a total of 2 hours after which TLC showed full conversion of the alcohol. The reaction mixture was transferred to a separatory funnel containing water and Diethyl ether. The phases were separated and the aqueous extracted twice with Diethyl ether. The combined organic phases were washed with sat. $NaHCO_3$ (aq.), water, and brine, then dried over Magnesium sulfate. The solvents were removed *in vacuo* and the crude purified by flash chromatography (Diethyl ether in petroleum ether) yielding the oxetane.

General procedure 3.2: oxidative cyclisation and preparation of furanaldehydes



To a dry flask was added the oxetane (0.2 mmol), acetonitrile (0.2 M compared to the oxetane) and 3-bromopyridine oxide (0.4 mmol). $Cu(MeCN)_4NTf_2$ (0.004 mmol) was then added and the reaction mixture was heated to reflux (82 °C). The reaction was followed by TLC until no starting material remained. The reaction mixture was then filtered through a silica gel pad which was rinced with ethyl acetate (final volume 10 mL). Solvent was removed *in vacuo*. NMR analysis of the crude mixture gave the ratio of oxidised product. 4,5-dihydrofuran-2-carbaldehyde was purified by flash chromatography using petroleum ether:ethyl acetate (90:10) as eluent.

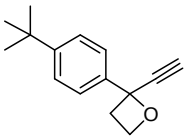
General procedure 3.3: oxidative cyclisation and preparation of α–β-unsaturated lactones



To a dry flask was added the oxetane (0.2 mmol), acetonitrile (0.2 M compared to the oxetane) and 4-methoxypyridine oxide (0.4 mmol). $Cu(MeCN)_4NTf_2$ (0.004 mmol) was then added and the reaction mixture was heated to reflux (82 °C). The reaction was followed by TLC until no starting material remained. The reaction mixture was then filtered through a silica gel pad which was rinced with ethyl acetate (final volume 10 mL). Solvent was removed *in vacuo*. NMR analysis of the crude mixture gave the ratio of oxidised product. 4,5-dihydrofuran-2-carbaldehyde was purified by flash chromatography using ethyl acetate : petroleum ether (10 : 90) as eluent.

2. Preparation of alkynyl oxetanes

2-(4-(*tert*-Butyl)phenyl)-2-ethynyloxetane (3.65) $C_{15}H_{18}O$ **MW = 214.3 g.mol^{-1}**



Procedure: see general procedure 3.1

Product: white solid

Yield: 14 % over 4 steps (m = 362 mg, n = 1.69 mmol)

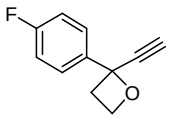
^{1}H NMR (400 MHz, $CDCl_3$):δ (ppm) 7.63 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 4.94-4.88 (m, 1H), 4.66 (dt, *J* = 8.4, 6.0 Hz, 1H), 3.26 (ddd, *J* = 11.2, 8.4, 6.0 Hz, 1H), 3.04 (ddd, *J* = 11.2, 8.4, 7.6 Hz, 1H), 2.98 (s, 1H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 151.2, 140.2, 125.4 (2C), 124.4 (2C), 85.5, 80.3, 76.5, 66.1, 38.1, 34.6, 31.4 (3C).

HRMS: $C_{15}H_{18}O$ [M^+]; calculated: 214.1358, found: 214.1356.

IR (CCl_4): ν (cm^{-1}) 3311, 2966, 2890, 1508, 1463, 1399, 1267.

2-Ethynyl-2-(4-fluorophenyl)oxetane (3.71) $C_{11}H_9FO$ **MW = 176.2 g.mol^{-1}**



Procedure: see general procedure 3.1 from commercially available 3-chloro-1-(4-fluorophenyl)-1-propanone

Product: colorless oil

Yield: 24 % over 3 steps (m = 128 mg, n = 0.72 mmol)

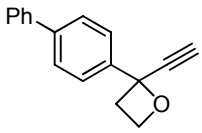
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.70-7.65 (m, 2H), 7.17-7.11 (m, 2H), 4.91 (ddd, *J* = 8.8, 7.6, 6.0 Hz, 1H)4.65 (dt, *J* = 8.8, 6.0 Hz, 1H), 3.26 (ddd, *J* = 11.2, 8.8, 6.0 Hz, 1H), 3.00 (s, 1H), 2.97 (ddd, *J* = 11.2, 8.8, 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 162.6 (d, $^1J_{CF}$ = 245.2 Hz), 139.1 (d, $^4J_{CF}$ = 3.1 Hz), 126.6 (d, $^3J_{CF}$ = 8.3 Hz, 2C), 115.3 (d, $^2J_{CF}$ = 21.5 Hz, 2C), 85.0, 80.0, 76.9, 66.0, 38.4.

HRMS: $C_{11}H_9FO$ [M^+]; calculated: 176.0637, found: 176.0638.

IR (CCl_4): ν (cm^{-1}) 3310, 3013, 2970, 2892, 1603, 1509, 1234, 1157.

2-ethynyl-2-(4-phenylphenyl)oxetane (3.69) $C_{17}H_{14}O$ **MW = 234.3 g.mol^{-1}**



Procedure: see general procedures 3.1

Product: yellow solid

Yield: 7 % over 4 steps (m = 160 mg, n = 0.68 mmol)

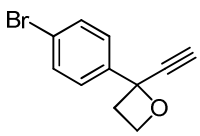
^{1}H NMR (400 MHz, $CDCl_3$):δ (ppm) 7.77-7.75 (m, 2H), 7.68-7.63 (m, 4H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.39 (tt, *J* = 2.4 Hz, *J* = 7.3 Hz, 1H), 4.91 (ddd, *J* = 6.0 Hz, *J* = 7.5 Hz, *J* = 8.5 Hz, 1H), 4.66 (ddd, *J* = 6.0 Hz, *J* = 6.0 Hz, *J* = 8.9 Hz, 1H), 3.28 (ddd, *J* = 6.2 Hz, *J* = 8.5 Hz, *J* = 11.0 Hz, 1H), 3.02 (ddd, *J* = 7.5 Hz, *J* = 8.8 Hz, *J* = 11.0 Hz, 1H), 2.99 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 142.3, 141.1, 140.7, 128.9 (2C), 127.5, 127.3 (2C), 127.2 (2C), 125.2 (2C), 85.3, 80.3, 76.8, 66.2, 38.3.

HRMS: $C_{17}H_{14}O$ [M^+]; calculated: 234.1045, found: 234.1044.

IR (CCl_4): ν (cm^{-1}) 3311, 3032, 2958, 2923, 2891, 1487, 1259.

2-(4-bromophenyl)-2-ethynyloxetane (3.73) $C_{11}H_9BrO$ **MW = 237.1 g.mol^{-1}**



Procedure: see general procedure 3.1

Product: yellow solid

Yield: 4 % over 4 steps (m = 72 mg, n = 0.30 mmol)

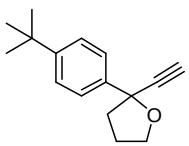
^{1}H NMR (400 MHz, $CDCl_3$):δ (ppm) 7.55-7.50 (m, 4H), 4.85 (ddd, *J* = 5.9 Hz, *J* = 7.5 Hz, *J* = 8.4 Hz, 1H), 4.59 (ddd, *J* = 5.9 Hz, *J* = 6.2 Hz, *J* = 8.9 Hz, 1H), 3.22 (ddd, *J* = 6.2 Hz, *J* = 8.5 Hz, *J* = 11.0 Hz, 1H), 2.94 (s, 1H), 2.90 (ddd, *J* = 7.5 Hz, *J* = 8.9 Hz, *J* = 11.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 142.3, 131.5, 126.4, 122.1, 84.7, 79.8, 76.9, 66.0, 38.2.

HRMS: $C_{11}H_9BrO$ [M^+]; calculated: 235.9837, found: 235.9840.

IR (CCl_4): ν (cm^{-1}) 3308, 2927, 2855, 1732, 1488, 1465, 1377, 1264.

2-(4-(tert-butyl)phenyl)-2-ethynyltetrahydrofuran $C_{16}H_{20}O$ **MW = 228.3 g.mol^{-1}**



Procedure: see general procedure 3.1

Product: white solid

Yield: 39 % over 4 steps (m = 665 mg, n = 2.91 mmol)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.42 (dt, *J* = 8.8, 2.0 Hz, 2H), 4.26-4.14 (m, 2H), 2.64 (s, 1H), 2.60-2.53 (m, 1H), 2.34-2.25 (m, 1H), 2.24-2.15 (m, 1H),2.13-2.04 (m, 1H), 1.37 (s, 9H).

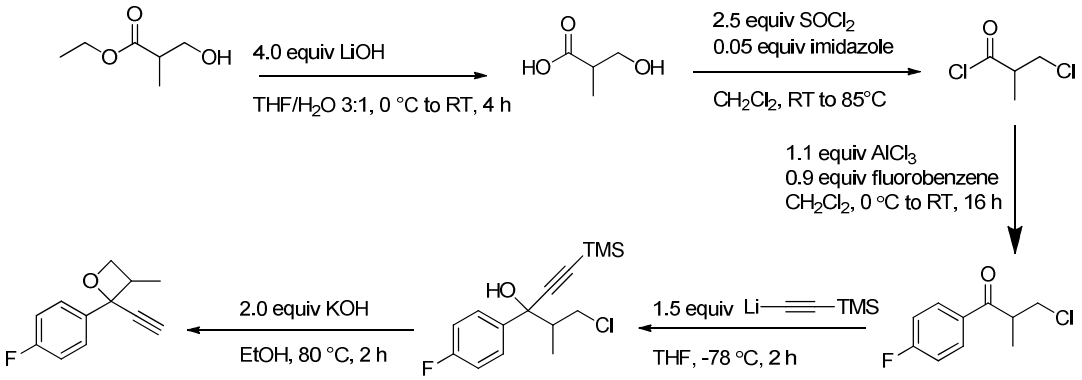
^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 150.5, 140.1, 125.2 (2C), 124.9 (2C), 86.3, 80.2, 72.9, 68.4, 42.5, 34.5, 31.4 (3C), 25.8.

HRMS: $C_{16}H_{20}O$ [M^+]; calculated: 228.1514, found: 228.1517.

IR ($CHCl_3$): ν (cm^{-1}) 3311, 2966, 2871, 1461, 1363, 1268, 1052.

2-ethynyl-2-(4-fluorophenyl)-3-methyloxetane (3.75)	$C_{12}H_{11}FO$	**MW = 190.2 g.mol^{-1}**

Procedure:



To a dry flask under nitrogen atmosphere containing ethyl 3-hydroxybutyrate in THf/H_2O (75/25) at 0°C was added LiOH. The mixture was stirred 30 min at 0°C then 4h at room temperature. The organic solvents were then removed *in vacuo*. The aqueous phase was diluted with water, acidified to pH 1 with HCl 37% and then extracted three times woth ethyl acetate. The combined organic phases were washed with brine and dried over magnesium sulfate. After filtration, the solvent were removed *in vacuo*. Crude 3-hydroxybutyric acid was obtained as a pale yellow oil that was furthered used without purification.

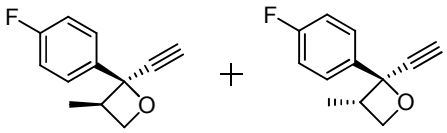
To the crude mixture obtained, dichloromethane and imidazole (0.05 equiv) were added and the mixture stirred at 0°C under nitrogen atmosphere. Then thionyl chloride (2.5 equiv) was added dropwise. The mixture was stirred at 0°C for 30 minutes and then heated at 85°C for 2h until no gas emission was observed. Excess $SOCl_2$ was removed *in vacuo*. The crude 3-chlorobutyryl chloride was then used without further purification.

To a dry flask under nitrogen atmosphere were added $AlCl_3$ (1.2 equiv) and CH_2Cl_2 (0.75 M compared to fluorobenzene). The mixture was cooled to 0 °C. Then the 3-chlorobutyryl chloride (1.1 equiv) was added followed by addition of fluorobenzene. The reaction was stirred 30 minutes at 0 °C. The ice bath was removed and the reaction stirred for 30 more minutes. After cooling to 0 °C, the reaction was slowly quenched with water. The mixture was poured into a separatory funnel containing H_2O and CH_2Cl_2. The phases were separated and the aqueous extracted twice with CH_2Cl_2. The combined organic phases were washed with water and sat. NaCl (aq.), then dried over Magnesium sulfate. The solvent was removed *in vacuo* and the crude purified by flash chromatography (EtOAc in petroleum ether) yielding the ketone.

To a dry flask under nitrogen atmosphere were added THF (0.25 M compared to ketone) and TMS-acetylene (1.5 equiv) and the mixture cooled to -78 °C. Then *n*BuLi (2.5 M in hexanes, 1.5 equiv) was added and the reaction stirred for 30 minutes. To this mixture was slowly added the ketone. The reaction was left stirring at -78 °C until no starting material remained in TLC (2h). The reaction was quenched with sat. NH_4Cl (aq.), then allowed to heat to room temperature before it was transferred

to a separatory funnel containing H_2O and Diethyl ether. The phases were separated and the aqueous extracted twice with Diethyl ether. The combined organic phases were washed with H_2O and brine, then dried over Magnesium sulfate. The solvents were removed *in vacuo* and the crude product carried forward without further purification.

The crude alcohol was dissolved in EtOH (0.25M) and KOH in pellets (2eq) was added. The reaction mixture was stirred at room temperature for 15 minutes. Then, the reaction mixture was heated at 80°C and stirred for 2 hours. The ethanol was then removed in vacuo. The mixture was dissolved in Diethyl ether and poured in a separatory funnel containing Diethyl ether and H_2O. The phases were separated and the aqueous phase extracted twice with Diethyl ether. The combined organic phases were washed with brine and dried over Magnesium sulfate. The solvent was removed *in vacuo* and the crude purified by flash chromatography yielding the final oxetane in a 8.5% yield over 5 steps.



Product: pale yellow oil

Yield: 8.5 % over 5 steps (m = 174 mg, n = 0.91 mmol). Product obtained as a mixture of diastereoisomers in a 1:1.33 ratio.

Major diastereoisomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.63-7.59 (m, 2H), 7.10-7.04 (m, 2H), 4.92 (qdd, *J* = 6.1 Hz, *J* = 6.5 Hz, *J* =7.6 Hz, 1H), 3.00 (dd, *J* = 7.6 Hz, *J* = 11.1 Hz, 1H), 2.93 (*J* = 6.5 Hz, *J* = 11.1 Hz, 1H), 2.93 (s, 1H), 1.68 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 162.4 (d, $^1J_{CF}$ = 244.7Hz), 139.5 (d, $^4J_{CF}$ = 3.2 Hz), 126.5 (d, $^3J_{CF}$ = 8.2 Hz, 2C), 115.3 (d, $^2J_{CF}$ = 21.5 Hz, 2C), 86.1, 76.0, 75.5, 73.4, 44.6, 24.0.

Minor diastereoisomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) 7.63-7.59 (m, 2H), 7.10-7.04 (m, 2H), 5.21 (qdd, *J* = 6.1 Hz, *J* = 6.9 Hz, *J* =7.9 Hz, 1H), 3.24 (dd, *J* = 6.9 Hz, *J* = 10.9 Hz, 1H), 2.91 (s, 1H), 2.60 (*J* = 7.9 Hz, *J* = 10.9 Hz, 1H), 1.50 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 162.5 (d, $^1J_{CF}$ = 245.0 Hz), 139.6 (d, $^4J_{CF}$ = 3.2 Hz), 126.8 (d, $^3J_{CF}$ = 8.3 Hz, 2C), 115.2 (d, $^2J_{CF}$ = 21.5 Hz, 2C), 85.6, 75.9, 75.8, 73.3, 45.8, 23.6.

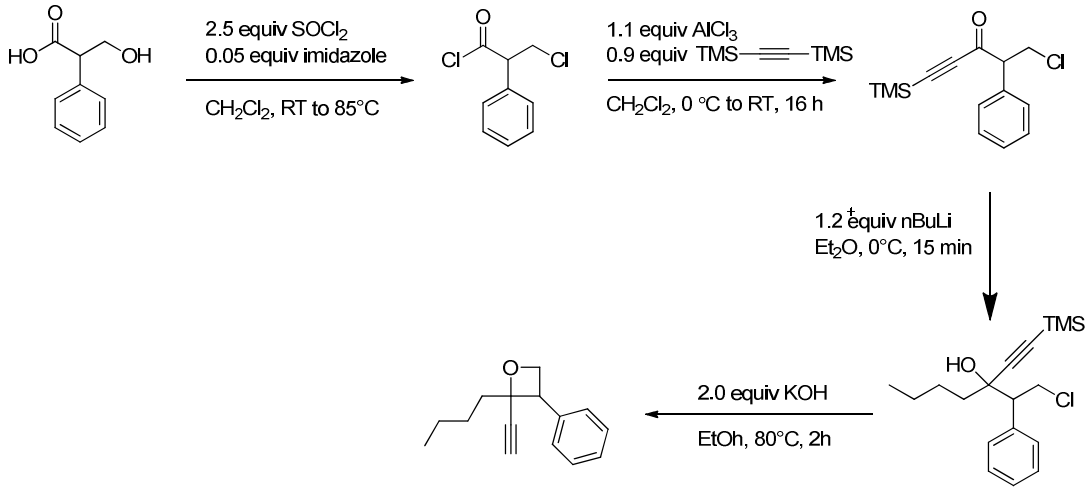
For both diastereoisomers:

HRMS: $C_{12}H_{11}FO$ [M^+]; calculated: 190.0794, found: 190.0794.

IR (CCl_4): ν (cm^{-1}) 3311, 3005, 2971, 2925, 1603, 1546, 1509, 1440, 1380, 1253, 1234, 1156.

2-butyl-2-ethynyl-3-phenyloxetane (3.83) $C_{15}H_{18}O$ **MW = 214.3 g.mol^{-1}**

Procedure:



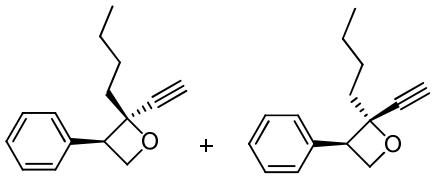
To tropic acid (10 mmol, 1.0 equiv) in a dry flask under nitrogen atmosphere were added dry dichloromethane (1 mL) and imidazole (0.05 equiv). The mixture was cooled to 0°C and then thionyl chloride (2.5 equiv) was added dropwise. The mixture was stirred at 0°C for 30 minutes and then heated at 85°C for 2h until no gas emission was observed. Excess thionyl chloride was removed *in vacuo*. 3-chloro-2-phenylpropanoyl chloride was then used without further purification.

To a dry flask under nitrogen atmosphere were added $AlCl_3$ (1.2 equiv) and dichloromethane (0.75 M compared to bis(trimethylsilyl)acetylene). The mixture was cooled to 0 °C. Then the 3-chloro-2-phenylpropanoyl chloride (1.1 equiv) was added followed by addition of bis(trimethylsilyl)acetylene. The reaction was stirred 30 minutes at 0 °C and TLC showed no remaining starting materialThe reaction was slowly quenched carefully with water at 0 °C. The mixture was then poured into a separatory funnel containing water and dichloromethane. The phases were separated and the aqueous extracted twice with dichloromethane. The combined organic phases were washed with water and brine then dried over Magnesium sulfate. The solvent was removed *in vacuo* and the crude purified by flash chromatography (ethyl acetate in petroleum ether) yielding the ketone.

A dry flask under nitrogen atmosphere containing dry diethyl ether (0.25M compared to ketone) was cooled to 0°C and *n*-butyllithium (1.2 equiv) was added. Ketone in solution in THF (1M) was then added dropwise over 15 minutes. The reaction mixture was then stirred at 0°C for 15 minutes until TLC showed no remaining strating material. The reaction was quenched with sat. NH_4Cl (aq.), then allowed to heat to room temperature before it was transferred to a separatory funnel containing water and diethyl ether. The phases were separated and the aqueous extracted twice with diethyl ether. The combined organic phases were washed with H_2O and brine, then dried over Magnesium sulfate. The solvents were removed *in vacuo* and the crude product carried forward without further purification.

The crude alcohol was dissolved in ethanol (0.25M) and KOH in pellets (2eq) was added. The reaction mixture was stirred at room temperature for 15 minutes. Then, the reaction mixture was heated at

80°C and stirred for 2 hours. The ethanol was then removed in vacuo. The mixture was dissolved in diethyl ether and poured in a separatory funnel containing diethyl ether and water. The phases were separated and the aqueous phase extracted twice with diethyl ether. The combined organic phases were washed with brine and dried over Magnesium sulfate. The solvent was removed *in vacuo* and the crude purified by flash chromatography yielding the final oxetane.



Product: yellow oil, mixture of diastereoisomers in a 1:2.85 ratio

Yield: 12 % over 4 steps (m = 255 mg)

Major diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41-7.35 (m, 3H), 7.33-7.28 (m, 2H), 4.87 (dd, *J* = 6.2 Hz, *J* = 8.0 Hz, 1H), 4.75 (dd, *J* = 6.2 Hz, *J* = 8.6 Hz, 1H), 4.08 (dd, *J* = 8.0 Hz, *J* = 8.6 Hz, 1H), 2.61 (s, 1H), 2.13-1.99 (m, 2H), 1.60-1.34 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 137.4, 128.5 (2C), 128.2 (2C), 127.4, 86.3, 82.6, 79.3, 71.2, 50.4, 42.9, 25.7, 22.8, 14.0.

Minor diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41-7.35 (m, 3H), 7.33-7.28 (m, 2H), 4.93 (dd, *J* = 6.4 Hz, *J* = 8.5 Hz, 1H), 4.77 (dd, *J* = 6.4 Hz, *J* = 7.4 Hz, 1H), 4.47 (dd, *J* = 7.4 Hz, *J* = 8.5 Hz, 1H), 2.85 (s, 1H), 2.13-1.99 (m, 2H), 1.60-1.34 (m, 4H), 0.74 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 136.0, 128.4 (2C), 128.1 (2C), 127.5, 86.2, 83.7, 75.8, 69.8, 50.8, 36.3, 25.1, 22.6, 13.8.

For both diastereoisomers

HRMS: $C_{15}H_{18}O$ [M^+]; calculated: 214.1358, found: 214.1354.

IR (CCl_4): ν (cm^{-1}) 3311, 3032, 2959, 2936, 2887, 2875, 1558, 1545, 1455, 1257.

2-butyl-2-ethynyloxetane (3.81)	$C_9H_{14}O$	**MW = 138.2 g.mol^{-1}**

Procedure :

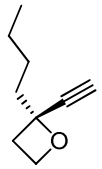
To a dry flask under argon atmosphere were added $AlCl_3$ (1.2 equiv) and dichloromethane (0.75 M compared to arene). The mixture was cooled to 0 °C. Then the acyl chloride (1.1 equiv) was added followed by addition of the bis(trimethylsilyl)acetylene. The reaction was stirred 30 minutes at 0 °C. The ice bath was removed and the reaction stirred for another hour until TLC showed no remaining starting material. After cooling to 0 °C, the reaction was slowly quenched with water. The mixture was poured into a separatory funnel containing water and dichloromethane. The phases were separated and the aqueous extracted twice with dichloromethane. The combined organic phases were washed with H_2O and brine then dried over Magnesium sulfate. The solvent was removed *in vacuo* and the crude purified by flash chromatography (ethyl acetate in petroleum ether) yielding the ketone.

A dry flask under nitrogen atmosphere containing dry diethyl ether (0.25M compared to ketone) was cooled to 0 °C and *n*-BuLi (2.5M in hexanes) (1.2 equiv) was added. Ketone in solution in THF (1M) was then added dropwise over 15 minutes. The reaction mixture was then stirred at 0 °C for 15 minutes until TLC showed no remaining strating material. The reaction was quenched with sat. NH_4Cl (aq.), then allowed to heat to room temperature before it was transferred to a separatory funnel containing water and diethyl ether. The phases were separated and the aqueous extracted twice with diethyl ether. The combined organic phases were washed with H_2O and brine, and then dried over Magnesium sulfate. The solvents were removed *in vacuo* and the crude product carried forward without further purification.

The crude alcohol was dissolved in ethanol (0.25M) and KOH in pellets (2eq) was added. The reaction mixture was stirred at room temperature for 15 minutes. Then, the reaction mixture was heated at 80 °C and stirred for 2 hours. The ethanol was then removed in vacuo. The mixture was dissolved in diethyl ether and poured in a separatory funnel containing diethyl ether and water. The phases were separated and the aqueous phase extracted twice with diethyl ether. The combined organic phases were washed with brine and dried over Magnesium sulfate. The solvent was carefully removed *in vacuo* and the crude purified by flash chromatography yielding the final oxetane.

Product: colorless oil.

Yield: 30% over 3 steps (m = 207mg)



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.66 (ddd, *J* = 6.0 Hz, *J* = 7.4 Hz, *J* = 8.6 Hz, 1H), 4.44 (ddd, *J* = 6.0 Hz, *J* = 6.3 hz, *J* = 8.8 Hz, 1H), 2.81 (ddd, *J* = 6.3 hz, *J* = 8.6 hz, *J* = 10.9 Hz, 1H), 2.73 (s, 1H), 2.64 (ddd, *J* = 7.4 hz, *J* = 8.8 Hz, *J* = 10.9 Hz, 1H), 1.95-1.80 (m, 2H), 1.52-1.30 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 85.6, 80.5, 75.2, 65.9, 41.7, 34.2, 25.7, 22.7, 14.0.

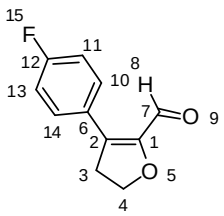
HRMS: $C_{15}H_{18}O_2$ [M^+]; calculated: 138.1045, found: 138.1040

HRMS: $C_9H_{14}O$ [$M+Na^+$]; calculated: 138.1045; not found

IR (CCl_4): ν (cm^{-1}) 3310, 2960, 2933, 2874, 2889, 1467, 1230, 968.

3. Preparation of furanaldehydes

3-(4-Fluorophenyl)-4,5-dihydrofuran-2-carbaldehyde (3.78)	$C_{11}H_9FO_2$	**MW = 192.2 g.mol^{-1}**



Procedure: see general procedures 3.2

Product: colorless solid

Yield: 80 % (m = 15.4 mg)

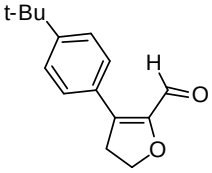
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.67 (s, 1H, **H8**), 7.44-7.39 (m, 2H, **H11 and H13**), 7.19-7.13 (m, 2H, **H10 and H14**), 4.59 (t, *J* = 9.6 Hz, 2H, **H4**), 3.32 (t, *J* = 9.6 Hz, 2H, **H3**).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.7 (**C7**), 163.1 (d, $^{1}J_{CF}$ = 248.7 Hz, **C12**), 149.9 (**C1**), 132.8 (**C2**), 130.0 (d, $^{3}J_{CF}$ = 8.1 Hz, 2C, **C10 and C14**), 128.0 (d, $^{4}J_{CF}$ = 3.3 Hz, **C6**), 116.1 (d, $^{2}J_{CF}$ = 21.7 Hz, 2C, **C11 and C13**), 68.5 (**C4**), 35.6 (**C3**).

HRMS: $C_{11}H_9FO_2$ [M^+]; calculated: 192.0587, found: 192.0590.

IR ($CHCl_3$): ν (cm^{-1}) 3054, 2964, 2857, 1750, 1671, 1602, 1510, 1239, 1159, 1097.

3-(4-(*tert*-Butyl)phenyl)-4,5-dihydrofuran-2-carbaldehyde (3.67) $C_{15}H_{18}O_2$ **MW = 230.3 g.mol^{-1}**



Procedure: see general procedure 3.2

Product: white solid

Yield: 85 % (m = 19.6 mg)

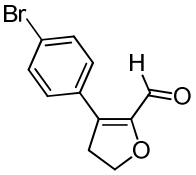
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.73 (s, 1H), 7.49 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.37 (dt, *J* = 8.4, 1.6 Hz, 2H), 4.57 (t, *J* = 9.6 Hz, 2H), 3.33 (t, *J* = 9.6 Hz, 2H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 182.0, 152.5, 149.8, 134.3, 129.0, 128.0 (2C), 125.9 (2C), 68.5, 35.5, 34.8, 31.2 (3C).

HRMS: $C_{15}H_{18}O_2$ [M^+]; calculated: 230.1307, found: 230.1307.

IR (CCl_4): ν (cm^{-1}) 2966, 2869, 1734, 1681, 1607, 1243.

3-(4-bromophenyl)-4,5-dihydrofuran-2-carbaldehyde (3.79) $C_{11}H_9BrO_2$ **MW = 253.1 g.mol^{-1}**



Procedure: see general procedure 3.2

Product: colorless oil

Yield: 79 % (m = 20.0 mg)

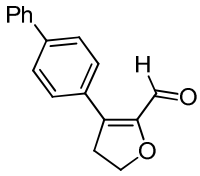
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.64 (s 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.54 (t, *J* = 9.8 Hz, 2H), 3.27 (t, *J* = 9.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.5, 150.2, 132.2, 132.1 (2C), 130.9 (2C), 129.6, 123.2, 68.6, 35.4.

HRMS: $C_{11}H_9BrO_2$ [M^+]; calculated: 251.9786, found: 251.9789.

IR (CCl_4): ν (cm^{-1}) 2964, 2925, 2899, 2850, 1686, 1587, 1487, 1244, 1167.

3-(4-phenylphenyl)-4,5-dihydrofuran-2-carbaldehyde (3.77) $C_{17}H_{14}O_2$ **MW = 250.3 g.mol^{-1}**



Procedure: see general procedure 3.2

Product: colorless oil

Yield: 88 % (m = 22.0 mg)

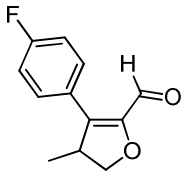
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.74 (s, 1H), 7.66-7.61 (m, 4H), 7.49-7.45 (m, 4H), 7.40-7.37 (m, 1H), 4.56 (t, *J* = 9.7 Hz, 2H), 3.33 (t, *J* = 9.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)181.8, 150.1, 142.0, 140.1, 133.5, 130.9, 129.0 (2C), 128.7 (2C), 127.9, 127.5 (2C), 127.0 (2C), 68.6, 35.5.

HRMS: $C_{17}H_{14}O_2$ [M^+]; calculated: 250.0994, found: 250.0986.

IR (CCl_4): ν (cm^{-1}) 3033, 2850, 1682, 1558, 1488, 1374, 1264, 1244, 1164.

3-(4-fluorophenyl)-4-methyl-4,5-dihydrofuran-2-carbaldehyde (3.80) $C_{12}H_{11}FO_2$ **MW = 206.2 g.mol^{-1}**



Procedure: see general procedure 3.2

Product: pale yellow oil

Yield: 72 % (m = 14.8 mg)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.60 (s, 1H), 7.37-7.32 (m, 2H), 7.13-7.08 (m, 2H), 4.89 (qdd, *J* = 6.3 Hz, *J* = 8.6 Hz, *J* = 9.7 Hz, 1H), 3.35 (dd, *J* = 9.8 Hz, *J* = 17;4 Hz, 1H), 2.88 (*J* = 8.5 Hz, *J* = 17.4 Hz, 1H), 1.49 (d, *J* = 6.3 Hz, 3H).

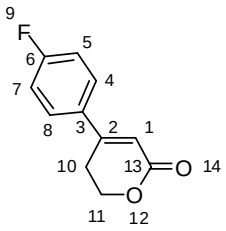
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 8, 181.8, 162.9 (d, $^1J_{CF}$ = 248.4 Hz), 149.2, 132.2, 129.9 (d, $^3J_{CF}$ = 8.1 Hz, 2C), 128.2 (d, $^4J_{CF}$ = 3.5 Hz), 115.9 (d, $^2J_{CF}$ = 21.7 Hz, 2C), 76.9, 42.6, 21.7.

HRMS: $C_{12}H_{11}FO_2$ [M^+]; calculated: 206.0743, found: 206.0738.

IR (CCl_4): ν (cm^{-1}) 2980, 2845, 1686, 1603, 1509, 1263, 1240, 1160.

4. Preparation of α–β-unsaturated lactones

4-(4-Fluorophenyl)-5,6-dihydro-2*H*-pyran-2-one (3.72) $C_{11}H_9FO_2$ **MW = 192.2 g.mol^{-1}**



Procedure: see general procedure 3.3

Product: colorless oil

Yield: 83 % (m = 15.9 mg)

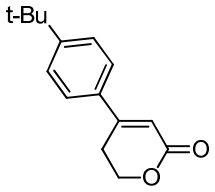
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61-7.56 (m, 2H, **H5 and H7**), 7.22-7.16 (m, 2H, **H4 and H8**), 6.38 (s, 1H, **H1**), 4.58 (t, *J* = 6.0 Hz, 2H, **H11**), 2.89 (t, *J* = 6.0 Hz, 2H, **H10**).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 164.9 (**C13**), 164.2 (d, $^1J_{CF}$ = 250.7 Hz, **C6**), 154.0, 132.2 (d, $^4J_{CF}$ = 3.4 Hz, **C2**), 128.0 (d, $^3J_{CF}$ = 8.5 Hz, 2C, **C4 and C8**), 116.2 (d, $^2J_{CF}$ = 21.7 Hz, 2C, **C5 and C7**), 114.9 (**C1**), 65.9 (**C11**), 26.4 (**C10**).

HRMS:$C_{11}H_9FO_2$ [M^+]; calculated: 192.0587, found: 192.0586.

IR (CCl_4):ν(cm^{-1}) 3054, 2954, 2905, 1720, 1703, 1602, 1510, 1226, 1163, 1090.

4-(4-(*tert*-Butyl)phenyl)-5,6-dihydro-2*H*-pyran-2-one (3.66) $C_{15}H_{18}O_2$ **MW = 230.3 g.mol^{-1}**



Procedure: see general procedure 3.3

Product: yellow solid

Yield: 74 % (m = 17.0 mg)

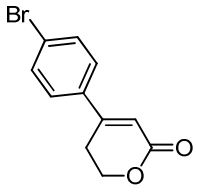
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 6.42 (s, 1H), 4.57 (t, *J* = 6.4 Hz, 2H), 2.91 (t, *J* = 6.4 Hz, 2H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.3, 155.1, 154.4, 133.0, 126.0 (2C), 125.9 (2C), 114.2, 66.1, 34.9, 31.2 (3C), 26.3.

HRMS: $C_{15}H_{18}O_2$ [M^+]; calculated: 230.1307, found: 230.1302.

IR (CCl_4): ν (cm^{-1}) 2966, 2870, 1731, 1363, 1218, 1091.

4-(4-bromophenyl)-5,6-dihydro-2H-pyran-2-one (3.74) $C_{11}H_9BrO_2$ **MW = 253.1 g.mol^{-1}**



Procedure: see general procedure 3.3

Product: light pink solid

Yield: 73 % (m = 18.5 mg)

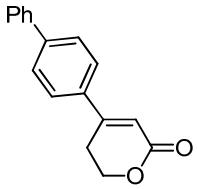
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 hz, 2H), 6.35 (t, *J* = 1.3 Hz, 1H), 4.52 (t, *J* = 6.2 Hz, 2H), 2.83 (dt, *J* = 1.3 Hz, *J* = 6.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 164.6, 154.0, 134.9, 132.3 (2C), 127.5 (2C), 125.2, 115.6, 66.0, 26.3.

HRMS: $C_{11}H_9BrO_2$ [M^+]; calculated: 251.9786, found: 251.9790.

IR (CCl_4): ν (cm^{-1}) 2987, 2897, 1735, 1588, 1491, 1397, 1264, 1217.

4-(4-phenylphenyl)-5,6-dihydro-2H-pyran-2-one (3.70) $C_{17}H_{14}O_2$ **MW = 250.3 g.mol^{-1}**



Procedure: see general procedure 3.3

Product: light yellow solid

Yield: 71 % (m = 17.8 mg)

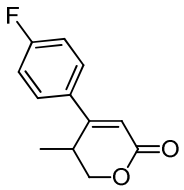
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.69-7.67 (m, 2H), 7.64-7.61 (m ,4H), 7.49-7.45 (m, 2H), 7.41-7.38 (m, 1H), 6.43 (t, *J* = 1.0 Hz, 1H), 4.55 (t, *J* = 6.2 Hz, 2H), 2.04 (dt, *J* = 1.0 Hz, *J* = 6.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.0, 154.7, 143.6, 139.8, 134.8, 129.0 (2C), 128.1, 127.7 (2C), 127.1 (2C), 126.5 (2C), 114.8, 66.0, 26.3.

HRMS: $C_{17}H_{14}O_2$ [M^+]; calculated: 250.0994, found: 250.0994.

IR (CCl_4): ν (cm^{-1}) 3033, 2927, 2855, 1732, 1558, 1544, 1275, 1263, 1217, 1091.

4-(4-fluorophenyl)-5-methyl-5,6-dihydropyran-2-one (3.76) $C_{12}H_{11}FO_2$ **MW = 206.2 g.mol^{-1}**



Procedure: see general procedure 3.3

Product: pale yellow oil

Yield: 89 % (m = 18.3 mg)

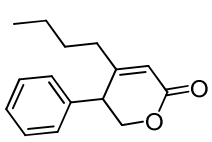
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54-7.51 (m, 2H), 7.16-7.11 (m, 2H), 6.31 (d, *J* = 2.1 Hz, 1H), 4.66 (qdd, *J* = 3.9 Hz, *J* = 6.3 Hz, *J* = 11.3 Hz, 1H), 2.77 (dd, *J* = 3.9 Hz, *J* = 17.5 Hz, 1H), 2.66 (ddd, *J* = 2.1 Hz, *J* = 11.3 Hz, *J* = 17.5 Hz, 1H), 1.53 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.6, 164.1 (d, $^{1}J_{CF}$ = 250.5 Hz), 153.4, 132.3 (d, $^{4}J_{CF}$ = 3.1 Hz), 128.0 (d, $^{3}J_{CF}$ = 8.5 Hz, 2C) 116.2 (d, $^{2}J_{CF}$ = 21.7 Hz, 2C), 114.7 (d, $^{5}J_{CF}$ = 1.6 Hz), 73.7, 33.5, 20.8.

HRMS: $C_{12}H_{11}FO_2$ [M^+]; calculated: 206.0743, found: 206.0737.

IR (CCl_4): ν (cm^{-1}) 2981, 2845, 1723, 1604, 1513, 1375, 1262, 1240, 1162, 1061.

4-butyl-5-phenyl-5,6-dihydro-2H-pyran-2-one (3.84) $C_{15}H_{18}O_2$ **MW = 230.3 g.mol^{-1}**



Procedure: see general procedure 3.3

Product: yellow oil

Yield: 67 % (m = 15.4 mg)

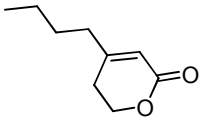
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37-7.29 (m, 3H), 7.21-7.19 (m, 2H), 6.01 (s, 1H), 4.59 (dd, *J* = 4.7 Hz, *J* = 11.2 Hz, 1H), 4.38 (dd, *J* = 4.2 Hz, *J* = 11.2 Hz, 1H), 3.53 (dd, *J* = 4.2 Hz, *J* = 4.7 Hz, 1H), 2.14 (t, *J* = 7.6 Hz, 2H), 1.51-1.38 (m, 2H), 1.35-1.20 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 164.6, 163.0, 137.3, 129.1 (2C), 128.2 (2C), 128.0, 116.6, 72.0, 44.2, 34.6, 28.7, 22.2, 13.8.

HRMS: $C_{15}H_{18}O_2$ [M^+]; calculated: 230.1307, found: 230.1300.

IR (CCl_4): ν (cm^{-1}) 3066, 3030, 2961, 2933, 2895, 2875, 1736, 1465, 1242, 1214.

4-butyl-5,6-dihydro-2H-pyran-2-one (3.82) $C_9H_{14}O_2$ **MW = 154.2 g.mol^{-1}**



Procedure: see general procedure 3.3

Product: yellow oil

Yield: 74 % (m = 11.4 mg)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.81-5.79 (m, 1H), 4.37 (t, *J* = 6.3 Hz, 2H), 2.37 (t, *J* = 6.4 Hz, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 1.54-1.46 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 164.9, 161.8, 115.7, 66.0, 36.4, 28.5, 28.0, 22.3, 13.8.

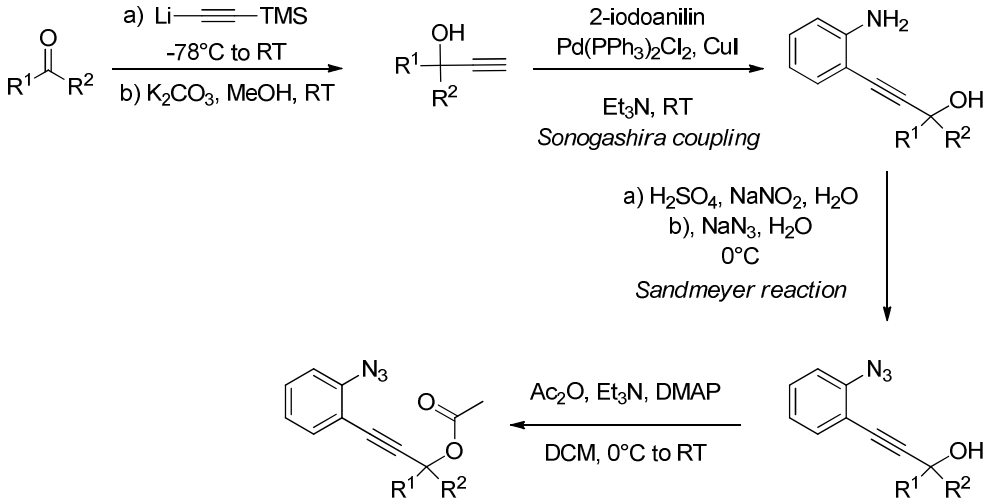
HRMS: $C_9H_{14}O_2$ [M^+]; calculated: 154.0994, found: 154.0988.

IR (CCl_4): ν (cm^{-1}) 2960, 2933, 2899, 2875, 2863, 1732, 1468, 1396, 1266, 1219, 1150, 1081.

Chapitre 4 : Quinolines synthesis from azidophenylalkynyl acetates

1. General procedures

General procedure 4.1:



Preparation:

Addition on the ketone

1.0 equiv. of a solution of butyllithium in hexanes is added to a solution of 1.1 equiv. of ethynyltrimethylsilane in THF at -78°C. The mixture is stirred at -78°C for 30 minutes. 1.0 equiv. of the ketone is then added and the resulting mixture stirred at -78°C and monitored by TLC. (The mixture's temperature can be raised to 0°C or RT depending on the duration of the addition). When the reaction is complete, $NH_4Cl_{(sat)}$ is added to the solution and the temperature is allowed to raise to RT. The phases are separated and the aqueous phase is extracted twice with diethyl ether. The combined organic phases are washed with brine and dried over Magnesium sulfate. After filtration, the solvents are evaporated and the crude is analyzed by NMR.

The crude can be used in the second step without further purification.

Deprotection of the silyl group

The substrate is dissolved in MeOH (0.5M) and 0.3 equiv. of K_2CO_3 is added. The mixture is stirred at RT until TLC shows no remaining starting material. The solvent is then evaporated under low pressure. $NH_4Cl_{(sat)}$ and diethyl ether are added to the mixture. The phases are separated and the aqueous phase is extracted twice with diethyl ether. The combined organic phases are washed with water, brine and dried over Magnesium sulfate. After filtration, the solvents are evaporated and the crude is analyzed by NMR. The product is purified by column chromatography using petroleum ether:ethyl acetate (80:20) as eluent.

Sonogashira coupling

1.0 equiv. of 2-iodoanilin is dissolved in triethylamine (0.3 M) and the solution is degased by bubbling N_2 for one hour. 0.02 equiv. of $Pd(PPh_3)_2Cl_2$ and 0.04 equiv. of copper iodide are then added and the mixture stirred for 5 minutes. 1.0 equiv. of the alkyne obtained in the previous step is then added pure or in a 1M solution in triethylamine (if solid). The reaction mixture is stirred at RT until TLC shows no starting alkyne remaining (2h to overnight). $NH_4Cl_{(sat)}$ and diethyl ether are added to the mixture. The phases are separated and the aqueous phase is extracted twice with diethyl ether. The combined organic phases are washed with water, brine and dried over Magnesium sulfate. After filtration, the solvents are evaporated and the crude is analyzed by NMR. The product is then purified by column chromatography using petroleum ether:ethyl acetate (85:15) as eluent.

Sandmeyer reaction

The anilin obtained in the previous step is dissolved in a sulphuric acid solution (10% in water). Acetonitrile can be added when the substrate is not soluble in the aqueous phase (up to 5mL). The mixture is stirred at 0°C and a 1.5M solution of 1.2 equiv. of sodium nitrite in water is added dropwise over 15 minutes. The resulting mixture is stirred at 0°C for 30 minutes. Then, 1.2 equiv. of a 1.5M solution of sodium azide in water is added dropwise over 15 minutes. The reaction mixture is stirred at 0°C for 30 minutes starting when no nitrogen degasing can be seen anymore.

The reaction is quenched by $Na_2S_2O_{3(sat)}$ and diethyl ether is added. The phases are separated and the aqueous phase is extracted twice with diethyl ether. The combined organic phases are washed with water, brine and dried over Magnesium sulfate. After filtration, the solvents are evaporated and the crude is analyzed by NMR.

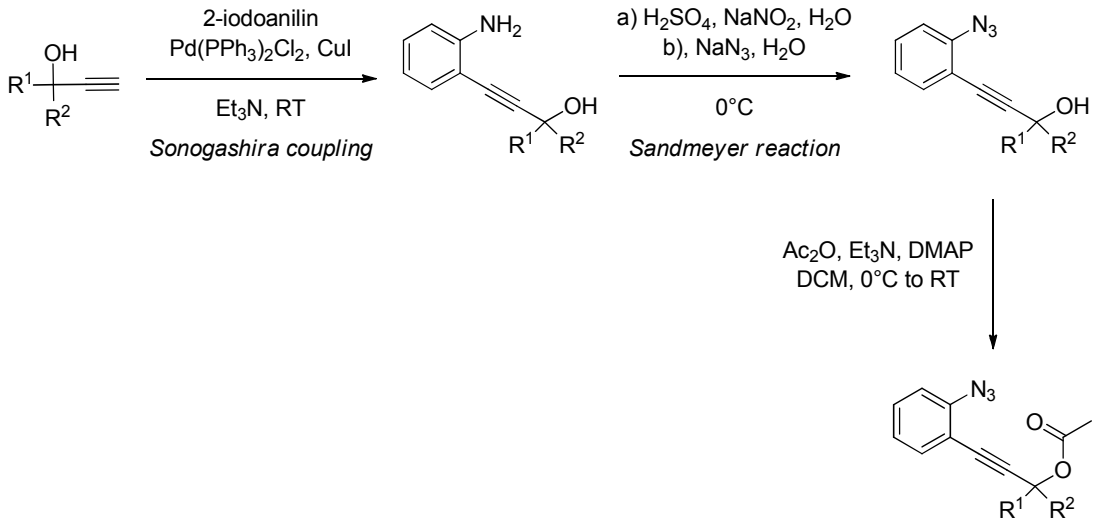
In most cases the next step can be carried out without further purification.

Acetylation

1.0 equiv. of the substrate is dissolved in dichloromethane (0.25M) and the solution is stirred under N_2 atmosphere at 0°C. 1.5 equiv. of triethylamine, 0.1 equiv. of DMAP and 1.5 equiv. of acetic anhydride are added. The reaction mixture is then heated to 40°C and stirred at this temperature until completion. $NH_4Cl_{(sat)}$ is then added to the mixture. The phases are separated and the aqueous phase is extracted twice with dichloromethane. The combined organic phases are washed with water, brine and dried over Magnesium sulfate. After filtration, the solvent is evaporated and the crude is analyzed by NMR.

The product is then purified on column chromatography using petroleum ether:ethyl acetate (98:2) as eluent.

General procedure 4.2 (when the propargyl alcohol is comercially available)



Sonogashira coupling

1.0 equiv. of 2-iodoanilin is dissolved in triethylamine (0.3 M) and the solution is degased by bubbling N_2 for one hour. 0.02 equiv. of $Pd(PPh_3)_2Cl_2$ and 0.04 equiv. of copper iodide are then added and the mixture stirred for 5 minutes. 1.0 equiv. of the alkyne obtained in the previous step is then added pure or in a 1M solution in triethylamine (if solid). The reaction mixture is stirred at RT until TLC shows no starting alkyne remaining (2h to overnight). $NH_4Cl_{(sat)}$ and diethyl ether are added to the mixture. The phases are separated and the aqueous phase is extracted twice with diethyl ether. The combined organic phases are washed with water, brine and dried over Magnesium sulfate. After filtration, the solvents are evaporated and the crude is analyzed by NMR. The product is then purified by column chromatography using petroleum ether:ethyl acetate (85:15) as eluent.

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The reaction is quenched by $Na_2S_2O_{3(sat)}$ and diethyl ether is added. The phases are separated and the aqueous phase is extracted twice with diethyl ether. The combined organic phases are washed with water, brine and dried over Magnesium sulfate. After filtration, the solvents are evaporated and the crude is analyzed by NMR. In most cases the next step can be carried out without further purification.