Selectivity of Grignard reagent formation – from semi-batch to continuous lab and pilot scale

Supplementary information

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Content

1 Grignard reagents

1.1 Allylmagnesium chloride **1**

Table 1: Synthesis parameters for allylmagnesium chloride.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	3-chloroprop-1-ene, 1.0 mol L^{-1}
thermostat temperature	15 °C
flow rate	2 mL min^{-1}

Table 2: Conversion and selectivity for allylmagnesium chloride synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	74	1	23
continuous lab scale	coarse	syringe pump	100	96	2	0

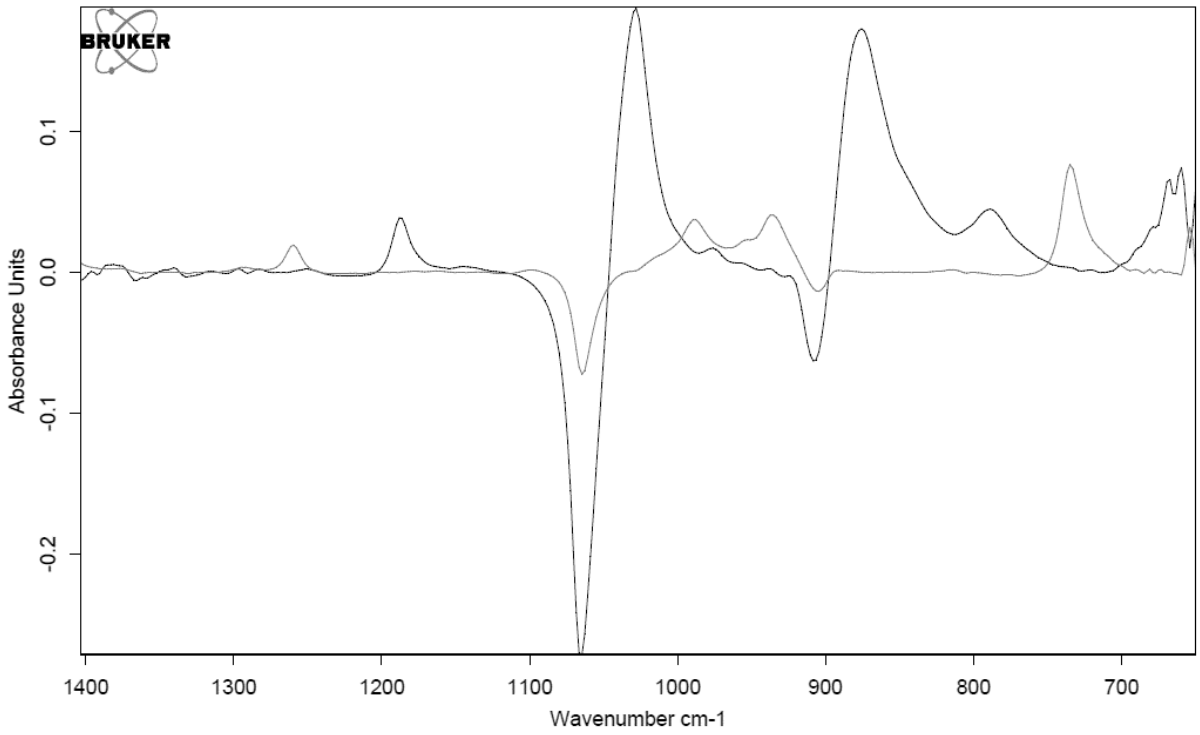

Figure 1: Infrared spectrum of allylmagnesium chloride (black) and 3-chloroprop-1-ene (grey) in THF.

1.2 Butylmagnesium bromide **2**

Table 3: Synthesis parameter for butylmagnesium bromide.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	bromobutane, 1.0 mol L^{-1}
thermostat temperature	batch: 20 °C lab scale: 20 °C, 30 °C
flow rate	4 mL min^{-1}

Table 4: Conversion and selectivity for butylmagnesium bromide synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	91	3	4
continuous lab scale	coarse	syringe pump	100	94	4	4

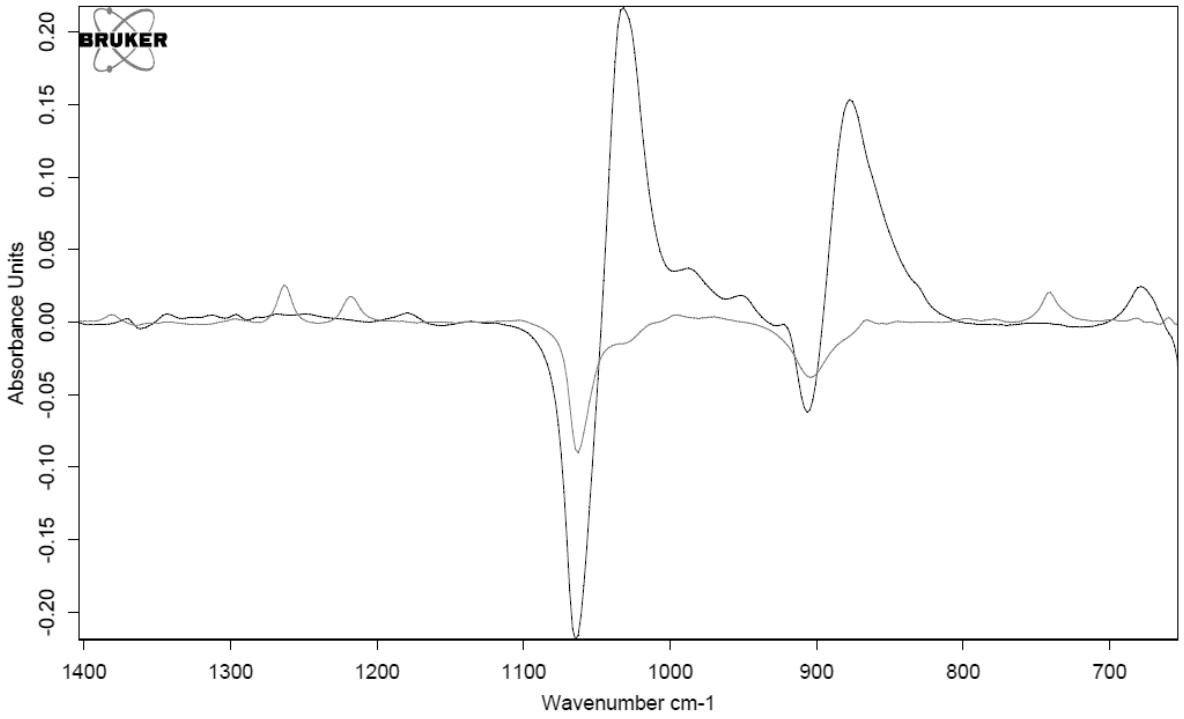

Figure 2: Infrared spectrum of butylmagnesium bromide (black) and 1-bromobutane (grey) in THF.

1.3 Butylmagnesium chloride **3**

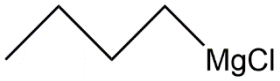

Table 5: Synthesis parameter for butylmagnesium chloride.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	chlorobutane, 1.0 mol L^{-1}
thermostat temperature	50 °C
flow rate	2 mL min^{-1}

Initiation of the reaction is done by adding a few milliliters of the pre-made Grignard reagent to the batch flask and the continuous lab scale reactor.

Table 6: Conversion and selectivity for butylmagnesium chloride synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	97	95	3	2
continuous lab scale	coarse	syringe pump	100	100	1	0

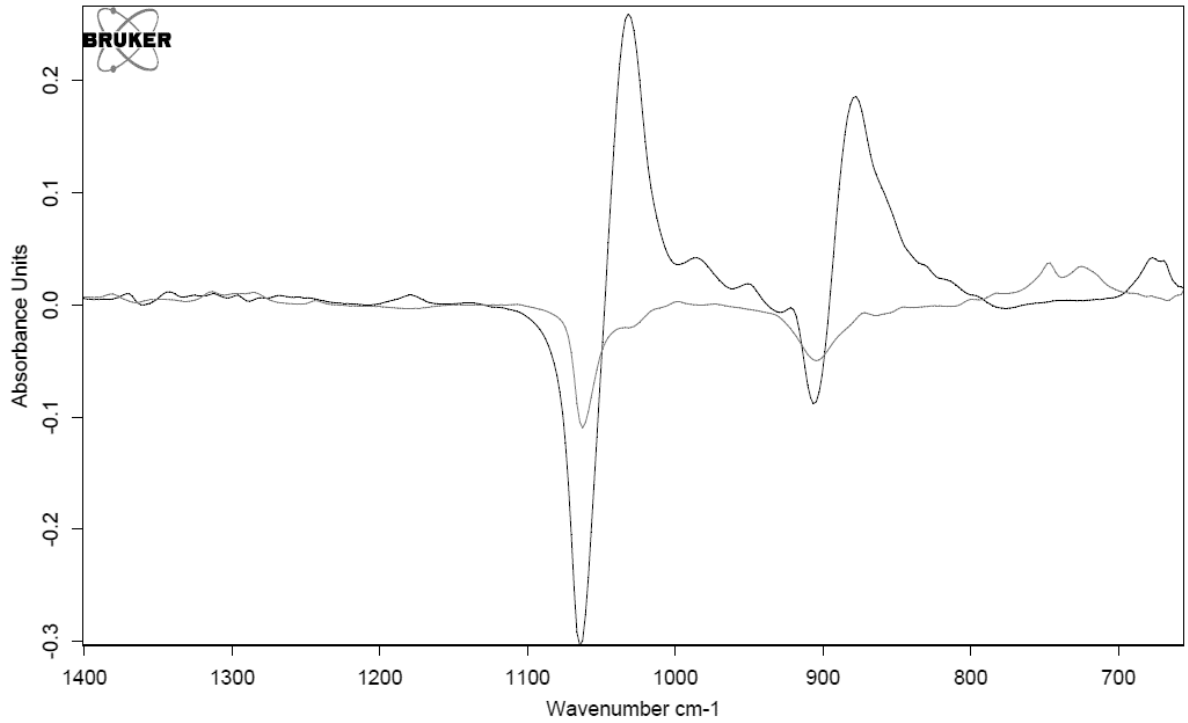

Figure 3: Infrared spectrum of butylmagnesium chloride (black) and 1-chlorobutane (grey) in THF.

1.4 2-Butylmagnesium chloride **4**

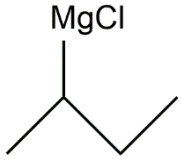

Table 7: Synthesis parameter for 2-butylmagnesium chloride.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	2-chlorobutane, 2.0 mol L^{-1}
thermostat temperature	20 °C
flow rate	1 mL min^{-1}

Table 8: Conversion and selectivity for 2-butylmagnesium chloride synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	89	5	2
continuous lab scale	coarse	syringe pump	97	95	3	2

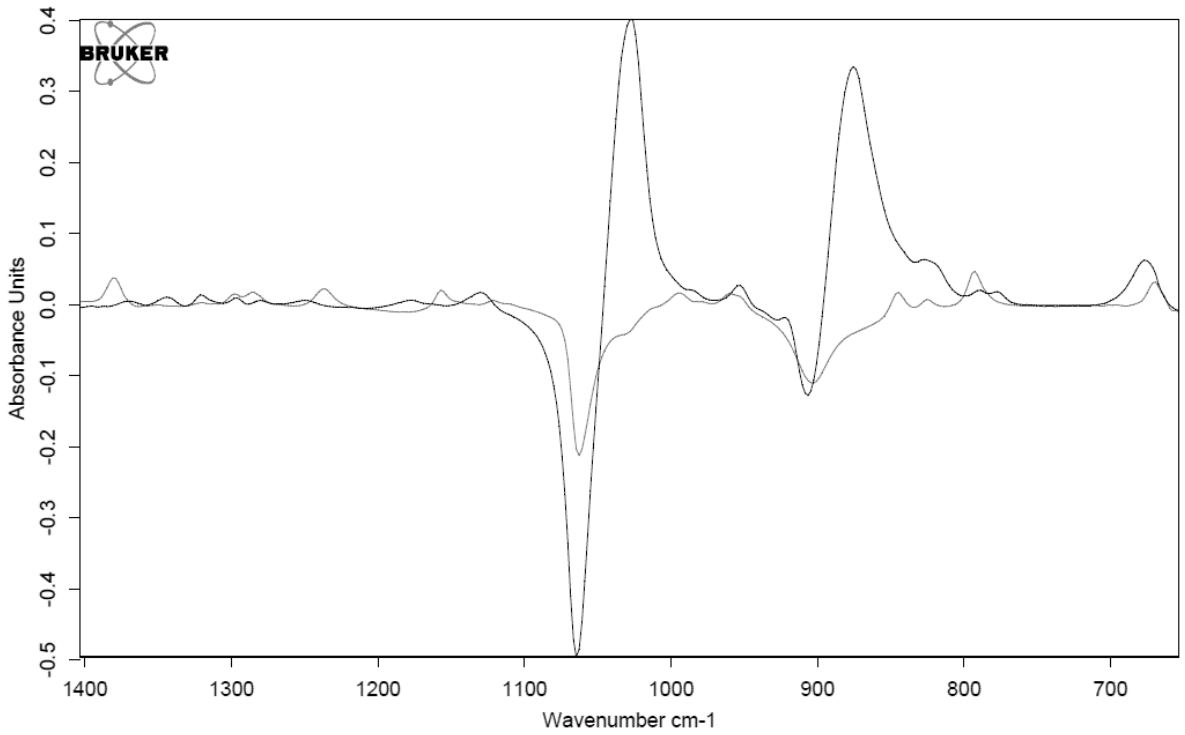

Figure 4: Infrared spectrum of 2-butylmagnesium chloride (black) and 2-chlorobutane (grey) in THF.

1.5 Ethylmagnesium bromide **5**

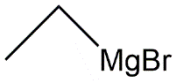

Table 9: Synthesis parameters for ethylmagnesium bromide.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	bromoethane, 1.0 mol L^{-1}
thermostat temperature	15 °C
flow rate	2 mL min^{-1} for semi-batch and continuous lab scale 74 mL min^{-1} for continuous pilot scale

Table 10: Conversion and selectivity of ethylmagnesium bromide synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	95	0	n.a.
continuous lab scale	coarse	syringe pump	100	98	0	n.a.
	fine	micro annular gear pump	100	91	0	n.a.
continuous pilot scale	coarse	micro annular gear pump	100	98	0	n.a.

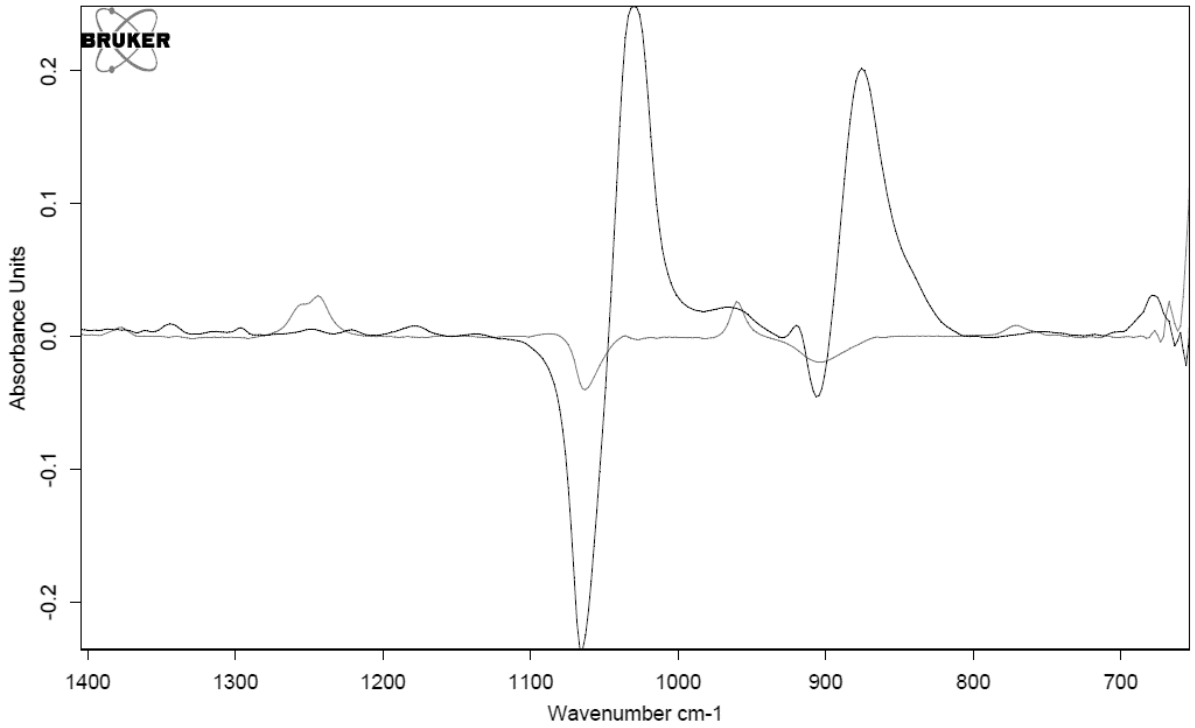

Figure 5: Infrared spectrum of ethylmagnesium bromide (black) and bromoethane (grey) in THF.

1.6 2-Methylallylmagnesium chloride **6**

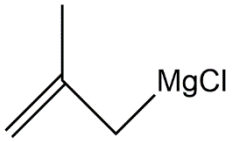

Table 11: Synthesis parameter for 2-methylallylmagnesium chloride.

parameter	**value**			
Mg turnings	coarse		fine	
solvent	THF			
halide and concentration	3-chloro-2-methylpropene			
	0.5 mol L^{-1}	2.0 mol L^{-1}	0.5 mol L^{-1}	2.0 mol L^{-1}
thermostat temperature	15 °C			
flow rate	1 mL min^{-1}			

Table 12: Conversion and selectivity for 2-methylallylmagnesium chloride synthesis (0.5 mol L^{-1}).

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	52	10	21
	fine	syringe pump	100	64	7	15
continuous lab scale	coarse	syringe pump	100	68	26	3
	fine	micro annular gear pump	100	72	22	1

Table 13: Conversion and selectivity for 2-methylallylmagnesium chloride synthesis (2.0 mol L^{-1}).

	Mg turnings	pump	conversion / %	selectivity / %		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	34	0	67
	fine	syringe pump	100	40	2	58
continuous lab scale	coarse	syringe pump	100	58	0	42
	fine	micro annular gear pump	100	72	1	28

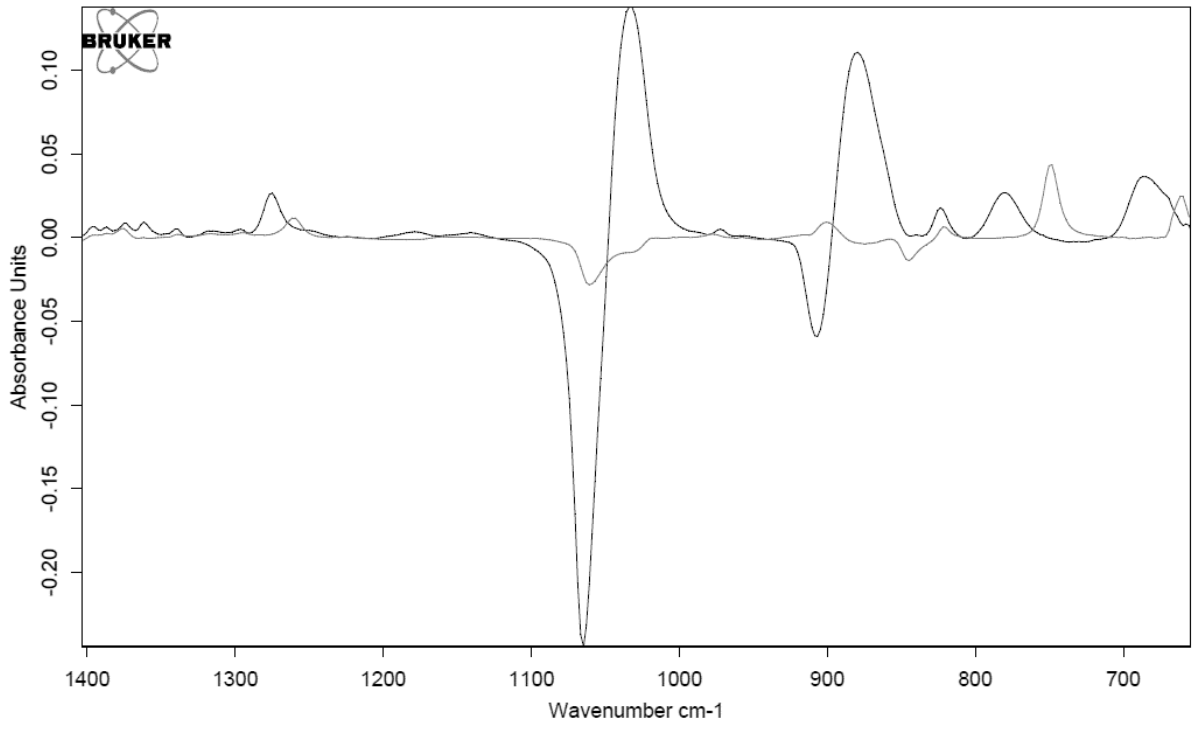

Figure 6: Infrared spectrum of 2-methylallylmagnesium chloride (black) and 3-chloro-2-methylpropene (grey) in THF.

1.7 Pentylmagnesium bromide **7**

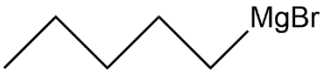

Table 14: Synthesis parameters for pentylmagnesium bromide.

parameter	**value**	
Mg turnings	coarse	
solvent	THF	diethyl ether
halide and concentration	bromopentane, 1.0 mol L^{-1}	
thermostat temperature	semi-batch: 20 °C continuous lab scale: 20 °C, 40 °C	15 °C
flow rate	2 mL min^{-1}	

Table 15: Conversion and selectivity of pentylmagnesium bromide synthesis in THF.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	92	0	8
continuous lab scale	coarse	syringe pump	100	96	0	4

Table 16: Conversion and selectivity of pentylmagnesium bromide synthesis in diethyl ether.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	88	0	12
continuous lab scale	coarse	syringe pump	100	86	0	16

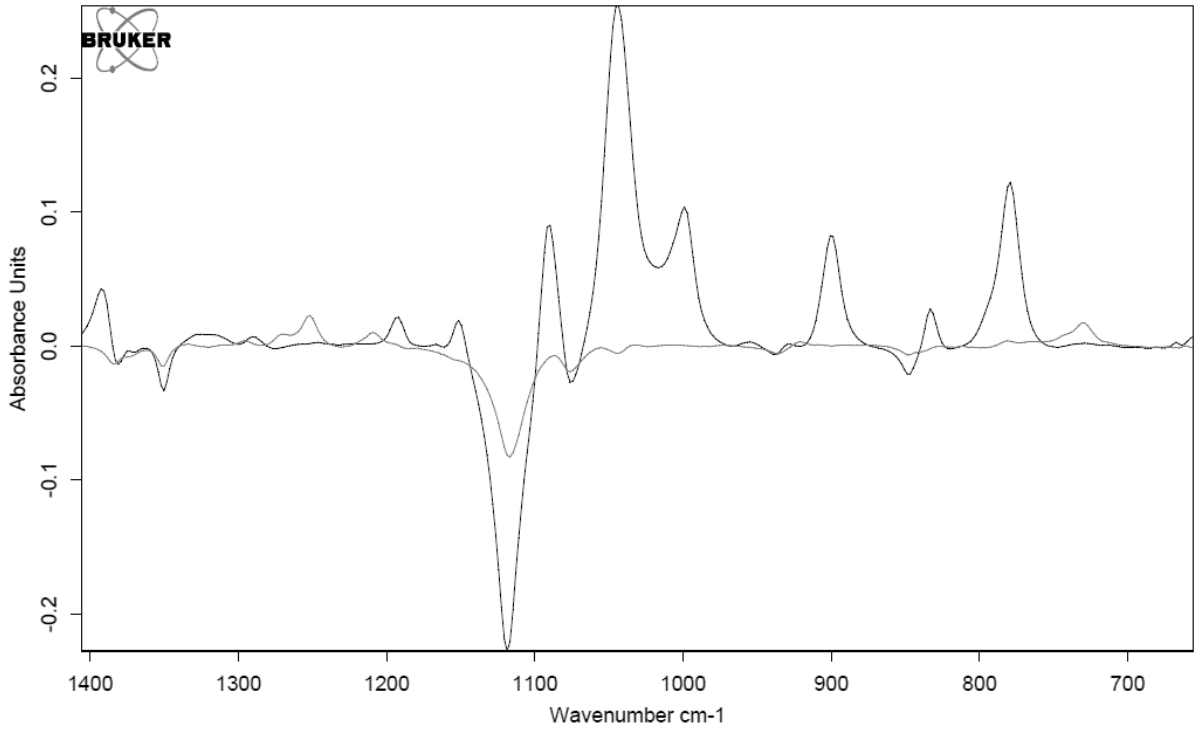

Figure 7: Infrared spectrum of pentylmagnesium bromide (black) and 1-bromopentane (grey) in diethyl ether.

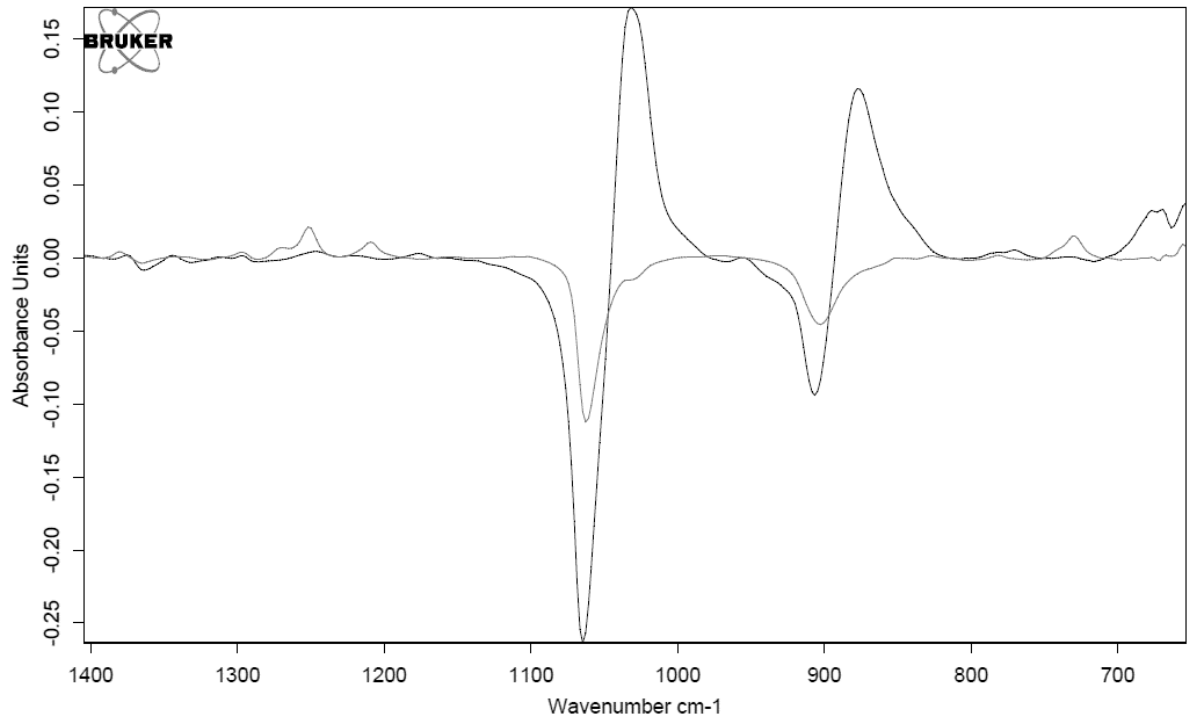

Figure 8: Infrared spectrum of pentylmagnesium bromide (black) and 1-bromopentane (grey) in THF.

1.8 Pentylmagnesium chloride **8**

Table 17: Synthesis parameters for pentylmagnesium chloride.

parameter	**value**	
Mg turnings	coarse	
solvent	THF	diethyl ether
halide and concentration	chloropentane, 1.0 mol L^{-1}	
thermostat temperature	45 °C	semi-batch: 20 °C continuous lab scale: 20 °C, 30 °C
flow rate	1.5 mL min^{-1}	2 mL min^{-1}

Initiation of the reaction is done by adding 30-40 mg iodine to the batch flask or by switching from pentylmagnesium bromide synthesis to pentylmagnesium chloride synthesis on continuous lab scale.

Table 18: Conversion and selectivity of pentylmagnesium chloride synthesis in THF.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	97	0	3
continuous lab scale	coarse	syringe pump	100	98	2	0

Table 19: Conversion and selectivity of pentylmagnesium chloride synthesis in diethyl ether.

	Mg turnings	pump	conversion / %	selectivity / %		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	85	100	0	2
continuous lab scale	coarse	syringe pump	98	99	0	1

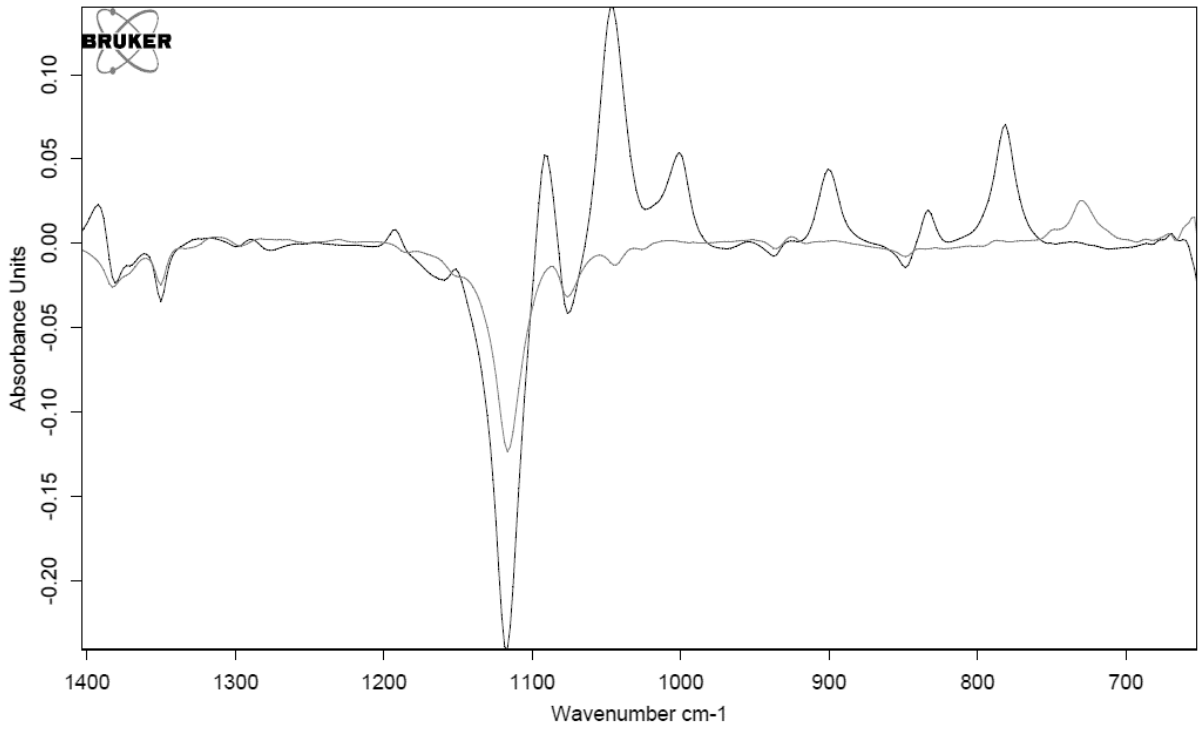

Figure 9: Infrared spectrum of pentylmagnesium chloride (black) and 1-chloropentane (grey) in diethyl ether.

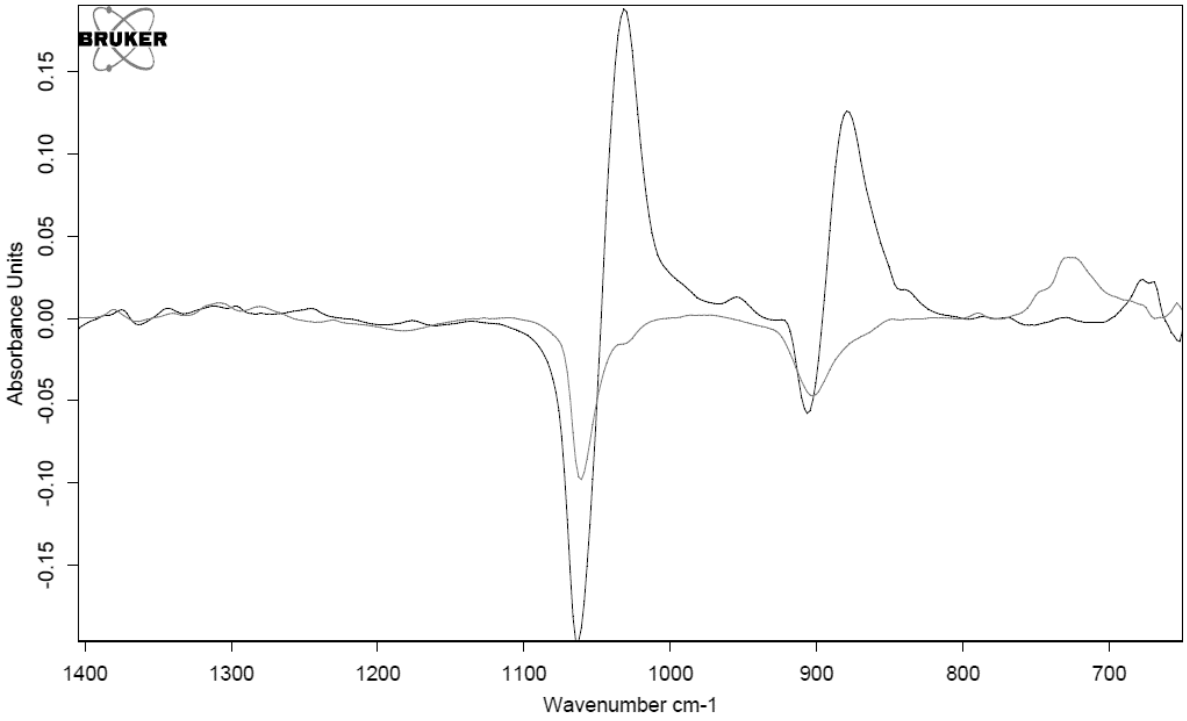

Figure 10: Infrared spectrum of pentylmagnesium chloride (black) and 1-chloropentane (grey) in THF.

1.9 Pentylmagnesium iodide **9**

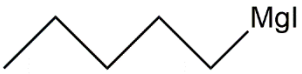

Table 20: Synthesis parameters for pentylmagnesium iodide.

parameter	**value**	
Mg turnings	coarse	
solvent	THF	diethyl ether
halide and concentration	iodopentane, 1.0 mol L^{-1}	
thermostat temperature	20 °C	15 °C
flow rate	2 mL min^{-1}	

Table 21: Conversion and selectivity of pentylmagnesium iodide synthesis in THF.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	30	77	13	5
continuous lab scale	coarse	syringe pump	-	-	-	-

Table 22: Conversion and selectivity of pentylmagnesium iodide synthesis in diethyl ether.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	64	2	32
continuous lab scale	coarse	syringe pump	98	63	10	27

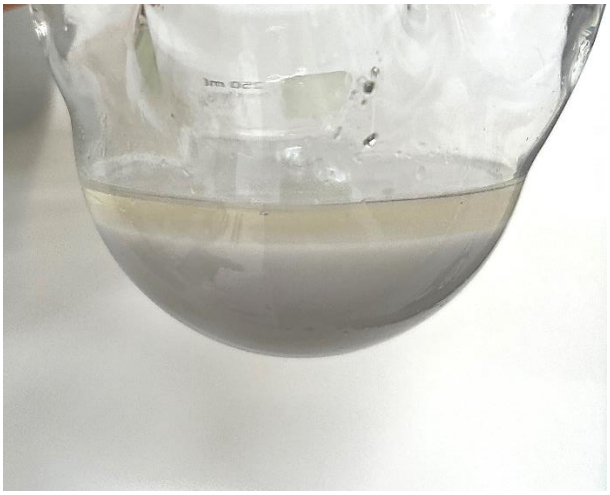

Figure 11: White precipitate during semi-batch synthesis of pentylmagnesium iodide in THF.

Figure 12: Precipitation during continuous lab scale synthesis of pentylmagnesium iodide in THF. Magnesium turnings are covered with white precipitate.

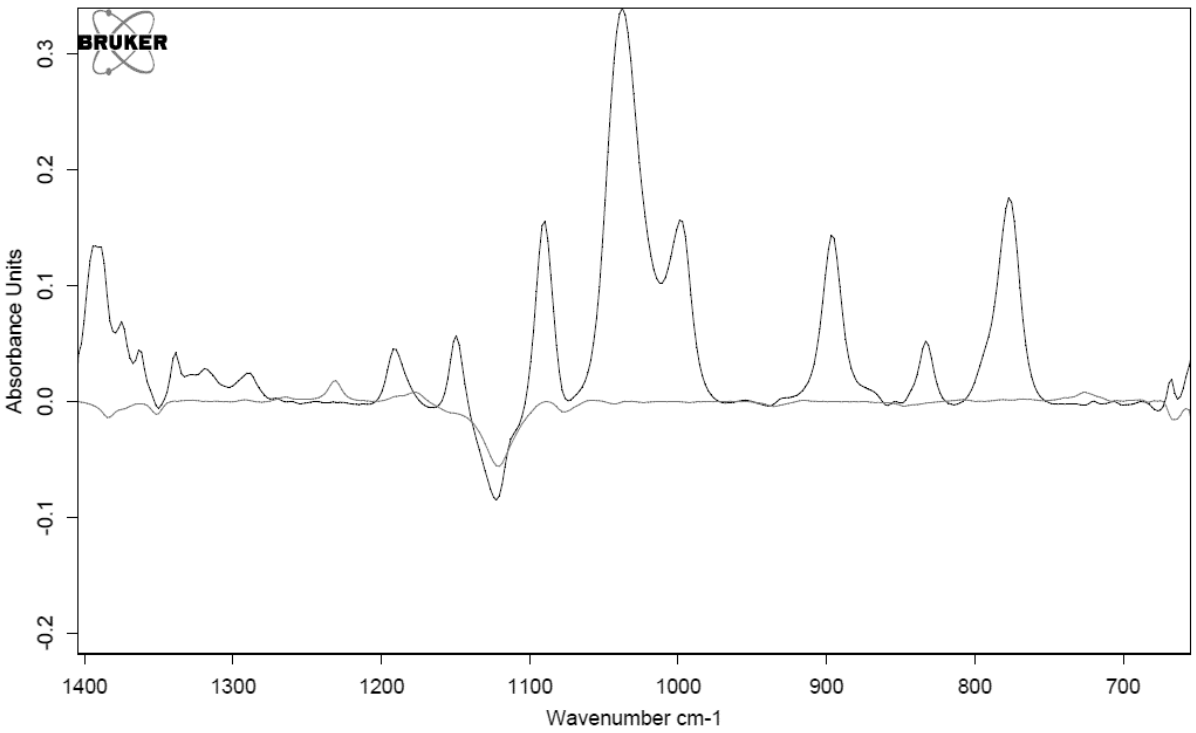

Figure 13: Infrared spectrum of pentylmagnesium iodide (black) and 1-iodopentane (grey) in diethyl ether.

1.10 Benzylmagnesium bromide **10**

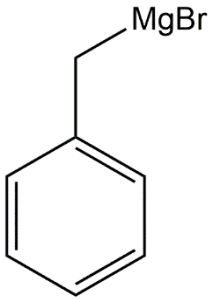

Table 23: Synthesis parameters for benzylmagnesium bromide.

parameter	**value**	
Mg turnings	coarse	fine
solvent	THF	
halide and concentration	(bromomethyl)benzene, 0.7 mol L^{-1}	
thermostat temperature	35 °C	
flow rate	2 mL min^{-1} for semi-batch and continuous lab scale 74 mL min^{-1} for continuous pilot scale	

Exemplary temperature profiles for the synthesis of benzylmagnesium bromide are displayed within chapter 2 of the ESI.

Table 24: Conversion and selectivity for benzylmagnesium bromide synthesis.

	Mg turnings	pump	conversion / %	selectivity / %		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	41	5	56
	fine	syringe pump	100	50	5	49
continuous lab scale	coarse	syringe pump	100	71	12	17
	coarse	micro annular gear pump	100	63	14	22
	coarse[1]	micro annular gear pump	100	94	0	6
	fine	micro annular gear pump	100	74	18	8
continuous pilot scale	coarse	micro annular gear pump	100	97	0	3

[1] Thermostat temperature: 60 °C & 25 °C instead of 35 °C.

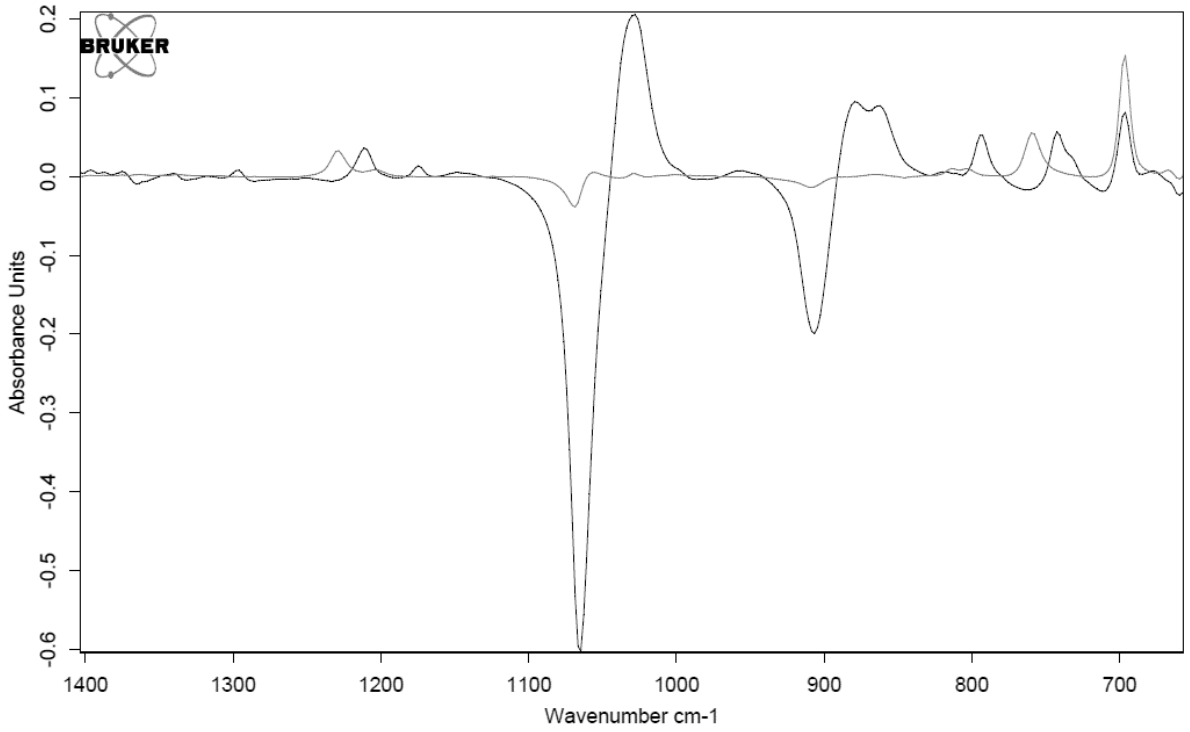

Figure 14: Infrared spectrum of benzylmagnesium bromide (black) and (bromomethyl)benzene (grey) in THF.

1.11 Benzylmagnesium chloride **11**

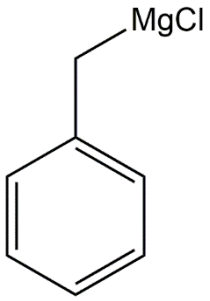

Table 25: Synthesis parameters for benzylmagnesium chloride.

parameter	**value**	
Mg turnings	coarse	fine
solvent	THF	
halide and concentration	(chloromethyl)benzene, 1.0 mol L^{-1}	
thermostat temperature	15 °C	
flow rate	1 mL min^{-1}	

Table 26: Conversion and selectivity for benzylmagnesium chloride synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	71	2	26
	fine	syringe pump	100	77	3	25
continuous lab scale	coarse	syringe pump	100	84	6	8
	fine	micro annular gear pump	100	90	4	6

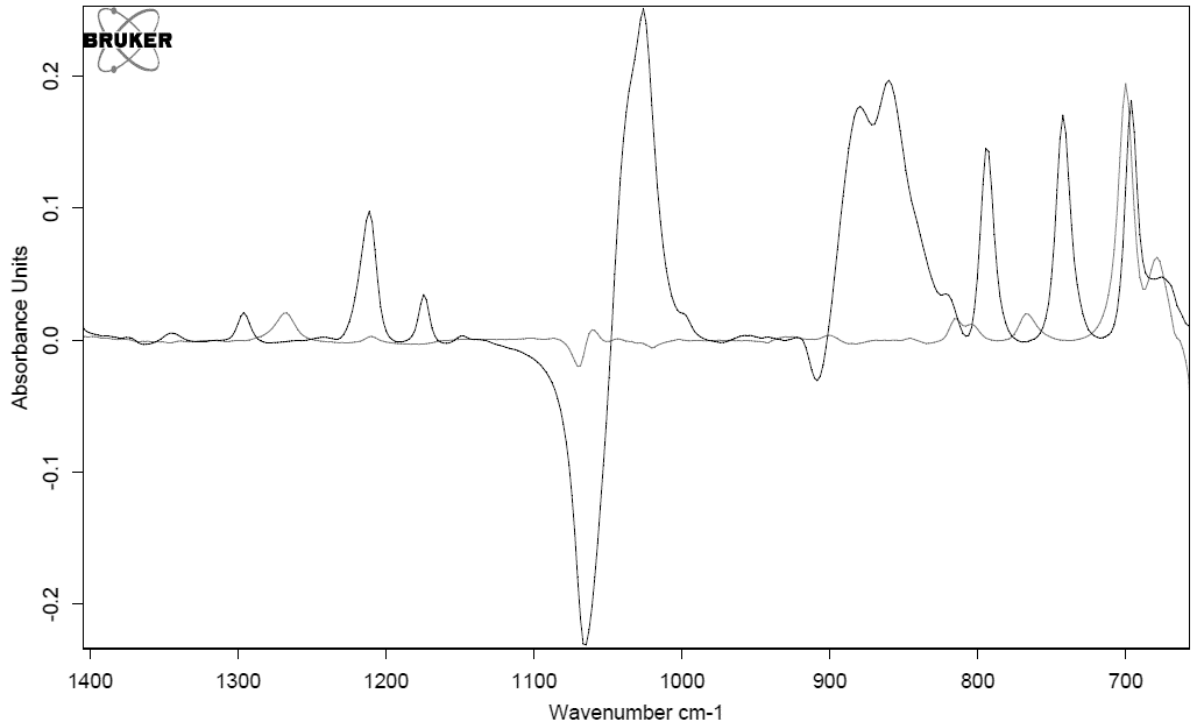

Figure 15: Infrared spectrum of benzylmagnesium chloride (black) and (chloromethyl)benzene (grey) in THF.

1.12 4-Fluorophenylmagnesium bromide **12**

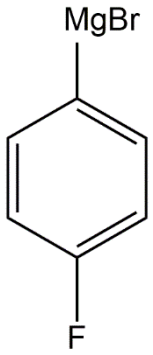

Table 27: Synthesis parameter for 4-fluorophenylmagnesium bromide.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	1-bromo-4-fluorobenzene, 1.0 mol L^{-1}
thermostat temperature	30 °C
flow rate	2 mL min^{-1} for semi-batch and continuous lab scale 74 mL min^{-1} for continuous pilot scale

Table 28: Conversion and selectivity for 4-fluorophenylmagnesium bromide synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	95	0	1
continuous lab scale	coarse	syringe pump	100	94	0	1
	fine	micro annular gear pump	100	90	3	2
continuous pilot scale	coarse	micro annular gear pump	100	98	1	1

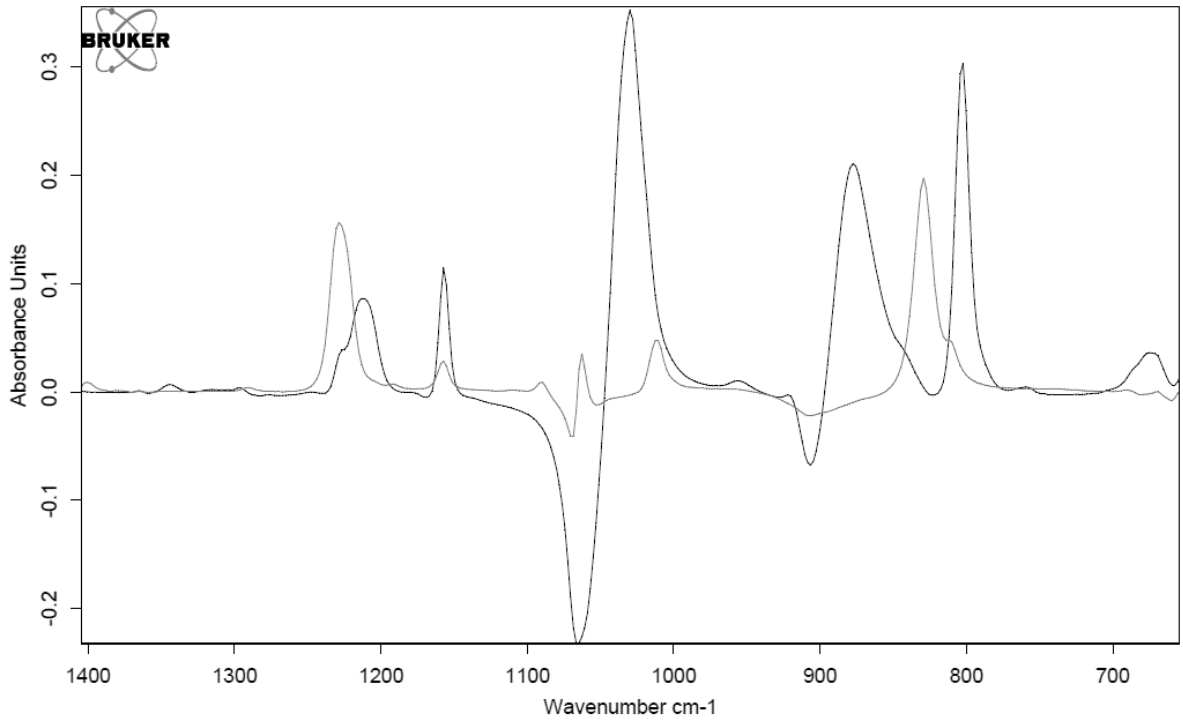

Figure 16: Infrared spectrum of 4-fluorophenylmagnesium bromide (black) and 1-bromo-4-fluorobenzene (grey) in THF.

1.13 4-Methoxyphenylmagnesium bromide **13**

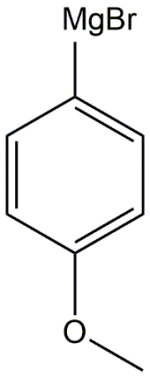

Table 29: Synthesis parameter for 4-methoxyphenylmagnesium bromide.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	1-bromo-4-methoxybenzene, 0.5 mol L^{-1}
thermostat temperature	35 °C
flow rate	4 mL min^{-1} for semi-batch and continuous lab scale 148 mL min^{-1} for continuous pilot scale

Table 30: Conversion and selectivity for 4-methoxyphenylmagnesium bromide synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	74	0	n.a.
	fine	syringe pump	100	82	1	n.a.
continuous lab scale	coarse	syringe pump	100	78	4	n.a.
		micro annular gear pump	100	75	5	n.a.
	fine	micro annular gear pump	100	89	0	n.a.
continuous pilot scale	coarse	micro annular gear pump	100	91	2	n.a.

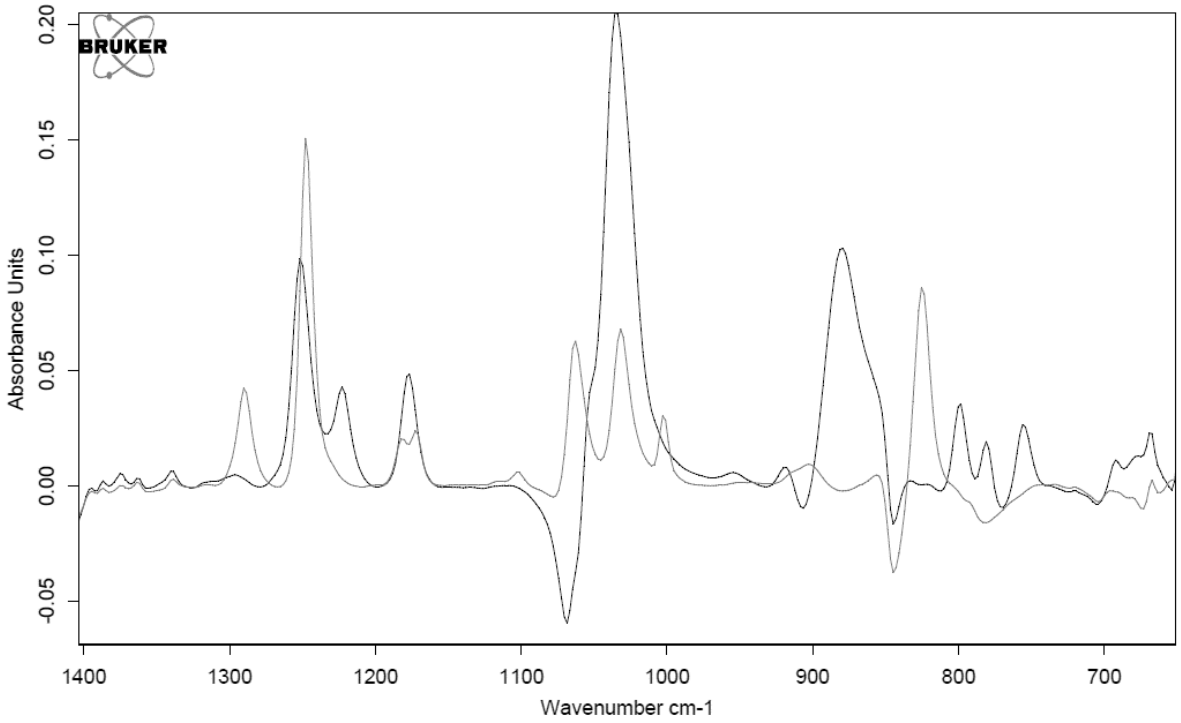

Figure 17: Infrared spectrum of 4-methoxyphenylmagnesium bromide (black) and 1-bromo-4-methoxybenzene (grey) in THF.

1.14 4-Methylphenylmagnesium bromide **14**

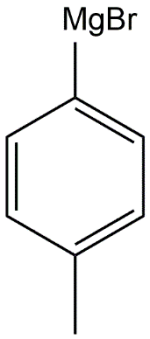

Table 31: Synthesis parameters for 4-methylphenylmagnesium bromide.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	1-bromo-4-methylbenzene, 1.0 mol L^{-1}
thermostat temperature	35 °C
flow rate	2 mL min^{-1}

Table 32: Conversion and selectivity of 4-methylphenylmagnesium bromide synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	95	n.a.	0
continuous lab scale	coarse	syringe pump	100	99	n.a.	2

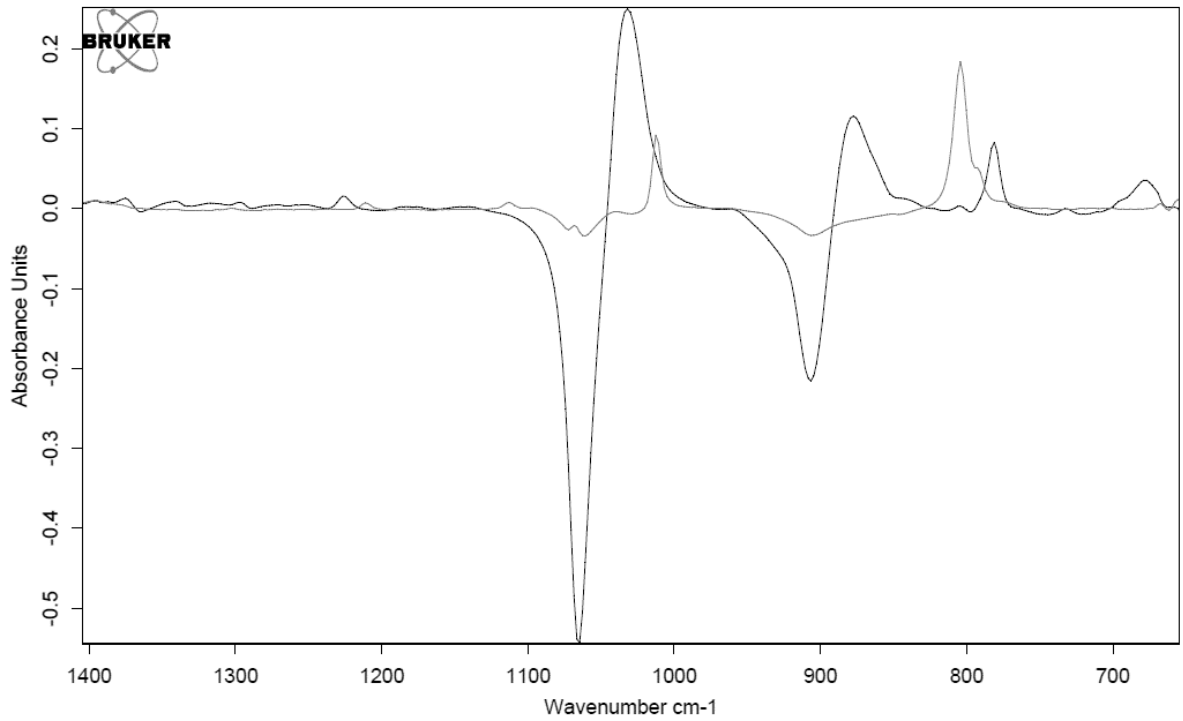

Figure 18: Infrared spectrum of 4-methylphenylmagnesium bromide (black) and 1-bromo-4-methylbenzene (grey) in THF.

1.15 Phenylmagnesium bromide **15**

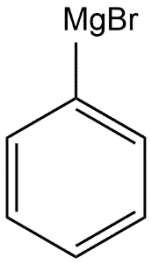

Table 33: Synthesis parameters for phenylmagnesium bromide.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	bromobenzene, 1.0 mol L^{-1}
thermostat temperature	35 °C for semi-batch and continuous lab scale continuous pilot scale: 1 module 35 °C 2 and 4 modules: 35 °C, 25 °C
flow rate	2 mL/min for semi-batch and continuous lab scale continuous pilot scale: 1 module mL min^{-1} 2 modules 74 mL min^{-1} or 100 mL min^{-1} 4 modules 200 mL min^{-1}

Table 34: Conversion and selectivity of phenylmagnesium bromide synthesis.

		Mg turnings	pump	conversion / %	selectivity / %		
					Grignard reagent	alcohol	Wurtz
semi-batch lab scale		coarse	syringe pump	100	99	0	1
continuous lab scale		coarse	syringe pump	100	96	0	1
		coarse	micro annular gear pump	100	92	1	3
continuous pilot scale	1 module	coarse	micro annular gear pump	100	99	0	0
	2 modules[2]	coarse	micro annular gear pump	100	99	0	0
	2 modules[3]	coarse	micro annular gear pump	100	99	0	0
	4 modules	coarse	micro annular gear pump	100	99	0	0

[2] Flow rate = 74 mL min^{-1}.

[3] Flow rate = 100 mL min^{-1}.

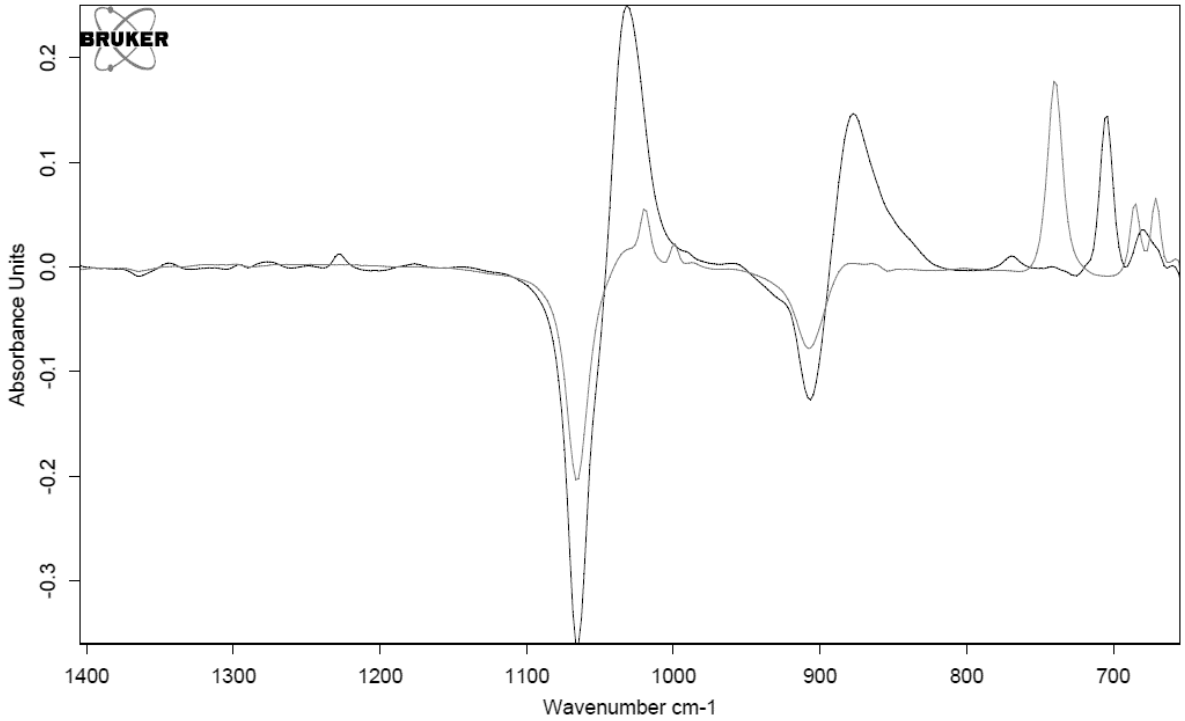

Figure 19: Infrared spectrum of phenylmagnesium bromide (black) and bromobenzene (grey) in THF.

1.16 2-Thienylmagnesium bromide **16**

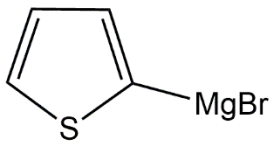

Table 35: Synthesis parameter for 2-thienylmagnesium bromide.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	2-bromothiophene, 1.0 mol L^{-1}
thermostat temperature	20 °C
flow rate	2 mL min^{-1}

Table 36: Conversion and selectivity for 2-thienylmagnesium bromide synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	97	n.a.	1
continuous lab scale	coarse	syringe pump	100	96	n.a.	0

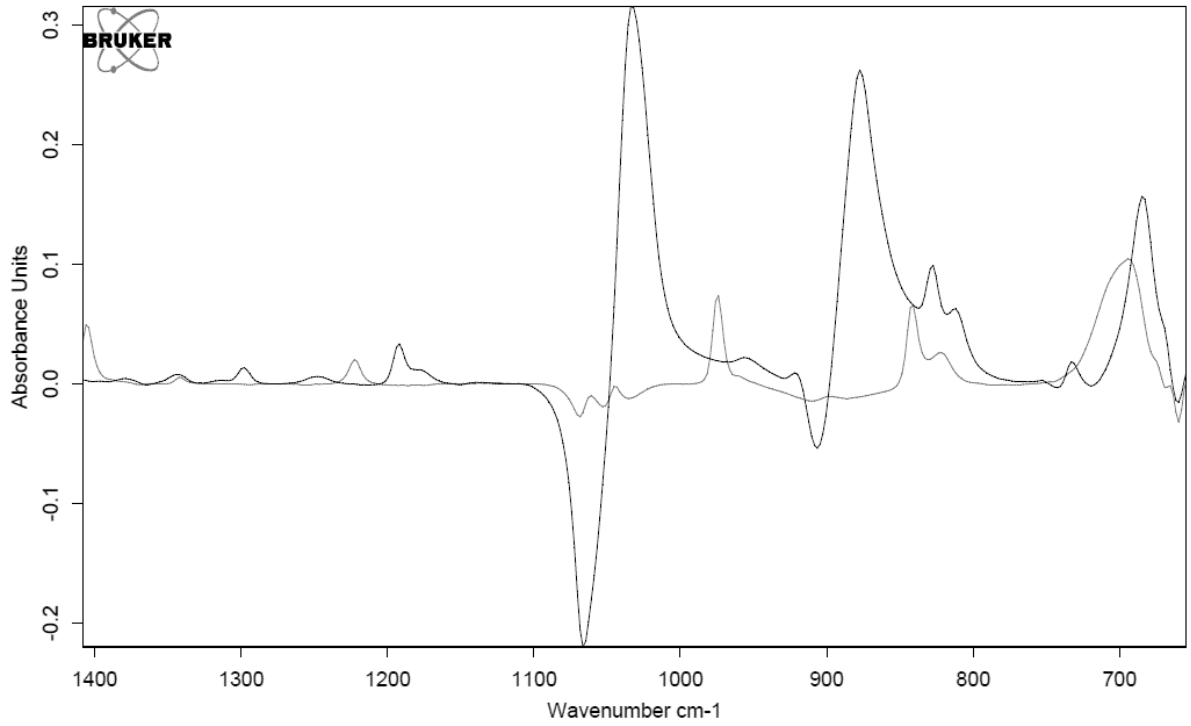

Figure 20: Infrared spectrum of 2-thienylmagnesium bromide (black) and 2-bromothiophene (grey) in THF.

1.17 2,4,6-Trimethylphenylmagnesium bromide **17**

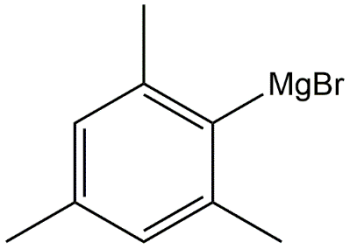

Table 37: Synthesis parameters for 2,4,6-trimethylphenylmagnesium bromide.

parameter	**value**
Mg turnings	coarse
solvent	THF
halide and concentration	2-bromo-1,3,5-trimethylbenzene, 1.0 mol L^{-1}
thermostat temperature	40 °C
flow rate	2 mL min^{-1}

Table 38: Conversion and selectivity for 2,4,6-trimethylphenylmagnesium bromide synthesis.

	Mg turnings	**pump**	**conversion / %**	**selectivity / %**		
				Grignard reagent	alcohol	Wurtz
semi-batch lab scale	coarse	syringe pump	100	91	n.a.	n.a.
continuous lab scale	coarse	syringe pump	100	96	n.a.	n.a.

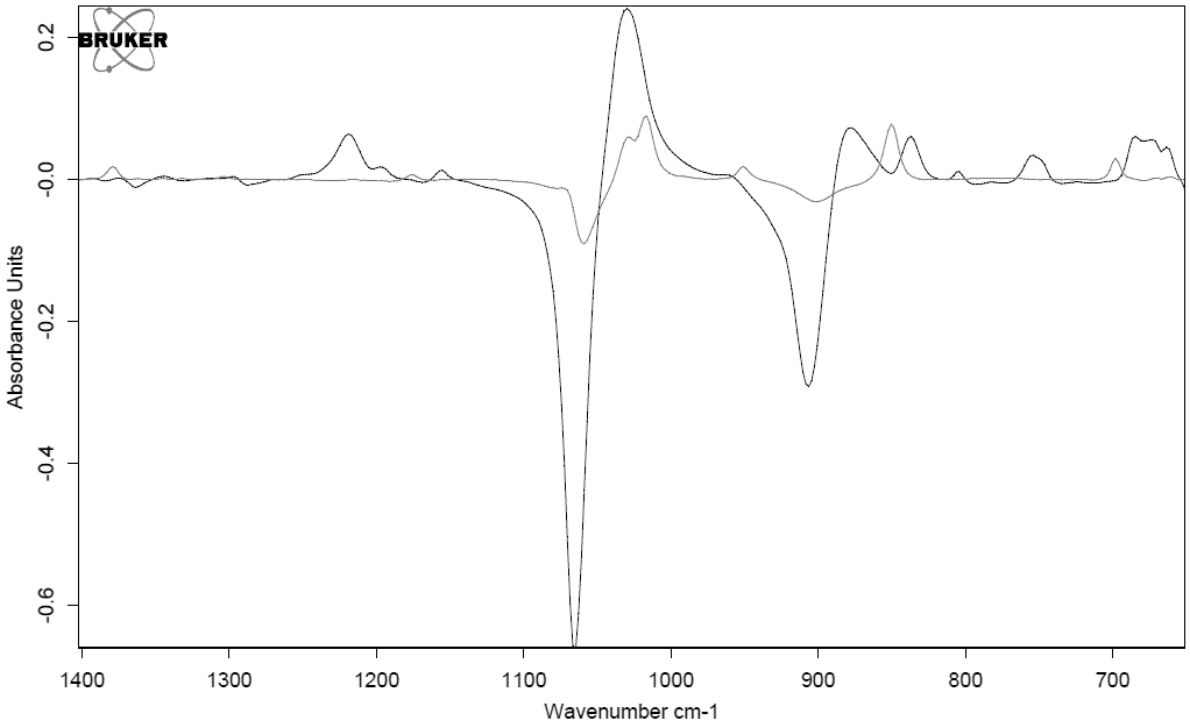

Figure 21: Infrared spectrum of 2,4,6-trimethylphenylmagnesium bromide (black) and 2-bromo-1,3,5-trimethylbenzene (grey) in THF.

2 Exemplary temperature profiles for benzylmagnesium bromide synthesis

The temperature profiles for the synthesis of benzylmagnesium bromide on continuous lab and pilot scale are displayed in figures 22-24. Temperatures are measured along the magnesium bed with temperature T1 (continuous lab scale) or M1U (continuous pilot scale) being close to the specific reactor inlet and temperature T4 (continuous lab scale) and M2O (continuous pilot scale) being close to the reactor outlet.

For pilot scale, the displayed temperature values for M1U (module 1 bottom), M1O (module 1 top), M2U (module 2 bottom) and M2O (module 2 top) are mean values of six temperatures each.

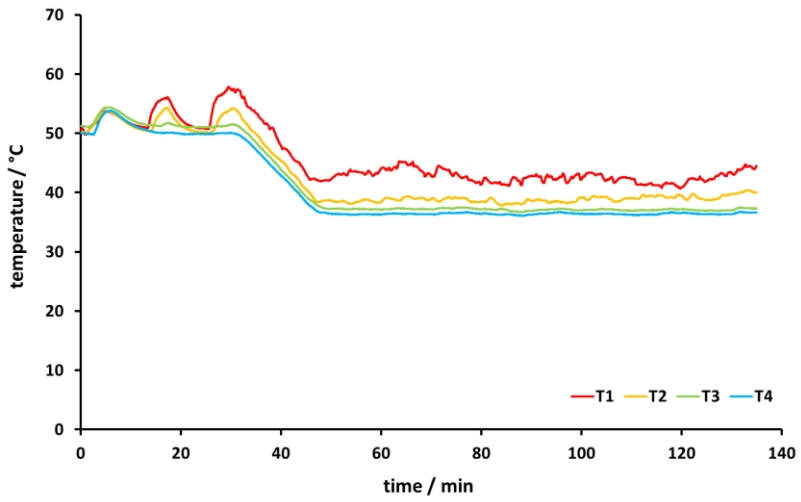

Figure 22: Temperature profile of continuous lab scale synthesis of benzylmagnesium bromide.

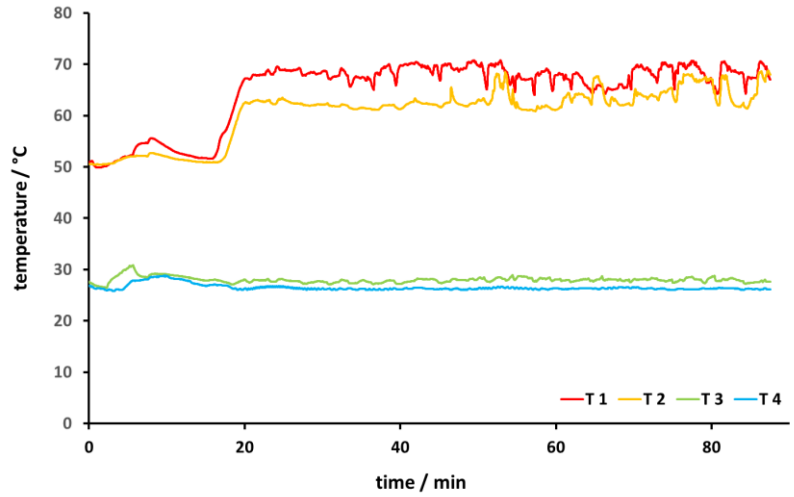

Figure 23: Temperature profile of continuous lab scale synthesis of benzylmagnesium bromide at elevated thermostat temperature.

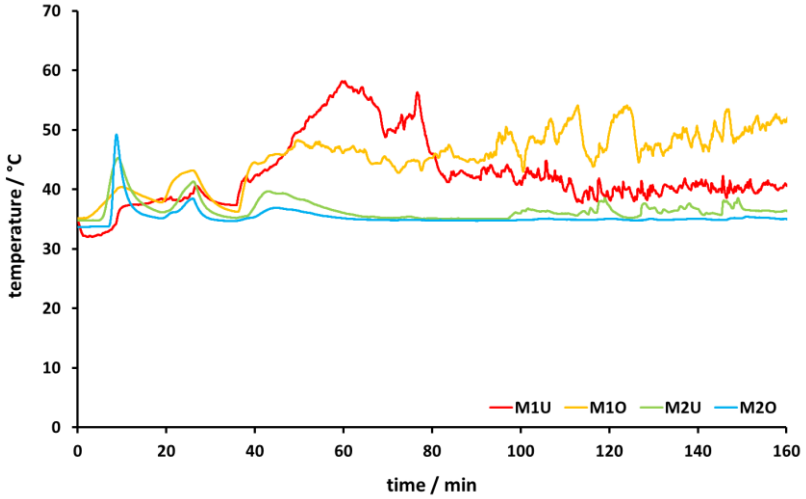

Figure 24: Temperature profile of continuous pilot scale synthesis of benzylmagnesium bromide.