



Selective monosubstitution on a trichlorosilane with highly reactive organolithium compounds in a microflow reactor

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Abstract

Organolithium compounds have been used successfully in flow chemistry since the recent past. Most of the studies dealt with the use in halogen-lithium exchanges. So far, however, there has been a lack of use in substitution reactions. The use of flow microreactors makes the highly reactive organolithium compounds more controllable and thus creates new synthetic possibilities.

Keywords Organosilanes · Substitutions · Selectivity · Microreactor · Continuous flow

Introduction

Chlorosilanes are probably the most commonly used starting materials for the preparation of organosilanes in preparative chemistry. This is especially due to their good availability on a large scale via the Müller-Rochow synthesis and their high reactivity towards electrophiles. **1** However, there is a problem of unwanted and uncontrolled multiple substitution of multiple chlorinated silicon compounds, which is particularly evident for highly reactive nucleophiles like Grignard reagents or lithium alkyls, to name a few. **2** The cause of this problem has not yet been fully clarified, but there are many indications of an extremely fast reaction and very low activation barriers. **3**.

So far, this problem has been avoided by low reaction temperatures, excess of halosilanes and the use of more unreactive or sterically demanding reagents. **4** Another step towards a controllable synthesis of special organosilanes *via* the reaction of chlorosilanes with organolithium compounds

is to consider the importance of fast mixing to achieve a better control on the fast reaction time. In a conventional batch system, this must be questioned as the multiple substitution observed could be caused by inhomogeneous mixing. However, it should be kept in mind that complete mixing at the molecular level may not be possible at all. Due to the aggregation of the lithium alkyls **5**, theoretically, there is always a local excess of organolithium reagent, even with equimolar amounts to the halosilane. The influence of the aggregation of lithium alkyls on the selectivity of the reaction has not yet been resolved.

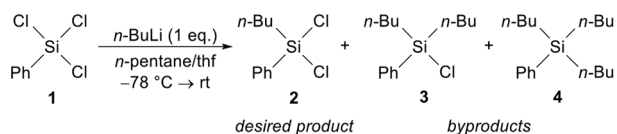
Results and Discussion

We want to present our latest results on the selective monosubstitution of trichlorophenylsilane (**1**) with *n*-butyllithium in a microflow reactor. Flow chemistry has shown great success and advantages in the application for halogen-lithium exchanges and other reaction types. **6** However, an application for substitution reactions has so far rarely been found in the literature, although there should be a great potential in this area. Therefore, we want to explore the potential of flow chemistry for substitution reactions with highly reactive reagents in order to obtain high selectivity and conversion even under mild conditions. Flow chemistry offers a multitude of advantages such as more efficient and faster mixing, better heat dissipation and a more resource-efficient and safe reaction management.

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Scheme 1 Undesired multiple substitution using the chosen model system of the reaction of trichlorophenylsilane (**1**) with *n*-butyllithium.

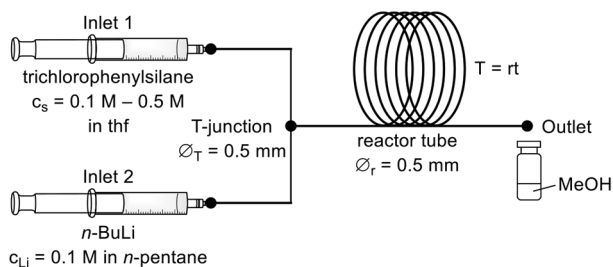


Fig. 1 Flow reactor setup for the substitution of trichlorophenylsilane (**1**) with *n*-BuLi.

In order to be able to recognize a possible improvement in the selectivity regarding the mono substitution under flow conditions compared to a conventional batch system, the reaction in the flask was first carried out at low temperatures of $-78\text{ }^\circ\text{C}$ (Table 1). There was a considerable difference whether the reaction is carried out in *n*-pentane or thf. Under the same conditions, much higher selectivity towards the monosubstituted product **2** can be obtained in a non-polar solvent such as *n*-pentane (61%). Considering the aggregation behaviour of lithium alkyls in dependence of the solvent, it seems reasonable that a molecule of **1** exists among a hexameric aggregate of *n*-butyllithium in pentane or a tetrameric aggregate in thf solution. Despite these local excess concentrations of lithium alkyls, selective mono substitution should generally be possible as the experimental results indicate (Table 1). Nonetheless, this also underlines the importance of a fast mixing, especially for polar solvents, in order to avoid multiple substitutions and reach high selectivities under mild conditions.

The flow reaction was carried out under ambient conditions using syringe pumps for each reactant, i.e. chlorosilane in thf and *n*-butyllithium in *n*-hexane/*n*-pentane. A T-junction with an inner diameter of 0.5 mm was employed in order to mix the reactants before they were led into the microreactor. The microreactor consisted of an FEP tube with 0.5 mm inner diameter that was coiled around a support

structure with 90° bends (coiled flow inverter) in order to narrow the residence time distribution (RTD) and enhance radial mixing due to emerging Dean vortices. **7** The FEP tube was 550 mm long and the total volumetric flow rate varied in the range of $9\text{--}50\text{ ml}\cdot\text{min}^{-1}$. At the outlet, samples were taken with vials containing methanol in order to stop the reaction and allow an easier analysis of the chlorosilanes as the respective methoxy silanes by means of GC/EI-MS and NMR. A scheme of the microfluidic structure is shown in Fig. 1.

Since the reaction is highly sensitive towards oxygen and moisture, the reactants were stored in flasks that were continuously flushed with argon before being manually drawn into the syringes. In addition, the FEP tubes were rinsed with diethyl ether (dried over sodium) before each set of experiments in order to remove possible moisture deposits from the ambient air. Oxygen- and moisture-free equipment is crucial to avoid side reactions and the formation of solids that could clog the microreactor. The problem of solid lithium chloride formation from the main reaction was avoided by using low reactant concentrations and keeping the amount of solid in a range that dissolves in the solvent: $c_{n\text{-BuLi}} = 0.1\text{--}0.2\text{ M}$ and $c_{\text{Silane}} = 0.1\text{--}0.6\text{ M}$. Each operating point was sampled three times in order to ensure the reproducibility of the experimental results.

In order to investigate the influence of the flow rate on selectivity and conversion a set of experiments with varying total flow rates was carried out. If mixing was already completed in the T-junction, no effect of flow rate (and residence time) on conversion and selectivity should be observed, provided that the reaction is close to equilibrium at the outlet of the T-junction for the investigated residence times. The corresponding residence times for each run are summarized in the Supporting Information. This behavior can be seen in Fig. 2 for initial reactant concentrations of 0.2 M. It can be concluded that the T-junction is suitable as a mixing element for the examined operating conditions and the mixing occurs within a few milliseconds. Since the molar proportions of the reactants and products have not changed at different flow rates, it can also be concluded that the reaction takes place on a similar time scale of very few milliseconds. The behavior shown in Fig. 2 could not be observed in preliminary tests with a T-junction with an adjacent straight tube and an inner diameter of 1.25 mm. At low flow rates, the conversion of chlorosilane decreased and more disubstituted and even trisubstituted product was formed, indicating

Table 1 Product distribution of the reaction of trichlorophenylsilane (**1**) and *n*butyllithium in a conventional batch system ($-78\text{ }^\circ\text{C}$ to rt, 20 h). *The conversion *X* is calculated from the remaining amount of **1** ($X = 100\% - 1$); the selectivity *S* is calculated as the formed amount of **2** among all formed products **2–4**. For more details see the Supporting Information.

#	solvent	2 [%]	3 [%]	4 [%]	<i>X</i> * [%]	<i>S</i> * [%]
1	<i>n</i> -pentane	47	30	0	77	61
2	thf	10	37	9	56	18

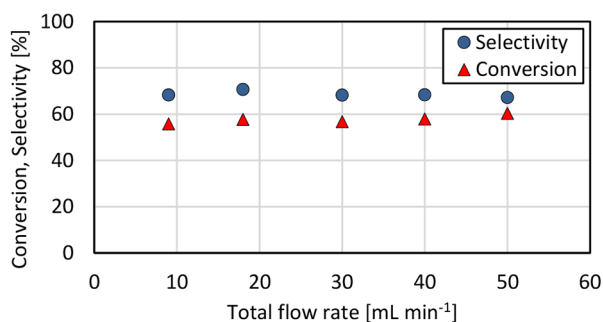


Fig. 2 Conversion of trichlorophenylsilane (**1**) and selectivity of *n*-butyllithium towards monosubstituted product **2** over total flow rates (thf, rt). The respective residence times for each run are summarized in the Supporting Information.

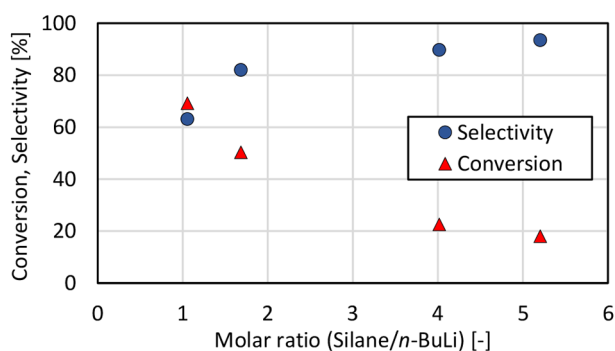


Fig. 3 Conversion of trichlorophenylsilane (**1**) and selectivity of *n*-butyllithium towards monosubstituted product **2** over initial ratio of **1** and *n*-butyllithium (thf, rt).

poor mixing. This shows the importance of a suitable mixing unit for optimizing the selectivity towards the monosubstituted product. As the reaction is so fast, the impact of the RTD properties of the microreactor decreases while other advantages such as heat transfer and safety aspects should be prioritized.

To draw conclusions regarding the kinetics and the reaction mechanism, the selectivity of *n*-butyllithium towards the monosubstituted product was optimized in another set of experiments by changing the molar ratio of the reactants. The concentration of *n*-butyllithium was set to 0.1 M (solved in *n*-pentane) and the concentration of chlorosilane to 0.1 M, 0.2 M, 0.4 M and 0.6 M (solved in thf). The results regarding the conversion of chlorosilane **1** and the selectivity of *n*-butyllithium are shown in Fig. 3 for a total flow rate of 18 ml·min⁻¹ and a total residence time of 3.6 ms.

Note that the depicted molar ratios were calculated from the analysis via GC-EIMS/NMR assuming a complete conversion of *n*-butyllithium and can deviate from the initially set concentrations. This deviation might come from the volatility of the solvents required to prepare the reactant solutions, minor inaccuracies of the analytics and

volumetric flow rates of the pumps. Regardless of this, it is observed that a selectivity of 63% can be obtained at equimolar ratios. Thus, performing the substitution in a micro-flow reactor gives access to similar selectivity compared to a conventional batch system with the major advantage of much milder conditions.

In addition, the polarity of the solvent in flow does not seem to have any influence on the product distribution, since a selectivity of 63% can also be obtained if both reactants are solved in thf. By changing the solvent of *n*-butyllithium from *n*-pentane to thf, a change in the *n*-BuLi aggregation towards smaller aggregates is also to be expected. Since the change of solvent did not result in any change in the selectivity, another hint to a subordinate role of the aggregation of the lithium alkyls in the uncontrolled multiple substitution on chlorosilanes is given. Furthermore, the selectivity can be increased to 93% with a higher molar ratio of chlorosilane to *n*-butyllithium at the expense of less conversion of chlorosilane **1**. This result does not seem surprising when considering conventional reaction systems since more chlorosilane obviously favours the formation of monosubstituted product. However, the flow chemistry makes the reaction much more resource-efficient, since it is easier to separate and recycle the starting material and byproducts than it is in a batch system. In addition, the use of flow chemistry allows the reaction to be carried out at room temperature, whereas conventional batch systems can only achieve the same efficiency at very low temperatures of usually $-78\text{ }^{\circ}\text{C}$.

It could also be observed that in the concentration range of $c_{\text{Silane}} = 0.1\text{--}0.6\text{ M}$ and $c_{n\text{-BuLi}} = 0.1\text{ M}$ the concentration profiles of **1**, **2** and **3** can be well described with a reaction order of 2 or 3 and a 1.47 times higher reaction rate constant k_1 (formation of the monosubstituted product **2**) to the reaction rate constant k_2 (formation of the disubstituted product **3**), suggesting a lower activation energy for the formation of the disubstituted product **3** compared to the monosubstituted product **2**. More information regarding the formation of the trisubstituted product **4**, i.e. experiments with an excess of *n*-butyllithium, is required in order to draw a clearer picture of the ongoing processes, which will be subject of future work.

Utilizing flow chemistry for the investigated selective mono substitution reaction of polychlorinated silanes with lithium alkyls shows a good example for the usefulness of water and oxygen free flow chemistry in organometallic applications. The necessity of low reactions temperatures of the usual $-78\text{ }^{\circ}\text{C}$ in a traditional batch system to gain high selectivity has shown to be avoided by usage of flow microreactor systems. Not only does it enable to conduct lithium chemistry at ambient conditions, but it also allows for highly selective reactions reducing the effort in downstream processing significantly. Mixing was found to be the

key process to achieve high selectivity towards the mono-substituted product while further improvement was made by adjusting molar ratios of the reactants. The generation of trisubstituted product could successfully be inhibited in all experiments. By reducing the amount of polysubstituted products, the crucial separation steps are reduced to the separation of chlorosilane and monosubstituted chlorosilane. The aggregation of lithium alkyls seems to play a subordinate role in the investigated reaction system as no influence on selectivity by changing the solvent was observed. It could also be observed that in the investigated concentration range the concentration gradient over the time can be described well with a reaction order of 2 or 3 and a ratio of the reaction rate constants of 1:0.67. Further clear conclusions regarding kinetics and reaction mechanism were not possible at this point and will be investigated in future work.

It is evident that flow chemistry with its inherent advantages in terms of mixing and heat transfer gives new impulses to organometallic chemistry and provides several benefits that wait to be exploited.

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Code Availability Not applicable.

Declarations

Conflicts of interest / competing interests The authors declare that they have no known conflicts of interest or competing interests.

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