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The direct access to alkenes from HF_2C- or Cl_3C-substituted arenes and an organo sodium reagent

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The investigation of an organo sodium reagent with starting materials, such as aryl–CH_{3-n}(Hal)$_n$ led to an unprecedented alkene synthesis for n = 2 (Hal = F) and for n = 3 (Hal = Cl), while the trifluoromethyl group n = 3 (Hal = F) proved to be inert under the identical reaction conditions. The alkene synthesis could be realised for a range of substrates bearing other functional groups that exhibit low reactivities towards organo sodium reagents.

Reagents with alkali metal carbon bonds, such as in alkyl lithium or alkyl sodium species, are among the most reactive nucleophiles utilised broadly in organic synthesis. Alkyl lithium reagents are in use in organic synthesis and methodology for decades whereas alkyl sodium reagents are far less explored and are far less involved in synthetic methodologies. This large discrepancy is largely based on the much lower stability and higher reactivity of alkyl sodium reagents compared to the corresponding alkyl lithium reagents. Significant improvements have been reported by *Hevia*, *Asako*, *Takai* and others for the stabilisation of various types of alkyl sodium reagents by nitrogen-containing ligands, such as TMEDA (N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine) and Me_5tren (N^1-(2-(dimethyl-lamino)ethyl)-N^1,N^2,N^2-trimethyl-ethane-1,2-diamine), for applications in batch synthesis (Scheme 1).[1,2]

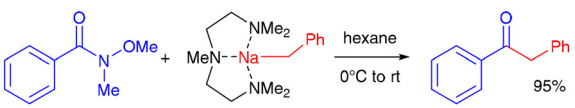
As an example, the freshly prepared, ligand-stabilized benzyl sodium reagents can be reacted with *Weinreb* amides for the efficient synthesis of ketones in a batch-type transformation.

To circumvent the use of complex amines for the stabilisation of alkyl sodium reagents, the use of a flow reactor allows the generation of such highly reactive alkyl sodium reagents *in situ*. The *Knochel* group pioneered in this respect and in a number of outstanding reports this approach for the synthesis of alkyl sodium reagents and their transformations in organic synthesis were described.[3] Therein, the use of a flow reactor, where the reactive species are formed over a defined period of time, which is controlled by the flow rate through a flow bed reactor, is of high importance (Scheme 2). These highly reactive sodium reagents, such as **2**, are generated from a simple alkyl chloride precursor (*e.g.* **1**), and then brought to reaction with electrophiles, such as epoxides or oxetanes,[4] or the sodium reagents are reacted with (hetero)aryl bromides for Br–Na exchange reactions or for the direct deprotonation of arenes (= sodiation) to name a few possible follow-up transformations.[5]

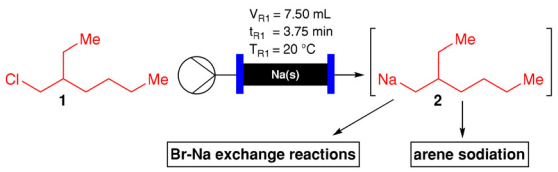
In this report, we describe the transformations of alkyl sodium reagent **2** which is generated in a flow bed reactor with starting materials bearing multiple benzylic halide bonds.[6]

The CF_3 group is inert towards many reagents, and no reaction was observed when the alkyl sodium reagent **2** was added to Ph–CF_3 (see Table 1, entry 1). Therefore, we investigated the transformation of **2** with Ph–CCl_3 in *n*-hexane at room temperature for 16 hours reaction time (Scheme 3) and the results of this investigation are described below.

After aqueous work-up we identified the alkene **4a** ($E:Z$ = >95 : <5) as product formed in the transformation (11%, Table 1, entry 4) alongside a large amount of the Wurtz-type



Scheme 1 Ketone synthesis from a Weinreb amides and a benzyl sodium reagent in a batch reaction.



Scheme 2 Generation of an organo sodium reagent in a flow reactor and follow-up transformations.

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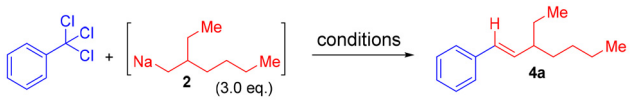
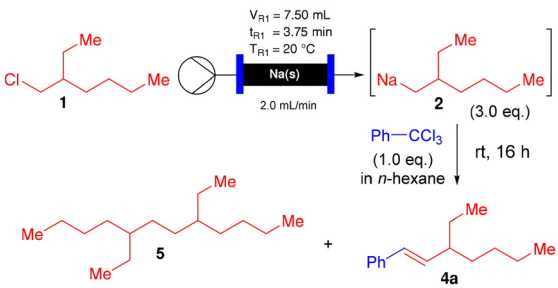
Table 1 Optimisation of the alkene synthesis of the organo sodium reagent **2** with (trichloromethyl)benzene



Entry	Conditions[a]	Yield[b]
1	Ph–CF_3 as starting material[c]	0%
2	−78 °C[c]	7%
3	0 °C[c]	12%
4	rt (= 20 °C)[c]	11%
5	50 °C[c]	11%
6	No TMEDA additive, rt	33%
7	2.0 eq. of **2**	22%
8	3.0 eq. of **2**	33%
9	3.5 eq. of **2**	43%
10	6.0 eq. of **2**	37%
11	THF as solvent	13%
12	With molecular sieves 4 Å	40%
13	With NaH (1.0 eq.) as base	36%
14	With 2,6-lutidine (1.0 eq.) as base	36%
15	With $BF_3{\cdot}OEt_2$ (0.5 eq.)	43%
16	1,2-Dimethoxyethane as solvent	20%
17	1.0 mL min^{-1} flow rate	40%
18	Less concentrated (10 mL) *n*-hexane	38%
19	Higher concentrated (1 mL) *n*-hexane	39%
20	Inversed addition of $PhCCl_3$ at 20 °C	36%
21	**2** cooled to 0 °C then addition of $PhCCl_3$	44%
22	**2** cooled to −78 °C then addition of $PhCCl_3$	51%

[a] Other reaction conditions: $PhCCl_3$ (0.5 mmol), *n*-hexane (3 mL), N_2 atm., rt, 16 h. [b] Determined by GC analysis of the crude mixture with mesitylene as internal standard added after the reaction. [c] TMEDA (1.1 eq.) were added.

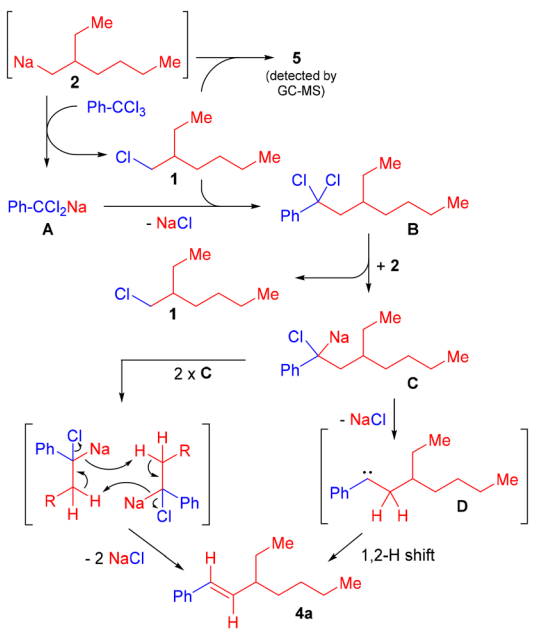


Scheme 3 Reaction of $PhCCl_3$ with the organo sodium reagent **1** generated in a flow reactor.

coupling product **5** as well as the starting material **1** (detected by GC-MS analysis) and some side-products formed in minor amounts. This unusual transformation of a benzylic CCl_3 group towards an alkene caused us to optimise this reaction with the alkyl sodium reagent **2** to minimize the amount of the Wurtz-type side-product **5** and to increase the yield of the desired alkene **4a**. The results of this investigation are summarized in Table 1.

As can be seen from Table 1, the modification of the reaction temperature had rather limited influence on the performance of the formation of **4a** (entries 2–5) so that the following optimisation efforts were performed at room temperature. When the amount of the alkyl sodium reagent **2** was increased up to 3.5 equivalents with respect to the Ph–CCl_3 starting material, a steady increase in the yield of **4a** (detected by GC analysis) was observed. However, a further increase of the amount of **2** to 6.0 eq. resulted in no further increase in the yield of **4a**. Accordingly, the optimization was continued with 3.5 eq. of **2** at room temperature. The change of the solvent towards THF (entry 11), the addition molecular sieves or bases (entries 12–14), nor the addition of a *Lewis* acid (entry 15) were ground-breaking to increase the yield of **4a**. Also 1,2-dimethoxyethane as solvent did not influence the yield of **4a** significantly (entry 16). The reduction of the flow rate (entry 17) as well as the modification of the concentration of the $PhCCl_3$ in *n*-hexane (entries 18/19) had also little effect on the yield of **4a** and we finalized our attempt to optimize the yield of **4a** by inverse addition at different temperatures (entries 20–22), but to no avail. Unfortunately, we could not identify reaction conditions where the alkene **4a** was formed in good to very good yields and the Wurtz byproduct **5** could be suppressed.

From a mechanistic point of view, the reaction of **2** with Ph–CCl_3 could proceeds *via* a Cl–Na exchange reaction to afford a carbenoid-type intermediate [**A** = Ph–CCl_2Na] and regenerate the alkyl chloride starting material **1** (Scheme 4). These two compounds could then undergo a nucleophilic substitution to generate the carbon–carbon single bond in **B**. Upon the addition of another equivalent of **2**, another Cl–Na exchange seems to occur to generate a second carbenoide-type intermediate **C**. The formation of the final alkene **4a** could then proceed *via* an α-elimination of NaCl affording the carbene **D** and a 1,2-H-shift leading to the formation of the alkene **4a**.



Scheme 4 Proposed reaction mechanism for the formation of **4a** from **2** and (trichloromethyl)benzene.

Alternatively, an intermolecular reaction of two carbenoide-type intermediates (2 × **C**) can be envisaged, to realize the 1,2-hydrogen transfer. These assumptions have to be taken into account based on experiments with a deuterium-marked alkyl chloride **1-D$_2$** as well as the quenching of the reaction with D_2O are considered (see below).

(Difluoromethyl)benzene, unlike (fluoromethyl)benzene, is relatively affordable and was chosen as starting material for the transformation with the alkyl sodium reagent **2** (Scheme 5). The result of the first test reaction with (difluoromethyl)benzene was surprising, in that respect that again the alkene **4a** was formed as main product; albeit in higher yields (>50%) compared to the transformations with (trichloromethyl)benzene.[7]

We then performed an optimisation with respect to the equivalents of **2** needed and the reaction temperature to obtain **4a** in good yields. The results of these experiments are summarised in Table 2.

The results illustrate that also for this transformation towards **4a** the amount of **2** is decisive. The highest yield of **4a** (80%) was isolated when 5.0 equivalents of **2** were applied while the temperature of the addition had only a minimal effect on the yield of **4a**. Accordingly, we assumed that the other parameters investigated in Table 1 for the transformation of (trichloromethyl)benzene with **2** would behave similarly and decided not to run those experiments again. Although we identified 5.0 eq. of **2** to give the highest yield, we decided to reduce the amount of **2** to 3.5 eq. and perform the reactions of **2** with some other functionalised arenes bearing the CHF_2 group. The selection for the CHF_2-functionalised arenes were made with respect to the hitherto known reactivity of **2** towards functional groups and naturally, functional groups, such as carbonyl groups and other carbonyl derivatives in a broad sense were not considered at this point. The results of the transformations of **2** with those selected CHF_2-functionalised arenes are summarized in Scheme 6.

With 3.5 eq. of the organo sodium reagent **2** applied, the product **4a** could be isolated in 70% yield. Electron donation groups, such the methyl substituent in **4b** or the methoxy substituent in **4c** reduced the yield only slightly.

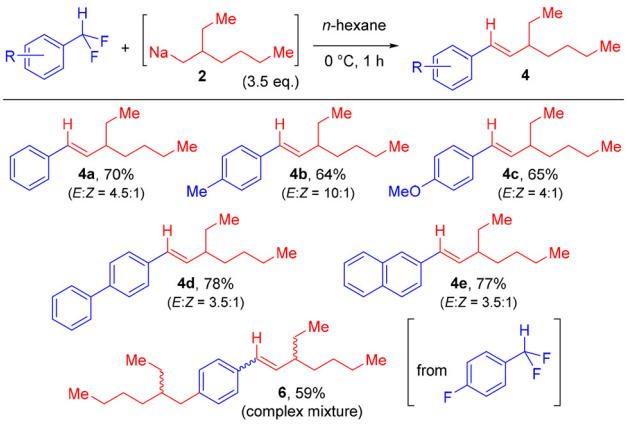
The difluoromethyl-substituted biphenyl derivative **4d** as well as the product **4e** bearing a naphthyl moiety could be isolated in reasonable 78% and 77% yield, respectively. When we applied (difluoromethyl)-4-fluorobenzene as starting material, we experienced an unusual result. The 4-fluoro substituent seems to have reacted with the organo sodium reagent **2**, resulting in the introduction of an additional alkyl substituent in **6**. The product **6** was isolated in 59% total yield as a mixture consisting of various stereoisomers.[8]

From a mechanistic point of view, it seems reasonable that the C–H acidity of the aryl–C**H**F$_2$ proton is enhanced and that a deprotonation with **2**, reacting as a strong base, is possible. Thereby a similar species to the Ph–CCl_2Na species **A** is formed alongside the corresponding alkane, which was detected by GCMS analysis. A carbon–carbon bond formation with the intermediate Ph–CF_2Na and **2** must therefore proceed *via* a carbene-type intermediate to form the intermediate **C′** (see Scheme 7).[9] Only if we assume that similar intermediates of type **C**/**C′** are formed the results of the deuterium-labelling experiments can be explained. Therefore, we prefer a concerted intermolecular reaction from **C** and **C′** realizing the hydrogen transfer/β-elimination process to afford the observed product **4a** in one step.

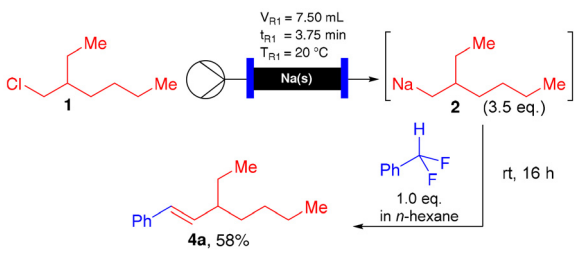
Table 2 Optimisation of the alkene synthesis of the organo sodium reagent **2** with (difluoromethyl)benzene

Entry	Conditions[a]	Yield[b]
1	2.5 eq. of **2**	53%
2	4.0 eq. of **2**	73%
3	4.5 eq. of **2**	74%
4	5.0 eq. of **2**	80%
5	0 °C	74%
6	−78 °C	75%
7	0 °C, 1 h	74%

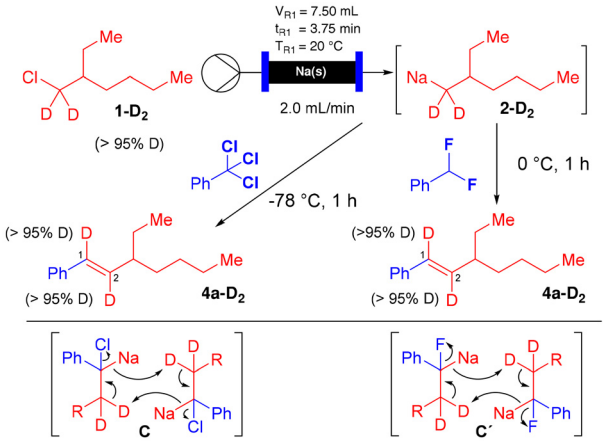
[a] Other reaction conditions: $PhCHF_2$ (0.5 mmol), *n*-hexane (3 mL), N_2 atm., rt, 16 h. [b] Determined by GC analysis of the crude mixture with mesitylene as internal standard, added after the reaction.



Scheme 6 Scope and limitation of the alkene synthesis of the organo sodium reagent **2** with (difluoromethyl)benzene derivatives.



Scheme 5 Application of (difluoromethyl)benzene with the organo sodium reagent **2** generated in a flow reactor.



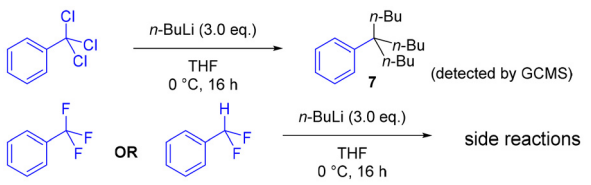
Scheme 7 Control experiments of (trichloromethyl)benzene and (difluoro-methyl)benzene with the deuterated version of the organo sodium reagent **2-D$_2$** for the synthesis of **4a-D$_2$**.

When the chlorinated starting material **1** for the synthesis of **2** was substituted with the dideuterated derivative (for the synthesis of the organo sodium reagent **2-D$_2$**), the corresponding dideuterated alkene **4a-D$_2$** was isolated in 45% yield from $PhCCl_3$ and in 65% yield from $PhCHF_2$, respectively (Scheme 7). By ^{1}H and ^{2}H NMR analysis the deuterium incorporation of >95% for the 1-position and >95% for the 2-position was observed when (difluoromethyl)-benzene was applied as starting material. The result that led to the mechanistic proposal is that the same reaction utilizing (trichloromethyl) benzene as starting material led to an almost identical ^{1}H and ^{2}H NMR with >95% deuterium incorporation for the 1-position and >95% for the 2-position.

On the other hand, when the non-deuterated organo sodium reagent **2** was reacted with (trichloromethyl)benzene and the mixture was quenched with D_2O, no deuterium incorporation in the resulting alkene **4a** was obtained.

This means that one deuterium atom in both cases migrates from the 2-position into the benzylic carbon at C1 and that no anionic intermediates are present when the reactions are quenched with H_2O or D_2O.

In comparison to the transformations with the organo sodium reagent **2**, the reactions with *n*-BuLi gave deviating results (Scheme 8). First, the transformation of $PhCCl_3$ with *n*-BuLi led to the alkane **7** instead of the alkene **4a** when reacted with **2**. Second, the application of (trifluoromethyl) benzene which was inert when reacting with **2** reacted with



Scheme 8 Comparison of the reported transformations utilising *n*-BuLi instead of **2**.

n-BuLi to a number of unidentified products (GCMS analysis). Third, also the transformation of (difluoromethyl)benzene with *n*-BuLi led to a number of products (GCMS analysis) did not lead to the alkene **4a** as was observed when the organo sodium reagent **2** was used. The steric hindrance of **2** is higher as in *n*-BuLi but it seems somewhat unlikely that this difference is crucial for the different reaction pathways of **2** and *n*-BuLi observed in this short study.

In summary, we have identified a reaction pathway from (trichloromethyl)benzene and more efficiently from (difluoromethyl)benzene and derivatives towards identical alkenes. The experiments with deuterium-labelled starting material **2** resulted in almost identical ^{1}H and ^{2}H NMR spectra which led us to the conclusion that similar reaction pathways are at work. The reactivity of the organo sodium reagent **2** towards many functional groups is known but the combination of the herein presented reactivity and the known transformation with additional functional groups could open up new pathways to access complex structures in such reaction utilizing organo sodium reagents.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6ob00838k.

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7 The higher homologues (tribromomethyl)benzene and (triiodomethyl)benzene were not investigated based on the high price for the bromo-derivative while the triiodomethyl-derivative seems not to be commercially available. Also, these compounds are rarely used as starting materials in organic synthesis. Therefore, we pointed our attention towards fluorinated toluene derivatives. For a reference concerning exchange reactions of $PhCCl_3$, see: ; K. K. K. Goh, A. Sinha, C. Fraser and R. D. Young, *RSC Adv.*, 2016, **6**, 42708.

8 The mixture consists of *E*/*Z* isomers as well as diastereomers based on the two stereogenic centers so that up to eight isomers are possible (see SI).

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