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Exploring Multistep Continuous Flow Hydrosilylation Reactions Catalyzed by Tris(pentafluorophenyl)borane

Lewis C. Wilkins, Joseph L. Howard, Stefan Burger, Louis Frentzel-Beyme, Duncan L. Browne* and Rebecca L. Melen*

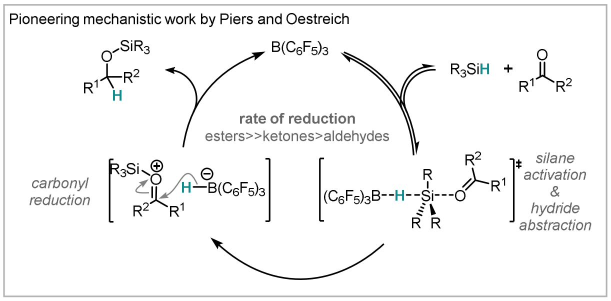
School of Chemistry, Main Building, Park Place, Cardiff University, Cardiff, CF10 3AT, U.K.
E-mail: MelenR@Cardiff.ac.uk or DLBrowne@cardiff.ac.uk

Abstract: Exploring the combination of continuous-flow processes with the boron Lewis acid catalyzed hydrosilylation of aldehydes and ketones has delivered a robust and generally applicable reaction protocol. Notably this approach permits ready access to high temperatures and pressures and thus allows improved reactivity of substrates that were previously recalcitrant under the traditional approach. Efforts to quench the output from the flow reactor with water showed surprising tolerance leading to the application of continuous-flow systems in a multistep imine formation/hydrosilylation processes to generate the corresponding secondary amines from their aldehyde and aniline precursors.

Keywords: hydrosilylation; frustrated Lewis pairs; catalysis; multistep continuous flow; $B(C_6F_5)_3$

Highly Lewis acidic boranes containing perfluorinated aryl groups, including the archetypal Lewis acid tris(pentafluorophenyl) borane, $B(C_6F_5)_3$, have enjoyed widespread applications in both organic and organometallic chemistry.[1] Research in one of our groups has focused on the use of $B(C_6F_5)_3$ in the reactions with various unsaturated frameworks[2] while others have proven it to be an excellent catalyst for the installation of C–Si,[3] O–Si[4] and even N–Si bonds (*en route* to hydrogenation).[5] Pioneering work in this field by Piers *et al.* demonstrated how $B(C_6F_5)_3$ can catalyze the hydrosilylation of aromatic aldehydes, ketones and esters.[4] It was seen through quantitative rate studies that this transformation proceeds through an alternative mechanism to that of conventional Lewis acid catalysis (Scheme 1).[5a,6] In these initial findings, the hydrosilylated products were recovered in good to excellent yields (*ca*. 80%). These results were later reinforced by the work of Oestreich *et al*. through further studies expounding the S_N2-Si mechanism by which this hydrosilylation occurs,[7] with in-depth computational analyses by Fujimoto *et al*. supporting this hypothesized silane activation by $B(C_6F_5)_3$.[8]

Whilst these established synthetic routes have been explored using traditional batch methods, they have not previously been investigated using novel processing methods, such as continuous-flow. In recent years, the adoption of continuous-flow techniques has increased amongst both academic and industrial research groups.[9] In light of this, continuous-flow reactors have become more ubiquitous as the advantages offered by such systems are becoming recognized across different fields.[10]

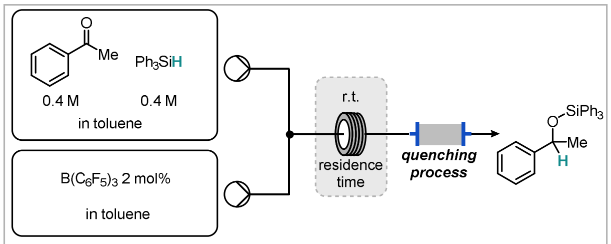

Pioneering mechanistic work by Piers and Oestreich
$B(C_6F_5)_3$
R_3SiH +
rate of reduction
esters>>ketones>aldehydes
carbonyl reduction
silane activation & hydride abstraction
$(C_6F_5)_3B$
$H-B(C_6F_5)_3$
R_3Si

Scheme 1. Previous work into the mechanism of borane catalyzed hydrosilylation.

In certain instances this symbiotic relationship has led to increased conversion, selectivity and reaction rates, but perhaps more importantly, flow chemistry can provide an automated platform that permits machines to conduct laborious or repetitive processes[11] whilst also enabling multistep syntheses.[12] These systems are able to negate many manual handling steps,[13] and through the construction of setups with interchangeable modular sections, vast libraries of compounds can be achieved. In addition, an important application of continuous-flow processing is the permittance of high temperatures and pressures, higher than is conventionally tolerated under standard batch reactions. The superheating of solvents under high pressures more often leads to faster reaction rates being observed, making the adoption of such techniques incredibly attractive to the synthetic chemist. Indeed, the use of a back-pressure regulator (BPR) allows the pressure of the reactor coil to be maintained throughout the reactor setup enabling easily scalable high temperature and pressure conditions.[14] This also highlights a further potential benefit of continuous-flow reactor technology, that is to maintain an improved safety profile whilst conducting ‘forbidden’ chemistries.[15] This current work explores the combination of the two fields of main group catalysis and continuous-flow chemistry for a multistep condensation/hydrosilylation processes.

Prior to translating into a continuous process, investigations were conducted through conventional techniques to check for incompatibilities. Acetophenone was selected as the model ketone for testing. In agreement with previous findings, optimal conditions include 2 mol% catalyst loading with a concentration of 0.2 M in toluene, notably this procedure did not lead to any formation of precipitates or particulates. To achieve comparable conditions for use in flow, 5 mL of a 0.4 M solution of ketone/aldehyde and silane was combined with 5 mL of the $B(C_6F_5)_3$ solution (2 mol%) to produce a reaction stream of 0.2 M. The silane/substrate and borane streams were combined using a T-piece resulting in a combined flow rate of 0.166 mL/min. The combined reaction stream was then passed through a reaction coil (5 mL) giving a residence time of 30 minutes. Collection of the product stream commenced after 36 mins under presumed steady-state conditions.

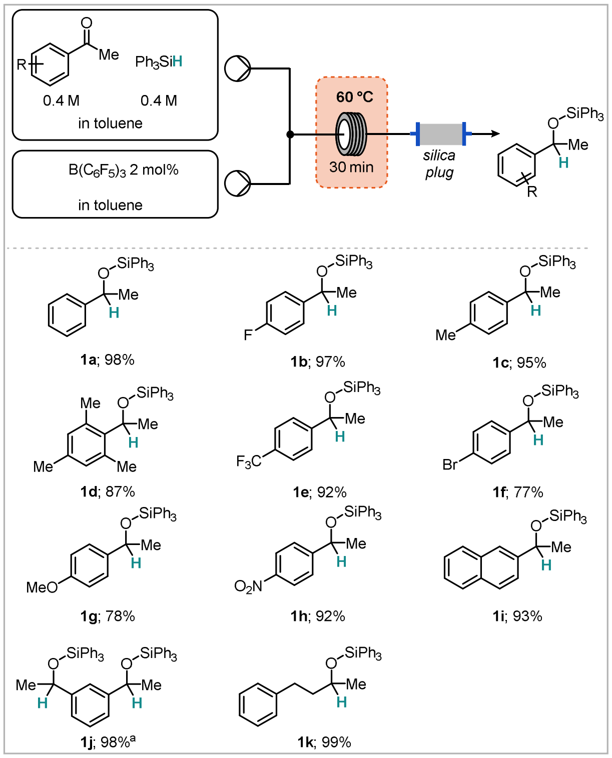
Initial analysis *via* ^{1}H NMR spectroscopy returned agreeable results for the screening of acetophenone at r.t. giving good conversion (85%). This was optimized further by conducting the reaction at 60 °C, which resulted in essentially quantitative conversion to the silyl ether **1a** (98%). At this juncture, it was imperative that the correct catalyst quenching protocol was developed to ensure that the conversion measurement was a true representation of the flow process and not a combination of the flow and continued reaction in the collection vessel. In order to design this quenching protocol, three methods were explored to irreversibly bind the borane catalyst; 1) the addition of water, 2) dropping into a slurry of CsF in MeCN, and 3) passing through a short silica plug (Figure 1). It was observed that reactivity continued with the former two processes, NMR ratios of products to starting materials continued to change following the 'quench' procedure. The catalyst was also observable in the ^{11}B and ^{19}F NMR spectrum. Indeed, this observation has recently been reported by both Ingleson and Ashley.[16] However, when being filtered through a short silica plug, any further catalytic activity was prevented and the catalyst was completely removed from the crude reaction mixture as evidenced in the ^{11}B and ^{19}F NMR spectra.



quench species	**quench protocol**	**observation**
H_2O	dropped into water	reaction continues
Fluoride	dropped into slurry of CsF in MeCN	reaction continues
Silica gel (retention)	***dropped through a silica gel pipette***	***reaction ceases***

Figure 1. Quenching protocols to terminate catalytic activity.

With an optimized quenching protocol, the scope of the process was then explored to see if a range of reactants would remain in solution in the flowing stream. Across a small range of both ketone and aldehyde substrates spanning electronic and steric properties, the reaction proceeded successfully (>90%) and importantly, no precipitate formation was observed. As originally reported by Piers, we have found ketones to be more reactive to reduction via this approach than aldehydes. This is particularly notable in the example of the mesityl derivatives, **1d** and **2d**, where application of identical conditions led to conversions of 87% and 62% for the ketone and aldehyde derivatives respectively (Figures 2 and 3). This reversal of the typical reactivity is truly remarkable. Notably, both the 1,3 bisacetylbenzene and homobenzylic ketone substrates underwent reduction in excellent conversion. Relatively low conversions (78% and 55%) were seen for the respective ketone and aldehyde moieties featuring activated aryl groups (**1g** and **2g** where R = *p*-MeOC$_6$H$_4$, Figures 1 and 2). These results agree with previous findings whereby a deactivated aldehyde or ketone is necessary to facilitate effective hydride transfer.[4]



[a] Using same reaction conditions with 2 equivalents of silane.

Figure 2. Continuous-flow hydrosilylation of ketones Conversion measured *via* ^{1}H NMR spectroscopy.

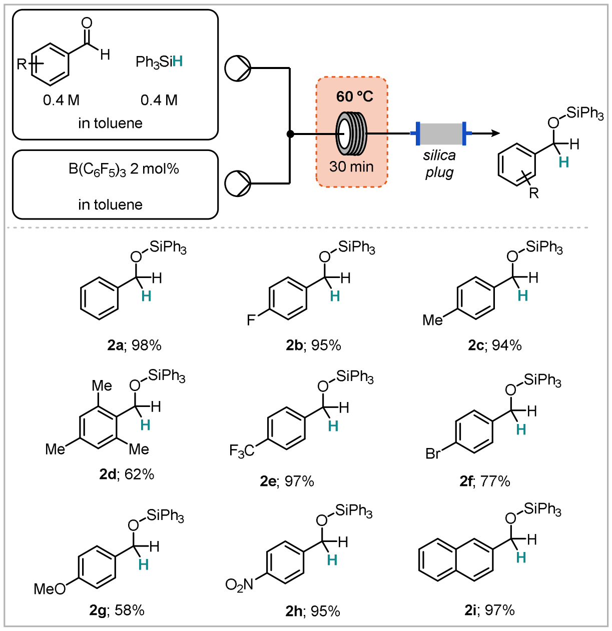
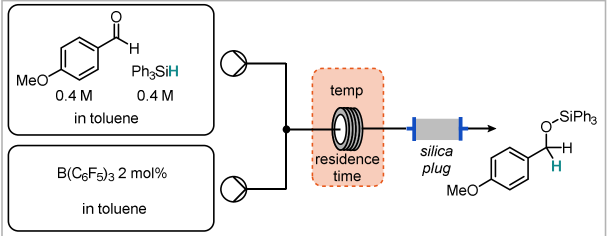


Figure 3. Continuous-flow hydrosilylation of aldehydes using. Conversion measured *via* ^{1}H NMR spectroscopy.

It was hypothesized that simple modification of the reactor setup could overcome this shortfall in reaction performance. Modifications consisted of the inclusion of high pressure HPLC pumps and a back-pressure regulator (BPR) thus permitting easy reach of higher pressures and thus temperatures past the atmospheric pressure boiling point of the solvent. With this modified setup, the reactor could hydrosilylate *p*-anisaldehyde within 5 minutes affording a 67% conversion at a reaction temperature of 150 °C and 130 PSI (Figure 4).

Returning to our earlier observations on quenching, we were intrigued by the idea that the borane remained catalytically active in the presence of water. Thus our investigations turned to applying this setup to condensation reactions whereby the side formation of water would not impede catalytic activity.[16] Therefore, the reactor setup was again adapted, now for a multistep process whereby a third stream was included to deliver a third reagent.[12] This modification allowed us to generate secondary imines from their aniline and aldehyde counterparts in the first reaction coil (along with the H_2O byproduct) followed by $B(C_6F_5)_3$ catalyzed hydrosilylation in the second reactor coil (Figure 5).


MeO
H
O
Ph3SiH
0.4 M
0.4 M
in toluene
B(C6F5)3 2 mol%
in toluene
temp
residence time
silica plug
SiPh3
O
H
H
MeO

Entry	Temp	Time	Back Pressure	Conversion
1	60 °C	30 min	0	58%
2	60 °C	5 min	0	14%
3[a]	**150 °C**	**5 min**	**130 PSI**	**67%**

a) Flow system uses back pressure regulator, HPLC pumps and stainless steel reactor coil

Figure 4. Comparison between low pressure/temperature and high pressure/temperature systems. Conversion measured *via* ^1H NMR spectroscopy.

A less bulky silane (Me_2PhSiH) was used during this method in order to maximize reactivity and reduce any unfavorable steric occlusion brought about by the substituent on nitrogen and the newly installed silane moiety.[17] A mixture of aldehyde (0.4 M) and Me_2PhSiH (0.48 M) in toluene was combined with a stream of the aniline substrate in toluene (0.48 M) using a T-piece joint. Passage through a short residence coil afforded the requisite imine formation whereupon a 2 mol% stream of $B(C_6F_5)_3$ was combined, this reaction mixture then proceeded to reactor coil 2, which was heated to 150 °C with a residence time of 10 minutes, the output stream was cooled to ambient temperature before passing through the back-pressure regulator (130 PSI), and filtering through a plug of silica to remove the catalyst.

In general, this method generates the desired secondary amine with good conversions as measured by ^1H NMR spectroscopy as well as isolated yields, up to 89%, with the exceptions being strongly electron withdrawing or donating groups on the aniline reagent (*p*-OMe = 45%, *p*-CF_3 = 34%). Indeed, in the case of the *p*-CF_3 substituted aniline the product stream also contained hydrosilylated aldehyde, the system could likely be independently optimized for these electronic biases. Increasing the length or temperature of reactor coil 1 would result in more complete conversion to the imine prior to the second step reaction. Although this pathway proceeds *via* a condensation reaction, the borane does not appear to suffer from any 'poisoning' from the water by-product during the reaction. The radial chart (Figure 5) shows a number of reaction parameters comparing batch to flow processing of this tandem imine formation/hydrosilylation process. Clearly the flow approach allows more convenient access to the lesser-used processing windows of high temperatures and pressures and thus delivers enhanced conversions with the same loading of catalyst but in a significantly shorter reactor time.

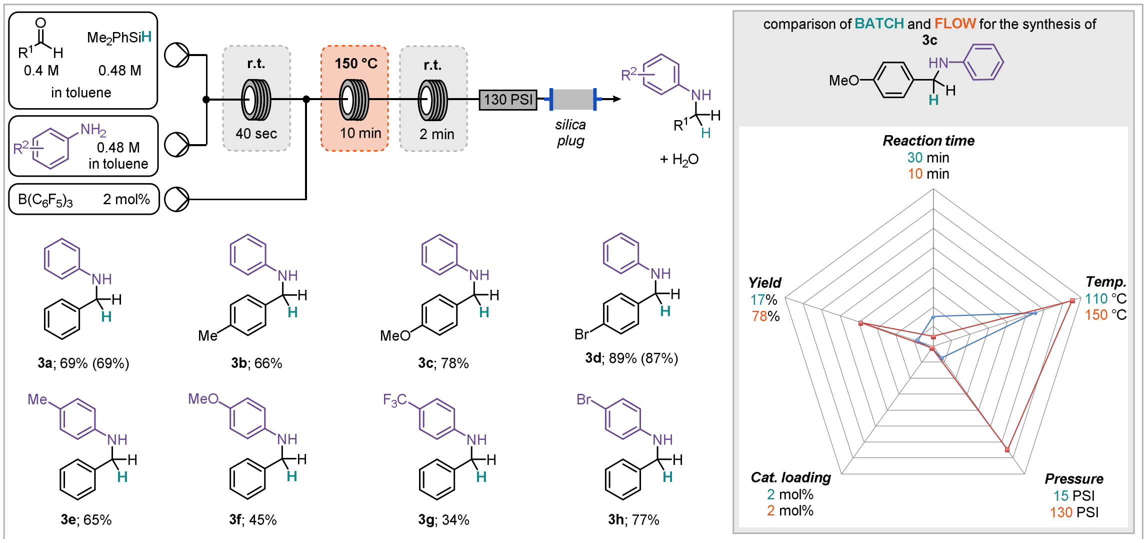

R1
O
H
Me2PhSiH
0.4 M
0.48 M
in toluene
R2
NH2
0.48 M
in toluene
B(C6F5)3
2 mol%
r.t.
40 sec
150 °C
10 min
r.t.
2 min
130 PSI
silica plug
R2
NH
R1
H
H
+ H2O
3a; 69% (69%)
3b; 66%
3c; 78%
3d; 89% (87%)
3e; 65%
3f; 45%
3g; 34%
3h; 77%
Me
MeO
Br
F3C
comparison of BATCH and FLOW for the synthesis of 3c
MeO
HN
H
H
Reaction time
30 min
10 min
Temp.
110 °C
150 °C
Pressure
15 PSI
130 PSI
Cat. loading
2 mol%
2 mol%
Yield
17%
78%

Figure 5. Tandem $B(C_6F_5)_3$ catalysis to give **3** alongside radial chart comparing batch and flow systems. Conversion measured *via* ^1H NMR spectroscopy isolated yields indicated in parentheses.

In summary, we have demonstrated the productive combination of main-group chemistry with multistep flow techniques. This has led to the rapid processing of substrate examples that are problematic under more traditional conditions. Finally, we have demonstrated that the release of water as a byproduct through a condensation reaction is compatible with a $B(C_6F_5)_3$ catalyst and thus a multistep flow process for the formation of secondary amines was realized.

Experimental Section

General procedure for hydrosilylation of aldehydes and ketones

A solution of triphenylsilane (1.0 equiv.) and aldehyde or ketone (1.0 equiv.) (0.4 M, toluene) was prepared along with a separate solution of tris(pentafluorophenyl)borane (0.008 M, 2 mol%, toluene). 5 mL aliquots of each solution were combined at matched flow-rates using a T-piece adapter *via* syringe pump with a combined flow rate of 0.166 $mLmin^{-1}$. The mixed reaction stream then proceeded to a 5 mL tubular reaction coil where it was heated to 60 °C and left to collect as waste for 36 minutes (to allow the system to reach steady-state) before the output was directed through a short plug of silica gel (to remove catalyst) and collected in a flask for 12 minutes (2 mL). The solvent was removed *in vacuo* followed by NMR spectroscopy to ascertain the conversion.

General procedure for tandem imine formation, hydrosilylation and hydrolysis.

A solution of the aldehyde (0.4 M, 1 equiv.) and dimethylphenylsilane (0.48 M, 1.2 equiv., toluene), aniline (0.48 M, 1.2 equiv., toluene) and $B(C_6F_5)_3$ (0.008 M, 2 mol%, toluene) were loaded into the sample loop of stream A, B and C respectively. The pumps were set to a flow rate of 0.17 $mLmin^{-1}$ and the temperature of the heated coil set to 150 °C. Streams A and B were set to inject, followed by stream C after 41 s. After waiting for 7 mL (14 min) to be collected as waste (to allow the system to reach steady-state), the output was directed through a plug of silica gel (to remove the catalyst) and the solution collected for 8 minutes (4 mL). The solvent was removed under reduced pressure and mesitylene (74 µL, 0.064 g, 0.53 mmol) added as an internal standard. NMR conversions were determined by ^{1}H NMR spectroscopy. Isolated yields were obtained by column chromatography on silica gel using an ethyl acetate/petroleum ether eluent (1:4 for **3a**, 1:9 for **3d**) and dried *in vacuo*.

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Notes and references

Corresponding Authors:
Dr Rebecca L. Melen:
E-mail: MelenR@cardiff.ac.uk
Dr Duncan L. Browne:
E-mail: DLBrowne@cardiff.ac.uk

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