In situ sulfidation of Pd/C: A straightforward method for chemoselective conjugate reduction by continuous hydrogenation

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Supporting Information. Experimental procedures, compound characterisation and GreenMotion™ analysis.

Abstract

A method has been developed for the in situ sulfidation of Pd/C under continuous flow. The approach provides a cheap, sustainable and operationally convenient method for chemoselective conjugate reduction by continuous hydrogenation. High conversions and excellent selectivities were obtained for olefin reduction in α/β-unsaturated carbonyl compounds in the presence of hydrogenatively sensitive functionalities. The methodology was analysed with a green metric system to highlight the sustainability features of the process.

Key Words

Hydrogenation; Continuous-Flow; Chemoselective; Conjugate-Reduction; Chalcones.

Synopsis

α/β-Unsaturated carbonyl compounds are chemoselectively hydrogenated in continuous-flow via catalyst modification with diphenyl sulfide.

Introduction

Over the past few decades there has been increasing pressure on pharmaceutical manufacturers to apply green metrics and improve efficiencies across the spectrum of chemical processes that they employ.[1–3] Consequently, an emphasis has been placed on the implementation of continuous manufacturing.[4–9] As a result, many enabling technologies have become available to drive this new agenda.[10–33] Catalytic heterogeneous hydrogenation is a key process technology that has benefitted from the growing popularity and commercial availability of miniaturised continuous hydrogenation reactors. Consequently, there is a growing literature precedent describing continuous hydrogenation processes.[34–38] Previous work from our group on continuous hydrogenation has largely focused on the use of supercritical fluids (SCFs)[39,40] and includes the large-scale hydrogenation of isophorone[41] and the reductive cyclisation of levulinic acid to Ɣ-valerolactone.[42] With the increasing expertise and knowledge, contract development and manufacturing organisations (CDMOs), which have historically taken a risk adverse approach to the adoption of new technologies, are turning to continuous manufacturing and applying green metrics to improve their own processes. As part of our ongoing drive towards greener continuous process improvement we were keen to investigate the reduction of Michael acceptors *via* continuous hydrogenation; in particular, a process relevant to our collaboration with industrial partners - the conjugate reduction of chalcones to dihydrochalcones. Dihydrochalcones are members of the flavonoid family and are widely distributed throughout the plant kingdom.[43] They exhibit a variety of biological properties including: antimicrobial, anti-inflammatory, antioxidant, antiplasmodial and antiviral activities and make up the core of many active pharmaceutical ingredients (Figure 1).[44–46] The most appealing method to access dihydrochalcones is conjugate reduction of chalcones, which can themselves be easily synthesised *via* the Claisen-Schmidt condensation between benzaldehyde and acetophenone derivatives.[47] The conjugate reduction of chalcones presents a challenge however, as the benzylic nature of the ketone functionality renders these substrates highly susceptible to over-reduction. This presents a significant challenge, particularly on large scale when employing traditional batch manufacturing approaches. Indeed, the difficulties associated with the chemoselectivity of this transformation are well documented.[48–50]

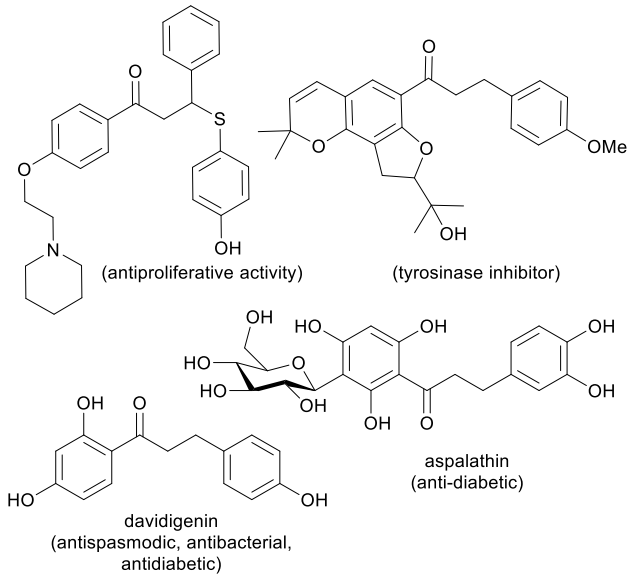


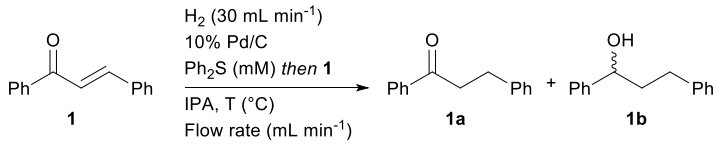
Fig. 1. Examples of biologically active molecules containing the dihydrochalcone scaffold.

Whilst a number of methods have been reported for chemoselective conjugate reduction *via* homogenous catalysis, few of these are currently amenable to a continuous-flow protocol. For example, a number of approaches have been developed that utilise bisphosphine ligated CuH catalysts.[51,52] These highly carbophilic reducing agents have seen great utility in the asymmetric conjugate reduction of a range of α/β-unsaturated carbonyl compounds including ketones,[53] esters[54] and carboxylic acids.[55] To the best of our knowledge however, no continuous-flow procedure has been reported that capitalises on this approach. Studies by Winterbottom and co-workers on the heterogeneous conjugate reduction of cinnamaldehyde focused on the effect of Fe and K salts and quinolone as additives on the chemoselectivity of the process.[56] The most selective conditions utilised potassium acetate as the additive and yielded 85% selectivity for conjugate reduction. Microfluidic enone reductions have been reported by Kobayashi and co-workers[57] and a continuous-flow procedure that utilises maghemite-Pd nanocomposites has also been developed for the conjugate reduction of α/β-unsaturated esters.[58] An asymmetric conjugate reduction, with continuous recovery of the chiral auxiliary has been recently reported where α/β-unsaturated amides are generated *in situ* from the corresponding acyl chloride and a chiral amine.[59] A continuous flow procedure for the ThalesNano H-Cube™ was reported by Bäckvall and co-workers, where nanopalladium supported on amino-functionalised mesocellular foam (Pd^0-AmP-MCF) was employed.[60] Whilst this was shown to be an effective method, the fabrication of bespoke catalyst cartridges was required *via* collaboration with ThalesNano. Furthermore, the selectivity was somewhat limited; in the case of chalcone (**1**), a 9:1 ratio of ketone:alcohol was produced. The deuteration of chalcones has also been performed in an H-Cube™ reactor, where D_2 was generated by the electrolysis of D_2O.[61]

Our strategy for developing a chemoselective conjugate reduction by continuous hydrogenation was inspired by a series of reports by Sajiki and co-workers, where various sulfur species were employed as additives in Pd/C catalysed hydrogenation in batch format.[62–64] Crucially for this study, it was shown that diphenyl sulfide imparts excellent selectivity when employed as an additive in the Pd/C catalysed conjugate reduction of chalcone (**1**). Sulfur species are well known to poison many metal catalysts, hence the advent of ultralow sulfur gasoline and diesel, which serves to prolong the lifetime of catalytic-converters in automotive exhaust streams. On the other hand, there are in fact many cases where sulfur additives can act as activity promotors and/or selectivity modifiers *via* modulation of the electronic environment and/or the orientation of catalytic metal centres.[65] The interplay between these distinct modes of action can allow for precise tuning of catalyst activity and sulfur additives have seen great utility in a range of chemoselective hydrogenations.[66] Examples include the conjugate reduction of enones,[62] hydrodeoxygenation of fructose,[67] the partial hydrogenation of alkynes,[68,69] nitro-reduction in the presence of alkenes[70] and alkene reduction in the presence of aryl chlorides, nitriles, benzyl esters and *N*-Cbz protecting groups.[63] We envisaged that if this powerful approach could be incorporated into a flow procedure, it would constitute a highly convenient method for conjugate reduction by continuous hydrogenation.

Results and Discussion

Initially, the reduction of chalcone (**1**) was investigated under a continuous flow protocol in the absence of an additive. Reactions were performed using a ThalesNano H-Cube™ hydrogenation reactor, which generates hydrogen on demand by the electrolysis of water. At 3 mL min^{-1} flow rate, high selectivity for the desired ketone **1a** was observed however the reaction proceeded only to 16% conversion (Table 1, Entry 1). Increasing the residence time by reducing the flow rate to 1 mL min^{-1} had only a minimal effect on both conversion and selectivity. (Table 1, Entry 2). A further reduction of the flow rate to 0.5 mL min^{-1} led to an improved conversion (46%) but in this case a mixture of the ketone **1a** and the alcohol **1b** was obtained (Table 1, Entry 3). Similarly, increasing the temperature to 50 °C gave an improved conversion, but at the cost of selectivity (Table 1, Entry 4). It was apparent at this early stage in the investigation that precise control of the reaction parameters alone would be unlikely to provide satisfactory selectivity in the reduction. This led us to investigate the use of an additive and in light of the excellent results reported for the corresponding batch process (*vide supra*), we selected diphenyl sulfide.



Entry	T (°C)	Flow Rate (mL min^{-1})	Ph_2S (mM)	Product Ratio [%]		Total Conversion [%]
				1a	1b	
1	20	3.0	-	>95%	<5%	16%
2	20	1.0	-	>95%	<5%	22%
3	20	0.5	-	83%	17%	46%
4	50	0.5	-	74%	26%	88%
5	50	0.5	2.5	>95%	<5%	36%
6	100	0.5	2.5	>95%	<5%	86%
7	100	0.5	0.5	63%	37%	>95%
8	**100**	**0.5**	**1.25**	**>95%**	**<5%**	**>95%**

Table 1. Optimisation of reaction conditions. All reactions were performed on 0.5 mmol scale. Conversions and product ratios were determined by ^{1}H NMR analysis.

One challenge in incorporating a potential catalyst poison into a continuous flow protocol is that continuous pumping of the additive across the catalyst bed can result in a cumulative suppression of catalyst activity, making it challenging to maintain steady-state conditions in the reactor. Following preliminary investigations, we developed a procedure that consisted of pre-treatment of the catalyst bed for 20 minutes with a solution of diphenyl sulfide at 0.5 mL min^{-1} flow rate (Figure 2). Following this period of conditioning, the starting material was processed as an additive-free solution under the same reaction conditions (Table 1). When the sulfide was employed at 2.5 mM, excellent selectivity (>95%) for the desired ketone **1a** was observed, albeit with only moderate conversion (36%, Table 1, Entry 5). The conversion was improved to 86%, without a deleterious effect on the selectivity, by increasing the temperature to 100 °C (Table 1, Entry 6). Full conversion of the starting material was observed when the sulfide was employed at the lower concentration of 0.5 mM but under these conditions the selectivity was poor (Table 1, Entry 7). This implies that alongside improving the selectivity, the incorporation of diphenyl sulfide leads to a suppression in the desired olefin hydrogenation. The optimal conditions were found when the additive was employed at 1.25 mM and the substrate was processed at 100 °C (Table 1, Entry 8). Under these conditions, full conversion of the starting material and >95% selectivity for the targeted ketone **1a** was observed.

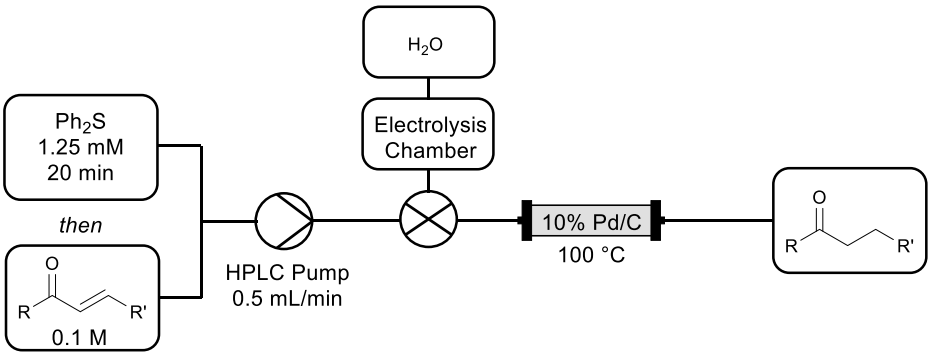
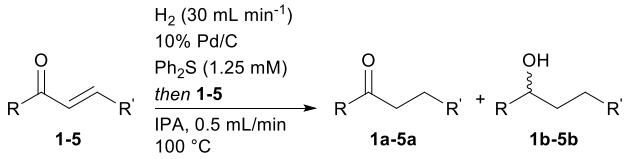
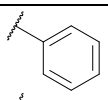
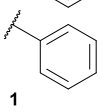
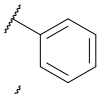
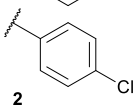
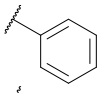
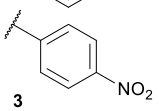
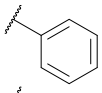
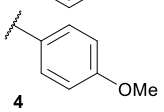


Fig. 2. Flow schematic. Hydrogen gas is generated by electrolysis of water and then mixed with the liquid stream before being passed through the catalyst cartridge.

With the optimised conditions in hand, the substrate scope of the methodology was investigated. Initially a series of chalcone derivatives were targeted in order to establish the effects of electron-donating and -withdrawing substituents at various positions on the phenyl rings. In general, high conversions and selectivities were obtained across the series (Table 2).



Entry	Substrate	Product Ratio [%]		Total Conversion [%]
		1a-5a	1b-5b	
1	R =  R' =  **1**	**1a** >95%	**1b** <5%	>95% (84%)[a]
2[b]	R =  R' =  **2**	**2a** >95%	**2b** <5%	>95%
3[b]	R =  R' =  **3**	-	-	Complex mixture
4	R =  R' =  **4**	**4a** 95%	**4b** 5%	94%

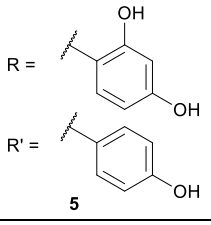
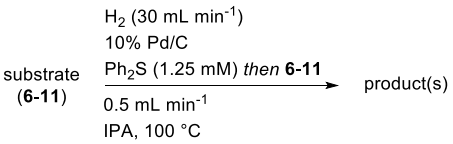
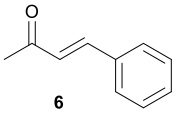
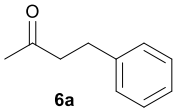
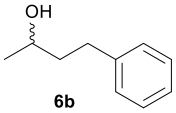
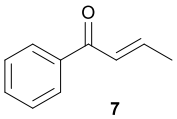
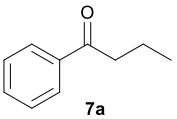
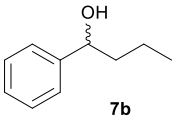
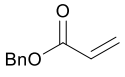
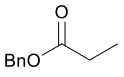
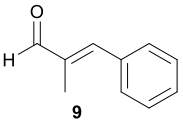
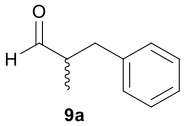
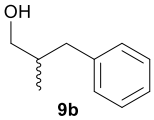
5	 **5**	**5a** >95%	**5b** <5%	60%

Table 2. Substrate scope for the conjugate reduction of chalcones **1-5**. Conversions and product ratios were determined by ^{1}H NMR analysis. [a]Isolated yield following column chromatography. [b]For solubility reasons, the reaction was performed in EtOAc.

The chemoselective conjugate reduction of the *p*-chloro derivative **2** demonstrates that the hydrogenatively unstable aryl chloride functionality is tolerated under the reaction conditions; the hydrodehalogenated species was not observed. In the case of the *p*-nitro derivative **3**, a complex mixture of products was obtained, which is consistent with the results obtained from the batch procedure reported by Sajiki and co-workers.[63] Electron-donating substituents were well tolerated, with the *p*-methoxy derivative **4** yielding the targeted dihydrochalcone **4a** in 94% conversion and with >95% selectivity. We next turned our attention to the conjugate reduction of isoliquiritigenin (**5**), a commonly occurring natural product with a range of useful pharmacological properties that include anti-inflammatory and anti-cancer activity.[71] This compound was transformed into the respective dihydrochalcone, davidigenin (**5a**) (Figure 1), which is itself a naturally occurring anti-spasmodic that exhibits antidiabetic and weak antibacteral activity.[72]

Next, the scope of the optimised hydrogenation conditions was investigated with a range of non-chalcone derivatives (Table 3).



Entry	Substrate	Product Ratio [%]		Total Conversion [%]
		A	B	
1	 **6**	 **6a** >95%	 **6b** <5%	>95%
2	 **7**	 **7a** 83%	 **7b** 17%	>95%
3	 **8**	 **8a** >95%	-	>95%
4	 **9**	 **9a** 91%	 **9b** 9%	88%

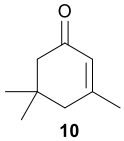
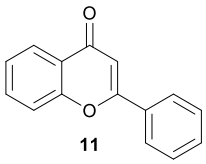
5	 **10**	-	-	<5%
6	 **11**	-	-	<5%

Table 3. Additional substrate scope for conjugate reduction of Michael Acceptors. Conversions and product ratios were determined by ^{1}H NMR analysis.

Pleasingly, the 1- and 4-phenyl butenones **6** and **7** were each hydrogenated to full conversion and with good selectivity (83% and >95%, respectively) (Table 3, Entries 1-2). The methodology can also be extended to α/β-unsaturated esters, as evidenced by the chemoselective hydrogenation of benzyl acrylate (**8**) (Table 3, Entry 3). This example also demonstrates that the sensitive benzyl ester functionality remains intact under the reaction conditions, with no sign of debenzylation occurring. When the methodology was applied to 2-methyl-cinnamaldehyde (**9**), the reaction reached 88% conversion and the targeted aldehyde **9a** was obtained with 91% selectivity over the corresponding alcohol **9b**. A limit to the methodology was found when the conditions were applied to the hydrogenation of less activated enones; in the cases of isophorone (**10**) and flavone (**11**) the major component recovered was starting material (Table 3, Entries 5-6).

Fig. 3. Analysis of the sustainability profile of the process using the metric tool Green Motion™.

Using the metric tool Green Motion™, we have evaluated the methodology with respect to sustainability (Figure 3).[73] This metric combines the twelve principles of green chemistry[74] with a penalty point system; the lower the impact to the environment, the higher the rating (100 being ideal). The process adheres well to the principles of green chemistry and therefore scores highly, with key sustainability features including:

- High selectivity, therefore reduced waste – low E-factor (Principle 1)[75]
- Hydrogenation with H_2 - high atom economy (Principle 2)[76]
- Low toxicity of reagents (Principle 3)
- Catalytic quantity of the auxillary diphenyl sulfide (Principle 5)
- Operation at atmospheric pressure and, despite heating, no cooling is required (Principle 6)
- Use of a renewable solvent (Principle 7)
- Catalytic reagents (Principle 9)
- No storage of H_2 - reduced chance of accidents (Principle 12)

A detailed description of the process involved in the GreenMotion™ assessment is available in the *Supporting Information*. It should be noted that the low score obtained for "Raw materials" is inherent, as the starting material, chalcone (**1**), is of synthetic origin. Overall the methodology scored highly at 77/100 which according to the guidelines laid out within the Green Motion™ metric[73] validates that the process can be considered green.

Conclusions

In conclusion, a procedure has been developed for the *in situ* sulfidation of Pd/C in continuous flow. The approach provides a straightforward and sustainable method for conjugate reduction by continuous hydrogenation. The methodology was initially showcased with a selection of chalcone derivatives and then shown to be extendable to other α/β-unsaturated carbonyl compounds. In general, high total conversions and excellent chemoselectivities were obtained. A number of hydrogenatively sensitive functionalities such as aryl ketones, benzyl esters and aryl halides were shown to be tolerated well under the reaction conditions. Analysis of the methodology with the metric GreenMotion™ highlighted a number of key sustainability features, confirming that the approach can be considered green. Work is on-going to up-scale this process (targeting ca. 1 kg day^{-1}) using a custom-built trickle-bed hydrogenation reactor and these studies will be reported in due course.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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