Fukuyama Reduction and Integrated Thioesterification/Fukuyama Reduction of Thioesters and Acyl Chlorides Using Continuous Flow

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S *Supporting Information*

ABSTRACT: Fukuyama reduction of thioesters has been achieved using a polymer-supported Pd[0] catalyst (Pd/XAD-4), and continuous flow conditions. The generality of this reaction is good with a range of aldehydes prepared in excellent yields. In addition, an integrated multistep thioesterfication/Fukuyama reduction has been developed that allows acyl chlorides to be directly converted to the corresponding aldehydes. Integral to this process is the use of polymer-supported amine and isocyanate reagents to achieve thioesterification and scavenge unreacted thiol. In addition, catch-and-release purification has been employed to enable isolation of the aldehyde from silylthioether byproducts without the need for chromatographic purification.

KEYWORDS: *Fukuyama reduction, heterogeneous catalysis, multistep continuous flow, thioesterification, catch-and-release*
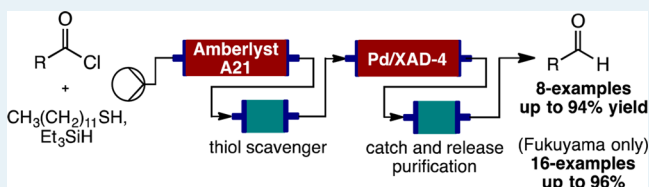
The manipulation of oxidation state is a necessary aspect of chemical synthesis. Ideally, this is married to key bond-forming events; however, in many contexts, isolated functional group oxidation state changes are unavoidable.[1] This is evident with the carbonyl group and, as a consequence, numerous techniques for reduction and oxidation of carbonyls are known.[2]

Catalytic oxidations and reductions have the capacity to enhance efficiency and have received significant attention. The Fukuyama reduction is a valuable Pd-catalyzed transformation for the conversion of thioesters (i.e., **1**) to aldehydes (i.e., **2**) without overreduction to the alcohol (Scheme 1).[3,4] The

Scheme 1. Reaction Design
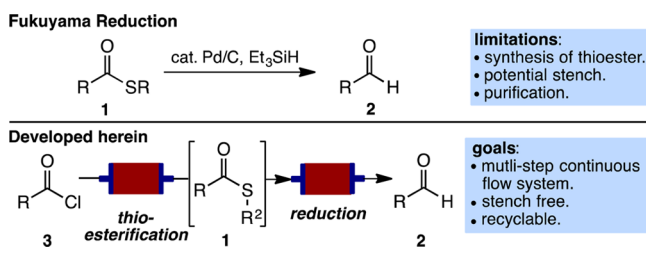
selective reduction of carboxylic acids and esters to aldehydes can be a challenge, with commonly used metal hydride reagents complicated by issues of chemoselectivity, and the requirement for cryogenic conditions.[5] Although recent studies from Jamison have examined the utility of continuous flow approaches with the DiBAL-H reduction,[6b] this elegant procedure remains constrained by the inherent chemoselectivity of aluminum hydride reagents.[6] For example, chemoselective reductions of substrates bearing keto or

aldehyde functionality is rarely possible. Although the Fukuyama reduction displays desirable chemoselectivity, particularly with respect to carbonyl functionality, its uptake has been limited by a number of factors. These include the use of odorous thiols, with first-generation approaches,[3,4] its multistep nature, requiring first preparation of the thioester, and issues associated with purification when using higher boiling odorless thiols.[7,8]

As part of our studies on the discovery of novel catalysts[9] and technologies[10] to address challenges in chemical synthesis, we recently investigated the application of continuous flow techniques to the reduction of carboxylic acid substrates (i.e., thioester **1** and acyl chloride **3**) to aldehydes (i.e., **2**) using the Fukuyama reduction.[11] Continuous flow techniques have a number of features that we considered potentially adventitious with respect to the Fukuyama reduction.[12,13] In particular, the capacity to develop multistep strategies,[14] thereby avoiding the isolation of undesirable intermediates (i.e., thioester **1**), and the application of inline purification approaches. In addition, it was envisaged that the linear scalability of continuous flow processes might allow methods with broad applicability to be developed. Herein, we report our studies on this topic that have led to the development of a continuous flow Fukuyama reduction (**1** → **2**) and integrated thioesterification/Fukuyama reduction (**3** → **2**).

Studies commenced with the identification of a suitable polymer-supported palladium source to serve as the heterogeneous catalyst for the reduction.[15] Initial studies with Pd monoliths gave promising results;[16] however, it was found that
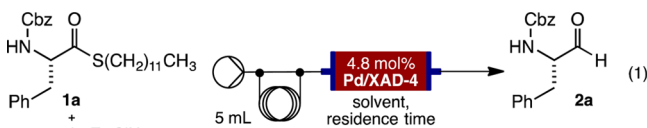
Pd/XAD-4 gave similar outcomes, and was significantly simpler to prepare.[17] TEM analysis of this catalyst was undertaken, indicating the presence of palladium nanoparticles with 2−10 nm particle size, consistent with previous preparations (Figure 1).[17] In addition, inductively coupled plasma atomic emission spectroscopy (ICP-AES) allowed the palladium composition to be determined (0.92 wt % Pd).
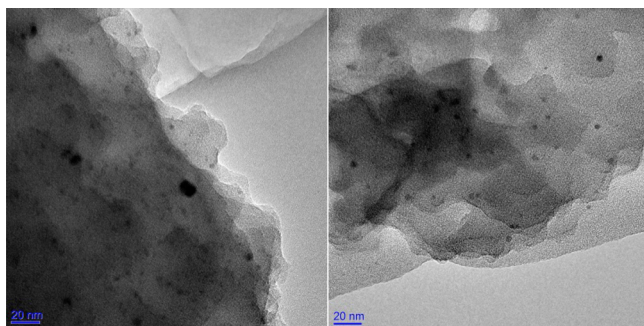
Figure 1. TEM images of Pd particles on Amberlite XAD-4. Accelerating voltage 200 kV utilizing LaB₆ thermal emitter.

Development of a continuous flow Fukuyama reduction was undertaken with Cbz-protected phenylalanine thioester **1a** (Table 1). This substrate has been applied to the odorless variant of the traditional Fukuyama reduction,[3,4,7] hence facilitating direct comparison to existing methods. All reactions were performed on a commercially available flow chemistry synthesis platform or a bespoke flow device comprising a tubular (PTFE) reactor. Optimization commenced with examination of the solvent. Although acetonitrile gave a modest isolated yield of aldehyde **2a** (Table 1, entry 1), CH₂Cl₂, THF, acetone, and dioxane gave the product in good to excellent yield (Table 1, entries 2−5), with THF providing **2a** in the highest isolated yield (Table 1, entry 3). When the stoichiometry of Et₃SiH was reduced, the reaction failed to reach completion. Next, residence times were varied from 15 to 180 min (Table 1, entries 6−8), with 60 min proving optimal. Finally, the recyclability of the column was investigated using

Table 1. Continuous Flow Fukuyama Reduction of Thioester 1a

entry	solvent	residence time	run	% yield 2a[a]
1	CH₃CN	60		42
2	CH₂Cl₂	60		71
3	**THF**	**60**		**96**
4	Acetone	60		80
5	Dioxane	60		80
6	THF	15		53
7	THF	30		78
8	THF	180		96
9	THF	60	5	90[b]
10	THF	60	10	91[b]

[a]Isolated yield following column chromatography. [b]conversion as determined by ¹H NMR analysis.

the optimal conditions. The yield of **2a** was determined after each run over ten experiments, with no significant decrease observed (Table 1, entries 3 cf. 9 and 10). Reanalysis of the used column by ICP-AES allowed palladium composition to be determined and the degree of leaching ascertained. The used column contains 0.87 wt % Pd, indicating around 0.54% leaching per run. Finally, the enantiopurity of **2a** was determined using HPLC over chiral stationary phases, demonstrating negligible racemization, with the aldehyde isolated in 99% enantiomeric excess.

Using a single Pd/XAD-4 column, the generality of the Fukuyama reduction was investigated with aromatic and aliphatic thioesters (Table 2). Benzoic acid-derived thioester

Table 2. Scope of the Continuous Flow Fukuyama Reduction
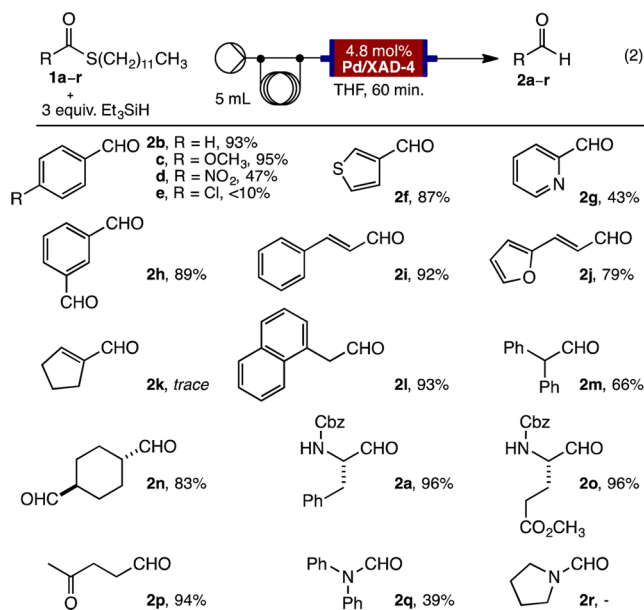
[a]Isolated yield following column chromatography.

1b and electron-rich thioester **1c** were reduced in excellent yields to aldehydes **2b** and **c**, while the electron-poor *p*-nitrobenzaldehyde (**2d**) formed in modest yield, accompanied by a variety of materials, presumably from reductions about the nitro group. In contrast, the *para*-chloro substituent (i.e., **1e**), significantly retarded the reaction, with <10% of the expected aldehyde formed as a mixture with unreacted starting material. When this reaction was attempted using reported batch conditions,[7] no conversion of the thioester was observed. Next, thioesters bearing coordinating functionality were examined, with 3-thiophene aldehyde **2f** formed in 87% yield, and 2-picolinic acid-derived thioester (i.e., **1g**) providing the corresponding aldehyde **2g** in modest yield. Reduction of dithioester **1h** could be achieved, providing dialdehyde **2h** in 89% yield, whereas the cinnamic acid thioester **1i** and α,β-unsaturated furyl thioester **1j** were reduced chemoselectively to provide aldehydes **2i** and **2j** in good yield. Surprisingly annulation about the α,β-unsaturated thio esters was not tolerated, with cyclopentenal **2k** formed in trace quantities. Benzylic thioesters were reduced smoothly, providing **2l** and **m**, in 93 and 66% yield respectively, while the aliphatic dithioester **1n** was reduced to dialdehyde **2n** in 83% yield. The reaction shows good functional group tolerance with amino acid

Table 3. Continuous Flow Thioesterification

Tris(2-aminoethyl)amine (**4**)   (Aminomethyl)polystyrene (**5**)   Amberlyst A21 (**6**)

entry	resin	equiv	acid chloride	% yield 1^a
1	tris(2-aminoethyl)amine **4**	1.5	PhCOCl (**3b**)	47
2	aminomethyl **5**	3.5–5	PhCOCl (**3b**)	40
3	**Amberlyst A21 (6)**	**7.6**	**PhCOCl (3b)**	**99**
4	Amberlyst A21 (**6**)	7.6	$p(MeO)C_6H_4COCl$ (**3c**)	96
5	Amberlyst A21 (**6**)	7.6	$pNO_2C_6H_4COCl$ (**3d**)	98
6	Amberlyst A21 (**6**)	7.6	PhCH=CHCOCl (**3i**)	91
7	Amberlyst A21 (**6**)	7.6	Ph_2NCOCl (**3q**)	99

^{a}Isolated yield following column chromatography.

derivatives and ketone containing substrates, reduced smoothly to afford aldehydes **2a**, **o**, and **p** in 96, 96, and 94% yield, respectively. This highlights the utility of the procedure, which allows the synthesis of aldehydes inaccessible using DiBAL-H reductions (i.e., **2o** and **2p**). Finally, thiocarbamates proved to be poor substrates for the reduction, with **2q** isolated in modest yield, while the aliphatic variant (i.e., **2r**) failed to form.

Having realized the continuous flow Fukuyama reduction, attention was directed to the multistep conversion of acyl chlorides to aldehydes via the thioester.[14] To achieve this transformation, three polymer-supported amine bases, tris(2-aminoethylamine) **4**, aminomethyl **5**, and Amberlyst A21 **6**, were trialed using benzoyl chloride **3b** and dodecanethiol as substrates (Table 3, entries 1–3). Using Amberlyst A21, the expected product (**1b**) was formed in quantitative yield (Table 2, entry 3). The generality of this reaction was examined with electron-rich benzoyl chloride **3c** (Table 3, entry 4), electron-poor benzoyl chloride **3d** (Table 3, entry 5), cinnamoyl chloride **3i** (Table 3, entry 6), and carbamoyl chloride **3q** (Table 3, entry 7), all giving the expected thioesters in excellent yield.

An integrated multistep thioesterification/Fukuyama reduction was trialed by linking the supported catalysts discussed previously and exploiting the optimized conditions (Table 1, entry 3 and Table 3, entry 3). Unfortunately, it was only possible to isolate benzaldehyde (**2b**) in 45% yield (Scheme 2). It was proposed that this was a consequence of thiol poisoning of the catalyst. Consistent with this was the observation that decreasing the Pd loading to 1 mol % decreased the yield further, while increasing the loading allowed quantitative conversion.

Scheme 2. Multistep Thioesterification/Fukuyama Reduction of 3b without Scavengers
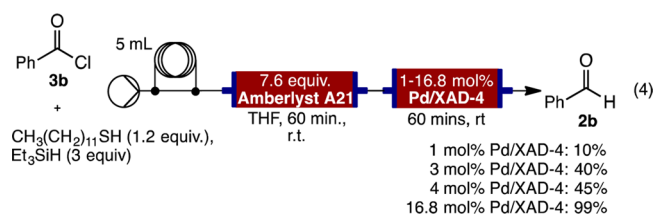
To allow more efficient conditions to be developed, particularly ones that did not lead to destruction of the previously reusable Pd/XAD-4 catalyst, studies were directed toward a continuous flow system in which unreacted thiols are scavenged. In addition to removing unreacted thiol, we took this opportunity to examine the purification of the aldehyde product. The Fukuyama reaction is known to be plagued by issues associated with the separation of the aldehyde from the silythioether, particularly when working with high molecular weight odorless thiols.[7,8] Although chromatographic approaches and derivatization studies have been developed to address this challenge, we envisaged an inline catch-and-release strategy[18] to allow the aldehyde to be purified more efficiently. In addition, although Pd leaching was moderate, it was decided to also introduce a palladium scavenger to the system.

A number of thiol scavenger resins were trialed under batch conditions. Eventually, it was found that polymer-supported isocyanate **7** in the presence of triethyl amine allowed rapid consumption of free thiol. Thus, following the Amberlyst A21 (**6**) column, an isocyanate column was introduced along with a stream of Et_3N (Table 4) to allow unreacted thiol to be removed. The use of Quadrapure IDA resin to remove trace metals is established,[19] and was introduced following the Pd/XAD-4 column. Finally, after optimization, it was found that primary amine resin **4** at 60 °C led to complete sequestration of the aldehyde. The immobilized imine product could then be released by exposure to a mixture of formic acid, methanol, and water. Application of these conditions in an integrated continuous flow system was then examined exploiting a range of acyl chlorides. This system gave outcomes similar to that of the isolated Fukuyama reduction (Table 2). Thus, benzoyl chlorides **3b**, **c**, and **h** gave aldehydes (i.e., **2b** and **c**) and dialdehyde **2h** in excellent yields, as did cinnamoyl chloride (**3i**). Similarly, aliphatic acyl chlorides **3l**, **m**, and **p** reacted smoothly to give the expected aldehydes (Table 4). When the reduction of activated phenylalanine was examined, the expected aldehyde **2a** formed in 94% yield. Unfortunately, the enantiopurity of this compound was compromised, with the catch/release protocol shown to lead to erosion in optical purity.[20] In all cases, yields were comparable to those achieved when performing the thioesterification and Fukuyama reduction as discrete steps. Although the system is reusable and one series of columns was used for all experiments, regeneration of

Table 4. Integrated Multistep Thioesterification/Fukuyama Reduction
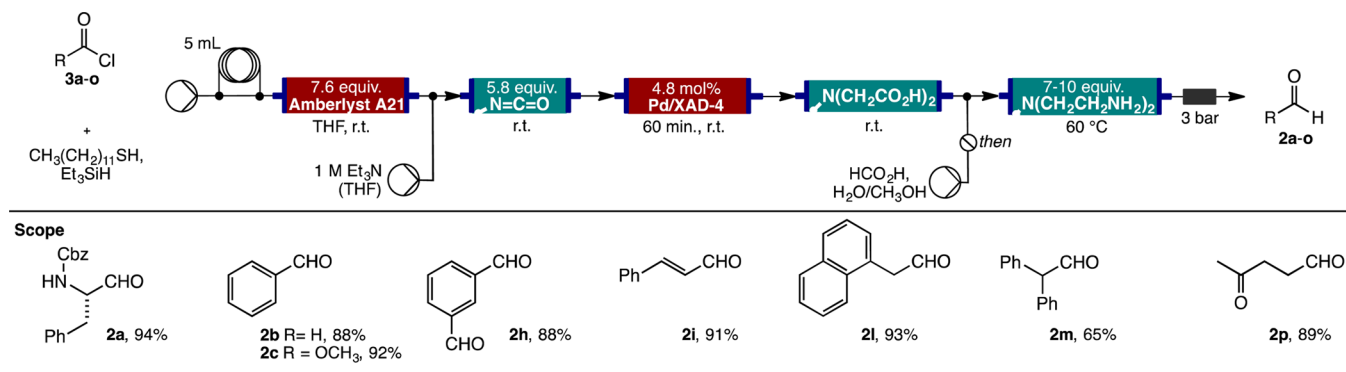
columns 1, 2, and 5 was undertaken after each run using standard washing techniques.[21]

Reduction of acid oxidation state substrates to the aldehyde is a routine, but often challenging, transformation in organic synthesis. As a consequence, overreduction to the alcohol, then oxidation to the aldehyde, is often applied. Through our studies, we have developed continuous flow strategies to achieve the synthesis of aldehydes from either thioester starting materials (i.e., **1**) or acyl chlorides (i.e., **3**) using the Fukuyama reduction. Both approaches exploit immobilized catalysts that are highly reusable, with a single system used for all scope investigations. Pivotal to the success of these approaches has been the development of continuous flow thioesterification, thiol capture, and catch-and-release purification strategies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization of all new compounds and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org..

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(20) Only partial resolution of the *R* and *S* signals was possible from the HPLC of this sample, indicating an ee of around 84%, as opposed to 99% from the isolated reduction.

(21) For full details, see the Supporting Information.