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Article

Scalable Palladium-Catalyzed C(sp3)−H Carbonylation of Alkylamines in Batch and Continuous Flow

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ABSTRACT: Development of scalable processes for C(sp3)−H oxidative carbonylation of alkylamines is reported to provide convenient access to the β-lactam scaffol d. A study of the kinetics of the process revealed that the reaction is CO-limited even at elevated pressures and that there is an optimal CO concentration for the most effective outcome—this understanding led to an increase in the turnover number from 7 to 420 in the optimized process. Two scalable processes were then developed: a batch process, characterized by a very low catalyst loading, and a continuous process for an oxidative C−H carbonylation reaction that uses a copper-tube-flow reactor as a heterogeneous source of Cu^{2+} oxidant. The continuous process was tested on oxidative carbonylation of several alkylamines, yielding very good results with virtually no optimization required. This study thereby builds upon the utility of flow chemistry applications to oxidative carbonylations and scalable metal-catalyzed processes more generally.

KEYWORDS: *oxidative carbonylation, flow chemistry, process optimization, β-lactams, C−H activation*

INTRODUCTION

Few reactions have had as significant an impact in synthetic chemistry as carbon−carbon bond formation via metal-catalyzed carbonylation. Insertion of CO into intermediate metal−carbon bonds to generate carbonyl groups via oxidative carbonylation is widely practiced at a laboratory scale, resulting in atom-efficient routes to a range of aromatic and aliphatic substrates including alcohols, diols, amines, and amino-alcohols.[1−5] Despite these obvious advantages, we cite Ullmann's Encyclopedia of Industrial Chemistry: "an industrial application of the oxidative carbonylation is not yet in sight".[6] This is due to the notorious complexity and inefficiency of oxidative carbonylations: the reactions are multiphase, often involving solid, liquid, and gas phases and, generally, are poorly understood from a mechanistic perspective. This makes predicting the conditions for scale-up and increasing efficiency of these reactions highly empirical and uncertain.

When reactions are controlled by kinetics, predicting scale-up is fairly straightforward. For reactions where the mechanism can be hypothesized and verified, it is feasible to predict the conditions of scale up from first principles.[7] Alternatively, when the mechanism is unknown, the tools of kinetic profiling coupled with in situ analytics allow the development of semiempirical kinetic expressions that are appropriate for scaling.[8,9] Neither of these approaches would work in the case of multiphase reactions when the rate-controlling step may alter between kinetics and mass transfer during the reaction. Hence, to successfully develop a reliable scaled-up multiphase reaction such as oxidative carbonylation, it is necessary to (i) experimentally study these reactions under a much broader range of conditions than is normally feasible in a standard synthetic chemistry laboratory, as this may allow to uncover transitions between mass transfer and kinetics and (ii) explicitly account for potential mass transfer limitations when designing experiments based on the reaction profiling methodology.

Enabling tools for these studies include continuous-flow and pressurized reactor vessels. A broad range of operating conditions (temperature, pressure, contact time, mixing efficiency) can be attained in flow processes in small-scale reactors,[10−13] which has previously been shown to benefit oxidative carbonylations[14] and other CH activation processes.[15−20] Alternatively, if short reaction times are not required, the conditions of intensive mixing and broad ranges of temperatures and pressures can be attained in small-scale pressurized batch reactors.

Hence, in this study, to develop a generic scalable process for oxidative carbonylation for the reactions of interest in synthetic chemistry, we extended the reaction profiling methodology to explicitly account for the possibility of mass transfer limitations and deliberately studied the reaction over a broad range of conditions that were intended to answer the questions about the relevance of two interfaces in this reaction system—gas−liquid and solid−liquid. This led us to develop two scalable processes: (i) a continuous-flow process for catalytic oxidative C(sp3)−H carbonylation using a copper-tube reactor as a source of Cu(II) cooxidant and (ii) a batch process, which is characterized by a significantly lower (compared to flow) catalyst loading; see Figure 1.

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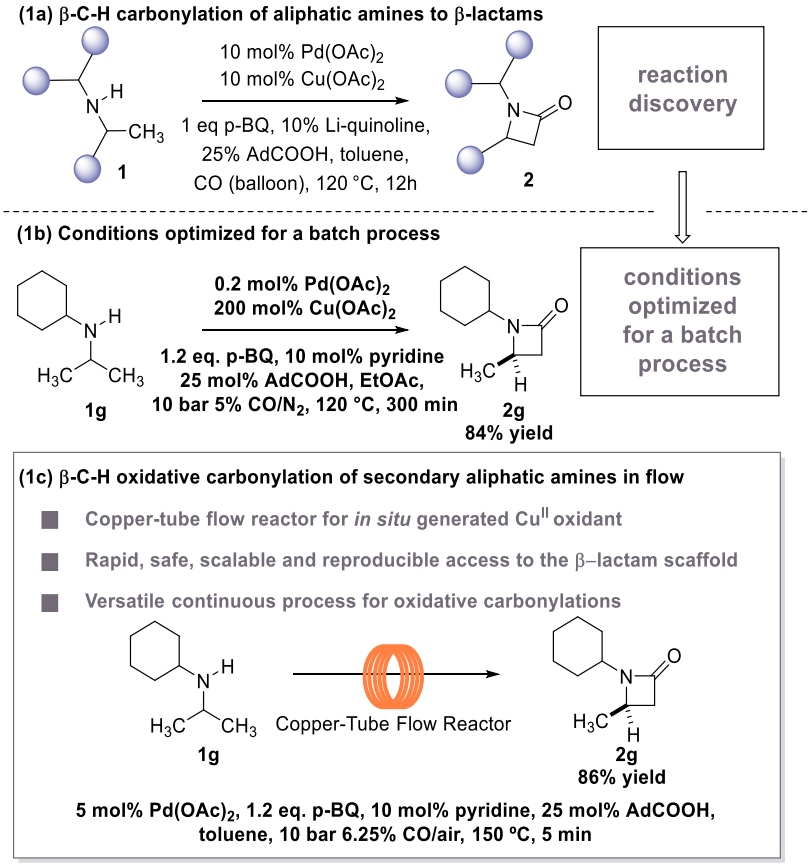

Figure 1. *β*-C−H oxidative carbonylation of aliphatic amines to *β*-lactams. Yields are given for the isolated compounds ((g) corresponds to a substrate number used in a later table). *P*-BQ: *p*-benzoquinone, AdCOOH: 1-adamantanecarboxylic acid, Li-Q: lithium-quinoline.

BUILDING PROCESS KNOWLEDGE

The suggested mechanism for this transformation, based on our previous study,[21] is shown in Figure 2. After the generation of catalytically active $Pd(O_2CR)_2$ species, subsequent addition of the aliphatic amine and CO results in the anhydride formation shown as reaction (**a**) in Figure 2. Carbamoylation, shown as the transformation (**b**) then establishes the resulting intermediate for reversible C−H activation (**c**) with the addition of *p*-BQ. Reductive elimination (**d**) occurs forming the resulting *β*-lactam, as Pd is recycled through off-cycle redox processes involving Cu(II), thereby reforming the active Pd species.

To build process understanding, we applied the reaction progress kinetic analysis methodology[9] and investigated the reactions at elevated pressures of CO in batch. In our previous studies of a similar system, we observed formation of a catalytically inactive bis-amine-palladium complex, being a product of coordination of two molecules of the alkylamine to the palladium catalyst.[7,22] Formation of this off-cycle intermediate results in a negative order influence of the concentration of the starting material on the apparent reaction rate. Since the formation of the bis-amine-palladium complex is also possible in this reaction, we anticipated similar behavior forming $Pd(I)_2$. As predicted, the concentration of the starting material proved to have an apparent negative order; see Figure 3a.

The influence of the concentration of the palladium catalyst on the reaction rate shows a complex behavior. The increase from 2.5 to 5 mol % caused an acceleration of the reaction; however, the increase was significantly smaller than expected (see Figure 3b). A further increase in the catalyst concentration did not bring any significant change to the reaction rate. This behavior could be explained by a mass-transfer-related limitation, most likely due to either the solubility or flux of carbon monoxide to the liquid phase. Should our hypothesis be true, an increase in CO partial pressure should result in an increase in the observed reaction rate.

Investigating the influence of pressure, we observed that the increase in pressure not only increased the initial reaction rate but also resulted in higher yields; see Figure 3c. This positive trend reversed after around 10 bar, where a significant decrease of the yield was observed, presumably owing to a strongly reductive nature of carbon monoxide that can reduce Pd(II) to Pd(0). Pd(0) upon precipitation and aggregation forms so-called palladium black.

The increase of total pressure increases the oxygen partial pressure and hence the concentration of dissolved oxygen, which can also increase the apparent reaction rate. This could, potentially, accelerate the oxygen−copper−palladium redox cycle to generate a more active palladium catalyst. To exclude this possibility, we ran several experiments wherein the concentration of copper (II) acetate was varied at the same partial pressure of oxygen. There was no increase in the observed reaction rate; see Figure 3d. Hence, we concluded that the reoxidation of palladium is not a turnover limiting step.

The presence of 5 mol % of the ligand, Li-quinoline (Li-Q), increased the yield of the reaction by more than 20%, although further increase in its concentration did not improve the yield

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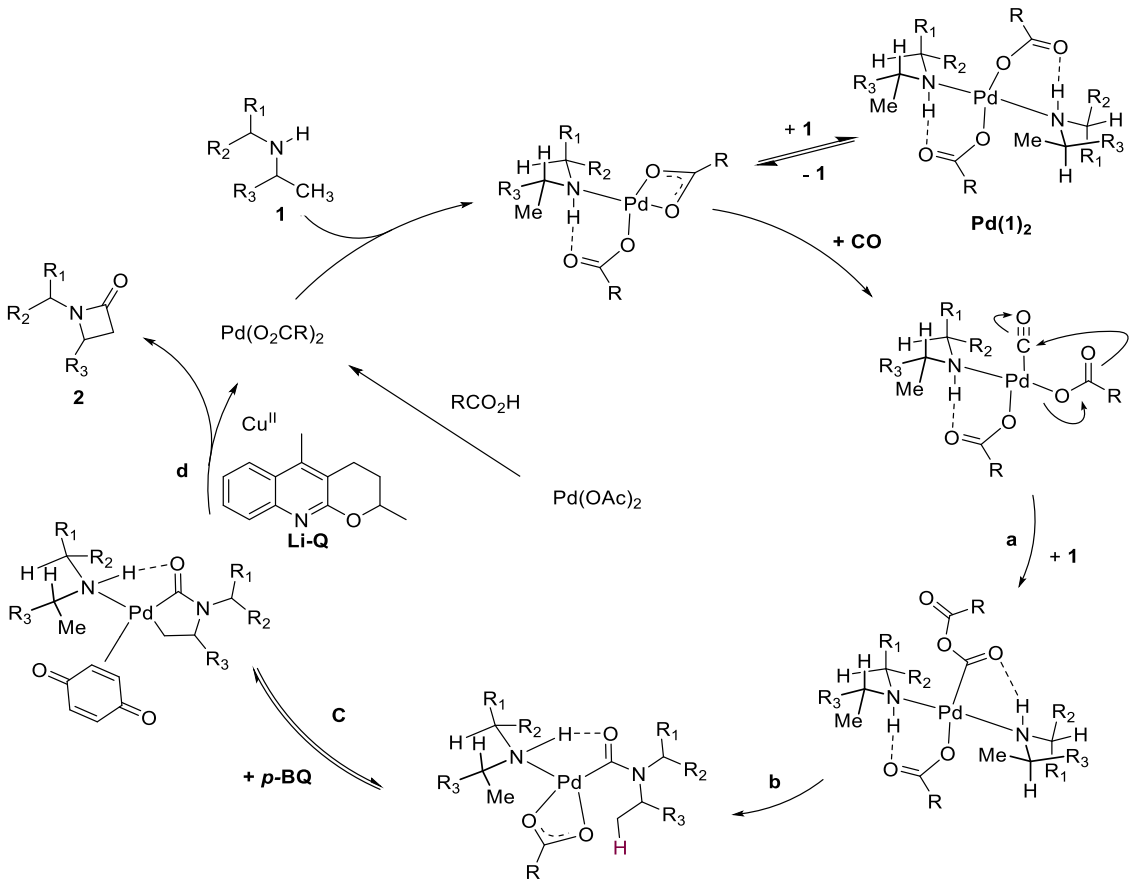

Figure 2. Suggested mechanism for the formation of a β-lactam, **2**, from an aliphatic amine, **1**. Reaction types: (**a**) anhydride formation, (**b**) carbamoylation, (**c**) C−H activation, and (**d**) reductive elimination.

further; see Figure 3e. The rate is zero-order with respect of the ligand. Similarly, 1,4-benzoquinone, which was required in slightly higher than stoichiometric amount to achieve highest yields, proved to have no influence on the rate of the reaction; see Figure 3f. This suggests that both Li-quinoline and *p*-benzoquinone enter the catalytic cycle after the turnover limiting step and thus can be omitted in setting up the kinetic model. When testing the effects of 1-adamantanecarboxylic acid, an initially positive influence was observed on both the yield and reaction rate. However, at concentrations more than double of the concentration of the catalyst, the trend reversed and the yield as well as the rate decreased; see Figure 3g.

The estimation of activation energy for the observed reaction rate, using gPROMS Model Builder 4.0.0,[23] gave a very low value of 5 kJ mol^{-1}. Combined with the apparent zero order of influence of several reaction species on the reaction rate, this suggests that the reaction is starved of one of the reactants. The positive order of the partial pressure of CO on the observed reaction rate most likely means that the limiting factor is the rate of feed of CO into the liquid phase.

To test this hypothesis, we ran the reaction with several solvents characterized by different CO solubilities. In the absence of other possible influences of a solvent on the catalytic reaction, the solvents characterized by a lower solubility of CO should result in a slower reaction. Due to the lack of reliable literature data on Henry's law coefficients for CO in standard organic solvents, an a priori thermodynamic method was used to predict them.[24,25] Solvents were selected that were known to give good performance in other reported carbonylation processes while avoiding solvents that are less environmentally friendly. From the selection tested, only benzene- and ester-derived solvents gave measurable reactivity, Table 1, in which more than 0% yield was obtained. DMF, DMSO, and MeCN presumably coordinated with the Pd(II) species forming kinetically stable complexes, thus prohibiting the reaction. The reaction in ethyl acetate was slower than the reaction in toluene, which is consistent with the predicted CO solubility in EtOAc being significantly lower than in toluene. A greater observed reaction rate in toluene further supports the hypothesis that the overall reaction was starved of CO, leading to lower yields of the β-lactam product.

This CO deficiency may be one reason for severe inefficiencies of oxidative carbonylation processes performed at ambient pressure, as even at elevated pressure, our model reaction appears to be CO-limited. The observed reaction rate of the investigated carbonylation reaction reached a maximum yield at a total pressure of ∼10 bar; further increase in pressure resulted in the decrease of the yield. This observation enabled the identification of the optimal pressure/concentration of CO for this process. Based on the available heuristics, a set of optimal conditions were identified; see Table 2.

PROCESS OPTIMIZATION

The amount of catalytic palladium used, arising from the amount of the precatalyst 5−10 mol % palladium(II) acetate used, is still a significant amount of rare metal and raises issues of sustainability (resource use) and safety (Pd toxicity) for potential industrial applications.[26] Therefore, it is highly

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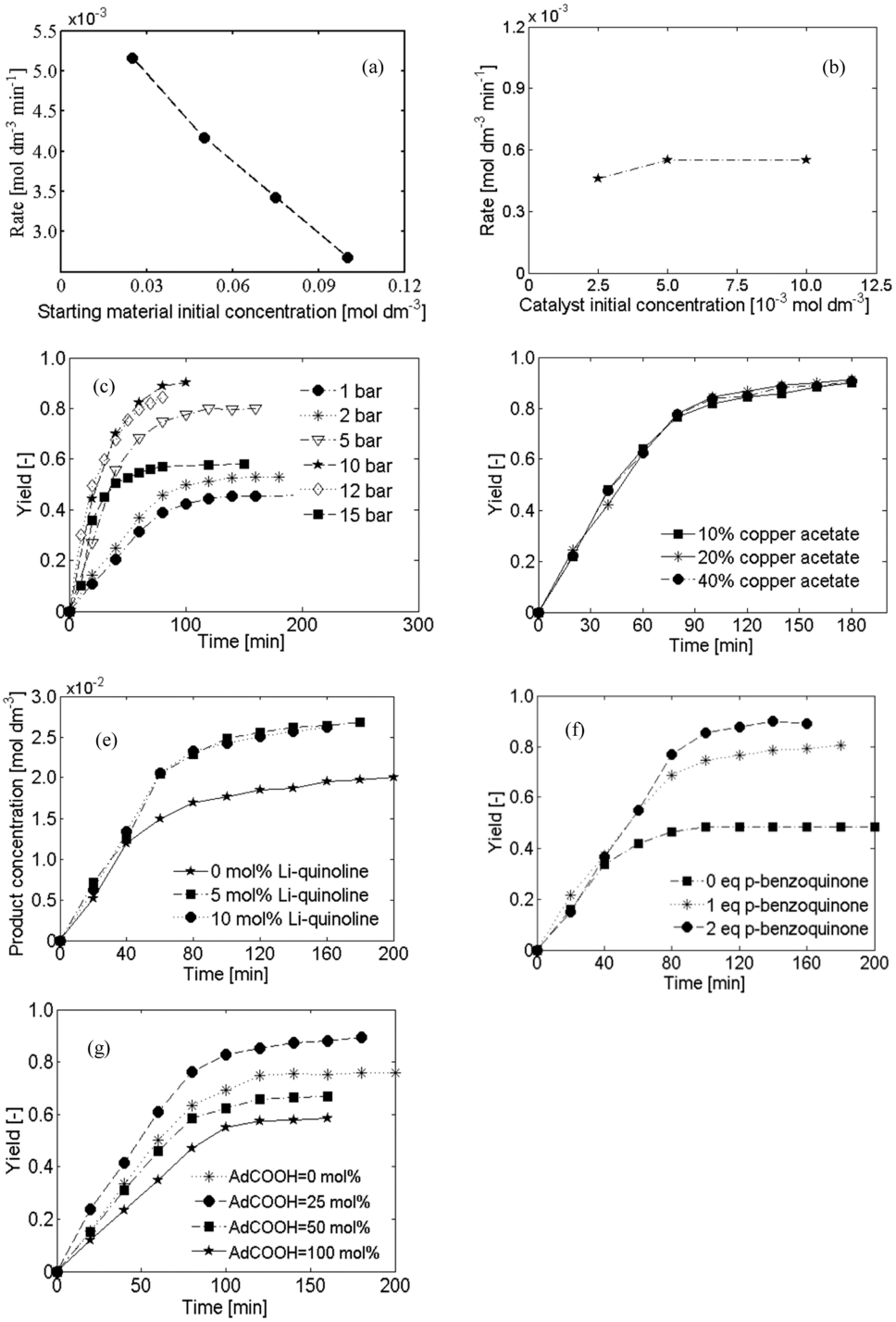

Figure 3. Results of the reaction progress kinetic analysis. Trendlines added for the convenience of the eye. Labels (a)−(g) are used in the text. Starting material in (a): *N*-cyclohexyl-isopropylamine, catalyst in (b): $Pd(OAc)_2$.

desirable to increase the turnover number (TON) using conditions given in Table 2 as the standard starting point. Gaunt and co-workers discovered that the yield of this reaction can be increased using nitrogen ligands, namely, Li-quinoline or quinuclidine.[27] However, the mechanism of this influence still remains unknown. We questioned whether the ligand plays a direct role in the formation of the product or rather coordinates with the palladium species after product formation, preventing the formation of insoluble species prior to oxidation back to the active catalyst; zero-order influence of Li-quinoline on the apparent reaction rate may suggest the latter.

To test our hypothesis, we replaced the expensive Li-quinoline with a much cheaper and environmentally friendly amine-derived ligand, pyridine. Despite using this much more general ligand, we achieved even better results in comparison to the standard conditions, attaining and increase in TON from the initial 8−28; see Table 3, entry 5. As pyridine can be used as a ligand, this supports the hypothesis that the role of the ligand is not directly connected to the formation of the product, but nitrogen ligands help to solubilize the Pd(0) species and prevent formation of palladium black. In the course of further tests, we discovered that this ligand is suitable only

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Org. Process Res. Dev. 2023, 27, 649−658

Table 1. Henry's Law Coefficients Predicted by COSMO RS at 120 °C[a]

solvent	Henry's law coefficient [bar]	measurable reactivity
toluene	697.9	yes
p-xylene	672.8	yes
acetonitrile	1529.2	no
ethyl acetate	1019.5	yes
isopropyl acetate	918.0	yes
THF	957.9	no
DMF	1391.0	no
DMSO	1776.3	no

[a]Reactions performed using standard conditions (Figure 1a) at 10 bar of 6.25% v/v CO balanced by air.

Table 2. Standard Conditions Used in Process Optimization[a]

N-cyclohexyl-isopropylamine	0.05 mol dm^{-3}
$Pd(OAc)_2$	0.005 mol dm^{-3} (10 mol %)
$Cu(OAc)_2$	0.0025 mol dm^{-3} (5 mol %)
p-benzoquinone	0.075 mol dm^{-3} (150 mol %)
AdCOOH	0.015 mol dm^{-3} (30 mol %)
Li-quinoline	0.0025 mol dm^{-3} (5 mol %)
CO/air 6.25% v/v	10 bar
temperature	120 °C

[a]The reactions were conducted at a 20 mL scale using a 2 cm cross-shaped magnetic bar at an agitation rate of 300 rpm.

for some selected substrates, but this is still an important observation as this significantly decreases the cost and environmental impact of the overall process.

With the awareness of the solubility issues of Pd(0) complexes and whether all catalytically active species are indeed soluble in toluene, we decided to test other solvents that may be suitable for this reaction. We discovered that by replacing toluene with ethyl acetate, we can achieve an increase in TON and lower the catalyst loading to 1 mol % without a significant decrease in the yield. The reactions in ethyl acetate required much longer reaction times than the reactions under the same conditions in toluene; for the same conditions, we require 300 min in EtOAc vs 120 min in toluene.

Finally, we investigated the effect of the gas phase composition on the TON. We questioned whether removal of oxygen from the system could potentially increase catalyst stability. However, the removal of the gas phase oxidant would require an increase in the concentration of the copper oxidant to a stoichiometric amount to allow the catalytic cycle to proceed but would prohibit formation of water as a byproduct from reoxidation of copper. Experimental results then confirmed that TON was significantly higher in this case, and for an optimal set of conditions, the catalyst loading was as low as 0.2 mol %; see Table 3, entry 7.

PROCESS DESIGN

With the understanding that the limiting factor precluding intensification of the reaction is mass transfer between the gas and the liquid phases, we studied the possibility of translating the process into continuous flow. This would allow us to enhance mass transfer, improve process safety, and ensure scalability of the process. Continuous-flow processes are also easier to control and more reproducible.[28] Significant attention has been paid to development of flow chemistry methods for challenging chemical transformations and extensive literature reports from this field are available.[12,28−34] Generally, there are very few examples of multiphase catalytic flow processes that include continuous liquid phase, dispersed gas phase, and dispersed solid phase, as the majority of the studies, including those by us, were performed with gas−liquid or liquid−liquid flows through a stationary solid phase.[35] Additionally, some interest has been paid to coflow of dispersed solids in gas−liquid biphasic main flow.[36] In this work, we chose to reduce the number of phases, which will reduce the overall complexity for the process scale up—full reaction setup information is described in the Supporting Information.

Reduction of the number of phases could neither be achieved by increasing the pressure to the point of full dissolution of the gas phase due to a rather narrow range of the tolerated CO concentrations nor by implementing membrane systems to continuously deliver gaseous reactants to the liquid phase due to inevitable membrane clogging and further pressure requirements. Therefore, we experimented with the use of heterogeneous precursors of Cu(II) salts instead of the continuous delivery of solids.

We initially probed this method by introducing a copper wire into a tubular reactor with a gas−liquid slug flow based on our previous positive results using copper wire in a continuous polymerization reaction.[37] The in situ oxidized metallic copper was able to reoxidize the palladium catalyst; see Table 4, entry 1. However, the system proved to be stable only for short periods of time. Despite this, we were encouraged by the positive initial results and elected to expand the contact area between the gas and liquid reactants and the heterogeneous precursor of the copper oxidant. We were inspired by the use of a copper-tube-flow reactor (CuTFR) by Zhang et al.[38] and Gemoets et al.[39] for this purpose and we used this setup for the reaction, demonstrating the first report of a triphasic (solid−liquid−gas) system incorporating a CuTFR. Accordingly, the use of a CuTFR resulted in a significant improvement of

Table 3. Selected Results from Process Optimization[a]

entry	process option	catalyst loading (Pd/Cu) [mol %]	additives [mol %]	time [min]	TON [-]	yield of **2g** [%]
1	initial conditions (Figure 1a)	10/10	10 Li-quinoline	360	7	68
2	10 bar CO/air	5/5	5 Li-quinoline	75	17	84
3	10 bar CO/N_2	5/200	5 Li-quinoline	85	17	86
4	1−10 bar CO	10/200	10 Li-quinoline	1440		trace
5	(2) + pyridine	3/5	10 pyridine	150	28	85
6	(3) + pyridine	1/200	10 pyridine	200	78	78
7	(5) + EtOAc (Figure 1b)	0.2/200	10 pyridine	300	420	84*

[a]The reactions were performed using 1.5 equiv of *p*-BQ and 25 mol % AdCOOH, T = 120 °C. Yields marked with an asterisk are given for the isolated compound, where others are determined by gas chromatography. Entries 2 and 3 consist of 6.25% v/v CO and 5% v/v CO, respectively.

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Org. Process Res. Dev. 2023, 27, 649−658

Table 4. Development of the Flow Process[a]

entry	process option	catalyst loading (Pd/Cu) [mol %]	time [min]	yield of **2g** [%]
1	flow (using copper wire)	10/-	20	80
2	flow (using CuTFR) (Figure 1c)	5/-	5	86*

[a]The reactions were performed using 1.2 equiv of *p*-BQ and 25 mol % AdCOOH. T = 150 °C. The reactions were performed in toluene using 6.25% v/v CO/air mixture. Yield marked with an asterisk is given for the isolated compound, where others are determined by gas chromatography.

stability of the system and in the increase in the observed reaction rate; see Table 4, entry 2. The layer of oxidized Cu was regenerated in situ by the oxygen present in the gas phase and proved to be stable for at least 8 h when run continuously.

This CuTFR-enabled flow process provides an easy access to the in situ generated Cu(II) species that are also widely used as oxidants in other related processes, where we believe it could also provide significant benefits in the development of these continuous-flow oxidative chemical systems. The removal of the third phase and operation in the so-called "slug flow" regime increased the mass transfer between the gas and the liquid phases significantly, resulting in an increased productivity.[40] In the continuous-flow setup, toluene was used instead of EtOAc to allow operation at short residence times, which also led to a significant reduction of Cu leaching. After designing this flow process, we decided to demonstrate a selected substrate scope; see Figure 4. A full, original substrate scope

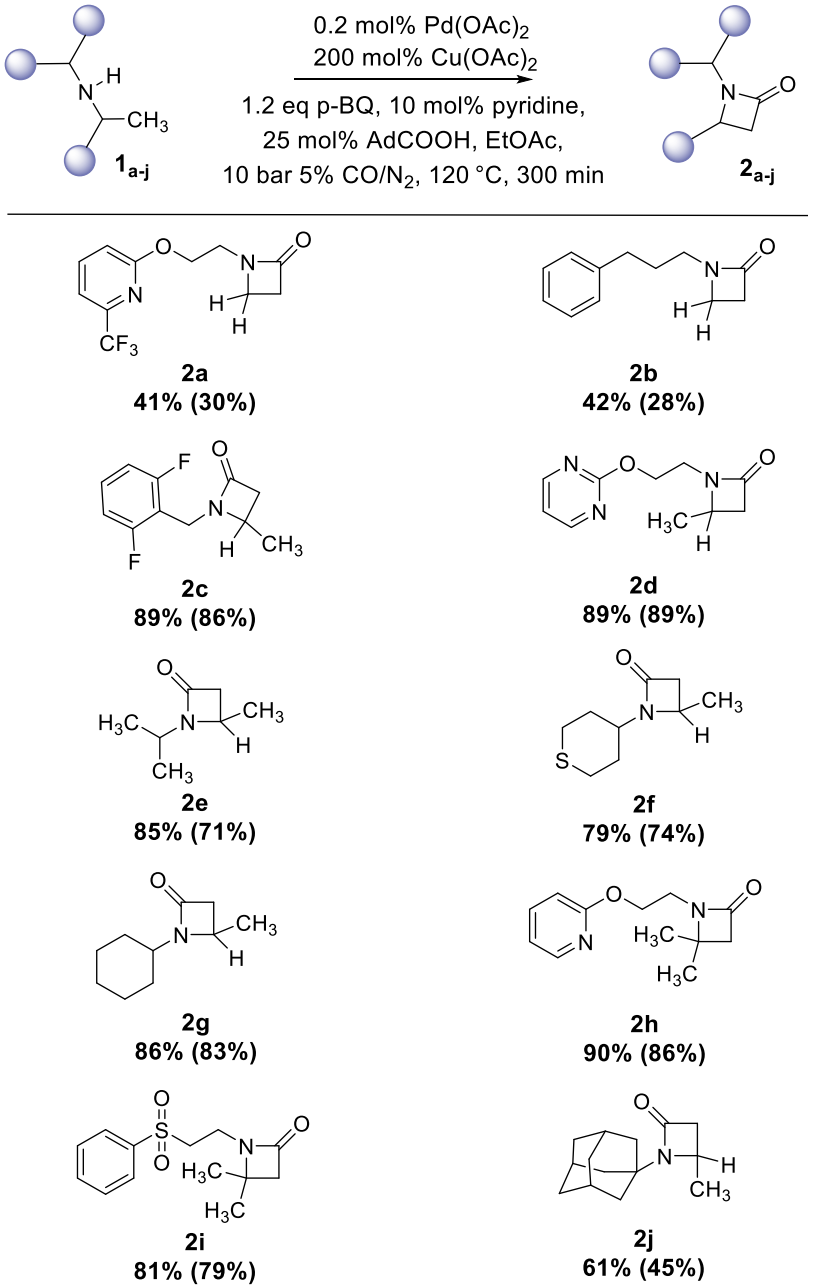

Figure 4. Selected substrate scope in flow. Yields are given for the isolated compounds. Yields in brackets are from the initial report of Gaunt and co-workers.[27]

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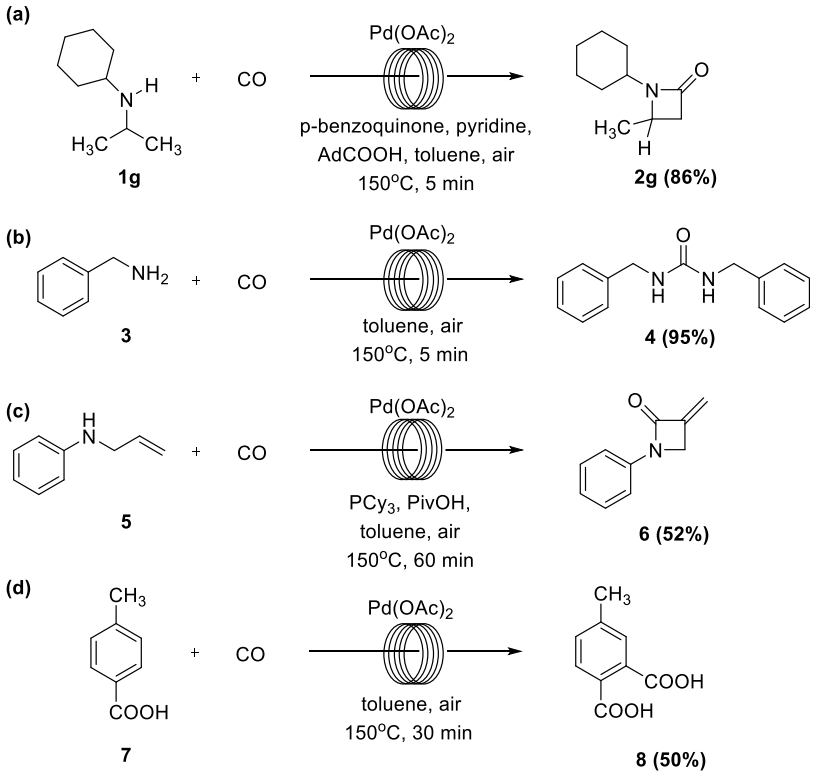

Figure 5. Selected scope of the process. Yields are given for the isolated compounds. Tests performed under 7 bar of 6.25% v/v CO balanced by air: (a) carbonylation to *β*-lactams, (b) carbonylation to ureas, (c) carbonylation of *N*-allylamines, and (d) carboxylation to benzoic acids.

described by Gaunt and co-workers was replicated,[27] wherein this new continuous-flow setup of all substrates tested worked equally well or better than in the original batch-setting report.

We investigated the utility of the CuTFR-enabled flow process on other, mechanistically distinct, reactions, as shown in Figure 5. The process worked well, where virtually no further optimization was required. First, the carbonylation of secondary amines to the corresponding ureas was tested and full conversion was achieved with almost quantitative yields within 5 min.[41] Furthermore, the oxidative carbonylation of *N*-allylamines for the synthesis of *β*-lactams was conducted under slightly adjusted conditions using tricyclohexylphosphine (PCy3) and pivalic acid (PivOH) for 60 min residence time to produce the desired products in comparable yields to the conventional solution-based protocol.[42] Finally, the C(sp2)−H carboxylation of benzoic acids to give the *ortho*-phthalic acid product was successfully demonstrated using the same CTFR-enabled flow process.[43] In all cases, the reaction conditions used here were different from those in the original published reports but our modified protocol performed equally well or better for each reaction.

As we were aware of both the advantages and disadvantages of flow chemistry,[10,44] including at times prohibitively expensive setup costs or expertise barriers, we also developed a batch process for the C(sp3)−H carbonylation of alkylamines (Figure 1b). After evaluation of the reaction setup, optimal conditions could be characterized by very low Pd(II) catalyst loading, high yield, and reasonable time for reaction completion. On the scalability of the batch process, we found that upon maintaining constant or greater surface-to-volume ratio ($\geq$0.56 cm^{-1}) or mass transfer coefficient ($k_La \geq 0.085$ min^{-1}) as well as energy dissipation rate, the protocol can be scaled without further chemistry considerations. However, despite the advantages of this optimized process, the batch protocol has some significant drawbacks that may be prohibitive for scale-up. Specifically, the operation in batch at elevated pressures of CO mixture and using temperatures above the boiling point of the solvent raises safety concerns.

■ ENVIRONMENTAL IMPACT

While the technological benefits of the new processes are fairly apparent, we also wanted to screen the environmental impacts of the two new process options for oxidative carbonylation chemistry. The environmental impacts of the optimized flow and batch reaction protocols were compared with that of our starting process[11] using a life cycle assessment (LCA) methodology. We screened life cycle impacts with respect to the production of 1 kg of 1-cyclohexyl-4-methylazetidin-2-one (functional unit), using Umberto 5.6, ReCiPe 2008[45] impact assessment methodology, and Ecoinvent 3.2 database for the inventory. For all molecules missing from Ecoinvent, simplified life cycle inventories were developed. Details of the models are described in the Supporting Information. Although using additional metrics may help to give a more complete framing of the environmental impacts of these processes, using LCA alone gives a very accurate and broad evaluation of these measures.[46]

The results of calculations of ReCiPe environmental impacts show that the impact of the flow process is half of the original process, and most of the impacts of the batch process are even smaller. Looking at the contributions of the individual processes to the impacts, we note that the impacts are dominated by the manufacture of Pd (Figure S4).

We then modeled recovery of Pd and Cu[47] and reevaluated the impacts of the batch and flow processes, assuming Pd and Cu are partially recovered. This resulted in the life cycle

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impacts for the optimized flow and batch processes to become very similar (Figure S5). It must be emphasized that life cycle impact analysis provides a significantly more accurate and realistic evaluation of the environmental impact of the new processes, compared to simplified proxy metrics, such as the process mass index (PMI), defined as the mass of raw materials normalized to the mass of the product and favored by fine chemical and pharmaceutical industries. We have evaluated PMIs for the three processes. The PMI for the original process was 13.9; for the optimized flow process (without metal recovery), it was also 13.9, and for the optimized batch process (also without metal recovery), it was 18.5. However, as we see from the life cycle assessment study, the mass indicator is providing incorrect guidance in the processes under consideration. This illustrates that the simplified metrics, such as PMI is not accounting for the life cycle impacts of molecules upstream of the process under consideration. Despite the larger amounts of molecules being used in the newly developed processes, due to changes in the molecules used, the overall life cycle impacts were significantly reduced—this is shown in Figure 6.

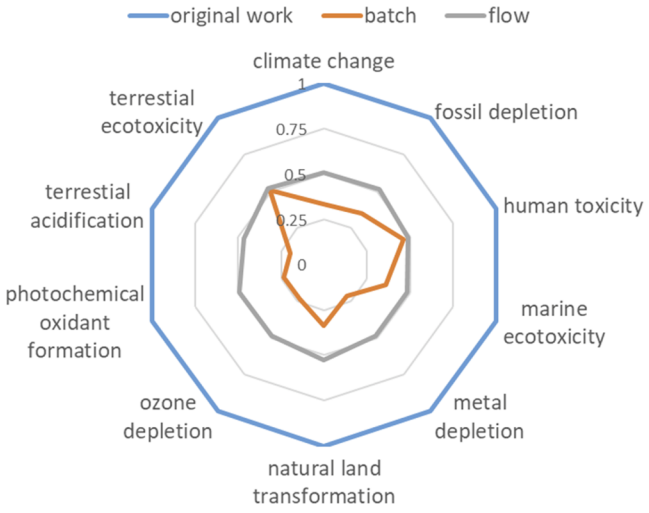

Figure 6. Comparative analysis of environmental impacts of the original reaction, the optimized flow, and batch protocols.

DISCUSSION AND CONCLUSIONS

A kinetic study and optimization of the reaction based on the available process information allowed a process design that resulted in two competitive process options for the β-C−H oxidative carbonylation of secondary amines. A simple and broadly applicable batch process allowed the reduction in Pd loading down to 0.2 mol % at the expense of a much larger amount of copper catalyst used. On the other hand, the continuous-flow process allowed in situ generation of the copper-based oxidant from cheap and widely available heterogeneous precursors. The copper-tube-flow reactor can be easily replaced by, for example, copper-based static mixers. This would further increase the scope of the process.

Both identified processes have potential broad applicability scope and can serve as exemplar solutions to the problem of difficult scale-up of oxidative carbonylation reactions. When generating small quantities in the range of milligrams or grams, the safe, robust, and flexible flow process can be of great use. For larger scales, the batch protocol may be easier to implement, subject to the available pressure and safety monitoring equipment. The commonly used equipment available in most production facilities and research institutions is designed for operation under similar conditions, and upon further scale-up, can serve as a viable process. Furthermore, these newly developed processes are also significantly more environmentally friendly when compared with originally published conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.2c00378.

Models for life cycle inventory; ReCiPe impact categories; analysis of life cycle impacts; and impacts when considering metal recovery (PDF)

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Notes

The authors declare no competing financial interest.

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