ORGANIC
LETTERS

2013
Vol. 15, No. 11
2794–2797

Modernized Low Pressure Carbonylation Methods in Batch and Flow Employing Common Acids as a CO Source

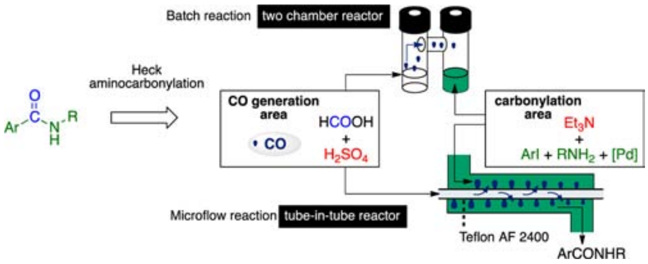
Célia Brancour,[†] Takahide Fukuyama,*,[†] Yu Mukai,[†] Troels Skrydstrup,[‡] and Ilhyong Ryu*,[†]

Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan, and Center for Insoluble Protein Structure (inSPIN), Interdisciplinary Nanoscience Center and Department of Chemistry, Aarhus University, Gustav Wieds Vej 14, 8000 Aarhus, Denmark

fukuyama@c.s.osakafu-u.ac.jp; ryu@c.s.osakafu-u.ac.jp

Received April 23, 2013

ABSTRACT



Carbonylation reactions, such as Heck, Sonogashira, and radical carbonylations, were successfully carried out in a "two-chamber reactor" where carbon monoxide was produced *ex situ* by the Morgan reaction (dehydration of formic acid by sulfuric acid). By a subsequent application in a microflow system using a "tube-in-tube" reactor where gas-permeable Teflon AF2400 was used as the inner tube, it is demonstrated that formic acid/sulfuric acid can be employed concomitantly with an amine base such as triethylamine in the Heck aminocarbonylation of aryl iodide.

Carbon monoxide (CO) has proven to be a practical carbonyl source for the preparation of a wide variety of carbonyl compounds, which involve aldehydes, ketones, carboxylic acids, and their derivatives.[1] However, both academic and industrial research have demonstrated a certain reluctance to study such reactions, due to the difficulty in handling the odorless, toxic, and flammable CO gas. Nevertheless, methods have been developed for carrying out carbonylation reactions without the direct use of gaseous CO.[2] Such transformations exploit *in situ* generated carbon monoxide from a variety of CO precursors,[3] including aldehydes,[3a−c] formates,[3d] formamides,[3e−g] and metal carbonyls such as $Mo(CO)_6$ and $W(CO)_6$.[3h] However, these alternative reagents have been involved in protocols that include the mixing of substrates, catalysts, and other additives in the same reaction vessels, which could limit the applications of carbonylation reactions.

Recently, one of us has reported a new and practical approach for carbonylation reactions, consisting of using a two-chamber reactor (COware) with two new solid CO precursors. This reactor allowed the *ex situ* generation of CO (in the decarbonylation chamber) while the gas was consumed in the other chamber during the carbonylation reaction.[4] This concept was exemplified with a number of

---

[†] Osaka Prefecture University.

[‡] Aarhus University.

(1) (a) Kollár, L. *Modern Carbonylation Methods*; Wiley-VCH: Weinheim, 2008. (b) Beller, M. *Catalytic Carbonylation Reaction*; Springer-Verlag: Berlin, 2006. (c) Fukuyama, T.; Ryu, I. Carbon Monoxide. *e-eros, Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: DOI: 10.1002/047084289X.rc013.pub2.

(2) For reviews, see: (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580. (b) Morimoto, T.; Fujioka, M.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *Pure Appl. Chem.* **2008**, *80*, 1079.

(3) (a) Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3806. (b) Shibata, T.; Toshida, N.; Takagi, K. *Org. Lett.* **2002**, *4*, 1619. (c) Morimoto, T.; Yamasaki, K.; Hirano, A.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K.; Harada, Y.; Fukumoto, Y.; Chatani, N.; Nishioka, T. *Org. Lett.* **2009**, *11*, 1777. (d) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687. (e) Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* **2002**, *4*, 2849. (f) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232. (g) Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607. (h) Wieckowska, A.; Fransson, R.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2011**, *76*, 978.

10.1021/ol401092a

Pd-catalyzed carbonylation transformations and, interestingly, demonstrated that *stoichiometric* or *substoichiometric* amounts of CO (1.0–1.5 equiv) could be used. This easy-to-use and safe reactor has paved the way for a new age of low-pressure carbonylation reactions, whereby CO gas can be delivered by decarbonylation reactions, or by decomplexation from a metal carbonyl complex.[5]

In contrast, we were interested in more common reagents that are cheap and readily available. From this perspective, our idea was to exploit the well-known dehydration of formic acid in sulfuric acid at elevated temperatures (Morgan reaction)[6] for CO generation (Figure 1). Herein, we report selected examples of carbonylation reactions with CO issued from formic acid decomposition in both the two-chamber reactor and in a microflow tube-in-tube reactor. Furthermore, we demonstrate for the first time that radical mediated carbonylations can also be run effectively in a two-chamber system, COware.

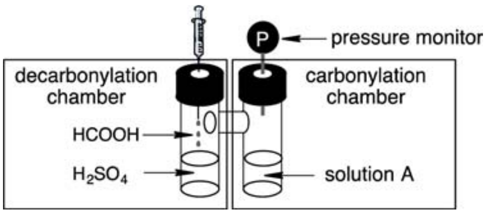
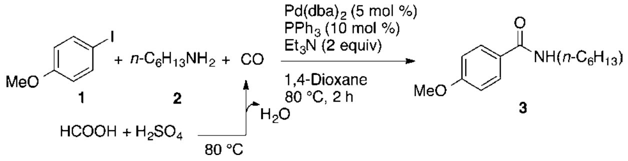


Figure 1. CO generation from formic acid in two-chamber reactor.

We first focused our attention on the Heck aminocarbonylation of aryl iodide that has previously been reported by Skrydstrup and co-workers and later by the Larhed group, investigating the amount of acid necessary for proper CO delivery (Table 1).[4,5] For this, we examined the carbonylation of 4-iodoanisole (**1**) with *n*-hexylamine (**2**) in the presence $Pd(dba)_2$ and triethylamine for our CO-generator system based on the Morgan reaction. We were pleased to see that the desired amide **3** was obtained in quantitative yield after only 2 h of the reaction (entry 1) with 4 equiv of formic acid and sulfuric acid. The internal pressure inside the reactor could be measured by applying a pressure monitor connected to the reactor.[7] With the 4 equiv of formic acid and sulfuric acid, the pressure inside the reactor increased to 3.3 atm (entry 1). Lowering the equivalents of acids to 3 also provided the amide **3** in high yield, whereas this yield significantly decreased with 2 equiv of acids, which caused a pressure drop to ca. 2 atm (entries 2 and 3). An excess of sulfuric acid allowed the formation of the carbonylated product in a good yield of 89% (entry 4). In light of these results, we have confirmed that the internal pressure was not the limiting factor for obtaining the product in high yields, whereas a sufficient volume of sulfuric acid was essential to lead to the complete decomposition of formic acid, and thereby allowing for a continuous consumption of the diatomic reagent during the Heck carbonylation reaction.

Table 1. Conditions for Decarbonylation Reaction in the Two-Chamber Reactor



entry[a]	**1**:H_2SO_4:HCO_2H	pressure (atm)	yield of **3** (%)[b]
1	1:4:4	3.3	quant.
2	1:3:3	2.6	97
3	1:2:2	2.0	59[c]
4	1:4:2	2.0	89

[a] Reaction conditions: 4-Iodoanisole (0.5 mmol), *n*-hexylamine (2 equiv), dioxane (1.5 mL). [b] Isolated yield. [c] NMR yield.

The setup was then tested for the carbonylative Sonogashira reaction. Inspired by quality work from the Yang group,[8] describing the efficient carbonylative coupling between an aryl iodide and a terminal alkyne in water, we attempted to carry out this reaction in the two-chamber reactor (Scheme 1). Thus, iodobenzene (**4**) and 1-octyne (**5**) were placed in the carbonylation chamber in the presence of palladium chloride. Yang and co-workers report that this coupling reaction reaches completion at room temperature, but in our system, the decarbonylation chamber required heating at 80 °C for 15 min in order to encourage the generation of CO. Then, the decarbonylation chamber was cooled to room temperature by a water bath, and the coupling reaction was carried out at room temperature for 24 h. The desired alkynyl ketone **6** was obtained in a high yield of 91%.

We are also pleased to report the first application of radical carbonylation reactions using a two-chamber reactor, as it was possible to carry out thermal-initiated and irradiation-initiated carbonylations of organo iodides using formic acid as a CO-precursor (Scheme 2). In our previous report about the hydroxymethylation of alkyl iodides mediated by tetrabutylammonium borohydride, we have demonstrated that an atmospheric pressure of CO could lead to the desired homologated alcohols.[9] In order

---

[4] (a) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061. (b) Hermange, P.; Gogsig, T. M.; Lindhardt, A. T.; Taaning, R. H.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 2444. (c) Nielsen, D. U.; Taaning, R. H.; Lindhardt, A. T.; Gogsig, T. M.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 4454. (d) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114. (d) Gøgsig, T. M.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 798.

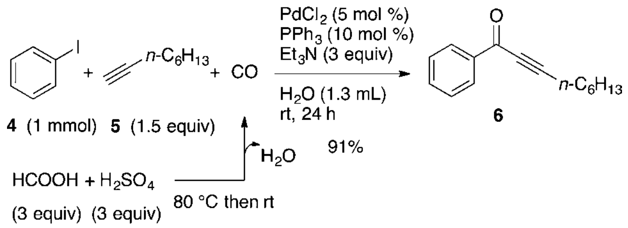
[5] $Mo(CO)_6$ was recently adapted as the CO source in the two-chamber reactor; see: Nordeman, P.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2013**, *77*, 11393.

[6] (a) Morgan, J. S. *J. Chem. Soc., Trans* **1916**, *109*, 274. For mechanistic studies, see: (b) Kaushik, S. M.; Rich, R. L.; Noyes, R. M. *J. Phys. Chem.* **1985**, *89*, 5722. (c) Bowers, P. G.; Hodes, K. *J. Phys. Chem.* **1988**, *92*, 2489.

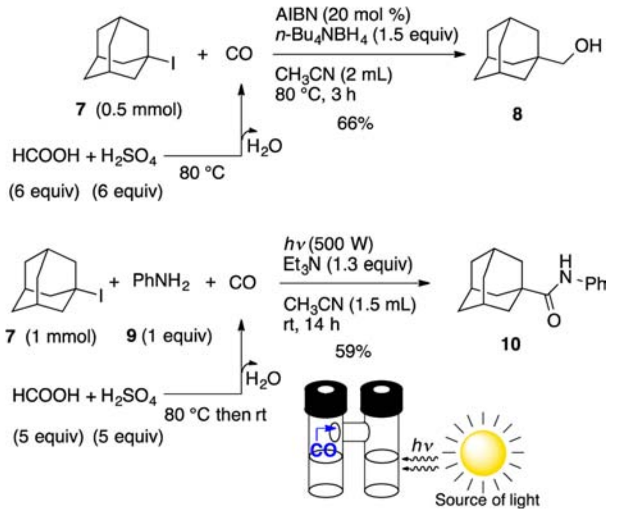
[7] The CO pressure was measured without carrying out the aminocarbonylation reaction.

[8] Liang, B.; Huang, M.; You, Z.; Xiong, J.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 6097.

Scheme 1. Carbonylative Sonogashira Reaction in a Two-Chamber Reactor



Scheme 2. Radical-Mediated Carbonylation in a Two-Chamber Reactor



to apply this reaction in COware, 1-iodoadamante (**7**), tetrabutylammonium borohydride, and AIBN were placed in the carbonylation chamber and heated at 80 °C for 3 h. The homologated alcohol **8** was obtained in a 66% yield. Further studies have led us to take advantage of the transparent glass of the reactor in order to test the efficiency of photoirradiation-initiated carbonylation in COware. In our previous work, we have demonstrated the efficient iodine transfer carbonylation of alkyl iodides in the presence of amines under photoirradiation that could afford amides in good yields.[10,11] Thus, 1-iodoadamante (**7**), aniline (**9**), and triethylamine were placed in the carbonylation chamber and submitted to 500 W-Xenon lamp irradiation. After 14 h of mixing at room temperature, the desired amide **10** was obtained in a 59% yield. The pressure inside the reactor was measured to be 6.5 atm for this amount of acids.

Finally, we focused our attention on a microflow system for the carbonylation reaction based on the Morgan reaction. Advantageously, continuous-flow processes offer the possibility to increase the production of desired compounds, meanwhile allowing precise control of the reaction conditions (temperature and residence time) and improving yields and safety.[12,13] Therefore, in recent years, we[14] and other groups[15] reported carbonylation reactions applying a microflow system. Here, we investigated the Heck aminocarbonylation of an aryl halide in order to estimate the efficiency of our microflow device with *ex situ* generated CO based on the Morgan reaction. At first sight, such a flow reaction would be incompatible with the present CO generation system because it would involve the mixing of sulfuric acid with triethylamine. Therefore, in order to prevent this parasite acid/base reaction, a dual flow system was applied. By analogy to the two-chamber reactor, this dual flow system would provide one flow dedicated to the CO generation reaction while the other flow would allow the carbonylation reaction. For this, we prepared a "tube-in-tube" reactor with an outside stainless steel tube for the carbonylation flow and an inner PTFE tube which is exclusively permeable to gas, for the decomposition of formic acid (Figure 2). For the inner PTFE tube, Teflon AF 2400 was employed, which has previously been used in a microflow reaction by Ley and co-workers[16] with gaseous CO,[16a] CO_2,[16b] ozone,[16c] H_2,[16d] and others.

Our continuous microflow "tube-in-tube" reactor is simple to prepare and consists mainly of two Swagelock T-pieces, a Hastelloy mixer (150 μm width, MiChS β 150),[17] and two sections of tubing (outer = stainless steel tube; 3.17 mm o.d., 2.0 mm i.d., inner = Teflon AF-2400; 1 mm o.d., 0.8 mm i.d., 53 cm length) as shown in Figure 3. Applying this apparatus, we could easily carry out the aminocarbonylation of

---

(9) Kobayashi, S.; Kawamoto, T.; Uehara, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 1548.

(10) For a review, see: Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16.

(11) Ryu, I.; Nagahara, N.; Kambe, N.; Sonada, S.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* **1998**, 1954.

(12) For recent reviews, see: (a) Wirth, T. *Microreactors in Organic Synthesis and Catalysis*; Wiley-VCH: Weinheim, 2008. (b) Hessel, V.; Renken, A.; Schouten, J. C. Yoshida, J. *Micro Process Engineering*; Wiley-VCH: Verlag, 2009. (c) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300. (d) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem.—Eur. J.* **2008**, *14*, 7450. (e) Lin, W.-Y.; Wang, Y.; Wang, S.; Tseng, H.-R. *Nano Today* **2009**, *4*, 470. (f) McMullen, J. P.; Jensen, K. F. *Annu. Rev. Anal. Chem.* **2010**, *3*, 19. (g) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, 675. (h) Yoshida, J. *Chem. Rec.* **2010**, *10*, 332. (i) Wegner, J.; Ceylan, S.; Kirschning, S. *Chem. Commun.* **2011**, *47*, 4583. (j) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7502. (k) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17. (l) Ley, S. V. *Chem. Rec.* **2012**, *12*, 378. (m) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38.

(13) For our reviews, see: (a) Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151. (b) Fukuyama, T.; Ryu, I. *Green Process Synth.* **2012**, *1*, 412.

(14) (a) Rahman, M. T.; Fukuyama, T.; Kamata, N.; Sato, M.; Ryu, I. *Chem. Commun.* **2006**, 2236. (b) Fukuyama, T.; Rahman, M. T.; Kamata, N.; Ryu, I. *Beilstein J. Org. Chem.* **2009**, *5*, Article No. 34. (c) Fukuyama, T.; Mukai, Y.; Ryu, I. *Beilstein J. Org. Chem* **2011**, *7*, 1288.

(15) (a) Miller, P. W.; Long, N. J.; de Mello, A. J.; Vilar, R.; Gee, A.; Passchier, J. *Chem. Commun.* **2006**, 546. (b) Miller, P. W.; Long, N. J.; de Mello, A. J.; Vilar, R.; Audrain, H.; Bender, D.; Passchier, J.; Gee, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2875. (c) Murphy, E. R.; Martinelli, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1734. (d) Miller, P. W.; Jennings, L. E.; de Mello, A. J.; Gee, A. D.; Long, N. J.; Vilar, R. *Adv. Synth. Catal.* **2009**, *351*, 3260. (e) Takebayashi, Y.; Sue, K.; Yoda, S.; Furuya, T.; Mae, K. *Chem. Eng. J.* **2011**, *180*, 250.

(16) (a) Koos, P.; Gross, U.; Polyzos, A.; O'Brien, M.; Baxendale, I.; Ley, S. V. *Org. Biomol. Chem.* **2011**, *9*, 6903. (b) Polyzos, A.; O'Brien, M.; Peterson, T. P.; Baxendale, I.; Ley, S. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 1190. (c) O'Brien, M.; Baxendale, I.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596. (d) O'Brien, M.; Taylor, M.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 1250.

(17) MiChS Co., Ltd. http://www.michs.jp/index_en.html (accessed May 17, 2013).

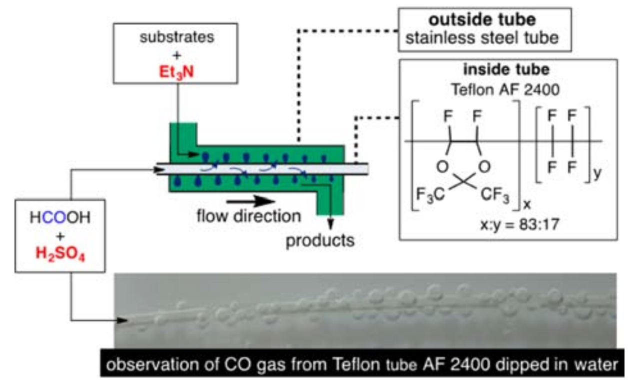


Figure 2. Principle of *ex situ* flow carbonylation using tube-in-tube reactor and illustration of permeativity of Teflon AF 2400 with generated CO.

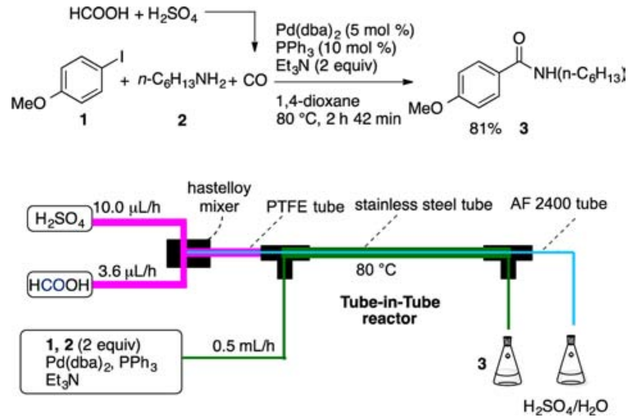


Figure 3. Microflow system for carbonylation reaction with formic acid/sulfuric acid using "tube-in-tube" reactor.

4-iodoanisole **1** to obtain the amide **3** in a good yield of 81%. To our knowlegde, this is the first time that a microflow Heck carbonylation could be performed in presence of sulfuric acid, thanks to the Teflon AF-2400 that has high chemical compatibility. It is noteworthy that the reaction time was calculated as a function of the volume of the outside tube; however, it was difficult to determine the residence time for this reaction since CO was formed progressively and consumed in the occurring carbonylation reaction. Nevertheless, the residence time inside the reactor is less than 2 h 42 min for this particular system.

In summary, through these selected examples of Pd catalyzed and radical carbonylations, we have demonstrated that the classical CO-generation system based on the Morgan reaction ($HCOOH/H_2SO_4$) is a useful tool for carbonylation in a modern double chamber system using COware. Furthermore, we have adapted the CO-generation system to a continuous microflow system using a modern "tube-in-tube" reactor, equipped with a CO gas permeable PTFE inner tube. The latter is an unprecedented example of Heck aminocarbonylation that combines simultaneously a strong acid with a base. Moreover, the decomposition of formic acid in sulfuric acid is a convenient reaction that gives rise to pure carbon monoxide, along with water. Thus, in combination with safe and easily handled equipment, common acids can serve as a CO source so that chemists can avoid the use of CO cylinders for low pressure carbonylation reactions.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the MEXT and the JSPS.

Supporting Information Available. The experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.