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Quinolin-8-yl Formate: A New Option for Small-Scale Carbonylation Reactions in Microwave Reactors

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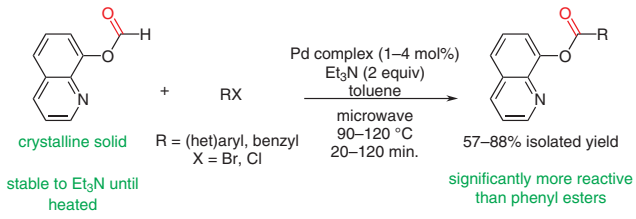

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Abstract A convenient procedure for conducting small-scale carbonylations of aryl or benzyl halides in a microwave reactor by using quinolin-8-yl formate is described. The resulting 8-acyloxyquinolines were shown to be more reactive than phenyl esters in acyl-transfer reactions, and their utility for the production of esters and amides was demonstrated.

Key words carbonylation, microwave heating, palladium catalysis, carbon monoxide surrogates, benzylic halides, aryl halides

The incorporation of carbon monoxide (CO) into organic molecules through palladium catalysis, first reported by Heck in 1974,[2,3] has grown to be a mainstay of synthetic organic chemistry. Many mild methods now exist that permit reliable alkoxycarbonylations, aminocarbonylations, reductive carbonylations, and even carbonylative variants of C–C cross-couplings to be conducted with a range of aryl or heteraryl halides or pseudohalides.[4,5] The challenges associated with handling a highly toxic, odorless gas have, however, driven many groups to explore alternatives to the use of high-pressure CO sources, especially in small-scale settings.[6]

We were particularly interested in the nearly simultaneous reports by the groups of Manabe and Tsuji of the use of phenyl formate (**1**) and its derivatives in palladium-catalyzed carbonylations.[7,8] Our interest in this chemistry was driven in part by Eli Lilly and Company's investment in automated organic synthesis[9] and by our hope that the resultant phenyl esters would prove to be versatile intermediates for automated synthesis.

Although our efforts to employ these methods in microwave reactors within our automated synthesis laboratory met with some modest success, we quickly realized two major limitations: (a) phenyl formate is too viscous to permit easy dispensing, and (b) phenyl esters lacked reactivity in subsequent reactions.

A follow-up publication by Manabe addressed both of these issues through the use of crystalline 2,4,6-trichlorophenyl formate, however this material is reported to liberate CO at room temperature on mixing with a base.[10] For safety reasons, we did not want to use any method that might result in pressurized vessels outside the containment of our microwave reactors. This left us searching for a phenyl formate derivative that was crystalline, provided more-activated products than phenyl formate, and was stable to mild base until heated.[11] Our attention was quickly drawn to quinolin-8-yl formate (2), shown in figure 1.

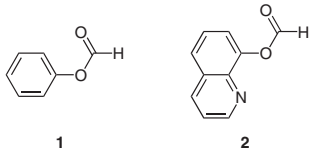

Figure 1 Phenyl formate (**1**) and quinoline-8-yl formate (**2**)

To the best of our knowledge, the only report of the use of **2** prior to our work was in a 1980 study of its reaction with $RhCl(PPh_3)_3$. Although experimental details of the preparation of **2** were extremely limited, a melting point of 102–103 °C was reported, indicating a solid with at least modest thermal stability.[12]

We were also encouraged by a separate report that 8-acyloxyquinolines (the expected products from carbonylations using **2**) are effective reagents for acylation of amines under extremely mild conditions.[13] Although the authors stated that the quinoline nitrogen 'greatly facilitated' the formation of amides, no head-to-head comparisons of the formation of amides from 8-acyloxyquinolines with those

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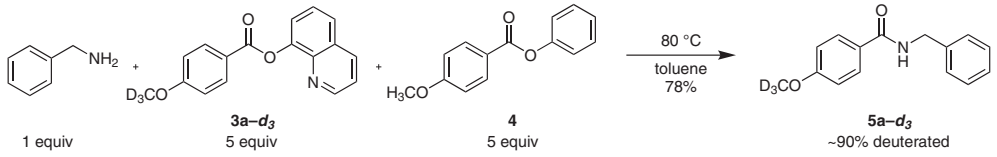
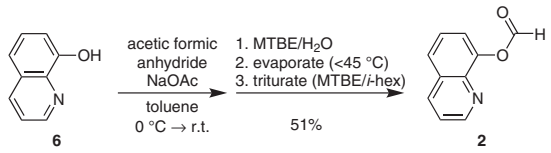


Scheme 1 Competition between 8-acyloxyquinolinyl and phenyl esters

from the parent phenyl esters were presented. Because our goal was to identify a reagent that could provide aryl esters that were more reactive than phenyl esters, we conducted the competition experiment shown in Scheme 1 to confirm the enhanced reactivity of **3a** relative to **4**.

When a solution containing five equivalents of **3a**-d_3 and five equivalents of nonlabeled **4** was treated with benzylamine at 80 °C, the resulting amide **5** was shown by ^{1}H NMR and LCMS to contain approximately 90% deuterium on the methoxy group, consistent with the 8-acyloxyquinoline **3a** reacting nearly an order of magnitude faster than the parent phenyl ester **4**.

Having verified the enhanced reactivity of 8-acyloxyquinolines, we next sought a safe and scalable synthesis of **2**. The original report on **2** indicated that it had been prepared from 8-hydroxyquinoline (**6**), sodium hydride and acetic formic anhydride in THF, but no details of the purification were provided.[12] As shown in Scheme 2, we found that the sodium hydride could be replaced by sodium acetate, and that a serviceable yield of **2** could be obtained after a simple aqueous workup and trituration. To obtain **2** in high purity, it was crucial to avoid the use of base in the workup and to avoid heat during evaporation of the MTBE. This procedure has been conducted on 50 g scale within Lilly and has been scaled up at an external manufacturer to produce a kilogram of **2**.



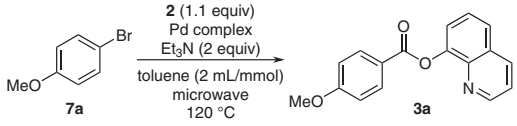
Scheme 2 Preparation of quinolin-8-yl formate (**2**)

Material prepared in this manner was consistently found to contain <1% of residual quinolin-8-ol (**6**), which could be easily quantified by comparing the ^{1}H NMR signals of residual **6** with the ^{13}C satellites from the corresponding signals of **2**. Having obtained **2** as a pure solid, we found that it could be stored in a freezer under nitrogen at –30 °C for two years with less than 1% reversion to **6**. A sample of solid **2** stored at room temperature was found to contain less than 10% of **6** after 14 days.

Because we were interested in developing a carbonylation method for use in microwave tubes, we also wanted to verify the solution stability of **2** in the presence of base at room temperature. This point was important to avoid possible unsafe buildup of pressure in the tubes during handling by users and also to ensure that CO was not being lost before the tubes were capped. We were happy to find that a solution of **2** and Et_3N (2 equiv) in toluene-d_8 showed no decomposition after three hours at room temperature. In contrast, treatment of **2** with DBU under the same conditions resulted in an immediate yellow color and >75% conversion into **6** and CO in less than ten minutes.

Satisfied that **2** met our criteria of being stable to mild base at room temperature and of giving rise to products with enhanced reactivities compared with phenyl esters, we began to explore its use in the Pd-catalyzed carbonylation of 4-bromoanisole (**7a**) as shown in Table 1. Because of success with use of the (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (Xantphos) ligand in previous carbonylations,[14] including those using phenyl formate[7] or *N*-hydroxysuccinate formate,[11] we chose to use a convenient second-generation Buchwald palladacycle precatalyst based on Xantphos.[15] We were pleased to obtain a 91% conversion into **3a** after just 20 minutes of heating with 3 mol% of the catalyst (Table 1, entry 1). Reducing the catalyst loading to 1 mol% still resulted in a 40% conversion after just 20 minutes (entry 2). The surprising difference between entries 2 and 3 of Table 1 highlights an issue rarely addressed in the field of CO-generating reactions: *when conducted in sealed vessels, reaction performance can depend upon scale.* Given that carbonylation reactions are known to be inhibited by high CO pressures,[16] this should not come as a sur-

Table 1 Initial Exploration of the Conditions for Carbonylation Reactions



Entry	Pd complex (loading)	Time (min)	Scale[a] (mmol)	Conversion[b] (%)
1	Xantphos-Pd-G2[c] (3%)	20	2.0	91
2	Xantphos-Pd-G2 (1%)	20	2.0	40
3	Xantphos-Pd-G2 (1%)	20	1.0	86

[a] All reactions were conducted in a Biotage Initiator microwave reactor with 2–5 mL tubes.
[b] Calculated from uncorrected integrations of **3a** and **7a** obtained by GC/MS.
[c] Chloro[(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II)

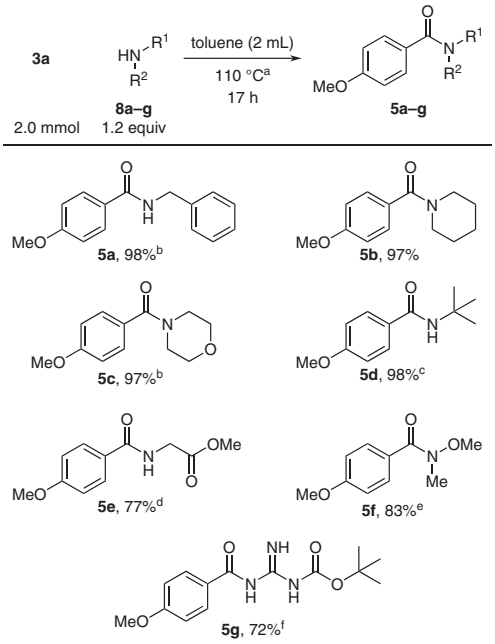
prise, as reducing the scale decreases the amount of CO that can be generated while simultaneously increasing the volume of headspace in the vessel.

Our observations suggest that the optimal conditions for these reactions are those in which pressures above 5 bar (as measured in the microwave reactor) are avoided. In practice, this can be achieved by reducing the scale of the reaction, by using a larger microwave tube,[17] or by increasing the catalyst loading.[18]

Our studies of the substrate scope for carbonylations with **2** are summarized in Table 2.[19] Noteworthy is the use of only 1.1 equivalents of **2** relative to the halide, suggesting efficient capture of the CO liberated in our reactions. A series of 4-substituted bromobenzene derivatives performed well (Table 2, entries 1–5), although slightly higher catalyst loadings and/or lower reaction temperatures were found to be required with electron-donating substituents. An excellent selectivity for bromide over chloride was observed (entry 2), whereas nitrile and methyl ester functionalities survived (entries 3 and 4). Substitution at the 2-position with methoxy or methyl was also tolerated, but these reactants performed better at lower temperatures and with *rac*-BINAP as the ligand (entries 6 and 7). Upon using 2.2 equivalents of **2**, a modest 57% yield of the phthalate derivative **3h** was obtained from 1,2-dibromobenzene. 2-Bromothiophene and 2-bromofuran each provided a good yield of the corresponding ester with only 1 mol% of catalyst (entries 10 and 11), whereas methyl 6-bromopicolinate provided a more modest yield of the carbonylation product **3l** (entry 12). Benzyl chloride was an excellent substrate under our conditions, proving 82% of the phenylacetate derivative **3m** in only 20 minutes with 1 mol% of Pd (entry 13).

Next, we turned our attention towards demonstrating the utility of our carbonylation products. Scheme 3 shows a range of amides that could be prepared from **3a** in good to excellent yields by simply heating a modest excess of the amine with the active ester and, in some cases, triethylamine. Nearly quantitative yields of the corresponding amides were obtained from benzylamine, piperidine, morpholine, and *tert*-butylamine. When the hydrochloride salt of methyl glycinate was used, the addition of 1.5 equivalents of Et_3N to neutralize the salt provided a good yield of amide **5e**. Amines with poor solubility in toluene could also be employed, but polar solvents were required. The Weinreb amide **5f** was prepared by heating **3a** with 3.5 equivalents of methoxy(methyl)amine hydrochloride and 5 equivalents of K_3PO_4 in DMF at 80 °C, whereas the N,N′-diacylguanidine **5g** was obtained by using acetonitrile as solvent at 80 °C.

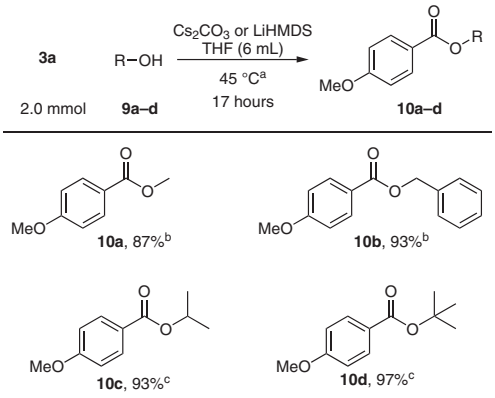
We also demonstrated that **3a** could be transesterified to give alkyl esters under mild conditions, as shown in Scheme 4. For methanol or benzyl alcohol, treatment with Cs_2CO_3 in THF at 45 °C was enough to achieve high yields of



Scheme 3 Reactions of **3a** with amines.
[a] Reactions were conducted in sealed microwave tubes.
[b] Et_3N (1.0 equiv) was added.
[c] *t*-$BuNH_2$ (1.8 equiv) was used.
[d] The HCl salt of methyl glycinate was used, along with Et_3N (1.5 equiv).
[e] Methoxy(methyl)amine hydrochloride (3.5 equiv) and K_3PO_4 (5 equiv) in DMF (6 mL) at 80 °C.
[f] Conducted in MeCN at 80 °C.

the desired esters. With isopropanol and *t*-butanol, LiHMDS was used to preform the lithium alkoxides, after which the desired esters were obtained in excellent yield.

Finally, we wondered if it might be possible to prepare ketones from **3a** by the addition of Grignard or lithium reagents.[20] Although our attempts to achieve this directly or

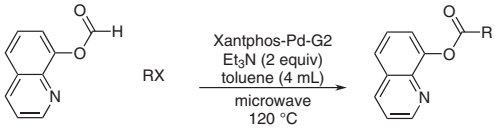


Scheme 4 Reactions of **3a** with alcohols
[a] Reactions were conducted in sealed microwave tubes.
[b] Alcohol (1.2 equiv) and Cs_2CO_3 (2.0 equiv) were used.
[c] Alcohol (1.3 equiv) and LiHMDS (1.2 equiv) were used.

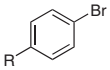
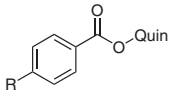
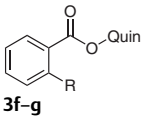
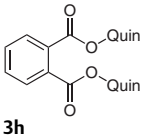
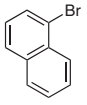
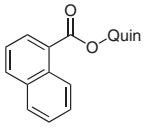
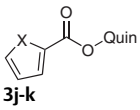
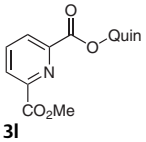
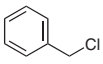
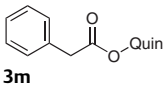
with the aid of a metal catalyst failed to bear fruit, we were able to develop a one-pot, two-step procedure via the morpholinoamide intermediate **5c**,[21] as shown in Scheme 5. Heating **3a** in THF with morpholine followed by simply cooling the tube in an ice bath and adding 2.4 equivalents of BuLi provided a 67% yield of ketone **11**.

In conclusion, we have shown that quinolin-8-yl formate (**2**) is a safe and effective reagent for small-scale carbonylations of aryl or heteroaryl bromides in a microwave

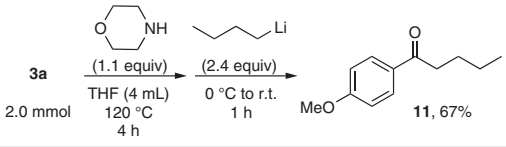
Table 2 Substrate Scope for Carbonylations Using **2**



2 (2.0 mmol) **7a–m** (1.1 equiv) **3a–m**

Entry	Substrate		Product	Pd loading (mol%)	Yield (%)
1		R = MeO (**7a**)	 **3a–e**	2[a]	88
2		R = Cl (**7b**)		1[b]	84
3		R = CN (**7c**)		1[b]	83
4		R = CO_2Me (**7d**)		1[b]	72
5		R = NMe_2 (**7e**)		3[a,c]	67
6		R = MeO (**7f**)	 **3f–g**	3[c,d,e]	71
7		R = Me (**7g**)		3[c,d,e]	77
8		**7h**	 **3h**	4[d,f]	57
9		**7i**	 **3i**	1[a]	88
10		X = S (**7j**)	 **3j-k**	1[b]	88
11		X = O (**7k**)		1[b]	73
12		**7l**	 **3l**	1[d]	61
13		**7m**	 **3m**	1[b]	82

[a] Reaction time 60 min.
[b] Reaction time 20 min.
[c] At 95 °C.
[d] Reaction time 120 min.
[e] The catalyst was *rac*-BINAP-Pd-G3 [Methanesulfonato[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl](2'-amino-1,1'-biphenyl-2-yl)palladium(II)].
[f] 1,2-Dibromobenzene (1.0 mmol), **2** (2.2 equiv), and Et_3N (3 equiv) were used.



Scheme 5 One-pot two-step ketone synthesis from **3a**

reactor. Importantly, we verified that this reagent will not begin to generate CO pressure in the reactions until they are heated. We also demonstrated the ease with which a representative 8-acyloxyquinoline product from these carbonylations could be converted into a range of amide and ester derivatives or even a ketone. We expect that this method will be useful in medicinal-chemistry laboratories, as well as in other settings where it is desirable to avoid the use of high-pressure CO sources.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707187.

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(11) N-Hydroxysuccinimidyl formate has also been reported to act as a solid CO surrogate that yields active esters, but it liberates CO at room temperature when treated with Et3N; see Supporting Information of: Barré, A.; Tînțaș, M.-L.; Alix, F.; Gembus, V.; Papamicaël, C.; Levacher, V. *J. Org. Chem.* **2015**, *80*, 6537.
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(16) Barnard, C. F. J. *Org. Process Res. Dev.* **2008**, *12*, 566.
(17) It is crucial that reactions are always conducted at or above the minimum working volume for the tube size chosen to avoid overheating and possible vessel failure due to incorrect temperature measurements in the microwave.
(18) When using high loadings of Xantphos-Pd-G2, small amounts of 8-quinolyl benzoate derived from phenyl transfer from the ligand were sometime seen. For an earlier report of phenyl transfer from Xantphos in carbonylations, see reference 11.
(19) **Quinolin-8-yl 4-Methoxybenzoate (3a); Typical Procedure**
4-Bromoanisole (378 mg, 2.02 mmol), quinolin-8-yl formate (**2**, 383 mg, 2.21 mmol, 1.1 equiv), and Xantphos-Pd-G2 (36 mg, 0.040 mmol, 2.0 mol%) were added to a 2–5 mL Biotage microwave tube (Part no. 351521) under N_2. Toluene (4.0 mL) and Et_3N (0.56 mL, 4.0 mmol, 2.0 equiv) were added sequentially, and the tube was capped and heated in a Biotage Initiator microwave at 120 °C for 60 min. When heating was complete and the microwave cavity had been opened, significant solid formation was observed in the tube. The contents of the tube were transferred to a separatory funnel with CH_2Cl_2 (30 mL), and the resulting mixture was washed with H_2O (20 mL). The organic layer was separated and injected directly onto a silica column (80 g). The product was eluted with a 0–10% gradient of MeCN in CH_2Cl_2 then dried at 35 °C under a vacuum to give an off-white solid; yield: 496 mg (88%).
^1H NMR (400 MHz, $CDCl_3$): δ = 8.88 (dd, *J* = 4.3, 1.6 Hz, 1 H), 8.29 (d, *J* = 9.0 Hz, 2 H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.74 (dd, *J* = 7.4, 2.2 Hz, 1 H), 7.52–7.59 (m, 2 H), 7.41 (dd, *J* = 8.4, 4.3 Hz, 1 H), 7.00 (d, *J* = 9.0 Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.4, 164.1, 150.8, 148.0, 141.8, 136.2, 132.9, 129.8, 126.5, 126.1, 122.1, 121.9, 121.9, 114.1, 55.7.
(20) A conversion of 8-acyloxyquinolines into ketones by using organoaluminum reagents has been reported; see: Tolstikov, G. A.; Valitov, F. Kh.; Kuchin, A. V. *Zh. Obshch. Khim.* **1982**, *52*, 1328.
(21) For an early example of the conversion of a morpholinoamide into a ketone, see: Pettit, G. R.; Baumann, M. F.; Rangammal, K. N. *J. Med. Chem.* **1962**, *5*, 800.

