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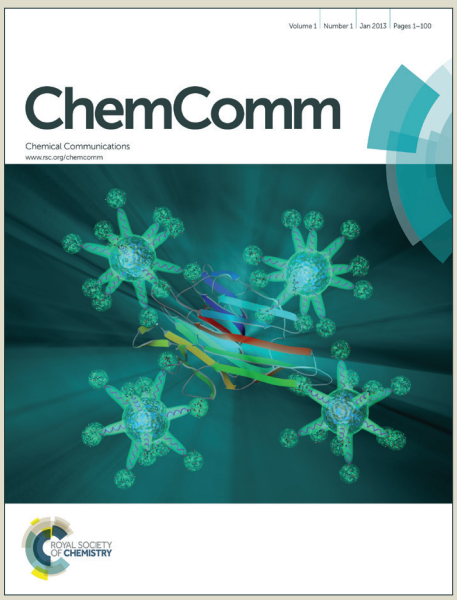

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Concise Synthesis of Cyclic Carbonyl Compounds from Haloarenes Using Phenyl Formate as the Carbonyl Source

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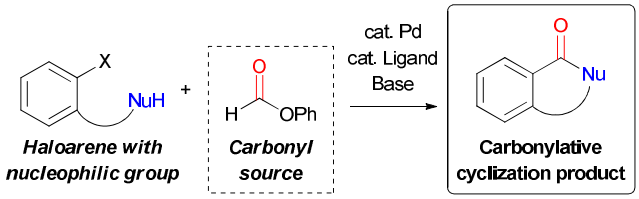
Various cyclic carbonyl compounds were concisely synthesized by carbonylative cyclization of haloarenes bearing nucleophilic moieties under Pd catalysis. Broad substrate scope and a feasible large-scale synthesis clearly demonstrate the high applicability of the reaction as a general, user-friendly method for access to cyclic carbonyl compounds.

Metal-catalyzed carbonylation using carbon monoxide (CO) is established as a fundamental synthetic method for the construction of carbonyl compounds.[1] Carbonylative cyclization of haloarenes containing a nucleophilic moiety, under an atmosphere of CO, is one application of metal-catalyzed carbonylations that can afford various cyclic carbonyl compounds in a single step.[2] Due to the importance of these compounds as useful building blocks and biologically active compounds, it is highly desirable to develop a practical and robust method for their synthesis.

Because CO gas is difficult to handle and highly toxic, several molecules that can act as CO surrogates have been investigated and the subject continues to attract much attention from synthetic chemists.[3] These molecules include formic acid,[4] acetic formic anhydride,[5] formic acid esters[6] and amides,[7] metal carbonyls,[8] aldehydes,[9] acyl chlorides,[10] and silacarboxylic acids.[11] Recently, we and Tsuji et al. have reported that phenyl formate could act as an easy-to-handle CO surrogate by generating CO through reaction with weak bases, and that the CO thus generated could be used for Pd-catalyzed aryloxycarbonylation.[12] We have also developed 2,4,6-trichlorophenyl formate[13] and *N*-formylsaccharin[14] as highly reactive CO surrogates useful for carbonylative transformations. The use of formic acid derivatives as CO surrogates does not require external CO gas and also benefits from a feasible scale-up, without the need for specialized pressure-resistant equipment, as well as the efficient production and consumption of CO within the reaction system, which ensures a high level of safety and practicality.[15]

Although use of CO surrogates for carbonylative cyclization would provide useful methods to synthesize cyclic carbonyl compounds, it has not been explored extensively. Since the side reactions might occur between the CO surrogate and the nucleophilic moieties of the haloarene substrates, to form other formyl compounds that cannot generate CO, identification of the appropriate CO surrogates and reaction conditions is the key to success. We describe herein a general, practical synthetic method for cyclic carbonyl compounds via a carbonylative cyclization, using Pd catalyst and phenyl formate as a commercially available and inexpensive CO surrogate (Scheme 1). The reaction can be applied to haloarenes bearing carbon, nitrogen, and oxygen nucleophiles under relatively mild conditions, demonstrating its generality and broad substrate scope.



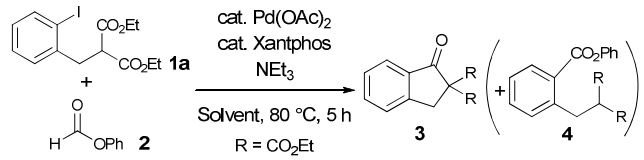
Scheme 1. Carbonylative cyclization using phenyl formate as the carbonyl source

We chose iodoarene **1a**, containing a tethered malonate moiety, as the model compound. In pioneering work by Negishi, the carbonylative cyclization of **1a** was conducted under a pressurized CO atmosphere (40 atm).[16] While this demonstrated the feasibility of the reaction, it is desirable to eliminate the need for CO gas. Later, Morimoto achieved this by applying aldehydes to the reaction as CO surrogates.[17] Although this method avoided the use of gaseous CO, a high temperature (130 °C) was required for the generation of CO from the aldehydes, which could impact the functional group tolerance of the method and, thus, limit the scope. We chose phenyl formate as the CO surrogate, because it is relatively stable and easy to handle and is easily converted to CO, as discussed above.

Firstly, the solvent was screened for the model reaction of 1a in the presence of Pd(OAc)2, Xantphos,[18] and NEt3 (Table 1). To our delight, polar solvents generally afforded the desired cyclic carbonyl product **3**

in moderate to high yield, without the use of a high pressure of CO gas, at 80 °C (entries 4–7). However, in most cases, this was accompanied by the formation of phenoxycarbonylated byproduct **4**. This could be ascribed to the competing intermolecular attack of a phenoxide ion, generated from **2**, on the Pd intermediate, rather than the desired intramolecular attack of the tethered nucleophile. Gratifyingly, the use of DMSO was effective for the selective formation of **3** (entry 7), and was thus revealed to be the optimal solvent.

Table 1. Effect of solvents on carbonylative cyclization[a]



Entry	Solvent	Yield of **3** (%)	Yield of **4** (%)
1	toluene	7	18
2	DCE	24	38
3	THF	7	15
4	CH_3CN	53	29[b]
5	DMF	59	26
6	NMP	57	12
7	DMSO	81	trace

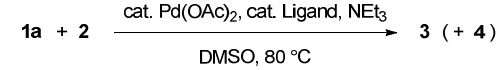
[a] The reaction was performed using iodoarene **1a** (0.30 mmol), **2** (2.0 equiv), $Pd(OAc)_2$ (3 mol %), Xantphos (6 mol %), and NEt_3 (2.0 equiv) in solvent (1.0 mL) at 80 °C for 5 h. The yields of **3** and **4** are isolated yields. [b] NMR yield (mesitylene as an internal standard).

Since ligands greatly affected the course of our previously developed carbonylative transformations, a ligand screening was conducted (Table 2). In the absence of ligands, a low conversion of **1a** was obtained (entry 1). The monodentate triarylphosphines and triaryl phosphite gave **3** in a higher yield than trialkylphosphines and XPhos (entries 2–7). Screening of bidentate phosphines revealed that DPPF and Xantphos afforded the best yields for **3**, with the yield deteriorating for others (entries 8–13). A brief examination of the Pd/P ratio showed that a five-fold amount of phosphino group to Pd metal was most effective for the reaction, with the yield of **3** reaching 84% (entry 14). The reason of the best Pd/P ratio with 1/5 is unclear at this moment.

We next attempted to apply the reaction to bromoarene **1b** (Table 3), as bromoarenes are easier to access and less expensive than iodoarenes. However, only a trace amount of **3** was detected (entry 1). Most alterations to the reaction parameters, such as the temperature and base, to improve the yield were in vain. However, to our delight, the use of P(*t*-Bu)$_3$·HBF$_4$[19] drastically improved the yield, which soared to 87% (entry 2). By varying the amount of ligand used, 15 mol % was found to be optimum (entry 3).

With the optimal conditions for both iodo- and bromoarenes in hand, a variety of haloarenes with different nucleophilic moieties were screened to examine the scope of the carbonylative cyclization (Table 4). Malonate **5**, with a tether containing one more carbon, reacted to afford tetralone **6**, albeit in a moderate yield (entry 1). Benzamide derivatives **7** and **9** gave phthalimides **8** and **10** in high yields (entries 2 and 3). Iodoarene **11**, bearing a different nitrogen nucleophile, was smoothly converted to 1*H*-isoindol-1-one **12** (entry 4). Indole-

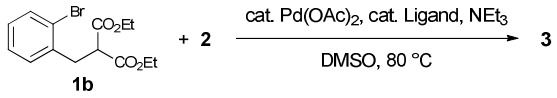
Table 2. Effect of ligands on carbonylative cyclization[a]



Entry	Ligand	Yield of **3** (%)	Yield of **4** (%)
1	–	14	trace
2	PPh_3	76	8
3	PCy_3	5	trace
4	P(*t*-Bu)$_3$·HBF$_4$	40	16
5	$P(OPh)_3$	72	4[b]
6	P(4-F-C_6H_4)$_3$	70	6[b]
7	XPhos	43	2[b]
8	DPPE	5	trace
9	DPPP	26	2[b]
10	DPPB	22	2[b]
11	DPPPE	53	12
12	DPPF	81	5
13	Xantphos	81	trace
14[c]	Xantphos	84	trace
15[d]	Xantphos	79	trace

[a] The reaction was performed using iodoarene **1a** (0.30 mmol), **2** (2.0 equiv), $Pd(OAc)_2$ (3 mol %), ligand (Pd/P = 1/4), and NEt_3 (2.0 equiv) in DMSO (1.0 mL) at 80 °C for 5 h. The yields of **3** and **4** are isolated yields. [b] NMR yield (mesitylene as an internal standard). [c] Pd/P = 1/5. [d] Pd/P = 1/6.

Table 3. Optimization of reaction conditions for carbonylative cyclization of bromoarene **1b**[a]

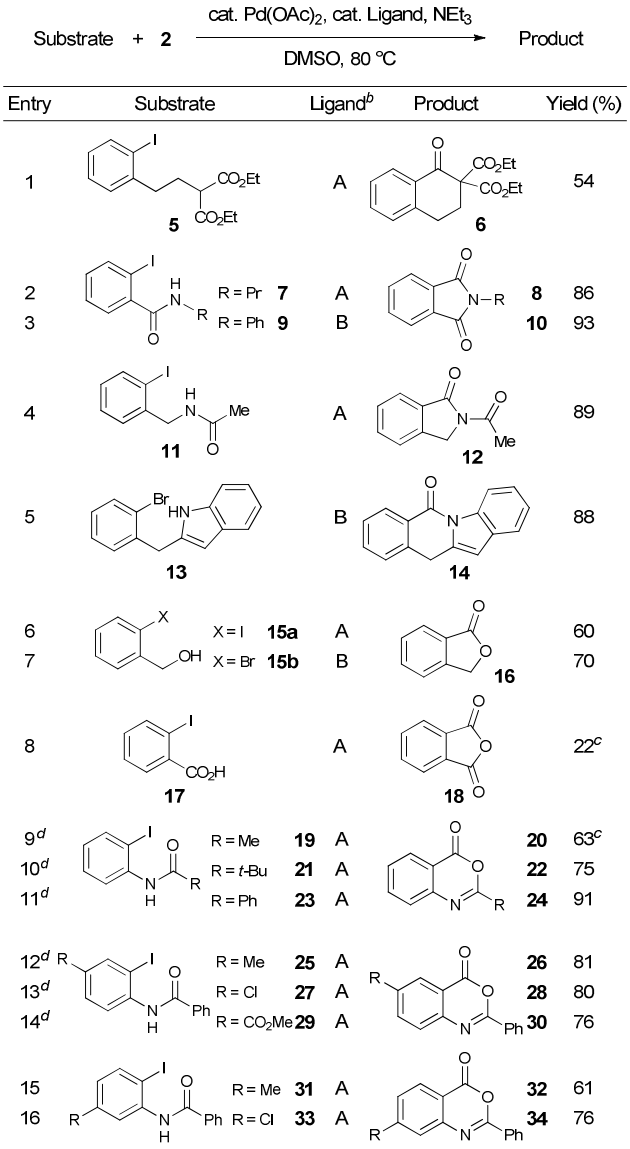


Entry	Ligand (mol %)	Yield (%)
1	Xantphos (6)	trace
2	P(*t*-Bu)$_3$·HBF$_4$ (12)	87
3	P(*t*-Bu)$_3$·HBF$_4$ (15)	93
4	P(*t*-Bu)$_3$·HBF$_4$ (18)	93

[a] The reaction was performed using bromoarene **1b** (0.30 mmol), **2** (2.0 equiv), $Pd(OAc)_2$ (3 mol %), ligand, and NEt_3 (2.0 equiv) in DMSO (1.0 mL) at 80 °C for 5 h. Yields of **3** are isolated yields.

substituted bromoarene **13** efficiently reacted to afford an interesting tetracyclic product **14** (entry 5). Aliphatic alcohols **15a** and **15b**, although they were deemed to be difficult substrates due to a potential competing transesterification with phenyl formate, gratifyingly afforded phthalide **16** in good yields (entries 6 and 7). The reaction of 2-iodobenzoic acid (**17**) afforded a low yield of phthalic anhydride (**18**) (entry 8), which could be ascribed to the low nucleophilicity of the carboxylate ion. To demonstrate the reaction for another class of oxygen nucleophiles, several anilides were tested for the synthesis of 4*H*-3,1-benzoxazin-4-one derivatives, a class of compounds that are known to have interesting bioactivities.[20] The synthesis of several 4*H*-3,1-benzoxazin-4-ones was thus successfully performed (entries 9–16), which was the novel method using a CO surrogate.[21] In some cases, DMF was found to be the optimal solvent (entries 9–14), which is discussed later, while substitution with electron-donating or -withdrawing groups did not greatly affect the reaction, indicating a broad substrate scope.

Table 4. Scope of substrates for carbonylative cyclization [a]

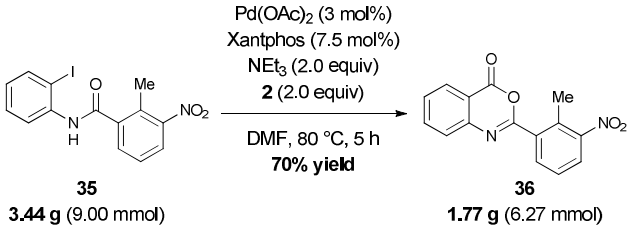


Entry	Substrate	Ligand[b]	Product	Yield (%)
1	**5**	A	**6**	54
2	R = Pr **7**	A	**8**	86
3	R = Ph **9**	B	**10**	93
4	**11**	A	**12**	89
5	**13**	B	**14**	88
6	X = I **15a**	A	**16**	60
7	X = Br **15b**	B	**16**	70
8	**17**	A	**18**	22[c]
9[d]	R = Me **19**	A	**20**	63[c]
10[d]	R = *t*-Bu **21**	A	**22**	75
11[d]	R = Ph **23**	A	**24**	91
12[d]	R = Me **25**	A	**26**	81
13[d]	R = Cl **27**	A	**28**	80
14[d]	R = CO_2Me **29**	A	**30**	76
15	R = Me **31**	A	**32**	61
16	R = Cl **33**	A	**34**	76

[a] The reaction was performed using substrate (0.30 mmol), **2** (2.0 equiv), $Pd(OAc)_2$ (3 mol %), ligand (Pd/P = 1/5), and NEt_3 (2.0 equiv) in DMSO (1.0 mL) at 80 °C for 5 h. The yields of the product are isolated yields. [b] A, Xantphos; B, P(*t*-Bu)$_3$•HBF_4. [c] NMR yield (mesitylene as an internal standard). [d] DMF was used as the solvent.

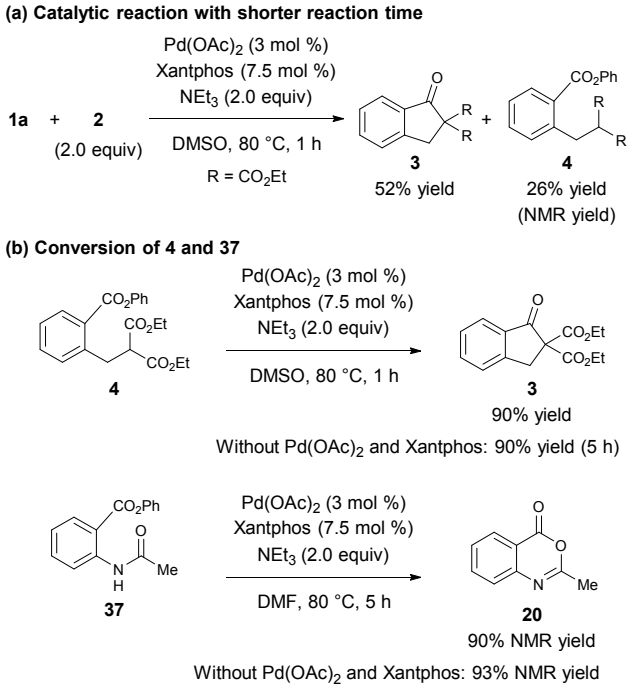
The catalytic reaction did not require external CO gas or pressure-resistant equipment, demonstrating a high level of safety and expediency. To increase its practicality, a large-scale synthesis of biologically active compound **36**, which inhibits the growth of prostate cancer cells,[22] was conducted (Scheme 2). A gram-scale synthesis of **36** proceeded with 70% yield to afford 1.77 g in a single run.

To get insight into the reaction mechanism of the carbonylative cyclization, the reaction was quenched after 1 h so that it could be analyzed in its early stages. Byproduct **4** was observed by NMR in 26% yield, along with cyclized product **3** (Scheme 3, (a)). Furthermore, when **4** was isolated and subjected to the catalytic reaction conditions



Scheme 2. Gram-scale synthesis of biologically active compound **36**.

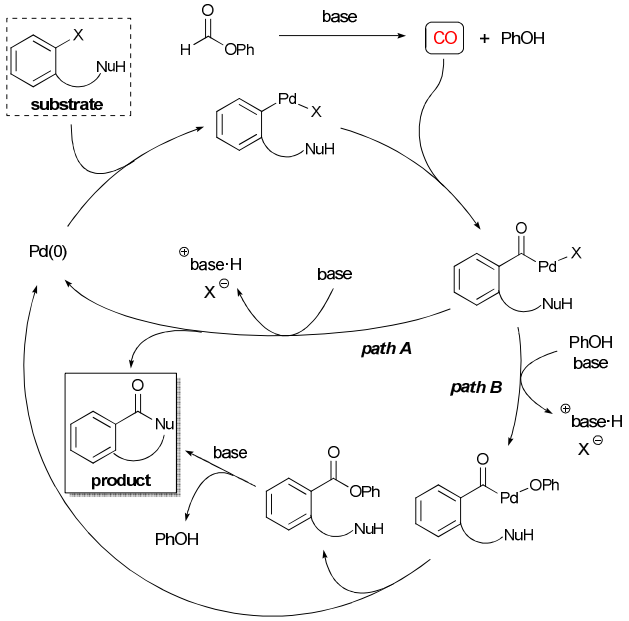
or conditions without the Pd catalyst, **3** was obtained in 90% yield (Scheme 3, (b)). These results strongly indicate that the reaction proceeds along a pathway from **4** to **3**, probably through a base-catalyzed Dieckmann condensation under the catalytic reaction conditions. Similarly, the reaction of isolated **37** also afforded ring-closing product **20** in high yield (Scheme 3, (b)).



Scheme 3. Formation of byproduct **4** and conversion of **4** and **37**.

The present mechanism is assumed to proceed as shown in Scheme 4. We believe that the carbonylation step proceeds in a similar manner to the previously reported Pd-catalyzed alkoxycarbonylation.[12a] Two pathways could be considered for the nucleophilic attack, one of which proceeds via an intramolecular attack of the tethered nucleophilic moiety on the acylpalladium intermediate (Scheme 4, path A). The other proceeds via the formation of the phenoxycarbonylated byproduct by nucleophilic attack of a phenoxide ion, generated in situ, which is followed by intramolecular attack of the tethered nucleophile on the carbonyl group of the byproduct (Scheme 4, path B). The presence of the latter path was confirmed experimentally for the reactions of **1** and **19**, based on the results shown in Scheme 3. We assume that the presence of path B allows the reaction to occur without the necessity for high CO pressure as, while the reported reaction of **1a** only proceeded under

high CO pressure,[16] the present method does not require this. Therefore, phenyl formate is not simply a CO surrogate, but also generates phenol during the reaction, which promotes the reaction under mild conditions.



Scheme 4. Assumed reaction mechanism.

In conclusion, a variety of cyclic carbonyl compounds could be accessed via a concise, Pd-catalyzed carbonylation and cyclization of haloarenes bearing nucleophilic moieties. All the reactions could be performed using phenyl formate as a CO surrogate, eliminating the need for external CO gas, demonstrating high levels of efficiency and practicality. Notably, the catalytic reaction provided several biologically active compounds, such as 4*H*-3,1-benzoxazin-4-one derivatives. This general, user-friendly carbonylative cyclization protocol for the synthesis of cyclic carbonyl compounds would be preferable to that using CO gas, and will accelerate the generation of libraries containing a wide array of cyclic carbonyl products.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/c000000x/

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