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Concise Report

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Palladium-Catalyzed Carbonylation of Multifunctionalized Substituted Alkynes to Quinolinone Derivatives under Mild Conditions†

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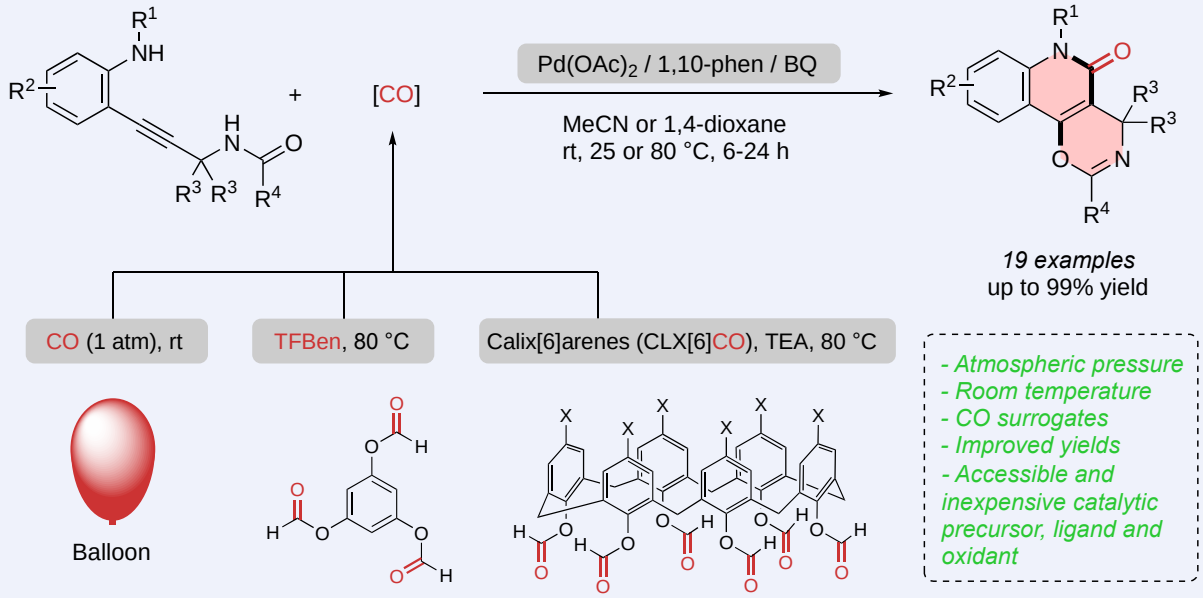
Keywords

Pd-catalysis | Carbonylation | Alkynes | CO surrogates | 6-*endo-dig* | Calixarenes | C1 building blocks | Domino reactions

Comprehensive Summary



A highly selective palladium-catalyzed carbonylation of 2-alkynylanilines bearing an amide moiety to condensed six-membered heterocyclic structures has been developed under mild conditions (room temperature and atmospheric pressure of CO). The carbonylative protocol is also compatible with CO surrogates, such as benzene-1,3,5-triyl triformate (TFBen) or the newly developed calix[6]arenes functionalized with six formate groups (CLX[6]CO), which are both capable to release CO *in situ*. A series of tricyclic fused heterocycles containing the important oxazino-quinolinone scaffold have been selectively obtained (only the 6-*endo-dig* cyclization mode has been observed) in good to excellent yields (up to 99%).

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† Dedicated to the Special Issue of C1 Chemistry.

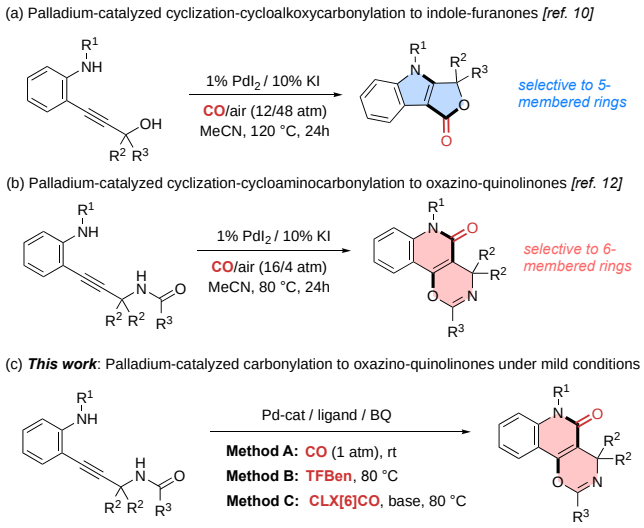
Background and Originality Content

Transition metal-catalyzed carbonylation reactions are widely exploited for the synthesis of value-added carbonylated compounds (*i.e.*, esters, amides, acids, ketones), including industrial products (fine and bulk chemicals).[1] In this context, a major role is played by palladium-based catalysts in combination with the use of gaseous carbon monoxide (CO), an inexpensive and largely available carbonylating agent that ensures excellent versatility and high atom economy.[2] Carbon monoxide is, however, an odorless and toxic gas, which imposes certain limitations on its use in academic laboratories and fine chemical industry, especially when employed at high pressure and temperature.[3] In the last decades, with the aim to reduce the risks related to the direct use of gaseous carbon monoxide, alternative CO surrogates have been developed.[4] Generally, CO substitutes can generate carbon monoxide directly in the reaction vessel (*in situ*) or in a different pot (*ex situ*). Skrydstrup and co-workers have developed a two-chamber system (COware) in which gaseous CO is separately produced (*ex situ*) from properly designed CO surrogates (*i.e.*, COgen) and consumed in a second vessel, where the desired carbonylation takes place.[5] This method has been successfully applied to the synthesis of labeled carbonyl-containing compounds and pharmaceuticals under mild conditions.[6] On the other hand, protocols based on the *in situ* CO generation approach may reduce the number of necessary manipulations, allowing a consistent simplification of the reaction setup. Certain limitations may arise from the fact that the reaction conditions of decarbonylation (temperature, catalysts, additives) need to be compatible with those of carbonylation. Among the most promising CO substitutes,[4] TFBen (benzene-1,3,5-triyl triformate) has been recently proposed by Wu[4b,7] as an efficient CO surrogate for *in situ* carbonylation processes. An doubtless advantage of TFBen is represented by the fact that its decarbonylation is followed by the generation of low-reactive phloroglucinol as co-product, which shows good compatibility with common carbonylation procedures.[4b] In this context, the discovery of new and mild carbonylation protocols based on the *in situ* generation of CO from easily available CO surrogates is still of high interest.

In the continuous effort to develop atom-efficient and sustainable carbonylative strategies to high value-added compounds,[2d,l,8] we reported several palladium-catalyzed carbonylation cascades to fused polyheterocycles[9] such as indole-furanones,[10] furobenzo-furanones,[11] oxazino-quinolinones[12] and *S,O*-bicyclic heterocycles[13] starting from easily accessible precursors. Specifically, indole-furanone derivatives have been obtained by a sequential cyclization-cycloalkoxycarbonylation catalyzed by the PdI_2/KI system (Scheme 1a).[10] Remarkably, the process is selective toward the formation of 5-membered heterocycles. On the other hand, under milder reaction conditions, the carbonylation of secondary anilines *ortho* functionalized with an *N*-acyl propargylamine moiety has led to condensed 6-membered ring products (Scheme 1b).[12] All the above-mentioned carbonylative transformations are based on the use of PdI_2/KI that represents an efficient and versatile catalytic system for a large variety of homogeneous oxidative carbonylation processes employing molecular oxygen as the terminal oxidant.[2d,l,8b-d,9-13] Recently, a new heterogeneous PdI_4^{2-}–based catalytic system has also been developed for the oxidative carboxylation reaction of alkynes to 2-ynamides.[14]

In the present work, we have found an alternative catalytic system for the selective carbonylative cyclization of 2-alkynyl anilines bearing an amide moiety, using benzoquinone (BQ) as the external oxidant under very mild conditions (Scheme 1c, *this work*). The developed protocol suggests the use of CO at atmospheric pressure and room temperature, or alternatively, CO surrogates for the synthesis of fused oxazino-quinolinone derivatives.

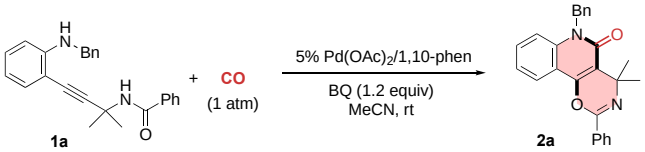
Scheme 1 Palladium-catalyzed carbonylative access to condensed 5 and 6 membered heterocycles



Results and Discussion

We started our study by testing commercially available $Pd(OAc)_2$ as the source of Pd(II), under atmospheric pressure of CO. *N*-Benzylaniline **1a**, bearing a propargylamide moiety in *ortho*-position, was selected as a model substrate. After several attempts, when $Pd(OAc)_2$ was employed in combination with 1,10-phenanthroline, we were pleased to observe full conversion of **1a** to oxazino-quinolinone **2a**. The transformation was complete in 6 h at room temperature with 5 mol% of $Pd(OAc)_2$ and 5 mol% of 1,10-phenanthroline in acetonitrile (Table 1, entry 1). 1,10-Phenanthroline is likely responsible for the enhanced stability of Pd(0) species in solution, preventing the aggregation and precipitation of Pd black. A reduced catalyst loading resulted in the almost quantitative formation of the product **2a** after an extended reaction time (Entries 2 and 3). Interestingly, very good results were also obtained with $Pd(TFA)_2$ and 2,2'-bipyridine (bpy) (Entries 4 and 5). It is worth noting that the process proceeded selectively *via* the 6-*endo-dig* cyclization pathway, as seen under

Table 1 Optimization study for the synthesis of **2a** with gaseous CO[a]



Entry	Variation from standard conditions[a]	Time/h	Yield of **2a**[b]/%
1	—	6	99 (95)[c]
2	2 mol% of $Pd(OAc)_2$/1,10-phen	16	99
3	1 mol% of $Pd(OAc)_2$/1,10-phen	24	96
4	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	6	99
5	bpy instead of 1,10-phen	8	95
6	UHP (2 equiv) instead of BQ	8	9
7	SPC (2 equiv) instead of BQ	8	7
8	$K_2S_2O_8$ (2 equiv) instead of BQ	8	4

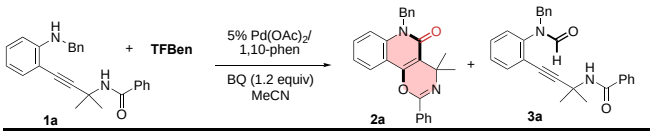
[a] Standard conditions: **1a** (0.3 mmol, 1 equiv), $Pd(OAc)_2$ (0.015 mmol, 5 mol%), 1,10-phenanthroline (0.015 mmol, 5 mol%), 1,4-benzoquinone (0.36 mmol, 1.2 equiv), MeCN (3 mL), CO balloon (1 atm), rt, 6 h. [b] ^1H NMR yield. [c] Isolated yield in parentheses.

the previously reported reaction conditions,[12] but now a higher yield has been achieved (95% *vs* 83%). At last, a few attempts to substitute 1,4-benzoquinone with a more sustainable oxidant were made. Unfortunately, urea hydrogen peroxide (UHP) and sodium percarbonate (SPC) provided low yields of the desired product **2a** (Entries 6 and 7), while potassium persulfate turned out to be unable to restore the active Pd(II) catalytic species (Entry 8).

Delighted by the obtained results, we proceeded with the investigation of CO substitutes. Aryl formates have been proven to be interesting and practical CO surrogates,[4g] as they can be decomposed to CO and phenol derivatives by heating or in the presence of a base. One of the most attractive analogues is benzene-1,3,5-triyl triformate (TFBen),[4b] that contains three formate functions and thus can theoretically generate a triple amount of CO respect to monoformates. Additionally, TFBen decomposes easily due to keto-enolic tautomerism of its decarbonylation product, phloroglucinol. This is also responsible for its low nucleophilicity, making phloroglucinol unreactive under typical carbonylative conditions.

Freshly prepared TFBen was then reacted with **1a** at room temperature under inert atmosphere. Unfortunately, the formation of **2a** was not detected neither with 1.2 nor with 3 equivalents of TFBen (Table 2, entries 1 and 2). The major product of the reaction was found to be formamide **3a**, which formation is owed to the TFBen deformylation. Pleasingly, the formation of **2a** was instead observed by heating the reaction mixture at 60 °C (Entry 3). Under these conditions, the competitive formylation of the starting material was reduced, and **2a** was isolated in 50% yield. The yield of **2a** was further increased to 95% by uprising the temperature to 80 °C (Entry 4). An attempt to halve the amount of TFBen resulted in a significant reduction in the yield of the carbonylation product (Entry 5).

Table 2 Optimization study for the synthesis of **2a** with TFBen[a]



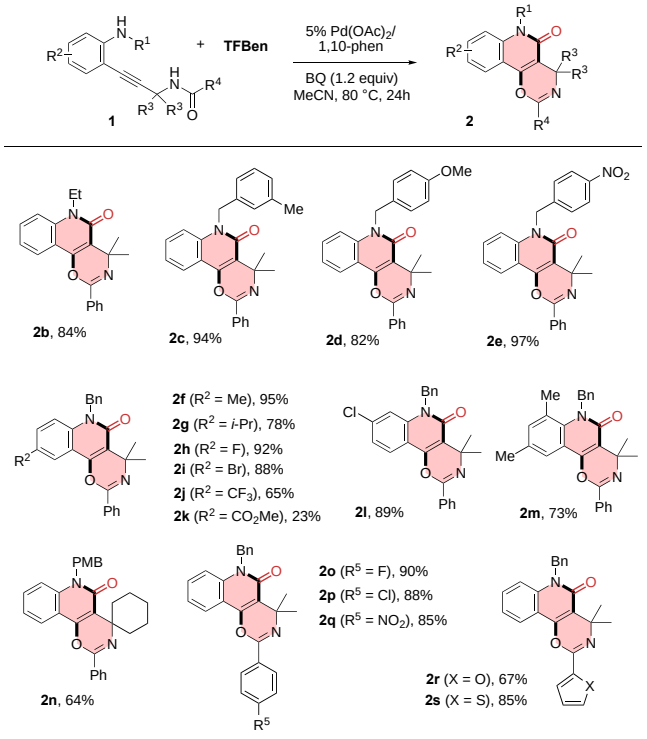
Entry	TFBen (equiv)	*T*/°C	Conv. of **1a**[b]/%	Yield of **2a**[b]/%	Yield of **3a**[b]/%
1	1.2	rt	38	—	31
2	3	rt	44	—	36
3	3	60	100	56 (50)[c]	22
4	**3**	**80**	**100**	**95 (90)[c]**	**trace**
5	1.5	80	82	64 (59)[c]	trace

[a] Standard conditions: **1a** (0.3 mmol, 1 equiv), TFBen, $Pd(OAc)_2$ (0.015 mmol, 5 mol%), 1,10-phenanthroline (0.015 mmol, 5 mol%), 1,4-benzoquinone (0.36 mmol, 1.2 equiv), acetonitrile (3 mL), 24 h under nitrogen. [b] ^{1}H NMR yield. [c] Isolated yield in parentheses.

To demonstrate the general applicability of our mild carbonylative conditions, the reaction scope was evaluated using TFBen as CO substitute (Table 2). Therefore, the optimized conditions (Table 2, entry 4) were applied to compounds **1b—q**, most of which displayed remarkable reactivity, allowing excellent yields for most substrates (Table 3).

Several ED and EW groups on the benzyl fragment (R^1) demonstrated great compatibility with the carbonylative double cyclization process (**2b—e**). Similarly, substituents of different nature (alkyl, halogen) were well tolerated in *para* (Me, *i*-Pr, F, Br), *meta* (Cl) and *ortho* (Me) positions respect to the nitrogen of the aniline moiety. Strong electron-withdrawing groups such as CF_3 and CO_2Me, decreasing the nucleophilicity of the nitrogen, led to a reduced formation of the product (65% and 23%, respectively for **2j** and **2k**). The presence of two alkyl groups at the propargylic position turned out to be essential for the transformation. The substrate bearing a cyclohexane moiety gave the corresponding product **2n** in a satisfactory yield, while unsubstituted substrates (R^3 = H) were unreactive under these conditions.[16] Several products bearing various substituents at the amide moiety were successfully synthesized under the carbonylation conditions. Specifically, **2o—q** with *para*-substituted aryls were obtained in good yields (85%—90%). In addition, the installation of a heteroaryl fragment was compatible in this carbonylation process, as products **2r** and **2s**, containing respectively the 2-furyl and 2-thiophen units, were isolated in 67% and 85% yields.

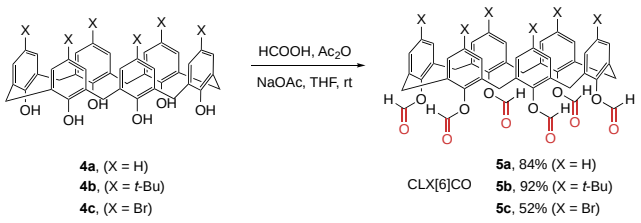
Table 3 Substrate scope with TFBen



[a] Standard conditions: **1** (0.3 mmol, 1 equiv), TFBen (0.9 mmol, 3.0 equiv), $Pd(OAc)_2$ (0.015 mmol, 5 mol%), 1,10-phenanthroline (0.015 mmol, 5 mol%), 1,4-benzoquinone (0.36 mmol, 1.2 equiv), MeCN (3 mL), 80 °C, 24 h under nitrogen. Isolated yield.

With the aim to discover new efficient CO substitutes, a series of calix[6]arene hexaformates (CLX[6]CO) has been prepared. We anticipate that these peculiar derivatives 1) are highly stable and therefore can be stored for a long time, even at room temperature, 2) bear six formate groups that potentially can release six CO molecules, 3) once decarbonylated, can in principle be recovered at the end of the reaction by simple filtration, thanks to low solubility of calixarenes in organic solvents, and lastly, 4) the rate of CO release can be modulated by changing the nature of the *para*-substituents at the aromatic rings.

Scheme 2 Synthesis of calixarene-based CO surrogates **5a—c** from **4a—c**



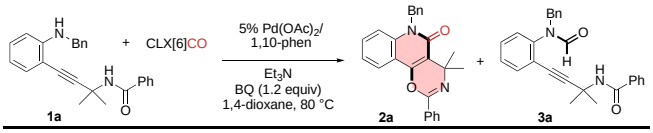
The esterification of hydroxy groups of calix[6]arenes **4a—c** was performed using formyl acetate (see SI for details). The cor-

responding products **5a—c** were obtained in yields ranging from 52% to 92%. The electronic effect of the substituents at the *para* position to hydroxyls turned out to directly affect the efficiency of the esterification. CLX[6]CO **5a** and **5b**, with respectively R = H and *t*-Bu, were obtained in high yields (84% and 92%), while the Br group dramatically decreased the yield of **5c** (Scheme 2).

The obtained CLX[6]CO **5a—c** were found to be highly insoluble in acetonitrile, while they could be dissolved in 1,4-dioxane upon heating. Since 1,4-dioxane is a common solvent for carbonylation reactions,[15] it was selected as an alternative reaction medium for the subsequent tests.

Contrarily to TFBen, under similar reaction conditions, CLX[6]CO **5** did not lead to the *in situ* CO generation upon simple heating (Table 4, entry 1). However, a common base (Et_3N) promoted the decarbonylation of **5** at gentle heating, thus providing the formation of a small quantity of **2a** together with a comparable amount of **3a** (Table 4, entry 2). While CLX[6]CO **5b** with a *t*-Bu substituent in place of H turned out to be even less efficient under the same conditions (Table 4, entry 3), surrogate **5c** having a Br group on each one of the *para*-position of phenolic fragments, enabled a synthetically useful yield of **2a** and a remarkable selectivity (Table 4, entry 4). Although the yield in this case is lower, in comparison with those obtained starting from TFBen (58% *vs* 90%), the advantage of the use of CLX[6]CO **5c** consists in the easy recovery of the decarbonylated material as it is practically insoluble in 1,4-dioxane and can be collected at the end of the reaction by filtration.

Table 4 Optimization study for the synthesis of **2a** with CLX[6]CO **5a—c**[a]



Entry	CLX[6]CO	Et_3N (equiv)	Conv. of **1a**[b]/%	Yield of **2a**[b]/%	Yield of **3a**[b]/%
1	**5a**	—	8	—	traces
2	**5a**	3	39	21 (15)[c]	14
3	**5b**	3	30	10	13
4	**5c**	**3**	**74**	**62 (58)[c]**	**7**

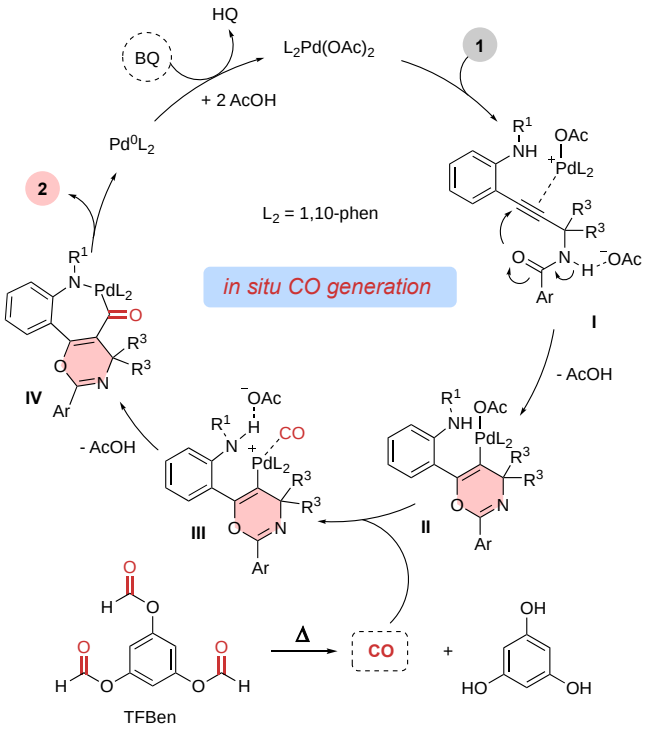
[a] Standard conditions: **1a** (0.3 mmol, 1 equiv), CLX[6]CO **5** (0.45 mmol, 1.5 equiv), $Pd(OAc)_2$ (0.015 mmol, 5 mol%), 1,10-phenanthroline (0.015 mmol, 5 mol%), 1,4-benzoquinone (0.36 mmol, 1.2 equiv), Et_3N, 1,4-dioxane (3 mL), 80 °C, 24 h under nitrogen. [b] ^1H NMR yield. [c] Isolated yield in parentheses.

Based on the previous studies,[7,12] a reaction pathway is proposed (Scheme 3). Initially, the triple bond of **1** coordinates Pd(II) leading to complex **I**. The most favorable route[12] involves the nucleophilic attack of the oxygen of the amide group on the activated triple bond following the 6-*endo-dig* cyclisation pathway to afford the σ-vinylpalladium complex **II**. The carbon monoxide thermically generated from TFBen,[4b,7] enters in the coordination sphere of palladium forming complex **III**. Consecutive CO migratory insertion and reductive elimination/nucleophilic displacement lead to the formation of product **2** and Pd(0) species. The final oxidation of palladium(0) by 1,4-benzoquinone regenerates the active palladium(II) species.

Conclusions

In the present study, a new carbonylative protocol for the synthesis of fused oxazino-quinolinone derivatives has been developed. Selective carbonylative domino 6-*endo-dig* cyclization has been achieved under mild conditions (atmospheric pressure and mild reaction temperature). Gaseous CO has been successfully replaced with TFBen, that is able to generate CO *in situ* without any additional activator. Hexa-formate calix[6]arenes

Scheme 3 Proposed reaction pathway



have been employed for the first time as solid carbonylating agents that can be recovered as insoluble decarbonylated material at the end of the process.

Experimental

General procedure for the oxidative carbonylation using gaseous carbon monoxide

In a 45 mL Schlenk tube under nitrogen, palladium acetate (0.015 mmol, 3.4 mg) and 1,10-phenanthroline (0.015 mmol, 2.7 mg) were dissolved in 3 mL of acetonitrile. The solution was stirred for 5 min at room temperature, and then **1** (0.3 mmol) and 1,4-benzoquinone (0.36 mmol) were added. The reaction then was purged with CO for ~30 s and, finally, a balloon charged with CO (1 atm) was attached to the tube. Full conversion of **1** was observed after 2—6 h of reaction time. The resulting mixture was filtered through a Celite® pad and concentrated *in vacuo*. The product **2** was isolated by flash column chromatography on SiO_2 using mixtures of hexane/ethyl acetate as eluent.

General procedure for the oxidative carbonylation using TFBen as a CO source

In a 10 mL tube under nitrogen, palladium acetate (0.015 mmol, 3.4 mg) and 1,10-phenanthroline (0.015 mmol, 2.7 mg) were dissolved in 3 mL of acetonitrile. The solution was stirred for 5 min, and then **1** (0.3 mmol), 1,4-benzoquinone (0.36 mmol) and freshly prepared TFBen (0.9 mmol) were added. The tube was immediately sealed, and the reaction mixture was heated at 80 °C. After 24 h of stirring, the mixture was cooled to room temperature, filtered through a pad of Celite®, and concentrated under reduced pressure. The product **2** was isolated by flash column chromatography on SiO_2 using mixtures of hexane/ethyl acetate as eluent.

General procedure for the oxidative carbonylation using CLX[6]CO 5a—c as a CO source

In a 10 mL tube under nitrogen, palladium acetate (0.015 mmol, 3.4 mg) and 1,10-phenanthroline (0.015 mmol, 2.7 mg) were dissolved in 3 mL of acetonitrile. The solution was stirred for

5 min, and then **1** (0.3 mmol), 1,4-benzoquinone (0.36 mmol), TEA (0.9 mmol) and **5a—c** (0.45 mmol) were added. The tube was immediately sealed, and the reaction mixture was heated at 80 °C. After 24 h of stirring, the mixture was cooled to room temperature, the decarbonylated calix[6]arene was collected on a fritted glass filter, and the filtrate was additionally filtered through a pad of Celite®, and concentrated under reduced pressure. The product **2** was isolated by flash column chromatography on SiO_2 using mixtures of hexane/ethyl acetate as eluent.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202300337.

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