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Synthesis of 4-Quinolones via a Carbonylative Sonogashira Cross-Coupling Using Molybdenum Hexacarbonyl as a CO Source

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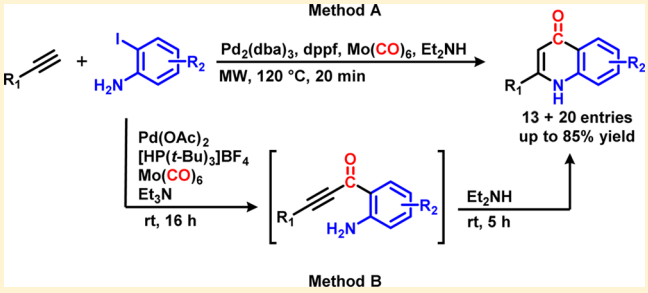
Supporting Information

ABSTRACT: A palladium-catalyzed CO gas-free carbonylative Sonogashira/cyclization sequence for the preparation of functionalized 4-quinolones from 2-iodoanilines and alkynes via two different protocols is described. The first method (A) yields the cyclized products after only 20 min of microwave (MW) heating at 120 °C. The second method (B) is a gas-free one-pot two-step sequence which runs at room temperature, allowing the use of sensitive substituents (e.g., nitro and bromide groups). For both protocols, molybdenum hexacarbonyl was used as a solid source of CO.



INTRODUCTION

4-Quinolones are commonly used in the pharmaceutical chemistry as a versatile scaffold with a wide range of biological activities, e.g., antibacterial,[1] antimalarial,[2] and anticancer.[3] As a result, the synthesis of 4-quinolones has attracted considerable interest, and there are several synthetic procedures available in the literature.[4] The most general method for the preparation of 2-substituted-4-quinolones is the condensation of anilines with *β*-keto esters followed by cyclization of the formed *β*-arylaminoacrylates. However, the reaction often performs poorly when using electron-deficient anilines.[5,6] Further strategies include the heterocyclization of 2-aminochalcone[7] and the palladium-catalyzed carbonylation of *N*-tosyl-*o*-iodoanilines with allenes.[8]

In addition, the palladium(0)-catalyzed multicomponent[9] carbonylative coupling of terminal acetylenes (**1**) with 2-iodoanilines (**2**) under elevated pressures of carbon monoxide has previously been described as a method to prepare functionalized 4-quinolones (**3**)[8,10,11] (Scheme 1, reactions a, b). This approach was first reported for aryl iodides, which were carbonylatively coupled to terminal acetylenes using $PdCl_2(PPh_3)_2$ or $Pd(dppf)Cl_2$ in neat diethylamine with in situ cyclization of the formed intermediate alkynone to generate 4-quinolones (**3**).[10−12] (Scheme 1, reaction a). The methodology was later adapted by Genelot and co-workers to enable the use of precatalyst, $Pd(dppp)Cl_2$ under milder conditions using a two-step procedure, providing **3** from **4** after addition of Et_2NH (Scheme 1, reaction b[13]). This synthetic protocol was applied in the preparation of the key quinolone substructure of the serine protease inhibitor BILN 2061.[14] However, the published carbonylative reactions require high pressures of CO gas, making them less attractive for lab-scale medicinal chemistry.

Palladium(0)-catalyzed carbonylation reactions, involving an aryl halide (or pseudohalide), CO, and a nucleophile, are commonly used for the synthesis of a multitude of arylcarbonyl derivatives (e.g., amides, esters, acids, ketones, etc.).[15−19] However, since many carbonylation reactions are performed above atmospheric pressure, specialized equipment which can withstand elevated pressures is often required to enable safe handling. In addition, CO is a highly toxic and flammable gas, which is invisible, odorless, and tasteless. As a result, the interest in solid reagents which release CO in a controlled manner has increased in the last decades.[19−31] $Mo(CO)_6$ has been successfully used in several different carbonylative reactions, e.g., aminocarbonylations,[32−36] amidocarbonylations,[37] and carbonylative cross-couplings.[20,38,39]

In addition to this work, a nongaseous Sonogashira carbonylative coupling providing alkynones using $Mo(CO)_6$ has been described by Iizuka et al. (Scheme 1, reaction c).[20] Nonetheless, one of the potential disadvantages of $Mo(CO)_6$ is its ability to reduce nitro-containing aromatic substrates.[40−42] In our group, we recently used a bridged two-chamber system,[43] originally developed by Skrydstrup et al.,[22−24] where CO is released from $Mo(CO)_6$ in one of the two compartments. The solid CO-source is separated from the reaction mixture and carbonylation occurs after free diffusion of the gas between the two chambers.[43] Using CO generated from COgen[22,24] ex situ in a two-chamber system, Neumann et al. recently reported a carbonylative Sonogashira for the preparation of alkynones from aryl bromides with excellent functional group tolerance (Scheme 1, reaction c).[44] Despite the advantage with the two-chamber procedure, it nevertheless demands specialized glassware and it is therefore of practical

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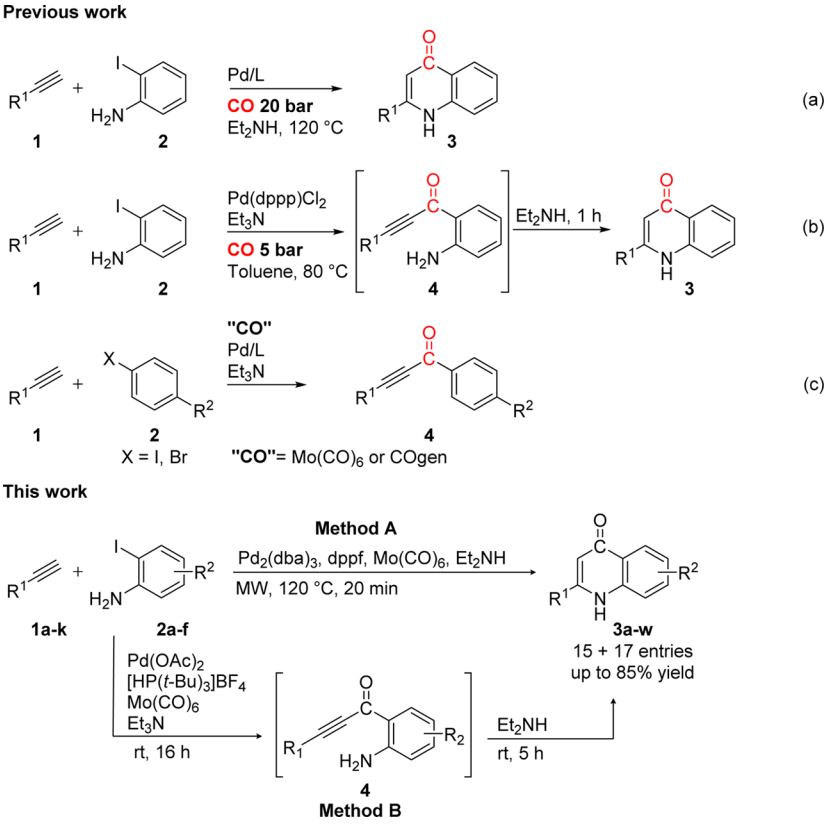
Scheme 1. Palladium(0)-Catalyzed Carbonylative Sonogashira Cross-Couplings, Cyclizations, and the Method Developed Herein



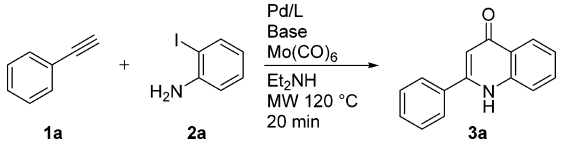
value to develop carbonylative reactions which can be conducted in a standard single vial system and tolerate sensitive functional groups.

In this study, we present two approaches for the preparation of 4-quinolones (**3**) using nongaseous $Mo(CO)_6$-promoted carbonylative methods. The first protocol provides the desired compounds after only 20 min of microwave (MW) heating whereas the second procedure is a one-pot two-step approach which operates at ambient temperature and tolerates sensitive functional groups, i.e., nitro groups and bromides. Both methods furnished a diverse set of 4-quinolone products in moderate to good yields.

RESULTS AND DISCUSSION

Initially, the feasibility of the carbonylative reaction was evaluated using a model reaction and microwave heating at 120 °C for 20 min in sealed vials. Phenylacetylene (**1a**, 2 equiv) and 2-iodoaniline (**2a**) were treated with various palladium catalysts (10 mol %) in the presence of base (3 equiv) and $Mo(CO)_6$ (2 equiv) with diethylamine (1.5 mL) as the solvent. The results of the screening are presented in Table 1. When $Pd(dppf)Cl_2$ was employed using sodium acetate as the base, the product **3a** was obtained in 76% isolated yield (entry 1). Changing to a triphenylphosphine catalytic system ($Pd(OAc)_2$ and PPh_3) only furnished trace amounts of the product (entry 2). When $Pd[(t\text{-}Bu)_3P]_2$ or a phosphine-free ligand system with $Pd_2(dba)_3$ was used, moderate yields were obtained (entries 3 and 4, 52% and 41%, respectively). Upon changing the base to Cs_2CO_3 with $Pd(dppf)Cl_2$ as the catalytic species, 82% of **3a** was isolated after chromatography (entry 5). DBU was found to be deleterious for the reaction (entry 6). Finally, when

Table 1. Optimization of the Reaction Conditions for the Synthesis of 4-Quinolone 3a from 1a and 2a Using MW



entry	Pd/L[a]	base	yield (%)[b]
1	$Pd(dppf)Cl_2$	NaOAc	76
2	$Pd(OAc)_2$, PPh_3[c]	NaOAc	trace
3	$Pd[(t\text{-}Bu)_3P]_2$	NaOAc	52
4	$Pd_2(dba)_3$	NaOAc	41
5	$Pd(dppf)Cl_2$	Cs_2CO_3	82
6	$Pd(dppf)Cl_2$	DBU	–
7	$Pd_2(dba)_3$[d], dppf[c]	Cs_2CO_3	85
8	–	Cs_2CO_3	–

Reaction conditions: 2-Iodoaniline **2a** (0.5 mmol), phenylacetylene (1 mmol), base (1.5 mmol), $Mo(CO)_6$ (1 mmol), Et_2NH, 120 °C, 20 min. [a]10 mol % of palladium catalyst. [b]Isolated yield. [c]20 mol %. [d]5 mol %.

$Pd_2(dba)_3$ (5 mol %) was used with an excess (20 mol %) of dppf, the desired product was isolated in 85% yield (entry 7). $Mo(CO)_6$ has been reported to have catalytic activity in carbonylation reactions.[45−47] Therefore, a control reaction without the addition of a palladium catalyst was performed, but no conversion of aryl iodide was observed (entry 8).

Based on the reaction conditions developed, the scope of the microwave-heated carbonylative method A was investigated next. When the aromatic 1-ethynyl-4-fluorobenzene (**1b**) was reacted with **2a**, 4-quinolone **3b** was obtained in 70% yield. The

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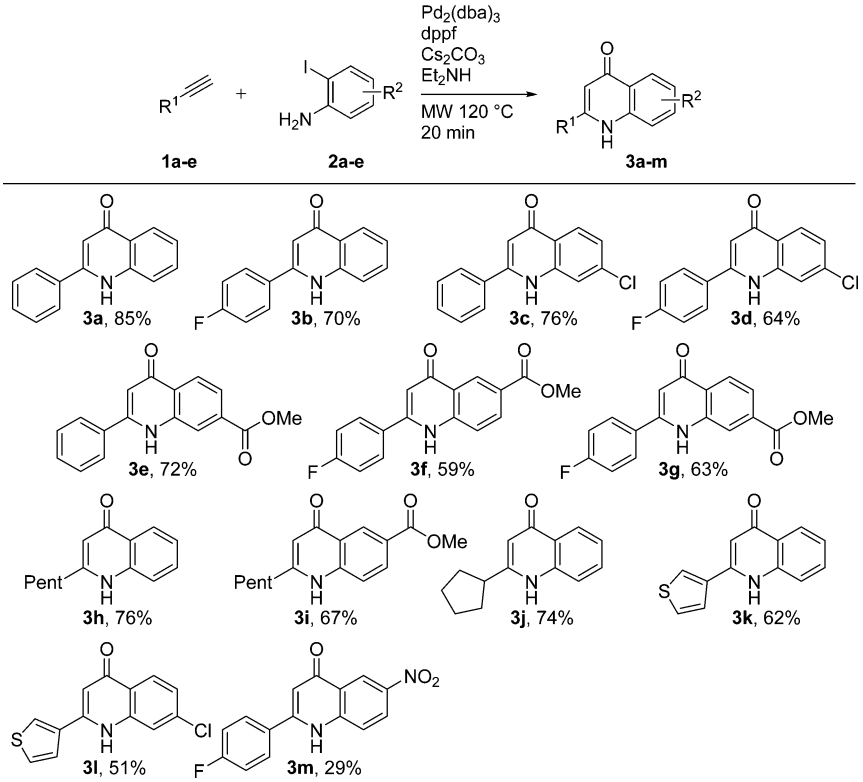
Table 2. Scope of the $Mo(CO)_6$-Mediated Reaction of 2-Iodoanilines with Acetylenes Using MW (Method A)[a,b]



[a]Reaction conditions: **1** (1 mmol), **2** (0.5 mmol), 5 mol % $Pd_2(dba)_2$, 12 mol % dppf, $Mo(CO)_6$ (1 mmol), Et_2NH, 120 °C, 20 min. [b]Isolated yield.

chloro-substituted 2-iodoanline (**2b**) gave products **3c**,**d** in 64−76% yield. Methyl ester-substituted 2-iodoanilines (**2c** and **2d**) furnished the 6- or 7-substituted 4-quinolones **3e**−**g** and **3i** in 59−72% yield. In addition, the aliphatic alkynes, 1-heptyne (**1c**) and cyclopentylacetylene (**1d**), performed well in the reaction and furnished products **3h**−**j** in 67−76% yield. Moreover, when 3-ethynylthiophene (**1e**) was used, **3k** and **3l** were obtained in 62% and 51% yield, respectively. In contrast, 2-iodo-4-nitroaniline (**2e**) gave product **3m** in a low yield of 29%. The lower isolated yield was probably due to the known thermally induced reduction of the nitro group by $Mo(CO)_6$.[41,43]

To further expand the preparative scope of the reaction, we sought to develop an alternative method (method B) that would tolerate the use of reduction-prone and other sensitive moieties. On the basis of the work by Iizuka et al. (Scheme 1, c),[20] we believed that 2-iodoanilines could also be used in a gas-free $Mo(CO)_6$-mediated procedure at room temperature to yield the arylalkynone intermediate (**4**) followed by subsequent cyclization induced by diethylamine. With the aim to develop method B to be carried out at room temperature, the use of a catalyst with stabilizing bidentate dppf was not optimal. Gratifyingly, the desired product **3m** was obtained in 67% when **2e** and **1b** were stirred in acetonitrile with triethylamine, $Pd(OAc)_2$, $[HP(t\text{-}Bu)_3]BF_4$, and $Mo(CO)_6$ at room temperature for 16 h followed by the addition of 3.5 equiv of diethylamine. Minor adjustments to the ligand loading and the amount of diethylamine led to a reliable protocol, which furnished nitro group containing **3m** in 79% isolated yield (Table 3), a considerable increase in yield compared to when the MW-heated protocol was used (29%, see Table 2).

Next, we wanted to investigate the scope and limitations of the reaction using various 2-iodoanilines (Table 3). In general, the reaction was found to be insensitive toward changes in the electronic properties of the aniline. The unsubstituted 2-phenyl-4-quinolone was obtained in 84% (**3a**) which is comparable to the result obtained using method A (85%, see Table 2). Anilines bearing electron-withdrawing substituents afforded the desired product in 68−79% yield (**3c**, **3m**, and **3n**−**o**) with the exception of the methyl ester (**3p**) which was obtained in 32% isolated yield. When compound **3p** was produced by method B, unidentified byproducts were formed, which were difficult to separate from the product. In addition, the compounds were poorly soluble in most common organic solvents which gave broad bandwidth on the silica column. These two factors contributed to the low yield. The electron-donating methyl-substituted aniline also performed well and the product was isolated in 75% (**3q**). Due to the mild reaction conditions nitro groups were well tolerated and no reduced byproducts could be observed by LC-MS or ^1H NMR (**3m**−**n**; both obtained in 79%). Furthermore, 6-bromo-2-phenyl-quinolin-4(1*H*)-one (**3o**) was prepared in 68% yield and no traces of dehalogenated or other byproducts resulting from palladium-mediated activation of the Ar−Br bond were detected (LC-MS).

To further evaluate the scope of the reaction we investigated the performance of various alkyne substrates in the reaction (Table 3). Aliphatic 1-heptyne and cyclopentylacetylene were transformed into the desired products in moderate to good yields (**3h** and **3j**; 50% and 71%, respectively). Electron-poor arylacetylenes performed well in the reaction (**3b**, **3m**, **3s**, **3t**; 72−84%) which may be related to the acidity of the acetylenic proton. In contrast, electron-rich arylacetylenes in general gave slightly lower yields (**3r**, **3x**,**3y**; 50−72%). Although the yield of aniline **3x** is probably related to the formation of unidentified byproducts or coordination to the metal catalyst.

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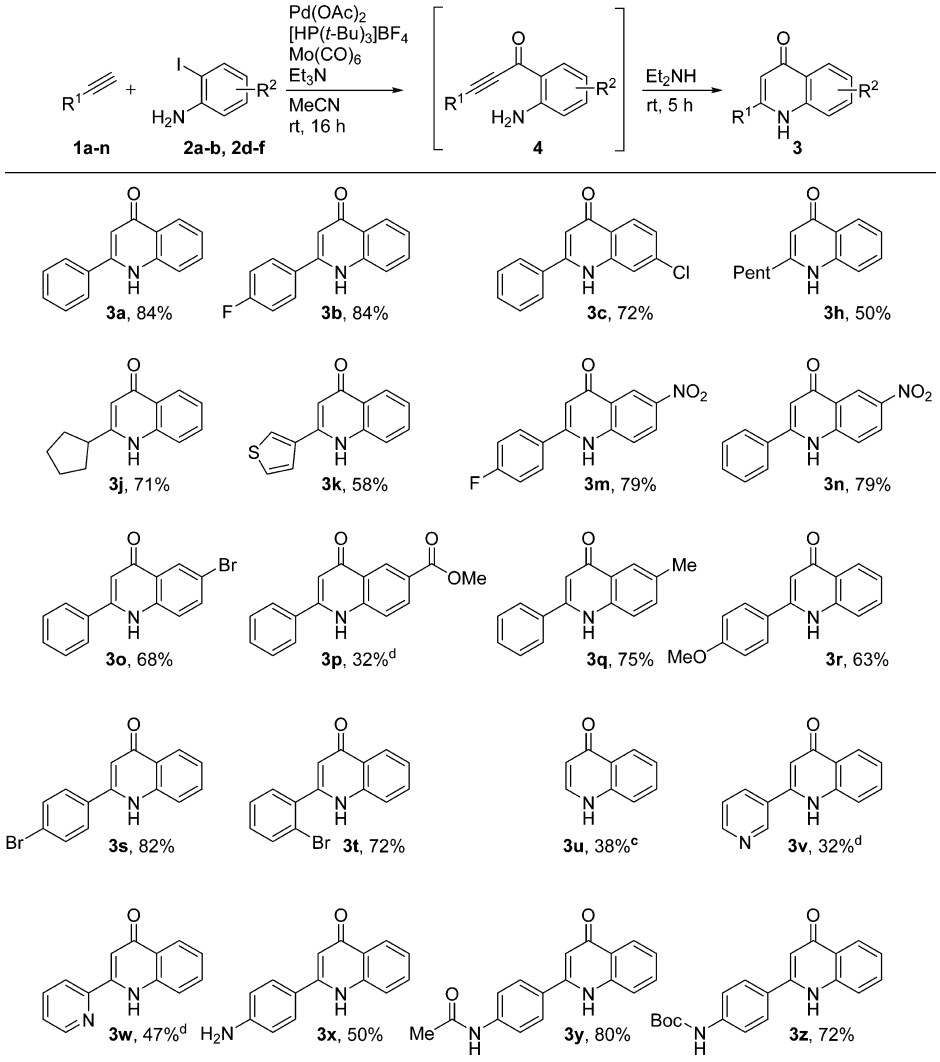
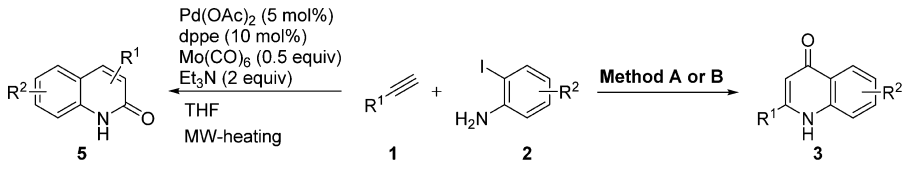
Table 3. Scope and Limitations of the $Mo(CO)_6$-Mediated Carbonylative Two-Step Protocol (Method B)[a,b]



[a]Reaction conditions: (i) **1** (1 mmol), **2** (0.5 mmol), 3 mol % $Pd(OAc)_2$, 6 mol % $[HP(t\text{-}Bu)_3]BF_4$, $Mo(CO)_6$, Et_3N, MeCN, rt, 16 h. (ii) Et_2NH, rt, 5 h. [b]Isolated yield. [c]Prepared from trimethylsilyacetylene (**1h**). [d]The reaction gave full conversion of the limiting reagent, but a problematic purification in combination with low solubility contributed to the low yield.

Scheme 2. Comparison of the Synthesis of 2-Quinolones (5) and 4-Quinolones (3) from 1 and 2



Chen et al. 2010[47]

Demonstrating mild conditions, 1-bromo 4-ethynylbenzene (**1f**) and 1-bromo-2-ethynylbenzene (**1g**) were used to prepare aryl bromide products **3s** and **3t** in high yields (82% and 72%, respectively). Moreover, the Boc-protected aniline was well tolerated in the reaction (**3z**; 72%). The parent compound quinolin-4(1*H*)-one (**3u**) could be prepared from trimethylsilylacetylene (TMS-acetylene) (**1h**) and was isolated after spontaneous deprotection of the TMS group under basic reaction conditions in 38% yield. In conjuction, when TBDMS-protected and free propargyl alcohol were tested as substrates in method B, only traces of the alkynone intermediate were observed after the initial carbonylative Sonogashira cross-soupling. Various heterocycles could, however, also be incorporated albeit in low to moderate yields (**3k**, **3v**, **3w**; 32−58%).

These results compare favorably to the pressurized CO-gas carbonylations in the literature in which five examples of **3** were obtained in yields of 26−75% (one example was obtained in 98% when isolated as a hydrochloride salt).[13] Notably, 2-phenyl-quinolin-4-one (**3a**) has previously been obtained in 62% yield;[13] however, using our nongaseous carbonylation method B, we were able to isolate the same compound in an improved yield of 84% (Table 3).

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Several attempts were made to adapt the developed protocol to 2-bromoanilines. However, no conversion of starting material was observed, and the desired product could not be detected even at elevated temperatures.

Interestingly, Chen et al. have reported a $Mo(CO)_6$-mediated protocol for the synthesis of 2-quinolones (**5**) from **1** and **2** using similar reaction conditions as in method A but using a tertiary amine base (Scheme 2).[48] Under those conditions, a mixture of 3- and 4-substituted 2-quinolones (**5**) were obtained following a noncarbonylative Sonogashira cross-coupling and a carbonylative cyclization. In contrast, the formation of 2-quinolones was never detected (confirmed by NMR) using the protocol described herein, not even when Et_3N was used in place of Et_2NH. Under our conditions (A and B) we firmly believe that a carbonylative Sonogashira reaction yields the alkynone (**4**) which is subsequently cyclized by addition of diethylamine. This is in accordance with previous studies showing that arylalkynones with *ortho*-amine or hydroxyl substituents can be cyclized in a 6-*endo*-*trig* mode to yield 4-quinolones and flavones, respectively, by the addition of secondary amines such as diethylamine.[11,13,49] To confirm that the reaction follows the proposed mechanism, alkynone **4a** was also prepared using our method B in 72% yield and subsequently cyclized to **3a** in 82% isolated yield.

■ CONCLUSION

We report two new methods for the CO gas-free carbonylative heteroannulation using $Mo(CO)_6$ as a convenient solid source of CO. Method A rapidly produces products in the absence of sensitive functional groups, and as a complement, method B tolerates nitro and bromide substituents. The developed protocols have a broad scope, and quinolones can be obtained in moderate to good yields from a wide variety of 2-iodoanilines and alkynes, including electron-rich and electron-poor anilines, arylacetylenes, aliphatic alkynes, and heterocyclic alkynes. Despite the use of a one-pot system, we could prepare nitro-substituted quinolones in good yields using method B. The problem with $Mo(CO)_6$-mediated nitro reduction has previously been solved by separating $Mo(CO)_6$ from the reaction mixture in a two-chamber system.[43] However, due to the mild reaction conditions employed in method B, nitro-substituted quinolones were obtained and no reduced by-products could be detected. Finally, several bromo-substituted quinolones, suitable for subsequent functionalization, were prepared in good yields.

■ EXPERIMENTAL SECTION

General Information. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F-254 plates and visualized with UV light. Flash column chromatography was performed on silica gel 60 (40−63 μm). ^1H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively. The chemical shifts for ^1H NMR and ^{13}C NMR are referenced to TMS via residual solvent signals (^1H, MeOD at 3.31 ppm, $CDCl_3$ at 7.26 ppm, and DMSO-d_6 at 2.50 ppm; ^{13}C, MeOD at 49.0 ppm, $CDCl_3$ at 77.0 ppm, and DMSO-d_6 at 39.5 ppm). Analytical HPLC/ESI-MS was performed using electrospray ionization (ESI) and a C18 column (50 × 3.0 mm, 2.6 μm particle size, 100 Å pore size) with CH_3CN/H_2O in 0.05% aqueous HCOOH as mobile phase at a flow rate of 1.5 mL/min. High resolution molecular masses (HRMS) were determined on a mass spectrometer equipped with an ESI source and 7-T hybrid linear ion trap (LTQ). Compounds **1m**,[50] **1n**,[51] **2g**,[52] **3a**,[53] **3b**,[54] **3c**,[55] **3h**,[56] **3k**,[57] **3n**,[13] **3o**,[6] **3q**,[55] **3r**,[55] **3s**,[54] **3u**,[53] **3v**,[57] **3w**,[57] and **4a**[13] are known, and spectral data were in agreement with the proposed structures and matched those reported in the literature.

Caution! The closed-vessel carbonylation reactions described in this paper should not be repeated on a larger scale or at higher temperatures than reported, as this could result in an explosion unless an appropriate pressure-relief device is used.

*N-(4-Ethynylphenyl)acetamide (**1m**).* The title compound was obtained as a white solid (720 mg, 90%) according to the literature.[50]

*tert-Butyl(4-ethynylphenyl)carbamate (**1n**).* The title compound was obtained as a white solid (620 mg, 57%) according to the literature.[51]

*2-Iodo-4-methylaniline (**2g**).* Prepared according to a published procedure.[58] Beige solid (759 mg, 64%).[52]

General Procedure for the Preparation of 4-Quinolones Using Method A. To a 0.5−2 mL Smith microwave vial were added corresponding 2-iodoaniline (0.5 mmol), corresponding ethylene (1.0 mmol, 2 equiv), tris(dibenzylideneacetone)dipalladium(0) (9.2 mg, 0.01 mmol), 1,1′-bis(diphenylphosphino)ferrocene (11.2 mg, 0.02 mmol), $Mo(CO)_6$ (132 mg, 0.5 mmol, 1 equiv), cesium carbonate (490 mg, 1.5 mmol, 3 equiv), and 1.5 mL of diethylamine. The vial was purged with nitrogen, capped, and irradiated in a Smith Initiator at 120 °C for 20 min. The reaction mixture was poured over water and extracted with chloroform (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with $CHCl_3$/MeOH (100:1−20:1) to yield the desired products.

General Procedure for the Preparation of 4-Quinolones Using Method B. A mixture of 2-iodoaniline (0.5 mmol), $Pd(OAc)_2$ (3 mg, 0.01 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (9 mg, 0,03 mmol), and $Mo(CO)_6$ (198 mg, 0.75 mmol) in a sealed vial was evacuated and backfilled with nitrogen three times. Acetonitrile (2 mL), the alkyne (1 mmol), and triethylamine (0.14 mL, 1 mmol) were added through the septa by a syringe. The reaction mixture was stirred at ambient temperature for 16 h whereafter all starting material had been consumed (LC-MS). Diethylamine (0.26 mL, 2.5 mmol) was added to the reaction mixture, and stirring was maintained at rt for 5 h. The reaction mixture was poured over water and extracted with chloroform (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with $CHCl_3$/MeOH (100:1−20:1) to yield the desired products.

*2-Phenylquinolin-4(1H)-one (**3a**):*[53] Prepared from **1a** and **2a** using method A or B, yielding **3a** as a tan powder. Method A (94 mg, 85%); 5 mmol of **2a** (957 mg, 87%); method B: 1 mmol of **2a** (185 mg, 84%); IR ($MeOH/CHCl_3$) cm^{-1} 1633.

*2-(4-Fluorophenyl)quinolin-4(1H)-one (**3b**):*[54] Prepared from **1b** and **2a** using method A or B, yielding **3b** as a tan powder. Method A (84 mg, 70%) and method B (106 mg, 84%); ^{13}C NMR (DMSO-d_6) δ 176.9, 163.4 (d, J = 248.2 Hz), 149.0, 140.5, 131.9, 130.7 (d, J = 3.1 Hz), 129.9 (d, J = 8.8 Hz), 124.8, 124.7, 123.3, 118.7, 116.0 (d, J = 21.8 Hz), 107.4.

*7-Chloro-2-phenylquinolin-4(1H)-one (**3c**):*[55] Prepared from **1a** and **2b** using method A or B, yielding **3c** as a tan powder. Method A (97 mg, 76%) and method B (95 mg, 72%); ^1H NMR ($CDCl_3$/methanol-d_4 + 1 drop of concd HCl) δ 8.26−8.23 (m, 1H), 8.14 (d, J = 8.9 Hz, 1H), 7.81−7.74 (m, 2H), 7.50−7.38 (m, 4H), 7.27 (s, 1H); ^{13}C NMR ($CDCl_3$/methanol-d_4 + 1 drop of concd HCl) δ 169.8, 156.7, 141.3, 140.5, 132.7, 130.8, 129.4, 128.6, 128.3, 125.3, 119.2, 118.0, 104.2; HRMS (ESI) calcd for $C_{15}H_{11}ClNO$ $[M + H]^+$ m/z 256.0529, found m/z 256.0535; LC purity (254 nm) >99%.

*7-Chloro-2-(4-fluorophenyl)quinolin-4(1H)-one (**3d**).* Prepared from **1b** and **2b** using method A, yielding **3d** as a yellow powder (88 mg, 64%); ^1H NMR (DMSO-d_6) δ 11.70 (br s, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.96−7.87 (m, 2H), 7.78 (s, 1H), 7.44 (t, J = 8.8 Hz, 2H), 7.36 (dd, J = 8.6, 1.7 Hz, 1H), 6.37 (s, 1H). Due to low solubility in common organic solvents, a ^{13}C NMR spectrum could not be obtained for **3d**. This problem is known in the literature for quinolones;[55] HRMS calcd $C_{15}H_{10}ClFNO$ $[M + H]^+$ 274.0435, found 274.0437; LC purity (254 nm) = 98%.

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*Methyl 4-Oxo-2-phenyl-1,4-dihydroquinoline-7-carboxylate (**3e**).* Prepared from **1a** and **2c** using method A, yielding **3e** as a yellow powder (101 mg, 72%); ^{1}H NMR (DMSO-d_6) δ 11.98 (br s, 1H), 8.72 (d, J = 1.8 Hz, 1H), 8.18 (dd, J = 8.7, 2.1 Hz, 1H), 7.85 (d, J = 8.7 Hz, 3H), 7.70−7.50 (m, 3H), 6.42 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 176.8, 165.8, 150.8, 143.4, 133.8, 131.6, 130.7, 129.0, 127.5, 127.2, 124.2, 124.1, 119.4, 108.4, 52.2; HRMS calcd $C_{17}H_{14}NO_3$ $[M + H]^+$ 280.0974, found 280.0971; LC purity (254 nm) = 99%.

*Methyl 2-(4-Fluorophenyl)-4-oxo-1,4-dihydroquinoline-6-carboxylate (**3f**).* Prepared from **1b** and **2d** using method A, yielding **3f** as a yellow powder (87 mg, 59%); ^{1}H NMR (DMSO-d_6) δ 11.99 (br s, 1H), 8.71 (d, J = 2.0 Hz, 1H), 8.17 (dd, J = 8.7, 2.1 Hz, 1H), 7.93 (dd, J = 8.7, 5.4 Hz, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.44 (t, J = 8.8 Hz, 2H), 6.43 (s, 1H), 3.90 (s, 3H). Due to low solubility in common organic solvents, a ^{13}C NMR spectrum could not be obtained for **3f**. This problem is known in the literature for quinolones;[55] HRMS calcd $C_{17}H_{13}FNO_3$ $[M + H]^+$ 298.0879, found 298.0883; LC purity (254 nm) = 97%.

*Methyl 2-(4-Fluorophenyl)-4-oxo-1,4-dihydroquinoline-7-carboxylate (**3g**).* Prepared from **1b** and **2c** using method A, yielding **3g** as a tan powder (93 mg, 63%); ^{1}H NMR (DMSO-d_6) δ 12.00 (br s, 1H), 8.71 (s, 1H), 8.17 (d, J = 10.8 Hz, 1H), 7.97−7.88 (m, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.44 (t, J = 8.8 Hz, 2H), 6.43 (s, 1H), 3.90 (s, 3H). Due to low solubility in common organic solvents, a ^{13}C NMR spectrum could not be obtained for **3g**. This problem is known in the literature for quinolones;[55] HRMS calcd $C_{17}H_{13}FNO_3$ $[M + H]^+$ 298.0879, found 298.0883; LC purity (254 nm) = 96%.

*2-Pentylquinolin-4(1H)-one (**3h**):*[56] Prepared from **1c** and **2a** using method A or B, yielding **3h** as a tan powder. Method A (82 mg, 76%) and method B (54 mg, 50%).

*Methyl 4-Oxo-2-pentyl-1,4-dihydroquinoline-6-carboxylate (**3i**).* Prepared from **1c** and **2d** using method A, yielding **3i** as a gray powder (92 mg, 67%);^{1}H NMR (DMSO-d_6) δ 11.74 (br s, 1H), 8.66 (s, 1H), 8.11 (d, J = 10.7 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 6.00 (s, 1H), 3.88 (s, 3H), 2.65−2.53 (m, 2H), 1.74−1.61 (m, 2H), 1.37−1.28 (m, 4H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 176.7, 165.8, 154.5, 143.1, 131.3, 127.3, 123.9, 123.6, 118.5, 108.7, 52.2, 33.2, 30.7, 27.9, 21.8, 13.9; HRMS calcd $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.1443, found 274.1440; LC purity (254 nm) = 95%.

*2-Cyclopentylquinolin-4(1H)-one (**3j**).* Prepared from **1d** and **2a** using method A or yielding **3j** as a white powder. Method A (79 mg, 74%) and method B (82 mg, 71%); ^{1}H NMR (DMSO-d_6) δ 11.37 (br s, 1H), 8.08−8.02 (m, 1H), 7.67−7.57 (m, 2H), 7.28 (ddd, J = 8.1, 6.2, 1.9 Hz, 1H), 5.98 (d, J = 1.7 Hz, 1H), 3.07−2.92 (m, 1H), 2.16−1.97 (m, 2H), 1.90−1.60 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 177.0, 156.7, 140.2, 131.4, 124.69, 124.66, 122.7, 117.9, 105.4, 43.4, 32.0, 24.9; HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$ m/z 214.1232, found m/z 214.1229; LC purity (254 nm) >99%.

*2-(Thiophen-3-yl)quinolin-4(1H)-one (**3k**):*[57] Prepared from **1e** and **2a** using method A or B, yielding **3k** as an off-white powder. Method A (70 mg, 62%) and method B (67 mg, 58%).

*7-Chloro-2-(thiophen-3-yl)quinolin-4(1H)-one (**3l**).* Prepared from **1e** and **2b** using method A, yielding **3l** as a brown powder (67 mg, 51%); ^{1}H NMR (DMSO-d_6) δ 11.55 (br s, 1H), 8.41−8.27 (m, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 4.3 Hz, 2H), 7.70 (d, J = 5.1 Hz, 1H), 7.34 (dd, J = 8.6, 1.8 Hz, 1H), 6.51 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 176.5, 173.6, 145.1, 141.1, 136.3, 135.0, 128.2, 127.0, 126.6, 126.3, 123.5, 117.7, 107.0; HRMS calcd $C_{13}H_9ClNOS$ $[M + H]^+$ 262.0093, found 262.0096; LC purity (254 nm) = 99%.

*2-(4-Fluorophenyl)-6-nitroquinolin-4(1H)-one (**3m**).* Prepared from **1b** and **2e** using method B. Yellow powder (519 mg, 79%); ^{1}H NMR (DMSO-d_6) δ 8.49 (d, J = 2.7 Hz, 1H), 7.96 (dd, J = 9.2, 2.7 Hz, 1H), 7.69 (s, 1H), 7.35−7.15 (m, 4H), 6.71 (d, J = 9.2 Hz, 1H), 5.81 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 187.4, 161.9 (d, J = 244.4 Hz), 161.8, 155.3, 134.6, 133.1 (d, J = 3.5 Hz), 130.1 (d, J = 8.3 Hz), 126.9, 126.7, 120.0, 115.9, 115.1 (d, J = 21.6 Hz), 93.8; HRMS (ESI) calcd for $C_{15}H_{10}FN_2O_3$ $[M + H]^+$ m/z 285.0675, found m/z 285.0670; LC purity (254 nm) = 96%.

*6-Nitro-2-phenylquinolin-4(1H)-one (**3n**):*[13] Prepared from **1a** and **2e** using method B. Yellow powder (208 mg, 79%); IR (MeOH/$CHCl_3$) cm^{-1} 3019, 1616, 1512, 1319.

*6-Bromo-2-phenylquinolin-4(1H)-one (**3o**):*[6] Prepared from **1a** and **2f** using method B. Yellow powder (100 mg, 68%); ^{13}C NMR ($CDCl_3$/methanol-d_4 + 1 drop of concd HCl) δ 168.8, 156.2, 138.7, 137.9, 132.7, 130.8, 129.5, 128.4, 126.0, 121.8, 121.6, 120.8, 104.6.

*Methyl 4-Oxo-2-phenyl-1,4-dihydroquinoline-6-carboxylate (**3p**).* Prepared from **1a** and **2d** using method B. Off-white powder (46 mg, 32%); ^{1}H NMR (DMSO-d_6) δ 8.76 (d, J = 2.0 Hz, 1H), 8.19 (dd, J = 8.7, 2.1 Hz, 1H), 7.91−7.81 (m, 3H), 7.65−7.56 (m, 3H), 6.44 (s, 1H), 3.94 (s, 3H). Due to low solubility in common organic solvents, a ^{13}C NMR spectrum could not be obtained for **3p**. This problem is known in the literature for quinolones;[55] HRMS (ESI) calcd for $C_{17}H_{14}NO_3$ $[M + H]^+$ m/z 280.0974, found m/z 280.0968; LC Purity (254 nm) >95%.

*6-Methyl-2-phenylquinolin-4(1H)-one (**3q**):*[55] Prepared from **1a** and **2g** using method B. Off-white solid (91 mg, 75%).

*2-(4-Methoxyphenyl)quinolin-4(1H)-one (**3r**):*[55] Prepared from **1i** and **2a** using method B. Beige solid (83 mg, 63%).

*2-(4-Bromophenyl)quinolin-4(1H)-one (**3s**):*[54] Prepared from **1f** and **2a** using method B. Tan powder (124 mg, 82%); ^{13}C NMR (DMSO-d_6) δ 176.9, 148.8, 140.5, 133.3, 131.92, 131.90, 129.5, 124.9, 124.7, 124.0, 123.3, 118.7, 107.4.

*2-(2-Bromophenyl)quinolin-4(1H)-one (**3t**).* Prepared from **1g** and **2a** using method B. Dark red solid (111 mg, 72%); ^{1}H NMR (DMSO-d_6) δ 7.70−7.61 (m, 2H), 7.41 (td, J = 7.5, 1.2 Hz, 1H), 7.31 (ddd, J = 8.0, 7.4, 1.8 Hz, 1H), 7.23 (dd, J = 7.5, 1.7 Hz, 1H), 7.08 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 6.61 (dd, J = 8.3, 1.2 Hz, 1H), 6.51 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 6.42 (br s, 1H), 5.87 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 188.4, 158.4, 149.8, 138.3, 132.0, 131.3, 129.7, 129.44, 129.38, 127.4, 121.9, 121.7, 116.3, 114.4, 93.2; HRMS (ESI) calcd for $C_{15}H_{11}BrNO$ $[M + H]^+$ 300.0024 m/z, found 300.0027 m/z; LC purity (254 nm) >99%.

*Quinolin-4(1H)-one (**3u**):*[53] Prepared from **1h** and **2a** using method B. Yellow powder (28 mg, 38%).

*2-(Pyridin-3-yl)quinolin-4(1H)-one (**3v**):*[57] Prepared from **1j** and **2a** using method B. Tan powder (33 mg, 32%).

*2-(Pyridin-2-yl)quinolin-4(1H)-one (**3w**):*[57] Prepared from **1k** and **2a** using method B. Tan powder (51 mg, 47%).

*2-(4-Aminophenyl)quinoline-4(1H)-one (**3x**).* Prepared from **1l** and **2a** using method B. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with 3 × 25 mL EtOAc. The combined organic phases were extracted with 3 × 25 mL of 1 M HCl (aq). The combined aqueous phases were made basic with 6 M NaOH (aq). After cooling, the formed precipitate was collected by filtration and washed with MeCN. The precipitate was dissolved in chloroform and methanol and heated with activated charcoal to remove any residual molybdenum residues, yielding **3x** as a yellow solid (61 mg, 50%); ^{1}H NMR (DMSO-d_6) δ 11.43 (br s, 1H), 8.08 (dd, J = 8.1, 1.5 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.69−7.56 (m, 3H), 7.31 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 6.76- 6.69 (m, 2H), 6.29 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 176.4, 151.3, 150.6, 140.5, 131.4, 128.3, 124.5 (two overlapping signals found by HMBC), 122.9, 120.1, 118.5, 113.6, 104.8; IR (DMSO) cm^{-1} 3428 (broad signal), 1629; HRMS (ESI) calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$ 237.1028 m/z, found 237.1038 m/z; LC purity (254 nm) >99%.

*N-(4-(4-Oxo-1,4-dihydroquinolin-2-yl)phenyl)acetamide (**3y**).* Prepared from **1m** and **2a** using method B yielding **3y** as a beige solid (107 mg, 80%); ^{1}H NMR (DMSO-d_6) δ 11.61 (br s, 1H), 10.24 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 15.9 Hz, 5H), 7.68 (ddd, J = 8.4, 6.9, 1.6 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 176.9, 168.7, 149.5, 141.3, 140.5, 131.7, 128.3, 127.9, 124.8, 124.7, 123.1, 118.9, 118.6, 106.6, 24.1; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$ 279.1134 m/z, found 279.1143 m/z; LC purity (254 nm) >99%.

*tert-Butyl (4-(4-Oxo-1,4-dihydroquinolin-2-yl)phenyl)carbamate (**3z**).* Prepared from **1n** and **2a** using method B yielding **3z** as a white solid (120 mg, 72%); ^{1}H NMR (DMSO-d_6) δ 11.57 (br s, 1H), 9.70 (s, 1H), 8.10 (dd, J = 8.1, 1.5 Hz, 1H), 7.82−7.75 (m, 3H), 7.71−

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7.64 (m, 3H), 7.33 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 6.33 (d, J = 1.8 Hz, 1H), 1.52 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 176.8, 152.6, 149.6, 141.7, 140.5, 131.6, 127.9, 127.3, 124.8, 124.7, 123.1, 118.6, 117.9, 106.5, 79.5, 28.1; IR (MeOH/$CHCl_3$) cm^{-1} 3268, 3019, 2943, 1720, 1633, 1216, 1158; HRMS (ESI) calcd for $C_{20}H_{21}N_2O_3$ $[M + H]^+$ 337.1552 m/z, found 337.1566 m/z; LC purity (254 nm) >99%.

*1-(2-Aminophenyl)-3-phenylprop-2-yn-1-one (**4a**):*[13] A mixture of **2a** (110 mg, 0.50 mmol), $Pd(OAc)_2$ (4.2 mg, 0.02 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (9.6 mg, 0.03 mmol), and $Mo(CO)_6$ (204 mg, 0.77 mmol) in a sealed vial was evacuated and backfilled with nitrogen three times. Acetonitrile (2 mL), **1a** (0.11 mL, 1.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) were added through the septa by a syringe. The reaction mixture was stirred at ambient temperature for 20 h whereafter all starting material had been consumed (TLC). The reaction mixture was poured over water and extracted with chloroform (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with CH_2Cl_2 to yield **4a** as an orange solid (80 mg, 72%).

*Cyclization of **4a**.* Diethylamine (80 μL, 0.77 mmol) was added to a solution of **4a** (34 mg, 0.15 mmol) in acetonitrile (2 mL) and stirred at rt for 22 h. The reaction mixture was filtered over activated charcoal and concentrated under reduced pressure to yield **3a** (28 mg, 82%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra and chromatograms of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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