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Title: Embedded Alkylamino-Directed One-Pot Reaction of N-Alkyl Anilines with CO, Amines and Aldehydes Leading to 2,3-Dihydroquinazolin-4(1H)-ones

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Alkylamino-Directed One-Pot Reaction of *N*-Alkyl Anilines with CO, Amines and Aldehydes Leading to 2,3-Dihydroquinazolin-4(1*H*)-ones

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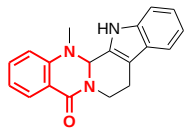
Abstract. An economical and efficient approach to pharmaceutically and biologically significant 2,3-dihydroquinazolin-4(1*H*)-ones has been disclosed. The one-pot multicomponent reaction was performed through a palladium-catalyzed *ortho*-selective oxidative carbonylation of *N*-substituted anilines with CO and primary amines, and subsequent condensation with aldehydes in MeCN by using alkylamino as the directing group, KI/AcOH as the additives, and $Cu(OAc)_2$ as the oxidant. This intriguing straightforward method features embedded directing strategy, simple starting materials, mild conditions, high atom/step economic economy, broad substrate scope and good product diversity.

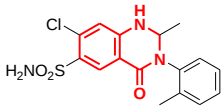
Keywords: C-H activation; 2,3-dihydroquinazolin-4(1*H*)-ones; embedded directing group; *N*-alkyl anilines; palladium

2,3-Dihydroquinazolin-4(1*H*)-ones (DHQAs) are an important class of nitrogen-containing heterocycles with a wide range of pharmaceutical and biological activities such as anticancer,[1] antitumor,[1b,2] antihypertensive,[3] anti-inflammatory,[4] antibacterial,[5] antifungal,[6] antipsychotic,[3b] antihistaminic,[7] antiviral,[8] anti-Plasmodium,[9] diuretic,[1b,3a,10] vasodilating,[11] analgesic,[4c] anthelmintic[12] effects and cathepsins B & H,[13] cholinesterases,[14] coagulation factor Xa,[15] HIV-1 reverse transcriptase,[16] inosine 5'-monophosphate dehydrogenase,[17] protein kinase C-θ,[18] transient receptor potential melastatin 2[19] inhibition. For example, evodiamine[2a,4a,20] and metolazone[10b,21] are typical representatives of clinically significant DHQA medications (Figure 1).

Due to their immense and important biological activities, the synthesis of DHQAs has attracted

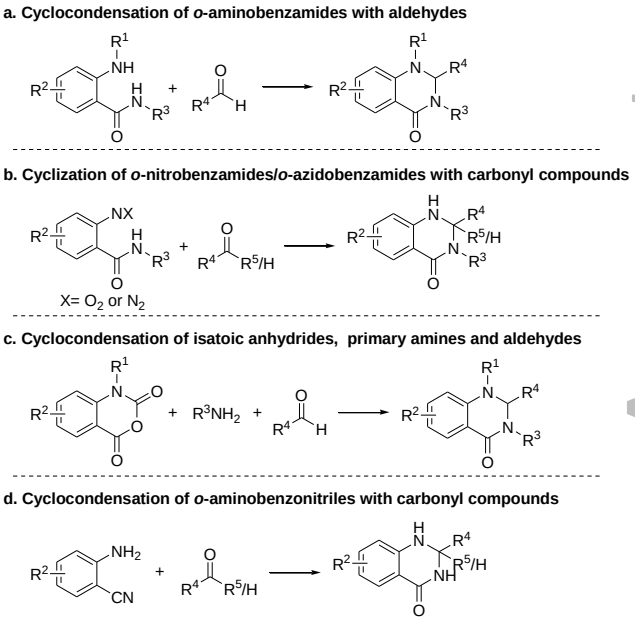


Evodiamine
(anti-cancer/antitumor/inflammatory/ obesity/cardiovascular diseases/ microbial/Alzheimer's disease agents)



Metolazone
(anti-hypertensive, saluretic, diuretic, treatment of severe refractory congestive cardiac failure)

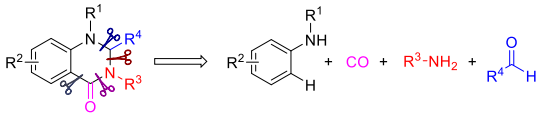
Figure 1. Representative examples of clinically significan DHQA medications.



Scheme 1. Previous synthetic approaches to DHQAs.

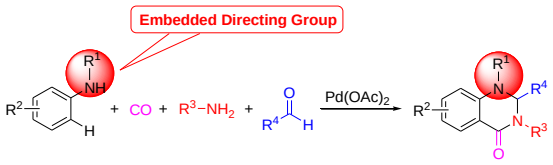
considerable interests. Among the established

synthetic protocols, the typical procedures involve cyclocondensation of *o*-amino-benzamides (usually obtained by ammonolysis of isatoic anhydride) with aldehydes (Scheme 1a),[3a,22] reductive cyclization of *o*-nitrobenzamides or *o*-azidobenzamides with carbonyl compounds (Scheme 1b),[23] cyclocondensation of isatoic anhydrides, primary amines (or ammonium salts) and aldehydes (Scheme 1c),[2b,5a,22a,24] and cyclocondensation of *o*-aminobenzonitriles with carbonyl compounds (Scheme 1d).[25] Despite the above advances, however, one major drawback associated with all the above approaches is that the N^1-containing starting materials applied in these protocols are usually complex, costly, and lack structural diversity. In addition, these synthetic strategies also suffer from certain limitations such as harsh reaction conditions, lengthy steps, tedious procedures for preparation of catalysts and tedious work-up conditions. Moreover, most of the efforts mainly focus on the development of various catalytic systems at present, no report has been found on the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by employing simple, cheap and readily available starting materials from the source. An intriguing question is whether simple *N*-substituted anilines, CO, amines and aldehydes can be used as the substrates for straightforward construction of DHQAs (Scheme 2), which, to the best of our knowledge, has not been explored to date. This proposed protocol would provide an entirely new facile, practical and efficient approach to such compounds with high atom/step economy if it works. However, there are at least three big challenges should be addressed: 1) There should be enough energy (using appropriate catalytic system) to activate CO under mild conditions; 2) The *ortho*-selective C-H carbonylation of *N*-substituted anilines with CO should be controlled; 3) The reaction system should avoid the formation of 1,3-dialkylureas via transition metal-catalyzed oxidative carbonylation of amines under the necessary oxidative reaction conditions.



Scheme 2. Retrosynthetic analysis of DHQAs.

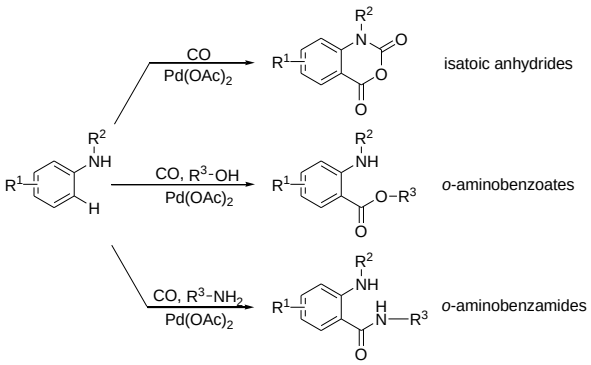
Because of the above challenges, such straightforward route to DHQAs under mild condition has not been realized, although it would substantially broaden bioactive DHQAs library. Herein, we demonstrate the first example of a straightforward method for synthesis of DHQAs through a Pd-catalyzed one-pot reaction of simple *N*-alkyl anilines, CO, amines and aldehydes (Scheme 3). This reaction successfully combines Pd-catalyzed *ortho*-selective C-H carbonylation, amidation and cycloaminoacetal formation. The alkylamino group of *N*-alkyl anilines was used as an embedded directing group (DG) to trigger the *ortho*-selective C-H functionalization reactions.



Scheme 3. Embedded alkylamino-directed Pa-catalyzed reaction to DHQAs.

During the past decades, the direct transformation of inert C-H bonds into carbon-carbon and carbon-heteroatom bonds via transition-metal-catalyzed activation & functionalization under the influence of the given DG has emerged as a powerful and valuable tool to simplify the synthesis of complex molecules dramatically.[26] However, the DGs applied in this strategy are usually difficult to be integrated into the desired products, thereby, result in additional synthetic steps being often required to both install the DGs into the starting materials and remove them after C-H functionalization. Compared to the traditional DGs, so called embedded DGs, which can be integrated into the corresponding products, show unparalleled superiority.

Recently, Guan's, Lei's and our groups have found that *N*-alkyl anilines can be used for the Pd-catalyzed *ortho*-selective C-H carbonylation with CO for the synthesis of isatoic anhydrides, *o*-aminobenzoates and *o*-aminobenzamides (Scheme 4).[27] Based on these studies, we envision that alkylamino group may be used as embedded DG to synthesize DHQAs (Scheme 3).



Scheme 4. Pd-catalyzed *ortho*-selective C-H carbonylation of *N*-alkyl anilines.

We began our study by testing the Pa-catalyzed oxidative carbonylation of *N*-methylaniline **1a** with CO (bubble), aniline **2a**, and benzaldehyde **3a**. The results were summarized in Table 1. To our delight, when the reaction conducted at 70 °C in MeCN with KI/HCl as the additive and $Cu(OAc)_2$ as the oxidant

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for 8 h, the desired product 1-methyl-2,3-diphenyl-DHQA (**4-1a**) could be obtained in 23% yield (entry 1) together with a certain amount of 1,3-diphenylurea and 1-methyl-1,3-diphenylurea and a small amount of *N*-methyl isatoic anhydride and 2-(methylamino)benzoic acid as by-products. Single crystals of **4-1a** were obtained by slow evaporation of the ethanol solution at room temperature. The Oak Ridge Thermal Ellipsoid Plot (ORTEP) drawing of **4-1a** is given in Figure 2.[28] Further screening of the acid additive among $FeCl_3$, TsOH, citric acid, and AcOH revealed that AcOH emerged as the most effective acid additive (entries 2-5). However, the reaction failed to proceed in the absence of KI or AcOH, indicating that both KI and AcOH were indispensable during this transformation (entries 6 and 7). Next, the effect of the common solvents such as MeCN, toluene, 1,4-dioxane, DMF, and DMSO on the reaction was examined (entries 5, 8-11) and the results showed that MeCN worked most effectively (entry 5), followed by DMF (entry 10). Finally, we explored the oxidant performance among $Cu(OAc)_2$, O_2, $Cu(OAc)_2/O_2$, $CuCl_2$, and $CuBr_2$ (entries 5, 12-15). Compared with the inferior efficacy of O_2 (entry 12), $Cu(OAc)_2$ gave the best result (entry 5), the combination of $Cu(OAc)_2/O_2$ failed to further increase the product yield (entry 13), while $CuCl_2$ and $CuBr_2$ didn't work at all. Scale-up experiment could afford the target product **4-1a** in 36% yield under the optimized reaction conditions (See SI, page S2).

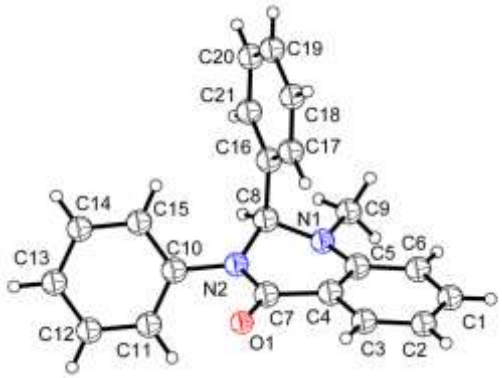
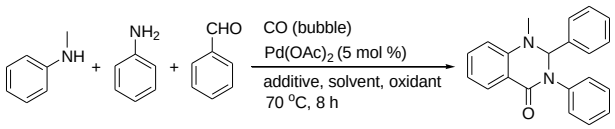


Figure 2. X-ray crystal structure of **4-1a**. The level set for thermal ellipsoids of all non-hydrogen atoms is 30%.

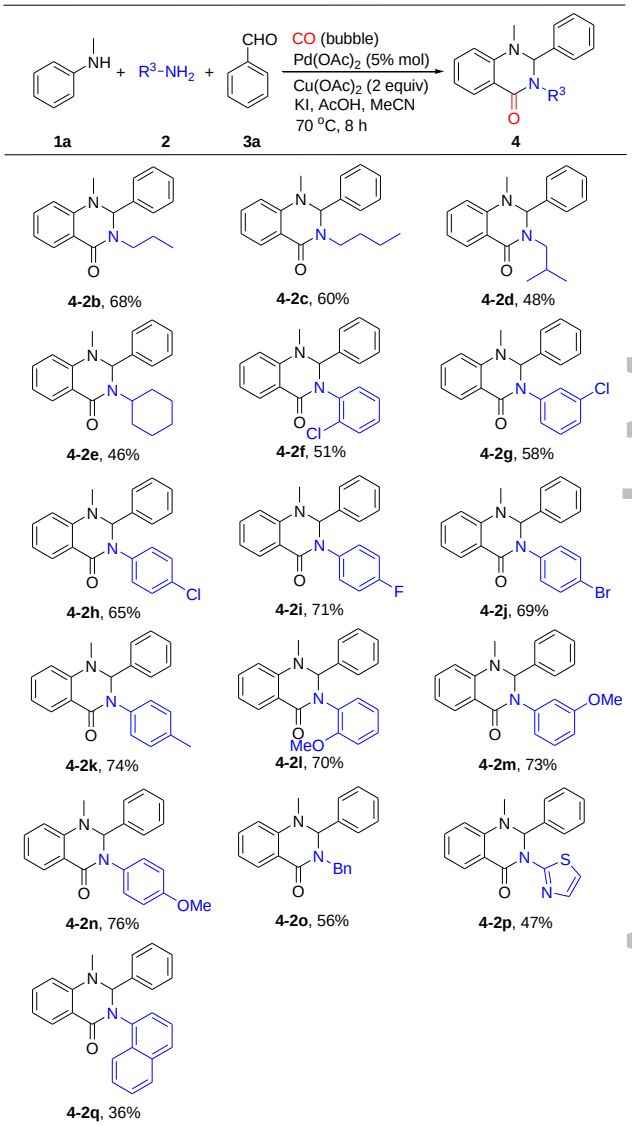
Table 1. Optimization of reaction conditions.[a]



entry	additive	solvent	oxidant	Yield(%)[b]
1	KI/HCl	MeCN	$Cu(OAc)_2$	23
2	KI/$FeCl_3$	MeCN	$Cu(OAc)_2$	0
3	KI/TsOH	MeCN	$Cu(OAc)_2$	0
4	KI/citric acid	MeCN	$Cu(OAc)_2$	0
5	KI/AcOH	MeCN	$Cu(OAc)_2$	78
6	KI	MeCN	$Cu(OAc)_2$	0
7	AcOH	MeCN	$Cu(OAc)_2$	0
8	KI/AcOH	Toluene	$Cu(OAc)_2$	15
9	KI/AcOH	1,4-dioxane	$Cu(OAc)_2$	44
10	KI/AcOH	DMF	$Cu(OAc)_2$	63
11	KI/AcOH	DMSO	$Cu(OAc)_2$	42
12	KI/AcOH	MeCN	O_2	28
13	KI/AcOH	MeCN	$Cu(OAc)_2/O_2$	78
14	KI/AcOH	MeCN	$CuCl_2$	0
15	KI/AcOH	MeCN	$CuBr_2$	0

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), **3a** (1.5 mmol), additive (KI: 0.2 mmol, liquid acid: 5.0 mL, solid acid: 1.0 mmol), solvent (10.0 mL), oxidant (solid oxidant 2.0 mmol, O_2 bubble), the mixture of **2a** and acid were added dropwise. [b] Isolated yield.

Table 2. Scope of amines.[a]



[a] Reaction conditions: **1a** (1.0 mmol), **2** (3.0 mmol), **3a** (1.5 mmol), KI (0.2 mmol), AcOH (5 mL), MeCN (10.0 mL), the mixture of **2** and AcOH were added dropwise. [b] Isolated yield.

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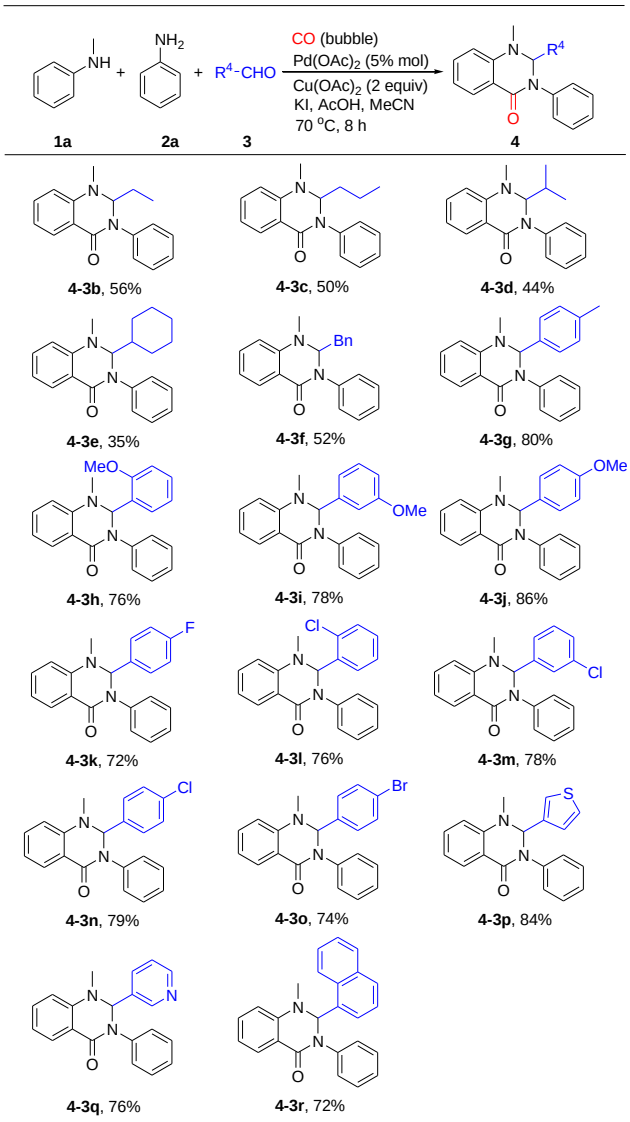
With the optimized reaction conditions in hand, we first turned our attention to investigate the generality of this transformation. The scope of amines (**2b-q**) was firstly examined. As shown in Table 2, both aliphatic amines and aromatic amines could be well tolerated with this protocol, affording the desired products mostly in moderate to good yields (**4-2b-q**). Steric effects seemed to have a certain impact on the transformation; the greater the steric hindrance of the amines was, the slightly lower the reactivity they became. Although the product yields obtained from the aromatic amines bearing the electron-donating groups (**4-2k-n**) were a little higher than those bearing the electron-withdrawing group (**4-2f-j**), their difference was not obvious, indicating that this transformation was not very sensitive to the electronic effects of the amines. When benzylamine was applied in this reaction, the desired product **4-2o** was obtained in 56% yield accompanied by an increased amount of byproduct 1,3-dibenzylurea compared with the case of aniline, revealing that the competitive self carbonylation enhanced to some extent due to its high reactivity. Finally, heteroaromatic amine thiazol-2-amine and polycyclic aromatic amine naphthalen-1-amine were also evaluated in this transformation to give the desired products **4-2p** and **4-2q** in 47% and 36% yields, respectively; the high steric hindrance of naphthalen-1-amine may be responsible for the low yield of the corresponding product **4-2q**.

Table 3. Scope of aldehydes.[a]



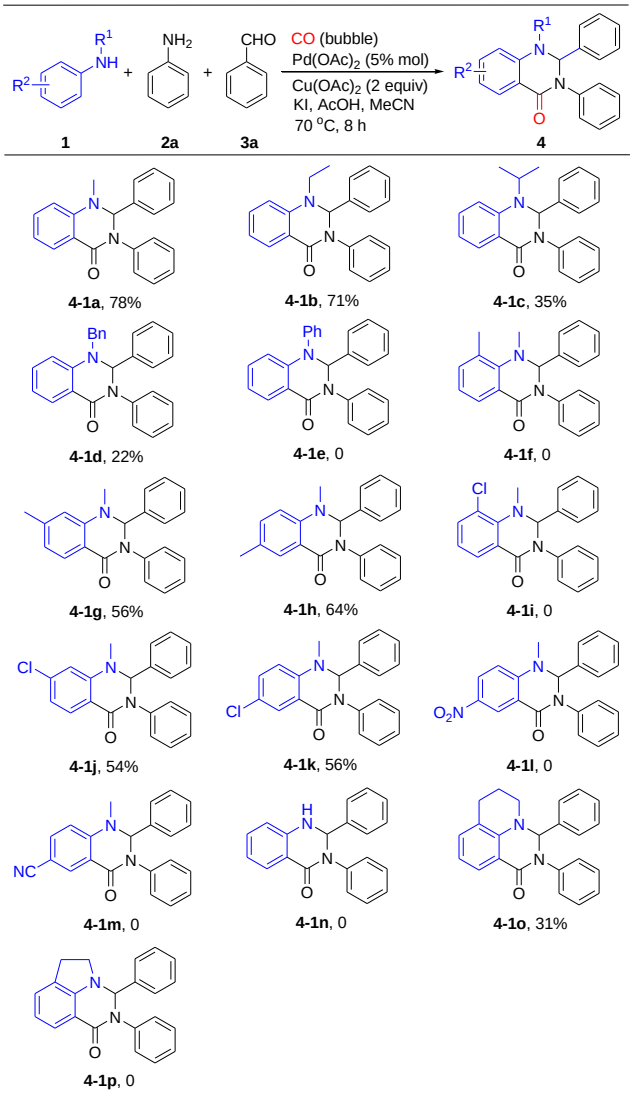
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), **3** (1.5 mmol), KI (0.2 mmol), AcOH (5 mL), MeCN (10.0 mL), the mixture of **2a** and AcOH were added dropwise. [b] Isolated yield.

Next, we evaluated the scope of aldehydes (**3b-r**) and the results were summarized in Table 3. Generally, aliphatic aldehydes worked less effectively than the aromatic ones. Higher volatility and/or steric hindrance may be accounted for the unsatisfactory performance of the aliphatic aldehydes (**4-3b-f**). Satisfyingly, however, aromatic aldehydes could be well tolerated with the transformation, affording the desired products in very high yields (**4-3g-r**). Although the type and position of the substituents on the benzene ring of the aromatic aldehydes seemed to have a certain impact on this reaction, it didn't make much difference. Satisfactorily, heteroaromatic aldehydes such as thiophene-3-carbaldehyde (**3p**) and 3-pyridinealdehyde (**3q**) together with polycyclic 1-naphthaldehyde (**3r**) could work effectively, affording the desired products in yield of 84%, 76%, and 72%, respectively.

Subsequently, this protocol was surveyed with a variety of *N*-substituted anilines (**1a-l**) to further demonstrate its generality (Table 4). We were pleased to find that the reaction could proceed smoothly with *N*-methyl/ethyl aniline, affording the desired **4-1a** and **4-1b** in 78% and 71% yield, respectively. However, the product yields decreased accordingly with the increase of the *N*-substituents bulk (**4-1c**, **4-1d**, **4-1e**), indicating that this transformation was very sensitive to steric hindrance to the embedded DGs, which also was confirmed by the different performance of *N*-substituted anilines bearing *ortho*-, *meta*-, and *para*-substituents at the benzene ring during this transformation (**4-1f**~**4-1k**). No obvious difference was observed in product yields when the transformation performed with the *N*-substituted anilines containing electron-donating methyl substituent and those containing weak electron-withdrawing chlorine substituent at the benzene ring, respectively (**4-1f** *vs* **4-1i**, **4-1g** *vs* **4-1j**, **41-h** *vs* **4-1k**), however, when the *N*-substituted anilines bearing strong electron-withdrawing group such as $-NO_2$ and –CN were applied in this protocol, no desired product could be obtained (**4-1l, 4-1m**). The reaction failed to give the desired product when aniline was applied instead of *N*-substituted aniline owing to the self carbonylation of aniline to afford 1,3-diphenylurea was predominated under the current conditions (**4-1n**). Further extension of this transformation to cyclic *N*-substituted anilines such as 1,2,3,4-tetrahydroquinoline (**1o**) and indoline (**1p**) revealed

that the former could tolerate this protocol, while the latter failed to work in this system.

Table 4. Scope of *N*-substituted anilines.[a]



[a] Reaction conditions: **1** (1.0 mmol), **2a** (3.0 mmol), **3a** (1.5 mmol), KI (0.2 mmol), AcOH (5 mL), MeCN (10.0 mL), the mixture of **2a** and AcOH were added dropwise. [b] Isolated yield.

In summary, an economical and efficient relay reaction has been developed for the synthesis of DHQAs through a palladium-catalyzed *ortho*-selective C-H functionalization of *N*-substituted anilines with CO, amines and aldehydes based on the embedded directing strategy. This embedded alkylamino-directed carbonylation reaction tolerates a wide range of functional groups and is a reliable method for the rapid elaboration of simple substrates into various substituted DHQAs, which are important potential biologically active molecules. The mild conditions, use of simple and readily available substrates, and multi-component one-pot reaction manner make this transformation very green and practical.

Experimental Section

General procedure for the synthesis of 2,3-dihydroquin-azolin-4(1*H*)-ones

N-Substitutedaniline (1.0 mmol), aldehyde (1.5 mmol), $Pd(OAc)_2$ (0.05 mmol), $Cu(OAc)_2$ (2.0 mmol), KI (0.2 mmol) and CH_3CN (10 mL) were charged in a 50 mL three-necked round-bottom flask equipped with a stir bar and a condenser. The mixture of AcOH (5 mL) and a primary amine (3.0 mmol) was added into a constant pressure dropping funnel, which was then connected with one neck of the flask. Another neck was equipped with a T-branch pipe connected with a CO balloon. The flask was then evacuated and back-filled with CO three times, followed by stirring at 70 °C for 8 h with continuous bubble of CO and slow dripping of AcOH and the primary amine. Then the reaction mixture was cooled to room temperature and the CO balloon was removed. A small amount of black powder of suspected metallic Cu and Pd could be detected in the reaction mixture according to the XPS study (See SI, page S2-S3). Subsequently, saturated NaCl solution (30 mL) was added into the flask and the mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding 2,3-dihydroquin-azolin-4(1*H*)-ones **4** with petroleum ether/ethyl acetate (15:1) as the eluent.

Acknowledgements

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[28] Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1876985. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk).

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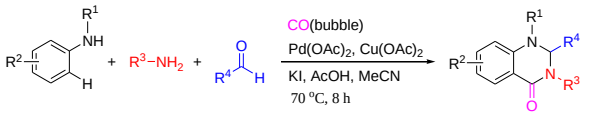

49 examples, up to 86% yield

- simple raw materials and low cost
- high atom economy and step economy
- one-pot manner and mild conditions
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