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Palladium-catalyzed carbonylative synthesis of quinazolines: Silane act as better nucleophile than amidine

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ABSTRACT

A palladium-catalyzed reductive carbonylation reaction has been developed for the synthesis of quinazolines. With N-(2-iodophenyl)benzimidamide as starting materials, a series of quinazolines were obtained through the aromatic aldehyde intermediates in moderate to good yields with good functional group compatibilities. In this system, silane act as better nucleophile than amidine.

During the past decades, transition-metal-catalyzed carbonylation reactions have proven to be one of the powerful methods for the construction of carbonyl-containing compounds and have attracted lots of attentions for their widely application in both academic and industrial fields. [1] Among all the carbonylation reactions, the synthesis of aromatic aldehyde by reductive carbonylation is considered to be unique and interesting. One representative example was developed by Beller's group, [2] a general and practical palladium-catalyzed reductive carbonylation of aryl and heteroaryl bromides in the presence of syngas. Furthermore, several other methods have been reported for the preparation of aromatic aldehydes by different research groups as well. [3] Recently, we also explored a few reductive carbonylation reactions for the synthesis of aromatic aldehydes. [4] Additionally, the synthesis of bis(indolyl)methanes, [5] and chalcone [6] have also been developed *via* the aldehyde-mediate palladium-catalyzed reductive carbonylation reactions.

Quinazolines, a valuable class of nitrogen-containing compounds which play an important role in pharmaceutical industry due to their wide range biological and medicinal activities such as antibacterial, [7] anticancer, [8] anticonvulsant, [9] anti-inflammatory, [10] antimalarial, [11] antitubercular, [12] and antiviral properties. [13] Therefore, numerous protocols for the preparation of quinazolines has been developed during these years. [14] Although much efforts have been put on this area, [15–17] the exploration of novel catalytic system remains an active field of research. Considering the straightforward and effective utilization of palladium-catalyzed reductive carbonylation, an aldehyde mediate quinazolines synthesis came to our mind (Scheme 1, eq a). In our approach, it is noteworthy that the reaction could potentially undergo another competitive pathway (Scheme 1, eq b). [18] We reasoned that this pathway may be suppressed by the selection of hydrogen source. Under these backgrounds, we wish to disclose here a palladium-catalyzed quinazolines synthesis *via* a reductive carbonylation process with aromatic aldehydes as the key intermediates.

Initially, we carried out this reductive carbonylation reaction with *N*-(2-iodophenyl)benzimidamide **1a** (prepared from *o*-iodoaniline and benzonitrile) as model substrate, $Pd(OAc)_2$ as the catalyst, PPh_3 as the ligand, $Mo(CO)_6$ as the CO source, Et_3SiH as the hydrogen source, Et_3N as the base in DMF at 120 °C for 16 h, the target product **2a** was obtained in 5% yield (Table 1, entry 1). Next, different silanes were studied (Table 1, entry 2–4), 19% yield of **2a** was observed with Ph_2SiH_2 as the hydrogen source (Table 1, entry 2). Delightly, when using 3 equivalent of $Mo(CO)_6$, the quinazoline product was detected in 47% yield (Table 1, entry 5). Palladium catalysts, such as $Pd(TFA)_2$, $PdCl_2$, $PdBr_2$, and $Pd(acac)_2$ were then examed, resulting the desired quinazoline in lower yields (Table 1, entry 6–9). Subsequently, various mono- and bidentate phosphine ligands were examined, PCy_3 and Xphos resulted the corresponding product in 18% and 26% yields (Table 1, entry 10–11), while $BuPAd_2$ gave a comparable yield as PPh_3 (Table 1, entry 12). Gratifyingly, $P(C_6F_5)_3$ appeared to be the best ligand in this reaction, producing the corresponding product in 56% (Table 1, entry 13). Compare to monodentate ligands, the use of bidentate ligands decreased the product yield (Table 1, entry 14–15).

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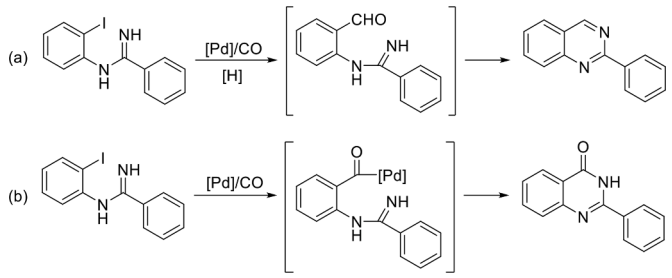
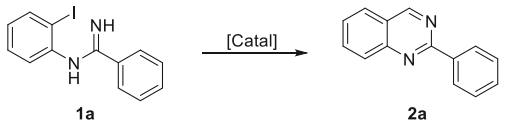


Scheme 1. Silane nucleophile vs amine nucleophile.

Table 1
Screening of reaction conditions.[a].



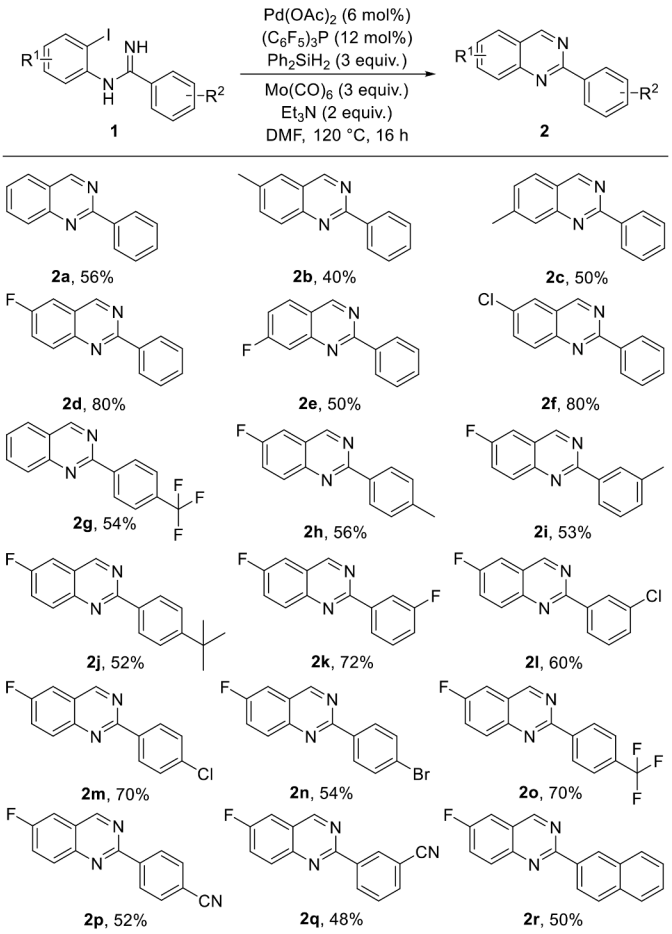
1a 2a

Entry	Catalyst	Ligand	[H]	Solvent	Yield (%)
1	$Pd(OAc)_2$	PPh_3	Et_3SiH	DMF	5
2	$Pd(OAc)_2$	PPh_3	Ph_2SiH_2	DMF	19
3	$Pd(OAc)_2$	PPh_3	iPr_3SiH	DMF	6
4	$Pd(OAc)_2$	PPh_3	PHMS	DMF	trace
5[b]	$Pd(OAc)_2$	PPh_3	Ph_2SiH_2	DMF	47
6[b]	$Pd(TFA)_2$	PPh_3	Ph_2SiH_2	DMF	30
7[b]	$PdCl_2$	PPh_3	Ph_2SiH_2	DMF	25
8[b]	$PdBr_2$	PPh_3	Ph_2SiH_2	DMF	18
9[b]	$Pd(acac)_2$	PPh_3	Ph_2SiH_2	DMF	25
10[b]	$Pd(OAc)_2$	PCy_3	Ph_2SiH_2	DMF	18
11[b]	$Pd(OAc)_2$	Xphos	Ph_2SiH_2	DMF	26
12[b]	$Pd(OAc)_2$	$BuPAd_2$	Ph_2SiH_2	DMF	47
13[b]	$Pd(OAc)_2$	$P(C_6F_5)_3$	Ph_2SiH_2	DMF	56
14[b]	$Pd(OAc)_2$	DPPF	Ph_2SiH_2	DMF	19
15[b]	$Pd(OAc)_2$	DPPP	Ph_2SiH_2	DMF	30
16[b]	$Pd(OAc)_2$	$P(C_6F_5)_3$	Ph_2SiH_2	DMSO	5
17[b]	$Pd(OAc)_2$	$P(C_6F_5)_3$	Ph_2SiH_2	DMA	17
18[b]	$Pd(OAc)_2$	$P(C_6F_5)_3$	Ph_2SiH_2	dioxane	6
19[b]	$Pd(OAc)_2$	$P(C_6F_5)_3$	Ph_2SiH_2	CH_3CN	4
20[b]	$Pd(OAc)_2$	$P(C_6F_5)_3$	/	CH_3CN	0

[a] Reaction conditions: *N*-(2-iodophenyl)benzimidamide **1a** (0.5 mmol), catalyst (6 mol%), ligand (12 mol% for monodentate ligand; 6 mol% for bidentate ligand), [H] (3 equiv.), $Mo(CO)_6$ (1.5 equiv.), Et_3N (2 equiv.), solvent (2 mL), 120 °C, 16 h. Isolated yields.
[b] $Mo(CO)_6$ (3 equiv.).

Furthermore, solvent screening showed that DMF tend to be the best solvent (Table 1, entry 16–19). This catalytic system showed very good selectivity towards the generation of aromatic aldehyde intermediate, even without Ph_2SiH_2, only trace amount of product from pathway b was observed (Table 1, entry 20).

With the optimal reaction conditions in hand, we next went on our studies on the substrate scope. As shown in Scheme 2, *o*-iodoaniline rings, which had substituents such as methyl, fluoro, and chloro groups at different positions worked well to give the corresponding products in moderate to good yields (**2a-2f**). Next, a series of groups substituted on the aryl group bonded at the C═NH carbon were examined. Substrates with electron-donating groups, including methyl and *tert*-butyl provided the final products in moderate yields (**2h-2j**). The halogen substituents could also tolerate well to afford the desired products in moderate to good yields no matter their positions on the aryl rings (**2l-2 m**). The reaction also proceeded well with electron-deficient groups, 52–70% yields of the desired products were obtained from the corresponding nitrile and trifluoro substituents (**2 g, 2o-2q**). Furthermore, 2-naphthyl group was tested, and the target product was produced in 50% yield (**2r**). It is also important to note that 10% of the desired product was obtained when *N*-(2-iodophenyl)acetimidamide was tested as the substrate.

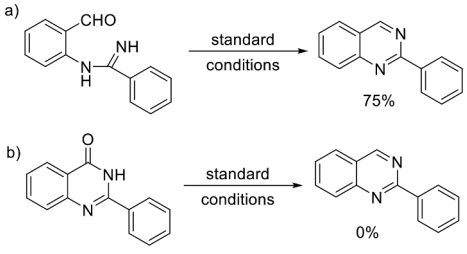


[a] Reaction conditions: *N*-(2-iodophenyl)benzimidamides **1** (0.5 mmol), $Pd(OAc)_2$ (6 mol%), $P(C_6F_5)_3$ (12 mol%), Ph_2SiH_2 (3 equiv.), $Mo(CO)_6$ (3 equiv.), Et_3N (2 equiv.), DMF (2 mL), 120 °C, 16 h. Isolated yields.

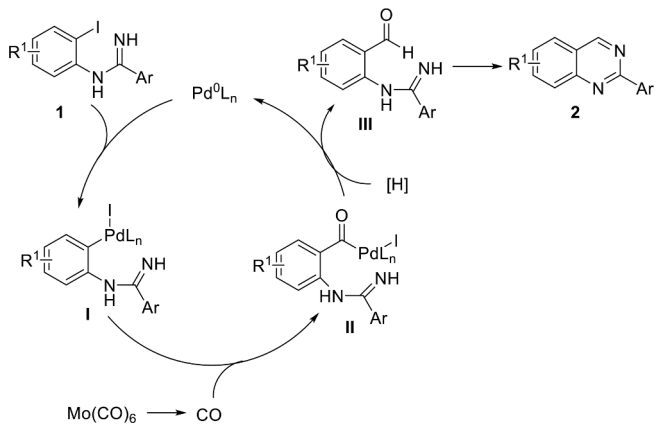
Scheme 2. Substrate scope.[a]

For the reaction pathway, it's important to mention that *N*-(2-formylphenyl)benzimidamide can be detected when we decreased the reaction temperature to 80 °C. With *N*-(2-formylphenyl)benzimidamide as the starting material under our standard conditions, 2-phenylquinazoline can be obtained in 75% yield (Scheme 3a). Additionally, no 2-phenylquinazoline could be detected when 2-phenylquinazolin-4(3*H*)-one was reacted under our standard conditions (Scheme 3b).

Based on the above results, a plausible reaction mechanism was proposed in Scheme 4. First, the oxidative addition of Pd(0) with **1** to afford arylpalladium species **I**, followed by a CO (generated from Mo $(CO)_6$) insertion to provide acylpalladium complexes **II**. Subsequently,



Scheme 3. Control experiments.



Scheme 4. Plausible reaction mechanism.

the aromatic aldehyde intermediates **III** were produced in the presence of Ph_2SiH_2 with the release of Pd(0) for the next catalytic cycle. Finally, an intramolecular condensation happened to give the desired final quinazoline products **2**.

In conclusion, a palladium-catalyzed reductive carbonylative process has been explored for the synthesis of quinazolines. With Ph_2SiH_2 as the hydrogen source, aromatic aldehydes were generated as the key intermediates, which then underwent dehydrative cyclization to give the final quinazoline products. The reaction proceeded smoothly, and a series of quinazolines were produced in moderate to good yields with good functional group tolerance.

General procedure

$Pd(OAc)_2$ (6 mol%), tris(pentafluorophenyl)phosphine (12 mol%), *N*-(2-iodophenyl) benzamidines **1** (0.5 mmol), and $Mo(CO)_6$ (1.5 mmol) were added to an oven-dried tube (15 mL), which was then placed under vacuum and refilled with nitrogen for three times. Then Ph_2SiH_2 (1.5 mmol), Et_3N (1 mmol) and DMF (2 mL) were added into the tube *via* a syringe. The reaction mixture was stirred at 120 °C for 16 h. After the reaction was completed, the reaction mixture was concentrated under vacuum. The crude mixture was purified by silica gel column chromatography ($PE/Et_2O = 50/1$) to provide the desired quinazoline products **2**.

CRediT authorship contribution statement

Jia-Ming Lu: Data curation, Formal analysis. **Yong-Wang Huo:** Data curation, Formal analysis. **Xinxin Qi:** Funding acquisition, Supervision, Writing - original draft. **Xiao-Feng Wu:** Funding acquisition, Supervision, Writing - original draft.

Declaration of Competing Interest

We have no conflict of interest to declaration!

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2021.111627.

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