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Quinazoline-directed regioselective arylation via palladium catalysis: synthesis of 2-(1-biaryl)-4-arylquinazolines

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ABSTRACT

Quinazoline was used as a directing group for palladium-catalyzed ortho-mono-arylation of 2,4-disubstituted quinazoline via C–H bond activation. The reaction proceeded well with a broad substrate scope in a highly regioselective manner to provide a direct way to access highly functional quinazoline core structure derivatives.

1. Introduction

In the past few decades, transition metal-catalyzed C–H bond activation for the construction of C–C bond provided the most directed route to prepare various natural and unnatural chemical compounds.[1] Tremendous efforts have been devoted to this area and great achievements for aryl–aryl bond formation have been developed.[2] In most cases, *ortho*-directing group was necessary for the high regioselectivity and efficiency.[1,2] The discovery and development of novel directing group could always induce great possibility for a variety of catalytic variants. Commonly, the established directing group can be divided into two types: the first one is an open chain[3] containing heteroatom (*O*, *N*, *S* etc.) which have coordination ability; the second type is a heterocycle.[4–9] Pyridine was the earliest one employed for both Pd[4] and Ru[5] catalysis, and then benzoxazole[6] was utilized by Wu et al. for the palladium-catalyzed ortho-arylation. At the same time, oxazoline[7] and purine[8] were found also effective for the ruthenium-catalyzed similar transformation. Our group reported an example of the benzothiazole group can play the directing role.[9] Steady progress has been achieved, however, the selectivity between mono- and di-arylation remains as a significant challenge. Thus, there is still great room for the development of novel directing group with unique character, especially for the tunable ability to render regioselective mono-arylation via C–H activation.

On the other hand, quinazoline or quinazolinone core structures are known to exhibit a wide range of important potential biological activities.[10] In recent years, we focused on the development of quinazoline derivatives syntheses. We reported rhodium-catalyzed regioselective direct C–H amidation of 2,4-diarylquinazoline with sulfonyl azides for the selectively synthesis of mono- and diamidation quinazoline derivatives regulated by steric hindrance.[11]

As a part of our continuous work, we herein demonstrate an efficient and highly regioselective palladium-catalyzed ortho-mono-arylation of 2,4-disubstituted quinazolines.

2. Results and discussion

At the beginning, 1-iodo-4-methylbenzene **2a** was selected as the arylation agent to react with 2,4-diphenylquinazoline **1a** in the presence of palladium acetate as the catalyst. We were pleased to find 15% yield of ortho-mono-arylation product **3a** was isolated when Ag_2CO_3 was used as the oxidant in TFA (Table 1, entry 1). Despite the yield was not satisfied, the reaction proceeded clearly

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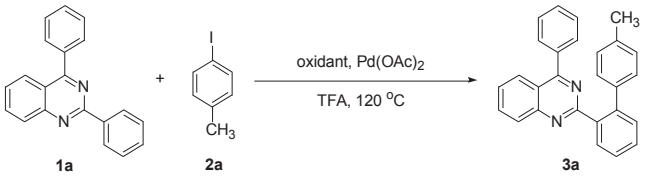
Table 1
Optimization of reaction conditions[a]



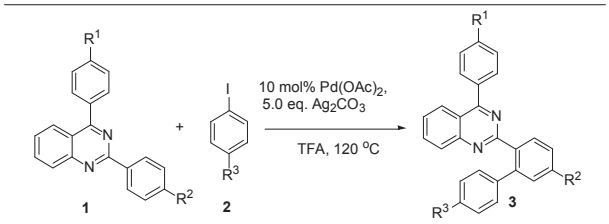
Entry	**2a** (equiv)	Oxidant (equiv)	$Pd(OAc)_2$ (equiv)	T (°C)	t (hour)	Yield (%)[b]
1	1.5	Ag_2CO_3 (2.0)	5%	120	12	15
2	1.5	CuI (2.0)	5%	120	12	0
3	1.5	$K_2S_2O_8$ (2.0)	5%	120	12	0
4	1.5	$AgBF_4$(2.0)	5%	120	12	9
5	1.5	Ag_2O (2.0)	5%	120	12	10
6	1.5	AgOTf (2.0)	5%	120	12	8
7	1.5	AgOAc (2.0)	5%	120	12	11
8	1.5	Ag_2CO_3 (2.0)	5%	120	12	Trace
9	1.5	Ag_2CO_3 (5.0)	5%	120	12	36
10	3.0	Ag_2CO_3 (5.0)	5%	120	12	68
11	**3.0**	**Ag_2CO_3 (5.0)**	**10%**	**120**	12	**79**
12	3.0	Ag_2CO_3 (3.0)	10%	120	12	63
13	3.0	Ag_2CO_3 (5.0)	10%	110	12	70
14	3.0	Ag_2CO_3 (5.0)	10%	110	18	71
15	3.0	Ag_2CO_3 (5.0)	10%	100	18	61
16	3.0	Ag_2CO_3 (5.0)	10%	90	18	Trace
17	3.0	Ag_2CO_3 (5.0)	10%	80	24	Trace
18	3.0	Ag_2CO_3 (5.0)	10%	140	12	72
19	3.0	Ag_2CO_3 (5.0)	10%	130	14	78
20	3.0	Ag_2CO_3 (5.0)	10%	120	10	79
21	3.0	Ag_2CO_3 (5.0)	10%	120	9	76
22	3.0	Ag_2CO_3 (5.0)	10%	120	8	62

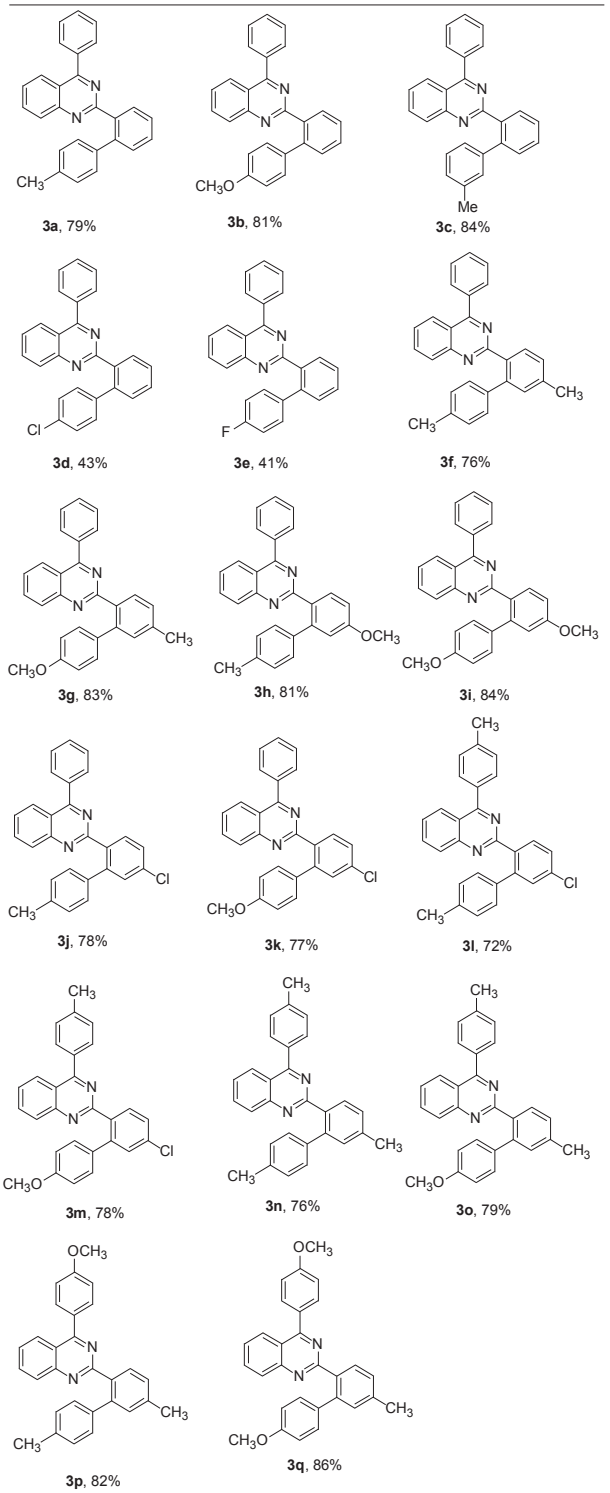
[a] All the reactions were performed in 0.2 mmol scale, standard conditions: 2,4-diphenylquinazoline **1a** and 1-iodo-4-methylbenzene **2a**, catalyst $Pd(OAc)_2$, in TFA.
[b] Isolated yield.

to provide the mono-arylation product with high regioselectivity. Unfortunately, when CuI or $K_2S_2O_8$ was used as the oxidant, there was no reaction occurred (entries 2–3). Then, several kinds of Ag source were screened and Ag_2CO_3 provided the most promising result (Table 1, entries 4–7). When HAc was used instead of TFA, the reaction rate decreased dramatically and only trace amount of **3a** was detected (Table 1, entry 8). Then, the reagents and catalyst loading were assessed to enhance the reaction efficiency (Table 1, entries 9–12). The highest yield of 79% was obtained with 3.0 equiv of **2a** and 5.0 equiv of Ag_2CO_3 catalyzed by 10 mol % $Pd(OAc)_2$ in TFA as solvent at 120 °C (Table 1, entry 11). Finally, the influence of reaction temperature was also examined, and we found it had a pivotal role in this catalytic transformation (Table 1, entries 13–19). Average 9 percent of yield decreased with 10 °C reaction temperature reduced (Table 1, entries 1, 13, 14 vs 15), and the reaction could not process any further below 100 °C (Table 1, entries 16 and 17). However, when the reaction temperature was elevated to 140 °C, the yield decreased and no di-arylated product was observed (entry18). Finally, the reaction time was optimized, and found that 9–12 h was appropriate.

With the optimized conditions in hand, the reaction scope was further explored, and the results were summarized in Table 2. A broad range of quinazolinones and iodobenzenes could be well tolerated in this catalytic system. At the outset, a group of iodobenzenes was assessed, and evidently, the electron-rich reagents provided higher yields than electron-poor ones (Table 2, entries **3a**–**e**). No product was obtained when hetero-aryl iodide such as 2-iodo-pyridine was used (not list in Table 2). After finishing the above examination, we moved on to check the mother aromatic ring of the quinazolinone. As a consequence 1-iodo-4-methylbenzene and 1-iodo-4-methoxylbenzene were selected to probe the substrates scope of quinazoline. Generally, the electronic properties of the mother ring of quinazoline have little influence on

Table 2
Substrate exploration[a]





[a] All the reactions were performed in the presence of 10 mol% $Pd(OAc)_2$ and 5.0 equiv of Ag_2CO_3 in TFA at 120 °C for 12 hours, isolated yield.