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Switching the Chemoselectivity in the Amination of 4-Chloroquinazolines with Aminopyrazoles

Zhenlu Shen,*,† Yiming Hong,† Xiaofei He,† Weimin Mo,† Baoxiang Hu,† Nan Sun,† and Xinquan Hu*,†,‡

College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, China, and State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China

zhenlushen@zjut.edu.cn; xinquan@zjut.edu.cn

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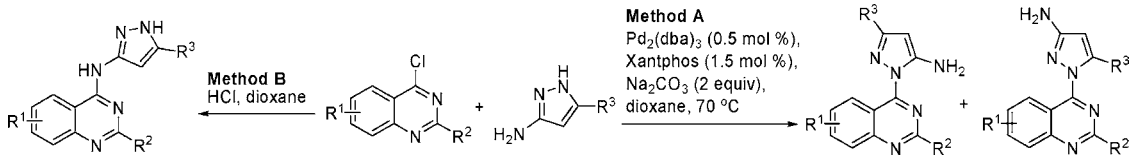
ABSTRACT



The chemoselectivity in the amination of 4-chloroquinazolines with 3-amino-1*H*-pyrazoles was studied. Under the conditions of $Pd_2(dba)_3$/Xantphos/Na_2CO_3, 4-chloroquinazolines underwent selective amination with the cyclic secondary amino group of 3-amino-1*H*-pyrazoles, whereas 4-chloroquinazolines were exclusively aminated with the primary amino group of 3-amino-1*H*-pyrazoles via S_NAr substitution in the presence of HCl.

Nitrogen-containing heterocycles are present in a variety of biologically active compounds that can be used in a wide range of therapeutic areas.[1] 4-Aminoquinazoline derivatives are an important class of nitrogen-containing heterocyclic compounds, which display a wide variety of biological activities.[2] Especially, 4-(3′-chloro-4′-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline (Gefitinib, ZD1839, Iressa), developed from 4-aminoquinazolines, has already been approved by the FDA for nonsmall-cell lung cancer treatment.[3] *N*-Arylpyrazoles and *N*-arylamino-pyrazoles, the other classes of nitrogen-containing heterocyclic compounds, are important structural classes in pharmaceuticals and agrochemicals including Celebrex, Pyracolfos, and Fipronil.[4] More recently, pyrazoloquinazolines (Figure 1) containing quinazoline and pyrazole motifs have been studied as they exhibited high antitumor activity, and several examples for synthesis of pyrazoloquinazoline derivatives **1** were reported via the S_NAr (nucleophilic aromatic substitution) reaction of 5-substituted-3-amino-1*H*-pyrazoles with electron-deficient 4-chloroquinazolines.[5]

† Zhejiang University of Technology.
‡ Chinese Academy of Sciences.

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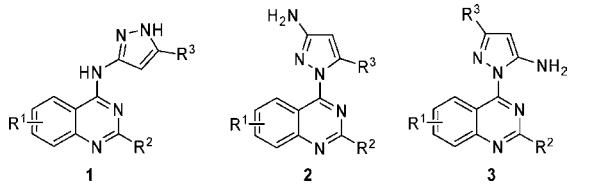


Figure 1. Structures of pyrazoloquinazoline derivatives.

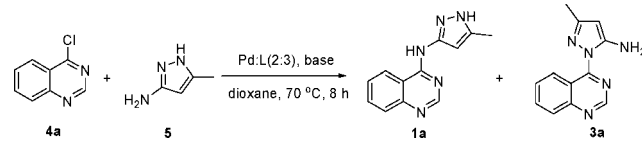
The Buchwald−Hartwig reaction, namely, Pd-mediated N-arylamination/N-heteroarylamination reaction, is one of the most widely used methods of forming C−N bonds between amines (alkylamines, arylamines, heteroarylamines) and arylhalides (heteroarylhalides).[6] However, only a few reports have involved the Pd-catalyzed selective amination between aryl halides and amine substrates bearing both a primary and a secondary amine functional group. Senanayake et al. have reported a selective amination reaction of 1-(4-fluorobenzyl)-2-chlorobenzamidazole and bromobenzenes with 4-aminopiperidine and some other acyclic diamines using Binap/$Pd_2(dba)_3$ as catalyst. It was found that the only primary amine was selectively involved in the C−N bond formation.[7] The chemoselectivity of the Pd-mediated reaction of bromobenzene with various heterocyclic diamines was studied by Rouden et al.[8] They found that 3-aminopyrrolidine underwent N-arylation at the secondary amine position regardless of the ligand employed, whereas the more flexible 3-aminoazepinine proceeded the arylation at its primary amine position. When 3-aminopiperidine or 4-aminopiperidine was used, the chemoselectivity could be tuned by either the choice of ligands or the aryl halide partners. Very recently, Buchwald et al. have reported the coupling of three diamine substrates and chlorobenzene with a Pd-Brettphos catalyst, and high levels of chemoselectivity for the arylation of a primary amine over a secondary amine were achieved.[9]

Preparation of pyrazoloquinazolines **2** or **3** via C−N bond formation between the NH− group of 5-substituted-3-amino-1*H*-pyrazoles and 4-chloroquinazolines is yet to be explored. To our knowledge, only one example of the Pd-catalyzed cross-coupling of aminopyrazole with aryl halide has been reported to date.[10] Furthermore, 4-chloroquinazolines were rarely employed as aryl halide substrates for the Buchwald−Hartwig reaction.[11] Herein, we describe our study on the Pd-catalyzed cross-coupling reaction between aminopyrazoles and 4-chloroquinazolines. A significant chemoselectivity was observed in the amination of 4-chloroquinazolines with 3-amino-1*H*-pyrazoles, and different pyrazoloquinazolines (**1**−**3**) can be selectively formed by variations of the reaction conditions.

In our initial screening experiments, 4-chloroquinazoline (**4a**) and 3-amino-5-methyl-1*H*-pyrazole (**5**) were used as the model substrates for investigating the effects of various ligands, palladium sources, and bases in the Pd-catalyzed cross-coupling reaction (Table 1). It is well-known that amination of aryl halides via a direct S_NAr substitution could be promoted with either acid or base. Thus, **1a** (amination product with the primary amino group) was the only observed product in the presence of Na_2CO_3 without the employment of palladium precatalyst and ligand (entry 1, Table 1).

With $Pd(OAc)_2$/Xantphos/Na_2CO_3 as the reaction conditions, a mixture of **1a** and **3a** (amination product with the cyclic secondary amino group) in a 6:1 ratio was obtained.

Table 1. Pd-Catalyzed Cross-Coupling of **4a** with **5** under Various Conditions[a]



4a 5 1a 3a

entry	Pd	ligand	base	convn (%)[b]	ratio **1a/3a** (%)[b]
1	-	-	Na_2CO_3	>99	100:0
2	$Pd(OAc)_2$	Xantphos	Na_2CO_3	>99	86:14
3	$Pd_2(dba)_3$	Xantpos	Na_2CO_3	>99	5:95
4	$Pd_2(dba)_3$	dppe	Na_2CO_3	>99	92:8
5	$Pd_2(dba)_3$	dppp	Na_2CO_3	>99	99:1
6	$Pd_2(dba)_3$	dppf	Na_2CO_3	>99	85:15
7	$Pd_2(dba)_3$	Binap	Na_2CO_3	>99	89:11
8	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	>99	17:83
9	$Pd_2(dba)_3$	Xantphos	K_3PO_4	>99	15:85
10	$Pd_2(dba)_3$	Xantphos	NaOAc	68	60:40

[a] **4a** (0.5 mmol), **5** (1.1 equiv), Pd (1 mol %), ligand (1.5 mol %), base (2 equiv). [b] Conversion and ratio of **1a**/**3a** were determined by HPLC.

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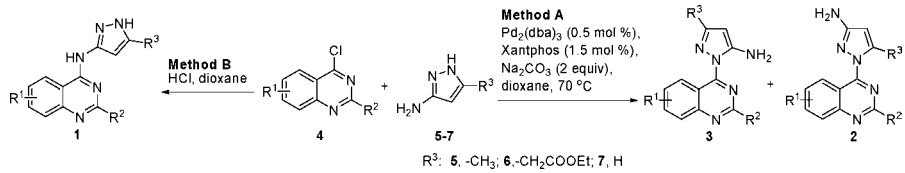
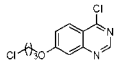
Table 2. Chemoselective Amination of **4** with Aminopyrazoles[a]



entry	4-chloroquinazolines	3-amino-pyrazoles	Method A			Method B		
			time (h)	products	yield (%) [b]	time (h)	products	yield (%) [b]
1	 **4a**	**5**	8	**3a**	73	7	**1a**	70
2	 **4b**	**5**	12	**3b**	80	7.5	**1b**	72
3	 **4c**	**5**	12	**3c** [c]	84	7.5	**1c**	76
4	 **4d**	**5**	12	**3d**	79	8	**1d**	70
5	 **4e**	**5**	7	**3e**	81	5	**1e**	77
6	 **4f**	**5**	7	**3f**	82	5	**1f**	75
7	 **4g**	**5**	7	**3g**	77	5	**1g**	71
8	 **4h**	**5**	7	**3h**	78	7.5	**1h**	75
9	 **4i**	**5**	8	**3i**	84	4	**1i**	76
10	 **4j**	**5**	8	**3j**	70	4	**1j**	71
11	**4a**	**6**	12	**3k**	62	5	**1k**	62
12	**4h**	**6**	8	**3l**	70	4	**1l**	61
13	**4i**	**6**	8	**3m**	61	2	**1m**	62
14	**4a**	**7**	5	**3n**, **2n**	88 (15,73)	4	**1n**	75
15	**4c**	**7**	4	**3o**, **2o**	85 (28,57)	4	**1o**	71
16	**4f**	**7**	4.5	**3p**, **2p**	84 (21,63)	3	**1p**	80
17	 **4k**	**5**	4	**3q**	71	18	**1q**	26 [12]

[a] **4** (0.5 mmol), aminopyrazoles (1.1 equiv). [b] Isolated yield, values in parentheses are isolated yields of **3** and **2**, respectively. [c] The structure of **3c** was confirmed by the NOE spectrum (see Supporting Information).

Screening of the palladium source revealed that the $Pd_2(dba)_3$/Xantphos/Na_2CO_3 system significantly increased the formation of **3a**, and the ratio of **1a**/**3a** was 1:19 (entry 3, Table 1). This result indicated that use of Pd^0 instead of Pd^{2+} species as catalyst precursor significantly promoted the selective arylation on the cyclic secondary amine group. As the ligand nature can also affect the C−N bond coupling, we examined this reaction in the presence of various bidentate phosphine ligands. Much to our surprise, when other ligands, such as dppe, dppp, dppf, or Binap, were employed, arylation on the cyclic secondary amine group was not favored (ratio 11:1 to 6:1, entries 4−7, Table 1). Xantphos, a common ligand applied in transition-metal-catalyzed cross-coupling reactions,[13] provided its unique chemoselectivity in this amination with the cyclic secondary amine, which could be attributed to its wide bite angle and the formation of a *trans*-chelating Xantphos−Pd(II)(Ar)Cl complex.[9,14]

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Using Cs_2CO_3 or K_3PO_4 as base in combination with $Pd_2(dba)_3$/Xantphos, the reactions also afforded **3a** as the major product albeit with the decreased chemoselectivity (ratio ca. 1:5 and 1:6, entries 8 and 9, Table 1). This could be attributed to the stronger basicity of Cs_2CO_3 and K_3PO_4 over Na_2CO_3, which promoted the rate of the competitive S_NAr substitution. With NaOAc as the base, a relative lower conversion (68%) was observed with a 6:4 ratio of **1a**/**3a** (entry 10, Table 1). The weak basicity of NaOAc not only slowed down the S_NAr substitution but also disfavored the reductive elimination step in the Pd-mediated Buchwald−Hartwig reaction.[6b]

Considering its high selectivity in the reaction of **4a** and **5**, the $Pd_2(dba)_3$/Xantphos/Na_2CO_3 system was our choice for further experimentation. We then explored the substrate scope of the reaction with a series of 4-chloroquinazolines and various 3-amino-1*H*-pyrazoles with the optimized conditions. As shown in Table 2, various 4-chloroquinazolines underwent selective amination with **5** to provide pyrazoloquinazoline derivatives **3a**−**j** in good isolated yields (method A, entries 1−10, Table 2). Only reaction time showed the effects of substituents to the activity. When the benzene ring of **5** was bearing the electron-donating group, a longer reaction time was needed to complete the reaction (entries 2−4, Table 2). It is noteworthy that substrates **4e**, **4f**, and **4i** containing two C−Cl bonds provided exclusively the coupling products at the more activated C-4 position (entries 5 and 6, Table 2). The reactions between 4-chloroquinazolines and ethyl 2-(3-amino-1*H*-pyrazol-5-yl) acetate (**6**) gave the selective amination products **3k**−**m** in 61−70% yields (entries 11−13, Table 2). These yields were slightly lower than those with **5** as nucleophile, which might be caused by the hydrolysis of the ester group during the reaction.

When 3-amino-1*H*-pyrazole (**7**) was used as the nucleophile to couple with **4a**, two products were formed. On the basis of the NMR and MS data, these two compounds were assigned the regioisomers of amination with the cyclic secondary amino group, **3n** and **2n**.[15] The isolated yields of **3n** and **2n** were 15% and 73%, respectively (entry 14, Table 2). Similar results were also obtained when **4c** and **4f** were aminated with **7** (entries 15 and 16, Table 2), while the isomerization products were not observed in the amination of **4** with **5** or **6**. According to the reported mechanism of Pd-mediated N-arylation of diamines, Pd initially coordinated with the primary amino group, and the resulted Pd complex would undergo the amine exchange to coordinate with the cyclic secondary amine under the relatively high reaction temperature.[8a] However, the coordination would preferentially occur at the less hindered cyclic secondary amine away from the substituent in the 5-substituted-3-amino-1*H*-pyrazoles due to the tautomerization of the pyrazole ring and thus produced **3**. This phenomenon was also observed in the Cu-catalyzed N-arylation of pyrazoles.[16] When 5-unsubstituted-3-amino-1*H*-pyrazole was employed as the nucleophile, Pd could coordinate with either cyclic secondary amines during the tautomerization but favored the original one and thus formed **2** as the major product. Analogue 2,4-dichloropyrimidine **4k** was also tested to react with **5**, and the C−N bond formation between the C−Cl on the C-4 position of **4k** and the cyclic secondary amino group of **5** yielded 1-(2-chloropyrimidin-4-yl)-3-methyl-1*H*-pyrazol-5-amine (**3q**, 71%).

As comparative experiments, the direct S_NAr substitution reactions between 4-chloroquinazolines and 3-amino-1*H*-pyrazoles were also carried out in the presence of HCl (Method B). All reactions can smoothly proceed to give the desired pyrazoloquinazoline **1** in moderate to good yields (Method B, entries 1−17, Table 2).

In summary, the chemoselectivity of amination of 4-chloroquinazolines with 3-amino-1*H*-pyrazoles strongly depends on the reaction conditions (Pd-catalyzed amination versus S_NAr). 4-Chloroquinazolines are predominantly aminated with the cyclic secondary amino group of 3-amino-1*H*-pyrazoles under the conditions of the $Pd_2(dba)_3$/Xantphos/Na_2CO_3 system, while amination products with the primary amino groups of 3-amino-1*H*-pyrazoles are exclusively formed in the presence of HCl.

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Supporting Information Available: Synthetic procedure and complete characterization data for entries in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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