



Gold(I)-catalyzed direct C–H arylation of pyrazine and pyridine with aryl bromides

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ABSTRACT

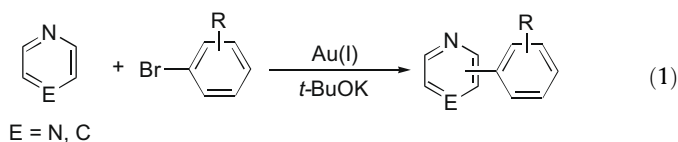
An efficient procedure for the direct C–H arylation of electron-poor aromatics such as pyrazine and pyridine with aryl bromides is described. In the presence of catalytic amount of Cy_3PAuCl and with the use of *t*-BuOK as base, pyrazine undergoes the direct C–H arylation with aryl bromides at 100 °C, and the yields of the arylated products depend on the nature of aryl bromides. In the cases of electron-rich aryl bromides used, the arylated pyrazines can be obtained in good to high yields. For electron-poor aryl bromides, the addition of $AgBF_4$ is the crucial point to accelerate the coupling reaction to give the arylated products in moderate yields. Pyridine also reacts with electron-rich aryl bromides catalyzed by Cy_3PAuCl to give a mixture of arylated regioisomers in moderate yield. However, in order to realize the direct C–H arylation of pyridine with electron-poor aryl bromides, the addition of silver salt as additive and a milder reaction temperature (60 °C) are required.

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Transition-metal-catalyzed direct arylation of aromatic compounds by C–H activation with aryl halides has recently become one of the most important and attractive research topic in synthetic chemistry.¹ Because such $C(sp^2)$ – $C(sp^2)$ bond formation procedure gives hydrogen halides (HX) as the by-product having the higher atom-efficiency than other often employed procedures such as Suzuki–Miyaura,² Stille³ cross-coupling reactions, in which not only is the reaction partner of organometallic derivatives aryl-M (M = B(OH)₂, SnR₃) required to be pre-prepared, but also the reaction gives organometallic salt (MX), which has a higher molecular weight than HX as the by-product. Therefore, the direct C–H arylation of aromatics with aryl halides is an economical procedure and a powerful tool for synthesis of biaryl molecules,⁴ particularly for the synthesis of aryl-heteroaryl compounds by employing different heteroaromatics. For example, the direct C–H arylation of furans,⁵ thiophenes,^{5a,6} pyrrole,^{5b} indolizines,⁷ thiazoles,^{6b,8} and oxazoles⁹ with aryl halides has been developed for the synthesis of their corresponding arylated derivatives. However, until recently, the reported procedures are limited to electron-rich aromatics and heteroaromatics having active C–H bond, the examples for the direct C–H arylation of electron-poor heteroaromatics such as pyrazine and pyridine with aryl halides are rare.¹⁰

Recently, gold(I) and gold(III) compounds have been proven to be the versatile catalysts in diverse organic syntheses,¹¹ but there is no report on the gold-catalyzed direct C–H arylation of aromatics

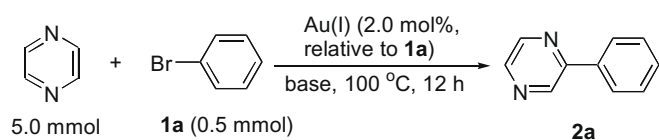
with aryl halides. In the continuation of our study of C–C bond formation of aromatics via activation of C–H bond¹² and of the purpose of developing the efficient catalytic system for the direct C–H arylation of electron-poor heteroaromatics, we now report our new findings of Cy_3PAuCl -catalyzed direct C–H arylation of pyrazine and pyridine with aryl bromides promoted by use of *t*-BuOK as base (Eq. (1)).



Initially, the reaction of bromobenzene (**1a**) with an excess amount of pyrazine (as solvent) under different reaction conditions was studied and the results were summarized in Table 1. Entries 1–6 demonstrated that Ph_3PAuCl showed no catalytic activity at all under nitrogen at 100 °C without base or even with the presence of bases such as Bu_3N , Pr_2NEt , K_2CO_3 , Na_3PO_4 , and CS_2CO_3 , which are usually employed as promoter in cross-coupling reaction of aryl halides. In these cases, the starting materials were recovered completely. However, when *t*-BuOK was used, Ph_3PAuCl showed an obvious catalytic activity to catalyze the formation of 2-phenylpyrazine (**2a**) in 51% GC yield, indicating the occurrence of direct C–H arylation of pyrazine with **1a** (entry 7). GC–MS and GC analyses of the reaction mixture revealed that **1a** was converted in almost quantitative yield, and the formation of *t*-butoxybenzene (9%, based on **1a**), benzene (34%, based on **1a**) and diphenyl (3%,

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Table 1
Gold(I)-catalyzed reaction of pyrazine with bromobenzene (**1a**)^a

Entry	Catalyst	Base (mmol)	Yield (%) ^b
1	Ph ₃ PAuCl	—	0
2	Ph ₃ PAuCl	Bu ₃ N (1)	0
3	Ph ₃ PAuCl	^t Pr ₂ NEt (1)	0
4	Ph ₃ PAuCl	K ₂ CO ₃ (1)	0
5	Ph ₃ PAuCl	Na ₃ PO ₄ (1)	0
6	Ph ₃ PAuCl	Cs ₂ CO ₃ (1)	0
7	Ph ₃ PAuCl	<i>t</i> -BuOK (1)	51
8	(<i>o</i> -Tolyl) ₃ PAuCl	<i>t</i> -BuOK (1)	55
9	Cy ₃ PAuCl	<i>t</i> -BuOK (1)	90 (81)
10	—	<i>t</i> -BuOK (1)	35
11	Cy ₃ PAuCl	<i>t</i> -BuOK (0.5)	46
12	Cy ₃ PAuCl	Bu ₃ N (1)	0
13	Cy ₃ PAuCl	Cs ₂ CO ₃ (1)	0

^a Reactions were carried out using 0.5 mmol of bromobenzene (**1a**), 5 mmol of pyrazine, 0.01 mmol of catalyst, and 1.0 mmol or 0.5 mmol of base.

^b GC yield based on the amount of **1a** charged. Number in parenthesis is isolated yield.

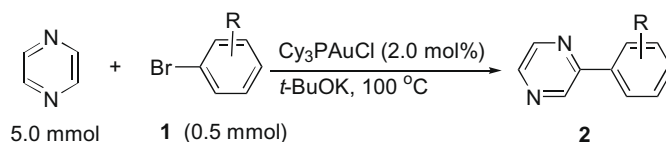
based on **1a**), as by-products was also observed. The formation of *t*-butoxybenzene is due most likely to the nucleophilic substitution of **1a** with *t*-BuOK under the reaction conditions, and benzene comes from the hydrodebromination of **1a** with *t*-BuOK as reductant.^{4e} The formation of diphenyl is considered to be from the Ullmann-type coupling reaction of **1a**.

As shown in entry 8, (*o*-tolyl)₃PAuCl, which is ligated by more basic phosphine displayed a slightly higher catalytic activity than Ph₃PAuCl to afford **2a** in 55% GC yield. Fortunately, when Cy₃PAuCl was used, **2a** was formed in 90% GC yield, along with the formation of *t*-butoxybenzene (4%) and trace amount of benzene (entry 9). During the preparation of this Letter, Itami and co-workers reported that *t*-BuOK was the efficient base to promote the direct C–H arylation of pyrazine with **1a** under microwave irradiation to afford **2a** in 54% yield, thus we examined the reaction without Cy₃PAuCl at 100 °C for 12 h. Indeed, a low yield of **2a** was obtained (entry 10). In addition, decreasing the amount of *t*-BuOK to 1.0 equiv of **1a** resulted in the decrease in the yield of **2a** to 46% (entry 11 vs entry 9). Moreover, the use of Bu₃N and Cs₂CO₃ to replace *t*-BuOK as bases led to no formation of **2a** at all (entries 12 and 13).

These obtained results indicate that the present direct arylation of pyrazine with aryl bromides is highly base dependent, pointing to the uniqueness of *t*-BuOK.

In addition, when the reaction was carried out using an excess amount of **1a** (5 equiv, as solvent) under the reaction conditions indicated in entry 9, only trace amount of **2a** was determined in the reaction mixture by GC–MS analysis, and the major product was *t*-butoxybenzene.

The results of Cy₃PAuCl-catalyzed direct C–H arylation of pyrazine with a variety of aryl bromides were summarized in Table 2. The coupling reaction of pyrazine with 2-bromotoluene (**1b**), which is a sterically hindered aryl bromide, also occurred under the reaction conditions indicated in entry 9 of Table 1, albeit slowly, resulting in the formation of **2b** in 58% isolated yield (Table 2, entry 1). A satisfactory yield of **2b** could be achieved by prolonging the reaction time to 24 h (Table 2, entry 2).¹³ The corresponding arylated product **2c** was isolated in 82% yield from the reaction of pyrazine with 3-bromotoluene for 24 h (**1c**) (Table 2, entry 3). In

Table 2
Cy₃PAuCl-catalyzed reaction of pyrazine with aryl bromide^a

Entry	Ar-Br	Time (h)	Product	Yield ^b (%)
1		12		58
2		24		82
3	3-Me, 1c	24	3-Me, 2c	86
4		24		44
5		12		64
6	4-OMe, 1f	12	4-OMe, 2f	60
7		12		56
8	2-Br, 1h	12	2h	40
9		12		<5
10 ^c	4-Cl, 1i	12	4-Cl, 2i	36
11 ^c	2-Cl, 1j	12	2-Cl, 2j	25
12 ^c		24		31
13 ^c		24		24

^a Reactions were carried out using 0.5 mmol of aryl bromide, 5 mmol of pyrazine, 0.01 mmol of Cy₃PAuCl, and 1.0 mmol of *t*-BuOK.

^b Isolated yield based on the amount of **1** charged.

^c AgBF₄ (2 mol %) was added.

the cases of 1-bromo-2,4-dimethylbenzene (**1d**), 1-bromo-2-methoxybenzene (**1e**), and 1-bromo-4-methoxybenzene (**1f**) used, the coupling reactions afforded the desired products in moderate yields after 12 or 24 h (Table 2, entries 4–6). In addition, the moderate yields of 2-(1-(naphthyl)pyrazine (**2g**) and 2-(2-(naphthyl)pyrazine (**2h**) could be obtained from the reactions of pyrazine with 1-bromonaphthalene (**1g**) and 2-bromonaphthalene (**1h**) for 12 h (Table 2, entries 7 and 8).

In contrast to electron-rich aryl bromides, electron-poor aryl bromides are apparently easier to undergo the hydrodebromination, since the reaction of pyrazine with 1-bromo-4-chlorobenzene (**1i**) gave only small amount of the corresponding arylated product **2i** under a similar reaction conditions. In this case, chlorobenzene

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