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

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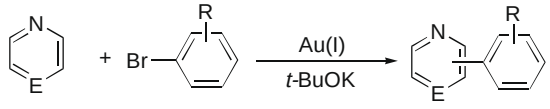
ABSTRACT

An efficient procedure for the direct C–H arylation of electron-poor aromatics such as pyrazine and pyridine with aryl bomides 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.

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] Stille[3] cross-coupling reactions, in which not only is the reaction partner of organometallic derivatives aryl-M (M = $B(OH)_2$, SnR_3) 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 oxazoles[9] 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 bond[12] 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)).



(1)

E = N, C

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, $^iPr_2NEt$, 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 phenylation 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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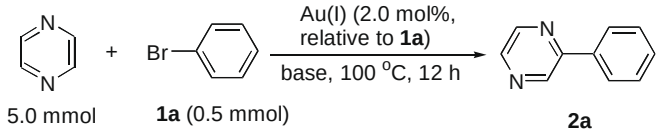
Table 1
Gold(I)-catalyzed reaction of pyrazine with bromobenzene (**1a**)[a]



Entry	Catalyst	Base (mmol)	Yield (%)[b]
1	Ph_3PAuCl	—	0
2	Ph_3PAuCl	Bu_3N (1)	0
3	Ph_3PAuCl	$^iPr_2NEt$ (1)	0
4	Ph_3PAuCl	K_2CO_3 (1)	0
5	Ph_3PAuCl	Na_3PO_4 (1)	0
6	Ph_3PAuCl	Cs_2CO_3 (1)	0
7	Ph_3PAuCl	*t*-BuOK (1)	51
8	(*o*-Toly)$_3$PAuCl	*t*-BuOK (1)	55
9	Cy_3PAuCl	*t*-BuOK (1)	90 (81)
10	—	*t*-BuOK (1)	35
11	Cy_3PAuCl	*t*-BuOK (0.5)	46
12	Cy_3PAuCl	Bu_3 N (1)	0
13	Cy_3PAuCl	Cs_2CO_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**.

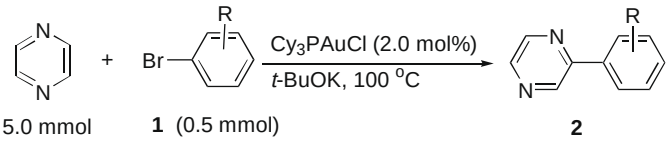
As shown in entry 8, (*o*-tolyl)$_3$PAuCl, which is ligated by more basic phosphine displayed a slightly higher catalytic activity than Ph_3PAuCl to afford **2a** in 55% GC yield. Fortunately, when Cy_3PAuCl was used, **2a** was formed in 90% GC yield, along with the formation of *t*-butoxybenzene (4%) 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 Cy_3PAuCl 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 Bu_3N and Cs_2CO_3 to replace *t*-BuOK as bases led to no formation of **2a** at all (entries 12 and 13).

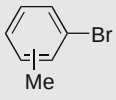
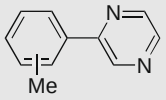
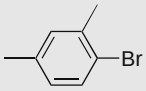
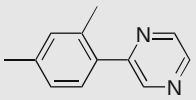
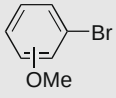
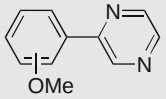
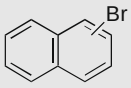
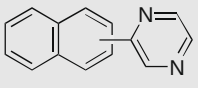
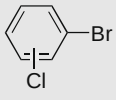
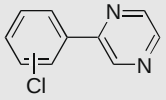
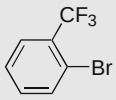
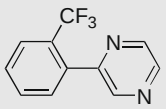
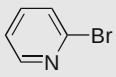
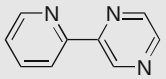
These obtained results indicate that the present direct arylation of pyrazine with aryl bromides is highly base dependent, pointing to the uniqueness of *t*-BuOK.

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 Cy_3PAuCl-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
Cy_3PAuCl-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, **1 h**	12	**2 h**	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 Cy_3PAuCl, and 1.0 mmol of *t*-BuOK.
[b] Isolated yield based on the amount of **1** charged.
[c] $AgBF_4$ (2 mol %) was added.

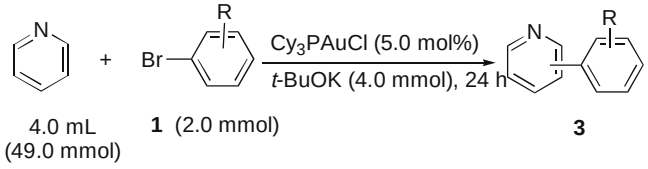
the cases of 1-bromo-2,4-dimethylbenzene (**1d**), 1-bromo-2-methoxybenzene (**1e**), and 1-bromo-4-methoxybenzene (**1f**) used, the coupling reactions afforded the desired products in moderate yields after 12 or 24 h (Table 2, entries 4–6). In addition, the moderate yields of 2-(1-naphthyl)pyrazine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

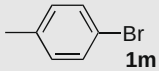
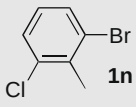
was the major product formed after 12 h with complete conversion of **1i** (Table 2, entry 9). Because there were some reports on the significant difference in the catalytic activity between R_3PAuCl and $R_3PAuCl/AgBF_4$,[14] the reaction of pyrazine with **1i** was repeated by addition of catalytic amount of $AgBF_4$ to the reaction mixture, and the arylated product **2i** was obtained in 36% isolated yield, along with the formation of chlorobenzene (Table 2, entry 10). These results indicated that $Cy_3PAuCl/AgBF_4$ could accelerate the direct C–H arylation of pyrazine with electron-poor aryl bromide. Indeed, other electron-poor aryl bromides such as 1-bromo-2-chlorobenzene (**1j**), 1-bromo-2-trifluromethylbenzene (**1k**), and 2-bromopyridine (**1l**) reacted with pyrazine to give the corresponding coupled products in fair yields (Table 2, entries 11–13).

Encouraged by the successful direct C–H arylation of pyrazine with aryl bromides, we next examined the reaction of pyridine with aryl bromides, and the results are summarized in Table 3. As is apparent from these results, the reactivity of pyridine is much more sluggish than that of pyrazine, and most of the reactions gave three arylated regioisomers in the order of *o*-arylpyridine (**3**) > *m*-arylpyridine (**3′**) > *p*-arylpyridine (**3″**). In the presence of 5.0 mol % of Cy_3PAuCl, the reaction of pyridine (as solvent) with **1a** at 100 °C for 24 h produced a mixture of regioisomers in 57% of total GC yield with *o*-(**3a**), *m*-(**3a′**), and *p*-phenylpyridine (**3a″**) in a ratio of 44:35:21 (Table 3, entry 1). The formation of *t*-butoxybenzene as the major by-product was also observed (31% GC yield). The reactions with **1b**, **1c**, and 4-bromotoluene (**1m**) afforded arylated pyridines in the total isolated yield of 26%, 32%, and 48%, respectively (Table 3, entries 2–4). Reactions with electron-poor aryl bromides at 100 °C produced small amount of desired arylated pyridine only, and the formation of *t*-butoxyarenes was found in almost quantitative yield. For example, heating a mixture of pyridine, **1i**, and *t*-BuOK in the presence of Cy_3PAuCl at 100 °C afforded 1-chloro-4-*t*-butoxybenzene as major product (>90%), only small amount of arylated pyridines (**3e**) was detectable by GC and GC–MS (Table 3, entry 5). The addition of $AgBF_4$ (5 mol %) was ineffective at this reaction temperature, but decreasing the reaction temperature to 60 °C resulted in the formation of desired arylated pyridines in 38% total isolated yield (Table 3, entries 6 and 7). In addition, it was found that $AgClO_4$ and $AgNO_3$ displayed the similar role as $AgBF_4$ did (Table 3, entries 8 and 9). Finally, the reaction of pyridine with 2-bromo-6-chlorotoluene (**1n**) to afford selectively 2-chloro-6-(2-pyridinyl)toluene (**3f**) in 32% isolated yield (Table 3, entry 10).

Table 3
Cy_3PAuCl-catalyzed reaction of pyridine with aryl bromide[a]



4.0 mL (49.0 mmol) **1** (2.0 mmol) **3**

Entry	Ar-Br	Temp (°C)		Yield[b](%) *o*-(3)	*m*-(3′)	*p*-(3″)
1	**1a**	100	**3a**	24 (25)	14 (20)	11 (12)
2	**1b**	100	**3b**	14	8	4
3	**1c**	100	**3c**	15	10	7
4	 **1m**	100	**3d**	22	17	9
5	**1i**	100	**3e**	(<5)	—	—
6[c]	**1i**	100	**3e**	(<5)	—	—
7	**1i**	60	**3e**	20 (24)	13 (17)	5 (8)
8[d]	**1i**	60	**3e**	(19)	(14)	(5)
9[e]	**1i**	60	**3e**	(19)	(13)	(4)
10[c]	 **1n**	60	**3f**	32	—	—

[a] Reactions were carried out using 2.0 mmol of aryl bromide, 0.1 mmol of Cy_3PAuCl, and 4.0 mmol of *t*-BuOK in 4.0 mL of pyridine for 24 h.
[b] Isolated yield based on the amount of 1 charged. Numbers in parentheses are GC yields.
[c] $AgBF_4$ (5 mol %) was added.
[d] $AgClO_4$ (5 mol %) was added.
[e] $AgNO_3$ (5 mol %) was added.

Since the free radical mechanism was proposed in other reaction systems for the direct C–H arylation of pyrazine and pyridine,[10] the present Cy_3PAuCl-catalyzed reactions of pyrazine and pyridine with **1a** in the presence of 1,2-dihydroxybenzene (10 mol %, as radical inhibitor) were examined again. It was found that **2a** was formed in 65% GC yield, while **3a** could not be detected at all by GC and GC–MS. On the basis of these results, the pathway involving the formation of radical aryl by the electron transfer from Au(I)[15] to aryl halides, and the reaction of radical aryl with pyridine to give arylated product **3** is highly probable. However, the mechanism for the Au(I)-catalyzed direct C–H arylation of pyrazine with aryl bromides remains to be elucidated.

In conclusion, in this Letter, we have developed the direct C–H arylation of pyrazine and pyridine with a wide range of aryl bromides catalyzed by Cy_3PAuCl in the presence of *t*-BuOK as base. For the reactions of pyrazine with electron-rich aryl bromides, Cy_3PAuCl served as an efficient catalyst to produce the arylated pyrazines in good to high yields. For the reaction of pyrazine with electron-poor aryl bromides, the nucleophilic substitution of aryl bromides with *t*-BuOK became the main reaction, but by the addition of $AgBF_4$, the direct C–H arylation could be improved. In addition, in the case of pyridine employed, Cy_3PAuCl could also catalyze the reaction with electron-rich aryl bromides such as bromobenzene, bromotoluene at 100 °C to afford a mixture of the arylated regioisomers in moderate yield, but in the case of electron-poor aryl bromides used, the addition of $AgBF_4$ and a milder reaction temperature (60 °C) are required to realize the coupling reaction.

*(1) A typical experimental procedure for arylation of pyrazine with bromobenzene (**1a**) to afford phenylpyrazine (**2a**)* (Table 1, entry 9): A mixture of pyrazine (400.0 mg, 5.0 mmol), bromobenzene (**1a**) (78.5 mg, 0.5 mmol), Cy_3PAuCl (6.0 mg, 0.01 mmol), and *t*-BuOK (112.0 mg, 1.0 mmol) under nitrogen in a screw-capped thick-walled Pyrex tube was heated at 100 °C (oil bath temperature) with stirring; the mixture became homogeneous within a few minutes and turned to deep-red. After heating for 12 h, the reaction mixture was cooled and diluted with CH_2Cl_2 (4.0 mL), and then both *n*-hexadecane (22.6 mg, 0.1 mmol), and *n*-octadecane (25.5 mg, 0.1 mmol) were added as internal standards for GC analysis. After GC and GC–MS analyses, the mixture solution was passed through a short silica pad. The filtrate was then concentrated and pyrazine was recovered (ca. 80%), the residue was then subjected to preparative TLC isolation (silica gel, eluted with a mixture solvent of ethyl acetate and petroleum ether (1:4) to give **2a** as a white solid (63.2 mg, 0.41 mmol, 81%). GC analysis of the reaction mixture revealed that **2a** was formed in 90% GC yield. Compound **2a**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 8.01–8.04 (m, 2H), 7.48–7.53 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 144.3, 143.1, 142.4, 136.5, 130.1, 129.2, 127.1. GCMS *m/z* (% relative intensity): 156 (M^+, 36), 129 (11), 103 (81), 91 (11), 80 (25), 77 (18).

*(2) A typical experimental procedure for arylation of pyridine with bromobenzene (**1a**) to afford o-, m-, p-phenylpyrazine (**3a**)* (Table 3, entry 1). A mixture of pyridine (4.0 mL), bromobenzene (**1a**) (314.0 mg, 2.0 mmol), Cy_3PAuCl (52.0 mg, 0.1 mmol) and *t*-BuOK

(448.0 mg, 4.0 mmol) under nitrogen in a screw-capped thick-walled Pyrex tube was heated at 100 °C (oil bath temperature) with stirring for 24 h. After work-up as described above, three phenylpyridines **3a** (as yellow oil, 74.5 mg, 0.48 mmol, 24%), **3a′** (as yellow oil, 43.4 mg, 0.28 mmol, 14%), and **3a″** (as white solid, 34.2 mg, 0.22 mmol, 11%) were isolated. GC analysis of the reaction mixture revealed that a mixture of three phenylpyridines in 57% of total GC yield with *o*- (**3a**), *m*- (**3a′**), and *p*-phenylpyridine (**3a″**) in a ratio of 44:35:21 was obtained. Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (dt, 1H, J = 4.8, 1.3 Hz), 7.94–8.00 (m, 2H), 7.73–7.65 (m, 2H), 7.48–7.36 (m, 3H), 7.21–7.14 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 149.7, 139.4, 136.8, 129.0, 128.8, 127.0, 122.1, 120.6. GCMS *m/z* (% relative intensity): 155 (M^+, 100), 127 (16), 102 (12), 77 (10); **3a′**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.60 (m, 1H), 7.90–7.86 (m, 1H), 7.60–7.57 (m, 2H), 7.51–7.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 148.4, 137.9, 136.8, 134.6, 129.2, 128.3, 127.3, 123.7. GC–MS *m/z* (% relative intensity): 155 (M^+, 100), 127 (17), 102 (5), 77 (20). Compound **3a″**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, 2H, J = 6.2 Hz), 7.68–7.61 (m, 2H), 7.52–7.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 148.5, 138.2, 129.3, 129.2, 127.1, 121.8. GCMS *m/z* (% relative intensity): 155 (M^+, 100), 140 (5), 127 (16), 115 (12), 77 (2).

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Supplementary data

General method, characterization data, and charts of ^{1}H, ^{13}C NMR for all products are concluded. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.059.

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