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A Study on the Selectivity of Arylzinc Reagents in Cross-coupling Reactions with Chemically Equivalent and Pseudo-equivalent Dibromopyridines

Hye-Soo Jung and Seung-Hoi Kim*

*Department of Chemistry, Dankook University, 119 Dandaero Cheonan 330-714, Korea. *E-mail: kimsemail@dankook.ac.kr*
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Heterocyclic compounds bearing a pyridine moiety have shown a broad range of biological activities as a result of diverse substitutents containing numerous different types of functionalities.[1] Consequently, new practical synthetic approaches for constructing pyridine complex molecules are of high value. To this end, transition-metal-catalyzed cross-coupling reactions of various organometallics with halopyridines have been frequently utilized as one of the efficient protocols.[2]

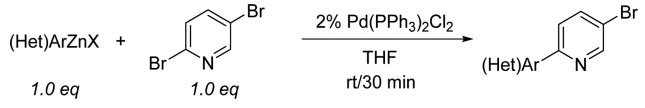
In spite of the high value of using halopyridines, recent researches have been intensively focused on the site-selective cross-coupling reactions with organometallic reagents because the most of pyridine derivatives found in natural compounds and material chemistry have at least two different types of substitutents on a pyridine ring. To install the diverse functionalities on a pyridine ring utilizing the cross-coupling protocol, regioselectivity of the reaction is highly demanded, especially in the case of using multiple halogenated pyridines. Due to the significance of this approach, there are many valuable reviews emphasizing the regioselectivity of the cross-coupling reactions with multiple halogenated compounds.[3]

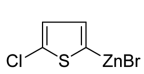
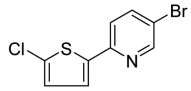
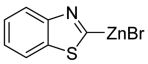
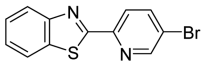
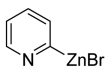
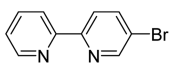
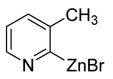
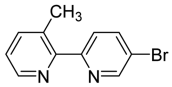
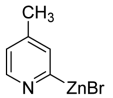
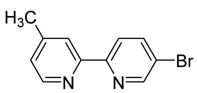
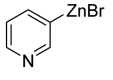
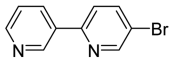
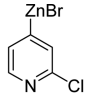
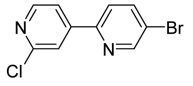
Among the halogenated pyridines, dibromopyridines have been the most popular substrates in the site-selective cross-coupling reactions of organometallic reagents.[4] Therefore, our attention was focused naturally on these substrates to investigate the site-selectivity in the cross-coupling of organozinc reagents. Notwithstanding the significance and popularity, a limited number of studies on the site-selective cross-coupling reactions were performed using dibromopyridines. More interestingly, to the best of our knowledge, only a few scattered examples of Negishi coupling products utilizing dibromopyridines were appeared.[4d,4k]

To investigate the site-selectivity in the cross-coupling reaction of organozincs with dibromopyridines, we first began with 2,5-dibromopyridine (**I**) bearing chemically pseudo-equivalent two carbon-bromine bonds. For the coupling reactions, a typical Pd-catalyzed reaction conditions was employed since, as well known, Pd-catalyzed version of Negishi coupling offers the most favorable reactivity in terms of yield and reactivity. The results are summarized in Table 1.

Initial study was carried out at room temperature in the presence of 2 mol % of $Pd(PPh_3)_2Cl_2$ in THF and the coupling was generally completed in 30 min. As shown in Table 1, substituted phenylzinc iodides[5] were successfully coupled with **I** and, as expected, the substitution took place at the C2-position affording the corresponding 2-aryl-substituted 5-bromopyridines (**1a-1e**) as a major product in each reaction in good yields (entries 1-5, Table 1). High preference for the

Table 1. Coupling reactions of (Het)ArZnX with 2,5-dibromopyridine



Entry	Organizinc	Product[a]	Yield (%)[b]
1	X: 2-CO_2Et	**1a**	67
2	4-CO_2Et	**1b**	85
3	4-Cl	**1c**	84
4	4-CF_3	**1d**	79
5	4-F	**1e**	88
6		 **1f**	89
7		 **1g**	65
8		 **1h**	70
9		 **1i**	33
10		 **1j**	65
11		 **1k**	64
12		 **1l**	60

[a]Characterization of regioselectivity, see ref. 8. [b]isolated yield

2-position over 5-position has been frequently observed from the previous examples,[6] and it was Table 1. Coupling reactions of (Het)ArZnX with 2,5-dibromopyridine also observed consistently throughout this study. According to the GC-MS analysis of the reaction mixture, undetectable amount of di-substituted product was observed from all of the couplings described in Table 1. In addition, a variety of different types of heteroarylzinc halides were coupled with **I** under the same conditions (Table 1).

With these promising results obtained from the couplings with 2,5-dibromopyridine (**I**) in hand, our studies were expanded to assess whether this protocol could be used for 2,6-dibromopyridine (**II**) possessing chemically equivalent two carbon-bromine bonds. To adapt this synthetic strategy to making unsymmetrically and/or symmetrically disubstituted pyridines through a site-selective coupling reaction, an effective reaction conditions for a high selectivity should be installed first. Thus, as depicted in Table 2, a catalyst screening test was performed prior to the general application of this strategy to 2,6-dibromopyridine.

The result clearly showed that the best selectivity (mono- *vs* di-substitution) was achieved from using $Pd(PPh_3)_2Cl_2$ among the various transition metal catalysts examined in this study According to the test, it could be concluded that a cold reaction temperature was a little better in selectivity. At a prolonged reaction time at 0 °C, however, the increment of dicoupled product was higher than that of mono-coupled product.

As shown in Table 3, the monocoupled products (**3a-3g**) were obtained in moderate to good isolated yields utilizing the arylzinc halides bearing a various functional group (entries 1-7, Table 3) except 4-cyanophenylzinc bromide (entry 2, Table 3). Even though, according to the GC-MS analysis, 10-15% of dicoupled molecule was generally observed in the rest of the couplings, no effort was executed to isolate the product.

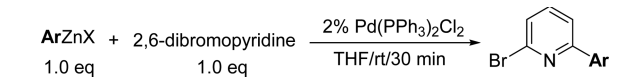
For the comparative analysis of the isolated products of mono- *vs* di-coupling, a couple of selected cross-coupling

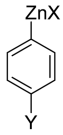
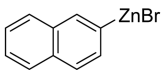
Table 2. A catalyst screening test[a]

Entry	Catalyst (2 mol %)	results (%)[b]			
		P1	P2	P3	Py
1	$Pd(PPh_3)_2Cl_2$	47	20	11	16
2[c]	$Pd(PPh_3)_2Cl_2$	42	15	10	27
3	$Pd(PPh_3)_4$	35	26	4	13
4	$Pd(OAc)_2$/SPhos[d]	20	19	30	25
5	$Ni(dppe)Cl_2$	3	27	20	41
6	$Ni(acac)_2$	5	6	5	45
7	$Fe(acac)_2$	3	3	2	76
8	$Co(dppe)Cl_2$	5	1	2	75
9	$Ni(PPh_3)_2Cl_2$	4	24	28	36

[a]carried out at rt for 30 min unless mentioned. [b]calculated based on the area ratios of GC-MS analysis. [c]carried out at 0 °C. [d]4 mol % used.

Table 3. Coupling reactions of arylzincs with 2,6-dibromopyridine

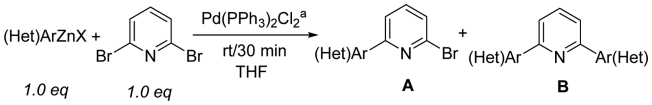


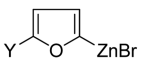
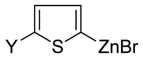
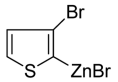
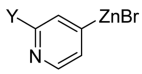
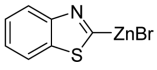
Entry	ArZnX			Product	Yield (%)[a]
1		X = I	Y = CO_2Et	**3a**	50
2		X = Br	Y = CN	**3b**	10(78)[b]
3		X = I	Y = OMe	**3c**	46
4		X = Br	Y = F	**3d**	45
5		X = I	Y = Cl	**3e**	55
6		X = I	Y = Br	**3f**	74
7				**3g**	33

[a]isolated (based on arylzinc). [b]homo-coupling product in parenthesis

reactions were carried out using an organozinc reagent, 5-ethoxycarbonyl-2-furylzinc bromide, under the same conditions (entries 1 and 2, Table 4). Unlike others in Table 4, a considerable amount of dicoupled product was observed from these reactions. A further study on the scope of regio-

Table 4. Coupling of Heteroarylzincs with 2,6-dibromopyridine



Entry	Organozinc		Product	Yield (%)[b]	
				A	B
1		Y : —CO_2Et	**4a**	53(40)[c]	23(10)[c]
2			**4b**	67	14
3		Y : —CO_2Et	**4ca**	52	- [d]
4		—Br	**4d**	77	- [d]
5		—Cl	**4e**	84	- [d]
6			**4f**	65	- [d]
7		Y : 2-ZnBr	**4g**	53	- [d]
8		3-ZnBr	**4h**	40(29)[c]	- [d]
9		Y : CH_3	**4i**	44	- [d]
10		Cl	**4j**	60	- [d]
11			**4k**	72	- [d]

[a]2 mol % used. [b]isolated yield (based on 2,6-dibromopyridine). [c]2 mol % $Pd(PPh_3)_4$ used. [d]no isolation performed

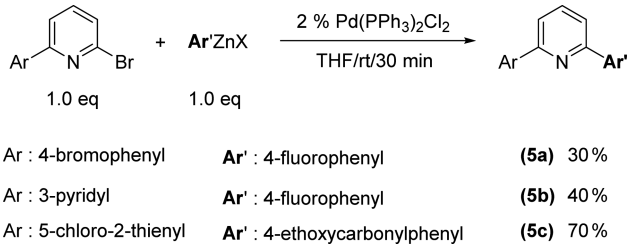


Figure 1. Preparation of unsymmetrically 2,6-disubstituted pyridines.

selectivity in the cross-coupling reaction of 2,6-dibromopyridine (**II**) was carried out with a wide range of heteroarylzinc reagents under the same reaction conditions described above. The results are summarized in Table 4. No further effort has been performed for the isolation of dicoupled one.

To figure out any difference in reactivity between Pd(II)- and Pd(0)-catalyst, coupling reactions of 5-ethoxycarbonyl-2-furylzinc bromide and 3-pyridylzinc bromide were carried out separately in the presence of Pd (0)-catalyst as well as Pd (II)-catalyst (entries 1 and 8, Table 4).

Our strategy could be also extended to the preparation of unsymmetrically disubstituted pyridines possessing two different substitutents at 2- and 6-positions. As illustrated in Fig. 1, coupling reaction of an appropriate organozinc reagent with one of the pyridine derivatives obtained from the previous monocoupling reaction provided the corresponding unsymmetrically disubstituted pyridines (**5a-5c**, Fig. 1) in moderate yields.

In conclusion, site-selective coupling reactions of arylzincs and heteroarylzincs with both chemically equivalent and pseudo-equivalent carbon-bromine bonds have been explored. A high site-selectivity was observed using 2,5-dibromopyridine in the presence of Pd(II)-catalyst under mild conditions. The coupling reactions employing the same equivalent of organozinc and 2,6-dibromopyridine were also successfully demonstrated and the results showed that the monocoupled compound was obtained as a major product over dicoupled one under the same conditions. Most of the monocoupled products obtained in this study may potentially be further transformed to the highly substituted pyridine derivatives due to the presence of a bromine atom on the pyridine ring. Further applications of the strategy are presently being investigated.

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