Tetrahedron Letters 49 (2008) 4302–4305

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: http://www.elsevier.com/locate/tetlet

Efficient homo-coupling reactions of heterocyclic aromatic bromides catalyzed by $Pd(OAc)_2$ using indium

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A R T I C L E I N F O

Article history:
Received 7 March 2008
Revised 21 April 2008
Accepted 22 April 2008
Available online 24 April 2008

Keywords:
Catalytic reaction
Indium
Heterocyclic biaryls
Homo-coupling reaction
Palladium

A B S T R A C T

Homo-coupling reactions of heterocyclic aromatic bromides smoothly proceeded with cat-$Pd(OAc)_2$, indium, and LiCl in DMF to afford exclusively symmetric biaryls possessing heterocyclic aromatic ring in good to excellent yields.

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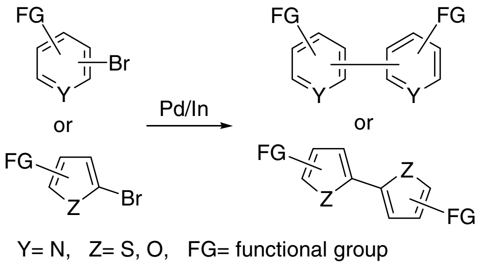
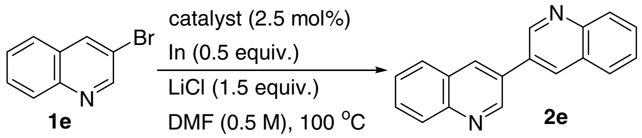
Development of efficient synthetic methods for biaryls possessing heterocyclic aromatic ring is highly required because these compounds are of importance in natural products as well as in molecular recognitions and in asymmetric reactions.[1] Although efficient synthetic method of symmetric biaryls with aromatic halides catalyzed by copper reagents has been well known as the Ullmann reaction, the use of high temperatures (neat, >200 °C), poor substrate scope, and the need to use stoichiometric amounts of copper reagents has limited the utility of these reactions in some cases.[2] In addition, the transition metal-catalyzed cross-coupling reaction of aryl halides with arylmetals, including arylboronic acids,[3] arylstannanes,[4] arylzinc,[5] aryl Grignard regents,[6] and so on,[7] is one of the effective methodologies for the synthesis of symmetric and unsymmetric biaryls. However, the direct dimerization of aryl halides without the additional step related to preparation of arylmetals is considered to be a more convenient and straightforward for the synthesis of symmetric biaryls. Recently, we reported that treatment of aryl iodides and vinyl iodides and bromides with indium in the presence of Pd-catalyst and LiCl efficiently produced symmetric biaryls and 1,3-diene derivatives through the homo-coupling reactions in good to excellent yields.[8] However, in the



Scheme 1. Homo-coupling reactions of heterocyclic aromatic bromides using cat-Pd and indium.

Table 1
Reaction optimization of homo-coupling reactions of 3-bromoquinoline



Entry	Catalyst	Time (h)	Yield[a] (%)
1	Pd–C	20	24(38)[b] (21)[c]
2	$PdCl_2$	2	78(15)[c]
3	**$Pd(OAc)_2$**	**1**	**91**
4	$Pd_2dba_3CHCl_3$	2	90
5	$Pd(PPh_3)_4$	2	85(5)[c]
6	$(\pi\text{-ally})_2PdCl_2$	2	87(3)[c]

[a] Isolated yield.
[b] Isolated yield of quinoline.
[c] Recovery yield of 3-bromoquinoline.

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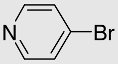
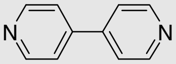
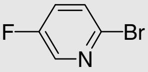
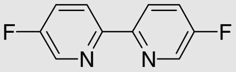
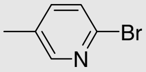
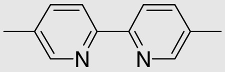
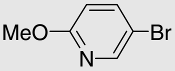
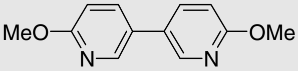
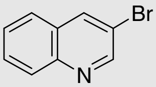
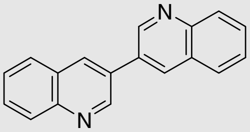
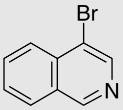
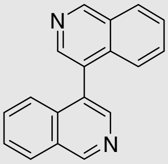
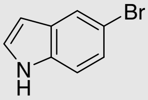
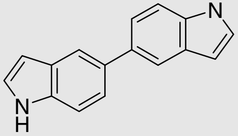
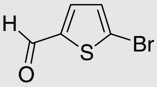
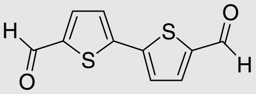
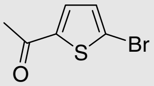
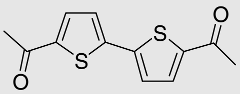
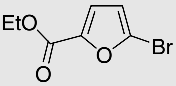
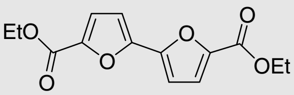
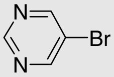
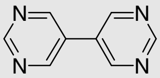
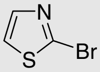
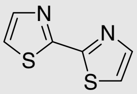
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.123

cases of heterocyclic aromatic bromides, the symmetric heterocyclic biaryls were produced in lower yields together with reduction products and the longer reaction time was required. Therefore, there is still a strong need for a preparative method of homo-coupling products of the heterocyclic aromatic bromides despite the recent progress of synthesis of symmetric biaryls.[9] In continuation of our studies directed toward the development of efficient indium-mediated reactions,[10] we described herein an efficient synthetic method of symmetric biaryls possessing heterocyclic aromatic ring from treatment of heterocyclic aromatic bromides with indium in the presence of Pd-catalyst and LiCl (Scheme 1).

Table 2
Homo-coupling reactions of heterocyclic aromatic bromides[a]

Entry	Substrate		Time (h)	Product		Yield (%)[b]
1		**1a**	3		**2a**	71(13)[c]
2			2.5			90[d]
3		**1b**	1		**2b**	89
4		**1c**	0.5		**2c**	94
5		**1d**	1		**2d**	87
6		**1e**	1.5		**2e**	91
7		**1f**	3		**2f**	92
8		**1g**	5		**2g**	80
9		**1h**	1.5		**2h**	71
10		**1i**	6		**2i**	76
11		**1j**	4		**2j**	85(8)[e]
12		**1k**	3		**2k**	71
13		**1l**	16		**2l**	72

[a] The reaction was performed with 1 equiv of substrate (1.0 mmol), 0.5 equiv of In and 1.5 equiv of LiCl in the presence of 2.5 mol % $Pd(OAc)_2$ in DMF at 100 °C, unless otherwise noted.

[b] Isolated yield.

[c] Recovery yield of 4-bromopyridine.

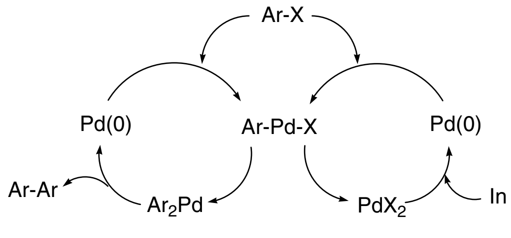
[d] 1 equiv In and 5 mol% $Pd(OAc)_2$ was used.

[e] Isolated yield of ethyl 2-furancarboxylate.

Our initial study focused on homo-coupling reaction of 3-bromoquinoline (**1e**) and the results are summarized in Table 1. Although 4,4′-dimethoxy-1,1′-biphenyl from homo-coupling reaction of 4-iodoanisole using indium in the presence of cat-Pd/C was produced in 91% yield,[8] the homo-coupling product **2e** of 3-bromoquinoline (**1e**) under the same reaction conditions was obtained only in 24% yield together with quinoline (38%) and **1e** (21%) even at 100 °C for 20 h in DMF (entry 1). Therefore, new optimum reaction conditions for biaryls possessing heterocyclic aromatic ring were highly required. Of the reactions screened, the best results were obtained with 2.5 mol % $Pd(OAc)_2$ with indium (0.5 equiv) and LiCl (1.5 equiv) in DMF at 100 °C for 1.5 h under a nitrogen atmosphere, producing the homo-coupling product **2e** in 91% yield (entry 3). 2.5 mol % of $Pd_2dba_3CHCl_3$, $Pd(PPh_3)_4$, and $(\pi\text{-allyl})_2PdCl_2$ gave the desired product **2e** in good yield, while a longer reaction time was needed to complete the reaction (entries 4–6).

To demonstrate the efficiency and scope of the present method, we applied the above catalytic reaction system to a variety of heterocyclic aromatic bromides. The results are summarized in Table 2. 4-Bromopyridine (**1a**) produced 4,4′-bipyridine (**2a**) in 71% yield together with recovered **1a** (13%) under the optimum reaction conditions (entry 1), while the use of 1 equiv indium and 5 mol % $Pd(OAc)_2$ gave **2a** in 90% yield (entry 2). 2-Bromo-5-fluoropyridine (**1b**) gave the homo-coupling product **2b** in 89% yield (entry 3).[11] 2-Bromo-5-methylpyridine (**1c**) and 2-bromo-5-methoxypyridine (**1d**) were treated with $Pd(OAc)_2$, indium, and LiCl to provide the desired products **2c** and **2d** in 94% and 87% yields, respectively (entries 4 and 5). 4-Bromoisoquinoline (**1f**) turned out to be compatible with the employed reaction conditions (entry 7). The homo-coupling reaction of 5-bromoindole (**1g**) having aryl bromide moiety works equally well to give rise to the heterocyclic biaryl **2g** in 80% yield (entry 8). The presence of various carbonyl groups, such as aldehyde, ketone, and ester groups, on the heterocyclic aromatic rings did not largely affect on the efficiency of the present reactions. 5-Bromo-2-thiophene-carboxaldehyde (**1h**) and 5-acetyl-2-bromothiophene (**1i**) gave the homo-coupling products **2h** and **2i** in 71% and 76% yields (entries 9 and 10) under the optimum reaction conditions. It is noteworthy that protection of aldehyde and ketone group on substrates is not necessary. The use of ethyl 5-bromo-2-furoate (**1j**) afforded the symmetric biaryl **2j** having furan moieties in 85% yield together with recovered **1j** in 8% yield (entry 11). Subjecting 5-bromopyrimidine (**1k**) to $Pd(OAc)_2$, indium, and LiCl in DMF for 3 h produced 5,5′-bipyrimidine (**2k**) in 71% yield (entry 12). In the case of 2-bromothiazole (**1l**), 2,2′-bithiazole (**2l**) was obtained in 72% yield (entry 13). However, a longer reaction time (16 h) at 100 °C in DMF was required to complete the homo-coupling reaction.

Although the mechanism of the coupling reactions has not been established, we believe that this transformation most likely proceeded via a direct electron transfer from indium to palladium(II), which completed the catalytic cycle (Scheme 2).[5b,12] In addition, potential for single electron transfer to generate radical or arylindium species can be considered.



Scheme 2. Proposed catalytic cycle.

In summary, we have developed efficient homo-coupling reactions of heterocyclic aromatic bromides using indium in the presence of cat-$Pd(OAc)_2$ and LiCl in DMF at 100 °C, producing exclusively homo-coupling products in good to excellent yields, in which Csp^2–Csp^2 bonds were formed.[13] It is noteworthy that protection of aldehyde and ketone group on substrates is not necessary.

Acknowledgments

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2005-041-C00255) and the Korea Science and Engineering Foundation (KOSEF) through the National Research Lab. Program funded by the Ministry of Science and Technology (No. M10600000203-06J0000-20310). The NMR data were obtained from the central instrumental facility in Kangwon National University. Dr. Sung Hong Kim at the KBSI (Daegu) is thanked for obtaining the MS data.

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11. A mixture of **1b** (176.0 mg, 1.0 mmol), $Pd(OAc)_2$ (5.61 mg, 0.025 mmol), indium (57.4 mg, 0.5 mmol) and lithium chloride (63.5 mg, 1.5 mmol) in dry DMF (2 mL) was stirred at 100 °C for 1 h under a nitrogen atmosphere. The reaction mixture was quenched with $NaHCO_3$ (satd aq). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic phase was washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and filtered. The residue was purified by silica gel column chromatography (EtOAc–hexane = 1:2) to give **2b** (85.5 mg, 89%). Mp 153–154 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 2H), 7.98 (t, J = 7.9 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.4, 146.0, 145.8, 139.8, 139.7, 130.7, 130.6, 110.2, 109.9; IR (film) 3071,1584, 1466 cm^{-1}; MS(EI) calcd for $C_{10}H_6F_2N_2$ M^+: 192; found, 192.12.
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