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# Palladium-catalyzed functionalization of 5- and 7-azaindoles

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**Abstract**

Palladium-catalyzed functionalization at the 2-position of various 5- and 7-azaindoles was performed by Suzuki, Heck, and Stille reactions. The 2-substituted azaindoles were obtained with 5% $Pd(OAc)_2$, LiCl, and KOAc in DMF at 110°C with moderate to high yields. 

There has arisen considerable synthetic interest in azaindoles, primarily as bioisosteres for indoles, in which adoption of an additional nitrogen atom in the aromatic ring confers its own unique properties to the systems. Azaindoles have been used for various pharmaceutical agents, such as anti-inflammatory agents,[1] anti-psychotic agents,[2] etc.[3] Since natural azaindoles are relatively scarce, most of the azaindoles have been prepared traditionally via classical methods such as the Fisher, Madelung, and Reissert procedures, which, in spite of their synthetic value, generally suffer from harsh reaction conditions and modest yields.[4] Recently, palladium-mediated cyclizations with alkynes have been of great interest for the preparation of azaindole derivatives[5] with modified synthetic procedures for indoles.[6] However, few transition metal mediated functionalization of azaindoles have been described in the literature.[7] In particular, reports on the functionalization at the 2-position of 5- and 7-azaindoles are very limited in the literature.[8] Herein, we report the facile functionalization at the 2-position of 5- and 7-azaindole derivatives, which is based on palladium-mediated coupling reactions.

The 2-iodo-3-substituted azaindoles were obtained by the reaction of 2-trimethylsilyl-3-substituted azaindoles with ICl at room temperature within 1 h for the palladium-catalyzed functionalization (Eq. (1)). Heating the reaction mixture[5a] resulted in some chloride which was unreactive towards further elaboration.[9]

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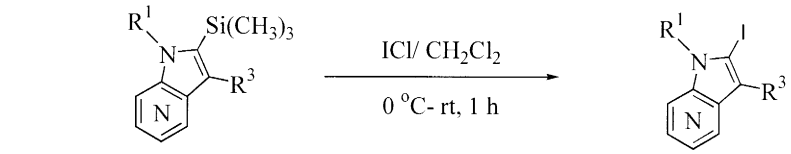


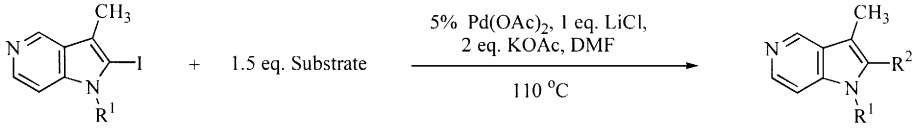

(1)

$R^1$ = H, $CH_3$, Bn
$R^3$ =$CH_3$, $CH_2CH_2N_3$, Ph, *etc.*

75-93%

Initial palladium-catalyzed coupling reactions were performed with various 2-iodo-3-methyl-5-azaindoles and boric acids, alkenes, and organotin derivatives. The results are summarized in Table 1.

Table 1
Palladium-catalyzed functionalization at the 2-position of 5-azaindoles




| Entry[a] | Substrate | $R^1$ | $R^2$ | Reaction time (h) | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 | $PhB(OH)_2$ | H | Ph | 60 | <5[b] |
| 2 | " | $CH_3$ | " | 16 | 75 |
| 3 | " | Bn | " | 60 | 64 |
| 4 | 2-$CH_3PhB(OH)_2$ | $CH_3$ | 2-$CH_3Ph$ | 74 | 52 |
| 5 | 4-$CH_3OPhB(OH)_2$ | " | 4-$CH_3OPh$ | 48 | 59 |
| 6 | 3-$NO_2PhB(OH)_2$ | " | 3-$NO_2Ph$ | 48 | 49 |
| 7 | " | Bn | " | 60 | 58 |
| 8 | 4-$FPhB(OH)_2$ | $CH_3$ | 4-FPh | 48 | 63 |
| 9 | $CH_2$=$CHSn(Bu)_3$ | " | $CH=CH_2$ | 48 | 62 |
| 10 | $CH_2$=$CHCH_2Sn(Bu)_3$ | " | $CH_2CH=CH_2$ | 48 | 49 |
| 11 | $PhSn(CH_3)_3$ | " | Ph | 48 | 68 |
| 12 | $CH_2$=$CHCO_2CH_3$ | " | $CH=CHCO_2CH_3$ | 38 | 81 |
| 13 | $CH_2$=$CHCO_2CH_3$ | Bn | $CH=CHCO_2CH_3$ | 24 | 78 (6:1)[c] |
| 14 | $CH_2$=$CHCOCH_3$ | " | $CH=CHCOCH_3$ | 24 | 72 (10:1)[c] |

[a] All reactions were run on a 0.5 mmol scale.
[b] Starting material was recoved with trace amount of desired product.
[c] The reaction provided two steroisomers (*trans*:*cis*) in the ratio of the numbers in parenthesis.

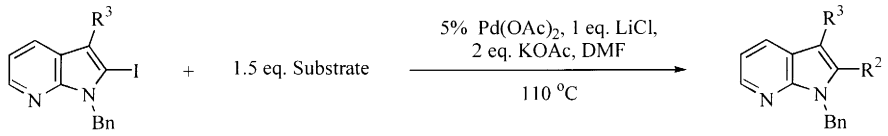
The reaction using 2-iodo-3-methyl-5-azaindoles with the phenylboric acid provided 3-methyl-2-phenyl-5-azaindoles (entries 1–3). The reaction of 2-iodo-3-methyl-1*H*-5-azaindole provided a trace amount of 3-methyl-2-phenyl-1*H*-5-azaindole and most of the starting material was recovered even after 60 h (entry 1). Probably, 1*H*-azaindole readily forms a complex with the palladium catalyst and the complex cannot proceed in the catalytic cycle. Also, the reaction of 1-benzyl-2-iodo-5-azaindole required a longer reaction time for completion compared to the reaction of 2-iodo-1-methyl-5-azaindole (entries 2 and 3). We examined a possible introduction of various phenyl groups at the 2-position of 5-azaindoles,

which could not easily be introduced by previous methods (entries 4–8). The Suzuki coupling reactions proceeded very well with various phenylboric acids, but the reaction with sterically more hindered *ortho*-substituted boric acid required a longer reaction time (entries 4 and 5).

Then Stille coupling reactions were also examined to introduce aryl or alkenyl groups at the 2-position of 5-azaindoles. The reactions provided not only an aromatic group but also an alkenyl group at the 2-position of 5-azaindoles in moderate yields (entries 9–11). Finally, the Heck reactions were examined (entries 12–14). The reactions using 1-benzyl-2-iodo-5-azaindole and vinyl olefins provided high yields of 2-substituted 5-azaindoles with *trans*:*cis* isomers in the ratio of 6–10:1.

In order to synthesize pharmaceutically useful 2-substituted 7-azaindole derivatives, the standard palladium-catalyzed reaction condition was also applied to 2-iodo-3-substituted 7-azaindoles with phenylboric acids, organotins, and olefin derivatives. The results are summarized in Table 2.

Table 2
Palladium-catalyzed functionalization at the 2-position of 3-substituted 7-azaindoles




| Entry[a] | Substrate | $R^2$ | $R^3$ | Reaction time (h) | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 | $PhB(OH)_2$ | Ph | $CH_3$ | 5 | 83 |
| 2 | " | " | $CH_2CH_2N_3$ | 24 | 81 |
| 3 | " | " | $CH_2CH_2OAc$ | 24 | 86 |
| 4 | $4\text{-}CH_3OPhB(OH)_2$ | $4\text{-}CH_3OPh$ | Ph | 18 | 60 |
| 5 | $4\text{-}FPhB(OH)_2$ | 4-FPh | Ph | 36 | 60 |
| 6 | $CH_2{=}CHCH_2Sn(Bu)_3$ | $CH_2CH{=}CH_2$ | $CH_3$ | 8 | 80 |
| 7 | $CH_2{=}CHSn(Bu)_3$ | $CH{=}CH_2$ | Ph | 4 | 84 |
| 8 | " | " | $\text{-}CH_2CH_2$morpoline | 4 | 66 |
| 9 | $PhSn(CH_3)_3$ | Ph | $CH_2CH_2OAc$ | 7 | 84 |
| 10 | 2-$FurylSn(Bu)_3$ | 2-Furyl | Ph | 36 | 71 |
| 11 | $CH_2{=}CHCO_2CH_3$ | $CH{=}CHCO_2CH_3$ | Ph | 12 | 92 |
| 12 | $CH_2{=}CHCOCH_3$ | $CH{=}CHCOCH_3$ | $CH_3$ | 12 | 72 |
| 13 | $CH_2{=}CHCHOHCH_3$ | $CH_2CH_2COCH_3$ | $CH_3$ | 12 | 52 |

[a] All reactions were run on a 0.5 mmol scale.

The reaction using various 2-iodo-7-azaindoles with phenylboric acids provided 2-phenyl-3-substituted 7-azaindoles in moderate to high yields (entries 1–5). Generally, the Suzuki coupling reaction of 7-azaindoles provided higher yields of 2-phenyl-7-azaindoles and required shorter reaction times compared to the reaction of 5-azaindoles. The Stille reaction was also examined (entries 6–10), and provided various 2-substituted 7-azaindoles in high yields within 8 h (entries 6–9, except for entry 10). Finally, the Heck reaction was examined with 2-iodo-7-azaindoles and terminal olefins (entries 11–13). This reaction provided 2-alkyl-7-azaindoles in high yields.

In summary, the functionalizations at the 2-position of 5- and 7-azaindoles were easily performed by

palladium-catalyzed Suzuki, Stille, and Heck reactions. This synthetic method is especially useful for the preparation of various 2-aryl 5- or 7-azaindoles, which cannot be synthesized easily with conventional synthetic methods.

## Acknowledgements

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9. The chloride and iodide were not separable by chromatography and the chloride was isolated after the coupling reaction. Three equivalents of fresh iodine monochloride were used. The reaction did not proceed in the presence of the hydroxymethyl or piperazinylethyl groups at the 3-position. For similar iododesilylation, see: Alimardanov, A.; Negishi, E.-i. *Tetrahedron Lett*. **1999**, *40*, 3839.