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Pd-Catalyzed Regioselective Direct Double C−H Arylation of 6,7-Benzindoles

Ping-Gui Li,*[a],[b] Youqing Yang,[a] Shuai Zhu,[b] Hong-Xi Li,[b] Liang-Hua Zou*[b]

ABSTRACT: A palladium-catalyzed protocol for the first direct diarylation of 6,7-benzindoles with aryl iodides at the C4 and C5 positions was developed. The key to this strategy was the employment of pivaloyl as the directing group at the C3 position and the blocking effect at the C6 and C7 positions. The reaction proceeded very well, providing a series of diarylated 6,7-benzindoles without prefunctionalization at the reactive sites. Several examples on the unexpected monoarylation of 6,7-benzindoles at the C5 position were also presented.

Introduction

Indoles and their derivatives represent a class of significant building blocks in natural products in a wide range of biologically active compounds for vegetal, animal and human health (pharmaceuticals and agrochemicals).[1] Therefore, the development of effective methods for the regioselective functionalization of indoles has attracted considerable attention.[2] It has been well-recognized that controlling positional selectivity exhibits as a big challenge due to the presence of multiple C-H bonds with subtle differences in activation barrier.[3] As for indoles, there are six sites for the functionalization of indoles involving sites C2 and C3 (pyrrole core) and sites C4-C7 (benzene core). Normally, metalation preferentially occurs at the C3[4] and/or C2[5] position due to the usual reactivity of indoles. However, it remains a big challenge to develop a strategy for the direct functionalization of C-H bonds on the benzene core rather than the pyrrole core.[6]

In order to override this intrinsic selectivity and realize the functionalization of indoles at various sites, many strategies have been developed by employing a directing group at the N-atom and/or C3 position to block the reactivity. For example, the regioselectivity at the C7 position was realized to achieve successful C-H borylation,[6a],[6b],[7] olefination,[6h] amidation,[6i],[6j] and arylation[8] by introducing directing groups, such as silyl, pivalyl and P(O)^{t}Bu$_2$, on the indole N-atom. Meanwhile, the C6-selective C-H olefination,[6f] borylation,[6c] alkylation[9] and arylation[10] of indoles have also been reported. Recently, the investigators continued to contribute to the research on the direct C-H arylation of indoles at the C4 and C5 positions with the aid of a pivaloyl directing group at the C3 position.[11] To date, the direct arylation of indoles at all positions have been achieved, while there are little reports on the diarylation of indoles and their derivatives.[12] Based on our previous work,[8],[10],[11],[13] the investigators were intrigued to determine whether the site-selective diarylation of indole could occur. Herein, we report a Pd-catalyzed strategy for the direct diarylation of 6,7-benzindoles at the C4 and C5 positions by installing a pivaloyl directing group at the C3 position.

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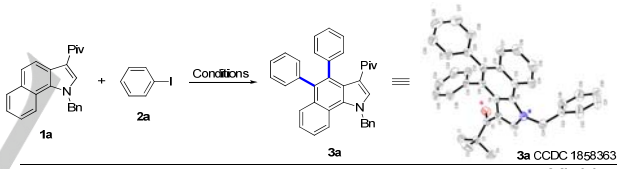
Results and Discussion

The initial screening and optimization of the reaction conditions was conducted with compound **1a** and iodobenzene (**2a**) as substrates (Table 1). Using **1a** and **2a** at a 1:3 ratio (on a 0.1 mmol scale), with $Pd(OAc)_2$ (0.05 eq) as catalyst, DBU (1.0 eq) as base, Ag_2O (1.2 eq) as oxidant, and HFIP as solvent, product **3a** was obtained in 25% yield at 80 °C (Table 1, entry 1). It was noteworthy that other solvents, such as DMSO, DMF, toluene, dioxane and CH_3CN, were all ineffective for this reaction (Table 1, entries 2-6). Later, various palladium catalysts were screened in the reaction, showing that $PdCl_2$(dppf) was the best for this reaction (Table 1, entries 7-10). The yield dropped slightly in the absence of molecular sieves (Table 1, entry 11), but no better yield was obtained when the reaction temperature was enhanced to 100 °C (Table 1, entry 12). Further optimization by adding various ligands did not improve the reaction. The use of other bases instead of DBU, such as Na_2CO_3 and Cs_2CO_3, led to lower yields (Table 1, entries 13 and 14). Performing the reaction in the absence of a base decreased the yield of **3a** significantly (Table 1, entry 15).

Table 1.Screened reaction conditions.[a]

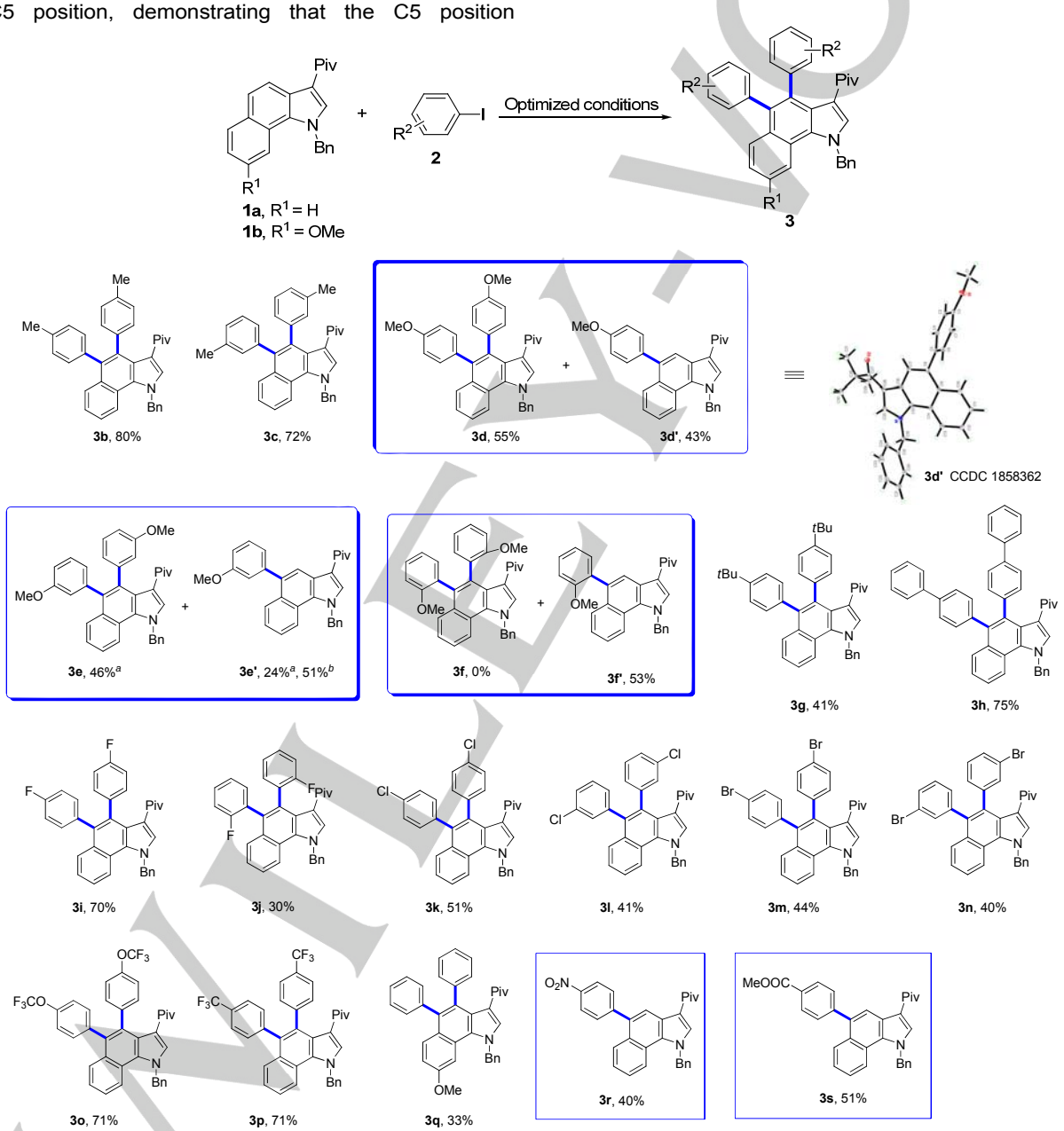


Entry	Catalyst	Base	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	DBU	HFIP	25
2	$Pd(OAc)_2$	DBU	DMSO	0
3	$Pd(OAc)_2$	DBU	DMF	0
4	$Pd(OAc)_2$	DBU	toluene	0
5	$Pd(OAc)_2$	DBU	dioxane	0
6	$Pd(OAc)_2$	DBU	CH_3CN	0
7	$PdCl_2$	DBU	HFIP	33
8	Pd(IPr)(allyl)Cl	DBU	HFIP	45
9	Pd $(PPh_3)_4$	DBU	HFIP	31
10	**$PdCl_2$(dppf)**	**DBU**	**HFIP**	**65**
11	$PdCl_2$(dppf)	DBU	HFIP	50[c]
12	$PdCl_2$(dppf)	DBU	HFIP	63[d]
13	$PdCl_2$(dppf)	Na_2CO_3	HFIP	61
14	$PdCl_2$(dppf)	Cs_2CO_3	HFIP	36
15	$PdCl_2$(dppf)	/	HFIP	32

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), catalyst (0.05 eq), DBU (1.0 eq), Ag_2O (1.2 eq), 4 Å MS (100 mg), solvent (1 mL), 12 h, 80 °C, Ar atmosphere. [b]After column chromatograph. [c]The reaction was carried out without 4 Å MS. [d]At 100 °C. DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene. HFIP: Hexafluoroisopropanol.

With the optimized reaction conditions in hand (Table 1, entry 10), the scope of the reaction of compound **1a** with a variety of aryl iodides **2** was investigated. The results are summarized in scheme 1. Many substrates with various electron-donating or electron-withdrawing substituents were applied to the reaction system to synthesize a series of diarylated 6,7-benzindoles. The reaction of substrates with the methyl group afforded the corresponding products **3b**

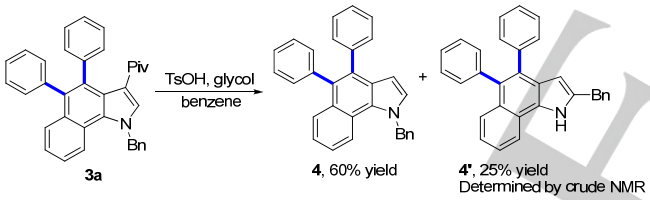
and **3c** in 80% and 72% yields, respectively. For substrates with the methoxyl group at the *para*-position, reaction conditions needed to be slightly modified by enlarging the ratio of *para*-methoxyiodobenzene to 5:1 and diarylated product **3d** and monoarylated product **3d'** were both obtained in 55% and 46% yields, respectively. For substrates with the methoxyl group at the *meta*-position, trace diarylated product **3e** and 51% yield of monoarylated product **3e'** were obtained under the optimized reaction conditions. By increasing the reaction scale to 0.3 mmol, diarylated product **3e** and monoarylated product **3e'** were both obtained in 46% and 24% yields, respectively. The structure of **3d'** was determined by X-ray crystallographic analysis, and surprisingly, the first reaction site occurred at the C5 position, demonstrating that the C5 position appeared to be more active than the C4 position. The difficulty in the second arylation might result from the steric hinderence of methoxy group at the C4 position when monoarylated product **3e'** was formed. The reaction of the substrate with the methoxy group at the *ortho*-position was further verified the present hypothesis, in which only monoarylated product **3f'** was formed in 53% yield. The substrate with *tert*-butyl yielded product **3g** in an acceptable yield of 41%. Interestingly, the substrate with diphenyl group exhibited more efficiency in the reaction, affording product **3h** in 75% yield. Unfortunately, the reaction of compound **1a** with bromobenzene only provided trace amounts of products **3a** because of the relatively inert reactivity of bromobenzene.



Scheme 1. The scope of the substrate in the reaction. Reaction conditions: **1a** (0.10 mmol), **2** (0.3 mmol), $PdCl_2$(dppf) (0.005 mmol), Ag_2O (0.12 mmol), DBU (0.1 mmol), HFIP (1 mL), 80 °C, 12 h. [a]0.3 mmol scale. [b]Merely a 51% yield of monoarylated product **3e'** was obtained at the 0.1 mmol scale.

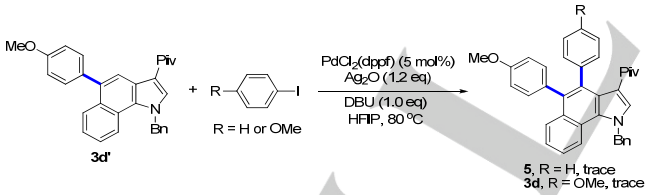
In addition, substrates with various electron-withdrawing substituents were also effective in the reaction (scheme 1). Reaction partners with halide atoms, such as -F, -Cl and –Br, were all effective for the reaction, providing the corresponding products **3i**-**n** in acceptable yields. Strong electron-withdrawing substituent groups, such as $–OCF_3$ and $–CF_3$, were well tolerated in the procedure, providing the desired products **3o** and **3p** both in 71% yields. Furthermore, another 6,7-benzindole substrate **1b** with the methoxyl group was also successfully employed in the reaction system, affording the desired product **3q** in 33% yield. As an exception, products **3r** and **3s** were exclusively afforded through the C5-monoarylation of substrates with nitro- and the ester group at *para*-position in 40% and 51% yields, respectively. It appears that there was no straightforward correlation between the stereoelectronic properties of the substrate and reaction efficiency, but apparently steric factors played an important role in the reaction.

Finally, the pivaloyl group was readily removed from products **3a** by a reverse Friedel-Crafts reaction in the presence of *p*-toluenesulfonicacid and glycol in benzene to give a 60% yield of compound **4**, along with a 25% yield of compound **4'**, which was observed by crude NMR (Scheme 2). The latter was formed *via* 1,2-migration of the benzyl group in the process.[14] Furthermore, in order to investigate the reactivity of monoarylated compound **3d'** and explore the possibility for the synthesis of structurally divergent molecules, control reactions was carried out using **3d'** as substrate under the optimized conditions, albeit provided only trace amouts of products **5** and **3d**, respectively (Scheme 3). This phenomenon appeared unexpectedly, showing that the doube C-H arylation might be realized almost simultaneously *via* an active intermediate state.



3a **4**, 60% yield **4'**, 25% yield Determined by crude NMR

Scheme 2. Removal of the directing group from compound **3a**.



3d' **5**, R = H, trace **3d**, R = OMe, trace

Scheme 3. Direct arylation of monoarylated compound **3d'**.

Regarding the mechanism, two steps might be involved for the selectivity of the diarylation reaction. First, Pd^{II} coordinates to the pivaloyl group of the substrate, followed by the C-H activation at the indole C5 position and oxidative addition by ArI to afford C5-arylated products through reductive elimination with regeneration of the active Pd^{II} species by Ag_2O. In the following step, the second arylation may proceed at C4 position through similar palladium catalysis. The steric factor accounts for the exclusive formation of momoarylated product **3f'** due to the hinderance of the methoxy group at the C5 position.

Conclusions

In summary, we have developed a palladium-catalyzed procedure for the direct diarylation of 6,7-benzindoles with aryl iodides at the C4 and C5 positions. The present study is the first to perform the diarylation of indole cycles and the key to this strategy resulted from the employment of pivaloyl as the directing group at the C3 position and the blocking effect of the phenyl ring at the C6 and C7 positions. Furthermore, a series of diarylated 6,7-benzindoles were prepared in good yields. As for several substrates, the monoarylation reaction unexpectedly took place at the C5 position of 6,7-benzindoles, demonstrating that the C5 site might be more active than the C4 site. Studies aimed at the extension of such synthetic procedures to heterocycles and small molecules to prepare more complex materials, especially indole-core-containing rigid fused rings for organic electronics, are of great value and currently underway in our laboratory.

Experimental Section

Take the synthesis of **3a** for example. To a 25 mL Schlenk tube was added 100 mg 4 Å MS (activated by heating to 600 °C for 5 minutes under vaccum) and purged with argon for three times. Then the tube was added compounds **1a** (34.1 mg, 0.10 mmol), iodobenzene (61.2 mg, 0.30 mmol), $PdCl_2$(dppf) (3.7 mg, 5 mol%), Ag_2O (27.8 mg, 1.2 equiv), DBU (15.2 mg, 1.0 equiv) and HFIP (1 mL) and the mixture was stirred at 80 ºC for 12 h and then cooled to rt, diluted with ethyl acetate. The resulting solution was filtered through celite, concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate = 10:1) afforded product **3a** as a white solid (32.1 mg, 65% yield).

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Keywords: 6,7-Benzindole • Diarylation • C-C coupling • C-H activation • Palladium

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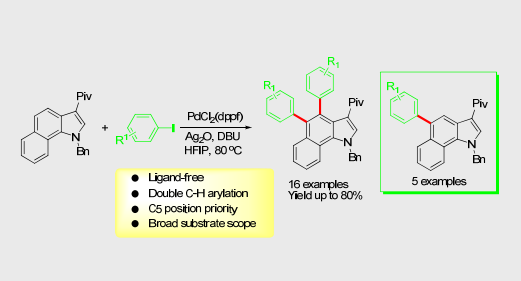

Palladium-catalyzed direct diarylation and monoarylation of 6,7-benzindoles were developed under “ligand-free” catalytic conditions. The introduction of pivaloyl as the directing group at the C3 position and the blocking effect at the C6 and C7 positions played an important role in the reaction. It was found that C5 position might be more active than C4 position. The pivaloyl group could be readily removed by a reverse Friedel-Crafts reaction.

Selective Arylation

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