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Palladium-catalyzed synthesis of carbazoles from *N*-(2-halophenyl)-2,6-diisopropylanilines via C–C cleavage

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ABSTRACT

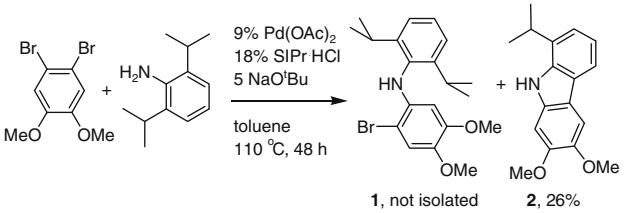
The synthesis of 1-isopropyl-substituted carbazoles by the palladium-catalyzed dealkylative cyclization of *N*-(2-halophenyl)-2,6-diisopropylanilines is described. The reaction involves intramolecular C–C bond formation, coupled with the cleavage of a C–X bond and a C–C bond, and is proposed to proceed through the formation of a dearomatized intermediate.

The palladium-catalyzed formation of carbon–carbon bonds via intramolecular C–X/C–H cross-coupling[1,2] has emerged as an efficient and versatile method for the synthesis of carbazoles, as well as a variety of other heterocycles and carbocycles. Analogous cyclizations involving C–C cleavage[3] rather than C–H cleavage have not been demonstrated, however. The development of catalytic transformations involving carbon–carbon bond cleavage is challenging, though several successful strategies have been advanced, involving the relief of ring strain, chelation assistance, and β-hydrocarbyl elimination.[4,5]

In the course of the synthesis of a series of bidentate N-heterocyclic carbene–pyridine ligands,[6] we attempted the palladium-catalyzed mono-amination of 4,5-dibromoveratrole with 2,6-diisopropylaniline, employing the conditions reported by Bielawski and co-workers,[7] which provide highly efficient tetra-aminations of 1,2,4,5-tetrabromobenzene (Scheme 1). The expected product **1** was not formed in a significant amount; instead we isolated the carbazole **2** in 25% yield, formed via loss of an *ortho*-isopropyl group, whose structure has been confirmed by X-ray crystallography.[8] This unexpected transformation warranted further investigation because the cleaved sp^2–sp^3 carbon–carbon bond is unactivated and sterically hindered. Herein, we report the studies on the scope of this reaction and discuss a possible mechanism for the formation of the carbazole product.

Presumably, the first step in carbazole formation is the originally expected mono-amination reaction giving **1**, followed by C–C bond-forming cyclization with loss of bromide and the isopropyl group. As such, we exposed the minimally functionalized substrate **1a** to similar conditions (Table 1, entry 1), and were pleased to observe smooth formation of the carbazole product **2a**. This transformation is closely related to palladium-catalyzed cyclizations of 2,6-dimethyl-substituted *N*-(2-bromophenyl)-anilines, recently reported by Bedford et al.[9] In the Bedford study, carbazole formation results from the cleavage of an *ortho*-methyl group, which competes with an unusual [2+2] cyclodimerization process. In contrast, carbazole **2a** was the sole product observed in the crude NMR spectrum when **1a** was subjected to the conditions shown in Scheme 1.

For optimization of the reaction parameters, we focused on substrate **1a**, varying the base, solvent, ligand, and palladium source (Table 1). Of several bases commonly employed in palladium-catalyzed cross-coupling, only NaO^{t}Bu was effective (entries 1–4). Toluene was an effective solvent, but no formation of **2a** was observed using either dioxane or *N*-*N*′-dimethylformamide (entries 5 and 6). A screen of several commercially available ligands (entries 7–14) revealed that only bulky, monodentate phosphines



Scheme 1. Unexpected formation of carbazole.

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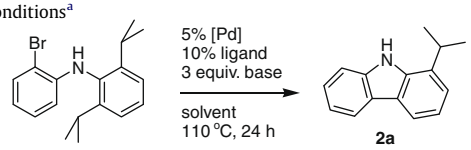
Table 1
Survey of conditions[a]



1a **2a**

Entry	Base	Solvent	Ligand	Pd source	Yield (%)
1	NaO^{t}Bu	Toluene	SIPr·HCl	$Pd(OAc)_2$	73
2	$CsCO_3$	Toluene	SIPr·HCl	$Pd(OAc)_2$	8
3	NaOMe	Toluene	SIPr·HCl	$Pd(OAc)_2$	0
4	K_3PO_4	Toluene	SIPr·HCl	$Pd(OAc)_2$	4
5	NaO^{t}Bu	Dioxane	SIPr·HCl	$Pd(OAc)_2$	0
6	NaO^{t}Bu	DMF	SIPr·HCl	$Pd(OAc)_2$	0
7	NaO^{t}Bu	Toluene	PPh_3	$Pd(OAc)_2$	0
8	NaO^{t}Bu	Toluene	DPEPhos	$Pd(OAc)_2$	0
9	NaO^{t}Bu	Toluene	SPhos	$Pd(OAc)_2$	62
10	NaO^{t}Bu	Toluene	BINAP	$Pd(OAc)_2$	0
11	NaO^{t}Bu	Toluene	PCy_3	$Pd(OAc)_2$	34
12	NaO^{t}Bu	Toluene	dppp	$Pd(OAc)_2$	0
13	NaO^{t}Bu	Toluene	SIMes·HCl	$Pd(OAc)_2$	0
14	NaO^{t}Bu	Toluene	P^{t}Bu$_3$·HBF$_4$	$Pd(OAc)_2$	37
15	NaO^{t}Bu	Toluene	SIPr·HCl	$Pd_2(dba)_3$[b]	77

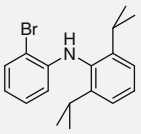
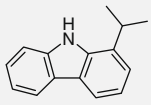
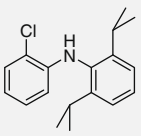
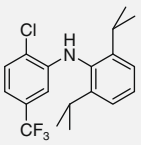
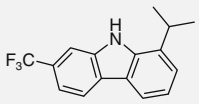
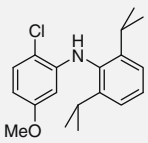
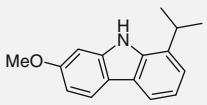
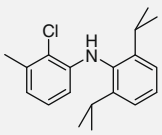
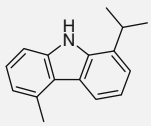
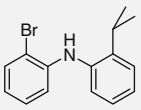
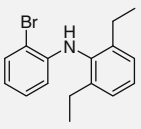
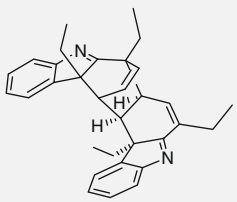
[a] Yields were measured by GC, using tetradecane as internal standard.
[b] Loading of $Pd_2(dba)_3$ was 2.5 mol %.

promote the formation of the carbazole. The monodentate phosphine ligand SPhos[10] was effective (entry 9), while PCy_3 and P^{t}Bu$_3$ were somewhat effective (entries 11 and 14). Bidentate ligands are completely ineffective (entries 8, 10, and 12). Surprisingly, the N-heterocyclic carbene ligand SIMes·HCl is completely ineffective (entry 13), although the structurally similar SIPr·HCl was the most effective (entry 1). $Pd_2(dba)_3$ was approximately equally effective as palladium source, as compared to $Pd(OAc)_2$ (entry 1 vs entry 15).

With optimized conditions in hand, we set out to examine the scope of the reaction (Table 2). The chloro-substituted substrate **1b** was efficiently transformed to **2a**. Substitution of the arene backbone with electron-withdrawing (**1c**) or electron-donating (**1d**) groups gave a moderately less efficient transformation. Substrate **1e**, with an *ortho*-methyl substituent, was converted much more slowly. Only a trace amount of carbazole **2e** was formed under the standard conditions, but a short screen of bulky monodentate ligands revealed that PCy_3 promotes the cyclization, albeit extremely inefficiently (entry 5). Substrate **1f**, with only one *ortho*-isopropyl substituent, gave exclusive C–H cleavage: carbazole **2a** was isolated in 29% yield under the standard conditions, while unsubstituted carbazole that would be formed via C–C cleavage was not observed in the crude reaction mixture, by NMR or GC–MS. This indicates that in intramolecular competition, the previously known cyclization via C–H cleavage[11–17] is significantly faster than the presently studied transformation.

Light was shed on the mechanism of this unusual transformation when the 2,6-diethyl-substituted substrate **1g** was subjected to the standard conditions. No carbazole (**2g**) was formed; rather, the dimerized product **3g** was isolated in 60% yield. X-ray crystallography confirmed the structure as a Diels–Alder dimer of the putative initial product **4** (Scheme 2, top). Analysis of the crude reaction mixture by ^{1}H NMR and thin-layer chromatography confirms the presence of a compound that is converted to **3g** upon concentration, whose ^{1}H NMR spectrum is consistent with that of structure **4**. Presumably, **4** is formed via a palladium-catalyzed dearomatization, and dimerizes upon rotary evaporation at elevated temperature. Attempts to isolate **4** in pure form were hampered by dimerization to **3g**. Analysis of the crude reaction mixtures for the isopropyl-substituted substrates **1a–e** by GC–MS and ^{1}H NMR showed no analogous dearomatized intermediate. In

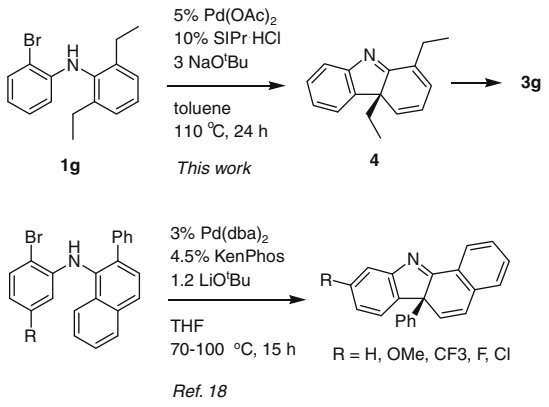
Table 2
Cyclization of various substrates[a]

Entry	Reactant	Product
1	 **1a**	 **2a**, 73%
2	 **1b**	**2a**, 73%
3	 **1c**	 **2c**, 47%
4	 **1d**	 **2d**, 63%[b]
5	 **1e**	 **2e**, 14%[c]
6	 **1f**	**2a**, 29%
7	 **1g**	 **3g**, 60%

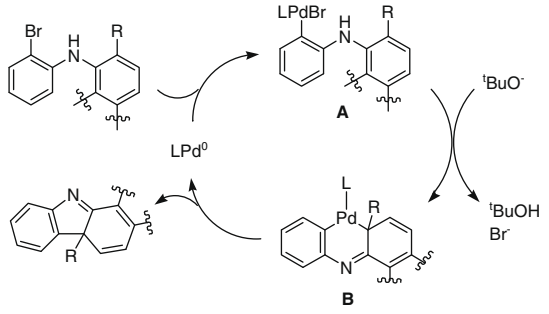
[a] Reaction conditions: Amine (0.40 mmol), $Pd(OAc)_2$ (5 mol %), SIPr·HCl (10 mol %), and NaO^{t}Bu (3 equiv) in toluene (35 mL). Stirred at 110 °C for 20 h. Isolated yields are given.
[b] Performed using 10% $Pd(OAc)_2$ and 20% SIPr·HCl.
[c] Performed using 10% $Pd(OAc)_2$ and 20% PCy_3.

the recent study by Bedford et al.,[9] substrate **1g** was transformed to 1-ethyl-9*H*-carbazole via cleavage of an ethyl group under nearly identical conditions to those in Table 2, in complete contrast to our observations. The key difference appears to be the reaction workup: our workup consisted of filtering the reaction mixture through a plug of silica gel, while the authors of the prior study employed acidic aqueous conditions.

The putative formation of product **4** is also analogous to a transformation of *N*-aryl-naphthylamines recently reported by Buchwald and co-workers,[18] promoted by the combination of palladium, a bulky monodentate phosphine, and a *t*-butoxide salt (Scheme 2, bottom). The authors proposed the reaction mechanism shown in Scheme 3, which is consistent with our observations and



Scheme 2. Formation of dearomatized products.



Scheme 3. Proposed mechanism.

with those of the Bedford and co-workers[9] study. Initial oxidative addition at the C–Br bond to LPd^0 gives intermediate **A**. Next, deprotonation at nitrogen increases the nucleophilicity of the aromatic carbons in the *ortho* and *para* positions, facilitating displacement of bromide by an *ortho*-carbon to give metallacycle **B**. Carbon–carbon bond-forming reductive elimination completes the catalytic cycle, giving the dearomatized carbazole. In the Buchwald study, the additional fused aromatic ring reduces Diels–Alder reactivity, so dearomatized carbazoles are isolated. In the present work, diethyl-substituted **4** dimerizes to form the isolated product, **3g**. Although carbazoles **2a–e** were the only products isolated in the cyclization reactions of diisopropyl-substituted substrates **1a–e**, we propose that the same mechanistic pathway operates: diisopropyl-substituted, dearomatized carbazoles analogous to **4** are formed initially, then are transformed to **2a–e** by the loss of the isopropyl group, presumably by an S_N1 mechanism, followed by protonation at nitrogen.

In summary, we have described a novel palladium-catalyzed transformation, where 2-halo-*N*-(2,6-diisopropylphenyl)anilines cyclize to give carbazoles via C–X/C–C cross-coupling. In the proposed mechanism, palladium facilitates the formation of a dearomatized carbazole intermediate; rearomatization then provides the driving force for carbon–carbon bond cleavage and the formation of the resulting carbazole.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.098.

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10. Abbreviations: SPhos = (2-dicyclohexylphosphino)-2′,6′-dimethoxy-1,1′-biphenyl; DPEPhos = bis(2-diphenylphosphinophenyl)ether; XantPhos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene; BINAP = *rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; SIMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazolinium chloride; SIPr = 1,3-bis(2,6-diisopropylphenyl)-imidazolinium chloride; dppp = 1,3-bis(diphenylphosphino)propane; dba = dibenzylideneacetone.
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