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Cyclopentadiene–Phosphine/Palladium-Catalyzed Cleavage of C–N Bonds in Secondary Amines: Synthesis of Pyrrole and Indole Derivatives from Secondary Amines and Alkenyl or Aryl Dibromides

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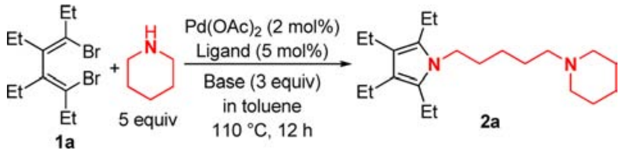
Supporting Information

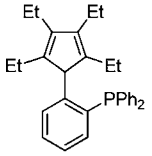
ABSTRACT: An efficient Pd-catalyzed cleavage of C(sp^3)–N bonds in secondary amines and a consequent C(sp^2)–N and C(sp^3)–N coupling process was developed. Various secondary amines could be used to react with alkenyl or aryl dibromides, affording pyrroles and indoles in high yields. Cyclopentadiene–phosphine ligands, a new type of P–olefin ligand, were found to be able to promote the efficiency of this Pd-catalyzed process remarkably. A reactive Pd complex coordinated with a cyclopentadiene–phosphine ligand was successfully isolated and structurally characterized.

The cleavage of C–N bonds is of significant synthetic interest because such bonds are common in organic chemistry and usually unreactive.[1−8] The cleavage of C–N bonds in tertiary amines using stoichiometric[3] or catalytic[4−6] amounts of transition-metal complexes has been reported, leading to various important N-heterocycles. However, to the best of our knowledge, there is no report in the literature on transition-metal-catalyzed cleavage and synthetic applications of C(sp^3)–N bonds in secondary amines.[1b,7,8] Since a secondary amine contains one N–H bond and two C–N bonds, efficient selective cleavage of the C–N bonds and further synthetic applications would be very attractive for both mechanistic studies and synthetic chemistry. Herein we report the first example of catalytic cleavage of the C(sp^3)–N bonds in secondary amines and a consequent C(sp^2)–N and C(sp^3)–N coupling process, which results in the high-yield formation of pyrroles and indoles. In addition, cyclopentadiene–phosphine ligands, a new type of mixed P–olefin ligand,[9,10] were synthesized and found to be able to promote the efficiency of this catalytic process remarkably.

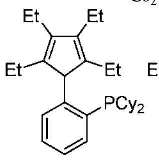
Table 1. Optimization of the Reaction Conditions



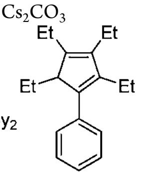
entry	ligand	base	yield of **2a** (%)[a]
1	–	LiO*t*-Bu	0
2	PPh$_3$	LiO*t*-Bu	32
3	Xantphos	LiO*t*-Bu	0
4	XPhos	LiO*t*-Bu	18
5	SPhos	LiO*t*-Bu	29
6	DavePhos	LiO*t*-Bu	16
7	**L1**	LiO*t*-Bu	75 (62[b])
8	**L2**	LiO*t*-Bu	52
9	**L3**	LiO*t*-Bu	0
10	**L4**	LiO*t*-Bu	38
11	**L1**	NaO*t*-Bu	0
12	**L1**	KO*t*-Bu	0
13	**L1**	K$_3$PO$_4$	14
14	**L1**	Cs$_2$CO$_3$	0



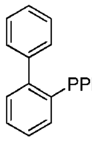
L1



L2



L3



L4

[a]GC yields. [b]Isolated yield.

As shown in Table 1, when dibromide **1a**[11] was treated with piperidine, an unexpected pyrrole derivative, **2a**, was obtained. Obviously, an unprecedented coupling process involving amination, C–N bond cleavage and C–N bond formation took place. After screening various reaction conditions, we found that our newly designed and synthesized phosphine–cyclopentadiene ligands **L1** and **L2** [see the Supporting Information (SI) for detailed synthetic procedures] were the best for this reaction (entries 7 and 8). Many other ligands, including commonly used ones such as PPh$_3$, Xantphos, XPhos, SPhos, and DavePhos, gave low yields or no product at all (entries 2–6). Ligands such as **L3** and **L4** also showed very low or zero efficiency (entries 9 and 10). These results demonstrated that both the P moiety and the cyclopentadiene moiety are necessary for the high-efficiency realization of this Pd-catalyzed coupling process. In addition, this transformation is very sensitive to the base, and LiO*t*-Bu was found to be most effective. Excess piperidine (>5 equiv) is required to achieve a clean reaction. The optimal reaction conditions were found to be Pd(OAc)$_2$ (2 mol %), **L1** (5 mol %), and LiO*t*-Bu (3 equiv) in 2 mL of 1:9 piperidine/toluene at 110 °C for 12 h (entry 7; see the SI for

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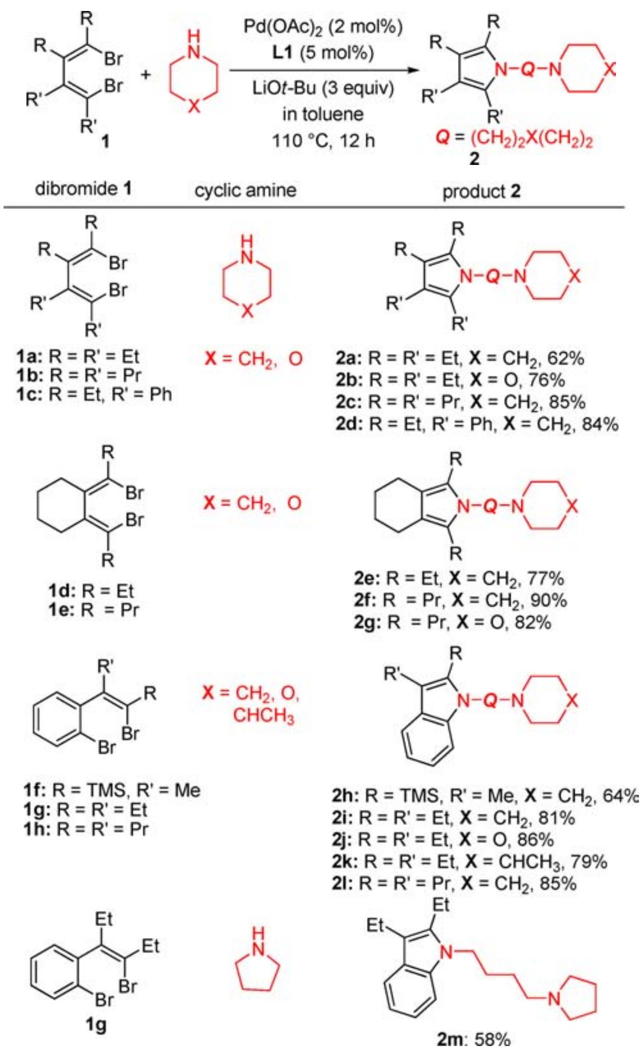
details). Under these optimized conditions, pyrrole derivative **2a** was obtained in 62% isolated yield.

The scope of the this Pd-catalyzed coupling process was investigated under the optimized reaction conditions, and the results are summarized in Tables 2–4. A variety of dibromides **1a–h** were applied. Table 2 shows results obtained from the reaction of dibromides **1a–h** with various cyclic secondary amines, including piperidine, 4-methylpiperidine, morpholine, and pyrrolidine. A wide variety of pyrrole derivatives (**2a–d**), 4,5,6,7-tetrahydroisoindole derivatives (**2e–g**), and indole derivatives (**2h–m**) were obtained in good to excellent isolated yields. In addition, acyclic secondary amines R''_2NH (R″ = Et, Pr, Bu, and *i*-Pr) were investigated (Table 3). No reaction took place when *i*-Pr_2NH was used (unreacted dibromide **1a** was recovered), probably because of steric effects. It should be noted that the formation of R''_3N was observed in all of these reactions. For example, when **1a** was treated with Pr_2NH, Pr_3N was formed in 85% GC yield along with **3b** in 69% isolated yield. The formation of R''_3N sheds light on the reaction mechanism.

Table 2. Pd-Catalyzed Reaction of Dibromides 1 with Cyclic Amines



We then applied acyclic secondary amines R^1R^2NH possessing two different substituents with the aim of investigating the chemoselective cleavage of C(sp^3)–N bonds. As shown in Table 4, when dibromide **1a** was treated with Me(Et)NH, the *N*-ethylpyrrole derivative **3a** was obtained in 65% isolated yield as the only pyrrole derivative product. Obviously, selective cleavage of the Me–N bond in Me(Et)NH took place. In the case of Et(Pr)NH, a 2:3 mixture of the two pyrrole derivatives **3a** and **3b** was formed. When Me(Ph)NH was used, the cleavage took place exclusively at the weaker Me–N bond (the bond energy is 71.4 kcal/mol for Me–N vs 100.1 kcal/mol for Ph–N),[12a,b] affording the corresponding *N*-phenylpyrrole derivative **3j** in 57% isolated yield. In addition, the tertiary amine Me_2NPh was formed in 75% GC yield. In contrast, when Et(Ph)NH was used, no remarkable reaction took place. These results demonstrate that the bulkiness of the N-substituent and the C–N bond energy determine which C–N bond in R^1R^2NH is more readily cleaved.[12] The formation of Me_2NPh again sheds light on the reaction mechanism.

Table 3. Pd-Catalyzed Reaction of Dibromides 1 with Dialkylamines R''_2NH

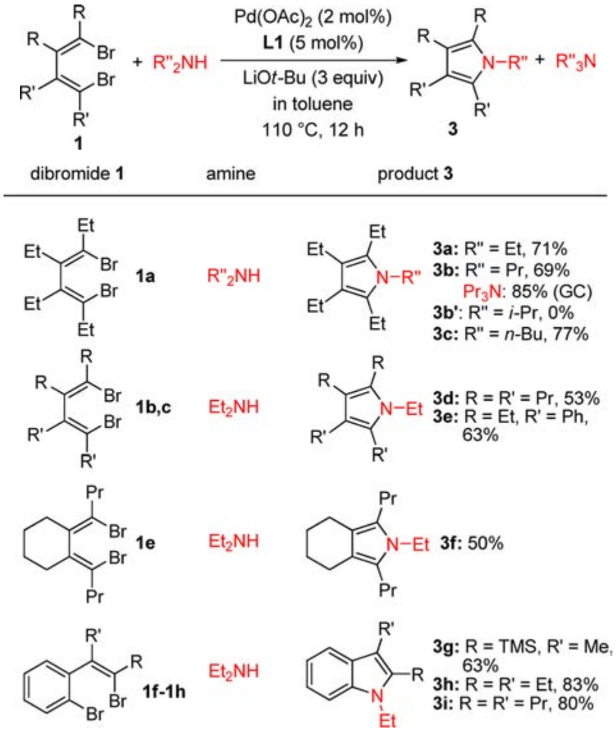
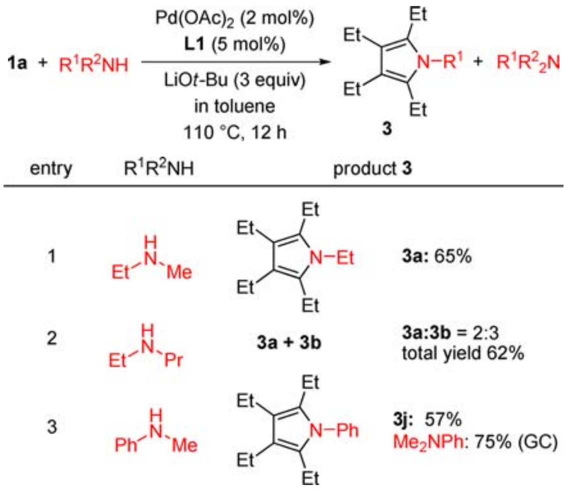
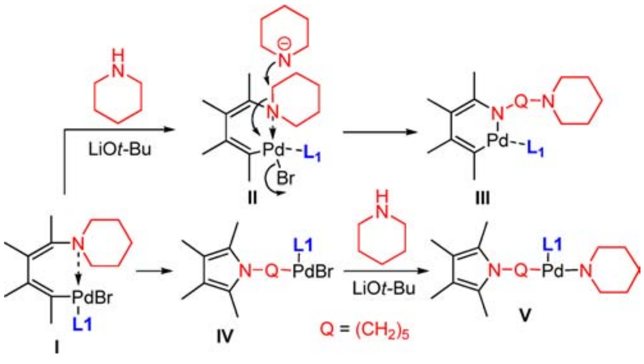


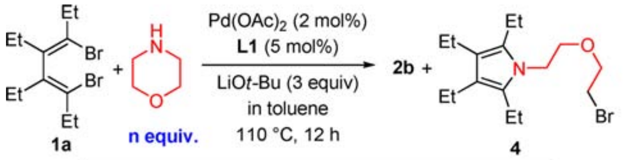
Table 4. Selectivity of Amines R^1R^2NH with Two Different Substituents



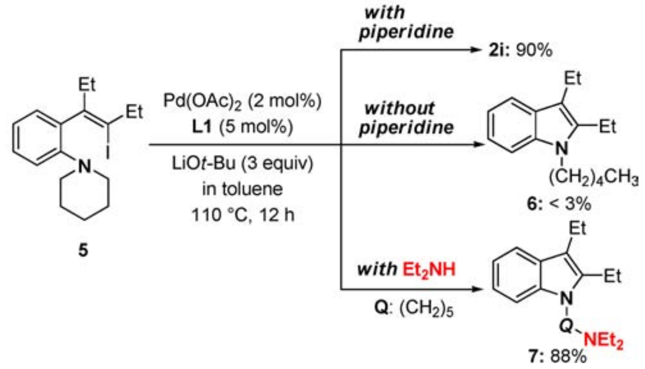
Scheme 1. Proposed Key Intermediates



Scheme 2. Mechanistic Study

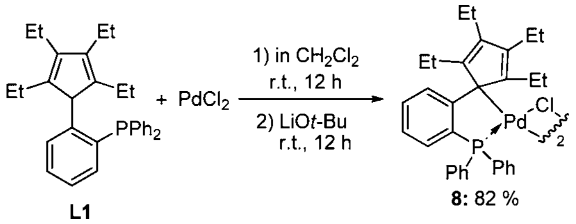


morpholine **n** equivalents	yield of **2b**	yield of **4**
n = 5	76%	trace
n = 2	52%	11%
n = 1	27%	19%



It is obvious that the new type of mixed P–olefin ligand is very effective for this Pd-catalyzed coupling process. However, it is not clear yet how this ligand works together with the palladium. Scheme 1 shows proposed key intermediates. Intermediate **I** would be formed from dibromide **1** and a secondary amine via an oxidative addition/amination/oxidative addition process.[13] Nucleophilic attack of piperidine anion on intermediate **I** would generate six-membered palladacycle **III**, which could then undergo reductive elimination to form the product. Although this mechanism is readily acceptable, an alternate path via intermediates **IV** and **V** is also possible[14,15] since compound **4**, which might be formed via reductive elimination of **IV**,[15] was obtained when a smaller amount of morpholine was used (Scheme 2). Under the same reaction conditions, compound **5** (a precursor of **I**) gave **2i** in 90% isolated yield with piperidine. In sharp contrast, no formation of **2i** was observed without piperidine; a trace amount of deiodination product and a small amount (<3% yield) of **6** were observed. When Et$_2$NH was used, indole derivative **7** was obtained. These results indicate that although the proposed intermediate **IV** is possible, its formation is slow and would be facilitated by its subsequent reaction with the amine.

Furthermore, as shown in eq 1, Pd–**L1** complex **8** was obtained and structurally characterized (see the SI for details).



(1)

Complex **8** is a dimer with two bridging chloride atoms. The five-membered cyclometalated ring is puckered, and the C_σ–Pd–P bite angle is 84.7(3)°. The length of the Pd–C_σ bond is 2.090(10) Å, similar to those in other five-membered azapalladacycles.[16] Notably, **8** (2 mol %) efficiently catalyzed the couplings of piperidine with **1a** and **1g** to give **2a** and **2i** in 62 and 83% isolated yields, respectively.

In summary, we have developed the first transition-metal-catalyzed cleavage of C(sp^3)–N bonds in secondary amines. A new type of cyclopentadiene–phosphine ligand was synthesized and found to promote the efficiency of this catalytic process remarkably. This finding represents an unprecedented route for the synthesis of a wide variety of pyrrole and indole derivatives with useful N-substitution.[17] Further studies of the reaction mechanism and synthetic applications are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, X-ray data for **L1** and **8** (CIF), and scanned NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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