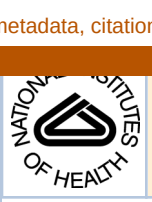

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Simple, Efficient Protocols for the Pd-Catalyzed Cross-Coupling Reaction of Aryl Chlorides and Dimethylamine

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Abstract

Simple and efficient procedures for the Pd-catalyzed cross-coupling reaction of aryl chlorides and dimethylamine are described. At room temperature with a strong base, *t*-BuXPhos is employed as the supporting ligand; at 110 °C with a weak base, XPhos is employed as the supporting ligand. In each of these cases, commercially available solutions constitute the source of the dimethylamine, and recently disclosed precatalysts constitute the source of the ligand and Pd. This work further expands the utility of these precatalysts in reactions that benefit from an easily activated source of $L_1Pd(0)$.

Biarylmonophosphine ligands are components of some of the most active catalytic systems for the formation of C(aryl)–N bonds (Figure 1).[1] We recently disclosed a new class of palladium precatalysts based upon biarylmonophosphines that is easily activated and ensures the formation of the active mono-ligated Pd(0) complex.[2, 3] Activation of these precatalysts is achieved by deprotonation of the amine complex, followed by the reductive elimination of a molecule of indoline (Scheme 1). These precatalysts are particularly useful in situations where reactions must be conducted under mild conditions that normally preclude the efficient generation of Pd(0), or where it is necessary to generate the active Pd(0) species in the absence of potentially inhibitory ligands such as dba[4] or PPh_3.[2, 5, 6]

Dimethylaniline is a common subunit of biologically active organic compounds.[7] In light of the ubiquity of $Ar–NMe_2$ groups in the substructure of biologically interesting molecules, we were surprised that there was no general process available for the Pd-catalyzed C–N bond-forming cross-coupling reaction between dimethylamine and an aryl halide.[8] Herein, we report efficient, general, and experimentally simple procedures to effect the cross-coupling of aryl chlorides and dimethylamine using the recently reported precatalysts. One procedure employs the *t*-BuXPhos-derived precatalyst (**6**) and a strong base at room temperature. The second procedure employs the XPhos version of the precatalyst (**7**) and a weak base at 110 °C.

Using precatalysts derived from biarylphosphines **1**-**5**, we attempted the direct cross-coupling reaction of dimethylamine and 4-chloroanisole. In these reactions, a 2 M solution of dimethylamine in THF was employed in combination with a 1 M solution of LHMDS in THF at room temperature. As shown in Table 1, the *t*-BuXPhos precatalyst (**6**) was most active, with complete conversion of 4-chloroanisole observed in less than 20 minutes. The XPhos and RuPhos precatalysts (**7** and **10**, respectively) can also be successfully employed

under these conditions, although reaction times in excess of 5 h are required to achieve complete conversion to product.

Based upon our success in using precatalyst **6** to effect the cross-coupling of dimethylamine and 4-chloroanisole, we employed it in cross-coupling reactions of dimethylamine and a variety of aryl and heteroaryl chlorides. Using 1 mol % Pd, we found that the cross-coupling reactions proceed efficiently with deactivated aryl chlorides (entry 1), *ortho*-substituted aryl chlorides (entry 4), as well as a variety of heteroaryl chlorides (entries 3, 5-7). All of these reactions were complete in less than 2 hours at room temperature. The solutions of dimethylamine and LHMDS used in these reactions are commercially available and were used as received (See Supporting Information).

Because LHMDS is not compatible with substrates bearing base-sensitive functional groups, we also investigated conditions for the arylation of dimethylamine that would permit the use of a weak base. Although the *t*-BuXPhos precatalyst (**6**) created the most efficient catalytic system at room temperature, we found that the XPhos precatalyst (**7**) afforded the optimal catalytic system with weak bases at elevated temperatures. Using 2 mol % **7** with K_3PO_4•H_2O, cross-coupling reactions of aryl chlorides and dimethylamine were performed efficiently at 110 °C (Table 3). We found that the use of rigorously anhydrous conditions leads to drastically diminished yields. Employing K_3PO_4•H_2O is required to obtain consistent yields. Under these conditions, potentially base-sensitive functional groups can be tolerated (entries 4 and 6). Additionally, dimethylamine can be successfully cross-coupled to deactivated aryl and heteroaryl chlorides (entries 1 and 5, respectively) using the combination of a weak base and an elevated temperature. Although no problems were observed during the course of these reactions, a blast shield should be employed as an additional precaution when conducting these sealed, high temperature reactions.

In summary, we have developed simple procedures for the efficient cross-coupling reaction of dimethylamine and aryl and heteroaryl chlorides. Separate methods have been developed that use a strong base at room temperature and a weak base at an elevated temperature. These procedures constitute the first general methods to form dimethylanilines via the cross-coupling reaction of aryl halides and dimethylamine. Commercially available reagents were exclusively used in these reactions. Additionally, palladacyclic precatalysts were employed as sources of highly active, mono-ligated Pd(0).[3] Such palladacycles are easily activated and permit the formation of Pd(0) complexes in the absence of potentially inhibitory ligands such as dba and PPh_3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1 a). Jiang, L.; Buchwald, SL. Metal-Catalyzed Cross-Coupling Reactions. 2nd ed. de Meijere, A.; Diederich, F., editors. Wiley-VCH; Weinheim: 2004. b) Surry DS, Buchwald SL. Angew. Chem. Int. Ed. 2008; 47:6338.

2. Biscoe MR, Fors BP, Buchwald SL. J. Am. Chem. Soc. 2008; 130:6686. [PubMed: 18447360]

3. Precatalysts **7** and **9** are currently commercially available from Strem. We expect **6** to be available in the near future.

4. Amatore C, Broeker G, Jutand A, Khalil F. J. Am. Chem. Soc. 1997; 119:5176.

5. Fors BP, Watson DA, Biscoe MR, Buchwald SL. J. Am. Chem. Soc. 2008; 130:13552. [PubMed: 18798626]

6. Martin R, Buchwald SL. Org. Lett. 2008; 10:4561. [PubMed: 18808127]

7. A Scifinder search generated approximately 40,000 hits for molecules containing the Ar–NMe_2 subunit, whose biological activities have been studied.

8 a). To the best of our knowledge, there have been only 4 examples of dimethylaniline formation via the direct Pd-catalyzed C–N cross-coupling reaction of dimethylamine and an aryl halide: Hosokawa S, Ogura T, Togashi H, Tatsuta K. Tetrahedrom Lett. 2005; 46:333. b) Thanh NC, Ikai M, Kajioka T, Fujikawa H, Taga Y, Zhang Y, Ogawa S, Shimada H, Miyahara Y, Kuroda S, Oda M. Tetrahedron. 2006; 62:11227. c) Joubert N, Pohl R, Klepetarova B, Hocek M. J. Org. Chem. 2007; 72:6797. [PubMed: 17665955] d) Li JJ, Wang Z, Mitchell LH. J. Org. Chem. 2007; 72:3606. [PubMed: 17417910]

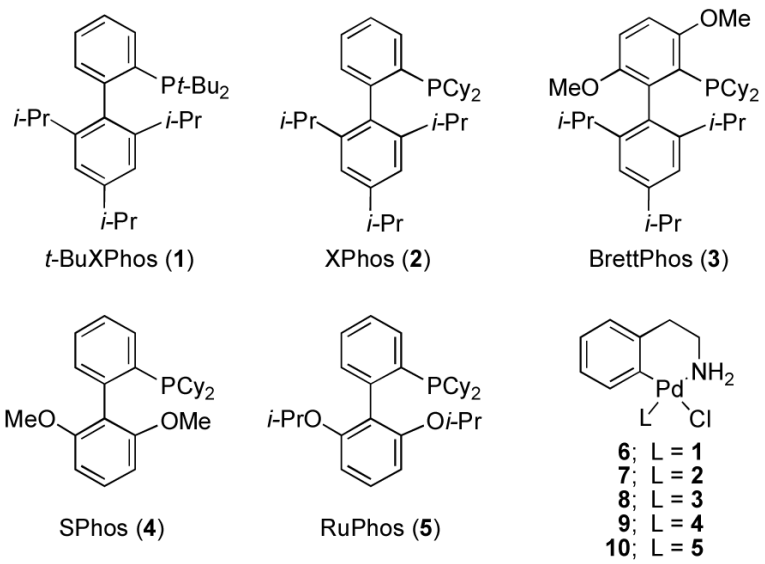
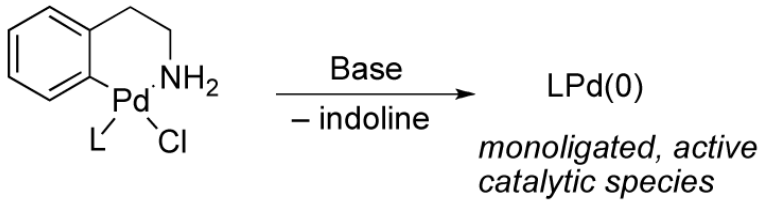


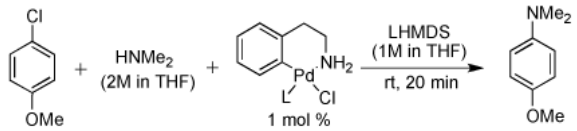
Figure 1.



Scheme 1.
Base-Mediated Activation of Precatalysts 6-10.

Table 1

Ligand Screen in the Cross-Coupling of Dimethylamine and 4-Chloroanisole at Room Temperature.

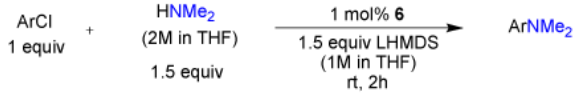


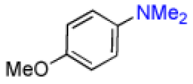
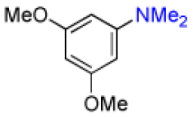
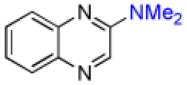
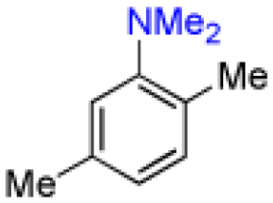
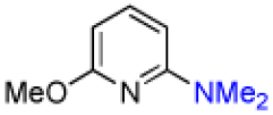
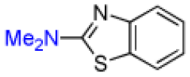
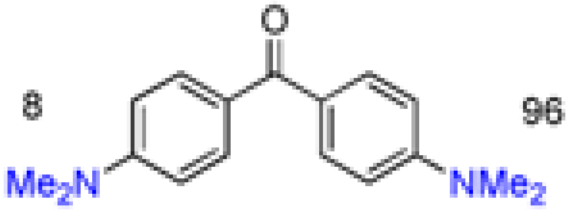
Entry	Precatalyst	Conversion[a] (%)
1	*t*-BuXPhos; **6**	100
2	XPhos; **7**	20
3	BrettPhos; **8**	1
4	SPhos; **9**	16
5	RuPhos; **10**	25

[a] Determined by GC

Table 2

Cross-Coupling Reactions of Dimethylamine and Aryl Chlorides with LHMDS at Room Temperature.



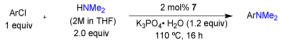
entry	product	yield[a] (%)
1		99
2		97
3		88
4		81[b]
5		97
6		99
7		96
8		96

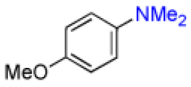
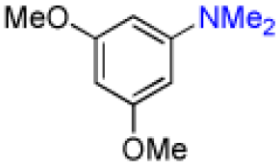
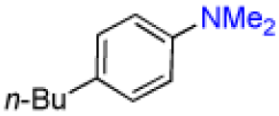
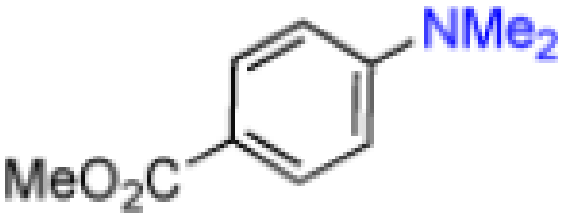
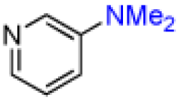
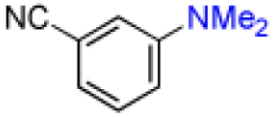
[a] Average isolated yields from 2 runs.

[b] Volatile product.

Table 3

Cross-Coupling Reactions of Dimethylamine and Aryl Chlorides using $K_3PO_4 \cdot H_2O$ at 110 °C.



entry	product	yield[a] (%)
1		83
2		90
3		95
4		82[b]
5		70[c]
6		94

[a] Average isolated yields of 2 runs.

[b] 6 h reaction time.

[c] Volatile product.