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Umpolung Amination: Nickel-Catalyzed Coupling Reactions of *N,N*-Dialkyl-*N*-chloroamines with Diorganozinc Reagents

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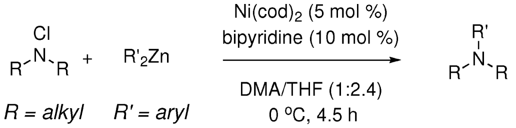
Nitrogen−carbon bond-forming reactions are important for their use in the synthesis of natural products and medicinal chemistry targets, as demonstrated by the breadth of research interest in this area in recent years.[1] The Buchwald−Hartwig amination, cross-coupling of aryl halides with amines, is an efficient method for this bond construction.[1b−d] An umpolung strategy, reaction of an electrophilic nitrogen source with a nucleophilic organometallic reagent, would provide a complementary method for the formation of anilines under nonbasic conditions. We report the use of *N*,*N*-dialkyl-*N*-chloroamines as electrophilic nitrogen sources for the amination of diarylzinc reagents in the presence of a Ni catalyst (eq 1). A one-pot procedure for chlorination and coupling of the amine with diarylzinc is also presented.



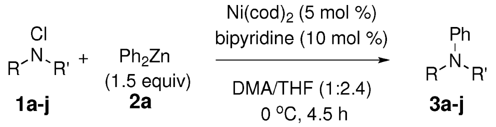
(1)

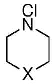
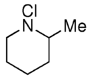
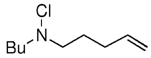
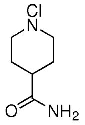
Umpolung amination reactions have received significant attention recently because of the utility an electrophilic amination provides in forming N−C bonds.[2] Johnson and co-workers have reported Cu- and Ni-catalyzed amination of organozinc reagents using *N*,*N*-dialkyl-*O*-acyl hydroxylamine derivatives.[3,4] Lei and co-workers recently published a Cu-catalyzed arylation of *N*-chloroamides with phenylboronic acid derivatives to form secondary amides.[5,6]

The coupling of *N*-chloroamines would be a significant advance in umpolung amination because these substrates are straightforward to prepare and isolate by treatment of the corresponding amines with bleach followed by extraction.[7] Prior investigations into coupling of *N*-chloroamines with organometallic reagents provided the desired anilines in low yields (10−20%).[3a,5] We hypothesized, however, that under the appropriate reaction conditions, oxidative addition of Ni(0) with the chloroamine would occur, allowing for cross-coupling to form the requisite C−N bond.[8,9] Gratifyingly, we found that the reaction of *N*,*N*-dibutyl-*N*-chloroamine (**1a**) with phenylzinc chloride, using a bipyridine-ligated Ni catalyst, afforded the desired product in modest yield (Table 1, entry 1).

The reaction conditions were optimized for the coupling of **1a**. Several solvents were surveyed, and a DMA/THF solvent mixture was found to be optimal.[10] A variety of ligands were examined, with bipyridine producing the highest yield.[11] Phosphines were ineffective as ligands for this reaction.[12] Either phenylzinc bromide or diphenylzinc could be utilized as a coupling partner (entries 2 and 3). The amount of diphenylzinc could be reduced to 1 equiv with increased reaction time (entry 4); use of less diphenylzinc resulted in a lower yield because of competitive formation of biphenyl as a byproduct under the reaction conditions. Control experiments revealed that the bipyridine-ligated Ni catalyst was necessary for the reaction to proceed.[13]

Table 1. Amination of Diorganozinc Reagents



entry	substrate		product	yield (%)[a]
1[b]	ClNBu$_2$	**1a**	**3a**	55
2[c]		**1a**	**3a**	87
3		**1a**	**3a**	90
4[d]		**1a**	**3a**	90
5		**1b**, X = O	**3b**	86
6		**1c**, X = CH$_2$	**3c**	82
7		**1d**, X = N(Boc)	**3d**	87
8[e]		**1e**, X = NCl	**3e**	73
9	ClNMeBu	**1f**	**3f**	63
10	ClNMeBn	**1g**	**3g**	49
11		**1h**	**3h**	51
12		**1i**	**3i**	70
13		**1j**	**3j**	60

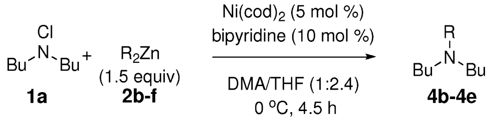
[a] Isolated yield after column chromatography. [b] Reaction conditions: PhZnCl (2.5 equiv), DMA/THF (1:2), rt, 16 h. [c] Reaction conditions: PhZnBr (1.6 equiv), DMA/THF (1:2.4), 0 °C, 8 h. [d] Reaction conditions: Ph$_2$Zn (1 equiv), DMA/THF (1:1.6), 0 °C, 6 h. [e] Using 3 equiv of Ph$_2$Zn.

With an optimized catalyst system in hand, a number of arylations of *N*,*N*-dialkyl-*N*-chloroamines were examined. Acyclic as well as cyclic *N*-chloroamines proved to be effective in this reaction. Boc-protected nitrogens were well-tolerated in this reaction (entry 7). The diminished yield with *N*-methyl-*N*-chlorobenzylamine (**1g**) was attributed to the formation of benzaldehyde during the course of the reaction.[14] Electron-poor *N*-chloroamines such as *N*-chloroamides and *N*-chlorosuccinimide (NCS) did not undergo coupling under the current reaction conditions.[15]

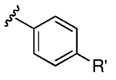
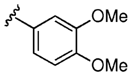
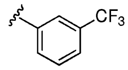
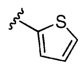
The functional-group tolerance of this reaction is highlighted in entries 12 and 13. Substrates with a terminal alkene, such as **1i**, were tolerated in this reaction. Coupling of the *N*-chloroamine occurred, and no cyclization with the olefin was observed. This result contrasts with previous work by Göttlich and co-workers, who reported that under transition metal-catalyzed conditions, *N*-chloroamines were found to cyclize onto terminal olefins and rearrange to form substituted piperidines.[16,17] Substrate **1j** with a

10.1021/ja907038b CCC: $40.75

Table 2. Amination of Diorganozinc Reagents

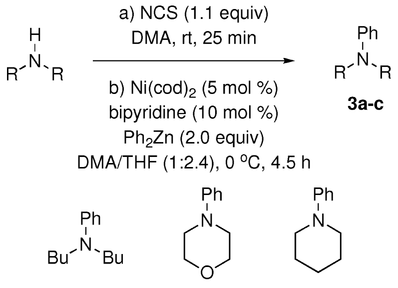


1a **2b-f** **4b-4e**

entry	R	substrate	product	yield (%)[a]
1		**2b**, R' = Me	**4b**	80
2		**2c**, R' = MeO	**4c**	95
3		**2d**, R' = F	**4d**	76
4		**2e**	**4e**	81[b]
5		**2f**	**4f**	82
6		**2g**	**4g**	59

[a] Isolated yield after column chromatography. [b] Yield determined by ^1H NMR spectroscopy by comparison to an internal standard.

Scheme 1. One-Pot Chlorination and Arylation of Amines



3a-c

79 % 78 % 81 %

free amide was also a competent substrate, affording the tertiary amine in good yield.[18]

An array of diarylzinc reagents were found to be effective under the reaction conditions (Table 2). Electron-donating substituents (entries 1, 2, and 4) as well as electron-withdrawing substituents (entries 3 and 5) were tolerated, providing coupling products in good yields. A meta-substituted diarylzinc reagent (entry 5) and a heterocyclic organozinc (entry 6) also reacted to afford the corresponding tertiary amines in good yield.

Development of a one-pot chlorination and arylation reaction would be attractive for certain applications, as isolation of the *N*-chloroamines would no longer be necessary. In preliminary studies, we observed that NCS did not undergo the Ni-catalyzed coupling reaction. On the basis of this observation, we hypothesized that NCS could oxidize the amine to the *N*-chloroamine and that the byproduct, succinimide, would be a spectator in the subsequent coupling reaction. To test this hypothesis, dibutylamine was reacted with NCS for 25 min, after which catalyst and a solution of diphenylzinc in THF were added (Scheme 1). The desired aniline **3a** was isolated in 79% yield. The one-pot procedure was also applied in coupling of morpholine and piperidine, yielding the corresponding anilines in 78 and 81% yields, respectively. Therefore, the reaction is adaptable, allowing amination of diarylzinc reagents to be accomplished using either amines or *N*-chloroamines as starting materials.

The Ni-catalyzed amination of *N*-chloroamines with diorganozincs provides a system for the formation of tertiary anilines. This umpolung strategy for aniline synthesis employs a readily available catalyst and ligand and provides a mild and convenient complement to amination reactions of aryl halides. Either isolated *N*-chloroamines or a one-pot procedure starting from the corresponding amine and NCS can be utilized, increasing the versatility of the method. Further work in our laboratories will focus on expanding the scope of this reaction to include primary and aryl *N*-chloroamines as well as studying the mechanism of this transformation.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) For Cu-catalyzed amination using hydroxylamines, see: (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364. (c) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (d) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.

(4) For Ni-catalyzed amination using hydroxylamines, see: Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799.

(5) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. This method was *not* effective with **1a** (11% yield).

(6) *N*-Arylsuccinimide has been observed as a minor byproduct (8% yield) in NCS-mediated, Pd-catalyzed oxidative functionalization of C−H bonds. See: Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.

(7) *N*-Chloroamines can be prepared by treating the corresponding amines with bleach. See: Zhong, Y.-L.; Zhou, H.; Gauthier, D. R.; Lee, J.; Askin, D.; Dolling, U. H.; Volante, R. P. *Tetrahedron Lett.* **2005**, *46*, 1099.

(8) Our working hypothesis was based on a cross-coupling mechanism for the transformation that would be initiated by oxidative addition of the Ni catalyst into the N−Cl bond by a single-electron-transfer (SET) mechanism. For studies of oxidative addition of alkyl halides by an SET mechanism, see: (a) Stille, J. K.; Cowell, A. B. *J. Organomet. Chem.* **1977**, *124*, 253. (b) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brancond, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175. For the reaction of NBS with Ni(0) complexes, see: (c) Weston, C. W.; Verstuyft, A. W.; Nelson, J. H.; Jonassen, H. B. *Inorg. Chem.* **1977**, *16*, 1313. For reductive elimination of Ni amido complexes, see: (d) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421.

(9) A viable alternative mechanism involves S_N2 attack of an arylnickel complex on the *N*-chloroamine (see ref 3d).

(10) DMA appears to play a key role in the reaction.

(11) See the Supporting Information for details of the ligand screen.

(12) *N*-Chloroamines are known to oxidize phosphines. See: Sopchik, A. E.; Bentrude, W. G. *Tetrahedron Lett.* **1980**, *21*, 4679.

(13) In the absence of $Ni(cod)_2$ and/or bipyridine, reaction of **1a** with diphenylzinc under the standard reaction conditions afforded <5% yield of **3a**.

(14) ^1H NMR spectroscopy of the unpurified reaction mixture revealed that benzaldehyde was formed in 23% yield in this reaction. Its formation is tentatively attributed to β-hydride elimination from a Ni amido complex to form *N*-methylbenzaldimine, which was hydrolyzed upon aqueous workup.

(15) Electron-withdrawing substituents on N substantially slow the reductive elimination from arylpalladium amido complexes. See: Yamashita, M.; Cuevas Vicario, J. V.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 16347.

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(17) Cyclization of these substrates frequently proceeds by a radical mechanism (see ref 16c).

(18) Preparation of **1j** takes advantage of the chemoselectivity of the *N*-chlorination reaction toward the more nucleophilic nitrogen.

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