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Zinc Trimethylsilylamide as a Mild Ammonia Equivalent and Base for the Amination of Aryl Halides and Triflates

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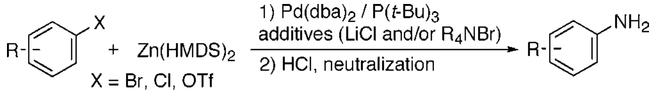
ABSTRACT



We report that Zn[N(SiMe$_3$)$_2$]$_2$ is a mild ammonia equivalent and base for the palladium-catalyzed amination of aryl halides and triflates. In contrast to LiN(SiMe$_3$)$_2$, the combination of Zn[N(SiMe$_3$)$_2$]$_2$ and LiCl coupled with aryl halides and triflates containing base-sensitive functionality in high yields. In addition, aryl bromides coupled with aryl and alkylamines with the combination of Zn[N(SiMe$_3$)$_2$]$_2$ and LiCl as base. These aminations occurred without racemization of the enolizable stereocenter of an optically active ester.

Palladium-catalyzed C−N bond formation has developed into a general and efficient way to prepare arylamines from aryl halides.[1−5] While a variety of amines and other nitrogen nucleophiles undergo this reaction in the presence of base, ammonia does not form primary arylamines. Thus, reactions have been conducted with ammonia surrogates, such as allylamine[6] or benzophenone imine.[7,8] Recently, we reported the synthesis of primary arylamines catalyzed by Pd(dba)$_2$ and P(t-Bu)$_3$ with lithium bis(trimethylsilyl)amide (LiN(SiMe$_3$)$_2$) as an ammonia equivalent. This reagent is inexpensive, and the aryl silylamine is easily deprotected.[9] Buchwald reported a similar coupling with catalysts containing 2-phosphinobiphenyl ligands.[10] While LiN(SiMe$_3$)$_2$ coupled with a range of aryl halides under mild conditions with low catalyst loading, the strong basicity of the reagent prevented reactions with aryl halides bearing base-sensitive functional groups or enolizable hydrogens.[9,10]

Recently, we developed conditions for the coupling of zinc enolates with aryl halides.[11] The functional group compatability of the α-arylation of carbonyl compounds with zinc enolates was greater than that with alkali metal enolates.[12] With this result in mind, we sought conditions to use zinc

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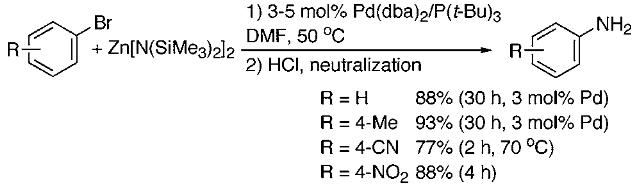
10.1021/ol050141b CCC: $30.25

Scheme 1



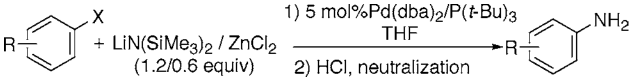
bis(trimethylsilyl)amides and perhaps zinc aryl and alkylamides to improve the tolerance of the coupling to form C−N bonds to sensitive functionality. We report the development of conditions to conduct the coupling of aryl halides and triflates with zinc silylamide as reagent and the coupling of aryl and alkylamines with zinc silylamide as base. These conditions increase the scope of the synthesis of primary arylamines and help alleviate racemization of enolizable stereocenters during coupling of alkyl and arylamines.

We first investigated the potential of zinc bis(hexamethyldisilazide) as a reagent for the synthesis of primary arylamines. To do so, we conducted reactions with a series of ligands in different media (see the Supporting Information). In the presence of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ as catalyst, the reaction of $Zn[N(SiMe_3)_2]_2$ with aryl bromides in DMF formed the corresponding silylamine derivatives upon mild heating. The primary arylamines were isolated after hydrolysis with acid (Scheme 1). Under these conditions, the reaction proceeded with aryl halides possessing functionality, such as cyano and nitro groups, that were incompatible with $LiN(SiMe_3)_2$ as reagent.

Although these results showed that the use of $Zn[N(SiMe_3)_2]_2$ could create a mild route to primary arylamines, reactions of $Zn[N(SiMe_3)_2]_2$ required higher concentrations of catalyst or longer reaction times than those of $LiN(SiMe_3)_2$.[8] Fortunately, reactions of the combination of $LiN(SiMe_3)_2$ and $ZnCl_2$, which we examined originally as a means to generate $Zn[N(SiMe_3)_2]_2$ in situ, revealed two sets of conditions to conduct the couplings at room temperature with less catalyst than the reactions of $Zn[N(SiMe_3)_2]_2$ alone.

The first set of conditions involves the reaction of a zinc silylamide generated in situ by combining $LiN(SiMe_3)_2$ and $ZnCl_2$ prior to the addition of the aryl halide. The results of reactions under these conditions (Table 1) show that the reaction is suitable for the conversion of a series of base-sensitive aryl halides to the corresponding amines. The reaction of $LiN(SiMe_3)_2$ and $ZnCl_2$ with 1-bromo-4-nitrobenzene (entry 1 and 2), 1-bromo-3-nitrobenzene (entry 3), 4-bromobenzonitrile (entry 4), and methyl and ethyl 4-bromobenzoate (entry 5 and 6) occurred in excellent yield.

Table 1. Coupling of Aryl Halides and $LiN(SiMe_3)_2$ in the Presence of $ZnCl_2$



entry	R	X	*T* (°C)	time (h)	isolated yield (%)
1	4-NO_2	Br	rt[a]	2	95
2[b]			50	8	90
3	3-NO_2	Br	rt	2	91
4	4-CN	Br	rt	1	90
5	4-CO_2Et	Br	rt	3	90
6	4-CO_2Me	Br	rt	2	91
7	4-NO_2	Cl	50	4	92
8	4-CN		50	12	80
9	4-Me	Br	rt	18	(71)[c]

[a] 25 °C. [b] The amount of $Pd(dba)_2$ was 2 mol %. [c] Conversion.

These reactions are easily executed without a drybox because the silylamide and $ZnCl_2$ are commercially available as THF solutions. Further, one can conveniently store a stock solution of $LiN(SiMe_3)_2$ and $ZnCl_2$ in THF (see the Supporting Information). The reaction described in entry 1 of Table 1 conducted with a stock solution of $LiN(SiMe_3)_2$ and $ZnCl_2$ in THF stored for 2 days formed 4-nitroaniline in a 87% isolated yield.

Although the conditions of the reactions in Table 1 are convenient and convert base-sensitive, activated aryl halides to the corresponding anilines, the rates of reactions of unactivated aryl halides were slower than desired. For example, 4-bromotoluene reacted with $LiN(SiMe_3)_2$ and $ZnCl_2$ (entry 9 of Table 1) to convert only 71% of the aryl bromide after 18 h. By comparison, the reaction of $LiN(SiMe_3)_2$ was complete in only 6 h. Thus, we sought conditions to further increase the reactivity of the zinc silylamides.

For reasons we do not yet understand, the palladium-catalyzed reactions of aryl halides with the combination of $Zn[N(SiMe_3)_2]_2$ and LiCl, which contains the same stoichiometry as $LiN(SiMe_3)_2$ and $ZnCl_2$, occurred faster than those of $LiN(SiMe_3)_2$ and $ZnCl_2$. The functional group tolerance of the reactions of $Zn[N(SiMe_3)_2]_2$ and LiCl remained as high as that of the reactions of $Zn[N(SiMe_3)_2]_2$ alone or that of the reactions of the combination of $LiN(SiMe_3)_2$ and $ZnCl_2$.

The reactions of $Zn[N(SiMe_3)_2]_2$ and LiCl occurred in the highly polar DMF and the less polar THF, but reactions in THF were faster than those in DMF. The reaction of 4-bromobenzonitrile with $Zn[N(SiMe_3)_2]_2$ and added LiCl in DMF was 90% complete (87% yield by GC) in 12 h at 50 °C with 2 mol % catalyst, while the same reaction in THF was complete in only 45 min at 50 °C and within 3 h at ambient temperature.

Examples of the reaction of $Zn[N(SiMe_3)_2]_2$ and LiCl with electron-rich and electron-poor aryl bromides to form the corresponding primary arylamines are shown in Table 2. These reactions occurred in high yield in the presence of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ as catalyst. Like those of $LiN(SiMe_3)_2$, these reactions did not occur with ortho-substituted aryl halides, due to the bulk of the reagent. However, bromoarenes that did not react with the highly basic $LiN(SiMe_3)_2$, such as bromobenzonitrile and bromonitrobenzene (entries 1 and 2), reacted in high yield with $Zn[N(SiMe_3)_2]$ and LiCl.

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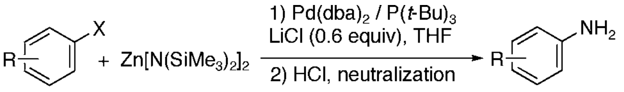
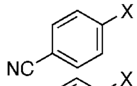
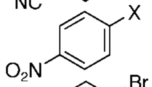
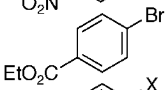
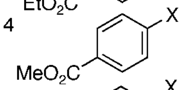
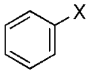
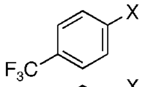
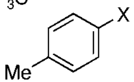
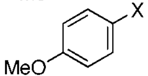
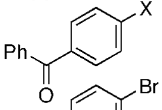
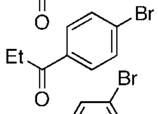
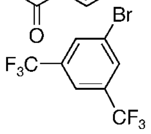
Table 2. Coupling of Aryl Halides and $Zn[N(SiMe_3)_2]_2$ in the Presence of LiCl Using $Pd(dba)_2$ and $P(t\text{-}Bu)_3$[a]



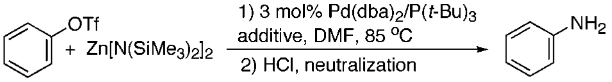
entry	aryl bromide		catalyst loading	temp	time	isolated yield
1		X=Br X=Br X=Cl	2 mol% 1 mol% 1 mol%	50 °C 50 °C 90 °C	45 min 2 h 6 h	97% 95% 97%
2		X=Br X=Cl	1 mol% 1 mol%	50 °C 90 °C	2 h 3 h	95% 92%
3			1 mol%	70 °C	3 h	93%
4		X=Br X=Cl	1 mol% 1 mol%	50 °C 90 °C	6 h 18 h	91% 85%
5		X=Br X=Cl	1 mol% 1 mol%	50 °C 90 °C	6 h 12 h	91% 90%
6		X=Br X=Cl	2 mol% 1 mol%	50 °C 90 °C	4 h 18 h	90% 88%
7		X=Br X=Cl	2 mol% 1 mol%	50 °C 90 °C	9 h 12 h	93% 90%
8		X=Br X=Cl	2 mol% 1 mol%	70 °C 90 °C	12 h 24 h	87% 88%
9		X=Br X=Cl	1 mol% 1 mol%	70 °C 90 °C	12 h 12 h	93% 80%
10			1 mol%	50 °C	6 h	92%
11			2 mol%	50 °C	6 h	94%

[a] Reactions were conducted with 0.50 mmol of ArX, 0.30 mmol of $Zn[N(SiMe_3)_2]_2$, 0.30 mmol of LiCl, and a 1:1 ratio of Pd/L in 1.0 mL of THF.

Although bromoacetophenone did not react, 4-bromopriopiophenone did react in high yield without formation of products from enolate coupling (entry 10). Thus, couplings of the zinc amides can occur with substrates containing slightly hindered enolizable hydrogens. Electron-neutral bromotoluene and electron-rich bromoanisole also reacted in high yield.

The coupling of aryl triflates with $LiN(SiMe_3)_2$ in the presence of any catalyst and the coupling of aryl triflates with amines in the presence of palladium catalysts containing tri-*tert*-butylphosphine have not been reported.[13] The accelerating affect of added halides on the oxidative addition of phenyl triflate to a palladium(0) complex with a hindered monodentate phosphine[14] led us to test the coupling of aryl triflates with silylamides in the presence of added halides (Scheme 2). The reaction of phenyl triflate with $Zn[N(SiMe_3)_2]_2$ without any added halide formed only 5% of the arylsilylamine after 12 h at 85 °C. However, the same reaction conducted with added Bu_4NBr was complete in 6 h; 94% yield of aniline was isolated after hydrolysis. The same reaction with added LiCl occurred in high yield after 12 h. Because LiCl accelerated the reactions of $Zn[N(SiMe_3)_2]_2$ (vide supra) and Bu_4NBr accelerated the addition of PhOTf,[14] we tested reactions with a combination of the two salts. Although the ions must exchange in solution, the reactions with the combination of salts were compete in a shorter 3 h.

Scheme 2



no additive	5% (GC yield, 12 h)
Bu_4NBr (2 equiv)	94% (6 h)
LiCl + Bu_4NBr (1 equiv)	95% (3 h)
LiCl (2 equiv)	85% (12 h)

Table 3. Coupling of Aryl Triflates and $Zn[N(SiMe_3)_2]_2$ in the Presence of Halide Salts (Scheme 2)[a]

entry	R =	additive	time (h)	isolated yield (%)
1	*p*-tolyl	Bu_4NBr (2 equiv)	6	97
2		LiCl/Bu_4NBr (1 equiv)	4	97
3		LiBr (2 equiv)	12	89
4	*m*-tolyl	Bu_4NBr (2 equiv)	9	90
5		LiCl/Bu_4NBr (1equiv)	6	91
6	2-naphthyl	LiBr (2 equiv)	12	92
7		Bu_4NBr (2 equiv)	9	95
8		LiCl/Bu_4NBr (1 equiv)	3	93
9	4-MeOC_6H_4	Bu_4NBr (2 equiv)	24	89
10	3-MeOC_6H_4	Bu_4NBr (2 equiv)	24	85
11		LiCl/Bu_4NBr (1 equiv)	24	90
12	$3\text{-CF}_3C_6H_4$	Bu_4NBr (2 equiv)	6	91
13	4-CNC_6H_4	Bu_4NBr (2 equiv)	9	87
14	3-CNC_6H_4	Bu_4NBr (2 equiv)	12	70

[a] Reactions were conducted under the same conditions as those in Scheme 2: ArOTf (0.50 mmol), $Zn[N(SiMe_3)_2]_2$ (0.30 mmol), $Pd(dba)_2$ (0.015 mmol), $P(t\text{-}Bu)_3$ (0.015 mmol), DMF (1.0 mL), and additives.

Table 3 shows the results from reactions of various aryl triflates with $Zn[N(SiMe_3)_2]_2$ in the presence of added halides. In most cases, the highest yields were obtained from reactions conducted with a mixture of LiCl and Bu_4NBr, but good yields were also obtained from reactions with LiCl or Bu_4NBr alone. Aryl triflates with electron-withdrawing groups, such as trifluoromethyl or cyano, decomposed in the reactions conducted with added LiCl, but high yields were obtained from reactions of these aryl triflates with added Bu_4NBr.

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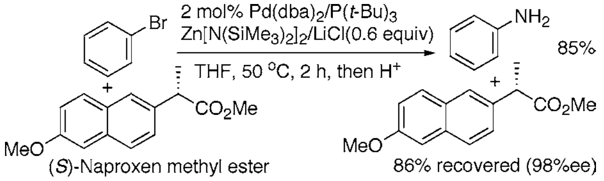
(14) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194.

Scheme 3



The coupling of aryl halides with basic reagents racemizes or epimerizes enolizable stereocenters. To determine if the zinc amides reduce the level of this racemization, we investigated the coupling of $Zn[N(SiMe_3)_2]_2$ in the presence of an optically active ester. For simplicity, we conducted the reaction of bromobenzene in the presence of the methyl ester of (*S*)-naproxen (Scheme 3). This reaction formed aniline in 85% yield without significantly racemizing the ester. The chiral ester was recovered (86%) in 98% enantiomeric excess. When the same reaction was conducted with $LiN(SiMe_3)_2$, the naproxen derivative was obtained in only 2% ee, and the aniline was formed in only 58% yield.

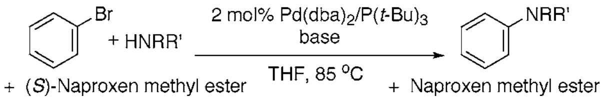
In addition to serving as a surrogate for ammonia, one could envision $Zn[N(SiMe_3)_2]_2$ as a weak base or a source of zinc amide for the coupling of amines with aryl halides. We have not investigated these reactions in detail, but preliminary data show that reactions of amines can be conducted with $Zn[N(SiMe_3)_2]_2$ under conditions that are less basic than those of reactions with other bases that induce the C−N coupling chemistry. Both aromatic and aliphatic amines couple under these conditions without competing transfer of the $N(SiMe_3)_2$ unit, and this selectivity suggests that this method may prove to be general.

The reaction of bromobenzene with aniline in the presence of 0.6 equiv of $Zn[N(SiMe_3)_2]_2$ and 2 mol % $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ in THF for 20 min at 85 °C or 2 h at 50 °C formed the corresponding arylamine in 88−91% yield. To determine the relative basicity of these conditions to those with alkoxide, carbonate and phosphate bases, we conducted related reactions of bromobenzene with aniline, morpholine and dibutylamine in the presence of the methyl ester of (*S*)-naproxen (Table 4).

The reaction of bromobenzene with aniline in the presence of alkoxide or Cs_2CO_3 as base at 85 °C led to nearly complete racemization of the ester. In contrast, the reaction of aniline with $Zn[N(SiMe_3)_2]_2$ or with K_3PO_4 as base at 85 °C occurred in good yields and with nearly complete retention of the stereochemistry of the ester. Although $Zn[N(SiMe_3)_2]_2$ is more expensive than K_3PO_4, the greater solubility of the zinc silylamide makes it suitable for assembly of reactions with stock solutions.

The reations of alkylamines in the presence of the different bases further distinguished reactions with the different bases (Table 4). The reaction of PhBr with morpholine or dibutylamine with the carbonate base at 85 °C formed the coupled product in good yield, but almost completely racemized the ester. The same reactions conducted with K_3PO_4 base also measurably racemized the ester. In contrast, the reaction with $Zn[N(SiMe_3)_2]_2$ as base formed the coupled product in good yield at either 50 or 80 °C, and at either temperature the naproxen derivative was recovered in high ee. The naproxen was recovered in 98% ee from the reaction of morpholine at 50 or 85 °C, and in 97% ee at 50 °C or 94% ee at 85 °C from the reaction of dibutylamine.

Table 4. Amination of Bromobenzene with Amines in the Presence of Chiral Ester



entry	amine	base (equiv)	time	yield of amine (%)	recovered naproxen ester (%) (% ee)
1[a]	$PhNH_2$	$Zn[N(SiMe_3)_2]_2$ (0.6)	20 min	91	98 (99% ee)
2		K_3PO_4 (2.5)	2 h	99	98 (97% ee)
3		Cs_2CO_3 (2.5)	2 h	92	90 (25% ee)
4[b]		NaOtBu (1.2)	2 h	32	63 (2% ee)
5[a]	morpholine	$Zn[N(SiMe_3)_2]_2$ (0.6)	6 h	87	95 (98% ee)
6		K_3PO_4 (2.5)	12 h	87	98 (87% ee)
7		Cs_2CO_3 (2.5)	18 h	87	76 (6% ee)
8[a,b,c]	Bu_2NH	$Zn[N(SiMe_3)_2]_2$ (0.6)	12 h	78	88 (97% ee)
9[c]		K_3PO_4 (2.5)	12 h	90	92 (88% ee)
10		Cs_2CO_3 (2.5)	12 h	90	93 (27% ee)

[a] LiCl (0.6 equiv) was added. [b] The reaction was conducted at 50 °C. [c] The reaction was conducted with 3 mol % catalyst.

Thus, we have shown that zinc bis(hexamethyldisilazide) is a mild ammonia surrogate and base for the amination of aryl halides. With $Zn[N(SiMe_3)_2]_2$ and added halide, the scope of substrates that undergo reaction to form silyl-protected anilines has been broadened to include aryl halides with base-sensitive functional groups and enolizable hydrogens. Further, the coupling of silylamides with aryl triflates occurred for the first time. Finally, we showed that the combination of $Zn[N(SiMe_3)_2]_2$ and added halide is mild enough as a base to allow coupling of aryl and alkylamines with aryl halides with minimal racemization of an additive with an enolizable stereocenter. Further studies on the scope of the reactions of silylamides are in progress.

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

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