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Communication

Palladium-Catalyzed Amination

Pd-PEPPSI-IPent^{Cl}-Catalyzed Amination Using Aminotriphenylsilane as an Ammonia Surrogate

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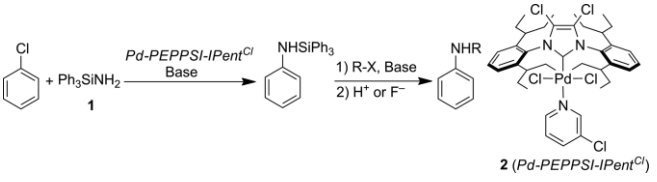
Abstract: Coupling of Ph_3SiNH_2 with aryl halides by using *Pd-PEPPSI-IPent*^{Cl} {dichloro(3-chloropyridyl)[4,5-dichloro-1,3-bis(2,6-dipent-3-ylphenyl)imidazol-2-ylidene]palladium(II)} yields triphenylsilyl-protected anilines. These triphenylsilyl protected anilines can be isolated, alkylated without over-alkylation, and the protecting group can be removed under mild acidic conditions or in the presence of fluoride to afford the secondary aniline product.

Introduction

In the past decade, the Pd-catalyzed coupling of primary alkylamines and ammonia with aryl halides and pseudo halides has been well developed.[1–8] Prior to the advent of catalysts for the direct amination with ammonia, a wide variety of ammonia equivalents were developed to obtain primary arylamines from aryl halides. The ammonia equivalents are first coupled to an aryl halide and the masking removed to yield the primary arylamine. Reagents that have been successfully used as ammonia equivalents include: *tert*-butyl sulfinamide,[9] allylamine,[10] benzophenone imine,[11,12] lithium bis(trimethylsilyl)amide (LiHMDS),[13] zinc bis(trimethylsilyl)amide (ZnHMDS),[14] and aminotriphenylsilane.[15]

While ammonia equivalents require additional synthetic operations compared to direct amination with ammonia, there are several advantages to their use. Ammonia equivalents are easier to handle than ammonia, they are not required in large excess, they do not readily undergo a second undesired coupling that plagues ammonia, and they are typically coupled under milder conditions than ammonia.

Aminotriphenylsilane was first disclosed by Buchwald's group in 2001 as a substitute for LiHMDS, which is too sterically demanding to couple with *ortho*-substituted aryl halides.[15] We envisaged that instead of immediately cleaving the silyl group off to yield the primary arylamine, the product could undergo alkylation before removing the silyl group, thereby mitigating over-alkylation concerns (Scheme 1).[16–29]



Scheme 1. Amination, alkylation, and silyl group removal.

Results & Discussions

The coupling of **1** with aryl chlorides was first attempted with a variety of bases commonly employed in Buchwald–Hartwig amination (Table 1). *Pd-PEPPSI-IPent*^{Cl} was selected as catalyst because it is known to be highly efficient for the amination and sulfination of sterically encumbered substrates.[30–33] While NaO*t*Bu gave conversion to product, the triphenylsilyl group of the reactant or product was slowly removed resulting in large amounts of 4-*tert*-butyl aniline and diarylamine. The bulkier iPr_3SiNH_2 was coupled successfully, but it also gave the same undesired products as **1**. LiHMDS was the most effective base for this reaction, likely because **1** is deprotonated prior to coordination to palladium.[15]

Reaction conditions were then optimized for the use of LiHMDS (Table 2). The reaction with **3**, which is slightly deactivated (i.e., the ring is electron-rich), went to completion in toluene at 100 °C. If the precatalyst was first activated with di-*n*-butylmagnesium the coupling was found to proceed well at room temperature (entry 1, Table 2).

LiHMDS prohibits the use of many aryl chlorides with base-sensitive functional groups. Hartwig and Lee reported ZnHMDS as a functional group-tolerant substitute for LiHMDS.[14] ZnHMDS, formed in situ by the addition of $ZnCl_2$ to LiHMDS, suppressed base-mediated decomposition of methyl *p*-chlorobenzoate (entries 4–7, Table 2). In order to aid the dissolution

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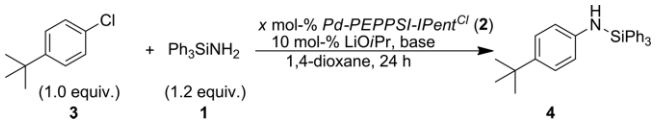
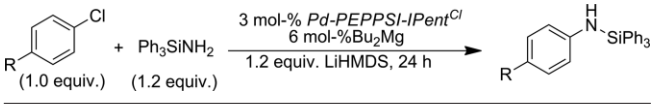
Table 1. Optimization of the reaction conditions for the coupling of 4-*tert*-butylchlorobenzene with aminotriphenylsilane.[a]



Entry	**2** [mol-%]	Base (equiv.)	Temp. [°C]	Conversion [%]
1	1	Cs_2CO_3 (3.0)	80	0
2	1	Cs_2CO_3 (3.0)	100	0
3	3	K_3PO_4 (1.2)	100	0
4	1	NaBHT (1.2)	90	< 5
5[b]	1	NaO*t*Bu (1.2)	30	< 5
6	1	NaO*t*Bu (1.2)	100	10[c]
7	3	NaO*t*Bu (1.2)	100	45[d]
8	3	LiHMDS (1.2)	100	100

[a] Aryl-Cl (0.1 M), conversion determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] The precatalyst was first activated by stirring with LiO*i*Pr at 95 °C for 5 min. [c] 40 % of **3** was converted to bis[4-(*tert*-butyl)-phenyl]amine. [d] 35 % of **3** was converted to bis[4-(*tert*-butyl)-phenyl]amine.

Table 2. Optimization of the reaction conditions with ZnHMDS for base-sensitive substrates.[a]



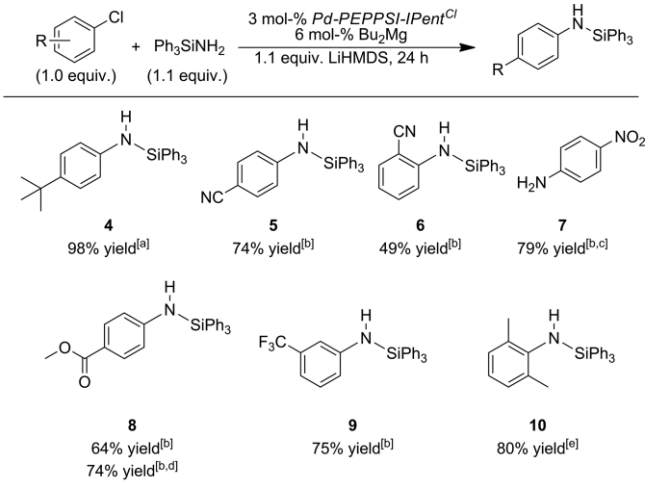
Entry	R	Solvent	$ZnCl_2$ [equiv.]	Temp. [°C]	Conversion [%]
1	$-C(CH_3)_3$	toluene	–	r.t.	100
2	$-CO_2CH_3$	toluene	–	r.t.	0
3	$-CO_2CH_3$	toluene	0.6	r.t.	0
4	$-CO_2CH_3$	THF	0.6	r.t.	45
5	$-CO_2CH_3$	DME	0.6	r.t.	50
6	$-CO_2CH_3$	DME	0.6	80	65
7	$-CO_2CH_3$	1:1 THF/ toluene	0.6	60	65

[a] 4-*tert*-Butylchlorobenzene (0.625 M); conversion determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

of $ZnCl_2$ the use of ethereal solvents were necessary. Dimethoxyethane (DME) or a 1:1 mixture of toluene and THF proceeded equally well, but the co-solvent system was chosen for convenience, because precatalyst activation works well in toluene, and both LiHMDS and $ZnCl_2$ are commercially available as THF solutions.

Having established two procedures for the coupling of **1**, a variety of sterically and electronically diverse aryl halides were examined (Table 3). Hindered 2,6-dimethylchlorobenzene reacted well in the absence of $ZnCl_2$ to provide **10**. Substrates bearing nitrile (**5**, **6**), nitro (**7**), and ester (**8**) substituents were coupled successfully, although column chromatography of the silylated 4-nitroaniline resulted in hydrolysis, and hence, 4-nitroaniline was isolated. In order to minimize hydrolysis on silica gel, triethylamine (1 %) was added to the eluent. Although the products all hydrolyze readily in dilute acid, they are bench stable with no loss of the triphenylsilyl group from **4** or **8** after one year of storage in a vial in air.

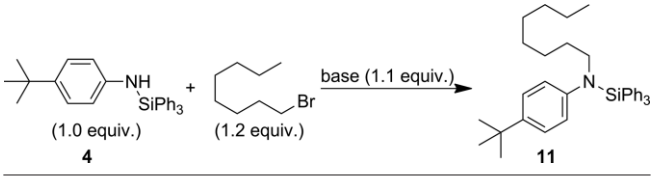
Table 3. Amination reactions with Ph_3SiNH_2 and aryl halides.



[a] Aryl-Cl (0.625 M), toluene, room temp. [b] 0.55 equiv. $ZnCl_2$, 65 °C, 1:1 toluene/THF. [c] Silylated product could not be isolated. [d] 3 mol-% *Pd-PEPPSI-IHept*^{Cl} (see the Supporting Information for structure). [e] Toluene, 100 °C.

Alkylation of **4** was attempted with 1-bromooctane (Table 4) and no conversion was observed with potassium or cesium carbonate in refluxing dichloromethane or acetonitrile. The use of dimethylformamide (DMF) as solvent at elevated temperatures resulted in partial desilylation of the reactant and subsequent over-alkylation of the unprotected aniline, which highlights the need for the silyl group. Deprotonation of the starting silylamine was then examined to generate a better nucleophile. Deprotonation with NaH caused partial loss of the silyl group before alkylation was complete, whereas deprotonation with LiHMDS at room temperature followed by addition of 1-bromooctane gave 60 % conversion to product.

Table 4. Optimizing of alkylation reaction conditions by using 1-bromooctane as substrate.[a]



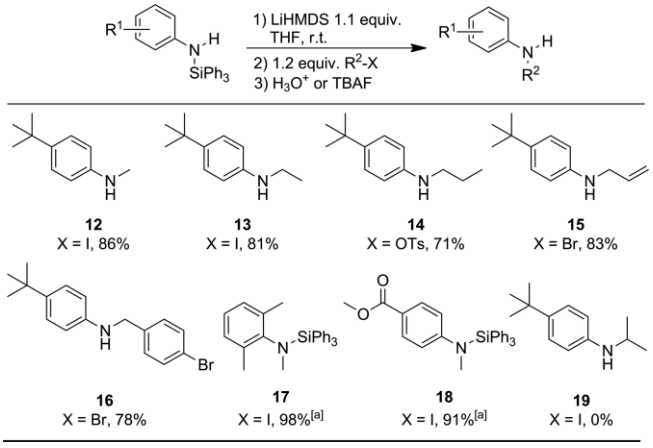
Entry	Base	Solvent	Temp. [°C]	Conversion [%]
1	Cs_2CO_3	CH_2Cl_2	40	0
2	K_2CO_3	MeCN	reflux	0
3	Cs_2CO_3	MeCN	reflux	0
4	K_2CO_3	DMF	120	0
5	Cs_2CO_3	DMF	120	0
6	NaH	THF	60	< 5
7	LiHMDS	Et_2O	r.t.	0
8	LiHMDS	THF	r.t.	60[a]

[a] Conversion determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

By using LiHMDS to deprotonate the silylated amine, primary (**12–14**, **17**, **18**), allylic (**15**), and benzylic (**16**) bromides, iodides, and tosylates were successfully alkylated (Table 5). Isolation of **17** shows that alkylation of sterically hindered aryl halides is

possible and that the triphenylsilyl group is not lost during the alkylation. Compound **18**, which contains an electron-withdrawing and base-sensitive ester group, was also alkylated in high yield.

Table 5. Alkylation of triphenylsilyl-protected anilines with alkyl bromides, iodides, or tosylates.



[a] Product isolated without silyl group removal.

Removal of the triphenylsilyl group from the amine can be accomplished by addition of HCl (1 M) or a slight excess of tetrabutylammnonium fluoride (TBAF) to the reaction mixture. Acid-catalyzed desilylation was faster (5 to 10 min) and simpler than the desilylation with TBAF, which can require up to 2 h to reach completion.

Conclusion

Aminotriphenylsilane is a convenient ammonia equivalent that can be coupled by using *Pd-PEPPSI-IPent*^{Cl} and LiHMDS. Addition of $ZnCl_2$ expands the substrate scope to include base-sensitive substrates. The silyl-protected products are useful intermediates for selective N-alkylation, which can then be easily deprotected by acid or with fluoride.

Experimental Section

General Procedure for the Amination of Aryl Halides with Aminotriphenylsilane and LiHMDS: In a glovebox, a vial (*V* = 8 mL) containing a Teflon-coated magnetic stir bar was charged with LiHMDS (44.9 mg, 0.275 mmol), sealed, and removed from the glovebox. The vial was then charged with aminotriphenylsilane (75.7 mg, 0.275 mmol), *Pd-PEPPSI-IPent*^{Cl} (6.5 mg, 3 mol-%), and the aryl halide (if solid, 0.25 mmol, 1 equiv.). The vial was sealed with a Teflon-coated screw cap and backfilled with argon (3 ×). The aryl halide (if liquid, 0.25 mmol, 1 equiv.) and toluene (4 mL) were then added with a syringe. The vial was then placed in a pre-heated oil bath at the given temperature and the reaction was stirred for 24 h. The mixture was then cooled to room temp., diluted with CH_2Cl_2, filtered through a plug of silica with ethyl acetate containing 1 % triethylamine, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography on silica gel by using an eluent containing 1 % triethylamine to yield the desired product.

General Procedure for Amination of Aryl Halides with Aminotriphenylsilane, LiHMDS, and $ZnCl_2$: An oven-dried argon-filled vial (A, *V* = 8 mL) containing a Teflon-coated magnetic stir bar was charged with LiHMDS in THF (1.0 M, 0.275 mL, 0.275 mmol), 0.5 M $ZnCl_2$ in THF (0.275 mL, 0.138 mmol), and THF (1.45 mL) with a syringe and the resultant solution was stirred for 20 min. A separate oven-dried argon filled vial (B, *V* = 8 mL) containing a Teflon-coated magnetic stir bar was charged with *Pd-PEPPSI-IPent*^{Cl} (6.5 mg, 3 mol-%). The vial was sealed with a Teflon-coated screw cap and backfilled with argon (3 ×). Toluene (2 mL) and *n*Bu_2Mg in heptanes (1.0 M, 15 µL, 6 mol-%) were added with a syringe and the solution was stirred for 10 min. An oven-dried argon-filled vial (C, *V* = 8 mL) containing a Teflon-coated magnetic stir bar was charged with aminotriphenylsilane (75.7 mg, 0.275 mmol) and the aryl halide (0.25 mmol, 1 equiv.). The vial was sealed with a Teflon-coated screw cap and backfilled with argon (3 ×). The contents of vial B were transferred with a syringe to vial C. The contents in vial A were then transferred to vial C with a syringe. Vial C was then placed in a pre-heated oil bath at 65 °C and was stirred for 24 h. The reaction mixture was then cooled to r.t., diluted with CH_2Cl_2, filtered through a plug of silica with ethyl acetate containing 1 % triethylamine, and the filtrate concentrated in vacuo. The crude product was purified with a flash chromatography on silica gel by using an eluent containing 1 % triethylamine to yield the desired product.

General Alkylation Procedure: An oven-dried argon-filled vial (*V* = 8 mL) containing a Teflon-coated magnetic stir bar was charged with the silylated amine (1 equiv.). The vial was sealed with a Teflon-coated screw cap and backfilled with argon three times. THF was then added with a syringe to dilute the silylated amine to 1.0 M. LiHMDS in THF (1.0 M, 1.1 equiv.) and the electrophile (1.2 equiv.) were then added with a syringe and the reaction progress was monitored by TLC. When the reaction was judged complete, either aqueous HCl (5 equiv., 1.0 M) or TBAF in THF (5 equiv., 1.0 M) were added and the resultant mixture was stirred until complete removal of the triphenylsilyl group was confirmed by TLC analysis. The reaction mixture was then diluted with diethyl ether, 0.1 M NaOH was added, and the layers were separated. The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to yield the desired product.

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Keywords: Ammonia equivalent · *N*-Alkylation · Amination · N-heterocyclic carbene · Cross-coupling · Palladium

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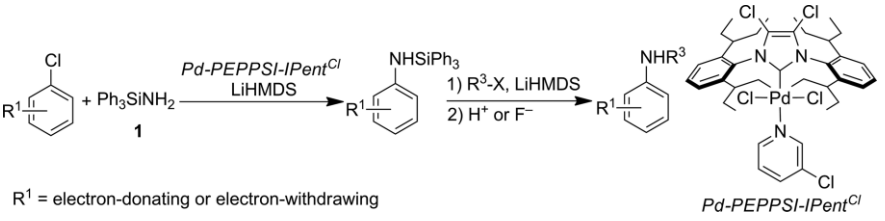

R^1 = electron-donating or electron-withdrawing

Triphenylsilyl-protected anilines were obtained from the cross-coupling of aminotriphenylsilane with aryl halides in the presence of *Pd-PEPPSI-IPent^{Cl}* {dichloro(3-chloropyridyl)[4,5-dichloro-1,3-bis(2,6-dipent-3-ylphenyl)imidazol-2-ylidene]palladium(II)}. The silylated products were then alkylated without over-alkylation, yielding the secondary amines after hydrolysis under mild acidic conditions.

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