Amination Reactions

DOI: 10.1002/anie.201103700

Titanium-Mediated Amination of Grignard Reagents Using Primary and Secondary Amines**

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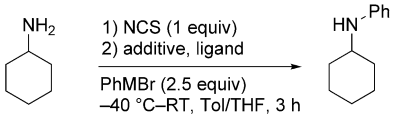
The synthesis of anilines through the formation of an aryl–nitrogen bond is a powerful method for the preparation of natural products and pharmaceutical targets.[1] Although palladium catalysis has proven to be an expedient and practical method for this type of bond construction,[1b–d] the use of electrophilic aminating reagents with nucleophilic organometallic reagents presents an alternative strategy.[2–4] This approach typically requires synthesis and isolation of the electrophilic nitrogen source; methods that use amines directly increase the appeal of this strategy. Transition-metal-catalyzed amination of organometallic reagents with *N*-chloroamines has been demonstrated by a number of research groups.[5] Although several of these methods were amenable to generation of the *N*-chloroamines in situ, none of these reports utilized the nonisolable primary *N*-chloroamines; thus establishing the need for a new method to address these challenging substrates.[6] Herein, we report the one-pot chlorination and titanium-mediated coupling of Grignard reagents with amines, including primary amines.

Our investigations began with examination of the reaction between *N*-chlorocyclohexylamine and Grignard or arylzinc reagents in the presence of a series of catalysts or promoters (Table 1). A one-pot procedure to prepare the electrophilic *N*-chloroamines in situ was utilized. In the absence of additive, no desired aniline was formed (Table 1, entry 1). Notably, in the presence of either nickel catalyst or diamine ligand, negligible to modest yields of desired product were observed (Table 1, entries 2 and 3).[7] We hypothesized that an aryltitanium intermediate may provide a suitably nucleophilic reaction partner that could best decomposition of the *N*-chloroamine (Scheme 1).[8–10] Use of $[Ti(OiPr)_4]$ with Grignard reagent provided the best yield of the desired product (Table 1, entry 6).[11]

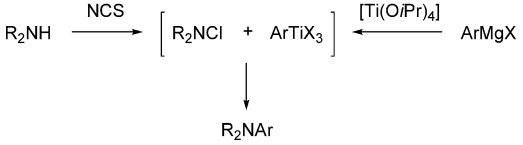
A series of primary amines reacted smoothly under the one-pot procedure (Table 2). Steric bulk on the adjacent carbon atom is well-tolerated, with α,α-disubstituted amines providing some of the best yields (Table 2, entries 5–7).

Table 1: Optimization with Cyclohexylamine.



Entry	M	Additive (equiv)	Ligand (equiv)	Yield [%]
1	Mg	none	none	< 5
2	Zn	$[Ni(cod)_2]$ (0.1)	bipyridine (0.1)	50
3	Mg	none	TMEDA (10)	< 5
4	Zn	$[Ti(OiPr)_4]$ (1)	none	29
5	Mg	$[Ti(OiPr)_4]$ (1)	none	56
6	Mg	$[Ti(OiPr)_4]$ (2.5)	none	74

cod = cycloocta-l,5-diene, NCS = *N*-chlorosuccinimide, THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Tol = toluene.



Scheme 1. Titanium-mediated amination of Grignard reagents. $[Ti(OiPr)_4]$ with Grignard reagent provided the best yield of the desired product (Table 1, entry 6).[11]

Configuration is conserved when starting with a chiral amine (Table 2, entry 10).[12] The reaction conditions tolerate protected alcohols and amines as well as a terminal alkyne (Table 2, entries 9–12). Use of unbranched primary amines generally resulted in lower yields.[13]

Next we turned our attention to functionalized secondary amines, including the synthesis of the biologically active biarylpiperazine substructure (Table 3). Functionalized cyclic and acyclic secondary amines were found to be very effective substrates under the reaction conditions. Diallylamine, a substrate that shows potential for being part of a protecting group strategy, gave the desired aniline in good yield (Table 3, entry 2). Primary nitriles were well tolerated (Table 3, entry 3), as were ethyl and benzyl carbamates (Table 3, entries 5 and 9). Arylpiperazines that incorporate functional groups including pyridine, nitrile, and 2-furanyl underwent smooth cross-coupling under the reaction conditions and provided biarylpiperazines (Table 3, entries 6–8). These types of structures are of particular interest because of the myriad of biological activities associated with the biarylpiperazine pharmacophore.[14] The synthesis of an *N*-aryl homopiperazine was also examined (Table 3, entry 9), thus demonstrating

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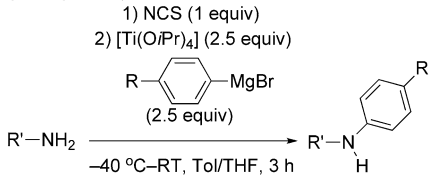
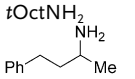
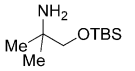
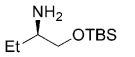
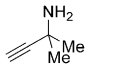
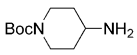
[**] We thank Pfizer for financial support and Dr. John Greaves for mass spectrometry analyses. T.J.B. acknowledges Allergan for a Graduate Fellowship. We thank Sigma–Aldrich for donation of functionalized amines.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103700.

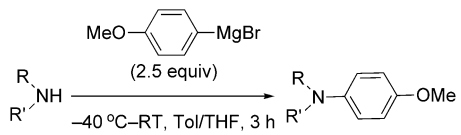
Table 2: Scope of primary amines.

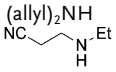
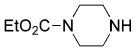
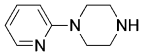
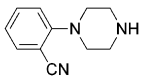
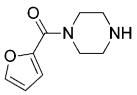
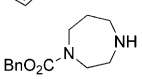


Entry	R	Amine	Product	Yield [%]
1	H	$CyNH_2$	**1a**	74
2	H	$sBuNH_2$	**1b**	70
3	MeO	$CyNH_2$	**2a**	66
4	MeO	$sBuNH_2$	**2b**	64
5	MeO	$tBuNH_2$	**2c**	73
6	MeO	$tAmNH_2$	**2d**	64
7	MeO	$tOctNH_2$	**2e**	67
8	MeO		**2f**	63
9	MeO		**2g**	61
10	MeO		**2h**	55
11	MeO		**2i**	55
12	MeO		**2j**	59

Boc = *tert*-butoxycarbonyl, Cy = cyclohexyl, *s*Bu = *sec*-butyl, *t*Am = *tert*-amyl, TBS = *tert*-butyldimethylsilyl, *t*Bu = *tert*-butyl, *t*Oct = *tert*-octyl.

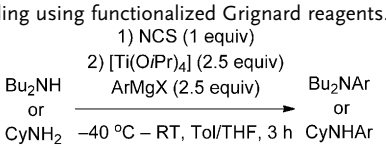
Table 3: Coupling of functionalized secondary amines.

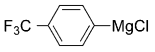
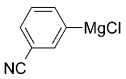
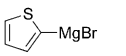
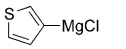
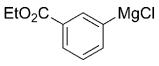


Entry	Amine	Product	Yield [%]
1	nBu_2NH	**3a**	78
2	$(allyl)_2NH$	**3b**	76
3		**3c**	75
4		**3d**	80
5		**3e**	77
6		**3f**	80
7		**3g**	75
8		**3h**	66
9		**3i**	72

Bn = benzyl.

Table 4: Coupling using functionalized Grignard reagents.

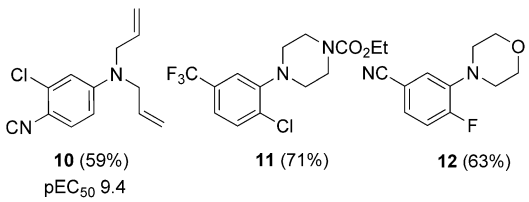


Entry	Amine	ArMgX	Product	Yield [%]
1	nBu_2NH		**4a**	80
2	$CyNH_2$		**4b**	59
3	nBu_2NH		**5a**	66
4	$CyNH_2$		**5b**	61
5	nBu_2NH		**6**	86
6	nBu_2NH		**7**	63
7	nBu_2NH		**8**	58
8	nBu_2NH		**9**	59

access to another substructure with application in medicinal chemistry.[15]

Examination of the scope with respect to the Grignard reagent was then performed (Table 4). Grignard reagents were prepared conventionally from aryl halides and magnesium turnings or by using the magnesium halogen exchange procedure developed by Knochel and co-workers.[16,17] In general, the highest yields were obtained when using secondary amines as coupling partners (Table 4, entries 1–4). Substitution in the *para*, *meta*, and *ortho* positions of the aryl Grignard reagent was well tolerated (Table 4, entries 1–4, 7, and 8). Trifluoromethyl-, nitrile-, and ester-substituted as well as thienyl-substituted Grignard reagents gave good yields. *o*-Bromophenylmagnesium bromide, a reagent of limited stability, provided the desired product, albeit in modest yield (Table 4, entry 7).

An androgen receptor modulator and two analogues were prepared to demonstrate the synthetic utility of this method. Androgen receptor agonist **10** has been previously prepared by an S_NAr reaction (Scheme 2).[18,19] Using our method, aniline **10** was prepared from diallylamine and the suitably functionalized Grignard reagent in 59% yield. To highlight this method as a complementary approach for the synthesis of electron-deficient anilines, we prepared two additional analogues, **11** and **12**, using our method. The synthesis of **11** and



Scheme 2. Androgen receptor antagonist and analogues.

12 by an S_NAr reaction would be challenging because they contain *meta*-electron-withdrawing groups and compound **12** contains an aryl fluoride.

The titanium-mediated amination of Grignard reagents presents a method for the synthesis of secondary and tertiary anilines. This electrophilic amination strategy for aniline synthesis employs inexpensive, commercially available reagents and provides a mild and convenient complement to S_NAr methodology. No prior isolation of the *N*-chloroamines was necessary, thus allowing for a diverse substrate scope. Further work in our laboratories will be focused on applying the use of *N*-chloroamines to other practical carbon–nitrogen bond-forming reactions.

Experimental Section

Representative procedure for the titanium-mediated amination of Grignard reagents: Cyclohexylamine (45.7 μL, 0.40 mmol, 1.0 equiv), *N*-chlorosuccinimide (53.4 mg, 0.40 mmol, 1.0 equiv) and toluene (1 mL) were added to an oven-dried vial (7 mL) under N_2. After stirring for 20 min, to a separate oven-dried vial (7 mL) under N_2, was added 1 mL of toluene, a 0.7 M solution of *p*-methoxyphenylmagnesium bromide in THF (1.43 mL, 1.0 mmol, 2.5 equiv), and [Ti(O*i*Pr)$_4$] (296 μL, 1.0 mmol, 2.5 equiv). Then the titanium-Grignard mixture was cooled to −40 °C while stirring. After five additional min, the *N*-chloroamine was cooled to −40 °C and the titanium solution was added by syringe. The bath temperature was allowed to warm slowly to RT (over about 1 h). After 3 h, the reaction was quenched with of aqueous saturated K_2CO_3 (2 mL). The reaction mixture was diluted with EtOAc (10 mL) and filtered. The layers were separated and the aqueous layer was extracted (2 × 10 mL EtOAc) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification was performed by chromatography on silica gel with a gradient from neat hexanes to (95:5) hexanes/EtOAc to afford **2a** as a pale yellow oil (54 mg, 66% yield).

Representative Knochel procedure for Mg–Br exchange[16]: *i*PrMgCl·LiCl (5.0 mL, 1.0 M, 5 mmol) and 3-bromo-4-fluorobenzonitrile (1.00 g, 5 mmol) were added to a flame-dried flask (25 mL) that had been cooled to 0 °C. The reaction was stirred for 3 h at 0 °C and then titrated with I_2. The Grignard reagent was then used in the amination reaction as described above. For best results the *i*PrMgCl·LiCl should be freshly prepared from isopropyl chloride and magnesium turnings in the presence of one equivalent of lithium chloride. Commercially available *i*PrMgCl with LiCl (1 equiv) added gave irreproducible results. The exchange could be monitored using ^{1}H NMR spectroscopy by taking a small aliquot of the Grignard reagent solution quenched with methanol and then analyzing the sample for the disappearance of the starting aryl bromide. For magnesium–iodine exchange, the exchange was performed at −40 °C for 45 min with commercially available *i*PrMgCl.

Received: May 31, 2011
Published online: July 18, 2011

Keywords: amination · anilines · Grignard reagents · *N*-chloroamines · titanium

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[12] See the Supporting Information for details.

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