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Aaron Schechter^a, David Goldrich^a, Jessica R. Chapman^b, Beatrix M. Uberheide^b & Daniel Lim^a

^a Department of Chemistry, Yeshiva University, New York, New York, USA

^b Proteomics Resource Center, New York University School of Medicine, New York, New York, USA Accepted author version posted online: 01 Dec 2014.Published online: 12 Jan 2015.

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MgBr₂ · OEt₂: A LEWIS ACID CATALYST FOR THE *O*- AND *N*-Boc PROTECTION OF PHENOLS AND AMINES

Aaron Schechter,¹ David Goldrich,¹ Jessica R. Chapman,² Beatrix M. Uberheide,² and Daniel Lim¹

¹Department of Chemistry, Yeshiva University, New York, New York, USA ²Proteomics Resource Center, New York University School of Medicine, New York, New York, USA

GRAPHICAL ABSTRACT



Abstract $MgBr_2 \cdot OEt_2$ efficiently catalyzes the O- and N-tert-butoxycarbonylation of functionalized phenols and amines. The presented procedure is operationally simple and done under solvent-free conditions.

Keywords: Amines; Boc; di-tert-butyl dicarbonate; Lewis acid; phenols; protecting group

INTRODUCTION

An important aspect of the total synthesis of molecules is the development and implementation of functional-group protection strategies. It has become imperative to develop protecting group strategies for commonly encountered functional groups in organic synthesis, such as alcohols and amines.^[1,2] The *tert*-butoxycarbonyl (Boc) group is one of the most important protecting groups available for organic synthesis. Among carbonic acid derivatives used as protecting groups, *tert*-butyl carbonates

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Address correspondence to Daniel Lim, Department of Chemistry, Yeshiva University, 500 W. 185th St., New York, NY 10033, USA. E-mail: dlim@yu.edu

(O-Boc alcohols) and *tert*-butyl carbamates (N-Boc amines) are of great importance in organic chemistry.^[3]

Although there are a number of protecting groups for the alcohol functional group, organic *tert*-butyl carbonates, or *O*-Boc, derivatives have gained increasing use and importance in the past few years both in industry and in academic research.^[4] This is due to their increased stability in comparison to the corresponding esters under basic conditions.^[5] Likewise, *tert*-butyl carbamates, or *N*-Boc, derivatives are extensively used for protecting amino groups, because of their stability in basic environments and ability to assist in developing orthogonal functional-group protection strategies.^[6] A majority of the *O*- and *N*-Boc methodologies work in basic media or in the presence of a Lewis base.^[7,8] In some cases, preparation of organic carbonates and carbamates have required the use of toxic reagents, such as phosgene, pyridine, and carbon monoxide.^[9] Thus much effort has been devoted to developing more environmentally friendly procedures for their synthesis.^[10]

Although there are a variety of base-mediated reaction conditions available for *O*- and *N*-Boc protection in the literature, a number of novel modes of catalyzing the Boc protection of phenols and amines have been reported.^[11] For example, the use of Lewis acids to catalyze the Boc protection of alcohols and amines has shown great promise.^[12] However, it is important to note that one of the more interesting limitations in the Lewis acid–catalyzed Boc protection is that *O*-Boc formation does not become feasible as phenols form the *tert*-butyl ethers with Boc₂O in the presence of a strong Lewis acid. In contrast, *O*-Boc formation occurs with the use of a mild Lewis acid, which may require heating.^[13,14]

Because of the very attractive nature of the *N*-Boc group, apart from the classical base-induced procedures, only a handful of Lewis acids have been used as catalysts for the *N*-Boc protection of amines.^[12] In contrast to Lewis acid catalysis, there have been a few examples of organocatalytic *O*- and *N*-tert-butoxycarbonylation protocols that have been reported using reagents such as CBr₄, PPh₃, and I₂.^[15]

Herein we report $MgBr_2 \cdot OEt_2$ as a novel Lewis acid catalyst for the *O*- and *N*tert-butoxycarbonylation of phenols and amines under neat and neutral conditions at room temperature. We deliberately chose these reagents because they are compatible with the capacity to retain their activity even in the presence of oxygen- and nitrogen-containing compounds. $MgBr_2 \cdot OEt_2$ is commercially available, inexpensive, and generates no toxic by-products on aqueous workup, which would allow us to conduct the reactions open to the atmosphere using untreated, reagent-grade solvent if necessary.

DISCUSSION

To explore the use of $MgBr_2 \cdot OEt_2$ toward the preparation of O-Boc-protected phenols we chose 4-nitrophenol as a test substrate and treated it with equimolar amounts of Boc₂O and $MgBr_2 \cdot OEt_2$ in CH₂Cl₂ (Table 1, entry 1). The O-Bocprotected phenol product was obtained in good yield, 72%, after column chromatography. After exploring the effects of catalyst loading we discovered an optimum catalytic amount of 10 mol% of $MgBr_2 \cdot OEt_2$ was sufficient to afford the desired product in excellent yield at room temperature (88% yield after column

MgBr₂·OEt₂-CATALYZED O- AND N-Boc PROTECTION

	OH NO ₂	MgBr ₂ · OEt ₂ Boc ₂ O	- OBoc NO ₂ 2	
try	% Catalyst	Solvent	Time (h)	% Yield

Table 1. MgBr₂·OEt₂-catalyzed O-Boc protection

Entry	% Catalyst	Solvent	Time (h)	% Yield ^b
1	100	CH ₂ Cl ₂	0.5	72
2	25	CH_2Cl_2	1	80
3	10	CH_2Cl_2	16	88
4	10	None	16	88

^aReactions were run with 1.0 mmol of alcohol and 1.0 mmol of Boc₂O.

^bIsolated yield after coloumn chromatography.

chromatography). We were also pleased to discover that the same results could be obtained when the reaction was repeated without solvent. Typically, shortly after the introduction of a catalytic amount of $MgBr_2 \cdot OEt_2$ into the reaction mixture there is evolution of gas that took place, which was followed by the formation of the corresponding *O*-Boc derivative. All products were characterized by instrumental techniques such as infrared (IR), ¹H NMR, ¹³C NMR, and mass spectrometry.

Having found suitable reaction conditions with $MgBr_2 \cdot OEt_2$ as a Lewis acid catalyst, we decided to explore the ease at which the alcohol group of various phenols can be manipulated in the presence of other functional groups. We planned to test the compatibility of the reaction conditions with various functional/protecting groups such as nitro, carboalkoxy, bromo, methoxy, acetyl, formyl, acetamido, and nitrile (Table 2, entries 1–10). The desired *O*-Boc compounds were formed in good to excellent isolated yields (80–95%) with excellent chemoselectivity and no competitive side reactions. These conditions were also applied to a benzyl alcohol derivative, along with an Fmoc-protected tyrosine methyl ester (Table 2, entries 11 and 12). Unfortunately, for both cases heating was necessary to obtain moderate to good yields of the respective *O*-Boc products.

With the optimized reaction conditions for *O*-Boc protection of phenols in hand, we then evaluated the scope of the reaction using a variety of structurally divergent amines and Boc_2O (Table 3), ranging from aromatic, aliphatic, and heterocyclic to amino acid methyl esters. All substrates reacted to give the corresponding *N*-Boc adducts within 3 h in moderate to excellent isolated yields.

Thus, the following mechanism can be proposed for the reaction. Both carbonyl oxygen atoms of Boc_2O are activated by $MgBr_2 \cdot OEt_2$ (Scheme 1, **21**) initially, making the carbonyl group more susceptible to nucleophilic attack by a phenol or amine. This facilitates extrusion of *tert*-butanol and carbon dioxide as leaving





Entry	Substrate	Product	% Yield ^b
1	HO	2	88
2	HO	3	95
3	HO	4	85
4	HO	5	95
5	HO	6	92
6	OH I	7	90
7	HO	8	85
8	HO	9	82

(Continued)

Entry	Substrate	Product	% Yield ^b
9	HO	10	80^c
10	HO	11	80
11	СІ ОН	12	72 ^{<i>c</i>}
12	NHFmoc	13	68°

^aReactions were run with 1.0 mmol of alcohol and 1.0 mmol of Boc₂O for 16 hours.

^bIsolated yield after column chromatography.

^cHeated at 60 °C.

entities, eventually leading to formation of *O*- or *N*-Boc-protected product 24 (Scheme 1).

 $MgBr_2 \cdot OEt_2$ shows promising results for the protection of various electronically and structurally diverse phenols and amines, as *O*- and *N*-Boc derivatives in moderate to excellent isolated yields. In contrast to the existing methods, this new method offers the following advantages: (i) it is mild and operationally simple; (ii) it is inexpensive, has lower catalyst loading, and uses a readily available and environmentally benign catalyst under solvent-free conditions; (iii) it displays chemoselectivity; (iv) it has wide substrate scope; and (v) it has no side reactions.

In conclusion, we have described a simple procedure for the O- and N-Boc protection of phenols and amines using MgBr₂·OEt₂ under solvent-free conditions. Further work is in progress to explore this novel catalyst for use in other organic transformations. We believe that our protocol will be a valuable contribution for the O- and N-Boc protection of phenols and amines both in academia and industries.

EXPERIMENTAL

 Boc_2O (1.0 mmol) was added to a mixture of phenol or amine (1.0 mmol) and $MgBr_2 \cdot OEt_2$ (0.1 mmol) in a round-bottom flask, at which point an evolution of gas

Table 2. Continued

10 % MgBr₂ · OEt₂ Boc₂O R−NH₂			
Entry	Substrate	Product	% Yield ^b
1	NNH	14	90
2	NH ₂	15	85
3	NH2	16	74
4	⊂ N H	17	80
5	H ₂ N	18	82
6		19	68

Table 3. MgBr₂ · OEt₂-catalyzed O-Boc protection of amines^a

occurs, and the reaction mixture was stirred magnetically at room temperature (if necessary, reactions was heated to ~ 60 °C). After complete consumption of the phenol or amine (by thin-layer chromatography, TLC; 3–16 h), the reaction mixture was diluted with water and extracted with EtOAc (3×20 mL), and the combined EtOAc extracts were dried with Na₂SO₄ and concentrated under vacuum rotary evaporation. The residue was isolated by column chromatography through a bed of silica gel and eluted with 5–30% ethyl acetate in hexane to afford the desired Bocprotected product.



Scheme 1. Proposed mechanism for O- and N-Boc protection.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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