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Copper(II) tetrafluoroborate as a novel and highly efficient catalyst for *N*-*tert*-butoxycarbonylation of amines under solvent-free conditions at room temperature

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Dedicated to Professor Goverdhan Mehta

Abstract—Commercially available copper(II) tetrafluoroborate hydrate was found to be a highly efficient catalyst for chemoselective *N*-*tert*-butoxycarbonylation of amines with di-*tert*-butyl dicarbonate under solvent-free conditions and at room temperature. Various aromatic amines were protected as their *N*-*tert*-butyl carbamates in high yields and in short times. No competitive side reactions such as isocyanate, urea, and *N*,*N*-di-*t*-Boc formation was observed. Chemoselective *N*-*tert*-butoxycarbonylation was achieved with substrates bearing OH and SH groups. Chiral α-amino acid esters afforded the corresponding *N*-*t*-Boc derivatives in excellent yields.

The presence of an amino group in various drug molecules and their key intermediates makes protection/deprotection[1] of the amine functionality a necessity during their synthesis. Although an easy process for the protection of amines is acylation,[2] liberation of the parent amino compound from the acylated derivatives requires harsh reaction conditions that are often detrimental to the purity of the product due to side reactions under strong alkaline/acidic conditions and at high temperatures.[3] Thus, it is desirable to have a protecting group that may be deprotected under mild conditions. *tert*-Butyl carbamates are stable in the presence of a wide range of nucleophiles and under alkaline conditions and are very labile under mild acidic conditions[1a] to liberate the parent amine. The resistance of the *N*-*t*-Boc functionality to nucleophilic attack allows synthetic manipulation of multifunctional substrates bearing the protected amine group.[4] *tert*-Butyl carbamate formation is achieved by treatment of an amine with di-*tert*-butyl dicarbonate [(Boc)$_2$O] in the presence of 4-dimethylaminopyridine (DMAP)[5] or organic/inorganic bases,[6] 4-dimethylamino-1-*tert*-butoxycarbonylpyridinium chloride[7]/tetrafluoroborate[8] in aqueous NaOH, 2-*tert*-butyloxycarbonyloxyimino-2-phenylacetonitrile in the presence of Et_3N in H_2O–dioxane,[9] *tert*-butyl 2-pyridyl carbonate in the presence of Et_3N in H_2O–DMF,[10] and *tert*-butyl 1-chloroalkyl carbonates in the presence of K_2CO_3 in H_2O–THF.[11] However, these methodologies have various drawbacks such as long reaction times, use of solvent, requirement to prepare the *tert*-butoxycarbonylation reagents,[8–11] etc. The high toxicity of DMAP[12] and the reagents derived from DMAP restrict its use. Further, the base catalysed reactions often lead to the formation of isocyanate,[5d,13] urea,[5d] and *N*,*N*-di-Boc derivatives.[5d,14]

We speculated that these disadvantages could be avoided by electrophilic activation of (Boc)$_2$O in the presence of a Lewis acid (Scheme 1). There are a few examples of Lewis acid catalysed *N*-*tert*-butoxycarbonylation of amines, including yttria–zirconia in MeCN,[15] $Zn(ClO_4)_2 \cdot 6H_2O$ in DCM[16] and $ZrCl_4$ in MeCN.[17] These require the use of solvent and the preparation of the catalysts,[15] are potentially hazardous[18,19] and require anhydrous conditions.[20]

We recently reported that commercially available Cu(BF_4)$_2 \cdot xH_2O$ is extremely effective for acetylation,[2f]

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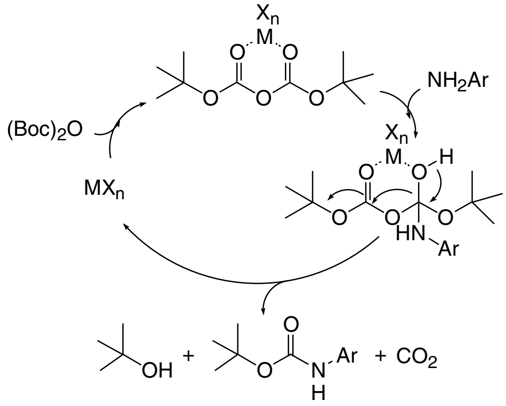

Scheme 1. Electrophilic activation of di-*tert*-butyl dicarbonate during Lewis acid catalysed *tert*-butyl carbamate formation from amines.

diacetate formation,[21] thia-Michael addition,[22] dithiolane formation[23] and acetal formation.[24] Herein we report an efficient methodology for the protection of amines as *tert*-butyl carbamates catalysed by $Cu(BF_4)_2{\cdot}xH_2O$ under solvent-free conditions and at room temperature.

Various amines were treated with $(Boc)_2O$ in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) at ~30–35 °C under neat conditions. The reactions were monitored by IR and GCMS. No isocyanate or urea formation was detected (IR, GCMS). The appearance of a base peak at m/z 57 along with the molecular ion peak in the GCMS confirmed the formation of *tert*-butyl carbamates. No significant amount of *N*,*N*-di-Boc aniline was formed (GCMS).[14] The results are presented in Table 1. The reactions could also be monitored visually. After addition of $(Boc)_2O$ (1 equiv) to the amine (solid or liquid) a clear solution was obtained. Effervescence occurred immediately after the addition of the catalyst to the reaction mixture, which solidified after the reaction was complete. Aromatic amines having various substituents such as OMe, Me, Cl, Br, F, OH and SH groups were converted to their *N*-*t*-Boc derivatives efficiently (entries 1–23). Amino groups attached to aromatic (entry 29) and non-aromatic (entry 30) heterocycles afforded quantitative yields. However, for antipyrine (entry 30), 2 equiv of $(Boc)_2O$ was required. In the case of amino-phenols (entries 13–15) and tyrosine methyl ester (entry 33), excellent chemoselectivity was observed and *N*-*t*-Boc derivatives were obtained as the sole products without competitive formation of *O*-*t*-Boc compounds.[5d,25] 4-Aminothiophenol (entry 16) was also chemoselectively *N*-*tert*-butyloxycarbonylated. However, with 2-aminothiophenol (entry 17), 2-hydroxybenzothiazole was isolated as the sole product (IR, NMR and MS). The presence of electron-withdrawing groups such as CN, COMe and NO_2 reduced the nucleophilicity of the nitrogen atom of the amino group significantly and these substrates required longer times and elevated temperatures to afford moderate yields (entries 24–28).

The mildness of the present methodology was exemplified by the formation of *N*-*t*-Boc derivatives of methyl and benzyl esters of chiral α-amino acids in high yields and optical purity (entries 31–34) as was evident by the comparison of the optical rotations.[15,26–29] The use of DMAP leads to racemisation of *N*-*t*-Boc protected amino-acids.[30]

The advantage of the use of $Cu(BF_4)_2{\cdot}xH_2O$ over the reported Lewis acid catalysts may be demonstrated by the following representative examples. Treatment of aniline with $(Boc)_2O$ in the presence of yttria–zirconia (20% by weight) afforded *tert*-butyl-*N*-phenylcarbamate in 90% yield after 14 h in MeCN.[15] A 92% yield could be obtained after 12 h in DCM on reaction in the presence of $Zn(ClO_4)_2$ (5 mol %).[16] In comparison, the use of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) afforded comparable yields after 5 min under solvent-free conditions. A more stringent test was *N*-*tert*-butoxycarbonylation of 4-nitroaniline. The $ZrCl_4$ (10 mol %) catalysed reaction carried out at 80 °C under neat conditions resulted in the formation of *N*-*t*-Boc-4-nitrophenylamine in 3% yield (GCMS) after 60 min whereas the desired product was obtained in 50% yield when the reaction was carried out in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol %) under identical experimental conditions.

We have described herein $Cu(BF_4)_2{\cdot}xH_2O$ as a highly efficient catalyst for the formation of *tert*-butyl carbamates from amines at room temperature. The advantages include (i) the use of a cheap, easy to handle and commercially available catalyst, (ii) solvent-free and room temperature reaction conditions, (iii) short reaction times and (iv) high yields. With the enforcement of tight legislation for environment protection in chemical transformations, the solvent-free reaction conditions employed in the present methodology constitutes a greener protocol for the desired transformation.[31]

Typical procedure for N-tert-butyloxycarbonylation of amines. To a magnetically stirred mixture of aniline (0.235 g, 2.5 mmol, 1 equiv) and $(Boc)_2O$ (0.545 g, 2.5 mmol, 1 equiv), $Cu(BF_4)_2{\cdot}xH_2O$ (6.0 mg, 0.025 mmol, 1 mol %) was added and the mixture was stirred at 30–35 °C until completion of the reaction (5 min, TLC, IR, GCMS). The mixture was diluted with EtOAc (25 mL), washed with water (2 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford *tert*-butyl-*N*-phenylcarbamate (white solid, 0.485 g, 98%, entry 1, Table 1), mp 132 °C. IR (KBr): 3314, 2985, 1689, 1598, 1531, 1245, 1150 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 1.51$ (s, 9H), 6.55 (br s, 1H), 6.99–7.04 (m, 1H), 7.24–7.36 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 28.32$, 80.45, 118.52, 122.98, 128.93, 138.32, 152.7. MS (EI): m/z 193 (M^+). This data is identical with those of an authentic sample.[16]

The remaining reactions were carried out following this general procedure. In most cases, the products obtained after workup were of sufficient purity (spectral data) and did not require any further purification. Wherever required (<90% conversion), purification was achieved by triturating with EtOAc–hexane or by passing through a column of silica-gel and eluting with hexane–EtOAc. On each occasion, the spectral data