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A mild and efficient chemoselective protection of amines as *N*-benzyloxycarbonyl derivatives in the presence of $La(NO_3)_3{\cdot}6H_2O$ under solvent-free conditions☆,☆☆

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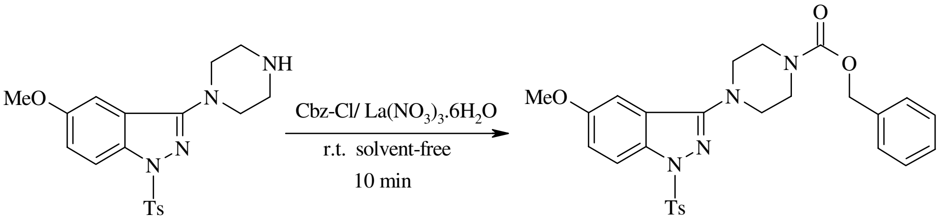
Abstract—A facile and versatile method for the chemoselective *N*-benzyloxycarbonylation of amines has been developed by treatment with benzyloxycarbonyl chloride (Cbz–Cl) in the presence of lanthanum(III) nitrate hexahydrate under solvent-free conditions. The method is general for the preparation of *N*-Cbz derivatives of aliphatic (acyclic and cyclic) and aromatic amines.

The benzyloxycarbonyl (Cbz) group is a very useful functionality for the protection of amines and amine derivatives.[1] This protecting group is very convenient, since it is easily removable by catalytic hydrogenation without any side reactions and is stable to basic and most aqueous acidic conditions. There are several methods available for the protection of amino groups as *N*-Cbz derivatives, which include LiHMDS as a base in THF–HMPA solvent[2] and β-cyclodextrin in aqueous medium.[3,4] The utility of a catalyst having Lewis acid character for the preparation of *N*-Cbz derivatives has not yet been properly explored.

In continuation of our work to develop new organic transformations,[5] we recently reported a mild, efficient and environmentally benign catalyst, lanthanum(III) nitrate hexahydrate, for the chemoselective tetrahydropyranylation of primary alcohols, chemoselective deprotection of acetonides and chemoselective acetylation of alcohols, phenols and amines.[6] These attractive features of lanthanum(III) nitrate hexahydrate prompted us to investigate the *N*-benzyloxycarbonylation of amines with Cbz–Cl under solvent-free conditions at room temperature (Scheme 1).

In general, the reactions were carried out by the addition of amines (1 mmol) to Cbz–Cl (1.2 mmol) in the presence of lanthanum(III) nitrate hexahydrate under solvent-free conditions at room temperature to give the corresponding carbamates in excellent yields



Scheme 1.

Keywords: $La(NO_3)_3{\cdot}6H_2O$; Amines; *N*-Benzyloxycarbonylation; Solvent-free conditions.

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☆☆ Reactions using lanthanum(III) nitrate hexahydrate Paper 6.

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Table 1. *N*-Benzyloxycarbonyl protection of amines in the presence of $La(NO_3)_3 \cdot 6H_2O$ under solvent-free conditions[a]

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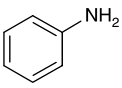
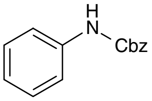
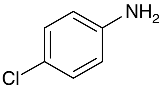
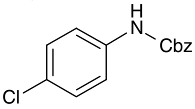
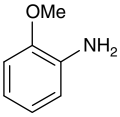
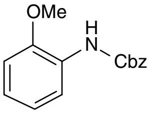
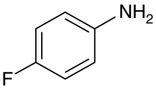
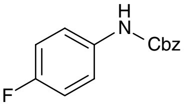
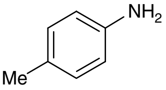
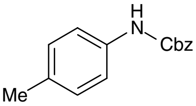
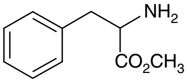
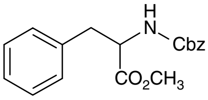
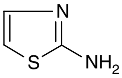
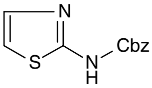
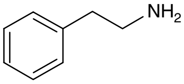
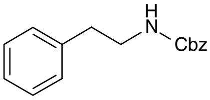
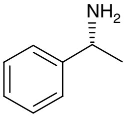
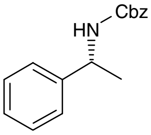
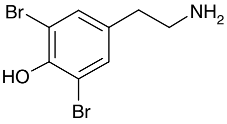
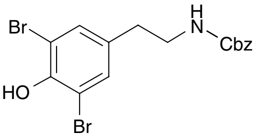
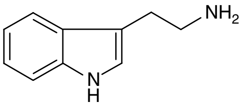
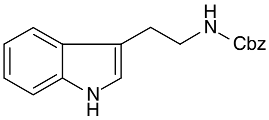
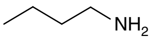
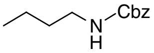
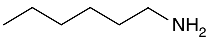
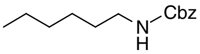
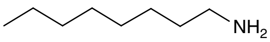
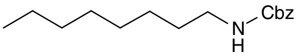
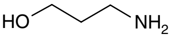
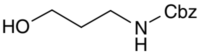
1			4	98
2			4	92
3			4	98
4			4	94
5			4	98
6			4	96
7			5	88
8			4	98
9			4	96
10			5	96
11			10	96
12			5	94
13			5	94
14			5	94
15			5	94

Table 1 (*continued*)

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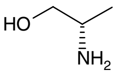
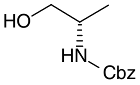
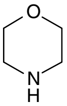
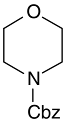
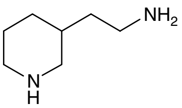
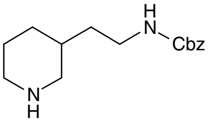
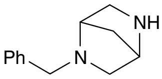
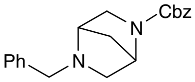
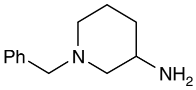
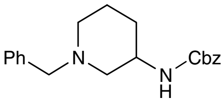
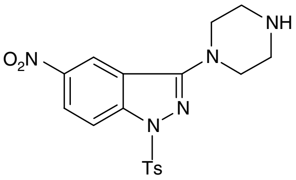
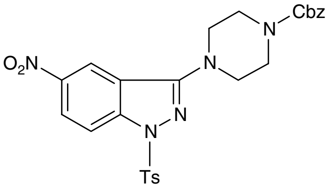
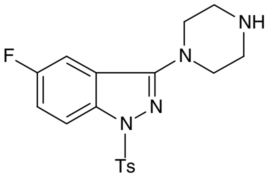
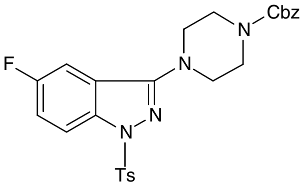
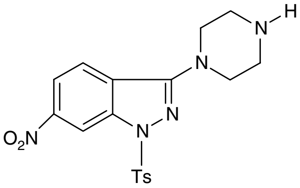
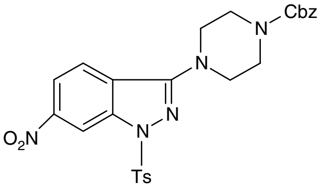
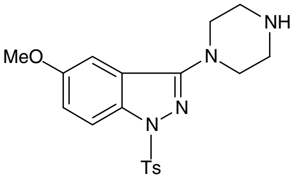
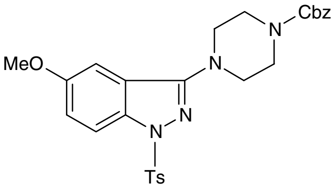
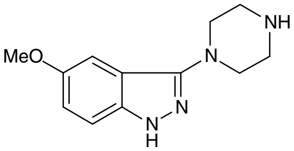
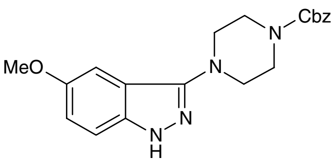
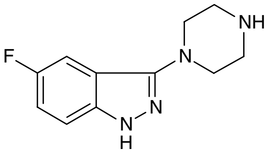
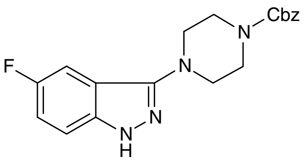
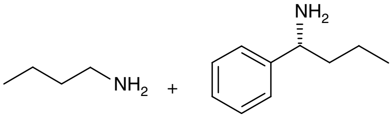
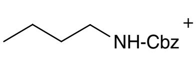
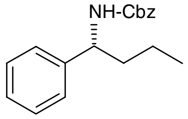
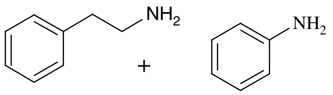
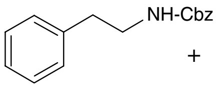
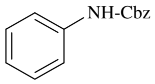
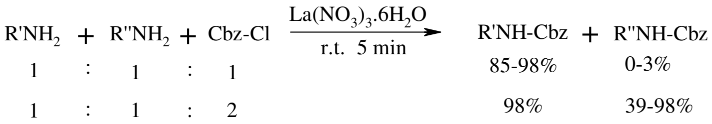
16			5	86
17			10	96
18			10	96
19			15	96
20			15	96
21			10	95
22			10	98
23			10	96
24			10	95
25			10	96
26			10	96

[a] All products were characterized by IR, NMR and mass spectroscopy.

[b] Isolated yields of products after column chromatography.

Table 2. Selective Cbz-protection of mixtures of amines

Entry	Mixture of amines	Products (% of isolated yield)	
1			
	+ 1 equivalent of CBzCl	(95)	(3)
	+ 2 equivalents of CBzCl	(95)	(98)
2			
	+ 1 equivalent of CBzCl	(99)	(0)
	+ 2 equivalents of CBzCl	(99)	(39)



$$R'NH_2 + R''NH_2 + Cbz\text{-}Cl \xrightarrow[\text{r.t. 5 min}]{La(NO_3)_3.6H_2O} R'NH\text{-}Cbz + R''NH\text{-}Cbz$$

R'NH₂	R''NH₂	Cbz-Cl	R'NH-Cbz	R''NH-Cbz
1	1	1	85-98%	0-3%
1	1	2	98%	39-98%

Scheme 2.

(86–98%, Table 1). The times required for derivatization were short (4–15 min). This method was compatible with various amines including aliphatic, aromatic and heteroaromatic examples.

Amino groups with different chemical natures further demonstrated the chemoselectivity of the reaction. Thus, in piperinyl indazoles only the aliphatic amino group was protected (Table 1, entries 25 and 26). In the case of tryptamine only the aliphatic amino group was protected (Table 1, entry 11). Similarly, in the case of an amino alcohol (Table 1, entry 15) and an amino phenol (Table 1, entry 10), only the amino groups were protected. In a separate experiment, a mixture of primary (1 mmol) and secondary (1 mmol) amines was treated with Cbz–Cl (1 mmol) in the presence of lanthanum(III) nitrate hexahydrate to give predominantly primary-Cbz-protected amine (95%) (Table 2, entry 1). However, if the reaction was carried out with 2 equiv of Cbz–Cl, both the primary and secondary amines were protected to give the corresponding carbamates. (Table 2, entry 1). In the case of a mixture of aliphatic and aromatic amines (1 mmol each), the reaction with Cbz–Cl (1 mmol) in the presence of lanthanum(III) nitrate hexahydrate, only the aliphatic amine was derivatized; however, if 2 mmol of Cbz–Cl was used, the aromatic amine was also partly converted (Scheme 2 , Table 2, entries 1 and 2).

In conclusion, we have described for the first time, lanthanum(III) nitrate hexahydrate as a remarkably efficient catalyst for Cbz-protection of a wide range of amines using Cbz–Cl. Aromatic amines containing electron-withdrawing groups also gave the desired derivatives in good yields. Chiral substrates were resistant to racemization and labile functionalities such as esters were compatible in this conversion. The protocol is highly chemoselective, involves simple experimental procedures, mild reaction conditions and gives excellent yields of Cbz-protected amines.

Typical experimental procedure: To a mixture of amine (1 mmol) and benzyloxycarbonyl chloride (Cbz–Cl) (1.2 mmol) was added finely powdered $La(NO_3)_3{\cdot}6H_2O$ (5 mol %) and the reaction was stirred under solvent-free conditions at room temperature for an appropriate amount of time (Table 1). After completion of the reaction as monitored by TLC, water was added to the reaction mixture and the product was extracted into ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product which was purified by silica gel column chromatography to afford the corresponding *N*-benzyloxycarbonyl protected amines.

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