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ARTICLE

tert-Butyl(3-cyano-4,6-dimethylpyridin-2-yl)carbonate as a green and chemoselective *N*-*tert*-butoxycarbonylation reagent

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The use of *tert*-butyl(3-cyano-4,6-dimethylpyridin-2-yl)carbonate as chemoselective *tert*-butoxycarbonylation reagent for aromatic and aliphatic amines has been demonstrated. To get insight into this reaction, *in situ* React IR technology was performed to confirm the affectivity and chemoselectivity of this novel Boc reagent. The reaction carried chemoselectively out in high yield under mild, environment-friendly conditions and was completed quickly within 1 hour. Simultaneously, the Boc carrier was easily recyclable which has great application prospects for industrial production.

Introduction

The $(Boc)_2O$, along with benzyl chloroformate (Cbz-Cl) and 9-fluorenylmethyl chloroformate (Fmoc-Cl), etc. are widespread reagents in organic synthesis and play significant roles in pharmaceutical and chemical industries [1]. They are widely used as *N*-protecting reagents in the syntheses of peptides, amino acids and other natural products because of different stability and availability [2].

Among various amine protecting groups, the *tert*-butoxycarbonyl (Boc) group has been employed extensively to decrease the nucleophilicity of the amino group, such as in both organic and peptide synthesis owing to the exceptional stability toward catalytic hydrogenation and resistance toward basic conditions and other nucleophilic reagents [3-8]. Removal of the Boc protecting group is easily performed by acid-catalyzed hydrolysis. Various reagents and methodologies developed for the preparation of *N*-*tert*-butyl carbamates using di-*tert*-butyl dicarbonate $(Boc)_2O$ have been carried out either in the presence of a base (DMAP, NaHMDS, K_2CO_3, NaOH, Et_3N) or more recently acid catalysts and miscellaneous reagents [9-11]. However, these methodologies have various drawbacks such as long reaction time, the use of many additives, the preparation of complex catalyst and lack of selectivity for amino and hydroxyl groups. Furthermore, some undesirable byproducts, for example, isocyanate, urea, and *N*,*N*-di-Boc derivatives, were simultaneously formed under the base catalyzed condition leading to lower reaction efficiency [12-14]. In addition, those protocols, featured by the high toxicity, unpleasant smell, non-recoverable and requirement of excess amount catalyst, aren't suitable for industrial application, especially from the perspective of green chemistry [15]. However, the most unfavorable shortcoming of $(Boc)_2O$ is the lack of selectivity for amino and phenolic hydroxyl groups. In 2001, Ouchi et al. disclosed that aromatic and aliphatic amine hydrochlorides and phenols were *tert*-butoxycarbonylation using 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) as reagent in the absence of a base [16]. However, lower atom economy is the main disadvantage of this method as waste of the isoquinoline, which is inconvenient to recycle, leading to the solvent waste and pollution, Simultaneously, the reaction was carried out in dichloroethane and benzene, which were undesirable solvents [17].

The goal of this study was to create a general atom economical method for the synthesis and selective protection of amines. Herein, we disclosed the use of *tert*-butyl(3-cyano-4,6-dimethylpyridin-2-yl)carbonate (BCMP) as a novel *tert*-butoxycarbonylation reagent for amines. By employing BCMP with different amines with hydroxyl moiety under mild temperature (78 °C), the desired *N*-Boc amines were obtained in high yields, especially the Boc carrier (3-cyano-4,6-dimethyl-2-hydroxypyridine, CDP, **1**) was insoluble in most solvents, which lead to safer processes and more easily available reactive reagents. Importantly, this reagent is general with respect to the amines, including the aromatic primary amines, aliphatic primary and secondary amines. This generality and chemoselectivity of the reagent allow preparation of many *N*-Boc amino acid esters and peptide. In considering the effect of

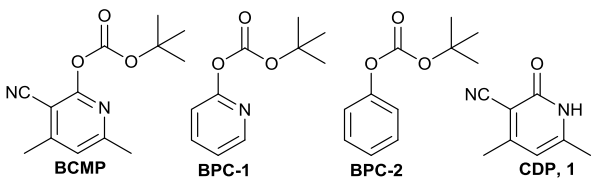

Fig. 1 Novel *tert*-butoxycarbonylation reagents and CDP.

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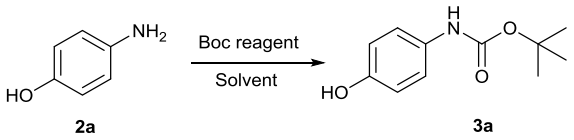
pyridine ring, cyano and methyl groups, we were drawn to use the *tert*-butyl pyridin-2-yl carbonate (BPC-1) and *tert*-butyl phenyl carbonate (BPC-2) as compared Boc reagents (**Fig. 1** and **Table 1**), which displayed weaker acylation reactivity and took longer time to give target compound than BCMP.

Results and Discussion

Identification of Reaction Conditions

The chemoselectivity of *tert*-butoxycarbonylation for amino and hydroxyl groups on an aryl ring was investigated using 4-aminophenol as a model substrate (**Table 1**). Preliminary experiments were carried out on 4-aminophenol with BCMP in toluene (entry **1**). The desired product *tert*-butyl (4-hydroxyphenyl)carbamate wasn't observed. Attempts to employ THF as solvent led to the similar result (entry **2**). However, a poorly soluble byproduct was obtained in the two entries. It was proved that the byproduct was Boc carrier of 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**1**, **Fig. 1**) by heating only BCMP in corresponding reaction conditions. The *N*-Boc product in 60% yield, along with unreacted starting material (entry **3**) was obtained by replacing THF with acetonitrile. It was shown that the solvent played an important role in the reaction according to the results of entries 1-3. Therefore, attempts to optimize the reaction through modification of the solvent proved successful. With the use of more environmentally friendly ethanol and methanol as solvents respectively, a target compound was obtained in the yield of 97% (entry **4**, **5**), suggesting that the O–H bond of solvent might be integral to its success. We postulated that hydrogen bond between ethanol and the carbonyl oxygen atoms of BCMP causes "electrophilic activation" making the carbonyl group more susceptible to nucleophilic attack since polar protic solvents could effectively selectively catalyze the *tert*-butoxycarbonylation of aromatic amines. Surprisingly, water, a strong polar solvent, was also favored (entry **6**). When the amount of BCMP was increased to 2 equiv, the desired compound **3a** was obtained in 96% yield and the phenolic hydroxyl couldn't be *tert*-butoxycarbonylated (entry **7**). Given the propensity of poor water solubility of compound, the *tert*-butoxycarbonylation was carried out in ethanol at reflux temperature. Certainly, for water-soluble amino acids, we preferred water as the solvent. Under these optimized conditions, the desired *tert*-butyl(4-hydroxyphenyl)carbamate **3a** was isolated in 97% yield. The ability of 4-aminophenol to participate in the reaction opens the possibility for *tert*-butoxycarbonylation.

Table 1. Optimization of reaction conditions [a]



2a **3a**

Entry	Boc reagent	Solvent	Temp (°C)	Time (h)	Yield (%) [b]
1	BCMP	toluene	reflux	24	--[c]
2	BCMP	THF	reflux	24	--[c]
3	BCMP	acetonitrile	reflux	10	60 [d]
4	BCMP	ethanol	reflux	2	97
5	BCMP	methanol	reflux	2	97
6	BCMP	H_2O	50	4	90
7 [e]	BCMP	ethanol	reflux	2	96
8	BPC-1	ethanol	reflux	10	54 [d]
9	BPC-2	ethanol	reflux	10	35 [d]

[a] Unless otherwise noted, 1 equiv of BCMP was used. [b] Isolated yield. [c] Almost no reactions were observed by TLC. [d] Isolated yield, along with unreacted starting material. [e] Conditions: 2 equiv of BCMP.

Identification of Conversion by React IR

In situ React IR technology was employed to monitor the conversion of 4-aminophenol to the corresponding *tert*-butyl(4-hydroxyphenyl)carbamate (**3a**). As seen in **Fig. 2** (A, 3D surface and B, 2D trends), less than 5 min after addition of BCMP to the 4-aminophenol in methanol start heating, a new, sharp peak appears at 1723 cm^{-1}. The intensity of this peak gradually increased as the reaction temperature was raised to reflux. Importantly, the disappearance of the 1770 and 1667 cm^{-1} band were marked by the appearance of three bands at 1723, 1622 and 1611 cm^{-1} corresponding to *tert*-butyl (4-hydroxyphenyl)carbamate (**Fig. 2**, **A**). We believed that the new IR absorption at 1723 cm^{-1} was attributable to the existence of carbamate carbonyl **3a**. The appearance of peaks at 1622 cm^{-1} 1611 cm^{-1} were responsible for amide N-H and benzene ring C-C, respectively. IR data of similar *N*-Boc compounds revealed that a stretch of 1723 cm^{-1} was highly characteristic of this type

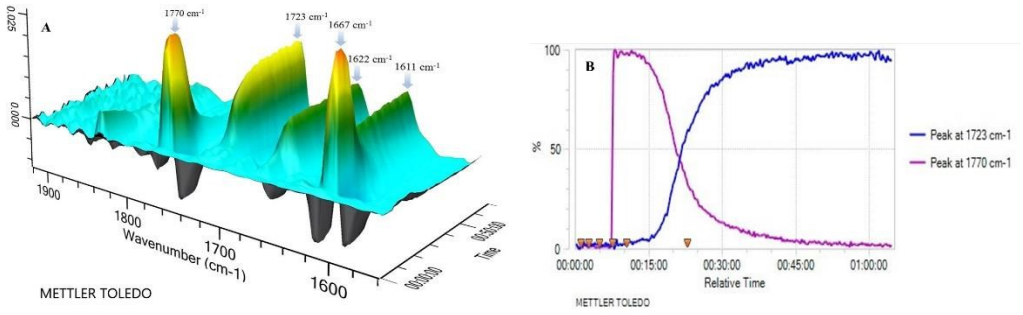


Fig.2 3D surface and 2D trends of ReactIR experiment.

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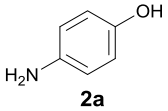
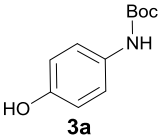
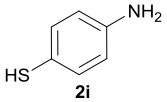
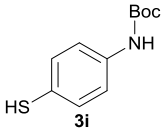
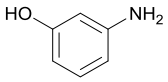
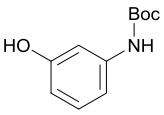
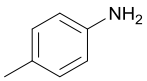
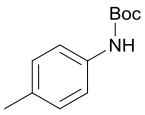
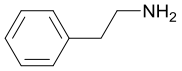
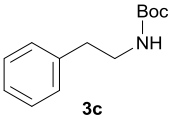
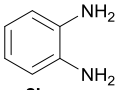
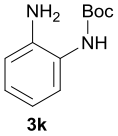
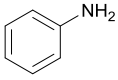
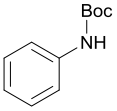
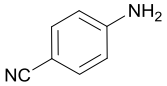
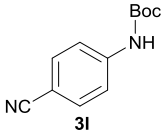
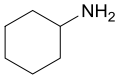
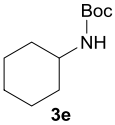
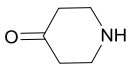
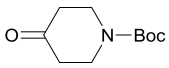
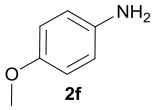
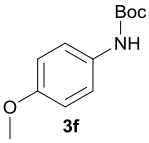
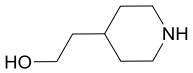
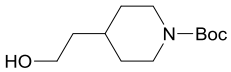
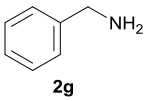
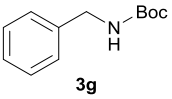
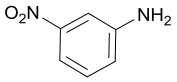
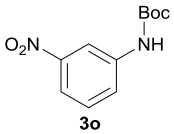
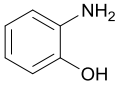
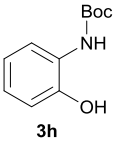
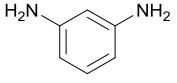
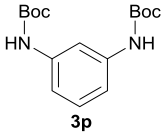
of carbamate carbonyl system. The conversion of BCMP before reflux reached 50% after only 15 min, and 100% after 30 min (**Fig. 2**, **B**). Thus, it was concluded that the conversion of 4-aminophenol to the corresponding *tert*-butyl(4-hydroxyphenyl)carbamate underwent quickly nucleophilic substitution to afford target compound.

***tert*-Butoxycarbonylation of Amines by BCMP**

The scope of the reaction with respect to aromatic primary amines, aliphatic primary and secondary amines is broad (**Table 2**), but alcohol, phenol, mercaptan, thiophenol and amide couldn't be *tert*-butoxycarbonylated by BCMP. Meanwhile, a more sterically encumbered compound such as 2,6-diisopropylaniline couldn't react in the case. A wide range of functional groups are tolerated, including hydroxy, methoxy, thiol, methyl, cyano, carbonyl and nitro groups. Both electron-rich and some electron-poor aniline participated equally well in the case. BCMP had high chemoselectively in aromatic amine to afford moderate to high yield.

The aromatic amine substituted with electron withdrawing group led to the lower yields, for example, **3l** and **3o** in 36% and 18% yield respectively. When the aromatic amine substituted with a stronger electron withdrawing group such as a nitro group in *para*-position **2v**, the *tert*-butoxycarbonylation couldn't occur. When the strong electron-withdrawing nitro group was in the *meta*-position of the amino group, producing a weaker electronic-withdrawing effect and a small amount of product could be obtained with 18% yield, such as **3o**. To our delight, ester compounds with weaker electron-withdrawing effect delivered the Boc product in moderate yield. Moreover, compared with the para-substitution, the electron-withdrawing substituent is in the meta position, leading to accelerating the reaction (e.g. **3t**, **3u**). In contrast, the aromatic amines

Table 2 Scope with Respect to amines [a]

Entry	Substrate	Product	Yield (%) [b]	Entry	Substrate	Product	Yield (%) [b]
1	 **2a**	 **3a**	97	9	 **2i**	 **3i**	91
2	 **2b**	 **3b**	94	10	 **2j**	 **3j**	95
3	 **2c**	 **3c**	99	11	 **2k**	 **3k**	85
4	 **2d**	 **3d**	97	12	 **2l**	 **3l**	36
5	 **2e**	 **3e**	98	13	 **2m**	 **3m**	96
6	 **2f**	 **3f**	100	14	 **2n**	 **3n**	95
7	 **2g**	 **3g**	97	15	 **2o**	 **3o**	18
8	 **2h**	 **3h**	89	16	 **2p**	 **3p**	88

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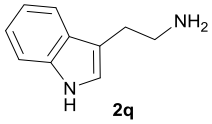
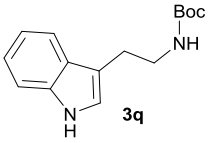
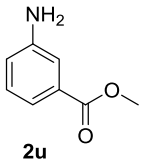
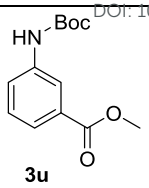
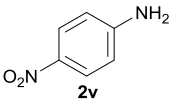
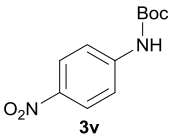
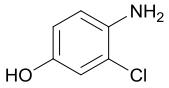
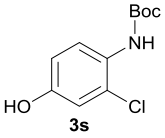
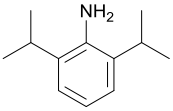
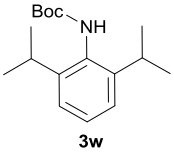
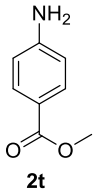
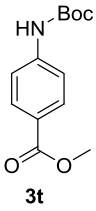
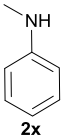
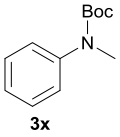
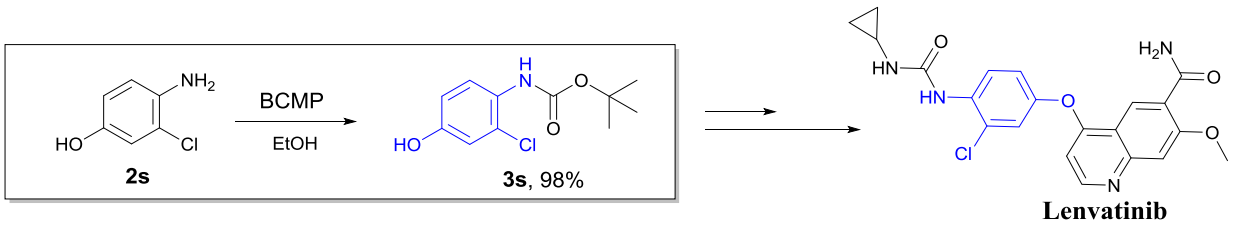
Entry	Substrate	Product	Yield (%) [b]	Entry	Substrate	Product	Yield (%) [b]
17	 2q	 3q	92	21	 2u	 3u	70
18	 2r	 3r	98	22	 2v	 3v	0
19	 2s	 3s	98	23	 2w	 3w	0
20	 2t	 3t	55	24	 2x	 3x	0

[a] Unless otherwise noted, the products were obtained by method A. Method A：A mixture of BCMP (2.02 mmol) and substituted amine (2.02 mmol) in ethanol (10 mL) was heated under reflux for 1 h; Isolated yield. [b] Almost no reactions were observed by TLC.

substituted with electron-donating group could increase the yield (**3f**). The methoxyl promoting the reaction resulted in 100% yield. Different results were observed for aromatic secondary amines. The *N*-methylaniline couldn't be protected with Boc in the general condition, which displayed the selectivity to aromatic primary amines.

1,2-Diaminobenzene, which has been used in this reaction with the use of 2 equiv BCMP, led to a more promising result. The mono-Boc product was isolated in 85% yield (**3k**), and importantly, the di-Boc product wasn't observed. This abnormal result led us to examine 1,3-diaminobenzene substrate. Interestingly, two amino groups were in the *meta*-position to give the di-Boc product in 88% yield, such as **3p**. We speculated that mono-Boc product of 1,2-diaminobenzene formed hydrogen bond with the *ortho*-amino group, which led to a decrease the nucleophilicity of the amino group, di-Boc product of 1,2-diaminobenzene couldn't been obtained.

Moreover, aliphatic primary amines also provided the *N*-Boc product under the general reaction conditions over 97% yields, such as **3c**, **3e** and **3g**. Further, aliphatic secondary amines also can be used in the reaction to afford *N*-Boc product in over 95% yields, such as **3m**, **3n** and **3r**. However, under this condition *tert*-butoxycarbonylation of phenol and 4-nitrophenol did not occur, resulting in the recovery of Boc carrier in 95% recovery rate. With these results in hand, we concluded that functional groups with weaker nucleophilicity than oxygen atom were failed to be *tert*-butoxycarbonylaed with Boc using BCMP as Boc reagent under the general condition.



Scheme 1. Synthetic method of Lenvatinib.

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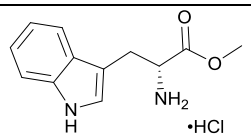
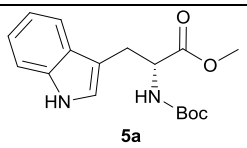
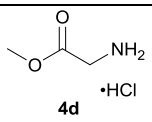
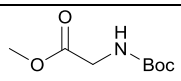
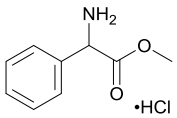
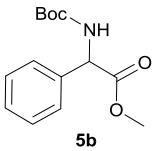
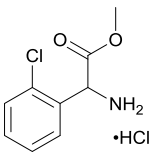
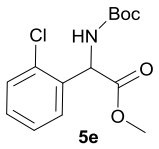
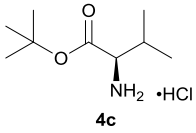
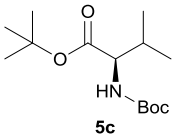
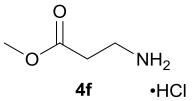
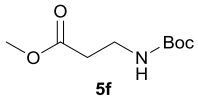
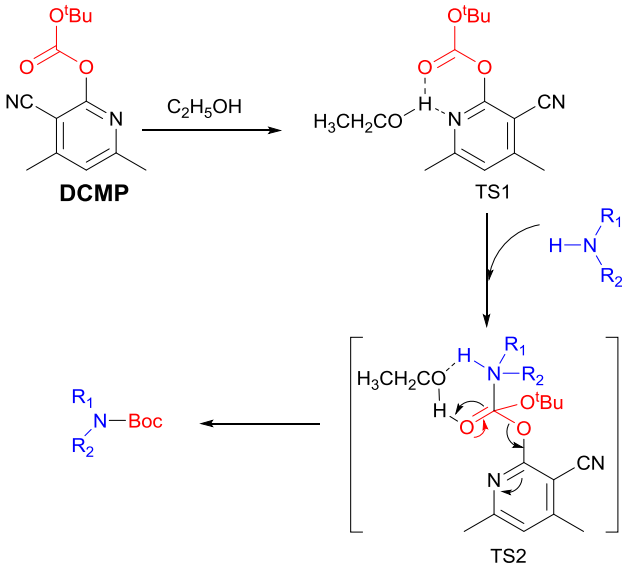
Table 3 Scope with Respect to Amino acids A [a]

Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	 **4a**	 **5a**	91	4	 **4d**	 **5d**	96
2	 **4b**	 **5b**	86	5	 **4e**	 **5e**	95
3	 **4c**	 **5c**	97	6	 **4f**	 **5f**	92

[a] Unless otherwise noted, the products were obtained by method B. Method B: A mixture of BCMP (2.02 mmol), potassium carbonate (2.02 mmol), amino acids ester hydrochlorides (2.02 mmol) in water (10 mL) was heated under reflux for 1 h. [b] Isolated yield.

There is clear relevance of **3s** from 4-amino-3-chlorophenol and the BCMP to the preparation of bioactive molecule. Lenvatinib [18] (**Scheme 1**) is an important medicinal agent used in the treatment of progressive radioiodine-refractory differentiated thyroid cancer. This compound can be readily prepared from *tert*-butyl (2-chloro-4-hydroxyphenyl)carbamate. As an illustration of the utility of our *tert*-butoxycarbonylation process, simple *tert*-butoxycarbonylation of 4-amino-3-chlorophenol provided in high yield the *tert*-butyl(2-chloro-4-hydroxyphenyl) carbamate. This result suggests that our new chemoselectivity *tert*-butoxycarbonylation method can be an alternative method for synthesis of Lenvatinib.

***tert*-Butoxycarbonylation of Amino Acids by BCMP**



Scheme 2. Plausible mechanism for *N*-Boc protection of amines

Simultaneously, the *tert*-butoxycarbonylation of amino acids ester hydrochlorides was undertaken. Screening experiments were made with *L*-Trp-OMe•HCl as a model compound using the equal amount of BCMP in ethanol. It was found the target compound was not observed, whereas additive of potassium carbonate (1 equiv) resulted in 80% yield (Method B). Use of water as a solvent provided a better result (91%) with reflux. On the basis of these results, the standard condition for the *tert*-butoxycarbonylation of several amino acid ester hydrochlorides with BCMP (1 equiv) and potassium carbonate (1 equiv) was in water under reflux. Thus, the *tert*-butoxycarbonylation of various amino acids in this study was normally performed, and the corresponding *N*-Boc-*L*-amino acid esters were obtained in high yields as shown in **Table 3**.

Possible Mechanistic Pathway

The role of ethanol may be explained by **Scheme 2** [19]. Hydrogen bond formation between ethanol and the carbonyl oxygen atoms of BCMP causes "electrophilic activation" making the carbonyl group more susceptible to nucleophilic attack (transition state 1, TS1). In turn, the oxygen atom of ethanol forms a hydrogen bond with the hydrogen atom of the amine and increases the electron density at the nitrogen atom creating nucleophilic activation (transition state 2, TS2). Then, intramolecular nucleophilic attack by the nitrogen atom on the carbonyl carbon followed by elimination of 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile forms the carbamate.

Conclusions

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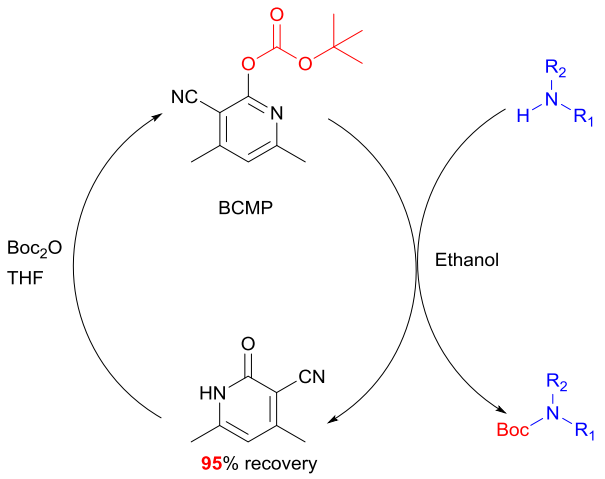

Scheme 3. Cyclic mechanism of Boc carrier.

In summary, we have developed a cyclic system for the selective *tert*-butoxycarbonylation of amines that utilizes readily available Boc reagent (BCMP) and related aromatic primary amines, aliphatic primary and secondary amines. This protocol proposes a highly chemoselective Boc reagent in C-N bond construction and provides the examples of *tert*-butoxycarbonylation of amines using readily available starting materials under mild reaction conditions and simple workup, which is a useful Boc reagent in the preparation of bioactive molecules such as peptide. The key to this discovery was the identification of a highly chemoselective Boc reagent and recyclable Boc carrier. The Boc carrier of 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile has poor solubility in most solvents which can be recycled just by filtration to achieve recycling in 95% recovery rate (**Scheme 3**) and has broad prospects for industrial application.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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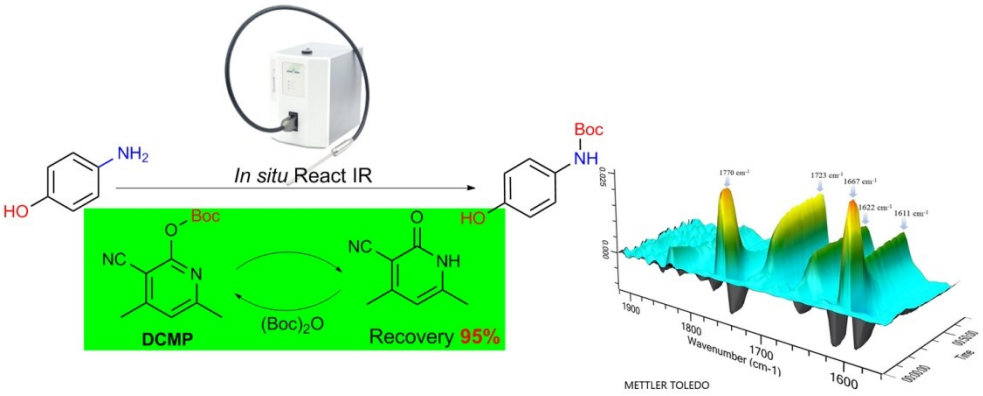

The use of *tert*-butyl(3-cyano-4,6-dimethylpyridin-2-yl)carbonate as chemoselective *tert*-butoxycarbonylation reagent for aromatic and aliphatic amines has been demonstrated (30 examples).