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Chemoselective *O-tert*-butoxycarbonylation of phenols using 6,7-dimethoxyisoquinoline as a novel organocatalyst

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ABSTRACT

The chemoselective *O-tert*-butoxycarbonylation of phenols using low levels (5–0.1 mol %) of 6,7-dimethoxyisoquinoline as a reusable organocatalyst is described.

1. Introduction

Among the carbonic acid derivatives used as protecting groups, *tert*-butyl carbonates and carbamates are of great importance in organic chemistry due to both their resistance to nucleophilic reagents and ease of removal under specific conditions.[1] We previously reported on the use of 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) prepared by the reaction of isoquinoline with Boc_2O as a novel and chemoselective *tert*-butoxycarbonylation reagent for acidic proton-containing substrates, such as phenols, amines, hydrochlorides, and carboxylic acids.[2] However, stoichiometric amounts of BBDI were needed for this reaction to proceed to completion. In view of the proposed mechanism of this reaction, we were prompted to investigate the organocatalyzed *O-tert*-butoxycarbonylation of phenols. The introduction of a Boc group into phenols is generally achieved by the reaction of Boc_2O in the presence of a phase transfer catalyst,[3] 4-dimethylaminopyridine (DMAP) as a catalyst[4] and $Zn(OAc)_2$[5] or $BiCl_3$[6] as Lewis acid catalyst. However, these conditions involve the *O-tert*-butoxycarbonylation of both aliphatic and aromatic hydroxyls, that is, they are not chemoselective. The chemoselective *O-tert*-butoxycarbonylation of phenols using triphenylphosphine or carbon tetrabromide as an organocatalyst was recently reported,[7] but these are not ideal reagents, in that they require the a high catalyst loading (10 mol %), involve long reaction time (12–72 h) at room temperature (~35–40 °C), and also involve the *O-tert*-butoxycarbonylation of benzyl alcohol. Accordingly, we wish to report herein on a method for the chemoselective *O-tert*-butoxycarbonylation of phenols using 6,7-dimethoxyisoquinoline as a novel organocatalyst in the presence of Boc_2O.

Based on our findings, the following mechanism is proposed for the *O-tert*-butoxycarbonylation of aromatic alcohols. BBDI is first protonated by an aromatic alcohol to form a cyclic six-membered intermediate **A**. The subsequent attack of the resulting aromatic alkoxide anion to the activated carbonyl of **A**, followed by cleavage gives rise to an *O*-Boc aromatic alcohol, isoquinoline, and *tert*-butyl alcohol.[2] Therefore, the liberated isoquinoline would be made available to again react with Boc_2O to regenerate BBDI (Scheme 1).

In practice, the *tert*-butoxycarbonylation of phenol (**1a**) was carried out using isoquinoline (5 mol %) as a catalyst in the presence of Boc_2O (120 mol %) in CH_2Cl_2 at room temperature for 10 h to give the *O*-Boc phenol **2a** in 71% yield. We screened a number of electron-donating substituted isoquinolines **3** for possible use in this reaction and the results are shown in Table 1. Among them, 6,7-dimethoxyisoquinoline (**3c**) gave the best results (entry 4). Presumably, because 6,7-dimethoxyisoquinoline contains an electron-rich nitrogen, the formation of a BBDI like reagent would be faster than that of the other candidates. Several solvents were tested for the reaction using **3c**, and CH_2Cl_2 and toluene afforded similar yields as shown in Table 1. On the other hand, the use of electron-deficient isoquinoline, such as 5-nitroisoquinoline (**3d**) afforded no product.

This *tert*-butoxycarbonylation reaction can be used to derivatize a variety of substituted phenols to provide *O*-Boc phenols in excellent yields with no damage of the substituted functional groups as exhibited in Table 2. A high chemoselectivity was demonstrated when **1g,h** were reacted in the presence of an aliphatic hydroxyl group to give **2g,h** with no detectable amounts of the alcoholic

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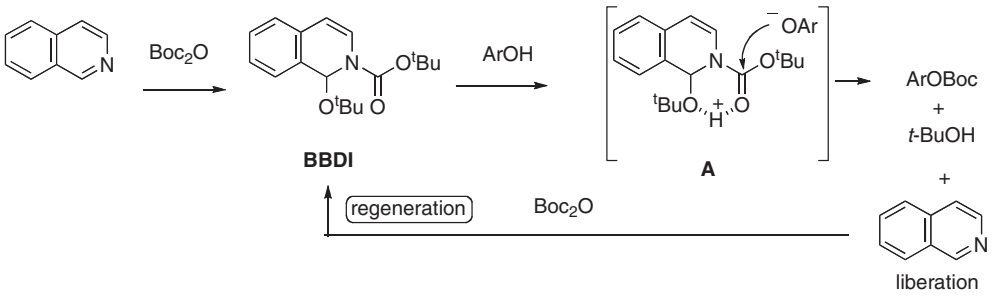
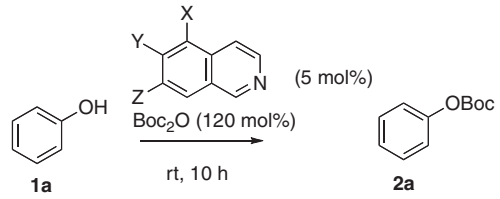


Scheme 1.

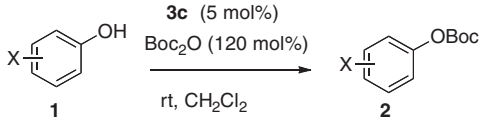
Table 1
tert-Butoxycarbonylation of **1a**



Entry	Organocatalyst	Solvent	Yield[a] (%)
1	X, Y, Z = H	CH_2Cl_2	71
2	X = OMe, Y, Z = H **3a**	CH_2Cl_2	77
3	X = H, Y = OMe, Z = H **3b**	CH_2Cl_2	86
4	X = H, Y, Z = OMe **3c**	CH_2Cl_2	93
5	X = H, Y, Z = OMe **3c**	THF	88
6	X = H, Y, Z = OMe **3c**	Toluene	92
7	X = H, Y, Z = OMe **3c**	MeCN	84
8	X = NO_2, Y, Z = H **3d**	CH_2Cl_2	0

[a] Isolated yields.

Table 2
tert-Butoxycarbonylation of **1** with 6,7-dimethoxyisoquinoline (**3c**) as an organocatalyst

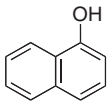
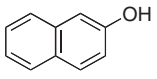
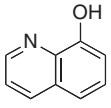
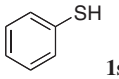
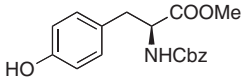


Entry	1	Time (h)	Yield[a] (%)
1	**1b**, X = 4-NO_2	5	96
2	**1c**, X = 4-CN	10	100
3	**1d**, X = 4-CO_2Me	10	95
4	**1e**, X = 4-OMe	10	98
5	**1f**, X = 4-Cl	10	90
6	**1g**, X = 4-CH_2OH	10	95
7	**1h**, X = 4-CH_2CH_2OH	10	95
8	**1i**, X = 4-$CONH_2$	10	97
9	**1j**, X = 4-OBn	10	100
10	**1k**, X = 4-CHO	10	93
11	**1l**, X = 2-NO_2	5	100
12	**1m**, X = 2-^{t}-Bu	10	93
13	**1n**, X = 2-OMe	10	91
14	**1o**, X = 2-Cl	10	97

[a] Isolated yields.

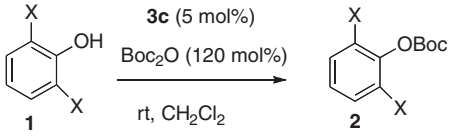
O-Boc being found (entries 6 and 7).[8] The nature of the substituents on the aromatic ring of **1** seems to have some influence on the reaction rate. For example, the presence of an electron-withdrawing group, such as a nitro group results in an accelerated reaction. The reaction is more rapid and more complete when more acidic phenol is used in the reaction (entries 1 and 11).

Table 3
tert-Butoxycarbonylation of **1p–t** with **3c** as an organocatalyst

Entry	1	Time (h)	Yield[a] (%)
1	 **1p**	10	96
2	 **1q**	10	100
3	 **1r**	10	95
4	 **1s**	10	98
5	 **1t**	10	90

[a] Isolated yields.

Table 4
tert-Butoxycarbonylation of 2,6-disubstituted phenols **1u–w**



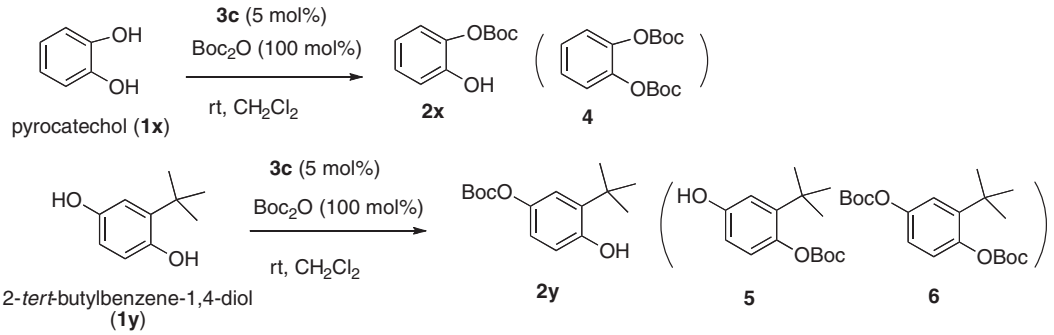
Entry	1	Time (h)	Yield[a] (%)
1	**1u**, X = Me	5	89
2	**1v**, X = *iso*-Pro	10	73
3	**1w**, X = *tert*-Bu	10	55
4	**1w**, X = *tert*-Bu	24	61

[a] Isolated yields.

In addition, miscellaneous compounds with phenol-like characteristics, such as naphtol and thiophenol could be *O*-butoxycarbonylated in high yields as exhibited in Table 3.

This *O*-butoxycarbonylation reaction is influenced by steric factors (Table 4). Namely, 2,6-disubstituted phenols underwent *O*-butoxycarbonylation at relatively slower rates and the reaction of 2,6-di-*tert*-butylphenol did not reach completion, even after a long reaction time of 24 h (entry 4).[3]

With the result in hand, the *O*-butoxycarbonylation of pyrocatechol (**1x**) and 2-*tert*-butylbenzene-1,4-diol (**1y**) was carried out in the presence of 1 equiv Boc_2O to provide the mono *O*-Boc products



Scheme 2.

Table 5
tert-Butoxycarbonylation of **1a** with **3c** in CH_2Cl_2 at room temperature

Entry	Catalytic loading (mol %)	Time (h)	Yield[a] (%)
1	5	10	93
2	1	31	91
3	0.5	72	94
4	0.1	96	88

[a] Isolated yields.

Table 6
tert-Butoxycarbonylation of **1a** reusing **3c** (5 mol %)in CH_2Cl_2 at room temperature

Entry	The number of times (reuses)	Time (h)	Yield[a] (%)
1	1	10	92
2	2	10	92
3	3	14	92
4	4	14	93
5	5	14	92

[a] Isolated yields.

2x (88%) and **2y** (95%), respectively, with no contamination by di-*O*-Boc derivative **4** and mono-*O*-Boc regioisomers **5** and **6** due to sterically hindered substituents, such as *O*-Boc and *tert*-butyl groups at the *ortho* position (Scheme 2). However, attempts to *O*-butoxycarbonylate of resorcinol and hydroquinone provided gave a mixture of mono- and di-*O*-Boc products under similar conditions.

Next, catalytic loading with **3c** was examined for the *O*-butoxycarbonylation of **1a** in CH_2Cl_2 at room temperature and the results are shown in Table 5. A very low catalyst loading (0.1 mol %) can be used, although the reaction time is long (entry 4). To our knowledge, this value of 0.1 mol % as an organocatalyst is quite small.

Lastly, the reuse of the organocatalyst was tested. After work-up, the aqueous layer, including 6,7-dimethoxyisoquinoline as the hydrochloride salt, was made basic by the addition of 10% NaOH, the solution extracted with ethyl acetate, and evaporated to yield the recovered 6,7-dimethoxyisoquinoline, which was then reused in subsequent reactions without further purification. The results are summarized in Table 6.[9] Although the reaction has been repeated only five times in this stage, it was expected that this procedure would be done in additional runs. In general, the reuse of a condensing reagent is difficult due to its transformation. Therefore, this operation is valuable and remarkable.

In summary, the chemoselective *O*-*tert*-butoxycarbonylation of phenols using 6,7-dimethoxyisoquinoline as a novel organocatalyst under mild condition was developed. This procedure has novel advantages over other catalysts use for this purpose in that the catalyst is reusable and can be used at very low catalyst loadings. In addition, since the recent Letter of the Suzuki–Miyaura coupling of aryl *tert*-butylcarbonates,[10] functionalized *O*-Boc phenols would be expected to be in widespread use as precursors to polysubstituted aromatic compounds.

2. Typical experimental procedures

In a flask were placed phenol (**1a**) (2.0 mmol), Boc_2O (2.4 mmol), and 6,7-dimethoxyisoquinoline **3c** (0.1 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (3 mL) was added and the resulting solution was stirred at room temperature for 10 h. Ethyl acetate (80 mL) was then added and the mixture was successively washed twice with 5% HCl (10 mL), brine (20 mL), twice with 10% NaOH (10 mL), and brine (20 mL). The solution was then dried over anhydrous Na_2SO_3 and evaporated. The residue was purified by flash column chromatography on silica gel to give *O*-Boc-phenol **2a** (361 mg, 93%) as a colorless oil.

Acknowledgment

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References and notes

1. (a) Wuts, P. G. M.; Green, T. W. *Greene's Protective Groups in Organic Synthesis*, 4rd ed.; Wiley: New York, NY, 2007; (b) Parrish, J. P.; Salvatore, R. N.; Jung, K. W. *Tetrahedron* **2000**, *56*, 8207; (c) Kocienski, P. J. *Protecting Groups*; Stuttgart: George Thieme, 2000.
2. (a) Ouchi, H.; Saito, Y.; Yamamoto, Y.; Takahata, H. *Org. Lett.* **2002**, *4*, 585; (b) Saito, Y.; Ouchi, H.; Takahata, H. *Tetrahedron* **2006**, *62*, 11599.
3. Houlihan, F.; Bouchard, F.; Frchet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153.
4. (a) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368; (b) Hansen, M.; Riggs, J. R. *Tetrahedron Lett.* **1998**, *39*, 2705.
5. Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Locatelli, M.; Melchiorre, P.; Palazzi, P.; Sambri, L. *Synlett* **2006**, 2104.
6. Suryakiran, N.; Prabhakar, P.; Venkateswarlu, Y. *Synth. Commun.* **2008**, *38*, 177.
7. (a) Chebolu, R.; Chankeshwara, S. V.; Chakraborti, A. K. *Synthesis* **2008**, 1448; (b) Chankeshwara, S. V.; Chebolu, R.; Chakraborti, A. K. *J. Org. Chem.* **2008**, *73*, 8615.
8. Even though reflux and the use of excess Boc_2O, di-Boc compound of **1g** was not detected.
9. The catalyst **3c** was recovered and reused as follows; ethyl acetate was added to the reaction, and the mixture was extracted twice with 5% HCl. The extracts were made basic by the addition of 10% NaoH and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous Na_2SO_3 and evaporated to yield **3c** (~95%). This procedure was repeated in future runs.
10. Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748.