### Letter

# A Simple and Powerful tert-Butylation of Carboxylic Acids and **Alcohols**

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Received: 08.08.2023

Accepted after revision: 29.08.2023

Published online: 29.08.2023 (Accepted Manuscript), 09.10.2023 (Version of Record) DOI: 10.1055/a-2161-9689; Art ID: ST-2023-08-0343-L

Abstract A simple and safe tert-butylation reaction was developed. Treatment of various free amino acids with 1.1 equivalents of bis(trifluoromethanesulfonyl)imide in tert-butyl acetate directly afforded tertbutyl esters with free amino groups guickly and in good yields. In addition, various carboxylic acids and alcohols without amino groups were converted into tert-butyl esters and ethers, respectively, in high yields in the presence of small catalytic amounts of bis(trifluoromethanesulfonyl)imide. All tert-butylation reactions of free amino acids, carboxylic acids, and alcohols proceeded much faster and in higher yields compared with conventional methods.

Key words tert-butylation, amino acids, tert-butyl esters, tert-butyl ethers, bis(trifluoromethanesulfonyl)imide

The *tert*-butyl ester group is widely used as a protecting group for carboxylic acids due to its excellent stability against various nucleophiles and reducing agents, as well as its convenient deprotection under acidic conditions.<sup>1</sup> It is therefore frequently used as a protecting group for the carboxylic acid functionality of amino acids.<sup>2</sup> Common methods for the formation of tert-butyl esters include the condensation of carboxylic acids with tert-butanol<sup>3</sup> or with bubbling isobutene gas in the presence of concd H<sub>2</sub>SO<sub>4</sub>.<sup>4</sup> In addition, the use of various tert-butylating agents, including di-tert-butyl dicarbonate (Boc<sub>2</sub>O),<sup>5</sup> tert-butylisourea,<sup>6</sup> tert-butyl trichloroacetimidate,7 N,N-dimethylformamide di-tert-butyl acetal,<sup>8</sup> 2-tert-butoxypyridine,<sup>9</sup> and tert-butyl acetoacetate,<sup>10</sup> as well as transesterification reactions<sup>11</sup> have been reported. However, these methods basically have to be conducted in organic solvents, and their applications to free amino acids that are insoluble in organic solvents are limited. There have been several examples of the direct formation of *tert*-butyl esters of free amino acids,<sup>12</sup> and the use of perchloric acid (HClO<sub>4</sub>) in tert-butyl acetate (tBuOAc) is an often-used condition.<sup>12a,13</sup> However, perchloric acid is a potentially hazardous reagent. Moreover, the reaction sometimes prematurely terminates, and yields and reaction rates also need to be improved. To proceed with the reaction efficiently, we considered it necessary to increase the solubility of free amino acids in organic solvents. The use of suitable organic acids to form salts was expected to increase solubility while also serving as an acid catalyst for tert-butylation reactions (Scheme 1). Here, we report our investigations of various acids for the direct tert-butylation

Scheme 1 The concept for the direct tert-butylation reaction of free amino acids

soluble salt

reaction of free amino acids.

-XH

appropriate acid (2)

1 free amino acids insoluble in organic solvent

As a substrate for the *tert*-butylation reaction, we chose 2-hydroxy-4-aminobutyric acid (HABA) (5) because the tert-butyl-protected HABA (6) was required for our synthetic investigations involving natural phytosiderophore mugineic acid analogues. First, hydrophobic acids to increase the solubility of the salt of 5 were examined in the reaction using t-BuOAc as both the solvent and the tert-butylating reagent. The addition of diphenyl phosphate or ptoluenesulfonic acid (TsOH) did not result in dissolution of 5 in t-BuOAc, and the desired 6 was not obtained at all (Table 1, entries 1 and 2). Because fluorinated acids increase the solubility of salts, trifluoroacetic acid (TFA) was next examined. The addition of 50 equivalents of TFA resulted in the dissolution of **5** in *t*-BuOAc, but the yield of **6** was only 7% (entry 3), suggesting that the acidity of TFA was insufficient for the generation of a *tert*-butyl cation from *t*-BuOAc.

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Therefore, to increase acidity and solubility, the acid was changed to bis(trifluoromethanesulfonyl)imide (Tf<sub>2</sub>NH). Treatment with 2.0 equivalents of Tf<sub>2</sub>NH readily dissolved 5, and the reactivity was dramatically enhanced to complete the reaction within two hours, giving the desired di-tertbutylated product 6 in 68% isolated yield as its Tf<sub>2</sub>NH salt (entry 4). The Tf<sub>2</sub>NH was readily removed from the salt by washing with 10% aqueous ammonia solution to give the free amine. To address the potential issue of the formation of a five-membered lactam, compound 6 was purified and stored in the form of its Tf<sub>2</sub>NH salt and desalinated prior to its use. In addition, decreasing the number of equivalents of  $Tf_2NH$  to 1.1 improved the yield to 86% (entry 5), and it was confirmed that the reaction was actually applicable on a gram scale. On the other hand, increasing the concentration in t-BuOAc (0.2 M) decreased the yield to 64% (entry 6). Furthermore, a similar reaction did not proceed at -20 °C (entry 7), and 6 was not obtained in other *tert*-butylating solvents such as t-BuOH or t-BuOMe (entries 8 and 9). On the other hand, Tf<sub>2</sub>NH did not dissolve **5** in dichloromethane  $(CH_2Cl_2)$ , and bubbling isobutene gas through the  $CH_2Cl_2$ solvent did not give 6 (entry 10). A similar fluorinated strong acid, trifluoromethanesulfonic acid (TfOH), also dissolved 5, although the resulting solution was slightly turbid, and 6 was obtained in 80% yield (entry 11). The conventional acid HClO<sub>4</sub> also gave the desired **6**, but the reaction was very slow and terminated prematurely; moreover, the yield was 61%, which is lower than that with Tf<sub>2</sub>NH or TfOH (entry 12). Other acids, such as H<sub>2</sub>SO<sub>4</sub>, HNO<sub>3</sub>, and CH<sub>3</sub>SO<sub>3</sub>H, did not give 6 (entries 13-15), suggesting that super-strong acidity is required in this reaction. The resulting 6 was used for the synthesis of mugineic acids and it was confirmed that racemization was not induced.

With the optimized conditions established, the reaction was applied to various free amino acids. In this investigation, the resulting tert-butyl esters of amino acids were successfully converted back into free amino groups, as there were no concerns regarding lactam formations (Scheme 2). The similar tert-butylation reactions of D-valine, L-leucine, and L-phenylalanine proceeded smoothly to give the desired *tert*-butyl esters 7, 8, and 9 with free amino groups in yields of 81, 74, and 86%, respectively. L-Phenylalanine tertbutyl ester 9 was converted into (+)- and (-)-Mosher amides, confirming that racemization had not occurred. Tertbutyl groups were easily introduced into free amino acids containing alcohol functionalities, resulting in the tert-butylation of both the carboxylic acid and alcohol groups. As a result, di-tert-butylated L-serine 10 was obtained in quantitative yield, whereas di-tert-butylated L-threonine 11 was obtained in 73% yield. In the case of amino acids possessing two carboxylic acid groups, such as L-aspartic acid and Lglutamic acid, both carboxylic acid groups were converted into their tert-butyl esters to give 12 and 13 in 77% yield and a modest yield, respectively. L-Cysteine, possessing a

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 Table 1
 Investigation of Appropriate Acids for the tert-Butylation Reaction

	CO₂H	acid	CO <sub>2</sub> <sup>t</sup> Bu	
	H <sub>2</sub> N 5 OH 5	solvent, 0 °C X <sup>-+</sup> H <sub>3</sub> N <sup>2</sup>	6 6	lu
Entry	Acid (equiv)	Solvent (0.1 M)	Time (h)	Yieldª (%)
1	(PhO) <sub>2</sub> P(O)OH (1.0	) <i>t</i> -BuOAc	24	-
2	TsOH (1.0)	<i>t</i> -BuOAc	72	-
3	TFA (50)	<i>t</i> -BuOAc	16	7
4	Tf <sub>2</sub> NH (2.0)	<i>t</i> -BuOAc	2	68
5	Tf <sub>2</sub> NH (1.1)	<i>t</i> -BuOAc	2.5	86
6	Tf <sub>2</sub> NH (1.1)	<i>t</i> -BuOAc (0.2 M)	18	64
7	Tf <sub>2</sub> NH (1.1)	<i>t</i> -BuOAc <sup>c</sup>	144	4 <sup>b</sup>
8	Tf <sub>2</sub> NH (1.5)	t-BuOH	24	-
9	Tf <sub>2</sub> NH (1.5)	<i>t</i> -BuOMe	24	-
10	Tf <sub>2</sub> NH (1.1)	$CH_2Cl_2^{d}$	144	-
11	TfOH	<i>t</i> -BuOAc	2	80
12	HClO <sub>4</sub> (1.2)	<i>t</i> -BuOAc	16	61
13	$H_2SO_4(1.1)$	t-BuOAc	72	-
14	HNO <sub>3</sub> (1.1)	<i>t</i> -BuOAc	24	-
15	CH <sub>3</sub> SO <sub>3</sub> H (2.0)	t-BuOAc	24	trace

<sup>a</sup> Isolated yield.

<sup>b</sup> NMR yield using pyrazine as an internal standard.

<sup>c</sup> The reaction was performed at –20 °C.

<sup>d</sup> Isobutene gas was bubbled through CH<sub>2</sub>Cl<sub>2</sub>.





thiol group, also smoothly dissolved and reacted, and the analogue **14**, in which the thiol group was also *tert*-butylated, was obtained in high yield. In the case of L-tyrosine which possesses a phenol group, product **15**, in which only the carboxylic acid was *tert*-butylated, was obtained as the major product in 68% yield, and **16**, in which both the phenol and the carboxylic acid group were *tert*-butylated, was also obtained as a minor product in 33% yield. On the other hand, the reaction of L-methionine was slow, and the desired *tert*-butyl ester **17** was obtained in only 7% yield as a Tf<sub>2</sub>NH salt. This substrate-scope investigation revealed that the *tert*-butylation reaction was applicable to various amino acids<sup>14</sup> other than L-methionine, due to the presence of the sulfide group.

In the *tert*-butylation reaction of free amino acids, 1.0 equivalent of Tf<sub>2</sub>NH was used for the soluble salt formation with amino groups, and the remaining 0.1 equivalent of Tf<sub>2</sub>NH made the reaction proceed. Therefore, a small catalytic amount of Tf<sub>2</sub>NH is considered sufficient for the tertbutylation reaction of carboxylic acids that do not have free amino groups. Thus, the Tf<sub>2</sub>NH-catalyzed tert-butylation reaction was applied to various carboxylic acids (Scheme 3). The conversion of hydrocinnamic acid, a simple carboxylic acid, into its tert-butyl ester 18 was achieved with just 2 mol% of Tf<sub>2</sub>NH, resulting in a 76% yield. A carboxylic acid possessing a ketone group was also converted into tert-butyl ester 19 in 79% yield by 5 mol% of Tf<sub>2</sub>NH, without affecting the ketone group. A bromo group also tolerated the reaction condition, and the tert-butyl ester 20 was obtained by treatment with 10 mol% of Tf<sub>2</sub>NH in 66% yield. A tertiary carboxylic acid and benzoic acid were also tert-butylated under catalytic conditions to give 21 and 22, respectively, in modest yields. The catalytic conditions were applicable to N-Cbz-protected amino acids, and the tert-butylation reactions of N-Cbz-L-serine and N-Cbz-L-azetidine-2-carboxylic acid were catalyzed by 5 mol% of Tf<sub>2</sub>NH to afford 23 and 24 in yields of 89 and 81%, respectively. Thus, the Tf<sub>2</sub>H-cata-





lyzed reaction was found to be applicable to various carboxylic acids that do not possess functional groups that could quench  $Tf_2NH$ , such as amino groups.<sup>15</sup>

Next, the catalytic conditions for the tert-butylation reaction were applied to alcohols. Although there have been several examples of the *tert*-butylation of alcohols,<sup>16</sup> the present reaction was expected to reduce both the catalyst loading and reaction time due to the high activity of Tf<sub>2</sub>NH. As the tert-butyl ethers of small alcohols are volatile and difficult to handle, high-molecular-weight alcohols were investigated this time (Scheme 4). The Tf<sub>2</sub>NH-catalyzed reaction of alcohols proceeded much faster than occurred with carboxylic acids. The reaction of decanol in the presence of only 2 mol% of  $Tf_2NH$  proceeded smoothly to afford *tert*-butyl ether **25** in 94% yield. In the presence of 1 mol% Tf<sub>2</sub>NH, benzyl alcohol underwent conversion to *tert*-butyl ether 26 with a yield of 75%. Importantly, no significant decomposition occurred due to the generation of the benzyl cation. Treatment by 1 mol% of Tf<sub>2</sub>NH of a propargyl alcohol afforded 27 in quantitative yield. In the case of diols, both alcohol groups were converted into tert-butyl ethers regardless of whether they were alkyl or propargyl alcohols, and di-tert-butyl ethers 28 and 29 were obtained in yields of 90 and 93%, respectively. The reaction of allylic alcohols also proceeded smoothly, and the allylic tert-butyl ether 30 was obtained in 88% yield. On the other hand, the reaction of phenol analogues stopped prematurely, as in the case of tyrosine 16, and the tert-butyl ether 31 was obtained in only 34% yield. Thus, it was revealed that the tert-butylation reaction of alcohols other than phenols proceeded smoothly and in high yields with very small amounts of  $Tf_2OH(1-2)$ mol%).17

Finally, the Tf<sub>2</sub>NH-catalyzed *tert*-butylation reaction was compared with the conventional method (Scheme 5). Previously, we prepared **34** from L-malic acid for the synthesis of natural phytosiderophoric mugineic acids<sup>18</sup> and





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the modified mugineic acid, proline deoxymugineic acid (PDMA), as fertilizers for desert soils.<sup>16</sup> The acetonide **32** derived from L-malic acid was heated to reflux in acetic acid and H<sub>2</sub>O to remove the acetonide group, and the solution was directly evaporated to give crude 33. Isobutene gas was bubbled through the dichloromethane solution of the resultant **33** in the presence of  $H_2SO_4$  to give **34** in 64% yield.<sup>19</sup> This method actually gave 34 on a gram scale, but repeated bubbling of isobutene gas was required and the reaction needed a very long time (7 days).<sup>16</sup> When we repeated the previous tert-butylation reaction and quenched at six days, **34** was obtained in 59% yield. On the other hand, the Tf<sub>2</sub>NHcatalyzed tert-butylation reaction of 33 proceeded much faster to give **34** in a very short time (3 h) with a higher (78%) yield (Scheme 5) (see the Supplementary Information, Scheme S1, for the time course of these reactions).



**Scheme 5** Comparison of If<sub>2</sub>NH-catalyzed *tert*-butylation reaction of **32** with the conventional method

In conclusion, a simple and safe tert-butylation reaction has been developed. The reaction employs Tf<sub>2</sub>NH as a reagent to generate soluble salts by reacting with the amino groups of amino acids in an organic solvent. Tf<sub>2</sub>NH also acted as a strong acid in this process. Additionally, tert-butyl acetate was used as both the solvent and the tert-butylation agent. The reaction enabled the direct conversion of free amino acids into tert-butyl esters. In addition, in the case of various carboxylic acids and alcohols without amino groups, a small catalytic amount of Tf<sub>2</sub>NH was sufficient to convert them into tert-butyl esters and ethers in high yields. All tert-butylation reactions of free amino acids, carboxylic acids, and alcohols proceeded much faster and in higher yields than did the conventional methods. The method developed in this study is a potential alternative to the conventional use of perchloric acid, simply by replacing it with bis(trifluoromethanesulfonyl)imide. However, this simple replacement dramatically increased the reaction rates and yields while providing safe conversions. Therefore, the authors consider that this information should be shared with a wide range of synthetic organic chemists.

# **Conflict of Interest**

2-Hydroxy-4-aminobutyric acid (HABA) (**5**) was provided by Aichi Steel Corporation, which is conducting cooperative research on the development of fertilizers for alkaline soils based on phytosiderophore mugineic acid analogues.

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## **Funding Information**

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This work was financially supported by JSPS KAKENHI (Grant Numbers JP21K19051 and JP22H00352), Adaptable and Seamless Technology transfer Program through Target-driven R&D (A-STEP) from the Japan Science and Technology Agency (JST) (Grant Number JPM-JTR214D), and the Research Clusters program of Tokushima University (No. 2201004).

### Acknowledgment

We thank to Drs. M. Suzuki and A. Mera of Aichi Steel Corporation for providing 2-hydroxy-4-amino butyric acid (HABA) (**5**).

### Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2161-9689.

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- (14) tert-Butyl 4-Amino-2-tert-butoxybutanoate (6); Typical Procedure

A suspension of 2-hydroxy-4-aminobutyric acid (HABA; **5**; 2.15 g, 18.0 mmol) in *t*-BuOAc (180 mL, 0.1 M) was cooled to 0 °C. and a solution of Tf<sub>2</sub>NH (5.58 g, 19.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (27 mL) at 0 °C was added to the suspension. The resulting mixture was stirred at 0 °C for 2.5 h and then slowly added to sat. aq NaHCO<sub>3</sub> (350 mL) at 0 °C (reverse addition). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 500 mL), and the combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (5:1, 2:1, to 0:1)] to give a white deliquescent Tf<sub>2</sub>NH salt; yield: 8.1 g (86%).

IR (KBr): 3187, 2980, 1721, 1621, 1350, 1229, 1197 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):  $\delta$  = 4.15 (dd, *J* = 7.3, 4.4 Hz, 1 H), 3.01 (td, *J* = 6.4, 1.5 Hz, 2 H), 2.03–1.85 (m, 2 H), 1.49 (s, 9 H), 1.21 (s, 9 H). <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD):  $\delta$  = 174.6, 125.0 (q), 122.5 (q), 119.9 (q), 117.4 (q), 83.2, 76.9, 71.0, 37.9, 32.3, 28.1, 28.0. HRMS-ESI: *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>27</sub>F<sub>6</sub>N<sub>2</sub>O<sub>7</sub>S<sub>2</sub>: 513.1164; found: 513.1155.

For the procedure to give **6** with a free amino group, see the Supporting Information.

(15) tert-Butyl 3-Phenylpropanoate (18); Typical Procedure

A solution of  $Tf_2NH$  (3.3 mg, 0.012 mmol) in  $CH_2Cl_2$  (0.15 mL) at 0 °C was added to a solution of hydrocinnamic acid (88.1 mg, 0.587 mmol) in *t*-BuOAc (5.9mL, 0.1 M). The mixture was

stirred at 0 °C for 16 h, then slowly added to sat. aq NaHCO<sub>3</sub> (7 mL) at 0 °C. The mixture was extracted with  $CH_2Cl_2$  (3 × 20 mL), and the combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (1:0, 20:1, to 10:1)] to give a colorless oil; yield: 92 mg (76%).

IR (KBr): 2978, 1732, 1367, 1147 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.34–7.28 (m, 2 H), 7.23–7.16 (m, 3 H), 2.91 (t, *J* = 7.6 Hz, 2 H), 2.54 (t, *J* = 7.6 Hz, 2 H), 1.41 (s, 9 H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 172.4, 140.9, 128.5, 128.4, 126.2, 80.4, 37.2, 31.2, 28.2. HRMS-ESI: *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>19</sub>O<sub>2</sub>: 207.1385; found: 207.1393.

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- (17) 1,6-Di-tert-butoxyhexane (29); Typical Procedure
- A solution of Tf<sub>2</sub>NH (6.6 mg, 0.023 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.15 mL) at 0 °C was added to a solution of hexane-1,6-diol (139 mg, 1.17 mmol) in *t*-BuOAc (11.7 mL, 0.1 M). The mixture was stirred at 0 °C for 16 and then slowly added to sat. aq NaHCO<sub>3</sub> (20 mL) at 0 °C. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL), and the combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (0:1, 20:1, to 10:1)] to give a colorless oil; yield: 250 mg (93%). IR (KBr): 2974, 1361, 1199, 1083 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):  $\delta$  = 3.32 (t, *J* = 6.8 Hz, 4 H), 1.56–1.47 (m, 4 H), 1.38– 1.30 (m, 4 H), 1.18 (s, 18 H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 72.4, 61.6, 30.8, 27.7, 26.2. HRMS-ESI: *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>31</sub>O<sub>2</sub>: 231.2324; found: 231.2315.
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