A simple and powerful *tert*-butylation of carboxylic acids and alcohols

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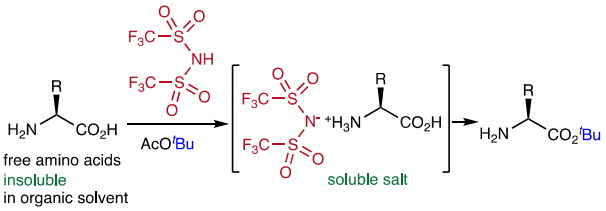

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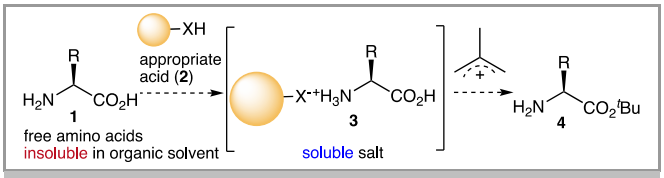
Abstract A simple and safe *tert*-butylation reaction was developed. Treatment of various free amino acids with 1.1 equiv of bis(trifluoromethanesulfonyl)imide in *tert*-butyl acetate directly afforded *tert*-butyl esters with free amino groups quickly and in good yields. In addition, various carboxylic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

Key words *tert*-butylation reaction, free amino acid, *tert*-butyl ester, *tert*-butyl ether, bis(trifluoromethanesulfonyl)imide

Tert-butyl ester is a widely utilized protecting group for carboxylic acids due to its excellent stability against different nucleophiles and reducing agents, as well as its convenient deprotection under acidic conditions.[1] It is therefore frequently used as a protecting group for the carboxylic acid functionality of amino acids.[2] Common methods for the formation of *tert*-butyl esters include condensation of carboxylic acids with *tert*-butanol[3] and isobutene gas bubbling in the presence of concd H_2SO_4.[4] In addition, *tert*-butylating agents have been reported, including di-*tert*-butyl dicarbonate (Boc_2O)[5], *tert*-butylisourea[6], *tert*-butyl trichloroacetimidate[7], *N,N*-dimethylformamide di-*tert*-butyl[8], 2-*tert*-butoxypyridine[9], and *tert*-butyl acetoacetate[10], as well as transesterifications[11]. 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 direct formations of *tert*-butyl esters of free amino acids,[12] and the use of perchloric acid ($HClO_4$) in *tert*-butyl acetate (AcO^{t}Bu) is an often-used condition.[12a,13] However, perchloric acid is the 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 formation of salts with suitable organic acids was expected to increase solubility while also serving as an acid catalyst for *tert*-butylation reactions (Scheme 1). Herein, we investigated various acids for the direct *tert*-butylation reaction of free amino acids.

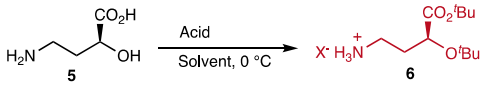


Scheme 1 The concept for the direct *tert*-butylation reaction of free amino acids.

As a substrate for the *tert*-butylation reaction, we chose 2-hydroxy-4-amino butylic acid (HABA) (**5**) because the *tert*-butyl protected HABA (**6**) was necessary for our synthetic investigations involving natural phytosiderophore mugineic acid analogs (Table 1). First, hydrophobic acids to increase the solubility of the salt of **5** were examined in the reaction using AcO^{t}Bu as both the solvent and the *tert*-butylating reagent. The addition of diphenyl phosphate or *p*-toluene sulfonic acid (*p*-TsOH) did not dissolve **5** in AcO^{t}Bu, and the desired **6** was not obtained at all (entries 1 and 2). As fluorinated acids increase the solubility of salts, trifluoro acetic acid (TFA) was next examined. The addition of 50 equiv of TFA actually dissolved **5** in AcO^{t}Bu, but the yield of **6** was only 7% (entry 3), suggesting that the acidity of TFA was insufficient for the generation of *tert*-butyl cation from AcO^{t}Bu. Thus, to increase acidity and solubility, the acid was changed to bis(trifluoromethanesulfonyl)imide (Tf_2NH). Treatment of 2.0 equiv of Tf_2NH readily dissolved **5**, and the reaction was dramatically enhanced to complete the reaction within 2 hours, giving the desired di-*tert*-butylated **6** in 68% isolated yield as a Tf_2NH salt (entry 4). The Tf_2NH salt was readily removed by washing with 10% aqueous ammonia solution to give free amine. To address the potential issue of 5-membered lactam formation, compound **6** was purified and stored in the

form of its Tf_2NH salt. Prior to usage, the compound was desalinated. In addition, decreasing the equivalent of Tf_2NH to 1.1 improved the yield to 86% (entry 5), and it was confirmed that the reaction was actually applicable to Gram scale. On the other hand, increasing the concentration in AcO^tBu (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 and ^{t}BuOMe (entries 8 and 9). On the other hand, Tf_2NH 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 $HClO_4$ also gave the desired **6**, but the reaction was very slow, it terminated prematurely, and the yield was 61%, which is lower than that with Tf_2NH or TfOH (entry 12). Other acids, such as H_2SO_4, HNO_3, and CH_3SO_3H, 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 confirmed that racemization was not induced.

Table 1 Investigation of appropriate acids for *tert*-butylation reaction.

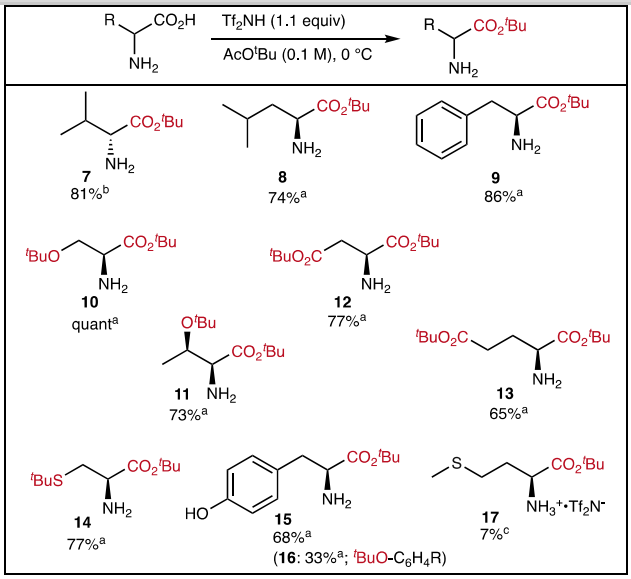


entry	Acid (equiv)	Solvent (0.1M)	Time (h)	Yield (%)[a]
1	$(PhO)_2P(O)OH$ (1.0)	AcO^tBu	24	0
2	*p*-TsOH (1.0)	AcO^tBu	72	0
3	TFA (50)	AcO^tBu	16	7
4	Tf_2NH (2.0)	AcO^tBu	2	68
5	Tf_2NH (1.1)	AcO^tBu	2.5	86
6	Tf_2NH (1.1)	AcO^tBu (0.2 M)	18	64
7	Tf_2NH (1.1)	AcO^tBu[c]	144	4[b]
8	Tf_2NH (1.5)	^{t}BuOH	24	0
9	Tf_2NH (1.5)	^{t}BuOMe	24	0
10	Tf_2NH (1.1)	CH_2Cl_2[d]	144	0
11	TfOH	AcO^tBu	2	80
12	$HClO_4$ (1.2)	AcO^tBu	16	61
13	H_2SO_4 (1.1)	AcO^tBu	72	0
14	HNO_3 (1.1)	AcO^tBu	24	0
15	CH_3SO_3H (2.0)	AcO^tBu	24	trace

[a]Isolated yield. [b]NMR yield using pyrazine as an internal standard. [c]The reaction was performed at -20 °C. [d]isobutene gas was bubbled through CH_2Cl_2.

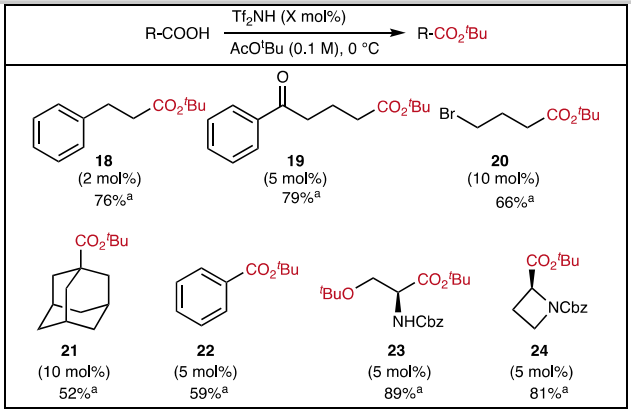
With the optimized conditions established, the reaction was applied to various free amino acids. In this investigation, the resulting *tert*-butyl esters of amino acids were successfully converted back into free amino groups, as there were no concerns regarding lactam formations (Table 2). The similar *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 81%, 74%, and 86% yields, respectively. L-Phenylalanine *tert*-butyl ester **9** was converted to (+)- and (-)-Mosher amides, confirming that racemization had not occurred. *Tert*-butyl groups were easily introduced into free amino acids containing alcohol functionalities, resulting in the *tert*-butylation of both carboxylic acids and alcohols. As a result, di-*tert*-butylated L-serine **10** was obtained in quantitative yield, while di-*tert*-butylated L-threonine **11** was obtained in 73% yield. In the case of amino acids possessing two carboxylic acids, such as L-aspartic acid and L-glutamic acid, both carboxylic acids were converted into *tert*-butyl esters to give **12** and **13** in 77% and modest yields, respectively. The amino acid possessing the thiol group, L-cysteine, also smoothly dissolved and reacted, and the analog **14,** in which the thiol group was also *tert*-butylated, was obtained in high yield. In the case of L-tyrosine possessing the phenol group, **15**, in which only the carboxylic acid was *tert*-butylated, was obtained as a major product in 68% yield, and **16**, in which both the phenol and the carboxylic acid 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_2NH salt. This substrate scope investigation revealed that the *tert*-butylation reaction was applicable to various amino acids,[14] except for L-methionine due to the presence of the sulfide group.

Table 2 Application of the *tert*-butylation reaction to various amino acids.



[a]Isolated yield. [b]NMR yield using pyrazine as an internal standard. [c]Isolated as a Tf_2NH salt

Table 3 Application of Tf_2NH-catalyzed *tert*-butylation reaction to various carboxylic acids.



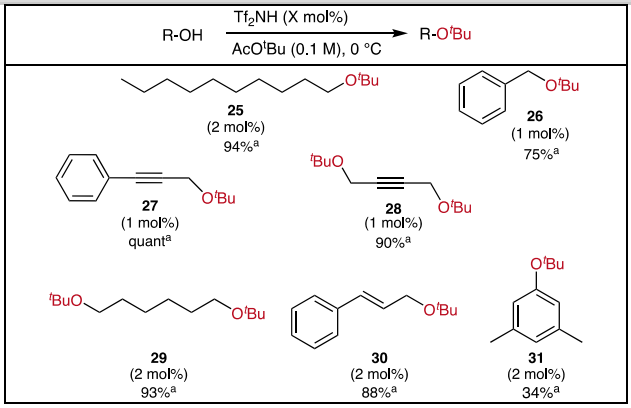
[a]Isolated yield.

In the *tert*-butylation reaction of free amino acids, 1.0 equiv of Tf_2NH was utilized for the soluble salt formation with amino groups, and the remaining 0.1 equiv of Tf_2NH made the reaction proceed. Therefore, a small catalytic amount of Tf_2NH is considered sufficient for the *tert*-butylation reaction of carboxylic acids that do not have free amino groups. Thus, the

Tf_2NH-catalyzed *tert*-butylation reaction was applied to various carboxylic acids (Table 3). The conversion of hydrocinnamic acid, a simple carboxylic acid, to *tert*-butyl ester **18** was achieved with just 2 mol% of Tf_2NH, resulting in an 76% yield. The carboxylic acid possessing a ketone group was also converted to *tert*-butyl ester **19** in 79% yield by 5 mol% of Tf_2NH without affecting the ketone group. The bromo group also tolerated the reaction condition, and *tert*-butyl ester **20** was obtained by treatment with 10 mol% of Tf_2NH in 66% yield. Tertiary carboxylic acid and benzoic acid were also *tert*-butylated under catalytic conditions to give **21** and **22** in modest yields. The catalytic conditions are applicable to *N*-Cbz-protected amino acids, and the *tert*-butylation reactions of *N*-Cbz-L-serine and *N*-Cbz-L-azatidine-2-carboxylic acid were catalyzed by 5 mol% of Tf_2NH to afford **23** and **24** in 89% and 81% yields, respectively. Thus, the Tf_2H-catalyzed reaction was found to be applicable to various carboxylic acids that do not possess functional groups that would quench Tf_2NH, such as amino groups.[15]

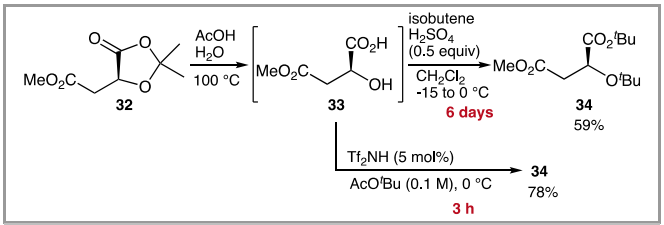
Next, the catalytic conditions of the *tert*-bulylation reaction were applied to alcohols. Although there have been several examples of *tert*-butylation of alcohols,[16] the present reaction was expected to reduce both catalyst loading and reaction time due to the high activity of Tf_2NH. As the *tert*-butyl ethers of small alcohols are volatile and difficult to handle, high-molecular-weight alcohols were investigated this time (Table 4). The Tf_2NH-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. Under the conditions of 1 mol% Tf_2NH, 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 of 1 mol% of Tf_2NH with propargyl alcohol afforded **27** in quantitative yield. In the case of diols, both alcohols were converted to *tert*-butyl ether regardless of alkyl or propargyl alcohols, and di-*tert*-butyl ether **28** and **29** were obtained in 90% and 93% yields, respectively. The reaction of allyl alcohols also proceeded smoothly, and allyl tert-butyl ether **30** was obtained in 88% yield. On the other hand, the reaction of phenol analog stopped prematurely as in the case of tyrosine **16**, and the *tert*-butyl ether **31** was obtained in 34% yield. Thus, it was revealed that the *tert*-butylation reaction of alcohols proceeded smoothly and in high yields by a very small amount of Tf_2OH (1~2 mol%), except for phenols.[17]

Table 4 Application of Tf_2NH-catalyzed *tert*-butylation reaction to various alcohols.



[a]Isolated yield.

Finally, the Tf_2NH-catalyzed *tert*-butylation reaction was compared to the conventional method. Previously, we prepared **34** from L-malic acid for the synthesis of natural phytosiderophore mugineic acids[18] and modified mugineic acid, proline deoxymugineic acid (PDMA), as fertilizers for desert soils.[16] The acetonide **32** derived from L-malic acid was heated to reflux in acetic acid and H_2O 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.[19] This method actually gave **34** on the Gram scale, but repeated bubbling of isobutene gas was required and the reaction needed a very long time (7 days).[16] When we repeated the previous *tert*-butylation reaction and quenched at 6 days, **34** was obtained in 59% yield. On the other hand, the Tf_2NH-catalyzed *tert*-butylation reaction of **33** proceeded much faster to give **34** in a very short time (3 h) in a higher (78%) yield (Scheme 2) (see Scheme S1 for the time course of these reactions).



Scheme 2 Comparison of Tf_2NH-catalyzed *tert*-butylation reaction of **32** with the conventional method

In conclusion, a simple and safe *tert*-butylation reaction was developed. The reaction employed Tf_2NH as a reagent to generate soluble salts by reacting with the amino groups of amino acids in an organic solvent. Tf_2NH also acted as a strong acid in this process. Additionally, *tert*-butyl acetate was utilized as both the solvent and the *tert*-butylation agent. The reaction enabled the direct conversion of free amino acids to *tert*-butyl esters. In addition, in the case of various carboxylic acids and alcohols without amino groups, a small catalytic amount of Tf_2NH was sufficient to convert to *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 high yields compared to conventional methods. The method developed in this study is a potential alternative to the conventional use of perchloric acid, simply 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.

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Supporting Information

Supporting information for this article is available online at

Conflict of Interest

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

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(14) **General Procedure for *tert*-butylation of amino acids to give *tert*-butyl esters as Tf_2NH salts**.
A suspension of 2-hydroxy-4-amino butylic acid (HABA) **5** (2.15 g, 18.0 mmol) in AcO^{t}Bu (180 mL, 0.1 M) was cooled to 0 °C. To the suspension was added a solution of Tf_2NH (5.58 g, 19.8 mmol) in CH_2Cl_2 (27 mL) at 0 °C. The mixture was stirred at 0 °C for 2.5 h and slowly added to saturated aqueous $NaHCO_3$ solution (350 mL) at 0 °C (reverse addition). The mixture was extracted with CH_2Cl_2 (500 mL x 3), and the combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 5/1, 2/1, to 0/1) to give **6** (8.1 g, 86%) as a white deliquescent material as a Tf_2NH salt.
Analytical Data
IR (KBr): 3187, 2980, 1721, 1621, 1350, 1229, 1197 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ 4.15 (dd, *J* = 7.3, 4.4 Hz, 1H), 3.01 (td, *J* = 6.4, 1.5 Hz, 2H), 2.03-1.85 (m, 2H), 1.49 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD): δ 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): $[M + H]^+$ calcd for C14H27F6N2O7S2, 513.1164; found, 513.1155.
The procedure to give **6** as a free amino group, see Supporting information.

(15) **General Procedure for *tert*-butylation of carboxylic acids**.
To a solution of hydrocinnamic acid (88.1mg, 0.587mmol) in AcO^{t}Bu (5.9mL, 0.1 M) was added a solution of Tf_2NH (3.3mg, 0.012mmol) in CH_2Cl_2 (0.15mL) at 0 °C. The mixture was stirred at 0 °C for 16 and slowly added to saturated aqueous $NaHCO_3$ solution (7 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (20 mL x 3), and the combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 1/0, 20/1, to 10/1) to give **18** (92mg, 76%) as a colorless oil.
Analytical Data
IR (KBr): 2978, 1732, 1367, 1147 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.28 (m, 2H), 7.23-7.16 (m, 3H), 2.91 (t, *J* = 7.6 Hz, 1H), 2.54 (t, *J* = 7.6 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 140.9, 128.5, 128.4, 126.2, 80.4, 37.2, 31.2, 28.2; HRMS-ESI (m/z): $[M + H]^+$ calcd for C13H19O2, 207.1385; found, 207.1393.

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(17) **General Procedure for *tert*-butylation of alcohols**.
To a solution of 1,6-hexyane diol (139 mg, 1.17 mmol) in AcO^{t}Bu (11.7 mL, 0.1 M) was added a solution of Tf_2NH (6.6 mg, 0.023 mmol) in CH_2Cl_2 (0.15 mL) at 0 °C. The mixture was stirred at 0 °C for 16 and slowly added to saturated aqueous $NaHCO_3$ solution (20 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (30 mL x 3), and the combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 0/1, 20/1, to 10/1) to give **29** (250 mg, 93%) as a colorless oil.
Analytical Data
IR (KBr): 2974, 1361, 1199, 1083 cm^{-1} ^{1}H NMR (500 MHz, CD_3OD): δ 3.32 (t, *J* = 6.8 Hz, 4H), 1.56-1.47(m, 4H), 1.38-1.30 (m, 4H), 1.18 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): 72.4, 61.6, 30.8, 27.7, 26.2; HRMS-ESI (m/z): $[M + H]^+$ calcd for C14H31O2, 231.2324; found, 231.2315.

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