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Graphical Abstract

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A Fast and Practical Synthesis of *tert*-Butyl Esters from 2-*tert*-Butoxypyridine using Boron Trifluoride·Diethyl Etherate under Mild Conditions

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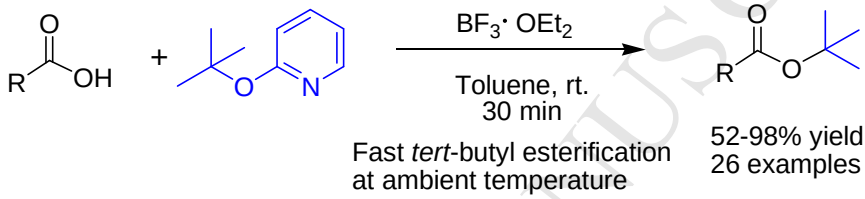

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ABSTRACT

A practical direct preparation of *tert*-butyl esters from 2-*tert*-butoxypyridine has been developed. This system features the use of boron trifluoride·diethyl etherate in toluene solvent to rapidly achieve the reaction at room temperature. Using this reaction protocol, a variety of *tert*-butyl esters were synthesized from several different carboxylic acids at high yields. This practical procedure provides a promising and effective approach to the protection of carboxylic acids with a *tert*-butyl group.

1. Introduction

Carboxylic acids are common structures in organic synthesis and pharmaceutical development. Protection and deprotection of this functional group are commonly performed during multistep syntheses. Esters, carboxylic acid derivatives, are widely used as carboxyl protecting groups. The conversion of carboxylic acid to *tert*-butyl ester is a particularly useful synthetic method because of the stability of the ester against nucleophilic attack and its easy cleavage. Several methods have been developed to remove the *tert*-butyl group from an ester. Traditional and simple strategies using strong acids such as CF_3COOH,[1] H_2SO_4,[2] and HNO_3[3] have been reported. Some Lewis acids such as MgI_2,[4] $TiCl_4$,[5] and $ZnBr_2$[6,7] have also been used for the deprotection of *tert*-butyl esters. Heating at 190–200 °C is a non-chemical method of cleaving the *tert*-butyl group.[8] Having various options for *tert*-butyl group removal provides advantages in multistep organic syntheses. The *tert*-butyl group has also been used in a wide range of organic reactions to protect carboxylic acids in the synthesis of bioactive compounds such as inhibitors of hepatitis C virus NS3 protease,[9] inhibitors of MMP-3, -6 and -9 subclasses of matrix metalloproteinases, which are related to dermal ulcers,[10] GABA-T inhibitors,[11] and HIV-gp120 discontinuous epitope mimics for the development of synthetic vaccines.[12]

Several synthetic methods for the preparation of *tert*-butyl esters have been reported (Scheme 1). Wright and co-workers reported a procedure to prepare *tert*-butyl esters promoted by reaction of an excess of *tert*-butyl alcohol and sulfuric acid in the presence of anhydrous magnesium sulfate.[13] Alternatively, isobutylene with concentrated H_2SO_4 in Et_2O has been shown to protect carboxylic acids with the *tert*-butyl group.[14] These methods use strong concentrated acid, which can obstruct the esterification of acid-sensitive functionalities. Also, isobutylene gas poses safety concerns for large-scale applications because of its high flammability and risk of explosion. Some methods of preparing *tert*-butyl esters have been reported that do not require strong acid or isobutylene gas such as the reaction of a carboxylic acid, *N*,*N'*-carbonyldiimidazole, and *t*-BuOH with DBU,[15] or reaction of an acid chloride, *tert*-BuOH, and AgCN in benzene.[16] However, these reactions still use expensive catalysts. Therefore, developing a new method that uses inexpensive starting materials as well as a short reaction time and mild conditions is an important challenge. In particular, discovery of new types of efficient reagents for the preparation of *tert*-butyl esters would be a valuable addition to organic chemistry. Lewis acids are potentially useful agents in the preparation of *tert*-butyl esters because they play an important role in various organic reactions.[17,18] Thus, we hypothesized that Lewis acids could be used for the high-yield synthesis of *tert*-butyl esters. Herein, we report a novel facile synthesis of *tert*-butyl esters from 2-*tert*-

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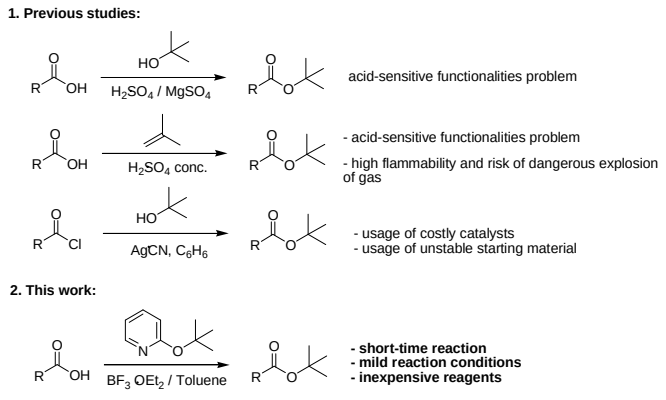
butoxypyridine and various carboxylic acids using the Lewis acid boron trifluoride·diethyl etherate under mild conditions in a short reaction time.

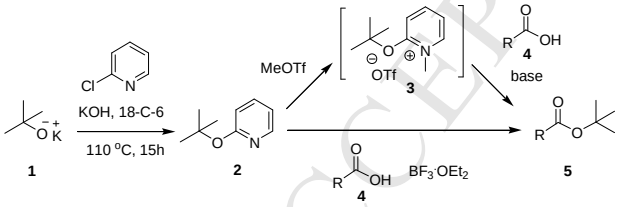


Scheme 1. Synthetic strategies of *tert*-butyl esters.

2. Result and Discussion

Dudley and co-workers first prepared benzyl esters from 2-benzyloxy-1-methylpyridine.[19] In the method, treatment of 2-benzyloxy-1-methylpyridine with MeOTf produced 2-benzyloxy-1-methylpyridinium triflate salt, one of the oxypyridinium salts and a key intermediate to achieve the desired reactions. This method was also employed to prepare allyl ester.[20] From the results of these reactions, we hypothesized that 2-*tert*-butoxypyridine could be used in the synthesis of *tert*-butyl esters.

Tert-butyl esters were prepared from potassium *tert*-butoxide in 2 steps, as shown in Scheme 2. In the reaction, potassium *tert*-butoxide was converted to 2-*tert*-butoxypyridine by previously reported method.[21] Treatment of potassium *tert*-butoxide with 2-chloropyridine in the presence of 18-crown-6 in toluene at 110 °C for 15 h generated 2-*tert*-butoxypyridine (compound **2**) in 54% yield. The purification of compound **2** was easily achieved via silica gel chromatography. Next, we employed the reported synthetic protocol using oxypyridinium salt to prepare *tert*-butyl ester.[19] Compound **2** was treated with carboxylic acid and MeOTf at room temperature. However, *tert*-butyl esterification at room temperature was inadequate (32% esterification after 20 h).



Scheme2. Synthesis of *tert*-butyl esters.

Thus, various reaction conditions for compound **2** were examined to yield *tert*-butyl esters (compound **5**). In an initial investigation, we carried out the esterification reaction with various commercially available reagents such as Lewis acids ($TiCl_4$, $AlCl_3$, $SnCl_4$, and BF_3·OEt_2) and bases (K_2CO_3, Et_3N, $NaHCO_3$, and DBU) to identify better reagents for *tert*-butyl ester formation. Benzoic acid was selected as a model substrate in our study. To a mixture of 1.35 equiv. of Lewis acid or base and 1.00 equiv. of benzoic acid in toluene, a 1.35 equiv. solution of compound **2** in toluene was added. After a 30-min reaction at room temperature, the yield of the desired product obtained after purification by flash column chromatography was calculated to determine the effect of each reagent on the esterification. The results are shown in Table 1. No change in the starting material was observed after 30 min when K_2CO_3, Et_3N, $NaHCO_3$, or DBU were used. Thus, we concluded that basic reagents were not a proper choice for this reaction. The addition of Lewis acids such as $SnCl_4$ resulted in small increased reaction yield for *tert*-butyl esterification, whereas none of the desired product was observed when the reaction was carried out with $TiCl_4$ or $AlCl_3$. Finally, the possibility of *tert*-butyl esterification using BF_3·OEt_2 was investigated. A yield of 94% of the desired product was observed, suggesting BF_3·OEt_2 as the most effective reagent for *tert*-butyl esterification.

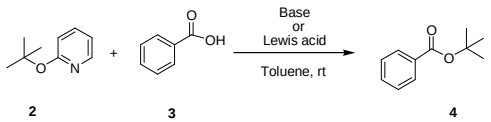
Next, screening for a reaction solvent effect was carried out. As shown in Table 2, reactions performed with BF_3·OEt_2 in THF, 1,4-dioxane, and chlorinated solvents (dichloromethane and dichloroethane) led to low yields of *tert*-butyl ester. When the reaction was carried out in MeCN, the desired product yield increased to 47%. Surprisingly, employing toluene as a solvent led to an accelerated reaction and gave significantly increased yield of the desired *tert*-butyl ester. The solvent screening study suggested that toluene was the best solvent for the reaction.

To provide a better understanding of the effect of BF_3·OEt_2 on the reaction, we investigated the use of different amounts of BF_3·OEt_2 (0.1 equiv, 0.5 equiv, 1.0 equiv, 1.35 equiv, and 2.0 equiv) in the *tert*-butyl esterification. As shown in Table 2, ester product yield increased in proportion to the amount of reagent (*i.e.*, 3% for 0.1 equiv of BF_3·OEt_2, 21% for 0.5 equiv of BF_3·OEt_2). The highest yield of *tert*-butyl ester was observed in the presence of 1.35 equiv and 2.0 equiv of BF_3·OEt_2 for 30 min (94% yield for both 1.35 and 2.0 equiv of BF_3·OEt_2). There was no significant difference in yield when employing 1.35 equiv or 2.0 equiv of BF_3·OEt_2. These results demonstrate that the synthetic yield of *tert*-butyl ester significantly depends on the amount of BF_3·OEt_2. Based on these results, 1.35 equiv. of BF_3·OEt_2 reagent was selected for further investigation in the *tert*-butyl ester synthesis.

Having determined the optimal conditions, we carried out esterification reactions with a variety of carboxylic acids including saturated or unsaturated ones, bulky ones, heterocyclic carboxylic acids, and aromatic carboxylic acids with electron-donating or electron-withdrawing groups. 1.00 equiv. of carboxylic acid substrate was treated with 1.35 equiv. of 2-*tert*-butoxypyridine and 1.35 equiv. of BF_3·OEt_2 in anhydrous toluene at room temperature. All *tert*-butyl esterification yields from carboxylic acids were determined after 30 min reaction time. As shown in Table 3, aromatic carboxylic acids containing electron-donating groups afforded the corresponding *tert*-butyl ester in very good yields ranging from 80 to 98% (Table 3, entries 2-5). Changing the substituents to electron-withdrawing groups led to similar results under the same conditions (Table 3, entries 6-10), suggesting that reactions using BF_3·OEt_2 with most substituted aromatic carboxylic acids will successfully produce the corresponding *tert*-butyl ester in excellent yield.

Furthermore, esterification of alkyl substituted carboxylic acids produced their corresponding *tert*-butyl esters in excellent yields. It is noteworthy that aliphatic acids were reactive in the esterification (Table 3, entries 11-12). Cyclohexane carboxylic acid as a cyclic substrate or aromatic substituted aliphatic acids also gave greater than 93% conversion yields in the reaction (Table 3, entries 13-15). The scope of this synthetic method was extended to unsaturated carboxylic acids containing sensitive and reactive π-bonds. Surprisingly, alkenyl and alkynyl substituted carboxylic acids converted to *tert*-butyl esters in high yields without any side reactions observed at the double or triple bond (84% yield for compound **5q** and 92% yield for compound **5r**).

Table 1. Screening of Lewis acids and bases for the *tert*-butyl esterification reaction[a]



2 3 4

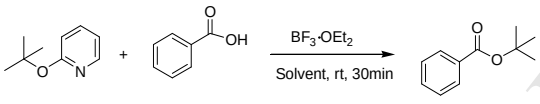
Entry	Base or Lewis acid	Time (min)	Temp.	Yield[b] (%)
1	K_2CO_3	30	r.t.	NR[c]
2	Trimethylamine	30	r.t.	NR[c]
3	$NaHCO_3$	30	r.t.	NR[c]
4	DBU	30	r.t.	NR[c]
5	$TiCl_4$	30	r.t.	NR[c]
6	$AlCl_3$	30	r.t.	NR[c]
7	$SnCl_4$	30	r.t.	4
8	$BF_3{\cdot}OEt_2$	30	r.t.	94
9	None	30	r.t.	NR[c]

[a]Reaction conditions: 1.35 mmol of compound **2**, 1.0 mmol of carboxylic acid, 1.35 mmol of base or Lewis acid, toluene (2 mL), room temperature, 30 min

[b]Product yield after purification by flash column chromatography.

[c]No reaction.

Table 2. Screening of solvents in the esterification reaction of benzoic acid and compound **2**[a]



2 4 5

Entry	Lewis acids (equiv)	Solvent	Temp.	Yield[b] (%)
1	$BF_3{\cdot}OEt_2$ (1.35)	THF	r.t.	4
2	$BF_3{\cdot}OEt_2$ (1.35)	MeCN	r.t	47
3	$BF_3{\cdot}OEt_2$ (1.35)	1,4-dioxane	r.t.	NR[c]
4	$BF_3{\cdot}OEt_2$ (1.35)	DCE	r.t.	25
5	$BF_3{\cdot}OEt_2$ (1.35)	CH_2Cl_2	r.t.	20
6	$BF_3{\cdot}OEt_2$ (1.35)	Toluene	r.t.	94
7	$BF_3{\cdot}OEt_2$ (2.0)	Toluene	r.t.	94
8	$BF_3{\cdot}OEt_2$ (1.0)	Toluene	r.t.	67
9[d]	$BF_3{\cdot}OEt_2$ (0.5)	Toluene	r.t.	21
10[d]	$BF_3{\cdot}OEt_2$ (0.1)	Toluene	r.t.	3
11	None	Toluene	r.t.	NR[c]

[a]Reaction conditions: 1.35 mmol of compound **2**, 1.0 mmol of carboxylic acid, solvent (2 mL), room temperature, 30 min

[b]Product yield after purification by flash column chromatography.

[c]No reaction.

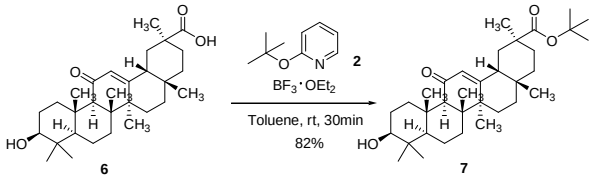
[d]Reaction performed for 6 h.

To demonstrate the efficiency of this method, we performed esterification reactions on carboxylic acids with bulky substituent groups for which steric effects usually obstruct the reaction. 3,5-dimethylbenzoic acid and 2,4,6-trimethylbenzoic acid, despite their bulky aromatic substrates, were converted to the desired products **5u** and **5v** in 81% and 82% yields, respectively (Table 3, entries 21-22). Moreover, diphenylacetic acid with its two bulky benzene groups, adamantine carboxylic acid, and 3-hydroxy-2,2-dimethylpropanoic acid were all utilized to form their corresponding esters in high yield under the same conditions (Table 3, entries 19, 20 and 23). These results indicated the importance of $BF_3{\cdot}OEt_2$ as a useful reagent for the synthesis of *tert*-butyl esters from bulky carboxylic acids during this mild reaction process with 2-*tert*-butoxypyridine.

Moreover, 2-furoic acid, a heterocyclic acid containing an oxygen, was investigated in our protocol to further expand the scope of the reaction utilizing $BF_3{\cdot}OEt_2$. It has been previously noted that the furan compound is not stable under acidic conditions and easily decomposes. In our investigation, remarkably, the treatment of 2-furoic acid with 2-*tert*-butoxypyridine readily achieved a 94% yield of the corresponding *tert*-butyl ester **5x** in 30 min without any observed by-products (Table 3, entry 24), demonstrating that $BF_3{\cdot}OEt_2$ is suitable for the synthesis of *tert*-butyl esters from different types of carboxylic acids under mild conditions.

Amino acids such as tyrosine and Boc-protected tyrosine were also utilized for *tert*-butyl esterification. The reaction of Boc-protected tyrosine produced its corresponding *tert*-butyl ester under the same conditions (Table 3, entry 25), while reaction of tyrosine with unprotected NH_2 produced *tert*-butyl protected amine compound as a main product. The results suggest that the new reaction method is more efficient at synthesis of *tert*-butyl ester from carboxylic acid than the class of reactions acting through the hydroxyl group. In this particular case, however, amine reacted with 2-*tert*-butoxypyridine more rapidly than carboxylic acid.

To further assess the utility of this synthetic procedure, 18*β*-glycyrrhetinic acid, a more complex bioactive compound, was used for the synthesis of *tert*-butyl ester. The desired *tert*-butyl ester was successfully obtained under the described reaction conditions while using an increased volume of toluene (Scheme 3).

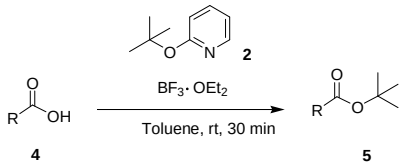


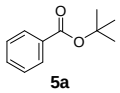
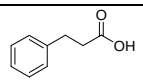
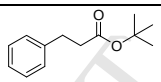
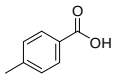
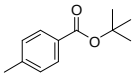
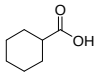
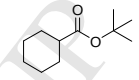
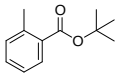
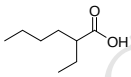
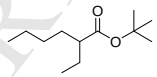
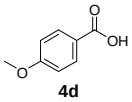
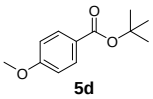
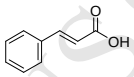
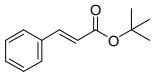
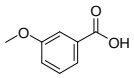
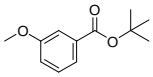
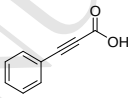
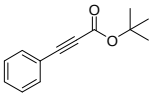
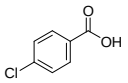
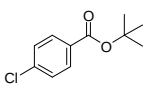
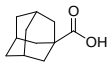
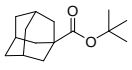
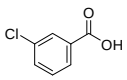
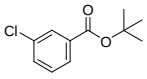
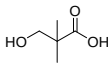
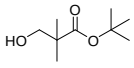
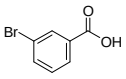
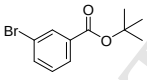
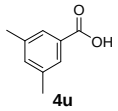
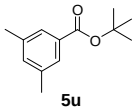
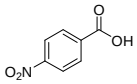
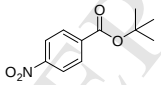
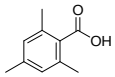
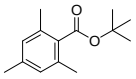
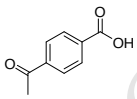
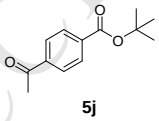
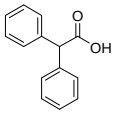
6 7

Scheme 3. Protection of a bioactive compound with *tert*-butyl ester

It has been reported that BF_3-pyridine complex can be prepared from the reaction of pyridine with $BF_3{\cdot}OEt_2$,[22] and that a BF_3-2-methoxypyridine complex was formed by interaction of BF_3 and 2-methoxypyridine.[23] Thus, a proposed reaction mechanism for this *tert*-butyl esterification based on our results and previous reports is shown in Scheme 4. The initial addition of $BF_3{\cdot}OEt_2$ to 2-*tert*-butoxypyridine **2** generates a BF_3-2-*tert*-butoxypyridine complex intermediate, which undergoes nucleophilic attack by the carboxylic acid to yield the *tert*-butyl ester product.

Table 3. Scope of tert-butyl esterification of carboxylic acid using 2-*tert*-butoxypyridine[a]

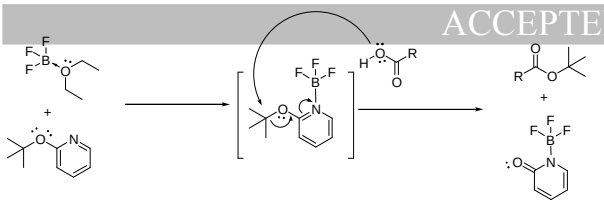


Entry	Carboxylic acid	Product	Yield[b] (%)	Entry	Carboxylic acid	Product	Yield[b] (%)
1	 **4a**	 **5a**	94	14	 **4n**	 **5n**	95
2	 **4b**	 **5b**	84	15	 **4o**	 **5o**	93
3	 **4c**	 **5c**	98	16	 **4p**	 **5p**	92
4	 **4d**	 **5d**	80	17	 **4q**	 **5q**	84
5	 **4e**	 **5e**	95	18	 **4r**	 **5r**	92
6	 **4f**	 **5f**	94	19[c]	 **4s**	 **5s**	85
7	 **4g**	 **5g**	83	20[c]	 **4t**	 **5t**	84
8	 **4h**	 **5h**	92	21	 **4u**	 **5u**	81
9	 **4i**	 **5i**	93	22[c]	 **4v**	 **5v**	82
10	 **4j**	 **5j**	95	23	 **4w**	**5w**	90
11	**4k**	**5k**	91	24	**4x**	**5x**	94
12	**4l**	**5l**	87	25	**4y**	**5y**	52
13	**4m**	**5m**	96				

[a]Reaction conditions: 1.35 mmol of compound **2**, 1.00 mmol of carboxylic acid, 1.35 mmol of BF_3·OEt_2, toluene (2 mL), room temperature, 30 min

[b]Product yield after purification by flash column chromatography.

[c]Reaction conditions: room temperature, 2h



Scheme 4. Proposed esterification mechanism using 2-*tert*-butoxypyridine with $BF_3{\cdot}OEt_2$.

3. Conclusion

In conclusion, rapid and practical *tert*-butyl esterification of diverse carboxylic acids has been successfully achieved via reaction with 2-*tert*-butoxypyridine in the presence of $BF_3{\cdot}OEt_2$. This synthetic method provides a new reaction system for protection of various carboxylic acids and has been shown to be effective for the preparation of *tert*-butyl esters at high yields under mild reaction conditions. We believe this novel, efficient, and readily applicable protocol will be useful for a broad range of carboxylic acid protections in a variety of organic syntheses.

4. Experimental

4.1. General information

Reagents and solvents were commercially available and used as received. Column chromatography was performed using silica gel 60 (0.040-0.063 mm) and eluted with proper mixture (CH_2Cl_2/hexane). All of the new compounds were identified by 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference, and high resolution mass spectroscopy. The identity of the known compounds was established by the comparison of their ^{1}H and ^{13}C NMR peaks with the authentic values.

4.2. Procedure for the preparation of 2-tert-butoxypyridine

A mixture of potassium *tert*-butoxide (9.88 g, 88.07 mmol) and 2-chloropyridine (5 g, 44.04 mmol) was added to toluene (100 mL), followed by 18-crown-6 (0.58 g, 2.20 mmol). The reaction mixture was heated at 110 °C for 15 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (200 mL), then washed with water (150 mL), followed by brine (150 mL). The organic layer was dried over anhydrous sodium sulfate and carefully concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography on silica gel with 0:5 to 1:5 ethyl acetate/hexane as eluent to yield the desired product **2** as a colorless oil (3.59 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) 8.15 (ddd, *J* =4.8 Hz, 2.0 Hz, 0.4 Hz, 1H), 7.52 (ddd, *J* = 9.2 Hz, 6.8 Hz, 1.6 Hz, 1H), 6.81 (ddd, *J* = 6.8 Hz, 5.2 Hz, 1.2 Hz, 1H), 6.67 (dt, *J* = 8.4 Hz, 0.8 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 146.5, 138.1, 116.2, 113.4, 79.4, 28.7 (3C). HRMS (ESI) m/z $(M+H)^+$ calcd for $C_9H_{14}NO$ = 152.1075, found 152.1077.

*4.3. General procedure for the preparation of tert-butyl ester compounds (**5a-5v**)*

Carboxylic acid (0.2 g, 1.64 mmol), *tert*-butoxypyridine (0.33 g, 2.21 mmol) and boron trifluoride diethyl etherate (0.31 g, 2.21 mmol) in dry $PhCH_3$ (2 mL) were added to a 20-ml vial. The reaction mixture was then allowed to stir at room temperature for 30 min before quenching with anhydrous $NaHCO_3$. The reaction mixture was diluted with ethyl acetate (30 mL), then washed with water (20 mL), followed by brine (20 mL). The organic layer was dried over anhydrous sodium sulfate and carefully concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography on silica gel with 0:4 to 1:4 dichloromethane/hexane as eluent to yield the desired product **5a** as a colorless oil.

*4.3.1. Tert-butyl benzoate (**5a**)*

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 8.02 (m, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.53 (m, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 1.63 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 132.4, 132.0, 129.4 (2C), 128.1 (2C), 80.9, 28.2 (3C). HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{15}O_2$ = 179.1072; found 179.1075.

*4.3.2. Tert-butyl 4-methylbenzoate (**5b**)*

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.90 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 142.9, 129.4 (2C), 129.3, 128.8 (2C), 80.6, 28.2 (3C), 21.6. HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{17}O_2$ = 193.1229; found 193.1227.

*4.3.3. Tert-butyl 2-methylbenzoate (**5c**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.84 (d, *J* = 7.6 Hz, 1H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7,24 (t, *J* = 7.6 Hz, 2H), 2.60 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.2, 139.2, 131.8, 131.5, 131.3, 130.3, 125.3, 81.0, 28.3 (3C), 21.7; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{17}O_2$ = 193.1229; found 193.1231.

*4.3.4. Tert-butyl 4-methoxybenzoate (**5d**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.96 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.6, 162.9, 131.3 (2C), 124.5, 113.4 (2C), 81.4, 55.4, 28.3 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{17}O_3$ = 209.1178; found 209.1182.

*4.3.5. Tert-butyl 3-methoxybenzoate (**5e**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.60 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.55 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.10 (ddd, *J* = 8.0, 2.8, 0.8 Hz, 1H), 3.87 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.6, 159.5, 133.4, 129.2, 121.8, 118.8, 114.0, 81.1, 55.4, 28.2 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{17}O_3$ = 209.1178; found 209.1180.

*4.3.6. Tert-butyl 4-chlorobenzoate (**5f**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.94 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.8, 138.8, 130.8 (2C), 130.5, 128.4 (2C), 81.4, 28.2 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{14}ClO_2$ = 213.0682; found 213.0685.

*4.3.7. Tert-butyl 3-chlorobenzoate (**5g**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.97 (t, *J* = 1.2 Hz, 1H), 7.90 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.51 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.4, 134.3, 133.8, 132.4, 129.5 (2C), 127.5, 81.7, 28.1 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{14}ClO_2$ = 213.0682; found 213.0686.

*4.3.8. Tert-butyl 3-bromobenzoate (**5h**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.13 (t, *J* = 1.6 Hz, 1H), 7.93 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.66 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.3, 135.3, 134.0, 132.4, 129.7, 128.0, 122.3, 81.7, 28.1 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{14}BrO_2$ = 257.0177; found 257.0179.

*4.3.9. Tert-butyl 4-nitrobenzoate (**5i**)*

White solid; m.p. 116 - 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.2 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.3, 137.4, 130.5 (2C), 123.3 (2C), 82.6, 28.1 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{14}NO_4$ = 224.0923; found 224.0935.

*4.3.10. Tert-butyl 4-acetylbenzoate (**5j**)*

White solid; m.p. 39-41°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 7.6 Hz, 2H), 2.65 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 164.8, 139.8, 135.8, 129.6 (2C), 128.0 (2C), 81.7, 28.1 (3C), 26.8; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{17}O_3$ = 221.1178; found 221.1180.

*4.3.11. Tert-butyl heptanoate (**5k**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (t, J = 7.6 Hz, 2H), 1.59 (t, J = 7.6 Hz, 2H), 1.46 (s, 9H), 1.35-1.25 (m, 6H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 79.8, 35.6, 31.5, 28.7, 28.1 (3C), 25.1, 22.5, 14.0; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{23}O_2$ = 187.1698; found 187.1697.

*4.3.12. Tert-butyl undecanoate (**5l**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (t, J = 7.2 Hz, 2H), 1.59 (t, J = 7.6 Hz, 2H), 1.46 (s, 9H), 1.35-1.23 (m, 14H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 79.8, 35.6, 31.9, 29.6, 29.5, 29.3 (2C), 29.1, 28.1 (3C), 25.1, 22.7, 14.1; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{15}H_{31}O_2$ = 243.2324; found 243.2328.

*4.3.13. Tert-butyl 2-phenylacetate (**5m**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 3.56 (s. 2H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 134.7, 129.2 (2C), 128.4 (2C), 126.8, 80.8, 42.7, 28.0 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{17}O_2$ = 193.1229; found 193.1232.

*4.3.14. Tert-butyl 3-phenylpropanoate (**5n**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.26-7.20 (m, 3H), 2.94 (t, J = 8.0 Hz, 2 H), 2.57 (t, J = 8.0 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 140.8, 128.4 (2C), 128.3 (2C), 126.1, 80.3, 37.1, 31.1, 28.1 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{19}O_2$ = 207.1385; found 207.1388.

*4.3.15. Tert-butyl cyclohexanecarboxylate (**5o**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (tt, J = 10.8, 3.6 Hz, 1H), 1.90-1.83 (m, 2H), 1.80-1.70 (m, 2H), 1.66-1.60 (m, 1H), 1.45-1.34 (m, 11H), 1.34-1.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 79.5, 44.1, 29.1 (2C), 28.1 (3C), 25.8, 25.5 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{21}O_2$ = 185.1542; found 185.1545.

*4.3.16. Tert-butyl 2-ethylhexanoate (**5p**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17-2.10 (m, 1H), 1.63-1.50 (m, 2H), 1.50-1.40 (m, 11H), 1.35-1.25 (m, 4H), 0.90 (td, J = 7.6, 2.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 79.7, 48.2, 31.9, 29.6, 28.1 (3C), 25.7, 22.6, 13.9, 11.8; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{25}O_2$ = 201.1855; found 201.1857.

*4.3.17. Tert-butyl cinnamate (**5q**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 16.0 Hz, 1H), 7.55-7.50 (m, 2H), 7.42-7.37 (m, 3H), 6.40 (d, J =16.0 Hz, 1H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 143.5, 134.7, 129.9, 128.8 (2C), 127.9 (2C), 120.2, 80.5, 28.2 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{17}O_2$ = 205.1229; found 205.1231.

*4.3.18. Tert-butyl 3-phenylpropiolate (**5r**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dt, J = 6.8, 1.6 Hz, 2H), 7.42 (tt, J = 7.2, 2.0 Hz, 1H), 7.38 (tt, J = 6.8, 1.6 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 132.8 (2C), 130.3, 128.5 (2C), 120.0, 83.8, 83.5, 82.0, 28.1 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{15}O_2$ = 203.1072; found 20.1075.

*4.3.19. Tert-butyl adamantane-1-carboxylate (**5s**)*

White solid; m.p. 42 - 44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 1.86 (d, J = 6.8 Hz, 6H), 1.75-1.65 (m, 6H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 79.3, 41.1, 38.9 (3C), 36.6 (3C), 28.1 (3C), 28.0 (3C). HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{15}H_{25}O_2$ = 237.1855; found 237.1859.

*4.3.20. Tert-butyl 3-hydroxy-2,2-dimethylpropanoate (**5t**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 2H), 2.57 (br s, 1H), 1.47 (s, 9H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 80.8, 69.7, 44.4, 28.0 (3C), 22.2 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_9H_{19}O_3$ = 175.1334; found 175.1337.

*4.3.21. Tert-butyl 3,5-dimethylbenzoate (**5u**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 2H), 7.17 (s, 1H), 2.38 (s, 6H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 137.8, 134.0 (2C), 131.9, 127.1 (2C), 80.7, 28.2 (3C), 21.2 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{19}O_2$ = 207.1385; found 207.1387.

*4.3.22. Tert-butyl 2,4,6-trimethylbenzoate (**5v**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 2.34 (s, 6H), 2.30 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 138.6, 134.4 (2C), 132.6, 128.3 (2C), 81.4, 28.3 (3C), 21.1, 19.5 (2C); HRMS (ESI) m/z (M+H)+ calcd for $C_{14}H_{21}O_2$ = 221.1542; found 221.1545.

*4.3.23. Tert-butyl 2,2-diphenylacetate (**5w**)*

White solid; m.p. 81 - 83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.31 (m, 8H), 7.31-7.25 (m, 2H), 4.95 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 139.3 (2C), 128.6 (4C), 128.5 (4C), 127.0 (2C), 81.3, 58.1, 28.0 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{18}H_{21}O_2$ = 269.1542; found 269.1546.

*4.3.24. Tert-butyl furan-2-carboxylate (**5x**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 1.6, 0.8 Hz, 1H), 7.09 (dd, J = 3.2, 0.8 Hz, 1H), 6.48 (dd, J = 4.0, 2.0 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 146.0, 145.7, 116.9, 111.5, 81.9, 28.2 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_9H_{13}O_3$ = 169.0865, found 169.0869.

*4.3.25. (R)-tert-butyl 2-(tert-butoxycarbonylamino) -3-(4-hydroxyphenyl)propanoate (**5y**)*

Colorless solid; m.p. 100-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 8.0 Hz, 2H, 2-CH= tyrosine), 6.75 (d, J = 8.0 Hz, 2H, 2-CH= tyrosine), 6.22 (br s, OH phenol), 5.05 (d, J = 8.4 Hz, 1H, NH), 4.42 (d, J = 7.2 Hz, 1H, -CH-NH), 3.05-2.95 (m, 2H, -CH2-), 1.44 (s, 9H, -C$(CH_3)_3$ Boc), 1.43 (s, 9H, -C$(CH_3)_3$ ester); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 155.3, 155.0, 130.6 (2C), 127.8, 115.3 (2C), 82.2, 80.0, 55.1, 37.7, 28.3 (3C), 28.0 (3C); HRMS (ESI) m/z (M+H)+ calcd for $C_{18}H_{28}NO_5$ = 338.1967; found 338.1970.

*4.3.26. Tert-butyl 18β-glycyrrhetinate (**7**)*

White solid. m.p. 229 - 231 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (s, 1H), 3.25 (dd, J = 10.8, 5.6 Hz, 1H), 2.80 (dt, J = 13.2, 3.2 Hz, 1H), 2.36 (s, 1H), 2.19-2.11 (m, 1H), 2.09-1.99 (m, 1H), 1.98-1.91 (m, 1H), 1.90-1.79 (m, 2H), 1.72-1.57 (m, 4H), 1.53-1.43 (m, 11H), 1.43-1.34 (m, 6H), 1.33-1.24 (m, 2H), 1.24-1.08 (m, 10H), 1.07-0.94 (m, 5H), 0.82 (s, 6H), 0.75-0.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.23, 175.7, 169.6, 128.4, 80.1, 78.8, 61.8, 54.9, 48.5, 45.4, 44.3, 43.2, 41.3, 39.1 (2C), 37.8, 37.1, 32.8, 31.8, 31.2, 28.8, 28.3, 28.1 (4C), 27.3, 26.5, 26.4, 23.4, 18.7, 17.5, 16.4, 15.6; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{34}H_{55}O_4$ = 527.4100; found 527.4102.

Conflicts of interest

There are no conflicts to declare..

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/

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