Using Benzotriazole Esters as a Strategy in the Esterification of Tertiary Alcohols

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Abstract: Benzotriazole esters formed in situ were found to be efficient intermediates in the esterification of tertiary alcohols using 4-(dimethylamino)pyridine (DMAP) as the base. These mild and basic reaction conditions allow the conversion of various substrates into esters in good yield.

Key words: esterification, hindered alcohols, 1-hydroxybenzotriazole, carbodiimides, hydrotalcites

The esterification of organic acids with tertiary alcohols is a persistent problem in organic synthesis and has therefore been the object of interest over the past year. It is well known that the *tert*-butyl group has been extensively used for carboxylic acid protection due to its relative resistance to nucleophilic attack and its ready removal under mild acidic conditions.[1] The simple reaction of a carboxylic acid and isobutylene in the presence of an acid catalyst is the most straightforward way to obtain these esters.[2]

Alternatively, a series of procedures has been introduced to synthesize not only solely esters of *tert*-butyl alcohol, but other sterically hindered alcohols as well. These protocols include transesterification with lithium[3] and potassium alkoxides;[4] transesterification in the presence of perchloric acid;[5] transesterification mediated by metal,[6] *N*-heterocyclic carbene[7] and iodine catalysts;[8] transesterification using Meldrum's acid;[9] dehydration by means of carbodiimides;[10] direct esterification of carboxylic acids using diphenylammonium triflate in fluorous media;[11] the use of Al-MCM-41,[12] silica chloride[13] or Keggin, Dawson and Preyssler heteropolyacids[14] to catalyze the direct esterification of carboxylic acids; esterification in enzymatic mediums;[15] esterification with anhydrides in the presence of Lewis acids,[16] montmorillonite K10 and KSF,[17] Si-MCM-41,[18] alumina,[19] magnesium bromide,[20] neutral ionic liquid [BMIm]BF_4,[21] pentaalkylguanidines[22] and cyclocopolymer containing pyrrolidinopyridine;[23] esterification of anhydrides in the absence of solvent and catalyst;[24] obtaining esters from carbonates;[25] activating alcohols by employing *N*,*N*-dimethylformamide di-*tert*-butyl acetal[26] or *tert*-butyl trichloroacetimidate;[27] using *tert*-butyl bromide in a nucleophilic substitution reaction;[28] esterification by an oxidation–reduction process in the presence of an alkoxydiphenylphosphine;[29] and, finally, using an acyl chloride or bromide[30] over alumina to obtain the ester (Scheme 1).

In this context, we considered the possibility of developing a new protocol for the esterification of sterically hindered alcohols using benzotriazole esters as a strategy. It is well known that carbodiimides and 1-hydroxybenzotriazole (HOBt) can be used in the formation of the peptide bond.[31] The easy access to that bond has been attributed to the high reactivity of benzotriazole esters **I** and **II** (Scheme 2), which are formed from the dehydration of carboxylic acid by means of a carbodiimide. In a recent publication, Chan and Cox described the influence of HOBt in the formation of the amide bond.[32] They demonstrated, by calorimetric procedure, that the reaction rate is independent of the HOBt concentration; however, HOBt is necessary to obtain high yields. In an attempt to synthesize a Weinreb active amide of *N*-trityl-protected phenylalanine using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), Liskamp and co-workers[33] isolated the corresponding intermediates **I** and **II**. The latter intermediate reacted with potassium *tert*-butoxide to provide the *tert*-butyl ester of *N*-tritylphenylalanine. Finally, we recently reported that the use of benzotriazole esters **I** and **II** in the synthesis of macrolactones afforded excellent yields in the cyclization of ω-hydroxy acids.[34] With this interesting background, we wondered whether this approach could also be used in the esterification reactions of other tertiary alcohols. Fully aware of the benefits and difficulties of this reaction, we decided to pursue an answer. The following is a description of the efficient esterification process of tertiary alcohols by the use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and HOBt to achieve the formation of intermediates **I** and **II**. A representative example of the original process is depicted in Scheme 2.

We initially investigated the intermolecular reaction of *tert*-butyl alcohol and phenylacetic acid (**1**) in the presence of EDC, HOBt and 4-(dimethylamino)pyridine (DMAP). Taking into consideration that the intermediates **I** and **II** are the precursors of the final product, it was necessary to identify the best solvent for their formation. In

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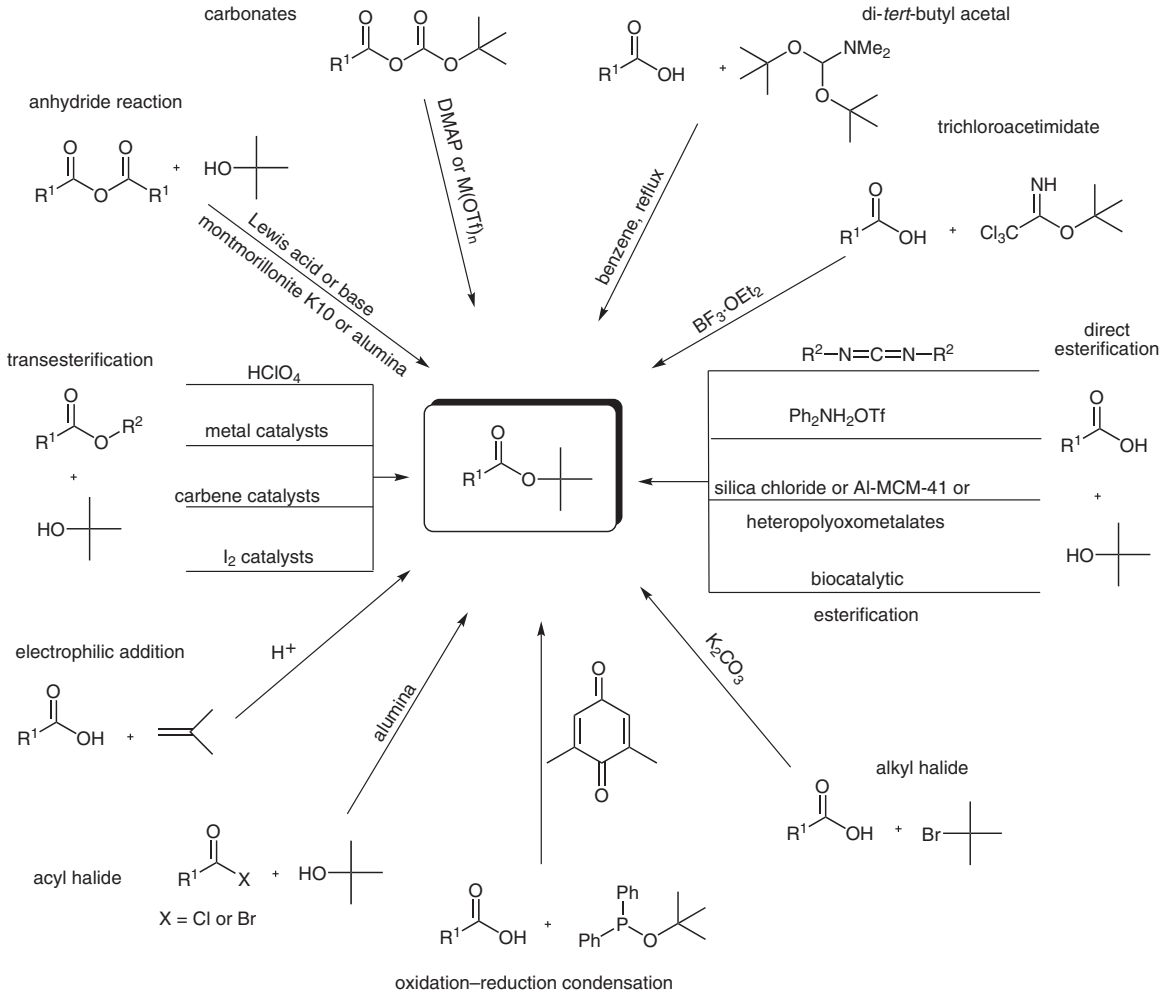
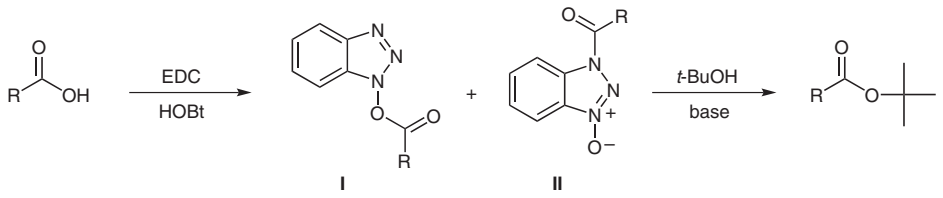


Scheme 1 Esterification strategies

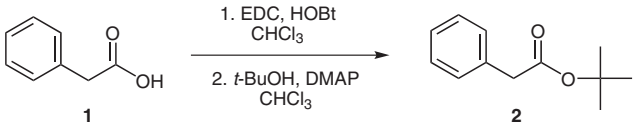
order to do this, we compared three different solvents: tetrahydrofuran, chloroform and dichloromethane. In general, each of these solvents can be used as a medium for ester formation with HOBt; however, only chloroform gave a 98% yield of intermediates **I** and **II**. These results were confirmed by the use of NMR spectroscopy, in which the raw material from the ester formation was analyzed. Once we identified the best solvent for the formation of the benzotriazole esters, we studied the reaction of these intermediates with *tert*-butyl alcohol, which involved stirring the following for 30 minutes at room temperature: one equivalent of carboxylic acid, one equivalent of EDC and one equivalent of HOBt in chloroform. Subsequently, *tert*-butyl alcohol and DMAP were added and the reaction mixture was stirred for 18 hours. Our initial survey revealed that temperature has an influence on the development of the reaction (Table 1, entries 1 and 3), that variations in the concentration of *tert*-butyl alcohol and DMAP have an effect on the reaction yield (Table 1, entries 2, 4–6) and that the use of four or eight equivalents of *tert*-butyl alcohol and DMAP gives the best results (Table 1, entries 7 and 8). These results contrast with that obtained in the esterification of the same carboxylic acid with *tert*-butyl alcohol in the absence of HOBt, where the formation of product **2** was not observed.

It is important to note that, when the reaction was carried out with 3, 4 or 8 equivalents of DMAP, the formation of side product **3** was observed, as a consequence of the enolate acylation of ester **2** with intermediates **I** and **II** (Scheme 3, eq 1). A similar behavior has been observed



Scheme 2 General transesterification process

Table 1 Esterification of Phenylacetic Acid (**1**) with *tert*-Butyl Alcohol in the Presence of DMAP[a]



1 2

Entry	DMAP (equiv)	*t*-BuOH (equiv)	Temp	Time (h)	Yield[b] (%)
1	1	2	r.t.	48	15
2	1	2	reflux	18	50
3	2	2.5	r.t.	48	21
4	2	2.5	reflux	18	51
5	2	4	reflux	18	61
6	3	6	reflux	18	65
7	4	4	reflux	18	89
8	8	8	reflux	18	84

[a] Reaction conditions: phenylacetic acid (1 mmol), EDC (1 mmol), HOBt (1 mmol), $CHCl_3$, r.t., 30 min, and then *t*-BuOH, DMAP.
[b] Yield of isolated product after chromatographic purification.

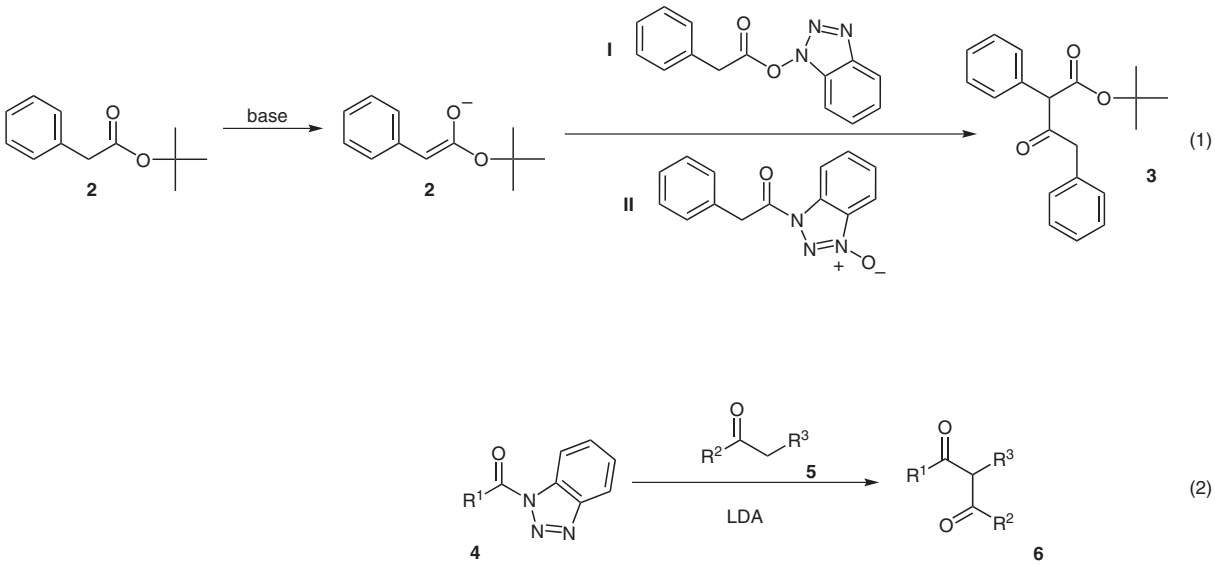
with 1-acylbenzotriazoles, such as compound **4**,[35] which are efficient C-acylation reagents for the regioselective conversion of ketones **5** into β-diketones **6** when lithium diisopropylamide is used as a base (Scheme 3, eq 2). With this observation, our group glimpsed the possibility of obtaining β-oxo esters from carboxylic acids in the presence of HOBt.

At this point in our research, we considered the possibility of using other bases. Therefore, a screen of alternative bases for the esterification reaction was conducted, focusing on the replacement of DMAP with triethylamine or *N*,*N*-diisopropylethylamine (DIPEA). Thus, when phenylacetic acid (**1**) was reacted with *tert*-butyl alcohol under reflux in the presence of EDC and HOBt, ester **2** was obtained in 48% yield after 18 hours (Table 2, entry 1). The yield increased to 82% when four equivalents of triethylamine were used (Table 2, entry 2). Similar results were obtained when the reaction was carried out in the presence of DIPEA (Table 2, entries 3 and 4). Additionally, we used a calcined hydrotalcite Mg^{2+}/Al^{3+} ratio $x = 0.33$ as the base instead of DMAP (Table 2, entries 5 and 6). Hydrotalcites are materials that have basic properties and can be used instead of classic bases, which are needed for the reaction to take place.[36] Hydrotalcites have the following advantages: ease of separation of the products, reduction of waste streams, possible regeneration of the catalyst and low cost. The aforementioned hydrotalcite was used, taking into consideration that the basicity of the calcined product can be modified by changing the Al/Mg ratio.[37] As shown in Table 2 (entry 5), the reaction performed with the calcined hydrotalcite afforded the corresponding ester in 80% yield; however, the use of commercial hydro-

Table 2 Esterification of Phenylacetic Acid (**1**) with *tert*-Butyl Alcohol in the Presence of Other Bases or Hydrotalcites[a]

Entry	Base	Equivalents	Yield[b] (%) of **2**
1	Et_3N	1	48
2	Et_3N	4	82
3	DIPEA	1	43
4	DIPEA	4	79
5	hydrotalcite, $x = 0.33$	200 mg/mmol	80
6	hydrotalcite (Aldrich)	200 mg/mmol	20

[a] Reaction conditions: phenylacetic acid (1 mmol), EDC (1 mmol), HOBt (1 mmol), $CHCl_3$, r.t., 30 min, and then *t*-BuOH (4 mmol), base or hydrotalcite, reflux, 18 h.
[b] Yield of isolated product after chromatographic purification.



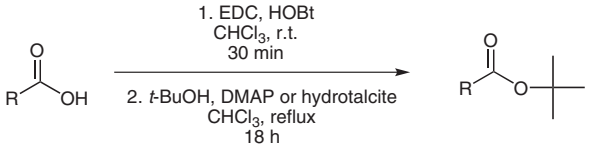
Scheme 3 Side product in the esterification reaction

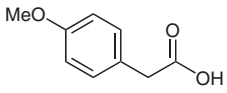
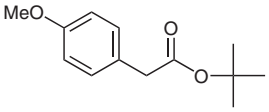
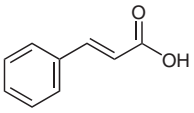
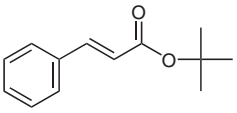
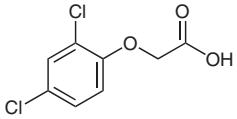
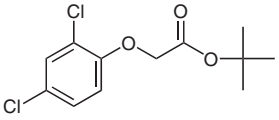
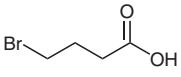
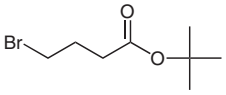
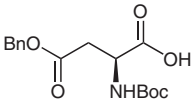
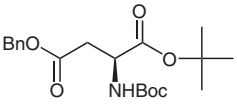
talcite resulted in ester **2** in poor yield (20%, entry 6). This result, obtained with calcined hydrotalcite, increases the already diverse range of possibilities for the use of solid catalysts in the esterification of tertiary alcohols, specifically *tert*-butyl alcohol.

Following the discovery of these results, we tried to extend the methodology to other carboxylic acids (Table 3). (4-Methoxyphenyl)acetic acid (**7**) can also be esterified with *tert*-butyl alcohol in the presence of DMAP or calcined hydrotalcite, under the same reaction conditions used for phenylacetic acid (**1**), giving the ester **8** in 45% yield with DMAP and 40% yield with calcined hydrotalcite (Table 3, entry 1). When the reaction was carried out with cinnamic acid (**9**), the yields were 60% and 55%, respectively (Table 3, entry 2). The *tert*-butyl esters can be generated in a low yield when (2,4-dichlorophenoxy)acetic acid (**11**) and 4-bromobutanoic acid (**13**) are used as starting materials (Table 3, entries 3 and 4), with DMAP or calcined hydrotalcite as the base. The reaction of the glutamic acid derivative **15** was also probed under the standard conditions in the presence of the following three bases: DMAP, DIPEA and calcined hydrotalcite. Ester **16** was obtained in 95%, 90% and 80% yield, respectively (Table 3, entry 5). In this case, there was complete racemization of ester **16** when DMAP was used as the base. The use of DIPEA allowed us to obtain the ester in an enantiomeric excess of 70%; however, when the reaction was carried out in the presence of calcined hydrotalcite, ester **16** was obtained as a single enantiomer.

To test the scope of this protocol in biologically relevant molecules, the esterification of Naproxen (**17**) was tested under the standard conditions. To our delight, ester **19** was obtained in 95% yield when DMAP was used as the base and 79% yield with calcined hydrotalcite as the base (Table 4, entry 1). We also demonstrated that the esterification reaction could be successfully achieved in a good yield with other tertiary alcohols. Thus, Naproxen (**17**) was treated with 2-methylbutan-2-ol (**20**) in the presence of DMAP or calcined hydrotalcite to provide ester **21** in 75% and 58% yield, respectively (Table 4, entry 2). In the same context, the reaction was performed using another sterically hindered alcohol, norethisterone (17α-ethynyl-19-nortestosterone, **23**) (Table 4, entry 3). Norethisterone (**23**) belongs to the first generation of synthetic progestins; this compound is still widely employed as a contragestational agent as well as in hormone replacement therapy.[38] Additionally, it has been demonstrated that norethisterone induces in vitro transactivation of an estrogen-regulated reporter vector transiently cotransfected with the estrogen receptor α or estrogen receptor β in African green monkey kidney CV-1 cells.[39] In the case of the reaction of alcohol **23** with acetic acid (**22**), the yield of ester **24** was 93% when DMAP was used as the base and 90% with calcined hydrotalcite as the base (Table 4, entry 3). Ester formation

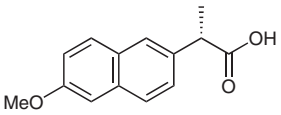
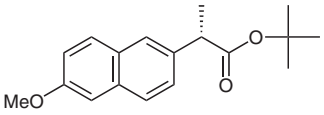
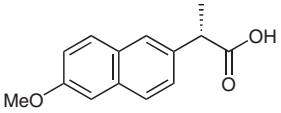
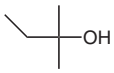
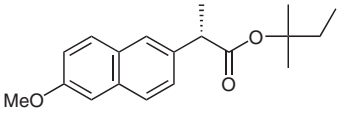
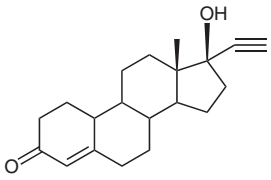
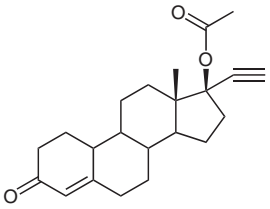
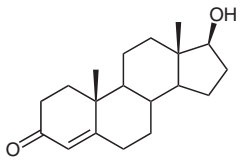
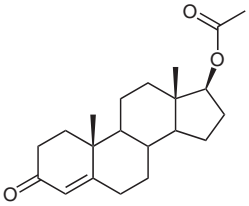
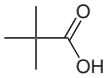
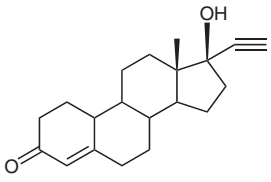
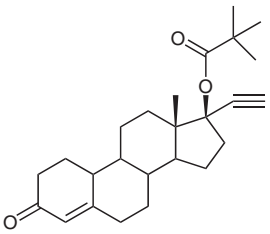
Table 3 Esterification of Various Carboxylic Acids with *tert*-Butyl Alcohol in the Presence of DMAP or Calcined Hydrotalcite[a]



Entry	Acid		Ester product		Base	Yield[b] (%)
1	**7**		**8**		DMAP hydrotalcite	45 40
2	**9**		**10**		DMAP hydrotalcite	60 55
3	**11**		**12**		DMAP hydrotalcite	25 25
4	**13**		**14**		DMAP hydrotalcite	20 18
5	**15**		**16**		DMAP DIPEA hydrotalcite	95 90 80

[a] Reaction conditions: carboxylic acid (1 mmol), EDC (1 mmol), HOBt (1 mmol), $CHCl_3$, r.t., 30 min, and then *t*-BuOH (4 mmol), DMAP (4 mmol) or hydrotalcite (200 mg), reflux, 18 h.
[b] Yield of isolated product after chromatographic purification.

Table 4 Esterification of Sterically Hindered Alcohols Using Benzotriazole Esters[a]

Entry	Acid	Alcohol	Ester product	Base	Yield[b] (%)
1	**17** 	**18** 	**19** 	DMAP hydrotalcite	95 79
2	**17** 	**20** 	**21** 	DMAP hydrotalcite	75 58
3	**22** 	**23** 	**24** 	DMAP hydrotalcite	93 90
4	**22** 	**25** 	**26** 	DMAP hydrotalcite	95 90
5	**27** 	**23** 	**28** 	DMAP hydrotalcite	– –

[a] Reaction conditions: carboxylic acid (1 mmol), EDC (1 mmol), HOBt (1 mmol), $CHCl_3$, r.t., 30 min, and then alcohol (1 mmol), DMAP (4 mmol) or hydrotalcite (200 mg), reflux, 18 h.
[b] Yield of isolated product after chromatographic purification.

was not observed when both the acid and the alcohol are sterically hindered (Table 4, entry 5). Finally, the reaction was carried out with testosterone (**25**) in the presence of 1 equivalent of acetic acid (**22**), which resulted in the ester product **26** in 95% yield with DMAP as the base and 90% yield with calcined hydrotalcite as the base (Table 4, entry 4).

In summary, a method for the esterification of tertiary alcohols has been described. The reaction conditions have been optimized, leading to an efficient procedure. The reaction is broad in scope and uses commercially available reagents. Additionally, a calcined hydrotalcite was used as the base, replacing DMAP, with excellent results for the formation of such esters. To further demonstrate the synthetic value, we have shown that the method can be used in the esterification of biologically relevant molecules.

All reactions were conducted under a dried argon stream. All chemicals were purchased from Aldrich Chemical Co. and used without further purification, unless stated otherwise. Yields refer to the chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. All glassware utilized was flame-dried before use. Reactions were monitored by TLC carried out on 0.25-mm E. Merck silica gel plates. Developed TLC plates were visualized under a shortwave UV lamp and by heating plates that were dipped in $Ce_2(SO_4)_3$ solution. Flash column chromatography was performed using silica gel (230–400) and employed a solvent with polarity correlated with TLC mobility. Optical rotations were measured at 589 nm on a Jasco DIP-370 digital polarimeter using a 100-mm cell. NMR experiments were conducted on a Varian 300-MHz instrument using $CDCl_3$ (99.9% D) as the solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm, ^1H; 77.00 ppm, ^{13}C) or TMS as internal reference (0.00 ppm). Chemical shifts are relative to the solvent peak and are in parts per million (ppm). Mass spectra were recorded on a Jeol JS102 high-resolution mass spectrometer.

Esterification Reaction; General Procedure

In a round-bottom flask, 1 equivalent of the carboxylic acid was added, followed by 1 equivalent of HOBt and EDC in anhyd $CHCl_3$ (30 mL), under argon atmosphere, and the mixture was stirred for 30 min; then, DMAP (4 equiv) was added and the tertiary alcohol (1 equiv) was injected via syringe. The reaction mixture was refluxed for 18 h. At the end of the reaction time, the solvent was

evaporated and the mixture was dissolved in Et_2O (30 mL). The organic layer was washed with 10% $NaHCO_3$ soln (2 × 10 mL), 10% citric acid soln (2 × 10 mL), 10% K_2CO_3 soln (2 × 10 mL) and brine (2 × 10 mL), then dried (anhyd Na_2SO_4), and the solvent was removed by evaporation. The residue was purified by flash chromatography on silica gel to afford the pure ester.

***tert*-Butyl Phenylacetate (2)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.24 (m, 5 H), 3.52 (s, 2 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 134.7, 129.2, 128.4, 126.8, 80.7, 42.6, 28.0.

HRMS (FAB): *m*/*z* calcd for $C_{12}H_{16}O_2$: 192.1150; found: 192.1152.

***tert*-Butyl 3-Oxo-2,4-diphenylbutanoate (3)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.05 (m, 10 H), 4.72 (s, 1 H), 3.78 (d, *J* = 15.9 Hz, 1 H), 3.71 (d, *J* = 15.9 Hz, 1 H), 1.44 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.1, 170.0, 139.5, 134.1, 129.8, 129.2, 128.9, 127.6, 127.2, 82.1, 60.4, 48.7, 28.8.

HRMS (FAB): *m*/*z* calcd for $C_{20}H_{22}O_3$: 310.1569; found: 310.1566.

***tert*-Butyl (4-Methoxyphenyl)acetate (8)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (m, 2 H), 6.84 (m, 2 H), 3.78 (s, 3 H), 3.46 (s, 2 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 158.5, 130.1, 126.8, 113.8, 80.6, 55.2, 41.7, 28.0.

HRMS (FAB): *m*/*z* calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1250.

***tert*-Butyl (*E*)-Cinnamate (10)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (m, 5 H), 6.44 (d, *J* = 15.9 Hz, 1 H), 6.37 (d, *J* = 16.1 Hz, 1 H), 1.54 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 143.5, 129.9, 128.8, 127.9, 118.3, 80.5, 28.2.

HRMS (FAB): *m*/*z* calcd for $C_{13}H_{16}O_2$: 204.1150; found: 204.1145.

***tert*-Butyl (2,4-Dichlorophenoxy)acetate (12)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 2.6 Hz, 1 H), 7.15 (dd, *J* = 9, 2.6 Hz, 1 H), 6.75 (d, *J* = 9 Hz, 1 H), 4.58 (s, 2 H), 1.47 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 152.5, 130.2, 127.4, 126.7, 124.1, 114.4, 82.8, 66.7, 28.0.

HRMS (FAB): *m*/*z* calcd for $C_{12}H_{14}Cl_2O_3$: 276.0320; found: 276.0321.

***tert*-Butyl 4-Bromobutanoate (14)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45 (t, *J* = 6.8 Hz, 2 H), 2.40 (t, *J* = 7.2 Hz, 2 H), 2.13 (quint, *J* = 6.8 Hz, 2 H), 1.45 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.4, 85.2, 59.3, 34.5, 33.1, 27.5.

HRMS (FAB): *m*/*z* calcd for $C_8H_{15}BrO_2$: 222.0255; found: 222.0259.

***tert*-Butyl 2-[(Benzyloxy)carbonyl]-1-(*tert*-butoxycarbonyl)ethylcarbamate (16)**

$[\alpha]_D^{25}$ +2.34 (*c* 1.95, EtOAc) {Lit.[40] $[\alpha]_D^{25}$ +2.34 (*c* 1.95, EtOAc)}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35 (m, 5 H), 5.45 (d, *J* = 8.4 Hz, 1 H), 5.15 (d, *J* = 12.2 Hz, 1 H), 5.1 (d, *J* = 12.2 Hz, 1 H), 4.45 (dt, *J* = 8.4, 4.8 Hz, 1 H), 3.0 (dd, *J* = 16.8, 4.3 Hz, 1 H), 2.82 (dd, *J* = 16.8, 4.8 Hz, 1 H), 1.44 (s, 9 H), 1.41 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 169.9, 155.4, 135.5, 128.5, 128.3, 128.3, 82.3, 79.8, 66.6, 50.5, 37.1, 28.3, 27.8.

HRMS (FAB): *m*/*z* calcd for $C_{20}H_{29}NO_6$: 379.1995; found: 379.1992.

***tert*-Butyl 2-(6-Methoxy-2-naphthyl)propanoate (19)**

$[\alpha]_D^{25}$ +26.8 (*c* 1.0, CH_2Cl_2) {Lit.[41] $[\alpha]_D^{25}$ +26.9 (*c* 1.0, CH_2Cl_2)}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (m, 3 H), 7.40 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.11 (m, 2 H), 3.90 (s, 3 H), 3.73 (q, *J* = 7.2 Hz, 1 H), 1.51 (d, *J* = 7.2 Hz, 3 H), 1.38 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 157.5, 136.3, 133.5, 129.2, 128.9, 126.9, 126.3, 125.7, 118.7, 105.6, 80.4, 55.3, 46.4, 27.9, 18.5.

HRMS (FAB): *m*/*z* calcd for $C_{18}H_{22}O_3$: 286.1569; found: 286.1562.

***tert*-Pentyl 2-(6-Methoxy-2-naphthyl)propanoate (21)**

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.66 (m, 3 H), 7.40 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.10 (m, 2 H), 3.90 (s, 3 H), 3.75 (q, *J* = 7 Hz, 1 H), 1.71 (q, *J* = 7.2 Hz, 2 H), 1.55 (d, *J* = 7.1 Hz, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 0.75 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 157.5, 136.3, 133.5, 129.2, 126.7, 126.4, 125.8, 118.7, 105.6, 82.9, 55.3, 46.5, 33.5, 25.5, 25.3, 18.4, 8.0.

HRMS (FAB): *m*/*z* calcd for $C_{19}H_{24}O_3$: 300.1725; found: 300.1720.

17α-Ethynyl-19-nortestosterone Acetate (24)

$[\alpha]_D^{25}$ –33.1 (*c* 1.0, $CHCl_3$) {Lit.[42] $[\alpha]_D^{25}$ –33.0 (*c* 1.0, $CHCl_3$)}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83 (s, 1 H), 2.75 (m, 1 H), 2.61 (s, 1 H), 2.48 (m, 1 H), 2.41 (m, 1 H), 2.29 (m, 1 H), 2.28 (m, 2 H), 2.11 (m, 1 H), 2.05 (s, 3 H), 2.04 (m, 1 H), 1.93 (m, 1 H), 1.86 (m, 1 H), 1.85 (m, 1 H), 1.77 (m, 2 H), 1.74 (m, 1 H), 1.57 (m, 2 H), 1.37 (m, 2 H), 1.28 (m, 1 H), 1.12 (m, 1 H), 0.935 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.9, 168.7, 166.3, 124.0, 83.4, 82.1, 70.5, 49.5, 47.4, 46.9, 43.3, 39.3, 36.6, 35.0, 33.8, 33.0, 31.3, 29.4, 26.6, 23.3, 20.4, 13.2.

HRMS (FAB): *m*/*z* calcd for $C_{22}H_{28}O_3$: 340.2038; found: 340.2035.

Testosterone Acetate (3-Oxo-4-androsten-17β-yl Acetate (26)

$[\alpha]_D^{25}$ +82.3 (*c* 1.0, $CHCl_3$) {Lit.[43] $[\alpha]_D^{25}$ +82.2 (*c* 1.0, CH_2Cl_2)}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.72 (s, 1 H), 4.60 (dd, *J* = 9.2, 7.9 Hz, 1 H), 2.40 (ddd, *J* = 16.8, 16.7, 5.2 Hz, 1 H), 2.39 (m, 1 H), 2.35 (ddd, *J* = 16.8, 5.1, 3.3 Hz, 1 H), 2.28 (ddd, *J* = 14.6, 4.3, 2.3 Hz, 1 H), 2.18 (dddd, *J* = 13.8, 9.5, 9.2, 6 Hz, 1 H), 2.04 (s, 3 H), 2.04 (ddd, *J* = 13.4, 5.2, 3.3 Hz, 1 H), 1.83 (m, 1 H), 1.79 (dt, *J* = 12.8, 6.8 Hz, 1 H), 1.70 (ddd, *J* = 16.8, 13.4, 5.1 Hz, 1 H), 1.66 (m, 1 H), 1.55 (m, 2 H), 1.52 (m, 1 H), 1.41 (m, 1 H), 1.36 (m, 1 H), 1.19 (s, 3 H), 1.18 (m, 1 H), 1.07 (m, 1 H), 1.04 (m, 1 H), 0.95 (m, 1 H), 0.84 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.2, 171.0, 170.7, 124.0, 82.4, 53.8, 50.3, 42.5, 38.6, 36.7, 35.8, 35.5, 33.9, 32.7, 31.5, 27.5, 23.5, 21.1, 20.6, 17.4, 12.0.

HRMS (FAB): *m*/*z* calcd for $C_{21}H_{30}O_3$: 330.2195; found: 330.2193.

Mg–Al Hydrotalcite[34]

Hydrotalcite was characterized by powder X-ray diffraction with Cu Kα radiation, using a Siemens diffractometer in the range from 4 to 70° (2θ). FT-IR spectra were recorded on a Nicolet Magna 750 spectrometer; data collection was performed using DRIFT and KBr disc techniques. DTA and TGA analyses were carried out on a Du-Pont thermobalance, using He flow at a heating rate of 10 °C/min. Specific surface areas were calculated by N_2 adsorption at 75.25 K (BET method) using a Micromeritics ASAP 2000 instrument; the samples were first outgassed at 523 K. Mg–Al hydrotalcite with *x* = Mg/Al ratio 0.33 was prepared by coprecipitation following the procedure described by Reichle.[44] $Mg_{10}Al_2(OH)_{24}CO_3{\cdot}6H_2O$: $Al(NO_3)_3{\cdot}9H_2O$ (0.01 mol) and $Mg(NO_3)_2{\cdot}6H_2O$ (0.05 mol) were dissolved in deionized H_2O (70 mL). A second deionized H_2O solution (100 mL) of Na_2CO_3 (0.1 mol) and NaOH (0.35 mol) was prepared. The first solution was slowly added to the second solution.

The resulting mixture was heated at 338 K with vigorous stirring for 18 h. After the heating period, the slurry was cooled to r.t., washed with deionized H_2O until pH 9 and dried at 383 K for 18 h. Hydrotalcites were activated by calcination at a rate of 2 °C/min up to 773 K and maintained for 2 h in a flow of air. Samples were then cooled in dry nitrogen and stored.

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