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Triphenylphosphine dibromide: a simple one-pot esterification reagent

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ABSTRACT

We report a one-pot, expedient protocol for the conversion of carboxylic acids to their esters using excess triphenylphosphine dibromide, base, and the alcohol. The reaction gave the esterified product in moderate-to-high yields (30–95%). For chiral acids, the reaction proceeded with little or no racemization. Use of a chiral alcohol in this transformation gave the ester with retention of configuration of the stereogenic center. Information is presented indicating that esterification proceeds through the intermediate generation of an acyloxyalkoxyphosphorane and where steric interactions play an important role in the energetics of the reaction.

1. Introduction

Esterification reactions are among the oldest and most often used reactions in organic chemistry.[1] Numerous and diverse methods have been advanced for this transformation, assuring that most esters can be prepared. Nonetheless, a simpler, general method would facilitate future synthetic studies.

We sought a readily available esterification reagent that could convert carboxylic acids to their alkyl esters. We report herein that treating aliphatic and aromatic acids with triphenylphosphine dibromide[2] (**1**), an excess of the primary, secondary, or tertiary alcohols, and a base provided the esterified products in a one-pot reaction. For optically active aliphatic acids, esterification proceeded with little or no racemization. Use of a chiral alcohol in this reaction gave the ester with retention of configuration of the stereogenic center. The conditions and scope of the esterification reactions provided information on the probable pathway for these transformations.

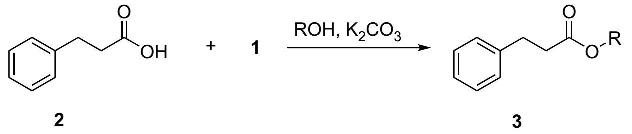
Ph_3PBr_2

1

2. Results and discussion

We first examined aliphatic acids and used 3-phenylpropionic acid (**2**) as the prototype. Treatment of **2** with **1** (5 equiv), K_2CO_3 (11 equiv), and excess MeOH (148 equiv) at room temperature (1 day) gave the esterified product **3a** in 79% yield after purification (Table 1). Substitution of primary alcohols (EtOH, *n*-BuOH, allyl alcohol, 2-chloroethanol, 2-methoxyethanol) for MeOH provided the corresponding esters **3b**–**3f** in 45–95% isolated yields. Similarly, the secondary alcohol, *iso*-propanol, gave ester **3g** in 88% yield. Finally, use of *t*-BuOH produced ester **3h** in 63% yield. Our finding that *tert*-butyl esters are prepared by this method is important since the acid-sensitive *tert*-butyl group has proven to be useful in synthesis.[4]

Table 1
Esterification of **2** to give **3**[a]



Entry	Alcohol	Product	Purified yield[b] (%)
1	MeOH	**3a**[c]	79
2	EtOH	**3b**[d]	95
3	*n*-BuOH	**3c**[e]	63
4	$CH_2{=}CHCH_2OH$	**3d**[f]	53[g]
5	$ClCH_2CH_2OH$	**3e**[h]	82
6	$MeOCH_2CH_2OH$	**3f**[i]	45
7	*i*-PrOH	**3g**[d]	88
8	*t*-BuOH	**3h**[c]	63

[a] All reactions were conducted by treating **2** with an excess of alcohol (6 mL, 63–148 equiv), **1** (5 equiv), and K_2CO_3 (11 equiv) at room temperature for 1 day.
[b] The products were purified by medium-pressure liquid chromatography (MPLC).
[c] Ref. 3a.
[d] Ref. 3b.
[e] Ref. 3c.
[f] Ref. 3d.
[g] Compound **3d** was purified by two MPLCs.
[h] Ref. 3e.
[i] Ref. 3f.

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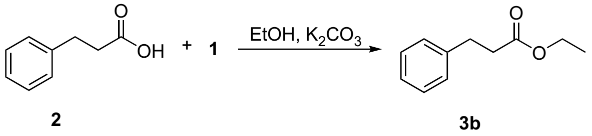
Table 2
Esterification conditions for the conversion of **2** to **3b**[a]

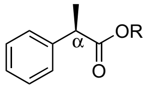


Entry	**1** (equiv)	K$_2$CO$_3$ (equiv)	Rxn Temp (°C)	Rxn time (h)	Yield[b] (%)
1	2	2	22	24	40
2	5	5	22	24	42
3	5	5	82	24	34
4	5	5	22	72	23

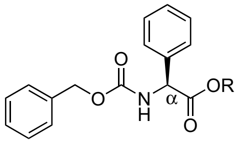
[a] All reactions were run in acetonitrile using **2** (1 mmol, 1 equiv) and EtOH (5 equiv).
[b] Isolated yields after MPLC.

The effect of the number of equivalents of **1**, K$_2$CO$_3$, and alcohol as well as the reaction conditions on the efficiency of the esterification process was briefly examined (Table 2). Employing the conversion of **2** to **3b** as a test case, we observed lower yields of the esterified product (40–42%) compared with the 95% yield for **3b** listed in Table 1 as we decreased either the number of equivalents of **1** and K$_2$CO$_3$ or the number of equivalents of EtOH (Table 2, entries 1 and 2). Efforts to improve the reaction efficiency by increasing the reaction temperature or reaction time (Table 2, entries 3 and 4) led to even lower yields of **3b** (Table 2, entries 3 and 4).

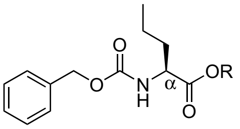
We asked the question whether the esterification procedure would proceed without racemization for optically active acids that had a chiral center at the C(α) site. To find out, we treated (*R*)-(−)-2-phenylpropionic acid (**4**), (*S*)-Cbz-phenylglycine (**5**), and (*S*)-Cbz-norvaline (**6**) with **1**, EtOH, and K$_2$CO$_3$ (room temperature, 1 day). In all these cases, the reaction gave the optically pure esters **7**[5] (73% yield, er $\geq$96.4%), **8**[6] (79% yield, er $\geq$99.8%), and **9**[7] (77% yield, er $\geq$97.6%).[8]



4 R = H
7 R = Et

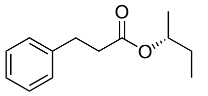


5 R = H
8 R = Et



6 R = H
9 R = Et

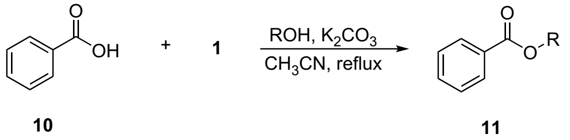
We determined if the esterification of **2** with a secondary, chiral alcohol proceeded with either retention or inversion of the stereogenic center in the alcohol. Using **2** and (*R*)-2-butanol we obtained **3i**[9] in 82% yield with complete retention of the 2-butoxy unit.



3i

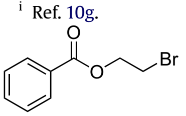
The reaction conditions needed to be modified in order to convert aromatic acids to their esters. Benzoic acid (**10**) served as our test substrate. Acetonitrile was used as the solvent, and the reaction mixture containing **10**, **1** (5 equiv), alcohol (5 equiv), and K$_2$CO$_3$ (11 equiv) was heated at reflux for 3 days. Moderate yields (35–80%) were obtained for most of the purified products **11** (Table 3). For most unsubstituted alcohols the yields appeared to be largely independent of the alcohol used. However, use of *t*-BuOH in this procedure did not provide ester **11h**. For 2-chloroethanol, we isolated a mixture of the 2-chloroethyl (**11e**) and 2-bromoethyl (**11i**) esters (NMR analysis). Similarly, when we used 2-methoxyethanol we isolated a mixture of the expected ester **11f** along with the corresponding 2-bromoethyl ester **11i** (NMR analysis).

Table 3
Esterification of **10** to give **11**[a]



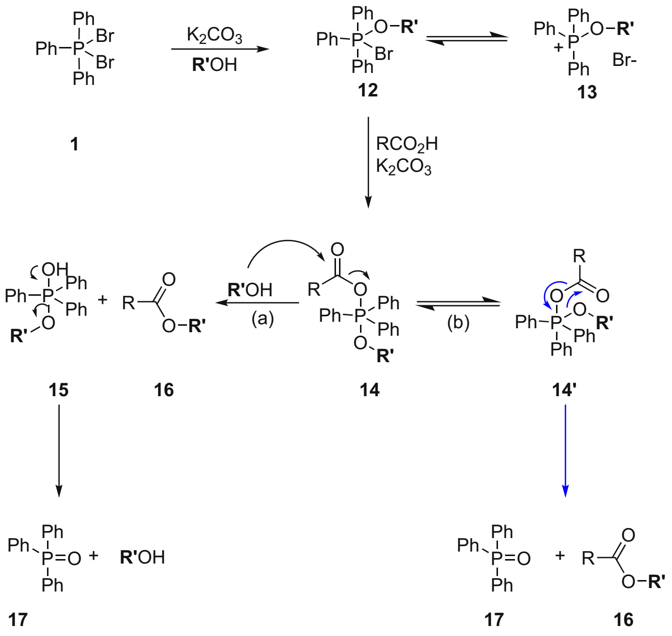
Entry	Alcohol	Product	Purified yield[b] (%)
1	MeOH	**11a**[c]	51
2	EtOH	**11b**[c]	80
3	*n*-BuOH	**11c**[d]	35
4	CH$_2$=CHCH$_2$OH	**11d**[e]	80
5	ClCH$_2$CH$_2$OH	**11e**[f]+**11i**[g]	Mixture
6	MeOCH$_2$CH$_2$OH	**11f**[h]+**11i**[g]	Mixture
7	*i*-PrOH	**11g**[c]	55
8	*t*-BuOH	**11h**[i]	0

[a] All reactions were conducted by treating **10** with an excess of alcohol (5 equiv), **1** (5 equiv), and K$_2$CO$_3$ (11 equiv) in acetonitrile at reflux for 3 days.
[b] The products were purified by MPLC.
[c] Ref. 10a.
[d] Ref. 10b.
[e] Ref. 10c.
[f] Ref. 10d.
[g] Ref. 10e.
[h] Ref. 10f.
[i] Ref. 10g.



11i

Phosphorus reagents (e.g., dihalophosphoranes, dialkoxyphosphoranes, Wittig reagents, trihalophosphines) have been used extensively in synthesis. In particular, treating carboxylic acids with **1** in aprotic solvents provides the acid halides.[11–13] Likewise, the dialkoxyphosphoranes and other similarly disubstituted reagents (e.g., bis(2,2,2-trifluoroethoxy)phosphorane,[14–16] 2,2,2-triphenyl-4,5-(2′,2″-biphenylene)-1,3,2-dioxaphospholane,[17] triphenylphosphine thiocyanogen,[18–22] triphenylphosphine ditriflate[23]) have been used to prepare carboxylic acid derivatives.



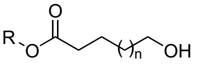
Scheme 1. Proposed pathway for **1**-mediated esterification processes.

In Scheme 1, we propose a pathway for the observed esterification reactions. In the initial step, **1** undergoes rapid halide exchange leading either to the monoalkoxy **12** or to the dialkoxy phosphorane,[24–26] which can possibly exist in equilibrium with the phosphonium salt **13**. The subsequent attack of **12** by the acid carboxylate provides intermediate **14**,[27] which can either react with the alcohol in solution (pathway a) or react with the appended phosphorane alkoxy unit by an intramolecular route after pseudorotation to give **14**′ to provide the esterified product **16** (pathway b). The pathway in Scheme 1 is similar, in part, to that proposed for the Mitsunobu reaction.[28] Unlike most Mitsunobu transformations, we observed retention of the stereogenic center [29] in **3i**.[9] We also discovered that **2** was converted to ester **3h** with *t*-BuOH (Table 1). Recently, Anders and co-workers have conducted a density functional analysis of the Mitsunobu reaction providing a rationale for both the typical inverted product and the atypical retention adduct.[30] Significantly, these investigators suggested that the retention product stems from an acyloxyalkoxyphosphorane species similar to **14** that undergoes Berry pseudorotation and intramolecular substitution.

The pathway outlined in Scheme 1 is consistent with the reported ease with which dihalophosphoranes react with alcohols,[24–26] and phosphorane-mediated mechanisms that activate carboxylic acid derivatives toward nucleophilic substitution reactions.[11–13,31,32] Several experimental observations supported the proposed pathway and provided insights into the controlling factors that governed this transformation. First, the yields for **3c** were independent of the order in which reagents were added. For example, we obtained **3c** in 63% yield after we added **1** to a reaction mixture consisting of **2**, *n*-BuOH, and K_2CO_3. Similarly, **3c** was produced in 70% yield after we premixed **1**, *n*-BuOH, and K_2CO_3 for 20 min before adding **2**. These results are consistent with the initial reaction of **1** with the alcohol rather than with the carboxylate. Second, we tested whether dialkoxyphosphoranes, similar to intermediate **12**, could convert carboxylic acids to the corresponding ester. Treatment of **2** with diethoxyphosphorane (DTPP, **18**) gave **3b** (85%), thus demonstrating that **18** and similar compounds can serve as esterification reagents. Indeed, the Evans laboratory reported that **18**-treated **19** provided the esterified product **20**.[33] The utility of **18** for ethyl esterification was not further explored. Third, we observed that **2** was converted to ester **3i**[9] with retention of the stereogenic center in the (*R*)-2-butanoxy group, and that **2** gave ester **3h** with *tert*-butanol. These collective findings suggested that the reaction proceeded through intermediate **14**.

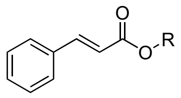
$PPh_3(OEt)_2$

18

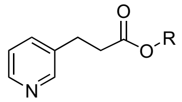


19 R = H
20 R = Et

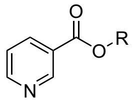
The different reactivities of **2** and **10** with **1** prompted us to determine if either electronic or steric factors governed the esterification process. We esterified *trans*-cinnamic acid (**21**), 3-(3-pyridyl)propionic acid (**22**), and nicotinic acid (**23**) under the same conditions employed for either **2** or **10**. The α,β-unsaturated acid **21** readily reacted with EtOH under the mild conditions used for the aliphatic acid **2** (room temperature, 1 day) to give **24**[34] (57%). The 3-pyridyl-substituted aliphatic acid **22** was converted to the ethyl **25a**[35] (76%), *iso*-propyl **25b** (75%), and *tert*-butyl **25c** (30%) esters at room temperature (1 day). Esterification of nicotinic acid (**23**) with EtOH and *iso*-propanol required the use of acetonitrile and heat (reflux, 3 days) to give the ethyl **26a**[36a] (40%) and *iso*-propyl **26b**[36b] (65%) esters, respectively. The esterification yields of **23** were similar to those of **10** (Table 3), demonstrating that substituting the phenyl group in **10** by the electron-deficient pyridine ring in **23** did not markedly affect this transformation. Collectively, these results showed that electronic effects produced by the R-substituent in carboxylic acids (RCO_2H) could not account for the different conditions needed for **2** or **10** esterification. Consistent with this notion is the finding that the pK_a values[37] for **2** and **10** fall within a narrow range (pK_a 4.2–4.4) indicating that under the mild basic conditions of our reactions both carboxylic acids are converted to the carboxylates.



21 R = H
24 R = Et

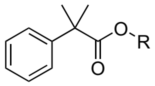


22 R = H
25a R = Et
25b R = *i*-Pr
25c R = *t*-Bu



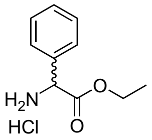
23 R = H
26a R = Et
26b R = *i*-Pr

We then asked whether steric factors affected esterification of **2** and **10**. In our proposed pathway (Scheme 1), **14** serves as the central intermediate. This species places the carboxylic acid R-substituent (alkyl, aryl) in proximity to one of the three phenyl groups in the proposed trigonal-bipyramidal intermediate **14**. X-ray crystallographic studies of disubstituted triphenylphosphoranes[25,38] show that the three phenyl groups are canted with respect to one another. If the esterification reaction proceeds through **14** then the phenyl R-substituent in **10** is likely to undergo an adverse steric interaction with one of the three phenyl groups in the triphenylphosphorane compared with the aliphatic R-substituent in **2**. We have modeled **14** intermediate for **2**, **10**, and **23** transformations using SPARTAN ’06 semi-empiric AM1 equilibrium geometry calculations and we found that the energy-minimized values for the central phosphorane intermediate for **10** and **23** to be appreciably higher than **2** (data not shown). To test this hypothesis further, we treated the tertiary-substituted aliphatic acid, 2-methyl-2-phenylpropionic acid (**27**) with **1** and EtOH and compared the ease of esterification of **27** with **4**. We found that **4** converted to the ethyl ester **7** (73%) under mild conditions (room temperature, 1 day) while **27** required acetonitrile and heat (60 °C, 3 days) to provide its corresponding ethyl ester **28**[39] (66%). Molecular-modeling studies indicated that the energy-minimized value for the intermediate **14** generated from **27** was higher than predicted from either **2** or **4**. These results, taken together, support the proposed pathway for esterification (Scheme 1) and provide evidence that the energetics for the formation of **14** govern the conditions required for esterification.[40]



27 R = H
28 R = Et

The efficiency of the **1**-mediated esterification reaction was compared with the established procedures. We chose (*S*)-Cbz-phenylglycine (**5**) as a test substrate since it contained a commonly used protecting group (Cbz) and a stereogenic center prone to racemization. First, using Fischer esterification conditions[41] (EtOH (115 equiv), HCl (20 equiv), 78 °C, 16 h) we obtained partially racemized ester **29**[42] in near quantitative yield and where the Cbz-group was removed. Second, when **5** was esterified with EtOH using the mixed anhydride procedure[43] ((i) isobutyl chloroformate (1.2 equiv), 4-methylmorpholine (1.2 equiv), −78 °C; (ii) EtOH (5 equiv), −78 °C to 22 °C, 4 h) we obtained partially racemized **8** in 61% yield. Third, addition of thionyl chloride (15 equiv) to a dichloromethane solution containing **5** and a catalytic amount of DMF (40 °C, 2 h), followed by concentration of the reaction mixture and addition of EtOH[44] led to a complex product mixture. Finally, treatment of **5** with thionyl chloride (2 equiv) and EtOH (35 equiv) at 22 °C (16 h)[45] gave optically pure **8** in 93% yield with little or no racemization.



29

The proposed pathway for esterification of carboxylic acids (Scheme 1) suggests that similar treatment of esters with **1** and alcohols would provide the trans-esterified products. We briefly explored this using acetonitrile as a solvent and a temperature maintained at reflux for 24 h. Treatment of **3a** with **1**, K_2CO_3 (6 equiv), and EtOH (5 equiv) gave **3b** (70%) along with the recovered methyl ester **3a** (<10%). When we substituted *n*-BuOH for EtOH we obtained a mixture of methyl (**3a**) and *n*-butyl (**3c**) esters in a 1:1.5 ratio, respectively, and an ~60% yield for **3c**.

3. Conclusions

In summary, we report a simple, one-pot experimental protocol for converting alkyl and aromatic acids to their alkyl esters using **1** and that proceeds with little or no racemization. Reagent **1** is commercially available and can be prepared from triphenylphosphine and Br_2 in near-quantitative yields.[25] The method relies on in situ conversion of **1** to an alkoxyphosphorane, which serves as the esterification agent. The described one-pot protocol has several important advantages over the conventional two-step procedure, which entails converting the acid to the acid halide with **1**[11–13] and then treating the isolated acid halide with the alcohol. These advantages include the procedure's simplicity as well as eliminating the need to handle and isolate acid halides, which are moisture sensitive and are lachrymators,[11–13] or the use of aprotic solvents to generate the acid halide. Our studies indicate that the reaction is governed, in part, by the energetics that form the initial pentavalent intermediate **14** containing the carboxylate and in which steric interactions have an important role. Finally, the different reactions reported for **1** among functional groups will affect the scope of this esterification process with respect to the permissible R-substituents in the starting acid.

4. Experimental

4.1. General procedures

Unless otherwise noted, all materials were used as-received from a commercial supplier without further purification. All reactions were monitored by analytical thin layer chromatography (TLC) plates (Aldrich, Cat # Z12272-6) and analyzed with 254 nm UV light. The reactions were purified by MPLC (CombiFlash *Rf*) with self-packed columns (silica gel from Dynamic Adsorbents Inc., Cat # 02826-25). Known compounds were characterized by ^{1}H NMR, ^{13}C NMR, and MS (when possible) and compared to their literature values. Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. Optical rotations were obtained on a Jasco P-1030 polarimeter. Proton (^{1}H NMR, 300 MHz) and carbon (^{13}C NMR, 75 MHz) nuclear magnetic resonance spectra were taken on a Varian Gemini 2000 spectrometer in $CDCl_3$. Chemical shifts (δ) were reported in parts per million relative to TMS as an internal reference. Coupling constants (*J*) were reported in hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), sept (septet), and m (multiplet). The high-resolution mass spectrum was recorded on a Bruker Apex-Q 12 Tesla FTICR by Dr. M. Crowe at the University of North Carolina, Chapel Hill, and the low-resolution mass spectra were recorded on a BioToF-II-Bruker Daltonics spectrometer by Dr. S. Habibi. Microanalysis was carried out by Atlantic Microlab, Inc. (Norcross, GA). The yields refer to the isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR.

4.2. General procedure for the esterification of aliphatic acids 2 and α,β-unsaturated acid 21

Reagent **1** (2.20 g, 5 mmol) was added to an alcoholic solution (6 mL) of K_2CO_3 (1.60 g, 11 mmol) and the acid (1 mmol). The reaction mixture was stirred at room temperature (24 h). The volatiles were removed and H_2O (25 mL) and CH_2Cl_2 (25 mL) were added to the residue. The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (25 mL). The organic layers were combined and concentrated in vacuo. The residue was purified by medium-pressure liquid chromatography (MPLC) with hexanes as the eluent to obtain a colorless oil. The compounds prepared by this method were consistent with those published. Representative examples are as follow:

4.2.1. *iso-Propyl 3-(pyridin-3-yl)propanoate (**25b**)*

R_f=0.37 (50% EtOAc in hexanes); IR (neat) 2779, 2392, 1731, 1579, 1429, 1376, 1186, 1035, 858, 802, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20 (d, *J*=6.3 Hz, 2C*H*$_3$), 2.61 (t, *J*=7.5 Hz, C*H*$_2$), 2.95 (t, *J*=7.5 Hz, C*H*$_2$), 5.00 (sept, *J*=6.3 Hz, OC*H*), 7.22 (dd, *J*=4.8, 7.8 Hz, *H*$_5$), 7.54 (dt, *J*=2.1, 7.8 Hz, *H*$_4$), 8.45–8.49 (m, *H*$_2$ and *H*$_6$); ^{13}C NMR ($CDCl_3$): δ 21.7 (2*C*H$_3$), 28.1 (*C*H$_2$), 35.7 (*C*H$_2$), 67.9 (*C*HO), 123.3, 135.8, 147.7, 149.9 (*C*$_5$H$_4$N), 171.8 (*C*(O)), the remaining pyridine resonance was not detected and is believed to overlap with nearby peaks; MS (M+H$^+$)(ESI$^+$) 194.2 [M+H$^+$] (calcd for $C_{12}H_{17}NO_2H^+$ 194.1). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.23; H, 7.88; N, 7.26.

4.2.2. *tert-Butyl 3-(pyridin-3-yl)propanoate (**25c**)*

R_f=0.38 (50% EtOAc in hexanes); IR (neat) 2924, 2860, 1727, 1456, 1369, 1254, 1152, 1031, 847, 801, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.41 (s, C(C*H*$_3$)$_3$), 2.56 (t, *J*=7.8 Hz, C*H*$_2$), 2.91 (t, *J*=7.8 Hz, C*H*$_2$), 7.21 (dd, *J*=4.8, 7.8 Hz, *H*$_5$), 7.53 (br d, *J*=7.8 Hz, *H*$_4$), 8.45–8.49 (m, *H*$_2$ and *H*$_6$); ^{13}C NMR ($CDCl_3$): δ 28.0 (C(*C*H$_3$)$_3$), 28.2 (*C*H$_2$), 36.5 (*C*H$_2$), 80.7 (O*C*(CH$_3$)$_3$), 123.3, 135.8, 147.7, 149.9 (*C*$_5$H$_4$N), 171.6 (*C*(O)), the remaining pyridine resonance was not detected and is believed to overlap with the nearby peaks; MS (M+H$^+$)(ESI$^+$) 208.2 [M+H$^+$] (calcd for $C_{12}H_{17}NO_2H^+$ 208.1). Anal. Calcd for $C_{12}H_{17}NO_2\cdot 0.07H_2O$: C, 69.09; H, 8.29; N, 6.71. Found: C, 69.21; H, 8.20; N, 6.32.

4.3. General procedure for the esterification of chiral acids

Reagent **1** (2.20 g, 5 mmol) was added to an alcoholic solution (6 mL) of K_2CO_3 (0.76 g, 5.5 mmol) and the acid (1 mmol). The reaction mixture was stirred at room temperature (24 h). The volatiles were removed, and H_2O (25 mL) and CH_2Cl_2 (25 mL) were added to the residue. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (25 mL). The organic layers were combined and concentrated in vacuo. The residue was purified by MPLC with hexanes as the eluent to obtain the esters. The compounds prepared by this method were consistent with those published.

4.4. General procedure for the esterification of aromatic acids 10, and acids 21 and 23

K_2CO_3 (1.60 g, 11 mmol) was added to a CH_3CN solution (6 mL) containing the acid (1 mmol). The mixture was stirred at room temperature (20 min), and **1** (2.20 g, 5 mmol) and the alcohol (5 mmol) were added. The reaction mixture was stirred at reflux (72 h). The volatiles were removed, and H_2O (25 mL) and CH_2Cl_2 (25 mL) were added to the residue. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (25 mL). The organic layers were combined and concentrated in vacuo. The residue was purified by MPLC with hexanes as the eluent to obtain a colorless oil. The compounds prepared by this method were consistent with those published.

4.5. General procedure for the esterification of aliphatic acids 2 with DTPP (18)

DTPP (**18**) (1.76 g, 5 mmol) was added to an alcoholic solution (6 mL) of the acid (1 mmol), and the reaction mixture was stirred at room temperature (24 h). The volatiles were removed and the residue was purified by MPLC with hexanes as the eluent to obtain a colorless oil.

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Supplementary data

Spectroscopic data (^{1}H and ^{13}C NMR) of all purified products and experimental details on the use of **18**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.062.

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