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Asymmetric reduction of 3-aryl-3-keto esters using *Rhizopus* species

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Abstract—Ethyl 3-aryl-3-oxopropanoates (aryl: phenyl, 2-fluorophenyl, 3-nitrophenyl, and 4-nitrophenyl) were reduced enantioselectively to the corresponding (*S*)-alcohols by the fungus *Rhizopus arrhizus* and other *Rhizopus* sp. The best results were generally obtained with *Rhizopus arrhizus* (wild type) and *Rhizopus nivius* NCIM 958 with 6 h incubation. A longer incubation period led to ester hydrolysis followed by decarboxylation and microbial reduction for all the substrates especially the 3-nitrophenyl ester.

1. Introduction

Optically active β-hydroxy esters/acids are important building blocks in organic synthesis, for example, in the syntheses of β-amino acids,[1a,b] β-lactams,[1c] and insect pheromones.[1d] The β-hydroxy acids are also important subunits[2a] of polyketide natural products such as amphotericin B,[2b] tylosin,[2c] and rosaramicin.[2d] Moreover, the stereogenicity in the β-hydroxy esters/acids can also assist in developing stereo-controlled construction of 1,3-diols[3a,b] and 1,3-amino alcohols,[3c,d] that are intermediates for a large number of antibiotics[4a,b] and chiral auxiliaries.[4c–f]

Optically active 3-aryl-3-hydroxy esters are precursors of worlds leading anti-depressant drugs like tomoxetine and fluoxetine hydrochlorides[5a] as well as other enantiopure pharmaceuticals such as *S*-1-benzyl-3-hydroxypyrrolidines.[5b,c] (*R*)-Tomoxetine is the first norepinephrine anti-depressant without any strong affinity for either α- or β-adrenergic receptors.[5d] In view of these medicinal importances, synthetic studies of these compounds have attracted considerable interest. Extensive effort in this field has resulted in fruitful synthetic methods for the synthesis of optically active 3-hydroxy esters or their derivatives, utilizing aldol reactions,[6a–c] as well as catalytic asymmetric hydrogenation[7a–e] and biological reduction[8a] of the corresponding 3-ketocarboxylates. Apart from these, biocatalytic deracemization[8b,c,d] and resolution[8e,f] of racemic 3-hydroxy esters have also been employed in some cases. Amongst these, the catalytic asymmetric hydrogenation route employs harsh conditions such as high temperature and pressure, and often requires preparation of the asymmetric catalysts. The microbial reduction, on the other hand, often provides the desired alcohols in low yields and/ or ees. Even then, the whole-cell-mediated enantioselective reduction of the 3-keto esters by an oxido-reductase enzyme is still attractive in terms of low cost, eco-friendly nature, and the availability of a large number of microorganisms with a wide substrate specificity.

During our work on microbial transformations,[9a–e] we found that the fungus *Rhizopus arrhizus* can efficiently carry out the asymmetric reduction of a wide variety of ketones including aliphatic 3-keto esters. The versatility of the fungus for asymmetric reduction was further exemplified using various 3-aryl-3-keto esters as substrates and the results are presented herein.

2. Results and discussion

One of the prime requirements of a microbial transformation is the optimization of the reaction parameters such as substrate structure, reaction conditions, etc. Hence, for the present study, we chose a series of 3-aryl-3-oxopropanoates **1a–d** and studied their bio-reduction with various *Rhizopus* species and strains (Scheme 1). Of the chosen substrates, the aromatic

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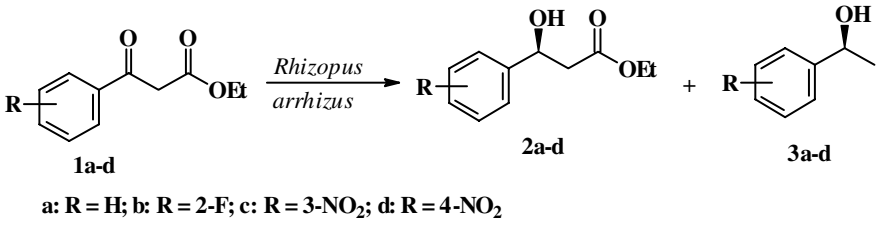

Scheme 1.

moieties of **1b–d** contained electron-withdrawing substituents (F and NO_2 groups) at different positions with respect to the keto group, while that in **1a** was unsubstituted. With all the substrates, the reactions were carried out for different periods (6 h to 7 days) using almost the same concentration (105–115 mg/150 mL microbial culture) of the substrates. After the usual work-up,[9a,e] the product alcohols **2a–d** were isolated from the respective substrates, purified by preparative TLC, and characterized by IR and ^{1}H NMR spectra. During the study, it was observed that irrespective of the microorganism used, microbial reduction of **1a–d** also furnished the 1-arylethanols **3a–d** along with the expected products **2a–d** as revealed by the GC analysis of the reaction mixtures. Presumably besides ketone reduction, the microorganisms also hydrolyzed the ester function of the substrates in a parallel reaction, the former being comparatively faster. The hydrolytic reaction furnished the corresponding keto acid, which on spontaneous decarboxylation followed by microbial reduction yielded **3a–d** with the respective substrates. The proposition was also confirmed by arresting the reaction at an appropriate time and analyzing the products with GLC. The extent of ester hydrolysis leading to the formation of the undesired side products **3a–d** was dependent on the nature of the substrates and the microorganisms, as well as the reaction time. These are discussed separately for each substrate in the following.

2.1. Reduction of ethyl benzoylacetate 1a

Initially the microbial reduction of **1a** was carried out with *R. arrhizus* (wild type) for different periods and the results are summarized in Table 1. Bioreduction for 2 days led to the formation of **2a** along with the alcohol **3a** in ~92:8 ratio (see Table 1, entry 1). From this, the desired hydroxy ester **2a** and the unreacted ketone **1a** were obtained in 24% and 57% isolated yields. Increasing the incubation time to 7 days led to complete decarboxylation of **1a**, and **3a** was obtained in 28% isolated yield. Apparently, during longer incubation, **2a** formed initially was reoxidized back to **1a** explaining the result. Formation of some highly polar compounds as an intricate mixture was noticed as expected with a multi-enzyme system. However, we did not analyze the composition of the mixture since this was of no interest in the present study.

Table 1. The course of microbial asymmetric reduction of ethyl benzoylacetate **1a** by different *Rhizopus* species

Entry	Organism	Time	Yield[a] (%)	**2a**:**3a**[b]
1	*R. arrhizus* (wild type)	2 d	24.0	91.7: 8.3
2	*R. arrhizus* (wild type)	1 d	41.1	98.1:1.9
3	*R. arrhizus* (NCIM 877)	1 d	49.0	97.8: 2.2
4	*R. arrhizus* (NCIM 878)	1 d	51.8	97.5:2.5
5	*R. arrhizus* (NCIM 879)	1 d	51.8	92.3:7.7
6	*R. arrhizus* (NCIM 997)	1 d	50.5	97.7:2.3
7	*R. oryzae* (NCIM1009)	1 d	31.6	95.7:4.3
8	*R. nivius* (NCIM 958)	1 d	43.2	98.1:1.9
9	*R. nivius* (NCIM 959)	1 d	76.5	97.5:2.5
10	*R. arrhizus* (wild type)	6 h	33.2	100:0
11	*R. nivius* (NCIM 958)	6 h	43.2	100:0

[a] Isolated yield without considering recovered substrate.
[b] Based on GLC analyses.

To avoid the formation of **3a**, the reduction was carried out by reducing the incubation period to 1 d, and also using various other *Rhizopus* species and strains (see Table 1, entries 2–9) under the same conditions. Very recently, we were able to improve the enantioselectivity of a *Rhizopus* mediated hydrolysis protocol by proper choice of a microbial strain.[9d] Hence, a similar strategy was extended for the present work. All the microorganisms transformed **1a** to **2a**, albeit in varying yields and different amounts of the undesired alcohol **3a**. Considerably less decarboxylation (<2%) was observed with *R. arrhizus* (wild type) and *R. nivius* NCIM 958 (see Table 1, entries 2 and 8), which afforded **2a** in ~41–43% yields.

The fungi *R. arrhizus* NCIM 877, NCIM 878, and NCIM 997 were also efficient (2.2–2.5% decarboxylation) providing **2a** in good yields (~50%) (see Table 1, entries 3, 4, and 6). With *R. nivius* NCIM 959, **2a** was obtained in excellent yield (~76%) (see Table 1, entry 9), but with less enantiopurity (data not shown). However, *R. arrhizus* NCIM 879 and *R. oryzae* NCIM 1009, were less efficient furnishing substantial amounts of **3a** (**2a**:**3a** 92:8 and 96:4, respectively, see Table 1, entries 5 and 7). Subsequently, the reduction was carried out for 6 h, using *R. arrhizus* (wild type) and *R. nivius* NCIM 958, the best two microorganisms only. Under this condition although the **2a** was obtained in 33% and 43% yields, respectively, formation of **3a** was not observed (see Table 1, entries 10 and 11).

2.2. Reduction of ethyl 2-fluorobenzoylacetate 1b

Similarly the microbial reduction of **1b** was carried out with various organisms and results obtained are shown in Table 2. In this case, *R. arrhizus* (wild type) produced both **2b** and **3b** in 9:1 ratio after 2 days of incubation (see Table 2, entry 1), while complete decarboxylation was noticed after only 4 days. Overall, substrate **1b**

Table 2. The course of microbial asymmetric reduction of ethyl 2-fluorobenzoylacetate **1b** by different *Rhizopus* species

Entry	Organism	Time	Yield[a] (%)	**2b**:**3b**[b]
1	*R. arrhizus* (wild type)	2 d	47.7	90.1:9.9
2	*R. arrhizus* (wild type)	1 d	76.2	91.9:8.1
3	*R. arrhizus* (NCIM 877)	1 d	68.9	92.2:7.8
4	*R. arrhizus* (NCIM 878)	1 d	43.8	75.5:24.5
5	*R. arrhizus* (NCIM 879)	1 d	52.3	79.0:21.0
6	*R. arrhizus* (NCIM 997)	1 d	70.0	73.9:26.1
7	*R. oryzae* (NCIM 1009)	1 d	32.7	58.3:41.7
8	*R. nivius* (NCIM 958)	1 d	76.4	92.7:7.3
9	*R. nivius* (NCIM 959)	1 d	69.5	91.0:9.0
10	*R. arrhizus* (wild type)	6 h	51.5	96.5:3.5
11	*R. arrhizus* (NCIM 877)	6 h	42.1	93.8:6.1
12	*R. nivius* (NCIM 958)	6 h	61.7	100:0
13	*R. nivius* (NCIM 959)	6 h	69.8	100:0

[a] Isolated yield without considering recovered substrate.
[b] Based on GLC analyses.

was more susceptible to decarboxylation even after 1 day incubation with all the fungi. As earlier, in this case also, *R. arrhizus* (wild type) and *R. arrhizus* NCIM 877, *R. nivius* NCIM 958 and 959 produced less amount of **3b** (**2b**:**3b** = 91–93:7– 9) after 1 day incubation (see Table 2, entries 2, 3, 8, and 9). Compound **1b** was more reactive than **1a** as was evident from the significantly higher yields (68–76%) of **2b** with several microorganisms as well as of the undesired alcohol **3b**. In this case also, the fungi *R. arrhizus* NCIM 878 and 879, as well as *R. oryzae* NCIM 1009 were very poor, furnishing **2b** in lower yields (44%, 52%, and 33%, respectively) and substantial amounts of **3b** (see Table 2, entries 4, 5, and 7). Hence the reduction was carried out for 6 h with *R. arrhizus* (wild type), *R. arrhizus* NCIM 877, and *R. nivius* NCIM 958 and 959. Amongst these, only *R. nivius* NCIM 958 and 959 furnished **2b** exclusively in good yields (62–70%, see Table 2, entries 12 and 13), while with *R. arrhizus* (wild type) and NCIM 877, both **2b** and **3b** were formed in 94–96:3–6 ratio (see Table 2, entries 10 and 11).

2.3. Reduction of ethyl 3-nitrobenzoylacetate 1c

Surprisingly, in the microbial reduction of **1c**, ester hydrolysis was the predominant reaction with most of the microorganisms leading to substantial amount of **3c** (see Table 3). Thus, all the *Rhizopus* species along with *R. oryzae* NCIM 1009 were very poor both in terms of the yields of **2c** as well as relative higher concentrations of **3c** even after 1 d of incubation (see Table 3, entries 2–7). Only *R. nivius* NCIM 958 and 959 were far superior furnishing **2c** and **3c** in a comparatively lower relative proportions (93:7 and 96:4, respectively). However, formation of **3c** could not be avoided even with these microorganisms, and the amount of undesired 1-arylethanol was more than that with **1a**. When the reaction was carried out with *R. nivius* NCIM 958 and 959 for 6 h, although the ratio of **2c**:**3c** improved marginally, the yields of **2c** were also reduced (see Table 3, entries 10 and 11). Thus, overall a 1 d incubation with *R. nivius* NCIM 958 or 959 was the best method for the asymmetric reduction of **1c**.

Table 3. The course of microbial asymmetric reduction of ethyl 3-nitrobenzoylacetate **1c** by different *Rhizopus* species

Entry	Organism	Time	Yield[a] (%)	**2c**:**3c**[b]
1	*R. arrhizus* (wild type)	2 d	11.5	54.9:45.1
2	*R. arrhizus* (wild type)	1 d	31.2	57.4:42.6
3	*R. arrhizus* (NCIM 877)	1 d	24.4	45.65:51.56
4	*R. arrhizus* (NCIM 878)	1 d	18.7	47.0:53.0
5	*R. arrhizus* (NCIM 879)	1 d	19.2	42.5:57.5
6	*R. arrhizus* (NCIM 997)	1 d	37.9	66.6:33.4
7	*R. oryzae* (NCIM 1009)	1 d	38.1	62.8:37.2
8	*R. nivius* (NCIM 958)	1 d	63.8	93.2:6.8
9	*R. nivius* (NCIM 959)	1 d	69.2	95.9:4.1
10	*R. arrhizus* (NCIM 958)	6 h	28.1	98.7:1.3
11	*R. nivius* (NCIM 959)	6 h	42.4	97.4:2.6

[a] Isolated yield without considering recovered substrate.
[b] Based on GLC analyses.

2.4. Reduction of ethyl 4-nitrobenzoylacetate (1d)

Surprisingly, unlike compound **1c**, the microbial reduction of the corresponding 4-nitro substrate **1d** proceeded almost uneventfully and very little formation of **3d** was observed (see Table 4). Amongst the microorganisms tested, microbial reduction of **1d** for 1 d with *R. arrhizus* NCIM 879 and 997 as well as *R. oryzae* NCIM 1009 produced **2d** and **3d** in 92–98:2–8 ratio (see Table 4, entries 5–7). However, even then **1d** was obtained in 56–63% yields. On the other hand, under the same conditions, the other *R. arrhizus* species (wild type, NCIM 877 and 878) afforded **2d** exclusively in 64%, 66%, and 46% yields, respectively (see Table 4, entries 2–4). The fungi *R. nivius* NCIM 958 and 959 were found to be the best as they produced **2d** exclusively in 80% and 74% yields (see Table 4, entries 8, 9). Thus, with most of the microorganisms the yields of the desired product **2d** were excellent (64–80%).

2.5. Determination of absolute configurations and enantiomeric purities of 2a–d

The absolute configurations of **2a** and **2d** were assigned as (*S*) by comparison of the chiroptical data with those reported.[10,8d] For the determination of the % ees of **2a**–**d**, these were converted into the corresponding MTPA esters[11] with (*R*)-MTPA. The % ees were then assessed by the ^{1}H NMR analyses of the respective MTPA esters. The

Table 4. The course of microbial asymmetric reduction of ethyl 4-nitrobenzoylacetate **1d** by different *Rhizopus* species

Entry	Organism	Time	Yield[a] (%)	**2d**:**3d**[b]
1	*R. arrhizus* (wild type)	2 d	25.7	92.9:7.1
2	*R. arrhizus* (wild type)	1 d	64.1	100:0
3	*R. arrhizus* (NCIM 877)	1 d	65.8	100:0
4	*R. arrhizus* (NCIM 878)	1 d	46.5	100:0
5	*R. arrhizus* (NCIM 879)	1 d	56.8	97.8:2.2
6	*R. arrhizus* (NCIM 997)	1 d	63.7	95.6:4.4
7	*R. oryzae* (NCIM1009)	1 d	60.3	91.8:8.2
8	*R. nivius* (NCIM 958)	1 d	79.9	100:0
9	*R. nivius* (NCIM 959)	1 d	73.9	100:0

[a] Isolated yield without considering recovered substrate.
[b] Based on GLC analyses.

Table 5. Optimized results of asymmetric microbial reduction of 3-aryl-3-keto esters

Product	Organism	Time	Yield (%)	% ee[a] (config.)
2a	*R. arrhizus* (wild type)	6 h	33.2	95.1 (*S*)
2a	*R. nivius* (NCIM 958)	6 h	43.5	90.9 (*S*)
2b	*R. nivius* (NCIM 958)	6 h	61.8	>98.0 (*S*)
2b	*R. nivius* (NCIM 959)	6 h	69.8	92.1 (*S*)
2c	*R. nivius* (NCIM 958)	6 h	28.1	94.2 (*S*)
2c	*R. nivius* (NCIM 959)	6 h	42.4	87.9 (*S*)
2d	*R. arrhizus* (wild type)	1 d	64.1	95.0 (*S*)
2d	*R. arrhizus* (NCIM 877)	1 d	65.8	94.2 (*S*)
2d	*R. nivius* (NCIM 878)	1 d	46.5	93.6 (*S*)
2d	*R. nivius* (NCIM 958)	1 d	79.9	>98.0 (*S*)
2d	*R. nivius* (NCIM 959)	1 d	73.9	91.7 (*S*)

[a] Based on ^{1}H NMR analyses of respective (*R*)-MTPA esters.

results on the % ees and yields of the desired alcohols **2a**–**d** are summarized in Table 5. In the ^{1}H NMR spectra, the methoxyl resonances of the (*R*)-MTPA esters of **2a**–**d** appeared as two singlets at δ 3.52–3.54 (major) and at δ 3.42–3.43 (minor). The relative intensities of these resonances furnished the respective % ees. Given that the compounds **2a** and **2d** possessed (*S*) configuration, the downfield methoxyl resonances were attributed to those of (*S*)-carbinols. Based on these, the esters **2b**,**c** were also assigned (*S*) configuration. These results are in accordance with our previous report.[9c]

3. Conclusion

Thus, the above studies demonstrated that the whole-cell system of different *Rhizopus* species can accomplish the asymmetric transformation of the 3-aryl-3-keto esters **1a**–**d** in highly enantioselective manner. Besides being environment-friendly, the protocol is very simple even to an organic chemist and furnishes the 3-aryl-3-hydroxy esters **2a**–**d** in satisfactory yields. Although, some of the organisms produced undesired 1-arylethanols via an ester hydrolysis/decarboxylation/reduction protocol, the course of the reaction can be controlled by judicious choice of microorganism and incubation period. Amongst the chosen microorganisms, *R. arrhizus* (wild type) and *R. nivius* NCIM 958 and 959 were very promising for this purpose. In spite of its several attractive features, the microbial reductive methodology has not been extensively used for the asymmetric synthesis of the pharmaceutically important 3-aryl-3-hydroxy esters. The previous reports[8a] suffer from lack of generality and wide applicability.

In general, baker's yeast is extensively used for the asymmetric reduction of alkyl 3-keto esters.[12a,12b] Amongst the aryl 3-keto esters, only **1a** could be reduced under fermenting condition.[10a] However, the reaction did not take place with non-fermenting yeast in an organic solvent.[10b] Further, the baker's yeast mediated method often suffers from poor chemical yields, varying enantioselectivity (70–97%), and tedious isolation protocol.[12a,b] In comparison, the present method provides an efficient alternative for the designated targets with excellent reproducibility under an operationally simple condition.

4. Experimental

4.1. General experimental details

All the substrates and (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) (Aldrich, Fluka, and Lancanster) were used as received. Other reagents were of AR grade. The extracts were dried over anhydrous Na_2SO_4. The *Rhizopus* cultures were received from National Collection of Industrial Microorganisms, National Chemical Laboratory, Pune, India. The fungus from PDA slants was cultivated on 150 mL sterilized modified Czepak Dox medium in 500 mL Erlenmeyer flasks at room temperature on a rotary shaker (150 rpm).[9a–e] The IR spectra were scanned as films on a Nicolet FT-IR model Impact 410 spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard with a Brucker AC-200 (200 MHz) spectrometer. The optical rotations were recorded with a Jasco 360 DIP digital polarimeter. The GLC analyses were carried out with a Shimadzu gas chromatograph GC-16A (3% OV-17 column, 90–240 °C, temp. program. 4 °C/min rate, 40 ml/min N_2).

4.2. General procedure for microbial reduction

In five cotton plugged Erlenmeyer flasks containing the 72 h grown *Rhizopus* culture (150 mL) was added each substrate **1a**–**d** (550 ± 20 mg) in ethanol (5 mL) in equal amounts. The mixtures were incubated on a rotary shaker (90–95 rpm) at room temperature for the desired period as indicated in Tables 1–4. At the end of incubation, the mycelial mass was removed, washed with water, squeezed, and extracted with ethyl acetate. The aqueous washings were combined with the aqueous filtrate and extracted with $CHCl_3$ (3× 50 mL). The organic extract was washed with water, brine, dried, and concentrated to obtain a residue. This was subjected to preparative TLC (silica gel, 15% EtOAc/hexane, visualization by UV exposure) to furnish the respective products **2a**–**d**.

4.3. Ethyl (*S*)-3-hydroxy-3-phenylpropionate 2a

Colorless oil; $[\alpha]_D^{22}$ −42.3 (*c* 0.96, $CHCl_3$) (95.1% ee) (lit. [10a]) $[\alpha]_D^{20}$ −25.8 (*c* 1.3, $CHCl_3$); IR: 3349, 3091, 3065, 3030, 1736 cm^{-1}; ^{1}H NMR: δ 1.26 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.71 (d, *J* = 4.26 Hz, 2H, CH_2CO_2Et), 3.04 (br s, 1H, OH), 4.17 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 5.13 (dd, *J* = 4.26, 8.0 Hz, 1H, CHOH), 7.25–7.37 (m, 5H, ArH); MS (EI, 70 eV): *m*/*z* (%) 194 (100, M^+), 165 (6), 147 (13), 120 (19), 107 (97), 105 (65), 79 (49), 77 (38), 60 (11).

4.4. Ethyl (*S*)-3-hydroxy-3-(2′-fluorophenyl)propionate 2b

Colorless oil; $[\alpha]_D^{22}$ −49.7 (*c* 2.71, $CHCl_3$) (>98% ee); IR: 3347, 3065, 1731 cm^{-1}; ^{1}H NMR: δ 1.24 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.74 (d, *J* = 4.5 Hz, 2H, CH_2CO_2Et), 3.28 (br s, 1H, OH), 4.16 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 5.39 (dd, *J* = 4.5, 8.0 Hz, 1H, CHOH), 6.95–7.56 (m, 4H, ArH); MS (EI, 70 eV): *m*/*z* (%) 212 (22, M^+), 195 (38), 165 (6), 153 (22), 138 (9), 125 (100), 123 (74), 97 (69), 88 (36), 77 (27), 60 (27).

4.5. Ethyl (*S*)-3-hydroxy-3-(3′-nitrophenyl)propionate 2c

Colorless oil; $[\alpha]_D^{22}$ −34.8 (*c* 1.20, $CHCl_3$) (94% ee); IR: 3436, 3091, 1730, 1530, 1350 cm^{-1}; ^1H NMR: δ 1.27 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.58 (br s, 1H, OH), 2.72 (d, J = 4.4 Hz, 2H, CH_2CO_2Et), 4.20 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.22 (dd, J = 4.4, 7.8 Hz, 1H, CHOH), 6.95–7.56 (m, 4H, ArH); MS (EI, 70 eV): *m/z* (%) 239 (34, M^+), 192 (26), 152 (67), 150 (100), 77 (37).

4.6. Ethyl (*S*)-3-hydroxy-3-(4′-nitrophenyl)propionate 2d

Colorless oil; $[\alpha]_D^{22}$ −30.1 (*c* 4.28, $CHCl_3$) (>98% ee); (lit.[8d] $[\alpha]_D^{20}$ +23.1 (*c* 1.0, $CHCl_3$) for (*R*)-isomer); IR: 3458, 3117, 3082, 1728, 1352 cm^{-1}; ^1H NMR: δ 1.27 (t, J = 7.6 Hz, 3H, OCH_2CH_3), 2.00 (br s, 1H, OH), 2.73 (dd, J = 4.6 Hz, 2H, CH_2CO_2Et), 4.19 (q, J = 7.6 Hz, 2H, OCH_2CH_3), 5.22 (dd, J = 4.6, 7.8 Hz, 1H, CHOH), 7.55 (d, 2H, J = 8.6 Hz, ArH), 8.21 (d, J = 8.6 Hz, 2H, ArH); MS (EI, 70 eV): *m/z* (%) 239 (30, M^+), 192 (34), 165 (29), 152 (75), 150 (100), 88 (46), 77 (34), 43 (22).

4.7. General procedure for preparation of the MTPA esters

A mixture of (*R*)-MTPA (25 mg) and $SOCl_2$ (0.250 mL) in toluene (2 mL) was refluxed for 3 h. After removing the excess $SOCl_2$ in vacuo, the resultant MTPA chloride was taken in CH_2Cl_2 (0.5 mL) and added to a solution of the alcohol (15 mg), pyridine (0.1 mL), and 4,4-dimethylaminopyridine (1–2 crystals) in CH_2Cl_2 (0.250 mL). After stirring the mixture for 16 h at room temperature, the excess pyridine was removed by purging with N_2 gas, and the residue subjected to preparative thin-layer chromatography (silica gel, 10% EtOAc/hexane) to isolate the respective MTPA esters. The ^1H NMR analyses were carried out with the pure samples.

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