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Asymmetric reduction of halo-substituted arylalkanones with *Rhizopus arrhizus*

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ABSTRACT

The *Rhizopus arrhizus*-mediated asymmetric reduction of various haloaryl alkanones furnished the respective (*S*)-carbinols with good to excellent enantioselectivities. It was found that the reaction course was primarily governed by the relative position of the halogen with respect to the carbonyl group, and its size. The relative order of efficacies of the nature of the halogen and their substitution pattern were Br > Cl > F and *o*- > *p*- > *m*-. The *ortho*-effect was the most predominant factor in the stereochemical outcome of the reaction, which was also confirmed with some non-halo-substituted acetophenones.

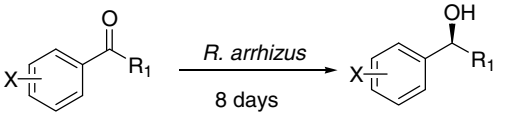
1. Introduction

The asymmetric reduction of the ubiquitous carbonyl group is of prime importance in asymmetric syntheses as the resultant chiral alcohols are often useful target bioactive compounds or their precursors.[1a,b] Chirality is a key factor in many of the pharmaceutical compounds, and production of single enantiomers of molecules has assumed great significance.[2] The enzymatic production of chiral alcohols via the asymmetric reduction of prochiral carbonyl compounds has some noteworthy advantages over conventional catalysts as they work under mild reaction conditions, and the reactions are often highly stereoselective.[3] To this end, the use of whole-cell microorganisms holds good promise as these are available in a large variety, and possess the inherent and stable co-factor regeneration system.[4]

Previously, we have established the versatility of the fungus *Rhizopus arrhizus* in the stereoselective reduction of a wide variety of ketones and keto esters.[5a–f] It was found that the *p*-substituted arylalkanones were good substrates for the fungus. However, the enantioselectivity of the reduction was governed by the substrate structures, that is, size of the aryl and alkyl groups as well as the electronic nature of the substituents. It was envisaged that a similar study with the *o*- or *m*-substituted arylalkanones would establish the scope and limitations of this protocol, while addressing the issue of the role of steric factor of the substituents. For this, we have undertaken the bioreduction of various *o*- or *m*-halo arylalkanones, and the results are presented herein.

2. Results and discussion

Herein, we chose a series of halo-substituted acetophenones **1b–l** and propiophenones **3b–k**, and studied their bioreduction with *R. arrhizus* and compared the results with those from the respective unsubstituted arylalkanones **1a** and **3a** (Scheme 1). The choice of the substrates was decided by our earlier observation[5c] that *p*-haloarylalkanones were superior substrates for *R. arrhizus*. However, the predominant *ortho*-effect (vide infra) was also confirmed with the methyl- and nitro-substituted acetophenones **1m–q**. It was felt that the bioreduction of the chosen substrates would provide valuable information on the relative influences of the steric and electronic factors of the substituents on the reaction. Further, the product alcohols are also important intermediates for the syntheses of various pharmaceutical products.[6a–f] The *R. arrhizus*-mediated reductions of **1a** and **3a** and the *p*-substituted arylethanones were previously reported by us.[5c] However, since the results of a microbial transformation often depend on various factors, we included the substrates for the present studies. The results presented are those obtained in the new experiments.



1a-q $R_1 = CH_3$
3a-k $R_1 = Et$

2a-q $R_1 = CH_3$
4a-k $R_1 = Et$

Scheme 1. See Table 1 for X.

The biotransformation of each of the substrates was carried out using *R. arrhizus* in a modified Czepek Dox medium for different incubation periods to optimize the yield and the enantiomeric purity. The best results were obtained after incubating the substrates for 8 days and the optimized results are shown in Table 1. The product alcohols were isolated and purified by preparative TLC. Overall, the chosen substrates can be broadly divided into two categories, and the results obtained with them are discussed separately.

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Table 1
Course of asymmetric reduction of substituted arylalkanones

Entry	Substrate	X	R_1	Product	Yield[a] (%)	ee[b] (%)
1	**1a**	H	Me	**2a**	63	75
2	**1b**	2-F	Me	**2b**	73	96
3	**1c**	3-F	Me	**2c**	66	40
4	**1d**	4-F	Me	**2d**	48	72
5	**1e**	2-Cl	Me	**2e**	77	97
6	**1f**	3-Cl	Me	**2f**	78	48
7	**1g**	4-Cl	Me	**2g**	80	85
8	**1h**	2-Br	Me	**2h**	73	>99
9	**1i**	3-Br	Me	**2i**	71	60
10	**1j**	4-Br	Me	**2j**	72	88
11	**1k**	2,4-Dichloro	Me	**2k**	32	94
12	**1l**	2,3,4-Trichloro	Me	**2l**	15	92
13	**1m**	2-Me	Me	**2m**	25	>99
14	**1n**	3-Me	Me	**2n**	65	33
15	**1o**	4-Me	Me	**2o**	72	72
16	**1p**	3-NO_2	Me	**2p**	98	10
17	**1q**	4-NO_2	Me	**2q**	85	65
18	**3a**	H	Et	**4a**	58	84
19	**3b**	2-F	Et	**4b**	61	92
20	**3c**	3-F	Et	**4c**	61	79
21	**3d**	4-F	Et	**4d**	61	85
22	**3e**	2-Cl	Et	**4e**	62	96
23	**3f**	3-Cl	Et	**4f**	60	75
24	**3g**	4-Cl	Et	**4g**	59	95
25	**3h**	2-Br	Et	**4h**	58	>99
26	**3i**	3-Br	Et	**4i**	53	86
27	**3j**	4-Br	Et	**4j**	54	95
28	**3k**	2,4-Dichloro	Et	**4k**	16	92

[a] Isolated yields.
[b] Based on ^{1}H NMR analysis of the corresponding (*R*)-MTPA esters.

2.1. Reduction of unsubstituted and halo-substituted acetophenones 1a–l

All the acetophenones **1a**–**l** were amenable to the *R. arrhizus*-mediated reduction to furnish the alcohols **2a**–**l**, albeit in different yields and enantiomeric excesses (ees). In general, the presence of the electron-withdrawing halogens increased the reactivity of the ketones as revealed from the better yields of **2b**–**j** compared to 1-phenylethanol **2a**. However, the presence of an *m*-halogen substitution in the substrates drastically reduced the enantioselectivity of the reaction. The *o*-substituted substrates gave the best yields and ee, irrespective of the nature of the halogen. For example, the *o*-substituted substrates **1b**, **1e** and **1h** gave better results than those possessing the halogens at the *m*- or *p*-position with respect to the acetyl group. With regard to the effect of different halogens in the same substitution pattern (comparison between *o*-, *m*- and *p*-series with different halogens), the ee increased with the increase in size of the halogens (F < Cl < Br). Thus, the acetophenones with *o*-, *m*- and *p*-bromo substituents furnished the corresponding 1-arylethanols with better ees compared to the fluoro- and chloro-substituted substrates. The effect of the *o*-substitution was so predominant that the nature of the halogen atom did not have much significance on the course of the reaction (Table 1, entries 2, 5 and 8). The effect of the nature of halogen was more evident with the *m*- and *p*-substituted substrates. In these cases, the yields and % ees of the products increased when increasing the size of the halogens. The inclusion of more halogen substituents had a detrimental effect on the yield of the reaction, although the reaction proceeded with excellent enantioselectivity. Thus, the dichloro and trichloro compounds **1k** and **1l** furnished alcohols **2k** and **2l** with poor yields (32% and 15%), but good (94% and 92%) ees, respectively (Table 1, entries 11 and 12). The present results with **1a**, **1d**, **1g** and **1j** correlated well with our previous results,[5c] establishing the reproducibility of our protocol.

2.2. Reduction of unsubstituted and halo-substituted propiophenones 3a–k

In order to test the scope of the above results, the biotransformation was also carried out with the propiophenones **3a**–**k**. The results of the *R. arrhizus*-mediated reduction followed a similar trend as the acetophenones. In all cases, the corresponding alcohols **4a**–**k** were obtained with good ees. Compared to the acetophenones, the yields of the products were significantly less with these substrates. The enantioselectivity, however, appeared to be sensitive to the alkyl chain length. Thus, ees of the products **4a**–**k** were better than those of the corresponding phenylethanols, irrespective of the nature of halogen group (Table 1, compare entries 2–10 vs 18–28). These results are consistent with our previous report,[5c] where a similar relationship of yields and ees with the size of the alkyl group was observed. In this case, the reduction of the dichlorinated substrate **3k** proceeded with poor yield but good ee (16% and 92%, respectively).

2.3. Reduction of methyl- and nitro-substituted acetophenones 1m–q

The predominant role of the *o*-substitution on the *R. arrhizus*-mediated reduction of acetophenones was further confirmed with the methyl- and nitro-substituted ketones **1m**–**q**. Amongst the methylacetophenones **1m**–**o**, the *o*-substituted ketone **1m** gave product **2m** with 99% ee, albeit in a low yield. In contrast, the reduction of the *m*- and *p*-methyl ketones **1m** and **1n** gave products **2m** and **2n** in good yields, but low ees (Table 1, entries 13–15). Likewise, the *m*- and *p*-nitro ketones **2p** and **2q** could also be reduced in excellent yields, but with poor to modest ees. Unfortunately, *o*-nitroacetophenone could not be reduced at all (Table 1, entries 16 and 17), may be because, the presence of the sterically demanding nitro group at the *ortho*-position prevented the reduction.

2.4. Stereochemical assignment and estimation of enantiopurity of the products

For the determination of the % ees of the carbinols, these were converted into the corresponding MTPA esters[7] with (*R*)-MTPA. The % ees were assessed from the integration of the methoxy resonance of the ^{1}H NMR spectrum of the respective MTPA esters. The methoxy resonance of the MTPA esters appeared as well separated singlets at δ 3.44–3.48 for the minor enantiomers and at δ 3.54–3.59 for the major enantiomers.

The absolute configurations of the products **2a**–**k** were assigned as (*S*) by comparison of the chiroptical data with those reported.[8a,b] Given that all the above alcohols were levorotatory, the configurations of **2l** and **4b**–**k** were assigned in analogy. However, following two excellent reports,[9] we also confirmed the assignment of the configurations from the NMR spectral data of the corresponding (*R*)-MTPA esters of the alcohols. In the MTPA esters, the chemical shifts of the CH_3 protons in methylcarbinols, and the CH_2 protons in ethylcarbinols showed consistent downfield shifts, with the major peak being more deshielded. In addition, the more downfield methoxyl resonances of the esters were also the major peaks. All these confirmed the (*S*)-configurations of the products **2b**–**q** and **4b**–**k**. Thus, the enantiopreference of the microbial reducing system was consistent, and independent of any change in the substituents.

2.5. Rationalization of enantioselectivity

The *R. arrhizus*-mediated bioreduction of the arylalkanones proceeded with moderate to excellent enantioselectivity to give the

(*S*)-carbinols. The enantiopreference of the fungus was the same as observed earlier by us[5a–f] and followed Prelog's rule.[10] The enantioselectivity was excellent for the *o*-substituted substrates, and significantly better than those observed for the *m*- and *p*-substituted substrates. The % ees were governed by the size, rather than the electronegativity of the halogen groups. The larger halogens gave products with better ees, although their respective electronegativities decreased progressively. Thus, the extent of asymmetric induction could be correlated to the van der Waals molecular volume of the halogens. The bulk of a substituent will be more predominant when it is located *ortho* to the acyl group.[6d] This explains the significantly better results with the *o*-substituted substrates. The electronegativity factor may also play a marginal role, and could possibly explain the better reactivity of the substituted substrates, especially the *p*-halogenated substrates over their *m*-halogenated counterparts. The high ees observed in the reduction of the polychlorinated substrates such as **1k**, **1l** and **3k** also confirmed the *ortho*-effect. The poor reactivity of these substrates might be due to their low solubility in the aqueous reaction medium and/or increased molecular size, rendering them less permeable to the cells.

3. Conclusion

Overall, the fungus *R. arrhizus* has been found to be an excellent bioreduction system for the asymmetric reduction of arylalkanones containing substitution with halogens at different positions. The protocol was highly reproducible and furnished the products in high yields for all substrates. Excellent (>95%) enantioselectivity was obtained with the *ortho*-substituted substrates, while reduction of the *para*- and *meta*-substituted compounds proceeded with good and modest enantioselectivity, respectively. Compared to the electronic features, the sizes of the halogens played a crucial role in governing the course of the reaction. Thus, the relative order of efficacies of the nature of the halogens and their substitution pattern were Br > Cl > F and *o*- > *p*- > *m*-. Finally, another important factor of the *Rhizopus*-catalyzed reduction is its good reproducibility in terms of both conversion and ee, as evident from the comparison of the present and previous[4c] results on the bioreduction of **1a** and **3a**.

4. Experimental

4.1. General

All the substrates (Fluka and Lancanster) and (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, Fluka) were used as received. Other reagents were of AR grade. The fungus, *R. arrhizus*, was obtained from the National Collection of Industrial Microorganisms, National Chemical Laboratory, Pune, India. The fungus from PDA slant was cultivated on 150 mL sterilized modified Czepak-Dox medium in 500 mL Erlenmeyer flasks at room temperature on a rotary shaker (150 rpm).[4c–e] The extracts were dried over anhydrous Na_2SO_4. The IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrophotometer. The ^{1}H NMR spectra in $CDCl_3$ were recorded with a Bruker Ac-200 (200 MHz) spectrometer. The optical rotations were recorded with a Jasco DIP 360 digital polarimeter.

4.2. General procedure for microbial reduction

In five cotton plugged Erlenmeyer flasks containing the 72 h grown *R. arrhizus* culture (150 mL) was added each substrate (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 8 days. Substrate and organism controls were also run simultaneously in each case. 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 (2 × 20 mL), brine (1 × 5 mL), dried and concentrated to obtain a residue. This was subjected to preparative TLC (silica gel, 15% EtOAc/hexane, visualization by UV exposure) to obtain the respective product alcohols. The optical and spectral data of **2a**, **2d**, **2g**, **2j** and **4a** were similar to those reported by us.[5c]

4.3. (*S*)-1-(2′-Fluorophenyl)ethanol 2b[8a]

Colourless liquid; $[\alpha]_D^{25} = -43.5$ (*c* 1.39, $CHCl_3$), {lit.[8a] $[\alpha]_D = -44.5$ (*c* 0.78, MeOH, >99 % ee)}; ^{1}H NMR: δ 1.49 (d, *J* = 6.5 Hz, 3H), 2.37 (br, 1H), 5.16 (q, *J* = 6.5 Hz, 1H), 7.04–7.24 (m, 3H), 7.44 (m, 1H).

4.4. (*S*)-1-(3′-Fluorophenyl)ethanol 2c[8a,c]

Colourless liquid; $[\alpha]_D^{25} = -24.4$ (*c* 1.24, $CHCl_3$), {lit.[8c] $[\alpha]_D = -28.0$ (*c* 0.98, MeOH, >72 % ee)}; ^{1}H NMR: δ 1.45 (d, *J* = 6.5 Hz, 3H), 2.37 (br, 1H), 4.84 (q, *J* = 6.5 Hz, 1H), 6.88–6.98 (m, 2H), 7.14 (m, 1H), 7.27 (m, 1H).

4.5. (*S*)-1-(2′-Chlorophenyl)ethanol 2e[8a,d,e]

Colourless liquid; $[\alpha]_D^{27} = -57.75$ (*c* 1.46, $CHCl_3$), {lit.[8a] $[\alpha]_D = -62.7$ (*c* 1.14, $CHCl_3$, >99 % ee)}; ^{1}H NMR: δ 1.45 (d, *J* = 6.4 Hz, 3H), 2.40 (br, 1H), 5.26 (q, *J* = 6.4 Hz, 1H), 7.14 (m, 3H), 7.33 (m, 1H).

4.6. (*S*)-1-(3′-Chlorophenyl)ethanol 2f[8a,e]

Colourless liquid; $[\alpha]_D^{27} = -28.3$ (*c* 1.48, $CHCl_3$), {lit.[8a] $[\alpha]_D = -43.5$ (*c* 1.08 $CHCl_3$, >99% ee)}; ^{1}H NMR: δ 1.43 (d, *J* = 6.5 Hz, 3H), 2.52 (br, 1H), 4.80 (q, *J* = 6.3 Hz, 1H), 7.19–7.29 (m, 3H), 7.33 (m, 1H).

4.7. (*S*)-1-(2′-Bromophenyl)ethanol 2h[8a,e]

Colourless liquid; $[\alpha]_D^{25} = -50.45$ (*c* 1.33, $CHCl_3$), {lit.[8a] $[\alpha]_D = -54.6$ (*c* 1.23, $CHCl_3$, 99% ee)}; ^{1}H NMR: δ 1.47 (d, *J* = 6 Hz, 3H), 2.23 (br, 1H), 5.21 (q, *J* = 6 Hz, 1H), 7.10 (m, 1H), 7.27 (m, 1H), 7.59 (m, 2H).

4.8. (*S*)-1-(3′-Bromophenyl)ethanol 2i[8a]

Colourless liquid; $[\alpha]_D^{25} = -25.7$ (*c* 1.33, $CHCl_3$), {lit.[8a] $[\alpha]_D = -28.6$ (*c* 1.78, EtOH, >99 % ee)}; ^{1}H NMR: δ 1.44 (d, *J* = 6.1 Hz, 3H), 2.24 (br, 1H), 4.82 (q, *J* = 6.1 Hz, 1H), 7.14–7.29 (m, 2H), 7.35 (m, 1H), 7.50 (m, 1H).

4.9. (*S*)-1-(2′,4′-Dichlorophenyl)ethanol 2k[8b]

Colourless liquid; $[\alpha]_D^{25} = -52.4$ (*c* 0.55, $CHCl_3$); ^{1}H NMR: δ 1.46 (d, *J* = 6.4 Hz, 3H), 1.94 (br, 1H), 5.25 (q, *J* = 6.4 Hz, 1H), 7.26–7.34 (m, 2H), 7.53 (m, 1H).

4.10. (*S*)-1-(2′,3′,4′-Trichlorophenyl)ethanol 2l

White solid; $[\alpha]_D^{25} = -42.9$ (*c* 0.21, $CHCl_3$); ^{1}H NMR: δ 1.47 (d, *J* = 6.4 Hz, 3H), 2.05 (br, 1H), 5.25 (q, *J* = 6.4 Hz, 1H), 7.25–7.51 (m, 2H).

4.11. (*S*)-1-(2′-Methylphenyl)ethanol 2m

Colourless liquid; $[\alpha]_D^{25} = -71.9$ (*c* 1.06, $CHCl_3$); ^1H NMR: δ 1.46 (d, *J* = 6.4 Hz, 3H), 1.75 (br, 1H), 2.34 (s, 3H), 5.12 (q, *J* = 6.4 Hz, 1H), 7.11–7.25 (m, 3H), 7.49–7.55 (m, 1H).

4.12. (*S*)-1-(3′-Methylphenyl)ethanol 2n

Colourless liquid; $[\alpha]_D^{25} = -34.5$ (*c* 1.18, $CHCl_3$); ^1H NMR: δ 1.48 (d, *J* = 6.4 Hz, 3H), 1.92 (br, 1H), 2.36 (s, 3H), 4.85 (q, *J* = 6.4 Hz, 1H), 7.07–7.28 (m, 4H).

4.13. (*S*)-1-(4′-Methylphenyl)ethanol 2o[8f,g]

Colourless liquid; $[\alpha]_D^{25} = -45.3$ (*c* 1.26, $CHCl_3$), {lit.[8h] $[\alpha]_D^{20} = -55.4$ (*c* 1.97, $CHCl_3$)}; ^1H NMR: δ 1.46 (d, *J* = 6.4 Hz, 3H), 1.94 (br, 1H), 4.84 (q, *J* = 6.4 Hz, 1H), 7.11–7.25 (m, 4H).

4.14. (*S*)-1-(3′-Nitrophenyl)ethanol 2p

Colourless liquid; $[\alpha]_D^{25} = -4.9$ (*c* 1.22, $CHCl_3$); ^1H NMR: δ 1.53 (d, *J* = 6.4 Hz, 3H), 1.95 (br, 1H), 5.01 (q, *J* = 6.4 Hz, 1H), 7.47–7.55 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.24 (s, 1H).

4.15. (*S*)-1-(4′-Nitrophenyl)ethanol 2q[8g]

Colourless liquid; $[\alpha]_D^{25} = -22.4$ (*c* 1.42, $CHCl_3$); {lit.[8h] $[\alpha]_D^{20} = -27.3$ (*c* 2.42, $CHCl_3$)}; ^1H NMR: δ 1.50 (d, *J* = 6.6 Hz, 3H), 1.94 (br, 1H), 5.0 (q, *J* = 6.6 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 8.25 (d, *J* = 8.2 Hz, 2H).

4.16. (*S*)-1-(2′-Fluorophenyl)propanol 4b

Colourless liquid; $[\alpha]_D^{25} = -32.3$ (*c* 1.16, $CHCl_3$); ^1H NMR: δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.72–1.86 (m, 2H), 2.19 (br, 1H), 4.92 (t, *J* = 6.5 Hz, 1H), 6.99–7.25 (m, 3H), 7.42 (m, 1H).

4.17. (*S*)-1-(3′-Fluorophenyl)propanol 4c

Colourless liquid; $[\alpha]_D^{25} = -31.3$ (*c* 1.13, $CHCl_3$); ^1H NMR: δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.67–1.81 (m, 2H), 2.23 (br, 1H), 4.56 (t, *J* = 6.5 Hz, 1H), 6.90–7.04 (m, 3H), 7.26 (m, 1H).

4.18. (*S*)-1-(4′-Fluorophenyl)propanol 4d

Colourless liquid; $[\alpha]_D^{25} = -37.7$ (*c* 0.75, $CHCl_3$); ^1H NMR: δ 0.88 (t, *J* = 7.7 Hz, 3H), 1.58–1.86 (m, 2H), 2.11 (br, 1H), 4.55 (t, *J* = 6.6 Hz, 1H), 6.96–7.05 (m, 2H), 7.24–7.31 (m, 2H).

4.19. (*S*)-1-(2′-Chlorophenyl)propanol 4e

Colourless liquid; $[\alpha]_D^{25} = -33.8$ (*c* 1.24, $CHCl_3$); ^1H NMR: δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.71–1.82 (m, 2H), 2.06 (br, 1H), 4.62 (t, *J* = 6.4 Hz, 1H), 7.21–7.32 (m, 3H), 7.43 (m, 1H).

4.20. (*S*)-1-(3′-Chlorophenyl)propanol 4f

Colourless liquid; $[\alpha]_D^{25} = -29.7$ (*c* 1.14, $CHCl_3$); ^1H NMR: δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.63–1.85 (m, 2H), 2.09 (br, 1H), 4.55 (t, *J* = 6.5 Hz, 1H), 7.16–7.27 (m, 3H), 7.32 (m, 1H).

4.21. (*S*)-1-(4′-Chlorophenyl)propanol 4g

Colourless liquid; $[\alpha]_D^{25} = -38.4$ (*c* 1.09, $CHCl_3$); ^1H NMR: δ 0.87 (t, *J* = 7.4 Hz, 3H), 1.60–1.84 (m, 2H), 2.19 (br, 1H), 4.53 (t, *J* = 6.5 Hz, 1H), 7.20–7.32 (m, 4H).

4.22. (*S*)-1-(2′-Bromophenyl)propanol 4h

Colourless liquid; $[\alpha]_D^{25} = -28.2$ (*c* 1.17, $CHCl_3$); ^1H NMR: δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.68–1.90 (m, 2H), 2.12 (br, 1H), 4.61 (t, *J* = 6.3 Hz, 1H), 7.22–7.35 (m, 2H), 7.42–7.51 (m, 2H).

4.23. (*S*)-1-(3′-Bromophenyl)propanol 4i

Colourless liquid; $[\alpha]_D^{25} = -24.3$ (*c* 0.97, $CHCl_3$); ^1H NMR: δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.62–1.85 (m, 2H), 2.14 (br, 1H), 4.53 (t, *J* = 6.5 Hz, 1H), 7.15–7.25 (m, 2H), 7.37–7.41 (m, 1H), 7.48 (1H).

4.24. (*S*)-1-(4′-Bromophenyl)propanol 4j

Colourless liquid; $[\alpha]_D^{25} = -30.5$ (*c* 0.98, $CHCl_3$); ^1H NMR: δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.61–1.84 (m, 2H), 2.02 (br, 1H), 4.54 (t, *J* = 6.5 Hz, 1H), 7.17–7.25 (m, 2H), 7.43–7.49 (2H).

4.25. (*S*)-1-(2′,4′-Dichlorophenyl)-1-propanol 4k

Colourless liquid; $[\alpha]_D^{25} = -39.85$ (*c* 0.27, $CHCl_3$); ^1H NMR: δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.61–1.87 (m, 2H), 2.00 (br, 1H), 5.01 (t, *J* = 6.0 Hz, 1H), 7.23–7.34 (m, 2H), 7.49 (1H).

4.26. 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 methanol-free 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 was 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.

4.27. (*R*)-MTPA ester of 2b

^1H NMR: δ 1.54 and 1.61 (two d, *J* = 6.8 Hz, 3H), 3.46 and 3.57 (two s, 3H), 6.03 (q, *J* = 6.8 Hz, 1H), 6.88–7.04 (m, 3H), 7.15–7.40 (m, 6H).

4.28. (*R*)-MTPA ester of 2c

^1H NMR: δ 1.55 and 1.61 (two d, *J* = 6.8 Hz, 3H), 3.48 and 3.56 (two s, 3H), 6.07 (q, *J* = 6.8 Hz, 1H), 6.88–7.04 (m, 2H), 7.15–7.40 (m, 7H).

4.29. (*R*)-MTPA ester of 2e

^1H NMR: δ 1.61 (d, *J* = 6.6 Hz, 3H), 3.47 and 3.59 (two s, 3H), 6.46 (q, *J* = 6.6 Hz, 1H), 6.90–7.08 (m, 3H), 7.19–7.37 (m, 6H).

4.30. (*R*)-MTPA ester of 2f

^1H NMR: δ 1.55 and 1.61 (two d, *J* = 6.6 Hz, 3H), 3.48 and 3.58 (two s, 3H), 6.03 (q, *J* = 6.6 Hz, 1H), 7.11–7.28 (m, 3H), 7.31–7.39 (m, 6H).

4.31. (*R*)-MTPA ester of 2h

^1H NMR: δ 1.60 (d, *J* = 6.6 Hz, 3H), 3.59 (s, 3H), 6.38 (q, *J* = 6.6 Hz, 1H), 7.13–7.26 (m, 2H), 7.36–7.56 (m, 7H).

4.32. (*R*)-MTPA ester of 2i

^{1}H NMR: δ 1.55 and 1.61 (two d, J = 6.6 Hz, 3H), 3.48 and 3.58 (two s, 3H), 6.02 (q, J = 6.6 Hz, 1H), 7.16–7.27 (m, 2H), 7.34–7.48 (7H).

4.33. (*R*)-MTPA ester of 2k

^{1}H NMR: δ 1.59 (d, J = 6.6 Hz, 3H), 3.48 and 3.58 (two s, 3H), 6.39 (q, J = 6.6 Hz, 1H), 7.03–7.12 (m, 2H), 7.26–7.49 (m, 6H).

4.34. (*R*)-MTPA ester of 2l

^{1}H NMR: δ 1.59 (d, J = 6.6 Hz, 3H), 3.47 and 3.58 (two s, 3H), 6.35 (q, J = 6.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.29–7.44 (m, 5H).

4.35. (*R*)-MTPA ester of 2m

^{1}H NMR: δ 1.55 and 1.59 (two d, J = 6.2 Hz, 3H), 2.37 (s, 3H), 3.57 (s, 3H), 6.28 (q, J = 6.2 Hz, 1 H), 7.05–7.18 (m, 1H), 7.22–7.32 (m, 7H), 7.35–7.42 (m, 1H).

4.36. (*R*)-MTPA ester of 2n

^{1}H NMR: δ 1.57 and 1.59 (two d, J = 7.2 Hz, 3 H), 2.29 (s, 3H), 3.47 and 3.57 (two s, 3H), 6.04 (q, J = 7.2 Hz, 1H), 7.00–7.42 (m, 9H).

4.37. (*R*)-MTPA ester of 2o

^{1}H NMR: δ 1.57 and 1.59 (two d, J = 7.0 Hz, 3H), 2.31 (s, 3H), 3.46 and 3.56 (two s, 3H), 6.08 (q, J = 7.0 Hz, 1 H), 6.88–7.02 (m, 2H), 7.22–7.28 (m, 5H), 7.38–7.50 (m, 2H).

4.38. (*R*)-MTPA ester of 2p

^{1}H NMR: δ 1.59–1.69 (two overlapping d, 3H), 3.47 and 3.58 (two s, 3H), 6.16 (q, J = 6.4 Hz, 1H), 7.30–7.78 (m, 7H), 8.06–8.20 (m, 2H).

4.39. (*R*)-MTPA ester of 2q

^{1}H NMR: δ 1.50 and 1.62 (two d, J = 6.6 Hz, 3H), 3.47 and 3.57 (two s, 3H), 6.12 (q, J = 6.6 Hz, 1H), 7.25–7.69 (m, 7H), 8.12–8.32 (m, 2H).

4.40. (*R*)-MTPA ester of 4b

^{1}H NMR: δ 0.91 and 0.95 (two t, J = 7.2 Hz, 3H), 1.79–2.27 (m, 2H), 3.44 and 3.56 (two s, 3H), 6.16 (t, J = 6.8 Hz, 1H), 6.99–7.21 (m, 3H), 7.28–7.47 (m, 6H).

4.41. (*R*)-MTPA ester of 4c

^{1}H NMR: δ 0.85 and 0.93 (two t, J = 7.2 Hz, 3H), 1.78–2.31 (m, 2H), 3.47 and 3.57 (two s, 3H), 5.80 (t, J = 7.0 Hz, 1H), 6.85–6.89 (m, 1H), 6.94–7.02 (m, 3H), 7.21–7.40 (m, 5H).

4.42. (*R*)-MTPA ester of 4d

^{1}H NMR: δ 0.92 (t, J = 7.2 Hz, 3H), 1.80–2.04 (m, 2H), 3.48 and 3.55 (two s, 3H), 5.80 (t, J = 7.2 Hz, 1H), 6.93–7.02 (m, 2H), 7.16–7.22 (m, 2H), 7.26–7.34 (m, 5H).

4.43. (*R*)-MTPA ester of 4e

^{1}H NMR: δ 0.91 and 0.97 (two t, J = 7.2 Hz, 3H), 1.84–2.24 (m, 2H), 3.45 and 3.57 (two s, 3H), 5.86 (t, J = 6.8 Hz, 1H), 7.17–7.28 (m, 3H), 7.31–7.45 (m, 6H).

4.44. (*R*)-MTPA ester of 4f

^{1}H NMR: δ 0.85 and 0.92 (two t, J = 7.2 Hz, 3H), 1.74–2.02 (m, 2H), 3.45 and 3.56 (two s, 3H), 5.75 (t, J = 7.2 Hz, 1H), 7.06–7.36 (m, 9H).

4.45. (*R*)-MTPA ester of 4g

^{1}H NMR: δ 0.92 (t, J = 7.2 Hz, 3H), 1.76–2.07 (m, 2H), 3.47 and 3.54 (two s, 3H), 5.78 (t, J = 6.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.31–7.39 (m, 5H).

4.46. (*R*)-MTPA ester of 4h

^{1}H NMR: δ 0.92 (t, J = 7.0 Hz, 3H), 1.82–2.36 (m, 2H), 3.54 (s, 3H), 5.89 (t, J = 6.6 Hz, 1H), 7.11–7.25 (m, 2H), 7.29–7.42 (m, 7H).

4.47. (*R*)-MTPA ester of 4i

^{1}H NMR: δ 0.89 and 0.94 (two t, J = 6.8 Hz, 3H), 1.86–1.97 (m, 2H), 3.46 and 3.58 (two s, 3H), 5.75 (t, J = 6.4 Hz, 1H), 7.15–7.21 (m, 2H), 7.27–7.45 (m, 7H).

4.48. (*R*)-MTPA ester of 4j

^{1}H NMR: δ 0.93 (t, J = 7.2 Hz, 3H), 1.76–2.06 (m, 2H), 3.47 and 3.58 (two s, 3H), 5.77 (t, J = 6.6 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.30–7.50 (7H).

4.49. (*R*)-MTPA ester of 4k

^{1}H NMR: δ 0.96 (t, J = 7.0 Hz, 3H), 1.82–1.93 (m, 2H), 3.49 and 3.57 (two s, 3H), 6.20 (t, J = 6.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.09 (dd, J = 8.4, 2.0 Hz, 1H), 7.25 (s, 1H), 7.37–7.41 (m, 5H).

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