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New synthetic routes towards various α-fluorinated aryl ketones and their enantioselective reductions using baker's yeast

Balaka Barkakaty, Yutaka Takaguchi and Sadao Tsuboi*

Department of Material and Energy Science, The Graduate School of Environmental Science, Okayama University, Tsushima, Okayama 700-8530, Japan

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Abstract—Highly electrophilic dichlorofluoromethyl aryl ketones were obtained by oxidation of dichlorofluoromethyl aryl alcohols. Subsequent dechlorination of these ketones using sodium formaldehyde sulfoxylate (Rongalite) and reductive dehalogenating system $SnCl_2$/Al led to various fluoromethyl aryl ketones and chlorofluoromethyl aryl ketones, respectively. Asymmetric reductions of these fluorinated ketones using the inexpensive baker's yeast produced the corresponding fluoromethyl aryl alcohols with different enantioselectivities.

1. Introduction

The success stories in achieving novel biological activities on introduction of a fluorine atom into different organic compounds have been so profound and fruitful that there has been a constant surge in research activities leading to the innovation of newer methods and synthetic techniques to incorporate a fluorine atom at different sites of various organic molecules.[1] More specifically, synthetic strategies or novel methodologies to attach the highly electronegative, low polarizable and hard fluorine atom near a carbonyl centre draw special attention due to the potentiality of such compounds to be used as important building blocks for other desired fluorinated targets. For example, since the synthesis of a number of biologically active compounds such as aminothiazoles, triazole, etc. relies on the nucleophilic displacements of α-halo carbonyl compounds, the presence of an adjacent fluoro atom in similar α-halo carbonyl synthons would pave the way for the synthesis of a gamut of novel fluoro containing biologically active compounds.[2] Furthermore, various condensation reactions are also possible due to the presence of highly acidic α-hydrogen atoms in α-fluorocarbonyl moieties, which makes the synthesis of α-fluorocarbonyl compounds a significant step towards numerous novel fluoro entities and thereby novel biological activities.[3]

The presence of a fluorine atom adjacent to a carbonyl group increases the electrophilicity of the carbonyl carbon considerably, thereby facilitating nucleophilic addition. Nucleophilic addition of an enzyme active site to the carbonyl group of fluorinated ketones has been suggested as being responsible for the inhibition of a variety of enzymes.[4] For example, some trifluoromethyl ketones were found to act as inhibitors of male responses to the pheromone of the processionary moth *Thaumetopea pityiocampa*.[5] The trifluoromethyl ketones are highly electrophilic compounds, which form stable hydrates or hemiketals in aqueous solutions with a serine residue of the enzyme.[6] The tetrahedral adducts formed in such reactions are similar to the transition state of the water addition to the carbonyl group of a peptide substrate.

However, there has already been a considerable effort on the introduction of a fluoro atom at the α-site of a carbonyl group by using various eletrophilic fluorinating agents.[7] Moreover, the synthetic utilization of environmentally hazardous chemicals such as trichlorofluoromethane (CFC-11) for the design of new fluoro compounds is emerging as a potential and useful fluorine fixation technique.[8] Recently, we have reported the reductive addition of $CFCl_3$ (CFC-11) to aromatic aldehydes using activated Al under ultrasonic irradiation.[9] This method leads to the formation of dichlorofluoromethyl aryl alcohols in reasonable to excellent yields. It indeed underscores one more important contribution towards safe and useful utilization of environmentally demanding compounds like CFC-11. Moreover, bioreductions of prochiral compounds to generate new chiral derivatives have always been the topic of immense scientific explorations. Among the various methods known so far, bioreduction by baker's yeast (*Saccharomyces cerevisiae*) is one of the most extensively studied and reported because of its easy availability, low cost, high efficiency in many cases and easy work-up procedure. We have already

* Corresponding author. Tel./fax: +81 86 251 8898; e-mail: stsuboi6@cc.okayama-u.ac.jp

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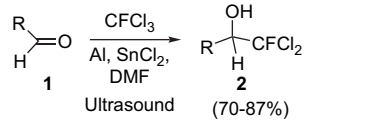
contributed a number of reports encompassing a wide range of useful substrates that permits asymmetric induction by the use of baker's yeast.[10] Herein, we wish to report novel strategies towards various α-fluorinated aryl ketones by selective dehalogenation of dichlorofluoromethyl aryl ketones and a comparative study of asymmetric baker's yeast reductions of the different kinds of α-fluorinated aryl ketones obtained from dichlorofluoromethyl aryl alcohols.

2. Results and discussion

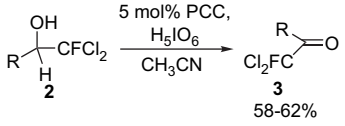
The starting compounds i.e., the dichlorofluoromethyl aryl alcohols were easily obtained by the reductive addition of $CFCl_3$ to aromatic aldehydes using $SnCl_2$ and activated Al in DMF under ultrasonic irradiation (Scheme 1) as reported in our previous work.[9]



1a: R = C_6H_5 **2a**: R = C_6H_5
1b: R = 4-$MeOC_6H_4$ **2b**: R = 4-$MeOC_6H_4$
1c: R = 4-BrC_6H_4 **2c**: R = 4-BrC_6H_4

Scheme 1.

The dichlorofluoromethyl aryl alcohols were then oxidized to the corresponding highly electrophilic dichlorofluoromethyl aryl ketones using 5 mol % of pyridinium chlorochromate (PCC) and 1.15 equiv of co-oxidant, H_5IO_6, in acetonitrile, as reported by Hunsen (Scheme 2).[11]

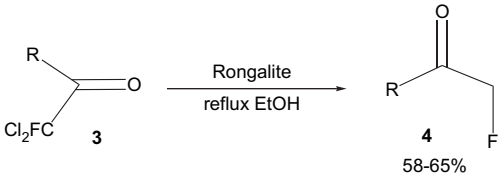


2a: R = C_6H_5 **3a**: R = C_6H_5
2b: R = 4-$MeOC_6H_4$ **3b**: R = 4-$MeOC_6H_4$
2c: R = 4-BrC_6H_4 **3c**: R = 4-BrC_6H_4

Scheme 2.

A number of methods were then investigated for the selective dechlorination reactions. For example, reduction with systems like Zn/AcOH, LAH, DIBAL-H, 10% Pd/C gave a mixture of products with very low selectivities. Reactions employing HI equivalents generated from NaI and H_2SO_4[12] and even by using Ph_3PHI[13] also failed to give the required conversions.

However, on using sodium formaldehyde sulfoxylate (Rongalite) in ethanol, selective dechlorination was observed leading to the formation of fluoromethyl aryl ketones (Scheme 3). Reductive dechlorination reactions of various halogenated ketones using Rongalite have been known,[14] but surprisingly, the synthetic utility of this reagent is not fully explored and have been limited only to a few examples to form R–CF_2H or R$COCF_2H$ moieties[15] and mostly in free-radical addition or cyclization reactions with perfluoroalkyl halides as starting materials.[16] In this paper, we investigated the utility of this reducing agent for the selective dechlorination of the dichlorofluoromethyl aryl ketones. After optimizing the conditions (Table 1), it was found that 2.0 equiv of Rongalite in reflux ethanol gave the corresponding fluoromethyl phenyl ketone (**4a**) from dichlorofluoromethyl phenyl ketone (**3a**) in moderate yields in less than 1 h.



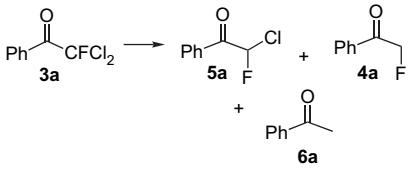
3a: R = C_6H_5 **4a**: R = C_6H_5
3b: R = 4-$MeOC_6H_4$ **4b**: R = 4-$MeOC_6H_4$
3c: R = 4-BrC_6H_4 **4c**: R = 4-BrC_6H_4

Scheme 3.

The mechanism of the dechlorination reactions by this reagent was supposed to be similar to that reported by Ait-Mohand et al.[15a] However, this particular system was applicable in the selective formation of fluoromethyl products only. As seen in Table 1, the reaction of dichlorofluoromethyl phenyl ketone **3a** with various amounts of Rongalite gave mixtures of fluoromethyl phenyl ketone **4a** with chlorofluoromethyl phenyl derivative **5a** or with acetophenone **6a** except entry 3 showing selective formation of **4a** with 2.0 equiv of Rongalite in reflux ethanol. The chlorofluoromethyl aryl ketones **4** were however obtained using the reductive dehalogenating system of $SnCl_2$/Al in DMF at 60 °C. Such a method was previously employed by Torii and co-workers for the mono-dechlorination of trichloromethyl carbinols employing $PbBr_2$/Al system in DMF.[17] We employed $SnCl_2$ for the required conversions instead of $PbBr_2$ because of lower toxicity of Sn compounds compared to that of Pb congeners (Scheme 4).

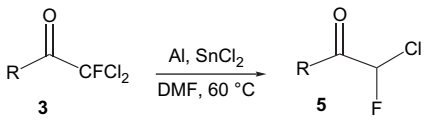
Next, we investigated the asymmetric reductions of the various kinds of α-fluorinated aryl ketones, obtained from the precursor compounds, dichlorofluoromethyl aryl alcohols, with baker's yeast. Baker's yeast produces many enzymes including many oxidoreductases[18,19] having diverse

Table 1. Reduction of dichlorofluoromethyl phenyl ketone[a] with Rongalite (NaO_2SCH_2OH)



Entry	Rongalite (equiv)	Time (min)	Product/%[b]
1	4.0	30	**4a**/10, **6a**/30
2	2.4	20	**4a**/50, **6a**/10
3	2.0	30	**4a**/60
4	1.0	30	**4a**/40, **5a**/20
5	2.0	180	**4a**/45, **5a**/20

[a] Carried out with dichlorofluoromethyl phenyl ketone **3a** (1.0 equiv) in absolute EtOH under reflux conditions except entry 5 at rt.
[b] Isolated yields based on amount of **3a** consumed.



3a: R = C_6H_5
3b: R = 4-$MeOC_6H_4$
3c: R = 4-BrC_6H_4

5a: R = C_6H_5
5b: R = 4-$MeOC_6H_4$
5c: R = 4-BrC_6H_4

Scheme 4.

activities. Therefore, the interaction of such whole-cells with the α-fluoro ketones having different steric demands with respect to the number of chlorine atoms in the α-position and also to the difference in nature of the substituents in the aromatic ring prompted us to carry out such kind of investigations (Scheme 5, Table 2).

3a: R = C_6H_5
X = Cl, Y = Cl
3b: R = 4-$MeOC_6H_4$
X = Cl, Y = Cl
3c: R = 4-BrC_6H_4
X = Cl, Y = Cl
5a: R = C_6H_5
X = Cl, Y = H
4a: R = C_6H_5
X = H, Y = H
4b: R = 4-$MeOC_6H_4$
X = H, Y = H
4c: R = 4-BrC_6H_4
X = H, Y = H

7a: R = C_6H_5
X = Cl, Y = Cl
7b: R = 4-$MeOC_6H_4$
X = Cl, Y = Cl
7c: R = 4-BrC_6H_4
X = Cl, Y = Cl
8a: R = C_6H_5
X = Cl, Y = H
9a: R = C_6H_5
X = H, Y = H
9c: R = 4-BrC_6H_4
X = H, Y = H

Scheme 5.

The baker's yeast reductions of the various kinds of dichlorofluoromethyl aryl ketones (**3**), chlorofluoromethyl aryl ketones (**5**) and the fluoromethyl aryl ketones (**4**) produced the corresponding asymmetric alcohols **7**, **8** and **9**, respectively, with different enantioselectivities and with no dehalogenated products. It was seen that in case of the dichlorofluoromethyl aryl ketones, the chemical yields (35–38%) as well as the optical yields (47–55%) of the chiral products did not depend on the nature of the substituents on the aromatic rings. But, the low optical yields (47–55%) in case of **3a**, **3b** and **3c** to give **7a**, **7b** and **7c**, respectively, and a slight improvement to 62% (with respect to the reduced carbonyl centre) in case of **5a** forming the corresponding diastereomeric chiral alcohol **8a** and a sharp increase to 92% and 94% in case of **4a** and **4c** forming **9a** and **9c**, respectively, reflected the dependence of such enzymatic selective reductions on steric factors of the substituents flanking the carbonyl centre. However, in the case of 2-fluoro-1-(4-methoxyphenyl) ethanone (**4b**), even being activated by the α-fluoro atom, no reaction occurred. In fact, this result is consistent with some other reported reductions of baker's yeast, which suggested that in systems such as 1-(4-methoxyphenyl)-1-ethanone[20] or 1-(1,3-benzodioxol-5-yl)-1-ethanone,[21] the carbonyl carbon is deactivated by the presence of electron donating substituents to undergo a nucleophilic attack by the hydride atom mediated by *S. cerevisiae*. In case of the dichlorofluoromethyl aryl ketone having the methoxy substituent (**3b**), the carbonyl group was however effectively reduced by the baker's yeast to give **7b** as a result of additional activation provided by the two chloro and one fluoro atoms attached to the carbonyl moiety.

Table 2. Baker's yeast reductions of various fluoromethyl aryl ketones

Substrate	R	X	Y	Time (days)	Product/yield (%)[a]	ee%[b,c]
3a	C_6H_5	Cl	Cl	3	**7a**/35	55
3b	4-$MeOC_6H_4$	Cl	Cl	3	**7b**/38	47
3c	4-BrC_6H_4	Cl	Cl	3.5	**7c**/36	50
5a	C_6H_5	Cl	H	3	**8a**/38	62[d]
4a	C_6H_5	H	H	2	**9a**/44	92
4b	4-$MeOC_6H_4$	H	H	5	No reaction	
4c	4-BrC_6H_4	H	H	2	**9c**/46	94

[a] Isolated yields based on starting materials consumed.
[b] Enantiomeric excess based on ^{1}H NMR analysis of the corresponding MTPA ester.
[c] Stereochemistry of each of the chiral product was found to be (*R*).
[d] Diastereomeric mixture with respect to the halogenated chiral centre while the stereospecificity of the reduced carbonyl centre was deduced as (1*R*). Separation of the diastereomeric mixture of **8a** was not possible even by HPLC technique.

However, it is often found that the stereoselectivity and regioselectivity associated with the reduction of an artificial substrate by a whole yeast is not always satisfactory[22] and could be improved further by various methods such as the use of isolated enzymes[23] instead of whole-cells, use of organic media,[24] addition of other compounds,[25] use of different carbon sources for the regeneration of the co-enzyme,[26] etc. But all these methods are not feasible in terms of practical utility to obtain high enantioselectivities and high chemical yields of the required compounds in terms of energy, time and expenses. Therefore, as obtained by our reported method, enantiomeric excesses (92% and 94%) for compounds **4a** and **4c** using baker's yeast with moderate chemical yields of 44% and 46%, respectively, offers a much easier, practically viable and an economical approach to obtain the required compounds.

The absolute configuration of the stereogenic centre of each homochiral aryl dichlorofluoromethyl aryl alcohol was deduced as *R* by comparing the sign of their specific rotations with that obtained for previously reported homochiral aryl trichloromethyl aryl alcohols[27] and that of trifluoromethyl aryl alcohols.[28] The configurations of other chiral halohydrins were also confirmed by comparison of the sign of the specific rotations with similar[29] and other authentic samples.[30] The enantiomeric excess of each of the chiral halohydrin was determined by ^{1}H NMR analysis of the corresponding MTPA ester by the chiral derivatization method using the Mosher's ester.[31] Furthermore, since no dehalogenated product was detected in the reaction products of the baker's yeast reductions, the results indicated that the reduction occurred via a hydride transfer mechanism and not an electron transfer as was demonstrated previously by Moran et al. in the case of α-haloacetophenones.[30]

3. Conclusions

In conclusion, we have shown here the synthetic utilization of our previously synthesized dichlorofluoromethyl aryl alcohols towards various α-fluorinated aryl ketones by employing very simple, facile and selective methodologies. These building blocks are expected to act as valuable starting materials for the synthesis of numerous novel fluorinated biologically active compounds. Asymmetric reductions of the various kinds of α-fluorinated aryl ketones with the inexpensive baker's yeast produced various chiral fluoro hydrins with different enantioselectivities depending on the steric size of the substituents on the α-carbon atom i.e., the number of chloro atoms attached to it. Although the presence of an electron donating group on the aromatic ring did not alter the reactivity in case of dichlorofluoromethyl aryl ketone but in case of fluoromethyl aryl ketone, the presence of an electron donating group such as –MeO totally deactivated the carbonyl moiety to such nucleophilic hydride addition mediated by the baker's yeast.

4. Experimental

4.1. General

^{1}H and ^{19}F (external C_6F_6) NMR spectra were recorded on JEOL JNM-AL300 spectrometer. FTIR spectra were recorded on a Thermo Nicolet Avatar 360T2 infrared spectrophotometer. Elemental analyses were performed on a Perkin–Elmer 2400 series II CHNS/O analyzer. For thin layer chromatography, aluminium sheets (Merck silica gel coated 60 F254) were used and the plates were visualized with UV light and phosphomolybdic acid (5% in EtOH). Merck silica gel 60 N (spherical, neutral) (40–50 μm) was used for the flash chromatography.

4.2. Materials

Trichlorofluoromethane and absolute ethanol were obtained from commercial source and stored over 4-Å molecular sieves. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Acetonitrile, DMF and methanol were dried and purified by standard procedures before use.

4.3. Preparation of dichlorofluoromethyl aryl alcohols 2a–c. General procedure

All compounds were synthesized according to the procedure described in Ref. 9.

4.3.1. Products 2a–c. Products **2a–c** were identified by comparison of their spectral data with authentic samples as given in Ref. 9.

4.4. Preparation of dichlorofluoromethyl aryl ketones 3a–c. General procedure

To 20 ml of acetonitrile was added 2.1 g (9.2 mmol) of H_5IO_6 and stirred vigorously at room temperature for 15 min. Dichlorofluoromethyl phenyl alcohol **2a** (1.64 g, 8.0 mmol) was then added (in ice-bath) followed by addition of 86 mg (5 mol %) PCC in 5 ml acetonitrile (in two portions), reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 3.5 h. The reaction mixture was then diluted with 100 ml ethyl acetate and washed with 1:1 brine/water, saturated aqueous Na_2SO_3 solution and brine. Then the organic extract was dried over anhydrous $MgSO_4$ and concentrated to give the crude product. The crude product was purified by silica gel flash column chromatography (hexane/EtOAc, 4:1) to yield 60% of **3a** (0.67 g, 3.25 mmol; based on starting material **2a** consumed).

4.4.1. 2,2-Dichloro-2-fluoro-1-phenylethanone (3a). Yield 60% (3.5 h); IR (neat): 3077, 2985, 1721, 1593, 1445, 1248, 1116, 1042, 944, 865, 807, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.17 (m, 2H), 7.66 (m, 1H), 7.52 (m, 2H); ^{19}F NMR ($CDCl_3$) δ 138.36. Anal. Calcd for $C_8H_5Cl_2FO$: C, 46.41; H, 2.43. Found: C, 46.76; H, 2.39.

4.4.2. 2,2-Dichloro-2-fluoro-1-(4-methoxyphenyl) ethanone (3b). Yield 62% (2.5 h); IR (neat): 3074, 2946, 2844, 1704, 1593, 1564, 1462, 1260, 1186, 1116, 1030, 984, 869, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.17 (d, J=9.3 Hz, 2H), 6.98 (d, J=7.5 Hz, 2H), 3.93 (s, 3H); ^{19}F NMR ($CDCl_3$) δ 138.78. Anal. Calcd for $C_9H_7Cl_2FO$: C, 45.60; H, 2.98. Found: C, 45.45; H, 2.92.

4.4.3. 2,2-Dichloro-2-fluoro-1-(4-bromophenyl) ethanone (3c). Yield 58% (3.5 h); IR (neat): 3088, 2977, 1713, 1598, 1449, 1249, 1120, 1095, 1074, 1036, 991, 863, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, J=8.1 Hz, 2H), 7.67 (m, 2H); ^{19}F NMR ($CDCl_3$) δ 138.25. Anal. Calcd for $C_8H_4BrCl_2FO$: C, 33.61; H, 1.41. Found: C, 33.27; H, 1.19.

4.5. Preparation of fluoromethyl aryl ketones 4a–c. General procedure

Into a three-necked flask equipped with a reflux condenser and a nitrogen inlet were added under nitrogen, dichlorofluoromethyl phenyl ketone **3a** (51.5 mg, 0.25 mmol) in 5 ml of absolute EtOH. Then after 5 min of stirring, Rongalite (59 mg, 0.50 mmol) was added and the solution was heated at reflux until complete consumption of starting material (30 min, TLC). The solution was then filtered and evaporated to dryness. The crude product was filtered through a short pad of silica gel eluting with hexane/EtOAc (4:1) to give 60% (21 mg, 0.15 mmol) of **4a**.

4.5.1. 2-Fluoro-1-phenylethanone (4a). Yield 60% (30 min). The compound was identified by comparison of its spectral data with authentic sample as given in Ref. 7b.

4.5.2. 2-Fluoro-1-(4-methoxyphenyl) ethanone (4b). Yield 65% (45 min); IR (neat): 2951, 2852, 1684, 1597, 1470, 1429, 1256, 1169, 1095, 964, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.90 (d, J=8.4 Hz, 2H), 6.97 (d, J=9.0 Hz, 2H), 5.48 (d, J=47.1 Hz, 2H), 3.90 (s, 3H); ^{19}F NMR ($CDCl_3$) δ 29.56. Anal. Calcd for $C_9H_9FO_2$: C, 64.28; H, 5.39. Found: C, 63.95; H, 5.28.

4.5.3. 2-Fluoro-1-(4-bromophenyl) ethanone (4c). Yield 58% (40 min); IR (neat): 3075, 3040, 2941, 1699, 1587, 1411, 1242, 1075, 986, 819 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.77 (m, 2H), 7.65 (m, 2H), 5.48 (d, J=47.1 Hz, 2H);

^{19}F NMR ($CDCl_3$) δ 29.28. Anal. Calcd for C_8H_6BrFO: C, 44.27; H, 2.79. Found: C, 43.98; H, 2.43.

4.6. Preparation of chlorofluoromethyl aryl ketones 5a–c. General procedure

A two-necked flask was charged with $SnCl_2$ (24 mg, 0.25 mmol) and Al powder (6.8 mg, 0.25 mmol) in DMF (1 ml) and allowed to stir at room temperature for 3 min. Then the starting material dichlorofluoromethyl phenyl ketone **3a** (51.5 mg, 0.25 mmol) in 1 ml of DMF was added and the reaction mixture was heated at 60 °C until completion of reaction (1.5 h, TLC). The reaction was quenched with two drops of aqueous 5% hydrochloric acid and the mixture was extracted with EtOAc. The combined extracts were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc, 4:1) to give 55% (24 mg, 0.14 mmol) of **5a**.

4.6.1. 2-Chloro-2-fluoro-1-phenylethanone (5a). Yield 55% (1.5 h); IR (neat): 2970, 1698, 1587, 1430, 1178, 985, 656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, J=8.1 Hz, 2H), 7.67 (m, 1H), 7.51 (m, 2H), 6.83 (d, J=50.7 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ 53.07. Anal. Calcd for C_8H_6ClFO: C, 55.67; H, 3.50. Found: C, 55.64; H, 3.19.

4.6.2. 2-Chloro-2-fluoro-1-(4-methoxyphenyl) ethanone (5b). Yield 52% (1.5 h); IR (neat): 2939, 1688, 1601, 1569, 1425, 1182, 980, 853, 630 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.07 (d, J=8.4 Hz, 2H), 6.99 (d, J=9.0 Hz, 2H), 6.78 (d, J=50.7 Hz, 1H), 3.90 (s, 3H); ^{19}F NMR ($CDCl_3$) δ 54.55. Anal. Calcd for $C_9H_8ClFO_2$: C, 53.35; H, 3.98. Found: C, 53.46; H, 3.67.

4.6.3. 2-Chloro-2-fluoro-1-(4-bromophenyl) ethanone (5c). Yield 56% (1 h); IR (neat): 2967, 1703, 1591, 1436, 1187, 989, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.67 (m, 2H), 6.76 (d, J=50.7 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ 53.93. Anal. Calcd for $C_8H_5BrClFO$: C, 38.21; H, 2.00. Found: C, 38.27; H, 1.89.

4.7. General procedure for the synthesis of 7a–c, 8a, 9a, 9c

To a stirring mixture of KH_2PO_4 (40 mg), $NH_4H_2PO_4$ (40 mg), $MgSO_4$ (20 mg), $CaCO_3$ (12 mg), glucose (1.0 g) and water (24 ml) was added baker's yeast (1.0 g) at 38 °C. After stirring for 30 min, dichlorofluoromethyl phenyl ketone **3a** (62 mg, 0.30 mmol) was added and the reaction mixture was stirred at 38 °C. Baker's yeast (1.0 g) and glucose (1.0 g) were added after every 24 h. After three days of stirring, the reaction mixture was treated with Celite for 1 h and filtrated. The filtrate was then extracted six times with EtOAc and washed with brine. The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated. The residual crude products were purified by flash column chromatography to give 35% (22 mg, 0.11 mmol) of **7a**.

4.7.1. (*R*)-2,2-Dichloro-2-fluoro-1-phenylethanol (7a). Spectral data as for racemic compound in Ref. 9: $[\alpha]_D^{20}$ −2.44 (*c* 1.5, $CHCl_3$).

4.7.2. (*R*)-2,2-Dichloro-2-fluoro-1-(4-methoxyphenyl) ethanol (7b). Spectral data as for racemic compound in Ref. 9: $[\alpha]_D^{22}$ −12.52 (*c* 1, $CHCl_3$).

4.7.3. (*R*)-2,2-Dichloro-2-fluoro-1-(4-bromophenyl) ethanol (7c). Spectral data as for racemic compound in Ref. 9: $[\alpha]_D^{25}$ −1.82 (*c* 1, $CHCl_3$).

4.7.4. (1*R*)-2-Chloro-2-fluoro-1-phenylethanol (8a). $[\alpha]_D^{23}$ −22.93 (*c* 0.5, $CHCl_3$); IR (neat): 3445, 3067, 1478, 1365, 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 5H), 6.15 (d, J=48 Hz, 1H), 4.93 (m, 1H), 2.63 (s, 1H); ^{19}F NMR ($CDCl_3$) δ 70.92. Anal. Calcd for C_8H_8ClFO: C, 55.03; H, 4.62. Found: C, 54.89; H, 4.78.

4.7.5. (*R*)-2-Fluoro-1-phenylethanol (9a). The product was identified by comparison of its spectral data with the authentic samples as given in Ref. 30. $[\alpha]_D^{25}$ −49.9 (*c* 1.2, $CHCl_3$) (lit. −50.6).[30]

4.7.6. (*R*)-2-Fluoro-1-(4-bromophenyl) ethanol (9c). $[\alpha]_D^{25}$ −25.94 (*c* 0.9, $CHCl_3$); IR (neat): 3403, 2930, 1708, 1589, 1490, 1301, 898 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.28 (m, 2H), 4.99 (m, 1H), 4.43 (m, 2H), 3.21 (s, 1H); ^{19}F NMR ($CDCl_3$) δ 67.33. Anal. Calcd for C_8H_8BrFO: C, 43.86; H, 3.68. Found: C, 43.84; H, 3.76.

4.8. Determination of enantiomeric purity of α-fluoro aryl alcohols 7a–c, 8a, 9c (derivatization method)

Chiral derivatization of each α-fluoro aryl alcohol was carried out by the chiral derivatization method using the Mosher's ester[31] on a 70 μmol scale. The resulting MTPA ester was analyzed by ^{1}H NMR spectroscopy.

4.8.1. MTPA ester of 7a. ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 13H), 6.38 (d, J=10.2 Hz, 0.29H), 6.31 (d, J=9.6 Hz, 1H), 3.56 (d, J=1.2 Hz, 0.87H), 3.43 (d, J=1.2 Hz, 3H).

4.8.2. MTPA ester of 7b. ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 9.52H), 6.90 (m, 0.72H), 6.83 (m, 2H), 6.40 (d, J=10.2 Hz, 0.38H), 6.33 (d, J=9.9 Hz, 1H), 3.84 (s, 1H), 3.82 (s, 3H), 3.62 (d, J=1.5 Hz, 3H), 3.56 (d, J=1.5 Hz, 1H).

4.8.3. MTPA ester of 7c. ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 4H), 7.40 (m, 9H), 6.33 (d, J=9.6 Hz, 0.33H), 6.24 (d, J=10.2 Hz, 1H), 3.63 (d, J=1.2 Hz, 3H), 3.49 (d, J=1.2 Hz, 0.33H).

4.8.4. MTPA ester of 8a. ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 12.4H), 6.37 (m, 0.6H), 6.142 (m, 1.24H), 3.62 (s, 3H), 3.48 (s, 0.7H).

4.8.5. MTPA ester of 9c. ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 9.3H), 6.22 (m, 1H), 6.08 (m, 0.03H), 4.65 (m, 2H), 4.51 (m, 0.06H), 3.61 (s, 3H), 3.48 (s, 0.09H).

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