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One-step synthesis of homochiral *O*-aryl and *O*-heteroaryl mandelic acids and their use as efficient ^{1}H NMR chiral solvating agents

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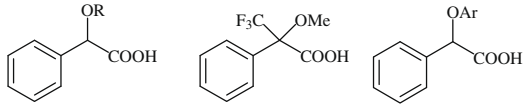
ABSTRACT

Job and Buchwald's one-step copper-promoted arylation of hydroxyl groups was explored and modified so that it could be applied to the coupling of mandelic acid with several halobenzenes and haloheteroarenes. A number of new homochiral *O*-aryl and *O*-heteroaryl mandelic acids, generally presenting high enantiomeric purities, were obtained. Although yields were moderate at the best, ranging from 9% to 41%, the reaction was convenient enough to prepare new mandelic acid derivatives, some of which performed as efficient chiral solvating agents (CSAs) for the direct ^{1}H NMR ee value determination of several clinically and pharmacologically relevant amines.

1. Introduction

Mandelic acid *O*-derivatives and analogs are well-known chiral solvating agents (CSAs) for the direct ^{1}H NMR determination of the enantiomeric composition of several classes of homochiral compounds.[1,2] Commercially available *O*-methyl mandelic acid (also referred to as α-methoxyphenylacetic acid, MPA, **1a**),[3] *O*-acetyl mandelic acid (OAMA, also named α-acetoxyphenylacetic acid, **1b**),[3–6] and α-trifluoromethyl-*O*-methyl mandelic acid (also known as α-methoxy-α-trifluoromethylphenylacetic acid, MTPA, or Mosher's reagent, **2**)[7–14] are generally used as CSAs for the determination of the enantiomeric purity of amines.



1
a: R = Me
b: R = Ac

2

3
a: Ar = *p*-ClC$_6$H$_4$
b: Ar = 2-naphthyl

However, when applied to the formation of diastereomeric salts with mexiletine, an antiarrhythmic drug, and related compounds, they caused only poor chemical shift non-equivalences and were unable to offer sufficient chiral discrimination for ee value determinations, regardless of the experimental conditions used.[15] Over the last few years, *O*-aryl mandelic acids **3** have been reported as efficient CSAs for the determination of the ee values of some clinically[15–18] or pharmacologically[15,16,19,20] relevant amines. In particular, (*S*)-*O*-(*p*-chlorophenyl)mandelic acid **3a** was successfully used to assess the ee values of mexiletine and two of its analogs,[15,16] *para*-hydroxymexiletine, a major mexiletine metabolite,[18] a prolinoxylidide acting as a voltage-gated sodium channel blocking agent,[19] and some 4-methylpiperidine derivatives reported as σ-receptor ligands.[20] (*R*)-*O*-(2-Naphthyl)mandelic acid **3b** was used as an alternative to chiral CZE analysis to assess the ee value of the so-called hydroxymethylmexiletine, one of the major metabolites of mexiletine.[18] Homochiral forms of **3a** were obtained in yields ranging from low to moderate by chemical,[21] lipase-mediated,[22] and dynamic kinetic[23] resolution of racemic **3a**, **3a** methyl ester, and the **3a** imido derivative of (*S*)-4-isopropyl-1,3-oxazolidin-2-one, respectively. The two latter procedures are less time-consuming than the former, but gave only poorly enriched optically active forms (ee values 25% and 47%, respectively). Compound (*S*)-**3a** was also obtained by Mitsunobu oxidoreductive condensation of 4-chlorophenol with (*R*)-ethyl mandelate followed by hydrazinolysis of the thus-obtained **3a** ethyl ester. However, partial racemization occurred (**3a** enantiomeric purity 41%) and the chemical yield was low (17%).[24] Recently, Durst's four-step procedure[25] was applied to the preparation of highly enriched forms of (*S*)-**3a**,[15] and (*R*)- and (*S*)-**3b**.[26] Looking for a more straightforward entry to *O*-aryl and *O*-heteroaryl mandelic acids **4a–h**, we considered Job and Buchwald's one-step copper-promoted coupling of alcohols[27] and aminoalcohols[28] with iodoarenes. Here we report the statistical experimental design (DoE) assisted exploration of Job and Buchwald's procedure. Optimal experimental conditions were found and used in a modified Job and Buchwald's procedure to obtain highly enriched homochiral 2-substituted phenylacetic acids **4a–h** which were tested as ^{1}H NMR CSAs to afford good chiral

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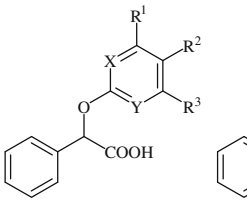
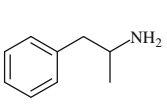
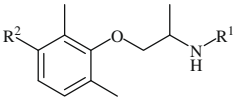
discrimination on amphetamine **5**, mexiletine **6**, two newly synthesized mexiletine metabolites—the so-called *N*- and *m*-hydroxymexiletines **7** and **8**, respectively, and other biologically relevant amines **11**–**13** (Table 3) as well.



4a-h



5



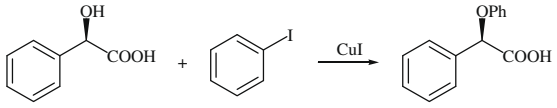
6: $R^1 = R^2 = H$
7: $R^1 = OH$; $R^2 = H$
8: $R^1 = H$; $R^2 = OH$

2. Results and discussion

2.1. One-step preparation of *O*-aryl and *O*-heteroaryl mandelic acids

Job and Buchwald's conditions used for the copper-catalyzed coupling of aryl iodides with aliphatic alcohols[27] were initially examined. The previously used catalyst system for carbon–oxygen bond formation consisted of copper(I) iodide, 1,10-phenanthroline as a bidentate nitrogenous ligand, and cesium carbonate as a base in refluxing toluene. In our initial screening experiments, homochiral mandelic acid (*R*)-**9** and iodobenzene **10a** were chosen as test substrates and subjected to the conditions previously established for enantiospecific cross-coupling of aryl iodides with aliphatic alcohols, namely, 10 mol % CuI, 20 mol % 1,10-phenanthroline, and 2.0 equiv of Cs_2CO_3, in refluxing toluene for 40 h (Table 1, entry 1).[27] Unfortunately, the reaction afforded the desired product (*R*)-**4a** in low yield (24%) and partially racemized form (24% enantiomeric purity). To avoid partial racemization, the reaction temperature was lowered to 80 °C but unreacted (*R*)-**9** was recovered (entry 2). Job and Buchwald's procedure for O-arylation of amino alcohols[28] was then applied: our first attempt to couple (*R*)-**9** with **10a** in refluxing butyronitrile for 14 h resulted in good yield (80%) but poor enantiomeric purity (36%) (entry 3). Several commonly used inorganic bases were screened for the coupling reaction. In summary, we found that the use of Cs_2CO_3 was crucial for the success of the reaction (entry 3), Rb_2CO_3 was considerably less effective (entry 9), while $CsHCO_3$, Li_2CO_3, K_2CO_3, K_3PO_4, and $BaCO_3$ afforded no product at all (entries 4–8). The organic base *i*Pr_2NEt was ineffective under our conditions (entry 10). With the best base determined, in an effort to understand how certain changes in the reaction conditions would affect the outcome of the coupling process, a statistical experimental design (DoE) was used in order to achieve both higher enantiomeric purity and yield. This allowed us to search for the optimal experimental conditions while performing a relatively low number of experiments. A two-level full factorial design was used and the influence of selected variables, namely, the molar ratio between mandelic acid and aryl iodide (0.8–1.2), temperature (60–100 °C), and time (5–40 h), was investigated. The results showed that temperature and reaction time were the key variables influencing the yield and enantiomeric purity, while the mandelic acid/aryl iodide ratio had no effect. In particular, we found that temperature and time were directly correlated to the yield but inversely correlated to the enantiomeric purity. A reaction time of 15 h and a temperature of 75 °C provided the best compromise between the two conflicting goals giving the desired product (*R*)-**4a** in a small amount (17% yield), but enough to be used as a chiral solvating agent, and with the highest ee (entry 11), which could be increased further to 98% by recrystallization. When 2-acetylcyclohexanone was used as a ligand,[29] the coupling reaction afforded no product (entry 12). The established optimal reaction conditions, namely, 5 mol % CuI, 2.0 equiv of Cs_2CO_3, and 1.0 equiv of iodobenzene in butyronitrile at 75 °C for 15 h, were then applied to the synthesis of a series of *O*-aryl and *O*-heteroaryl mandelic acids (Table 2). A variety of aryl and heteroaryl halides **10a–h** were used, with F, Br, or I as leaving groups. Both electron-donating and electron-withdrawing substituents were tolerated on the aryl halide reactants giving almost comparable yields of the corresponding *O*-alkyl derivatives (entries 2, 3, 5, 7, and 8). Generally, when a nuclear nitrogen atom was present at the 2-position with respect to the halogen, the highest yields were observed (entries 4–7). In particular, 2-iodopyridine (entry 6) was at least twice as reactive as iodobenzene (entry 1). It is notable that the coupling proceeded even with the sterically hindered substrate 2-bromo-3-nitropyridine **10g** (entry 7).

Table 1
Selection of ligands, bases, solvents, temperatures, and times of reaction in the O-arylation of (*R*)-mandelic acid with iodobenzene

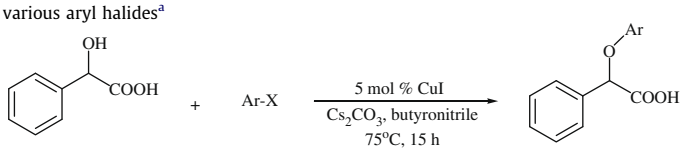


(*R*)-**9** **10a** (*R*)-**4a**

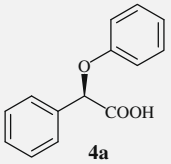
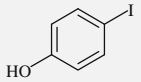
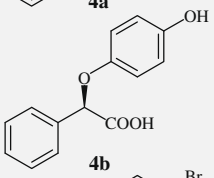
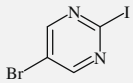
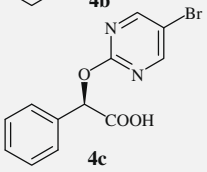
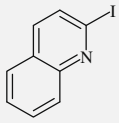
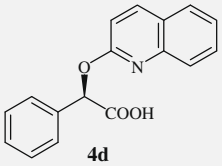
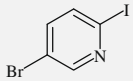
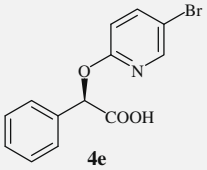
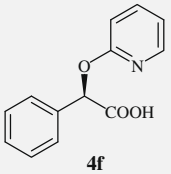
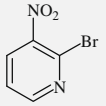
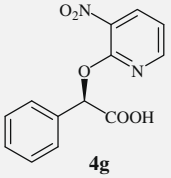
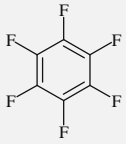
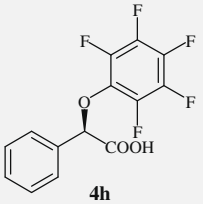
Entry	Ligand	Base	Solvent	Temp (°C)	Time (h)	Yield[a] (%)	Enantiomeric purity[b,c] (%)
1	1,10-Phenanthroline	Cs_2CO_3	Toluene	110	40	24	24[b]
2	1,10-Phenanthroline	Cs_2CO_3	Toluene	80	24	0	—
3	—	Cs_2CO_3	Butyronitrile	125	14	80	36[b]
4	—	$CsHCO_3$	Butyronitrile	100	16	0	—
5	—	Li_2CO_3	Butyronitrile	100	16	0	—
6	—	K_2CO_3	Butyronitrile	110	28	0	—
7	—	K_3PO_4	Butyronitrile	100	40	<1	n.d.[d]
8	—	$BaCO_3$	Butyronitrile	80	16	0	—
9	—	Rb_2CO_3	Butyronitrile	100	16	15	0.5[b]
10	—	*i*Pr_2NEt	Butyronitrile	80	15	0	—
11	—	Cs_2CO_3	Butyronitrile	75	15	17	93[c]
12	2-Acetylcyclohexanone	Cs_2CO_3	Butyronitrile	75	15	<1	n.d.[d]

[a] Yield of the isolated product.
[b] Expressed as a ratio of the observed specific rotation to the highest specific rotation value available.[15]
[c] Ee evaluated by CZE, CSA: 2-hydroxypropyl-β-cyclodextrin.
[d] Not determined.

Table 2
Arylation of homochiral mandelic acid with various aryl halides[a]



(*R*)- and (*S*)-**9** **10a–h** (*R*)-**4a–h** and (*S*)-**4b–h**

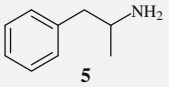
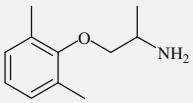
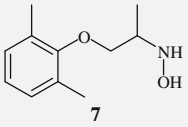
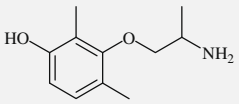
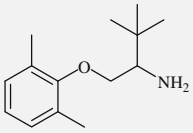
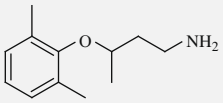
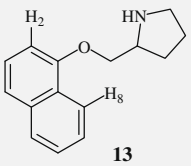
Entry	ArX	Compound	% Conversion[b]	% Yield[c]	% ee
1	 **10a**	 **4a**	27	17	93[d]
2	 **10b**	 **4b**	29 (29)	24 (15)	99[d]
3	 **10c**	 **4c**	22 (45)	12 (24)	99[d,e]
4	 **10d**	 **4d**	54 (38)	29 (33)	98[d,e]
5	 **10e**	 **4e**	39 (28)	34 (16)	99[d]
6	 **10f**	 **4f**	60	41 (45)	98[d]
7	 **10g**	 **4g**	65 (34)	30 (26)	98[d,e]
8	 **10h**	 **4h**	15 (16)	9 (10)	96[d]

[a] All reactions were carried out using 1 mmol of homochiral mandelic acid, 1.0 equiv of aryl halide, 2.0 equiv of Cs_2CO_3, and 2.0 mL of butyronitrile; for the sake of simplicity, only the structures of the (*R*)-enantiomers obtained starting from (*R*)-**9** have been reported for each entry; ee values refer to (*R*)-**4a–h**.
[b] Determined by ^{1}H NMR for the (*R*)-enantiomer and, in parentheses, for the (*S*)-enantiomer.
[c] Isolated product yield after preparative layer chromatography.
[d] Ee evaluated by CZE, CSA: 2-hydroxypropyl-β- or γ-cyclodextrin.
[e] Ee evaluated by HPLC on the corresponding methyl ester, chiral stationary phase: Daicel Chiralpak IA.

2.2. *O*-Aryl and *O*-heteroaryl mandelic acids as chiral shift reagents

Some of the carboxylic acids obtained were evaluated as CSAs for direct ^{1}H NMR ee determinations (Table 3). Initially, the case of commercially available amphetamine **5** was investigated. To the best of our knowledge, cyclodextrins[30] and *tert*-butylphenylphosphinothioic acid[31] were previously used as CSAs for the determination of amphetamine enantiomeric composition by NMR spectroscopy. However, baseline resolution has never been observed: when the above reported CSAs were used, the $\Delta\delta$ values 0.010 and 0.057, respectively, were found for **5** methyl doublets. Similarly, when **4a** was used as the CSA, insufficient chemical shift differences, that is, non-equivalences, were obtained ($\Delta\delta$ 0.021, Fig. 1A and Table 3). On the contrary, the non-equivalence produced by **4d** ($\Delta\delta$ 0.112, Fig. 1B and Table 3) was significantly higher than that measured with **4a** and the methyl signals of **5** were baseline resolved. Compound **4d** gave good results also in the case of mexiletine **6** whose methyl doublet $\Delta\delta$ value was higher than that previously described using another series of aryl mandelic acids

Table 3
Magnitude of non-equivalences determined in the presence of (*R*)-CSAs

Entry	Amine	Affected protons	Acid	$\Delta\delta$[a]
1	 **5**	C*H*$_3$CH	**4a**	0.021
			4d	0.112
2	 **6**	C*H*$_3$CH	**4d**	0.123
			3a	0.101
		C*H*$_3$Ar	**4d**	0.033
			3a	0.046
3	 **7**	C*H*$_3$CH	**3a**	0.022
			4f	0.023
			4a	0.022[c]
			4d	0.055
			1b	0.013
			3b	0.008
			–[b]	0.008
			2	0.018
		C*H*$_3$Ar	**3a**	0.005
			4f	0.016
			4a	0[c]
			4d	0.019
			1b	0
			3b	0.012
			–[b]	0
			2	0
4	 **8**	C*H*$_3$CH	**4d**	0.296
5	 **11**	C*H*$_3$C	**4d**	0.063
		C*H*$_3$Ar	**4d**	0.058
6	 **12**	C*H*$_3$CH	**4d**	0.082[d]
			4a	0[d]
			1b	0
7	 **13**	Ar *H*C-2	**3a**	0.089
			4h	0.119
		Ar *H*C-8	**3a**	0
			4h	0.050

[a] Spectra were registered in $CDCl_3$, unless otherwise noted.
[b] 1-(Anthracen-9-yl)-2,2,2-trifluoroethanol (Pirkle's alcohol) was used as the CSA.
[c] Solvent, benzene-d_6.
[d] Solvent, toluene-d_8.

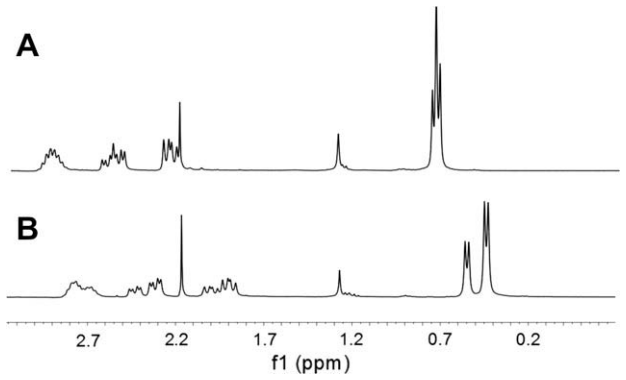


Figure 1. Variation of $\Delta\delta$ ($CDCl_3$) for the methyl doublets of amphetamine **5** diasteromeric salts with acid **4a** (A) and **4d** (B). Observed $\Delta\delta$ values are reported in Table 3.

(entry 2).[15] Given the good results obtained in the enantiodiscrimination of **5** and **6**, we became interested in checking the applicability of these compounds to the case represented by *N*-hydroxy mexiletine **7**, a major mexiletine metabolite.[32]

Our first attempts to determine the enantiomeric composition of **7** by capillary electrophoresis and chiral HPLC failed. Entry 3 in Table 3 shows the results obtained with several CSAs. *O*-Heteroaryl derivatives performed better than their corresponding carbon ring equivalents (cf. **4a** and **4f**, **4d** and **3b**), thus indicating the beneficial role played by a nitrogen atom in the OAr ring. The best result was obtained when **4d** was used as the CSA ($\Delta\delta$ 0.055, Fig. 2D and Table 3), suggesting that this quinoline derivative might be efficient as a CSA on relatively weak bases such as the hydroxylamine **7** (pK_a 5.15 ± 0.02, see Section 4).

For compounds **8** and **11**, the non-equivalences produced on the methyl signals in the presence of **4d** were 0.296 and 0.063, respectively, the former being the highest $\Delta\delta$ value obtained in our study. Most likely, the hydroxyl group of **8** contributes to the stabilization of the diastereomeric complexes. Generally, the largest chemical shift differences were induced by **4d** on protons adjacent to the basic center of the molecule. In most cases also protons that were more distant from nitrogen showed spectral non-equivalences, but were not sufficiently resolved to allow accurate integration. An exception was observed with the mexiletine analog **12** (entry 6): despite the formal displacement of the stereocenter from the basic group by insertion of two methylene spacers, chemical shift non-equivalences were good for the methyl doublets. The efficiency of **4d** might be ascribed to the large anisotropic effect of the quinoline ring.[33]

Classic aryloxyaryl acids could sometimes be ineffective for amines without singlets or doublets in a free high field region of the ^{1}H NMR spectrum. This is the case for amine **13**, which presents a series of multiplets in the region between 0 and 5 ppm, and whose only useful signals are in the aromatic region. As a result, we prepared acid **4h**, whose hydrogen atoms of the aryloxy moiety were substituted by fluorine ones, in order to not obscure resonances of interest in the region between 6 and 7 ppm. This acid was able to baseline resolve the doublet signal of the *H*C-2 on the aromatic ring (Fig. 3B and Table 3).

Acids **3a**, **4d**, and **4h** were also applied to the determination of the ee values of amines **6**,[16] **8**,[34] **12**,[35] and **13**[36] (Table 3). It is worth noting that, for each of these compounds, the (*R*)-enantiomer presented a downfield sense of the non-equivalence. This finding could be used to correlate absolute configuration within this series. ^{1}H NMR analyses were performed at room temperature and no deconvolution software was required.

2.3. Synthesis of *N*-hydroxymexiletine

Compound (*RS*)-**7** was synthesized following the synthetic route shown in Scheme 1. It starts from commercially available 2-[({[(*tert*-butoxycarbonyl)amino]oxy}carbonyl)oxy]-2-methylpropane **14**, which was submitted to a Mitsunobu[37] reaction with 1-(2,6-dimethylphenoxy)propan-2-ol **15**, prepared as previously described.[38] Deprotection of **16** gave (*RS*)-**7**.

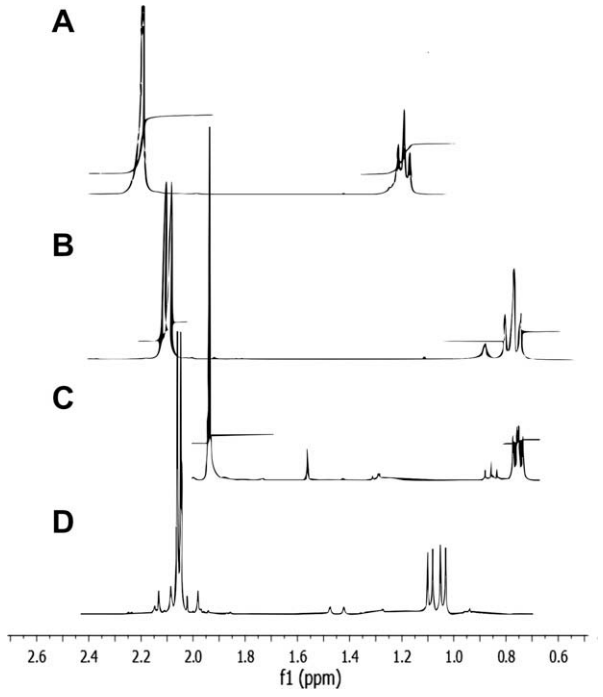


Figure 2. Variation of $\Delta\delta$ ($CDCl_3$, or benzene-d_6 for spectrum C) for the methyl doublets and methyl singlets of *N*-hydroxymexiletine (**7**) diasteromeric salts with acids **3a** (A), **4f** (B), **4a** (C), and **4d** (D). $\Delta\delta$ values are reported in Table 3.

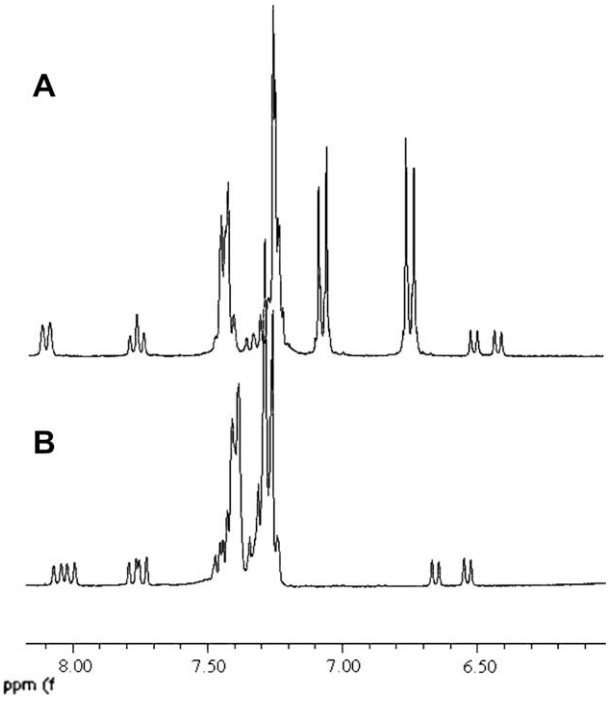
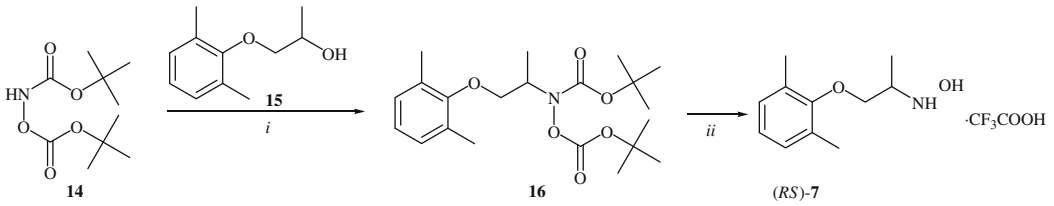


Figure 3. Variation of $\Delta\delta$ ($CDCl_3$) for the *H*C-2 and *H*C-8 doublets of compound **13** diasteromeric salts with acids **3a** (A) and **4h** (B). $\Delta\delta$ values are reported in Table 3.



Scheme 1. Synthesis of (*RS*)-*N*-hydroxymexiletine [(*RS*)-**7**]. Reagents and conditions: (i) TPP, DIAD, anhydrous THF, 0 °C, 2 h; (ii) CF_3COOH 99%/HCOOH 98%, 0 °C, 4 h.

3. Conclusion

In conclusion, a simple procedure for the rapid synthesis of highly enantiomerically enriched *O*-aryl and *O*-heteroaryl mandelic acids has been developed. In a one-pot process, aryl and heteroaryl halides can be coupled to homochiral mandelic acid in yields ranging from 9% to 41% and in excellent enantiomeric purity, making this a superior method to those described previously.[15,21–26] The method reported herein proceeds smoothly using a diverse array of aryl and heteroaryl halides; it seems to be applicable to both electron-deficient and electron-rich substrates, and to sterically hindered substrates as well. Some of the thus-obtained mandelic acid derivatives **4a,d,f,h** were tested as CSAs for direct ^{1}H NMR ee determinations of amines. Generally, CSA usefulness is limited by two main drawbacks: (1) small separations of the NMR signals of diastereomeric salts, which compel to record spectra at low temperature and/or to use computer-aided deconvolution procedures and (2) low solubility of the diastereomeric complexes in non-polar solvents, generally required to maximize the observed anisocrony.[2] *O*-Aryl mandelic derivatives **4d** and **4h** do not suffer from these drawbacks. In particular, **4d** gave chiral discrimination from sufficient to excellent on amines **5–12**, allowing ee value determination even in a case where the stereocenter was displaced from the amine group by two carbon units **12**.[35] The quinidine derivative **4d** was even successful with amphetamine **5** and the hydroxylamine **7**. Thus, **4d** might be able to allow ee value determinations on weak amines. The fluorine-containing CSA **4h** was applied to ee value determination of naphthyloxy methyl pyrrolidine **13**[36] due to its ability to split signals on the aryloxy moiety. In conclusion, our modified Job and Buchwald's one-step copper-promoted arylation of mandelic acid may serve as a straightforward route to efficient CSAs and let envisage the possibility for researchers to obtain CSAs specifically tailored on their own homochiral amines.

4. Experimental

4.1. Chemistry

All chemicals were purchased from Sigma–Aldrich or Lancaster. Compound **10d** was obtained from 2-chloroquinoline following a previously reported procedure.[39] The solvents were of RP grade unless otherwise indicated. The structures of the compounds were confirmed by routine spectroscopic analyses. Only spectra for compounds not described previously are given. Melting points were determined on a Gallenkamp melting point apparatus in open glass capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin–Elmer (Norwalk, CT) Spectrum One FT spectrophotometer and band positions are given in reciprocal centimeters (cm^{-1}). Routine ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-VX spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively, using $CDCl_3$, DMSO-d_6, or CD_3OD (where indicated) as a solvent. Chemical shifts are reported in parts per million (ppm) relative to the residual non-deuterated solvent resonance: $CDCl_3$, δ 7.26 (^{1}H NMR) and δ 77.2 (^{13}C NMR), unless otherwise indicated; CD_3OD, δ 3.30 (^{1}H NMR) and 46.3 (^{13}C NMR); DMSO-d_6, δ 2.47 (^{1}H NMR). *J* values are given in Hertz. The ee values of (*R*)-**4a–h** and (*S*)-**4f** were determined by CZE on a BioFocus 3000 CE system (Bio-Rad, USA). A fused silica capillary of 69.7 cm (effective length 65.2 cm) and 0.05 mm i.d. (Quadrex Corporation) thermostated at 20 °C was used as a separation tube. The samples (0.1 mg/mL) were pressure injected (15 psi/s) and detected at 214 nm. As background electrolyte, phosphate buffer (0.035 M), at pH 6.2, and the chiral selector 2-hydroxypropyl-β-cyclodextrin (40 mg/mL) were used, unless otherwise indicated. HPLC analyses were performed with an Agilent chromatograph (model 1100), equipped with a diode array detector, on a Daicel Chiralpak IA column (flow rate 0.7 mL/min, λ 230 nm, eluent 95:5 hexane/*i*PrOH, unless otherwise indicated). The ee values of (*R*)-**4b–d,g** and (*S*)-**4b,d** were determined by HPLC analysis after derivatization to methyl esters by reaction with an ether solution of diazomethane. In order to register ^{1}H NMR spectra of the diastereomeric salts, compounds **5–8** and **11–13** were dissolved with 2 equiv of CSA in the appropriate deuterated solvent and the spectra were registered at 25 °C. EIMS spectra were recorded on a Hewlett-Packard 6890-5973 MSD gas chromatograph/mass spectrometer at low resolution. Elemental analyses were performed on a Eurovector Euro EA 3000 analyzer. Optical rotations were measured on a Perkin Elmer (Norwalk, CT) Mod 341 spectropolarimeter; concentrations were expressed in g/100 mL, and the cell length was 1 dm, thus $[\alpha]_D^{20}$ values were given in units of 10^{-1} deg cm^2 g^{-1}. Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040–0.063 mm, Merck, Darmstadt, Germany) using the technique described by Still et al.[40] Preparative layer chromatography analyses were performed on 2 mm precoated silica gel on glass plates (20 × 20 cm) (Kieselgel 60F_{254}, Merck). TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel 60F_{254}, Merck).

4.1.1. General procedure for the preparation of *O*-aryl mandelic acids 4a–h

A mixture of homochiral mandelic acid **9** (2.45 mmol), aryl halides **10a–h** (2.45 mmol), Cs_2CO_3 (4.90 mmol), and CuI (5%) in butyronitrile (2 mL) was heated to 75 °C under an N_2 atmosphere for 15 h. The solvent was then removed under vacuum; the residue was taken up with water and washed two times with EtOAc. The aqueous phase was acidified in citric acid and extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The yield of the crude product was determined by ^{1}H NMR. The residue was then purified by preparative layer chromatography (EtOAc) to give the desired product (**4a–h**).

4.1.2. (−)-(*R*)-2-Phenoxy-2-phenylacetic acid (−)-(*R*)-4a

Yield: 17%; mp 109–111 °C ($CHCl_3$/hexane), lit:[15] 117–118 °C (hexane) for the *S* enantiomer; $[\alpha]_D^{20} = -114$ (*c* 1, MeOH), ee 93% (CZE), lit:[15] $[\alpha]_D^{20} = +120$ (*c* 1.1, MeOH), ee 97% (HPLC) for the (*S*)-enantiomer. Spectroscopic data were in agreement with those reported in the literature for the *S* enantiomer.[15]

4.1.3. (−)-(*R*)-2-(4-Hydroxyphenoxy)-2-phenylacetic acid (−)-(*R*)-4b

Yield: 24%; mp 181–182 °C; $[\alpha]_D^{20} = -101$ (*c* 1, MeOH), 99% ee (CZE); IR (KBr): 3259 (OH), 1721 (C=O) cm^{-1}; ^{1}H NMR (CD_3OD):

δ 5.56 (s, 1H), 6.65–6.70 (m, 2H), 6.80–6.85 (m, 2H), 7.30–7.40 (m, 3H), 7.50–7.60 (m, 2H); ^{13}C NMR (CD_3OD): δ 79.5 (1C), 115.6 (2C), 116.9 (2C), 127.2 (2C), 128.4 (2C), 128.6 (1C), 136.7 (1C), 150.8 (1C), 152.0 (1C), 172.8 (1C); GC–MS (70 eV) (methyl ester) *m/z* (%) 258 (M^+, 24), 121 (100). Anal. Calcd for ($C_{14}H_{12}O_4 \cdot 0.3H_2O$): C, 67.42; H, 5.08. Found: C, 67.38; H, 5.12.

4.1.4. (+)-(*S*)-2-(4-Hydroxyphenoxy)-2-phenylacetic acid (+)-(*S*)-4b

Yield: 15%; mp 187–188 °C; $[\alpha]_D^{20} = +115$ (*c* 1, MeOH), 98% ee (HPLC: flow rate 1.5 mL/min, eluent 97:3 hexane/*i*PrOH). Spectroscopic data were in agreement with those found for (−)-(*R*)-**4b**.

4.1.5. (−)-(*R*)-2-(5-Bromopyrimidin-2-yloxy)-2-phenylacetic acid (−)-(*R*)-4c

Yield: 12%; mp 140–141 °C; $[\alpha]_D^{20} = -102$ (*c* 1, MeOH), 99% ee (CZE), 98% ee (HPLC); IR (KBr): 2964 (OH), 1717 (C=O) cm^{-1}; ^{1}H NMR: δ 6.12 (s, 1H), 6.70 (br s, 1H), 7.30–7.50 (m, 3H), 7.55–7.70 (m, 2H), 8.56 (s, 2H); ^{13}C NMR: δ 77.4 (1C), 113.2 (1C), 127.9 (2C), 129.0 (2C), 129.6 (1C), 133.6 (1C), 160.0 (2C), 162.8 (1C), 173.8 (1C); GC-MS (70 eV) (methyl ester) *m/z* (%) 322 (M^+, 11), 263 (100). Anal. Calcd for ($C_{12}H_9BrN_2O_3 \cdot 0.33H_2O$): C, 45.74; H, 3.09; N, 8.89. Found: C, 45.76; H, 3.18; N, 8.64.

4.1.6. (+)-(*S*)-(5-Bromopyrimidin-2-yloxy)phenylacetic acid (+)-(*S*)-4c

Yield: 24%; mp 133–134 °C; $[\alpha]_D^{20} = +105$ (*c* 1, MeOH). Anal. Calcd for ($C_{14}H_9BrN_2O_3 \cdot 1.33H_2O$): C, 43.26; H, 3.53; N, 8.41. Found: C, 43.27; H, 3.57; N, 8.05. Spectroscopic data were in agreement with those found for (−)-(*R*)-**4c**.

4.1.7. (−)-(*R*)-2-Phenyl-2-(quinolin-2-yloxy)acetic acid (−)-(*R*)-4d

Yield: 39%; mp 122–123 °C ($CHCl_3$/hexane); $[\alpha]_D^{20} = -167$ (*c* 1, MeOH), 98% ee (capillary electrophoresis: pH 5.5, 2-hydroxypropyl-γ-cyclodextrin), 98% ee (HPLC: flow rate 0.6 mL/min); IR (KBr): 2906 (OH), 1724 (C=O) cm^{-1}; ^{1}H NMR: δ 6.43 (s, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 7.35–7.45 (m, 3H), 7.58 (t overlapping t at 7.59, *J* = 7.6 Hz, 1H), 7.59 (t overlapping t at 7.58, *J* = 7.8 Hz, 1H), 7.60–7.70 (m, 2H), 7.74 (d overlapping d at 7.77, *J* = 6.9 Hz, 1H), 7.77 (d overlapping d at 7.74, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 9.00 (br s, 1H); ^{13}C NMR: δ 75.8 (1C), 112.8 (1C), 124.8 (1C), 125.7 (1C), 127.6 (2C), 128.0 (2C), 129.0 (2C), 129.3 (1C), 129.9 (1C), 134.9 (1C), 139.7 (1C), 146.1 (1C), 160.7 (1C), 175.5 (1C). Anal. Calcd for ($C_{17}H_{13}NO_3 \cdot 0.66H_2O$): C, 70.09; H, 4.96; N, 4.81. Found: C, 70.21; H, 4.66; N, 4.77.

4.1.8. (+)-(*S*)-2-Phenyl-2-(quinolin-2-yloxy)acetic acid (+)-(*S*)-4d

Yield: 33%; mp 123–124 °C ($CHCl_3$/hexane); $[\alpha]_D^{20} = +173$ (*c* 1, MeOH), 98% ee (HPLC: flow rate 0.6 mL/min). Anal. Calcd for ($C_{17}H_{13}NO_3 \cdot 0.25H_2O$): C, 71.95; H, 4.79; N, 4.94. Found: C, 71.89; H, 4.79; N, 4.84. Spectroscopic data were in agreement with those found for (−)-(*R*)-**4d**.

4.1.9. (−)-(*R*)-2-(5-Bromopyridin-2-yloxy)-2-phenylacetic acid (−)-(*R*)-4e

Yield: 34%; mp 164–165 °C; $[\alpha]_D^{20} = -104$ (*c* 1, MeOH), 99% ee (CZE: pH 5.5); IR (KBr): 3162 (OH), 1745, 1705 (C=O) cm^{-1}; ^{1}H NMR: δ 6.15 (s, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 7.35–7.45 (m, 3H), 7.55–7.60 (m, 2H), 7.70 (dd, *J* = 8.8, 2.5 Hz, 1H), 8.17 (d, *J* = 1.9 Hz, 1H), 8.70 (br s, 1H); ^{13}C NMR: δ 75.8 (1C), 113.0 (1C), 113.1 (1C), 127.9 (2C), 129.0 (2C), 129.5 (1C), 134.4 (1C), 141.9 (1C), 147.4 (1C), 161.2 (1C), 175.3 (1C); MS (70 eV) (methyl ester) *m/z* (%) 321 (M^+, 28), 121 (100).

4.1.10. (+)-(*S*)-2-(5-Bromopyridin-2-yloxy)-2-phenylacetic acid (+)-(*S*)-4e

Yield: 16%; mp 166–167 °C; $[\alpha]_D^{20} = +102$ (*c* 1, MeOH). Spectroscopic data were in agreement with those found for (−)-(*R*)-**4e**.

4.1.11. (−)-(*R*)-2-Phenyl-2-(pyridin-2-yloxy)acetic acid (−)-(*R*)-4f

Yield: 41%; mp 107–108 °C; $[\alpha]_D^{20} = -148$ (*c* 1, MeOH), 98% ee (CZE: pH 5.5); IR (KBr): 3442 (OH), 1733 (C=O) cm^{-1}; ^{1}H NMR: δ 6.23 (s, 1H, C*H*), 6.91 (d overlapping apparent t at 6.92, *J* = 7.8 Hz, 1H), 6.92 (apparent t overlapping d at 6.91, *J* = 6.6 Hz, 1H), 7.35–7.45 (m, 3H), 7.55–7.65 (m, 3H), 8.12 (dd, *J* = 5.5, 1.4 Hz, 1H), 9.12 (br s, 1H); ^{13}C NMR: δ 75.5 (1C), 111.5 (1C), 118.0 (1C), 127.9 (2C), 129.0 (2C), 129.3 (1C), 134.8 (1C), 139.3 (1C), 146.8 (1C), 162.4 (1C), 175.8 (1C); GC-MS (70 eV) (methyl ester) *m/z* (%) 243 (M^+, 44), 184 (100). Anal. Calcd for ($C_{13}H_{11}NO_3 \cdot 0.25H_2O$): C, 66.80; H, 4.96; N, 5.99. Found: C, 66.74; H, 4.92; N, 5.91.

4.1.12. (+)-(*S*)-Phenyl(pyridin-2-yloxy)acetic acid (+)-(*S*)-4f

Yield: 45%; mp 108–109 °C; $[\alpha]_D^{20} = +147$ (*c* 1, MeOH), 98% ee (CZE: pH 5.5). Anal. Calcd for ($C_{13}H_{11}NO_3 \cdot 0.10H_2O$): C, 67.58; H, 4.89; N, 6.06. Found: C, 67.63; H, 4.88; N, 6.03. Spectroscopic data were in agreement with those found for (−)-(*R*)-**4f**.

4.1.13. (−)-(*R*)-2-(3-Nitropyridin-2-yloxy)-2-phenylacetic acid (−)-(*R*)-4g

Yield: 30%; mp 113–114 °C; $[\alpha]_D^{20} = -141$ (*c* 1, MeOH), 98% ee (CZE: pH 5.5), 98% ee (HPLC); IR (KBr): 2922 (OH), 1706 (C=O) cm^{-1}; ^{1}H NMR: δ 6.10 (br s, 1H), 6.35 (s, 1H), 7.13 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.35–7.50 (m, 3H), 7.65–7.75 (m, 2H), 8.35–8.45 (m, 2H); ^{13}C NMR: δ 76.4 (1C), 118.0 (1C), 127.5 (2C), 129.0 (2C), 129.5 (1C), 133.4 (1C), 134.0 (1C), 135.8 (1C), 151.6 (1C), 155.0 (1C), 174.3 (1C); MS (70 eV) (methyl ester) *m/z* (%) 288 (M^+, <1), 124 (100). Anal. Calcd for ($C_{13}H_{10}N_2O_5 \cdot 0.66H_2O$): C, 54.55; H, 3.99; N, 9.79. Found: C, 54.81; H, 3.88; N, 9.45.

4.1.14. (+)-(*S*)-2-(3-Nitropyridin-2-yloxy)-2-phenylacetic acid (+)-(*S*)-4g

Yield: 26%; mp 111–112 °C; $[\alpha]_D^{20} = +142$ (*c* 1, MeOH). Spectroscopic data were in agreement with those found for (−)-(*R*)-**4g**.

4.1.15. (−)-(2*R*)-2-(Pentafluorophenoxy)-2-phenylacetic acid (−)-(*R*)-4h

Yield: 9%; mp 100–101 °C; $[\alpha]_D^{20} = -157$ (*c* 1, MeOH), 96% ee (CZE: pH 5.5); IR (KBr): 3205 (OH), 1745, 1710 (C=O) cm^{-1}; ^{1}H NMR: δ 4.95 (br s, 1H), 5.78 (s, 1H), 7.35–7.45 (m, 3H), 7.45–7.55 (m, 2H); ^{13}C NMR: δ 82.5 (1C), 127.9 (2C), 129.2 (2C), 130.4 (1C), 133.5 (1C), 136.5 (2C), 139.8 (2C), 139.9 (1C), 143.5 (1C), 173.1 (1C); MS (70 eV) (methyl ester) *m/z* (%) 332 (M^+, <1), 149 (100).

4.1.16. (+)-(2*S*)-2-(Pentafluorophenoxy)-2-phenylacetic acid (+)-(*S*)-4h

Yield: 10%; mp 98–99 °C; $[\alpha]_D^{20} = +134$ (*c* 1, MeOH). Spectroscopic data were in agreement with those found for (−)-(*R*)-**4h**.

4.1.17. (*RS*)-*tert*-Butyl [2-(2,6-dimethylphenoxy)-1-methylethyl]-[(*tert*-butoxycarbonyl)oxy]carbamate 16

To a stirred solution of 2-[({[(*tert*-butoxycarbonyl)amino]oxy}-carbonyl)oxy]-2-methylpropane **14** (1.80 g, 7.7 mmol), (*RS*)-1-(2,6-dimethylphenoxy)propan-2-ol **15** (0.92 g, 5.1 mmol), and triphenylphosphine (2.02 g, 7.7 mmol) in dry THF (120 mL), under an argon atmosphere, a solution of DIAD (1.55 g, 7.7 mmol) in dry THF (60 mL) was added dropwise. The mixture was stirred at 0 °C for 2 h. The solvent was then evaporated under reduced pressure, after which Et_2O was added and the precipitate formed was filtered off. The filtrate was evaporated in vacuo and the residue was

purified by flash chromatography (eluent EtOAc/petroleum ether 0.5:9.5) to give 1.73 g of a colorless oil (86%): IR (neat): 1789 (OCOO), 1740 (NHCOO) cm^{-1}; ^1H NMR: δ 1.47 (br s overlapping br s at 1.52, 9H), 1.52 (br s overlapping br s at 1.47, 12H), 2.27 (s, 6H), 3.60–3.75 (m, 1H), 3.75–3.90 (m, 1H), 4.55–4.75 (m, 1H), 7.06 (m, 1H), 6.95–7.05 (m, 2H); MS (70 eV) *m/z* (%) 205 (M^+-190, 4), 57 (100).

4.1.18. (*RS*)-1-(2,6-Dimethylphenoxy)-*N*-hydroxypropan-2-amine trifluoroacetate (*RS*)-7·CF_3COOH

(*RS*)-*tert*-Butyl [2-(2,6-dimethylphenoxy)-1-methylethyl][(*tert*-butoxycarbonyl)oxy]carbamate (*RS*)-**16** (0.80 g, 2.0 mmol) was dissolved, under an argon atmosphere, in a mixture of 98% HCOOH (20 mL) and 99% CF_3COOH (15 mL). The reaction mixture was stirred at 0 °C for 4 h. The solvent was removed under vacuum; the residue was taken up with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give (*RS*)-**7**·CF_3COOH as a slightly yellowish solid, which was recrystallized from iPr_2O/hexane to give 0.36 g (58%) of white crystals: IR ($CHCl_3$): 3232 (OH), 1668 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.34 (br d, J = 5.5 Hz, 3H), 2.22 (s, 6H), 3.60–3.80 (br s, 1H), 3.80–4.00 (m, 2H), 6.95–7.0 (m, 1H), 7.0–7.05 (m, 2H), 11.0 (br s, 1H), 11.3 (br s, 2H). Anal. Calcd for ($C_{13}H_{18}F_3NO_4$): C, 50.48; H, 5.87; N, 4.53. Found: C, 50.78; H, 5.94; N, 4.62.

4.2. Physicochemical data

The pK_a value for compound **7** was obtained by a pH metric technique using a GlpK_a apparatus (Sirius Analytical Instruments Ltd, Forrest Row, East Sussex, UK).[41–44] Due to the low solubility of the compound investigated in aqueous medium, methanol was used as a cosolvent for pK_a measurements. Three separate solutions of a concentration approximately 10^{-5} M, in 10–30% w/w (MeOH/H_2O), were prepared. They were then acidified with 0.5 M HCl to pH 3. The solutions were then titrated with 0.5 M KOH to pH 12. The initial pK_a value, which is the apparent ionization constant relative to the mixture of the solvents, was obtained by Bjerrum Plot, that is, the curve obtained by the difference between the curve of titration of the ionizable substance and that of the blank solution. This value was then optimized by a weighed nonlinear least-squares procedure (Refinement Pro 1.0 software) to obtain a pK_a value in the absence of a cosolvent, by extrapolation using the Yasuda–Shedlovsky equation.[45] All titrations were carried out at 25 ± 0.1 °C under nitrogen gas atmosphere to exclude CO_2.

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