Optically Active Amines. 34.[1] Application of the Benzene Chirality Rule to Ring-Substituted Phenylcarbinamines and Carbinols

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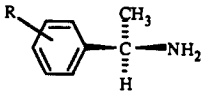
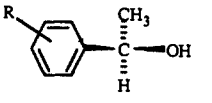
Abstract: The negative sign of the ^1L_b Cotton effects (CEs) from about 250 to 270 nm in the circular dichroism (CD) spectra of (*R*)-α-phenylethylamine and (*R*)-α-phenylethyl alcohol and other phenylalkylcarbinamines and carbinols is determined by vibronic borrowing from allowed transitions at shorter wavelength. On ring substitution, bond transition moments are induced in the benzene ring bonds adjacent to the attachment bond of the chiral group, resulting in enhanced coupling of the ^1L_b transition with the chiral group. A sign reversal for the ^1L_b CEs on para substitution with an atom or group with a positive spectroscopic moment (Cl, CH_3) can be viewed as the overshadowing of the vibronic contribution by an induced contribution of opposite sign. On para substitution with a group with a negative spectroscopic moment (CF_3, CN), the sign of the ^1L_b CEs is unchanged since the vibronic and induced contributions have the same sign. Meta substitution by an atom or group will result in bond moments in an opposite sense from that caused by the same atom or group in the para position. Thus on meta substitution by a group with a positive spectroscopic moment (Cl, CH_3), both the vibronic and induced contributions have the same sign, and the sign of the ^1L_b CEs is the same as that of the unsubstituted parent. For meta substitution by a group with a negative spectroscopic moment (CF_3, CN), the sign of the induced contribution is opposite to that of the vibronic contribution. In the case of CF_3 and CN groups, the latter is more important than the former, and the sign of the ^1L_b CEs is the same as that of the unsubstituted parent. Ortho substitution again reverses the sense of the induced bond transition moments from that induced by the same meta substituents. Thus, provided the position of the substituent and its spectroscopic moment are taken into account the absolute configuration of substituted phenylmethylcarbinamines and carbinols can often be assigned.

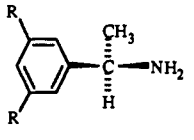
The circular dichroism (CD) spectra of (*R*)-α-phenylethylamine [(*R*)-**1a**] and its hydrochloride and (*R*)-α-phenylethyl alcohol [(*R*)-**2a**] shows a number of negative Cotton effects (CEs) from



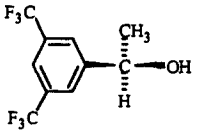
(*R*)-**1a**, R = H
b, R = *p*-Cl
c, R = *p*-CH_3
d, R = *p*-CF_3
e, R = *p*-CN
f, R = *m*-Cl
h, R = *m*-CF_3
i, R = *m*-CN
j, R = *o*-Cl
l, R = *o*-CF_3



(*R*)-**2a**, R = H
b, R = *p*-Cl
c, R = *p*-CH_3
d, R = *p*-CF_3
f, R = *m*-Cl
g, R = *m*-CH_3
h, R = *m*-CF_3
j, R = *o*-Cl
k, R = *o*-CH_3
l, R = *o*-CF_3



(*R*)-**1m**, R = Cl
n, R = CH_3
o, R = CF_3



(*R*)-**2o**

about 255 to 270 nm (Figure 1) associated with transitions of the benzene chromophore from its lowest energy vibrational mode in the ground state to the totally symmetric vibrational modes in the ^1L_b electronically excited state,[1-3] the lowest energy of these being associated with the ^1L_b band origin.[4] Occasionally, additional, weak CD maxima with signs opposite to that of the ^1L_b band origin are observed within the ^1L_b band (Figure 1). These latter maxima are the result of transitions to nontotally symmetric vibrational modes in the electronically excited state.[4] The discussion below, however, is concerned only with CEs associated with transitions to totally symmetric vibrational modes.

Other chiral phenylalkylcarbinamines and their salts and phenylalkylcarbinols of the same generic configuration as (*R*)-**1a** and (*R*)-**2a** in which the alkyl group is in a higher oxidation state or is larger in effective bulk size than is a methyl group also show negative ^1L_b CEs.[5-9] On ring substitution, however, the sign of the ^1L_b CEs may be the same or different from that of the unsubstituted parent.[1,3,9-16] Since a change in sign has been related to the spectroscopic moment[17] and ring position of the additional substituent,[1,9,16] the sign of the ^1L_b may be used to assign the absolute configuration of a chiral center contiguous to a substituted benzene ring provided the position of the substituent and its

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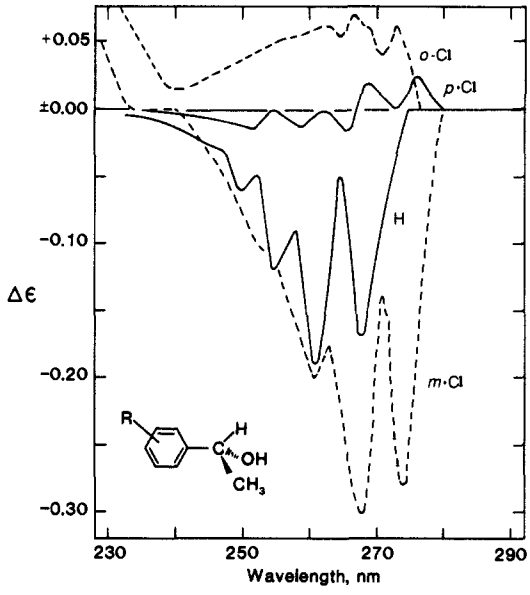


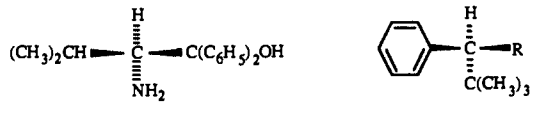
Figure 1. Circular dichroism spectra of (*R*)-α-phenylethyl alcohol [(*R*)-**2a**], (*R*)-α-(*p*-chlorophenyl)ethyl alcohol [(*R*)-**2b**], (*R*)-α-(*m*-chlorophenyl)ethyl alcohol [(*R*)-**2f**], and (*R*)-α-(*o*-chlorophenyl)ethyl alcohol [(*R*)-**2j**]. Data for (*R*)-**2a** and (*R*)-**2b** are from ref 1.

spectroscopic moment are taken into account.

To illustrate the full scope and limitation of this method, we now report the CD of a number of ring-substituted phenylmethylcarbinamines and their hydrochloride salts and phenylmethylcarbinols.

Results and Discussion

Synthesis and Absolute Configurations. The chiral carbinamines and carbinols prepared in connection with this work are shown in Table I together with their respective enantiomeric excess (ee). Most were prepared by asymmetric reduction of the corresponding ring-substituted acetophenone *O*-methyloxime or acetophenone with borane in tetrahydrofuran, using (*S*)-2-amino-3-methyl-1,1-diphenyl-1-butanol [(*S*)-**3**] as the chiral auxillary,[20,21] the latter prepared from L-valine.[20]



Asymmetric reduction of the corresponding *O*-methyloximes gave the chiral amines [(*S*)-**1f,h,l,o**] with the *S* configuration, the same generic configuration as that found on reduction of the *E* isomer of similar oxime ethers, using (-)-morephedrine as the chiral auxillary.[22] Racemic amines (±)-**1i** and (±)-**1j** were prepared by reductive amination of the corresponding acetophenones using respectively ammonia and sodium cyanohydridoborate[23] and the Leuckart reaction.[24] The racemates were resolved by fractional crystallization of their *N*-acetyl-L-leucinate[25] salts.

Table I. Phenylalkylcarbinamines and Phenylalkylcarbinols[a]

compd	name	α^{21-27}_{D},[b] deg	% ee[c]
(*S*)-**1f**	(*S*)-α-(*m*-chlorophenyl)ethylamine	-12.6[d]	80
(*S*)-**1h**	(*S*)-α-(*m*-(trifluoromethyl)phenyl) ethylamine	-12.1[d]	87
(*S*)-**1i**	(*S*)-α-(*m*-cyanophenyl)ethylamine	-18.0[d]	95[e]
(*R*)-**1j**	(*R*)-α-(*o*-chlorophenyl)ethylamine	+55.9	94[e]
(*S*)-**1l**	(*S*)-α-(*o*-(trifluoromethyl)phenyl) ethylamine	-14.9[d]	76
(*S*)-**1o**	(*S*)-α-(3,5-bis(trifluoromethyl)phenyl)-ethylamine	-9.8[d]	71
(*R*)-**2c**	(*R*)-α-(*p*-methylphenyl)ethyl alcohol	+8.5[d]	25[f]
(*R*)-**2f**	(*R*)-α-(*m*-chlorophenyl)ethyl alcohol	+41.2	94
(*R*)-**2g**	(*R*)-α-(*m*-methylphenyl)ethyl alcohol	+10.6[d]	55[g]
(*R*)-**2h**	(*R*)-α-(*m*-(trifluoromethyl)phenyl) ethyl alcohol	+33.9	91
(*R*)-**2j**	(*R*)-α-(*o*-chlorophenyl)ethyl alcohol	+18.5[d]	70
(±)-**2k**	(±)-α-(*o*-methylphenyl)ethyl alcohol	±0.0[d]	0
(*R*)-**2l**	(*R*)-α-(*o*-(trifluoromethyl)phenyl) ethyl alcohol	+8.4[d]	35
(*S*)-**2l**	(*S*)-α-(*o*-(trifluoromethyl)phenyl) ethyl alcohol	-23.3[d]	94[e]
(*R*)-**2o**	(*R*)-α-(3,5-bis(trifluoromethyl)phenyl)-ethyl alcohol	+21[h]	94
(*S*)-**4**	(*S*)-α-phenylneopentyl alcohol	-13.3[i]	49[j]

[a] Prepared by asymmetric syntheses or as noted by resolution. [b] Observed rotation: neat, 1 dm or as noted otherwise. [c] Enantiomer excess determined by the ^{1}H NMR method or as noted otherwise. [d] Length: 0.5 dm. [e] Prepared by resolution. [f] On the basis of the rotatory power given in ref 18, this carbinol would have an ee of 37%. [g] On the basis of the rotatory power given in ref 18, this carbinol would have an ee of 52%. [h] Specific rotation: *c* 1.01 g/100 mL of CH_3OH. [i] Specific rotation: *c* 9.00 g/100 mL of benzene. [j] On the basis of the maximum rotatory power given in ref 19 as 100% ee.

The absolute configurations of the previously unreported amines were established by application of the *N*-salicylidenamino chirality rule[26] to an interpretation of the CD spectra of their *N*-salicylidene derivatives. The latter were formed in situ in methanol, and the *S* configuration was assigned to that enantiomer showing strong positive CEs near 255 and 315 nm.[26]

The asymmetric reduction of the ring-substituted acetophenones with the chiral auxillary (*S*)-**3** invariably gave the *R* configuration, the same configuration as that obtained on reduction of methyl phenyl and *n*-alkyl phenyl ketones with (*S*)-**3**.[20] The effective bulk size of the alkyl group, however, is crucial, and reduction of pivalophenone (*tert*-butyl phenyl ketone) gave (*S*)-α-phenylneopentyl alcohol[8] [(*S*)-**4a**] with an ee of 49%.[19] The nature and position of a ring-substituent on the acetophenone do affect the ee of the resulting carbinol. Reduction of acetophenones with the electron-withdrawing chloro and trifluoromethyl substituents in the meta or 3,5-positions gave carbinols (*R*)-**2f,h,o** with an ee greater than 90%. For these same substituents in the ortho position the ee's of the carbinols (*R*)-**2j,l** were 70 and 35%, respectively. In the case of (*R*)-**2l**, the ee was too low for CD measurements, and the enantiomer [(*S*)-**2l**] was obtained by resolution. Similarily, reduction of *p*- and *m*-methylacetophenone gave the corresponding carbinols (*R*)-**2c** and (*R*)-**2g** with ee of 25 and 55%, respectively, while reduction of *o*-methylacetophenone gave the racemic carbinol [(±)-**2k**].

Enantiomers of the methyl-substituted α-phenylethyl alcohols (**R**)-**2c,g,k** were previously reported,[27] and their ee's and absolute configurations were assigned earlier.[18,27,28] The absolute configurations of the chloro-substituted alcohols (*R*)-**2f,j** were established by their conversion on catalytic hydrogenolysis to the deschloro analogue (*R*)-**2a**, while the absolute configurations of the trifluoromethyl-substituted carbinols (*R*)-**2h**, (*R*)-**2o**, and (*S*)-**2l** were assigned by comparison of the CD spectra of their

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Table II. Spectral Data for Phenylmethylcarbinamines and Phenylmethylcarbinols in Methanol

		^1L_b band origin			
		carbinamines [(*R*)-**1**]		carbinols [(*R*)-**2**]	
code	subst	EA λ_{max}, nm (ϵ^a)	CD λ_{max}, nm ($\Delta\epsilon^b \times 10^2$)	EA λ_{max}, nm (ϵ^a)	CD λ_{max}, nm ($\Delta\epsilon^b \times 10^2$)
		No Additional Substituent			
a		267 (86)[c]	268 (−11)[c,d]	267 (90)[e]	268 (−17)[e]
		Para Substituted			
b	Cl	276 (240)[c]	276 (+6.1)[c]	275 (240)[e]	276 (+2.5)[d,e]
c	CH_3	273 (310)[c]	273 (+2.7)[c,d]		
d	CF_3	268 (240)[c]	269 (−18)[c,d]	269 (280)[e]	268 (−12)[d,e]
e	CN	279 (380)[f]	279 (−11)[d,f]		
		Meta Substituted			
f	Cl	274 (200)	274 (−24)[d]	274 (200)	274 (−28)
h	CF_3	271 (550)	271 (−11)[d]	270 (600)	271 (−15)
i	CN	282 (1000)	282 (−8.5)[d]		
		Ortho Substituted			
j	Cl	273 (160)	273 (+5.8)	273 (160)	273 (+6.7)
k	CH_3			270 (150)[g]	273 (+4.0)[g]
l	CF_3	271 (950)	270 (−25)[d]	271 (940)	270 (−13)[d]
		3,5-Disubstituted			
m	Cl	278 (140)[c]	280 (−36)[c,d]		
n	CH_3	274 (170)[c]	275 (−26)[c]		
o	CF_3	272 (320)	271 (−7.6)[d]	272 (580)	273 (−15)

[a] Molar absorptivity. [b] Molar dichroic absorption adjusted to 100% ee. $\Delta\epsilon = [\theta]/3300$ where $[\theta]$ is the molecular ellipticity. [c] Data from ref 16. [d] Enantiomer used. [e] Data from ref 1. [f] Data from ref 14. [g] Data from ref 15; solvent not specified.

p-nitrobenzoyl derivatives with those of (*R*)-**2a,b,f,j**. For these derivatives the *R* configuration is assigned to those enantiomers showing a negative CE near 260 nm.[29]

It should be noted that all of these carbinols and carbinamines in Table I, and the others listed only in Table II, with the *R* configuration, ring-substituted or not, are dextrorotatory as the neat liquid or in a solvent with sodium D light. Thus they all obey Brewster's rules of atomic asymmetry,[30] the sequence of polarizability being OH, $NH_2 > C_6H_5 > CH_3 > H$.[31]

As a whole, the asymmetric reduction of the *O*-methyloximes was less satisfactory than the reduction of the ketones. The latter required only a catalytic amount of the chiral auxillary,[21] while the former needed an equimolar amount of the auxillary and a longer reaction time. In comparison to the corresponding ketone, the reduction of the oxime also gave a product with a lower ee, and its isolation often required a more extensive purification procedure.

The enantiomeric excesses shown in Table I for the previously unreported carbinamines and carbinols were established by the proton nuclear magnetic resonance method of Jacobus, Raban, and Mislow,[32] using the diastereomeric amides and esters prepared from (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[33] and the respective amines and alcohols.

Interpretation of Circular Dichroism Spectra. The molar absorptivites (ε) and molar dichroic absorptions (Δε) are shown in Table II for the ^1L_b band origins for the (*R*)-phenylmethylcarbinamines and (*R*)-phenylmethylcarbinols, regardless of the absolute configurations of the amines and alcohols actually used. Complete electronic absorption (EA) and CD data have been reported elsewhere for some of the amines and their hydrochlorides and some of the carbinols. For the others, complete EA and CD data are given in the Experimental Section.

Table III. Rotational Contributions to the ^1L_b Cotton Effects of Ring-Substituted Phenylalkylcarbinamines and Phenylalkylcarbinols of the Same Generic Absolute Configuration as (*R*)-α-Phenylethylamine and (*R*)-α-Phenylethyl Alcohol

	substituent		
contribution[a]	para	meta[b]	ortho
No Additional Ring Substituent			
vibronic	−	−	−
induced	0	0	0
Substitution by a Group with a Positive Spectroscopic Moment[c]			
vibronic	−	−	−
induced	+	−	+
Substitution by a Group with a Negative Spectroscopic Moment[c]			
vibronic	−	−	−
induced	−	+	−

[a] For the enantiomers the respective signs for the contributions are reversed. [b] The signs are the same for the 3,5-disubstituted compounds. [c] See ref 17 for spectroscopic moments.

For the EA spectra, Sklar has shown that the intensity of the forbidden ^1L_b (B_{2u}) transition can be divided into two parts.[34] One part is attributed to vibronic borrowing from nearby transitions at shorter wavelength. The second part of the intensity is attributed by Sklar to a migration moment (spectroscopic moment) induced in the ring by a substituent on the ring that destroys its symmetry.[34]

In a similar way, the CD spectra associated with the ^1L_b transition may be divided into two parts, a vibronic borrowing contribution and an induced contribution. Earlier work indicates that the sign and magnitude of the ^1L_b CEs of phenylalkylcarbinamines[9,16] and -carbinols[1] without additional ring substituents are determined by vibronic borrowing[35,36] from transitions at shorter wavelengths. Thus both (*R*)-**1a** and (*R*)-**2a** show negative ^1L_b CEs (Table II). On para substitution by a group with either a positive or a negative spectroscopic moment,[17] electric transition moments are induced in the ring bonds adjacent to the attachment bond of the chiral group,[37,38] resulting in enhanced coupling of the ^1L_b transition with the chiral group. The reversal of the sign of the ^1L_b CEs on para substitution of (*R*)-**1a** and (*R*)-**2a** by a group with a positive spectroscopic moment[17] (Cl and CH_3) (Figure 1) thus can be viewed as the overshadowing of the negative vibronic rotational strength by the positive induced contribution, and (*R*)-**1b**, (*R*)-**1c**, and (*R*)-**2b** have positive ^1L_b CEs. On para substitution by a group with a negative spectroscopic moment[17] (CF_3 and CN), bond moments of an opposite sense are induced, and the negative induced contribution to the ^1L_b rotational strength has the same sign as the vibronic contribution. Thus (*R*)-**1d**, (*R*)-**1e**, and (*R*)-**2d** have negative ^1L_b CEs, the same sign as those for (*R*)-**1a** and (*R*)-**2a**.

Meta substitution by an atom or group will result in bond moments in an opposite sense from that caused by the same group in the para position.[1,38,39] Thus on meta substitution by a chlorine atom on (*R*)-**1a** and (*R*)-**2a**, both the vibronic and induced contributions to the ^1L_b CEs are negative, and as predicted (*R*)-**1f** and (*R*)-**2f** show strong negative ^1L_b CEs (Figure 1). For meta substitution by a group with a negative spectroscopic moment (CF_3 and CN), the induced contribution is of opposite sign to that of the vibronic contribution, but the sign of the ^1L_b CEs of (*R*)-**1h**, (*R*)-**1i**, and (*R*)-**2h** is unchanged from that of (*R*)-**1a** and (*R*)-**2a**. Similar ^1L_b CEs are observed when two groups are meta (3,5-disubsituted) to the chiral group. For (*R*)-**1m** and (*R*)-**1n**, both the vibronic and induced contributions are negative, and the ^1L_b CEs are negative. Both (*R*)-**1o** and (*R*)-**2o** also show negative ^1L_b CEs although the induced contribution is positive.

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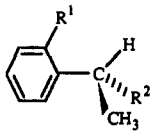
Ortho substitution again reverses the sense of the induced bond moments[1,38,39] from that induced by the same meta substituent. Thus the sign of the ^1L_b CEs of the *o*-chloro-substituted carbinamine (*R*)-**1j** and the *o*-chloro- and *o*-methyl-substituted carbinols (*R*)-**2j** and (*R*)-**2k** have the same sign as the para-substituted isomer (Figure 1), the induced contribution being more important than the vibronic contribution. Both (*R*)-**1l** and (*R*)-**2l** show, as predicted, strong negative ^1L_b CEs, both the vibronic and induced contributions being negative.

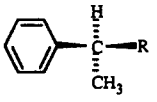
A summary of the respective rotational contributions to the ^1L_b CEs for chiral phenylalkylcarbinamines and their salts and phenylalkylcarbinols is given in Table III. This table applies to all phenylalkylcarbinamines and phenylalkylcarbinols without and with an additional ring substituent of the same generic configuration as (*R*)-**1a** and (*R*)-**2a**. Since in the preferred conformation



Ia, $R^1 = H$; $R^2 = NH_2$

b, $R^1 = H$; $R^2 = OH$

c, $R^1 = CH_3$; $R^2 = OH$



(*S*)-**5a**, R = $N(CH_3)_2$

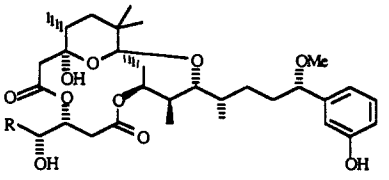
b, R = OCH_3

c, R = $N(CH_3)_3I$

of (*R*)-**1a** and (*R*)-**2a** (Ia and Ib) the hydrogen atom at the chiral center nearly eclipses the phenyl ring plane,[15] a change in the effective bulk size of the alkyl group or the amino group or the change of the hydroxyl group to an alkoxyl group is also predicted to result in a preferred conformation in which the hydrogen atom at the chiral center nearly eclipses the benzene ring plane.[40-47] Thus (*S*)-α-phenylneopentylamine[9] [(*S*)-**4b**], (*S*)-*N*,*N*-dimethyl-α-phenylethylamine[48] [(*S*)-**5a**], (*S*)-α-phenylneopentyl alcohol[8] [(*S*)-**4a**], and (*S*)-1-methoxy-1-phenylethane[49] [(*S*)-**5b**] all show positive ^1L_b CEs. The respective hydrochloride salts of phenylalkylcarbinamines, including (*S*)-*N*,*N*,*N*-trimethyl-α-phenylethylammonium iodide[48] [(*S*)-**5c**], also show ^1L_b CEs of the same sign as the corresponding amines.[9,14,16]

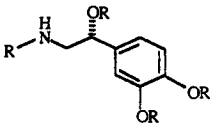
Empirical potential function calculations favor a preferred conformation Ic for (*R*)-α-(*o*-methylphenyl)ethyl alcohol [(*R*)-**2k**] in which the hydrogen atom at the chiral center eclipses the benzene ring plane and is proximal to the *o*-methyl group.[15] Thus ring substitution of a phenylalkylcarbinamine, its salt, or a phenylalkylcarbinol is also not expected to alter greatly the preferred conformation from that in which the hydrogen atom at the chiral center nearly eclipses the benzene ring plane.[40,44,46] Any change in the sign of the ^1L_b CEs from that of the unsubstituted parent as the result of benzene ring substitution by an atom or group similar to those in Table II is primarily the result of the interplay of the vibronic and induced contribution to the ^1L_b CEs and not due to change in the conformational equilibrium from that of the parent phenylalkylcarbinamine or phenylalkylcarbinol.

If the vibronic and induced contributions have the same sign, the sign of the ^1L_b CEs for a particular ring-substituted phenylalkylcarbinamine or -carbinol can be predicted with certainty. Thus, the chiral center contiguous to the benzene ring in oscillatoxin A (**6a**) and debromoaplysiatoxin (**6b**), both **6a** and **6b** showing positive ^1L_b CEs, can be confirmed as having the *S* configuration.[50] This configurational assignment was originally made on the unjustified assumption that the ^1L_b CEs of **6a** and **6b**, with the same generic configuration as (-)-noradrenaline



6a, R = H

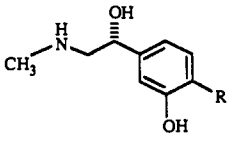
b, R = CH_3



(*R*)-**7a**, R = H

b, R = CH_3

hydrochloride [(*R*)-**7a**·HCl] and (*R*)-calipamine hydrochloride [(*R*)-**7b**·HCl], would have the same sign as the ^1L_b CEs of (*R*)-**7a**·HCl and (*R*)-**7b**·HCl. Since the spectroscopic moment of a hydroxyl group is positive,[17] both the vibronic and induced contributions to the ^1L_b CEs are positive (Table III) for the configuration shown for **6a** and **6b**. The *S* absolute configuration can thus be unambiguously assigned to the carbinol chiral center in **6a** and **6b**. Likewise, the levorotatory isomers of phenylephrine (**8a**) and its hydrochloride (**8**·HCl) were also assigned the *R* absolute configuration because of the similarity of their ORD curves to that of (-)-adrenaline hydrochloride [(*R*)-**8b**·HCl].[51] Using the benzene chirality rule, both (*R*)-**8a** and (*R*)-**8a**·HCl are predicted to show positive ^1L_b CEs.



(*R*)-**8a**, R = H

b, R = OH

When the vibronic and induced contributions to the ^1L_b CEs are of opposite sign (Table III), a prediction as to the sign of the ^1L_b CEs shown by a particular enantiomer is ambiguous. However, all of the phenylalkylcarbinamines and carbinols so far reported that are para or ortho substituted with an atom or group with a positive spectroscopic moment[17] (CH_3, F, Cl, Br, OH, and OCH_3) show ^1L_b CEs of opposite sign to that of the unsubstituted parent.[1,3,9-16] For the few phenylalkylcarbinamines and -carbinols with a group with a negative spectroscopic moment[17] (CN and CF_3) in the meta position (Table I), the sign of the ^1L_b CEs is not changed from that of the unsubstituted parent.

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Boiling points are uncorrected. Rotatory powers at the sodium D line were measured with an Autopol III automatic polarimeter and a 1-dm sample tube or as otherwise noted. Proton magnetic resonance (^1H NMR) spectra were obtained in chloroform-*d* with tetramethylsilane as an internal standard on a JEOL JNM-FX 90Q or Bruker AM-200, AM-300, or AM-400 spectrometer, and all compounds had ^1H NMR spectra consistent with their assigned structures. The gas chromatography (GC) was done with a Shimadzu mini-2 GC fitted with a Supelco 60-m VOCOL glass capillary column (0.75-mm ID) operating at a column temperature of 185 °C with helium as the carrier gas and 3 mL/s flow rate. Electronic absorption (EA) spectra were measured with a Cary Model 14 spectrophotometer with matched 1-cm cells and the normal variable slit. Circular dichroism (CD) spectra were obtained at 25-28 °C with a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory. The sample cell was 1 cm and the slit was

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Table IV. Circular Dichroism Data of the *N*-Salicylidene Derivatives of Ring-Substituted Phenylmethylcarbinamines

amine	*N*-salicylidene derivative substituent	spectrum,[a] λ_{max}, nm ([θ][b]) band I	band II
(*S*)-**1f**	*m*-Cl	317 (+18 000)	253 (+31 000)
(*S*)-**1h**	*m*-CF_3	315 (+19 000)	253 (+31 000)
(*S*)-**1i**	*m*-CN	317 (+22 000)	253 (+38 000)
(*R*)-**1j**	*o*-Cl	317 (−12 000)	254 (−36 000)
(*S*)-**1l**	*o*-CF_3	315 (+20 000)	265 (+25 000)[c]
(*S*)-**1o**	3,5-$(CF_3)_2$	318 (+18 000)	252 (+33 000)

[a] Derivatives formed in situ in methanol with $c = 1.23 \times 10^{-3}$ to 2.32×10^{-3} g/100 mL for the *N*-salicylidene derivative. [b] Molecular ellipticity adjusted to 100% ee. [c] CEs also at 272 nm ([θ] +25 000) and 249 nm ([θ] +18 000).

programmed for a spectral band width of 1.5 nm. Cutoff was indicated when the dynode voltage reached 400 V. Circular dichroism measurements began at 300 nm and the molecular ellipticities ([θ]) have been corrected to 100% enantiomeric excess (ee) for the chiral amines, alcohol, amine hydrochlorides, and *N*-salicylidene derivatives of the amines.

The EA and CD of the amine hydrochlorides were obtained by formation of the salt by addition of 2 drops of concentrated hydrochloric acid to a solution of the amine in 10 mL of methanol. Concentrations given with the CD spectra are for grams of amine per 100 mL of methanol.

The *N*-salicylidene derivatives of the enantiomeric amines were formed in situ[52] by warming the amines (ca 0.1 mmol) with about 25% molar excess of salicylaldehyde in methanol (10 mL) for 10 min. The molecular ellipticities [(θ)] for bands I and II at 315 and 255 nm, respectively, are shown in Table IV. The *p*-nitrobenzoyl derivatives of the enantiomeric alcohols were prepared and isolated as previously described,[29] and the physical and spectral properties of the derivatives are shown in Table V.

The percent enantiomeric excess of the chiral amines and alcohols was determined by ^{1}H NMR of the respective (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid[33] derivative. The doublet due to the α-methyl group of the amine or alcohol moiety at 1.4–1.7 ppm of the amide or ester was the absorption used for comparison.

Preparation of Substituted Acetophenone *O*-Methyloximes. Ethanol was added to a mixture of the substituted acetophenone (0.10 mol), methoxylamine hydrochloride (9.2 g, 0.11 mol), and sodium acetate hydrate (11.0 g, 0.11 mol) in 100 mL of water until the solution became clear. The mixture was boiled for about 20 h and then extracted with ether (3 × 50 mL). The ether solution was washed with 5% $NaHCO_3$ (30 mL), dried ($MgSO_4$), and evaporated. Distillation of the residue gave the oxime ether in 60–80% yield.

Asymmetric reduction of the *O*-methyloximes was done according to the procedure of Itsuno.[20] This reduction yielded an amine containing about 5% of an impurity, which from the ^{1}H NMR of the product appeared to be the corresponding *N*-methoxyamine. The amine was separated from the impurity by partitioning the crude reaction product between 0.001 N HCl and ether (5–6×) in a countercurrent extraction. The combined aqueous fractions were made basic and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated, and the resulting oil was distilled to give the pure amine.

Asymmetric Reduction of Substituted Acetophenones. Borane (35 mmol) in tetrahydrofuran (35 mL) was added to a stirred solution of the chiral auxiliary, (*S*)-2-amino-3-methyl-1,1-diphenyl-1-butanol[20] [(*S*)-**3**; 0.82 g, 3.2 mmol] in tetrahydrofuran (50 mL) under nitrogen at 0 °C, and the solution was allowed to gradually warm to room temperature and then stirred for an additional 3–4 h. The substituted acetophenone (0.032 mol) was dissolved in tetrahydrofuran (20 mL) and added slowly (1–2 mL/min) to the reaction mixture. Ten to fifteen minutes after the addition of the ketone, the reaction was quenched by pouring the solution into ice (100 g) and 6 N hydrochloric acid (50 mL). The tetrahydrofuran was allowed to evaporate (~24 h), and the mixture was extracted with ether (2 × 50 mL). The aqueous layer was retained for recovery of (*S*)-**3**·HCl. The ether solution was washed with 5% $NaHCO_3$ (20 mL), dried ($MgSO_4$), and evaporated. The resulting oil was distilled to give the pure alcohol.

(*S*)-α-(*m*-Chlorophenyl)ethylamine [(*S*)-1f]. The *O*-methyloxime of *m*-chloroacetophenone had bp 126–128 °C (15 mmHg); ^{1}H NMR (90 MHz) δ 2.19 (s, 3 H, CH_3), 4.00 (s, 3 H, OCH_3), 7.25–7.66 ppm (m, 4 H, Ar). Asymmetric reduction of this oxime gave (*S*)-**1f**: bp 116–118 °C (18 mmHg); α^{21}_D −12.6° (neat, 0.5 dm), 80% ee; ^{1}H NMR (300 MHz) δ 1.37 (d, 3 H, *J* = 6.5 Hz, CH_3), 1.56 (s, 2 H, NH_2), 4.10 (q, 1 H, *J* = 6.6 Hz, CH), 7.24 (m, 3 H, Ar), 7.36 ppm (d, 1 H, *J* = 1.6 Hz, Ar); EA max (CH_3OH) 274 nm (ε 200), 267 (260), 260 (210), 254 (150), 248 (90); CD (CH_3OH, *c* 0.0680) $[\theta]_{280}$ ±0, $[\theta]_{274}$ +790, $[\theta]_{272}$ +400, $[\theta]_{267}$ +860, $[\theta]_{264}$ +475, $[\theta]_{260}$ +570, $[\theta]_{255}$ + 300 (sh), $[\theta]_{240}$ ±0, $[\theta]_{233}$ −340; EA max (CH_3OH–HCl) 274 nm (ε 280), 267 (330), 260 (250), 255 (170), 249 (110); CD (CH_3OH–HCl, *c* 0.0680) $[\theta]_{280}$ ±0, $[\theta]_{274}$ +490, $[\theta]_{271}$ +240, $[\theta]_{267}$ +490 $[\theta]_{263}$ +280, $[\theta]_{260}$ +310, $[\theta]_{238}$ ±0, $[\theta]_{228}$ −90.

(*S*)-α-(*m*-(Trifluoromethyl)phenyl)ethylamine [(*S*)-1h]. The *O*-methyloxime of *m*-(trifluoromethyl)acetophenone had bp 86–88 °C (10 mmHg); ^{1}H NMR (90 MHz) δ 2.24 (s, 3 H, CH_3), 4.02 (s, 3 H, OCH_3), 7.46–7.92 ppm (m, 4 H, Ar). Asymmetric reduction of this oxime gave (*S*)-**1h** (19%): bp 88–92 °C (22 mmHg); α^{27}_D −12.1° (neat, 0.5 dm), 87% ee; ^{1}H NMR (90 MHz) δ 1.40 (d, 3 H, *J* = 7.0 Hz, CH_3), 1.58 (s, 2 H, NH_2), 4.20 (q, 3 H, *J* = 7.0 Hz, CH), 7.48 (m, 3 H, Ar), 7.62 ppm (s, 1 H, Ar); EA max (CH_3OH) 271 nm (ε 550), 263 (630), 258 (480), 252 (290); CD (CH_3OH, *c* 0.0492) $[\theta]_{278}$ ±0, $[\theta]_{271}$ +370, $[\theta]_{267}$ +240, $[\theta]_{263}$ +390, $[\theta]_{258}$ +260 (sh), $[\theta]_{251}$ +120 (sh), $[\theta]_{245}$ ±0, $[\theta]_{235}$ −230; EA max (CH_3OH–HCl) 269 nm (ε 420), 262 (480), 257 (360), 250 (220), 245 (120); CD (CH_3OH–HCl, *c* 0.0492) $[\theta]_{274}$ ±0, $[\theta]_{269}$ +190, $[\theta]_{266}$ +110, $[\theta]_{262}$ +210, $[\theta]_{258}$ +140, $[\theta]_{256}$ +180, $[\theta]_{239}$ ±0, $[\theta]_{220}$ −320.

(±)-α-(*m*-Cyanophenyl)ethylamine [(±)-1i]. Sodium cyanohydridoborate (2.9 g, 0.046 mol), *m*-acetylbenzonitrile (9.4 g, 0.065 mol), ammonium acetate (40 g, 0.52 mol), and ammonium chloride (10 g, 0.19 mol) were dissolved in methanol (150 mL) and enough glacial acetic acid was added (~10 mL) to adjust the pH to 6.0. The reaction was stirred at 40 °C for 48 h and then quenched by adjusting the pH to <2.0. The methanol was evaporated and the mixture was made basic with 3 N sodium hydroxide (pH >10) and then extracted with ether (3 × 50 mL). The ether was dried ($MgSO_4$) and then evaporated to give an oil that was distilled to give (±)-**1i** (1.38 g, 15%): bp 72–80 °C (0.2 mmHg). This synthesis was aso accomplished with the Leuckart reaction,[24] but it gave equally poor yields.

(*S*)-α-(*m*-Cyanophenyl)ethylamine [(*S*)-1i]. *N*-Acetyl-L-leucine (3.1 g, 0.018 mol) and (±)-**1i** (2.6 g, 0.018 mol) were dissolved in hot ethanol (125 mL). On cooling, a solid precipitated which was recrystallized (3×) from ethanol to give the pure salt (1.5 g, 53%): $[\alpha]^{26}_D$ −14° (*c* 1.0, CH_3OH). The salt was decomposed in 3 N sodium hydroxide (20 mL), and the amine was extracted into ether (2 × 30 mL). The ether was dried ($MgSO_4$) and evaporated, and the residue was distilled to give (*S*)-**1i** (0.23 g, 18%): α^{26}_D −18.0° (neat, 0.5 dm), 95% ee; ^{1}H NMR (90 MHz) δ 1.38 (d, 3 H, *J* = 6.6 Hz, CH_3), 1.70 (s, 2 H, NH_2), 4.18 (q, 1 H, *J* = 6.6 Hz, CH), 7.40–7.58 ppm (m, 3 H, Ar), 7.68 (s, 1 H, Ar); EA max (CH_3OH) 282 nm (ε 1000), 274 (1080), 268 (790); CD (CH_3OH, *c* 0.0185) $[\theta]_{286}$ ±0, $[\theta]_{282}$ +280, $[\theta]_{278}$ +220, $[\theta]_{272}$ +320, $[\theta]_{269}$ +180, $[\theta]_{266}$ +220, $[\theta]_{255}$ ±0, $[\theta]_{245}$ −680; EA max (CH_3OH–HCl) 280 nm (ε 1000), 273 (1100), 267 (790), 259 (560); CD (CH_3OH–HCl, *c* 0.0370) $[\theta]_{284}$ ±0, $[\theta]_{280}$ +330, $[\theta]_{276}$ +190, $[\theta]_{272}$ +360, $[\theta]_{268}$ +250, $[\theta]_{265}$ +270, $[\theta]_{257}$ +170 (sh), $[\theta]_{240}$ ±0, $[\theta]_{239}$ −120.

(*R*)-α-(*o*-Chlorophenyl)ethylamine [(*R*)-1j]. Racemic **1j** was prepared (55%) from *o*-chloroacetophenone with use of a variation of the Leuckart reaction[24] and had bp 117–120 °C (23 mmHg). Racemic **1j** (25.0 g, 0.161 mol) and *N*-acetyl-L-leucine (27.8 g, 0.161 mol) were mixed in hot water (250 mL), and the solution was heated to boiling. Cooling overnight gave a precipitate, and recrystallization of this solid (3×) from water gave the pure salt (7.5 g, 28%): $[\alpha]^{25}_D$ +8.5° (*c* 1.0, 10 mL of CH_3OH w/2 drops 20% KOH). Decomposition of the salt gave (*R*)-**1j** as an oil: bp 115–116 °C (22 mmHg); α^{26}_D +55.9° (neat), 94% ee; ^{1}H NMR (200 MHz) δ 1.36 (d, 3 H, *J* = 6.6 Hz, CH_3), 1.53 (s, 2 H, NH_2), 4.52 (q, 1 H, *J* = 6.6 Hz, CH), 7.13–7.33 (m, 3 H, Ar), 7.50 ppm (dd, 1 H, *J* = 7.7 and 1.6 Hz, Ar); EA max (CH_3OH) 273 nm (ε 160), 265 (210), 263 (200), 259 (180); CD (CH_3OH, *c* 0.0576) $[\theta]_{277}$ ±0, $[\theta]_{273}$ +190, $[\theta]_{269}$ +150, $[\theta]_{265}$ +170, $[\theta]_{258}$ +150 (sh), $[\theta]_{236}$ ±0, $[\theta]_{231}$ −300; EA max (CH_3OH–HCl) 274 nm (ε 220), 267 (280), 262 (230); CD (CH_3OH–HCl, *c* 0.0660) $[\theta]_{281}$ ±0, $[\theta]_{277}$ −70,[53] $[\theta]_{275}$ ±0, $[\theta]_{273}$ +180, $[\theta]_{268}$ +40, $[\theta]_{266}$ +180, $[\theta]_{262}$ +95, $[\theta]_{258}$ +130, $[\theta]_{253}$ +60 (sh), $[\theta]_{244}$ ±0, $[\theta]_{228}$ −110.

(*S*)-α-(*o*-(Trifluoromethyl)phenyl)ethylamine [(*S*)-1l]. The *O*-methyloxime of *o*-(trifluoromethyl)acetophenone had bp 100–102 °C (20 mmHg); ^{1}H NMR (200 MHz) δ 2.18 (s, 3 H, CH_3), 3.97 (s, 3 H, OCH_3), 7.36–7.69 ppm (m, 4 H, ArH). Asymmetric reduction of this oxime gave (*S*)-**1l** (16%): bp 85–87 °C (23 mmHg); α^{27}_D −14.9° (neat, 0.5 dm), 76% ee; ^{1}H NMR (400 MHz) δ 1.39 (d, 3 H, *J* = 6.5 Hz, CH_3), 1.54 (s, 2 H, NH_2), 4.57 (q, 1 H, *J* = 6.4 Hz, CH), 7.32 (t, 1 H, *J* = 7.6 Hz, Ar), 7.57 (m, 2 H, Ar), 7.77 ppm (d, 1 H, *J* = 7.8 Hz, Ar); EA

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(53) This negative maximum is assumed not to be associated with the ^1L_b band origin of the preferred conformer.

Table V. Physical Properties of *p*-Nitrobenzoate Derivatives of Ring-Substituted Phenylmethylcarbinols

		p-nitrobenzoate derivative			
				spectra,[a] λ_{max}, nm (ϵ or $[\theta]^b$)	
carbinol	substituent	mp,[c] °C	$[\alpha]^{21-26}_D$,[d] deg	EA	CD
(*R*)-**2f**	*m*-Cl	44–45	−71	261 (15 000)	263 (−7 700)
(*R*)-**2h**	*m*-CF_3	56–57	−58	258 (15 000)	263 (−11 000)
(*R*)-**2j**	*o*-Cl	99–100	−64	258 (14 000)	256 (−6 800)[e]
(*S*)-**2l**	*o*-CF_3	127–128	+70	263 (16 000)	265 (+17 000)[e]
(*R*)-**2o**	3,5-$(CF_3)_2$	90–91	−64	258 (15 000)	260 (−14 000)

[a] Methanol as solvent. [b] Molecular ellipticity with $c = 2.40 \times 10^{-3}$ to 3.18×10^{-3} g/100 mL. [c] Recrystallized from ethanol. [d] c = 0.95–1.10 g/100 mL in methanol. [e] Center CE of multiple CEs of the same sign from 280 to 250 nm.

max (CH_3OH) 271 nm (ϵ 950), 264 (1060), 259 (760); CD (CH_3OH, c 0.0210) $[\theta]_{280}$ ±0, $[\theta]_{270}$ +830, $[\theta]_{267}$ +780, $[\theta]_{264}$ +970, $[\theta]_{259}$ +710 (sh), $[\theta]_{240}$ ±0, $[\theta]_{224}$ +1100; EA max (CH_3OH–HCl) 269 nm (ϵ 680), 263 (730), 258 (560), 250 (350); CD (CH_3OH–HCl, c 0.0420) $[\theta]_{273}$ ±0, $[\theta]_{269}$ +340, $[\theta]_{266}$ +210, $[\theta]_{262}$ +340, $[\theta]_{258}$ +240 (sh), $[\theta]_{249}$ +130 (sh), $[\theta]_{240}$ ±0, $[\theta]_{223}$ −80.

(*S*)-α-(3,5-Bis(trifluoromethyl)phenyl)ethylamine [(*S*)-1o]. The *O*-methyloxime of 3,5-bis(trifluoromethyl)acetophenone had bp 101–103 °C (21 mmHg); ^{1}H NMR (90 MHz) δ 2.26 (s, 3 H, CH_3), 4.05 (s, 3 H, OCH_3), 7.86 (s, 1 H, Ar), 8.11 ppm (s, 2 H, Ar). Asymmetric reduction of this oxime gave (*S*)-**1o** (15%): bp 90–93 °C (23 mmHg); α^{27}_D −9.8° (neat, 0.5 dm), 71% ee; ^{1}H NMR (90 MHz) δ 1.42 (d, 3 H, J = 6.6 Hz, CH_3), 1.57 (s, 2 H, NH_2), 4.30 (q, 1 H, J = 6.6 Hz, CH), 7.76 (s, 1 H, Ar), 7.85 ppm (s, 2 H, Ar); EA max (CH_3OH) 272 nm (ϵ 320), 265 (360), 258 (280), 250 (170); CD (CH_3OH, c 0.0642) $[\theta]_{281}$ ±0, $[\theta]_{277}$ −70,[53] $[\theta]_{275}$ ±0, $[\theta]_{271}$ +250, $[\theta]_{268}$ +110, $[\theta]_{264}$ +270, $[\theta]_{260}$ +200, $[\theta]_{258}$ +220, $[\theta]_{251}$ +120 (sh), $[\theta]_{245}$ ±0, $[\theta]_{235}$ −580; EA max (CH_3OH–HCl) 270 (180), 263 (220), 257 (170), 250 (120); CD (CH_3OH–HCl, c 0.128) $[\theta]_{278}$ ±0, $[\theta]_{270}$ +220, $[\theta]_{266}$ +170, $[\theta]_{263}$ +260, $[\theta]_{257}$ +220 (sh), $[\theta]_{250}$ +130 (sh), $[\theta]_{245}$ ±0, $[\theta]_{235}$ −230.

(*R*)-α-(*p*-Methylphenyl)ethyl Alcohol [(*R*)-2c]. Asymmetric reduction of *p*-methylacetophenone gave (*R*)-**2c** (59%): bp 100–104 °C (15 mmHg); $[\alpha]^{21}_D$ +16° (c 1.00, CH_3OH); α^{20}_D +8.5° (neat, 0.5 dm), 25% ee [lit.[18] α^{25}_D +4.24° (neat, 1 cm), 92% ee]; ^{1}H NMR (90 MHz) δ 1.48 (d, 3 H, J = 6.6 Hz, $CHCH_3$), 1.79 (s, 1 H, OH), 2.34 (s, 3 H, CH_3), 4.86 (q, 1 H, J = 6.6 Hz, CH) 7.20 ppm (dd, 4 H, J = 8.1 and 12.3 Hz, Ar).

(*R*)-α-(*m*-Chlorophenyl)ethyl Alcohol [(*R*)-2f]. Asymmetric reduction of *m*-chloroacetophenone gave (*R*)-**2f** (74%): bp 122–124 °C (14 mmHg); α^{24}_D +41.2° (neat), 94% ee; ^{1}H NMR (90 MHz) δ 1.47 (d, 3 H, J = 6.6 Hz, CH_3), 1.99 (s, 1 H, OH), 4.85 (q, 1 H, J = 6.6 Hz, CH), 7.25 (m, 3 H, Ar), 7.36 ppm (s, 1 H, Ar); EA max (CH_3OH) 274 nm (ϵ 200), 267 (260), 260 (200), 253 (150), 247 (110); CD (CH_3OH, c 0.0326) $[\theta]_{280}$ ±0, $[\theta]_{274}$ −940, $[\theta]_{271}$ −450, $[\theta]_{268}$ −1000, $[\theta]_{263}$ −550, $[\theta]_{261}$ −620, $[\theta]_{254}$ −290 (sh), $[\theta]_{240}$ ±0, $[\theta]_{234}$ ±0, $[\theta]_{229}$ +170.

(*R*)-α-(*m*-Methylphenyl)ethyl Alcohol [(*R*)-2g]. Asymmetric reduction of *m*-methylacetophenone gave (*R*)-**2g** (61%): bp 100–103 °C (14 mmHg); $[\alpha]^{22}_D$ +23.4° (c 1.00, CH_3OH): α^{20}_D +10.6° (neat, 0.5 dm), 55% ee [lit.[18] α^{25}_D −2.27 (neat, 1 cm) for the enantiomer, 56% ee]; ^{1}H NMR (90 mHz) δ 1.48 (d, 3 H, J = 6.2 Hz, $CHCH_3$) 1.86 (s, 1 H, OH), 2.36 (s, 3 H, CH_3), 4.85 (q, 1 H, J = 6.6 Hz, CH), 7.03–7.25 ppm (m, 4 H, Ar).

(*R*)-α-(*m*-(Trifluoromethyl)phenyl)ethyl Alcohol [(*R*)-2h]. Asymmetric reduction of *m*-(trifluoromethyl)acetophenone gave (*R*)-**2h** (67%): bp 100–104 °C (14 mmHg); α^{23}_D +33.9° (neat), 91% ee; ^{1}H NMR (200 MHz) δ 1.48 (d, 3 H, J = 6.4 Hz, CH_3), 2.42 (s, 1 H, OH), 4.91 (q, 1 H, J = 6.4 Hz, CH), 7.46 (m, 3 H, Ar), 7.62 ppm (s, 1 H, Ar); EA max (CH_3OH) 270 nm (ϵ 600), 263 (660), 259 (460), 257 (460); CD (CH_3OH, c 0.0320) $[\theta]_{275}$ ±0, $[\theta]_{271}$ −510, $[\theta]_{268}$ −340, $[\theta]_{264}$ −540, $[\theta]_{243}$ ±0, $[\theta]_{229}$ ±0, $[\theta]_{223}$ +200.

(*R*)-α-(*o*-Chlorophenyl)ethyl Alcohol [(*R*)-2j]. Asymmetric reduction of *o*-chloroacetophenone gave (*R*)-**2j** (44%): bp 120–122 °C (17 mmHg); α^{26}_D +18.5° (neat, 0.5 dm); 70% ee; ^{1}H NMR (200 MHz) δ 1.43 (d, 3 H, J = 6.4 Hz, CH_3), 2.51 (s, 1 H, OH), 5.25 (q, 1 H, J = 6.4 Hz, CH), 7.15–7.31 (m, 3 H, Ar), 7.54 ppm (dd, 1 H, J = 7.4 and 1.7 Hz, Ar); EA max (CH_3OH) 273 nm (ϵ 160), 269 (170), 264 (220), 262 (210), 257 (190), 253 (150); CD (CH_3OH, c 0.0556) $[\theta]_{277}$ ±0, $[\theta]_{273}$ +220, $[\theta]_{271}$ +120, $[\theta]_{268}$ +220 (sh), $[\theta]_{266}$ +240, $[\theta]_{263}$ +180, $[\theta]_{262}$ +220, $[\theta]_{256}$ +170 (sh), $[\theta]_{240}$ +60, $[\theta]_{228}$ +380.

(±)-α-(*o*-Methylphenyl)ethyl Alcohol [(±)-2k]. Asymmetric reduction of *o*-methylacetophenone gave (±)-**2k** (12%): bp 107–111 °C (12 mmHg); α^{20}_D ±0.0° (neat, 0.5 dm) [lit.[28] $[\alpha]^{20}_D$ +10.30 (neat), 14% ee]; ^{1}H NMR (90 MHz) δ 1.46 (d, 3 H, J = 6.7 Hz, $CHCH_3$), 1.74 (s, 1 H, OH), 2.34 (s, 3 H, CH_3), 5.10 (q, 1 H, J = 6.7 Hz, CH), 7.04–7.52 ppm (m, 4 H, Ar). The yield for this preparation was unusually low because the alcohol had a tendancy to dehydrate and form the corresponding styrene.

(±)-α-(*o*-(Trifluoromethyl)phenyl)ethyl Alcohol [(±)-2l]. To methylmagnesium bromide in tetrahydrofuran (110 mL, 3.0 M) cooled in an ice bath was added dropwise α,α,α-trifluoro-*o*-tolualdehyde (50.0 g, 0.287 mol) in tetrahydrofuran (50 mL). The reaction was allowed to warm to room temperature and stirred under nitrogen for 1 h. The reaction was quenched by pouring the solution over ice (100 g) and 6 N hydrochloric acid (50 mL) and extracted with ether (3 × 50 mL). The ether was dried ($MgSO_4$) and evaporated, and the residue was distilled to give (±)-**2l** (44.6 g, 82%): bp 82–84 °C (10 mmHg).

(±)-α-(*o*-(Trifluoromethyl)phenyl)ethyl Acid Phthalate. A mixture of (±)-α-(*o*-(trifluoromethyl)phenyl)ethyl alcohol ((±)-**2l**; 44.0 g, 0.231 mol), phthalic anhydride (34.3 g, 0.232 mol), and pyridine (36.0 g, 0.455 mol) was stirred for 24 h at room temperature and then 6 h at 90 °C. The pyridine was allowed to evaporate, and a crystalline solid precipitated. Recrystallization from methanol–water–acetic acid (70:25:5) gave the acid phthalate ester (58.0 g, 74%): mp 142–143 °C.

(*S*)-α-(*o*-(Trifluoromethyl)phenyl)ethyl Alcohol [(*S*)-2l]. (*S*)-(−)-α-Phenylethylamine (*S*)-**1a** (10.8 g, 0.0892 mol) was mixed with racemic (±)-α-(*o*-(trifluoromethyl)phenyl)ethyl acid phthalate (30.2 g, 0.0893 mol) in hot 95% ethanol (150 mL). On cooling, a crystalline solid precipitated, and recrystallization (2×) from 95% ethanol gave the salt (11.1 g, 54%): $[\alpha]^{24}_D$ +40° (c 1.0, CH_3OH). The salt was decomposed with methanol (50 mL) and 3 N hydrochloric acid (150 mL). Extraction with ether (3 × 100 mL) and evaporation of the ether yielded an oil that was boiled for 4 h in 30% sodium hydroxide (100 mL). After cooling the mixture was extracted with ether (2 × 50 mL), and the ether was dried ($MgSO_4$) and evaporated. The residue was distilled to obtain (*S*)-**2l** (2.68 g, 32%): α^{24}_D −23.3° (neat, 0.5 dm); 94% ee; ^{1}H NMR (300 MHz) δ 1.46 (d, 3 H, J = 6.3 Hz, CH_3), 2.18 (s, 1 H, OH), 5.31 (q, 1 H, J = 6.2 Hz, CH), 7.35 (t, 1 H, J = 7.6 Hz, Ar), 7.58 (m, 2 H, Ar), 7.81 ppm (d, 1 H, J = 7.9 Hz, Ar); EA max (CH_3OH) 271 nm (ϵ 940), 264 (970), 258 (670), 251 (360), 244 (170); CD (CH_3OH, c 0.0315) $[\theta]_{275}$ ±0, $[\theta]_{270}$ +430, $[\theta]_{267}$ +340, $[\theta]_{263}$ +480, $[\theta]_{257}$ +360 (sh), $[\theta]_{250}$ +220 (sh), $[\theta]_{235}$ ±0, $[\theta]_{222}$ ±0.

(*R*)-α-(3,5-Bis(trifluoromethyl)phenyl)ethyl Alcohol [(*R*)-2o]. Asymmetric reduction of 3,5-bis(trifluoromethyl)acetophenone gave (*R*)-**2o** (74%), which was purified by sublimation: mp 48–50 °C; $[\alpha]^{26}_D$ +21° (c 1.01, CH_3OH), 94% ee; ^{1}H NMR (300 MHz) δ 1.55 (d, 35 H, J = 6.5 Hz, CH_3), 2.05 (s, 1 H, OH), 5.05 (q, 1 H, J = 6.4 Hz, CH), 7.79 (s, 1 H, Ar), 7.85 ppm (s, 2 H, Ar); EA max (CH_3OH) 272 nm (ϵ 580), 265 (640), 259 (480); CD (CH_3OH, c 0.0300) $[\theta]_{280}$ ±0, $[\theta]_{273}$ −500, $[\theta]_{269}$ −430, $[\theta]_{265}$ −530, $[\theta]_{245}$ ±0, $[\theta]_{225}$ ±0.

(*S*)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol [(*S*)-3] was prepared from L-valine methyl ester hydrochloride and phenylmagnesium bromide according to the procedure used by Itsuno.[54] The crude product was recrystallized from 90% ethanol to give (*S*)-**3** (49%): mp 94–95 °C; $[\alpha]^{21}_D$ −121° (c 0.621, $CHCl_3$) [lit.[54] mp 94–95 °C; $[\alpha]^{25}_D$ −127.7° (c 0.639, $CHCl_3$)].

(*S*)-α-Phenylneopentyl Alcohol [(*S*)-4a]. Asymmetric reduction of pivalophenone gave (*S*)-**4a** (24%), which was purified by sublimation: mp 36–40 °C; $[\alpha]^{24}_D$ −13.3° (c 9.00, benzene), 49% ee [lit.[19] $[\alpha]^{20}_{578}$ −27.3° (c 9, benzene) for 100% ee]; ^{1}H NMR (90 MHz) δ 0.91 (s, 9 H, CCH_3), 1.88 (s, 1 H, OH), 4.38 (s, 1 H, CH), 7.29 ppm (s, 5 H, Ar).

Hydrogenolysis of (*R*)-α-(*m*-Chlorophenyl)ethyl Alcohol [(*R*)-2f]. A mixture of (*R*)-**2f** (1.0 g, 6.4 mmol), absolute ethanol (15 mL), potassium hydroxide (1.5 g, 27 mmol), and 10% palladium on carbon (0.10 g) was stirred under an atmosphere of hydrogen (727 mmHg and 24 °C) for 4–6 h at which time essentially 1 molar equiv (166 mL) of hydrogen had been consumed. The catalyst was removed by filtration, and the filtrate was evaporated. The remaining oil was dissolved in ether (30 mL) and

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washed with saturated brine (1 × 15 mL). The ether solution was dried ($MgSO_4$) and evaporated. The residue was an oil and had α^{22}_D +21.1° (neat, 1 dm). Analysis of the product by GC showed that the hydrogenolysis was essentially complete. A peak with a retention time of 3.8 min was present, corresponding to α-phenylethyl alcohol (**2a**), but the peak corresponding to the retention time of **2f** (5.9 min) was absent.

Hydrogenolysis of (*R*)-α-(*o*-Chlorophenyl)ethyl Alcohol [(*R*)-2j]. The hydrogenolysis of (*R*)-**2j** was accomplished by using the same general procedure used for the hydrogenolysis of (*R*)-**2f**. The product oil has α^{22}_D +24.3° (neat, 1 dm), and GC analysis showed that the hydrogenolysis was complete. The peak corresponding to the retention time of α-phenylethyl alcohol (**2a**) was present, but the peak corresponding to the retention time of **2j** (5.5 min) was absent.

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Neutralization–Chemical Reionization Mass Spectrometry

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Abstract: A neutralization–reionization scheme for tandem mass spectrometry has been developed which uses proton-transfer rather than electron-transfer reactions. The neutralization reaction is an endothermic transfer of a proton from protonated peptides to ammonia carried out at beam energies close to threshold. The ammonia collision gas also serves as a reagent gas in a collision chamber that is also a chemical ionization source. As the kinetic energies of neutralized molecules are reduced by additional collisions, they are reprotonated in the same chamber by the reverse, exothermic reaction. The method has the advantages that the neutralization and reionization reactions can be carried out in a single chamber, that proton-transfer reactions are compatable with the protonated species produced by soft ionization techniques, and that additional fragmentation is observed. The method is referred to as neutralization–chemical reionization mass spectrometry (NCRMS).

Recently, research groups at Cornell[1,2] introduced a technique for tandem mass spectrometry known as *neutralization–reionization mass spectrometry* (NRMS), in which a mass selected high energy ion beam from MS1 is neutralized by collision with a metal vapor and then reionized and mass analyzed in MS2. The collision chamber consists of two regions.[3] Collision with vaporized metals in the first chamber favors *charge exchange* over *collision induced dissociation* (CID). Reionization by collision with O_2, the most efficient of the target gases tested,[4,5] occurs in the second chamber, producing fragment ions as well for structural information. Both charge-transfer processes (neutralization and reionization) take place at high kinetic energy and involve electron transfer. In McLafferty's experiments, mass analyses in MS2 were performed with an electric sector only.

Both positive and negative ions may be used in neutralization–reionization schemes.[6] Thus, McLafferty et al.[7] used a (+NR+) scheme to study the interconversion (isomerization) of gas-phase neutral C_6H_6O isomers (phenol and cyclohexa-2,4-dienone), prepared from their radical cations by 9.9 keV collision with mercury vapor. Alternatively, Harrison and co-workers[8] have obtained (+NR+) and (+NR−) spectra of $[SF_5]^+$ and (−NR+) and (−NR−) spectra of $[SF_5]^-$. In their experiments, O_2 was used as both the neutralization and reionization gas. The processes were, however, carried out in separate chambers and deflector electrodes were used between the chambers to remove ions surviving the neutralization collisions.

Recently we introduced the use of *endothermic ion–molecule reactions* as an alternative to both *low-energy* and *high-energy* CID for inducing fragmentation in peptides and proteins.[9] In that scheme we assumed that in the protonated, even-electron molecular ions (MH^+) of peptides produced by *fast atom bombardment* the protons were localized primarily at the amide bonds. Such ions could then be reacted with ammonia in a collision chamber, where the proton-transfer reaction

$$MH^+ + NH_3 \rightarrow M + NH_4^+ \quad (1)$$

would occur at a relative energy in the center-of-mass frame, E_{cm}

$$E_{cm} = (E_{lab}M_n)/(M_{ion} + M_n) \quad (2)$$

M_n is the mass of the (target) neutral

M_{ion} is the mass of the (projectile) ion

whose threshold could be estimated from the reaction

$$NH_4^+ + CH_3CONH_2 \rightarrow NH_3 + CH_3CONH_3^+ \quad (3)$$

which is exothermic (ΔH = −2.2 kcal/mol = −0.10 eV).[10] The reaction between peptides and ammonia proceeds via a long-lived, proton-bound *collision complex*, MNH_4^+, and for leucine enkephalin thresholds for the appearance of both the MNH_4^+ and NH_4^+ ions were measured at relative kinetic energies of 0.18 eV.[9] The assumption that protons were transferred from an amide bond

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