Asymmetric Hydrogenation

(*R*)-Binap-Mediated Asymmetric Hydrogenation with a Rhodacarborane Catalyst in Ionic-Liquid Media**

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The reduction of ketones to alcohols under homogeneous catalysis is an important synthetic step in the chemical industry, and recent emphasis placed upon the asymmetric hydrogenation of prochiral substrates as pharmaceutical precursors enhances the importance of this chemistry.[1] Aside from the discovery of new asymmetric hydrogenation reactions, there remains the challenge of separating the reaction products from an expensive chiral catalyst[2] for purposes of recycling. Novel reaction media or polymer-immobilized catalysts may play an important role in this regard. More specifically, salts that are liquids at ambient temperature have received much attention because of their potential as direct replacements for conventional solvents and as a means to immobilize transition-metal catalysts in biphasic processes.[3–5] Many organic reactions have been carried out in ionic liquids, such as hydrogenation,[6,7] oxidation,[8] epoxidation,[9] and hydroformylation reactions.[10] The use of ionic-liquid media for other classic transformations, such as Friedel–Crafts acylation[11] and alkylation[12] reactions, allylation,[13,14] Diels–Alder,[15] and Heck[16] reactions, as well as Suzuki[17] and Trost–Tsuji coupling[18] reactions in ionic liquids have also been reported. In contrast, relatively little attention has been given to the use of ionic-liquid reaction media in the catalytic hydrogenation of ketones.

As has been repeatedly demonstrated in the past, ketones do not easily undergo homogeneous hydrogenation in the presence of simple transition-metal catalysts. Rhodium was successfully employed for this purpose under 1 atm of H_2, in

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complexes in which the metal center was made electron rich by using ligands of the fully alkylated bidentate diphosphane type.[1] In contrast with these results, we describe herein 1) the hydrogenation of aromatic ketones in the presence of a catalyst derived from a previously described rhodacarborane catalyst[19] precursor with a suicide alkene ligand: [*closo*-1,3-{μ-(η^2-3-CH_2=$CHCH_2CH_2$)}-3-H-3-PPh_3-3,1,2-$RhC_2B_9H_{10}$] (**1**); 2) the use of ionic-liquid reaction media: 1-methyl-3-octylimidazolium tetrafluoroborate ($OMIM^+BF_4^-$, **2**), 1-butyl-3-methylimidazolium hexafluorophosphate ($BMIM^+PF_6^-$, **3**), and the new liquid salt comprised of 1-carbadodecaborate ions[20] and *N*-*n*-butylpyridinium (BP) ions, $BP^+CB_{11}H_{12}^-$ (**4**); 3) the introduction of molecular asymmetry in the catalytic hydrogenation by complexation of the rhodium center of the catalyst with the optically active (*R*)-binap ligand, (*R*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (**5**); and 4) the comparison of these ionic liquids with tetrahydrofuran as reaction media, and comparison of the performance of the catalyst derived from **1** with that derived from [{Rh(cod)Cl}$_2$] (cod = 1,5-cyclooctadiene) under otherwise identical conditions.

The robust rhodacarborane catalyst systems developed by Hawthorne and co-workers,[21] such as [*closo*-3-H-3,3-$(Ph_3P)_2$-3,1,2-$RhC_2B_9H_{11}$], are understood mechanistically in the hydrogenation and isomerization of alkenes, as well as in the hydrogenolysis and hydrosilanolysis of alkenyl carboxylates. The complex **1** stands out among rhodacarborane catalyst precursors because of its η^2-3-CH_2=CH-$(CH_2)_2$ alkene ligand, which is linked to the *nido*-7,8-$C_2B_9H_{11}^{2-}$ dicarbollide module at the 7-vertex. Saturation of this alkenyl ligand under hydrogenation conditions removes it from the manifold of competitive ligands and creates a catalyst system that has only one triphenylphosphane ligand per rhodium atom, which results in its enhanced reactivity with alkene substrates. This alkene-hydrogenation catalyst is among the most reactive known.[19] The corresponding *closo* rhodacarborane catalyst systems, which contain two triphenylphosphane ligands per rhodium atom, are also quite active and robust in alkene hydrogenation.[21] As discussed below, **1** was used in this study because the bidentate ligand (*R*)-binap displaces all ligands originally attached to the rhodium center of **1** other than the hydride and the dicarbollide, in situ, to generate an active chiral catalyst. Hydrogenation of the coordinated suicide alkene ligand present in **1** simplifies this process.

The application of ionic-liquid media in the hydrogenation of aromatic ketones was explored by using the known liquid salts **2** and **3** as reaction media. The new liquid salt **4** was also prepared for use in this study, as it was thought that a beneficial interaction of the B–H bonds of the *closo*-$CB_{11}H_{12}^-$ ion with the rhodium center in the catalyst derived from **1** may occur, and that **4** should otherwise be chemically inert under the conditions used. The salt **4** was readily prepared by the metathesis reaction of *N*-*n*-butylpyridinium chloride with Cs^+*closo*-$CB_{11}H_{12}^-$ as a solution in CH_2Cl_2. Pure **4** is a colorless solid that melts at 21 °C.[22] This novel ionic liquid will undoubtedly find use in catalytic reactions other than those described herein.

The use of the catalyst precursor **1** in the hydrogenation of aromatic ketones in ionic-liquid reaction media provides both a potential new route to the corresponding alcohols and the opportunity to include optically active phosphanes, such as **5**, in the rhodacarborane catalyst system as structural components. This modification provided effective chiral catalysts that promoted the asymmetric hydrogenation of prochiral ketones under mild conditions. Both acetophenone and ethyl benzoylformate were hydrogenated in the presence of the catalyst precursor **1**[23] and (*R*)-binap (150 mol% relative to **1**), in the reaction media **2**, **3**, **4**, and tetrahydrofuran at 50 °C under H_2 (12 atm) within 12 h. In **2**, **3**, and **4**, the desired products (*R*)-phenylethanol and ethyl (*R*)-mandelate were formed in quantitative chemical yields and with very high *ee* values. The use of tetrahydrofuran led to both diminished chemical yields and diminished *ee* values. Reaction mixtures were monitored and product mixtures analyzed by GC.[24] Typical hydrogenation results for acetophenone are reported in Table 1, for which reaction rates are shown in Figure 1. The catalyst and (*R*)-binap were recycled in the ionic-liquid experiments by volatilization and removal of the reaction product under high vacuum, followed by the addition of fresh ketone. Six such cycles were carried out without degradation of catalyst activity or selectivity.

Table 1: Rhodium-catalyzed hydrogenation of acetophenone (A) and ethyl benzoylformate (B).[a]

Solvent	Conversion [%][b]	*ee* [%][c]	TOF [h^{-1}][d]
$OMIM^+BF_4^-$ **2**	100(A,B)	97.3(A), 99.3(B)	194(A), 201(B)
$BMIM^+PF_6^-$ **3**	100(A,B)	97.8(A), 98.2(B)	207(A), 213(B)
$BP^+CB_{10}H_{12}^-$ **4**	100(A,B)	99.1(A), 99.5(B)	239(A), 306(B)
tetrahydrofuran	82(A), 87(B)	91.3(A), 85.7(B)	96(A), 107(B)

[a] Mole ratio of catalyst/(*R*)-binap/acetophenone = 1:1.5:1000; reaction conditions: H_2 (12 atm), 50 °C, 12 h; [**1**] = 8.1×10^{-4} M; [**5**] = 1.21×10^{-3} M. [b] Determined by GC. [c] Determined by GC on a Chirasil DEX-CB column.[24] [d] Turnover frequency (= moles of hydrogenation product per mole of Rh per hour) was determined after 3 h.

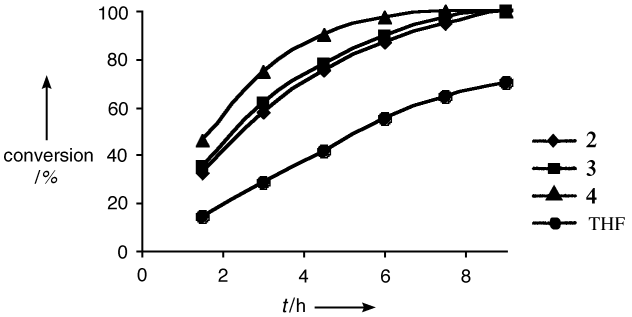


Figure 1. The course of acetophenone hydrogenation under standard conditions in the ionic-liquid media $OMIM^+BF_4^-$ (**2**), $BMIM^+PF_6^-$ (**3**), and $BP^+CB_{11}H_{12}^-$ (**4**), and in tetrahydrofuran.

The conversion, *ee* values, and turnover frequency observed when **1** and [{Rh(cod)Cl}$_2$] were used as catalyst precursors in the hydrogenation of acetophenone in the reaction media **2** and tetrahydrofuran are reported in Table 2. Thus, the replacement of **1** with [{Rh(cod)Cl}$_2$] as the catalyst precursor caused a severe decrease in performance in both reaction media examined. These observations strongly sug-

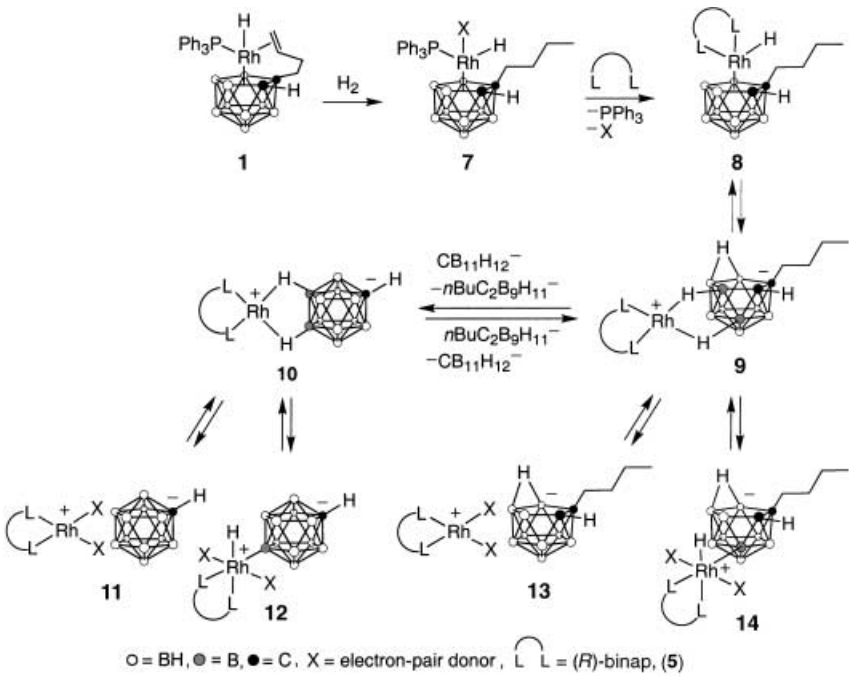
Table 2: Hydrogenation of acetophenone catalyzed by [{Rh(cod)Cl}$_2$] and by **1** in the ionic liquid OMIM$^+$BF$_4^-$ **2** (I) and in THF (II).[a]

Catalyst	Conversion [%][b]	*ee* [%][c]	TOF [h^{-1}][d]
1	100(I), 82(II)	97.3(I), 91.3(II)	194(I), 96(II)
[{Rh(cod)Cl}$_2$]	17(I), 8(II)	10.3(I), 5.7(II)	16(I), 11(II)

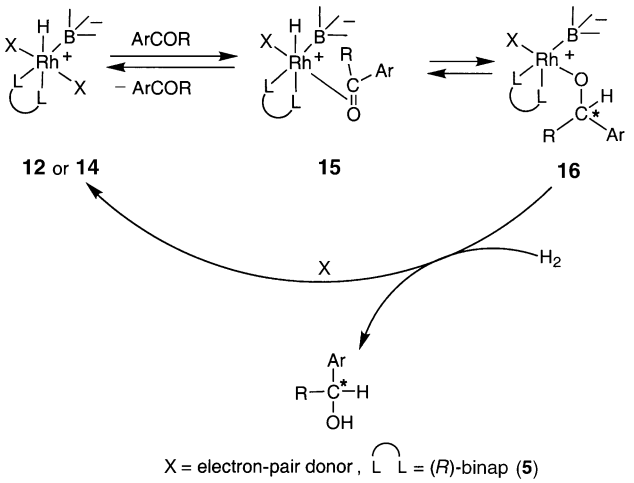
[a] Mole ratio of catalyst/(*R*)-binap/acetophenone = 1:1.5:1000; reaction conditions: H_2 (12 atm), 50 °C, 12 h. [b] Determined by GC. [c] Determined by GC on a Chirasil DEX-CB column.[24] [d] Turnover frequency was determined after 3 h.

gest that the hydrogenation processes in which **1** and [{Rh(cod)Cl}$_2$] serve as catalyst precursors differ in their mechanism. We are as yet unable to explain the significant increase in performance that results from the substitution of the ionic liquid **2** for tetrahydrofuran as the reaction medium for rhodacarborane-catalyzed reactions. However, it seems likely that an ionic medium better supports zwitterionic intermediates. The most efficient ionic-liquid reaction medium studied was **4**, which has a large number of available B–H bonds that may be involved in the reaction, as discussed below.

If it is assumed that ketone hydrogenation catalyzed by rhodacarboranes resembles rhodacarborane-catalyzed alkene hydrogenation and many other reactions that share its unusual mechanistic features,[21] the mechanisms shown in Schemes 1 and 2 can be proposed. The established mechanisms of rhodacarborane-catalyzed reactions[21] involve the presence of equilibrium concentrations of active zwitterionic [B-RhL$_2$-H] species formed by the oxidative addition of [L$_2$Rh]$^+$ to electron-rich terminal B–H bonds of the many isoelectronic, isomeric, and substituted variants of the parent *nido*-7,8-$C_2B_9H_{12}^-$ ion **6**.



Scheme 1. Fate of the rhodacarborane catalyst precursor **1** under the reaction conditions and equilibria leading to the possible catalytic species **12** and **14**.



Scheme 2. Proposed mechanism for the asymmetric hydrogenation of prochiral ketones in the presence of the rhodacarborane catalysts **12** and/or **14**.

As previously established, *closo*-rhodacarborane catalyst precursors, such as **8**, reductively eliminate Rh^{III} to produce mixtures of Rh^I *exo-nido* isomers, such as **9**, in which the [L$_2$Rh]$^+$ center is attached to the *nido* anion cage by a pair of three-center two-electron Rh–H–B bonds (Scheme 1). These species do not provide catalysis by dissociation to active [L$_2$RhX$_2$]$^+$ (X = electron pair donor) ion-pair species **13**, but rather undergo reversible oxidative addition of Rh^I to the coordinated terminal B–H bonds. The result is a set of catalytically active *exo-nido* Rh^{III} hydride derivatives **14**. Alkene hydrogenation and related reactions have been shown to proceed by a metathesis mechanism involving species such as **14**, which are regenerated in a separate catalytic cycle.[21] In reactions in which **4** was used as the ionic-liquid medium, reaction of the solvent *closo*-$CB_{11}H_{12}^-$ ion through its B–H donors with the [L$_2$RhX$_2$]$^+$ could possibly lead to the conversion of **9**, **13**, and **14** into the analogues **10**, **11**, and **12**, respectively. Of the latter group, species **12** would be expected, by analogy, to exhibit catalytic activity.

A generalized mechanism for the asymmetric hydrogenation of the aromatic ketones described in this study is proposed in Scheme 2. Species **12** and **14** are generalized, as shown, and the coordination of the ketone is followed by hydride transfer from the rhodium center of the catalyst to the carbonyl carbon atom of the ketone. Reversal of this last step is prevented by rapid irreversible H_2 metathesis, which regenerates the rhodium hydride species (either **12** or **14**). This metathesis step involves the formal addition of a proton to the complexed oxygen atom of the alkoxy group and the simultaneous formal addition of a hydride ion to Rh^{III}. This process is similar to the observed metathesis of the RhO(CO)CH$_3$ species involved in catalytic alkenyl acetate hydrogenolysis.[21] The precise stereochemical role of the (*R*)-binap

ligand in these hydrogenation reactions is not yet understood. However, its remarkable effect can be seen in the essentially quantitative chemical yields and superb *ee* values recorded in Table 1. The observed reaction rates and *ee* data show that ketone hydrogenation is both more rapid and stereochemically more selective in the ionic liquid **4** than in the other reaction media studied (Figure 1 and Table 1). This suggests that **12** may play an important role under hydrogenation conditions.

In summary, we have synthesized a new carborane-based room-temperature ionic liquid **4**, and used this salt as the reaction medium in the asymmetric hydrogenation of unsymmetrical aryl ketones in the presence of the chelating ligand (*R*)-binap and a previously known[19] rhodacarborane catalyst. The extraordinary performance of this catalyst system warrants further synthetic and mechanistic studies, which are in progress.

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Keywords: asymmetric catalysis · carboranes · hydrogenation · ionic liquids · P ligands · rhodium

[1] a) Q.-H. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385 – 3466; b) T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, *J. Am. Chem. Soc.* **2002**, *124*, 6508 – 6509; c) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 41 – 75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40 – 73.

[2] H. B. Kagan in *Comprehensive Organometallic Chemistry, Vol. 8* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, pp. 463 – 498.

[3] J. D. Holbrey, K. R. Seddon, *Clean Prod. Processes* **1999**, *1*, 223 – 236.

[4] T. Welton, *Chem. Rev.* **1999**, *99*, 2071 – 2083.

[5] P. Wasserscheid, W. Keim, *Angew. Chem.* **2000**, *112*, 3926 – 3945; *Angew. Chem. Int. Ed.* **2000**, *39*, 3772 – 3789.

[6] C. J. Adams, M. J. Earle, K. R. Seddon, *Chem. Commun.* **1999**, 1043 – 1044.

[7] Y. Chauvin, L. Mussmann, H. Olivier, *Angew. Chem.* **1995**, *107*, 2941 – 2943; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2698 – 2700.

[8] J. Howarth, *Tetrahedron Lett.* **2000**, *41*, 6627 – 6629.

[9] G. S. Owens, M. M. Abu-Omar, *Chem. Commun.* **2000**, 1165 – 1166.

[10] C. C. Brasse, U. Englert, A. Salzer, H. Waffenschmidt, P. Wasserscheid, *Organometallics* **2000**, *19*, 3818 – 3823.

[11] C. J. Adams, M. J. Earle, G. Roberts, K. R. Seddon, *Chem. Commun.* **1998**, 2097 – 2098.

[12] C. E. Song, W. H. Shim, E. J. Roh, J. H. Choi, *Chem. Commun.* **2000**, 1695 – 1696.

[13] W. Chen, L. Xu, C. Chatterton, J. Xiao, *Chem. Commun.* **1999**, 1247 – 1248.

[14] C. M. Gordon, A. McCluskey, *Chem. Commun.* **1999**, 1431 – 1432.

[15] M. J. Earle, P. B. McCormac, K. R. Seddon, *Green Chem.* **1999**, *1*, 23 – 25.

[16] A. J. Carmichael, M. J. Earle, J. D. Holbrey, P. B. McCormac, K. R. Seddon, *Org. Lett.* **1999**, *1*, 997 – 1000.

[17] C. J. Mathews, P. J. Smith, T. Welton, *Chem. Commun.* **2000**, 1249 – 1250.

[18] C. de Bellefon, E. Pollet, P. Grenouillet, *J. Mol. Catal. A* **1999**, *145*, 121 – 126.

[19] a) M. S. Delaney, C. B. Knobler, M. F. Hawthorne, *Inorg. Chem.* **1981**, *20*, 1341 – 1347; b) M. F. Hawthorne, M. S. Delaney, US Patent 4363747, **1982**.

[20] A. S. Larsen, J. D. Holbrey, F. S. Tham, C. A. Reed, *J. Am. Chem. Soc.* **2000**, *122*, 7264 – 7272.

[21] J. A. Belmont, J. Soto, R. E. King, A. J. Donaldson, J. D. Hewes, M. F. Hawthorne, *J. Am. Chem. Soc.* **1989**, *111*, 7475 – 7486.

[22] **4**: A solution of (*N*-*n*-butyl-C_5H_5N)$^+$$Cl^-$ (1.40 g, 8.16 mmol) in dry CH_2Cl_2 (30 mL) was added to a stirred solution of $Cs^+CB_{11}H_{12}^-$ (2.26 g, 8.19 mmol) in dry methanol (120 mL), and the mixture was stirred at room temperature for 20 h. All solvents were then evaporated under reduced pressure, and the resulting viscous residue was dissolved in CH_2Cl_2 and purified by column chromatography (SiO_2; CH_2Cl_2/Et_2O 4:1). The solvent was removed under reduced pressure and the product was dried under high vacuum for 2 days to give (*N*-*n*-butylpyridinium)$^+$-*closo*-$CB_{11}H_{12}^-$ (**4**; 2.10 g, 92 %) as a colorless sticky liquid with the dynamic viscosity $\mu = 250$ cP (0.01 g cm^{-1} s^{-1}; measured on a CV-100 Caulking Viscometer at 20 °C; estimated error: ± 2 %). The liquid solidified at 21 °C to give **4** as a colorless waxy solid. Elemental analysis: calcd for $C_{10}H_{26}B_{11}N$ (279.246): C 43.01, H 9.39, N 5.02; found: C 43.10, H 9.41, N 5.08; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.92$ (m, 2H, N-C_{py}-H), 8.18 (m, 1H, C_{py}-H), 7.75 (m, 2H; C_{py}-H), 4.46 (t, 2H; N-CH_2), 2.92 (s, 1H; B-CH), 1.65 (m, 2H; N-C-CH_2-), 1.03 (m, 2H; N-C-C-CH_2-), 0.56 (t, 3H; CH_3), 0.20–3.60 ppm (m, 11H; BH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.37$ (*C*-C-C-C-N), 19.24 (C-*C*-C-C-N), 33.59 (C-C-*C*-C-N), 55.67 (C-B), 61.89 (C-C-C-*C*-N), 128.58 (C_{py}), 144.72 (C_{py}), 145.41 ppm (C_{py}); IR (KBr): $\tilde{\nu} = 2955$ s, 2894 m, 2592 vs (νBH), 1588 m, 1501 m, 1455 m, 1409 m, 1322 s, 1250 vs, 1086 s, 927 s, 886 s, 835 vs, br, 692 s, 636 s, 518 s, 497 s cm^{-1}.

[23] Typical procedure: a solution of the catalyst precursor (8.1 μmol) in THF (2.53 mL), a solution of (*R*)-binap (12 μmol, 4.5 mM) in THF (2.64 mL), and an ionic liquid (10 mL) were placed in a 100-mL glass autoclave equipped with a magnetic stirring bar, a pressure gauge, and a gas inlet tube to be attached to a hydrogen source. The THF solvent was removed under reduced pressure, and the vessel was filled with argon. Acetophenone (975 mg, 8.12 mmol) was then added under a stream of argon, and the mixture was degassed by placing the autoclave under vacuum and filling it with argon three times, followed by evacuating it and filling it with hydrogen twice. After this procedure, the vessel was placed under H_2 pressure (12 atm) and the reaction mixture was stirred vigorously at 50 °C for 12 h. After the mixture had cooled to room temperature, the hydrogen gas was vented carefully. The yield and enantiomeric excess of the product was determined by GC analysis and the residue was distilled to give (*R*)-1-phenylethanol. The selective reduction of ethyl benzoylformate was carried out by a similar procedure to give ethyl-(*R*)-mandelate. When THF (15 mL) was used as the reaction medium, the degassing process was carried out at −78 °C. Chloro(1,5-cyclooctadiene)rhodium(I) dimer, [{Rh(cod)Cl}$_2$], was used as received from Sigma-Aldrich Pte., Ltd.

[24] GC column: Chirasil-DEX CB, 25 m, CHROMPACK; carrier gas: helium; column temperature: 105 °C; injection temperature: 200 °C; retention time, t_R, of (*R*)-1-phenylethanol: 17.8 min, (*S*)-1-phenylethanol: 20.5 min, acetophenone: 8.3 min, ethyl (*R*)-mandelate: 25.6 min, ethyl (*S*)-mandelate: 28.7 min, ethyl benzoylformate: 14.8 min.

