Enantioenriched Calcium-(*R*)-5,5′,6,6′,7,7′,8,8′-Octahydro-BINOL (H_8-BINOL): An Efficient Catalyst for the Creation of a Quaternary Stereocenter[#]

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Abstract: An efficient catalyst for the creation of a quaternary stereocenter has been developed utilizing easily available, eco-friendly $CaCl_2$ and applied for enantioselective carbon-carbon bond forming reactions. Among the surveyed ligands, it was found that (R)-5,5′,6,6′,7,7′,8,8′-octahydro-BINOL-Ca (**2f**) gave maximum ee (72%) with excellent yields.

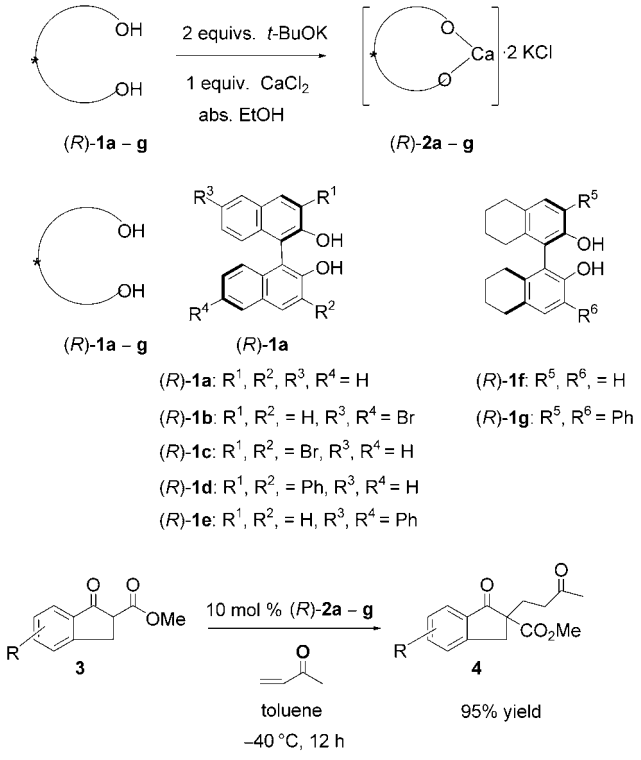
Keywords: calcium chloride; Michael reaction; (*R*)-octahydro-BINOL (H_8-BINOL); quaternary stereocenter

Introduction

Chiral tertiary carbon centers are ubiquitous in most biologically active natural products.[1] To generate a fully substituted carbon center retaining its stereointegrity is still a great challenge to the synthetic chemist. The most reliable and frequently used reactions for the synthesis of quaternary stereocenters are the conjugate addition of activated carbon nucleophiles to an acceptor, i.e., the Michael reaction. Much progress has been made in the development of catalytic as well as auxiliary-mediated[2] asymmetric Michael reactions.[3] Among these, extensively investigated and the most important reported to date are reactions catalyzed by (i) (*R*)-tol-BINAP-Pd,[4] (ii) chiral biquinoline *N,N*-oxide-$Sc(OTf)_3$,[5] (iii) lanthanum-sodium-heterobimetallic complexes,[6] and (iv) *N*-spiro C_2-symmetric chiral quaternary ammonium salts.[7] In spite of these impressive developments, there is a still great demand for new processes.

Results and Discussion

In our ongoing study of enantioenriched calcium-BINOL complexes,[8] we envisioned to study the activation of the addition of 1-oxoindan-2-carboxylate **3** to methyl vinyl ketone by modifying the BINOL scaffolds. Herein, we disclose our results regarding enantioenriched the calcium-octahydro-BINOL (H_8-BINOL) complex (**2f**) for the synthesis of quaternary stereocenters.



Scheme 1.

The enantioenriched catalysts (*R*)-**2a**–**g**, were prepared using the dipotassium salt of the binaphthol (**1a**–**g**) and calcium chloride in absolute ethanol at room temperature (Scheme 1). In order to examine their ability to generate a quaternary stereocenter, 10 mol %

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of this catalyst (*R*)-**2a**–**g** was tested on the model substrates methyl 1-oxoindan-2-carboxylate (**3**) and methyl vinyl ketone in toluene at $-40\,^{\circ}C$. The results of our investigation are summarized in Table 1. Among the surveyed ligands, it was found that octahydro-BINOL-Ca (**2f**) gave the maximum ee (72%) with excellent yields (93%). Electronically activated (entries 2 and 3), as well as sterically differentiated catalysts (entries 4 and 5) gave only moderate ees. Partially hydrogenated 3,3′-substituted H_8-BINOL-Ca (entry 7) did not improve the ee of the adduct **4**. Use of more than 10 mol % of the catalyst did not give any increase in enantioselectivity of the product. A catalyst loading of 5 mol % decreased the rate as well as the selectivity of the reaction.

Using 10 mol % H_8-BINOL-Ca (*R*)-**2f** as the catalyst, a series of different solvent systems was evaluated. In polar solvents the rate of the reaction was very fast, but with drastically decreasing ee of the adduct **4** [THF (22% ee, 90% yield), DME (20% ee, 95% yield), and DMF (32% ee, 68% yield)]. The reaction did not progress at all in acetonitrile. Toluene turned out to be the solvent of choice in terms of the yield, selectivity, and time, except in the case of entry 2, Table 2 (52% ee, 85% yield); CCl_4 seems appropriate. A wide variation in the chiral induction was observed with changes in the temperature. The best results were obtained at $-40\,^{\circ}C$. At $-78\,^{\circ}C$ the reaction was very sluggish. At elevated temperature, i.e., more than $-40\,^{\circ}C$ the ee of the product **4** decreased. Additives like EtOH or 2-propanol gave the racemic product. The addition of external salts such as LiCl, KCl and KF was screened to obtain best results. These salts also significantly improved the rate of the reaction at lower temperatures but lead to virtually racemic product **4**. The synergetic effect of a catalytic amount of bases like $NaHCO_3$, Na_2CO_3 and K_2CO_3 was tested but gave no further improvement of product ee. Use of an excess of the acceptor methyl vinyl ketone (2 equivs.) helped to improve yield and optical purity of the product.

Having the best reaction conditions in hand, the scope of this reaction was extended to various cyclic β-keto esters and methyl vinyl ketones as the acceptor.[9] Our results are shown in Table 2. The nature of the ester group of the β-keto esters (donor) affected the ee of the product. Higher enantioselectivity was observed using methyl esters, when compared to the higher homologues of the ester group (entries 1–3). Interestingly, a chlorine substituent at the *para* position of the methyl 1-oxoindan-2-carboxylate gave the adduct (entry 4d) in high yield with a good ee. Five-membered keto esters (entries 7 and 8) resulted in products in excellent yields with a more reasonable ee than the six-membered keto esters (entries 9 and 10).

Table 1. List of ligand calcium complexes (*R*)-**2a**–**g** screened for Michael addition between **3** and methyl vinyl ketone.

Entry	Catalyst[a]	Time	ee [%]	Yield [%][b]
1	(*R*)-**2a**	15 h	40	95
2	(*R*)-**2b**	18 h	46	87
3	(*R*)-**2c**	10 h	35	90
4	(*R*)-**2d**	20 h	22	68
5	(*R*)-**2e**	12 h	65	85
6	(*R*)-**2f**	12 h	72	93
7	(*R*)-**2 g**	10 h	58	65

[a] 10 mol% of catalyst used.
[b] Yields of isolated product.

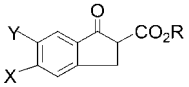
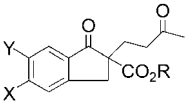
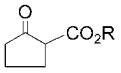
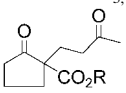
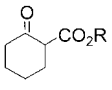
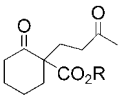
Attempts to obtain a suitable crystal structure of catalyst (*R*)-**2f** failed. But significant information was obtained through surface structure investigations by the ESCA method, which not only gives information about the elements present but also about the oxidation states and chemical environment of the elements.[11] The ESCA survey scan shows peaks characteristic of C 1 s (285 eV), O 1 s (530 eV), Ca 2p (350 eV), K 2p (294 eV) and Cl 2p (200 eV). A high-resolution narrow scan for C 1 s shows peaks due to C–C/C–H (at 284.6 eV) and C–O (at 285.6 eV). In addition to C 1 s peaks, peaks corresponding to K 2p are also observed at (293.7 eV and 296.4 eV) which can be attributed to K $2p_{3/2}$ and K $2p_{1/2}$. Use of the XPS technique for O 1 s shows two peaks on deconvolution, which are associated with C–O (530.7 eV) and Ca–O (532.3 eV). The narrow scan of Ca 2p shows two peaks for Ca $2p_{3/2}$ (347.3 eV) and Ca $2p_{1/2}$ (351.0 eV) that correspond to Ca–O bonds. Similarly, a narrow scan spectrum of Cl 2p also shows peaks corresponding to Cl $2p_{3/2}$ (198.4 eV) and Cl $2p_{1/2}$ (199.9 eV), which can be attributed to the K–Cl bond. From these ESCA studies, it was established that calcium metal is in its +2 oxidation state bonded to the oxygen atoms of the binaphthyl moiety. Further evidence can be obtained from the ESCA spectrum for O 1 s which clearly depicts the presence of K and Cl in the form of KCl salt. This supports the nature of the catalyst in which the calcium replaces the potassium in the dipotassium salt of (*R*)-**1f** to form KCl and the active catalyst containing calcium metal.

The ESCA spectra of calcium-(*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-BINOL catalyst [(*R*)-**2f**] can be found in the Supporting Information.

Conclusion

In conclusion, we have demonstrated the potential of the (*R*)-5,5′,6,6′,7,7′,8,8′-octahydroBINOL-Ca (**2f**) complex-catalyzed enantioselective Michael addition for the creation of a quaternary stereocenter. This monometallic catalyst works not only as a Lewis acid but also as a Brønsted base. This calcium complex is reasonably robust and to the best of our knowledge this is the first time that calcium is used for the construction of quaternary carbon centers in high to moderate enantiose-

Table 2. Asymmetric Michael addition of β-keto esters to methyl vinyl ketone.[a]

Entry	β-Keto esters	Adducts[c]	$[\alpha]_D^{25}$	% [ee][d]	Yield [%][b]
	 **3a–f**	 **4a–f**			
1	**3a** R = CH_3, X = Y = H	**4a** R = CH_3, X = Y = H	+55.5 (*c* 2, benzene)	72 (*R*)	93
2	**3b** R = *i*-Pr, X = Y = H	**4b** R = *i*-Pr, X = Y = H	+46.2 (*c* 2, benzene)	68 (*R*)	91[e]
3	**3c** R = *t*-Bu, X = Y = H	**4c** R = *t*-Bu, X = Y = H	+36.1 (*c* 2, benzene)	62 (*R*)	86
4	**3d** R = CH_3, X = Cl, Y = H	**4d** R = CH_3, X = Cl, Y = H	+52.8 (*c* 2, benzene)	–	90
5	**3e** R = CH_3, X = Br, Y = H	**4e** R = CH_3, X = Br, Y = H	+48.3 (*c* 2, benzene)	–	82
6	**3f** R = CH_3, X = H, Y = OCH_3	**4f** R = CH_3, X = H, Y = OCH_3	+24.3 (*c* 2, benzene)	–	80
	 **5a–c**	 **6a – c**			
7	**5a** R = CH_3	**6a** R = CH_3	+14.8 (*c* 5, $CHCl_3$)	80 (*S*)	88
8	**5b** R = Et	**6b** R = Et	+13.4 (*c* 5, $CHCl_3$)	78 (*S*)	82
	 **7a, b**	 **8a, b**			
9	**7a** R = CH_3	**8a** R = CH_3	+28.0 (*c* 2, CCl_4)	–	80
10	**7b** R = Et	**8b** R = Et	+32.6 (*c* 2, CCl_4)		76

[a] 10 mol % of catalyst used.
[b] Yields of isolated products.
[c] All the adducts gave satisfactory analytical data.
[d] Enantiomeric excess (ee) values were determined by the optical rotation and the absolute configuration was assigned by comparison with values known from the literature.[10]
[e] The reaction was carried out in CCl_4 instead of toluene.

lectivity with excellent product yields. Further studies are in progress to enhance the enantioselectivity.

Experimental Section

General Procedure for Asymmetric Michael Addition

To a mixture of (*R*)-(+)-5,5′,6,6′,7,7′,8,8′-octahydro-BINOL (**1f**; H_8-BINOL; 50 mg, 0.177 mmol, 10 mol %) and potassium *t*-butoxide (38.2 mg, 0.34 mmol), absolute ethanol (6 mL) was added at room temperature under an argon atmosphere. After stirring for 30 min, ethanol was removed under reduced pressure and to the residue; solid $CaCl_2$ (19.6 mg, 0.177 mmol) was added, followed by the addition of absolute ethanol (6 mL). The white suspension was stirred for 3 h at ambient temperature and then subsequent evaporation of ethanol under reduced pressure gave a white powder. To this solid catalyst, toluene (10 mL) was added under an argon atmosphere and the mixture was stirred overnight at ambient temperature. This reaction mixture was cooled at −40 °C for 10 min followed by addition of a toluene solution (0.5 mL) of methyl 1-oxoindan-2-carboxylate (336 mg, 1.77 mmol) at the same temperature. After 5 min, methyl vinyl ketone (248.12 mg or 0.29 mL, 3.54 mmol) was added dropwise *via* a syringe. The reaction mixture was stirred at −40 °C for 12 h. The reaction was quenched with saturated NH_4Cl solution, extracted with EtOAc and the extracts dried over anhydrous Na_2SO_4. After concentration, the residue was subjected to column chromatography (silica gel 60–120 mesh) which gave a white solid; yield: 415 mg (93%); $[\alpha]_D^{25}$: +55.5 (*c* 2, benzene)].[12]

Methyl 1-oxo-2-(3-oxobutyl)indan-2-carboxylate **(4a):** Yield: 415 mg (93%); mp 104.5–107 °C; $[\alpha]_D^{25}$: +55.5 (*c* 2, benzene) [lit.[5a]: +29.8(*c* 1.24, benzene)]; IR: ν = 1742,1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.21 (s,3H), 2.19–2.27 (m, 2H), 2.45–2.76 (m, 2H), 3.04 (d, *J* = 17.8 Hz,1H), 3.67 (d, *J* = 17.8 Hz,1H), 3.70 (s, 3H), 7.39–7.79 (4H, m); ^{13}C NMR ($CDCl_3$, 75 Hz): δ = 28.6, 29.8, 37.8, 38.7, 52.7, 59.1, 124.8, 126.4, 127.9, 135.0, 135.5, 152.5, 171.5, 202.2, 207;3. EI- MS: *m/z* = 260(M^+), 190.

Isopropyl 1-oxo-2-(3-oxobutyl)indan-2-carboxylate **(4b):** Yield: 464.4 mg (91%); $[\alpha]_D^{25}$: +46.2 (*c* 2, benzene) [lit.[5a]: +31.9 (*c* 1.21, benzene)]; IR: ν = 1742, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.17 (d, *J* = 5.9 Hz, 6H), 2.11 (s, 3H), 2.17–2.23 (m, 2H), 2.43–2.68 (m, 2H), 3.01 (d, *J* = 17.2 Hz, 1H), 3.63 (d, *J* = 17.2 Hz, 1H), 5.01 (sept, *J* = 5.9 Hz, 1H), 7.37–7.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.5, 21.6, 28.5, 30.0, 37.9, 38.9, 59.3, 69.2, 124.7, 126.3, 127.8, 135.0, 135.3, 152.5, 170.4, 202.3, 207.5; EI-MS: *m/z* = 288 (M^+), 218, 176.

tert-*Butyl 1-oxo-2-(3-oxobutyl)indan-2-carboxylate* (4c): Yield: 460 mg (86%); $[\alpha]_D^{25}$: +36.1 (*c* 2, benzene) [lit.[5a]: + 47.1 (*c* 1.21, benzene)]; IR (KBr): ν = 1712, 1370, 1154 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.39 (s, 9H), 2.13 (s,3H), 2.15–2.21 (m, 2H), 2.44–2.69 (m, 2H), 3.00 (d, *J* = 17.2 Hz, 1H), 7.37–7.77 (m,4H); ^{13}C NMR($CDCl_3$, 75 MHz): δ = 27.9, 28.5, 30.0, 38.0, 38.9, 59.9, 82.0, 124.6, 126.2, 127.7, 135.1, 135.2, 152.5, 170.0, 202.6, 207.0; EI-MS: *m/z* = 246 (M^+), 200, 176, 157.

***Methyl 5-chloro-1-oxo-2-(3-oxobutyl)indan-2-carboxylate* (4d):** Yield: 468 mg (90%); $[\alpha]_D^{25}$: +52.8 (*c* 2, benzene); IR: ν = 1712, 1370, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.09 (s, 3H), 2.21 (t, 2H), 2.45–2.76 (m, 2H), 3.05 (d, *J* = 17.5 Hz,1H), 3.67 (d, *J* = 17.5 Hz, 1H), 3.70 (s, 3H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.49 (s,1H), 7.78 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.9, 24.8, 28.7, 37.9, 50.7, 66.3, 126.0, 128.6, 129.8, 135.3, 138.0, 174.5, 200.7, 207.1; EI-MS: *m/z* = 296 (M + 2), 294.7 (M^+), 176.

***Methyl 5-bromo-1-oxo-2-(3-oxobutyl)indan-2-carboxylate* (4e):** Yield: 490.5 mg (82%); $[\alpha]_D^{25}$: +48.3 (*c* 2, benzene); IR: ν = 1712, 1370, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.09 (s, 3H), 2.21 (t, 2H), 2.45–2.76 (m, 2H), 3.05 (d, *J* = 17.5 Hz, 1H), 3.67 (d, *J* = 17.5 Hz, 1H), 3.70 (s, 3H), 7.33–7.39 (m, 2H), 7.73 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.9, 24.8, 28.5, 37.9, 50.7, 66.3, 127.3, 128.9, 130.6, 131.5, 136.2, 141.7, 174.5, 200.7, 207.1; EI-MS: *m/z* = 341 (M + 2), 339 (M^+), 176.

***Methyl 5-methoxy-1-oxo-2-(3-oxobutyl)indan-2-carboxylate* (4f):** Yield: 410.6 mg (80%); $[\alpha]_D^{25}$: +24.3 (*c* 2, benzene); IR: ν = 1712, 1370, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.09 (s, 3H), 2.21 (t, 2H), 2.45–2.76 (m, 2H), 3.05 (d, *J* = 17.5 Hz, 1H), 3.67 (d, *J* = 17.5 Hz, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 6.71 (s, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.9, 24.8, 29.4, 37.8, 50.8, 56.1, 66.2, 111.2, 113.7, 129.4, 129.6, 140.5, 166.2, 174.5, 200.7, 207.2; EI-MS: *m/z* = 290 (M^+).

***Methyl 2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate* (6a):** Yield: 330.5 mg (88%); $[\alpha]_D^{25}$: +14.8 (*c* 5, $CHCl_3$); IR: ν = 2966, 2890, 1735, 1421, 1407, 1358, 1317, 1276, 1248, 1163, 1147, 1116, 929, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.62–1.69 (m, 1H), 1.85–1.97 (m, 1H), 2.11 (s, 3H), 2.16 (s, 3H), 2.28–2.38 (m, 4H), 2.55–2.57 (m, 1H); ^{13}C NMR($CDCl_3$, 75 MHz): δ = 19.09, 25.84, 27.30, 29.65, 31.21, 38.08, 38.31, 67.11, 204.33, 206.86, 215.72; EI-MS: *m/z* = 212 (M^+).

***Ethyl 2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate* (6b):** Yield: 328.4 mg (82%); $[\alpha]_D^{25}$: +13.4 (*c* 5, $CHCl_3$) [lit.[9b]: + 19.5 (neat)]; IR: ν = 2976, 1748, 1717, 1448, 1406, 1367, 1318, 1260, 1232, 1165, 1116, 1029, 861 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, 3H), 1.82–2.03 (m, 4H), 2.03–2.13 (m, 1H), 2.12 (s, 3H), 2.24–2.49 (m, 4H), 2.69 (ddd, *J* = 18, 9.6, 6.0 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.29, 18.84, 26.24, 29.00, 33.22, 37.07, 38.01, 58.23, 60.23, 170.47, 206.61, 213.75; EI-MS: *m/z* = 226 (M^+), 208, 198, 169, 156, 152, 141, 137, 125, 110, 55, 43.

***Methyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate* (8a):** Yield: 320 mg (80%); $[\alpha]_D^{25}$: +28.0 (*c* 2, CCl_4); IR: ν = 2940, 2867, 1711, 1445, 1367, 1244, 1212, 1188, 1168, 1137, 1096, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.79–1.82 (m, 4H), 2.09 (s, 3H), 2.01–2.23 (m, 6H), 2.45–2.70 (m, 2H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.4, 24.8, 26.1, 27.0, 29.0, 37.8, 38.0, 50.7, 62.1, 176.0, 207.1, 211.3; EI-MS: *m/z* = 226 (M^+).

***Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate* (8b):** Yield: 323 mg (76%); $[\alpha]_D^{25}$: +32.6 (*c* 1.8, CCl_4); IR: ν = 2940, 2867, 1711, 1445, 1367, 1244, 1212, 1188, 1168, 1137, 1096, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.24 (t, 3H), 1.38–1.48 (m, 1H), 1.56–1.65 (m, 2H), 1.68–1.76 (m, 1H), 1.81 (ddd, *J* = 14, 10, 5.4 Hz, 1H), 1.92–2.01 (m, 1H), 2.05 (ddd, *J* = 14, 10, 5 Hz, 1H), 2.09 (s, 3H), 2.33 (ddd, *J* = 18, 10,5.4 Hz, 1H), 2.39–2.50 (m, 3H), 2.55 (ddd, *J* = 18, 10, 5.2 Hz, 1H), 4.11–4.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.47, 21.90, 26.85, 27.72, 29.14, 35.86, 37.99, 40.30, 59.25, 60.64, 171.22, 206.67, 206.87; EI-MS: *m/z* = 240 (M^+), 212, 194, 170, 151, 124.

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[12] While isolating product **4**, the ligand (*R*)-(+)-5,5′,6,6′,7,7′,8,8′-octahydro BINOL (**1f**; H_8-BINOL) was also eluted through column chromatography and its optical purity was found to be 99%.

