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Chiral Crown Complexes catalyse Michael Addition Reactions to give Adducts in High Optical Yields

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Summary Chiral crowns complexed to potassium bases catalyse with high turnover numbers the Michael additions of a β -ketoester to methyl vinyl ketone, and of two phenylacetic esters to methyl acrylate, to give products of 99–60% optical purity with a configurational bias rationalizable on the basis of steric effects.

INTRAMOLECULAR asymmetric induction has been used in synthesis for over a century,¹ and rationalizations of the direction of configurational bias have existed for nearly three decades.^{2,3} Stoichiometric asymmetric reagents for nucleophilic additions to carbonyl groups by H⁻ and R⁻ donors have proven to be synthetically useful and interpretable.^{4–6} Abiotic asymmetric catalysis as a phenomenon has long been known, but is stereospecific enough to be generally useful and interpretable only in the hydrogenation of alkenes,⁷ in epoxidations of allyl alcohols,⁸ and in Michael additions to $\alpha\beta$ -unsaturated ketones. Bergson⁹ reported the first example of chiral catalysis of the Michael reaction, and Wynberg reported optical purities of products as high as 76% enantiomeric excess (e.e.) in the cinchona alkaloid-catalysed additions of β -ketoesters to methyl vinyl ketone.¹⁰

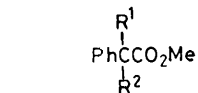
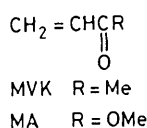
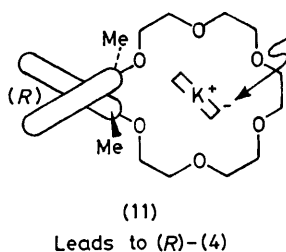
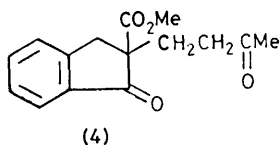
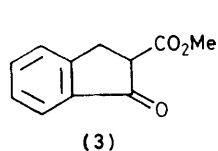
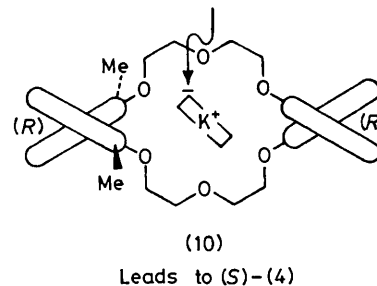
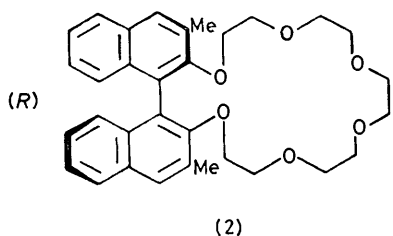
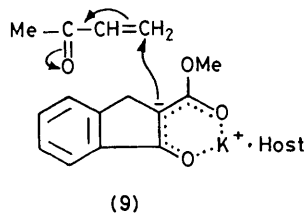
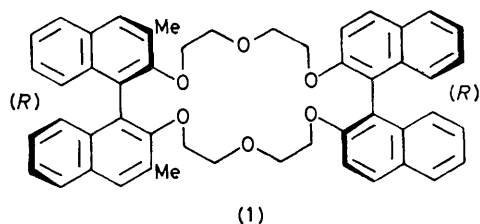
We report that potassium salt bases complexed to designed chiral hosts catalyse Michael additions (Table). Our best

chemical and optical yields are close to quantitative, and our highest catalytic turnover number (CTN) is 55.† Hosts (1)¹¹ and (2)¹² of maximum rotations and established configurations complexed with KOCMe₃ or KNH₂ are the catalysts. Carbon acids (3), (5), and (7), when added to methyl vinyl ketone (MVK) or methyl acrylate (MA) in toluene in the presence of the catalysts, gave products (4), (6), or (8) whose configurations and maximum rotations are reported or calculable (footnotes f–h to the Table). Optical yields were determined from optical rotations of nonfractionated products.

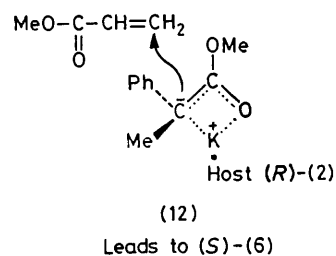
Catalyst (SS)-(1)·KOCMe₃ and MVK gave (*R*)-(4) with an optical yield of ca. 99% e.e. [$\Delta(\Delta G^\ddagger) > 2$ kcal mol⁻¹] and CTN = 10 at -78 °C (run 1). At 25 °C in run 2, (*R*)-(4) was produced with 67% e.e. and CTN = 15. Thus the lower temperature provided the higher stereospecificity. In runs 3 and 4, carbon acid (5) reacted with MA to give (*S*)-(6) with (*R*)-(2)·KNH₂ as catalyst. Optical yields of 83 and 73% e.e., and CTN values of 7 and 6, respectively, were realized. The asymmetric induction is insensitive to large changes in the relative amounts of host and base (Table).

In runs 5–10, carbon acid (7) was added to MA to give (*S*)-(8). The reactions were catalysed by (SS)-(1)·KOCMe₃, (*R*)-(2)·KOCMe₃, or (*R*)-(2)·KNH₂. Optical yields are

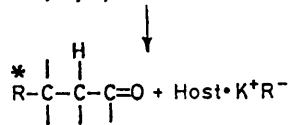
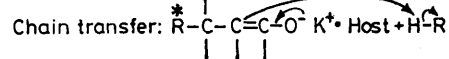
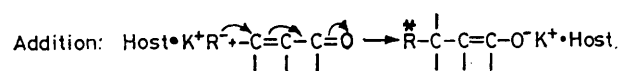
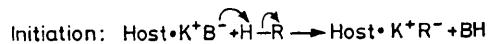
† Thoroughly dried solvents and reagents were used in reactions carried out under argon. Product esters gave the expected 200 MHz ¹H n.m.r. spectra. Run 7 illustrates a procedure. To 10 ml of liquid NH₃ at -78 °C were added 14.7 mg of K. After the metal had reacted, 1.5 ml of PhCH₂CO₂Me in 10 ml of toluene was added dropwise. The solution, stirred under argon, was allowed to warm to 25 °C to evaporate NH₃, and cooled to -78 °C. Host (*R*)-(2) (599 mg) was added, followed (after 15 min) by 0.93 ml of MeO₂CCH=CH₂ in 8 ml of toluene (dropwise, 15 min). The mixture was stirred for 30 min and poured into 35 ml of water saturated with NH₄Cl. The toluene layer combined with a toluene wash solution was dried (MgSO₄), evaporated at 40 °C, and the product chromatographed on silica gel (dry column, 18 by 1.5 inches, CH₂Cl₂). The middle (product) fraction was again chromatographed (gel permeation, 18 ft by 3/8 inch column, Styragel SX-12, CH₂Cl₂) to give 800 mg (96%) of (*S*)-(8), [α]_D²⁵ + 55.7° (c 4.1, EtOH). The host remained at the origin on the dry column, was recovered by EtOAc elution, purified by gel permeation chromatography on Styragel 100 Å (CH₂Cl₂), and gave the same rotation before and after use.



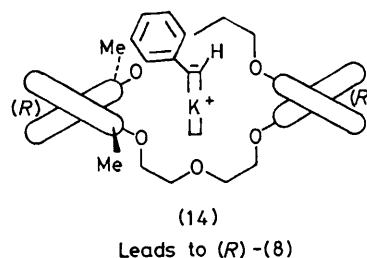
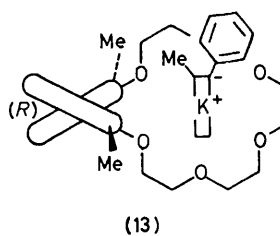
- (5) $\text{R}^1 = \text{H}, \text{R}^2 = \text{Me}$
 (6) $\text{R}^1 = [\text{CH}_2]_2\text{CO}_2\text{Me}, \text{R}^2 = \text{Me}$
 (7) $\text{R}^1 = \text{R}^2 = \text{H}$
 (8) $\text{R}^1 = [\text{CH}_2]_2\text{CO}_2\text{Me}, \text{R}^2 = \text{H}$



minimal since optically active (8), once formed, racemized somewhat or underwent further addition to MA.† Manipulation of the relative amounts of reactants, their states of dilution, the temperature, solvent, and reaction times pro-



SCHEME



† Small amounts of $\text{PhC}(\text{CO}_2\text{Me})(\text{CH}_2\text{CH}_2\text{CO}_2\text{Me})_2$ were isolated from some runs. When (R)-(8) of rotation $[\alpha]_{589}^{25} + 52.6^\circ$ (*c* 5, EtOH) was subjected to the conditions of run 7, except that the $\text{MeO}_2\text{CCH}=\text{CH}_2$ was omitted and the stirring time at -78°C was extended from 0.5 to 2 h, (R)-(8) was recovered (90%) and gave $[\alpha]_{589}^{25} + 32.8^\circ$ (38% racemized).

vided optical yields of 65 to 60% e.e. [$\Delta(\Delta G^\ddagger) = ca. 0.6$ kcal mol⁻¹], CTN values of 55—8, and chemical yields of 100—80%.[§]

These reactions probably go by the catalytic chain reaction mechanism indicated (Scheme). In (9), the configuration-determining step for the production of (4) is

embracing K⁺ symbolizes the plane of the four-membered ring of the ion pair which in the complex is perpendicular to the best plane of the host's oxygens. The relative positions of the Me and Ph groups in (13) are dictated by the lower steric requirements of Me and the large steric requirements of the naphthalene face against which the methyl

TABLE. Chiral catalysis of Michael additions in toluene as solvent.

		Run									
		1	2	3	4	5	6	7	8	9	10
Catalyst complex	Host	(SS)-(1)	(SS)-(1)	(R)-(2)	(R)-(2)	(SS)-(1)	(R)-(2)	(R)-(2)	(R)-(2)	(R)-(2)	(R)-(2)
	Base	KOBu ^t	KOBu ^t	KNH ₂	KNH ₂	KOBu ^t	KOBu ^t	KNH ₂	KNH ₂	KNH ₂	KNH ₂
Reactants	R-H	(3)	(3)	(5)	(5)	(7)	(7)	(7)	(7)	(7)	(7)
	Carbonyl ^a	MVK	MVK	MA	MA	MA	MA	MA	MA	MA	MA
mmol of catalyst complex	Host	0.20	0.17	1.16	0.26	0.28	0.29	1.16	0.40	0.26	0.36
	Base	0.20	0.17	0.38	0.26	0.23	0.23	0.38	0.40	0.26	0.24
mmol of reactants	R-H	5.00	3.45	10.6	3.6	10.6	10.6	10.6	42	3.6	3.6
	Carbonyl	10.0	8.6	3.4	2.25	5.5	5.5	3.4	22	2.2	2.2
Conditions	Toluene (ml)	25	25	20	15	30	40 ⁱ	20	200	15	20
	Temp./°C	-78	25	-78	-78	-78	-78	-78	-78	-78	-100
	t/h	120	96	4	5	5	0.8	0.5	0.8	0.5	0.5
Product	Structure	(R)-(4) ^f	(R)-(4)	(S)-(6) ^g	(S)-(6)	(S)-(8) ^h	(S)-(8)	(S)-(8)	(S)-(8)	(S)-(8)	(S)-(8)
	Yield ^b /%	48	75	80	75	80	90	96	100	95	94
	E.e. ^c /%	ca. 99	67	83	73	65	62	63	60	60	65
$\Delta(\Delta G^\ddagger)$ ^d kcal mol ⁻¹		> 2	1.0	0.9	0.7	0.6	0.6	0.6	0.6	0.6	0.5
CTN ^e		10	15	7	6	19	22	9	55	8	9

^a MVK is methyl vinyl ketone and MA is methyl acrylate. ^b Chemical yields (not maximized) are based on minimum reactant. ^c Enantiomeric excess. Should new 'maximum' rotations be reached in the future, as sometimes happens, our % e.e. values can be recalculated accordingly. ^d $\Delta(\Delta G^\ddagger) = RT \ln$ (dominant enantiomer/subordinate enantiomer). ^e Catalyst turnover number (CTN) equals (mmol product)/(mmol catalyst complex). Values were not maximized. ^f Our % e.e. values are based on (R)-(4) having a maximum rotation of $[\alpha]_D^{25} + 77.0^\circ$ (*c* 2, C₆H₆) (ref. 10). ^g G. Otani and S.-I. Yamada, *Chem. Pharm. Bull. Jpn.*, 1973, **21**, 2119 gave the maximum rotation and absolute configuration of (R)-PhCMe(CO₂H)CH₂CH₂CO₂H as $[\alpha]_D - 22.3^\circ$ (*c* 0.6, EtOH). Ester (S)-(+)-(6) produced in run 3 was hydrolysed to this acid to give $[\alpha]_D + 16.5^\circ$ (*c* 1.2, EtOH). This ester with Eu(tfc)₃ [tris(trifluorocamphorato)europium] and ¹H n.m.r. spectroscopy provided a maximum rotation for (S)-(6) of $[\alpha]_D + 22.5^\circ$ (*c* 3.0, EtOH). Our % e.e. is based on our value for (S)-(6). The maximum ester rotation when used to calculate the maximum rotation of (S)-PhCMe(CO₂H)CH₂CH₂CO₂H gives $[\alpha]_D^{25} + 20.0^\circ$ (*c* 1.2, EtOH). ^h K. Kawazu, T. Fujita, and T. Mitsui, *J. Am. Chem. Soc.*, 1957, **81**, 932 reported the maximum rotation and absolute configuration of (S)-(+)-(8). We base the % e.e. for (S)-(8) on a value of $[\alpha]_D^{25} + 89^\circ$ (*c* 5, EtOH). This value does not vary from *c* 1 to *c* 5, EtOH. ⁱ 5% (v/v tetrahydrofuran).

formulated. Structures (10)[¶] and (11)[§] rationalize on steric grounds the configurational direction of the asymmetric induction. The rectangle embracing K⁺ symbolizes the plane of the ion pair (six-membered ring) which is visualized as being roughly parallel to the planes of the naphthalene rings in the complex. In (10) and (11), the cross sections of these planes are drawn. The C⁻ occupies the position in the complex sterically most amenable to electrophilic attack on one face of its plane. The face of this ion is *sided* because of the location of the naphthalene barriers. In (12), the configuration-determining step is formulated for the production of (6). Formulae (12) and (13) rationalize on steric grounds how the configuration of host (R)-(2) leads to (S)-(6) as the dominant enantiomer. The rectangle

group rests. The electrophile approaches the carbanion from the side opposite the K⁺ (the top), as is indicated in (12). When H is substituted for the Me group attached to C⁻ in (12) and (13), (8) is the product, and the model is compatible with the configurations of catalyst and product. Formula (14)[¶] similarly rationalizes how the configuration of host (RR)-(1) leads to (R)-(8) as the dominant enantiomer.

These results indicate that chiral hosts which complex potassium bases can be designed and synthesized. These chiral complexes catalyse the Michael addition reaction with CTN values of 55—7 to produce products of 99—60% optical purity. The base strengths of these chiral catalysts can be adapted to the acid strengths of the carbon acid reactants. The hosts have been recovered and reused many times. The

[§] When Et₂O or THF were substituted for toluene in run 9, the chemical yields were 87 or 86%, and the optical yields, 48 or 45% e.e., respectively, the configurations being (S)-(8) [(R)-(2)·KNH₂ as catalyst]. Higher temperatures gave lower e.e. values. In a run made in toluene at -78 °C with (R)-(2)·K₂CO₃ as catalyst, (R)-(4) was produced from (3) and MVK in 100% yield, 39% e.e., and a CTN of 20.

[¶] In (10) and (14), (RR)-(1) is formulated [instead of the (SS)-(1) actually used] to simplify comparisons of the drawings.

direction of the configurational bias is rationalizable on the basis of steric differences in diastereomeric transition-state models for the complexes involved.

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