Chiral Michael Addition: Methyl Vinyl Ketone Addition Catalyzed by *Cinchona* Alkaloid Derivatives

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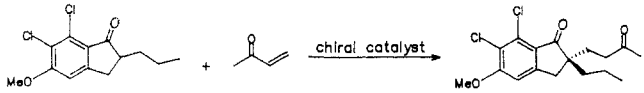
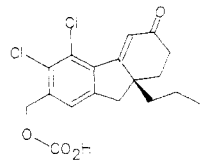
Chiral Michael additions of methyl vinyl ketone (MVK) to indanone 2-carboxylic esters are well precedented in the literature.[1] However, many of these methods are not applicable to 2-alkylindanones such as **1**, containing a proton less acidic than the β-keto ester.[2] Here we report



1 (R)-**2**

an addition of MVK to indanone **1** catalyzed by the quaternary salts of *Cinchona* alkaloids in 95% yield and up to 80% enantiomeric excess (ee). This chiral Michael addition,[3] followed by aldol condensation to complete the Robinson annelation, was the key step in our preparation of drug candidate **3**.[4]



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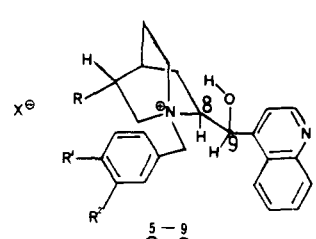
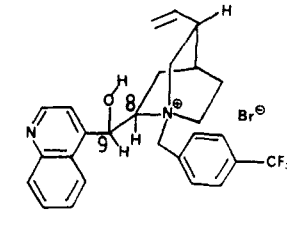
Cinchona alkaloids are not basic enough to catalyze Michael additions to the 2-propylindanone **1**. Wynberg reports[1b] that the corresponding quaternary salts are not as effective as catalysts as the free bases.[5] However, excellent results have been obtained in these laboratories in phase-transfer alkylations with quaternary *Cinchona* alkaloid catalysts[6] leading to a synthesis of **3** employing 1,3-dichloro-2-butene as an MVK surrogate. We now report that the Michael addition of **1** with MVK is possible, leading directly to the desired diketone **2**.

Table I. Enantiomeric Excess of 2 as a Function of Catalyst



5-9



4

	R	R^1	R^2	X	ee %
4					80 (*S*)
5	vinyl	Cl	Cl	Cl	20 (*R*)
6	ethyl	Cl	Cl	Cl	40 (*R*)
7	vinyl	CF_3	H	Br	40 (*R*)
8	ethyl	CF_3	H	Br	52 (*R*)
9	vinyl	CF_3	H	Cl	38 (*R*)

Results and Discussion

Reaction of the 2-propylindanone **1** with 1 equiv of methyl vinyl ketone in a two-phase toluene/50% aqueous NaOH system in the presence of 5.6 mol % of the *Cinchona* alkaloid catalyst [*p*-(trifluoromethyl)benzyl]-cinchoninium bromide (**4**) gave the MVK adduct **2** in 95% yield and 80% ee. As predicted by the proposed ion-pairing mechanism,[6] the *S* isomer predominated.

Encouraged by the excellent yield and clean reaction with MVK, we turned our attention to the desired *R* isomer. The enantiomeric *Cinchona* alkaloids are not available from natural sources. Cinchonine and cinchonidine are epimeric at C8 and C9 and these centers control the absolute stereochemistry.[6] The first catalyst investigated in the cinchonidinium series was (3,4-dichlorobenzyl)cinchonidinium chloride (**5**). An excellent yield of **2** was obtained, but in a modest 20% ee. This reaction was relatively insensitive to a wide variety of reaction parameters studied in an effort to improve the optical yield. These included changes in the organic solvent, base, base strength, temperature, stirring rate, indanone concentration, and catalyst level.[7] Simple structural modifications in the catalyst, however, gave more notable increases in ee, up to 52%.

The Michael addition is catalytic and does not require excess base. It has been postulated that the catalyst species in these reactions is transported into toluene as a dimer between the cinchoninium halide and its zwitterionic oxide.[6b,8] While the catalysts **4-9** are not soluble in toluene, after being partitioned between toluene and aqueous base a homogeneous toluene solution of the dimeric, catalytic species is obtained and the excess base can be removed. The Michael addition of indanone **1** to methyl

(1) (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057. (b) Hermann, K.; Wynberg, H. *Helv. Chim. Acta* **1977**, *60*, 2208. (c) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238. (d) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1979**, *100*, 7071. (e) Kobayashi, N.; Iwai, K. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 923. (f) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (g) Colonna, S.; Annunziata, R. *Afinidad* **1981**, *38*, 501. (h) Kobayashi, N.; Iwai, K. *J. Polym. Sci., Polym. Lett. Ed.* **1982**, *20*, 85. (i) Hodge, E.; Khoshdel, E.; Waterhouse, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2205. (j) Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312. (k) Raguse, B.; Ridley, D. D. *Aust. J. Chem.* **1984**, *37*, 2059.

(2) Only one example of a chiral addition of MVK to 2-alkylindanones is reported involving the preparation of chiral (indanone)tricarbonylchromium complexes. Jaouen G.; Meyer, A. *Tetrahedron Lett.* **1976**, 3547. Meyer, A.; Hofer, O. *J. Am. Chem. Soc.* **1980**, *102*, 4410.

(3) For other examples of Michael additions to ketones stoichiometrically functionalized with chiral auxiliaries see: Hiroi, K.; Achiwa, K.; Yamada, S. *Chem. Pharm. Bull.* **1972**, *20*, 246. Enders, D. E.; Papandopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 2967. Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.

(4) Cragoe, Jr., E. J.; Stokker, G. E.; Gould, N. P. U.S. Pat. 4 316 043, 1982.

(5) Though there is little data for direct comparison, similar results are indicated with polymer bound *Cinchona* alkaloids (ref 1e) and their quaternary salts (ref 1i).

(6) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Dolling, U.-H.; Hughes, D. L.; Bhattacharya, A.; Ryan, K. M.; Karady, S.; Weinstock, L. M.; Grabowski, E. J. J. *Book of Abstracts*, 190th National Meeting of the American Chemical Society, Chicago, IL; American Chemical Society: Washington, DC, 1985; PETR12. (c) Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem., Int. Ed. Engl.* 1986, *25*, 476.

(7) Other solvents studied included methylene chloride, hexane, and methyl *tert*-butyl ether, but none led to satisfactory reaction. Changes in the base and especially the concentration of the aqueous base led to marked variation in the reaction rate (less concentrated base giving slower reaction) but with little change in asymmetric induction. Reduction of the temperature from 25 to 5 °C gave small increases in ee. These reactions were hampered, however, by decreased solubility of **1**. Less concentrated solutions gave no change in ee. Similarly, higher catalyst levels, up to stoichiometric amounts, did not give improved enantioselectivity. This reaction was not sensitive to stirring rate.

(8) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Grabowski, E. J. J.; Schoenewaldt, E. F. *Book of Abstracts*, 188th National Meeting of the American Chemical Society, Philadelphia, PA; American Chemical Society: Washington, DC, 1984; ORGN 225.

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vinyl ketone took place in this homogeneous system with no change in the optical yield. This modification, therefore, will allow the use of Michael acceptors that are not compatible with hydroxide bases.[9]

In summary, we have demonstrated a chiral catalytic process for the addition of MVK to indanone **1** which takes place in excellent chemical yield and up to 80% ee for the *S* enantiomer and 52% ee for the *R* enantiomer.

Experimental Section

Assays for Optical Purity. Assays for optical purity were obtained by chiral liquid chromatography. A poor separation of the enantiomers **2** was obtained on a Pirkle covalent *l*-leucine column (Regis Chemical) with 0.75% isopropyl alcohol in hexane. However, base line resolution of the diastereomeric ketals formed from **2** and (2*R*,3*R*)-(−)-2,3-butanediol[10] was obtained on a Pirkle ionic phenylglycine column with 88:12:0.5 hexane/chloroform/isopropyl alcohol, flow rate of 2 mL/min, UV detector at 254 nm. Retention times *S* enantiomer, 5.8 min; *R* enantiomer, 6.2 min.

Confirmation of the ee was obtained by NMR chiral shift studies on the enantiomeric mixture **2** with an equal weight (29 mol %) of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III) derivative. The shift was observed in the methyl group adjacent to the carbonyl with the *S* enantiomer shifting to lower field relative to the *R* enantiomer.

Catalysts. Catalysts **4** and **7** are commercially available from Chemical Dynamics Corporation, South Plainfield, NJ. Catalyst **5** was prepared from cinchonidine and 3,4-dichlorobenzyl chloride in refluxing THF. The reduced catalysts **6** and **8** were prepared by hydrogenation of **5** and **7**, respectively, at 40 psi with 10% Pt/C in methanol. Catalyst **9** was prepared from **7** on an ion-exchange resin.

Chiral Methyl Vinyl Ketone Additions. Preparation of 6,7-Dichloro-2,3-dihydro-5-methoxy-2-(3-oxobutyl)-2-propyl-1*H*-inden-1-one. Three sets of conditions were employed for the Michael additions: (1) liquid/liquid phase-transfer conditions using toluene/50% NaOH, (2) liquid/solid phase-transfer conditions using toluene/KOH pellets, and (3) homogeneous conditions using a solution of the preformed catalytic species. Liquid/solid conditions were equally effective as liquid/liquid in most cases and more convenient for large-scale work. Homogeneous conditions will allow the use of base-sensitive Michael acceptors and will facilitate the investigation of low-temperature reactions. All reactions were carried out under a nitrogen atmosphere.[11] The reaction was monitored by LC. Two systems have been developed for this purpose. Normal phase: μ-Porasil, 2:1 hexane/ethyl acetate, 2 mL/min, 300 nm, $t_r(1)$ = 2.7 min, $t_r(2)$ = 8.3 min. Reverse phase: Altex, Ultrasphere IP, 65:35 CH_3CN/H_2O with 0.1% H_3PO_4, 1.5 mL/min, 300 nm, $t_r(1)$ = 8.0 min, $t_r(2)$ = 6.5 min.

Liquid/Liquid Phase-Transfer System. The catalyst, dihydro-[*p*-(trifluoromethyl)benzyl]cinchonidinium bromide (**8**) (0.5 g, 0.9 mmol) followed by 25 mL of 50% aqueous NaOH, was added to a solution of 6,7-dichloro-2,3-dihydro-5-methoxy-2-propyl-1*H*-inden-1-one (**1**) (2.73 g, 10 mmol) in 70 mL of toluene. The mixture was stirred at 25 °C, and a solution of methyl vinyl ketone (0.72 g, 10 mmol)[12] in 30 mL of toluene was added dropwise over 0.5 h. The reaction was stirred for 5 min after the completion of the addition, and the reaction was shown to be complete by LC. The organic layer was separated and washed with 50 mL of 1 N HCl: LC assay, 93 wt % yield. An aliquot, removed and derivatized as the (2*R*,3*R*)-(−)-2,3-butanediol ketal,[10] assayed at 52% ee, the *R* enantiomer predominating. The toluene solution was dried over Na_2SO_4 and filtered and the solvent removed in vacuo to yield 3.3 g: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3 H, d, *J* = 7.3 Hz, $CH_2CH_2CH_3$), 1.00–1.30 (2 H, m, $CH_2CH_2CH_3$), 1.56 (2 H, m, CH_2CH_2CO), 1.89 (2 H, m, $CH_2CH_2CH_3$), 2.09 (3 H, s, $COCH_3$), 2.35 (2 H, m, CH_2CH_2CO), 2.90 (2 H, AB, indanone CH_2), 3.99 (3 H, s, OCH_3), 6.85 (1 H, s, Ar H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 17.6, 30.0, 30.8, 37.5, 38.4, 39.5, 52.7, 56.9, 106.6, 123.0, 126.5, 131.7, 154.6, 160.9, 205.4, 208.1. Anal. Calcd for $C_{17}H_{20}Cl_2O_3$: C, 59.49; H, 5.87; Cl, 20.66. Found: C, 59.36; H, 5.92; Cl, 20.60

Liquid/Solid Phase-Transfer System. The catalyst, dihydro(3,4-dichlorobenzyl)cinchonidinium chloride (**6**) (10 g, 0.020 mol) and 40 g of KOH pellets were added to a solution of indanone **1** (100 g, 0.366 mol) in 2.5 L of toluene. A solution of methyl vinyl ketone (26.17 g, 0.366 mol) in 100 mL of toluene was added over 10 min. The reaction was stirred at 25 °C and monitored by LC to completion (1.5 h). The solid KOH was filtered and washed with 200 mL of toluene. The combined organics were washed with 1 L of 1 N HCl: assayed as above, 92 wt % yield, 40% ee.

Homogeneous System. The catalyst, dihydro(3,4-dichlorobenzyl)cinchonidinium chloride (**6**) (0.5 g) was partitioned between 60 mL of toluene and 25 mL of 50% aqueous NaOH with vigorous stirring, under N_2, for 30 min.[13] The layers were allowed to settle, and the toluene layer was removed by syringe to a clean, dry, N_2-flushed flask containing indanone **1** (2.73 g, 0.010 mol). Methyl vinyl ketone was added (0.72 g, 0.010 mol) and the reaction stirred for 30 min until complete as determined by LC. The reaction mixture was washed with 50 mL of 1 N HCl: assayed as above, 94 wt % yield, 40% ee.

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Registry No. (±)-**1**, 101375-36-4; (*S*)-**2**, 104833-01-4; (*R*)-**2**, 101165-85-9; **4**, 95088-20-3; **5**, 104778-30-5; **6**, 104761-86-6; **7**, 101311-12-0; **8**, 104761-87-7; **9**, 104761-88-8; MVK, 78-94-4; (2*R*,3*R*)-(−)-$H_3CCH(OH)CH(OH)CH_3$, 24347-58-8; cinchonidine, 485-71-2; 3,4-dichlorobenzyl chloride, 102-47-6.

(9) Work in our laboratories has been carried out with methyl and ethyl acrylate as Michael acceptors. Under phase-transfer conditions, saponification of the esters was competitive with Michael addition.

(10) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. van Leusen, D.; Rouwetts, P. H. F. M.; van Leusen, A. M. *J. Org. Chem.* **1981**, *46*, 5159.

(11) Under phase-transfer conditions the indanone **1** can air oxidize to the 2-hydroxy compound.

(12) Use of excess MVK in the phase-transfer reactions led to over reaction products. In the homogeneous system, however, there is only a catalytic amount of base and excess MVK may be used.

(13) This reaction should not be prolonged since decomposition of the catalyst does take place under these conditions.

Cleavage of Methoxymethyl Ethers with BCl_3. A Convenient, Versatile Preparation of Chloromethyl Ether Derivatives

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In conjunction with our ongoing program directed toward the synthesis of potential reactivators of organophosphorous inhibited acetylcholinesterase,[1] we required a series of chloromethyl ethers **1** which were to be used to quaternize various oxime derivaties. Although the classical procedure for preparing type **1** compounds (eq 1)[2] generally

$$ROCH_2Cl$$
1, R = alkyl, aralkyl

(1) Bedford, C. D.; Harris, R. N., III; Howd, R. A.; Miller, A.; Nolen, H. W., III, *J. Med. Chem.* **1984**, *27*, 1431.

(2) (a) Henry, L. *Bull. Cl. Sci., Acad. R. Belg.* **1893**, *25*, 439. (b) Wedekind, E. German Patent 135 310, 1902. (c) Wedekind, E. *Ber.* **1903**, *36*, 1383. (d) Walker, J. F.; Chadwick, A. F. *Ind. Eng. Chem.* **1947**, *39*, 974. (e) Clark, F. E.; Cox, S. F.; Mack, E. *J. Am. Chem. Soc.* **1917**, *39*, 712. (f) Hill, A. J.; Keach, D. T. *J. Am. Chem. Soc.* **1926**, *48*, 257. (g) Kursanov, D. N.; Setkina, V. N. *J. Appl. Chem.* USSR (*Engl. Transl.*) **1943**, *16*, 36.

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