Chiral Synthesis via Organoboranes. 42. Selective Reductions. 57. Efficient Kinetic Resolution of Representative α-Tertiary Ketones with *B*-Chlorodiisopinocampheylborane

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Kinetic resolution of racemic α-tertiary ketones with 0.5−0.6 molar equiv of *B*-chlorodiisopinocampheylborane provides the product alcohols in very high diastereomeric and enantiomeric excess, with the unreacted ketone recovered in very high ee. For example, ethyl 1-methyl-2-oxocyclopentane- and -cyclohexanecarboxylates are partially reduced to recover the ketone in 91 to ≥99% ee and the product alcohols in up to 94% de, with >90% ee for the major diastereomer. Bicyclic ketones, such as 1-methyl- and 1-ethylnorcamphor, camphor, and camphenilone, are readily resolved to provide the ketone in 92 to ≥99% ee, with the product alcohol recovered in high de and ee. Dihydrospiro[bicyclo[3.2.1]octane-2,2′(3′*H*)-furan]-3-one is resolved to provide the ketone in ≥99% ee and the product alcohol in ≥99% de. In all the cases studied, the *R*-isomer of the ketone is recovered when $^{d}Ipc_2BCl$ is used for kinetic resolution, while $^{l}Ipc_2BCl$ provides the *S*-ketone. Optimum conditions for obtaining the product alcohol, or the ketone, or both, in very high yields and ee have been established.

Introduction

The efficient syntheses of enantiomerically pure multifunctional molecules containing a chiral quaternary carbon have long fascinated organic chemists because of their considerable utility as building blocks for several biologically important compounds.[2] Fujisawa's synthesis of malyngolide and frontalin by the bakers' yeast reduction of ethyl 2-cyclopentanethiocarboxylate followed by alkylation,[3] and Westermann's synthesis of the Nitraria alkaloids, nitramine and isonitramine, via a resolution of ethyl 1-(2-cyanoethyl)-2-oxocyclohexanecarboxylate with pig liver esterase,[4] are representative examples of these. Sakai and co-workers carried out the asymmetric alkylation of 2-oxocyclopentanecarboxylates by preparing their acetals with optically pure diols, prior to the alkylation,[5] and Enders et al. used RAMP-/SAMP-hydrazone to synthesize 2-alkyl-2-cyanocycloalkanones and other polyfunctionalized chirons in high ee.[6] α-Alkyl Dieckmann esters have been used as starting material in several syntheses.[5,7]

Enzymatic kinetic resolution via the hydrolysis of racemic keto esters is a commonly employed procedure in stereoselective organic synthesis.[4,8] However, kinetic resolution of racemic ketones using organic reagents has not been studied seriously.[9] The importance of these types of chiral α-tertiary alkyl ketones and alcohols persuaded us to develop a very simple approach for their easy access via asymmetric reduction. Almost a decade ago, as part of a study of the reduction of hindered ketones with (−)-*B*-chlorodiisopinocampheylborane ($^{d}Ipc_2BCl$; Aldrich; (−)-DIP-Chloride, (−)-**1**),[10] we observed the kinetic resolution of methyl 1-methyl-2-oxocyclopentanecarboxylate (**2**), in THF at −25 °C, providing the alcohol in 96% diastereomeric and 96% enantiomeric excesses (de and ee).[11] A systematic study of this reaction to optimize the conditions for the successful resolution of several cyclic α-alkyl-*β*-keto esters and bicyclic α-*tertiary* ketones with (+)- and (−)-**1** with the simultaneous preparation of the alcohols in high de and ≥95% ee has now been completed.

Results and Discussion

The reductions of the ketones or keto esters with 0.50 molar equiv of **1**, carried out under neat conditions at room temperature (rt) and monitored by ^{11}B NMR spectroscopy of a methanolyzed aliquot (*δ* 32), are complete in 2−12 h. The usual diethanolamine[10] or

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(10) (a) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. DIP-Chloride is the trademark of Aldrich Chemical Co. (b) The superscripts *d* and *l* refer to (+)- and (−)-α-pinene, respectively, used to prepare the corresponding (−)- and (+)-DIP-Chloride, respectively.

(11) Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J. *J. Org. Chem.* **1986**, *51*, 3394.

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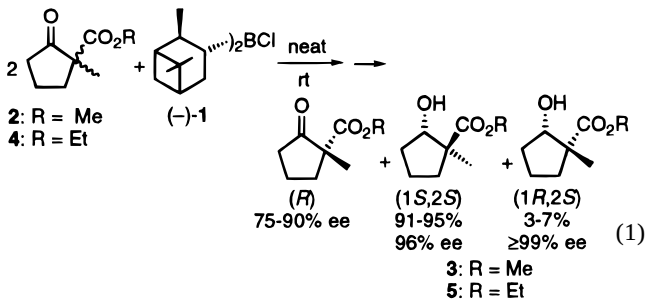
Table 1. Kinetic Resolution of α-Hindered Cyclic β-Keto Esters with (−)-1 under Neat Conditions at Room Temperature

				hydroxy ester, %				recovered keto ester		
keto ester	keto ester:reagent	yield,[a] %	*cis:trans*,[b] %	(1*S*,2*S*)	(1*S*,2*R*)	(1*R*,2*R*)	(1*R*,2*S*)	yield,[a] %	ee,[c] %	config
2	2:1	73	3:97	95	0	2	3	86	90	(*R*)
2	2:1.2	89	12:88	85	0	3	12	86	96	(*R*)
2	2:1.3	68	16:84	80	0	4	16	70	≥99	(*R*)
4	2:1	72	7:93	91	0	2	7	79	75	(*R*)[d]
4	2:1.2	80	9:91	88	0	3	9	89	96	(*R*)[d]
4	2:1.3	74	15:85	80	0	5	15	61	≥99	(*R*)[d]
4	2:1.3[e]	80	14:86	5	14	81	0	72	≥99	(*S*)[d]
6	2:1	75	5:95	84	0	11	5	81	72	(*R*)
6	2:1.2	85	3:97	83	0	14	3	91	91	(*R*)

[a] Isolated yield. [b] Determined as the TFA derivative on a Chiraldex-GTA capillary column. [c] Determined as such on a Chiraldex-GTA capillary column. [d] On the basis of analogy. [e] For a reaction using (+)-**1**.

acetaldehyde[12] workup provides diastereomeric mixtures of the product alcohol and the unreacted ketone. The ketone, product alcohol, and α-pinene, liberated during the reduction, are separated using column chromatography. The ee of the ketone is determined by gas chromatographic (GC) analysis on a Chiraldex-GTA capillary column.[13] The diastereomeric ratio of the alcohols is determined by GC analysis using a SPB-5 capillary column. Their ee values are determined by converting them either to the corresponding menthyl chloroformate (MCF)[14] or to the methoxy(trifluoromethyl)phenylacetates (MTPA derivative),[15] followed by analysis on a SPB-5 capillary column. Frequently, the alcohols are esterified to the corresponding trifluoroacetates and analyzed using a Chiraldex-GTA capillary column.

Kinetic Resolution of α-Hindered Cyclic β-Keto Esters. Methyl 1-Methyl-2-oxocyclopentanecarboxylate (2). We had reported the reduction of **2** with 0.50 molar equiv of (−)-**1**, at rt, when the major diastereomer of the alcohol was obtained in 93% ee.[11] But the configuration of the product alcohol and recovered ketone was not established. This reaction was repeated, complete in 2 h, to reproduce our earlier results (eq 1). The usual



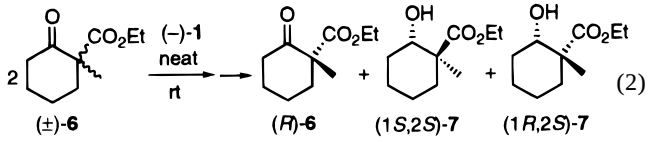
(1)

diethanolamine workup provides the recovered ketone in 86% yield with a 73% yield of methyl 1-methyl-2-hydroxycyclopentanecarboxylate (**3**). The diastereomeric ratio of the alcohols was determined by gas chromatographic and ^{1}H NMR spectroscopic comparison of the product alcohols with that obtained from the reduction with $NaBH_4$, as described in the literature.[16] The analysis shows that the reduction of **2** with 0.50 equiv of **1** provides 94% de for the (1*S*,2*S*)-*trans* isomer **3** in 96% ee. The configurations of all of the diastereomers of the product are assigned on the basis of the configuration of the recovered ketone coupled with the identification of the major diastereomer as the *trans*-alcohol. The proposed mechanism of reduction with ^{d}Ipc$_2$BCl supports this assignment.[10] This methodology is used to assign the configurations for all of the products reported herein. The *cis* isomer shows ≥99% ee. The excess ketone, recovered in 86% yield, is enriched in the (*R*)-isomer in 90% ee (eq 1). A good correspondence between the % ee of the recovered ketone and the product alcohols formed is obvious.

The efficiency of the kinetic resolution increases when 0.60 equiv of the reagent is used, al beit at the expense of the de and ee values of the product alcohol.[17] Utilization of 0.65 equiv of the reagent provides essentially optically pure ketone.

Ethyl 1-Methyl-2-oxocyclopentanecarboxylate (4). The effect of the ester grouping on the stereochemical outcome was tested by reducing **4**, the ethyl ester analog of **2**, with (−)-**1**. Essentially similar results are realized (eq 1). On the basis of the analogous reaction of **2**, we believe that we have recovered (*R*)-**4** in ≥99% ee.

Ethyl 1-Methyl-2-oxocyclohexanecarboxylate (6). The results are similar also for the reduction of the cyclohexane analog of **4**, namely **6** (eq 2). The diastereomeric ratio of the product alcohol is again determined by comparing it with the product obtained from the reduction of **6** with $NaBH_4$. Unlike **4**, the reduction of **6** with $NaBH_4$ produces the *cis* alcohol as the predominant isomer, as reported in the literature.[16] However, ^{d}Ipc$_2$BCl provides the (1*S*,2*S*)-isomer (*trans*) as the major diastereomer, consistent with the stereochemistry of the product obtained from **2** and **4**. The recovered ketone shows an ee of 91% (*R*) when 0.60 equiv of the reagent is used for kinetic resolution. The results of the kinetic resolution of these keto esters are summarized in Table 1.



(2)

Kinetic Resolution of Bicyclo[2.2.1]heptan-2-ones. Due to their application in the syntheses of several natural products,[18] medicinal compounds,[19] and chiral

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(13) Chiraldex-GTA is a trademark of Alltech Associates, Inc.
(14) Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978.
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(16) Nerdel, F.; Frank, D.; Barth, G. *Chem. Ber.* **1969**, *102*, 395.
(17) We had reported that the reaction of **2** with **1** in THF at −25 °C is complete in 60 h[11] and obtained the product alcohol in 96% de and ee. In this case the recovered ketone was also obtained in 96% ee.
(18) Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519.
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Table 2. Kinetic Resolution of α-Hindered Bicyclic Ketones with 1 under Neat Conditions at Room Temperature

				product alcohol					recovered ketone		
					endo[c]		*exo*[c]				
ketone	reagent	ketone:reagent	yield,[a] %	*endo:exo*[b]	(1*R*), %	(1*S*), %	(1*R*), %	(1*S*), %	yield,[a] %	ee,[d] %	config
1-methylnorcamphor (**8**)	(−)-**1**	2:1	89	9:91	9	0	5	86	97	63	(1*R*)
1-methylnorcamphor (**8**)	(−)-**1**	2:1.2	91	13:87	13	0	3	84	92	88	(1*R*)
1-methylnorcamphor (**8**)[e]	(−)-**1**	2:1.4	92	16:84	16	0	4	80	91	≥99	(1*R*)
1-methylnorcamphor (**8**)[e]	(+)-**1**	2:1.4	93	21:79	0	21	76	3	91	≥99	(1*S*)
1-ethylnorcamphor (**10**)	(−)-**1**	2:1:2	84	14:86	14	0	2	84	78	92	(1*R*)[f]
camphor (**12**)	(−)-**1**	2:1	94	1:99	1	0	3	96	89	66	(1*R*)
camphor (**12**)	(+)-**1**	2:1	95	2:98	0.2	1.8	96	2	91	64	(1*S*)
camphor (**12**)	(−)-**1**	2:1.2	94	3:97	3	0	4	93	94	98	(1*R*)
camphenilone (**14**)	(−)-**1**	2:1	91	94:6	2	92	6	0	92	78	(1*R*)
camphenilone (**14**)	(−)-**1**	2:1.2	92	86:14	2	84	14	0	98	97	(1*R*)
spirofuranone (**16**)	(−)-**1**	2:1.2	78	≥99:0	23	77	0	0	81	89	(1*R*)
spirofuranone (**16**)	(+)-**1**	2:1.2	84	≥99:0	78	22	0	0	94	94	(1*S*)
spirofuranone (**16**)[e]	(−)-**1**	2:1.45	90	≥99:0	29	71	0	0	96	≥99	(1*R*)

[a] Isolated yield. [b] Determined by analysis on a SPB-5 capilary column. [c] Determined as a derivative on a capillary column. [d] Determined by direct analysis on a Chiraldex-GTA capillary column. [e] At 0 °C. [f] On the basis of analogy.

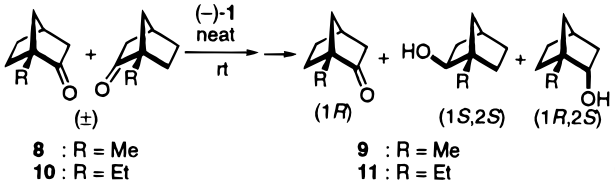
Table 3. Kinetic Resolution of Camphenilone with 1 under Different Conditions

				product alcohol					recovered ketone		
					endo[c]		*exo*[c]				
reagent	ketone:reagent	reactn temp	yield,[a] %	*endo:exo*[b]	(1*R*), %	(1*S*), %	(1*R*), %	(1*S*), %	yield,[a] %	ee,[d] %	config
(−)-**1**	2:0.9	rt	92	95:5	1	94	3	2	85	70	(1*R*)
(−)-**1**	2:1	rt	91	94:6	2	92	6	0	92	78	(1*R*)
(−)-**1**	2:1.1	rt	93	91:9	1	90	6	3	89	92	(1*R*)
(−)-**1**	2:1.1	0 °C	92	97:3	0	92	3	5	86	95	(1*R*)
(−)-**1**	2:1.2	rt	92	86:14	2	84	14	0	98	97	(1*R*)
(−)-**1**	2:1.2	0 °C	90	91:9	1	90	6	3	88	≥99	(1*R*)
(+)-**1**[e]	2:1.2	0 °C	95	91:9	90	1	3	6	98	≥99	(1*S*)
(−)-**1**	2:1.3	rt	87	82:18	2	80	14	4	90	≥99	(1*R*)

[a] Isolated yield. [b] Determined by analysis on a SPB-5 capillary column. [c] Determined as a derivative on a capillary column. [d] Determined by direct analysis on a Chiraldex-GTA capillary column. [e] Large-scale reaction, acetaldehyde workup.

auxiliaries,[20] the kinetic resolution of bicyclo[2.2.1]heptan-2-ones has been attempted in the past.[21] The applicability of **1** for the resolution of representative bicyclic ketones with an α-tertiary center in excellent de and ee is summarized in Tables 2 and 3. The discussion of the kinetic resolution of individual ketones is continued below.

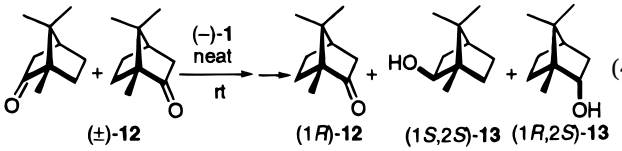
1-Methylnorcamphor. We had earlier reported that 1-methyl-2-norbornanone (**8**) is partially reduced with (−)-**1** in THF at rt to produce the (1*S*,2*S*)-isomer of the alcohol in 89% ee (eq 3).[11] Repetition of this reaction under neat condition at rt provides a 90% yield of the product alcohol showing an *exo*/*endo* ratio of 91:9, the *exo*-alcohol in 94% ee and the *endo*-isomer in ≥99% ee. The *exo*/*endo* ratio is determined by GC comparison with the product obtained from a sodium borohydride reduction of **8**.[22] The (1*R*)-isomer of the excess ketone is recovered in 95% yield and 63% ee. A reaction of the ketone with 0.60 molar equiv of the reagent provides the recovered ketone in 88% ee. Increasing the amount of the reagent to 0.70 equiv, while lowering the reaction temperature to 0 °C, provides enantiomerically pure **8**. The optical rotation of the sample of enantiopure **8** prepared by this procedure, $[\alpha]^{25}_D = -45.50$ (*c* 5.03, $CHCl_3$) for the (1*R*)-**8**, or $[\alpha]^{25}_D = +45.91$ (*c* 4.57, $CHCl_3$) for the (1*S*)-**8**, is lower than that calculated to be $[\alpha]^{22}_D = -52$ ($CHCl_3$) by Berson and co-workers.[23]



(3)

1-Ethylnorcamphor. The kinetic resolution of 1-ethyl-2-norbornanone (**10**) provides essentially similar results as the methyl analog (eq 3). On the basis of the analogous reaction of **8**, we believe that we have recovered (1*R*)-**10** in 92% ee.

Camphor. The reaction of camphor (**12**) with 0.50 molar equiv of (−)-**1** provides 99% of the *exo*-alcohol in 94% ee, and the excess ketone is recovered in 66% ee in the (*R*)-isomer. However, 0.60 molar equiv of **1** provides the recovered ketone, (1*R*)-**12**, in 98% ee (eq 4).



(4)

Camphenilone. The reaction of camphenilone (**14**) also provides similar results (eq 5). The reduction of **14**

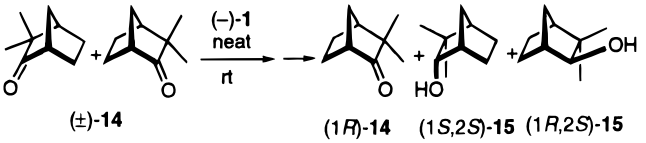
(20) (a) Hoffman, R. W.; Harold, T. *Chem. Ber.* **1981**, *114*, 375. (b) Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 2258. (c) Keegan, D. S.; Midland, M. M.; Werley, R. T.; McLoughlin, J. I. *J. Org. Chem.* **1991**, *56*, 1185. (d) ShengJian, L.; Yaozhong, J.; Aiqiao, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1467.

(21) Irwin A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 8476.

(22) The reduction of 1-methylnorcamphor and camphenilone with $NaBH_4$ in ethanol at rt provides the product alcohol with an *endo*/*exo* ratio of 95:5 and 96:4, respectively.

(23) A rotation of −12.5 (*c* 2.41, $CHCl_3$) is reported for partially pure (1*R*)-**8**. On the basis of this, the optical rotation of optically pure (1*R*)-**8** was calculated to be −52.0 (*c*, $CHCl_3$). Berson, J. A.; Walia, J. S.; Remanick, A.; Suzuki, S. *J. Am. Chem. Soc.* **1961**, *83*, 3986.

with 0.5 equiv of (−)-**1** provides 94% of the *endo*-alcohol in 96% ee as the major isomer. The *exo*/*endo* ratio is determined by GC comparison with the product obtained from a sodium borohydride reduction of **14**.[22] The recovered ketone is analyzed to be 78% ee in the (1*R*)-isomer. Increasing the reagent used to 60% improves the ee of the ketone, (1*R*)-**14**, to 92%.

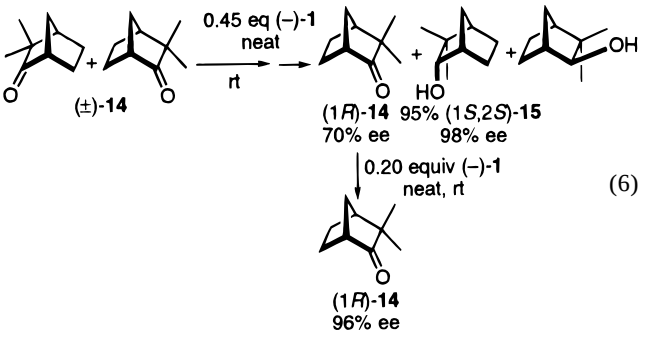


(5)

Effect of Stoichiometry. The effect of the stoichiometry and temperature on this kinetic resolution procedure was studied for the reduction of **14**. Thus, the treatment of **14** with 0.45−0.65 equiv of **1**, in increments of 0.05 equiv, at different temperatures clearly shows the effect on the % ee of the recovered ketone as summarized in Table 3. Optically pure **14** is obtained by carrying out the kinetic resolution either with 0.60 equiv of **1** at 0 °C or with 0.65 equiv of the reagent at rt.

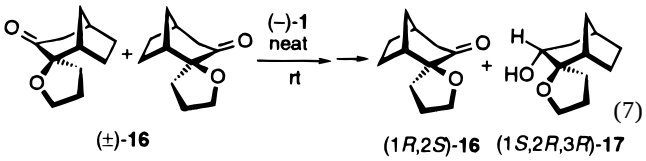
The product alcohol is obtained in higher diastereomeric excess by using slightly less than 0.50 equiv of the reagent and by conducting the reaction at the lower temperature.

Two-Step Kinetic Resolution. The procedures discussed thus far produce either the ketone or the alcohol in high ee. The ee of the recovered ketone is increased at the expense of the % de and % ee of the product alcohol. To achieve maximum optical purity for the alcohol and the ketone, a two-step procedure was developed. The reduction of **14** with 0.45 molar equiv of the reagent at rt provides 95% *endo*-**15** in 98% ee. The ketone and the alcohol are separated by column chromatography, and the recovered **14** is then treated with 0.20 equiv of **1** at rt and worked up when the % ee is improved from 70% to 96% (eq 6). Adopting this procedure, we can obtain both the product alcohol and the ketone in very high ee.



(6)

Dihydrospiro[bicyclo[3.2.1]octane-2,2′(3′*H*)-furan]-3-one (16). Recently, Paquette described the synthesis of dihydrospiro[bicyclo[3.2.1]octane-2,2′(3′*H*)-furan]-3-one (**16**) by an oxonium ion initiated pinacol-like rearrangement.[24] We considered **16** to be an ideal compound to test the capability of **1** for kinetic resolution since it contains an α-quaternary carbon center. So far, the kinetic resolution of ketones with $^{d}Ipc_2BCl$ provided the (*R*)-isomer for the quaternary center of the recovered ketone. In the case of **16**, we were interested in observing whether the chiral center at the 1-position of the starting norcamphor or the newly created α-chiral center controls the kinetic resolution. The reaction of **16** with 0.60 equiv of (−)-**1** provides the product alcohol in ≥99% de, and the excess ketone is recovered in 89% ee. Utilization of 0.7 equiv of **1** provides **16** in ≥99% ee (eq 7). The



(7)

stereochemistry of the recovered ketone and the product alcohol are determined as follows. Paquette has reported that the reduction of **16** with Dibal-H produces the *endo*-alcohol as the major isomer.[24] Comparison of the product obtained from the Dibal-H reduction with that realized from the DIP-Chloride reduction shows it to be exclusively *endo*. This is confirmed by an X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative (**18**)[25] of the alcohol obtained from the DIP-Chloride reduction of optically pure **16** recovered from kinetic resolution with (−)-**1**. The X-ray analysis confirms that the recovered ketone is 1*R*,2*S*, showing that the chirality at the 1-position still influences the rate of reduction.

In some of these kinetic resolution experiments, we utilized (+)-**1** ($^{l}Ipc_2BCl$) to yield the opposite isomer of the alcohol and recover the (*S*)-isomer of the ketone (Tables 1−3). The scaling up[26] of this kinetic resolution methodology was tested by resolving 0.5 mol of **14** with 0.6 equiv of (+)-**1** using acetaldehyde workup.[12] The alcohol is obtained in 95% yield, and the ketone is recovered in 98% yield and ≥99% ee, while the chiral auxiliary, α-pinene, is recovered in 95% yield in a readily recyclable form.

Conclusions

In conclusion, we have demonstrated the use of **1** for the kinetic resolution of representative α-tertiary cyclic and bicyclic ketones. Optimum conditions to obtain either the product alcohol or the ketone or both, in very high yields and ee, have been established. This procedure can be used as an excellent alternative to asymmetric alkylations of carbonyls for the generation of *tertiary* chiral centers. This adds to the attractiveness of our reagent, one that has already found a number of applications in organic syntheses.

Experimental Section

General Methods. Techniques for handling air-sensitive compounds have been previously described.[27] Analyses of the MTPA esters or MCF derivatives were performed on a gas chromatograph (GC) using a SPB-5 capillary column (30 m), at appropriate temperatures. Some of the product alcohols were converted to the trifluoroacetates and analyzed on a Chiraldex-GTA capillary column (23 m).

(24) (a) Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956.

(25) Paquette and co-workers could crystallize only the minor (15%) *exo*-isomer of **18** for X-ray data.

(26) DIP-Chloride has been utilized for preparative-scale reactions. For example, see: King, A. O.; Corley, E. G.; Anderson, R. K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; Labelle, M.; Prasit, P.; Zamboni, R. *J. Org. Chem.* **1993**, *58*, 3731.

(27) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975; Chapter 9.

Materials. Ethyl ether (EE) (Mallinckrodt) was used as received. (±)-Camphenilone was a sample previously obtained from the Chemical Samples Co. All other chemicals were purchased from Aldrich Chemical Co. α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) obtained from Aldrich Chemical Co. was converted to the acid chloride using Mosher's procedure.[15]

Kinetic Resolution of Ketones with 1. General Procedure. An oven-dried 50 mL round bottom flask equipped with a septum-capped side arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. The ketone (20 mmol) and DIP-Chloride (10 mmol) were transferred to the flask in a glovebag. The reaction mixture was stirred at appropriate temperatures until the reaction was complete as shown by the ^{11}B NMR spectrum of a methanolyzed aliquot (δ 32). EE (25 mL) was added, followed by diethanolamine (22 mmol), and the mixture was stirred for 2 h when the boron components precipitated as a complex. This precipitate was filtered and washed with pentane. The combined filtrates were concentrated and chromatographed using vacuum liquid chromatography on silica gel. α-Pinene was eluted with pentane, and the recovered ketone was eluted with pentane:EE (9:1), followed by elution of the alcohol with pentane:EE (1:1). The ketone was further purified by preparative GC on a SE-30 column, and the rotation was measured. The ee of the ketone was determined by analysis on a gas chromatograph using a Chiraldex-GTA capillary column (23 m). The *cis*/*trans* or *exo*/*endo* ratios of the alcohols were determined by a GC comparison (SPB-5 capillary column) with the product obtained from the reduction of the ketone with $NaBH_4$. The ee of the diastereomers were determined by converting the alcohol to the MCF, MTPA, or TFA derivative and analysis on a GC using an appropriate capillary column. The reactions of individual ketones are presented below.

Kinetic Resolution of Methyl 1-Methyl-2-oxocyclopentanecarboxylate (2). (a) 2:1 Reaction. The keto ester was prepared in 91% yield by the methylation of methyl 2-oxocyclopentanecarboxylate using NaH and iodomethane in THF, bp 80 °C/3.7 mmHg. **2** (28 mmol, 4.37 g) was treated with 4.5 g (14 mmol) of (−)-**1** at rt as described in the general procedure. The reaction was complete in 2 h. Workup and chromatography provided 1.62 g (73%) of the product hydroxy ester and 1.87 g (86%) of the recovered keto ester. Analysis of the TFA derivative of the alcohol on a Chiraldex-GTA column showed an isomeric composition of 95% (1*S*,2*S*)-**3**, 2% (1*R*,2*R*)-**3**, and 3% (1*R*,2*S*)-**3**. The recovered keto ester was analyzed on a Chiraldex-GTA capillary column which showed a composition of 95% of the (*R*)-isomer and 5% of the (*S*)-isomer. The spectral data of the recovered keto ester are identical to those of (±)-**2**.

(b) 2:1.3 Reaction. **2** (53.6 mmol, 8.36 g) was treated with 11.17 g (34.8 mmol) of (−)-**1** at rt. The reaction was complete in 12 h. Workup as above provided 2.05 g (70%) of the recovered keto ester and 3.74 g (68%) of the hydroxy ester. The keto ester was analyzed to be of ≥99% ee in the (*R*)-isomer. $[\alpha]^{22}_D = -11.41$ (*c* 4.98, $CHCl_3$) corresponds to an optical purity of ≥99% on the basis of the rotation reported in the literature.[3] The hydroxy ester showed an isomeric composition of 80% (1*S*,2*S*)-**3**, 4% (1*R*,2*R*)-**3**, and 16% (1*R*,2*S*)-**3**.

Kinetic Resolution of Ethyl 1-Methyl-2-oxocyclopentanecarboxylate (4). (a) 2:1 Reaction. The keto ester was prepared in 93% yield by the methylation of ethyl 2-oxocyclopentanecarboxylate using NaH and iodomethane in THF, bp 76 °C/2.1 mmHg. **4** (22 mmol, 3.75 g) was treated with 3.54 g (11 mmol) of (−)-**1** at rt as described in the general procedure. The reaction was complete in 2 h. Workup and chromatography provided 1.37 g (72%) of the product hydroxy ester and 1.48 g (79%) of the recovered keto ester. Analysis of the TFA derivative of the alcohol on a Chiraldex-GTA column showed an isomeric composition of 91% (1*S*,2*S*)-**5**, 2% (1*R*,2*R*)-**5**, and 7% (1*R*,2*S*)-**5**. The recovered keto ester was analyzed on a Chiraldex-GTA capillary column which showed a composition of 87.5% of the (*R*)-isomer and 12.5% of the (*S*)-isomer. The spectral data of the recovered keto ester are identical to those of (±)-**4**.

(b) 2:1.3 Reaction. **4** (126 mmol, 21.42 g) was treated with 26.27 g (81.9 mmol) of (−)-**1** at rt. The reaction was complete in 2 h. Workup as above provided 4.57 g (61%) of the recovered keto ester and 10.42 g (74%) of the hydroxy ester. The keto ester was analyzed to be of ≥99% ee in the (*R*)-isomer. $[\alpha]^{22}_D = -16.09$ (*c* 5.9, $CHCl_3$).[28] The hydroxy ester has an isomeric composition of 80% (1*S*,2*S*)-**5**, 5% (1*R*,2*R*)-**5**, and 15% (1*R*,2*S*)-**5**.

(c) 2:1.3 Reaction, with (+)-1. **4** (65.2 mmol, 11.09 g) was treated with 13.6 g (42.4 mmol) of (+)-**1** at rt. The reaction was complete in 2 h. Workup as above provided 2.79 g (72%) of the recovered keto ester and 5.84 g (80%) of the hydroxy ester. The keto ester was analyzed to be of ≥99% ee in the (*S*)-isomer. $[\alpha]^{22}_D = +15.99$ (*c* 4.2, $CHCl_3$).[28] ^{1}H NMR δ (ppm) ($CDCl_3$): 1.22−1.27 (t, 7.1 Hz), 1.31 (s), 1.82−2.58 (m), 4.12−4.20 (m). ^{13}C NMR δ (ppm) ($CDCl_3$): 13.97, 19.30, 19.48, 36.13, 37.56, 55.81, 61.20, 172.27, 215.73. Anal. Calcd for $C_9H_{14}O_3$: C, 63.31; H, 8.30. Found: C, 63.49; H, 8.38.

The hydroxy ester has an isomeric composition of 5% (1*S*,2*S*)-**5**, 81% (1*R*,2*R*)-**5**, and 14% (1*S*,2*R*)-**5**.

Kinetic Resolution of Ethyl 1-Methyl-2-oxocyclohexanecarboxylate (6). (a) 2:1 Reaction. The keto ester was prepared in 99% yield by the methylation of ethyl 2-oxocyclohexanecarboxylate using NaH and iodomethane in THF, bp 74−75 °C/1.9 mmHg. **6** (23 mmol, 4.23 g) was treated with 11.5 mmol (3.69 g) of (−)-**1** at rt as described in the general procedure. The reaction was complete in 3 h. Workup and chromatography provided 1.60 g (75%) of the product hydroxy ester and 1.71 g (81%) of the recovered keto ester. Analysis of the TFA derivative of the alcohol showed a composition of 84% (1*S*,2*S*)-**7**, 11% (1*R*,2*R*)-**7**, and 5% (1*R*,2*S*)-**7**. The recovered keto ester was analyzed on a Chiraldex-GTA capillary column which showed a composition of 86% of the (*R*)-isomer and 14% of the (*S*)-isomer. $[\alpha]^{25}_D = -85.40$ (*c* 5.85, $CHCl_3$) corresponds to an optical purity of ≥99% on the basis of the maximum rotation, $[\alpha]_D = +66.1$ ($CHCl_3$), reported in the literature for the (*S*)-isomer.[4] The spectral data of the recovered keto ester are identical to those of (±)-**6**.

(b) 2:1.2 Reaction. **6** (10.2 mmol, 1.88 g) was treated with 1.97 g (6.1 mmol) of (−)-**1** at rt. The reaction was complete in 3 h. Workup as above provided 0.69 g (91%) of the recovered keto ester and 0.96 g (85%) of the hydroxy ester. The keto ester was analyzed to be of 91% ee in the (*R*)-isomer. $[\alpha]^{25}_D = -105.86$ (*c* 6.83, $CHCl_3$) corresponds to an optical purity of ≥99% on the basis of the maximum rotation, $[\alpha]_D = +66.1$ ($CHCl_3$), reported in the literature for the (*S*)-isomer.[4] The hydroxy ester showed a composition of 83% (1*S*,2*S*)-**7**, 14% (1*R*,2*R*)-**7**, and 3% (1*R*,2*S*)-**7**.

Kinetic Resolution of 1-Methylnorcamphor (8). (a) 2:1 Reaction. This bicyclic ketone was prepared in 56% yield from norcamphor using a literature procedure, bp 60−63 °C/11 mmHg.[23] **8** (15 mmol, 1.86 g) was treated with 2.41 g (7.5 mmol) of (−)-**1** at rt as described in the general procedure. The reaction was complete within 2 h. Workup and chromatography provided 0.84 g (89%) of the product alcohol and 0.90 g (97%) of the recovered ketone. Gas chromatographic analysis of the alcohol showed a composition of 91% of the *exo* and 9% of the *endo* product. Analysis of its MCF derivative on a SPB-5 capillary column showed a composition of 86% (1*S*) and 5% (1*R*) of the *exo* product and 9% (1*R*) of the *endo* product. The recovered ketone was analyzed on a Chiraldex-GTA capillary column which showed an ee of 63% in the (1*R*)-isomer.

(b) 2:1.4 Reaction. **8** (80.5 mmol, 9.98 g) was treated with 18.08 g (56.4 mmol) of (−)-**1** at 0 °C. The reaction was complete in 5 h. Workup as above provided 2.72 g (91%) of the recovered ketone and 6.53 g (92%) of the alcohol. The ketone was analyzed to be of ≥99% ee in the (1*R*)-isomer. $[\alpha]^{25}_D = -41.70$ (*c* 3.18, EtOH). The optical rotation was noted in $CHCl_3$ also to compare with the calculated rotation reported in the literature.[23] $[\alpha]^{25}_D = -45.49$ (*c* 5.03, $CHCl_3$). Upon

(28) A rotation of $[\alpha]_D = +1.7$ (*c* 10.33, $CHCl_3$) is reported in the literature for **4** without any assignment of the configuration. Saigo, K.; Koda, H.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3119. On the basis of the analogy with other resolutions, we believe that (*R*)-**4** is obtained after kinetic resolution.

analysis as the MCF derivative on a SPB-5 capillary column, the alcohol showed a composition of 80% (1*S*) and 4% (1*R*) of the *exo* product and 16% (1*R*) of the *endo* product.

(c) 2:1.4 Reaction, with (+)-1. 8 (68.1 mmol, 8.45 g) was treated with 15.3 g (47.7 mmol) of (+)-**1** at 0 °C. The reaction was complete in 5 h. Workup as above provided 2.30 g (91%) of the recovered ketone and 5.58 g (93%) of the alcohol. $[\alpha]^{25}_D = +45.91$ (*c* 4.57, $CHCl_3$). Upon analysis as the MCF derivative on a SPB-5 capillary column, the alcohol showed a composition of 3% (1*S*) and 76% (1*R*) of the *exo* product and 21% (1*S*) of the *endo* product.

Kinetic Resolution of 1-Ethylnorcamphor (10). 2:1.2 Reaction. This bicyclic ketone was prepared in 50% yield from norcamphor using the same procedure used for the preparation of **8**, bp 71−73 °C/12 mmHg. This material showed identical properties to **10** reported in the literature.[29] **10** (9.6 mmol, 1.33 g) was treated with 1.85 g (5.8 mmol) of (−)-**1** at rt as described in the general procedure. The reaction was complete within 2 h. Workup and chromatography provided 0.68 g (84%) of the product alcohol and 0.41 g (78%) of the recovered ketone. Gas chromatographic analysis of the alcohol showed a composition of 86% of the *exo* and 14% of the *endo* product. Analysis of its MCF derivative on a SPB-5 capillary column showed a composition of 84% (1*S*) and 2% (1*R*) of the *exo* product and 14% (1*R*) of the *endo* product. The recovered ketone was analyzed on a Chiraldex-GTA capillary column which showed an ee of 92%. On the basis of analogy, we believe that this corresponds to the (1*R*)-isomer: $\alpha^{25}_D = -32.51$ (neat). The spectral data of the recovered ketone are identical to those of (±)-**10**.

Kinetic Resolution of Camphor (12). (a) 2:1 Reaction. 12 (17.2 mmol, 2.61 g) was treated with 2.76 g (8.6 mmol) of (−)-**1** at rt as described in the general procedure. The reaction was complete within 1 h. Workup and chromatography provided 1.25 g (94%) of the product alcohol and 1.16 g (89%) of the recovered ketone. Gas chromatographic analysis of the alcohol showed a composition of 99% of the *exo* and 1% of the *endo* product. Analysis of its MCF derivative on a SPB-5 capillary column showed a composition of 96% (1*S*) and 3% (1*R*) of the *exo* product and 1% of the (1*R*) *endo* product. The recovered ketone was analyzed on a Chiraldex-GTA capillary column which showed an ee of 66% in the (1*R*)-isomer.

(b) 2:1.2 Reaction. 12 (8.9 mmol, 1.36 g) was treated with 1.72 g (5.4 mmol) of (−)-**1** at rt. The reaction was complete in 2 h. Workup as above provided 0.51 g (94%) of the recovered ketone and 0.78 g (94%) of the alcohol (*exo*:*endo* 97:3). Analysis of the MCF derivative of the alcohol on a SPB-5 capillary column showed a composition of 93% (1*S*) and 4% (1*R*) of the *exo* product and 3% (1*R*) of the *endo* product. The ketone was analyzed to be of 98% ee in the (1*R*)-isomer. $[\alpha]^{25}_D = +43.39$ (*c* 4.48, EtOH) corresponds to an optical purity of 99.5% on the basis of the rotation of $[\alpha]^{20}_D = +43.6$ (*c* 5, EtOH) reported in the literature.[30]

Kinetic Resolution of Camphenilone (14). (a) 2:0.9 Reaction. 14 (79.9 mmol, 11.02 g) was treated with 11.53 g (35.9 mmol) of (−)-**1** at rt as described in the general procedure. The reaction was complete within 2 h. Workup and chromatography provided 4.63 g (92%) of the product alcohol and 5.15 g (85%) of the recovered ketone. Gas chromatographic analysis of the alcohol showed a composition of 5% of *exo* and 95% of *endo* product. Analysis of the MCF derivative of the alcohol on a SPB-5 capillary column showed a composition of 94% (1*S*) and 1% (1*R*) of the *endo* product and 3% (1*R*) and 2% (1*S*) of the *exo* product. The recovered ketone was analyzed on a Chiraldex-GTA capillary column which showed an ee of 70% in the (1*R*)-isomer.

The recovered ketone from the above reaction (1.9 g, 13.8 mmol) was treated with 0.88 g (2.8 mmol, 0.2 equiv) of (−)-**1**. The reaction was complete in 6 h, and workup provided 1.41 g (93%) of recovered ketone which was analyzed on a Chiraldex-GTA capillary column to show 96% ee in the (1*R*)-isomer.

(b) 2:1 Reaction. 14 (16.2 mmol, 2.23 g) was treated with 2.60 g (8.1 mmol) of (-)-**1** at rt. The reaction was complete in 2 h. Workup as above provided 1.03 g (92%) of the recovered ketone and 1.03 g (91%) of the alcohol. The ketone was analyzed to be of 78% ee in the (1*R*)-isomer: $[\alpha]^{23}_D = -55.97$ (*c* 2.58, EtOH) which corresponds to an optical purity of 79.5% on the basis of the maximum rotation reported in the literature, $[\alpha]^{24}_D = +70.4$ for *d*-camphenilone.[31] Analysis of the MCF derivative of the alcochol on a SPB-5 capillary column showed a composition of 92% (1*R*) and 2% (1*S*) of the *endo* product and 6% (1*S*) of the *exo* product.

(c) 2:1.2 Reaction, at 0 °C. 14 (9.3 mmol, 1.29 g) was treated with 1.80 g (5.6 mmol) of (−)-**1** at rt. The reaction was complete in 10 h. Workup as above provided 0.45 g (88%) of the recovered ketone and 0.70 g (90%) of the alcohol. The ketone was analyzed to be of ≥99% ee in the (1*R*)-isomer: $[\alpha]^{25}_D = -72.26$ (*c* 5.21, EtOH).[31] Analysis of the MCF derivative of the alcohol on a SPB-5 capillary column showed a composition of 90% (1*S*) and 1% (1*R*) of the *endo* product and 6% (1*R*) and 3% (1*S*) of the *exo* product.

(d) 2:1.3 Reaction, at rt. 14 (10.4 mmol, 1.43 g) was treated with 2.16 g (6.7 mmol) of (−)-**1** at rt. The reaction was complete in 2 h. Workup as above provided 0.46 g (90%) of the recovered ketone and 0.82 g (87%) of the alcohol. The ketone was analyzed to be of ≥99% ee in the (1*R*)-isomer: $[\alpha]^{25}_D = -72.19$ (*c* 3.01, EtOH).[31] Analysis of the MCF derivative of the alcohol on a SPB-5 capillary column showed a composition of 80% (1*S*) and 2% (1*R*) of the *endo* product and 14% (1*R*) and 4% (1*S*) of the *exo* product.

(e) Preparative Scale Kinetic Resolution of 14. 14 (0.5 mol, 69 g) was treated with 96 g (0.3 mol) of (+)-**1**, under neat conditions, at 0 °C. The reaction was complete in 10 h. Ethyl ether (200 mL) was added to the flask, followed by 20 mL of acetaldehyde (1.2 equiv) at 0 °C. The mixture was warmed to rt and stirred for 5 h. The ^{11}B NMR spectrum of a methanolzed aliquot (δ 18) showed complete elimination of α-pinene. The reaction mixture was then treated with 100 mL of 6 *N* NaOH and stirred for 1 h. The organics were extracted with EE, washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography on silica gel provided 77.5 g (95%) of α-pinene, 39.9 g (95%) of **15**, and 27.0 g (98%) of **14**. The ketone was analyzed to be of ≥99% ee in the (1*S*)-isomer: $[\alpha]^{25}_D = +72.17$ (*c* 3.5, EtOH).[31] Analysis of the MCF derivative of the alcohol on a SPB-5 capillary column showed a composition of 90% (1*R*) and 1% (1*S*) of the *endo* product and 6% (1*S*) and 3% (1*R*) of the *exo* product.

Kinetic Resolution of Dihydrospiro[bicyclo[3.2.1]-octane-2,2′(3′*H*)-furan]-3-one (16). (a) 2:1.2 Reaction. This bicyclic spiro ketone was prepared in 85% yield from norcamphor using a literature procedure.[24] **16** (17.7 mmol, 3.19 g) was treated with 3.42 g (10.7 mmol) of (−)-**1** at rt as described in the general procedure. The reaction was complete within 12 h. Workup and chromatography provided 1.52 g (78%) of the product alcohol and 1.02 g (81%) of the recovered ketone. Gas chromatographic analysis of the alcohol showed a composition of ≥99% of the *endo* product. Analysis of its TFA derivative on a Chiraldex-GTA capillary column showed a composition of 77% of (1*S*)-*endo* and 23% of (1*R*)-*endo*. The recovered ketone was analyzed on a Chiraldex-GTA capillary column which showed an ee of 89% in the (1*R*, 2*S*)-isomer. $[\alpha]^{25}_D = -16.52$ (*c* 6.0, $CHCl_3$). The spectral data of the recovered ketone are identical to those of (±)-**16**.

(b) 2:1.45 Reaction. 16 (35.2 mmol, 6.33 g) was treated with 8.17 g (25.5 mmol) of (−)-**1** at 0 °C as described in the general procedure. The reaction was complete in 5 d. Workup and chromatography provided 4.17 g (90%) of the product alcohol and 1.68 g (96%) of the recovered ketone. Gas chromatographic analysis of the alcohol showed a composition of ≥99% of the *endo* product. Analysis of its TFA derivative on a Chiraldex-GTA capillary column showed a composition of 71% of (1*S*)-*endo* and 29% of (1*R*)-*endo*. The recovered

(29) (a) Belikova, N. A.; Bobyleva, A. A.; Kalinichenko, A. N.; Platé, A. F.; Pekhk, T. I.; Lippmaa, E. T. *Zh. Org. Khim.* **1974**, *10*, 239. (b) Lippmaa, E. T.; Pekhk, T. I.; Belikova, N. A.; Bobyleva, A. A.; Kalinichenko, A. N.; Ordubadi, M. D.; Platé, A. F. *Org. Magn. Reson.* **1976**, *8*, 74.

(30) Poe, C. F.; Plein, E. M. *J. Phys. Chem.* **1934**, *38*, 883.

(31) Huckel, W. *Ann.* **1941**, *549*, 186.

ketone was analyzed on a Chiraldex-GTA capillary column which showed an ee of ≥99% in the (1*R*,2*S*)-isomer: $[\alpha]^{25}_{D} = -18.55$ (*c* 12.76, $CHCl_3$).

A sample of optically pure **16** prepared as above was reduced with (+)-**1** when the reaction was complete in 2 h, and a diethanolamine workup provided the product alcohol in 90% yield. This was then converted to its 3,5-dinitrobenzoate (**18**) using a standard procedure. The oily product obtained was crystallized from ethanol−water (mp 121−122 °C) and analyzed using X-ray crystallography. The details of the experimental procedures of X-ray data collection are provided in the supporting information.[32]

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Supporting Information Available: ^1H and ^{13}C NMR of (1*S*)-**4** and ORTEP diagram of compound **18** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951206Z

(32) The author has deposited atomic coordinates for structure **18** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.