mechanism seems to be a general one in the presence of bidentate phosphine ligands. In fact, in a very recent paper Ozawa and Hayashi invoked a similar mechanistic hypothesis in order to explain the outcome of the asymmetric Heck reaction of simple aryl triflates and aryl iodides with dihydrofuran in the presence of the $Pd(OAc)_2$/(R)-BINAP complex.[24a]

Conclusion

DPPP and DPPF have shown to be good ligands in the Heck reaction; this work represents the first example in which bidentate phosphines have been used with success in the reaction between aryl triflates and an electron-deficient olefin.[24]

The particular reactivity of the anthraquinoid system allowed us to study, under controlled conditions, the coordination-insertion step of the olefin onto the palladium(II) complex, and the effectiveness of the reaction resulted from a subtle balance between ligand and counterion in the oxidative addition intermediate.

The mechanism proposed is in agreement with the hypothesis of Ozawa and Hayashi and allows the clarification, to some extent, of the general mechanism of the arylation of olefin catalyzed by palladium complex in the presence of bidentate phosphine ligands. The procedure developed made possible the synthesis of the first anthracyclinone substituted at carbon 4 with a vinyl derivative. However, in anthracycline chemistry the Heck reaction is limited to the use of olefins able to accept electron back-donating from the metal.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. ^1H NMR spectra were recorded at 200 MHz in $CDCl_3$. HPLC analyses were performed with a LiChrosorb RP-18 (7-μm) column using $CH_3CN/CH_3OH/H_2O$ (51/15/33 by volume) as eluent. Purifications by flash chromatography were carried out on Merck silica gel 60 (230-400 mesh), as described by Still.[25] 4-Demethyl-4-(trifluoromethanesulfonyl)-13-dioxolanyldaunomycinone (2),[3] 1-(9,10-anthraquinoyl) triflate 7,[7] and $Pd(PPh_3)_2Cl_2$[26] were prepared according to published procedures. $Pd(OAc)_2$, DPPP, DPPF were purchased from Aldrich.

Representative Procedure for Palladium-Catalyzed Reaction with Methyl Acrylate (4). Methyl [1-(9,10-Anthraquinoyl)]propenoate (8) (Table I, Entry 3). To a stirred solution of triflate 7 (0.178 g, 0.5 mmol) in 8.4 mL of DMF under Ar at rt were sequentially added Et_3N (0.139 mL, 1.0 mmol), 4 (0.45 mL, 5.0 mmol), DPPP (0.0113 g, 0.0275 mmol), and $Pd(OAc)_2$ (0.0056 g, 0.025 mmol). The solution was stirred and heated at 60 °C for 1.5 h then cooled to rt. CH_2Cl_2 (40 mL) was added, and the resulting mixture was sequentially washed with 5% HCl (3 × 5 mL) and water until neutral. The solution was dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate (8/2) by volume) affording quinone 8 (0.137 g, 94%): yellow solid; mp 195-197 °C (MeOH); IR (Nujol) 1720, 1690, 1340, 1290 cm^{-1}; ^1H NMR δ 3.86 (s, 3 H), 6.27 (d, 1 H, J = 15.9 Hz), 7.65-7.90 (m, 4 H), 8.16-8.48 (m, 3 H), 8.69 (d, 1 H, J = 15.9 Hz). Anal. Calcd for $C_{18}H_{12}O_4$: C, 73.94; H, 4.14. Found: C, 73.91; H, 4.11.

The procedures for the palladium-catalyzed reactions of Table III and for triflate 2 were the same as described above with the exception that 3 equiv of the indicated salt were added just before the phosphine.

The reaction of 2 was carried out using the procedure described above in the presence of AcOLi and DPPF as ligand.

4-Demethoxy-4-[2'-(methoxycarbonyl)ethenyl]-13-dioxolanyldaunomycinone (5): 0.154 g, 62%; red solid; mp 214-216 °C dec; IR (KBr) 3470, 1716, 1610, 1575 cm^{-1}; UV (EtOH) 527, 492, 347, 264, 213 nm; λ_{max} 264 nm; ^1H NMR ($CDCl_3$) δ 1.48 (3 H, s), 1.98 (1 H, dd, J = 5.1, 14.7 Hz), 2.46 (1 H, dt, J = 2.0, 14.7 Hz), 2.79 (1 H, d, J = 18.9 Hz), 3.24 (1 H, dd, J = 2.1, 18.9 Hz), 3.34 (2 H, s), 3.80 (1 H, br s), 3.87 (3 H, s), 4.08 (4 H, s), 5.26 (1 H, dd, J = 1.5, 4.9 Hz), 6.24 (1 H, d, J = 15.9 Hz, 7.75-7.80 (2 H, m), 8.36-8.44 (1 H, m), 8.72 (1 H, d, J = 15.9 Hz), 13.35 (1 H, s), 13.54 (1 H, s); $[\alpha]_D$ = 195.0° (c 0.1 in dioxane). Anal. Calcd for $C_{26}H_{24}O_{10}$: C, 62.90; H, 4.87. Found: C, 62.85; H, 4.91.

By use of the same procedure in the presence of 3 equiv of LiCl instead of Et_3N and AcOH, compound 5 was isolated in 50% yield.

Acknowledgment. We thank Professor Gian Paolo Chiusoli for helpful and stimulating discussions.

Registry No. 2, 128065-73-6; 4, 96-33-3; 7, 123412-36-2; 8, 135340-33-9; 9, 84-65-1; DPPP, 6737-42-4; DPPF, 12150-46-8; $Pd(PPh_3)_2Cl_2$, 13965-03-2; $Pd(OAc)_2$, 3375-31-3; LiCl, 7447-41-8; LiBr, 7550-35-8; LiI, 10377-51-2; Et_4NCl, 56-34-8; AcOLi, 546-89-4; CH_2=CHO-t-Bu, 926-02-3; 1-(1-*tert*-butoxyethenyl)-9,10-anthracenedione, 135340-35-1.

(24) Bidentate phosphines were reported not to form effective catalyst for the Heck reaction, ref 5c. There are only two examples in the literature of arylation of olefins by aryltriflates. Interestingly, in both papers were used electron-rich olefins, enol ethers. See: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3654. For aryl iodides see: (c) Reference 19. (d) Karabellas, K.; Westerlund, C.; Hallberg, A. *Ibid.* **1985**, *50*, 3896.

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Lewis Acid Induced Ene Cyclization of ω-Olefinic Trifluoromethyl Ketones: Access to Bicyclic Compounds Bearing a CF_3 Group

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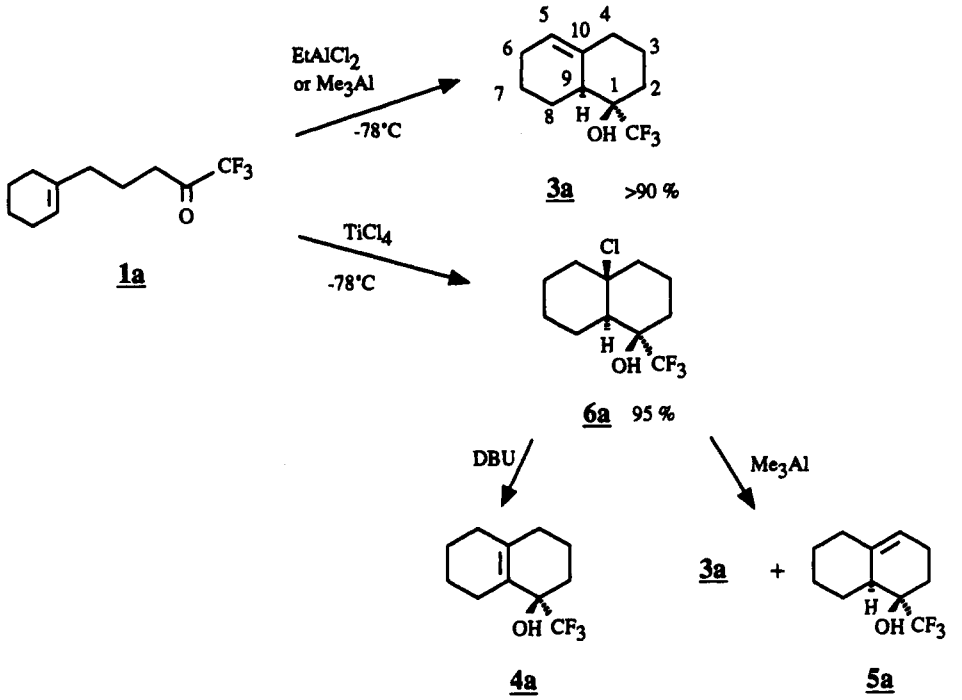
Received November 6, 1990

Lewis acid induced ene cyclization of ω-olefinic trifluoromethyl ketones provides (trifluoromethyl)decalins and (trifluoromethyl)hydrindans in high yield. δ-(1-Cyclohexenyl) trifluoromethyl ketone **1a** leads stereoselectively to 1-(trifluoromethyl)-1-hydroxy-$\Delta^{5,10}$-octalin **3a** or 10-chloro-1-(trifluoromethyl)-1-hydroxydecalin **6a**, depending on the choice of Lewis acid. γ-(1-Cyclohexenyl) trifluoromethyl ketone **2a** leads to a mixture of 9-chloro-1-(trifluoromethyl)-1-hydroxyhydrindans **10a** and **11a**. Similar reactions were performed successfully with the corresponding β-keto esters **1b** and **2b**.

Much attention has been focused on trifluoromethyl-substituted compounds because of the remarkable effect of such fluorinated groups on biological activity.[1a-c] The selective introduction of a CF_3 group into bioactive mol-

0022-3263/91/1956-5800$02.50/0

Scheme I



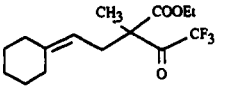
ecules has become a major goal in modern organofluorine chemistry. This inherent synthetic problem may be solved by direct fluorination of a carboxylic acid,[1d] by addition of a trifluoromethyl group, or by use of CF_3-containing building blocks.[1e] However, the synthesis of alicyclic trifluoromethylated compounds still remains a serious problem. For solving this specific problem, cyclization approaches are attractive.

Radical-induced cyclization[2] and annelation routes[3,4] have previously been employed for the construction of such compounds. We thought that a carbocationic cyclization would be a fruitful method for preparing trifluoromethylated polycyclic compounds.[5,6] In this connection, a strategy involving the cyclization of ω-unsaturated carbonyl compounds could permit easy access to functionalized alicyclic compounds. Lewis acid initiated ene reactions of ω-unsaturated aldehydes are well documented.[7,8] However, few examples have been reported with ω-unsaturated ketones because of their lower reactivity toward ene cyclization.[9,10] However, electron-deficient trifluoromethyl ketones turn out to be good enophiles for such Lewis acid promoted ene reactions.[11,12]

Reported herein are the results of a study of the ene cyclization of ω-cyclohexenyl trifluoromethyl ketones and related β-keto esters for preparing decalins and hydrindans bearing a CF_3 group.

Results

Trifluoromethyl ketones **1a** and **2a** were prepared by the KF-mediated hydrolysis of trifluoromethyl silyl enol ethers, obtained by the Wittig reaction of trimethylsilyl trifluoroacetate, as we have previously described.[13] Direct alkylation of ethyl 4,4,4-trifluoro-2-methyl-3-oxobutanoate[14] with 1-(bromomethyl)cyclohexene[15] led to keto ester **2b**. Similarly, alkylation with (2-bromoethylidene)cyclohexane[16] led to **1c** and, after partial isomerization of the double bond, to keto ester **1b** (*p*-toluenesulfonic acid at reflux of toluene); subsequent reactions were performed on a 80/20 mixture of **1b**/**1c** (**1c** did not react).



1c

For the structure determination of the products, the NMR spectral data were of particular value because of the presence of the trifluoromethyl group. First, coupling to

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(2) (a) Watanabe, Y.; Yokozawa, T.; Takata, T.; Endo, T. *J. Fluorine Chem.* **1988**, *39*, 431. (b) Morikawa, T.; Nishiwaki, T.; Kobayashi, Y. *Tetrahedron Lett.* **1989**, *30*, 2407. (c) Morikawa, T.; Uejima, U.; Kobayashi, Y. *Chem. Lett.* **1989**, 623.

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(10) Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364.

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(12) (a) Aubert, C.; Bégué, J. P. *Tetrahedron Lett.* **1988**, *29*, 1011. (b) Abonaddellah, A.; Aubert, C.; Bégué, J. P.; Bonnet-Delpon, D. *J. Chem. Soc., Perkin Trans. I* **1991**, 1397.

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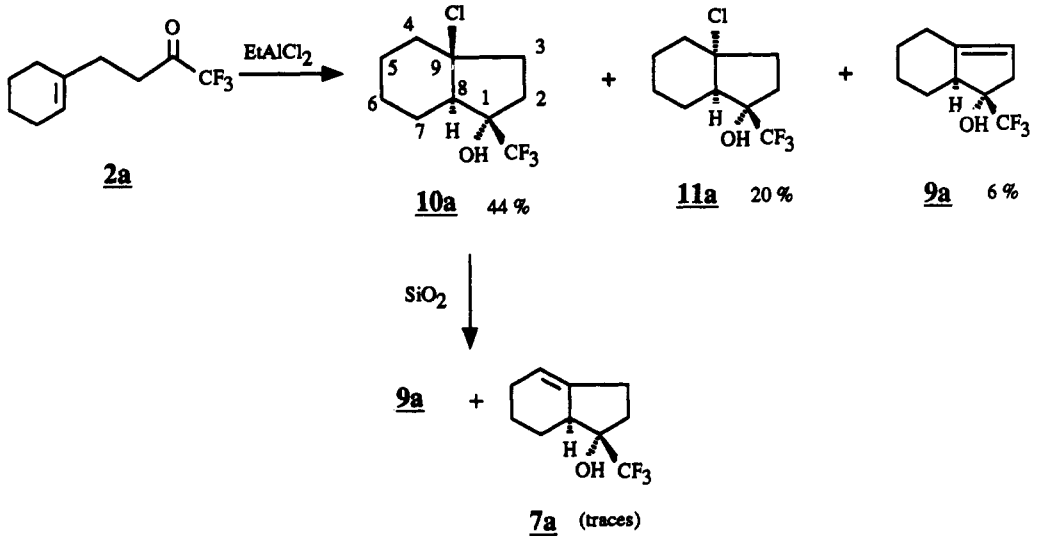
Table I. Cyclization of Compounds 1a, 1b, 2a, and 2b

run	compd	Lewis acid	(equiv)	T, °C (t, h)	products[a]		
1	1a	$EtAlCl_2$	(1.1)	-78 (0.7)	3a 90 (72)	6a 10 (7)	
2	1a	Me_3Al	(1.1)	-78 (1.5)	3a 99 (80)		
3	1a	$TiCl_4$[b]	(1)	-78 (1)	3a <3 (9)	5a <2 (8)	6a 95 (68)[c]
4	2a	$EtAlCl_2$	(1.1)	-78 (0.7)	9a 6 (36)	10a 44 (12)	11a 20 (18)[c,d]
5	2a	$TiCl_4$	(1)	-78 (0.5)	12a (65)[d]	(→ 13a (40)[c,d])	
6	1b[e]	$EtAlCl_2$[f]	(0.3)	0 (3)	3b 90 (65)	4b 5	6b 5
7	1b[e]	$TiCl_4$	(1)	-78 (2.5)	3b 20 (12)	4b 76 (50)	6b 4
8	2b	$EtAlCl_2$	(1)	0 (0.7)	8b 95 (74)	11b 5	
9	2b	$TiCl_4$	(1)	-78 (0.5)	8b 99 (92)		

[a] GC analysis, the parenthetic values are isolated yields. [b] Nearly same results when reaction was performed at -35 °C or with 0.3 equiv of $TiCl_4$ (see Experimental Section). [c] Products transformed after silica gel chromatography. [d] Yields from GC analysis obtained by using undecane as internal standard (after appropriate calibration). [e] Reactions performed on a mixture (80/20) of 1b and 1c. Yields were calculated from 1b. [f] When the bottle of $EtAlCl_2$ was not freshly opened, chloride 6b was major product.

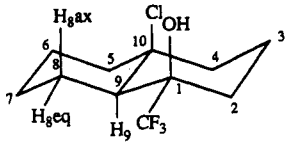
Scheme II



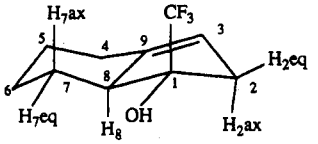
fluorine is transmitted through bonding electrons, and J_{C-F} is easily measured up to three bonds in ^1H-decoupled ^{13}C NMR spectra. Furthermore $^{19}F-^1H$ and $^{19}F-^{13}C$ coupling can occur by a direct through-space mechanism;[17a,b] long-range coupling constants can be observable, provided that there is a close spatial proximity of the two atoms.

Cyclization of Ketone 1a (Scheme I). At -78 °C, $EtAlCl_2$-, Me_2AlCl-, or Me_3Al-induced cyclization of 1a provided octalin 3a in very good yield (>90%, see Table I, runs 1 and 2), whereas reaction with $TiCl_4$ afforded chlorodecalin 6a (>95%), even with 0.3 equiv of the catalyst (run 3). Formation of this chlorodecalin became significant with $EtAlCl_2$, at -35 °C; in this case, 6a was accompanied by octalin 5a.

Dehydrohalogenation of chloride 6a with DBU led primarily to 4a, suggesting that the junction in 6a is trans. Chloride 6a could be partially converted to a mixture of 3a and 5a after elution on silica gel and completely by treatment with Me_3Al; these results indicate an identical configuration of C-9 and C-1 in 6a, 3a, and 5a. The cis relationship of the H-9 hydrogen and the CF_3 group was deduced from NMR data. A complete assignment of the ^1H and ^{13}C chemical shifts in 3a was made by 2D shift correlations. Selective irradiation of $H\text{-}8_{ax}$, $H\text{-}8_{eq}$, and H-9 protons, with simultaneous observation of the ^{19}F NMR signal of the CF_3 group, have been carried out. Irradiation of $H\text{-}8_{eq}$ converted the doublet due to the CF_3 group (^5J = 2.3 Hz) to a singlet. This through-space coupling[17] to an equatorial hydrogen is only possible with an equatorial CF_3 group. In the COSY spectrum of 3a the successive correlations starting from the single ethylenic proton led to the junction proton H-9 showing that the double bond belongs to the nonsubstituted cycle.



6a



9a

Cyclization of Ketone 2a (Scheme II). $EtAlCl_2$-(or $MeAlCl_2$)-induced cyclization of ketone 2a gave a mixture of chlorides 10a (44%), 11a (20%), and 9a (6%) (run 4). The major chloride 10a was unstable and underwent dehydrochlorination during silica gel chromatography to dehydrohydrindan 9a (36%) and traces of an isomer tentatively identified as 7a (^{19}F and MS). The position of the double bond in 9a was easily deduced from correlations of the ethylenic proton in the COSY spectrum. The trans relationship of H-8 and the CF_3 group was deduced from the shape of the ^{19}F NMR CF_3 signal. Irradiation of each of four different protons induced a decrease of ≈1.5 Hz in the half-height width of the CF_3 group signal ($W_{1/2}$ = 6 Hz). H-8 and $H\text{-}2_{ax}$ are coupled to the CF_3 fluorines via planar W orientation ^4J coupling; $H\text{-}2_{eq}$ and $H\text{-}7_{ax}$ are coupled through space. If the CF_3 group was equatorial, it would be coupled only to $H\text{-}2_{ax}$ and/or $H\text{-}8_{ax}$ through space.

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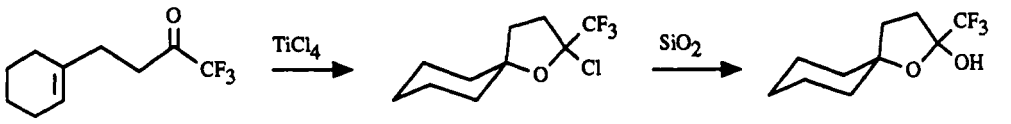
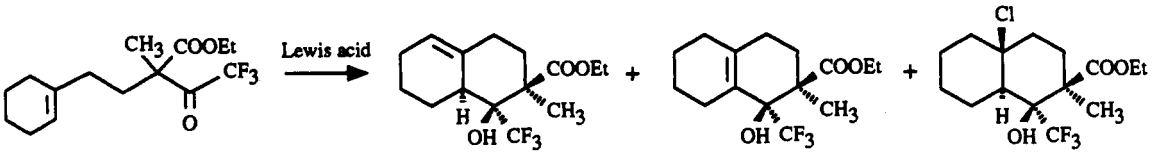
Scheme III



2a 12a 65 % 13a 40 %

Scheme IV



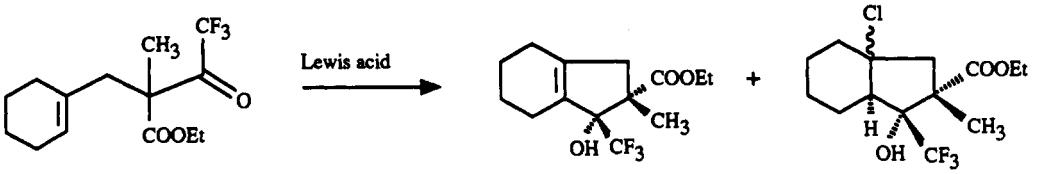
1b 3b 4b 6b

	3b	4b	6b
$EtAlCl_2$	90	5	5
$TiCl_4$	20	76	4

Scheme V

6b 3b 6 % + 4b 70 % + 6b 15 % + 5b 9 %

Scheme VI



2b 8b 11b

	8b	11b
$EtAlCl_2$	95 %	5 %
$TiCl_4$	100 %	0 %

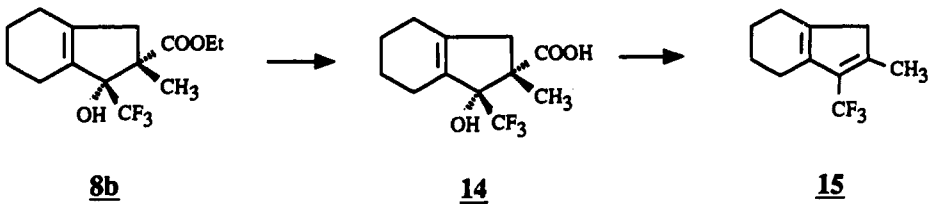
In the presence of $TiCl_4$ (run 5), cyclization of **2a** to form a hydrindan did not occur. Spiro compound **12a** (65%) was formed, probably via initial protonation of the double bond. This process could not be avoided by the use of freshly distilled $TiCl_4$. **12a** was converted to **13a** on silica gel column chromatography (Scheme III).

Cyclization of β-Keto Ester 1b (Scheme IV). With 0.3 equiv of $EtAlCl_2$ at 0 °C, the cyclization of keto ester **1b** selectively afforded 90% of **3b** (run 6) and traces of **4b** and chloride **6b**. At −78 °C, reaction was not complete after 5 h and a mixture of **1b** (30%), **3b** (14%), **4b** (6%), and **6b** (32%) was obtained (GC determination). With Me_2AlCl, the proportions of **4b** and **6b** increased. With Me_3Al, no cyclization occurred at 0 °C. With $TiCl_4$, 1 equiv of Lewis acid was necessary for significant amounts of cyclization, even at 0 °C, and **4b** was obtained as the major product (75%), along with **3b** (20%) and **6b** (5%) (run 7). Once formed, **3b** and **6b** were stable in the reaction medium ($EtAlCl_2$ or $TiCl_4$), even at room temperature. **6b** was converted with sodium ethoxide primarily into **4b** along with a small amount of **3b** and **5b** (Scheme V). This demonstrates that the ring junction in **6b** is trans and that the configurations of C-9, C-1, and C-2 are the same in **3b**, **5b**, and **6b**. In **3b**, the cis relationship between the hydroxyl group and the carbethoxy group was deduced from NMR data. The chemical shift of the OH proton is δ 6.20 at all concentrations and its exchange with D_2O is very slow. These observations indicate hydrogen bonding between the OH and COOEt groups. Furthermore, this OH signal is a doublet (J = 1.5 Hz), which becomes a singlet under irradiation of H-9. This ^4J coupling of planar W orientation is the outcome of the trans relationship between H-9_{ax} and the rigidly hydrogen-bonded OH.[18] Thus, the OH must be in the axial position and the COOEt group in the equatorial position, cis to the OH, in order to allow the hydrogen bond. This is confirmed with $^4J_{CF}$ and $^5J_{HF}$ coupling constants between the methyl substituent and the CF_3 group, reflecting a through-space effect only possible if these two groups are cis to each other.[17a,b] In **3b**, the position of the double bond has been deduced from the COSY spectrum as for **3a**.

Cyclization of β-Keto Ester 2b (Scheme VI). The cyclization of keto ester **2b** was found to proceed very selectively with both $EtAlCl_2$ and $TiCl_4$, to afford dehydrohydrindan **8b** (>95%) (runs 8 and 9) accompanied by

(18) Jackson, A. C.; Goldman, B. E.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 3988.

Scheme VII



8b 14 15

Type I Type II

Figure 1.

a trace amount of a byproduct that could be chloride **11b** in view of its retention time in GC and its MS. The hydroxyl group and the carbethoxy group in **8b** are also cis to each other as deduced from the formation of diene **15** in lactonization experiments (see Scheme VII)[19,20] and a strong hydrogen bond in the IR spectrum at low concentration.

Discussion

Ene Cyclization to Bicyclo[4.4.0]decane System (from 1a and 1b). With $EtAlCl_2$, $MeAlCl_2$, and Me_3Al at −78 °C, ketone **1a** undergoes a concerted ene process of type II (Figure 1)[8] through transition state A leading to ene adduct **3a** (path a, Figure 2). The same process occurs for **1b** with $EtAlCl_2$ and Me_2AlCl at 0 °C to afford **3b**. The cis relationship of CF_3 and H-9 is a consequence of the only possible six-center transition state A, which allows the allylic hydrogen to be transferred to the oxygen and provides good overlap between the ene and carbonyl π bonds. This configuration is the same as that of the alcohol resulting from the previously reported ene cyclization of the corresponding methyl ketone,[9] which occurs via the same mechanism.

The formation of a single stereoisomer of chlorodecalins **6a** and **6b** is rather unexpected. The formation of a chlorohydrin is generally assumed to be the result of a stepwise process proceeding through a carbocation intermediate.[8] The stereochemistry at the alcohol center is most often opposite that of the ene reaction product.[7b,8b] No stereoselectivity can be expected at the chloro center since the intermediate carbocation can be trapped from either face.[22a] In fact, the formation of **6a** and **6b** occurs with stereospecificity at the chloro center (C-10) with the same C-1 configuration as in **3a** and **3b**. This could a priori result from isomerization of the ene adduct by an intramolecular transfer of chloride from an axial alkoxide complexed product. However, the conversion of **3a** into **6a** or **3b** into **6b** was not observed in control experiments, e.g., when **3a** or **3b** was placed into the same medium. The stereoselective formation of **6a** and **6b** can be explained by a six-centered transition state including a chloride of the aluminum complex A (path b, Figure 2). The transfer of a chloride could be favored by a positive charge developing on C-10. The process leading to **6a** and **6b** seems to be energetically similar to the concerted ene process

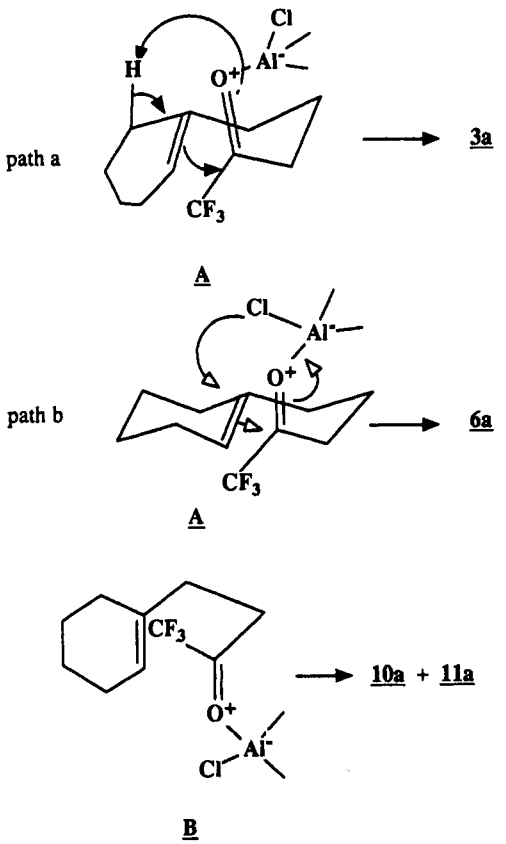


Figure 2.

(path a). From **1a**, at −78 °C, chlorodecalol **6a** was obtained in high yield with $TiCl_4$ and in low yield with $EtAlCl_2$ (**6a** becomes the major product only at −35 °C with $EtAlCl_2$). From **1b**, chlorodecalol **6b** is the major product with $EtAlCl_2$, provided that the reaction was performed at −78 °C (at 0 °C, **3b** is the major product). With $TiCl_4$, the major product **4b** cannot result from the concerted ene process, indicating the possibility of a stepwise process that has also a similar energetics to that of the concerted reactions.

The cyclization of ketone **1a** is easier than that of the corresponding β-keto ester **1b**: no cyclization occurred on treatment of **1b** with Me_3Al and the cyclization was slower than that for **1a** with $EtAlCl_2$, Me_2AlCl, or $TiCl_4$, allowing different processes to compete.

Complexation of the two carbonyl groups of β-keto ester **1b** by the Lewis acid explains the remarkably specific cis relationship between the hydroxy and ethoxycarbonyl groups in the observed products.[21] The cyclization process and the chelation effect allow the formation of a single stereoisomer with creation of two asymmetric centers in **3b** and three such centers in **6b**.

Ene Cyclization to Bicyclo[4.3.0]nonane System (from 2a and 2b). In **2a** and **2b**, the two-carbon chain length is too short to achieve both a good overlap between

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the two π systems and a proximity of any allylic hydrogen, since the type II process needs a minimum of a three-carbon loop.[7b] Therefore, only a two-step process can occur, and the resulting carbocation either eliminates to give the more stable ethylenic products or traps a chloride ion.

From **2a**, the trans configuration of H-8$_{ax}$ and CF_3 is the result of the opposite direction of the approach of the carbonyl group, allowing the best overlap between π systems, compared to the cyclization process leading to the bicyclo[4.4.0]decane system (complex B) (Figure 2).

The stereoselective intramolecular transfer of chloride is then not possible and trapping of chloride ion from both faces leads to a mixture of cis and trans chlorohydrindans **11a** and **10a**. Trans-fused chloride **10a** is unstable,[22] undergoing an elimination on silica gel to give **9a** and small amounts of **7a**.

From **2b**, the same cationic process occurs, but little or no chloride was formed. The ethylenic compound **8b** seems to be the more stable.[23] Surprisingly in contrast to the cyclization of **1b**, the ester group does not slow down the rate of cyclization in presence of $TiCl_4$ since the ene process can occur at −78 °C.

Comparison with Nonfluorinated Carbonyl Compounds. These results clearly show that trifluoromethyl ketones are more reactive than methyl ketones and have similar levels of reactivity to aldehydes.[9,10,24] Molecular orbital energy calculations show that the LUMO levels of aldehydes and ketones are very close.[25,26] The observed difference of reactivity can be explained by the steric effect of a methyl group. Although steric hindrance of a trifluoromethyl ketone is larger than that of a methyl ketone,[1c,26a] its LUMO energy is greatly reduced.[26b] The usual lower proton affinity (or metal affinity) of fluorinated ketones[27] makes this LUMO energy level difference only slightly smaller in the ketone–Lewis acid complex. Thus, the cyclizations of trifluoromethyl ketones and β-keto esters do not require such harsh conditions as their nonfluorinated analogues, and they occur in higher yields. That is particularly clear for β-keto esters.[18]

When a cationic process is involved, as in the cyclization of **2a** and **2b**, migration of a CF_3 group cannot occur and hence successive migrations are not observed, unlike the methyl ketones.[9]

The tertiary alcohol–Lewis acid complexes of methyl ketones are not stable and only Me_2AlCl is a useful catalyst since an irreversible loss of methane leads to a stable aluminum alkoxide.[9,10,18] However, in the fluorinated series, the resulting tertiary alcohol–Lewis acid complexes are stable because the powerfully electron-withdrawing CF_3 group prevents solvolysis or elimination. Thus, a large variety of Lewis acids can be used for the ene reaction of trifluoromethyl ketones.

Experimental Section

^1H (60 or 300 MHz), ^{19}F (56 MHz), and ^{13}C NMR (20 or 75 MHz) spectra were obtained with $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to Me_4Si and $CFCl_3$ (for ^{19}F NMR) as internal standards. In the ^{13}C NMR data, reported signal multiplicities are related to C–F coupling. In the case of determination of fine coupling constants an acquistion of 16K data points, a Lorenz–Gauss transformation of the FID, and a zero filling to 64K were performed in order to obtain a minimum resolution of 0.2 Hz/pt (^1H and ^{19}F) or 0.5 Hz/pt (^{13}C). COSY, COSYLR, and XHCORR Brucker programs were used for 2D NMR experiments. High resolution MS and GC/MS analyses were obtained at 70 eV EI (capillary column CPSIL-5, 25 m).[28] GC analysis was performed on a capillary column SE30, 10 or 25 m). FT IR spectra were recorded in CCl_4 or $CHCl_3$ solutions. $EtAlCl_2$, $MeAlCl_2$, Me_2AlCl, and Me_3Al (solutions in hexanes) and $TiCl_4$ (1 M solution in CH_2Cl_2) were purchased from Aldrich Chemical Co.

4-(1-Cyclohexenyl)-1,1,1-trifluorobutan-2-one (2a). A solution of crude 2-(1-cyclohexenyl)ethanol (containing 10% of 2-cyclohexylethanol) (21 g, 172 mmol), resulting from lithium–propylamine reduction of β-phenylethanol,[29] and triethylamine (31 mL) in CH_2Cl_2 (200 mL) were treated slowly, at 0 °C, with a solution of methanesulfonyl chloride (19 g, 166 mmol). The reaction mixture was stirred overnight at this temperature. After extraction (Et_2O), the organic layer was washed to neutrality and dried over $MgSO_4$. The crude mesylate (29 g, 85%) was obtained after rotary evaporation: ^1H NMR δ 1.2–2 (m, 10 H), 3.0 (s, 3 H, Me), 4.2 (t, ^3J = 6.5 Hz, 2 H, CH_2—O), 5.5 (m, 1 H, CH=C). This crude mesylate (29 g) was refluxed with NaI (31.5 g, 1.5 equiv) in acetone (250 mL) for 24 h. After filtration and evaporation of the acetone, the residual oil was extracted with pentane, washed successively with aqueous sodium thiosulfate solution and water, dried ($MgSO_4$), and filtered through silica gel. The crude 2-(1-cyclohexenyl)-1-iodoethane (28 g, 78%) was isolated after evaporation of the pentane: ^1H NMR δ 1.22–2.7 (m, 10 H), 3.0 (t, ^3J = 7 Hz, 2 H, CH_2—I), 5.5 (m, 1 H, CH=C). This crude iodide (28 g, 0.118 mol) and triphenylphosphine (31 g, 0.118 mol) were refluxed in toluene (500 mL) for 48 h. The solid phosphonium salt was filtered and washed several times with toluene. Recrystallization from a mixture of Et_2O–CH_2Cl_2 provided pure [2-(1-cyclohexenyl)ethyl]triphenylphosphonium iodide (34 g, 58%), mp = 174.5 °C. The corresponding phosphonium ylide was prepared[13] by refluxing this phosphonium salt (20 g, 40 mmol) and $NaNH_2$ (1.722 g, 1.1 equiv) in benzene (20 mL) with hexamethyldisilazane (0.1 mL) as catalyst, for 1 h. Then, the solution of ylide was added via a syringe to trimethylsilyl trifluoroacetate (7 mL, 1 equiv).[13] After rapid decoloration, the reaction mixture was maintained at reflux overnight. After addition of pentane, filtration on silica gel, and evaporation of solvent, the crude product was stirred in Et_2O (50 mL) in the presence of silica gel (5 g), KF (2 g), and H_2O (2 g) for 3 h. Chromatography on silica gel (pentane) gave the pure ketone **2a** (4.3 g, 54%): ^1H NMR δ 1.6–1.9 (m, 8 H), 2.4 (m, 2 H, CH_2CH_2CO), 3.8 (t, ^3J = 7 Hz, 2 H, CH_2CO), 5.6 (m, 1 H, CH=C); ^{19}F NMR δ −80.3; ^{13}C NMR δ 22.2, 22.7, 25.1, 28.2, 30.3, 34.8, 115.6 (q, ^1J = 292 Hz CF_3), 122.4, 134.2, 192.2 (q, ^2J = 34 Hz, -CO–CF_3); exact mass calcd for $C_{10}H_{13}F_3O$ 206.0919, found 206.0915.

Ethyl 4,4,4-Trifluoro-2-[2-(1-cyclohexenyl)ethyl]-2-methyl-3-oxobutanoate (1b). A solution of ethyl 4,4,4-trifluoro-2-methyl-3-oxobutanoate[14] (24.9 g, 0.12 mol) in anhydrous THF (60 mL) was added dropwise, under Ar, to a stirred suspension of NaH (2.88 g, 0.12 mol) in anhydrous THF. After complete addition, the reaction mixture was stirred for 3 h at rt. To this crude enolate were added HMPA (42 mL, 2 equiv) and then (2-bromoethylidene)cyclohexane[16] (23 g, 0.12 mol) and KI (0.2 g). The reaction mixture was refluxed and stirred for 24 h and finally hydrolyzed with 10% aqueous HCl (20 mL). After extractions with CH_2Cl_2, the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and distilled under reduced pressure (bp_{10} = 125–130 °C). The resulting crude product (24 g) was refluxed in benzene (200 mL) in the presence

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(28) In some cases GC/MS analyses do not provide a molecular ion but show an elimination of HCl, HF, and/or H_2O (**1b**, **2b**, **6a**, **6b**, **10a**, and **11a**) due either to the column used, or to the standard enregistration conditions.

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of *p*-toluenesulfonic acid (0.6 g) for 24 h. The solution was washed with $NaHCO_3$ and brine and dried ($MgSO_4$). Chromatography on silica gel (pentane) of this crude product gave a mixture (80/20) of **1b** and the nonisomerized ethylenic product **1c** (16 g, 43%). They have not been separated. **1b**: ^1H NMR δ 1.2 (t, J = 7 Hz, 3 H), 1.4 (s, 3 H, CH_3), 1.6 (m, 6 H), 1.9 (m, 6 H, 3 × CH_2CH=C), 4.1 (q, J = 7 Hz, 2 H), 5.3 (m, 1 H); ^{19}F NMR δ -73.6; ^{13}C NMR δ 13.7, 18.1, 22.4, 22.8, 25.2, 28.2, 31.9, 32.6, 56.0 (quat C), 62.0 (CH_2O), 115.8 (q, ^1J = 298 Hz, CF_3), 121.9, 136.2, 170.3, 190.0 (q, ^2J = 35 Hz, C=O); MS m/e 268 (4, M - 38), 109 (15), 108 (84), 93 (58), 79 (100), 67 (33), 55 (15); exact mass calcd for $C_{15}H_{21}O_3F_3$ 306.1443, found 306.1436. **1c**: ^1H NMR δ 1.2 (t, ^3J = 7 Hz, 3 H), 1.4 (s, 3 H), 1.5 (m, 6 H), 2.1 (m, 4 H), 2.6 (d, ^3J = 8 Hz, 2 H), 4.1 (q, ^3J = 7 Hz, 2 H), 4.9 (t, ^3J = 8 Hz, 1 H); ^{19}F NMR δ -72.9; ^{13}C NMR δ 13.8, 18.0, 26.7, 27.6, 28.5, 28.7, 31.7, 37.4, 56.4, 62.0, 112.9, 115.5 (q, ^1J = 298 Hz, CF_3), 144.9, 170.3, 190.0 (q, ^2J = 35 Hz, C=O); MS m/e 268 (2, (M - HF - H_2O), 109 (38), 108 (83), 93 (36), 79 (73), 67 (100), 55 (30).

Ethyl 4,4,4-Trifluoro-2-methyl-2-[(1-cyclohexenyl)-methyl]-3-oxobutanoate (2b). A solution of ethyl 4,4,4-trifluoro-2-methyl-3-oxobutanoate[14] (24.9 g, 0.08 mol) in anhydrous THF (30 mL) was added dropwise, under Ar, to a stirred suspension of NaH (1.92 g, 0.08 mol) in anhydrous THF (80 mL). After this addition, the reaction mixture was stirred for 3 h at room temperature. To this crude enolate were added HMPA (28 mL, 2 equiv) and then 1-(bromomethyl)cyclohexene[15] and KI (0.15 g). The reaction mixture was refluxed and stirred for 24 h and finally hydrolyzed with 10% aqueous HCl (20 mL). After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and distilled at reduced pressure (bp_{10} = 95–100 °C). Chromatography on silica gel (pentane) of this crude product (19 g) gave **2b** (12 g, 55%): ^1H NMR δ 1.1 (t, J = 7 Hz, 3 H, CH_3), 1.3 (s, 3 H, CH_3), 1.4 (m, 4 H), 1.7 (m, 4 H), 2.6 (m, 2 H), 4.2 (q, J = 7 Hz, 2 H), 5.4 (m, 1 H); ^{19}F NMR δ -73.2; C^{13} NMR δ 14.9, 18.3, 21.7, 22.7, 25.2, 29.4, 42.3, 56.2, 61.8, 115.6 (q, ^1J = 294 Hz, CF_3), 127.9, 131.6, 170.0 (COOEt), 190.0 (q, ^2J = 33 Hz, C=O); MS m/e 274 (M - 18, 4), 247 (M - 45, 4), 201 (100), 173 (10), 149 (21), 95 (26), 79 (67), 67 (38); exact mass calcd for $C_{14}H_{19}F_3O_3$ 292.1286, found 292.1277.

Lewis Acid Mediated Ketone and β-Keto Ester Cyclization: General Procedure. Reactions were performed in anhydrous solvents under Ar, with the reaction volume adjusted to produce a solution about 0.1–0.15 M in carbonyl compound. The solution was cooled to the desired temperature and the Lewis acid in solution was added dropwise via syringe through a septum cap. When the starting material had disappeared (followed by GC after rapid quenching of samples), ether (20 mL) was added and the mixture was hydrolyzed with saturated aqueous NH_4Cl and then allowed to warm to rt. The organic layer was washed with aqueous $NaHCO_3$ until neutral and then twice with brine, dried ($MgSO_4$), and concentrated by rotary evaporation of distillation. The crude product was further purified by column chromatography (silica gel 60, 70–230 mesh) using pentane and pentane–ether mixture as eluent.

Cyclization of 1a. (a) With $EtAlCl_2$. **1a** (220 mg, 1 mmol) in CH_2Cl_2 (10 mL), treated with $EtAlCl_2$ (1.1 mL of a 1 M solution in hexanes, 1.1 mmol) for 2 h at -78 °C, afforded, after workup and purification, **3a** (160 mg, 72%) and **6a** (17 mg, 7%).

The same reaction performed at -35 °C for 18 h afforded a mixture of **3a** (21%), **6a** (53%) and **5a** (26%) (GC analysis).

1-(Trifluoromethyl)-1,2,3,4,6,7,8,9-octahydronaphthalen-1-ol (3a): ^1H NMR δ 1.36 (m, 1 H, H-7_{ax}), 1.55 (br d, ^2J = 15 Hz, 1 H, H-8_{ax}), 1.6–1.76 (m, 4 H), 1.90 (m, 1 H, H-8_{eq}), 1.95 (m, 4 H + O*H*), 2.24 (br d, ^2J = 14 Hz, H-4_{eq}), 2.5 (br t, J = 6.8 Hz, 1 H, H-9), 5.70 (br s, 1 H, H-5); ^{19}F NMR δ -78.3 (d, J = 2.3 Hz); ^{13}C NMR δ 20.6 (C-3), 21.7 (C-7), 23.6 (q, ^4J = 2 Hz, C-8), 24.7 (C-6), 31.7 (q, ^3J = 2 Hz, C-2), 34.8 (C-4), 41.1 (C-9), 75.4 (q, ^2J = 26 Hz, C-1), 126.3 (C-5), 126.4 (q, ^1J = 287 Hz, CF_3), 134.1 (C-10); MS m/e 220 (55, M^+), 202 (80, M - 18), 151 (29, M - CF_3), 133 (38), 95 (100), 91 (74), 79 (71); exact mass calcd for $C_{11}H_{15}F_3O$ 220.1075, found 220.1070.

10-Chloro-1-(trifluoromethyl)decahydronaphthalen-1-ol (6a): ^1H NMR δ 1.26–2.20 (m, 14 H), 4.13 (bs, 1 H, O*H*); ^{19}F NMR δ -78.6; ^{13}C NMR δ 16.5 (C-3), 21.3 (C-6), 22.0 (q, ^4J = 2.7 Hz, C-8), 25.6 (C-7), 32.2 (q, ^3J = 2 Hz, C-2), 41.8 and 43.4 (C-4 and C-5), 46.5 (C-9), 75.8 (q, ^2J = 26 Hz, C-1), 77.9 (C-10), 125.7 (q, ^1J = 287 Hz, CF_3); MS m/e 220 (22, M - HCl), 203 (77, M - 53), 187 (100, M - CF_3), 151 (68, M - CF_3 - HCl), 133 (29), 108 (51), 91 (52), 79 (68); exact mass calcd for $C_{11}H_{16}ClF_3O$ 256.0842, found 256.0849.

(b) With Me_2AlCl. **1a** (220 mg, 1 mmol) in CH_2Cl_2 (10 mL), treated with Me_2AlCl (1.1 mL of a 1 M solution in hexanes, 1.1 mmol) for 1 h at -78 °C, afforded, after workup **3a** (90%) and **6a** (10%) (GC analysis).

(c) With Me_3Al. **1a** (220 mg, 1 mmol) in CH_2Cl_2 (10 mL), treated with Me_3Al (0.55 mL of a 2 M solution in hexanes, 1.1 mmol) for 1.5 h at -78 °C, afforded, after workup and purification, **3a** (175 mg, 80%).

(d) With $TiCl_4$. **1a** (220 mg, 1 mmol) in CH_2Cl_2 (8 mL), treated with $TiCl_4$ (0.11 mL, 1 mmol) for 1 h at -78 °C, afforded, after workup, crude **6a**. Chromatography on silica gel afforded **6a** (175 mg, 68%), **3a** (20 mg, 9%), and **5a** (18 mg, 8%), resulting from partial dehydrohalogenation. Performed with 0.3 equiv of $TiCl_4$, the reaction afforded at -78 °C **6a** (90%), **3a** (4%), and **5a** (5%) (GC analysis).

1-(Trifluoromethyl)-1,2,3,4,5,6,7,8-octahydronaphthalen-1-ol (4a). A solution of chloride **6a** (256 mg, 1 mmol) in benzene (10 mL) was refluxed in the presence of DBU (152 mg, 1 mmol) for 0.5 h. After cooling, the solution was washed with 5% aqueous H_2SO_4 and water, dried ($MgSO_4$), and concentrated under reduced pressure. Elution on silica gel (pentane) afforded 176 mg (80%) of a mixture of **3a** (9%), **5a** (12%), and **4a** (79%) (GC analysis). **4a**: ^1H NMR δ 1.40–2.20 (m, 14 H + O*H*); ^{19}F NMR δ -77.0; ^{13}C NMR δ 11.4, 22.1, 22.9, 23.7 (q, ^4J = 2.5 Hz, C-8), 30.7, 31.1, 33.7, 73.2 (q, ^2J = 28 Hz, C-1), 126.2 (q, ^1J = 287 Hz, CF_3), 124.8 (C-10), 138.6 (C-9); MS m/e 220 (11, M^+), 202 (4, M - 18), 151 (100, M - CF_3), 105 (7), 91 (21), 79 (18); exact mass calcd for $C_{11}H_{15}F_3O$ 220.1075, found 220.1073.

1-(Trifluoromethyl)-1,2,3,5,6,7,8,9-octahydronaphthalen-1-ol (5a). Chloride **6a** (256 mg, 1 mmol) in CH_2Cl_2 (10 mL) was treated with Me_3Al (1.1 mL of a 2 M solution in hexanes, 2 mmol) for 3 h at -78 °C and then for 10 h at 20 °C. After workup, elution on silica gel (pentane) afforded 165 mg (75%) of a mixture (40:60) of **3a** and **5a**. **5a**: ^1H NMR δ 1.30–2.40 (m, 14 H), 5.46 (m, 1 H); ^{19}F NMR δ -78.3; ^{13}C NMR δ 19.9, 26.0, 27.0 (q, J = 1.5 Hz), 27.2, 27.9 (q, J = 1.5 Hz), 36.0, 40.7 (C-9), 73.6 (q, ^2J = 27 Hz, C-1), 118.4 (C-4), 126.9 (q, ^1J = 286 Hz, CF_3), 137.2 (C-10); MS m/e 220 (32, M^+), 202 (33, M - 18), 160 (20), 151 (20, M - CF_3), 108 (88), 79 (100); exact mass calcd for $C_{11}H_{15}F_3O$ 220.1075, found 220.1074.

Cyclization of Ketone 2a. (a) With $EtAlCl_2$. A solution of **2a** (206 mg, 1 mmol) in CH_2Cl_2 (10 mL) was treated with $EtAlCl_2$ (1 mL of a 1 M solution in hexanes, 1 mmol) at -78 °C for 45 min, in presence of undecane (309 mg). Workup gave 183 mg of a mixture of products (GC yields: **9a** (6%), **10a** (44%), **11a** (20%). Chromatography on silica gel afforded chlorides **11a** (44 mg, 18%) and **10a** (29 mg, 12%) and 9:1 mixture of unsaturated compounds **9a** and an isomer, tentatively identified as **7a** (83 mg, 40%) (the chloride **10a** in the crude product was dehydrohalogenated on silica gel to give **7a** and **9a**).

1-(Trifluoromethyl)-1,2,4,5,6,7-hexahydroinden-1-ol (9a): ^1H NMR δ 1.1–1.4 (m, 3 H, H-5_{ax}, H-6_{ax}, O*H*), 1.82 (m, 2 H, H-5_{eq}, H-6_{eq}), 2.0 (m, 3 H, H-4_{ax}, 2 × H-7), 2.38 (m, 1 H, H-2_{ax}), 2.4–2.5 (m, 2 H, H-4_{eq}, H-8_{ax}), 2.85 (bd, ^2J = 17 Hz, 1 H, H-2_{eq}), 5.20 (m, 1 H, H-3); ^{19}F NMR δ -77.6 ($W_{1/2}$ = 6 Hz); ^{13}C NMR δ 25.7 (C-6), 27.3 (C-5), 28.9 and 29.0 (C-4 and C-7), 41.3 (C-2), 57.2 (C-8), 81.1 (q, ^2J = 28 Hz, C-1), 114.9 (C-3), 126.1 (q, ^1J = 281 Hz, CF_3), 144.7 (C-9); MS m/e 206 (11, M^+), 188 (13, M - 18), 138 (59), 137 (55, M - CF_3), 119 (19), 109 (17), 91 (64), 79 (100) 67, (63), 55 (39); exact mass calcd for $C_{10}H_{13}F_3O$ 206.0918, found 206.0902.

7a: ^{19}F NMR δ -77.6; MS m/e 206 (6, M^+), 188 (13, M - 18), 138 (30), 137 (38), 119 (26), 95 (21), 94 (29), 91 (71), 79 (100), 67 (35), 51 (34).

9-Chloro-1-(trifluoromethyl)octahydroinden-1-ol (11a): ^1H NMR δ 1.5 (m, 2 H), 1.6–2 (m, 6 H), 2.25 (m, 1 H, O*H*), 2.5 (m, 1 H); ^{19}F NMR δ -77.7; ^{13}C NMR δ 21.1, 22.5, 26.1, 34.8, 39.8, 40.1, 61.3, 81.5 (q, ^2J = 30 Hz, C-1), 82.9 (C-9), 125.5 (q, ^1J = 284 Hz, CF_3); MS m/e 206 (10, M - HCl), 189 (18), 137 (41, M - HCl - CF_3), 119 (15), 95 (100), 79 (54), 67 (69), 53 (37); exact mass calcd for $C_{10}H_{14}F_3ClO$ 242.0685, found 242.0680.

9-Chloro-1-(trifluoromethyl)octahydroinden-1-ol (10a): ^{19}F NMR δ -75.8; ^{13}C NMR δ 23.4, 23.9, 25.9, 33.8, 37.1, 39.0, 58.5,

82.8 (C-9), 85.0 (q, ^2J = 29 Hz, C-1), 125.6 (q, ^1J = 284 Hz, CF_3); MS *m/e* 206 (2, M - HCl), 189 (21), 186 (20), 158 (14), 156 (39), 157 (17), 155 (39), 95 (20), 79 (45), 67 (55), 55 (100); exact mass calcd for $C_{10}H_{14}F_3ClO$ 242.0685, found 242.0681.

(b) With $MeAlCl_2$. A solution of **2a** (206 mg, 1 mmol) in CH_2Cl_2 (10 mL) was treated with $MeAlCl_2$ (1.27 mL of a 1 M solution in hexanes, 1.27 mmol) at -78 °C for 7 h. Workup gave a crude product (190 mg), which was purified by chromatography on silica gel, affording starting material **2a** (25 mg, 12%), chlorides **11a** (48 mg, 20%) and **10a** (20 mg, 12%), and a 9:1 mixture of two unsaturated compounds, **9a** and an isomer, tentatively identified as **7a** (60 mg, 29%).

(c) With $TiCl_4$. A solution of ketone **2a** (206 mg, 1 mmol) in CH_2Cl_2 (10 mL) was treated with $TiCl_4$ (1 mL of a 1 M solution in CH_2Cl_2, 1 mmol) at -78 °C for 0.5 h. Workup gave crude **12a** (157 mg, 65%). Chromatography on silica gel afforded **13a** (89 mg, 40%).

2-Chloro-2-(trifluoromethyl)-1-oxaspiro[4.5]decane (12a): ^{19}F NMR δ -81.8; ^{13}C NMR δ 23.3, 25.0, 33.6, 36.2, 38.1, 38.15, 92.1 (*C*-O), 103.4 (q, ^2J = 36 Hz, *C*-Cl), 121.8 (q, ^1J = 281 Hz, CF_3); MS *m/e* 244 (9, M^+) and 242 (18, M^+), 213 (44)) and 215 (16), 207 (86), 201 (70) and 199 (100), 189 (37), 163 (13), 95 (27), 81 (28), 67 (39), 55 (90); exact mass calcd for $C_{10}H_{14}F_3OCl$ 242.0685, found 242.0680.

2-Hydroxy-2-(trifluoromethyl)-1-oxaspiro[4.5]decane (13a): ^{19}F NMR δ -85.3; ^{13}C NMR δ 23.4, 23.6, 25.2, 32.3, 33.1, 36.4, 38.9, 86.6 (*C*-O), 101.3 (q, ^2J = 41 Hz, CCF_3), 122.3 (q, ^1J = 286 Hz, CF_3); MS *m/e* 224 (9, M^+), 207 (30, M - OH), 195 (22), 181 (100), 115 (17), 81 (8), 69 (17), 55 (30); exact mass calcd for $C_{10}H_{15}F_3O_2$ 224.1024, found 224.1023.

Cyclization of β-Keto Ester 1b. (a) With $EtAlCl_2$. A solution of 430 mg of a mixture (80/20) of **1b** and **1c** (**1b**: 340 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was treated with $EtAlCl_2$ (0.42 mL of a 1 M solution in hexanes, 0.42 mmol) for 3 h at 0 °C. Workup gave a crude product (390 mg), which was purified by chromatography on silica gel; unreacted **1c** (80 mg) and **3b** (220 mg, 65%) were obtained. Traces of **4b** and **6b** were detected by GC analysis of the crude reaction product.

The same reaction from 450 mg of a mixture (80/20) of **1b** and **1c** (**1b**: 360 mg, 1.2 mmol) and $EtAlCl_2$ (1.5 mL, 1.5 mmol) for 5 h at -78 °C gave a crude product (410 mg). Chromatography on silica gel gave successively the starting mixture **1b** and **1c** (190 mg, 40/60 ratio), the chloride **6b** (90 mg, 25%), and **3b** (50 mg, 14%).

The same reaction performed with 1 equiv of $EtAlCl_2$ at 0 °C afforded **3b** (75%), **4b** (15%), and **6b** (10%) (GC analysis).

Ethyl 1-hydroxy-1-(trifluoromethyl)-2-methyl-1,2,3,4,6,7,8,9-octahydronaphthalene-2-carboxylate (3b): ^1H NMR δ 1.26 (t, *J* = 7 Hz, 3 H), 1.44 (q, $^5J_{HF}$ = 1.7 Hz, 3 H, CH_3), 1.6-2.0 (m, 8 H), 2.16 (m, 2 H), 2.66 (m, 1 H), 4.20 (q, *J* = 7 Hz, 2 H), 5.71 (m, 1 H), 6.25 (d, ^4J = 1.5 Hz, 1 H, O*H*, slow exchange); ^{19}F NMR δ -69.3; ^{13}C NMR δ 13.3 (CH_3CH_2), 16.1 (q, ^4J = 2.1 Hz, CH_3), 21.5 (C-7), 22.4 (q, ^4J = 2.2 Hz, C-8), 24.3 (C-6), 28.9 (C-3), 34.0 (C-4), 37.9 (C-9), 45.9 (C-2), 61.4 (CH_2-O), 78.9 (q, ^2J = 24 Hz, C-1), 125.2 (C-5), 126.0 (q, ^1J = 292 Hz, CF_3), 132.3 (C-10), 178.7 (COOEt); MS *m/e* 306 (3, M^+), 288 (10, M - 18), 268 (18, M - 18 - HF), 240 (17), 215 (66), 173 (15), 108 (60) 93 (46), 79 (100), 69 (25), 67 (25), 55 (15); exact mass calcd for $C_{15}H_{21}F_3O_3$ 306.1443, found 306.1436.

Ethyl 10-chloro-1-(trifluoromethyl)-1-hydroxy-2-methyldecahydronaphthalene-2-carboxylate (6b): ^1H NMR δ 1.32 (t, *J* = 7 Hz, 3 H), 1.45 (q, $^5J_{HF}$ = 2.5 Hz, 3 H, CH_3), 1.50-2.10 (m, 11 H), 2.19 (m, 1 H), 2.35 (m, 1 H), 4.23 (q, *J* = 7 Hz, 2 H), 5.45 (d, ^4J = 1.5 Hz, 1 H, O*H*); ^{19}F NMR δ -63.6; ^{13}C NMR δ 13.9 (CH_3CH_2), 21.8 (CH_3), 23.1, 23.2, 27.9, 29.4 (q, ^4J = 2.8 Hz, C-8), 40.2, 44.8, 50.5 (C-2), 54.9 (C-9), 61.9, 73.0 (C-10), 78.4 (q, ^2J = 25 Hz, C_1), 126.4 (q, ^1J = 290 Hz, CF_3), 180 (COOEt); MS *m/e* 288 (3, M - HCl - H_2O), 253 (55), 241 (29), 215 (89), 173 (100), 108 (60), 91 (30), 79 (85), 67 (40), 55 (32); exact mass calcd for $C_{15}H_{22}F_3O_3Cl$ 342.1209, found 342.1211.

(b) With Me_2AlCl. The same reaction performed with Me_2AlCl (1 equiv) at 0 °C for 3 h afforded **3b** (70%), **4b** (11%), and **6b** (19%) (GC analysis).

(c) With $TiCl_4$. A solution of **1b** and **1c** (80/20 mixture, 500 mg) (**1b**: 400 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) was treated with $TiCl_4$ (0.18 mL, 1.6 mmol), for 2.5 h at -78 °C. Workup and chromatography of the crude product (495 mg) gave unreacted **1c** (85 mg), **4b** (200 mg, 50%), **3b** (50 mg, 12%), and a trace of chloride **6b**.

Ethyl 1-(trifluoromethyl)-1-hydroxy-2-methyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-carboxylate (4b): ^1H NMR δ 1.2 (t, *J* = 7 Hz, 3 H), 1.4 (s, 3 H, CH_3), 1.6 (m, 4 H), 2.0 (m, 8 H), 4.1 (q, *J* = 7 Hz, 2 H), 5.7 (1 H, O*H*, slow exchange); ^{19}F NMR δ -70.6; ^{13}C NMR δ 13.3 (CH_3CH_2), 18.7 (q, ^4J = 2 Hz, CH_3), 21.7 (C-6), 22.5 (C-7), 23.7 (q, ^4J = 2 Hz, C-3), 27.1 (C-5), 28.0 (q, ^4J = 2 Hz, C-8), 30.2 (C-4), 47.3 (C-2), 61.0 (CH_2-O), 76.5 (q, ^2J = 26 Hz, C-1), 125.5 (q, ^1J = 289 Hz, CF_3), 127.5 (C-10), 134.6 (C-9), 177.9 (*C*OOEt); MS *m/e* 268 (5, M - 18 - HF), 253 (100), 241 (81), 215 (40), 173 (76), 145 (26), 135 (39), 107 (18), 91 (24), 79 (21), 55 (16); exact mass calcd for $C_{15}H_{21}F_3O_3$ 306.1443, found 306.1436.

Treatment of Chloride 6b with EtONa. A solution of chloride **6b** (30 mg, 0.8 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature, with a 1 M solution of sodium ethoxide in ethanol (2 mL), for 3 days. The reaction mixture was neutralized with aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated on reduced pressure. Analysis by coupled MS-GC of the resulting mixture (20 mg) showed **4b** (70%), **3b** (6%), **6b** (15%), and another product, probably the isomeric alkene **5b**.

Ethyl 1-(trifluoromethyl)-1-hydroxy-2-methyl-1,2,3,5,6,7,8,9-octahydronaphthalene-2-carboxylate (5b): ^{19}F NMR δ -69.3; MS *m/e* 268 (2, M - H_2O - HF), 253 (60), 215 (30), 174 (24), 173 (100), 145 (10), 121 (10), 91 (14), 79 (20).

Cyclization of β-Keto Ester 2b. (a) With $EtAlCl_2$. A solution of **2b** (435 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was treated with $EtAlCl_2$ (1.5 mL of a 1 M solution in hexanes, 1.5 mmol) for 45 min at 0 °C. After workup and chromatography compound **8b** (320 mg, 74%) was isolated, containing only traces (<3%) of **11b** (reaction is not complete at -78 °C).

Ethyl 1-(trifluoromethyl)-1-hydroxy-2-methyl-2,3,4,5,6,7-hexahydroindene-2-carboxylate (8b): ^1H NMR δ 1.2 (q, *J* = 7 Hz, 3 H), 1.3 (bs, 3 H, CH_3), 1.6 (m, 5 H), 1.9 (m, 4 H), 2.1 (d, *J* = 14 Hz, 1 H), 2.8 (d, *J* = 14 Hz, 1 H), 4.1 (q, *J* = 7 Hz, 2 H); ^{19}F NMR δ -73.4; ^{13}C NMR δ 13.7, 20.3, 21.5, 21.9, 22.2, 25.7, 45.9, 53.6, 61.3, 87.3 (q, ^2J = 28 Hz, C-1), 124.5 (q, ^1J = 288 Hz, CF_3), 132.1, 141.8, 176.0 (*C*OOEt); MS *m/e* 274 (33, M - 18), 254 (11), 227 (15), 201 (67), 200 (100), 181 (20), 173 (40), 149 (35), 131 (23), 121 (45), 105 (27), 91 (26), 79 (34), 77 (23); FT IR 3440 (br, bounded *OH*, 1710 *C*OOEt); exact mass calcd for $C_{14}H_{19}F_3O_3$ 292.1286, found 292.1277.

11b: MS *m/e* 274 (18, M - H_2O - HCl), 245 (4), 219 (13), 201 (100), 200 (50), 181 (13), 173 (28), 149 (12), 141 (7), 131 (16), 121 (18), 105 (26), 91 (24), 77 (26).

(b) With $TiCl_4$. A solution of **2b** (435 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was treated with $TiCl_4$ (0.18 mL, 1.5 mmol) for 30 min at -78 °C. After workup and chromatography, product **8b** (405 mg, 92%) was isolated.

1-(Trifluoromethyl)-1-hydroxy-2-methyl-2,3,4,5,6,7-hexahydroindene-2-carboxylic Acid (14). A solution of **8b** (500 mg) in EtOH (15 mL) and 20% aqueous KOH (1 mL) was stirred for 5 h at room temperature. After acidification with 2 M HCl (to pH 3), the product was extracted (CH_2Cl_2), and the organic extracts were dried ($MgSO_4$). Evaporation of the solvent afforded crude acid **14**; crystallization (pentane) gave pure acid **14** (170 mg): mp 103-4 °C; ^1H NMR δ 1.44 (m, 3 H, CH_3), 1.65 (m, 4 H), 2.05 (m, 5 H), 2.16 (d, ^2J = 14 Hz, 1 H), 3.05 (d, ^2J = 14 Hz, 1 H), 5.55 (br s, 1 H, COO*H*); ^{19}F NMR δ -73.3; ^{13}C NMR (acetone-d_6) δ 20.9 (C-6), 22.6 (C-5), 22.9 (C-4), 23.2 (C-7), 26.5 (Me), 46.7 (C-3), 55.2 (C-2), 87.9 (q, *J* = 29 Hz, C-1), 126.8 (q, ^1J = 294 Hz, CF_3), 132.6 (s, C-9), 143.1 (C-8), 176.7 (*C*OOH); exact mass calcd for $C_{12}H_{15}F_3O_3$ 264.0973, found 264.0976.

1-(Trifluoromethyl)-1-methyl-4,5,6,7-tetrahydroindene (15).[19,20] A solution of acid **14** (40 mg, 0.15 mmol) in dry pyridine (3 mL) was treated under an argon atmosphere at -10 °C with benzenesulfonyl chloride (55 mg, 0.3 mmol). The temperature of the reaction was maintained between -10 °C and -5 °C overnight. The mixture was poured over ice and extracted with Et_2O. The organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under atmospheric pressure. A crude product consisting primarily of diene **15** (20 mg, 65%) but contaminated with traces of other products

was obtained. 15: ^{1}H NMR δ 1.67 (m, 4 H), 2.12 (m, 3 H, CH_3), 2.25 (m, 4 H), 2.88 (m, 2 H); ^{19}F NMR δ -59.6; ^{13}C NMR δ 14.3, 22.6, 22.7, 23.1, 25.0, 48.7 (C-3), 123.7 (q, ^1J = 271 Hz, CF_3), 130.6 (q, ^2J = 36 Hz, C-1), 135.1 (C-8), 137.7 (C-9), 144.6 (C-2); MS m/e 202 (M^+, 71), 185 (M - 15, 38), 174 (M - 28, 23), 159 (30), 141 (12), 133 (41, M - CF_3), 115 (12), 105 (100), 91 (24), 79 (14), 77 (10), 69 (14); IR no C=O vibration.

Acknowledgment. We wish to thank Prof. Barry B. Snider for helpful criticisms during the preparation of the paper and Prof. Takeshi Nakai for stimulating discussions. We gratefully acknowledge M. Ourevitch (CERCOA) for 2D NMR experiments.

Supplementary Material Available: NMR data of products **1b**, **1c**, **2b**, **3a**, **5a**, **6a**, **9a**, **10a**, **11a**, **12a**, **13a**, **3b**, **4b**, **6b**, **8b**, **14**, and **15** (53 pages). Ordering information is given on any current masthead page.

Use of Sulfoxides as Cocatalysts in the Palladium-Quinone-Catalyzed 1,4-Diacetoxylation of 1,3-Dienes. An Example of Ligand-Accelerated Catalysis

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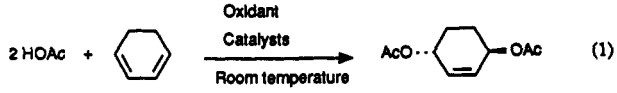
Received February 21, 1991

The use of sulfinyl quinones as cocatalysts in the palladium-catalyzed 1,4-diacetoxylation of 1,3-dienes improves the stereochemical outcome of the reaction by increasing the rate of the internal migration of the acetate nucleophile. A mechanism of the interaction between the sulfoxide and the intermediate (π-allyl)palladium complex, based on ^{1}H NMR results, is proposed.

Introduction

The palladium-catalyzed diacetoxylation of 1,3-dienes is a high-yielding regio- and diastereoselective reaction that gives access to synthetically useful products (eq 1).[1] To



(1)

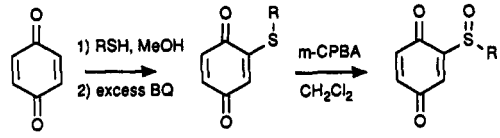
further improve the scope of this reaction, it was our objective to increase the reaction rate as well as to investigate the possibility of introducing enantioselectivity. The idea was to enhance the interaction between the intermediate (π-allyl)palladium complex and the quinone used as oxidant (or electron-transfer mediator), since this interaction is of importance for the selectivity of the reaction.[2]

Several reactions that employ 1,4-benzoquinones as stoichiometric oxidants or electron carriers in selective palladium-catalyzed oxidations have recently been developed in this group.[2-4] When the quinone is used in catalytic amounts, an external oxidant such as MnO_2[2] or molecular oxygen activated by a metal macrocycle[4] is employed (eq 1). In the present study molecular oxygen, activated by iron phthalocyanine (Fe(Pc)), was chosen as the external oxidant. This allows the progress of the reaction to be monitored by the oxygen consumption.

Results and Discussion

The interaction between the (π-allyl)palladium complex and the quinone can be enhanced by increasing the electron density of the quinone itself or by introducing an additional "handle" on the quinone in the form of a coordinating substituent. Previous investigations, in which a wide variety of quinones were employed, have shown that reaction rate and selectivity are markedly dependent upon the quinone substituents.[2] This might have steric as well as electronic reasons. The best results, regarding both rate and selectivity, were obtained for the unsubstituted 1,4-benzoquinone and for quinones with an electron-withdrawing and an electron-donating group in the 2- and 3-positions, respectively. This indicates that the electron density of the quinone may not be varied much.

It is known that sulfoxides form strong complexes with Pd(II),[5] and (π-allyl)palladium(sulfoxide) species have been characterized by NMR spectroscopy.[6] Other related, weaker complexating agents are nitriles[5b,7] and DMF.[5b,8] Since the sulfoxide group has good complexation properties we decided to study 2-sulfinyl-1,4-benzoquinones **2a-c**, which are readily available from 1,4-benzoquinone (eq 2).[9]



(2)

Since these chiral sulfinyl quinones may be useful in enantioselective reactions the *R*-(+)-enantiomer of *p*-

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0022-3263/91/1956-5808$02.50/0