The Wittig Reaction of Perfluoro Acid Derivatives: Access to Fluorinated Enol Ethers, Enamines, and Ketones

Jean-Pierre Bégué,* Danièle Bonnet-Delpon, Dany Mesureur, Gérard Née, and Sheng-Wen Wu

CERCOA-CNRS, 2 rue Henry Dunant, 94320 Thiais, France

Received November 27, 1991

The preparation of novel perfluoroalkyl-substituted compounds in good yields is described. This preparation involves the Wittig reaction of a phosphonium ylide with perfluoroalkyl acid derivatives. The influence of the structure of the starting alkylidenetriphenylphosphoranes, the perfluoroalkyl reagents, and the reaction conditions has been investigated. Trifluoroacetamides lead to a Z/E mixture of enamines **3**. Perfluoroalkyl esters (Rf = CF_3, C_2F_5, C_3F_7, C_7F_{15}, CF_2Cl) lead to only the (Z)-enol ethers **8–12** when reactions are performed with $NaNH_2$ as a base and to 1-perfluoroalkyl ketones **13–17** when reactions are performed with BuLi.

Introduction

Organofluorine compounds are of great interest to synthetic and medicinal chemists owing to the unique physical and biological properties imparted by fluorine atoms.[1,2] Polyfluorinated compounds have been prepared by fluorination or perfluoroalkylation of hydrocarbons and their halides. Synthesis using fluorine-containing building blocks is another approach. Our purpose is to contribute to this second approach by finding new syntheses for fluorinated building blocks. Among these, fluorinated ketones are the subject to renewed interest by organic chemists. This focus is derived not only from their roles as synthons in the preparation of more complex molecules but also from their own biological properties as enzyme inhibitors.[3]

The synthesis of fluorinated ketones has, for a long time, been difficult because the original methods were limited. However, new approaches were recently developed based upon the enhanced electrophilicity of the carbonyl carbon bearing fluorinated groups.[3] One of these involves the Wittig reaction, successfully effected on trifluoroacetic derivatives. Moreover, a Wittig approach has provided various other fluorinated synthons as described by several groups, notably Burton's,[4] Shen's,[5] Cambon's,[6] and our own group.[7-9]

Generally, the main limitation of a Wittig reaction with carboxylic acid derivatives is the poor reactivity of nonactivated esters, and especially amides, with alkylidenephosphoranes.[10] In this respect, the addition of a phosphorane to a carboxylic ester is possible only if the phosphorane is reactive enough, or if the ester is activated. With nonstabilized phosphoranes, nonactivated esters afford β-acyl alkylidenephosphoranes,[11] whereas no reaction occurs with stabilized phosphoranes. Activated esters react with stabilized phosphoranes providing enol ethers,[12,13] while with nonstabilized phosphoranes the nature of products is dependent on reaction conditions.[12,14]

The great electrophilicity of fluoroalkyl carboxylic acid derivatives enables phosphorus ylides to add to the carbonyl group of esters,[7,12] and even amides.[8] Thus, we have previously reported the preparation of trifluoromethyl trimethylsilyl enol ethers[7] and trifluoromethyl enamines,[8] from $CF_3COOSi(Me)_3$ and trifluoroacetamides, respectively. In this paper, we have examined in more detail the reaction between the ylides generated from phosphonium salts **1** and fluorinated amides, anhydrides, and esters. Our new investigations show that the structure of alkylidene phosphoranes **2**, the reaction conditions, the acylating reagent, and the fluoroalkyl group all have a significant role in determining the success and the course of the reaction. This study provides general and selective synthetic procedures for 1-perfluoroalkyl enol ethers, 1-trifluoromethyl enamines, and 1-perfluoroalkyl ketones.

Results

(a) From Amides (Scheme I). We have already reported the synthesis of trifluoromethylated enamines (Z/E mixture) using the condensation of various trifluoroacetamides with alkylidene phosphoranes, generated in "salt-free conditions" by $NaNH_2$–hexamethyldisilazane (HMDS).[8] From phosphoranes **2**, enamines **3** (morpholino) (57%), **4** (piperidino) (38%), and **5** (dibenzylamino) (19%) could be obtained (Rf = CF_3). The same reaction has been performed under other basic conditions and with other perfluoroalkyl groups. The desired reaction was achieved with alkylidene phosphorane **2a** generated from **1a** with n-BuLi in THF. The same Z/E enamines **3a** were obtained (59%) with the trifluoromethyl morpholinoamide. Surprisingly, with perfluoroalkyl morpholinoamides, only 6% of enamines **6a** (Rf = C_2F_5) and traces of enamines **7a** (Rf = C_3F_7) were obtained, regardless of the base used ($NaNH_2$ or BuLi).

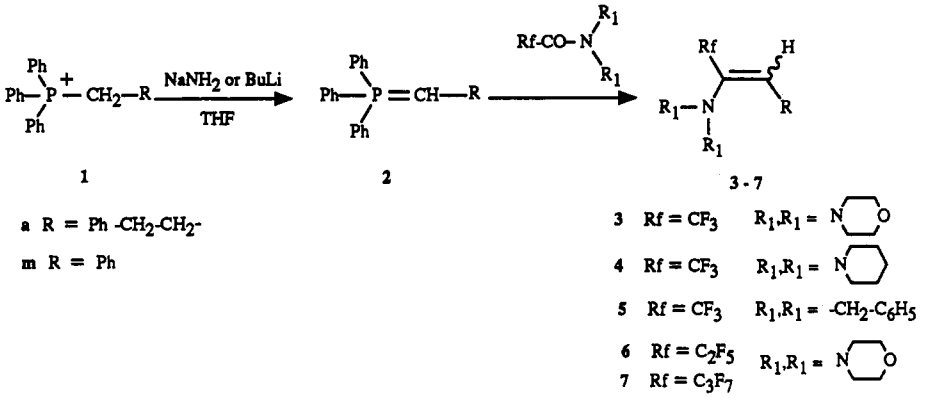
Hydrolysis of these enamines in acidic medium (HCl, 1 N) provides the corresponding fluorinated ketones in quantitative yield.

(b) From Trifluoroacetic Anhydride (Scheme II). Shen et al. described the addition of trifluoroacetic

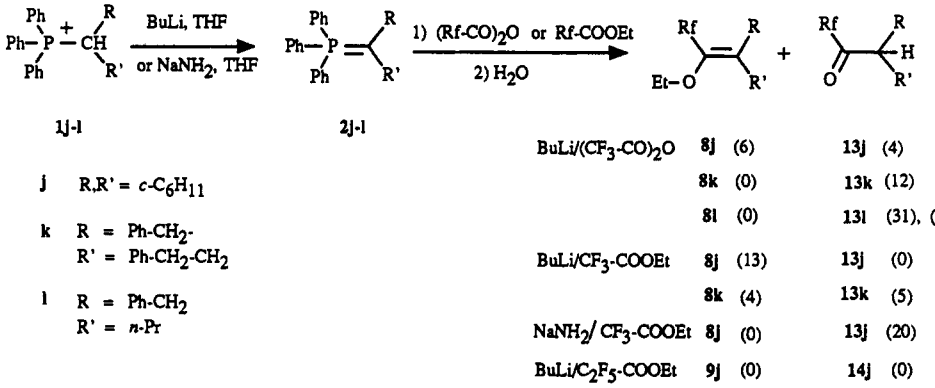
(1) Liebman, J. F.; Greenberg, A.; Dolbier, W. J., Jr. *Fluorine-containing Molecules, Structures, Reactivity, Synthesis and Applications*; VCH: New York, 1988.
(2) Banks, R. E.; Horwood, E. "*Organofluorine Compounds and their Industrial Applications*; Halsted Ed., New-York, 1979.
(3) Bégué, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207.
(4) (a) Burton, D. J.; Inouye, Y. *Tetrahedron Lett.* **1979**, 3397. Burton, D. J.; Cox, D. G. *J. Am. Chem. Soc.* **1983**, *105*, 650. Burton, D. J.; Herkes, F. E.; Klabunde, K. J. *J. Am. Chem. Soc.* **1966**, *88*, 5042. Burton, D. J.; Thenappan, A. *J. Org. Chem.* **1991**, *56*, 273. Jeong, I. H.; Burton, D. J.; Cox, D. G. *Tetrahedron Lett.* **1986**, *27*, 3709.
(5) (a) Shen, Y. C.; Xin, Y. K.; Cen, W. B.; Huang, Y. Z. *Synthesis* **1984**, 35. (b) Shen, Y. C.; Qiu, W. M. *J. Chem. Soc., Chem. Commun.* **1987**, 703. (c) Shen, Y. C.; Wang, T. *Tetrahedron Lett.* **1989**, *30*, 7203. (d) Shen, Y. C.; Qiu, W. M.; Xin, Y. K.; Huang, Y. Z. *Synthesis* **1984**, 924. (e) Shen, Y. C.; Liao, Q.; Qiu, W. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 695.
(6) (a) Trabelsi, H.; Rouvier, E.; Cambon, A. *J. Fluorine Chem.* **1986**, *31*, 351. (b) Trabelsi, H.; Bollens, E.; Rouvier, E.; Cambon, A. *J. Fluorine Chem.* **1986**, *34*, 265. (c) Trabelsi, H.; Bollens, E.; Cambon, A. *Synthesis* **1990**, 623.
(7) Bégué, J. P.; Mesureur, D. *J. Fluorine Chem.* **1988**, *39*, 271.
(8) Bégué, J. P.; Mesureur, D. *Synthesis* **1989**, 309.
(9) Bégué, J. P.; Bonnet-Delpon, D.; Sdassi, H. *Tetrahedron Lett.* **1992**, *33*, 1879.
(10) Murphy, P. J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1.
(11) (a) Wittig, G.; Schöllkopf, V. *Chem. Ber.* **1954**, *87*, 1318. (b) Bestmann, H. J.; Arnason, B. *Chem. Ber.* **1962**, *95*, 1513.
(12) Bestmann, H. J.; Dornauer, H.; Rostock, K. *Chem. Ber.* **1970**, *103*, 2011.
(13) Subramanyan, V.; Silver, E. H.; Soloway, A. H. *J. Org. Chem.* **1976**, *41*, 1272.
(14) (a) Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 1266. (b) Grell, W.; Machleidt, H. *Liebigs Ann. Chem.* **1966**, *693*, 134.

0022-3263/92/1957-3807$03.00/0

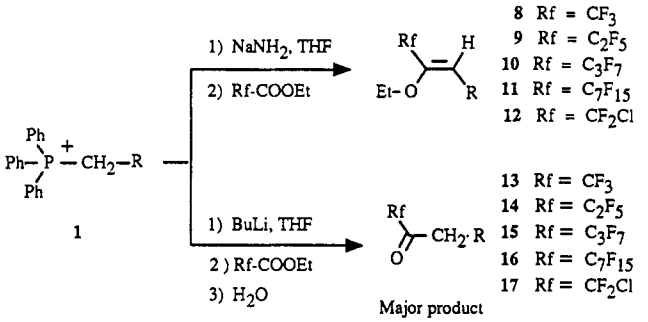
Scheme I



Scheme II



Scheme III



anhydride to phosphorane **2l**, leading to a 70% yield of ketone **13l**.[15] Only 30% of ketone **13l** was obtained when we tried to reproduce this experiment. The same reaction has been performed with two other α,α-dialkylidenephosphoranes **2j** and **2k**. The color of the ylide disappeared as soon as trifluoroacetic anhydride was added. However, after heating and basic hydrolysis, ketones **13j** and **13k** were obtained in very poor yields (≤10 %). The reaction failed with monoalkylidenephosphorane **2a**, generated from **1a** with BuLi, PhLi, or $NaNH_2$ and HMDS in THF. Although decoloration was fast after the addition of the anhydride, only traces of ketone **13a** were detected after workup.

(c) From Esters (Table I, Schemes II and III). The Wittig reaction was performed using salt-free conditions in THF (or benzene) with various perfluoroalkyl ethyl esters (Rf = CF_3, C_2F_5, C_3F_7, C_7F_{15}, CF_2Cl) and alkylidenephosphoranes **2**, generated from alkyltriphenylphosphonium salts **1** with $NaNH_2$ in the presence of catalytic amounts of HMDS (Table I). In all cases, enol ethers **8** (Rf = CF_3), **9** (Rf = C_2F_5), **10** (Rf = C_3F_7), **11** (Rf = C_7F_{15}), and **12** (CF_2Cl) were obtained in moderate to good yield (45–75%). It should be pointed out that for Rf = CF_3, reflux (6 h) was needed to obtain the enol ether, while reactions with other perhaloalkyls were performed at room temperature. The reaction is stereoselective: only the (*Z*)-enol ethers were obtained according to NMR data.[16] They are stable under acidic or basic hydrolysis. The reaction failed with $CF_2BrCOOMe$, probably due to the ease of difluorocarbene formation. α,α-Disubstituted phosphorane **2j** gave only 20% of enol ether **8j** (Scheme II); however, semistabilized and stabilized phosphoranes

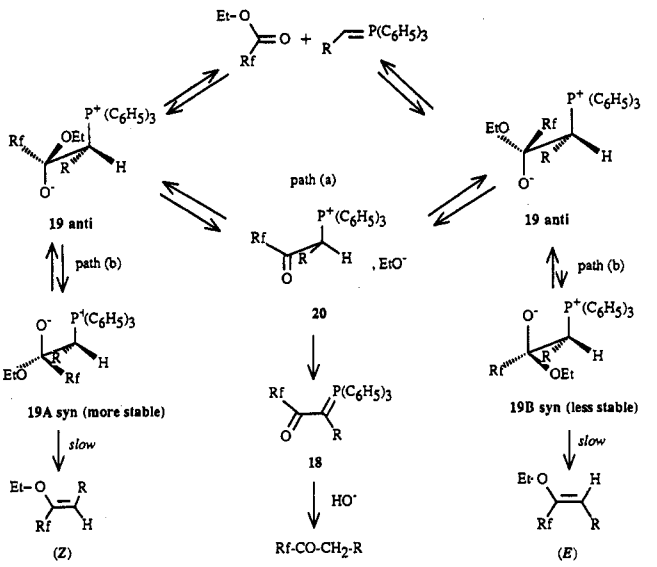


Figure 1. Reaction pathway for the addition of Rf–COOEt on alkylidene phosphorane.

(15) Qiu, W. M.; Shen, Y. C. *J. Fluorine Chem.* **1988**, *38*, 249.

(16) Bégué, J. P.; Bonnet-Delpon, D.; Ourevitch, M. *Res. Magn. Chem.* **1991**, *29*, 675.

Table I. Wittig Reaction with Fluorinated Esters Rf-COOEt and Alkylidene Phosphoranes 2 Generated with $NaNH_2$[a] and with BuLi (Scheme III)

phosphorane 2				enol ether		ketone	
no.	R	Rf	base	no.	(%)[b]	no.	(%)[b]
2a	$PhCH_2CH_2$	CF_3	$NaNH_2$	8a	(60)	13a	(0)
			BuLi	8a	(0)	13a	(60)
2a	$PhCH_2CH_2$	C_2F_5	$NaNH_2$	9a	(70)	14a	(0)
			BuLi	9a	(0)	14a	(57)
2a	$PhCH_2CH_2$	n-C_3F_7	$NaNH_2$	10a	(58)	15a	(0)
			BuLi	10a	(0)	15a	(72)
2a	$PhCH_2CH_2$	n-C_7F_{15}	$NaNH_2$	11a	(45)	16a	(0)
			BuLi	11a	(8)	16a	(45)
2a	$PhCH_2CH_2$	CF_2Cl[c]	$NaNH_2$	12a	(48)	17a	(0)
			BuLi	12a	(8)	17a	(44)
2b	4-(OMe)$C_6H_4CH_2CH_2$	CF_3	BuLi	8b	(0)	13b	(40)
2b	4-(OMe)$C_6H_4CH_2CH_2$	C_2F_5	BuLi	9b	(0)	14b	(43)
2c	3,4-$(OMe)_2C_6H_3CH_2CH_2$	CF_3	$NaNH_2$	8c	(55)	13c	(0)
			BuLi	8c	(0)	13c	(40)
2c	3,4-$(OMe)_2C_6H_3CH_2CH_2$	C_2F_5	BuLi	9c	(0)	14c	(47)
2d	3,4-$(OCH_2O)C_6H_3CH_2CH_2$	CF_3	BuLi	8d	(0)	13d	(40)
2d	3,4-$(OCH_2O)C_6H_3CH_2CH_2$	C_2F_5	BuLi	9d	(0)	14d	(54)
2e	c-C_6H_{11}	CF_3	$NaNH_2$	8e	(55)	13e	(0)
2e	c-C_6H_{11}	n-C_3F_7	$NaNH_2$	10e	(45)	15e	(0)
2f	c-$C_6H_{11}CH_2$	CF_3	$NaNH_2$	8f	(50)	13f	(0)
2g	$PhCH_2CH_2CH_2$	CF_3	BuLi	8g	(0)	13g	(52)
2h	$CH_3(CH_2)_3CH_2$	n-C_7F_{15}	BuLi	11h	(0)	16h	(57)
2i	$CH_3(CH_2)_4CH_2$	CF_3	BuLi	8i	(0)	13i	(40)
2i	$CH_3(CH_2)_4CH_2$	C_2F_5	BuLi	9i	(0)	14i	(49)
2m	Ph	CF_3	$NaNH_2$	8m	(55)	13m	(0)
			BuLi	8m	(29)	13m	(0)
2m	Ph	C_2F_5	BuLi	9m	(36)	14m	(0)
2n	3-$(CF_3)C_6H_4$	CF_3	BuLi	8n	(61)	13n	(0)
2o	4-(OMe)C_6H_4	CF_3	BuLi	8o	(33)	13o	(0)
2p	CO_2Et	CF_3	$NaNH_2$	8p	(30)	13p	(0)
			BuLi	8p	(0)	13p	(0)

[a] In some limited experiments, yields have been improved with the use of NaH. [b] Isolated yield. [c] Methyl ester.

2m and **2p** led to **8m** (55%) and **8p** (30%), respectively.

The same reaction was performed in THF with phosphoranes **2**, generated from **1** with BuLi (Table I). With nonstabilized phosphoranes **2a–i**, the reaction afforded, after a basic hydrolysis, perfluoroalkyl ketones in 40–70% yield, regardless of the Rf group of starting esters. Fluorinated β-acyl phosphorane **18a** (Figure 1) could be isolated when the hydrolysis was conducted in acidic medium. When Rf = C_7F_{15} and CF_2Cl, ketones **16a** and **17a** were accompanied with small amounts of enol ethers **11a** (8%) and **12a** (8%) respectively. In contrast, only enol ethers were obtained with semistabilized phosphoranes **2m–o** and with the α,α-disubstituted methylene phosphorane **2j** (Scheme II), this latter being poorly reactive (13% of **8j**). No reaction occurred with stabilized phosphorane **2p**.

Discussion

The course of the reaction between a phosphorane and a fluoroalkyl acid derivative depends on (i) the ability of this reagent to add on to the phosphorane and (ii) the transformation of the resulting adduct. This intermediate can undergo two main conversions discussed by Uijttewaal et al. in the case of nonfluorinated starting esters.[17,18] Path (a) from the anti conformer of the alkoxybetaine (Figure 1) requires the loss of the alkoxide anion. An acylated phosphonium salt is formed and is rapidly deprotonated to the stable acylated phosphorane (if an α-hydrogen is present). This process, first described by Wittig and Schöllkopf,[11a] has been developed by Bestmann.[11b] The presence of lithium salts is known to favor this path by stabilization of the anti conformer and complexation of the ethoxy group. Path (b), from the syn conformer or corresponding oxaphosphetane, affords enol ethers by loss of triphenylphosphine oxide. This path has been described in the case of activated esters[12] and/or stabilized and semistabilized phosphoranes.[13,19,20] It is favored when reactions are performed using salt-free conditions. We will discuss the influence of different factors upon yields and product distribution.

(1) Amides. Usually, the poor electrophilicity of amides does not allow a Wittig reaction to occur with alkylidenephosphoranes.[10] With perfluoroalkylamides, this reaction is possible to some extent. Reaction times are long (usually 24 h in boiling THF), and yields are strongly dependent on the nature of the amino residue as well as on the Rf chain. Yields dramatically decrease with increasing steric hindrance and increasing basicity of the amino group. The best results were found with the less basic morpholino residue (≈60%). More surprising are the very low yields with perfluoroalkylacetamides (Rf = C_2F_5 and Rf = C_3F_7). This could be explained by the lower electron-withdrawing character of Rf chains in relation to that of CF_3 group[21,22] as well as by a greater steric hindrance.

Only enamine formation was observed, even in the presence of lithium salts: the β-aminobetaines, resulting from the addition of phosphoranes with trifluoroacetamides, cannot form a β-acylphosphonium by the loss of an amide anion, as it is such a poor leaving group. The

(17) Uijttewaal, A. P.; Jonkers, F. L.; van der Gen, A. *J. Org. Chem.* **1978**, *43*, 3306.
(18) Uijttewaal, A. P.; Jonkers, F. L.; van der Gen, A. *J. Org. Chem.* **1979**, *44*, 3157.
(19) Le Corre, M. *Bull. Soc. Chim. Fr.* **1974**, 2005.
(20) Aitken, R. A.; Thom, G. L. *Synthesis* **1989**, 958.
(21) Naji, N.; Moreau, P. *J. Fluorine Chem.* **1988**, *38*, 19.
(22) (a) Zhukov, V. P.; Gubanov, V. A. *Tr. Inst. Khim., Ural. Nauchn. Tsentr, Akad. Nauk. SSSR* **1975**, *34*, 110. (b) Zhukov, V. P.; Gubanov, V. A. *J. Mol. Struct.* **1977**, *41*, 281.

Z/E ratio[8] could reflect the relative stabilities of corresponding aminobetaines (Figure 1 and discussion below).

The easy hydrolysis of 1-trifluoromethyleneamines affords a convenient access to trifluoromethyl ketones.

(2) Trifluoroacetic Anhydride. Perfluoroalkyl anhydrides (or chlorides) are described to be unreactive with methylenetriphenylphosphorane.[5d] They react well with α,α-dialkylidenephosphoranes to give fluorinated acylphosphonium salts[15,23,24] and with stabilized phosphoranes to give fluorinated acylphosphoranes.[5a,25,26] However we could not reproduce these experiments in such good yields. Furthermore, out attempts to acylate the nonstabilized alkylidenephosphorane **2a** with trifluoroacetic anhydride failed (salt-free conditions or the presence of lithium salts). We are unable to explain this result since anhydrides are better acylating agents than esters.

(3) Esters (Figure 1). Neither the Rf chain nor the alkoxy group of the ester (Me, Et, $SiMe_3$[7]) has a notable influence on the course of the reaction (products and yield). The success of the condensation is dependent on the phosphorane structure. Fluorinated esters easily add to methylenephosphorane[5d] and to alkylidenephosphoranes. Yields decrease in proportion to the steric hindrance (**2j,k**, Scheme II) and the stabilization of the phosphorane (**2m–p**) (Table I). The phosphorane structure affects the product distribution, but the determining factor for the reaction outcome is the presence (or absence) of lithium salts.

Reaction in the Presence of Lithium Salts. The presence of lithium salts slows down the rate of the condensation step (see Experimental Section). In most cases, the reaction product is the fluoroalkyl ketone obtained by the hydrolysis of the corresponding β-acylphosphorane **18**. We have verified the formation of this intermediate, before hydrolysis, in the case of the nonstabilized starting phosphorane **2a**. The presence of lithium salts is of crucial importance for the reaction to proceed along path (a) via ethoxide elimination. This has been verified by the isolation of enol ethers instead of ketones when HMPA was added to the reaction solution. The phosphorane structure, however, also has an influence on this selectivity. With α,α-disubstituted methylenephosphoranes and with phenylphosphoranes, the product is the enol ether instead of the expected ketone. This observation can be explained by substituent stabilization of the incipient double bond of enol ether. With phenylphosphoranes **2m,n,o** the yield decreases from 70% for the electron-withdrawing substituent CF_3 (**2n**) to 30% when the substituent is H or MeO (**2m**, **2o**). Yields are low with **2j** and **2k**, and no reaction occurs with carbethoxytriphenylphosphorane **2p** (Table I).

Reaction Using Salt-Free Conditions. With salt-free conditions, only the syn betaine can be stabilized by the formation of an oxaphosphetane or by electrostatic interactions. Furthermore, the lack of complexation of the R_1O group prevents its elimination. So, in all cases path b occurs (Table I) and leads to enol ethers. The reaction proceeds with a complete Z selectivity. We have checked that there is no previous formation of the (E) isomer and isomerization. This selectivity is thermodynamically controlled at the intermediate betaine level. The obtained (Z) isomer results from the decomposition of the less congested betaine **A** (Figure 1). Indeed, there is a great difference of stability between the **19A** and **19B** alkoxybetaines because of the strong steric interaction between the R substituent of the ylid and the Rf group. Even the CF_3 group van der Waals volume is nearly twice of that of a CH_3 group.[27,37] (It must be pointed out that this difference of stability is not so large between corresponding aminobetaines, steric hindrance of the CF_3 group being competitive with that of the amino group). The Z selectivity is the opposite of that which is usually observed in aldehyde series,[28] in which the kinetic formation of the more hindered betaine is favored and leads immediately to Z olefin (corresponding to E enol ether). In our case, we propose that the exclusive formation of the more stable alkoxybetaine **A** is explained by the relative rates of each step of the reaction sequence and by the reversibility of the condensation step. The stabilization by the Rf group of the tetrahedral alkoxyanion[27,29] slows down the decomposition of the betaine.[30,31] This is particularly striking when Rf = CF_3. Despite a fast condensation step, 4–6 h of reflux are necessary for the full decomposition into the enol ether.

The great stability of these intermediates prompted us to perform some preliminary ^{31}P NMR experiments in order to determine the nature of the intermediate. In a Wittig reaction between an aldehyde and a nonstabilized phosphorane, an oxaphosphetane is detected as the only observable intermediate (^{31}P NMR δ –60 to –65).[32,33] There is no support of this in the case of activated esters. Our experiments have been performed in C_6D_6 as a solvent for "salt-free conditions" (H_3PO_4 as external reference). The addition of CF_3COOEt to the phosphorane **2a** (^{31}P NMR δ +13.5) leads to a product whose signal (^{31}P NMR δ +24.3) could be attributed to a tetravalent phosphorus intermediate.[32,33] On heating, this signal disappears and is replaced by another signal (^{31}P NMR δ +28.4). Afterwards, the triphenylphosphine oxide signal (^{31}P NMR δ +30.9) appears together with a signal (^{31}P NMR δ –64.9) corresponding to a pentavalent phosphorus compound.[32,33] These NMR data strongly suggest an initial formation of a betaine and its isomerization (^{31}P NMR δ +24.3 → 28.4). As soon as it is converted into an oxaphosphetane, its decomposition into enol ether and triphenylphosphine oxide occurs.

Conclusion

With these systematic studies of the Wittig reaction of perfluoro acids derivatives we have brought out the main parameters that affect the yield and the product distribution of the reaction: the amino and Rf groups in the case of amides, the structure of the phosphoranes in the case of anhydrides, and the reaction medium for the esters. Using a good choice of these parameters, perfluoroalkyl carboxylic acid derivatives act as versatile and convenient agents for selective preparations of a variety of fluorinated synthons: fluoroalkyl enamines from amides, fluoroalkyl enol ethers from esters (under "free-salt" reaction condi-

(23) Shen, Y. C.; Qiu, W. M. *Tetrahedron Lett.* **1987**, *28*, 449.
(24) However, we were not able to obtain yields so good as these described by Shen.[15]
(25) Hamper, B. C. *J. Org. Chem.* **1988**, *53*, 5558.
(26) Huang, Y. Z.; Shen, Y. C.; Ding, W. Y.; Zheng, J. H. *Tetrahedron Lett.* **1981**, *22*, 5283.
(27) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320.
(28) (a) Schlosser, M. *Top. Stereochem.* **1970**, 1. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(29) (a) Salvador, R. L. Saucier M. *Tetrahedron* **1971**, *27*, 1221. (b) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898.
(30) Ramirez, F.; Smith, C. P.; Pilot, J. F. *J. Am. Chem. Soc.* **1968**, *90*, 6726.
(31) (a) Camps, F.; Canela, R.; Coll, J.; Messeguer, A.; Roca, A. *Tetrahedron* **1978**, *34*, 2179. (b) Camps, F.; Sanchez, F. J.; Messeguer, A. *Synthesis* **1988**, 823.
(32) (a) Vedejs, E.; Meier, G. P.; Snoble, K. A. *J. Am. Chem. Soc.* **1981**, *103*, 2823. Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1990**, *112*, 3905.
(33) Reitz, A. B.; Mutter, M. S.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1984**, *106*, 1873.

tions), and fluoroalkyl ketones from esters (in the presence of lithium salts).

Experimental Section

General. All the reactions were performed in an oven-dried apparatus that consisted of a three-necked flask equipped with an addition funnel, a Teflon-coated magnetic stir bar, and a reflux condenser connected to an Argon source and a mineral oil bubber. ^{19}F NMR, ^{1}H NMR, and ^{13}C NMR spectra were recorded on a 200-MHz multinuclear spectrometer. All chemical shifts are reported in parts per million downfield (positive) from the standard. ^{19}F NMR spectra are referenced with external $CFCl_3$, ^{1}H NMR and ^{13}C NMR spectra with tetramethylsilane, and ^{31}P NMR spectra with H_3PO_4. Multiplicities described in the ^{13}C NMR data concern J_{CF} coupling. GC–MS spectra were obtained at 70 eV, in the electron-impact mode. GC analyses were performed using 5% SE 30 or CP-SIL-5 capillary columns (10 or 25 m).

Materials. THF was purified by distillation from sodium benzophenone ketyl. $NaNH_2$ was washed with pentane from a suspension in toluene obtained from Fluka Co. Fluorinated esters are available from Aldrich Chemical Co. or prepared by classical procedures[34] and used after treatment with anhydrous Na_2CO_3.

Typical Procedure for the Preparation of 1-(Perfluoroalkyl)enamines: (*Z*)- and (*E*)-1,1,1,2,2-Pentafluoro-3-morpholino-6-phenyl-3-hexene (6a). Phosphonium salt **1a** (4.61 g, 10 mmol) was added to a suspension of $NaNH_2$ (0.39 g, 10 mmol) in THF (25 mL). Then HMDS (0.2 mL, 1.5 mmol) was added via syringe through a septum cap. The mixture was stirred and then heated at reflux until no more NH_3 evolved (usually 2–3 h). Morpholine pentafluoropropionylamide (2.33 g, 10 mmol) was added to the red ylide solution, and heating and stirring were maintained until the red color disappeared (about 72 h in this case). The mixture was concentrated under reduced pressure, and triphenylphosphine oxide was precipitated by the addition of pentane (100 mL). The solution was filtered through a silica gel column (pentane–ether (97:3)). Solvents were removed under reduced pressure, and the remaining oil was distilled in a bulb-to-bulb apparatus under reduced pressure to give 1.52 g of starting amide and a mixture (Z/E = 61/39) of the two enamines **6a** (0.24 g, 6%): bp 120–125 °C (1 mmHg); ^{19}F NMR δ −83.0 and −83.3 (CF_3), −110.3 and −112.5 (CF_2); ^{1}H NMR δ 2.48 and 2.62 (m, 8 H), 3.58 and 3.62 (t, J = 4.5 Hz, 4 H, OCH_2), 5.05 and 5.49 (t, J = 7.6 Hz, 1 H, CH=C), 7.14 (m, 5 H, C_6H_5); ^{13}C NMR δ 28.5 and 28.6, 35.6 and 35.8, 51.5 and 53.1, 66.6 and 67.0, 120.2, 125.8 and 125.9, 128.2, 129.9, 140.5 and 140.7. The same reaction performed with pentafluoropropionamide and the phosphorane **2a** generated with BuLi gave 0.24 g (6%) of **6a** and 1.59 g of starting amide. The same reaction performed with trifluoroacetylmorpholine and the phosphorane **2a** generated with BuLi gave 0.68 g of trifluoroacetamide and 3.72 g (59%) of **3a**.[8]

(*Z*)- and (*E*)-1,1,1,2,2,3,3-Heptafluoro-4-morpholino-7-phenyl-4-heptene (7a). Similarly, **7a** was prepared from **1a** (6.93 g, 15 mmol) and heptafluorobutyrylmorpholine (4.25 g, 15 mmol). After reflux (96 h), usual workup of the reaction mixture gave 2.84 g of starting amide and 0.23 g (4%) of **7a** (Z/E = 87/13): bp 125–130 °C (1 mmHg) (bulb-to-bulb distillation); ^{19}F NMR δ −80.3 and −80.5 (CF_3), −110.6 and −100.4 (CF_2), −125.0 and −126.8 (CF_2); ^{1}H NMR δ 2.49 (m, 4 H), 2.64 and 2.74 (t, J = 4.5 Hz, 4 H, NCH_2), 3.52 and 3.59 (t, J = 4.6 Hz, 4H, OCH_2), 5.50 and 5.85 (t, J = 7.5 Hz, 1 H, HC=C), 7.15 (m, 5 H, C_6H_5); ^{13}C NMR δ 28.7 and 29.8, 35.1 and 35.9, 51.1 and 53.5, 67.2 and 67.5, 126.7, 128.4, 130.7, 138.5 (t, J = 22.8 Hz, CH=CCF_2), 140.7. The same reaction performed with heptafluorobutyrylmorpholine and the phosphorane **2a** generated with BuLi gave 4.0 g of starting amide and 60 mg (1%) of **7a**.

Hydrolysis of Enamines 3. Typical Procedure: Preparation of Trifluoromethyl Ketone 13a. A solution of enamine **3a** (10 mmol) in Et_2O (20 mL) was stirred with 1 N HCl (20 mL) for 4 h at rt. After extraction (Et_2O), the organic layer was washed (brine) and dried (Na_2SO_4). Evaporation of the solvent and filtration on SiO_2 gave the ketone **13a**[7] in 95% yield.

Typical Procedure for the Reaction of α,α-Disubstituted Methylenephosphorane with Trifluoroacetic Anhydride: Reaction of Phosphonium 1j. Phosphonium salt **1j** (8.5 g, 20 mmol) was placed in a flame-dried and argon-flushed three-necked flask, and THF (50 mL) was added via syringe through a septum cap. Then PhLi (20 mmol, 15.4 mL of a solution 1.3 M in ether) was added dropwise. The mixture was vigorously stirred for about 0.5 h at rt until the solution was red and transparent. After the solution was cooled to −78 °C, 4.2 g (20 mmol) of TFAA was added. The mixture was stirred for 4 h at −78 °C and then allowed to warm to rt. NaOH (2%, 20 mL) was then added, and stirring was maintained overnight at rt. The ether layer was washed with water to neutral and dried. Evaporation of the solvent and silica gel column chromatography gave 0.42 g (10 %) of a mixture (60:40) of enol ether **8j** and ketone **13j**. **8j**: IR (neat) 1670 cm^{-1} (νC=C); ^{19}F NMR δ −58.7; ^{1}H NMR δ 1.15 (t, J = 7 Hz, 3 H, CH_3), 1.60 (m, 6 H), 2.30 (m, 4 H), 3.70 (q, J = 7 Hz, CH_2O). Anal. Calcd for $C_{10}H_{15}F_3O$: C, 57.68; H, 7.26; Found: C, 57.42; H, 7.11. **13j**: IR (neat) 1755 cm^{-1} (νC=O); ^{19}F NMR δ−80.0; ^{1}H NMR δ 1.19 (m, 6 H), 1.60 (m, 4 H), 2.4 (m, 1 H).

1,1,1-Trifluoro-2-benzyl-5-phenyl-2-pentanone (13k). Using Shen's procedure,[15] phosphonium salt **1a** (4.61 g, 10 mmol) was placed in a flame-dried and argon-flushed three-necked flask and THF (50 mL) was added via syringe through a septum cap. Then PhLi (10 mmol, 7.7 mL of a solution 1.3 M in ether) was added dropwise. The mixture was stirred at rt for 0.5 h until the solution was red. Then benzyl bromide (1.71 g, 10 mmol) in THF (5 mL) was added. The solution was stirred again for 0.5 h. Then PhLi 10 mmol (7.7 mL, 1.3 M) was added dropwise, and the mixture was stirred for 0.5 h until the solution became red. Then 2.1 g (10 mmol) of TFAA (in 5 mL of THF) was added, and the reaction mixture was maintained overnight at rt. Described workup of the reaction mixture gave 350 mg (12%) of **13k**: ^{19}F NMR δ −79.2; ^{1}H NMR δ 1.70–2.25 (m, 2 H), 2.32–3.7 (m, 5 H), 6.9–7.10 (m, 10 H); ^{13}C NMR δ 32.3, 33.1, 37.0, 51.9, 115.3 (q, ^{1}J = 293 Hz, CF_3), 126.3, 126.9, 128.3, 128.6, 128.7, 129.0, 137.7, 140.6, 194.4 (q, ^{2}J = 34 Hz, $COCF_3$). Anal. Calcd for $C_{18}H_{17}F_3O$: C, 70.54; H, 5.66. Found: C, 70.32; H, 5.78.

1,1,1-Trifluoro-2-benzyl-2-pentanone (13l). Similarly, **13l** was prepared from 3 mmol of **1l** (prepared from 3.5 mmol of **1h**, 3.5 mmol of PhLi, and then 3 mmol of benzyl bromide), 3 mmol of PhLi, and 3 mmol (0.63g) of TFAA. After hydrolysis with NaOH (5%, 10 mL), workup led to 0.24 g (31%) of **13l** (reported by Shen et al., 70%).[15]

General Procedure for the Preparation of Fluoroalkyl Enol Ethers. Phosphonium salt **1** (30 mmol) was added to a suspension of $NaNH_2$ (1.17 g, 30 mmol) in THF (80 mL). Then HMDS (0.6 mL) was added via syringe through a septum cap. The mixture was stirred and heated to reflux until no more NH_3 evolved (usually 2–3 h) and then cooled to rt. The red ylide solution was added dropwise into another flask containing alkyl perfluoroalkanoate[34] (30 mmol) in solution in THF (10 mL). After the end of the addition, the reaction medium was stirred again until the red color disappeared (4–6 h) at rt or at reflux in the case of ethyl trifluoroacetate. The mixture was concentrated under reduced pressure, and triphenylphosphine oxide was precipitated by the addition of pentane (30 mL). The solution was filtered through a silica gel column (pentane–Et_2O (97:3)). Evaporation of the solvent gave the residue which was purified by bulb-to-bulb distillation or by chromatography on silica gel (pentane) to afford the pure enol ether.

(*Z*)-1,1,1-Trifluoro-2-ethoxy-5-phenyl-2-pentene (8a). **8a** was prepared from 13.83 g (30 mmol) of **1a** and 4.26 g (30 mmol) of ethyl trifluoroacetate. Described workup of the reaction mixture gave 4.39 g (60 %) of (*Z*)-**8a**:[12,16] bp 80 °C (10 mmHg) (bulb-to-bulb distillation); IR (neat) 1670 cm^{-1} (νC=C); ^{19}F NMR δ −68; ^{1}H NMR δ 1.25 (t, J = 7 Hz, 3 H, CH_3), 2.51 (m, 2 H), 2.68 (m, 2 H), 3.80 (q, J = 7 Hz, 2 H, CH_2O), 6.3 (t, J = 7 Hz, 1 H, HC=C), 7.3 (m, 5 H); ^{13}C NMR δ 15.4, 26.7, 35.0, 69.8, 121.7 (q, ^{1}J = 275 Hz, CF_3), 126.3, 128.3, 128.5, 128.6, 128.7, 141.0, 143.4 (q, ^{2}J = 32 Hz, CCF_3).

(*Z*)-1,1,1,2,2-Pentafluoro-3-ethoxy-6-phenyl-3-hexene (9a). Similarly, **9a** was prepared from 13.83 g (30 mmol) of **1a** and 5.76 g (30 mmol) of ethyl pentafluoropropanoate. Workup of the reaction mixture gave 6.18 g (70%) of (*Z*)-**9a**: bp 85 °C (10 mmHg) (bulb-to-bulb distillation); IR 1665 cm^{-1} (νC=C); ^{19}F NMR δ −82.7

(34) (a) Henne, A. L.; Alderson, T.; Newman, M. S. *J. Am. Chem. Soc.* **1945**, *67*, 918. (b) Reid, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2069.

(CF_3), -117.0 (CF_2); ^1H NMR δ 1.25 (t, J = 7 Hz, 3 H, CH_3), 2.53 (t, J = 7.4 Hz, 2 H), 2.71 (t, J = 7.3 Hz, 2 H), 3.76 (q, J = 7 Hz, 2 H, OCH_2), 5.76 (t, J = 7.4 Hz, 1 H), 7.23 (m, 5 H); ^{13}C NMR 15.2, 27.2, 34.9, 70.4, 122.4, (CH=C), 128.2, 128.5, 140.6, 143.4 (t, ^2J = 23.7 Hz, CF_2C=C); MS m/e (rel intensity) 265 (20, M - F)), 249 (20), 175 (36), 91 (100). Anal. Calcd for $C_{14}H_{15}F_5O$: C, 57.14; H, 5.10. Found: C, 57.07; H, 4.99.

(Z)-1,1,1,2,2,3,3-Heptafluoro-4-ethoxy-7-phenyl-4-heptene (10a). Similarly, **10a** was prepared from 4.61 g (10 mmol) of **1a** and 2.42 g (10 mmol) of ethyl heptafluorobutanoate. Workup of the reaction mixture gave 2.0 g (58 %) of **(Z)-10a**: bp 85–88 °C (10 mmHg) (bulb-to-bulb distillation); IR 1670 cm^{-1} (νC=C); ^{19}F NMR δ -80.7 (t, J = 8 Hz, CF_3), -114.9 (m, C=CCF_2), 126.7 (m, CF_2); ^1H NMR δ 1.30 (t, J = 7 Hz, 3 H, CH_3), 2.60 (t, J = 7.4 Hz, 2 H), 2.80 (t, J = 7.3 Hz, 2 H), 3.87 (q, J = 7 Hz, 2 H, OCH_2), 5.80 (t, J = 7.4 Hz, 1 H), 7.32 (m, 5 H); ^{13}C NMR δ 15.2, 27.3, 35.0, 70.6, 122.9, (CH=C), 126.3, 128.5, 128.6, 140.9, 143.7 (t, ^2J = 23.5 Hz, CH=CCF_2); MS m/e (rel intensity) 329 (7, M - Me), 315 (100, M - Et), 299 (92, M - OEt), 130 (8), 117 (30), 105 (11), 91 (66). Anal. Calcd for $C_{15}H_{15}F_7O$: C, 52.33; H, 4.36. Found: C, 52.59; H, 4.50.

(Z)-1-(Pentadecafluoroheptyl)-1-ethoxy-4-phenylbutene (11a). Similarly, **11a** was prepared from 4.61 g (10 mmol) of **1a** and 4.42 g (10 mmol) of ethyl pentadecafluorooctanoate. Workup of the reaction mixture gave 1.96 g (44 %) of **11a**: bp 94–8 °C (10 mmHg) (bulb-to-bulb distillation); IR 1660 cm^{-1} (νC=C); ^{19}F NMR δ -80.9 (t, J = 9 Hz, CF_3), -113.8 (m, C=CCF_2), 121.8 (CF_2), 121.9 (CF_2), 122.1 (CF_2), 122.7 (CF_2), 126.8 (CF_2); ^1H NMR δ 1.19 (t, J = 7 Hz, 3 H, CH_3), 2.45 (t, J = 7.4 Hz, 2 H), 2.66 (t, J = 7.4 Hz, 2 H), 3.70 (q, J = 7 Hz, 2 H, OCH_2), 5.66 (t, J = 7.4 Hz, 1 H), 7.20 (m, 5 H); ^{13}C NMR δ 15.3, 27.3, 35.0, 70.6, 122.9 (CH=C), 126.3, 126.5, 128.4, 140.8, 143.8 (t, ^2J = 23.7 Hz, CH=CCF_2); MS m/e (rel intensity) 544 (M^+, 2), 515 (35, M - 29), 499 (20, M - OEt), 129 (50), 117 (11), 105 (8), 91 (100). Anal. Calcd for $C_{19}H_{15}F_{15}O$: C, 41.91; H, 2.76. Found: C, 42.33; H, 2.89.

(Z)-1-Chloro-1,1-difluoro-2-methoxy-5-phenyl-2-pentene (12a). Similarly, **12a** was prepared from 9.22 g (20 mmol) of **1a** and 2.90 g (20 mmol) of methyl chlorodifluoroacetate. Workup of the reaction mixture gave 2.38 g (48%) of **12a**: bp 100–5 °C (mmHg) (bulb-to-bulb distillation); IR (neat) 1665 cm^{-1} (νC=C); ^{19}F NMR δ -54.8 (CF_2); ^1H NMR δ 2.46 (t, J = 7.4 Hz, 2 H), 2.67 (t, J = 7.6 Hz, 2 H), 3.59 (s, 3 H, OCH_3), 5.61 (t, J = 7.4 Hz, 1 H), 7.20 (m, 5 H); ^{13}C NMR δ 26.7, 34.8, 61.7, 117.8 (CH=C), 123.6 (t, ^1J = 282 Hz, CF_2), 126.1, 128.1, 128.4, 140.7, 147.9 (t, ^2J = 25.1 Hz, CH=CCF_2Cl); MS m/e (rel intensity) 215 (4, M - OMe), 210 (39, M - Cl), 179 (9), 128 (3), 105 (10), 91 (100). Anal. Calcd for $C_{12}H_{13}F_2ClO$: C, 58.42; H, 5.27. Found: C, 58.84; H, 5.35.

(Z)-1,1,1-Trifluoro-2-ethoxy-5-(3,4-dimethoxyphenyl)-2-pentene (8c). Similarly, **8c** was prepared from 28.4 g (50 mmol) of **1c** and 7.1 g (50 mmol) of ethyl trifluoroacetate. Workup of the reaction mixture gave 8.36 g (55%) of **8c**: IR (neat) 1670 cm^{-1} (νC=C); ^{19}F NMR δ -69.7; ^1H NMR δ 1.2 (t, J = 7 Hz, 3 H, CH_3), 2.55 (m, 4 H), 3.70 (q, J = 7 Hz, 2 H, OCH_2), 3.85 (s, 6 H, CH_3O), 5.6 (t, J = 7 Hz, CH=C) 6.7 (m, 3 H, C_6H_3; ^{13}C NMR δ 14.6, 23.6, 33.8, 55.0, 55.1, 69.0, 111.0, 111.4, 120.7 (q, ^1J = 279 Hz, CF_3), 129.7, 147.2 (q, ^2J = 32 Hz, C=CCF_3), 148.6. Anal. Calcd for $C_{11}H_{15}F_3O_3$: C, 59.48; H, 6.20. Found: C, 59.85; H, 6.09.

(Z)-1,1,1-Trifluoro-2-ethoxy-3-cyclohexyl-2-propene (8e). Similarly, **8e** was prepared from 26 g (59 mmol) of **1e** and 8.41 g (59 mmol) of ethyl trifluoroacetate. Workup of the reaction mixture gave 7.23 g (55 %) of **8e**:[12] bp 82 °C (25 mmHg) (bulb-to-bulb distillation); IR (neat) 1670 cm^{-1} (νC=C); ^{19}F NMR δ -70.0; ^1H NMR δ 1.30 (t, J = 7 Hz, 3 H, CH_3), 1.6 (m, 6 H), 2.30 (m, 4 H), 2.45 (m, 1 H), 3.8 (q, J = 7 Hz, 2 H, CH_2O), 5.5 (d, J = 10 Hz, CH=C).

(Z)-1,1,1,2,2,3,3-Heptafluoro-5-cyclohexyl-4-ethoxy-4-pentene (10e). Similarly, **10e** was prepared from 6.6 g (15 mmol) of **1e** and 3.63 g (15 mmol) of ethyl heptafluorobutanoate. Workup of the reaction mixture gave 2.16 g (45%) of **10e**: bp 85–90 (25 mmHg) (bulb-to-bulb distillation); IR (neat) 1665 cm^{-1} (νC=C); ^{19}F NMR δ -79.7 (t, J = 8.9 Hz, CF_3), -113.3 (m, CF_2, CF_2C=C), 125.3 (m, CF_2); ^1H NMR δ 1.19 (t, J = 7 Hz, 3 H, CH_3), 1.1–1.4 (m, 6 H), 1.6 (m, 4 H), 2.4 (m, 1 H), 3.78 (q, J = 7 Hz, 2 H, OCH_2), 5.40 (d, J = 10.2 Hz, 1 H); ^{13}C NMR δ 14.9, 25.2, 25.5, 25.7, 25.8, 32.1, 34.6, 70.7, 112.3 (m, CF_2), 114.8 (m, CF_2), 120.5 (m, CF_3), 129.0 (CH=C), 141.4 (t, ^2J = 23.7 Hz, CH=C); MS m/e (rel intensity) 322 (M^+, 3), 321 (3), 293 (13), 276 (6), 153 (12), 95 (6), 83 (36), 67 (100). Anal. Calcd for $C_{13}H_{17}F_7O$: C, 48.45; H, 5.28. Found: C, 48.43; H, 5.32.

(Z)-1,1,1-Trifluoro-4-cyclohexyl-2-ethoxy-2-butene (8f). Similarly, **8f** was prepared from 5.0 g (10 mmol) of **1f** and 1.42 g (10 mmol) of ethyl trifluoroacetate. Workup of the reaction mixture gave 1.18 g (50 %) of **8f**: bp 120 °C (35 mmHg) (bulb-to-bulb distillation); IR (neat) 1670 cm^{-1} (νC=C); ^{19}F NMR δ -69.8; ^1H NMR δ 1.30 (t, J = 7 Hz, 3 H, CH_3), 1.6 (m, 6 H), 2.30 (m, 6 H), 2.45 (m, 1 H), 3.8 (q, J = 7 Hz, 2 H, CH_2O), 5.5 (t, 1 H, CH=C); ^{13}C NMR δ 14.9, 25.9, 26.0, 32.0, 32.8, 37.3, 69.2, 119.3, 120.9 (q, ^1J = 275 Hz, CF_3), 143.3 (q, ^2J = 32 Hz, C=CCF_3); MS m/e 237 (26, M + 1), 236 (15, M^+), 221 (15), 167 (16, M - CF_3), 83 (100). Anal. Calcd for $C_{12}H_{19}F_3O$: C, 61.10; H, 8.05. Found: C, 61.44; H, 7.88.

(2,2,2-Trifluoro-1-ethoxyethylidene)cyclohexane (8j). Similarly, **8j** was prepared from **1j** (8.5 g, 20 mmol) and 2.84 g of ethyl trifluoroacetate. Usual workup of the reaction mixture gave 0.83 g (20 %) of enol ether **8j**: bp 92–95 °C (10 mmHg) (bulb-to-bulb distillation).

(Z)-2-(Trifluoromethyl)-2-ethoxystyrene (8m). Similarly, **8m** was prepared from 7.8 g (20 mmol) of **1m** and 2.84 g (20 mmol) of ethyl trifluoroacetate. Usual workup of the reaction mixture gave 2.68 g (55%) of **8m**:[12] bp 103 °C (30 mmHg) (bulb-to-bulb distillation); IR (neat) 1660 cm^{-1} (νC=C); ^{19}F NMR δ -70.0; ^1H NMR δ 1.25 (t, J = 7 Hz, 3 H, CH_3), 3.8 (q, J = 7 Hz, 2 H, CH_2O), 5.6 (t, J = 7 Hz, 1 H, CH=C), 7.3 (m, 5 H).

Ethyl (Z)-Ethoxy-4,4,4-trifluoro-2-butenoate (8p). Similarly, **8p** was prepared from phosphonium salt **1p** (9.65 g, 22.5 mmol), $NaNH_2$ (0.88 g, 22.5 mmol), and ethyl trifluoroacetate (3.2 g, 22.7 mmol). After reflux (4 h), usual workup of the reaction mixture gave 1.25 g (30%) of enol ether **8p**:[12] ^{19}F NMR δ -73.

Typical Procedure for the Preparation of Fluoroalkyl Ketones: 1,1,1-Trifluoro-5-phenyl-2-pentanone (13a). Phosphonium salt **1a** (10.4 g, 22.6 mmol) was placed in a flame-dried and argon-flushed three-necked flask, and THF (50 mL) was added via syringe through a septum cap. Then BuLi (19 mL of a solution 1.2 M in hexane, 22.8 mmol) was added dropwise. The mixture was vigorously stirred for about 0.5 h at rt until the solution was red and transparent. The alkyl perfluoroalkanoate CF_3COOEt (3.2g, 22.6 mmol) in THF (10 mL) was added dropwise into the red ylide solution and stirred until the red color disappeared (usually 6 h at room temperature). Then the reaction was quenched with water and stirred again for 45 min. The aqueous layer was extracted three times with diethyl ether. The combined extracts were washed with brine until neutral. The ether solution was dried ($MgSO_4$) and concentrated. Triphenylphosphine oxide was precipitated by the addition of pentane (30 mL). The solution was filtered through a silica gel column in order to remove most of Ph_3PO. Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel eluted with pentane/Et_2O (30:1) to afford 2.92 g (60%) of the ketone **13a**:[7] bp 90 °C (10 mmHg); ^{19}F NMR δ -80.

1,1,1,2,2-Pentafluoro-6-phenyl-3-hexanone (14a). Similarly, **14a** was prepared from 13.83 g (30 mmol) of **1a**, 25 mL of BuLi (1.2 M in hexane), and 5.76 g of ethyl pentafluoropropionate. Hydrolysis and usual workup of the reaction mixture gave 4.55 g (57%) of **14a**: bp 92–95 °C (10 mmHg) (bulb-to-bulb distillation); IR (neat) 1760 cm^{-1} (νC=O); ^{19}F NMR δ -82.5 (CF_3), -123.3 (CF_2); ^1H NMR δ 1.95 (m, 2 H), 2.69 (m, 4 H), 7.1 (m, 5 H); ^{13}C NMR δ 23.9, 34.5, 36.5, 126.4, 128.4, 128.6, 140.7, 194.2 (t, ^2J = 26.5 Hz, $COCF_2$); MS m/e (rel intensity) 147 (6, M - C_2F_5), 119 (2), 104 (100), 91 (55). Anal. Calcd for $C_{12}H_{11}F_5O$: C, 54.12; H, 4.12. Found: C, 54.78; H, 4.24.

1,1,1,2,2,3,3-Heptafluoro-7-phenyl-4-heptanone (15a). Similarly, **15a** was prepared from 9.22 g (20 mmol) of **1a**, 16.8 mL of BuLi (1.2 M in hexane), and 4.84 g of ethyl heptafluorobutyrate. Hydrolysis and usual workup of the reaction mixture gave 4.55 g (72%) of **15a**: bp 96 °C (10 mmHg) (bulb-to-bulb distillation). IR (neat) 1755 cm^{-1} (νC=O); ^{19}F NMR δ -80.7 (CF_3), -121.1 (CF_2), -126.7 (CF_2); ^1H NMR δ 2.1 (m, 2 H), 2.72 (m, 4 H), 7.3 (m, 5 H); ^{13}C NMR δ 23.9, 34.4, 37.0, 108.5 (m, ^1J = 266 Hz, ^2J = 33.8 Hz, ^2J = 38.8 Hz), 108.7 (m, ^1J = 267.5 Hz, ^2J = 32.1 Hz), 117.5 (m, ^1J = 287.5 Hz, ^2J = 33.5 Hz), 126.3, 128.4, 128.5, 140.6, 193.3 (t, ^2J = 26.6 Hz, $COCF_2$); MS m/e (rel intensity) 147 (6, M - C_3F_7),

104 (100), 91 (58). Anal. Calcd for $C_{13}H_{11}F_7O$: C, 49.37; H, 3.48. Found: C, 49.20; H, 3.48.

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-Pentadecafluoro-11-phenyl-8-undecanone (16a). Similarly, **16a** was prepared from 4.61 g (10 mmol) of **1a**, 12 mL of BuLi (1.2 M in hexane), and 4.42 g of ethyl pentadecafluorooctanoate. Hydrolysis and usual workup of the reaction mixture gave 1.89 g (45 %) of **16a** [bp 90–92 °C (5 mmHg) (bulb-to-bulb distillation); IR (neat) 1760 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −80.9 (CF_3), −120.24 (CF_2), −121.4 (CF_2), −122.1 (2 × CF_2), −122.8 (CF_2), −126.2 (CF_2); ^1H NMR δ 1.91 (m, 2 H), 2.56 (t, J = 7.7 Hz, 2 H), 2.65 (t, J = 7.1 Hz, 2 H), 7.13 (m, 5 H); ^{13}C NMR δ 23.8, 34.3, 36.6, 126.1, 128.2, 128.4, 140.5, 194.0 (t, ^2J = 26.2 Hz, $COCF_2$). Anal. Calcd for $C_{17}H_{11}F_{15}O$: C, 39.53; H, 2.13. Found: C, 39.68; H, 2.23.] and 0.35 g (8%) of **11a**.

1-Chloro-1,1-difluoro-6-phenyl-2-pentanone (17a). Similarly, **17a** was prepared from 6.95 g (15 mmol) of **1a**, 12.5 mL of BuLi (1.2 M in hexane), and 2.17 g of methyl chlorodifluoroacetate. Hydrolysis and usual workup of the reaction mixture gave 1.52 g (44%) of **17a** [bp 100–105 °C (10 mmHg) (bulb-to-bulb distillation); IR (neat) 1750 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −66.6 (CF_2); ^1H NMR δ 1.95 (m, 2 H), 2.60 (m, 4 H), 7.2 (m, 5 H); ^{13}C NMR δ 24.3, 34.1, 34.4, 119.7 (t, ^1J = 288 Hz, CF_2), 126.2, 128.3, 140.8, 191.5 (t, ^2J = 26.1 Hz, $COCF_2$); MS m/e (rel intensity) 147 (23, M − CF_2Cl), 104 (100), 91 (90). Anal. Calcd for $C_{11}H_{11}ClF_2O$: C, 56.77; H, 4.73. Found: C, 56.84; H, 4.88.] and 0.28 g (8%) of **12a**.

1,1,1-Trifluoro-5-(4-methoxyphenyl)pentan-2-one (13b). Similarly, **13b** was prepared from 18.2 g (34 mmol) of **1b**, 32.2 mL of BuLi (1.05 M in hexane), and 4.8 g (34 mmol) of ethyl trifluoroacetate. Hydrolysis and usual workup of the reaction mixture gave 1.5 g (40 %) of **13b**;[35] bp 82 °C (0.5 mmHg) (bulb-to-bulb distillation); ^{19}F NMR δ −80.

1,1,1,2,2-Pentafluoro-6-(4-methoxyphenyl)-3-hexanone (14b). Similarly, **14b** was prepared from 9.15 g (17 mmol) of **1b**, 16.2 mL of BuLi (1.05 M in hexane), and 3.26 g (17 mmol) of ethyl pentafluoropropionate. Hydrolysis and usual workup of the reaction mixture gave 2.16 g (43%) of **14b**: bp 82–85 °C (0.5 mmHg) (bulb-to-bulb distillation); IR (neat) 1755 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −82.0 (CF_3), −123.3 (CF_2); ^1H NMR δ 1.98 (m, 2 H), 2.60 (t, J = 7.4 Hz, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 3.75 (s, 3 H), 6.9 (q, 4 H, C_6H_4); ^{13}C NMR δ 24.0, 33.5, 36.3, 55.0, 107.0 (q of t, ^1J = 267 Hz, ^2J = 40 Hz, CF_2), 113.9, 117.3 (t of q, ^1J = 287 Hz, ^2J = 40 Hz, CF_3), 129.3, 132.6, 158.1, 194.2 (q, ^2J = 26.5 Hz, $COCF_2$); MS m/e (rel intensity) 296 (M^+, 18), 295 (4), 134 (41), 121 (100), 91 (20), 77 (21). Anal. Calcd for $C_{13}H_{13}F_5O_2$: C, 52.70; H, 4.39. Found: C, 53.13; H, 4.51.

1,1,1-Trifluoro-5-(3,4-dimethoxyphenyl)-2-pentanone (13c). Similarly, **13c** was prepared from 7.8 g (13.7 mmol) of **1c**, 11.7 mL of BuLi (1.17 M in hexane), and 2 g (14 mmol) of ethyl trifluoroacetate. Hydrolysis and usual workup of the reaction mixture gave 1.5 g (40 %) of **13c**: bp 90–92 °C (0.5 mmHg) (bulb-to-bulb distillation); IR (neat) 1755 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −82.5; ^1H NMR δ 1.95 (m, 2 H), 2.69 (m, 4 H), 3.86 (s, 6 H, 2 × CH_3O), 6.75 (m, 3 H, C_6H_3); ^{13}C NMR δ 14.5, 23.9, 34.5, 36.5, 55.0, 55.2, 111.1, 111.5, 120.7 (q, ^1J = 279 Hz, CF_3), 129.5, 148.9, 194.4 (q, ^2J = 35 Hz, $COCF_3$). Anal. Calcd for $C_{11}H_{15}O_3F_3$: C, 56.52, H, 5.60. Found: C, 55.98; H, 5.60.

1,1,1,2,2-Pentafluoro-5-(3,4-dimethoxyphenyl)-3-hexanone (14c). Similarly, **14c** was prepared from 5.35 g (10 mmol) of **1c**, 7.9 mL of BuLi (1.2 M in hexane), and 1.92 g (10 mmol) of ethyl pentafluoropropionate. Hydrolysis and usual workup of the reaction mixture gave 1.54 g (47 %) of **14c**: bp 95–98 °C (0.5 mmHg) (bulb-to-bulb distillation); IR (neat) 1755 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −80.9 (CF_3), −122.1 (CF_2); ^1H NMR δ 1.89 (m, 2 H), 2.52 (t, J = 7.5 Hz, 2 H), 2.67 (t, J = 7.1 Hz, 2 H)m 3.78 (s, 6 H, 2 × CH_3O), 6.67 (m, 3 H); ^{13}C NMR δ 24.0, 34.0, 36.6, 55.8, 55.9, 110.3, 111.6, 120.3, 133.1, 147.5, 149.0, 194.0 (t, ^2J = 26 Hz, $COCF_2$); MS m/e (rel intensity) 327 (M^++1, 8), 326 (75), 325 (7), 207 (9), 164 (40), 151 (100), 121 (6), 107 (13). Anal. Calcd for $C_{14}H_{15}F_5O$: C, 51.53; H, 4.60. Found: C, 51.92; H, 4.81.

1,1,1-Trifluoro-5-[(3,4-methylenedioxy)phenyl]-2-pentanone (13d). Similarly, **13d** was prepared from 7.8 g (13.7 mmol) of **1d**, 11.7 mL of BuLi (1.17 M in hexane), and 2.0 g (14 mmol) of ethyl trifluoroacetate. Hydrolysis and usual workup of the reaction mixture gave 1.50 g (40%) of **13d**: bp 89–91 °C (0.5 mmHg) (bulb-to-bulb distillation); IR (neat) 1755 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −80.3; ^1H NMR δ 1.95 (m, 2 H), 2.69 (m, 4 H), 5.88 (s, 2 H, OCH_2O), 6.65 (m, 3H); ^{13}C NMR δ 23.8, 33.9, 36.1, 100.6, 107.9, 108.4, 115.8 (q, ^1J = 292 Hz, CF_3), 120.9 134.2, 145.7, 147.6, 193.9 (q, ^2J = 35 Hz, $COCF_3$). Anal. Calcd for $C_{12}H_{11}F_3O_3$: C, 55.39; H, 4.26. Found: C, 55.67; H, 4.25.

1,1,1,2,2-Pentafluoro-5-[(3,4-methylenedioxy)phenyl]-5-hexanone (14d). Similarly, **14d** was prepared from 5.52 g (10 mmol) of **1d**, 8.1 mL of BuLi (1.17 M in hexane), and 1.92 g (10 mmol) of ethyl pentafluoropropionate. Hydrolysis and usual workup of the reaction mixture gave 1.67 g (54%) of **14d**: bp 93–96 °C (10 mmHg) (bulb-to-bulb distillation). IR (neat) 1755 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −81.3 (CF_3), −122.4 (CF_2); ^1H NMR δ 1.91 (m, 2 H), 2.52 (t, J = 7.5 Hz, 2 H), 2.71 (t, J = 7.1 Hz, 2 H), 5.84 (s, 2 H), 6.58 (m, 3 H); ^{13}C NMR δ 23.8, 33.7, 36.1, 100.6, 106.7 (q of t, ^1J = 268 Hz, ^2J = 40 Hz, CF_2), 107.9, 108.4, 117.5 (t of q, ^1J = 288 Hz, ^2J = 40 Hz, CF_3), 120.9, 134.2, 145.7, 147.6, 193.9 (q, ^2J = 26 Hz, $COCF_2$); MS m/e (rel intensity) 310 (M^+, 54), 148 (45), 135 (100), 105 (14), 91 (30), 77 (34). Anal. Calcd for $C_{13}H_{11}F_5O_3$: C, 50.32; H, 3.55. Found: C, 50.74, H, 3.81.

1,1,1-Trifluoro-6-phenyl-2-hexanone (13g). Similarly, **13g** was prepared from 5 g (9.57 mmol) of **1g**, 8.2 mL of BuLi (1.17 M in hexane), and 1.36 g (9.6 mmol) of ethyl trifluoroacetate. Hydrolysis and usual workup of the reaction mixture gave 1.15 g (52%) of **13g**:[36] ^{19}F NMR δ −80.2.

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-Pentadecafluoro-8-tetradecanone (16h). Similarly, **16h** was prepared from 4.2 g (10.2 mmol) of **1h**, 8.5 mL of BuLi (1.2 M in hexane), and 4.42 g (10 mmol) of ethyl pentadecafluorooctanoate. Hydrolysis and usual workup of the reaction mixture gave 4.55 g (57%) of **16h**: bp 90–95 °C (25 mmHg) (bulb-to-bulb distillation); IR (neat) 1750 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −81.6 (CF_3), −120.9 (CF_2), −121.9 (CF_2), −122.7 (2 × CF_2), −123.3 (CF_2), −126.8 (CF_2); ^1H NMR δ 0.8 (t, J = 6.7 Hz, 3 H, CH_3), 1.22 (m, 4 H), 1.57 (m, 2 H), 2.63 (t, J = 7.2 Hz, 2 H); ^{13}C NMR δ 13.0, 21.7, 21.8, 30.4, 37.4, 193.6 (t, ^2J = 26.5 Hz, $COCF_2$); MS m/e (rel intensity) 449 (M^+ − F, 6), 99 (100), 71 (93), 57 (16). Anal. Calcd for $C_{13}H_{11}F_{15}O$: C, 33.33; H, 2.35. Found: C, 33.71; H, 2.36.

1,1,1-Trifluoro-2-nonanone (13i). Similarly, **13i** was prepared from 5.8 g (13.1 mmol) of **1a**, 12.6 mL of BuLi (1.05 M in hexane), and 1.86 g (13 mmol) of ethyl trifluoroacetate. Workup of the reaction mixture gave 1 g (40 %) of **13i**:[36] ^{19}F NMR δ −80.3.

1,1,1,2,2-Pentafluoro-3-decanone (14i). Similarly, **14i** was prepared from 4.41 g (10 mmol) of **1i**, 9.6 mL of BuLi (1.05 M in hexane), and 1.92 g (10 mmol) of ethyl pentafluoropropionate. Hydrolysis and usual workup of the reaction mixture gave 1.21 g (49%) of **14i**: bp 80 °C (25 mmHg) (bulb-to-bulb distillation); IR (neat) 1750 cm^{-1} ($\nu C{=}O$); ^{19}F NMR δ −82.6 (CF_3), −123.9 (CF_2); ^1H NMR δ 0.80 (t, J = 6.7 Hz, CH_3), 1.20 (m, 8 H), 1.59 (m, 2 H), 2.63 (t, J = 7.2 Hz, 2 H); ^{13}C NMR δ 13.5, 22.1, 22.3, 26.5, 26.7, 31.4, 37.0, 106.8 (t, ^1J = 267 Hz, CF_2), 117.7 (q, ^1J = 286 Hz, CF_3), 194.0 (t, ^2J = 26.5 Hz, $COCF_2$); MS m/e (rel intensity) 247 (M^+ + 1, 2), 246 (M^+, 1), 227 (5), 127 (24). Anal. Calcd for $C_{10}H_{15}F_5O$: C, 48.78; H, 6.10. Found: C, 48.70; H, 6.14.

Reaction of Phosphonium Salt 1j with BuLi and Ethyl Trifluoroacetate. Similarly, **1j** (8.5 g, 20 mmol), 20 mL of BuLi (1.0 M in hexane), and 2.84 g (20 mmol) of ethyl trifluoroacetate gave after hydrolysis and usual workup 0.54 g (13 %) of enol ether **8j**. The same reaction with PhLi instead of BuLi did not work. No reaction occurred with C_2F_5COOEt.

Reaction of Phosphonium Salt 1m with BuLi and Ethyl Trifluoroacetate. Similarly, phosphonium **1m** (7.89 g, 20 mmol) reacted with 16.8 mL of BuLi (1.2 M in hexane) and then with 2.84 g (20 mmol) of ethyl trifluoroacetate. Hydrolysis and usual workup of the reaction mixture gave 1.25 g (29%) of enol ether **8m**.[12]

Reaction of Phosphonium Salt 1m with BuLi and Ethyl Pentafluoropropionate. Similarly, phosphonium **1m** (3.9 g, 10

(35) Bonnet-Delpon, D.; Cambillau, C.; Charpentier, M.; Jacquot, R.; Mesureur, D.; Ourevitch, M. *J. Org. Chem.* **1988**, *53*, 1988.

(36) Bégué, J. P.; Charpentier, M.; Langlois, B.; Née, G. *J. Fluorine Chem.* **1989**, *44*, 377.

(37) (a) Bott, G.; Fields, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618. (b) Nagai, T.; Nishioka, G.; Ando, A.; Miki, T.; Kumadaki, I. *Chem. Pharm. Bull.* **1991**, *39*, 233.

mmol) reacted with 7.4 mL of BuLi (1.2 M in hexane) and then with 1.92 g (10 mmol) of ethyl pentafluoropropionate. Usual workup of the reaction mixture gave 0.95 g (36%) of enol ether **9m**.

Reaction of Phosphonium Salt 1n with BuLi and Ethyl Trifluoroacetate: (*Z*)-β-(Trifluoromethyl)-β-ethoxy-2-(trifluoromethyl)styrene (8n). Similarly, phosphonium **1n** (5 g, 11 mmol) in THF (17 mL) reacted with 7.4 mL of BuLi (solution 1.47 M in hexanes) and then with 1.56 g (11.3 mmol) of ethyl trifluoroacetate. Hydrolysis and usual workup gave 1.89 g (61%) of enol ether **8n**: IR (neat) 1660 cm^{-1} (νC=C); ^{19}F NMR δ −69.7; ^1H NMR δ 1.35 (t, J = 7 Hz, 3 H), 3.9 (q, J = 7 Hz, 2 H), 6.35 (s, 1 H), 7.2–8 (m, 5 H). Anal. Calcd for $C_{12}H_{10}F_6O$: C, 50.71; H, 3.55. Found: C, 51.41; H, 3.76.

Reaction of Phosphonium Salt 1o and Ethyl Trifluoroacetate: β-(Trifluoromethyl)-β-ethoxy-4-methoxystyrene (8o). Similarly, phosphonium salt **1o** (8 g, 17.3 mmol) in THF (27 mL) reacted with 14.8 mL of BuLi (1.17 M in hexanes) and then with 2.46 g (17.3 mmol) of trifluoroacetate in THF (18 mL). After 72 h, hydrolysis and usual workup give 1.14 g (33%) of **8o**: IR (neat) 1655 cm^{-1} (νC=C); ^{19}F NMR δ −69.5; ^1H NMR δ 1.30 (t, 3 H), 3.65–4.10 (s + m, 5 H), 6.30 (s, 1 H), 6.85 (m, 2 H), 7.45 (m, 2 H). Anal. Calcd for $C_{12}H_{13}F_3O_2$: C, 58.54; H, 5.32. Found: C, 59.42; H, 5.57.

Acknowledgment. We thank Professor Manfred Schlosser for a critical reading of this manuscript and Dr Micheline Charpentier-Morize for fruitful discussions.

Asymmetric Conjugate Additions to Chiral Bicyclic Lactams. Synthesis of Aracemic Trans-2,3-Disubstituted Pyrrolidines

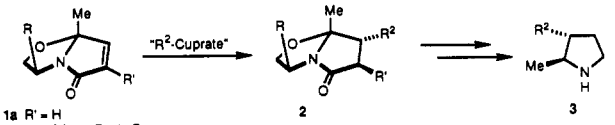
A. I. Meyers* and Lawrence Snyder

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received February 11, 1992

The trans-2,3-disubstituted pyrrolidine moiety, found in the pyrrolizidine alkaloids as well as other natural products, has been accessed from the α,β-unsaturated bicyclic lactams **1d** and **10**. Conjugate addition of lower order cyanocuprates to lactams **1d** and **10** resulted in endo entry of the cuprate with high diastereoselectivity. Other cuprates were investigated and resulted in diminished or opposite stereoselectivities. Further transformation of the β-substituted lactams provided the title compounds in good overall yield and high enantiomeric excess.

Conjugate additions utilizing cyanocuprates have received considerable attention in the past 20 years,[1] whereas higher order cyanocuprates have been in the spotlight for the past decade.[2] We now describe a study involving the conjugate addition of various organocuprates to the bicyclic lactams **1**[3] and the subsequent cleavage of the resultant β-substituted lactams **2** to trans-2,3-disubstituted pyrrolidines **3**.



1a R' = H
b R' = SOMe, R = i-Pr
c R' = CO_2Me, R = i-Pr
d R' = CO_2Bn, R = Ph

2 3

Initial attempts to add dialkyl organocuprates to lactam **1a** (R = i-Pr)[4] were unsuccessful due to facile 1,4-reduction to the enone furnishing the saturated lactam **4**. This reduction is not without precedent and presumably proceeds through an electron transfer from the cuprate to the π-system of the lactam (Scheme I).[5] Additional attempts to introduce alkyl groups (Gilman-type cuprates, lower order cyanocuprates, higher order cyanocuprates) with and without additives (TMSCl,[6] HMPA) to lactam **1a** (R = i-Pr, t-Bu, Ph) in a conjugate fashion also failed. However, it was observed earlier in our laboratory that addition of the lower order methyl cyanocuprate (MeCuCNLi) to lactam **1b** resulted in clean addition producing one diastereomer.[7]

Scheme I

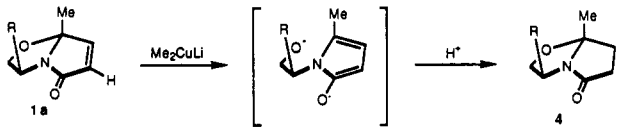


Table I. Effect of Cuprate Species on Cis/Trans Ratio of 5

lactam	cuprate	5 ratio (cis:trans)[a]
1c	Me_2CuLi	1:3
1c	$Me_2CuCNLi_2$	3:1
1c	MeCuCNLi	5:95
1d	n-PrCuCNMgBr	1:3

[a] Determined by 270- or 300-MHz NMR.

In a previous study from this laboratory the Diels–Alder cycloadditions to **1** were unsuccessful unless R′ was a

(1) Gorlier, J. P.; Hamon, L.; Levisalles, J.; Wagnon, J. *J. Chem. Soc., Chem. Commun.* **1973**, 88.
(2) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. Lipshutz, B. H. *Synthesis* **1987**, 325. Lipshutz, B. H. *Synlett* **1990**, 119.
(3) For earlier reports on the synthetic utility of the bicyclic lactams of type **1** see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.
(4) Sturgess, M. A.; Meyers, A. I. Colorado State University, unpublished results.
(5) Posner, G. H. *An Introduction to Synthesis using Organocopper Reagents*; Wiley: New York, 1980; pp 50–51.
(6) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.
(7) Midura, W.; Meyers, A. I. Colorado State University, unpublished results.

0022-3263/92/1957-3814$03.00/0