Tetrahedron Letters, Vol. 33, No. 52, pp. 8001-8004, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

An Application of the Trost Reaction to the Stereoselective Synthesis of *trans*-Tetrasubstituted Fluoroalkenes

Paul V. Fish, S. Pulla Reddy, Cheol H. Lee, and William S. Johnson*

Department of Chemistry, Stanford University, Stanford, California 94305, USA

Abstract: The coupling of β-fluoroallylic acetates (1) with stabilised ester-enolates (3), in the presence of catalytic palladium(0), gave tetrasubstituted fluoroalkenes (2) in good yield and with generally satisfactory *trans*-stereoselectivity.

The recent development of the fluorine atom as a highly effective cation-stabilising (C-S) auxiliary[1] which enhances yields and controls the regiochemistry of biomimetic polyene cyclizations that are applicable to the synthesis of polycyclic steroids and pentacyclic triterpenoids (*e.g.* Figure 1), stimulated our interest in the development of new methods for the stereoselective synthesis of fluoroalkenes.[2] In particular our attention was directed towards the formation of tetrasubstituted *trans*-fluoroalkenes, such as found in the polyene in Figure 1, as this unit allows for the incorporation of an angular methyl group in the cyclized product.

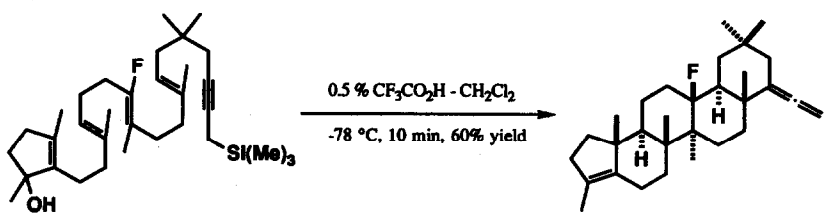


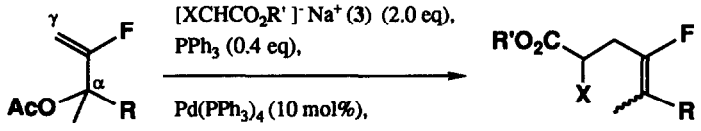
Figure 1: Example of a fluorine-mediated tetracarbocyclization.[1c]

Our initial efforts directed towards the synthesis of tetrasubstituted fluoroalkenes involving Claisen rearrangements (ortho ester,[3a] Eschenmoser,[3b] and Ireland-enolate[3c]) gave poor *trans*-selectivity, and Wittig rearrangements[4] gave, at best, a 70 : 30, *trans* : *cis* ratio.[1c] Hence, we decided to explore a conceptually different approach involving the palladium(0) catalysed alkylation of allylic acetates, *i.e.* the Trost reaction.[5] The first example, developed for a total synthesis of (±)-β-Amyrin,[1d] furnished a highly selective result and has led us to investigate the scope of this reaction which is the subject of the present communication.

Thus, the reaction of the sodium ester-enolates (3) with β-fluoroallylic acetates (1)[6] in the presence of catalytic tetrakis(triphenylphosphine)palladium(0) and triphenylphosphine, in THF at 80 °C, cleanly afforded the

coupled fluoroalkenes (2) in good yield and with generally satisfactory *trans*-stereoselectivity (Scheme 1).[7, 8] The results of such reactions with several esters and with a series of allylic acetates (1) are summarised (Table).[9]

Scheme 1: Synthesis of tetrasubstituted fluoroalkenes.



(1) (2)

Table:[a]

Entry	R	X	R'	Isolated yield (%)[b, c]	Selectivity[d] *trans* : *cis*[e]
1	R^1	COMe	Me	78	81 : 19
2	R^1	COR^2	Et	80	83 : 17
3	R^1	COPh	Et	(68)	83 : 17
4	R^1	CO_2Me	Me	69	67 : 33
5	R^1	CO_2Et	Et	67	63 : 37
6	R^1	CO_2-*t*-Bu	*t*-Bu	67	52 : 48
7	R^1	SO_2Ph	Me	60	56 : 44
8	*n*-Butyl	COR^2	Et	45 (67)	81 : 19
9	R^3	COR^2	Et	83	88 : 12
10	R^4	COR^2	Et	78	74 : 26
11	$-CH_2CH_2C{\equiv}CMe$	COR^2	Et	83	82 : 18
12	$-CH_2CH_2CH_2C{\equiv}CMe$	COR^2	Et	32 (79)	81 : 19
13	$-CH_2CH_2\overline{CH(OCH_2CH_2O)}$	COR^2	Et	79	78 : 22
14	Allyl	COR^2	Et	32	77 : 23
15	*i*-Propyl	COR^2	Et	(38)	78 : 22
16	Phenyl	COR^2	Et	25 (62)	86 : 14

(a), *Key* : R^1 = (*E*)-$CH_2CH_2C(Me)=CHCH_2C(Me)_2CH_2C{\equiv}CMe$; R^2 = (1-Methylcycloprop-1-yl); R^3 = (Z)-$CH_2CH_2C(Me)=CHCH_2C(Me)_2CH_2C{\equiv}CMe$; R^4 = (Z)-$CH_2CH_2CH=CHCH_2Si(Me)_3$; (b), Refers to chromatographically purified materials; (c), Yields in parenthesis determined by GC ; (d), Determined by GC and/or ^1H NMR (400MHz) analysis of the reaction product mixture; (e), Assigned on the basis of vinylic methyl and fluorine coupling values.

The reactions were regiospecific giving exclusively the fluoroalkene resulting from attack of the nucleophile at the least substituted carbon atom (γ-C) of the π-allylpalladium complex. The nature of the nucleophile appears to be the controlling factor with a higher degree of selectivity, in favour of the *trans*-

isomer, being observed for the β-ketoesters (Table, entries 1-3, 8-16). Dialkyl malonates gave only modest *trans*-selectivity and this selectivity decreased as the size of the alkyl group increased, Me > Et > *t*-Bu, (Entries 4-6). Methyl phenylsulphonylacetate showed little selectivity (Entry 7).

The sodium enolate derived from ethyl 3-(1-methylcycloprop-1-yl)-3-oxopropionoate[10], **3** (X = COR^2, R' = Et), was then coupled with several different α-substituted allylic acetates (**1**) and in all cases the reactions proceeded with a similar degree of selectivity (Table, entries 8-16). The most favourable examples involved either bulky α-substituents, or α-substituents incorporating a pendant π-donor ligand able to coordinate with the metal. Minor structural changes of the α-substituents remote from the allylic moiety also exhibited an influence on the selectivity (Table, entry 2 v 9). However, these effects appear to be very subtle. The selection of phosphine ligand additive also affects the coupling as the use of tri-*o*-tolylphosphine instead of triphenylphosphine (for Table, entry 2) greatly inhibited the reaction suggesting the formation of a highly hindered π-allylpalladium complex.

Another noteworthy feature, the Ireland-enolate Claisen rearrangement[3c] of acetate **1** (R = R^1) gave the fluoroalkenyl acid **2** (R = R^1, X = R' = H) in 69% yield and with good *cis*-stereoselectivity, 80 : 20, *i.e.* with the opposite selectivity to that of the Trost reaction. However, further investigaton indicated this substrate to be a special example as rearrangement of acetates **1** (R = *n*-Bu and Ph) gave approximately 1 : 1 mixtures of geometrical isomers. Hence, this alternative approach appears unlikely to be a general route to tetrasubstituted *cis*-fluoroalkenes.

In conclusion, the methodology described herein provides a useful route to functionalised tetrasubstituted fluoroalkenes and is currently being applied, in our laboratories, towards the biomimetic total synthesis of several complex polycyclic triterpenoids.

Typical Procedure:[11] A solution of the allylic acetate (0.40 mmol), triphenylphosphine (0.16 mmol, 0.4 eq) and tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 5 mol%) in anhydrous THF (2.0 mL) was stirred at 23 °C under Ar for 60 min. In a separate flask, the ester (0.80 mmol, 2.0 eq) was added dropwise to a stirred suspension of hexane-washed sodium hydride (0.82 mmol, 2.05 eq, 60 % dispersion in mineral oil) in anhydrous THF (3.0 mL) at 0 °C under Ar, and the resulting homogeneous solution was warmed to 23 °C and stirred for an additional 30 min. The solution of the sodio-derivative was then added to the former mixture in one portion, and the combination was then heated at reflux for 30-48 h. After 12 h, a second portion of tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 5 mol%) was added. The cooled mixture was diluted with ether (50 mL) and washed successively with saturated NH_4Cl (20 mL), saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$) and then evaporated to leave the *coupled fluoroalkene* which was purified by chromatography on silica gel.

Acknowledgements: This research was supported by the National Institutes of Health (DK 03787) and the National Science Foundation. HRMS were recorded by the Regional Mass Spectrometric Service at the University of California, San Francisco. We wish to thank Professor B. M. Trost for helpful discussions and his interest in this work. We are also grateful to Dr. F. W. John Demnitz for performing the indicated example, (Table, entry 13).

References and Notes:

1. (a), Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.*, in press; (b), Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.*, in press; (c), Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.*, in press; (d), Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.*, in press.

2. For representative procedures towards disubstituted ($RC(F)=CH_2$, RCH=CHF) or trisubstituted (RC(F)=CHR', RC(R')=CHF) fluoroalkenes see: (a), Cox, D. G.; Gurusamy, N.; Burton, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 2811-2812; (b), McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439-7440; (c), Boys, M. L.; Collington, E. W.; Finch, H.; Swanson, S.; Whitehead, J. F. *Tetrahedron Lett.* **1988**, *29*, 3365-3368; (d), Boche, G.; Fahrmann, U. *Chem. Ber.* **1981**, *114*, 4005-4009; (e), McCarthy, J. R.; Matthews, D. P.; Barney, C. L. *Tetrahedron Lett.* **1990**, *31*, 973-976; (f), Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1989**, *30*, 967-970; (g), Lee, S. H.; Schwartz, J. *J. Am. Chem. Soc.* **1986**, *108*, 2445-2447.

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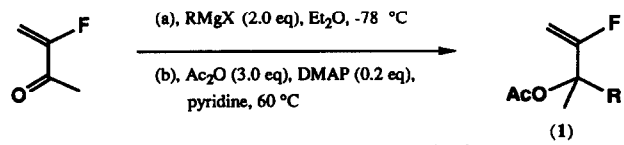
5. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730-4743 *et seq.*

6. The majority of the β-fluoroallylic acetates (1) were prepared by the Grignard reaction of 3-fluorobutenone (Bessiere, Y.; Savary, D. N. -H.; Schlosser, M. *Helv. Chim. Acta.* **1977**, *60*, 1739-1746.) with the respective organomagnesium halide, and subsequent acetylation of the resulting allylic alcohols.



(1)

The synthesis of acetates 1, (R = R^1, R^3) has been previously reported.[1c, d]

7. The stereochemistry of the tetrasubstituted olefinic bond has been defined, for the sake of clarity, in terms of the relative position of the vinylic methyl and fluorine groups. Note that the *trans*-configuration has the (Z)-assignment due to the priority of the fluorine atom.

8. The assignment of the fluoroalkene stereochemistry was based on the coupling constant observed between the vinylic methyl and fluorine groups (*trans*- ca 2.6 Hz, *cis*- ca 3.3 Hz) (*cf.* Emsley, J. W.; Philips, L.; Wray, V. *Fluorine Coupling Constants*; Pergamon Press: Elmsford, NY, 1977; pp. 187-194.). In addition, in our experience, the *trans*-fluoroalkenes invariably had the longer retention times on GC and were less mobile on TLC.

9. Satisfactory spectroscopic data, together with microanalytical and/or high resolution mass spectrometry data, were obtained for all new compounds.

10. A useful unit in polyene synthesis. See: (a), Brady, S. F.; Ilton, M. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882-2889; (b), Wolf, H.; Matzel, U.; Brunke, E. -J.; Klein, E. *Tetrahedron Lett.* **1979**, 2339-2342.

11. This is a generalised procedure based on the one reported in ref. 1d. The reaction (Table, entry 2) has also been performed on a relatively large scale (45 mmol) with just 5 mol% of $Pd(PPh_3)_4$ catalyst with neither decrease in yield nor loss of selectivity.

(Received in USA 9 September 1992)