Novel reductive olefination mediated by Ti(O-i-Pr)$_4$ and Ph$_3$P. One-pot synthesis of trifluoromethylated *trans*-allylic alcohols

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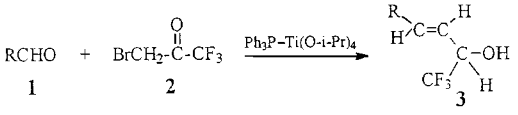
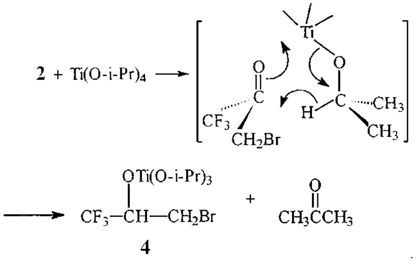
A novel reductive olefination mediated by Ti(O-i-Pr)$_4$ and Ph$_3$P and its application to the 'one-pot' synthesis of perfluoroalkylated *trans*-allylic alcohols are described.

One-pot synthesis has attracted much interest in recent years because it provides a simple and efficient route to compounds by including two or more transformations in a single operation to increase the complexity of a substrate starting from commercially available, relatively simple precusors.[1] In our laboratory 'one-pot' carbon–carbon double bond formation has been observed between α-bromo carboxylic derivatives (esters, amides and nitriles) and aldehydes in the presence of n-Bu$_3$P(As) and catalyst (Pd, Zn, Cd) forming α,β-unsaturated esters, amides and nitriles.[2] This reaction greatly simplifies the traditional Wittig reaction into a stereospecific alkenylation methodology and compresses the three steps of a Wittig reaction to a one-step, one-pot synthesis.[3] Allylic alcohols are employed as useful building blocks in many synthetic applications, particularly in the synthesis of biologically active compounds.[4] Therefore there has been much interest in the development of an effective 'one-pot' method for the preparation of allylic alcohols, especially fluoro species. Numerous methods by which to prepare allylic alcohols are known,[5] but either multiple steps are necessary or the starting materials are not commercially available. Very recently a new stereoselective method for the preparation of allylic alcohols using nickel catalyzed alkylative cyclization of ynals or coupling of aldehydes, alkynes and organozincs has been reported.[6] However, the syntheses of trifluoromethylated allylic alcohols[7a–d] and difluoro species[7e–h] are still limited. Herein we report a novel reductive olefination mediated by Ti(O-i-Pr)$_4$ and Ph$_3$P and its application to the 'one-pot' synthesis of trifluoromethylated *trans*-allylic alcohols (Scheme 1). The results are summarized in Table 1.



Scheme 1

At present, the tentative hypothesis shown in Schemes 2–4 appears to be consistent with the information currently available. The reaction is postulated to be initiated by the Meerwein–Pondorf–Verley-like reduction of 3-bromo-1,1,1-trifluoroacetone with Ti(O-i-Pr)$_4$ (Scheme 2).[8]



Scheme 2

The halophilic reaction occurred between intermediate **4** and the Ph$_3$P forming ion pair **5** and **6** as reported in the literature (Scheme 3).[9] Compound **6** might be stabilized by a strong electron-withdrawing trifluoromethyl group. Subsequently the active species **5** and **6** reacted with the aldehyde forming the six-membered intermediate **7**. After elimination of triphenylphosphine oxide and HBr the intermediate **8** was formed which was hydrolysed to give the product **3** (Scheme 4).[10]

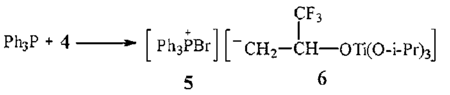
Table 1 Preparation of perfluoroalkylated allylic alcohols[a] mediated by Ti(O-i-Pr)$_4$ and Ph$_3$P

Compound	R	(Bp/°C)/(*p*/torr)	Yield (%)[b]
3a	C_6H_5	114–115/2.5[c]	90
3b	4-$CH_3C_6H_4$	110/2.5	99
3c	4-FC_6H_4	102–104/2.6	87
3d	4-ClC_6H_4	112/2.5	77
3e	4-$CH_3OC_6H_4$	120/2.5	54
3f	4-$NO_2C_6H_4$	103–104[d]	55
3g	3-BrC_6H_4	105/2.0	71
3h	3-ClC_6H_4	110/2.0	78
3i	2-BrC_6H_4	81/2.5	95
3j	(*E*)-$C_6H_5CH{=}CH$	118/2.5	81

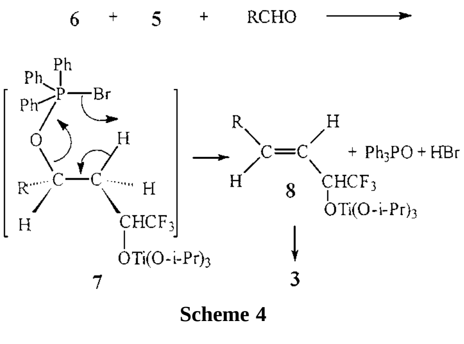
[a] All reactions were carried out neat at 80 °C for 24 h, using 1.0 equiv. of Ti(O-i-Pr)$_4$, Ph$_3$P, 3-bromo-1,1,1-trifluoroacetone and aldehyde. [b] Isolated yields. All new compounds were characterized by microanalyses, IR, NMR and mass spectroscopy. [c] Lit.[7a] data 76–77 °C/1 torr. [d] Mp.

3-Bromo-1,1,1-trifluoroacetone was proved to be able to react with Ti(O-i-Pr)$_4$ by independent experiment. When **2** was reacted with Ti(O-i-Pr)$_4$ at 80 °C for 2 h, **4** was isolated and characterized, [11] and further reacted with 4-chlorobenzaldehyde in the presence of Ph$_3$P giving the desired product **3d.**‡

A possible mechanism involving Ph$_3$P attack on 3-bromo-1,1,1-trifluoroacetone to give the enolate, followed by an aldol condensation, transferring the Ph$_3$PBr onto the hydroxylic oxygen, followed by elimination of HBr from **7,** and a Merrwein–Pondorf–Verley 1,2-reduction of the enone product, seems to be discounted, since in the absence of Ti(O-i-Pr)$_4$, no olefination occurred under the same conditions. If the above mentioned mechanism does occur, the olefination product



Scheme 3



Scheme 4

should be obtained in the absence of Ti(O-i-Pr)$_4$. The detailed mechanism is being pursued.

These studies provide, to our knowledge, the first example of organotitanium compounds combined with Ph$_3$P mediated reductive olefination giving trifluoromethylated *trans*-allylic alcohols efficiently and stereoselectively. This 'one-pot' synthesis is a very convenient starting point using commercially available substances for the preparation of trifluoromethylated allylic alcohols, and the widespread use of these allylic alcohols is quite important in organic synthesis. They are interesting fluorinated building blocks, not easily available by existing synthetic methods.

Notes and References

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‡ General experimental procedure: To a mixture of 3-bromo-1,1,1-trifluoroacetone (1 mmol), aldehyde (1 mmol) and Ph$_3$P (1 mmol) in a capped vessel under nitrogen was injected Ti(O-i-Pr)$_4$ (1 mmol). After stirring at 80 °C for 24 h, the reaction mixture was treated with 5% HCl (10 ml) and extracted with Et$_2$O (3 × 20 ml). The organic layer was washed with water (3 × 10 ml), dried and evaporated to remove the solvent. The residue was chromatographed on silica gel, and eluted with petroleum ether (60–90 °C)–ethyl acetate (95:5) to give the product.

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11 After fractional distillation under vacuum, a colorless oil **4** was obtained which was sensitive to moisture. Bp 110 °C/0.1 torr; δ_H(300 MHz, CDCl$_3$, TMS) 5.00–4.20 (m, 4H), 3.58 [dd, ^2J(H,H) 10.9, ^3J(H,H) 3.2, 1H], 3.10 [dd, ^2J(H,H) 10.6, ^3J(H,H) 8.8, 1H], 1.28 [d, ^3J(H,H) 6.1, 18H]; δ_F(60 MHz, CDCl$_3$, TFA) 0.3 [d, ^3J(H,F) 5.4].

Received in Cambridge, UK, 10th August 1998; 8/06271D