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A Facile and Mild Method for the Synthesis of Terminal Bromofluoroolefins via Diethylzinc-Promoted Wittig Reaction

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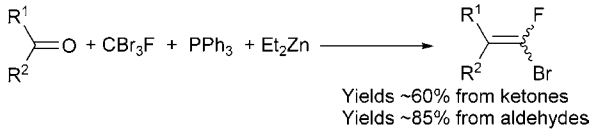
ABSTRACT



Synthesis of 1-bromo-1-fluoroolefins was achieved in good yields via a Wittig reaction promoted by diethylzinc, even with nonactivated aldehydes and ketones as starting materials.

Introduction of fluorine into molecules frequently leads to the discovery of novel and potent tools in various domains, from liquid crystalline materials[1] to biologically active agents, peptide isosteres,[2] or enzyme inhibitors.[3] A wide variety of methods have been developed for the preparation of fluorinated compounds.

Among them 1-bromo-1-fluoroolefins are very useful and versatile building blocks. Indeed, the olefins can be conveniently converted to various functionalized fluoroolefins, i.e., 1-substituted-1-fluoroolefins by the palladium-catalyzed cross-coupling reaction,[4] 1-fluorovinylphosphonates,[5] α-fluoro-α,β-unsaturated esters,[6] and fluorovinyl compounds via a carbenoid reaction.[7] Generally, the bromofluoroolefins are synthesized via Wittig reactions with triphenylphosphine, fluorotribromomethane, and appropriate aldehydes or ketones.[8] Another attractive method, giving good stereoselectivity, is brominative addition on unsaturated fluoroacids, followed by decarboxylative elimination.[9] An alternative approach is the elimination of a leaving group LG (acetate or tosylate) from RCH(LG)CBr_2F with a Grignard reagent.[10] All of these methods are very interesting but usually give low yields with nonactivated ketones or aliphatic aldehydes.

Herein we report a convenient and mild method to synthesize bromofluoroolefins via a Wittig reaction. The key factor in our improvement of this known reaction is the use of diethylzinc instead of zinc. This is, to our knowledge, the first report that diethylzinc can promote the Wittig reaction, producing the desired bromofluoroolefins in moderate to good yields depending on the nature of the carbonyl compound.

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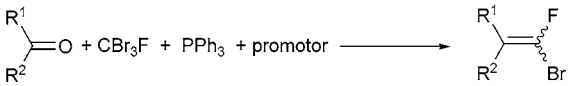
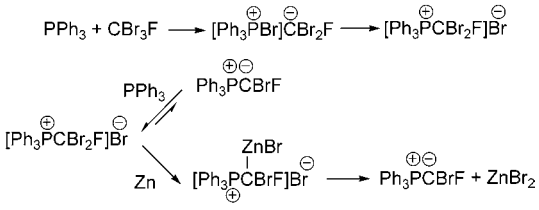
In our ongoing program on biological compound mimics, bromofluoroolefins are key intermediates. We tried first to obtain bromofluoroolefins via the more general method which is the Wittig reaction (Scheme 1). Using standard

Scheme 1. Synthesis of Bromofluoroolefins



conditions, described by Burton,[8] we studied the Wittig reaction of 3-phenylpropionaldehyde (1.0 equiv) with triphenylphosphine(3.0 equiv) and fluorotribromomethane (1.0 equiv) in the presence of activated zinc powder (3.0 equiv) in dry THF at room temperature under argon. The desired product was never observed in the reaction mixture, even after 24 h. Burton demonstrated in his review[8] that the yields of the Wittig reaction for nonactivated ketones or aliphatic aldehydes are often low. Therefore, we tested various Lewis acids to activate the substrate under the above reaction conditions. The results were very discouraging, and most of the Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $ZnCl_2$, $TiCl_4$, $TiCl(OiPr)_3$, $Ti(OiPr)_4$, $AlMe_3$, and Et_2AlCl had only a small effect on the reaction. The best result was obtained with use of Cp_2TiCl_2 as an activating agent, and 1-bromo-1-fluoro-4-phenylbutene was isolated in 65% yield when 3-phenylpropionaldehyde was treated with the mixture of $PPh_3/CBr_3F/Zn/Cp_2TiCl_2$ (3.0/1.0/3.0/1.0 equiv) in anhydrous THF under Ar at room temperature overnight. Unfortunately, the improvement obtained with titanocene chloride was not general and replacing 3-phenylpropionaldehyde by 2-acetylnaphthalene, a ketone, led to a lower yield (20%). In addition, the phosphonium salt could rarely be observed by ^{19}F NMR. The mechanism of the Wittig reaction in the absence or presence of activated zinc has been published[8,11−13] (Scheme 2).

Scheme 2. Formation of the Ylide with or without Zinc



The first step in the above mechanism is the formation of the phosphonium salt, through the rearrangement of the methide ion and the bromophosphonium cation obtained from the reaction between triphenylphosphine and tribromofluoromethane. In the presence of a second equivalent of triphenylphosphine, the phosphonium salt can be debrominated to give the ylide. This step is an equilibrium, which lies to the left, but in the presence of a trapping agent, i.e., an aldehyde, the equilibrium is shifted to the right. An alternative procedure with activated zinc to debrominate the phosphonium salt gives a stable solution of a metal-stabilized ylide. Phosphine and zinc are the two reagents used to debrominate the phosphonium salt derived from tribromofluoromethane, to form the key ylide intermediate.

Recently it was reported that the zinc carbenoid could be produced in situ from tribromofluoromethane treated with diethylzinc. The carbenoid was then added to the appropriate aldehydes or ketones to give the corresponding alcohols.[14] Another interesting paper reports that the zinc carbenoid derived from diethylzinc and chloroiodomethane could react with tetrahydrothiophene to give the corresponding sulfonium ylide.[15] In regard to these papers, we wondered whether diethylzinc could act as a debrominating agent of phosphonium derived from tribromofluoromethane to generate the reacting ylide. This might constitute an alternative to the classical condition.

In the first assay, we added dropwise diethylzinc (1 equiv) to a THF solution of triphenylphosphine, 3-phenylpropionaldehyde, and tribromofluoromethane (3/1/1 equiv, respectively) at room temperature. Using these conditions, the bromofluorovinyl Wittig product could be isolated in an encouraging 65% yield, the best ever obtained for that particular aldehyde. By optimizing the reaction conditions, changing the solvent (THF, CH_2Cl_2, Et_2O, diglyme), the temperature (from −78 to 100 °C), the nature of the phosphine (PPh_3, $P(NMe_2)_3$), and the number of equivalents, and employing the phosphonium salt instead of forming it in situ, the yields could be increased to 88% by using THF as solvent at room temperature with a 3-phenylpropionaldehyde/$Et_2Zn/CBr_3F/PPh_3$ ratio of 1.0/1.2/1.2/1.2. (see the typical procedure in ref 16).

Then, various aldehydes were subjected to these optimized reaction conditions, giving the corresponding bromofluoroolefins with high yields (Table 1). Under the above conditions, even nonactivated aldehydes could be converted to the corresponding bromofluoroalkenes (Table 1; entries 1−3). The reaction is general and can tolerate various functional groups such as ester, nitro, protected alcohol, and others with yields always around 80−90%.

Unfortunately, whatever the conditions and the aldehydes were, the stereoselectivity was never better than 70:30. At

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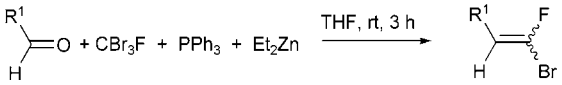
(16) To a solution of triphenylphosphine (2.4 mmol, 1.2 equiv), tribromofluoromethane (2.4 mmol, 1.2 equiv), and an appropriate aldehyde or ketone (2.0 mmol, 1.0 equiv) in anhydrous THF (30−40 mL) was added a solution of diethylzinc in hexanes or toluene (2.4 mmol, 1.2 equiv) dropwise via a syringe pump over 30 min at room temperature under argon. The mixture was stirred at room temperature for 30 min. The resulting solution was then quenched with methanol (10 mL), stirred for 30 min, and concentrated under reduced pressure. The residue was then chromatographed on silica gel (eluent: cyclohexane/ethyl acetate), affording the desired bromofluoroolefins.

Table 1. Reaction with Aldehydes



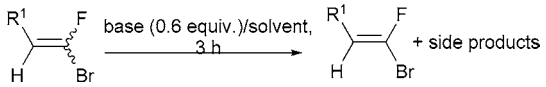
entry	R^1	yield[a] (%)	^{19}F (ppm), Z/E	Z/E[b]
1	$PhCH_2CH_2$	88	−71.7/−75.4	1.00/1.05
2	$TBDPSOCH_2CH_2$	90	−70.6/−75.0	1.00/0.88
3	$TBDPSOCH_2CH(CH_3)$	83	−71.7/−74.7	1.00/1.38
4	4-Br-C_6H_4	74	−66.2/−69.6	1.00/0.81
5	4-F-C_6H_4	73	−64.4/−67.2	1.00/0.96
6	4-NO_2-C_6H_4	85	−59.3/−62.3	1.00/0.73
7	4-$MeOC_6H_4$	94[c]	−68.2/−71.4	1.00/1.03
8	2-NO_2-C_6H_4	87	−64.3/−67.6	1.00/0.43
9	2-MeO-C_6H_4	91	−65.6/−69.5	1.00/0.72
10	3,4(OCH_2O)-C_6H_4	91	−67.6/−70.6	1.00/0.92
11	4-MeO_2C-C_6H_4	81	−62.2/−64.5	1.00/0.81
12	2-naphthyl	78	−65.1/−67.9	1.00/0.92

[a] Isolated yield. [b] Ratio determined by ^{19}F NMR or ^1H NMR. [c] Aldehyde/Et_2Zn/CBr_3F/PPh_3 ratio of 1.0/1.5/1.5/1.5.

that stage, we tried to find a general method to have access to each diastereoisomer in pure form. Numerous methods have been developed to obtain pure *E* or *Z* bromofluoroolefins from mixtures. Among them, the more attractive are separation by gas chromatography[17−19] and isomerization with a catalytic amount of bromine,[19] with palladium II[9] or with light.[17] However, none of these methods are general and adapted to variously functionalized bromofluoroolefins.[17] Instead of isomerizing or separating the two diastereoisomers, we decided to consume chemoselectively one of the two isomers. We found an interesting paper from Perichon's group where they dehydrobrominate 1,1-dibromoroalkenes to give the corresponding bromoalkynes.[20]

On the basis of the difference of reactivity between bromine and fluorine atoms, we decided to try the stereoselective dehydrobromination, and it worked. After optimization, the best bases to promote the transformation were DBU in DMSO at 95 °C or LiHMDS in THF at room temperature,

Table 2. Access to Pure *E* Isomer



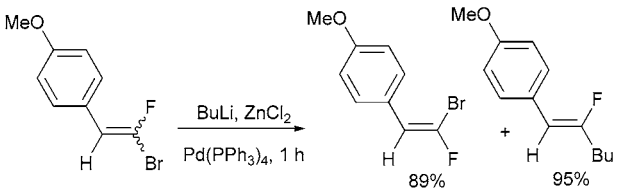
entry	R	base/solvent	yield[a] (%)
1	$PhCH_2CH_2$	LiHMDS/THF	88
2	$TBDPSO\text{-}CH_2CH_2$	LiHMDS/THF	98
3	4-NO_2-C_6H_4	DBU/DMSO	55
4	4-MeO-C_6H_4	DBU/DMSO	85
5	4-MeO_2C-C_6H_4	DBU/DMSO	83
6	4-MeO_2C-C_6H_4	LiHMDS/THF	98
7	2-naphthyl	DBU/DMSO	90
8	4-F-C_6H_4	DBU/DMSO	22
9	4-F-C_6H_4	LiHMDS/THF	67

[a] Based on starting *E* isomer.

yielding, after column chromatography, pure *E* isomer in good to excellent yields (Table 2). As byproducts, fluoroalkynes were expected, but we could not observe them, probably due to their instability.

The pure *Z* isomer could also be isolated by engaging the mixture of isomers in a palladium coupling reaction. In that case, only the *E* isomer reacted as already demonstrated by Burton et al.,[21] and we obtained the *Z* isomer unchanged (Scheme 3). In our hands, as an example, the yield of the

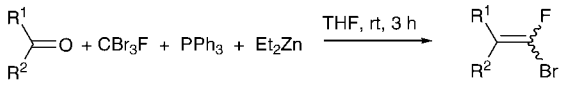
Scheme 3. Access to Pure *Z* Isomer

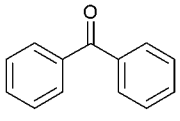
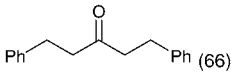
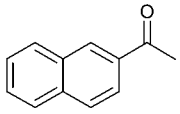
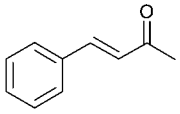
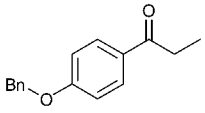
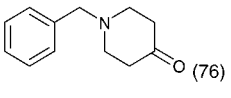
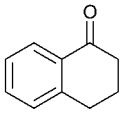
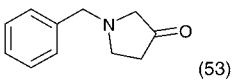
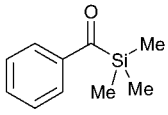
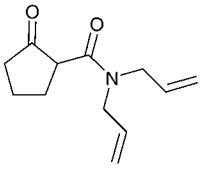


recovered pure Z isomer was 89% with 1-bromo-1-fluoro-2-(4-methoxyphenyl)ethene.

To broaden the scope of the reaction, we then subjected unactivated ketones to Wittig conditions with diethylzinc activation (Table 3).

Table 3. Reaction with Ketones



entry	starting ketones (isolated yields of the bromofluoroolefins)	entry	starting ketones (isolated yields of the bromofluoroolefins)
1	 (22)	6	 (66)
2	 (69)	7	 (39)
3	 (83)	8	 (76)
4	 (78)	9	 (53)
5	 (53)	10	 (0)

The yields of isolated bromofluoroalkene from aromatic or aliphatic ketones were often moderate to good. Nonethe-

less, the structure of the ketones could contain various functional groups such as amine, protected alcohol, etc. Interestingly, we also could obtain 1-bromo-1-fluoro-1,3-diene and 1-bromo-1-fluoro-2-trimethylsilylalkene in moderate yield via the reaction (Table 3; entries 7 and 5, respectively). However, the reaction was not suitable for easily enolizable substrates such as 2-oxocyclopentanecarboxylamide (Table 3; entry 10) or β-tetralone. In these particular cases, the α-hydrogen is probably too acidic and the ylide reacts first with it, instead of adding to the carbonyl group.

In conclusion, we found a novel and convenient method to synthesize 1-bromo-1-fluoroolefins via Et_2Zn-promoted Wittig reaction of CBr_3F/PPh_3 with aldehydes or ketones. The yields for the aldehydes are excellent, and those for ketones are good to moderate. The reaction could tolerate various functional groups, and could be a useful method to provide various fluorovinyl-containing building blocks. It is also, to our knowledge, the first example of using Et_2Zn as a promotor for the Wittig reaction.

Supporting Information Available: Analytical data for the bromofluoroolefins. This material is available free of charge via the Internet at http://pubs.acs.org.

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