Organic LETTERS

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Facile Regio- and Stereoselective Metal-Free Synthesis of All-Carbon Tetrasubstituted Alkenes Bearing a C(sp^3)−F Unit via Dehydroxyfluorination of Morita−Baylis−Hillman (MBH) Adducts

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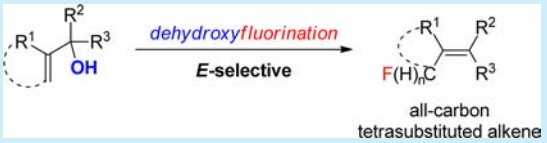
Supporting Information

ABSTRACT: Highly *E*-selective all-carbon tetrasubstituted alkenes with a C(sp^3)−F unit have been synthesized through a dehydroxyfluorination of Morita−Baylis−Hillman (MBH) adducts which can be readily prepared from α,β-unsaturated carbonyl compounds and α-keto esters. A variety of subsequent transformations afforded monofluoromethyl substituted heterocycles in high yields.

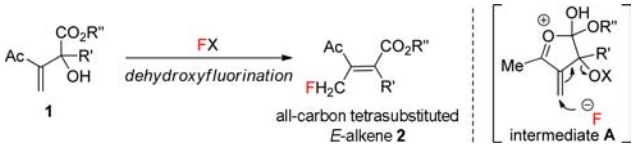


Alkenes represent one of the most versatile and widespread classes of organic compounds.[1] In current organic chemistry, tetrasubstituted alkenes have received considerable attention owing to their high potential when incorporated in liquid crystals, molecular devices, and pharmaceutical compounds.[2] Recent efficient approaches for their construction[3] mainly involve the use of transition metal intermediates via carbometalation of alkynes, or olefin metathesis. However, the regio- and stereocontrol of the tetrasubstituted alkenes is a key issue to be addressed in these methodologies.[3]

Fluorine-containing compounds are gaining much attention in material sciences and medicinal chemistry because the inclusion of a F atom into organic molecules dramatically changes the physical, chemical, and biological properties, for example, lipophilicity, bioavailability, and metabolic stability.[4] Alkenes with a C(sp^3)−F unit, allylic fluorides, have been identified as important building blocks for the preparation of biologically active compounds,[4,5] and transition-metal-mediated allylic fluorination has been recognized as a common and straightforward method for their construction. However, this method has proven to be challenging because of the dual reactivity profile of fluoride (nucleophile and base), leading to undesired products.[5e−h,j,k,n,o,r,s] Moreover, the practical use of toxic and expensive transition metal catalysts is best avoided to prevent residual metal impurities. Herein, we report a facile, nonmetallic synthesis of all-carbon tetrasubstituted alkenes **2** bearing a C(sp^3)−F unit from readily available allylic tertiary alcohols **1** by Deoxo-Fluor-mediated dehydroxyfluorination (Scheme 1).

The Morita−Baylis−Hillman (MBH) reaction is one of the most useful and atom economical carbon−carbon bond forming reactions between the α-position of an electron-deficient alkene, such as an enone, and the sp^2 carbon atom of an aldehyde.[6] Highly functionalized tertiary alcohols (MBH adducts) **1** are readily obtained from an MBH reaction using ketones such as an α-keto ester.[7,8] Dehydroxyfluorination of **1** via an S_N2' mechanism would readily provide all-carbon tetrasubstituted and vicinal fluorinated alkenes **2** (Scheme 1);

Scheme 1. Facile, Regio- and Stereoselective Synthesis of All-Carbon Tetrasubstituted Alkenes Bearing a C(sp^3)−F Unit



however, the regio- and stereocontrol is not always favorable because the fluorination steps could proceed through an S_N2', S_N2, S_Ni', and/or S_N1 mechanism.[5a,i,t,u] Byproducts resulting from carbonium type rearrangements and dehydration are also occasionally observed.[5a] We envisioned that the dehydroxyfluorination of **1** would proceed via a five-membered cyclic orthoester-like[9] intermediate **A** (Scheme 1), by interaction between two closely located carbonyl groups, followed by the smooth addition of fluoride to the double bond under the S_N2' mechanism, to predominantly afford *E*-alkenes **2**.

We started our study evaluating the reaction of MBH adduct **1a** as a model substrate with diethylaminosulfur trifluoride (DAST), which is a commonly used reagent for the dehydroxyfluorination of allylic alcohols (Table 1).[5a] Initial attempts yielded the desired **2a** in high conversion with high *E*-stereoselectivity (entries 1−3). The corresponding hydroxyl-fluoro exchanged regioisomer **3a**, generated via an S_N1-type process, was not obtained. Reducing the reaction temperature (entries 1 and 3) or decreasing the amount of DAST (entry 2) led to no significant improvement. When using bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) as the fluoride source,[10] **2a** was obtained in a higher yield (75%), compared with DAST, maintaining high stereoselectivity (*E*:*Z* = >20:1), as shown in entry 4. Although solvent such as $CHCl_3$, toluene, and THF (entries 5 and 8) gave a complex mixture or

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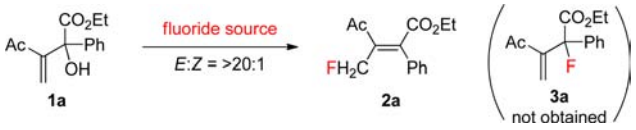
Table 1. Optimization for the Synthesis of Tetrasubstituted Alkenes[a]



entry	fluoride source (equiv)	solvent	temp (°C)	conversion (%)[b]	yield (%)[b]
1	DAST (1.8)	CH_2Cl_2	0 to 25	>99	55[c]
2	DAST (1.1)	CH_2Cl_2	0	82[d]	50
3	DAST (1.8)	$(ClCH_2)_2$	−20 to 0	>99	54
4	Deoxo-Fluor (1.8)	CH_2Cl_2	0	>99	75
5	Deoxo-Fluor (1.8)	$CHCl_3$ or toluene	0	>84	trace
6	Deoxo-Fluor (1.8)	$(ClCH_2)_2$	0	95	73
7	Deoxo-Fluor (1.8)	1,4-dioxane	10	>99	64
8	Deoxo-Fluor (1.8)	THF	0	83	20
9	Deoxo-Fluor (1.8)	diglyme	0	96	96[c]
10	Deoxo-Fluor (1.8)	diglyme	−10	87	80
11	Deoxo-Fluor (1.5)	diglyme	0	67	54

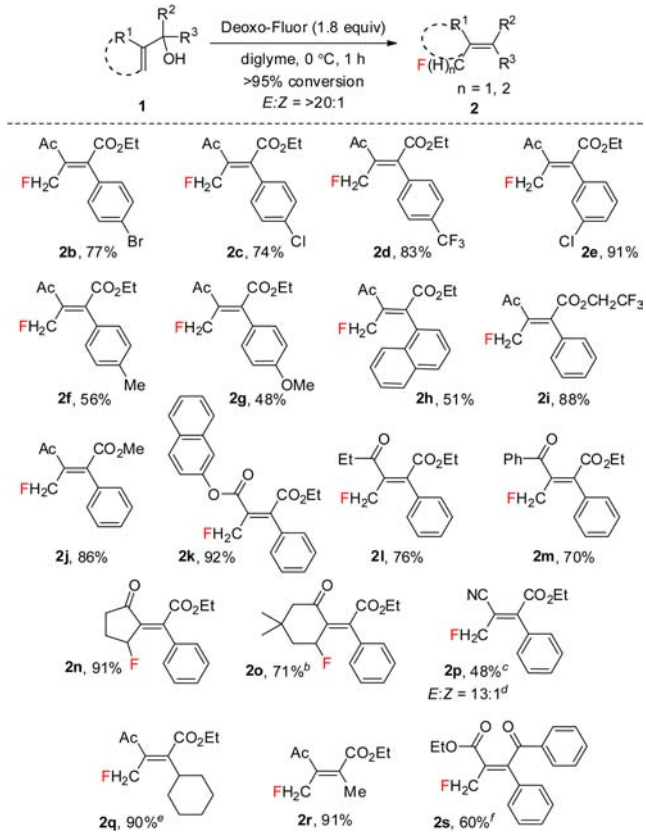
[a]The reaction was performed for 1 h under N_2 in the indicated solvent (0.2 M), DAST (diethylaminosulfur trifluoride); Deoxo-Fluor (bis(2-methoxyethyl)aminosulfur trifluoride). [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]Reaction was performed for 5 h.

low yield of **2a**, the use of diglyme had a beneficial impact, resulting in a 96% isolated yield of **2a** (entry 9). A lower temperature (entry 10) or decreased amount of Deoxo-Fluor (entry 11) resulted in lower yields.

Having optimized the dehydroxyfluorination conditions, we then investigated the substrate scope (Scheme 2). When alcohols bearing an electron-withdrawing group on the aryl unit **1b−e** (R^3 = 4-Br, 4-Cl, 4-CF_3, or 3-Cl−C_6H_4) were utilized, the corresponding alkenes **2b−e** were obtained in 74%−91% yields with excellent stereoselectivities (*E*:*Z* = >20:1). However, the alcohols with an electron-donating moiety on the aryl unit **1f−h** (R^3 = 4-Me-C_6H_4, 4-MeO-C_6H_4, or 1-Np) afforded alkenes **2f−h** in lower yields, presumably due to a competitive benzyl carbocation stabilization effect preventing the S_N2' fluorination. Trifluoromethyl, methyl ester, and benzoyl groups **1i−j** and **1s** (R^2 = $CO_2CH_2CF_3$, CO_2Me, or COPh) were easily introduced and conserved after the olefination giving **2i−j** and **2s**. Alcohols **1k−o** derived from acrylates and acyclic or cyclic enones (R^1 = CO_2R or COR) gave the corresponding alkenes **2k−o** in 70%−92% yields with excellent *E*-stereoselectivities. Cyano-substituted alcohol **1p** (R^1 = CN) gave **2p** in high regioselectivity (*E*:*Z* = 13:1).[11] Notably, the scope was further expanded by the use of aliphatic systems **1q,r** (R^3 = Cy or Me), which were found to smoothly deliver high yields of the alkenes **2q,r** without formation of any byproducts. The *E*-geometry of the tetrasubstituted alkenes was unambiguously determined by X-ray crystallographic analysis of **2q** (Figure 1).[12,13]

It was clear that substrates **1** possessing two carbonyl groups were effective in the regio- and stereoselective transformation. To clarify the role of these carbonyl groups in the reaction, we examined substrates **1t** and **1u** (Scheme 3), possessing one

Scheme 2. Substrate Scope of the Dehydroxyfluorination[a]



[a]The reaction was performed for 1 h under N_2 in diglyme (0.2 M). Isolated yields after column chromatography. [b] Performed at −20 °C for 1 h. [c] Performed at −40 °C for 1 h in CH_2Cl_2. [d] Determined by ^{1}H NMR. [e] Stirred for 2 h. [f] Stirred for 17 h, >90% conversion.

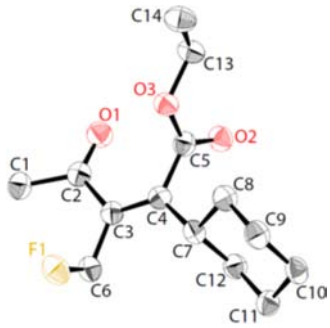
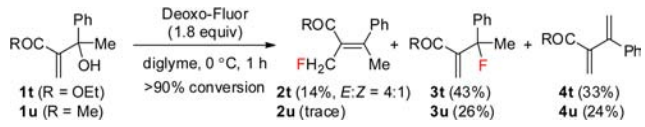


Figure 1. ORTEP drawing of tetrasubstituted alkene **2q**.

Scheme 3. Reaction of 1t and 1u with Deoxo-Fluor



carbonyl group under the optimized reaction conditions. Interestingly, the desired tetrasubstituted alkenes **2** were obtained in low or poor yields (**2t**: 14%; **2u**: trace), whereas the hydroxyl-fluoro exchanged products **3** and the dehydrated products **4** were mainly formed (**3t**: 43%, **4t**: 33%; **3u**: 26%, **4u**: 24%), respectively.

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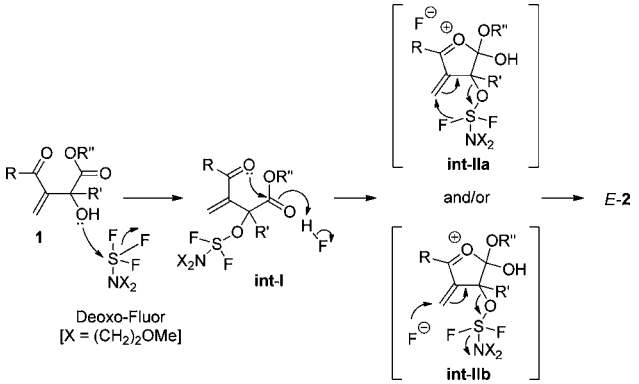
The sterically and thermodynamically unfavorable *E*-selective allylic fluorination mechanism has not been unequivocally established;[14] however, these results, along with previous reports,[5a,i,t,u,9,15] may be in agreement with a five-membered cyclic orthoester-like intermediate directing the observed *E*-stereoselectivity, as shown in Scheme 4. The OH of MBH

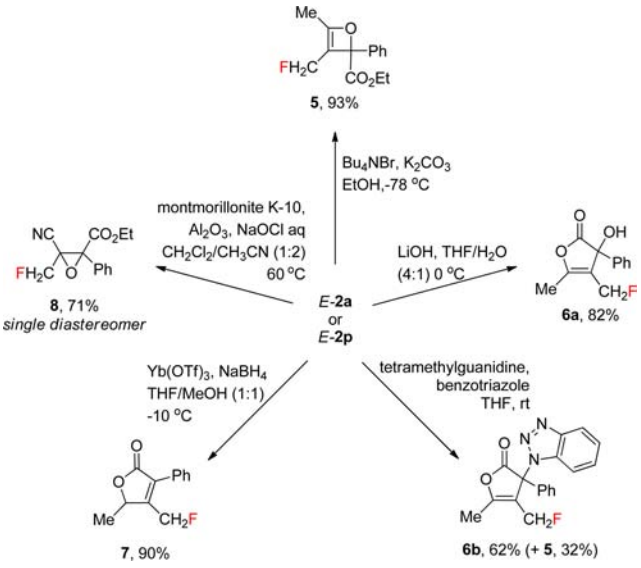
Scheme 4. Plausible Reaction Mechanism



adduct **1** reacts with the sulfur moiety of Deoxo-Fluor resulting in **int-I**. Due to the proximity of the two carbonyl groups, the formation of an orthoester-like intermediate **int-II** is possible.[16] The allylic fluorination most likely proceeds through **int-IIa** via a favorable six-membered transition state in a concerted manner to predominantly form the *E*-alkene, although a stepwise process through **int-IIb** would also be possible.

To demonstrate the significant synthetic utility of the tetrasubstituted alkenes **2** as building blocks, several transformations were carried out (Scheme 5). Base-mediated

Scheme 5. Synthetic Transformations of Alkenes 2



intramolecular cyclization of **2a** readily gave highly functionalized four-membered heterocycle,[17] oxetene **5**, in high yield. Domino oxo- or aza-Michael addition/intramolecular cyclization of the *in situ* generated enolate of **2a** afforded lactones **6** bearing a tetrasubstituted carbon. Ytterbium triflate promoted Luche reduction[18] of **2a** followed by intramolecular cyclization provided five-membered cyclic compound **7** in high yield. Finally, epoxidation of **2p** gave oxirane **8**, bearing two tetrasubstituted carbon stereogenic centers, as a single diastereomer in good yield.[19]

In summary, we have developed a facile method for the preparation of alkenes bearing four different C-substituents with high regio- and stereocontrol. A highly challenging $C(sp^3)$–F bond was also generated as part of the present synthetic method. Furthermore, the alkenes possessing a fluoromethyl group were successfully converted into structurally appealing 3-, 4-, or 5-membered heterocycles, exhibiting their importance as synthetic building blocks. Further investigations into the reaction mechanism and scope, as well as application to the synthesis of biologically active compounds, are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) XtalFluor-E as a fluoride source was tested but only gave the tetrasubstituted alkene **2a** in 14% yield.

(11) The formation of a five-membered cyclic orthoester-like intermediate requires the presence of two carbonyl groups; however, in the case of **1p** one of those is replaced with a CN group. Further investigation into the reaction mechanism of **1p** is currently underway.

(12) Crystallographic data of *E*-**2q** for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 977587. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk/data_request/cif.

(13) *E*-geometry on the olefin **2a** was also determined by NMR experiments (^{1}H–^{19}F HOESY); see Supporting Information.

(14) The MM2 investigation indicated that *Z*-**2a** is thermodynamically more stable than *E*-**2a** (ΔE = 3.09 kcal/mol).

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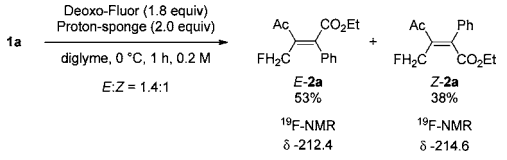
(16) Since the fluorination of **1a** in the presence of proton-sponge (2.0 equiv) gave an *E* and *Z* mixture of **2a** (total yield, 91%; *E*/*Z* ratio = 1.4:1), the *in situ* generation of HF seems important to activate the carbonyl group for the formation of **int-II**.



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