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Stereospecific Synthesis of Fluoroalkenes by Silver-Mediated Fluorination of Functionalized Alkenylstannanes

Heiko Sommer and Alois Fürstner*

Dedicated to Prof. Masakatsu Shibasaki on the occasion of his 70th birthday

Abstract: *The known procedures for the conversion of alkenylstannanes into the corresponding fluoroalkenes suffer from largely variable yields and a limited compatibility with functional groups; most notably, protodestannation becomes a serious issue whenever protic sites are present in the substrate. Outlined in this paper is a convenient alternative with a much improved application profile, which is largely unperturbed by free alcohols and amides of all sorts. Key to success is the use of F-TEDA-PF_6 in combination with non-hygroscopic and bench-stable silver phosphinate ($AgOP(O)Ph_2$) that acts as an essentially neutral, non-nucleophilic promotor and effective tin-scavenger at the same time. This new method opens many opportunities for late-stage fluorination of elaborate compounds far beyond the scope of the literature procedures, as witnessed by the preparation of a fluorinated macrolide antibiotic, a fluorinated prostaglandin derivative, and a set of fluorinated amino acid surrogates and peptide isosteres.*

Our group has recently described a practical, mild and scalable method for the ruthenium catalyzed *trans*-hydrostannation of internal alkynes.[1,2] This stereochemically unorthodox transformation is distinguished by high yields and an excellent compatibility with functional groups, including substituents that would not persist under free radical conditions.[1,2,3,4] Moreover, the addition process is also highly regioselective when working with unsymmetrical acetylene derivatives such as **A** that carry a protic group in vicinity to the reacting triple bond (Scheme 1): in this case, the tin moiety is faithfully delivered to the C-atom proximal to the –XH (X = O, NR) group, provided that $[Cp^*RuCl]_4$ is chosen as precatalyst. The massive steering effect originates from interligand hydrogen bonding

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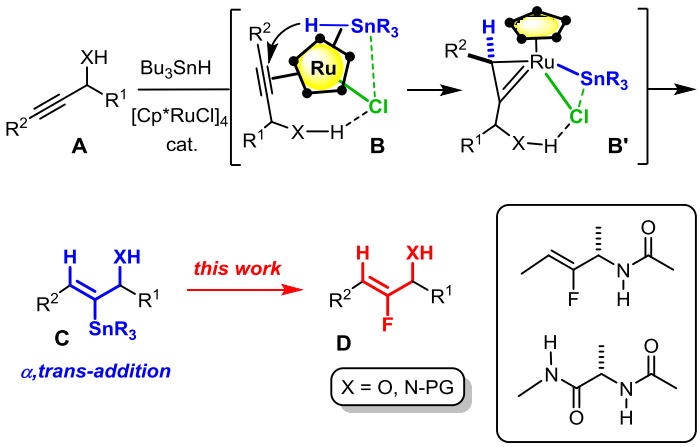
10.1002/chem.201605444

between the protic substituent and the polarized [Ru–Cl] unit, which imposes directionality onto the ligand sphere of the loaded complex of type **B**.[2]



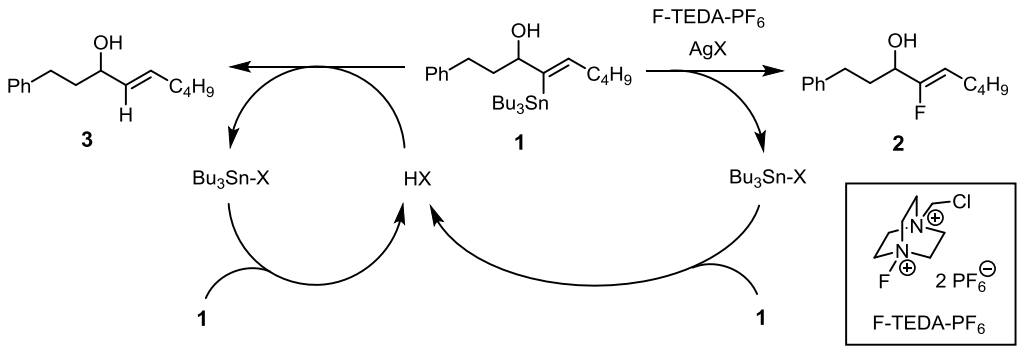
Scheme 1. Directed *trans*-hydrostannation/fluorination sequence; for X = N-PG, the resulting fluoroalkenes capture the polarity and conformation of an *s-trans* amide bond and hence represent valid peptide isosteres; PG = protecting group; • denotes a CMe unit

In order to harness the full potential of this remarkably selective transformation, it is necessary to develop adequate downstream chemistry for the resulting alkenylstannanes **C**.[5,6,7] In this context, we became interested in converting them into the corresponding alkenyl fluorides **D**: strategic placement of a fluorine atom adjacent to the hydroxyl substituent (X = O) is expected to result in increased (metabolic) stability since the induced electron-withdrawal within the σ-framework renders the allylic substituent less ionization-prone.[8] Moreover, fluoroalkenes with a flanking amido substituent (X = NR) are known to capture the polarization and conformation of an *s-trans* amide bond and hence serve as non-scissile, lipophilic and conformationally locked peptide isosteres (Scheme 1).[9,10] Most synthetic approaches to compounds of type **D** start from one of the few readily available small fluorinated building blocks and successively assemble the carbon framework from there on.[8-11] In conceptual terms, the proposed conversion of **C** into **D** is orthogonal in that the formation of the (polyfunctionalized) skeleton *precedes* the introduction of the fluorine substituent.[12] For this complementarity, the current method should be of interest for the life sciences at large.[13,14]

Surprisingly though, we had to learn that none of the literature methods that allow alkenyl tin derivatives to be converted into the corresponding fluorides proved adequate for the projected case.

10.1002/chem.201605444

Protocols relying on the use of elementary fluorine,[15] acetyl hypofluoride[16] or shock-sensitive caesium fluoroxysulfate[17] were neither deemed practical nor did the literature data look promising;[18] likewise, XeF_2 in combination with AgOTf is known to be low-yielding and unselective when applied to alkenylstannanes containing unprotected –OH groups.[19] Akin, the use of F-TEDA-BF_4 (Selectfluor®) or F-TEDA-PF_6 – with[20,21] or without[22,23] (stoichiometric or catalytic) AgOTf – engendered either decomposition or substantial proto-destannation when applied to model substrate **1** (Table 1, entries 1-7), although F-TEDA-PF_6/AgOTf is the reagent combination of choice for the (late stage) fluorination of various aryltin derivatives.[20] Since large amounts of alkene **3** are difficult to separate from the desired fluoroalkene **2**, its formation is a major complication in practical terms.



Scheme 2. Productive fluorodestannation mediated by AgX engenders lethal protodestannation whenever the Bu_3SnX primarily formed is prone to react with the protic substrate

We figured that the tin by-product formed in the transmetalation step might account for this inadequate situation, at least to a large extent (Scheme 2). Although previous screening campaigns had identified AgOTf as optimal promotor,[19,20] the resulting R_3SnOTf can react with compounds containing an unprotected –OH group such as **1** to release detrimental TfOH; this off-cycle event represents a potential suicide mechanism. The problem is all the more severe since early attempts to quench incidental Bronsted acids in the mixture with the help of heterogeneous bases have been reported to be of no avail; likewise, the use of excess 2,6-di-*tert*-butyl-4-methylpyridine in combination with XeF_2/AgOTf is known not to prevent protodestannation from occurring either.[19] Entries 5 and 7 in Table 1 confirm these prior failures.

10.1002/chem.201605444

Table 1. Optimization of the fluorodestannation of compound **1**[a]

Entry	AgX (eq.)	F-TEDA-PF_6 (eq.)	Additive (eq.)	3 (%)[b]	2 (%)[b]
1	---	2.0		---[c]	---[c]
2	AgOTs (2)	1.2		71	29
3	AgOTf (2)	1.2[d]		48	52
4	AgOTf (2)	1.2		35	65
5	AgOTf (0.1)	1.5	$NaHCO_3$ (2)	53	47
6	AgOTf (0.2)	1.2	$[Ph_2P(O)O][Bu_4N]$ (2)	59	41
7	AgOTf (0.2)	1.2	$[Ph_2P(O)O][Bu_4N]$ (2)/pyridine (0.2)[e]	67	33
8	$AgOP(O)Ph_2$ (2)	1.2		29	71
9	$AgOP(O)Ph_2$ (2)	2.0		<7%	>93 (78)[f,g]

[a] all reaction were carried out in acetone at ambient temperature; [b] ratio in the crude product, as determined by NMR, upon full conversion of the substrate; [c] complex mixture; [d] using F-TEDA-BF_4 instead of F-TEDA-PF_6; [e] 2,6-di-*tert*-butyl-4-methylpyridine; [f] slow addition of the stannane over 1 h; [g] isolated yield

Therefore we pursued a different strategy to remedy the problem, envisaging effective tin scavenging rather than post-facto neutralization of any Bronsted acid released in situ. Aware of the beneficial effect that certain phosphinate salts exert in exigent Stille reactions,[24,25,26] we turned our attention to this tin sequestering agent. Whereas addition of $[Ph_2P(O)O][Bu_4N]$ to a mixture of F-TEDA-PF_6 (or F-TEDA-BF_4) and AgOTf did not improve the outcome (entries 6, 7), replacement of AgOTf by $AgOP(O)Ph_2$ was rewarding. Specifically, addition of the alkenyltin derivative over the course of 1 h to a pre-stirred and hence homogenized mixture of $AgOP(O)Ph_2$ and F-TEDA-PF_6 in acetone furnished analytically pure fluoroalkene **2** in 78% yield on a 1 mmol scale (entry 9); under these conditions, competing protodestannation was marginal ($\leq$ 7% in the crude mixture, NMR). $AgOP(O)Ph_2$ is easy to prepare on multigram scale as a non-hygroscopic and bench-stable solid (see the Supporting Information);[27] since the resulting $R_3SnOP(O)Ph_2$ is poorly soluble and hence largely removed upon filtration of the crude mixture through a pad of silica, product purification is straightforward. These favorable attributes render the new procedure practical and robust.

10.1002/chem.201605444

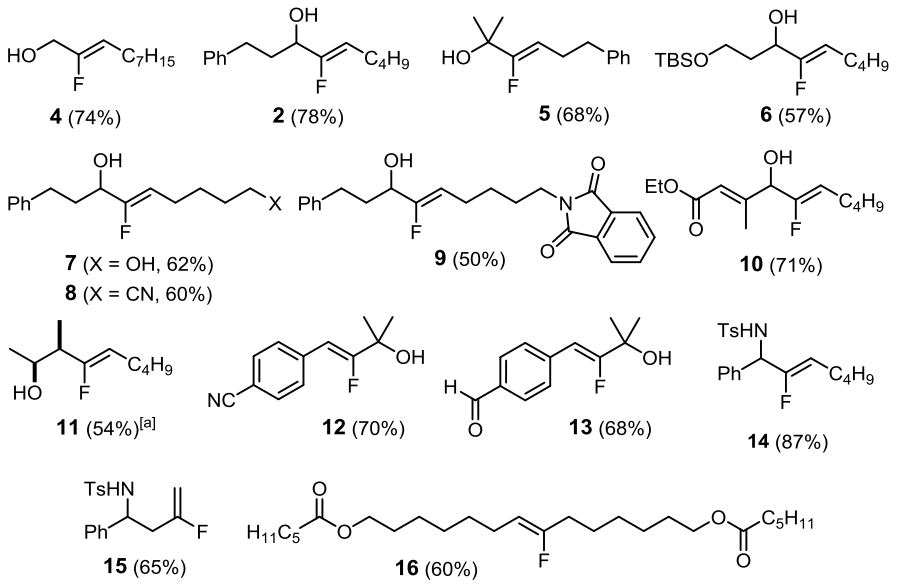


Figure 1. Model fluoroalkenes prepared by treatment of the corresponding alkenyltin derivatives with F-TEDA-PF_6 (2 eq.) and $AgOP(O)Ph_2$ (1.2 eq.) in acetone at ambient temperature; [a] the organotin substrate and the derived fluoroalkene were a 6:1 mixture of regioisomers; TBS = *tert*-butyldimethylsilyl; Ts = p-toluenesulfonyl;

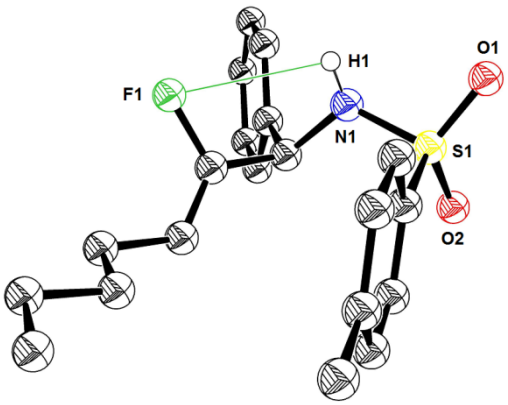


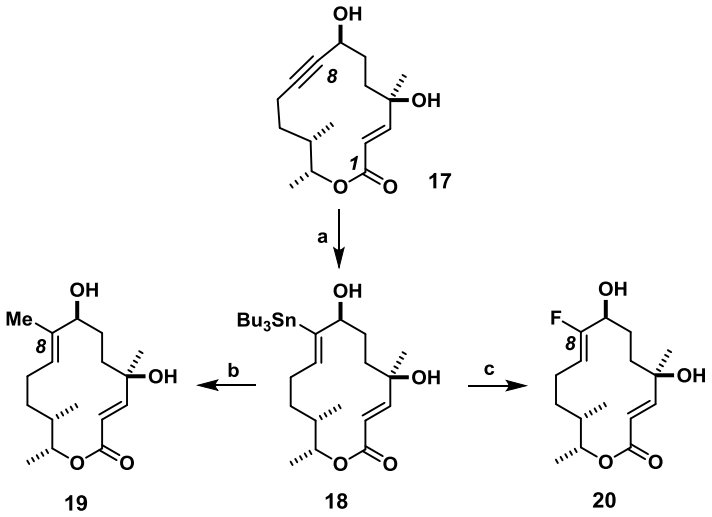
Figure 2. Structure of compound **14** in the solid state.

The scope of the new procedure is evident from the examples compiled in Figure 1. Protic sites in the substrate are well tolerated: this includes primary, secondary and tertiary alcohols at allylic, homoallylic and remote positions, as well as amides, carbamates, sulfonamides, and phosphonamides (see below); competing protodestannation was no serious issue in any of the cases investigated. Equally gratifying is the compatibility with functional groups such as aldehydes, esters, enoates, nitriles, phthalimide and even silyl ethers. These common protecting groups are

10.1002/chem.201605444

endangered by any recipe that comprises nucleophilic anions (most notably fluoride) or eventually releases acids such as HOTf or HF; moreover, they are cleaved when F-TEDA-BF_4 alone is used as [F^+] source.[22] Likewise, the sensitive doubly allylic alcohol in **10** proved stable and the pre-existing alkene passed uncompromised. Finally, compound **16** shows that the new procedure is not limited to alkenylstannanes bearing an allylic –OH or –NHR substituent but also works for "ordinary" substrates of this type.

The stereospecific nature of the fluorination was conclusively demonstrated by X-ray diffraction of compound **14** (Figure 2) and its stannylated precursor (see the Supporting Information), which are both *Z*-configured.[28] Another noteworthy feature of the structure of **14** in the solid state is the hydrogen bond between the sulfonamide NH proton and the flanking fluoride (2.671 Å). This interaction seems to impose a preferred conformation on the compound,[29] which is particularly relevant for the use of fluoroalkenes as peptide isosteres (see below).

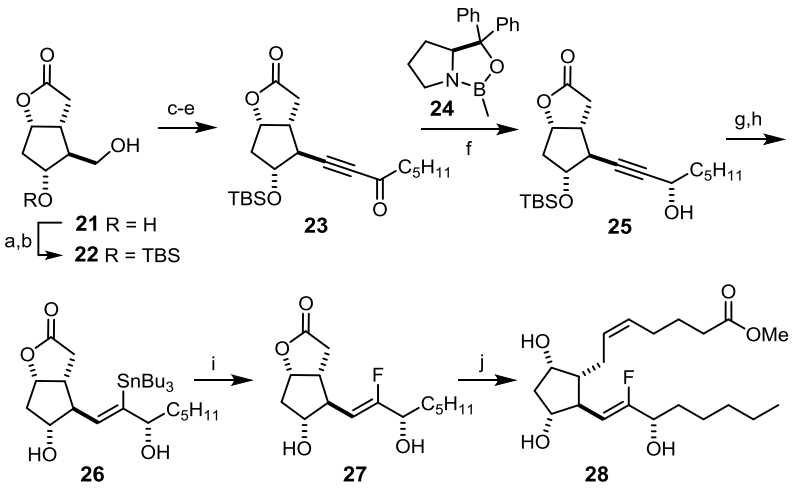


Scheme 3. a) Bu_3SnH, $[Cp^*RuCl_2]_n$ (5 mol%), CH_2Cl_2, 83%; b) $Pd(PPh_3)_4$ (5 mol%), $[Ph_2PO_2][NBu_4]$, CuTC, MeI, DMF, 92%; c) F-TEDA-PF_6, $AgOP(O)Ph_2$, acetone, 84%

The significance of the new method is further illustrated by selected applications to natural product chemistry. In a first foray, we prepared compound **20** as an analogue of the antibiotic 5,6-dihydrocineromycin B (**19**), in which the C8 methyl branch of the natural product is formally replaced by a stabilizing fluorine substituent.[30] As shown in Scheme 3, the alkenyltin derivative **18** formed by

10.1002/chem.201605444

hydroxyl-directed *trans*-hydrostannation of cycloalkyne **17** serves as common intermediate;[5] **17**, in turn is readily prepared by ring closing alkyne metathesis.[31,32] Fluoroalkene **20** complements a series of non-natural analogues of 5,6-dihydrocineromycin B (**19**) previously prepared in this laboratory;[5,6] collectively, these compounds illustrate the versatility of the emerging *trans*-addition chemistry in the context of diverted total synthesis.[33] As expected, the late-stage fluorination proceeded well in the presence of the two unprotected alcohols and the enoate subunit comprised in the macrocyclic ring of stannane **18**.



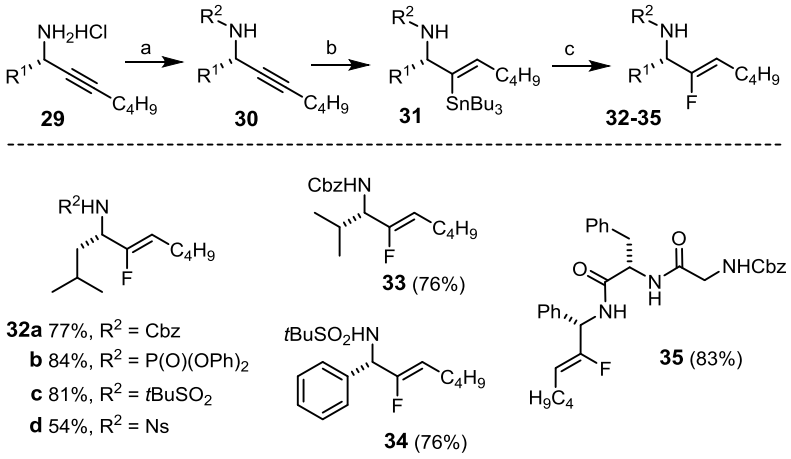
Scheme 4. a) TBSCl, imidazole, DMF; b) HOAc, aq. THF, 58% (over both steps); c) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60°C → RT; d) $(MeO)_2P(O)CHN_2$, KO*t*Bu, THF, −78°C → RT, 66% (over both steps); e) $PhSC(O)C_5H_{11}$, $(dppf)PdCl_2$ (10 mol%), $(2\text{-furyl})_3P$ (25 mol%), CuI, DMF/Et_3N (5:1), 68%; f) **24**, $BH_3{\cdot}Me_2S$, THF, −30°C, 82% (dr > 20:1); g) Bu_3SnH, $[Cp^*RuCl]_4$ (5 mol%), CH_2Cl_2, 62%; h) $TBAF{\cdot}3H_2O$, THF, 0°C → RT, 77%; i) F-TEDA-PF_6, $AgOP(O)Ph_2$, acetone, 67%; j) see ref.[34]; Cp* = pentamethylcyclopentadienyl; dppf = 1,1′-ferrocenediyl-bis(diphenylphosphine); TBAF = tetra-*n*-butylammonium fluoride

Next, we targeted compound **27** which is a known advanced building block for the synthesis of 14-fluoro-prostaglandin $F_{2\alpha}$ methyl ester (**28**); this analogue of natural PGE $F_{2\alpha}$ exhibits pronounced antifertility but reduced smooth-muscle activity.[34,35] Commercial Corey lactone **21** served as convenient point of departure,[36] which was converted into ynoate **23** by routine operations. CBS-reduction nicely set the (15*S*)-configuration (dr > 20:1),[37] a critical determinant for PG-receptor

10.1002/chem.201605444

affinity and specificity in mammals, and, in so doing, created the steering substituent for the subsequent *trans*-hydrostannation. As expected, this reaction furnished compound **26** essentially as a single isomer, which was desilylated prior to treatment with F-TEDA-PF_6/$AgOP(O)Ph_2$. Once again, the reaction proceeded smoothly in the presence of two unprotected secondary alcohols, which almost certainly preclude application of any other method for fluorodestannation known prior to this work.

From the conceptual viewpoint, a brief comparison with the literature route is informative, which used fluoroacetic acid as key building block for the preparation of **27**.[34] After conversion into a suitable phosphonate reagent, incorporation into the prostaglandin framework relied on a Horner-Emmons olefination that proved stereo-unselective and actually favored the undesired fluoroalkene isomer to a large extent (64:10); for its elaboration into **27**, the fluorine tag had to be carried through seven linear operations. The new strategy shown in Scheme 4 is orthogonal in that it introduces the fluorine substituent in the final step and avoids any selectivity issues by taking advantage of the virtues of ruthenium catalyzed alkyne *trans* hydrometalation.[12]



Scheme 5. a) see the Supporting Information; b) Bu_3SnH, $[Cp^*RuCl]_4$ (1 mol%), CH_2Cl_2; c) F-TEDA-PF_6, $AgOP(O)Ph_2$, acetone; Cbz = benzyloxycarbonyl; Ns = 2-nitrophenylsulfonyl

The use of small fluorinated building blocks also dominates the preparation of α-amino substituted fluoroalkene derivatives as non-hydrolyzable, lipophilic and conformationally rigid peptide isosteres for biochemical, biophysical and medicinal research.[9,38] Therefore it seemed worthwhile to check if

the new methodology provides opportunities in this area too. For proof-of-concept, we prepared several *N*-protected leucine- (**32**), valine- (**33**) and phenylalanine surrogates (**34**),[39] as well as a more elaborate tripeptide isostere (**35**) (Scheme 5). To this end, a series of secondary propargyl amines **29** was prepared by recourse to known methodology;[40] it is emphasized that the hexynyl residue in these model compounds was chosen only for practicality reasons. They were then either N-acylated with one of the protecting groups commonly used in peptide chemistry or coupled to a small peptide sequence (Z-Gly-Phe). The subsequent hydrostannations furnished the α,*trans*-adducts with high selectivity, which shows that the protic amide (peptide), sulfonamide or phosphonamide groups are adequate steering substituents for the chosen $[Cp^*RuCl]_4$ catalyst. The final introduction of the fluorine substituent with the help of F-TEDA-PF_6/AgOP(O)Ph_2 also worked well; only in the case of **35** was the crude product no more than ca. 80% pure, whereas protodestannation was subordinate in all other instances. In any event, this case study shows the ready availability of a library of valuable synthons and peptide isosteres by late-stage fluorination, which none of the established methods would be able to provide.[12,41]

Hence we conclude that the simple switch from AgOTf to AgOP(O)Ph_2 upgrades the performance and functional group compatibility of late-stage electrophilic fluorination of alkenyl tin derivatives to a significant extent; for the first time, even protic sites are tolerated without risking protodestannation to take over. When allied with powerful modern stannylation techniques such as the ruthenium catalyzed *trans*-hydrostannation of internal alkynes, this new procedure enables functionalization of elaborate and polyfunctionalized compounds, as illustrated by the preparation of a fluorinated macrolide antibiotic, a fluorinated prostaglandin derivative and a set of fluorinated amino acid and peptide isosteres. Further applications of this and related methodologies will be reported in due course.

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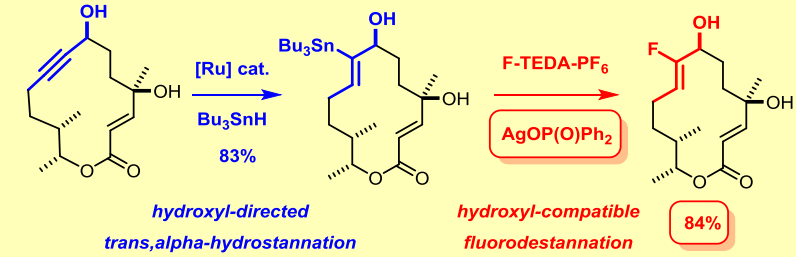
10.1002/chem.201605444

For the Table of Contents



On (late) stage: A highly regioselective net *trans*-addition of HF across a triple bond is achieved by a sequence of ruthenium-catalyzed *trans*-hydrostannation followed by fluorodestannation; the latter reaction hinges on the use of silver phosphinate as non-nucleophilic tin scavenger, whereas other promotors engender massive protodestannation if protic sites are present in the substrate.

Keywords: fluorination · peptide isosteres · silver · tin · *trans*-addition

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