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Enolizable β-Fluoroenones: Synthesis and Asymmetric 1,2-Reduction

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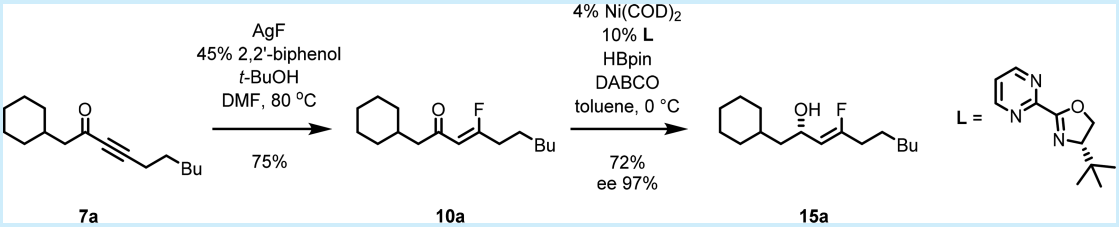
Supporting Information

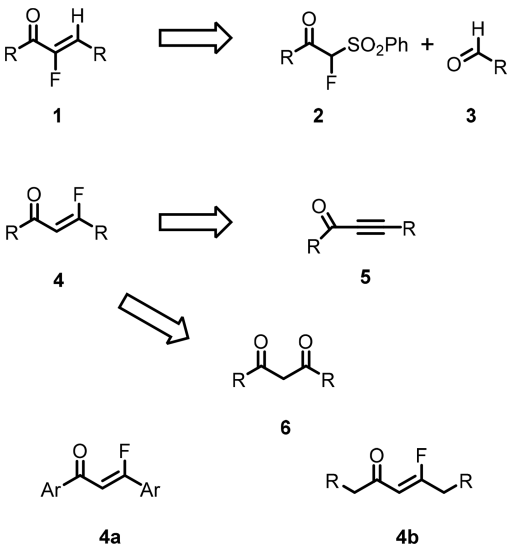


ABSTRACT: The hydrofluorination of enolizable ynones with AgF in *t*-BuOH/DMF is reported. The formation of furans as side products can be suppressed using 2,2′-biphenol. The corresponding β-fluoroenones were obtained with good *Z*-selectivity. A variety of functional groups are tolerated. β-Fluoroenones are vinylogous acid fluorides whose hydrolysis to vinylogous acids can be avoided under the reported reaction conditions. The asymmetric 1,2-reduction of β-fluoroenones to 3-fluoroallylic alcohols is possible with pinacolborane and a Ni(0) catalyst prepared from a pyrimidyloxazoline ligand.

The establishment of methods for the selective introduction of C−F bonds in organic molecules is an important task and constitutes a significant synthetic challenge due to the numerous applications of organofluorine compounds in life and material sciences.[1−3] Fluoroolefins are used as monomers in polymer chemistry and peptide mimics[4] and can be synthesized by olefin metathesis[5] or by olefination[6] of a carbonyl precursor. Methods for the synthesis of fluoroolefins as peptide mimetics require stereoselectivity (*E*,*Z*) and functional group tolerance (e.g., protected amines).

Fluoroenones such as **1** and **4** are valuable building blocks for the synthesis of fluoroorganics (Scheme 1). While α-fluoroenones **1** are readily available, e.g., by Julia−Kocienski olefination[6] from sulfone **2** and aldehyde **3**, the synthesis of β-fluoroenones **4** is less well developed. The addition of HF (hydrofluorination) to ynones **5** is a promising solution to this problem. The use of a 1,3 dicarbonyl precursor **6** is limited to symmetrical 1,3-dicarbonyl compounds or at least monoaryl ketones in order to avoid the formation of regioisomers.[7] Aryl β-fluoroenones have been prepared from 1,2-allenic ketones using TBAF.[8] The reaction of β-fluoroacroyl chlorides with organo cuprates[9a] and the copper-catalyzed fluoroolefination of silyl enol ethers[9b] are other entries to β-fluoroenones. The addition of DMPU/HF to triple bonds has been reported for propiolic esters to generate β-fluoroacrylates.[10] The gold-catalyzed hydrofluorination of arylalkylalkynes[11] has not been reported for ynones. Hydrofluorinations using $Bu_4NH_2F_3$[12] or Au(I)−NHC catalysis[13] have been limited to the preparation of diaryl β-fluoroenones **4a**. Recently, the gold-catalyzed hydrofluorination of electron-deficient alkynes using RuPhos-AuCl and $Et_3N{\cdot}3HF$ has been reported.[14] Here, a more general method to synthesize enolizable dialkyl-β-fluoroenones **4b** is presented.

Scheme 1. Synthetic Routes to Fluoroenones



Ynone **7a** was chosen as an enolizable test substrate to optimize the reaction conditions for the hydrofluorination. All ynones used within this study were synthesized from the corresponding Weinreb amides (Supporting Information (SI)). For ynone **7a**, the carboxylic acid **8** was converted into the Weinreb amide **9**, which upon treatment with the lithiated 1-octyne gave the desired ynone **7a** (Scheme 2).

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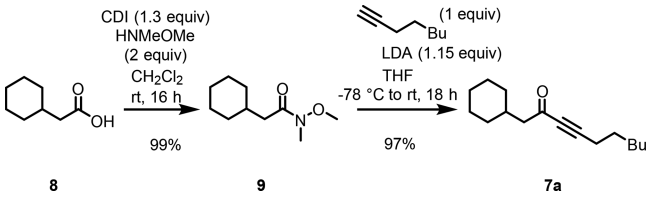
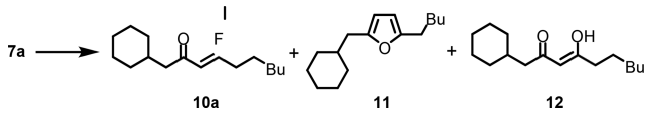
Scheme 2. Synthesis of Ynone 7a



The starting point for our hydrofluorination study was Jiang's observation that AgF in CH_3CN/H_2O leads to diaryl-β-fluoroenones **4a**.[15] With these conditions, the hydrofluorination of ynone **7a** led to a mixture of the (*Z*)-β-fluoro enone **10a** ($^3J_{\alpha HF}$ = 40 Hz), the furan **11**, and the β-hydroxy enone **12** (Table 1, entry 1).

Table 1. Optimizing Reaction Conditions for the Hydrofluorination of Ynone 7a



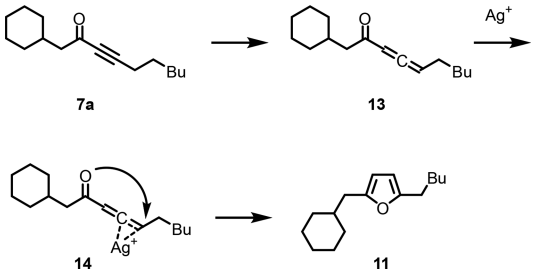
entry	conditions	yield of **10a** (%) (*Z*/*E*)	yield of **11** (%)	yield of **12** (%)
1	2 equiv of AgF, H_2O, DMF, 80 °C, 3.5 h	52 (7:1)	23	18
2	2 equiv of AgF, *t*-BuOH, DMF, 80 °C, 3.5 h	51 (5.4:1)	19	
3	2 equiv of AgF, 2 equiv of DTBPy[a] *t*-BuOH, CH_3CN, 80 °C, 2.5 h	18 (1:1.2)	55	
4	2 equiv of AgF, 0.1 equiv of BINOL *t*-BuOH, DMF, 80 °C, 5 h	74 (6.4:1)	2	
5	2 equiv of AgF, 2 equiv of BINOL *t*-BuOH, DMF, 80 °C, 5 h			
6	3 equiv of AgF, 0.45 equiv of 2,2′-biphenol, *t*-BuOH, DMF, 70 °C, 5 h	75 (10.0:1)	2	
7	RuPhosAuCl, $AgBF_4$, $Et_3N{\cdot}3HF$, *p*-Cl benzoic acid[b]	60 (19:1)		2

[a]DTBPy = 6,6′-di-*tert*-butylbipyridine. [b]$MeCN/CH_2Cl_2$ 4:1, 24 h, rt.[14]

The formation of the vinylogous acid **12** by partial hydrolysis of the vinylogous acid fluoride with water as cosolvent is not surprising. Remarkably, the hydrolysis was not complete under Jiang's conditions. Substitution of water by *t*-BuOH suppresses the hydrolysis side reaction (entry 2). Attempts to improve the reaction by addition of chelating ligands were undertaken next. For 6,6′-di-*t*-Bu-bipyridine the furan **11** was formed as the main product (entry 3). With 10% BINOL, the desired β-fluoroenone **10a** was produced in good yield and only with traces of side product (entry 4). The use of 2 equiv of BINOL, however, blocked the reaction (entry 5). With 2,2′-biphenol, the best yield was obtained (entry 6). Hydrofluorination using Toste's conditions[14] (entry 7) resulted in the formation of the desired product in moderate yield and good stereoselectivity. BINOL and 2,2′-biphenol can act as ligand and proton source.

The formation of furan **11** can be rationalized by rearrangement of the ynone **7a** to the allenone **13** under the reaction conditions (Scheme 3). The latter can undergo via **14**

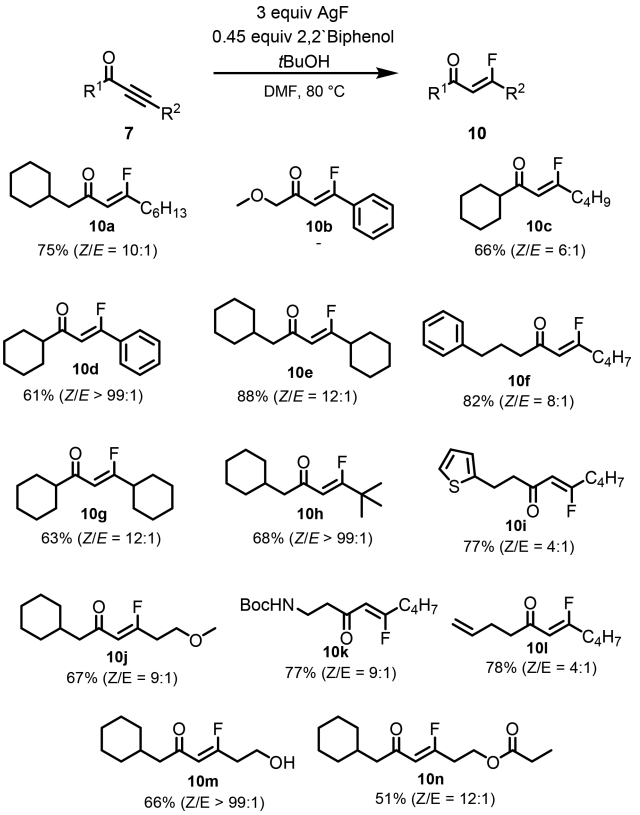
Scheme 3. Formation of the Furan Side Product 11



a Ag-mediated cyclization to form the 2,5-disubstituted furan.[16,17] The absence of an enolizable position in diaryl β-fluoroenones **4a** prohibits furan formation for these cases.

The scope and limitations of the optimized hydrofluorination conditions were studied for a series of ynones with different aliphatic substitution patterns and functional groups present (Scheme 4). Good to excellent *Z*/*E* selectivites were

Scheme 4. Scope and Limitations for Hydrofluorination of Ynones (7 → 10) Using Optimized Conditions



observed for all cases, except for **7b** where no hydrofluorination product **10b** could be obtained. A variety of functional groups were tolerated under the hydrofluorination conditions (**10i**, **10j**, **10k**, **10l**, **10m**, **10n**). Noteworthy is the excellent *Z*-selectivity for the case of the hydroxy-substituted substrate (**7m** → **10m**).

β-Fluoroenones could be valuable building blocks, e.g., as peptide mimetics, if a stereocontrolled functionalization could be achieved. In this context, a stereocontrolled 1,2-reduction of β-fluoroenones is of interest. This reaction is challenged by the competing 1,4-reduction, defluorination, and potential double bond *Z*/*E* isomerization. The stereocontrolled 1,2-reduction

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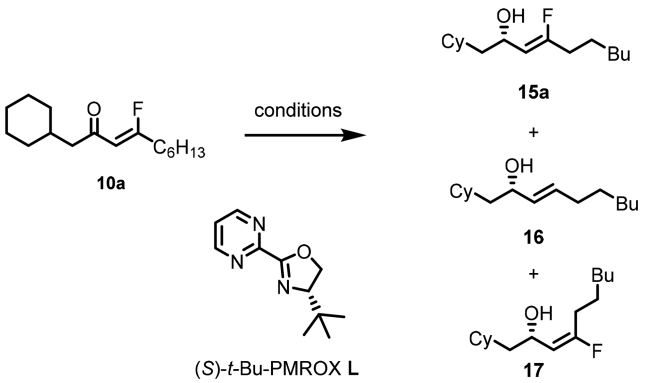
Org. Lett. XXXX, XXX, XXX−XXX

was studied and optimized for the case of the β-fluoroenone **10a** (Table 2). DIBAL-H was a suitable reagent for the racemic

Table 2. Optimizing Reaction Conditions for the Stereocontrolled 1,2-Reduction of β-Fluoroenone 10a



entry	conditions	yield of **15a** (%) (ee)	yield of **16** (%)	yield of **17** (%)
1[a]	1 equiv of DIBAH	75 (rac)		
2[b]	0.05 equiv of $RuCl_2$[(*S*)-DM-BINAP][(*S*)-DAIPEN]			
3[c]	0.05 equiv of RuCl(*p*-cymene)[Ts-DPEN]			
4[d]	1 equiv of (*S*)-(−)-*o*-Tol-CBS catalyst	99 (37)		
5[e]	3.6 equiv of (+)-*N*-methylephedrine	32 (−)		
6[f,g]	0.02 equiv of $Ni(COD)_2$, 0.024 equiv of **L**[j]	20 (83)	26	
7[f,h]	0.04 equiv of $Ni(COD)_2$, 0.10 equiv of **L**[j]	72 (97)	6	3
8[h,i]	0.04 equiv of $Ni(COD)_2$, 0.10 equiv of **L**[j]			

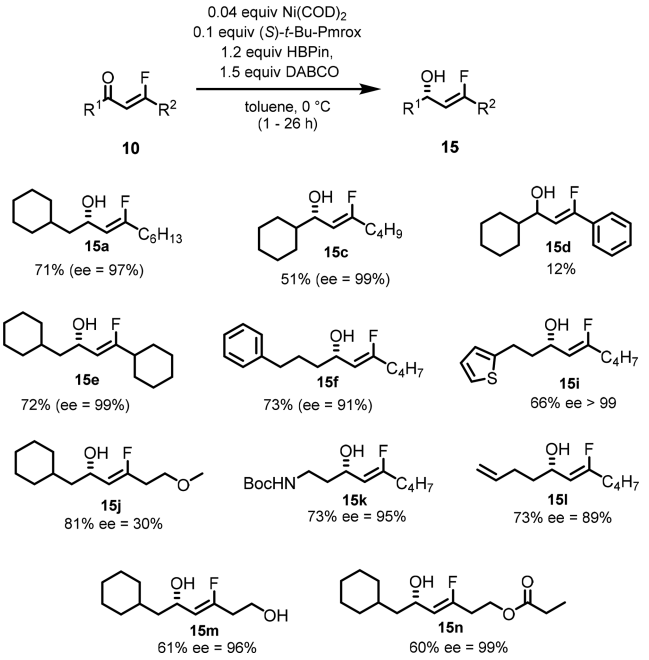
[a]Et_2O, −10 °C. [b]0.05 equiv of KO*t*Bu, H_2 (5 bar), *i*PrOH, 25 °C. [c]1.5 equiv of HCO_2H/NEt_3, CH_3CN, 25 °C. [d]1 equiv of $BH_3{\cdot}SMe_2$, THF, 0 °C. [e]3.3 equiv of LAH, 7.2 equiv pf 1,2,3,4-tetrahydrochinoline, Et_2O, −78 to +50 °C. [f]1.2 equiv of HBpin, 1.5 equiv of DABCO, toluene. [g]−25 °C. [h]0 °C. [i]1.5 equiv of DABCO, toluene. [j]**L** = (*S*)-*t*-Bu-PMROX.

1,2-reduction (entry 1).[18] Ru-catalyzed hydrogenation of β-fluoroenone **10a** under various conditions gave no conversion of the starting material (entries 2 and 3).[19]

The CBS reduction provided the desired fluoroallylic alcohol **15a** in very good yield, however, with only low enantioselectivity (entry 4).[20] A $LiAlH_4$ reduction using *N*-methylephedrine as chiral ligand was less effective (entry 5).[21] The NiH/PMROX-catalyzed 1,2-reduction of **10a** using Zhu's conditions[22] gave the desired product **15a** in low yield and good enantioselectivity (entry 6). Under these conditions, the defluorinated allylic alcohol **16** was formed as side product in nearly equal amounts. It was found that changing the catalyst loading to 4% $Ni(COD)_2$ and 10% (*S*)-*t*-Bu-PMROX resulted in a very good yield and excellent enantioselectivity (entry 7). Only traces of side products **16** and **17** were observed in this case. Without borane, no conversion of the starting material was observed (entry 8). The absolute configuration of **15a** was determined using Mosher-NMR analysis[23] (SI) and is in accordance with the prediction made by Zhu.[22]

The scope and limitations of the optimized conditions for the asymmetric 1,2-reduction were studied for a series of β-fluoroenones **10** (Scheme 5). Excellent enantioselectivities

Scheme 5. Scope and Limitations for Asymmetric 1,2-Reduction of β-Fluoroenones(10 → 15) Using Optimized Conditions

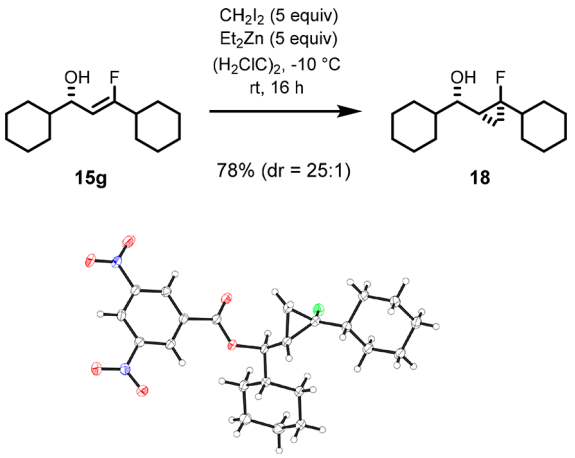


were obtained for the 3-fluoroallylic alcohols **15** for different aliphatic substitution patterns in the α′-position of the ketone, while an aromatic substituent in β-position (**15d**) resulted in low yield and no significant ee. A variety of functional groups were tolerated under the hydrofluorination conditions (**15i**, **15j**, **15k**, **15l**, **15m**, **15n**).

Chiral 3-fluoroallylic alcohols **15** offer a variety of synthetic applications in fluoroorganics. One example is the stereocontrolled cyclopropanation (**15g** → **18**), which exhibits a remarkably high diastereoselectivity (Scheme 6).

The relative configuration of the cyclopropanation product **18** was secured by X-ray crystallography of its 3,5-dinitrobenzoate (SI). While no stereoselective cyclopropanation of 3-fluoroallylic alcohols has been reported, the stereochemical outcome for (**15g** → **18**) is in agreement

Scheme 6. Diastereoselective Cyclopropanation of Fluoroallylic Alcohol 15g and X-ray Crystal Structure of the 3,5-Dinitrobenzoate of 18



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with the related Furukawa cyclopropanation of the corresponding 3-iodoallylic alcohols and 3-alkylallylic alcohols.[23,24]

In summary, the (*Z*)-selective hydrofluorination of enolizable ynones to *β*-fluoro enones has been achieved. The formation of furan byproducts was suppressed using 2,2′-biphenol as additive. An enantioselective 1,2-reduction of the *β*-fluoroenones to 3-fluoroallylic alcohols is possible with pinacolborane as hydride donor and a Ni(0)catalyst prepared from $Ni(COD)_2$ and (*S*)-*t*-Bu-PMROX. Both the hydrofluorination and the asymmetric 1,2-reduction exhibit a good functional group compatibility. These results offer synthetic access to chiral 3-fluoroallylic alcohols. The latter could have various applications in the synthesis of chiral fluoroorganics. One example given here is the diastereoselective Furukawa cyclopropanation to provide chiral fluorocyclopropanes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02435.

Experimental details; spectroscopic and analytical data of all new compounds (PDF)

Accession Codes

CCDC 1824992 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Author Contributions

Experimental work was done by L.Z. and C.M.; X-ray crystallography was done by K.H.

Notes

The authors declare no competing financial interest.

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