Electrochemical Synthesis of Glycosyl Fluorides Using Sulfur(VI) Hexafluoride as the Fluorinating Agent

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Abstract

This manuscript describes electrochemical synthesis of 17 different glycosyl fluorides in 73–98% yield on up to 5 g scale that relies on using SF_6 as an inexpensive and safe fluorinating agent. Subsequently carried cyclic voltammetry and related mechanistic studies suggest that the generated through the cathodic reduction of SF_6 active fluorinating species are transient under these reductive conditions, and that the sulfur and fluoride by-products are effectively scavenged by Zn(II) to generate benign salts.

Graphical Abstract
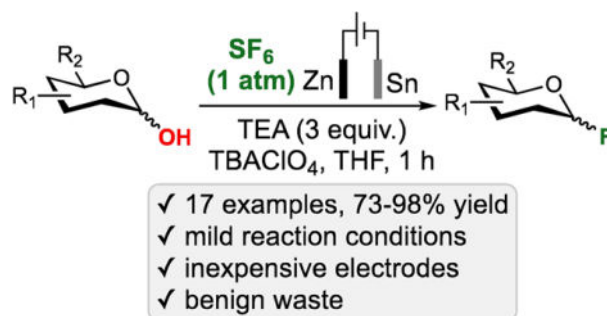
Keywords

Electrochemical; Fluorination; Sulfur(VI) Hexafluoride; Glycosyl Fluorides; Reduction

INTRODUCTION

With the increasing awareness about the impacts of the atmospheric greenhouse gasses on the climate changes, many recent efforts of the scientific community have focused on reducing the amount of greenhouse gas emission. Among the various problems associated with this topic that modern science and engineering face, the utilization of sulfur(VI) hexafluoride is one of the significant challenges.[1] Sulfur (VI) hexafluoride (SF_6), is a

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very stable and nontoxic gas that is produced on an industrial scale and used worldwide as a dielectric insulator.[2] Due to its chemical stability and high susceptibility to infrared light excitation, SF_6 is considered to be one of the strongest greenhouse gasses that is regulated by the Kyoto protocol.[3] Several recent studies have examined the possibility of degrading or converting SF_6; however, a feasible protocol is yet to emerge from these studies. The inertness of this gas presents a significant challenge as the majority of the examples describing SF_6 activation involve extreme reaction conditions (very high temperatures, pressures or UV radiation <190 nm) that are not desirable for the modern organic processes.[4] In addition, the decomposition of SF_6 results in fluorine and sulfur-containing waste, disposal of which is often a challenge. Therefore, the processes that do not simply decompose SF_6, but also take advantage of SF_6 as a chemical entity are highly desired.[5–10]

One of the practical uses of SF_6 as a chemical reagent was recently reported by Jamison and McTeague who demonstrated that photoredox activation of SF_6 with Ir(III)-based catalysts and blue LED light may result in active fluorinating species that mediate deoxyfluorination of allylic alcohols (Scheme 1A).[6] The idea of exploring SF_6 to generate stoichiometric fluorinating reagents for deoxyfluorination was subsequently explored by the Rueping group[7a] and Braun and Kemnitz.[7b] In addition, several different studies including the reduction of SF_6 with phosphide anions by Speed and coworkers[5i] and reductive deconstruction of SF_6 by Crimmin and coworkers[5j] have been reported. In parallel to the aforementioned studies, the Wagenknecht group described several different applications of SF_6 for the photochemical pentafluorosulfanylation of alkenes.[8]

Our group has long-standing interests in developing new organocatalytic methods and their application for the synthesis of carbohydrate derivatives.[10,11] As a part of these efforts, we recently investigated the possibility of developing new approach for the synthesis of glycosyl fluorides.[11] Glycosyl fluorides represent a unique class of glycosyl donors, which are stable to a variety of conditions, but could serve as highly active glycosylating agents upon activation with fluorophilic Lewis acids.[12] While there are many methods that are available for the synthesis of glycosyl fluorides, the deoxyfluorination-based reactions involving (diethylamino)sulfur(IV) trifluoride (DAST)[13] or HF•Py[14] are by far the most common and general. The use of these highly corrosive, reactive and toxic reagents for larger scale processes is not ideal, and our group recently explored the possibility of utilizing nontoxic and inexpensive SF_6 as a safer alternative. By using 4,4'-dimethoxybenzophenone as an inexpensive photocatalyst and DIPEA as the reducing agent, we achieved a photochemical activation of SF_6 with UVA LED source (λ_{max}=365 nm) that resulted in efficient fluorination of 16 protected carbohydrates containing a hydroxyl group at the anomeric position.[11] While this represented an efficient and safe method for utilizing SF_6 and producing valuable carbohydrate-based building blocks, this transformation had several limitations in comparison to the more traditionally employed DAST-mediated 2-deoxyfluorination reactions. These limitations included significantly extended reaction times, in particular on a larger scale, and, as the result of it, lower conversions. In addition, the reaction required using a large excess of DIEA (10 equiv.) and resulted in multiple side-products including the photocatalyst decomposition products and sulfur-containing waste. These limitations prompted us to search for the alternative new methods to achieve

SF$_6$ activation, and this manuscript describes electrochemical deoxyfluorination with SF$_6$ leading to the fast, efficient and scalable formation of glycosyl fluorides.[15] The use of zinc sacrificial anode provides an effective mean to scavenge sulfur and fluoride waste to form benign Zn(II) sulfides and fluorides, and this protocol holds promise as an inexpensive, safe and mild method for utilization of SF$_6$ for the fluorination of organic molecules.

RESULTS AND DISCUSSION

Our study commenced with subjecting the armed 2,3,4,6-tetra-O-benzyl-D-galactose **1a** to galvanostatic electrolysis in the atmosphere of SF$_6$ using platinum (Pt) anode(+) and cathode(−), DIPEA as the base, tetrabutylammonium perchlorate (TBAClO$_4$) as the electrolyte, and DCE as the solvent (Table 1, entry 1). Gratifyingly, the exposure of **1a** to the aforementioned reaction conditions for 1 h resulted in the formation of desired product **2a** albeit in only 32% yield. In attempts to optimize these conditions, we evaluated various solvents (cf. Table S1) and observed that using THF resulted in slightly faster reaction with ~70% consumption of the starting material and 35% yield of **2a** (Table 1, entry 2). The NMR analysis of the crude reaction indicated the formation of unidentified fluorine-containing debenzylation side-products in addition to **2a**. We surmised that the debenzylation reactions happen due to the anodic oxidation of **1a** and **2a**. Therefore, to minimize these undesired oxidation reactions, the use of sacrificial zinc (Zn) anode, which would get oxidized to produce Zn^{2+} cations, was evaluated next (Table 1, entry 3).[16] Excitingly, this modification dramatically improved the yield of **2a** and eliminated the formation of the side-products. Our further optimizations were focused on making this process more practical and identifying a less expensive type of the cathode (entries 4–6 and Table S2). While the use of C(−) instead of Pt(−) cathode led to a significant reduction in the yield (entry 4), we found that Sn(−) cathode provided **2a** in 84% yield (entry 5). Further attempts to optimize this yield by using magnesium as sacrificial anode[17] was not successful (entry 6), and, therefore, Zn(+) anode and Sn(−) cathode were selected as the optimal electrodes and other reaction parameters were optimized next.

While our attempts to improve the yield by replacing TBAClO$_4$ with other salts were not successful, other electrolytes such as TBAPF$_6$ were found to be compatible with the reaction conditions (cf. Table S4). It was also observed that the electrolysis time and the nature/quantities of the base could be used to improve the yield of **2a** (entries 7–9 and Table S3 Thus, **2a** could be produced in 93% yield if the amounts of DIEA and TBAClO$_4$ are reduced to 3 equivalents and 0.15 M, respectively, and the solution is electrolyzed for 1 h instead of 30 min (entry 7). DIEA could be substituted with less expensive triethylamine without the decrease in the yield of **2a** (entry 8). In addition, our subsequent studies indicated that triethylamine is preferred over DIEA for the fluorination of acetylated and PMB protected galactose derivatives **1k** and **1h** (Table S6). Amine base is not an essential component as the reaction progresses to 67% in the absence of triethylamine (Table 1, entry 9). However, the use of the amine base ensures a full progression of the reaction either by preventing the electrode passivation or by promoting the solvation of Zn^{2+} cation (Figure S1).

With the optimal conditions for the electrochemical fluorination of **1a** in hand, our subsequent studies were focused on evaluating the substrate scope of this reaction (Scheme

2). This evaluation revealed that this method is suitable for a variety of sugars and protecting groups typically employed in carbohydrate synthesis. The deoxyfluorination of perbenzylated D-galactose, D-glucose, D-mannose, D-xylose, L-fucose and L-rhamnose derivatives **1a–1f** and D-ribose derivative **1g** proceeded in excellent yields (91–98%) and resulted in the corresponding products **2a–2g**. While the PMB protecting groups are sensitive to both oxidative and reductive conditions, the deoxyfluorination of PMB-protected D-galactose, D-glucose and D-mannose derivatives **1h–1j** proceeded cleanly to provide the corresponding products in 96% yield.

The electrochemical fluorination conditions did not affect the acid-sensitive benzylidene acetal moiety present in **1p**, and glycosidic linkage present in perbenzylated cellobiose derivative **1q**, and the corresponding products were obtained in 96% and 84% yield correspondingly. Finally, the electrochemical fluorination conditions were compatible with disarmed peracetylated and perbenzylated glycosides **1k–1o** that were previously found to be significantly less reactive under the photochemical conditions, and the corresponding products **2k–2o** were obtained in 73–84% yields. It is important to emphasize that these transformations are amenable to scale up, and we were able to adopt an experimental setup developed by Baran and coworkers [18] and modified it to carry a 5 g scale deoxyfluorination of D-glucose derivative **1b** in 98% yield (*cf.* SI-III-e for additional details).

The results summarized in Scheme 2 suggest that the electrochemical fluorination with SF_6 proceeds with excellent efficiencies and under mild conditions, which makes it favorably comparable with the other popular deoxyfluorination protocols (*cf.* Table S8). Therefore, our subsequent studies were focused on understanding the reaction mechanism and showcasing the safety of this protocol by demonstrating that no toxic SF_n and SO_mF_n species are accumulated throughout the reaction (*cf.* Figure 1). Similar to the photochemical deoxyfluorination with SF_6, no active fluorinating species, such as SF_4, were detected by the ^{19}F NMR throughout the reaction. A control experiment with Zn(II) fluoride instead of SF_6 demonstrated that the presence of salt alone does not lead to the formation of glycosyl fluorides (cf. SI-Vb). The continuous electrolysis was essential for the progression of this reaction, and the formation of **2b** from **1b** stopped when the current was turned off (Figure 1A). While the photochemical activation of SF_6 with DMBP led to significant accumulation of the active fluorination species that reacted with triphenylphosphine to produce difluorotriphenylphosphine, only trace amounts of this compound were detected by ^{31}P and ^{19}F NMR after the treatment of the crude electrochemical fluorination mixture with PPh_3 (Figure 1B). This suggests that electrochemical conditions prevent accumulation of the active SF_n and SO_mF_n species by reducing them to Zn(II) fluorides and sulfides. To demonstrate this and to understand the role of the amine base in this process, we carried series of cyclic voltammetry (CV) studies (*cf.* Figure 1C and 1D, and Figure S6–S12). Based on the observation from chemical experiments, our initial assumption was that the amine base is not directly involved in the catalytic cycle, but it is important for preventing the electrode passivation. We first attempted to identify the half reduction potential of SF_6 by adopting the previously published experimental setup (Figure S6).[15b] The voltammogram showed irreversible reduction of SF_6 around –2.4 V (vs Fc^+/Fc), which is similar to the previously measured value (–2.17 V vs Fc^+/Fc). CV data for the reduction of SF_6 with

zinc as counter electrode in the absence of Et_3N revealed the current attenuation in the chronological order of the scan (Figure 1C). This suggests the electrode passivation via the formation of nonconducting zinc salts on its surface, which leads to the increased internal resistance. As expected, we observed consistent current throughout the scans when the CV experiment was repeated with Pt as counter electrode (Figure S8). Next, we conducted the CV experiment in the presence of triethyl amine for the reduction of SF_6 with zinc as counter electrode (Figure 1D). The current was dependent on the scan rate rather than the chronological order of the scan. With the slower scan rate, triethylamine has more time to either promote the solvation of zinc cation or scavenge the deposited zinc salts. This would prevent the electrode passivation and keep the resistance in the cell relatively steady, which enhances the current flow compared to faster scan rate. Since our method is under galvanostatic condition, triethylamine keeps the voltage steady and prevents the undesired reduction reactions. Based on these considerations, the tentative mechanism of this transformation is proposed in Figure 1D. SF_6 undergoes cathodic reduction that leads to SF_4 or related S(IV)- or S(II)-based active fluorinating agents. The various SF_n or SO_mF_n species resulting from the reduction of SF_6 and deoxyfluorination undergo subsequent reduction to S^{2-} and F^- anions that undergo binding to Zn^{2+} cations to form zinc(II) sulfides and fluorides and their complexes with triethylamine.

CONCLUSION

In conclusion, we have developed a mild and highly efficient protocol for the electrochemical utilization of SF_6 leading to the formation of 17 different glycosyl fluorides in 73–98% yield. To demonstrate the utility of this transformation, 5g scale synthesis of 2,3,4,6-*O*-tetrabenzyl-*D*-glucopyranosyl fluoride was accomplished in 98% yield. Subsequently carried cyclic voltammetry and other mechanistic studies were consistent with the cathodic reduction of sulfur(VI) fluoride and oxidation of Zn anode. These studies suggest that the generated from SF_6 active fluorinating species are transient under these reductive conditions, and that the sulfur and fluoride by-products are effectively scavenged by Zn(II) to generate benign and unreactive salts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources

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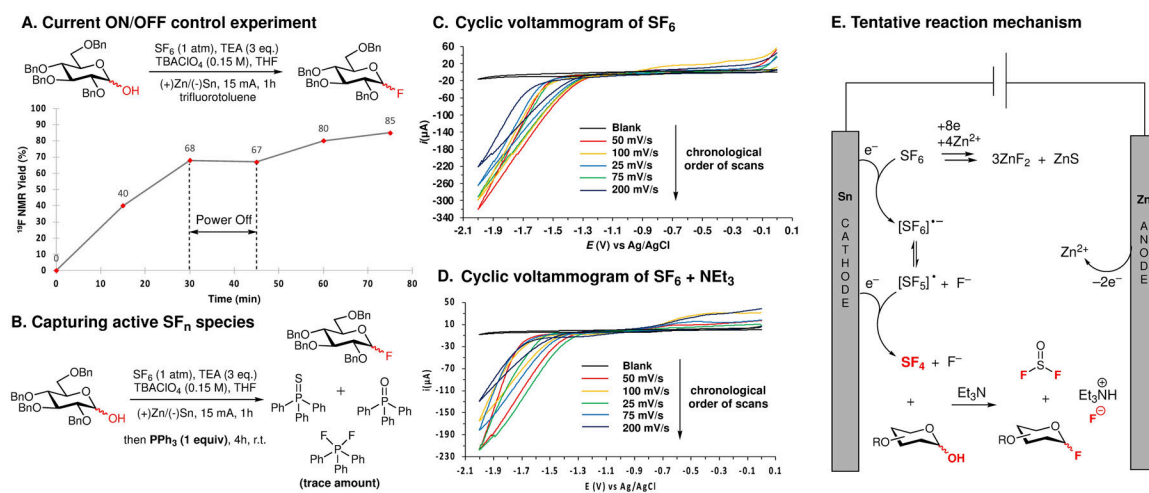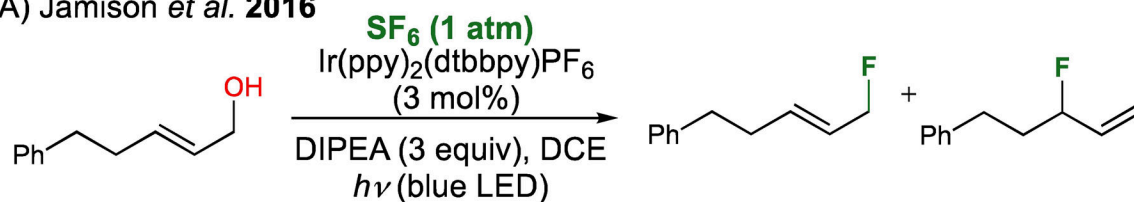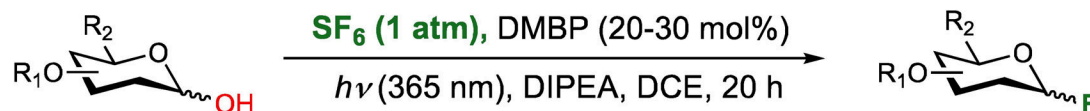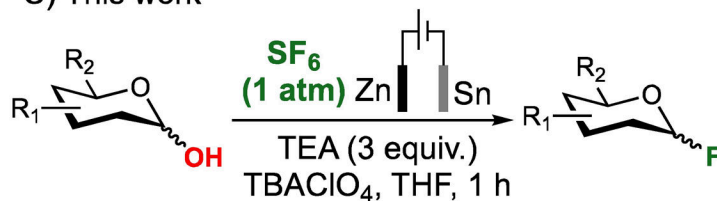
Figure 1.
Studies focused on understanding the reaction mechanism

A) Jamison *et al.* 2016

SF$_6$ (1 atm)
Ir(ppy)$_2$(dtbbpy)PF$_6$
(3 mol%)
⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯
DIPEA (3 equiv), DCE
$h\nu$ (blue LED)

B) Nagorny *et al.* 2021

SF$_6$ (1 atm), DMBP (20-30 mol%)
⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯
$h\nu$ (365 nm), DIPEA, DCE, 20 h

C) This work

SF$_6$
(1 atm) Zn ‖ Sn
⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯
TEA (3 equiv.)
TBAClO$_4$, THF, 1 h

✓ 17 examples, 73-98% yield
✓ fast reaction times
✓ mild reaction conditions
✓ inexpensive electrodes
✓ benign waste

Scheme 1.
Summary of deoxyfluorination with SF$_6$

SF₆ (1 atm), TEA (3 eq.)
TBAClO₄ (0.15 M), THF (3 mL)

(+)Zn/(−)Sn, 15 mA, 1h

1a-q → **2a-q**

2a
94%
(α:β = 1:1.6)

2b
98% **(5 g scale)**[b]
(α:β = 1:2.3)

2c
95%
(α:β = 22:1)

2d
98%
(α:β = 1:2.6)

2e
91%
(α:β = 2.3:1)

2f
93%
(α:β = 19:1)

2g
94%
(α:β = 1:17)

2h
96%
(α:β = 1:1.2)

2i
96%
(α:β = 1:1.4)

2j
96%
(α:β = 24:1)

2k
73%
(α:β = 1.9:1)

2l
76%
(α:β = 1:2.4)

2m
81%
(α:β = 20:1)

2n
79%
(α:β = 20:1)

2o
84%
(α:β = 21:1)

2p
96%
(α:β = 26:1)

2q
84%
(α:β = 1:3.3)
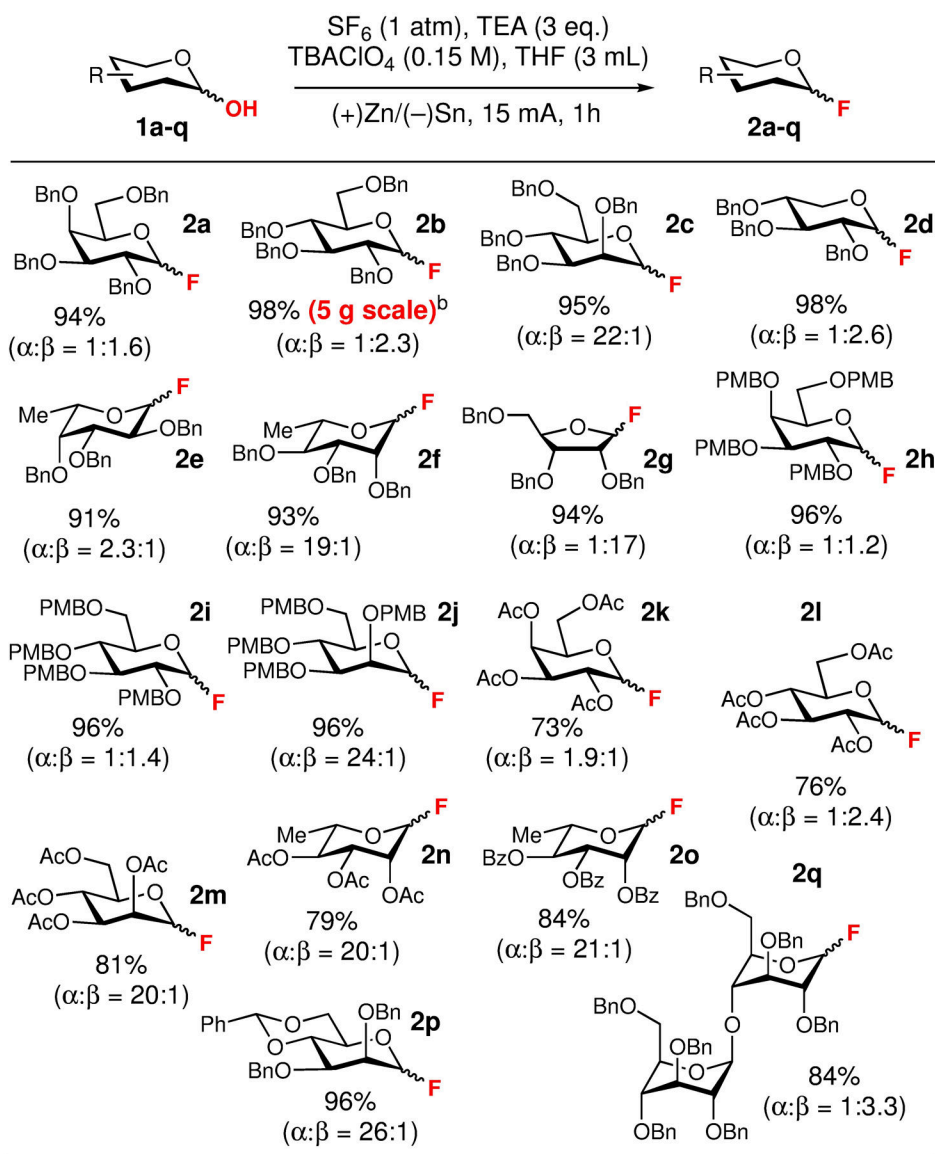
Scheme 2.
Substrate scope[a]

[a]The provided yields and diastereomeric ratios represent the average values over two runs on 0.1 mmol scale. For the specific yields and selectivities obtained for each individual run please refer to the SI. [b]This reaction was performed on 9.25 mmol (5.0 g) scale.

Table 1.

Reaction condition optimization
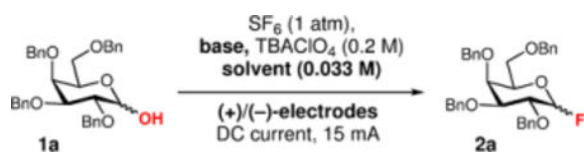
Entry	Conditions[a]	Yield[b]
1	(+)Pt/(−)Pt, DIEA (5 eq.), DCE, 1 h	32%[c]
2	(+)Pt/(−)Pt, DIEA (5 eq.) THF, 45 min	35% ($\alpha : \beta = 1:2.1$)[c]
3	(+)Zn/(−)Pt, DIEA (5 eq.) THF, 30 min	94% ($\alpha : \beta = 1 : 1.3$)
4	(+)Zn/(−)C, DIEA (5 eq.) THF, 30 min	22% ($\alpha : \beta = 1 : 1.3$)
5	(+)Zn/(−)Sn, DIEA (5 eq.) THF, 30 min	84% ($\alpha : \beta = 1 : 1.5$)
6	(+)Mg/(−)Sn, DIEA (5 eq.) THF, 30 min	66% ($\alpha : \beta = 1 : 1.2$)
7[d]	(+)Zn/(−)Sn, DIEA (3 eq.) THF, 1 h	93% ($\alpha : \beta = 1 : 1.3$)
8[d]	(+)Zn/(−)Sn, NEt$_3$ (3 eq.) THF, 1 h	93% ($\alpha : \beta = 1 : 1.6$)
9	(+)Zn/(−)Sn, no base THF, 1 h	67% ($\alpha : \beta = 1 : 1.2$)

[a]The reactions were carried on 0.1 mmol scale.

[b]Represents isolated yield.

[c]Determined by ^{19}F NMR with trifluorotoluene as internal standard.

[d]TBAClO$_4$ = 0.15M