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# Stereocontrolled generation of nucleophilic (*Z*)- or (*E*)-α-fluoroalkenylchromium reagents *via* carbon–fluorine bond activation: highly stereoselective synthesis of (*E*)- or (*Z*)-β-fluoroallylic alcohols†

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**Highly nucleophilic (*Z*)- or (*E*)-α-fluoroalkenylchromium species could be generated in a stereoselective manner *via* C–F bond activation of $CBrF_2$-containing molecules, and they reacted smoothly with various aldehydes to give (*E*)- or (*Z*)-β-fluoroallylic alcohol derivatives in high yields, respectively.**

Carbon–fluorine (C–F) bonds are the strongest single bonds in organic substances. Therefore, the carbon–fluorine (C–F) bond cleavage and its subsequent carbon–carbon (C–C) bond formation have been one of the most attractive and challenging issues because such a process offers great potential in providing novel synthetic methodologies in synthetic organic chemistry.[1]

To date, there have been substantial efforts to develop such transformations, but most of preceding examples are the reactions mediated or catalyzed by *late* transition metals, such as Cu,[2] Pd,[3] Ni,[4] Pt,[5] Rh,[6] Co,[7] Ir,[8] Fe.[9] In these cases, under the influence of *late* transition metals, the corresponding intermediary organometallics are characterized as *electrophilic*, which can react with nucleophiles, such as organolithium, Grignard reagent, organozinc, organoboronic acid, *etc.*, to afford the corresponding cross-coupling products (Fig. 1, Path A).[10] On the other hand, organometallic intermediates generated through an *early* transition metal-mediated C–F bond activation can be *nucleophilic*, and there are relatively few reports in this research area. (Fig. 1, Path B).[11]

In this communication we disclose facile methods for highly stereoselective generation of *nucleophilic* (*Z*)- or (*E*)-α-fluoroalkenylmetal species, *via* C–F bond activation with the early transition metal, $Cr^{(II)}$,[12] which react with a broad range of aldehydes, affording β-fluoroallylic alcohols (Table 1).

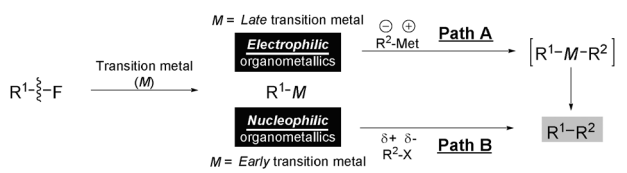
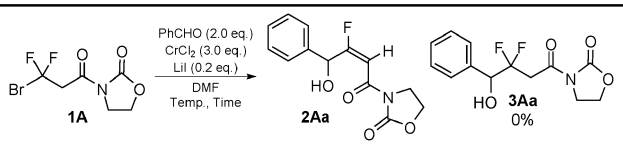



Fig. 1 Classification of carbon–fluorine bond activation.

Thus, treatment of **1A**[13] (1.0 equiv.) with 2.0 equiv. of benzaldehyde in the presence of 3.0 equiv. of $Cr^{(II)}Cl_2$ and 0.2 equiv. of LiI in DMF at −20 °C for 4 h gave the corresponding β-fluoroallylic alcohol **2Aa** in only 15% yield without recovery of **1A** (entry 1). In this case, any trace of fluorinated byproducts, including difluorinated coupling adduct **3Aa**, was not detected. While longer reaction time was ineffective (entry 2), raising the reaction temperature from −20 °C to 0 °C significantly improved the efficacy of the reaction; that is, **2Aa** was obtained in 86% yield (entry 3). The reaction also proceeded smoothly at ambient temperature (entry 4); however the reaction at 60 °C led to a significant decrease of the yield (entry 5). Unfortunately, a slight decrease of the yield was observed using a smaller equivalent of benzaldehyde (1.2 equiv.) (entry 7). In the absence of LiI, the reaction yield was sharply decreased to only 64% as well (entry 8). Finally the use of 4.0 equiv. of $Cr^{(II)}Cl_2$ led to the optimal reaction conditions (entry 9). To extend the scope of the

Table 1 Investigation of the reaction conditions




| Entry[a] | Temp. (°C) | Time (h) | Yield[b] (%) | Recovery of **1A**[b] (%) |
|---|---|---|---|---|
| 1 | −20 | 4 | 15 | Trace |
| 2 | −20 | 20 | 18 | Trace |
| 3 | 0 | 4 | 86 | Trace |
| 4 | r.t. | 4 | 84 | 0 |
| 5 | 60 | 4 | 27 | 0 |
| 6[c] | 0 | 4 | 13 | 21 |
| 7[d] | 0 | 4 | 76 | 4 |
| 8[e] | 0 | 4 | 64 | 9 |
| 9[f] | 0 | 4 | 89 | 0 |

[a] In every case, the *E*-isomer was obtained exclusively. [b] Determined by $^{19}F$ NMR. [c] Two equiv. of $CrCl_2$ was used. [d] The reaction was carried out in the presence of 1.2 equiv. of benzaldehyde. [e] Without LiI. [f] Four equiv. of $CrCl_2$ was used.

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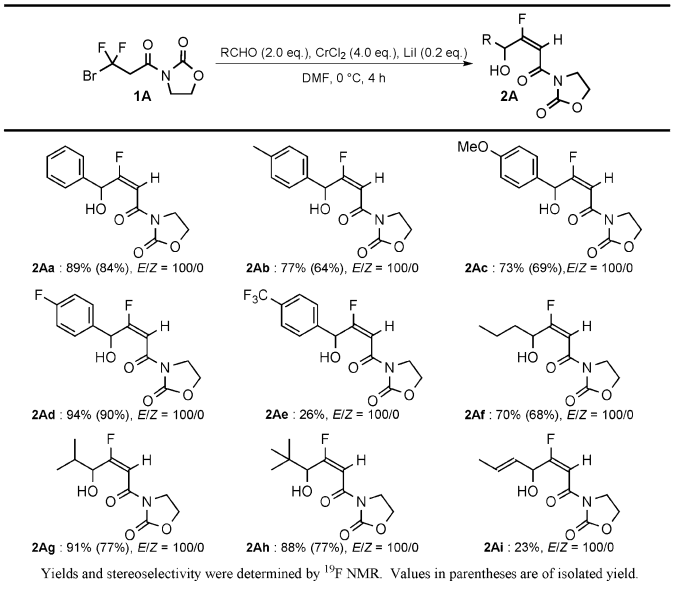
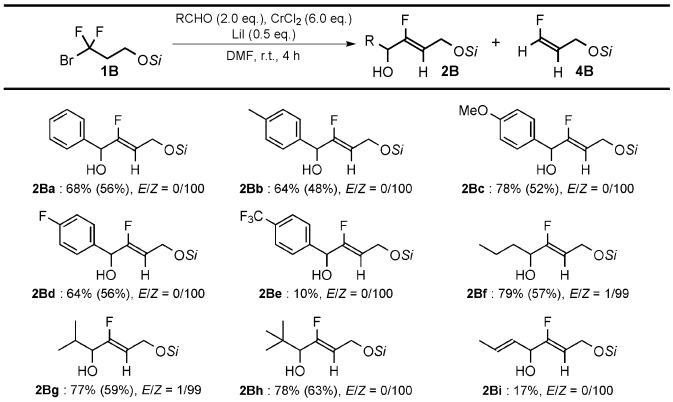
Table 2 Reductive coupling of **1A** with various aldehydes

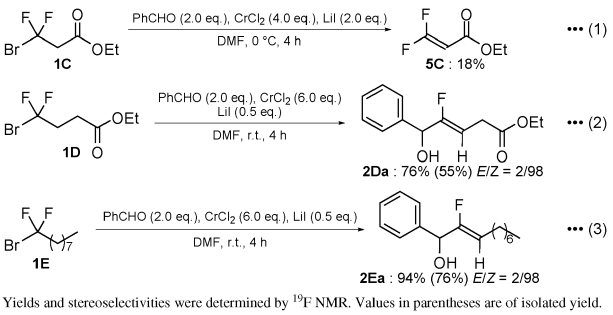



Yields and stereoselectivity were determined by $^{19}F$ NMR. Values in parentheses are of isolated yield.

Table 3 Reductive coupling of **1B** with various aldehydes




*Si* = *tert*-butyldiphenylsilyl. Yields and stereoselectivity were deteriubed by $^{19}F$ NMR. Values in parentheses are of isolated yield.




Yields and stereoselectivities were determined by $^{19}F$ NMR. Values in parentheses are of isolated yield.

Scheme 1 Screening of the substrates.

method, a broad range of aldehydes was tested for the present reductive coupling reaction. The results are summarized in Table 2.

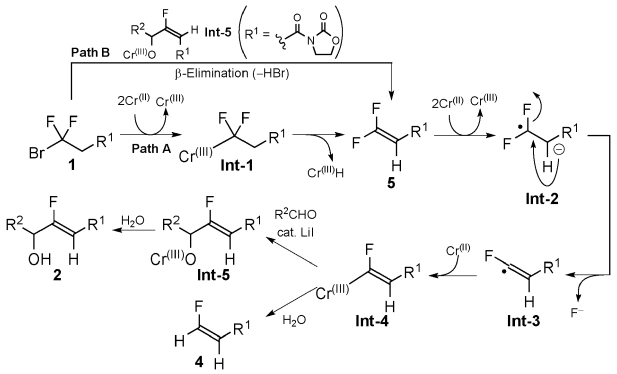
Aromatic aldehydes having an electron-donating group (Me and MeO) on the benzene ring could participate in the reaction to afford the desired products with high *E* stereoselection.[14] Also, *p*-fluorobenzaldehyde, which has an electron-withdrawing substituent, could be successfully applied for this reaction; however, a stronger electron-withdrawing $CF_3$ group as a substituent on the benzene ring led to a significant decrease of the yield. In the case of aliphatic aldehydes, the reaction with butanal, isobutyraldehyde, and pivalaldehyde took place very smoothly, regardless of the bulkiness of the substituent R in aldehydes, to obtain the corresponding alcohols in high to excellent yields. Disappointingly, crotonaldehyde was found to be unsuitable for the reaction, though its stereoselectivity was still high.

We also examined the reductive coupling reaction using the substrate **1B**[15] under similar reaction conditions as tabulated in Table 2. The results are listed in Table 3.

In sharp contrast to the results in Table 2, the reductive coupling proceeded in a highly *Z* selective fashion.[16] Thus, various aromatic aldehydes, such as benzaldehyde, *p*-tolualdehyde, *p*-anisaldehyde, and *p*-fluorobenzaldehyde, were all found to be good substrates as a reaction partner to give the corresponding (*Z*)-alcohols in acceptable yields. Similarly to the results shown in Table 2, the aromatic aldehyde with a $CF_3$ group at its *para* position is not suitable for this reaction. Various aliphatic aldehydes, such as butanal, isobutyraldehyde, and pivalaldehyde, could also be successfully applied for the reaction. However, α,β-unsaturated aldehyde showed poor yield in spite of the complete consumption of the starting compound **1B**. In all cases, a small amount of the byproduct **4B** was detected.

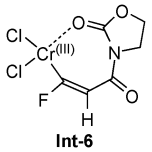
We also investigated the reductive coupling using other substrates, **1C**,[15] **1D**,[17] and **1E**[18] as shown in Scheme 1. It was revealed that **1C** gave β,β-difluoroacrylate **5C** in 18% yield as the sole product.[19] Very surprisingly, the substrate **1D**, which has just one-carbon elongated framework compared with **1C**, could participate in the reaction very nicely to give the corresponding adduct **2Da** in good yield. Additionally, **1E** was also found to be a good substrate for the reaction. In both cases, the β-fluoroallylic alcohols were obtained exclusively in a *Z* selective manner.

Although the detailed reaction mechanism must require for further investigation, our experimental results allow us to propose the following plausible reaction mechanism (Scheme 2).[20,21] Thus, the starting substrate **1** can be converted into difluorinated chromium species **Int-1** through the single electron transfer mechanism, followed by β-elimination, to give the corresponding difluoroalkene **5** (Path A). Again, single electron transfer takes place to




Scheme 2 A plausible reaction mechanism. (Halogen ligands on Cr were omitted.)




**Int-6**

Fig. 2 Chelation control.

afford the anion radical **Int-2**, which undergoes a smooth elimination of fluoride to provide a monofluorovinyl radical **Int-3**. Then a subsequent single electron transfer results in the formation of a thermokinetically stable (*E*)-fluorovinylchromium reagent **Int-4**, which can react with various aldehydes to yield the corresponding (*Z*)-β-fluoroallylic alcohol derivatives **2**, whereas unreacted vinylchromium provides (*Z*)-fluoroalkene **4** after quenching the reaction with $H_2O$.

In the case of the reaction with **1A**, however, β-elimination of **1** by the chromium alkoxide **Int-5** may play a role to provide difluoroalkene **5** due to a highly acidic α-proton of the carbonyl (Path B). Additionally, the Lewis acidic chromium metal can coordinate with the carbonyl oxygen of the oxazolidinone moiety to form a stable 7-membered intermediate **Int-6** (Fig. 2), which can react with aldehydes to produce (*E*)-β-fluoroallylic alcohols **2Aa–Ai.**

In summary, this communication reports the convenient $Cr^{(II)}Cl_2$-mediated generation of (*E*)- or (*Z*)-α-fluorovinylchromium species *via* C–F bond activation. These intermediates are very nucleophilic, which can react smoothly with various aldehydes, and β-fluoroallylic alcohols are afforded in moderate yields. Notably, the present methodology makes it possible to prepare both (*E*)- and (Z)-fluoroalkenes in a highly stereoselective manner.[22] Further studies on the reductive coupling are now underway in our laboratory.

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