# Synthesis of α-Alkylated (*Z*)-γ-Fluoro-β,γ-enoates through Organocopper Mediated Reaction of γ,γ-Difluoro-α,β-enoates: A Different Reactivity of $R_3Al$-Cu(I) and $Me_2CuLi$

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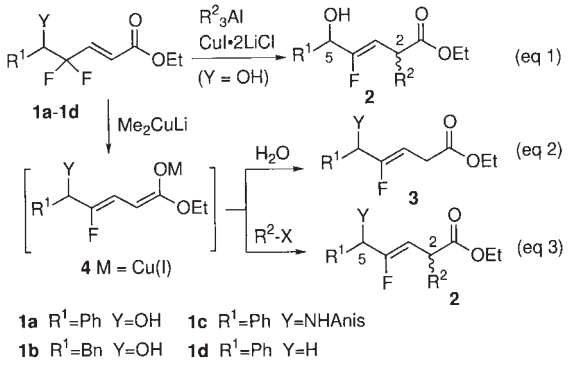
Reaction of γ,γ-difluoro-α,β-enoates having a δ-hydroxyl group with trialkylaluminum ($R_3Al$) in the presence of CuI•2LiCl proceeded in $S_N2'$-type manner to give α-alkylated (*Z*)-γ-fluoro-β,γ-enoates, while reductive defluorination of γ,γ-difluoro-α,β-enoates with $Me_2CuLi$ followed by reaction with alkyl halides provided the corresponding (*Z*)-α-alkylated products.

Fluoroolefin (-CF=CH-) is recognized to be an excellent steric and electronic mimic for an amide bond (-CO-NH-), while unlike the amide bond, fluoroolefin should be a nonhydrolyzable bond both chemically and enzymatically, and the lack of rotational freedom of this bond is also a different property from that of the amide bond.[1] Thus, utilization of (*Z*)-fluoroalkene dipeptide or depsipeptide isosteres as nonhydrolyzable and/or conformationally nonflexible replacements for the parent amide bonds has attracted much attention in the field of medicinal chemistry.[2–5] Not only as a replacement of amide bond, such functionalized fluorinated compounds can also be useful building blocks for a variety of fluorinated compounds. Although several reports have appeared for the synthesis of fluoroalkene dipeptide isosteres,[2–5] stereochemical control of the geometry of the fluoroolefin part and the relative configuration of the chiral centers as well as the use of readily obtainable starting material are major matters to be solved.

Recently, Otaka *et al.* demonstrated that γ,γ-difluoro-α,β-enoates can be converted to (*Z*)-γ-fluoro-β,γ-enoates utilizing organocopper mediated reduction[6] and to α-alkylated (*Z*)-γ-fluoro-β,γ-enoates utilizing organocopper reagent under reduction-oxidative alkylation conditions.[7] In the latter reaction, α-alkylated products were formed without any diastereo-selectivity (2,5-relative configuration) in moderate yields with concomitant formation of reduction product. We have independently developed a method for the construction of α-alkylated γ-fluoro-β,γ-enoates **2** using γ,γ-difluoro-α,β-enoate **1** (eq 1, eq 3).[8] As we wish to report in this paper, we found that reaction of γ,γ-difluoro-α,β-enoate having a δ-hydroxyl group with trialkylaluminum ($R_3Al$) in the presence of CuI•2LiCl proceeded in $S_N2'$-type manner to give the desired α-alkylated (*Z*)-γ-fluoro-β,γ-enoates (**2**, Y=OH) (eq 1). Furthermore, reductive defluorination of γ,γ-difluoro-α,β-enoates **1** with $Me_2CuLi$ followed by reaction with alkyl halides provided the α-alkylated (*Z*)-γ-fluoro-β,γ-enoates (**2**, Y=OH, NHAr, H) in good yields (eq 3).

As the substrates, we chose γ,γ-difluoro-α,β-enoates having a hydroxyl group (Y=OH, **1a**, **1b**)[9] or an amino group (Y=NHAnis, **1c**)[9] at the δ-position and without such a hetero-atom substituent (Y=H, **1d**)[10] to examine the reactivity of each compound in organocopper mediated reactions to convert to the α-alkylated γ-fluoro-β,γ-enoate **2**.

Reaction of **1a-d** with $Me_2CuLi$ (5 equiv) in THF gave the



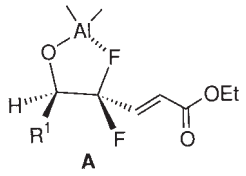

reductive elimination product **3** in high yields after aqueous work-up without the formation of the desired α-methylated product **2** (eq 2, see also Table 2), as in the reactions of similar substrates with organocopper reagent reported by Otaka.[6a,7] On the other hand, when the reaction was conducted using a combination of $R_3Al$ and CuI•2LiCl[11] in THF at 0 °C, direct introduction of the alkyl substituent from the aluminum reagent to the α-position via $S_N2'$-type reaction was achieved with the substrates having a hydroxyl group at the δ-position (**1a**, **1b**) (eq 1, Table 1).[12] Trimethylaluminum gave the α-methylated product **2a-1** (79%), **2b-1** (90%) in good yields, while tri-isobutylaluminum gave the α-alkylated product **2a-2** (25%), **2b-2** (58%) in moderate yields. In all cases, the reaction proceeds in completely *Z* selective manner. Regarding the diastereoselectivity, moderate selectivity (8-5.3 : 1) was observed with the phenyl derivative **1a** (entries 1, 2), but the reaction was almost nonselective in the case of the benzyl derivative **1b** (entries 3, 4). Since treatment of **1a** or **1b** with trialkylaluminum in THF followed by quenching with water resulted in a complete recovery of **1a** or **1b**, Cu(I) is a crucial additive for the reaction to proceed.[13]

Contrary to the above results, with the amino derivative **1c** and with the substrate lacking a δ-hydroxyl group **1d** α-alkylation did not occur under similar conditions ($Me_3Al$, CuI•2LiCl in THF) (entries 5, 6). Thus, a hydroxyl group at the δ-position in the substrate **1** seemed to be an essential functionality in the Cu(I)-promoted alkyl-transfer reaction with $R_3Al$. Although mechanistic detail are unclear at this moment,[14] it is likely that formation of a five-membered complex A involving the fluorine-aluminum coordination[15] is possibly the first step in the present reaction. By forming complex **A**, one of the two fluorine atoms should be activated as a leaving group and presumably the C-C double bond becomes more electrophilic, thereby complex **A** showed such reactivity toward copper reagent derived from $R_3Al$ and CuI•2LiCl, the nature of which is quite different from that of alkyllithium-based copper reagent such as $Me_2CuLi$.

**Table 1.** CuI•2LiCl mediated reaction of **1** with trialkylaluminum (eq 1)

| Entry | 1 | $R^2{}_3Al$ | 2 | $R^1$ | Y | $R^2$ | Yield/ %[a] | Ratio[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | $Me_3Al$ | **2a-1** | Ph | OH | Me | 79 | 8 : 1 |
| 2 | **1a** | $i$-$Bu_3Al$ | **2a-2** | Ph | OH | $i$-Bu | 25 | 5.3 : 1 |
| 3 | **1b** | $Me_3Al$ | **2b-1** | Bn | OH | Me | 90 | 1 : 1 |
| 4 | **1b** | $i$-$Bu_3Al$ | **2b-2** | Bn | OH | $i$-Bu | 58 | 1.5 : 1 |
| 5 | **1c** | $Me_3Al$ | **2c** | Ph | NHAnis | Me | 0[c] | — |
| 6 | **1d** | $Me_3Al$ | **2d** | Ph | H | Me | 0[d] | — |

[a]Isolated yield. [b]Diastereomer ratio was determined by $^1$H- and $^{19}$F-NMR. Stereochemistries were not determined. [c]Reduction product **3c** was isolated in 41% yield. [d]Recovery of the starting material.




**A**

As mentioned above, reaction of **1a-d** with $Me_2CuLi$ in THF gave the reductive elimination product **3** in high yields after aqueous work-up (Table 2, entries 1,2). For mechanistic considerations, Otaka postulated the generation of a stable Cu(I) or Cu(II) intermediate via two electron transfer for the Cu(I) intermediate and *via* single electron transfer for the Cu(II) intermediate, respectively.[7] Since Cu(II) species derived from ester enolate are known to be very unstable to readily decompose to Cu(I) and radical species,[16] it is likely that reaction of **1** with $Me_2CuLi$ generates the Cu(I) intermediate **4**, which would react with alkyl halides to give $\alpha$-alkylated (*Z*)-$\gamma$-fluoro-$\beta$,$\gamma$-enoate **2**. Thus, treatment of **1a** with $Me_2CuLi$ (5 equiv) in THF at $-20\,^\circ$C for 15 min followed by the reaction with methyl iodide (10 equiv) at $0\,^\circ$C for 2 h gave $\alpha$-methylated product **2a-1** in 93% yield (Table 2, entry 3). As shown in Table 2, not only $\delta$-hydroxylated derivatives **1a**, **1b**, but also the amino derivative **1c** and the substrate without an additional $\delta$-substituent, **1d**, provided the (*Z*)-$\alpha$-alkylated products in good yields without formation of a detectable amount of reduction product **3** (entries 3–7). Moderate diastereoselective alkylation (5-6 : 1) was observed only in the case of **1b** (entries 4,5).

In conclusion, we have shown efficient methods for the preparation of $\alpha$-alkylated (*Z*)-$\gamma$-fluoro-$\beta$,$\gamma$-enoates from $\gamma$,$\gamma$-difluoro-$\alpha$,$\beta$-enoates using Cu(I) mediated alkyl-transfer reaction with trialkylaluminum and $Me_2CuLi$ mediated reduction followed by alkylation with alkyl halide, respectively.

**Table 2.** $Me_2CuLi$ mediated reduction and $\alpha$-alkylation of **1** (eq 2, 3)

| Entry[a] | 1 | $R^2$-X | Product | $R^1$ | Y | $R^2$ | Yield/ %[b] | Ratio[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | — | **3a** | Ph | OH | — | 70 | — |
| 2[d] | **1a** | — | **3a** | Ph | OH | — | 64 | — |
| 3 | **1a** | MeI | **2a-1** | Ph | OH | Me | 93 | 1 : 1 |
| 4 | **1b** | MeI | **2b-1** | Bn | OH | Me | 75 | 6 : 1 |
| 5 | **1b** | BnBr | **2b-3** | Bn | OH | Bn | 78 | 5 : 1 |
| 6 | **1c** | MeI | **2c** | Ph | NHAnis | Me | 92 | 1.4 : 1 |
| 7 | **1d** | MeI | **2d** | Ph | H | Me | 95 | — |

[a]Entries 1, 2 correspond to eq 2 and entries 3-7 correspond to eq 3. [b]Isolated yield. [c]Diastereomer ratio was determined by $^1$H- and $^{19}$F-NMR. Stereochemistries were not determined. [d]$Me_3Al$ (2 equiv) was added.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

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