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Stereoselective construction of functionalized (*Z*)-fluoroalkenes directed to depsipeptide isosteres

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Abstract—Cu(I)-mediated alkyl-transfer reaction of trialkylaluminum (R_3Al) with (*E*)- or (*Z*)-4,4-difluoro-5-hydroxyallylic alcohol derivatives proceeded in an SN′-type manner to give the corresponding 2-alkylated (*Z*)-4-fluoro-5-hydroxyhomoallylic alcohol derivatives with 2,5-*syn*- or 2,5-*anti* selectivity, respectively. Oxidation of the primary hydroxyl group of the product to carboxylic acid was easily achieved without epimerization at the chiral centers. © 2002 Elsevier Science Ltd. All rights reserved.

Fluoroolefins (–CF=CH–) are considered to be ideal mimics for amide bonds (–CO–NH–) due to the close similarity of the steric and electronic properties.[1] Contrary to these similarities, fluoroolefins should be non-hydrolyzable bonds both chemically and enzymatically, and the lack of rotational freedom of this bond is also a different property from that of the amide bond. On the basis of these unique properties, utilization of (*Z*)-fluoroalkene dipeptide or depsipeptide isosteres as non-hydrolyzable and/or conformationally restricted replacements for the parent amide bonds has attracted much attention in the field of medicinal chemistry (Fig. 1).[2–5] For the synthesis of fluoroalkene dipeptide or depsipeptide isosteres,[2–5] there remains several problems to be solved with respect to the stereochemical control of the *Z*-configuration of the fluoroolefin part and the relative stereochemistry of the two chiral centers (2- and 5-positions), as well as the use of readily obtainable starting material.

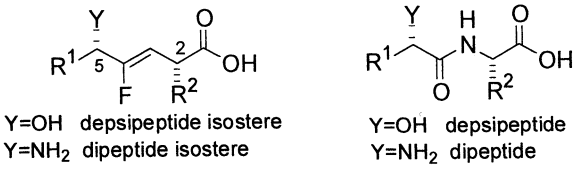
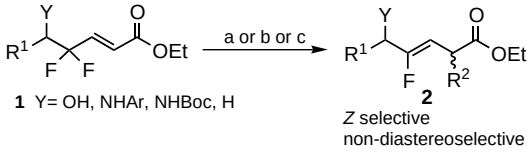


Figure 1. Displacement of amide bond by *Z*-fluoroolefin

Recently, we have reported that α-alkylated (*Z*)-γ-fluoro-β,γ-enoates **2** can be prepared from γ,γ-difluoro-α,β-enoates **1** upon treatment with trialkylaluminum (R_3Al) and Cu(I) or through Me_2CuLi-mediated reductive defluorination followed by α-alkylation with alkyl halide (Scheme 1, a or b).[6] As an alternative method for the synthesis of **2** from **1**, Otaka demonstrated the utilization of organocopper reagents under reduction–oxidative alkylation conditions (Scheme 1, c).[7] Although these reactions proceed with complete *Z* selectivity, low diastereoselectivity in each reaction is a severe problem to be solved.

Further efforts were made to develop a highly stereoselective preparation of these compounds, and we found that Cu(I)-mediated alkyl-transfer reaction of trialkylaluminum (R_3Al) with (*E*)-4,4-difluoro-5-hydroxyallylic alcohol derivatives **3** provides the corresponding 2-alkylated 4-fluorohomoallylic alcohol derivatives **4** in a completely *Z* and 2,5-*syn* selective manner (Scheme 2). In this paper, we report these promising results for the preparation of (*Z*)-fluoroalkene depsipeptide isosteres **5**.



Scheme 1. *Reagents and conditions*: (a) $R^2{}_3Al$, CuI·2LiCl (for Y = OH); (b) (1) Me_2CuLi, (2) R^2-X; (c) (1) [R_2Cu], (2) O_2.

Keywords: fluoroolefin; difluoroallyl alcohol; trialkylaluminum; cuprous iodide; depsipeptide.

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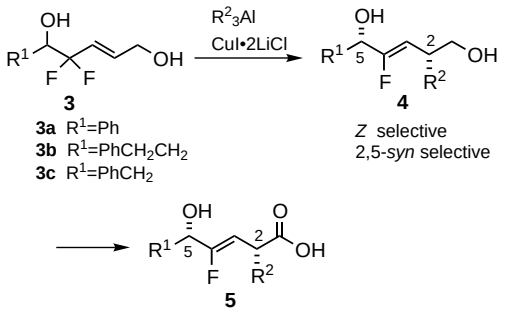
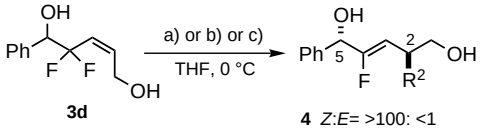


Scheme 2.

As the substrates, we chose both *E*- and *Z*-isomers of 4,4-difluoro-5-hydroxyallylic alcohol derivatives (**3a–c**[8] and **3d**[9]) to examine the reactivity and the stereochemical outcome in organocopper-mediated reactions to convert to the 2-alkylated 4-fluorohomoallylic alcohol derivative **4**.

In Table 1, preliminary results of reactions of (*E*)-difluoroallylic alcohols **3a–c** with $R^2{}_2CuLi$ (entries 8–10) and $R^2{}_3Al$–CuI·2LiCl (entries 2–7) are shown. Reaction of **3a** with Me_2CuLi proceeded smoothly (THF, 0°C, 2.5 h) to give the 2-methylated homoallylic alcohol **4a-1** in high yield (90%) with relatively high *Z* selectivity (*Z*/*E*=15), but with low diastereoselectivity (*syn*/*anti*=2 for the *Z* isomer) (entry 8). Similar high *Z* selectivity but almost no diastereoselectivity was observed in the reactions of **3a** or **3b** with alkyllithium-based copper reagents (entries 9 and 10). On the other hand, when the reaction of (*E*)-difluoroallylic alcohols **3a–c** was conducted using a combination of trialkylaluminum (R_3Al, 5–10 equiv.) and CuI·2LiCl[10](2.5 equiv.) in THF at 0°C for 15–20 h, the desired 4-fluoro-5-hydroxyhomoallylic alcohols **4a–c** were obtained in good to excellent yield (62–98%) with complete *Z*-selectivity and 2,5-*syn* diastereoselectivity (entries 2–7).[11] In the absence of CuI·2LiCl, no reaction occurred upon treating **3a** with Me_3Al resulting in the recovery of **3a** (entry 1). Thus, Cu(I) is a crucial additive for the alkyl-transfer reaction of trialkylaluminum to proceed.[12,13]



Scheme 3. *Reagents and conditions*: (a) Me_3Al, CuI·2LiCl, 22 h, **4a-1** 53%, *syn*/*anti*=1/11; (b) Me_2CuLi, 4 h, **4a-1** 76%, *syn*/*anti*=1/4.7; (c) *i*-Bu_3Al, CuI·2LiCl, 22 h, **4a-2** 30%, *anti* only.

The reactivity and stereochemical outcome of *Z*-isomer **3d** was compared with those of *E*-isomer **3a**. The results obtained are shown in Scheme 3. Reaction of *Z*-isomer **3d** under the similar conditions (Me_3Al, CuI·2LiCl, THF, 0°C, 22 h) proceeded more slowly than that of *E*-isomer **3a** to give the methylated 4-fluorohomoallylic alcohol **4a-1** in moderate yield (53%) along with the recovery of **3d** (41%). The stereochemistry of the product thus obtained indicated that the reaction proceeds in a highly *Z*-selective manner (*Z*/*E* >100) and in a relatively high *anti*-selective manner (*syn*/*anti*=1/11), opposite to that of *E*-isomer **3a** (Scheme 3). Using *i*-Bu_3Al instead of Me_3Al under similar conditions, **3d** gave the allylic substitution product **4a-2**, having *Z*-configuration and 2,5-*anti* relative stereochemistry, in 30% yield along with the recovery of **3d** (49%). As in the case of *E*-isomer **3a**, reaction of *Z*-isomer **3d** with Me_2CuLi proceeded with lower diastereoselectivity (*syn*/*anti*=1/4.7) to give **4a-1** in 76% yield (Scheme 3).

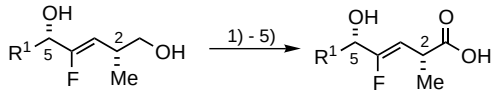
The results mentioned above indicated that using the *E*- or *Z*-isomer of 4,4-difluoro-5-hydroxyallylic alcohol **3**, both the *syn* or *anti* isomers of 2-alkylated (*Z*)-4-fluoro-5-hydroxyhomoallylic alcohol **4** are highly selectively constructed by the reaction with R_3Al and CuI·2LiCl, although the product yield should be improved in the case of the *Z*-isomer of **3**.

Oxidation of the primary hydroxyl group of **4** to carboxylic acid can be achieved by Jones' oxidation after protection of the secondary hydroxyl group as its acetate form to give the desired acid **5** (**5a-1** in 53% and

Table 1. Reaction of (*E*)-difluoroallylic alcohol **3a–c** with $R^2{}_3Al$-CuI·2LiCl or $R^2{}_2CuLi$

Entry	**1**	R^1	Reagent	**4**	R^2	Yield (%)[a]	*Z*/*E*[b]	*syn*:*anti*[b,c]
1	**3a**	Ph	Me_3Al	**4a-1**	Me	0[d]		
2			Me_3Al, CuI·2LiCl	**4a-1**	Me	98	>95	>95:1
3			*i*-Bu_3Al, CuI·2LiCl	**4a-2**	*i*-Bu	68	>95	>95:1
4	**3b**	$PhCH_2CH_2$	Me_3Al, CuI·2LiCl	**4b-1**	Me	65	>95	>95:1
5			*i*-Bu_3Al, CuI·2LiCl	**4b-2**	*i*-Bu	62	>95	>95:1
6	**3c**	$PhCH_2$	Me_3Al, CuI·2LiCl	**4c-1**	Me	98	>95	>95:1
7			*i*-Bu_3Al, CuI·2LiCl	**4c-2**	*i*-Bu	78	>95	>95:1
8	**3a**	Ph	Me_2CuLi	**4a-1**	Me	90	15	2:1
9			*n*-Bu_2CuLi[e]	**4a-3**	*n*-Bu	58	13	1.1:1
10	**3b**	$PhCH_2CH_2$	Me_2CuLi[e]	**4b-1**	Me	90	11	1:1

[a] Isolated yields.
[b] The ratio was determined by ^1H and ^{19}F NMR.
[c] For the *Z*-isomer.
[d] Recovery of **1a**.
[e] Me_3Al (2 equiv.) was added.



4a-1 R^1=Ph
4c-1 R^1=$PhCH_2$
5a-1 R^1=Ph
5c-1 R^1=$PhCH_2$

Scheme 4. *Reagents and conditions*: (1) TBDMSCl, imidazole, DMF; (2) Ac_2O, Et_3N, THF; (3) TBAF, THF; (4) CrO_3, H_2SO_4, acetone; (5) KOH, H_2O–MeOH, then 10% HCl.

5c-1 in 52% overall yield, respectively), without detectable epimerization at the chiral centers (Scheme 4).

In conclusion, we have developed a completely stereoselective synthesis of (*Z*)- and 2,5-*syn* 2-alkyl-4-fluoro-5-hydroxy-3-alkenoic acid through the Cu(I)-mediated allylic substitution reaction of trialkylaluminum with (*E*)-4,4-difluoro-5-hydroxyallylic alcohol derivative. The present reaction should provide an efficient method for the preparation of functionalized *Z*-fluoroolefins, which, in particular, are applicable to the preparation of depsipeptide isosteres. Investigation on the mechanistic details of the present reaction is currently in progress.

Acknowledgements

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8. (*E*)-Difluoroallylic alcohols **3a**–**c** were prepared by DIBAL reduction of the corresponding ester forms **1**. See Refs. 6 and 7.
9. (*Z*)-Difluoroallylic alcohol **3d** was prepared by a three-step procedure: (1) indium-mediated reaction of 4-bromo-4,4-difuoro-2-butyn-1-ol TBDPS ether with benzaldehyde; (2) hydrogenation (Pd–$BaSO_4$, quinoline); (3) TBAF, THF. For examples of indium-mediated difluoropropargylation of aldehydes, see: (a) Wang, Z.; Hammond, G. B. *Tetrahedron Lett.* **2000**, *41*, 2339–2342; (b) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547–6552.
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11. Typical procedure (Table 1, entry 2): Under an argon atmosphere, to a solution of **3a** (1 mmol) in THF at 0°C was added trimethylaluminum (5 mmol, 1 M hexane solution). After stirring for 10 min, a 0.5 M THF solution of CuI·2LiCl (2.5 mmol)[10] was added and the reaction mixture was stirred for 20 h at 0°C. Addition of 5% HCl and extractive work-up gave the crude product, which was purified by column chromatography (silica gel, hexane–AcOEt 1:1) to give **4a-1** in 98% yield.
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